OXIDATIVE DESULFURIZATION OF AZOLE-2-THIONES WITH BENZOYL PEROXIDE

by

DEREK MICHAEL WOLFE

(Under the Direction of Peter R. Schreiner)

ABSTRACT

1-Alkyl-3-methylimidazole-2-thiones were prepared in one pot and subsequently converted to 1-alkyl-3-methylimidazolium benzoates through a sequence consisting of an oxidative desulfurization with benzoyl peroxide and a novel anion exchange. Also reported are the outcomes of exchanges with other anions, acidifications of the imidazolium benzoates to other salts, and the syntheses of both 1,3-diphenylimidazolium and 3-alkylthiazolium salts from the corresponding azole-2-thiones. This oxidative desulfurization was also appropriate for the synthesis of neutral imidazoles from 1-alkylimidazole-2-thiones, which were prepared from amino acids by way of 2-thiohydantoins. Four such sequences are described, one of which constitutes a formal synthesis of three imidazole alkaloids from the sponge *Leucetta*. The merits of these routes in terms of both adaptability and operational simplicity are emphasized. A chiral imidazolium salt featuring camphor was pursued, but an imidazole-2-thione precursor suited to desulfurization could not be prepared; the desired salt could not be assembled with conventional methods, either. The unsuitability of some imidazolium ionic liquids in an adaptation of the phase transfer catalyzed halogenation is discussed in the context of γ-adamantane amino acids.

INDEX WORDS: Anion exchange, Desulfurizations, Heterocycles, Imidazoles, Ionic Liquids, Oxidations, Sulfur

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DEDICATION

For Mom and Dad

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In the late 90s, graduate students in the Department of Chemistry drew the same salary all the rest of their years in the Department as they did in their first. As I understand it, I entered with the first class that received annual cost of living raises. I'm grateful to whatever group of people saved me from subsisting on turn of the century dollars because it kept my name out of the AJC alongside the words "clandestine", "Airstream", and "Danielsville". I am appreciative that Dr. Schreiner gave me a great deal of latitude researchwise and did not breathe down my neck for results at the same time, and that he saw to it that I visited his labs in Giessen in 2003. I didn't want to go because of the time I thought I would waste in duplicating work here (going) and there (coming back); at the time, I didn't know how little whatever time was lost was going to figure into the span of my graduate career. Working abroad proved to be incalculably valuable for all the intangible reasons, and I couldn't / wouldn't have done it without Schreiner's insistence. When I went back in 2005, I rediscovered the value of working in labs full of people and having regular group meetings—which feels weird for me to admit, because I had always thought I was so dedicated to the discharge of my own brand of misanthropy. Team Giessen (if they are reading this) know who they are and I hope they are not offended that I do not thank each of them by name for their hospitality during my sojourns in 2003 and 2005.

I am, however, compelled to explicitly thank Binh Bui for putting me up in his apartment (on his floor) within walking distance of the Chemistry Building, and Dr. Andrey Fokin for brightening a room just by being in it. Fokin also gave Ellen Downs (now Ellen Beaulieu) and me countless hours of enjoyment as we repeated *ad nauseum* the phrase (with the best Russian

accents we could muster), "No, Peter! Peter, no!" This utterance came out over lunch one day when Schreiner made the observation that milk is white and opaque because it is an emulsion of fat and water, and that fat free milk gets its natural look from titanium dioxide added to it. Fokin came in on the tail end of Schreiner's comment, and took him to mean that skim milk is only titanium dioxide in water. A hilarious comedy of errors ensued. Fokin has been eminently quotable for as long as I've known him. Speaking in reference to my horror that he had just unsealed a steel canister of commercial methyl magnesium bromide only to go into it with a syringe he found hanging out, chilling under atmospheric conditions, Fokin also gave us the phrase that would be my epitaph were I of Russian extraction: "For Russian, is no big deal." As I recall, that reaction went in 78% yield; no big deal, indeed. Other combinations of words that are made cooler by Fokin saying them (and which I figure I will hear in my head for the rest of my life) are "boiling hot bromine", "was cheapest thing" (in reference to benzene–carbon tetrachloride mobile phases in silica gel chromatography), "this is how Russians discipline their children" (in reference to a picture of himself [shirtless] holding his daughter under a Siberian waterfall), and "tonight we will have party with meat, beer, everything."

The unflappable Boryslav Tkachenko and the inimitable Volker Lutz each visited Schreiner's labs here at Georgia and I appreciated their company immensely. Alexander Wittkopp and I only overlapped for a year or so, but I list him among my contemporaries and I feel as though I learned a great deal from him. None of it is coming to me right now, but I'm sure it's there. If nothing else, he gets my thanks for letting me sleep on the floor of his apartment in Munich for Oktoberfest 2005 because that's the rule: I sleep on your floor in Germany, you get acknowledged (*vide supra*). As I stop to think about it, it occurs to me that Ellen was the only coworker I ever had who was American born and bred, and if you have to

have coworkers, it's nice to have ones that get "it" for all the same reasons as you do, and she did. It was also fun to hear her say "*Ich bin Auslander!*" to Giesseners as they tried to make small talk. I never told her that, for want of an "*-in*" on "*Auslander*", she was saying, "I'm a boy from another country!" It's the simple pleasures that keep me going. Christopher Rinderspacher was my longest running (nigh constant) coworker. He also got "it", and got "it" so well and was around so often for so long that I expect to be diagnosed with schizophrenia and discover he was just an imaginary friend—in a *Fight Club* and not in an *A Beautiful Mind* kind of way. As the only other member of Team Georgia, and considering that no mortal power could have moved our research projects farther apart, he deserves special credit for feigning interest in what I was doing during what I guess qualify as impromptu group meetings.

I was primed for graduate school by the faculty of the Roanoke College Chemistry Department, Drs. Gary Hollis, Ben Huddle, Vern Miller, Ron Oetgen, and Jack and Gail Steehler. They were, and are, committed to getting undergraduates, including me, all the research experience the law allows, and they don't stop there—they had me back last April to give my first invited lecture. The invitation was extended by Hollis, who taught me Organic Chemistry and supervised my research project in college. The Roanoke College Chemistry Department and Hollis in particular have been instrumental to my development as a chemist. While I'm here, thanks are due Dr. David Gardner for waiving the prerequisites for his classes on immunology and cell physiology, and sparing me lab work in taxonomy and animal behavior. Dr. James Ogier didn't only teach me German, but he willingly did it privately in addition to his regular teaching load because I had Biochemistry in the same time slot. There will be some very confused authorities in Frankfurt if they ever run upon the real Ogier, because we look nothing alike. I feel he has only himself to blame.

At Georgia, the people who chaperoned me to this point (aside from Schreiner) were Drs. Geert-Jan Boons, Robert Phillips, and Paul Schleyer, none of whom will be available at the time appointed to defend this dissertation, and I appreciate their service to this point. I thank Schleyer in particular for both his class on the structure and energy of carbon compounds and the voluminous, largely first-hand account that is his lecture notes on structural and physical organic chemistry. It's a post-*Talladega Nights* world, and it would be great if Schleyer could be convinced to drop an occasional, "Did that blow your mind? *Because that just happened*!" in future lectures—especially in reference to anything planar / hypervalent carbon in nature, or pertaining to X-ray crystal structures being wrong. At the 11th hour, Drs. George Majetich and Vladimir Popik have come on board as my advisory committee. I am immensely grateful that they will give up an entire morning in July to, presumably, get me out of here, and that they will do so in exchange for only an offering of baked goods, juice, coffee, and their choice of 2% milk or aqueous titanium dioxide. I know a lot of words, and I can't come up with the precise ones to thank them.

I didn't have an IR spectrophotometer at my disposal during this experience, and I thank Brian Loudermilk and his major professor, Dr. James de Haseth, for allowing me access to theirs. Both crystal structures appearing in the chapter on γ-adamantane amino acids were taken *pro bono* by Jason Vohs of Dr. Greg Robinson's group.

And, finally, to my friends and / or roommates (primarily Jeremy, Riland, Barry), you're looking at the reason Grandma missed your birthday. May you all be given a long time to fear the expansion phases of Jupiter and of Camryn Manheim while experimenting with multiverses in your basement (singular) in a non-extradition country.

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CHAPTER 1

IONIC LIQUIDS

1.1. FUNDAMENTAL ASPECTS OF IONIC LIQUID CHEMISTRY

Articles appearing in *Green Chemistry* (at least in its early issues) contain a statement of the green context of the work. K. R. Seddon provided this context in a historical account from J. S. Wilkes regarding the evolution of modern ionic liquid (IL) chemistry and technology. In this statement, Seddon implied that the lack of both personal comments and critical analyses in reviews of the IL literature were unfortunate.[1] This may be the state of the review literature in general, but reviews dealing with ILs have become particularly formulaic. Historical dating of these materials comes first; depending on the author, ILs are either approaching 100 years old or they have been with us since the very dawn of man. A graph or table is used to illustrate the boom in references dealing with ILs over the past few years, and speaks to the legitimate problem that there is an unapproachable number of references for any real review of IL chemistry as a whole. Next come surveys of the physical properties of ILs and of the methods to prepare them. There is usually little attention paid to either the minor but inextricable inconveniencies or the prevailing but physically unrealistic notions associated with modern IL preparations. Still less often is there any serious consideration for the fact there are currently no codified, reliable conventions allowing descriptions of IL formulations in universally understandable terms. By way of unchecked enthusiasm, many authors go on to frame ILs as little less than the alkahest when they take up the issue of organic reactions in ILs. The starting

point for any discussion of organic reactivity in ILs is the set of reactions appearing in T. Welton's *Chemical Reviews* paper[2] and the book he co-edited with P. Wasserscheid.[3]

Mechanical as it is, there is no better way to introduce the topic of IL chemistry, and I will follow this formula almost to the letter, save adding critical analysis and opening with an analogy I believe offers a useful perspective on the current scramble to reevaluate the whole of chemistry in ILs. I imagine, but have not yet found the right sort of references to prove, any recounting of the emergence of ILs parallels the story of dimethylsulfoxide, which does not appear to have been reviewed for its own sake since H.-J. Niclas and coworkers did it in 1967.[4] Books with a focus on the inherent pharmacological value of dimethylsulfoxide and with its use in drug delivery are available from the scientific and popular literature,[5, 6] but these are only a few years newer. By the time of Niclas and coworkers' review, roughly 300 references entailing dimethylsulfoxide were available (Figure 1). The number of new references nearly tripled from the period 1962 – 1966 to the period 1967 – 1971, more than doubled across the next period, and has grown steadily in the last 30 years.

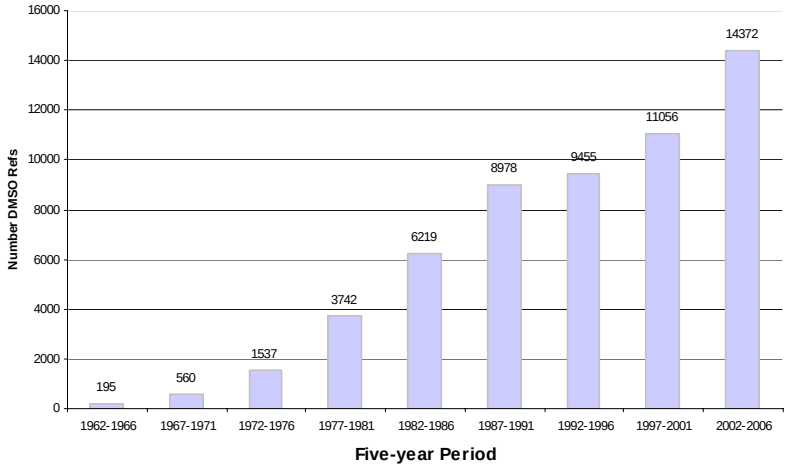


Figure 1. Abundance of DMSO references in five-year periods since 1962.

Today, attempting the second chapter of the 1967 review would be a fool's quest. Even in the absence of such a review, the characteristics of dimethylsulfoxide are widely known. It is a polar aprotic solvent that readily takes up organic and inorganic materials. It can be used as an emulsifier. It has its own characteristic acid–base chemistry, and F. G. Bordwell famously used this property to provide an alternative tabulation of pK_a values to those in water. Dimethylsulfoxide can also be used as an oxidizing agent, as seen in the Kornblum, Pfitzner–Moffatt, and Swern oxidations. The ylide derived from trimethylsulfoxonium derived from dimethylsulfoxide serves as a methylene transfer agent, as seen in the Corey–Chaykovsky and similar reactions. Dimethylsulfoxide's behavior in redox chemistry also means it cannot be combined with hydroiodic acid (DMSO + 2 HI → DMS + I_2 + H_2O), thiols (2 RSH + DMSO → RSSR + DMS + H_2O), or certain oxidizing agents.

The process of drying and distilling dimethylsulfoxide is notoriously tedious, and it is known in sum that dimethylsulfoxide, like every other solvent, possesses both inherent advantages and limitations. Dimethylsulfoxide is different from many other solvents in that it has not been used since time immemorial. It has come into wide use in less than one human lifetime. The citations from its first occurrences and from the development of an understanding of its properties can still be found. And so it is with ILs, except the understanding of their properties is in development right now. Hopefully, the day will come when the following properties and uses of ILs do not need an introduction, or at least not as much of one.

In introducing the topic as it was 25 years ago, D. G. Lovering observed there was an idea "often peddled in research theses . . . that [molten salt technology] started on the shores of ancient Phoenicia, where the glass industry was born." Continuing with the theme that the real dates of the first appearances of liquefied ion pairs are unknowable, he noted that the earliest

solder fluxes and smelting processes may have relied on liquid salt phases. He concluded an understanding of molten salts in the modern sense goes back at least to the 19th century, beginning with the work of H. Davy on the isolation of alkali metals from their molten hydroxides, of M. Faraday on the laws of electrolysis using molten lead halides, and the electrolytic preparation of aluminum introduced near the end of that century.[7] Narratives from Wilkes also provide examples of liquified ionic compounds reaching back many years.[1, 3] For example, he notes a byproduct sometimes separating from the mother liquors of classic Friedel–Crafts reactions—the "red oil"—is a liquefied arenium haloaluminate intermediate. He continues with the observations that simple alkylammonium chlorides and copper (I) chloride, both solids at room temperature, liquefy when mixed,[8] and that simple alkylammonium nitrates can melt around or below room temperature.

Welton points out that ethylammonium nitrate (EAN) in particular (mp 12 ^{o}C) was first described in 1914 by P. Walden.[2] It is frequently repeated that EAN is one of the oldest examples of an IL in the modern sense, if not the oldest, and that is more or less accurate. A translated passage from Walden's 1914 paper[9] is available from C. Reichardt,[10] and it shows Walden did not isolate EAN by any accident. He had deliberately pursued salts melting below 100 ^{o}C, which is the exact same arbitrary cutoff used in today's IL vernacular. Walden in fact sustained a program into the 1930s on what he variably called fused, low-melting, or molten salts, publishing at least eight more papers on the topic.[11-18] Reichardt also notes that P. C. Ray and J. N. Rakshit identified other liquid ammonium salts earlier in the same decade.[10] Walden made as much clear in his 1914 paper,[9] from which Reichardt translated the following statement: "The study of molten salts concerning conductivity, density, viscosity, etc., has been thoroughly studied during the last years . . . ."[10]

The lesson here is that the use of ionic compounds in the liquid state predates their recognition as such, but this recognition and even some of the current vocabulary describing these liquids—molten salts, fused salts, Coulomb(ic) liquids, ILs, room temperature ILs (RTILs), non-aqueous RTILs (NARTILs), organic ILs (OILs), and ambient temperature ILs (ATILs)—trace back nearly a century. An additional point authors usually make, though sometimes only implicitly, is that the historical record on these liquids shows they have always attracted a great deal of attention in applied science. For example, descriptions of molten salts in the most easily appreciated sense, melted inorganic salts, include the phase and mole fraction diagrams one would expect, as well as mathematical treatments of lattice, diffusion, and transport properties at high temperatures in fluids composed of ions.[7, 19-22] However, included in equal proportion in these references are accounts of these fluids applied to industrial processes requiring high temperatures, such as metal and petroleum refining. Lovering's comments in particular bear repeating in this regard.

Since molten salts are electrolytes in their most concentrated form, it follows they have been evaluated in electrochemical applications without interruption.[7, 19-23] Recent literature deals with general aspects of ILs as media for electrochemistry,[24-27] and with electrodeposition,[28-30] voltammetric studies,[31] energy storage,[32] and electrochemical generation of organic radical cations[33] in particular. It was the prospect of molten salt batteries that caught the interest of the U.S. Air Force (USAF) in the 1960s, but a practical implementation would require salts melting around room temperature. The oldest solution to this problem, which predates the USAF's interest, is the doping of salts with other salts to yield a mixture comprised only of ions that is liquid in a convenient temperature range. The aforementioned mixtures of simple alkylammonium chlorides and copper (I) chloride[8] are

examples, as are several salts of the formula $Na_{13}[(lanthanide)(TiW_{11}O_{39})_2]$, which were just reported in 2004;[34] many other compositions are known.[19]

Operating in part on funding from the USAF, R. A. Osteryoung was the first to consciously develop melts of organic salts with an eye towards energy storage. His first salts were mixtures of ethylpyridinium bromide and aluminum chloride that could melt below room temperature, depending on the proportions.[35, 36] Systems based on 1-butylpyridinium chloride and aluminum chloride, including a tidy example of a 1 : 1 "all-chloride" mixture that was liquid at room temperature,[1] followed.[37] C. L. Hussey introduced the terms "basic", "neutral", and "acidic" to describe mixtures of this type with a larger molar amount of salt than aluminum halide, equal mole fractions of each component, and more moles of aluminum halide than salt, respectively.[38] The rationale behind this terminology is that a substoichiometric amount of aluminum halide leaves some basic halide free, whereas an equimolar amount of aluminum halide should bind all free halide as the tetrahaloaluminate. When the aluminum halide is present in excess, some free Lewis acid will exist in the mixture, hence the name, and the relevant anions may be tetrahaloaluminates or heptahalodialuminates, which exist in equilibrium. The 1 : 1 mixture is conceptually easy because the concentrations of free halide and higher order metallates are both very small, and the only significant anion is the tetrahaloaluminate. The liquidity of these mixtures is explained in terms of charge delocalization. Dispersion of the formal charge of the cation throughout the pyridine ring and of the anion into four chlorines of the aluminate disrupts the Coulombic interactions that account for the generally high melting points of salts. This disruption allows the mixture to melt below room temperature. Following Osteryoung's examples, new room temperature molten salts were rationally designed based on charge distribution, and many cation motifs are in use today (Figure 2).

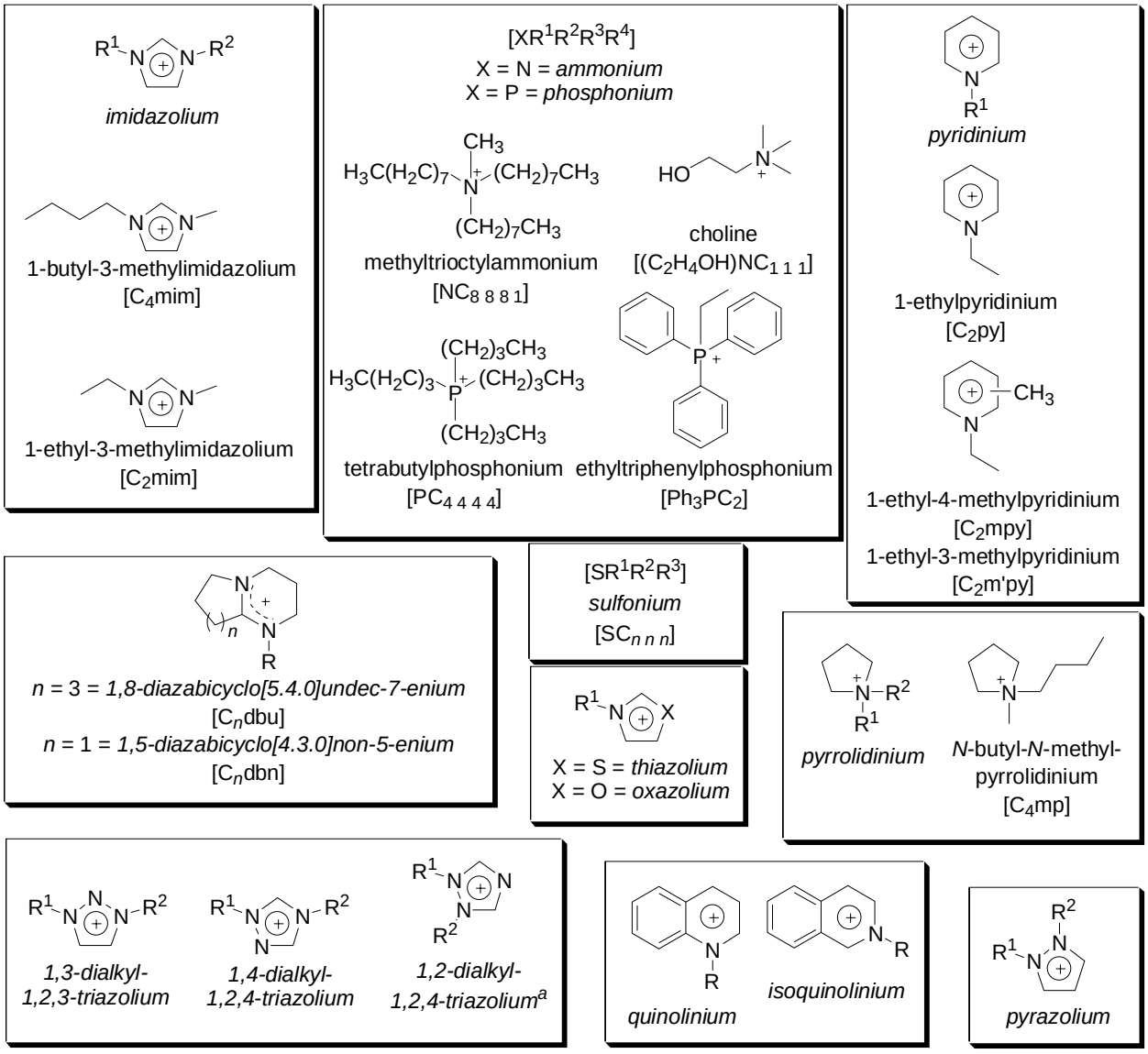


Figure 2. A selection of important cation motifs and some specific cations from the IL literature. [a]Although the 1,2-dialkyl-1,2,4-triazolium substructure is known, it has not yet appeared in the IL literature and is only included for completeness.

Figure 2 also introduces some of the most important cations by name, as well as the shorthand systems denoting them. The most common heterocyclic IL cations feature at least one saturated, linear, primary alkyl substitutent, and the cation is denoted by appending "C_n" to an abbreviation characteristic of the free heterocyclic base, where *n* is the number of carbon atoms in the normal alkyl chain. The abbreviation is flanked with brackets. For example, derivatives of 1-methylimidazole (mim), the 1-alkyl-3-methylimidazolium cations, are abbreviated "[$C_n$mim]"; derivatives of *N*-methylpyrrole (mp), the *N*-alkyl-*N*-methylpyrrolidinium cations, are abbreviated "[$C_n$mp]". All-letter abbreviations like [Bmim] (or [BMIM] or [bmim]) and [Emim] (or [EMIM] or [emim]) for [C_4mim] and [C_2mim] cations, respectively, appear regularly, but this convention is sometimes ambiguous. For example, [Hmim] properly denotes salts of acidified 1-methylimidazole, but it could be mistaken for 1-hexyl-3-methylimidazolium, [C_6mim], under an all-letter convention. Similarly, it is not immediately clear whether [Pmim] and its equivalents denote 1-propyl-3-methylimidazolium, [C_3mim], or 1-pentyl-3-methylimidazolium, [C_5mim]. Quaternary ammonium and phosphonium salts are similarly abbreviated except that the alkyl chain indicators follow the atomic symbol of the heteroatom; most authors order these chains from longest to shortest. Whenever these cations carry alkyl groups that cannot be conveniently reduced to this syntax, as is the case in cholines and quaternized salts derived from triphenylphosphine, the substituents with awkward abbreviations are commonly listed before the atomic symbol.

Wilkes, a professor at the USAF Academy, and M. Zaworotko, a professor at St. Mary's University visiting the USAF Academy, introduced tetrafluoroborate, hexafluorophosphate, and other air- and water-stable salts in 1992, alternately calling them "low melting salts" and "ionic liquids", but using the latter term in the title of their paper.[39] These and many more anions that

can be manipulated outside a drybox are in use today (Figure 3). Conventional abbreviations are used for all but one of the anions seen in Figure 3, and, like the cation abbreviations, they are bracketed in reference to ILs (e.g., [C_4mp][OTf] is *N*-butyl-*N*-methylpyrrolidinium triflate). Only dicyanamide ($(NC)_2N$) has a special abbreviation, [dca]. As the demarcation in Figure 3 suggests, ILs can be excluded from an aqueous environment, and IL hydrophobicity is generally an effect of the anion, but there are many exceptions to this pattern. For example, [BF_4] ILs are usually miscible with water, but some 1-octyl cations of substituted pyridines give [BF_4] ILs with water solubility lower than 2 g / 100 mL.[40] *bis*-Triflimide usually gives hydrophobic ILs, but this anion paired with *N*-ethyl-1,4-diazabicyclo[2.2.2]octanium gives a hydrophilic salt.[41] Other examples of departures from IL solubility rules are available.[42]

Almost all anions regularly featured in ILs delocalize charge by resonance or induction, but the halides appear frequently, and these salts melt at easily accessible temperatures despite their comparatively high charge density (Table 1). Unlike water solubility and miscibility, there is no clear pattern of certain cations or anions dictating melting points. There is also no indication that any ion has a characteristic influence over the *direction* of melting point change as its counterion is varied between pairs. For example, [C_4mim][OMs] (Entry 20) melts 18 ^oC higher than [C_4mim][Br] (Entry 15), whereas [C_2mim][OMs] (Entry 7) and [Bu_4N][OMs] (Entry 33) melt at 47 and > 20 ^oC lower than their respective bromides (Entries 2 and 28). 1-Ethyl-3-methylimidazolium iodide (Entry 3) melts around the same temperature (ca. 80 ^oC) as its respective chloride and bromide (Entries 1 and 2), whereas [C_4mim][I] (Entry 16) melts at more than 100 ^oC lower than [C_4mim][Cl] or [Br] (Entries 14 and 15, respectively).

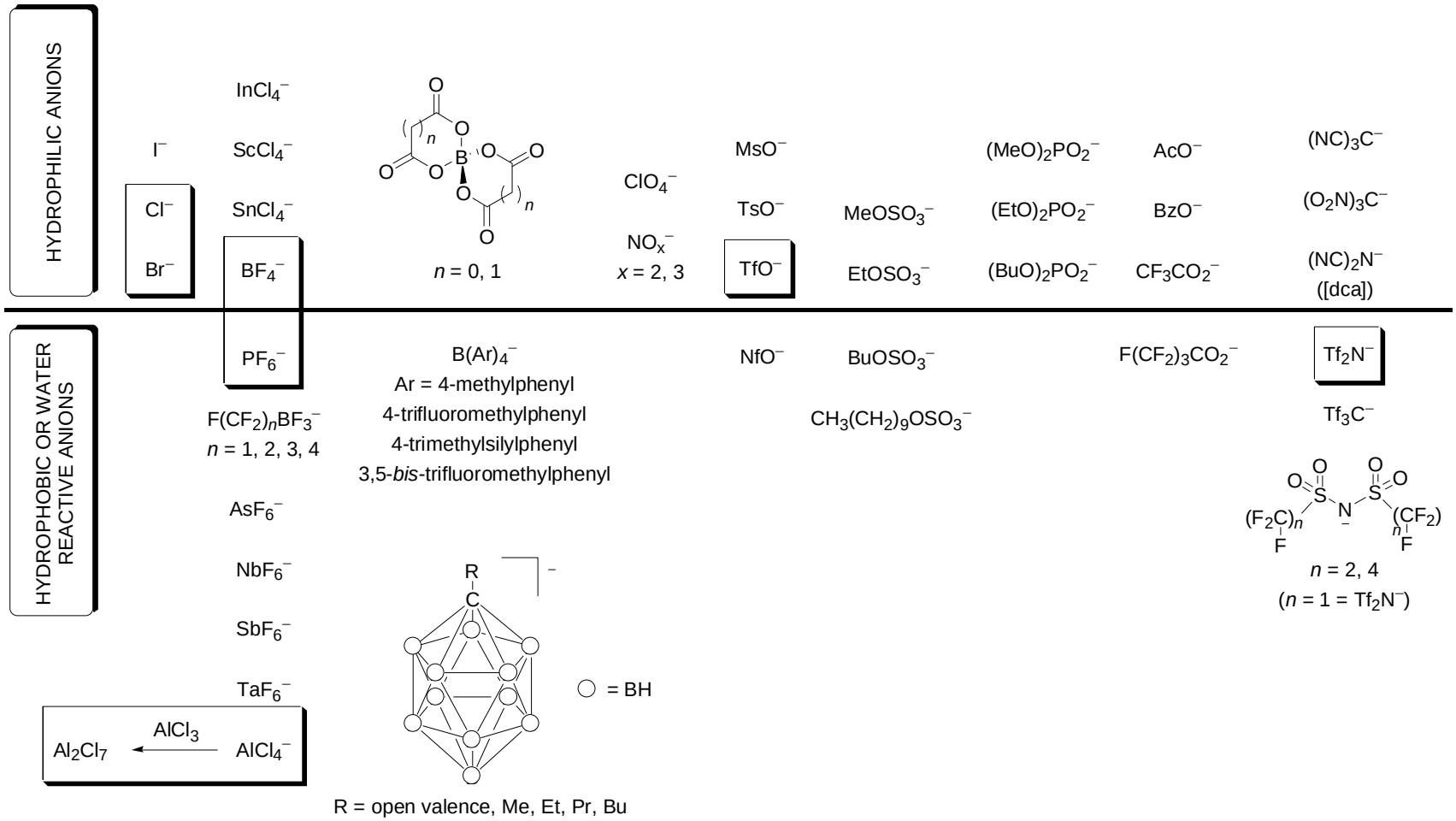


Figure 3. A selection of anions from the current IL literature. The most commonly appearing anions are marqueed.

Table 1.[a] Melting points of selected ion pairs

Entry	Cation	Anion	mp (°C)	Entry	Cation	Anion	mp (°C)	Entry	Cation	Anion	mp (°C)
1	C_2mim	Cl	79	14	C_4mim	Cl	60	27	Na	Cl	801
2	C_2mim	Br	82	15	C_4mim	Br	57	28	Bu_4N	Br	102 – 106
3	C_2mim	I	79 – 80	16	C_4mim	I	–72	29	C_3mim	I	< rt
4	C_2mim	$AlCl_4$	7	17	C_4mim	$AlCl_4$	–10	30	Na	$AlCl_4$	185
5	C_2mim	BF_4	15	18	C_4mim	BF_4	–80	31	Bu_4N	BF_4	155 – 161
6	C_2mim	PF_6	60	19	C_4mim	PF_6	–8 – 10	32	C_8mim	PF_6	< –40
7	C_2mim	OMs	35	20	C_4mim	OMs	75	33	Bu_4N	OMs	78 – 80
8	C_2mim	OTf	–9	21	C_4mim	OTf	16	34	Et_4N	OTf	161 – 163
9	C_2mim	ONf	28	22	C_4mim	ONf	20	35	C_2mpy	ONf	–6
10	C_2mim	NTf_2	< 0	23	C_4mim	NTf_2	–4	36	NC_{8881}	NTf_2	< –65
11	C_2mim	$N(CN)_2$	–21	24	C_4mim	$N(CN)_2$	–6	37	PC_{14666}	$N(CN)_2$	–50
12	C_2mim	$MeOSO_3$	–77	25	C_4mim	$MeOSO_3$	–5	38	Me_2SO_4		–32
13	C_2mim	$EtOSO_3$	–65	26[b]	C_4C_2im	$EtOSO_3$	–84	39	Et_2SO_4		–24

[a]Many ILs are now commercially available; accordingly, their melting point values can be found in commercial suppliers' catalogs. In the literature, there are at least two large compilations of IL physical data with an emphasis on melting points.[43, 44] One of these databases reports the library of ions in ILs was up to 276 cations and 55 anions as of 2006.[43] [b]C_4C_2im = 1-butyl-3-ethylimidazolium.

Over time, the terms used to describe these salts changed. "Molten salt" was initially favored by Wilkes, Osteryoung, and other early IL progenitors, but was gradually replaced with "ionic liquids", a convention surely meant to distinguish them from their predecessors, which were primarily inorganic salts or mixtures of them with melting points well above room temperature. In the current sense, a salt is supposedly only called an IL if it melts below 100 ^{o}C; otherwise, its melt is a molten salt, but neither of these standards are strictly followed. The primacy of certain salts and the vocabulary around them is clearest in a survey of the number of references indexed to certain cations on the SciFinder database. The database uses two variants of both terms, the looser definition being any salt solution with a high ionic strength. Only the tighter definition, discrete melted ion pairs, was used in the following analysis. As of May 2007, the term "ionic liquid" appeared in 3443 references, "ionic liquids" in 7565, "molten salt" in 12491, and "molten salts" in 6156. Using the more popular term from each set, and breaking up the numbers of references into five year periods over the last 30, it is clear the former, newer term started to appear more often than the latter, older term in the most recent five year period (Table 2). Some cations must have appeared in references using either term or both terms. For example, between 1977 and 1981, 172 references were published which featured ammonium cations, and this number is more than the total number of references using the term "ionic liquids". There are also dozens of other references to other organic cations, some of which necessarily fall under the "molten salt" umbrella. "Ionic liquids" would be the favored term for all of them today. In the most recent period, 2002 – 2006, there were 6380 references to "ionic liquids", which easily accommodates every occurrence of each cation surveyed, and leaves room for many more. By that time, the 1,3-dialkylimidazolium ILs—and especially the [$C_n$mim] subtype—were the most common cations in use.

Table 2. Number of references using the term "ionic liquids" or "molten salt", and the abundance of selected cations in these references in five year intervals since 1977.

Period	"Ionic liquids"	"Molten salt"	Cation class[a]								
			1,3-dialkyl-imidazolium	[$C_n$mim]	ammonium	pyridinium	pyrrolidinium	phosphonium	sulfonium	pyrazolium	triazolium[b]
1977–1981	20	**1050**	7	6	**172**	30	3	12	9	11	0
1982–1986	38	**1270**	52	52	**183**	55	4	11	5	8	0
1987–1991	31	**1402**	111	108	**232**	52	3	16	6	8	0
1992–1996	50	**1669**	188	186	**244**	46	2	18	10	7	4
1997–2001	452	**1778**	**411**	**400**	121	48	7	13	5	4	1
2002–2006	**6380**	2321	**3697**	**3579**	717	323	236	197	31	18	56
TOTALS	6971	9490	4466	4331	1669	554	255	267	66	56	61

[a]The number of references featuring each cation is the sum of references calling the salt(s) "ionic liquids" or a "molten salt". [b]As total 1,2,3- and 1,2,4-triazolium species.

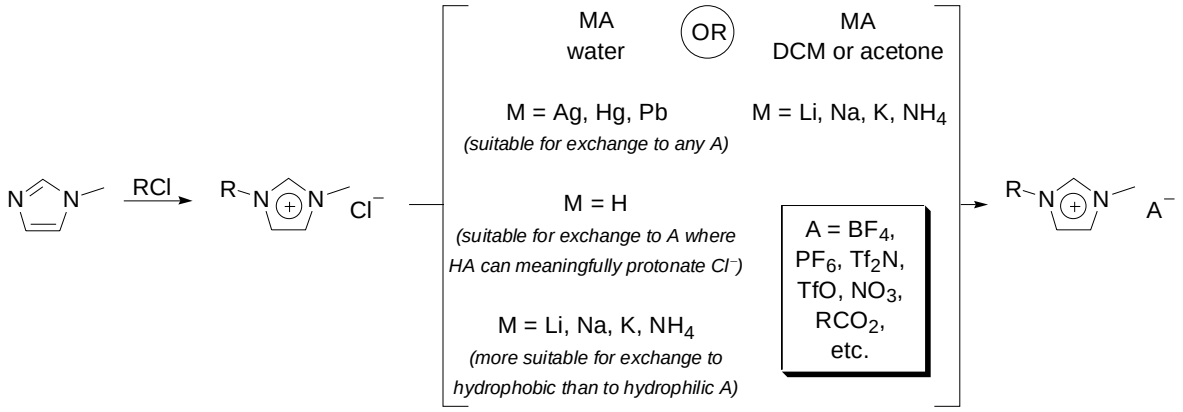
Some duplication across the topics "ionic liquids" and "molten salt" is guaranteed, but it is surprisingly small. Only 222 references out of 12491 "molten salt" references are crossindexed with "ionic liquid" or "ionic liquids"; 315 references out of 7565 "ionic liquids" references are crossindexed with "molten salt" or "molten salts". When these overlapping references were refined by date of publication, it was found the majority (134 and 224 crossindexed references, respectively) inexplicably came from the *most recent* (2002 and later) literature, well after a terminology convention was supposedly in place! However, as the abundances of several cations in Table 2 demonstrate, there was a time when the salts now called ILs must have been preferentially called molten salts. Although the literature is beginning to trend the other way, reports on ILs and on molten salts (each in the current usage) are generally sequestered at this moment. The terms "Coulomb(ic) liquids" and "fused salts" that were introduced earlier do appear, but comparatively rarely. Of these two terms, the latter is far more common, but appears in only 3845 *total* references, 1242 of which are in English. Interested parties are advised that the Library of Congress indexes molten salts under the term "fused salts", and ionic liquids under the term "ionic solutions".

The air and water stable ILs Wilkes and Zaworotko introduced in 1992 were imidazolium salts. To date over 4000 references feature imidazolium cations, and most of those concern a [$C_n$mim] cation. Wilkes reveals that imidazolium salts became popular because of the early emphasis on electrochemical applications, and these salts were sturdier in these applications than other organic salts because they had lower reduction potentials.[1, 3] They also had excellent thermal stability. In the last several years, the observation on new imidazolium ILs has been they reliably have low melting points and comparatively low viscosities. Thus, imidazolium salts are currently the state of the art in IL chemistry partly because they were preferred for the

USAF's electrochemical applications, and partly because this preference was reinforced as IL research expanded. Another contributor to the current popularity of [$C_n$mim] salts in particular is surely their economical synthetic accessibility. 1-Methylimidazole is a cheap heterocyclic base (ca. 0.12 USD / g), and is the cheapest commercially available 1-alkylimidazole (i.e., an imidazolium IL precursor with one of two alkyl groups already in place). These factors make it the logical starting point for imidazolium ILs, and it can only lead to [$C_n$mim] ILs. Note that, although the following descriptions of IL syntheses are biased towards the synthesis of [$C_n$mim] ILs, the exact same approaches are suitable for the synthesis of other ILs.

Osteryoung's method of quaternization followed by addition of a Lewis acid is appropriate for the synthesis of many chloro- or bromometallate ILs, but the most common ILs are prepared by sequential alkylation and anion exchange as represented in Scheme 1 for the synthesis of [$C_n$mim] ILs. It is sensible to accomplish the quaternization with an alkyl halide because halides can be conveniently exchanged for more desirable anions in several ways. This alkyl halide is usually a chloride because acids are an abundant source of desired anions, and chloride is more easily exchanged with acids than is bromide, which is more easily exchanged than iodide. It is technically facilitating to apply an alkyl chloride which boils above the melting point of the quaternized product because this alignment of properties allows a solventless preparation. For example, 1-chlorobutane (bp 80 ^{o}C) is suitable for such a reaction with 1-methylimidazole, and it is convenient to prepare a large volume of [C_4mim][Cl] (mp 60 ^{o}C) in a solventless reaction. The quaternized product can be purified by crystallization.

Both hydrophilic and -phobic ILs are accessible by the application of a soluble heavy metal salt of the desired anion to the quaternized halide in water. In this case, a heavy metal



Scheme 1. Quaternization and anion exchange synthesis of [C$_n$mim] ILs.

halide precipitate is removed by filtration, and this process is suitable for a wider array of anions than anion exchange with acid, although the pertinent salts are toxic, and are expensive to both procure and dispose. As one may expect, ILs that do not mix with water are the easier type to access. Recall that certain cations may force typically hydrophilic ILs from an aqueous environment, but water solubility is more commonly the effect of the IL anion. The hydrophobic ILs are synthesized by combining any form of the anion and the quaternized salt in water, whereupon the desired IL is released as a separate layer; the process is thermodynamically driven by a precipitation. For example, hexafluorophosphoric acid, or potassium or sodium hexafluorophosphate can be used for anion exchange to [PF_6] ILs; [NTf_2] ILs separate from aqueous mixtures of quaternized intermediates and lithium *bis*-triflimide (lead refs[45-49]).

The picture is more complicated for the syntheses of water soluble ILs. Most commonly, the conjugate acid of the desired anion is used for anion exchange. In this case, it is important that the acid utilized be nonvolatile, or that it be strong enough to irreversibly protonate halide so the desired anion will not be lost during the subsequent distillation of the exchanged hydrogen halide from the IL product, which is accomplished under reduced pressure. Anion exchanges to

hydrophilic ILs with alkali metals in water instead of acid are not necessarily thermodynamically driven as are the anion exchanges to hydrophobic ILs, but there is one example of a water soluble IL separating from an aqueous mixture which could be extended to the synthesis of others. J. Dupont and coworkers reported that $[C_4mim][BF_4]$ separated from a byproduct of aqueous potassium chloride formed upon the combination of concentrated aqueous solutions of $[C_4mim][Cl]$ and potassium tetrafluoroborate.[45]

Anion exchanges to water soluble ILs providing the desired anion as its alkali or ammonium salt in an organic solvent appear frequently. The procedure is also seen for the synthesis of water immiscible ILs, but there is no explanation why one would not use water and recover the desired IL as a molten precipitate. This tack is especially hard to understand considering the evident lack of attention paid to basic solubility phenomena in this paradigm. Supposedly, a quaternized intermediate and a source of the desired anion are stirred in an organic solvent (normally dichloromethane or acetone), what is presumed to be an alkali or ammonium halide precipitate is removed by filtration, and the desired IL is recovered after concentration of the filtrate. In other words, this anion exchange method is an attempt to wash a freely soluble ion pair off two less soluble salts, and only a rudimentary understanding of solubility is necessary to understand this approach is not necessarily as straightforward as is often represented. It is true that ILs are miscible with a variety of organic solvents, including dichloromethane and acetone, while the intermediate halide and a metal salt of the desired anion are each less so. However, the process is complicated by the fact that unexchanged salts can be taken into the organic phase as the IL forms. This potentiated dissolution is simply the classic approach to make salts melt at lower temperatures—by doping them with other salts—in the presence of a solvent, which could potentially take up the doped melt wholesale.

An analogy which seems appropriate and universally understandable can be drawn from the properties of slightly soluble salts in water. Stirring a suspension of lead (II) chloride (water sol @ 25 ^{o}C ≈ 1 g / 100 g) and barium (II) sulfate (water sol @ 25 ^{o}C ≈ 1 × 10^{-4} g / 100 g) would surely release some barium (II) chloride (water sol @ 25 ^{o}C ≈ 37.5 g / 100 g) from a precipitate enriched in lead (II) sulfate (water sol @ 25 ^{o}C ≈ 0.44 g / 100 g). But how thorough would this anion exchange be? The solubility products available from any physical chemistry handbook reflect the extent of dissolution of single salts in water, and probably cannot be used to derive an equilibrium constant for the release of one solute from two precipitates. An experiment is probably required to know for sure, but therein is the point. This hypothetical anion exchange to barium (II) chloride would run on exactly the same principle as the commonly seen anion exchanges to ILs in organic solvents from quaternized bases and either alkali metal or ammonium salts. The thermodynamics of the process are no better understood in the latter than in the former case, and too many papers have already appeared where its authors do not take these confounding factors into consideration. It is worth pointing out that, in the IL literature, this type of anion exchange is usually arbitrarily left for 24 to 48 hours. There is no indication whether that is enough time for the mixture to reach its equilibrium point, wherever it is.

Hence, this anion exchange looks ideal on its face, but there is every indication that on the way to the most common ILs, one organic soluble ion pair is not cleanly extracted upon contact of two organic insoluble salts, and that this process leads to an "ionic soup". However, it is possible that certain combinations of four ions in certain solvents or solvent mixtures may strongly favor either the release of a desired IL or the precipitation of the undesired ion pair, and cleanly (or, at least, more cleanly) separate a desired IL from the assortment of ions. Dupont and coworkers' observation that combining saturated solutions of [C_4mim][Cl] and potassium

tetrafluoroborate leads to the separation of a $[C_4mim][BF_4]$ layer is an example. There could also be other ways to improve anion exchange to ILs by the simple contact of two salts, which is an approach too appealingly simple to supplant despite its physically unrealistic implementations. Protocols for the synthesis of ILs using physical fields have appeared, and it is believable, but not yet incontrovertibly demonstrated, that the application of either microwaves[50-54] or ultrasound[55, 56] during the type of anion exchange at issue could force thorough separation of an inorganic halide from a desired IL.

To be absolutely clear, the problem with the widespread implementation of an oversimplified view of anion exchange (i.e., that a desired IL is quantitatively stirred into an organic solvent from two sparingly soluble or insoluble salts) is not that the process does not release some IL, or even that the resulting array of dissolved ions is not rich in the desired IL. It is that it must be an imperfect process, that the formulation surely requires a final purification, and that dutiful purifications are not performed often enough in the IL literature. The preceding is not meant to say ILs prepared by any other anion exchange do not require the same treatment. The following purification methods are effective and operationally simple, so it is fair to say IL preparations are easy, but not as much so as is too often represented.

Depending on the method of entry to the crude IL composition, it is contaminated with acid (including the protonated form of any unreacted heterocyclic base), or either an alkali / ammonium or heavy metal salt. Unreacted reagents will still be present in various forms, as will thermal decomposition products from the quaternization step. Heavy metal contaminants are the easiest to remove because ILs are generally soluble in, although not always miscible with, chloroform. Thus, an IL made from heavy metal anion exchange is dissolved in chloroform, cooled, filtered, and concentrated to extricate salts that cannot be removed with water. The

process is repeated until no more precipitate is released.[57] For the purification of ILs prepared by anion exchange with acid or alkali / ammonium salts, the pertinent acids and salts are soluble in water, which makes final purification easiest for ILs insoluble in water accessed by these exchanges. The IL is simply washed with water until the aqueous wash does not affect pH paper (signifying the removal of residual acid in any form), and until the wash does not give a precipitate when separated and treated with silver nitrate (signifying the removal of halide in any form). If only a small amount of IL is prepared, it is wise to wash it as a solution in a hydrophobic organic solvent. Note that herein is a good reason to perform anion exchanges with acid as opposed to alkali metals; any residual heterocyclic base will be removed in this step as its conjugate acid.

A salt formulation with high water solubility is freed of residual acid, alkali metal, or ammonium contaminants by dissolving it in a large volume of organic solvent (commonly dichloromethane), and repetitively washing the solution with a comparatively tiny volume of water (commonly less than 1% of the volume of dichloromethane).[58] Water selectively, but not exclusively, removes the inorganic contaminants harder than the desired IL, which is to say both the acid of the desired anion and the conjugate acid of the heterocyclic base, or the alkali / ammonium salt of the desired anion, depending on the anion exchange method employed. The process is complete when the water washes pass the pH and silver nitrate tests described above. Because the amount of water relative to the total volume of the separatory funnel used for the operation is so small, it is advisable to wash the funnel with water between each wash. A novel adaptation of this step is washing the organic extract with a solution of the sodium salt of the desired anion in water, which may improve the extent of anion exchange by essentially continuing the process in a separatory funnel.[46]

The order of the final steps in an IL preparation varies, but at some point there is a bulk drying step (with an inorganic sulfate or by simple distillation) and a vacuum drying step. The isolates are frequently some shade of yellow to red, and a decolorization step with adsorbents (silica gel, Celite, charcoal, or acidic or neutral aluminum oxide) is common. Some of these adsorbents can be used as dessicants, so a solution of the isolate in an organic solvent may be simultaneously dried and decolorized before concentration and drying under vacuum.

The preparation of $[C_4mim][PF_6]$ is the proverbial perfect storm, which likely explains why it is the most frequently utilized IL of the $[C_nmim]$ caste (Figure 4); by extension, it is probably the most common IL in use today. Aqueous $[C_4mim][Cl]$ is treated with hexafluorophosphoric acid or any aqueous hexafluorophosphate salt. The hydrophobic IL separates from the aqueous solution, and the isolate is washed with water without significant loss, and the specimen is decolorized and dried. Wasserscheid has commented that pure ILs should be colorless, but they are usually isolated on a spectrum of purity from dark red to faintly yellow.[3] He also comments that methods of IL preparation vary from lab to lab. The preceding account is rooted mostly in two papers from Welton and coworkers which are commonly cited in experimental sections.[58, 59] A useful 1999 paper from J. D. Holbrey and K. R. Seddon includes representative ^1H NMR chemical shifts and coupling constants for $[C_nmim]$ ILs, and a table of comparative microanalyses (which is not commonly utilized in IL characterizations) for ILs prepared by different anion exchange methods.[60]

P. J. Scammells and coworkers have called the assessment of IL purity a "neglected issue"[61] because there are few attempts to quantify the purity of an IL beyond physical appearance and superfluous peaks in ^1H and ^{13}C NMR spectra. The first of these qualities is

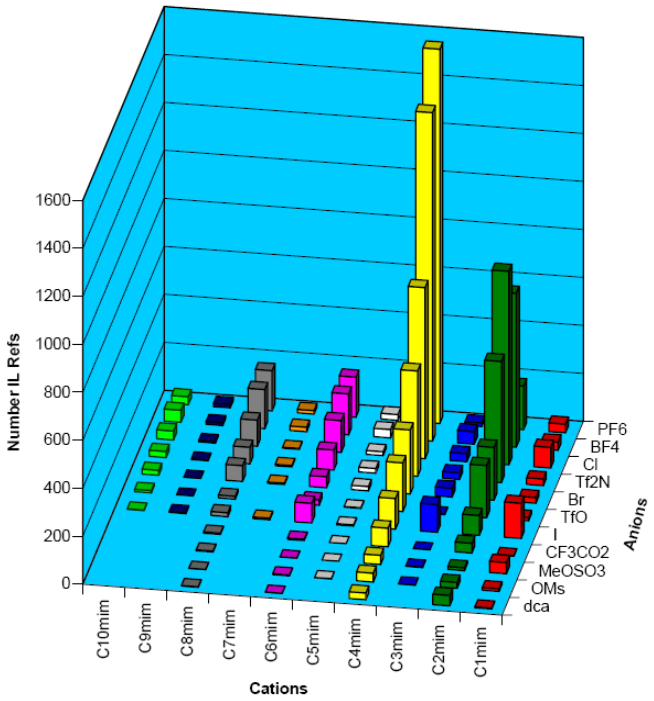


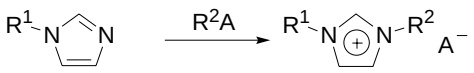
Figure 4. Abundance of [C$_n$mim] IL references as a function of ion pair. These values were found by searches for the corresponding structures on the SciFinder database on June 14, 2007.

unavoidably and unacceptably subjective, and the second can only detect impurities visible by the spectroscopic method, which most extraneous inorganic salts are not—and these are likely the most common contaminants. Melting points of intermediate halides or of anion exchanged ILs melting above room temperature may be measured by conventional methods, but the most common ILs require scanning calorimetry for this measurement (lead refs[45, 48, 62]), and most research groups do not make the investment for the instrument. Halides are of particular concern because of their effects on the physical properties of IL,[57] and because, unlike thermal decomposition products and residual solvents that may contaminate ILs, halides are invisible by NMR spectroscopy. More accurately, halides are invisible in the ^{1}H and ^{13}C NMR spectra that are usually collected; any attempt to quantify halide contamination utilizing the appropriate

NMR spectroscopy is not well known. Halides can have a direct effect on reactions performed in ILs. For example, P. J. Dyson and coworkers demonstrated the deleterious effect of halide contamination on hydrogenations with a certain ruthenium catalyst.[63] This example required halide free [C_4mim][BF_4] to make a comparison, and it was prepared by methylation of 1-butylimidazole with Meerwein's salt (Table 3, Entry 1).

Precisely because there are no commonly employed standards for batch analyses of ILs, the results from work not using ILs from commercial sources should be compared with caution. Many authors do not even provide the unique characterizations of their ILs for inspection. Consequently, even in the realm of detectable impurities, it is difficult to ascertain whether reported outcomes are due to the presence of ILs, or to contaminants in ILs, or to a combination of them in one particular IL formulation. Whenever results that are at variance are encountered, it should be borne in mind that these discrepancies could be the result of contaminants in the IL used. Ionic liquids which pass the same exacting analyses as new organic compounds are probably not necessary, and, depending on the application, colorless, nearly colorless, or even IL samples with qualitatively quiet ^{1}H and ^{13}C NMR spectra may not even be necessary. It would, however, be advantageous if there were a way to grade ILs akin to the systems in place for traditional solvents. Ionic liquids *can* pass microanalysis—the above references from both Dyson and Seddon are examples—but generally, even the purest ILs cannot be expected to pass. Tolerating a larger error in microanalyses of ILs than in the analysis of new compounds would be of little use unless there were some way to make clear whether the contaminants were organic (e.g., solvents, thermal decomposition products) or inorganic (e.g., acids, halides, adsorbents).

Table 3. Synthesis of inherently halide free ILs by direct alkylation of imidazoles.



Entry	R^1	R^2	A	Ref
1	*n*Bu	Me	$Me_2O{\cdot}BF_4$	[63]*a*
2	Me, Et	Me	Tf_2N	[64]
3	Me	Et	CF_3CO_2	[65]
4	Bu	Me	OTf	[66]
5	Me, Et, *n*Pr, *n*Bu	Me, Et	O_3SOR^2	[62]*b*
6	Me, Et, *n*Pr, *n*Bu, etc.	Me, Et, *n*Bu	$OP(O)(OR^2)_2$	[67]*c*
7	Et	Me	O_2COMe	[68]*d*

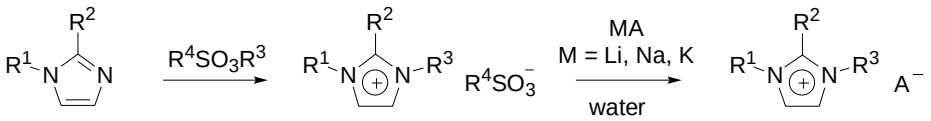
[a]The authors note that dimethyl ether was released as IL formed, and it was removed under vacuum to leave [C_4mim][BF_4]. [b]C(2)-Me ILs were also prepared. [c]1-Hexyl-, -octyl-, and -oligoethylene glycol imidazoles were also alkylated with trialkylphosphates. [d]In the original reference, these ILs were carried through to [(perfluoroalkyl)BF_3] ILs by acidification. A paper from different authors provides examples of further [$C_n$mim][$MeOCO_2$] ILs made in this way and their acidifications to other [$C_n$mim] ILs, as well as a discussion of mechanistic aspects of the reaction and its practical application to the synthesis of halide-free ILs.[69] More information pertinent to the mechanistic course of the reaction, but not specifically on the topic of these or any other ILs, is available.[70]

Ionic liquid formulations *could* be compared against electrochemical benchmarks and color assessments *could* be quantified with electronic spectroscopy. It is fair to say there is more of an effort by electrochemists than by organic chemists to measure the purity of ILs, but this is the case because the inherent electrochemical markers of the medium are part of the background for their subsequent experiments. In other words, their purity assessments of ILs are typically the blank run in whatever method is about to feature an IL.[3] Published examples of these blank runs are difficult to find, however. There is one example from 2006 which does not currently lead to additional references on the topic in either direction, but which describes the synthesis and evaluation of pyrrolidinium ILs by linear sweep voltammetry.[71] A. M. Bond writes there is an IUPAC electrochemical standard to compare IL formulations, which is voltammetric measurement of cobalticenium and ferrocene redox processes in the ionic liquid.[31] As of this writing, it does not appear to be widely used. When this electrochemical assessment does appear, it is only performed when there is a subsequent interest in voltammetry in the IL, and not in the purity of the IL for any other purpose. C. Hardacre and coworkers have described methods to detect halides electroanalytically and ion chromatographically,[72, 73] but these are not yet part of any standard operating procedure, either.

There are a few approaches to measure IL purity with instruments commonly available to organic chemists. Two recent papers concern the purification of ILs to the point they are invisible over most of the UV–visible range. The chronologically first compared the UV invisibility of ILs purified by different methods.[74] The newer paper reports the decolorization of ILs over a column layered with charcoal, silical gel, and Celite; the authors compare the UV spectra from the bulk and purified IL formulations.[48, 49] The quiet spectra contained in each of

these papers could serve as benchmarks to assess the purity of IL batches anywhere, but do not appear to have filled this role yet.

Dupont and coworkers introduced an IL preparation allowing meaningful purity assays by NMR spectroscopy. They prepared [RSO_3] ILs from the reactions of imidazoles and alkyl sulfonates, then exchanged the alkylsulfonate anion for another by stirring the [RSO_3] IL with a salt of a desired anion in water (Scheme 2). The final ILs were isolated by extraction of the aqueous mixture with dichloromethane.[75] The intermediate [RSO_3] ILs made by this route are inherently halide free, and it follows the final ILs are also. It is particularly noteworthy that this method could furnish inherently halide free ILs based on anions which are not (or not conveniently) available with a transferable alkyl group.



Scheme 2. Alkylation of imidazoles to [RSO_3] ILs and their subsequent anion exchange, as reported by Dupont and coworkers.[75]

The most significant feature of this IL synthesis is that it stoops to the level of widely available instrumentation to assess an IL sample by making the anion present following quaternization visible to NMR spectroscopy. The success of the anion exchange to ILs with anions invisible to NMR spectroscopy is evident from the presence or absence of alkylsulfonate signals in the ^{1}H and ^{13}C NMR spectra of the desired formulation. The authors went on to offer estimates of the purities of their final IL products using logic that runs as follows.[75] Since the natural abundance of ^{13}C is 1.11%, the intensity of two satellite *N*-(^{13}C)-methyl signals visible in

expansions of ^{1}H NMR spectra each represent 0.555% of the imidazolium salt present in the specimen (Figure 5). If no alkylsulfonate peak was visible relative to the *N*-(^{13}C)-methyl satellite signals, as in [C_4mim][PF_6] they prepared by the sequence in Scheme 2, they put the IL purity at > 99.4%. If an alkylsulfonate peak appeared, as in their [C_4mim][BF_4] sample, they related the intensity of that peak to that of the *N*-(^{13}C)-methyl satellite signal to estimate the amount of unexchanged [RSO_3] IL contaminating the isolate. The purity of their [C_4mim][BF_4] sample was estimated as > 98.5% (23.44 / 9.25 = 2.53; 2.53 × 0.555 = 1.41; 100 – 1.41 > 98.5). Presumably, the "intensities" were integrals, although the authors did not say so explicitly.

Dupont and coworkers did not measure the actual isotopic abundance of ^{13}C in their samples or correct for water present in the IL, so the values are only rough approximations, but they should not be drastically affected by variations across samples. This point is easy to make by playing with factors of 0.5 and 2.0. If their samples were actually 0.555% ^{13}C at the *N*-methyl carbon, the purities of the [PF_6] and [BF_4] ILs go up to > 99.7% and > 99.3%, respectively. If their samples were actually 2.22% ^{13}C at the *N*-methyl carbon, the purities of the [PF_6] and [BF_4] ILs go down to > 98.9% and > 97.2%, respectively. It should be noted these authors apparently represent the purity of their samples as a mole fraction, which is not how most people think about purity.

The gold standard in IL analysis is the appearance of NMR spectra, and this IL synthesis makes the appearance of those spectra more meaningful. The approach could be easily improved, however, by simply using an internal standard to find the absolute molar amounts of [C_4mim] and [RSO_3] species in the samples. Subtracting the latter (moles [C_4mim][RSO_3]) from the former (moles [C_4mim] salts total) would return the molar amount of desired [C_4mim] IL,

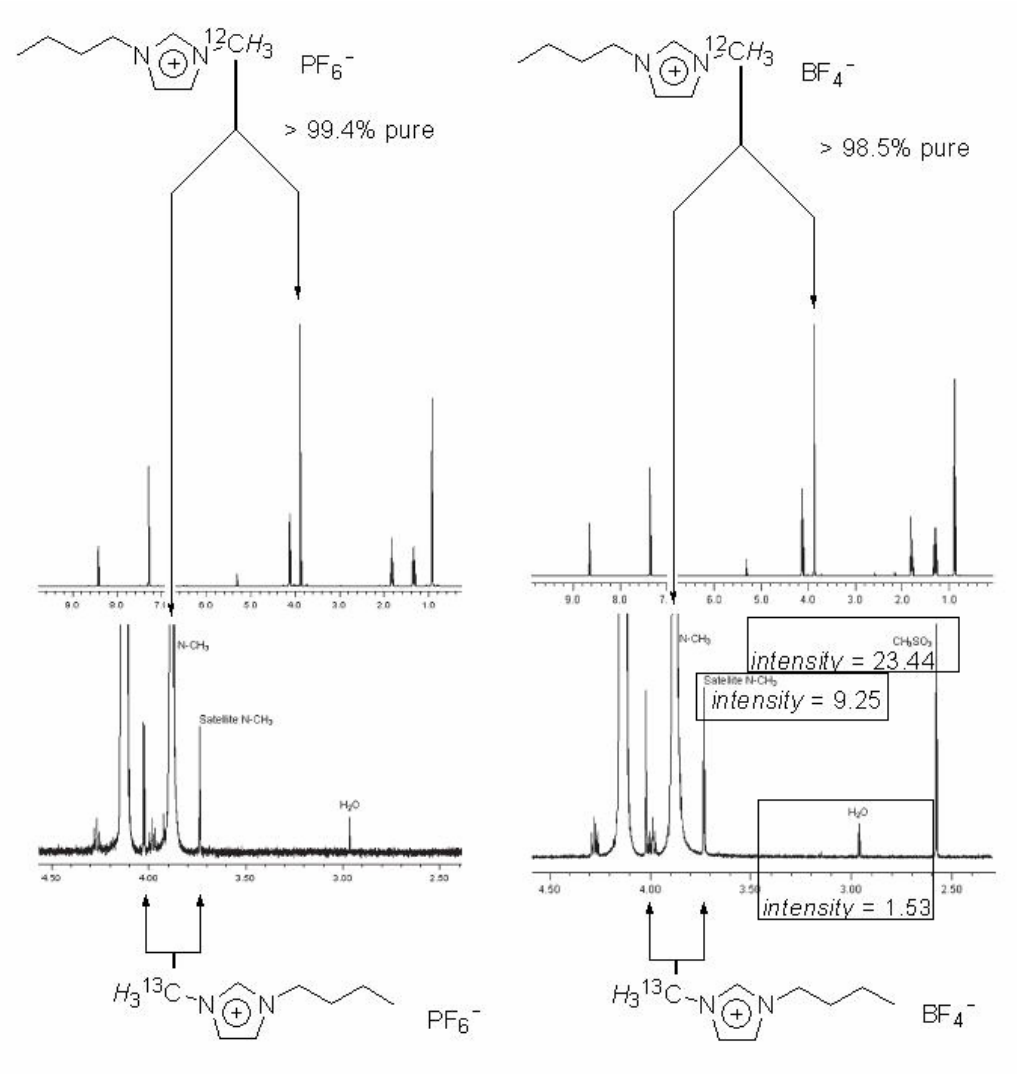


Figure 5. Annotated ^{1}H NMR spectra and expansions excerpted from Dupont and coworkers' report on the synthesis of [RSO_3] ILs and their subsequent anion exchange to other ILs.[75]

which could be converted into a purity indicator based on either a mole or mass fraction. Note that all three protons of a dialkylimidazolium ring can exchange with deuterium oxide, although the process requires supplied base[76, 77] or a palladium catalyst[78] to be synthetically useful; each of these protons can also exchange with superacidic deuterons.[79] Therefore, it would be critical to use the integrations of signals from the substitutents on nitrogen for this kind of quantification.

After criticizing the dominant and oversimplified perception of anion exchange from imidazolium halides to ILs with alkali / ammonium salts in an organic solvent as represented in Scheme 1, I should point out that Dupont's group's claims of anion exchanges from [RSO_3] ILs to others in high purity with little effort in purification is believably (but not certainly) as simple as presented. Recall that the shortcoming of the anion exchange method at issue is that the isolated ILs cannot be as pure as many authors would like to believe, and suitable measures to purify the IL are not taken often enough. The halide in particular is difficult to wash from an organic solution of the desired IL because the desired IL increases the solubility of halide salts in organic solvents. Dupont and coworkers claim to have isolated their ILs by simple extraction with dichloromethane following the combination of imidazolium alkylsulfonates and alkali salts of the desired anions in water. The synthesis of adequately pure hydrophobic ILs (e.g., [C_4mim][PF_6] in > 99.4% purity) by this simple approach is remarkable enough because no subsequent aqueous washes were necessary. Such was also the case in the synthesis of adequately pure hydrophilic ILs (e.g., [C_4mim][BF_4] in > 98.5% purity), but these syntheses are all the more remarkable because the desired IL does not form as a separate layer at the outset of anion exchange, and because the release of the desired IL to dichloromethane is not thermodynamically driven as it is in the synthesis of hydrophobic ILs.

For this representation to be true, all that is necessary is that the alkylsulfonate anion be sufficiently harder than the desired anion than is a halide. If salts of alkylsulfonates are sufficiently hard, the combination of an imidazolium alkylsulfonate and the alkali metal salt of a desired anion would be a mixture of four ions where the release of a desired IL in high purity is favored over the formation of an ionic soup. The far softer ion pair, the IL, would be more easily extracted from water, and the process would not be confounded by leaching of the alkali alkylsulfonate byproduct into dichloromethane.

Evidence that anionic sulfur oxide ILs are much harder than halide ILs came to light four years before the report from Dupont and coworkers,[75] when Wasserscheid and coworkers described a synthesis of $[C_4mim]_2[SO_4]$ by anion exchange of $[C_4mim][Cl]$ with an anion exchange resin in water. The product was dried by repetitive concentration from acetonitrile, in which it had no solubility.[80] It is otherwise unheard of that the imidazolium salts called ILs have low, let alone no, solubility in acetonitrile. An $[RSO_3]$ IL is not an $[SO_4]$ IL, but it does not have to be; the alkylsulfonate anion only has to be sufficiently hard, and it is believably so considering the apparent hardness of $[SO_4]$ ILs. Thus, the possibility of extracting one imidazolium IL from a combination of an $[RSO_3]$ IL and an alkali metal salt in water with an organic solvent is probably much higher than the possibility of extracting one imidazolium IL from a combination of an imidazolium halide and an alkali metal salt in the solid phase with an organic solvent.

It is certainly more believably successful than are the widespread descriptions of haphazard anion exchanges through quaternium halides and alkali / ammonium salts in an organic solvent. I debated the need to provide an exact example of such a misleading approach to anion exchange, but believe it could be instructive. Dupont and coworkers passed off a

particularly disingenuous anion exchange of [C_4mim][Cl] to [C_4mim][BF_4] in their 1996 *Polyhedron* paper.[81] They performed this "anion exchange" by combining [C_4mim][Cl] and sodium tetrafluoroborate in acetone, stirring the mixture 24 hours, then filtering it through Celite. There was no subsequent refinement of the sample because the IR and ^{1}H and ^{13}C NMR spectra were flawless. I have personally followed this example because it is so deceptively simple; the addition of any organic solvent less polar than acetone to the isolate forces an inorganic precipitate from the formulation. That some desired IL formed is a given; that the authors did not know or did not advise anybody working off their paper that further purification of it would be necessary is the problem. And this paper has been cited a disconcerting 496 times as of this moment—often as the source of the method for the IL preparation used in the citing reference.

As an aside, note that Wasserscheid and coworkers have provided an important confirmation. Magnesium or sodium sulfate often appears as a drying agent in recorded IL preparations with little concern for the ability of the desired IL to exchange to an [SO_4] IL. There is no way to be sure from the ^{1}H and ^{13}C NMR spectra of the isolates dried in this way, and the IR spectrum of a sample would be variably useful for finding sulfate depending on the identity of the desired anion. However, the empirical observation that discrete [SO_4] ILs do not even dissolve in acetonitrile suggests there is probably little cause for concern over their formation as byproducts when drying solutions of ILs in organic solvents over inorganic sulfates.

Considering the legitimate difficulty in a meaningful assessment of IL purity, it may be comforting to bear in mind what M. Maase said at an IL conference held in Salzburg, Austria in 2005: "The definition of purity strongly depends on the specific requirements of the targeted application. In the end, we do not sell purity—we sell performance."[82] To say performance is being sold is an understatement. Of the 7565 current references dealing with ILs indexed on the

SciFinder database, 847 are patents. In an interview with Thomson Scientific, Seddon was asked to reveal the proverbial secret to his success in developing ILs and applications for them; he says it was industry.[83] The commoditization of ILs was discussed four years ago.[84] Even the primary scientific literature clearly places a premium on applied science, as was the case with their molten salt predecessors. For starters, ILs are useful in analytical chemistry, where their negligible volatility and thermal stability make them suitable matrices for MALDI mass spectrometry and as stationary phases for gas chromatography; they are also media for non-aqueous capillary electrophoresis.[85-90] Wilkes writes that the ILs developed at the USAF Aacademy were not suitable for the applications they had in mind. Nonetheless, the references provided in the eighth paragraph of this chapter indicate ILs are still brought to bear on numerous electrochemical applications, including energy storage.

That said, it is not hard to glean from the literature that the primary marketable applications of ILs are *not* electrochemical, and that a recurring topic is sustainability—i.e., many of the following examples fall under the heading of green processes. A review of green industrial applications of ILs has appeared.[91] The connection between greenness and ILs is sometimes contrived, but there are many examples of truly green processes featuring ILs, and applications yet to come may have a large role in a sustainable economy. Having pointed out the green facet of ILs here, I will only emphasize it again as new ideas adding to the sustainability factor are introduced, and will otherwise leave it to the reader to determine the greenness of what follows and to imagine other logical adaptations.

Extractions with ILs get considerable attention,[92] especially in the dissolution and reconstitution of cellulose,[93] the sequestration of metals (actinides in particular),[94, 95] and the desulfurization of petroleum products. Ionic liquids are immiscible with alkanes, and in biphasic

mixtures of dodecane containing 500 ppm sulfur (as dibenzothiopehene) and an IL, up to 90% of the sulfur contaminant was released to the IL by simple mixing.[96-100] When ILs stable to hydrogen peroxide and acetic acid were used, the addition of this mixture oxidized sulfur contaminants, and improved the efficiency of their removal by the ILs.[101] Ionic liquids are also immiscible with supercritical carbon dioxide ($scCO_2$), which is miscible with gasoline and cannot be used for desulfurization directly. However, the sulfur contaminants removed from crude petroleum by an IL can be removed from the IL by $scCO_2$, and the IL can be recycled.[102] The use of ILs in the removal of sulfur compounds from petroleum products has been reviewed.[103]

Ionic liquids have been used for the lubrication of metal–metal contacts.[104, 105] Authors in this niche have leapt straight to detailed evaluations of the suitability of ILs to this purpose and have not said much about the thinking that led them to these investigations. For example, the first paper on the topic says only the negligible volatility, nonflammability, high thermal stability, low melting point, and wide liquidous range of ILs, and their miscibility with many organic compounds "potentially make them excellent lubricants."[106] Several reasons these properties are desirable can be imagined. Thermal stability and negligible vapor pressure mean ILs should degrade slowly and not evaporate when exposed to the heat present at the tribological junction; it also means ILs could function as persistent lubricants in the vacuum of space.[106] Low melting points make certain ILs suitable for the lubrication of equipment exposed to low temperatures, where glycols and mineral oils may freeze, and "wide liquidous range" combines the benefits of low melting point and negligible vapor pressure. Miscibility with organic compounds is presumably beneficial for degreasing joints, but it does not seem that critical a property because water could be used to remove many ILs. One of the qualities of ILs left off

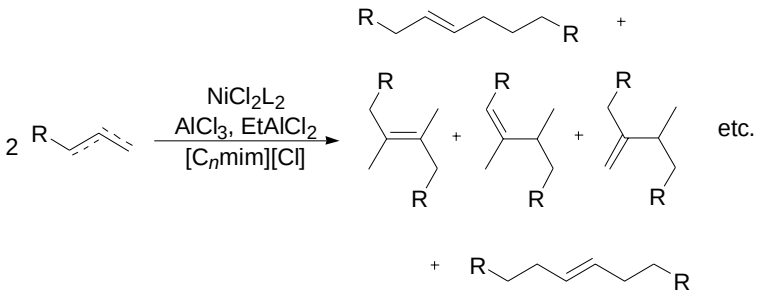
this list by authors in the area that should be a benefit is the sometimes high viscosity of ILs. Although this property is generally undesirable in the laboratory setting, it means ILs used as lubricants would stay in place as well as conventional greases. The potential redox chemistry between the IL and the metal surface, which degrades both sides of the interface, is the only significant criticism voiced to date.[107]

Ionic liquids can be suitable media for many processes in the course of petroleum refining or plastic recycling because strong acid catalysts and / or high temperatures are often required for these applications, and ILs tolerate both.[108-112] The most important example from this area is the use of an IL as the medium for propene and butene dimerizations in the Difasol process (Scheme 3, Figure 6). The overall conversion is identical to that of the Dimersol process, which is over 30 years old.[113] Both processes rely on a nickel catalyst, both were invented by 2005 Nobel Laureate in Chemistry Y. Chauvin, and both are usually considered alongside each other in the literature.[114-121] Chauvin credits H. Olivier-Bourbigou with developing the Difasol process as the subject of her graduate work in the 1990s.[122] She reviewed the topic in 2005.[123] These processes together account for over four megatons of hexenes and octenes produced annually at over 30 sites worldwide. The salient features of and differences between the two processes are as follows:

- Dimersol uses $[(PR_3)NiCH_2R']$[$AlCl_4$] as the cracking and reforming catalyst. No solvent is supplied for the reaction.
- The Dimersol catalyst has a tendency to leach into hydrocarbon products.
- The active catalyst in the Difasol process forms in a mixture of $Ni_2Cl_2(PR_3)_2$, [C_2mim][Cl], $AlCl_3$, and $EtAlCl_2$. It is most active in [$C_n$mim] chloroaluminates,

wherein >250 kg dimerized product is recovered per 1 g of catalyst. This mixture is fluid at the reaction temperature of –15 °C.

- In the Difasol process, an IL phase with entrained catalyst cleanly separates from the liquid hydrocarbon products in an overflow vessel.



Scheme 3. Dimerization of alkenes in [$C_n$mim] chloroaluminate ILs during the Difasol process.

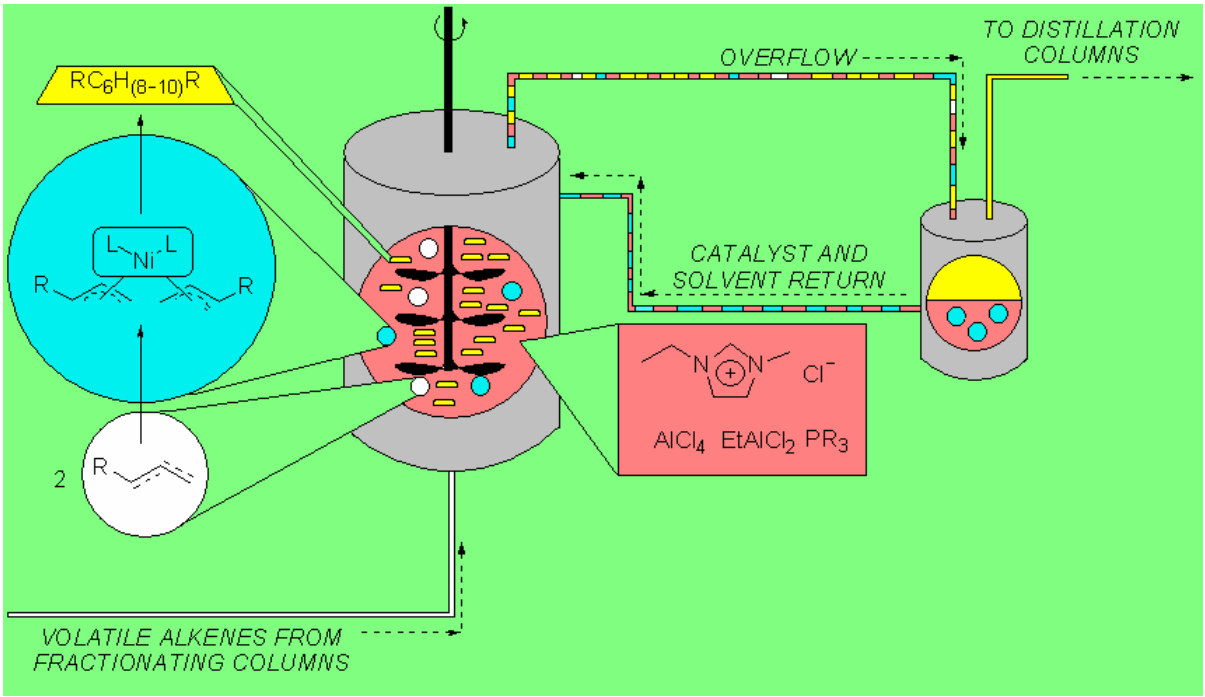
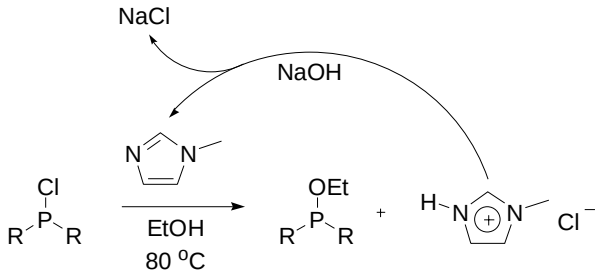


Figure 6. The Difasol process, adapated from graphics in Chauvin's Nobel Prize lecture.[124]

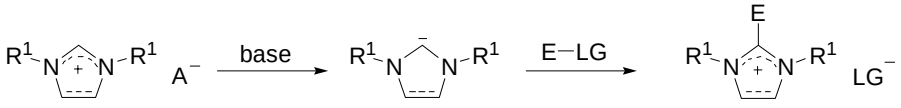
Maase and coworkers at BASF have described the advantages of 1-methylimidazole as an acid scavenger in processes they call biphasic acid scavenging utilizing ILs (BASIL).[125, 126] They originally conceived of the process to simplify the production of ethoxyphosphines from chlorophosphines (Scheme 4). When using triethylamine as the acid scavenger, the product had to be filtered from a barely workable ammonium chloride precipitate. 1-Methylimidazolium chloride ([Hmim][Cl]), however, melts at 75 ^{o}C, and this protonated byproduct separates from the phosphine product at a reaction temperature of 80 ^{o}C. Following phase separation, 1-methylimidazole is regenerated with sodium hydroxide and recycled. From a comment in a separate report,[127] it appears scavenged hydrogen chloride can be driven off by heating [Hmim][Cl] to regenerate the free base. Maase and coworkers also found the formation of IL hastened the substitution reaction, a phenomenon I will return to later, and "increased the yield per unit volume time from 8 to 690,000 kg $m^{-3}h^{-1}$," enabling BASF to carrying out a reaction "which previously needed a 20 m^3 batch vessel . . . in a little jet reactor the size of a thumb."[126] The authors say this thimble reactor is in continuous operation and is responsible for the preparation of over a megaton of phosphine products per year.



Scheme 4. BASF's BASIL process for the synthesis of ethoxyphosphines from chlorophosphines. "BASIL" is a descriptor applicable to any process forming a separate IL phase as a basic hetereocycle scavenges an acid generated during a reaction.

To this point, as in the literature in general, the reputed characteristics of ILs that make these applications possible have been parroted without consideration. For example, nonflammability is widely assumed to be an intrinsic property of ILs, and is desirable in high temperature or high friction settings like some of those described above. However, Wilkes, R. D. Rogers, A. Katritzky, and coworkers recently demonstrated that these salts can burn.[128] D. R. MacFarlane and Seddon recently said the only inherent characteristics of ILs are their liquidity below 100 ^{o}C (which is simply a definition), and that these liquids are conductive because they *contain* ions.[129] They were careful not to say ILs are truly made of only ions because one of the topics they took up was the very nature of the species in an IL, which is a question worth asking even if the bearing of irremovable impurities on IL ionicity is not considered. They scrutinized other properties frequently ascribed to ILs which are not absolute—nonvolatility and thermal stability foremost among them. Whether ILs are genuinely composed of ions and whether they are nonvolatile and thermally stable are best considered simultaneously, at least as far as [C$_n$mim] ILs are concerned, because the single greatest cause for concern presumably revolves around the N-hetereocyclic carbenes (NHCs) **1** (Table 4), which are formed by the deprotonation of imidazolium or -inium salts and *may* subsequently react with nearly anything (Scheme 5). A. J. Arduengo is widely credited with discovering isolable NHCs **1** (lead refs[130-132]) and recently reported on their heats of formation.[133] Carbenes **1** had actually been isolated and extensively characterized several years earlier (at least) by H.-W. Wanzlick, who published over 20 papers on the topic,[134] and by K. Öfele, who entered the field around the same time as Wanzlick (in 1968),[135] reviewed the topic in 2002 and 2003,[136, 137] and was still publishing as of 2006.[138]

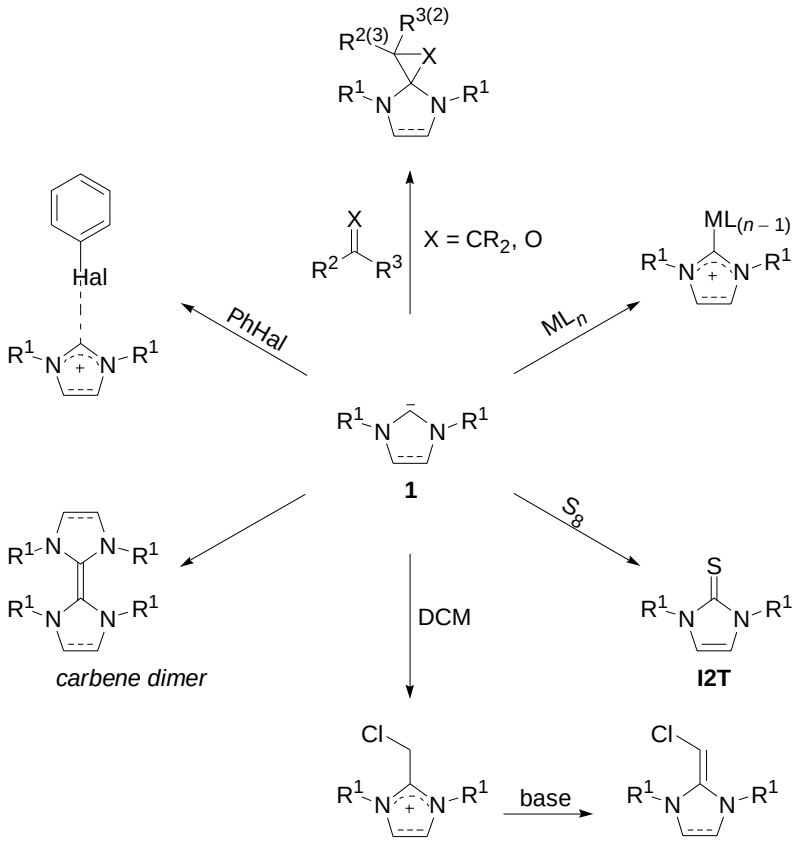
Table 4. Formation and some derivatizations of NHCs **1**.



1

R^1	A	base	E	LG	Yield	Ref
Ph	Cl	*t*BuOK in DMSO	HgCl	Cl	--[a]	[134]
Me	OTs	NaH in DMF	MeS	SO_3Na	100	[139]
Me	OTs	NaH in DMF	Cl_3CCCl_2	Cl	100	[139]
Me	OTs	NaH in DMF	CBr_3	Br	100	[139]
Me	OTs	NaH in DMF	Et	I	100	[139]
Me	OTs	NaH in DMF	Me	I	100	[139]
Me	OTs	NaH in DMF	Ac	OAc	50	[139]
Me	OTs	NaH in DMF	O_2[b]		96[b]	[139]
*i*Pr	--[c]	--[c]	$P(O)Cl_2$	Cl	68	[140]

[a]This mercury complex comes from the 20th paper in Wanzlick's series on nucleophilic carbenes, and many more relevant examples with yields can be found in that set. [b]The reaction of NHC **1** with molecular oxygen gives the imidazolone. [c]This example comes from the 50th paper in N. Kuhn's ongoing series on imidazole derivatives; as in the Wanzlick series, there are many more relevant examples in the earlier reports. There is no anion or base to speak of because the discrete NHC **1** (R^1 = *i*Pr) was used; it was prepared by reducing the corresponding imidazole-2-thione with elemental potassium.[141]



Scheme 5. More of the many possible reactions of NHCs **1** at C(2). Reactions at C(4)(5) are also known.[142, 143]

Carbenes **1** are strong but accessible bases. The pK_a of the C(2) proton of imidazolium salts is > 20 in water.[144] The groups of R. W. Alder and A. Streitwieser have put the basicity of NHCs **1** on a different relative scale by measuring their ability to deprotonate hydrocarbons to aromatic anions. Following the acid-base chemistry by NMR spectroscopy, Alder and coworkers report one NHC **1** (R^1 = *i*Pr) quantitatively deprotonated indene (pK_a 20.1), fluorene (pK_a 22.9), and 2,3-benzofluorene (pK_a 23.5) in DMSO, whereas 9-phenylxanthene (pK_a 27.7) and triphenylmethane (pK_a 20.6) were not deprotonated.[145] Streitwieser and Y.-J. Kim reaffirmed these results with the same carbene and similar fluorene compounds, and added computational data.[146] A. H. Cowley and coworkers have reported X-ray crystal structures of

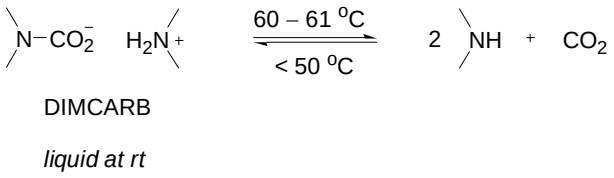
[C_1mim][fluorenide] and [indenide]; a carbene insertion product was observed along with the latter complex. They have also characterized 1,3-dimesitylimidazolium cyclopentadienide. All of these examples demonstrate these hydrocarbon anions are not sufficiently powerful bases to abstract protons from the corresponding imidazolium salts.[147]

Scheme 5 shows more of the reactions NHCs **1** have given. They can form epoxides with acetone and other C=O carbonyls, and cyclopropanes with alkenes. They can associate strongly with haloarenes and may even add to dichloromethane.[142, 143] They may dimerize.[148] They may add to elemental sulfur to deliver an imidazole-2-thione (**I2T**). The latter reaction can be accomplished thermodynamically from an imidazolium under the influence of pyridine[134] or potassium carbonate[149] in lieu of quantitative conversion of the relevant imidazolium salt to its NHC **1** with a powerful base. Kuhn has studied many of the reactions of NHCs **1** with main group elements,[150] but their most frequent occurrence in the literature is as ligands on transition metal, which may be from from either NHCs **1** or the corresponding carbene dimer.[151-155] However, NHCs **1** do not add to hydrocarbons or ethers, and upon exposure to alcohols, they only enter an acid-base equilibrium and are not materially changed. Desired reactions requiring NHCs **1** are normally accomplished in one vessel, but the carbenes can be isolable and even crystallized—facts borne out in several of the preceding references.

Therefore, the popular [$C_n$mim] ILs are only one step away from a carbene, which leads to the consideration that they are not genuinely ILs, but equilibrium mixtures of ILs and neutral carbenes separated from acids (i.e., "autoneutralization" products). This is an important point to bear in mind, but examples which follow will demonstrate the cause for concern is probably very low. There are apparently no examples of side reactions from NHCs **1** in [$C_n$mim] ILs except in instances where a base was applied and there was a substrate present to give a reaction with the

NHC faster than the desired reaction. Note that the preceding examples of **I2T**s prepared from imidazolium salts under the influence of pyridine or carbonate may suggest the prospect of reactions from NHCs **1** in [C$_n$mim] ILs would be more important than it actually is. These deprotonations were followed by a chemical reaction, and this reaction was the only one open; the net change is a better example of Le Chatelier's principle than of imidazolium C(2) acidity. Unless experimental evidence to the contrary comes to light (e.g., if there is a drastic reordering of acid strength in ILs), and excepting a few situations presented later where an imidazolium cation is paired with a strong base, the massive amount of knowledge on NHCs **1** must lead one to believe imidazolium and particularly [C$_n$mim] ILs are what they are called. For a semantic model, consider the fact water autoionizes. It is still called water without qualification.

Equilibration with neutral species is a central property of one IL, however. Dimethylammonium dimethylcarbonate (DIMCARB, Scheme 6) traces back to the patent literature of the late 1950s, was tapped as a solvent in the late 1980s,[156-158] and was recently seized upon as an IL.[159-161] DIMCARB is a stable liquid at room temperature, but decomposes to its gaseous components around 50 ^{o}C. Reportedly, it is easily reconstituted from these components, meaning this IL can be purified by distillation into a cold receiving vessel, which makes it the only example of a conveniently distillable IL (see below), especially on a preparative scale.



Scheme 6. DIMCARB and its components in equilibrium.

The frequent exposure of [$C_n$mim] ILs to high temperatures begs the question whether they are truly thermal stable or if they, too, decompose at higher temperatures. The corresponding thermal decomposition of [$C_n$mim] ILs would presumably proceed via NHCs **1**, if only because entropy favors bond cleavage at higher temperatures, and because it seems the most reasonable first step to release species that polymerize, cyclopropanate, hydrolyze, etc. M. J. Earle and Seddon and coworkers assessed the thermal stability and nonvolatility of these and other ILs in Kugelrohr distillations at roughly 300 ^{o}C. They found ILs could be distilled at rates on the order of milligrams per hour.[127] 1-Butyl-2,3-dimethylimidazolium ([C_4dmim]) and [C_4mp][NTf_2], and two [$C_n$dbu] ILs distilled cleanly. Most of the authors' examples came from the [$C_n$mim], [NR_4], and [PR_4] classes of ILs, and they found at least one IL from each class that distilled before decomposing and at least one other that decomposed extensively, confirming that IL thermal stability in general varies among ILs as a function of both the cation and anion. The report indicates [C_2mim], [C_4mim], and [C_6mim][NTf_2] were the ILs closest to what could really be understood as distillable, and may be taken as benchmarks. They were actually sublimed, but the endeavor required temperatures around 200 ^{o}C at pressures < 1.0 μbar, equating to boiling points around 800 ^{o}C at atmospheric pressure. As for the intermediacy of NHCs **1** while heating [$C_n$mim] ILs, no less than two other reports lay claim to detecting only ion pairs in the distilling vapor.[162, 163] In other words, not only are some [$C_n$mim] salts so thermally stable they can be recovered from a distillation unchanged, but they are not necessarily equilibrated with neutral species in the course of the distillation. In the end, it can only be assumed the [$C_n$mim] ILs that did decompose did so via the carbene. Thus, while certain ILs will vaporize before decomposing, and apparently will vaporize as ion pairs, even the most volatile salts are nonvolatile under ordinary conditions and effectively nonvolatile under extraordinary conditions.

These developments warrant special consideration from the standpoint of sustainability because any IL decomposition probably generates environmental culprits and certainly contributes to waste. Even though unverified assumptions of nonvolatility and high thermal stability encouraged the premature branding of ILs as inherently green solvents, the greenness of IL applications that are legitimately green need not be undermined by the occasional volatility or thermal instability of certain ILs. The obvious answer is to identify the pertinent ILs and avoid them the same way an effort is made to avoid benzene, dichloromethane, heavy metals, etc. The simple fact that some ILs will thermolyze, sometimes even at unremarkable temperatures, is just a practical consideration characteristic of the materials, like the diminished drying capacity of inorganic sulfates at elevated temperature, or the photolability of alkyl iodides, or the incompatibility of halocarbons with elemental sodium, or the basicity of dimethylsulfoxide.

It is also commonly assumed that ILs must be very polar. It turns out getting a clear picture of their place among other solvents as a function of polarity is difficult. The absolute position of an IL's polarity fluctuates with the method of quantification. Such is also the case with conventional liquids,[164] which it should be noted are often called "molecular liquids" in the IL literature to distinguish them from the ionic kind. Conventional solvents, however, generally stay within a familiar pattern (formamide > water > dipolar aprotic solvents DMSO, DMF, MeCN, acetone, etc. ≈ alcohols > halocarbons > ethers ≈ esters > hydrocarbons) even as the values of their polarity vary with the method of analysis. Ionic liquids do not hold to this trend. They have dielectric constants of 8.8 to 15, depending on the IL,[165-167] which puts their polarity in the range of dichloromethane / -ethane, *tert*-butyl alcohol, and isopropanol. On the other hand, no less than 117 data points on Reichardt's E_T scale were reviewed by Reichardt himself, and these measurements put each of six IL castes—[NR_4] (33 data points), [$C_n$dmim] (5 data

points), [C$_n$mim] (56), [PR$_4$] (11), pyridinium (6), and pyrrolidinium (6)—within a fairly tight range *starting* at a polarity between acetone and *N*,*N*-dimethylformamide (Table 5; see also Table 6).[10] Most of the ILs assayed had E_T^N values over 0.5, and the [C$_n$mim], pyridinium, and pyrrolidinium ILs were the most polar classes. Note that these ILs also have the highest dielectric constants. The striking difference is that the least polar ILs on the E_T scale were more polar than organic solvents that were more polar than the most polar ILs on the ε scale. In other words, depending on the measurement, the entire IL population can bounce from one side of intermediate polarity to the other.

Guidelines for IL solubility in other solvents are more useful than ordinary descriptors of polarity, and broad observations on them are presented in Table 6 alongside the dielectric constant of the relevant solvent. The halide ILs are generally less soluble in organic media than are other ILs, and Table 6 is split accordingly. The guidelines presented in Table 6 are very rough, indeed; there is at least one exception in every row of the "IL anion / Other" column, and if there are not already as many exceptions in the "IL anion / Halide" column, there eventually will be. However, Table 6 is accurate for the currently most frequently encountered ILs. Ionic liquid solubility is confused most in water and aqueous mixtures, but observations on the behaviors of IL and water mixtures are instructive. Bearing in mind the old trope "like dissolves like", it is tempting to expect ILs would dissolve inorganic salts very well just because they are salts. Not only is that not the case, but even hydrophilic ILs can be excluded from aqueous salt solutions,[45, 168, 169] so they do not necessarily contribute to inorganic salt dissolution in water.

Table 5.[a] E_T^N values for ILs compared to E_T^N values for conventional liquids.[10]

Liquid	E_T^N range for ILs	E_T^N value[b]	Liquid	E_T^N range for ILs	E_T^N value[b]
DCM	NA	0.31	1-heptanol	NA	0.55
acetone	NA	0.35	**[C*n*dmim] ILs**	**0.50 – 0.56**	**0.53**
[PC*n n n n*] ILs	**0.35 – 0.44**	**0.38**	EtOH	NA	0.66
DMF	NA	0.40	NMA	NA	0.66
DMSO	NA	0.44	**[C*n*mim] ILs**	**0.53 – 0.75**	**0.66**
MeCN	NA	0.47	**pyridinium ILs**	**0.63 – 0.69**	**0.66**
2-BuOH	NA	0.50	**pyrrolidinium ILs**[d]	**0.38 – 0.90**	**0.69**
[NC*n n n n*] ILs[c]	**0.38 – 0.63**	**0.50**	TFE	NA	0.90
*i*PrOH	NA	0.53	water	NA	1.00

[a]Reichardt stresses these values do not reflect 21 extrapolated values included in the full set of 117 data points. [b]As mean E_T^N value for IL class or specific E_T^N value for a conventional liquid. [c]The total set of 33 ammonium data points included in Reichardt's original tabulation contained 11 data points from lower ammonium salts which are not reproduced here. [d]As 1-(2-methoxyethyl)-1-methylpyrrolidinium salts only. A [C_4mpy] IL appearing in the complete set of six is omitted here and, apparently, in Reichardt's original tabulation, as well.

Table 6. Rough solubility guidelines for halide salts and other ILs in common solvents at room temperature, ordered by the dielectric constants (ε) of the latter.

		IL anion				IL anion	
ε	Solvent	Halide	Other	ε	Solvent	Halide	Other
ca. 2	$C_nH_{(2n+2)}$	insol.	insol.	10.42	DCE	[c]	∞
2.21	*p*-dioxane	insol.	insol.	12.5	*t*BuOH	[b]	∞
2.28	PhMe	insol.	insol.	18.3	*i*PrOH	[c]	∞
2.38	PhH	insol.	insol.	20.7	acetone	[c]	∞
4.34	Et_2O	insol.	insol.	24.6	EtOH	sol.	∞
4.81	$CHCl_3$	insol.	[a]	32.6	MeOH	sol.	∞
6	EtOAc	[b]	[c]	35.9	$MeNO_2$	sol.	∞
6.15	AcOH	sol.	∞	36.7	DMF	sol.	∞
7.2	DME	insol.	[c]	37.5	MeCN	sol.	∞
7.6	THF	insol.	[c]	47	DMSO	sol.	∞
9.08	DCM	[c]	∞	78.54	water	[d]	[e]

[a]Usually very soluble, not usually miscible. [b]Usually insoluble at room temperature, but seen often in crystallizations. [c]There are huge variations in the descriptions of these salts' solubilities in this solvent. The particular anion is critical in determining solubility here, and the history of the sample is usually relevant, as well. Inorganic contaminants lower IL solubility in this solvent, whereas contamination with polar organic solvents may homogenize this mixture. [d]Usually very sol., but solubility drops off with increasing carbon content in the cation. [e]Solubility ordinarily depends first on the particular IL anion (Fig. 2). The solubility of ILs with ordinarily hydrophilic anions can drop off with increasing carbon content in the cation. The solubility of ILs with ordinarily hydrophobic anions can be increased if the cation features alkyl subsitutents bearing polar groups, especially H–bonding sites.

These observations show ILs are neither the organic replacements for water nor the universal solvents for organic and inorganic materials one may have expected on first inspection. That and the fact that existing material indicators of absolute polarity do not apply to ILs can be taken to mean they are unrecognizable in any contemporary understanding of solvation. As a family, ILs may be considered something altogether new. Accordingly, ILs have been called "neoteric" solvents,[1] which is a handle also applied to both supercritical fluids and fluorous solvents.[170] In a different approach to setting these liquids apart from the more recognizable varieties, Reichardt has pictorially represented the distinctions between three classes of liquids (i.e., atomic, conventional (molecular), and ionic) (Figure 7).[10, 170]

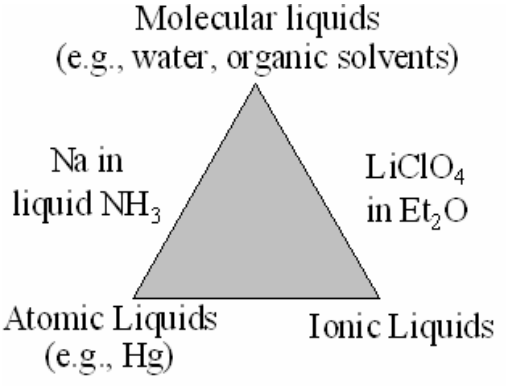


Figure 7. Reichardt's triangle relating atomic, conventional (molecular), and ionic liquids.[10, 170]

1.2. ORGANIC SYNTHESIS AND REACTIVITY IN IONIC LIQUIDS

Ionic liquids were first explored as reaction media by scientists at or associated with the USAF Academy, including Seddon, whose introduction to the topic resulted from his work at Oxford on vanadium phosphines of interest to the U.S. Navy. In a comment reminiscent of Max Planck's "desperate" foray into the consequences of energy quantization on mechanics, he told an interviewer from Thomson Scientific he conceived of ILs as solvents for organic synthesis as follows:

> We sent in reports to the U.S. Navy, which had funded the work, and about six months later, we got a letter back asking if we could make . . . potassium hexachloromolybdate . . . and I said sure. So I went to the library to see how to make these things and I discovered it was pretty well impossible. I'm sitting in the library with all these journals open, every known article on the subject, and I'm getting bored, thinking, "Me and my big mouth," and on the page opposite one of these articles was a paper by Bob Osteryoung on room temperature molten salts, which is what ionic liquids were then called. And I thought, "That's a jolly good idea—these would be an ideal environment in which to try and make these compounds." So I wrote a proposal to the U.S. Air Force and three weeks later they flew me out to their laboratories in Colorado. What I didn't know then was . . . they wanted the compound . . . to make batteries in room temperature molten salts. It was a complex coincidence. John Wilkes was also there, and Chuck Hussey from Mississippi was visiting the lab at the same time. And they taught me everything they knew about these room-temperature molten salts . . . . My one original thought was, "I bet these would be pretty good solvents for doing chemistry with." That was 1981.[83]

Molten salts in the current sense had also been recognized as reaction media,[171] but it should not be hard to appreciate that, as a practical matter, the useful properties molten salts possess could not be tapped until the advent of ILs. Many if not most of the 6000-plus IL references appearing between 2002 and 2006 (Table 2) deal with synthesis. The crown jewels of marketable IL applications, the Difasol and BASIL processes, are chemical reactions carried out in ILs. Reactions in ILs are reviewed frequently; a topic search on Thomson Scientific's Web of

Science finds 8,864 IL references. (The major difference between the SciFinder and Web of Science databases is that only the former includes patents and only the latter includes meeting abstracts.) Of the references indexed on Web of Science, 464 (one in 19) are reviews. MacFarlane and Seddon found a similarly gaudy rate of review, adding the observation, ". . . a review appears every two to three days . . . ."[129] An index of selected reviews is presented in Table 7. It should be apparent from Table 7 that most but not all of the reactions carried out in ILs are venerable reactions or concepts with a different solvent inserted. The examples that follow will show this change is by no means a trivial detail.

Moving organic reactions into ILs brings a new dimension to the relationship between ILs and sustainability. Because ILs are effectively nonvolatile, products that distill conveniently are easily recovered from the reaction mixture. Because ILs are insoluble in many organic solvents (e.g., alkanes, PhMe, and Et_2O), organic components are frequently removed from the reaction mixture not by a conventional workup, but by direct extraction from the IL. Utilizing organic solvents may seem to undermine the purported greenness of organic synthesis in ILs, but there is usually a workup following any reaction in any solvent, so this is, at worst, a zero sum game. There are also greener approaches to product isolation, most significantly using supercritical carbon dioxide to recover organic materials.[172] Recycling ILs sometimes requires repeating the washing, decolorizing, and drying steps described for their preparation, but this investment should always be less than the initial investment of reagents, solvents, materials, and electricity to prepare an IL, which is divided by as many recycles as a particular IL specimen can survive and still serve its purpose. Further, any other solvent needs similar treatment before use (if not by the end user, then by the chemical manufacturer), and these treatments can require the use of chemicals more hazardous than those necessary to treat used ILs. There are times,

Table 7. An index of selected IL reviews.

Emphasis	Review(s)
General interest	[2, 3, 42, 111, 173-180]
Processes catalyzed *in* and / or *by* ILs	[2, 177, 179, 181-191]
• Supported IL phase (SILP) catalysis	[192]
• IL supported synthesis (ILSS)	[193]
• Biocatalysis	[173, 194-199]
• Catalytic oxidations	[200]
• Metal catalyzed reactions in general	[201-204]
o Catalytic metal nanoparticles	[205-207]
o Metal catalyzed hydroformylation	[208]
o Metal catalyzed hydrogenation	[209, 210]
o Metal catalyzed C–C bond formation	[211, 212]
Physical field (MW, ultrasound, *h*ν) synthesis in ILs	[213-216]
Nucleophilic substitution (normally aliphatic) in ILs	[217, 218]
Electrophilic substitutions of arenes and heteroarenes in ILs	[219]
Synthesis of cyclic organic carbonates in ILs	[220]
Asymmetric synthesis in ILs	[221-224]
Carbohydrate chemistry in ILs	[225]
Amino acid esterification in ILs	[226]
Lewis base ILs	[41]
Reactions *of* ILs	[227]

however, when it is actually inadvisable to refine an IL sample. There is a general observation that ILs retain metal catalysts very well (as in the Difasol process). In cases where the banked catalytic activity could be compromised, it is wiser to reuse a recycled IL as is, with the possible exception of drying it under vacuum.

There is one problem with inviting reexaminations of old reactions in new solvents, however, and it is that the reactions in ILs that get noticed are those which appear to be directly and profoundly affected by the IL, and there is an unfortunate trend of many authors touting results diametrically opposed to existing data and sometimes to the very data they present. Consider that if just 10% of the IL literature from the last five years contains cherry-picked, doctored, exaggerated, or fraudulent data, then the garbage factor (Seddon's preferred phrase[3]) equates to more than 600 papers muddying the waters. As reviews of this literature as a whole or of freestanding fragments of it continue to appear (at a rate of 5% of all papers added to the IL literature), the garbage factor is compounded. To quote MacFarlane and Seddon, many of the papers in the IL literature are "highly derivative, or based on false, naïve assumptions," and there are "far too many papers . . . appearing with extravagant (verging on dishonest) claims."[129]

That said, improved yields, rates, and selectivities are commonly substantiated, and there are already many reproducible remarkable examples. It is hard to not be of two minds about the clamor to reevaluate synthetic mainstays in ILs. Even when they appear to chide the IL readership at large for unsubstantiated assertions, not even MacFarlane and Seddon are contesting the idea that ILs may impart drastic changes on organic reactions performed in them, or even that they may do so regularly. For example, in his interview with Thomson Scientific, Seddon was asked for a final thought on the topic, and gave the following response:

> If you are an industrialist and you have got a process that's giving you 100 percent yield that is working beautifully, then you don't need ionic liquids. If you have a problem; if the yield is too low; if the solvent you're using is going to be banned in two years because it's too toxic, then ionic liquids are an extremely attractive option for changing a known process or initiating a new one. Chemistry in ionic liquids is totally different than chemistry in the molecular environment of a normal solvent. The kinetics are different. The thermodynamics are different. The outcome is different. Everything is new.[83]

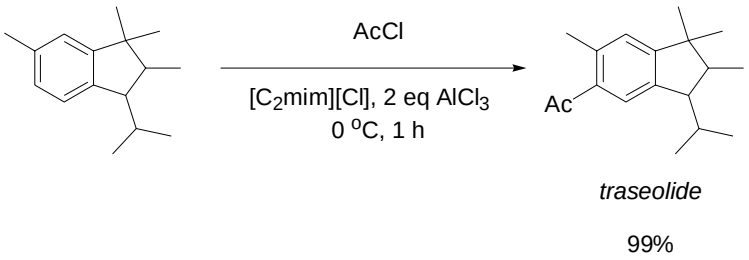
He ends on the very simple and believable assertion that chemistry could be fundamentally altered when conventional liquids are replaced with salts. The inconsistency is that he opened by dissuading anyone reading his comment from trifling with the alchemic properties of the media.

Hence, the larger issue is the dirth of models to explain reactivity in ILs, and the open questions are when and how these solvents materially change the chemical reactions performed in them. The need for new explanations for chemical reactivity in ILs has a parallel with the renewed interest in organic reactions in water. The simple explanation for many observations on organic reactivity in water is that it influences reactions by forcing the association of hydrophobic reagents which could disperse in an organic solvent, but there are also many outcomes from organic syntheses in water that defy this simple explanation.[228, 229] To quote MacFarlane and Seddon again, they write "the time for quiet contemplation is long overdue,"[129] clearly referring to the scarcity of attempts to understand the observed reaction outcomes in ILs and the physical properties that made them possible. Giving ILs their own classification, the neoteric brand, should be conceptually useful in developing an understanding of the physical properties of ILs and appreciating that chemical processes may be different in them than in conventional solvents. The new classification underscores the fact that chemists are outside their proverbial comfort zone.

New physical models to go along with new reactivity patterns in ILs usually do not appear in either designs or postmortems of reactions in ILs. However, in the last two years, reviews have appeared that seriously consider chemical reactivity in ILs as an effect of properties unique to the liquids.[174, 230, 231] In a course of research that has not received much attention yet, H. Zhao has taken an interest in classifying ions appearing in ILs as kosmotropic (order-making) or chaotropic (order-breaking).[232, 233] He recently found a correlation between these solvent properties and the enantioselectivity of enzymatic reactions in ILs.[234] It is probably a stretch to believe kosmo- / chaotropic indicators will correlate to the behaviors of reagents dissolved in ILs because the metric is specifically based on the effect an ion pair has on water. But it is enticing to imagine that some unit of measure previously uncommon to organic chemistry could be structured around a descriptive model and used to account for unique reactivities in ILs. Such a metric will be especially useful if it suggests what is reasonable to expect (or report or read) and what is not, and a quantifier attached to each ionic half of an IL will be all the more useful for this purpose. An article from M. Watanabe addressing the ionicity of ILs catalogs several physicochemical properties of ILs and defines two new ones which may prove helpful in developing a mechanistic interpretation of reactions in ILs.[235]

Acid catalyzed reactions appear to constitute the single largest class studied in ILs. There are hundreds of examples just from the reactions of aromatic and heteroaromatic compounds in ILs, and a review of this subset by G. I. Borodkin and V. G. Shubin is available.[219] Ionic liquids can feature strong Lewis or Brønsted acids within their structures, and these may be effective acid *catalysts*. One of many such examples comes from Wasserscheid, who reports that Friedel–Crafts alkylations of benzene with 1-decene under the influence of sulfuric acid are improved by the addition of a small amount of a $[HSO_4]$ or a $[B(HSO_4)_4]$ IL.[80]

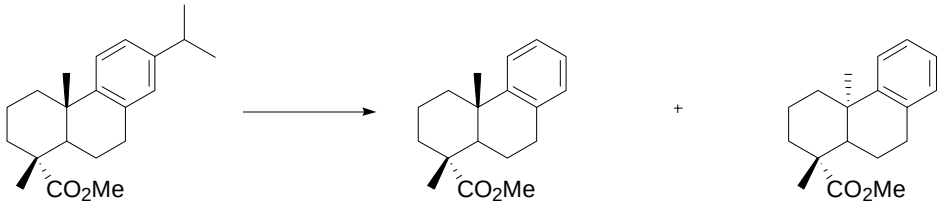
These acidic ILs may also be used as the *medium* for a reaction catalyzed by acid, and it follows that the reaction will be more efficient than the corresponding one in a conventional solvent because a catalyst has been loaded in solvent quantities. A catalytic liquefied acid solvent is used in the Difasol process (Figure 6), and references were provided above to other acidic ILs functioning as media for alkane cracking and alkene oligo- and polymerization, especially in the manufacture of petroleum products. The Friedel–Crafts reactions were the first reactions performed in ILs, which should not be surprising since the first ILs were chloroaluminate melts. The first examples came from Osteryoung, V. R. Koch, and L. L. Miller in 1976, and these Friedel–Crafts reactions were electroinitiated.[236] Ten years later, reactions promoted only by the chloroaluminate melts were reported,[237] and in 10 more years time, Friedel–Crafts acylations of ferrocene were reported in haloaluminate melts.[238] Earle, Seddon, and coworkers made their first entry to the series in 1998, reporting a synthesis of the indane fragrance traseolide in 99% yield after one hour at 0 ^{o}C (Scheme 7), an acylation of chlorobenzene in one day at room temperature, and on the reversibility of Friedel–Crafts acylations of anthracene, all in chloroaluminate ILs.[239] This was one of the last papers to legitimately open with the sentence, "The possibility of carrying out chemical transformations in low temperature ionic liquids has, to date, received little attention."



Scheme 7. The synthesis of traseolide from Earle, Seddon, and coworkers.[239]

Speaking of reversible Friedel–Crafts reactions in ILs, a process for the transfer of an acyl group from a congested aromatic ketone to an activated arene has been reported by K. K. Laali and V. D. Sarca.[240] Examples of the removal of an isopropyl group from methyl dehydroabietate at room temperature have also appeared (Table 8).[241] Chloroaluminate melts have also been used to access coumarins through the Pechmann condensation of phenols and ethyl acetoacetate,[242] and to cleave aryl methyl ethers.[243] Melts of $[(C_2H_4OH)NC_{1\ 1\ 1}][Cl]$ in zinc chloride gave Fischer indole adducts in an example with a unique emphasis on product separation; the indoles were sublimed from the medium.[244]

Table 8. Dealkylations of methyl dehydroabietate at room temperature.[241]



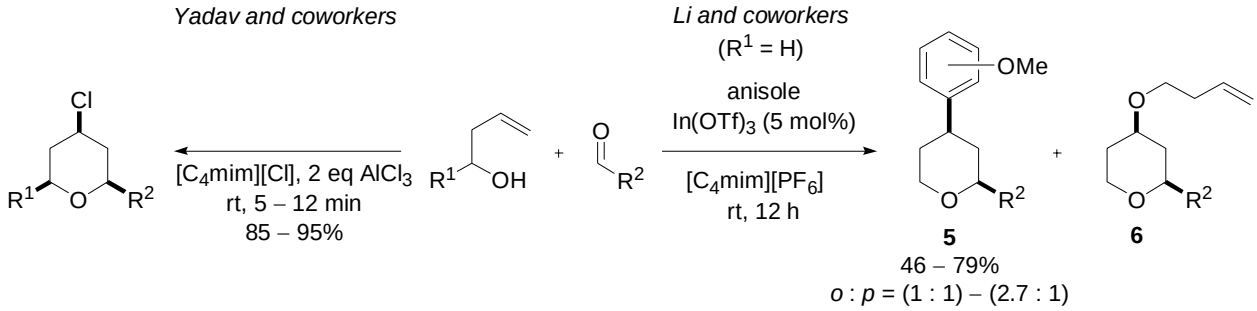
2 **3** **4**

Entry	Solvent	*i*Pr$^+$ scavenger	**2** : solvent : $AlCl_3$: *i*Pr$^+$ scavenger	*t* (h)	% conversion	**3** : **4**
1	PhH	PhH	1 : 352 : 5 : --	3	100	27 : 73
2	$[C_n$mim][X] *n* = 3, 5, 7 X = Cl, Br	PhMe	1 : 2 : 4 : 4	0.5	90 – 98	ca. 30 : 70
3	$[C_5$mim][I]	"	"	"	87	52 : 48
4	$[C_5$mim][BF_4] or [PF_6]	"	"	48	0	--
5	$[C_5$mim][BF_4]	"	1 : 7 : 14 : 4	15	90	85 : 15

Ionic liquids with no significant acidities of their own can also be used as media for acid catalyzed reactions; Entry 5 of Table 8 is one example. Other examples of acid catalyzed reactions in effectively neutral ILs include Friedel–Crafts alkenylations with alkynes and alkylations with alkenes, both under the influence of metal triflates,[245, 246] and Friedel–Crafts acylations under the influence of either metal triflates or *bis*-triflimides.[247, 248] There is a large number of references dealing with conversions of indoles and carbonyl compounds to *bis*-(indolyl)methanes in ILs (lead refs[249-251]). Fischer esterifications have been accomplished in ILs,[252] as have Pictet–Spengler syntheses by the application of phenyliodine (III) trifluoroacetate,[253] Hantzsch 1,4-dihydropyridine syntheses with 3,4,5-trifluorobenzeneboronic acid as the catalyst,[254] and syntheses of imidazo[1,2]pyridines from 2-aminopyridines and α-tosyloxyketones.[255]

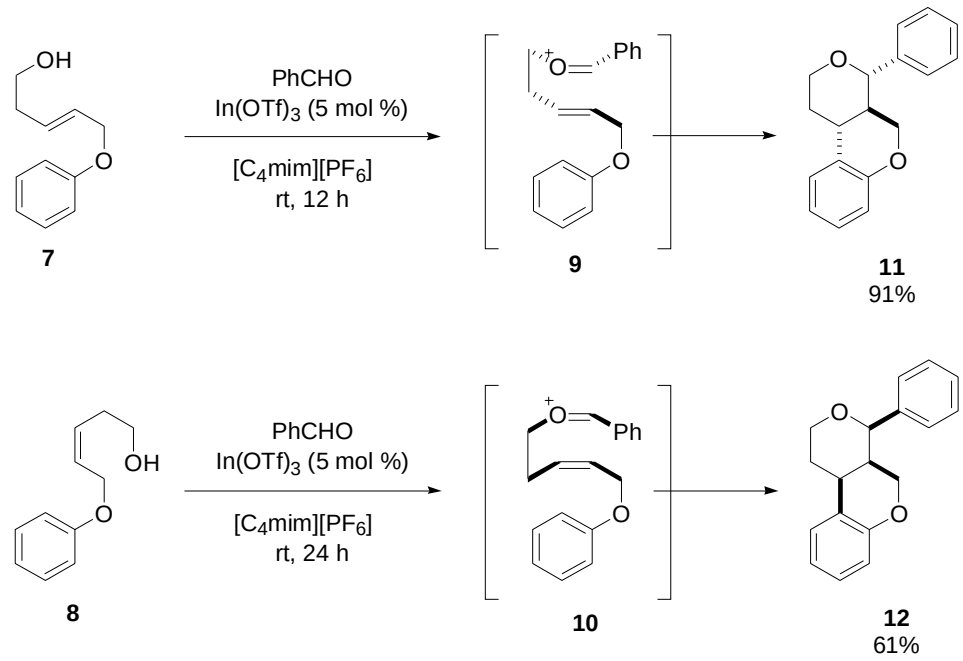
Prins reactions leading to tetrahydropyran derivatives have been carried out in ILs in at least two ways. J. S. Yadav and coworkers used acidic mixtures of $[C_4mim][Cl]$ and aluminum chloride to prepare *cis*-2,6-disubstituted-*cis*-4-chlorotetrahydropyrans (Scheme 8).[256] C.-J. Li and coworkers used indium (III) triflate in $[C_4mim][PF_6]$ for tandem Prins–Friedel–Crafts reactions leading to *cis*-1-substituted-4-aryltetrahydropyrans **5**.[257] The ratio of Prins–Friedel–Crafts adduct **5** to ether byproduct **6** varied with the solvent. This ratio was most strongly biased toward the desired product in reactions in $[C_4mim][PF_6]$ containing a catalytic amount of indium (III) triflate and 10 equivalents anisole, where the ratio **5** : **6** was 6 : 1.

Li and coworkers went on to show that ethers **7** and **8** react with benzaldehyde to provide 2,4-*cis* and 2,3,4-*cis* trisubstituted fused tetrahydropyrans **11** and **12**, respectively, as the only isolable products (Scheme 9). The authors did not rationalize the observed stereochemical



Scheme 8. Prins reactions in ILs leading to THP derivatives.[256, 257]

outcomes, but it appears from models of the intermediates that the phenyl ring introduced with benzaldehyde must be *cis* about the oxonium double bond. This geometry places the phenyl ring on the more congested side of the pi system in intermediate **10**. These compounds are related to the heterocyclic core of the reported structure of calyxin I. The efficiency and the potential synthetic usefulness of the conversions reported by Li's group notwithstanding, note that there have been structural revisions to some calyxin natural products.[258]



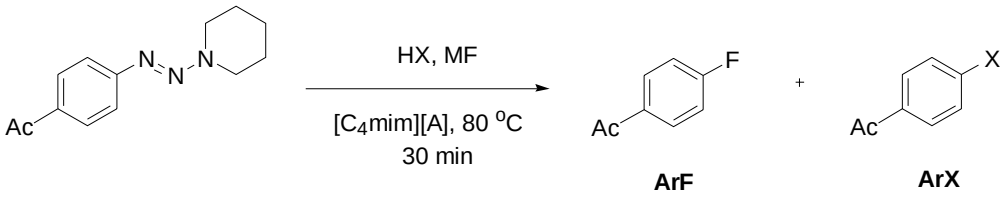
Scheme 9. Syntheses of fused tetrahydropyrans in $[C_4mim][PF_6]$ by Li and coworkers.[257]

D. Y. Chi, J. A. Katzenellenbogen, and coworkers have used the decomposition of triazines by acid in ILs as an alternative to the Balz–Schiemann variant of the Sandmeyer reactions (Table 9).[259] The authors note that a separate reference showed this reaction proceeded in 29% yield when performed with hydrogen fluoride–pyridine and silver (I) fluoride in the absence of IL; the yield was 24% with triflic acid and cesium fluoride. Note the importance of the IL anion in particular, which is revealed by the low yields in [C_4mim][OTf] or [NTf_2] (Entries 12 and 13). The variation in yield with IL anion and the success of several reactions without a fluoride salt (Entries 5, 6, 8 – 10) indicate the carbocation intermediate can be quenched by fluoride transfer from [BF_4] or [PF_6]. Thus, the benefit to doing this reaction in ILs with fluorous anions is that they provide a convenient source of fluoride in excess.

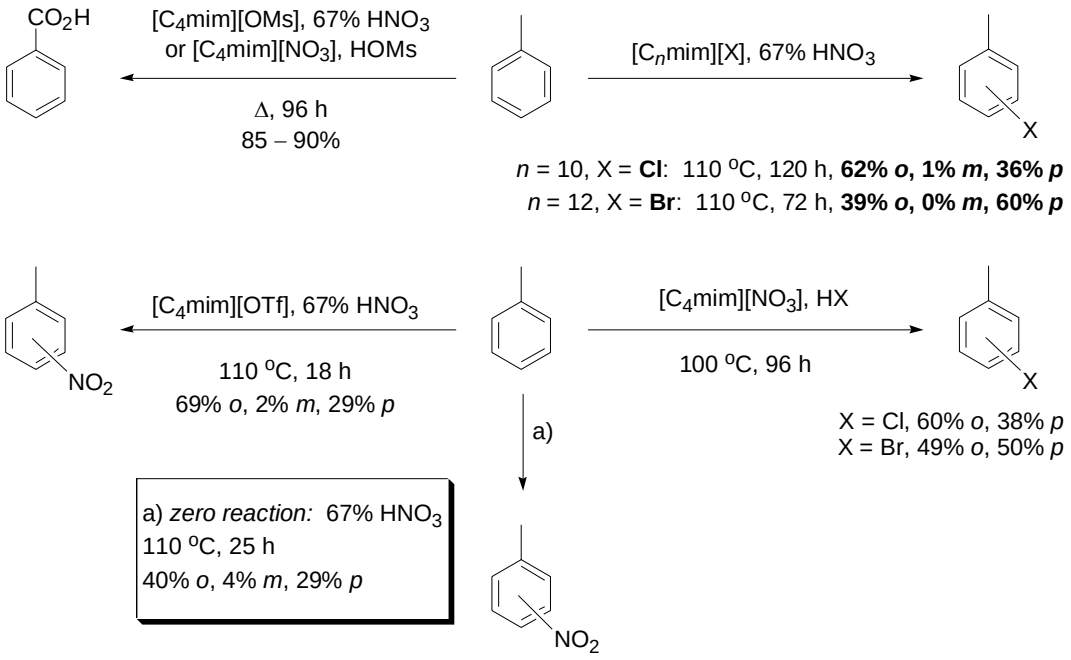
Several examples of acid catalyzed reactions in ILs come from a paper by Earle, S. P. Katdare and Seddon titled, "Paradigm Confirmed: The First Use of Ionic Liquids to Dramatically Influence the Outcome of Chemical Reactions".[260] They were able to selectively accomplish the electrophilic aromatic nitration or halogenation of toluene, or to oxidize it to benzoic acid depending on what inorganic acid and IL they put in the reaction mixture (Scheme 10). The recipes started with toluene and a [$C_n$mim] cation. Providing halide, nitrate, and an acidic proton delivered halotoluenes. Providing mesylate, nitrate and an acidic proton delivered benzoic acid. Toluene was nitrated by concentrated nitric acid in [C_4mim][OTf] in both higher yield and *ortho* : *para* ratio than by the zero reaction.

Note that the conversions included in Scheme 5 are only the most striking and comprise the most complete set of reactions from the Paradigm Confirmed paper; the authors provide additional observations and examples using other arenes. Many of their reactions show solvent

Table 9. Synthesis of fluoroarenes in ILs through the decomposition of triazenes.[259]



Entry	[A]	HX (eq)	MF (1.5 eq)	% Yield	
				ArF	**ArX**
1	$[BF_4]$	*p*-TsOH (1.5)	KF	73	15
2	$[BF_4]$	*p*-TsOH (1.5)	CsF	71	13
3	$[BF_4]$	*p*-TsOH (1.5)	TBAF	68	12
4	$[PF_6]$	*p*-TsOH (1.5)	KF	71	12
5	$[BF_4]$	*p*-TsOH (1.5)	--	77	12
6	$[BF_4]$	*p*-TsOH (1.2)	--	73	7
7	$[BF_4]$	*p*-TsOH (7.5)	--	0	93
8	$[BF_4]$	TfOH	--	65	10
9	$[BF_4]$	MsOH	--	70	9
10	$[BF_4]$	TFA	--	56	22
11	$[BF_4]$	AcOH	--	0	0
12	[OTf]	*p*-TsOH (1.5)	KF	29	26
13	$[NTf_2]$	*p*-TsOH (1.5)	KF	22	28



Scheme 10. Reactions of toluene which vary as a function of provided IL.[260]

quantities of ILs were not actually necessary. For example, at the lower limit, 0.11 equivalent [C_4mim][OTf] in toluene with three equivalents nitric acid gave a nitration with almost identical results to the one shown in Scheme 10. This implementation required only five more hours reaction time, which is still a more efficient process than the zero reaction, and led the authors to propose a catalytic effect from [C_4mim][OTf].

Programming an IL to drastically influence a chemical reaction was, is, and surely will continue to be a popular concept among chemists with an interest in ILs. Tuning or designing an organic synthesis that is ideal in one IL as an effect of that IL is similar in concept to streamlining a synthesis with cascade reactions.[261] Each of these pursuits requires idiosyncratic examples produced by conscious manipulation of reaction conditions. From the differential reactions presented in the "Paradigm Confirmed" paper,[260] some readers might not find the halogenations stunning because the results may have been expected from the beginning, but that

is part of the point. These examples have convenient explanations because combinations of an acidic proton, halide, and nitrate react to the corresponding hypohalous acid, which goes on to halogenate toluene. The authors stress that all of these reactions were performed open to the atmosphere, and imagine the reduced form of nitrogen oxide could be reoxidized in the aerated mixture. In their experimental protocol, they show a slight excess of nitrate was provided, so this reoxidation may be at work, but it is not clear whether it is critical.

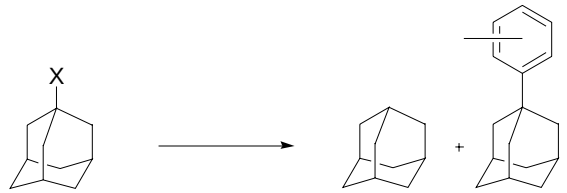
The oxidation of toluene by nitric acid in [C_4mim][OMs] as opposed to nitration in [C_4mim][OTf] is harder to explain. Regarding the latter, there is no inorganic redox process in the background, and the electrophilic nitration of toluene is straightforward; the presence of air does not appear to factor into this reaction at all. The obvious difference between [OTf] and [OMs] ILs is their basicity; the pK_as of triflic, nitric, and methanesulfonic acids are –14 (est), –1.3, and 2.6, respectively. Hence, nitric acid should have protonated [OMs] to methanesulfonic acid. If methanesulfonation of toluene had been observed, the explanation would be nitric acid ionized methanesulfonic but not triflic acid, but that was not observed. The authors only address the Etard-type reaction with the comment, "nitric acid acts as an oxidizing agent rather than a nitrating agent." Interestingly, their data do indicate the presence of air was important in this case, because the reaction of 5.0 mmol [C_4mim][NO_3], 7.5 mmol methanesulfonic acid, and 10.0 mmol toluene gave an 89% yield of benzoic acid based on toluene, so there must have been some cooxidation by air.

What could the explanation be? Lanthanide triflates are separately known as aromatic nitration catalysts,[262] and examples were provided earlier of Friedel–Crafts reactions affected by these catalysts in ILs. Of course, one would imagine the Lewis acidic metal cation is the functional side of the salt in those cases, but perhaps some properties of the triflate are important.

These properties could explain the effect of only a small amount of [C_4mim][OTf] on the nitration of toluene and account for the different course of reaction in [C_4mim][OTf] as opposed to [OMs]. The other half of an explanation would have to address why nitration did not occur in [C_4mim][OMs]—why mesylate favors oxidation or forbids nitration. The following comment is a strained explanation, but in the interest of mental exercise, note that Upjohn abandoned a drug called Freedox (tirilazad mesylate), which inhibited enzymatic aromatic nitration.[263, 264] The few available studies dealing with the mechanism of action do not address any specific role of the anion. Industry rarely does anything by accident, and it seems more likely the anion was selected for conferring some desirable physical property during preparation of the drug, such as crystallinity or solubility—not because mesylate was medicinally relevant—but there it is.

Laali, Sarca, and coworkers have studied Friedel–Crafts adamantylations in ILs.[265] Among their data are comparisons of adamantylations of toluene catalyzed by triflic acid in [C_4mim][OTf] versus dichloroethane, which show the formation of adamantane as a side product is disfavored in the IL (Table 10). The authors also studied competitive adamantylations of benzene or toluene in both [C_4mim][OTf] and dichloroethane, finding there was a much stronger preference for adamantylation of toluene over benzene in the IL as compared to the organic solvent (Table 11). Taken together, these observations could incorrectly suggest the adamantane carbocation is stabilized in [C_4mim][OTf], and can therefore react more selectively. Common ILs like [C_4mim][OTf] should actually be inhospitable media to cations because the anion of the IL is poorly coordinating. Friedel–Crafts and similar reactions can proceed efficiently in ILs partly because they tolerate (and can be tailored to provide) acids strong enough to force the existence of electrophilic species, and then *do not* stabilize the intermediate. The better explanation for both the observed regioselectivities in Table 10 and the selective reaction of

Table 10. Data on arene adamantylations at 60 – 65 °C from Laali, Sarca, and coworkers.[265]

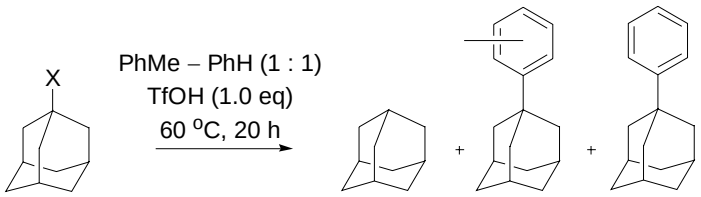


						Product distribution (% yields)		
Entry	X	Solvent	TfOH (eq)	PhMe (eq)	*t* (h)	AdH	*m*-tolyladamantane	*p*-tolyladamantane
1	OH	DCE	0.5	6	4	26	38	36
2	"	[C_4mim][OTf]	"	"	1	0	0	100
3	Cl	DCE	0.5	6	1.5	33	44	23
4	"	[C_4mim][OTf]	0.6	"	20	0	0	22
5	"	"	1.2	"	20	2	5	89
6	"	"	2.0	"	20	0	0	100
7	Br	DCE	0.5	6	1.5	42	36	22
8	"	[C_4mim][OTf]	1.2	"	20	0	2	14
9[a]	"	[C_4mim][OTf]	1.2	"	20	5	5	90

[a]Reaction at 80 °C.

toluene over benzene recounted in Table 11 is that [C_4mim][OTf] resolved the activation energies of competing processes than did dichloroethane, and not that [C_4mim][OTf] stabilized the intermediate carbocation to give more controlled reactions. This conclusion also explains why some of the reactions in [C_4mim][OTf] required longer reaction times and / or higher temperatures to proceed, but gave more selective adamantylations nonetheless. The lesser extent of adamantane formation in the reactions in [C_4mim][OTf] is more likely due to the fact the IL has no adequate source of hydride for transfer to the intermediate carbocation, unlike dichloroethane, and not due to any stabilization of the intermediate carbocation.

Table 11. Data on competitive adamantylations of PhMe and PhH from Laali, Sarca, and coworkers.[265]



		Product distribution (% yield)		
X	Solvent	AdH	tolyladamantanes	PhAd
OH	DCE	18.5	37.6	43.9
"	[C_4mim][OTf]	0.13	94.2	5.8
Cl	DCE	26.0	31.4	42.4
"	[C_4mim][OTf]	0	94.0	6.0
Br	DCE	26.5	28.4	45.1
"	[C_4mim][OTf]	0.1	94.4	5.6

There is further evidence for the instability of carbocations in ILs. X. Creary and coworkers detailed the formations and reactions of many carbocationic species in ILs.[266] Qualitatively, their results show carbocations do not persist in ILs; they quickly gave elimination in the presence of 2,6-lutidine or rearrangement in its absence. C. Chiappe, C. S. Pomelli, and coworkers followed the solvolysis of *bis*-(4-methoxyphenyl)chloromethane in mixtures composed of ILs, trifluoroethanol, and / or acetonitrile. The intermediate *bis*-(4-methoxyphenyl)methyl carbocation was trapped by trifluoroethanol up to an order of magnitude faster in mixtures containing ILs than in mixtures without them. Putting it succinctly, they conclude, "ILs, having a high ionizing power but a very low ability to interact with the formed carbenium ions, make these latter intermediates highly reactive species."[267] The ability of ILs to drive the formation of carbocations even when the outcome is not forced by a potent Lewis acid is likely due to the H–bond donating ability of the most popular ILs, which can assist the cleavage of a leaving group from an alkyl backbone. It follows that the instability of the resultant carbocation comes from the inability of the most popular IL anions to interact with it.

1.2.1. NUCLEOPHILIC SUBSTITUTION REACTIONS IN IONIC LIQUIDS

Since ILs stabilize anions, they should be expected to impede nucleophilic substitutions by them. This consequence is apparent in relative reaction rates drawn from several sources (Table 12). Most of this data comes from Welton and coworkers, particularly N. L. Lancaster.[218] They measured the rate constants of the S_N2 reactions of anions with methyl *p*-nitrobenzenesulfonate (*p*NBS) around room temperature using UV spectroscopy to follow the reactions.[59, 268-271] D. Landini and A. Maia have provided rate constants at 60 °C for reactions of anions with hexyl mesylate in [C_6mim] ILs, which they followed titrimetrically or with gas chromatography. For comparison to the rates in conventional solvents, they provided the rate constants of reactions for the same anions with octyl mesylate in chlorobenzene.[272] More data is available from the same group on similar reactions in methanol and dimethylsulfoxide.[273] Table 12 also draws on rate constants reported for similar reactions in acetonitrile[274] and in 1,1,1,3,3,3-hexafluoroisopropanol.[275]

Each of the papers these numbers come from present the measured rate constants as a function of the anion. There are some errors associated with this data treatment in the original references, and they contaminate the very comparisons of S_N2 reaction rates in ILs to those in conventional solvents the compilation in Table 12 is meant to allow. First, the leaving group varied among the references most useful for such comparisons. This variation is no small detail. For example, the rates of reactions presented in the acetonitrile period are 2 – 90 times slower than the same reactions with methyl iodide in place of methyl tosylate; the differences in relative rates as a function of leaving group can be even greater (up to 212 ×) with nucleophiles not considered in Table 12.[274] The data points selected for Table 12 always featured a sulfonate leaving group, but this constraint is no guarantee that the error is kept to a minimum as the exact leaving groups vary. The alkyl groups transferred also varied across (and within) the original references.

Table 12. Relative rates of S_N2 reactions (LG–TG + Cation–Anion → TG–Anion + Cation–LG) in either ILs or conventional liquids. The fastest combinations in conventional solvents are bolded and boxed; the fastest combinations in ILs are italicized and boxed. The slowest reaction overall is in black.[59, 268-275]

					Anion							
solvent	T (°C)	LG	TG	Cation	Cl	Br	I	CN	AcO	CF_3CO_2	SCN	N_3
DMSO	25	*p*NBS	Me	???[a]	17510	7607	**3735**	**344358**	**85603**	**944**	**564**	--
DCM	22	*p*NBS	Me	???[a]	**20817**	**8949**	1284	52335	5272	125	442	--
$[C_4mp][OTf]$	25	*p*NBS	Me	$[C_4mp]$	*1926*	*1167*	798	*37160*	*1751*	*134*	*119*	--
$[C_4mim][BF_4]$	25	*p*NBS	Me	$[C_4mim]$[b]	784	741	1047	--	--	--	--	--
$[C_4mp][NTf_2]$	25	*p*NBS	Me	$[C_4mp]$	761	440	366	30350	1051	49	90	--
PhCl	60	MsO	*n*Oc	$[NC_{8\,8\,8\,8}]$	720	389	132	--	--	--	15	**3035**
$[C_4dmim][NTf_2]$	25	*p*NBS	Me	$[C_4dmim]$	576	430	463	--	--	--	--	--
MeCN	25	TsO	Me	Ph_4As	447	97	--	--	5058	--	4	486
$[C_4mim][OTf]$	25	*p*NBS	Me	$[C_4mim]$[b]	383	611	*1204*	--	--	--	--	--
$[C_4mim][PF_6]$	25	*p*NBS	Me	$[C_4mim]$[b]	280	167	541	--	--	--	--	--
$[C_4mim][NTf_2]$	25	*p*NBS	Me	$[C_4mim]$[b]	241	379	451	7510	181	17	77	--
$[C_4mim][SbF_6]$	25	*p*NBS	Me	$[C_4mim]$[b]	224	239	350	--	--	--	--	--
PhCl	60	MsO	*n*Oc	$[C_8mim]$	146	138	62	--	--	--	14	696
DMSO	60	MsO	*n*Oc	$[PC_{4\,4\,4\,16}]$	70	45	10	658	--	--	5	263
$[C_6mim][ClO_4]$[c]	60	MsO	*n*Hx	$[C_6mim]$	14	10	16	--	--	--	3	*110*
MeOH	25	*p*NBS	Me	???[a]	8	32	117	315	13	1	45	0
$[C_6mim][PF_6]$[c]	60	MsO	*n*Hx	$[C_6mim]$	6	7	7	--	--	--	2	62
HFIP	50	*p*NBS	Me	$[NC_{1\,1\,1\,1}]$	2	9	76	--	--	--	--	--
MeOH	60	MsO	*n*Oc	$[PC_{4\,4\,4\,16}]$	2	4	11	8	--	--	3	12

[a]??? = The cation was assuredly an IL cation, but it is not always clear from the references which one. [b]For the measurements of the rate constants of substitutions by iodide, the anion was supplied as the $[C_2mim]$ salt. [c]The authors note the IL contained 2000 ± 100 ppm water.

The cations paired with the supplied anions were also inconsistent, which even values in Table 12 show can be a significant difference. The potential differences in reaction rates of anionic nucleophiles paired with different cations are most acutely seen in the S_N2 reactions of octyl mesylate with [C_8mim] as opposed to [$NC_{8\ 8\ 8\ 8}$] salts in chlorobenzene at 60 ^oC, where anions paired with the latter gave complete reactions two to five times faster for four of six anions (one set of reactions is omitted from Table 12).[272] For measurements of the rate constants in ILs, both research groups named above took pains to provide the anion in question as the salt of the same cation as that of the IL under investigation, the idea being that the rate constant measured reflected the inherent nucleophilicity of the anion in that IL. It is a novel approach, but bulletproof comparisons require the rate constant for the reaction of the anion at the center of a comparison supplied with the cation of *each* contrasted IL in *each* conventional solvent. That comparison would require the same number of rate constants in each of as many conventional solvents as the number of ILs for comparison. Besides that, it is not always possible to thusly limit the number of conceivable ion pairs in a reaction mixture and to ostensibly isolate the anion nucleophilicity from the effect of a cation. For example, the Welton group used [C_2mim][I] as the source of iodide for reactions in [C_4mim] ILs because [C_4mim][I] was difficult to obtain in adequately pure form.[59] Additionally, methyl *p*-nitrobenzenesulfonate, the favored electrophile of the Welton group, is insoluble in most ILs; it was added as a solution in dichloromethane.

None of the data extracted from the literature for Table 12 allows an unambiguous comparison of the S_N2 reaction of even one electrophile with one anion in one conventional solvent and one IL based on one cation paired with one anion, but the three periods from Landini and Maia concerning the reactions of [C_6mim] salts in chlorobenzene, [C_6mim][ClO_4], and

[C_6mim][PF_6] come closest. The only difference among them is the use of *n*-octyl as the transferred group in chlorobenzene and *n*-hexyl in the ILs, and none of the reactions within this set were faster in ILs than in chlorobenzene.

The preceding 1.75 pages of qualifiers notwithstanding, using these rate constants for a comparison of anion nucleophilicity in ILs against conventional solvents is still informative. From the tabulated data, it appears S_N2 reactions of anions in ILs are faster than the reactions in hydroxylic solvents, but the reaction rates are only available in two hydroxylic solvents. There are several examples of faster reactions in ILs than in nonhydroxylic conventional solvents as well, but the fastest of these are slower than the fastest reactions in conventional solvents; the difference is over an order of magnitude for four out of eight anions.

Although the supposition arguably plays fast and loose with the data, the data show that S_N2 reactions of anions are slower in ILs than in conventional solvents. Like the reactions in traditional solvents, the rates of reactions in ILs vary with the anionic nucleophile, its counterion, and the exact solvent. The order of anion nucleophilicity also varies from solvent to solvent, be it conventional or be it an IL. The significance of this variable reactivity is an eye of the beholder problem; Welton and coworkers observe that this type of variability means ILs could be tuned to optimize a specific nucleophilic substitution,[268] which is reminiscent of the Paradigm Confirmed paper.

The Welton group first rationalized the impediment to model S_N2 reactions by ILs in terms of the Hughes–Ingold rules, which they have alternately deemed useful if ILs are simply considered polar solvents for the exercise,[268, 269] or have called "crude" and reliant "on a rather vague, generalized idea of solvent polarity."[271] They have also considered the deleterious solvent effect as the result of the H–bond donating ability of the IL cation,[268-270] and with

conceptualizations of the reaction in terms of hard and soft ion coordination. The conclusion is that anion nucleophilicity is lower in ILs than in conventional solvents because it is stabilized by the IL cation. They state, "reaction rates will probably be greater in [ILs] composed of the least coordinating (poor hydrogen bond acids) cations."[268] Last year, they showed that the rates of some reactions between anions and methyl *p*-nitrobenzenesulfonate in ILs and in conventional solvents exhibit linear solvation energy relationships (LSERs) with the Kamlet–Taft parameters of the respective solvents. In those cases, the reaction rate depended most on the parameter α, a measure of H–bond donating ability, and the reaction rate was inversely proportional to it (Eqs. 1 – 7).[270] This observation has more empirical support in that the highest reaction rates in Table 12 for reactions in ILs featured [C_4mp] ILs, which should not be as powerful H–bond donors as [$C_n$mim] ILs. Welton and coworkers faithfully stress that S_N2 reactions of anions do not experience any "IL effect", by which they surely mean an enhancement, because they themselves documented the relative slowing of a model reaction in ILs.

$$\text{Anion} = Cl^- \ (R^2 = 0.98) \quad : \quad \Delta G_{298K}^{\ddagger} = 72.3 + 19.2\alpha \qquad (1)^{[270]}$$

$$\text{Anion} = AcO^- \ (R^2 = 0.95) \quad : \quad \Delta G_{298K}^{\ddagger} = 71.4025 + 19.9\alpha \qquad (2)^{[270]}$$

$$\text{Anion} = AcO^- \ (R^2 = 1.00) \quad : \quad \Delta G_{298K}^{\ddagger} = 90.0 + 21.6\alpha - 3.2\beta - 18.5\pi^* \qquad (3)^{[270]}$$

$$\text{Anion} = CF_3CO_2^- \ (R^2 = 0.97) \quad : \quad \Delta G_{298K}^{\ddagger} = 94.2 + 12.4\alpha - 12.8\pi^* \qquad (4)^{[270]}$$

$$\text{Anion} = SCN^- \ (R^2 = 0.91) \quad : \quad \Delta G_{298K}^{\ddagger} = 82.5 + 6.19\alpha \qquad (5)^{[270]}$$

$$\text{Anion} = CN^- \ (R^2 = 0.95) \quad : \quad \Delta G_{298K}^{\ddagger} = 16.8 + 15.7\alpha \qquad (6)^{[270]}$$

$$\text{Anion} = CN^- \ (R^2 = 0.98) \quad : \quad \Delta G_{298K}^{\ddagger} = 79.9 + 12.3\alpha - 12.8\pi^* \qquad (7)^{[270]}$$

These observations can be understood with the familiar terms used to describe these reactions in conventional solvents, where S_N2 reactions of anions are expected to be fastest in those dipolar aprotic solvents which strongly coordinate cations, namely dimethylsulfoxide, *N*,*N*-dimethylformamide, acetonitrile, and hexamethylphosphorus triamide and its phosphoramide. The rationale is that those solvents free the anionic nucleophile, destabilize it, and facilitate substitution by it. This effect is counterbalanced by any H–bond donation from the solvent, however, which deactivates anionic nucleophiles, which is why hydroxylic solvents can be relied upon to give slower S_N2 reactions.

There is also the matter of stabilizing the transition structure. The stabilization is greater in nonpolar solvents if charge is, by comparison to the reagents, dispersed or annihilated in the progression from reactants to transition structure. The stabilization is greater in polar solvents if charge is, by comparison to the reagents, localized or created in the progression from reactants to transition structure. In practice, the solvent effects that destabilize reagents and stabilize transition structures operate in balance, as evidenced by the dimethylsulfoxide and dichlormethane periods in Table 12. Within this framework, strongly H–bond donating ILs are the other side of the polar aprotic coin; they provide stabilizing interactions with anions and offer no stabilization for cations. Weakly H–bond donating ILs (like $[C_4mp]$ salts) may give faster reactions than strongly H–bond donating ILs, but are still expected to give much slower S_N2 reactions of anions than do conventional solvents, and there are many examples to this effect within Table 12.

In S_N2 reactions of neutral nucleophiles with neutral electrophiles, however, the situation is different because the forming charge in the transition structure should be stabilized by the IL. Still using *p*-nitrobenzenesulfonate as the electrophile, Welton and coworkers found the

methylations of neutral amines were several times faster in ILs than in acetonitrile, water, or dichloromethane (Table 13).[271] A. Skrzypczak and P. Neta have provided rate constants for the alkylation of 1,2-dimethylimidazole by benzyl bromide in several ILs and in conventional solvents; they also observed the reactions were fastest in ILs.[276] One more accumulation of rate constants for the S_N2 reactions of neutral nucleophiles with neutral electrophiles in ILs is available from F. D'Anna and coworkers, who report that nucleophilic *aromatic* substitutions of neutral 2^o amines for leaving groups at C(2) of 3- or 5-nitrothiophenes were faster in ILs than in methanol or benzene (Table 14).[277] Yadav and coworkers have provided 14 examples of nucleophilic aromatic substitutions in ILs.[278]

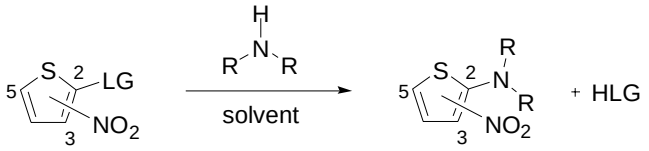
Empirical data also speaks to the facilitating effect of ILs on substitution reactions between two neutral species. Foremost among S_N2 reactions of neutral reagents is the original BASIL process (Scheme 4). Although an IL is not applied, [Hmim][Cl] formed in the course of the reaction is presumed to hasten of the reaction, which is why it can be carried out in a thimble reactor. D'Anna's group implied a Boulton–Katritzky reaction (Scheme 11) was faster in $[C_4mim][BF_4]$ and $[PF_6]$ than in conventional solvents; they provided rate constants for the reaction in these ILs, but did not compare them to those in traditional media.[279, 280] The displacement of nitrate from a rhodium complex by neutral pyridines was promoted in both $[C_6py][NTf_2]$ and $[C_4mim][PF_6]$ by comparison to dichloromethane. The authors took the opportunity to note this behavior could be useful for the generation of catalysts in ILs, and that competitive coordination of the metal center expected in conventional solvents should not occur in ILs.[281]

Table 13. Relative rates of S_N2 reactions between neutral nucleophiles and various electrophiles in either ILs or conventional liquids; the slowest reaction is in black.[271, 274, 276, 282]

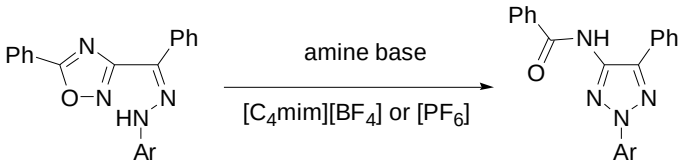
	Neutral Amine Nucleophiles					
	1°	2°		3°		Heterocyclic
solvent	$BuNH_2$[a]	Bu_2NH[a]	Pr_2NH[a]	Bu_3N[a]	Et_3N	dmim[b]
$[C_4dmim][BF_4]$	--	--	--	--	--	17778
$[C_4mim][BF_4]$	--	--	--	--	--	15556
$[C_8dmim][BF_4]$	--	--	--	--	--	15556
$[C_8mim][BF_4]$	--	--	--	--	--	12778
$[C_4mp][NTf_2]$	1989	2739	--	572	--	12778
$[C_4mim][PF_6]$	--	--	--	--	--	10556
$[C_4dmim][NTf_2]$	--	--	--	--	--	10556
$[C_8mim][PF_6]$	--	--	--	--	--	10000
$[C_8dmim][NTf_2]$	--	--	--	--	--	8333
$[C_4mim][NTf_2]$	--	--	--	--	--	7778
$[NC_{6\,4\,4\,4}][NTf_2]$	--	--	--	--	--	6667
$[C_4mp][OTf]$	5122	5778	--	2906	--	--
$[C_8mim][NTf_2]$	--	--	--	--	--	5556
$[C_4mim][OTf]$	2778	3006	--	294	--	--
MeCN	861	1011	--	143	26[c]	7
water	304	--	369	--	114[a]	--
DCM	92	252	--	111	--	--
propylene carbonate	--	--	--	--	--	14
NMF	--	--	--	--	--	4
EtCN	--	--	--	--	--	3
PrCN	--	--	--	--	--	3
$(CH_2OH)_2$	--	--	--	--	--	1
other alcohols[d]	--	--	--	--	--	0.10 – 0.44

[a]The electrophile was *p*NBS–Me; the reaction temperature was 25 °C. [b]The electrophile was BnBr; the reaction temperature was not specified. [c]The electrophile was TsOMe; the reaction temperature was 25 °C. [d]2-methoxyethanol, MeOH, EtOH, *n*PrOH, *i*PrOH, *n*HxOH, *n*OcOH

Table 14. Relative rates of S_NAr reactions between neutral nucleophiles and 2-substituted 3- or 5-nitrothiophenes in either ILs or conventional liquids; the slowest reaction is in black.[277]



			2° amine		
NO_2 position	LG	solvent	pyrrole	piperidine	morpholine
5	Br	$[C_4mim][BF_4]$	974	485	44.6
5	Br	MeOH	5.80	3.68	1
5	Br	$[C_4mim][PF_6]$	426	--	--
5	OMe	$[C_4mim][BF_4]$	13550	5657	--
5	OMe	MeOH	--	227	--
5	OPh	$[C_4mim][BF_4]$	4560	2930	228
5	OPh	MeOH	--	97.7	--
5	*p*-$O_2NC_6H_4O$	$[C_4mim][BF_4]$	10087	7172	566
5	*p*-$O_2NC_6H_4O$	MeOH	--	88.6	--
3	Br	$[C_4mim][BF_4]$	4964	1328	157
3	Br	MeOH	66.2	25.4	--
3	Br	PhH	242	61	--

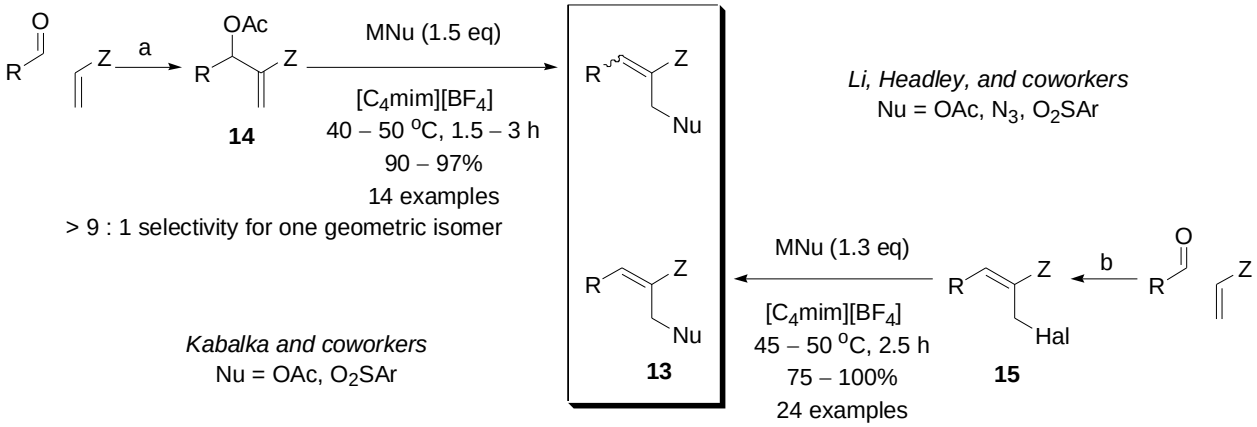


Scheme 11. A Boulton–Katritzky reaction D'Anna and coworkers report is facilitated in ILs.[279, 280]

Hence, the *current* indication is that the fastest reactions of anions with neutral electrophiles in ILs may be faster than the same reactions in some conventional liquids, but are always faster in some conventional solvent than in any IL. On the other hand, substitution reactions between two neutral reagents are usually faster in ILs than in conventional liquids. Returning to the concept of tunability, Welton and coworkers note that substitution reactions of both stripes should be optimal in ILs based on poorly H–bond donating cations and strongly H–bond accepting anions.[271]

However, the data above shows that model substitution reactions are only *relatively* slower or faster in ILs than in conventional solvents, but the *absolute* values of these rate constants usually only translate to a change in reaction time from milliseconds in fast solvents to hours in slow solvents. These relative rates are important in an industrial setting where the time required to accomplish an S_N2 reaction with an anionic nucleophile would be detrimental, but the relative hastening of an S_N2 reaction with a neutral nucleophile, as in the case of the original BASIL process, is advantageous. Both time frames are convenient in a laboratory setting, however, and there are a multitude of target- and methods-oriented results from academic chemists regarding substitution reactions in ILs. α,β-Unsaturated carbonyl compounds **13** are a unique example because they have been prepared in ILs in two ways (Scheme 12). G. W. Kabalka and coworkers prepared them from S_N2' reactions of Baylis–Hillman adducts, which led to a mixture of geometric isomers in the final product mixture. Regioselectivity was universally high (> 9 : 1) for one isomer or the other in each of their examples giving a reaction.[283] They recorded 16 examples, but the yield of the nucleophilic substitution on one compound **14** (R = octyl) by acetate was 0%; this electrophile also gave the lowest yield in the series of reactions between **14** and

tolylsulfinate. G. Li, A. D. Headley, and coworkers prepared **13** from the S_N2 reactions of electrophiles **15**, which were accessed in high geometric purity by a method of their own creation. Purified **15** of one configuration was used for the substitutions, leading to **13** as a single isomer.[284]



Scheme 12. Entry to compounds **13** from two directions.[283, 284] Reagents and conditions: a) Baylis–Hillman conditions; acetylation. b) $Ti(Hal)_4$, ≥ 85% yield, $E : Z \geq 9 : 1$

A selection of data from Chi and coworkers, who have written their own account of nucleophilic substitution reactions in ILs,[217] is presented in Tables 15 – 21. They have often claimed that nucleophilicities are "significantly enhanced" in ILs, even when the nucleophile is an anion (Tables 15 – 17).[285] They have emphasized their observation of the synthetic usefulness of fluoride nucleophilicity in particular (Table 15, Entries 1 – 5, 10),[286, 287] and have asserted that an increase in bromide nucleophilicity facilitates ether cleavages (Tables 18 and 19).[288] Specifically addressing the Chi group's claim of an increase in bromide nucleophilicity affording these ether cleavages, Welton and coworkers have written

that it is in "direct contradiction" to the available kinetic data,[269] but this statement could be extended to cover the Chi group's claims regarding the reactions of other anionic nucleophiles in Tables 15 – 17. Welton and coauthors are rightly offended that Chi and coworkers have often implied that the following results are somehow the effect of ILs alone. All of the collected kinetic data indicates the opposite, and Chi's group's own data show that either ILs or conventional solvents *alone* are *usually* inferior solvents for the reactions they perform, whereas *solvent mixtures* are advantageous for these reactions. Therein is why the model and applied data are not necessarily at odds. There are significant differences between the model environments used in the kinetic work and the environments provided for the development of synthetic methods and the synthesis of target molecules. The biggest such differences are that the applied examples were accomplished in solvent mixtures where the anionic nucleophiles were supplied as their alkali metal salts. By the same token, a reference claiming ILs facilitate substitution reactions in biphasic reaction mixtures is presumably beyond the reach of the model kinetic data.[289] Further, the following reactions were performed at high temperatures, where the H–bonding that is presumably the impediment to the nucleophilic substitution reactions of anionic nucleophiles in ILs may be disrupted.

Table 15. A selection of Chi and coworkers' data on substitutions by halides in conventional solvents, ILs, and their mixtures.[285, 286]

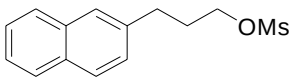
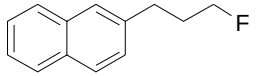
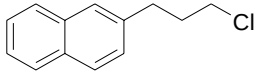
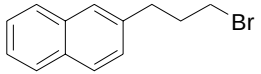
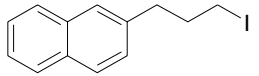
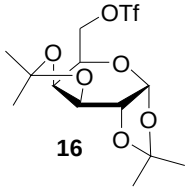
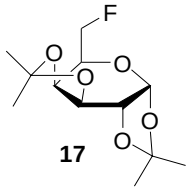
Entry	Electrophile	Nucleophile (5 eq)	T (°C)	*t* (h)	Solvent	Product	% Yield
1		CsF	100	48	MeCN		16
2		CsF	100	5	MeCN + 2 eq 18-crown-6		88
3		"	100	0.33	20 : 19 : 1 $[C_4mim][BF_4]$–MeCN–H_2O		95
4		"	25	48	"		58
5		KF	100	1.5	"		93
6		KCl	100	0.5	"		95
7		KBr	100	0.5	"		96
8		KI	100	0.25	"		93
9		KI	25	24	"		50
10	 **16**	CsF (3 eq)	80	1.5	MeCN + polymer bound $[C_6mim][BF_4]$	 **17**	94

Table 16. A selection of Chi and coworkers' data on substitutions by acetate in conventional solvents, ILs, and their mixtures. The nucleophile in each of these cases was 5 eq KOAc.[285]

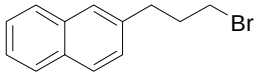
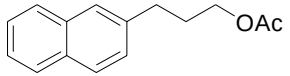
Entry	Electrophile	T (°C)	*t* (h)	Solvent	Product	% Yield
1		25	48	MeCN		0
2		25	48	PhH / water + 2 eq. TBABr		5
3		25	6	MeCN + 2 eq 18-crown-6		92
4		25	2	1 : 1 $[C_4mim][BF_4]$–MeCN		95
5		50	0.5	"		96
6		90	0.5	1 : 1 $[C_4mim][PF_6]$–MeCN		93
7		90	0.5	1 : 1 $[C_4mim][PF_6]$–*p*-dioxane		95
8		25	6	DMSO–d_6		99

Table 17. A selection of Chi and coworkers' data on substitutions by other anions in mixtures of ILs and conventional solvents.[285]

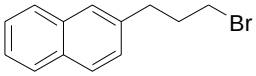
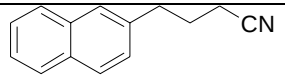
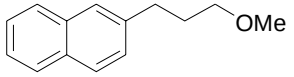
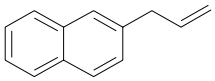
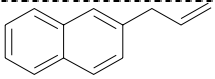
Entry	Electrophile	Nucleophile (5 eq)	T (^{o}C)	*t* (h)	Solvent	Product	% Yield
1		KCN	25	48	MeCN		0
2		"	50	1	1 : 1 [C_4mim][BF_4]–MeCN	"	93
3		KOMe	25	15	1 : 1 [C_4mim][BF_4]–MeOH		92
						"	80
4		"	70	25	"	and 	15
5		*t*BuOK	70	0.3	1 : 1 [C_4mim][BF_4]–*t*BuOH		95

Table 18. Chi and coworkers' optimization of aryl methyl ether cleavage in ILs at a reaction temperature of 115 °C.[288]

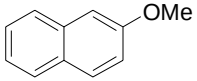
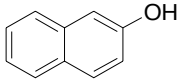
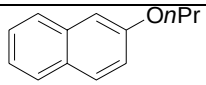
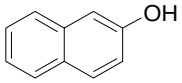
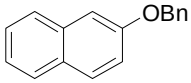
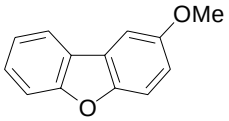
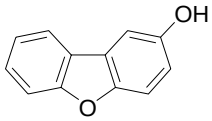
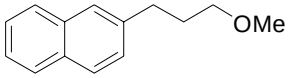
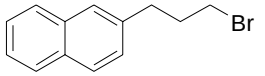
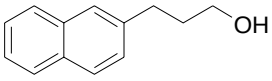
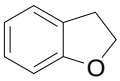
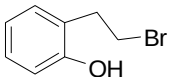
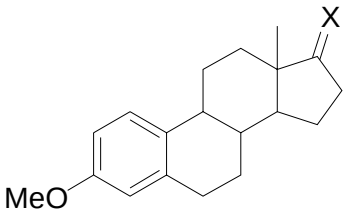
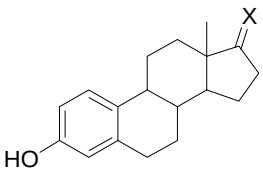
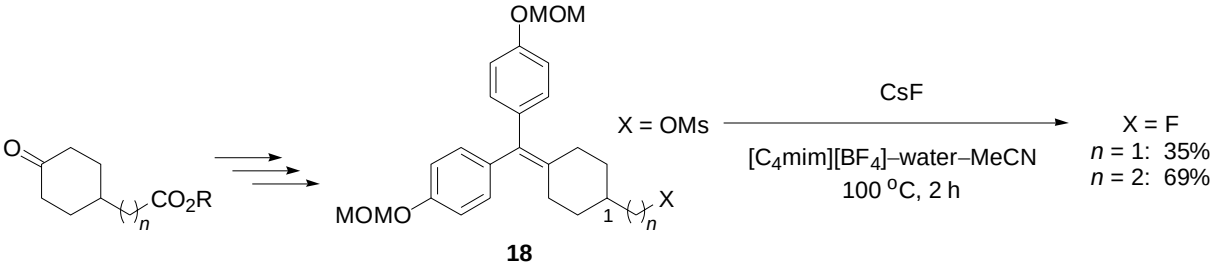
Entry	Ether	*t* (h)	Acid (eq)	[C_4mim][Br]	Solvent	Product	% Yield
1		48	47% HBr (2)	0	MeCN		19
2		22	*p*-TsOH, MsOH, 35% HCl or 50% H_2SO_4 (3)	0	[C_4mim][BF_4]		≤ 30
3		48	47% HBr (2)	0	PhH		34
4		48	47% HBr (2)	0	water		35
5		48	47% HBr (2)	0	DCE		37
6		9	47% HBr (2)	0	[C_4mim][BF_4]		97
7		14	*p*-TsOH, MsOH, 35% HCl or 50% H_2SO_4 (3)	3	[C_4mim][BF_4]		≥ 93

Table 19. Ether cleavages reported by Chi and coworkers at a reaction temperature of 115 °C in $[C_4mim][BF_4]$.[288]

			2 eq 47% HBr		3 eq *p*-TsOH + 3 eq $[C_4mim][Br]$	
Entry	Ether	Product	*t* (h)	% Yield	*t* (h)	% Yield
1			13	95	20	91
2			4	93	4	90
3			5	94	10	95
4		 	12	45 46	12	46 47
5			13	40	13	40
6	 X = O or OH, H	 X = O or OH, H	5	86	5	86

Aside from the potential effects of ionic strength, these examples from Chi's group do not have adequate explanations of their own. Temporarily allowing these results to pass unquestioned (i.e., assuming these reactions are not some of the "extravagent (verging on dishonest) claims" MacFarlane and Seddon had in mind), Chi and coworkers are correct that the fluoridations they demonstrate in ILs are potentially synthetically useful. Katzenellenbogen and coworkers (Chi is one of them) have used one of Chi's fluoridation methods on the way to analogs of cyclofenil, the free diphenol of C(1)-desalkyl **18** (Scheme 13).[290] Note that there is a separate claim of ILs facilitating nucleophilic substitutions by fluoride from R. Grée and coworkers.[291]



Scheme 13. Chi and coworkers' fluoridation protocol in Katzenellenbogen's synthesis of cyclofenil derivatives.[290]

This is a good time to pause for some of the "quiet reflection" MacFarlane and Seddon requested. Excepting the fluoridations, these reactions are only enhanced by comparison to certain reactions provided by the authors in context; they are not absolute improvements. For example, it is conceivable other organic soluble salts or other mixtures of traditional solvents could have given rise to the same results as the mixtures including ILs. Further, consider whether the iodidations in Table 15, Entries 8 – 9 constitute any "significant enhancement" over

a Finkelstein reaction. The substitutions with acetate in mixtures of ILs and acetonitrile or *p*-dioxane were more successful than those in acetonitrile alone or under the one condition of phase transfer catalysis reported, but these conversions required higher temperatures or longer reaction times than the same S_N2 reaction in dimethylsulfoxide (cf. Table 16, Entries 1 – 8). Are the ether cleavages in Tables 18 and 19 believable as alternatives to boron tribromide or lithium *n*-propylsulfide for the same conversions? These are reactions that simply are not markedly improved by employing an IL, and are probably the examples Welton and coworkers had in mind when they wrote that there is no "IL effect" on the substitution reactions of anionic nucleophiles with neutral electrophiles in ILs.

Chi's group has also provided less controversial examples in the reactions of several neutral hydroxylic nucleophiles (Tables 20 and 21).[292] One more reaction of an anionic nucleophile is included in Table 20, Entry 6, where acetate provided as the IL anion delivers an alkyl acetate, which is a novel adaptation of the substitution reaction in ILs. This approach does not truly get around the apparent limiting effect on the reaction from IL cation association with nucleophilic anion, but it does make supplying an excess of nucleophile convenient. Another example along this line is the use of $[C_4mim][SCN]$ as a source of thiocyanate; the IL was prepared by anion exchange of $[C_4mim][Cl]$ with potassium thiocayante in acetone.[293] High yields, usually > 90%, were reported following reactions at room temperature with 1.2 equivalents $[C_4mim][SCN]$, and ordinarily in ≤ 15 min.

The results in Tables 20 and 21 are generally straightforward, one exception being the substitution of an acetate for a bromide in 68% yield in a mixture of $[C_4mim][PF_6]$, acetonitrile, and water (Table 20, Entry 5). The authors theorize that hydrogen bromide released in the reaction afforded acetic acid by hydrolyzing acetonitrile. From there, they imagine acetic acid

Table 20. A selection of Chi and coworkers' data on substitutions in aqueous mixtures of ILs and conventional solvents.[292]

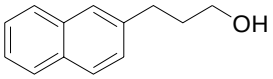
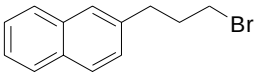
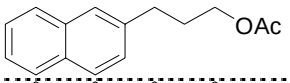
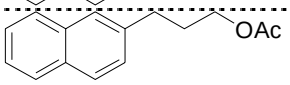
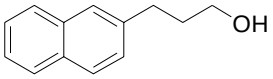
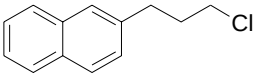
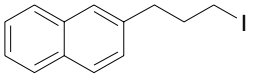
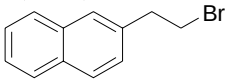
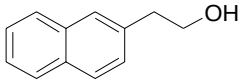
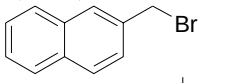
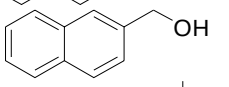
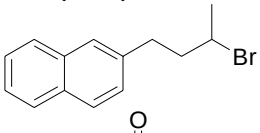
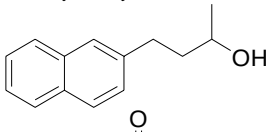
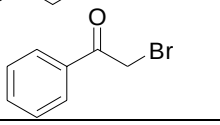
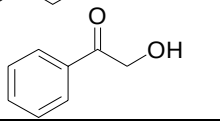
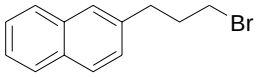
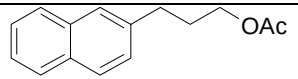
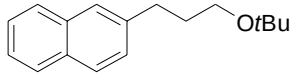
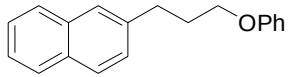
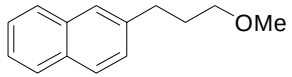
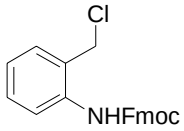
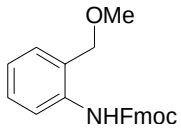
Entry	Electrophile	T (°C)	*t* (h)	Solvent	Product	% Yield
1		100	48	4.5 : 1 *p*-dioxane–**water**		< 8
2		110	65	4 : 1 [C_4mim][BF_4]–**water**		65
3		110	48	4 : 2.5 : 1 [C_4mim][BF_4]–MeCN–**water**		84
4		110	48	4 : 2.5 : 1 [C_4mim][BF_4]–acetone–**water**		92
					"	23
5		110	24	4 : 2.5 : 1 [C_4mim][**PF_6**]–**MeCN–water**	and 	68
6		110	0.33	4 : 2.5 : 1 [C_4mim][**OAc**]–*p*-dioxane–water		98
7		110	20	4 : 2.5 : 1 [C_4mim][BF_4]–*p*-dioxane–**water** + 3 eq $NaHCO_3$		95
8		110	65	4 : 2.5 : 1 [C_4mim][BF_4]–*p*-dioxane–**water**	"	94
9		110	48	"	"	5
10		100	18	"	"	95
11		110	72	"		80
12		90	3	"		91
13		110	48	"		95
14		100	12	"		68

Table 21. A selection of Chi and coworkers' data on substitutions by other neutral hydroxylic nucleophiles as mixtures with ILs. [292]

Entry	Electrophile	T (°C)	*t* (h)	Solvent	Product	% Yield
1		110	48	1 : 1 $[C_4mim][BF_4]$–**AcOH**		15
2		110	96	1 : 1 $[C_4mim][BF_4]$–***t*BuOH** + 3 eq $NaHCO_3$		25
3		100	48	1 : 1 $[C_4mim][BF_4]$–**PhOH**		0
4		100	48	1 : 1 $[C_4mim][BF_4]$–**MeOH**		94
5		110	4	"		83

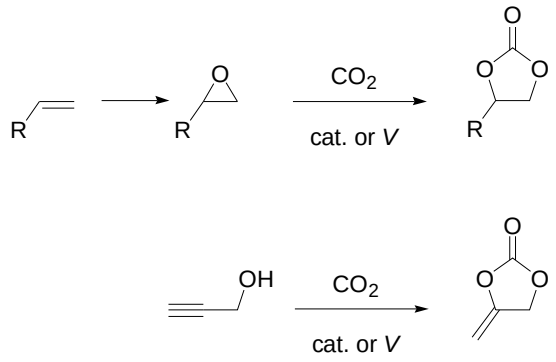
could have displaced bromide from the electrophile in a subsequent reaction (which seems like an unlikely prospect from some of the authors' other data—Table 21, Entry 1), or that acetic acid from the hydrolysis of acetonitrile could have esterified the desired hydrolysis product. That is also unlikely considering the volume of water available and that Fischer esterification is usually most productive under the influence of anhydrous oxo acids. It is certainly an intriguing result possibly resulting from the hydrolysis of acetonitrile. Hydrogen bromide is not believable as the acid catalyst for this hydrolysis, however, because it must have also been present in other reactions in the presence of acetonitrile, but this side reaction was only observed in one instance. The $[PF_6]$ counterion featured in this reaction can provide up to five equivalents of hydrofluoric acid through hydrolysis—a reaction which prompted R. P. Swatloski, J. D. Holbrey, and Rogers to point out "Ionic liquids are not always green".[294] The involvement of this acid may seem unlikely because hydrofluoric acid is supposedly so much weaker than hydrobromic, but there would be several equivalents available. Additionally, L. A. Carpino has noted the reputed weakness of hydrofluoric acid is unfair because concentrated forms of hydrogen fluoride behave as a stronger source of acid than its pK_a value would indicate.[295] It is also possible that pK_as are different in ILs and their mixtures than in water. Most importantly, Chi and coworkers provided examples regarding the uncommonly effective substitution reactions of fluoride in IL mixtures. It is possible hydrofluoric acid itself added to acetonitrile, and acetic acid formed following hydrolysis of an intermediate imidic acid fluoride.

In publishing the reactions of these neutral oxygen nucleophiles with alkyl halides, Chi and coworkers continued to claim "significant enhancement" of nucleophilicities in ILs, to which Welton and coworkers only replied it "is not possible to interpret [Chi's] data . . . quantitatively" because no careful kinetic measurements were made."[271] There are still some legitimate

criticisms of the data in these tables. First, water was always available in solvent amounts. Based on the existing data regarding the reaction of neutral nucleophiles with neutral electrophiles in ILs, a stoichiometric amount of water or a slight excess should have given a faster reaction in an IL than in either water or an aqueous mixture of one. Second, regarding the necessary conditions for reaction, the impression is given that the reactions require high temperatures. It does not seem that this must be the case, especially if an acid scavenger is applied (cf. Table 20, Entries 7 – 8), but the authors have not provided any optimization studies concerning reaction temperature. Third, the authors pointed out that a protected aniline (Table 21, Entry 5) was destroyed in 20 minutes at room temperature in methanolic sodium methoxide. Although survival of the Fmoc group during the substitution reaction in methanolic $[C_4mim][BF_4]$ is noteworthy in its own right, the authors have not provided realistic control experiments, such as methoxylation with tertiary amine bases or pyridine in methanol.

Among the many nucleophilic substitution reactions studied in ILs by Chi's group is the alkylation of metal carbonates to symmetric dialkyl carbonates.[296] Synthesis of organic carbonates in ILs is a topic with many examples, but usually insofar as addition reactions to cyclic carbonates are concerned (Scheme 14). The interest in the synthesis of cyclic carbontes in ILs is two-fold. The inherent synthetic value of dialkyl carbonates is the lesser of them. Authors in this field are more commonly interested in new methods of carbon fixation—that is, methods to entrain atmospheric carbon dioxide. That ILs would be applied to this purpose is not surprising because the people who study ILs are frequently concerned with finding green applications for them. But utilizing ILs for carbon fixation is not merely a contrivance. The fixing reaction is most conveniently accomplished when a Lewis acid catalyst or a voltage is applied, and ILs are excellent media for acid catalyzed and electrochemical processes. When the

reaction is complete, the carbonate separates from the IL, with the assistance of organic solvents or $scCO_2$ if required, and the IL is recycled, along with any Lewis acid that was applied (lead refs[220, 297-301])

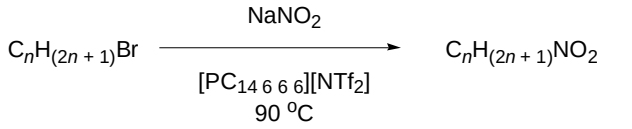


Scheme 14. Idealized reactions fixing carbon dioxide as a cyclic organic carbonate.

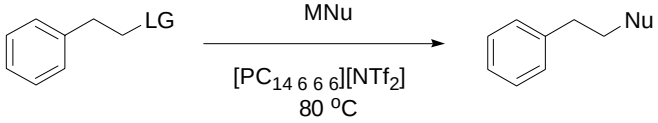
There are also several noteworthy examples of nucleophilic substitutions performed in $[PC_{14\ 6\ 6\ 6}][NTf_2]$ by J. McNulty and coworkers (Table 22).[302] Among the reactions they accomplished were smooth Kornblum reactions to prepare nitroalkanes in good yields, an observation which is accounted for by the oxophilicity of the $[PR_4]$ cation. In substitutions of neutral nucleophiles, they observed exhaustive alkylation of benzylamine. Following alkylations of carboxylates, the yields of ester products were not profoundly affected by the selection of ethyl, phenyl, electron-donated aryl, or electron-withdrawn aryl carboxylates. The syntheses of cyclohexyl and *tert*-butyl esters are particularly interesting.

McNulty and coworkers pointed out their phenethyl halides and pseudohalides did not eliminate to styrene, and other authors have also emphasized an apparent absence of elimination side products following substitution reactions in ILs. Chi makes the same observation regarding the hydrolysis of phenethyl bromide in aqueous mixtures of ILs (Table 20, Entry 11). This is a

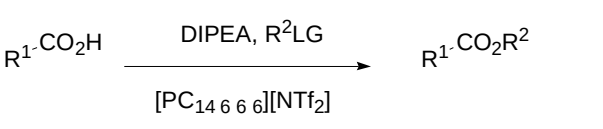
Table 22. Substitution reactions in $[PC_{14\,6\,6\,6}][NTf_2]$ from McNulty and coworkers.[302]



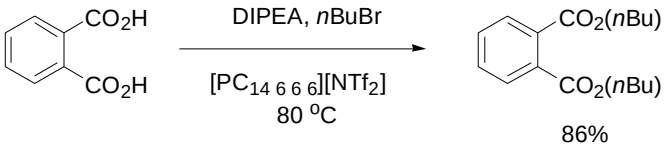
n	% Yield
7, 8, 12	90

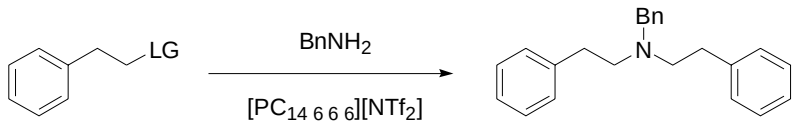


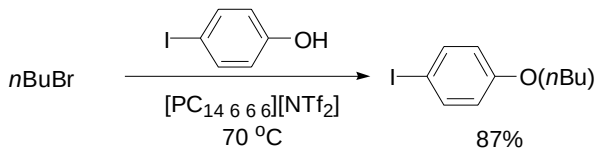
LG	MNu	% Yield
Br	KCN	92
OMs, OTs	KCN	85, 84
Br	NaN_3	95
OMs, OTs	NaN_3	87, 86
Br	$NaNO_2$	80



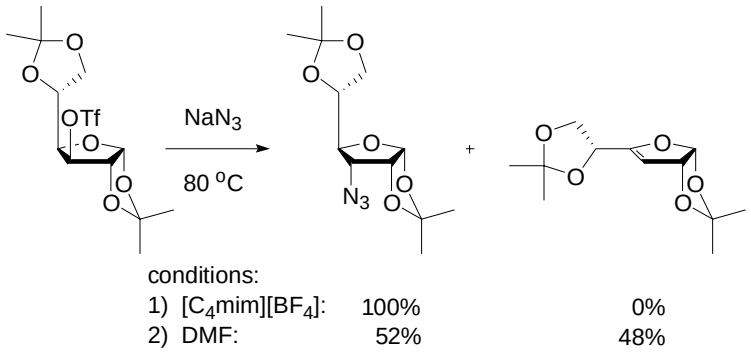
R^1	R^2LG	T (°C)	% Yield
p-$O_2NC_6H_4$	CyBr	70	80
"	CyOTs	80	77
"	*t*BuBr	50	70
EWG–Ar	7 more ex	30 – 80	77 – 95
EDG–Ar	10 ex	30 – 40	85 – 95
Et	2 ex	75	98
Ph	2 ex	75	98







curious fixation, however, because there is apparently only one example actually comparing the distribution of substitution and elimination products in one IL as opposed to one conventional solvent, which comes from Chiappe and coworkers (Scheme 15).[303] In light of this substitution reaction on the congested protected glucose triflate, the high yield Chi observed in the synthesis of protected galactosyl fluoride **17** from triflate **16** (Table 15, Entry 10) is potentially another example of a substance that would give more elimination product in a conventional solvent than in an IL, but a comparison is not available. Eliminations certainly *can* occur in ILs, however, as Creary and coworkers observed.[266]



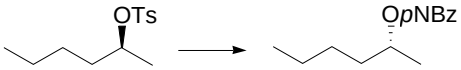
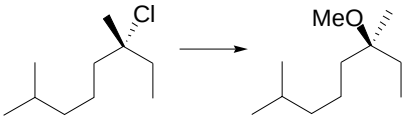
Scheme 15. Nucleophilic substitution of a protected glucose triflate by NaN_3 in $[C_4mim][BF_4]$ as opposed to substitution and elimination in DMF.[303]

In the same paper containing the reaction shown in Scheme 15, Chiappe and coworkers also observed elimination reactions; these side reactions were most significant in reactions of cyanide, and could be 100% of the isolated product. The larger context of these examples was understanding the mechanistic aspects of nucleophilic substitution reactions in ILs.[303] Observations from Chiappe's group suggest the actual mechanistic course of substitution reactions in ILs are in flux between pure S_N1 and S_N2, and that the composition of the

mechanism in action varies among ILs. Composite mechanisms have been discussed by T. W. Bentley and by W. P. Jencks with regard to the reactions in conventional solvents.[304, 305] The key piece of evidence offered by Chiappe and coworkers for the extension of this logic to nucleophilic substitution reactions in ILs is that, while keeping all other factors constant, more complete nucleophilic substitutions by azide were seen after equal reaction times with 1^o alkyl halides or pseudohalides than with 2^o alkyl halides or pseudohalides in some ILs, but a different order of completeness was observed in the same reaction in other ILs. If the reactions consistently occurred by either a pure S_N1 or S_N2 mechanism in ILs, or even by one hybrid mechanism between them, the more thorough reaction at the same reaction time should have always been observed for one type of electrophile or the other.

This hypothesis is potentially undermined by the result shown in Scheme 15, which looks to be a pure S_N2 reaction. The reaction could occur through an S_N1 mechanism or a composite mechanism close to it, but it is hard to believe this path would deliver a product with 100% inversion at the reactive center. There are other examples of Walden inversions in ILs which are usually taken by some authors as evidence that the preferred mechanism is a composite because configuration at the reactive center is inverted or lost to different degrees depending on the solvent (Table 23). Two of the available studies are based on inversions at 2^o stereogenic centers derived from (2*S*)-hexanol (Entries 1 – 3), which give some inversion and some loss of configuration to different extents in conventional solvents, too. As it happens, they give nearly complete inversion in the available examples, which suggests the reactions proceed by a nearly unadulterated S_N2 mechanism. In the one example comparing a Walden inversion in ILs across two temperatures (Entries 2 and 3), the data are a better indication that the S_N1 character of

Table 23. Walden inversions in ILs.

Entry	Process	Conditions	T (^{o}C)	% inversion	Ref
1		NaN_3 in $[C_4mim][NTf_2]$ or $[PF_6]$, or $[C_6py][NTf_2]$	80	96.5	[303]
2		*p*-NBzOH,[a] DIPEA $[PC_{14\,6\,6\,6}][NTf_2]$	80	96	[302]
3	"	*p*-NBzOH,[a] DIPEA $[PC_{14\,6\,6\,6}][NTf_2]$	50	> 99	[302]
4	 **19**	MeOH	40	88	[306]
5	"	MeOH, 0.019 mol % $[C_4mim][NTf_2]$	"	70	[306]
6	"	MeOH, 0.043 mol % $[C_4mim][NTf_2]$	"	57	[306]
7	"	MeOH, 0.12 mol % $[C_4mim][NTf_2]$	"	57	[306]
8	"	MeOH, 0.49 mol % $[C_4mim][NTf_2]$	"	39	[306]
9	"	MeOH, 0.72 mol % $[C_4mim][NTf_2]$	"	25	[306]

[a] *p*-NBzOH = *p*-nitrobenzoic acid

nucleophilic substitution in ILs is directly proportional to the temperature of the reaction than it is that nucleophilic substitutions in ILs are always better described by a composite mechanism.

Nucleophilic substitutions at the 3^{o} stereogenic center of linalool derivative **19** are more convincing. That the reaction gives a product mixture with a measurable enantiomeric excess is noteworthy because racemization through solvolysis of a 3^{o} carbocation in an S_N1 process would have been expected (Entries 4 – 9). However, any retention or loss of configuration is first connected to the reagent itself. In studying the relative rates of solvolysis of **19** in methanol, benzyl alcohol, and mixtures of them with an IL, the authors took an interest in this compound precisely because it characteristically gives a significant amount of inversion product by an S_N2 process on a 3^{o} alkyl halide. Note that the highest extent of inversion was achieved in neat methanol. Because the amount of cleanly inverted product went down with increasing IL content, it does indeed appear that the presence of IL pulls a customarily S_N2 reaction into the area between bimolecular substitution and an S_N1 process, which is evidence that ILs may confuse substitution mechanisms. Note that variable substitution reaction mechanisms in ILs could be another way to account for the apparent discrepancies between the model and the applied studies on substitution reactions of anions in ILs.

1.2.2. DIELS–ALDER REACTIONS IN IONIC LIQUIDS

From the examples of acid catalyzed reactions in ILs, it appears some ILs simultaneously force the formation of full or partial positive charges, especially on carbon and presumably through H–bond donation from the IL cation. The ionized or polarized species give an immediate reaction, presumably because the IL anion is poorly coordinating. It is clear from an analysis of substitution reactions in ILs that they favor reactions proceeding through transition structures polarized relative to the reagents. Therefore, ILs should be expected to promote Diels–Alder reactions, which are catalyzed by H–bond donors and are typically faster in polar solvents. The available data actually do not confirm this hypothesis, but the significance of some results is not entirely clear.

There is currently no thorough review confined to the topic of Diels–Alder reactions in ILs, although the examples feature prominently in the respective reviews of either reactions in ILs or Diels–Alder reactions. In 1989, D. A. Jaeger and C. E. Tucker used EAN (which they referred to as a fused salt) as a solvent for the reactions of cyclopentadiene with butenone and with methyl acrylate, concluding it gave better *endo* : *exo* selectivity (ca. 7 : 1) than nonpolar organic solvents.[307] In fact, the only data point they provided for comparison was from the same reaction in benzene, which did give a much lower stereoselectivity (*endo* : *exo* = 2.8 : 1). However, their results do show the stereoselectivity in this particular model reaction in EAN was similar to that of the reaction performed in methanol, formamide, and water, and was higher than in ethanol (*endo* : *exo* = 5.2 : 1). The approximate *endo* : *exo* benchmark culled from several model Diels–Alder reactions performed without solvent is 3 : 1. This stereoselectivity typically dips slightly when the reaction is instead performed in nonpolar organic solvents and goes up significantly when the reaction is instead performed in polar organic solvents. Hence, the

examples from Jaeger and Tucker reasonably extrapolate to their conclusion although the number of actual examples was limited.

In 1997, J. Howarth and coworkers reacted cyclopentadiene with crotonaldehyde and with methacrolein in dichloromethane under the influence of a catalytic amount of one of three imidazolium salts. They expected to capitalize on the H–bond donating ability of the C(2) imidazolium proton. However, they recovered low yields and variable stereoselectivities from the reactions after 48 hours at –25 ^{o}C; these indicators were even lower following heterogeneous reactions in diethyl ether.[308] Since 1999, reactions between model dienes and dieneophiles have been evaluated in [C$_n$mim] ILs,[309-315] [PR$_4$][OTs]s,[316] [(C$_2$H$_4$OH)NC$_{1\ 1\ 1}$][Cl] melts,[317] [C$_n$py] ILs,[312, 313, 318] and in [Hmim] ILs and its homologs (i.e., [HC$_n$im]).[319] A selection of yields and stereo- and regioselectivities is provided in Table 24, and comparisons are made to the same reactions in conventional solvents where data are available.

It is easy to get from the IL literature the impression that Diels–Alder reactions faithfully give high stereo- and regioselectivities in ILs, as if this is an intrinsic property of the media, and that they are inherently superior to conventional solvents for Diels–Alder reactions. Table 24 includes several examples of respectable yields and stereo- and regioselectivities, and some which demonstrate ILs *can* be superior to conventional solvents for many Diels–Alder reactions. However, ILs rarely even double the operable benchmark of *endo* : *exo* selectivity of 3 : 1, and similar outcomes are achievable by using polar conventional solvents for Diels–Alder reactions. It is often repeated in the IL literature that ILs "resemble" polar organic solvents, and those which are H–bond donors in particular.

Table 24. Selected data points for the Diels–Alder reaction in ILs, ordered by diene / dienophile pairs (continued on next page).

Entry	Solvent	Diene	Dienophile	*t* (h)	T (^{o}C)	Yield (%)	Selectivity[a] *N* / *X*	Selectivity[a] "*p*" / "*m*"	Ref
1	$[C_2mim][BF_4]$	cyclopentadiene	methyl acrylate	2	20	50	5.7	N/A	[309]
2	$[C_2mim][BF_4]$	cyclopentadiene	methyl acrylate	72	20	91	4.2	N/A	[309]
3	$[C_4mim][BF_4]$	cyclopentadiene	methyl acrylate	24	rt	97	3.5 – 4.9	N/A	[320]
4	$[C_4mim][PF_6]$	cyclopentadiene	methyl acrylate	24	rt	97	3.8 – 5.0	N/A	[320]
5	$[C_4mim][SbF_6]$	cyclopentadiene	methyl acrylate	24	rt	94	4.2	N/A	[320]
6	$[C_4mim][NTf_2]$	cyclopentadiene	methyl acrylate	24	rt	99	4.2 – 4.3	N/A	[320]
7	$[C_4mim][CF_3CO_2]$	cyclopentadiene	methyl acrylate	24	rt	96	4.2 – 4.4	N/A	[320]
8	$[C_2mim][Cl]$ + 1.05 eq $AlCl_3$	cyclopentadiene	methyl acrylate	22	rt(?)	32	4.88	N/A	[310]
9	$[C_2mim][Cl]$ + 1.05 eq $AlCl_3$	cyclopentadiene	methyl acrylate	72	rt(?)	95	5.25	N/A	[310]
10	$[C_2mim][Cl]$ + 1.12 eq $AlCl_3$	cyclopentadiene	methyl acrylate	22	rt(?)	53	19	N/A	[310]
11	$[C_2mim][Cl]$ + 1.12 eq $AlCl_3$	cyclopentadiene	methyl acrylate	72	rt(?)	79	19	N/A	[310]
12	$[C_4mim][OTf]$	cyclopentadiene	ethyl acrylate	18	20	96	6.0	N/A	[311]
13	$[C_4mim][OTf]$	cyclopentadiene	dimethyl maleate	18	20	98	4.2	N/A	[311]
14	$[C_4mim][OTf]$	cyclopentadiene	acrylonitrile	24	–15	96	2.4	N/A	[311]
15	$[C_4mim][PF_6]$	isoprene	DMAD[b]	2	80	98	N/A	N/A	[311]
16	$[C_4mim][OTf]$	isoprene	ethyl acrylate	24	70	97	N/A	2.5	[311]
17	$scCO_2$	isoprene	methyl acrylate	96	50	11	N/A	2.2	[316]
18	PhMe	isoprene	methyl acrylate	15	145	78	N/A	2.5	[316]
19	**$[PC_{4442}][OTs]$**	**isoprene**	**methyl acrylate**	**24**	**80**	**68**	N/A	**>99**	[316]

[a]*Endo* (*N*) / *exo* (*X*) or *para*-like (1,4-cycloadduct, "*p*") / *meta*-like (1,3-cycloadduct, "*m*") as appropriate. [b]DMAD = dimethyl acetylenedicarboxylate

Table 24. Selected data points for the Diels–Alder reaction in ILs, ordered by diene / dienophile pairs (continued from previous page).

Entry	Solvent	Diene	Dienophile	*t* (h)	T (°C)	Yield (%)	Selectivity[a]		Ref
							N / *X*	"*p*" / "*m*"	
20	$[C_4mim][PF_6]$	isoprene	butenone	18	20	11	N/A	4.0	[311]
21	$[C_4mim][PF_6]$ + 5 mol% ZnI_2	isoprene	butenone	6	20	98	N/A	20.0	[311]
22	PhMe	isoprene	butenone	15	120	71	N/A	2.4	[316]
23	**$[Ph_3PC_4][OTs]$**	**isoprene**	**butenone**	**17**	**80**	**87**	N/A	**>99**	[316]
24	$[PC_{4\,4\,4\,2}][OTs]$	isoprene	acrylonitrile	24	80	18	N/A	3.2	[316]
25	DCM	isoprene	acrylonitrile	72	20	12	N/A	1.8	[318]
26	$[C_2py][CF_3CO_2]$	isoprene	acrylonitrile	2	20	90	N/A	8.2	[318]
27	$[C_2py][CF_3CO_2]$	isoprene	acrylonitrile	24	20	97	N/A	3	[318]
28	$[C_2py][CF_3CO_2]$	isoprene	acrylonitrile	72	20	99	N/A	3	[318]
29	$[(C_2H_4OH)NC_{1\,1\,1}][Cl]$ + 200 mol% $SnCl_2$	isoprene	acrolein	24	rt	88	N/A	19	[317]
30	**$[(C_2H_4OH)NC_{1\,1\,1}][Cl]$ + 200 mol% $ZnCl_2$**	**isoprene**	**acrolein**	**0.9**	**rt**	**90**	**N/A**	**19**	[317]
31	**$[(C_2H_4OH)NC_{1\,1\,1}][Cl]$ + 200 mol% $ZnCl_2$**	**cyclopentadiene**	**butenone**	**0.1**	**rt**	**94**	**24**	**N/A**	[317]
32	DCM	myrcene	acrolein	6	30	7	N/A	2.6	[313]
33	DCM + $ZnCl_2$	myrcene	acrolein	6	30	69	N/A	11.5	[313]
34	$[C_4mim][Cl]$	myrcene	acrolein	4	15	4	N/A	3	[313]
35	$[C_4mim][Cl]$ + 200 mol % $ZnCl_2$	myrcene	acrolein	2	15	97	N/A	19	[313]

[a] *Endo* (*N*) / *exo* (*X*) or *para*-like (1,4-cycloadduct) / *meta*-like (1,3-cycloadduct) as appropriate.

For some pointed examples, note that boiling toluene gave a higher chemical yield than [C_4mim][PF_6] at room temperature in the reaction of isoprene with butenone (cf. Entries 20 and 22), but a lower yield than [Ph_3PC_4][OTs] at 80 °C in the same reaction (cf. Entries 22 and 23). Boiling toluene also gave a higher chemical yield than [$PC_{4\,4\,4\,2}$][OTs] at 80 °C in the reaction of isoprene with methyl acrylate (cf. Entries 18 and 19). On the other hand, regioselectivity was always higher in the ILs in these examples. Regioselection in the [PR_4] tosylates was particularly impressive because they *usually* gave > 99% 1,4-cycloadduct when the dienophile featured a C=O carbonyl.[316] However, this family gave low chemical yields in the reactions of isoprene with acrylonitrile, a C≡N carbonyl (e.g., Entry 24). This reaction proceeded in excellent yields in a different IL, [C_2py][CF_3CO_2] (Entries 26 – 28), which gave better yields than [C_2py][BF_4] (not included). The [C_2py] ILs had their own weakness, however, giving low yields in reactions of isoprene with methacrylic acid (not included). One point about Diels–Alder reactions in ILs should be obvious from the accumulated data: any quantifier of the success of Diels–Alder reactions in ILs varies as a function of the diene, the dienophile, and the IL, which means ILs are never necessarily better or worse media for the Diels–Alder reaction than are conventional solvents, although they can be either. Of course, this variability is seen in Diels–Alder reactions in conventional solvents, too.

As alluded to above, Diels–Alder reactions in [$C_n$mim] ILs would have been expected to be facilitated by H–bond donation from the C(2) imidazolium proton more than they apparently are.[321] This assumption was not truly invalidated by Howarth's report because the imidazolium salts assayed as Lewis acids were only present in catalytic amounts, and it is possible a solvolytic amount of imidazolium salt could efficiently catalyze Diels–Alder reactions. Unfortunately, the hallmarks of a Diels–Alder reaction catalyzed by an H–bond donor (namely increased rate, yield,

and regio- or stereoselectivity) are not always manifest in ILs. When they are, the effect is not usually overwhelming. Archetypal Diels–Alder reactions in [$C_n$mim] ILs may proceed in yields, reaction times, and stereo- or regioselectivities on par with H–bond donating organic solvents (e.g., Entries 1 – 7), or they may not come close (e.g., Entries 20 and 34). Also, this model does not account for the high stereo- and regioselectivities possible in [$C_n$py] (Table 7, Entry 26) or 1-alkyl-2,3-dimethylimidazolium ([$C_n$dmim], not shown) ILs, which can act as H–bond donors, but presumably not as well as can [$C_n$mim] ILs because they are such weaker Brønsted acids. Further, the best regioselectivities yet observed for the Diels–Alder reaction in ILs come not from Diels–Alder reactions in general in [$C_n$mim] ILs, but from the specific Diels–Alder reactions of C=O dienophiles in [PR_4] tosylates (Entries 19 and 23). These results may be better explained by theorizing that the oxophilic phosphonium center functioned as a Lewis acid, not that the reaction was directed by an H–bond donor.

In a paper revolving around solvent effects on the Diels–Alder reaction in [$C_n$mim] ILs,[320] Dyson and coworkers discussed several of the observations to that point (2005) while adding new experimental data. Further, to paraphrase, they imagined what the ideal Diels–Alder reaction in a [$C_n$mim] IL would require. They assumed it should be catalyzed by H–bond donation from the C(2) proton of an imidazolium cation, and that this donation would be maximized if the cation were paried with as poorly an H–bond accepting anion as possible. In the authors' words, "'Hardness' of the ionic liquids . . . leads to less interaction between the ionic liquids and the TS." This requirement was first articulated, at least in the context of Diels–Alder reactions in ILs, by Welton.[321] To test this theory, Dyson and coworkers took the highest wavenumber in the IR spectrum of several [$C_n$mim] ILs, the C(2)–H absorption, as a measure of the extent of ion pair association between the cation and the anion, and observed a loose

correlation between increasing wavenumber (freer cation) and increasing *endo* : *exo* selectivity in the reaction of cyclopentadiene and methyl acrylate in that IL. They observed the same rough correlation between the ^{1}H NMR chemical shift of the imidazolium C(2) proton and *endo* : *exo* selectivity. Note that this qualitative scale requires the chemical shift of the neat IL, because the value from a sample of IL dissolved in a solvent to collect the ^{1}H NMR spectrum will reflect any solvent effect on the IL.

Dyson and coworkers hypothesized that, because chloride is more strongly associating than other IL anions, contamination with it should interrupt any catalytic effect from H-bond donation by the IL cation. Indeed, when the model Diels–Alder reaction mixture was spiked with [C_4mim][Cl], selectivity decreased slightly. The authors were not very impressed by the slight dip in performance, even at a [C_4mim][Cl] concentration of 140 g [C_4mim][Cl] / kg [C_4mim][NTf_2] used as the reaction solvent. They went on to show that homogeneous Diels–Alder reactions in ILs proceeded with higher *endo* : *exo* selectivity than heterogeneous reactions in ILs, which is reminiscent of Howarth's report. They also demonstrated that increasing bulk around the cation lead to lower *endo* : *exo* selectivities, which is strong evidence that the cation does associate with the transition structure.

Some of the other preceding references on Diels–Alder reactions in ILs tabulated Kamlet–Taft parameters of those ILs and showed a correlation between these parameters and different markers of the Diels–Alder reactions under investigation. The Diels–Alder reaction was empirically faster and more stereo- or regioselective in an IL with a high value in the α parameter (H–bond donating ability) and a low value in the β parameter (H–bond accepting ability). Dyson and coworkers went farther and demonstrated that *endo* : *exo* selectivities of the Diels–Alder reactions of cyclopentadiene and methyl acrylate in seven [NTf_2] ILs and one

[SbF_6] IL could be numerically related to a different measure of solvent polarity (apparently of their own creation), Δ (Eq. 8).[320] They postulated if each of the four Δ values defining any IL were known, the *endo* : *exo* selectivity of the model Diels–Alder reaction in that liquid could be predicted, in the true sense. The parameters Δ come from normalized differences in ^{13}C NMR chemical shifts between certain organic solvents (chloroform, 1,2-dichloroethane, benzonitrile, toluene and fluoropyridines) dissolved in an IL against cyclohexane (Δ = 0) and dimethylsulfoxide (Δ = 1) dissolved in the same IL. Recall that Welton and coworkers found LSERs between the reaction rates of certain anions in nucleophilic substitution reactions in ILs and Kamlet–Taft parameters of the IL (Eqs. 1 – 7). Those LSERs showed the rate of reaction was inversely proportional to the H–bond donating ability of the IL cation, which was indicated by the Kamlet–Taft α parameter of the IL. There is no such explicit correlation between factors influencing ion pairing and *endo* : *exo* selectivity in ILs using the Δ scale in Equation 8, but from Dyson and coworkers' other work correlating wavenumbers in IR spectra and chemical shifts in ^1H NMR spectra, it is surely present implicitly.

$$endo\ /\ exo = 1.97(\Delta_a^N) + 3.03(\Delta_b^N) - 4.39(\Delta_c^N) + 1.87(\Delta_d^N) + 1.33 \qquad (8)^{[320]}$$

Thus, it seems strong H–bond donation from an IL cation is one requirement for an optimal Diels–Alder reaction in it, and this cation's free dissociation from a poorly coordinating anion is another. As far as the anion is concerned, this is a good time to ask, "How poorly coordinating is poorly enough?" The Diels–Alder reaction of cyclopentadiene and methyl acrylate in [C_4mim][SbF_6] only gave an *endo* : *exo* ratio of 4.2 : 1 (Table 24, Entry 5). Diels–Alder reactions in [C_4mim][OTf] also give good, but not great, stereoselectivities (Table 24,

Entries 12 – 14, 16). These are important examples since the anions are the conjugate bases of superacids, making it difficult to imagine much more separable ion pairs could exist. *If* ion pair dissociation is the main determinant of the outcome of Diels–Alder reactions in [$C_n$mim] ILs, these results should at least be very near the crest of the best possible outcomes of Diels–Alder reactions in ILs.

The ramifications of ion pairing effects and / or halide contamination are not limited to the Diels–Alder reaction, either. Recall that Dyson and coworkers provided one of the first examples of how damaging halide contamination could be to a chemical reaction in hydrogenations catalyzed by a ruthenium catalyst. Excess halide *deactivated* the metal.[63] The same group showed the presence of chloride *activated* a different ruthenium hydrogenation catalyst.[322] Additionally, all available data on nucleophilic substitutions of anions in ILs demonstrates that the most popular IL cations (even those which are not the strongest H–bond donors) coordinate halides *strongly*, but Dyson's group has also shown that [C_4mim] ILs may coordinate chloride too *weakly* to allow dissociation of chloride from yet another ruthenium catalyst.[323] Maddening as the effects of halides in ILs on chemical reactivity in ILs may be, the most pronounced and common effects of halide contamination are on the physical properties of ILs,[57] and particularly viscosity. The Diels–Alder reaction seems to be impervious to changes in IL viscosity.[321]

Although it is beginning to appear that ILs are not intrinsically ideal Diels–Alder catalysts, the effect of Lewis acids on the reaction in ILs is usually profound (cf. Table 24, Entries 20 and 21; 34 and 35). The [$(C_2H_4OH)NC_{1\ 1\ 1}$] ILs compounded from excess zinc chloride in particular gave noteworthy stereo- and regioselectivities (Table 24, Entries 29 – 31). Note that there can be no comparison to a zero reaction free of Lewis acid because choline

chloride does not melt; it decomposes at 302 – 305 ^{o}C, and therefore requires a dope to liquefy at a convenient temperature. The reaction of myrcene with acrolein was more improved by the application of zinc chloride to [C_4mim][Cl] than to dichloromethane (cf. Table 24, Entries 32 – 35), both of which gave unenviable results alone.

There are already several examples where returns in yield, selectivity, and shorter reaction time can be greater when a Lewis acid is applied to a Diels–Alder reaction in an IL than in a conventional solvent. For example, a survey of model Diels–Alder reactions of cyclopentadiene under the influence of Lewis acids in [C_6mim][BF_4] has appeared where the authors report lanthanum triflates (particularly triflates of cerium, yttrium, and scandium) were the most efficient catalysts (Table 25).[314] They compared the reactions of cyclopentadiene and butenone with the most successful conditions in conventional solvents to that point (2005). The most striking observation was the tiny amount of Lewis acid necessary (less than 1 mol %) to deliver Diels–Alder adducts in excess of 95% yield and up to 90% diastereomeric excess when the reaction was performed in an IL. It is conceivable the selectivity would have improved if the reactions had been attempted below room temperature with any commensurate loss in yields made up by continuing the reactions beyond the minute (*minute*!) timescale. Although the authors do not say as much, their observations on the activity of different Lewis acids in [C_6mim][BF_4] do not necessarily extend to other ILs, but this caveat does not undermine the dramatic effects they have shown are possible in ILs. The excellent capacity of ILs for Lewis acid retention and the subsequent recyclability of a catalytic IL phase bear repeating.

Table 25. Outcomes of the Diels-Alder reaction between cyclopentadiene and butenone in different systems, ordered by stereoselectivity.[314]

Solvent	Catalyst	Mol %	*t* (min)	T (^{o}C)	Yield (%)	*N* / *X*
H_2O	$InCl_3$	20.0	240	rt	84	6.7
DCM	$Sc(OTf)_3$	10.0	720	0 ^{o}C	96	8.1
[C_6mim][BF_4]	**$Ce(OTf)_4$·5 H_2O**	**0.5**	**5**	**rt**	**98**	**15.7**
[C_6mim][BF_4]	**$Ce(OTf)_4$·5 H_2O**	**0.2**	**60**	**rt**	**97**	**15.7**
[C_6mim][BF_4]	**$Y(OTf)_3$**	**0.5**	**15**	**rt**	**96**	**19**
[C_6mim][BF_4]	**$Sc(OTf)_3$**	**0.5**	**15**	**rt**	**98**	**19**
[C_6mim][BF_4]	**$Sc(NTf_2)_3$**	**0.5**	**15**	**rt**	**98**	**19**
DCM	$Sc(ONf)_3$	5.0	180	–20 ^{o}C	100	49
$CHCl_3$	$MeReO_3$	1.0	60	rt	95	> 99

Note the low 1,3- / 1,4-stereoselection in the reaction of myrcene and acrolein in [C_4mim][Cl] (Table 24, Entry 34) and the moderate and high *endo* : *exo* stereoselectivities for the reaction of cyclopentadiene and methyl acrylate in nearly neutral [C_2mim][$AlCl_4$] (Entries 8 and 9) and acidic [C_2mim][$AlCl_4$] (Entries 10 and 11). Correctly accounting for these results is difficult because the relevant literature summarized below does not truly make it clear whether chloroaluminate ILs can be effective Diels–Alder catalysts, or if Entries 10 and 11 are another example where an IL is "only" a better medium for a Diels–Alder reaction catalyzed by a Lewis acid.

We start at one end of the spectrum of claims regarding Diels–Alder reactions in ILs, where A. Kumar and S. Tiwari have boldly titled a paper "Diels–Alder Reactions Are Faster in

Water than in Ionic Liquids at Room Temperature," concluding that "water, and not a RTIL, is definitely the solvent of choice for carrying out Diels–Alder reactions."[324] They base this claim on only 18 of their own data points—three Diels–Alder reactions (cyclopentadiene with methyl, ethyl, or butyl acrylate) each in water or one of five ILs. The model reactions were indeed several times (4 – 8 ×) faster in water than in their selected ILs, and Diels–Alder reactions were 5 – 30 times faster in water than in ILs according to other references reporting comparative rate constants. However, the conclusion "water is definitely the solvent of choice" is unjustified if only because faster does not always equate to better. Moreover, in the face of the expanding library of ILs, it is conceivable an IL commonly giving faster Diels–Alder reactions than water will emerge. In fact, the Diels–Alder reactions in melts of $[C_2mim][Cl]$ and aluminum chloride reiterated above (Table 24, Entries 8 – 11) may qualify.

The Diels–Alder reactions of cyclopentadiene and methyl acrylate in approximately neutral $[C_2mim][AlCl_4]$ (Table 24, Entries 8 and 9) and the acidic IL (Entries 10 and 11) were reported by C. W. Lee in 1999, and were accompanied by a reported rate constant 10 times larger for the reaction in the acidic IL than in water; the reaction was roughly 2.5 times faster in water than in the neutral IL.[310] Lee ascribes the increased rate and *endo* : *exo* selectivity in the acidic IL to catalysis by the $[C_2mim]$ cation, and not by aluminum chloride. Lee claims no free molecular aluminum chloride was present, but does not divulge how its presence was ruled out. The concentration of aluminum chloride may have been very low, but it should not have been zero because there is an equilibrium among free halide, free aluminum chloride, tetrachloroaluminate, and heptachlorodialuminate in this type of IL formulation.[38] Even if the concentration of molecular aluminum chloride was very low at any given time in Lee's

experiments, interaction of either prevalent aluminate species with the dienophile may have lead to the release of free molecular aluminum chloride to catalyze the Diels–Alder reaction.

Hence, it is not easily knowable whether the result derives from performing the reaction in the IL or from the presence of Lewis acid. This legitimate ambiguity is probably why Kumar and Tiwari did not acknowledge the rate constant Lee reported. Interestingly, Kumar himself could have shone more light on the subject. Kumar and S. S. Pawar observed the Diels–Alder reactions of the four possible combinations of cyclopentadiene with methyl methacrylate or crotonate in [C_4py] or [C_2mim][Cl] all inverted from *exo* to *endo* selectivity when aluminum chloride was supplied.[312] The extent of inversion was commensurate with the amount of aluminum chloride added; *endo* : *exo* selectivity was universally higher in acidic melts and reached as high as 11.5 : 1 in [C_2mim][Cl] containing 60 mol % aluminum chloride. This observation is in line with Lee's earlier observations, indicates catalysis from some source, and could have been accompanied by a rate increase, but no kinetic measurements were made. It also does not elucidate whether the Diels–Alder reactions in chloroaluminate ILs are facilitated by IL or Lewis acid.

O. Acevedo, W. L. Jorgensen, and J. D. Evanseck recently studied the reaction of cyclopentadiene and methyl acrylate in mixtures of [C_2mim][Cl] and aluminum chloride and in water with QM / MM computations following Monte Carlo simulations.[325] Several points need to be aired out before considering them, however. The reference speaks of basic and acidic mixtures, but they appear to have actually computed the neutral and acidic mixtures. They describe computations of reactions in solvent boxes containing 192 ions each of [C_2mim] and an equal number of [$AlCl_4$] (neutral) or [Al_2Cl_7] (acidic) anions, which is problematic in comparing the computed system to the experimental results. The computational data reflects discrete

[C_4mim][Al_2Cl_7], whereas Lee's data was collected in [C_2mim][Cl] containing 1.12 eq aluminum chloride, wherein the IL could not have quantitatively been [C_4mim][Al_2Cl_7]. This difference is not just a semantic problem; the following rationalization is based on ion pairing, and the difference in basicity between [$AlCl_4$] and [Al_2Cl_7] is orders of magnitude. Note again that Kumar and Pawar used 1.5 eq aluminum chloride in [C_2mim] and [C_4py][Cl], which comes closer to an examination of the Diels–Alder reaction in [Al_2Cl_7] ILs, but they did not report any reaction rate constants.

The computations did not include discrete aluminum chloride, and the aluminates did not dissociate during simulation of the reaction. Under these constraints the barriers to reaction in the solvents investigated still ran as in Lee's experiments (i.e., [C_2mim][Al_2Cl_7] < water < [C_2mim][$AlCl_4$]). Acevedo, Jorgensen, and Evanseck found this barrier lowering resulted from an increase in the partial positive charge on the methyl acrylate carbonyl carbon from reagent to transition structure in [C_2mim][Al_2Cl_7]. The relevant aluminates were necessarily involved in solvation, but did not associate with the computed transition structure in any way recognizable as a catalyzing interaction. Instead, the barrier lowering was the effect of H–bonding between [C_2mim] and the dienophile. However, it was a C(4) / C(5) proton of the imidazolium, and not the C(2) proton, associated with the transition structure, and the H–bond from this proton to methyl acrylate was stronger than the H–bond from water. By extension, the material results of Lee's experiments may genuinely be an effect of whatever proportion of [C_2mim] cation existed as [C_2mim][Al_2Cl_7] and not of Lewis acid catalysis. If that is the case, the absence of a significant catalytic effect on Diels–Alder reactions in other [$C_n$mim] ILs needs an explanation.

Acevedo, Jorgensen, and Evanseck rationalize the efficiency of the acidic formulation as a Diels–Alder catalyst in terms of ion dissociation, which increases with an increasing mole

fraction of aluminum chloride. According to the papers from Welton and coworkers[321] and from Dyson and coworkers,[320] ion dissociation is a desirable property for Diels–Alder reactions in ILs, and Acevedo, Jorgensen, and Evanseck add that, in addition to H–bonds, they observed more solvent–solute interactions between the transition structure in the acidic IL (1.6 contacts) than in the neutral IL (0.6 contacts), which does speak to the need to fully dissociate the IL ion pair to stabilize the transition structure, but it also speaks to the need for an IL anion that will solvate an organic transition structure.[325]

Kumar's rebuke of ILs as solvents for the Diels–Alder reaction of cyclopentadiene with methyl acrylate shows the reaction is four to eight times slower in [$C_n$mim][BF_4]s and [PF_6]s than in water.[324] Lee found the same reaction in acidic mixtures of [C_2mim][Cl] and aluminum chloride was 10 times faster than in water,[310] and this result is in good agreement with the computational data from Acevedo, Jorgensen, and Evanseck.[325] If the answer is only ion pairing, then the simple conclusion is that the set of [$C_n$mim][BF_4] / [PF_6] / [$AlCl_4$] ILs are so much more strongly ion paired than [$C_n$mim][Al_2Cl_7] ILs that the Diels–Alder reaction is 40 – 80 times faster and *endo* : *exo* selectivities are 4 – 5 times greater in the last of these varieties. As foreshadowed, that does not explain why Diels–Alder reactions in [C_4mim] paired with [OTf] and [SbF_6] only give stereoselectivities comparable to those in ILs with what should be much more strongly coordinating anions. It seems reasonable to believe [C_4mim][OTf] and [SbF_6] are at the high end of divisibility, too, and yet the only recorded indicators of their effect on the Diels–Alder reaction are unremarkable. Why would the reaction in an acidic [C_2mim][Cl] melt with aluminum chloride proceed so much more quickly and with such higher stereoselectivity than the reaction in other [$C_n$mim] ILs based on anions from superacids?

Perhaps if the highest wavenumbers in the IR spectra or the ^{1}H chemical shifts of the C(2)—or, better yet, C(4) / C(5)—protons of all the relevant ILs were available for comparison, it would turn out the [$C_n$mim] salts of other conjugate bases of superacids are more strongly coordinated than may be expected, and that [Al_2Cl_7] is singularly dissociated. Perhaps if the four Δ parameters of [C_2mim][Al_2Cl_7] were known, Equation 8 would demonstrate that this IL is unique in its effect on Diels–Alder reactions by comparison to other [$C_n$mim] ILs, including those with anions from superacids.[320] It is also possible there is an optimum between ion dissociation and transition structure solvation. Maybe the disparities in the product selectivities and reaction rates of Diels–Alder reactions in the set [$C_n$mim][BF_4] / [PF_6] / [$AlCl_4$] and the set [$C_n$mim][SbF_6] / [OTf] as opposed to [$C_n$mim][Al_2Cl_7] result from the first set being too strongly associated to afford a catalytic effect, while the second features anions associating too poorly with the transition structure to stabilize it. Then the explanation would be that [$C_n$mim][Al_2Cl_7] ILs sit at the confluence of ions sufficiently poorly coordinating to separate into a catalytic [$C_n$mim] cation with an anion that adequately interacts with and stabilizes the transition structure. The computational results do show the transition structure was not only chelated by [C_2mim][Al_2Cl_7], but was better solvated all around.[325] For an analogy, consider that chlorinated hydrocarbon solvents dissolve nearly anything organic; highly fluorinated solvents only dissolve other highly fluorinated materials well. Changing the halogen bearing atoms in these solvents to a metal does not change the atoms projected onto a solute. It could be the case that fluorous solvents based on metals do not solvate most organic solutes any better than fluorous solvents based on carbon, and that [Al_nCl_m] ILs, like chlorinated hydrocarbons, make excellent solvents.

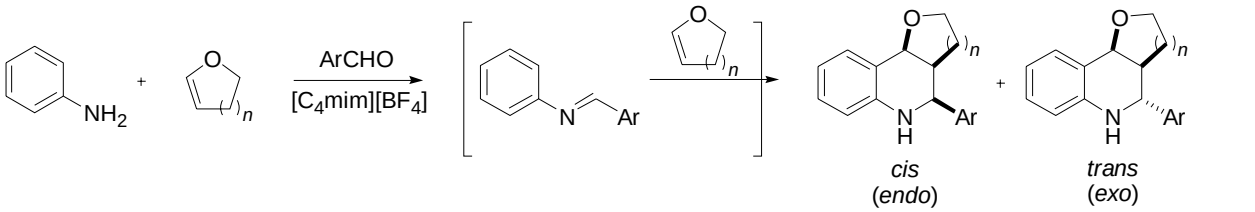
A more thorough explanation for the basis of the unique catalytic properties of [$C_n$mim][Al_2Cl_7]s versus other [$C_n$mim] ILs or evidence that Lee's examples were actually catalyzed by aluminum chloride will be necessary to clearly reconcile the existing data. The most straightforward entry to the necessary data would be more QM / MM computations, where it may be revealed chlorometallates are inherently more stabilizing solvents towards Diels–Alder transition structures than are fluorous anions. The simplest explanation, of course, is that the computed path is simply not the mechanistic course of the reaction in solution, and that Lee's examples were catalyzed by aluminum chloride. Recall that many other examples speak to the potency of Lewis acids on the Diels–Alder reaction in ILs.

The sum of these reports indicates there is *maybe* one example of a Diels–Alder reaction proceeding in an IL at a faster rate and with a higher stereoselectivity than the same reaction in water; if that is the only metric, then water is ordinarily a "better" solvent for Diels–Alder reaction than are ILs. It is not impossible that one or many ILs *may* emerge as effective catalysts for the reaction, but any IL that would be a powerful catalyst of the Diels–Alder reaction must (presumably) be constituted from a very good H–bond donating cation and a very poor H–bond accepting anion. These ions which readily dissociate from each other are also required to effectively solvolyze the transition structure. It is clear certain ILs *can* effectively direct the stereo- and regiochemical outcomes of Diels–Alder reactions in them, and that some of these Diels–Alder reactions are *commonly* superior to the *uncatalyzed* reaction in a conventional organic solvent by any measure. However, the observations simply do not support the notion that ILs faithfully afford Diels–Alder reactions without rival in conventional solvents. The [PR_4][OTs]s gave excellent yields and regioselectivities in some Diels–Alder reactions, but they are best suited to Diels–Alder reactions of unsaturated C=O compounds. Ionic liquids do seem

ideally suited for the execution of Diels–Alder reactions catalyzed by Lewis acids, partly because of the impressive outputs relative to the amount of catalyst invested, and partly because these Lewis acid catalysts may be conveniently recycled. The capacity for H–bond donation is believable as an intrinsic property of ILs and of the [$C_n$mim] ILs in particular, which appear to donate meaningful H–bonds from any hydrogen on the cation. However, it is not yet *definitively* known what effect this characteristic may have on Diels–Alder reactions in ILs.

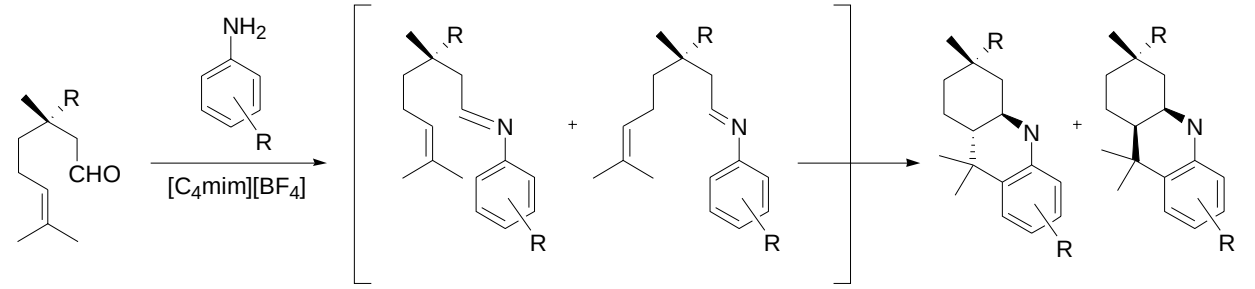
Ionic liquids have been used as media for Diels–Alder reactions leading to complex molecular targets. Yadav and coworkers first described the aza Diels–Alder reaction of *N*-phenyl aromatic aldimines with dihydrofuran and -pyran in [C_4mim][PF_6] with scandium triflate as a catalyst in 2002.[326] The aldimine was prepared and then subjected to the Diels–Alder reaction in the same pot, and a catalytic IL layer could be recycled following extraction of the product with ether. The next year they reported a successful three component coupling *without* supplied catalyst in under four hours total at room temperature (Scheme 16).[327] In the case of aza Diels–Alder reactions of dihydrofurans, only the *cis* enantiomers resulting from *endo* cycloaddition were isolated, which the authors stress could not be accomplished under conventional reaction conditions. In the dihydropyran series, they recovered a 4 : 1 or greater ratio of *cis* : *trans* diastereomers in six of seven trials. The same group reported octahydroacridine syntheses in as little as 20 minutes at room temperature (Scheme 17).[328] As in the syntheses in Scheme 16, the syntheses of octahydroacridines were accomplished in IL alone. The authors note the dehydrations required three hours in conventional solvents in the absence of an acid catalyst, and were not followed by cyclizations. The same group has used hetero Diels–Alder reactions to assemble tetrahydrochromanoquinolines[329] and

pyranocoumarins[330] in [C_4mim][BF_4], the latter of which was completed in the second stage of a tandem reaction started with a Knoevenagel condensation.



n = 1: 100% *endo* selectivity, 85 – 92% yield
n = 2: (3 : 1) – (9 : 1) *endo* selectivity, 80 – 91% yield

Scheme 16. Synthesis of hexahydropyrano- and -furanoquinolines by a three component reaction in [C_4mim][BF_4].[327]

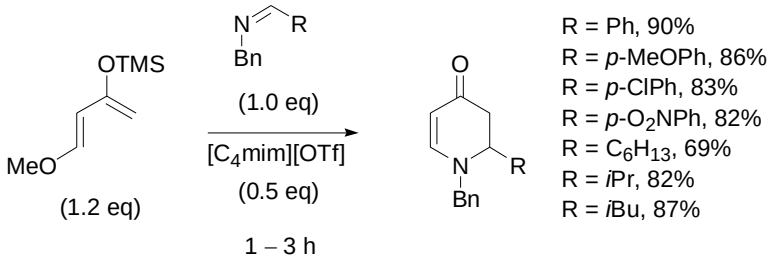


R = H: (1 : 1) – (4 : 1) *trans* : *cis* selectivity, 86 – 95% yield
R = Me: 100% *trans* selectivity, 70 – 97% yield

Scheme 17. Synthesis of octahydroacridines in [C_4mim][BF_4].[328]

Reactions of Danishefsky's diene with imines have been accomplished more easily in ILs than in conventional solvents with an acid catalyst. The first report came from T. Kitazume and F. Zulfiqar and utilized scandium triflate in ILs in a one pot procedure.[331] Newer conditions from a different group eliminate the Lewis acid altogether, and require a small amount of [C_4mim][OTf] on a molar basis (Scheme 18).[332] The yield was reduced nine-fold in the solventless reaction to *N*-benzyl protected pyridones. Note that a three component reaction was

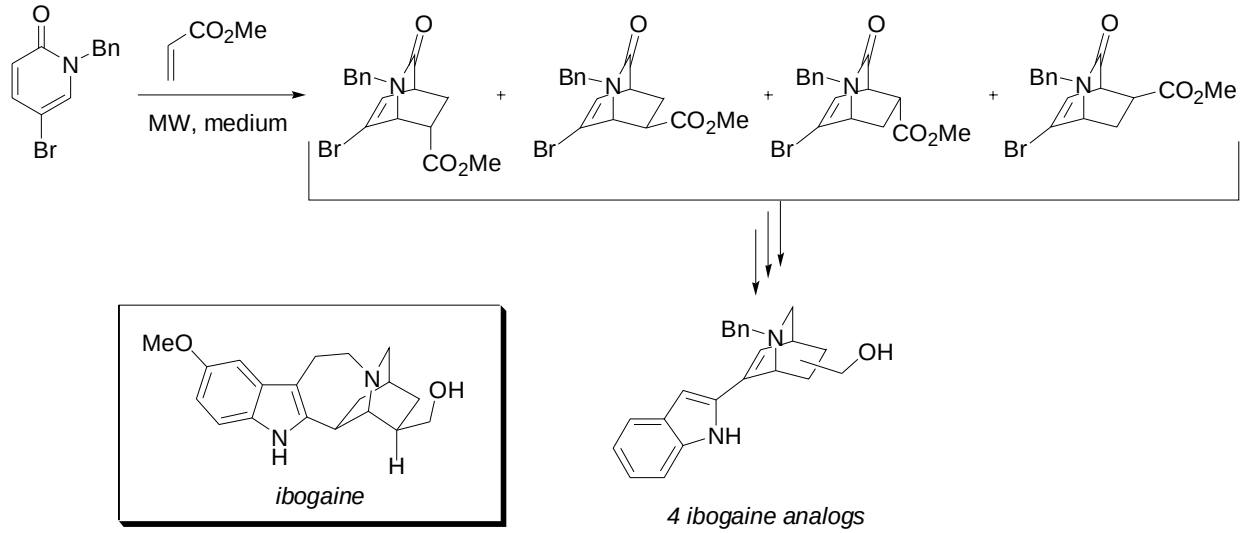
not feasible in this case. For an example with a contrary effect to those described above, note that ILs did not enhance the Diels–Alder reactions of 4-methylene-5-propylidene-2-oxazolidinone with representative dienophiles.[333]



Scheme 18. Reactions of Danishefsky's diene with imines in ILs.[332]

An emerging use of ILs is as additives to reaction mixtures under microwave irradiation, where they raise the maximum attainable temperature in the reaction solvent,[215, 334, 335] and many of the current examples along this line are of Diels–Alder reactions. For example, a 10% solution of $[C_4mim][PF_6]$ in toluene was recently evaluated in this capacity during a synthesis of ibogaine analogs (Table 26).[336]

Table 26. The results of a MW Diels–Alder step on the way to ibogaine analogs in PhMe containing [C_4mim][PF_6] and in other media.[336]



Medium	Conversion (%) over time			
	90 min	6 h	14 h	10 d
Montmorillonite clay	20	Polymerized	--	--
$MgSO_4$	20	Polymerized	--	--
Aluminum oxide (acidic)	20	Polymerized	--	--
DCM	--	11	--	--
Aluminum oxide (basic)	19	17	--	--
Silica gel	21	21	--	--
10% [C_4mim][PF_6] in PhMe	**11**	**45**	--	--
Aluminum oxide (neutral)	10	45	60	--
DCM (no MW, 120 ^oC, sealed tube)	--	--	--	84

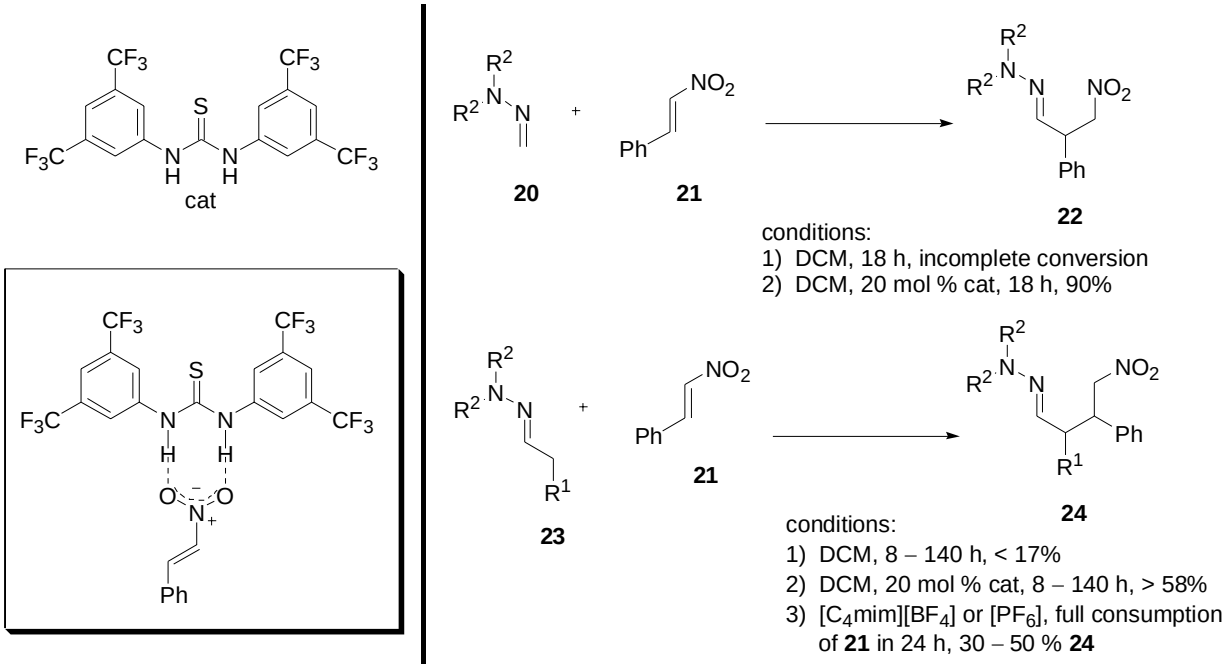
1.2.3. ADDITION REACTIONS IN, BASE STABILITY OF, AND SYNTHETIC CONCEPTS ADAPTED TO IONIC LIQUIDS

Addition reactions in ILs could be a testing ground to examine how reaction mechanisms may differ in them as opposed to conventional solvents and when ILs can be inherently catalyzing solvents, but many of the available examples are not comparative in nature. One thorough study comes from Chiappe and coworkers regarding addition reactions of two trihalides (Br_3^- and ICl_2^-) to unsaturated compounds.[337] They reported the rates of reaction of both trihalides increased by moving the reaction from dichloroethane to ILs, but that H–bonding was apparently only important in the reaction of iodine dichloride. This example warrants special attention from a practical standpoint, because the side reaction of nucleophilic substitution by chloride following iodine dichloride addition to an unsaturated system was suppressed in ILs.

Among the potentially instructive examples are results from a study of the Sakurai reaction of allyltrimethylsilane with α,β-unsaturated ketones in [C_4mim][PF_6] by Howarth and coworkers. These 1,4-additions always featured indium (III) chloride and chlorotrimethylsilane, and did not address any inherent catalyzing effect from H–bond donation by the cation.[338] Aldehydes have been converted to homoallyl ethers by their Sakurai reactions with allyltrimethylsilane in the presence of mild alkylating agents (orthoformates and trimethylsilyloxy compounds) in [C_4mim][OTf], but these products were also accessed in the presence of a Lewis acid (TMSOTf), and do not elucidate whether [$C_n$mim] had any catalyzing effect on the reaction.[339] The analogous addition reactions of tetraallylstannane to aldehydes have been accomplished in [C_4mim][BF_4] and [PF_6],[340] and their acyl substitution reactions on Weinreb amides were evaluated in the former IL by the same group.[341] The authors did not explicitly take up the issue of catalysis via H–bond donation from the IL cation and did not

compare the reactions of aldehydes in ILs to the same reactions in conventional solvents. From their work with the Weinreb amides, however, it does seem any effect from the IL cation could not have been very strong because the low to moderate yields recovered in methanol were not improved by conducting the same reactions in $[C_4mim][BF_4]$. B. C. Ranu and coworkers claim that Michael additions of thiols to α,β-unsaturated carbonyls are more effective in molten $[NC_{4\,4\,4\,4}][Br]$ than in a solventless reaction, but do not offer any comparisons to the reactions in conventional solvents.[342] Yadav and coworkers draw a similarly unsubstantiated conclusion from conducting the same additions in aqueous $[C_4mim][PF_6]$.[343]

S. Toma and coworkers studied the additions of aldehydes and ketones to β-nitrostyrenes under the influence of 2^o amine base catalysts without comparing these reactions to the same processes in conventional solvents.[344] However, they have since shown this same class of reaction can be more efficient in ILs than in dichloromethane when chalcone is the electrophile, and that active methylene compounds added to chalcone *without* any additional catalyst.[345] D. Pettersen, R. P. Herrera, and coworkers also reported on some additions to β-nitrostyrene (**21**) (Scheme 19).[346] They observed the additions of neutral hydrazones to **21** were uniformly faster and higher yielding under the influence of 20 mol % of a thiourea catalyst in dichloromethane than in dichloromethane alone, and that hydrazones derived from formaldehyde (**20**) added to **21** from the C=N carbonyl carbon. Enolizable hydrazones (**23**) added to **21** from their α carbons. The authors did not address whether the thiourea catalyst facilitated tautomerization of hydrazones **23**, but did imagine the catalyst activated the reaction through bidentate coordination of **21**.



Scheme 19. Additions of neutral hydrazones **20** or **23** to **21** in DCM, DCM + cat, or ILs.[346]

The observation relevant to organic synthesis in ILs is that **21** was entirely consumed 24 hours after **23** and **21** were combined in [C_4mim][BF_4] or [PF_6] without benefit of catalyst. For comparison, the reactions in dichloromethane loaded with thiourea catalyst required 8 – 140 h to complete. The authors note that the combination of catalyst and IL was not productive. However, the reactions in ILs gave lower yields of **24** than did the reactions in dichloromethane loaded with thiourea, which means the fate of some **23** was not clear. By this point in the study, the authors were apparently looking for adducts **24** from these reactions. It is possible the reaction of **23** with **21** proceeded through addition from the C=N carbonyl carbon of **23**, and the reaction actually gave homologs of **22** the authors did not expect. This presumed outcome would require several things. First, [C_4mim] would have to activate **21** in a manner analogous to the thiourea catalyst, which is possible because [$C_n$mim] ILs may donate H–bonds from their C(4) and C(5) protons. It would also be required that [C_4mim] *not* facilitate tautomerization and

electron donation from C(α) of **23** as efficiently as does the thiourea, thereby forcing reaction from the C=N carbonyl carbon. A caveat for the second of these requirements is that the thiourea actually did encourage tautomerization of **23**. That is a lot of "if"s, but, were it the case, the difference in yields of **24** would be explained by different directing effects. The authors did not report on any reaction of **20** and **21** in ILs, which may have provided a better comparison to divine any catalytic activity of the [C_4mim] ILs versus the thiourea catalyst.

Of course, another possible explanation is that free hydrazone base **23** deprotonated the [$C_n$mim] ILs to NHCs **1**, and their addition or cyclopropanation reaction with **21** account for the full consumption of it. That a base may deprotonate an imidazolium IL with a C(2) proton in any reaction combining them is an important practical matter to bear in mind, and some authors have wondered how much it matters. On one hand, ionic liquids which are themselves weak Lewis bases have some useful properties resulting from this characteristic,[41] but those ILs feature dicyanamide or carboxylates as anions, or an *N*-alkyl-1,4-diazabicyclo[2.2.2]octanium cation. None of these bases are what most people have in mind when they think about the compatability of imidazolium salts with base. The pK_as of both ammonium salts and cyanic acid, the conjugate acids of the strongest bases seen in ILs with any frequency, are around 10 in water. The pK_as of the imidazolium salts are > 20 in water.[144] Considering the basicity of NHCs **1**, it is unlikely that hydrazone **23** led to enough of it to consume **21**, or that carbenes are a cause for concern in the substitution reactions of neutral amines or of basic anions.

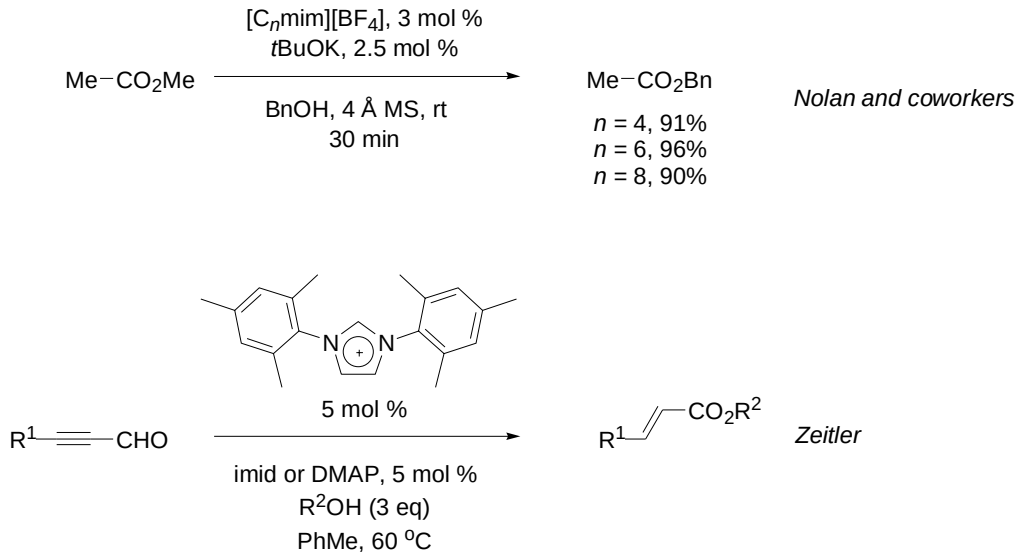
Toma and coworkers' examples of addition reactions catalyzed by 2^o amines in ILs are examples of the stability of imidazolium ILs to common bases. The spontaneous additions of active methylene compounds to chalcone they observed presumably proceeded through carbanions. Like ammonium salts and cyanic acid, the pK_as of these compounds are around 10.

There are also many examples of reactions in ILs in the presence of carbonate or hydroxide with either unpronounced or no ill effects from any carbene present.[347-358] At the limit, the ILs [C_4mim] and [C_2mim][OH] are known, the former reportedly being prepared by stirring potassium hydoxide and [C_4mim][Br] in dichloromethane for 10 hours, which indicates that the possible side reaction of NHCs **1** with dichloromethane (Scheme 5) is very slow. It is conceivable that these formulations would be more accurately described as solutions of NHC **1**, however.

Although it apparently is not in effect during the synthesis of [C_4mim][OH] in dichloromethane or in the other preceding examples combining imidazolium ILs, base, and a cosolvent that could conceivably escort NHCs **1** down a decomposition pathway, Le Chatelier's principle could complicate acid–base chemistry in imidazolium ILs. For example, pyridine and carbonate are too weak to quantitatively form NHC **1**, but the combination of imidazolium salts with elemental sulfur in their presence led to high yields of **I2T**s through a small but omnipresent population of NHCs **1** (Scheme 5).[134, 149] The side reactions open to mixtures of an imidazolium IL and base have received attention in some reviews, ordinarily alongside considerations of other limitations to the use of ILs.[61, 227, 359] Despite the possibility of myriad reactions of NHCs **1**, however, it appears the reactions of NHCs **1** are the most significant when the *only* reaction pathway open is that involving the carbene.

The population of NHC **1** which may exist in a mixture of an imidazolium IL and a base can also be synthetically useful. The relevance of NHCs **1** to synthetic chemistry in ILs in so many words has been reviewed by J. A. C. Clyburne and coworkers.[360] Redox processes of these carbenes have been reviewed insofar as they relate to catalytic reactions using them.[361] S. P. Nolan and coworkers have shown that NHCs **1** are useful as transesterification catalysts,

and that these may be derived from ILs in solution to give yields comparable or better to the reactions of the discrete carbenes (Scheme 20).[362] Scheme 20 also includes a conversion introduced by K. Zeitler which produces α,β-unsaturated esters from ynals under the influence of NHCs **1**.[363] She prepared a dimesityl NHC **1** in solution and did not report any processes with ILs. In light of Nolan and coworkers' transesterification, it is believable these reactions could have been accomplished by the formation of an NHC **1** from an IL in solution. Her results also stand out because the NHC **1** formed under the influence of imidazole or *N*,*N*-dimethylaminopyridine, which are weak bases. Mechanistic interpretations of these reactions demand exchange of a C–C bond for a C–O bond and expulsion of an NHC **1**, which is also the case in Stetter and benzoin reactions catalyzed by carbenes. Those reactions more commonly employ carbenes derived from thiazolium or triazolium salts, but NHCs **1** can be used.[364-366]



Scheme 20. Transesterifications in the presence of NHCs **1** reported by Nolan and coworkers,[362] and conversion of ynals to α,β-unsaturated esters reported by Zeitler.[363] Zeitler's paper includes one reaction proceeding in 18% yield (R^1 = CHO), and one proceeding in 90% yield (R^2 = *t*Bu), and nine giving a 50 ± 10% yield; *E* : *Z* regioselectivity was > 95 : 5.

When reactions which are not facilitated by NHCs are performed in an imidazolium IL containing base, NHCs **1** can be a nuisance, but some such reactions can still be successful. It is possible some carbenes simply do not form to an extent that permits thorough consumption of one or more reagents. A carbene may form but not irreversibly consume the reagents for the desired reaction, or an irreversible side reaction may be much slower than the desired. For example, Chi and coworkers reported high yields in the reactions of a bromopropylnaphthalene with potassium methoxide and *tert*-butoxide (Entries 3 – 5 of Table 17). Both of these bases must have led to populations of NHC **1** in [$C_n$mim] ILs, and substitution with an alkyl bromide is a reaction pathway open to a carbene. The authors do not acknowledge that they looked for this byproduct, but the yields of the products they did find mean it could not have given a substitution product in more than 5% yield in either of these reactions. In those examples, it is also possible the carbene formed ultimately served as a base to give elimination, or as an acid scavenger following alcoholysis.

There are many more examples of reactions in imidazolium ILs under basic conditions; all of those cataloged below proceed in > 50% yield, and most in > 80% yield. Kitazume and coworkers have shown that alkynes may add to carbonyl compounds under the influence of zinc triflate and 1,8-diazabicyclo[5.4.0]undec-7ene in [C_4mim][BF_4] and [PF_6], and that these ILs could give even better yields than the aprotic IL [C_2dbu][OTf]; the latter IL gave higher yields in Reformatsky reactions.[367] The same group used potassium carbonate and 1,8-diazabicyclo[5.4.0]undec-7ene to effect Horner–Wadsworth–Emmons reactions in [C_1dbu] and [C_2dbu][OTf], but these are aprotic ILs.[368] An example of a Horner–Wadsworth–Emmons reaction in [C_4mim][PF_6] is also available, wherein triethyl α-phosphonoesters (pK_{aDMSO} 18.6) were activated by deprotonation with lithium hydroxide (conjugate acid pK_{aDMSO} 32).[369] A

Wittig reaction in which the ylide was fashioned by the metathesis of ethyl diazoacetate and triphenylphosphine with an iron porphyrin catalyst in $[C_4mim][PF_6]$ has been reported; this reaction probably does not create conditions basic enough to raise eyebrows because pK_{aDMSO} of the conjugate acid is < 10.[370] Not only was the organometallic methylenation reagent *bis*-(iodozincio)methane ($CH_2(ZnI)_2$) not destroyed by the addition of roughly 0.5 equivalents $[C_4mim][PF_6]$, but it went on to give a higher yield of olefin product than the reaction in the absence of an IL.[371] Corey–Chaykovsky reactions have also been performed in $[C_4mim][PF_6]$ using potassium hydroxide as the base (the pK_{aDMSO} of $Me_3S(O)I$ is 18.2).[372] R. D. Singer and coworkers report that the chloride of $[C_6mim][Cl]$ displaced tributylstannate from trimethylsilyltributylstannane, and the products of 1,4-addition of this anion to α,β-unsaturated ketones were isolated in around 70% yields.[373]

Other examples of basic reactions in imidazolium or other ILs are not as successful, as some of the reviews cited above attest, and none of the successful examples are included to imply that conducting these reactions in ILs, especially imidazolium ILs, is not tempting fate. There is certainly a limit to what imidazolium ILs, at least, will tolerate. As of this writing, that limit appears to the reaction of diethylzinc with aldehydes in $[C_4mim][BF_4]$, from which T. H. Chan and coworkers recovered alcohols in yields somewhere between 30 and an incredible 99%.[374] These results can only be taken seriously because the authors documented the evolution of gas when adding diethylzinc to $[C_4mim][Br]$, provided characterizations of the zinc complexes of the resulting NHC **1**, and then went on to report that $[C_4mim][BF_4]$ did not behave the same way. They added that deprotonation of this IL by diethylzinc was possible in the presence of sodium bromide, and that it was important to have IL meticulously freed of bromide for successful additions. They did record another observation as odd as the fact that one

[$C_n$mim] IL was not destroyed by diethylzinc while another one was; the yields in aprotic ILs [C_4dmim] and [C_4py][BF_4] were lower than in [C_4mim][BF_4].

Grignard reactions in imidazolium ILs are presumably out of the question, but the addition of 5 mol % [C_4mim][$FeCl_4$] to aryl Grignard reactions caused them to add to alkyl halides in higher yields than they did without it.[375] Chan and coworkers have prepared and elaborated Grignard reagents in [C_4py] ILs.[376] Clyburne and coworkers used [PR_4] ILs for the reaction of phenyl magnesium bromide and *N*,*N*-dimethylformamide, and followed that synthesis of benzaldehyde with a sodium borohydride reduction in the IL.[377] V. Jurcik and R. Wilhelm have synthesized imidazolinium ILs bearing phenyl groups at C(2) to permit the use of strong bases in ILs.[378] (What is the effect of the C(2) phenyl group on the melting point of the salt? 1,3-Dimethyl-2-phenylimidazolinium bistriflimide melts around 30 ^{o}C.)

S. T. Handy has accomplished Grignard reactions in imidazolium ILs without a C(2) proton; he added solutions of commercial Grignard reagents to aldehydes in 1-butyl-2-isopropyl-3-methylimidazolium bistriflimide.[379] Handy cites an interesting precedent from M. Begtrup that led him to choose this IL. Some of Begtrup's work was included in the selected functionalizations of NHCs **1** in Table 4. Handy notes that he (Begtrup) showed that the [C_1mim] cation could be elaborated to the 1,3-dimethyl-2-isopropylimidazolium cation on treatment with excess sodium hydride and methyl iodide, but not further.[380] Handy took this observation to mean the 1,3-dimethyl-2-isopropylimidazolium cation was not deprotonated to the enediamine in the presence of a strong base. Begtrup's observation could have just as easily meant that the enediamine that would have resulted from deprotonation did not accept methyl iodide as an electrophile, but, in the event, Handy's reasoning was confirmed by his yields. He recovered 67 – 94% of the expected alcohols in reactions of carbonyl compounds with only 1.1

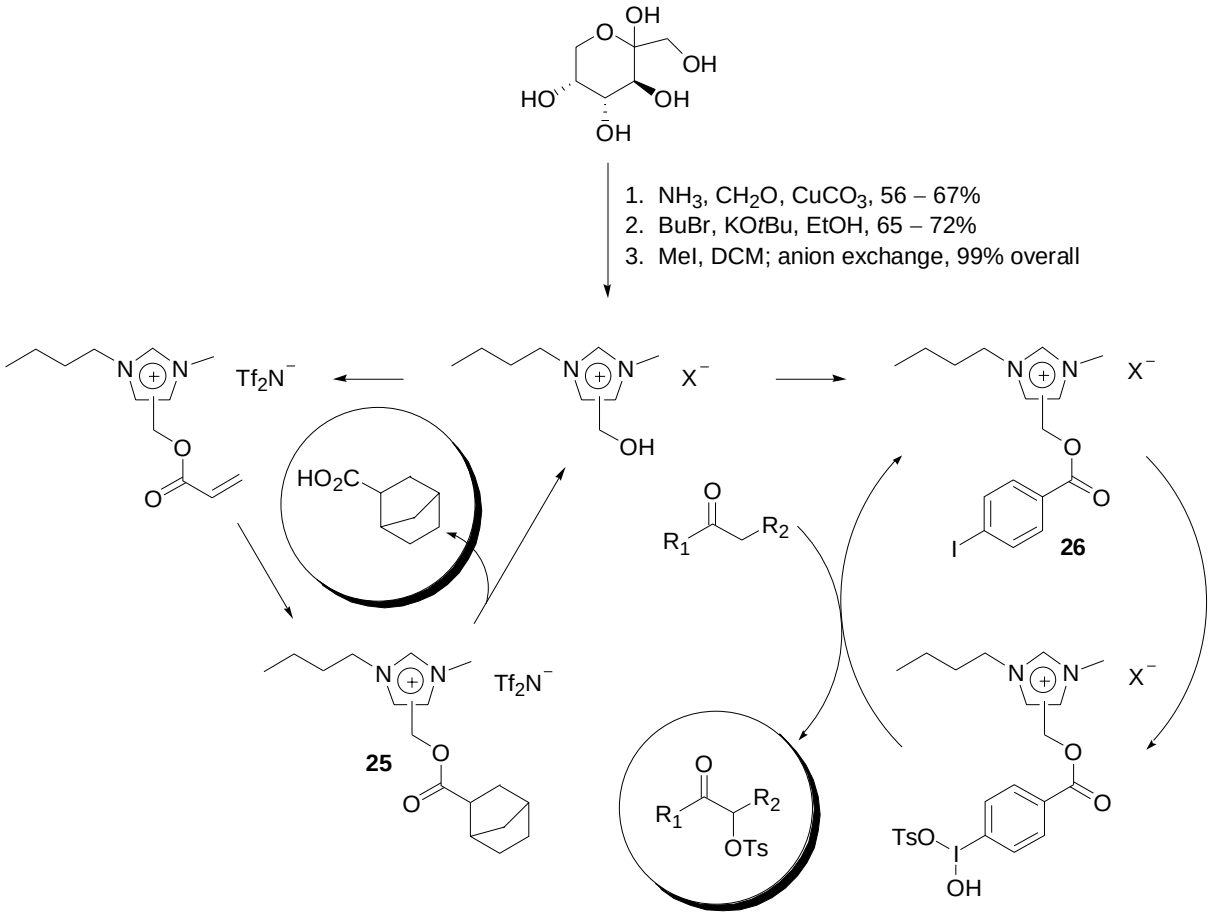
equivalents of Grignard reagent. This small excess of reagent does not leave much room to consider that Handy actually prepared an enediamine solvent from an imidazolium salt and a Grignard reagent, and then carried carbonyls through to alcohols by applying excess Grignard reagent.

Another interesting facet of that paper is that Handy did not prepare 1-butyl-2-isopropyl-3-methylimidazolium bistriflimide from a [C_4mim] salt even though he cites Begtrup. He prepared the IL from butylation and then methylation of 2-isopropyl imidazole.[379] A three component coupling of isobutyraldehyde, glyxoal, and butylamine to 1-butyl-2-isopropylimidazole proved unsatisfactory. This approach to a C(2)-substituted IL is curious because Handy had experience derivatizing the C(2) position of [$C_n$mim] ILs. He and M. Okello wrote a paper on the topic.[47] I emphasize alternative methods of IL synthesis like those from Jurcik and Wilhelm and from Handy because there are currently so few, and because the emerging applications of ILs described below can only benefit from more of them. Handy and coworkers have written about alternative syntheses of ILs while emphasizing the availability of some ions from biorenewable sources, and especially of cations from nicotine and fructose;[381-385] Chiappe, G. Imperato, and B. König recently wrote their own review on this theme.[386]

Handy's fructose ILs were used to support reagents for homogeneous synthesis in ILs, but the examples need to be prefaced by observing that there are a few different strategies in the family of supported syntheses which are tinted with ILs. Ionic liquids may be supported by polymers which contain one ion of an IL. The polymer could be insoluble and be used in a heterogeneous reaction (e.g., if the IL is supported by a Merrifield resin), or it could be a soluble polymer (e.g., PEG) and support the IL in a homogeneous reaction. It appears as though no ion common to IL chemistry other than imidazolium has been incorporated in a polymer so far, but

anions and other cations could appear as fragments of a polymer in the future. A derivatized resin was used by Chi's group in substitution reactions with polymer bound imidazolium tetrafluoroborate (e.g., Table 15, Entry 10). Another approach is the fixation of an IL phase to a heterogeneous support, and impregnation of the IL phase with a transition metal catalyst. In a reaction on a supported IL phase (SILP), the SILP serves to keep the catalyst in place and as the reaction medium during homogeneous catalysis. The SILP is itself kept in place by the heterogeneous support (lead ref[192]). As opposed to either of these approaches, the IL can be used as the supporting agent, which is what Handy and coworkers accomplished with imidazolium ILs derived from fructose (Scheme 21). There are many more examples of IL supported synthesis (ILSS, lead ref[193]). The advantage to this method is that judicious design of the synthetic method can furnish products (e.g., **25**) or valuable intermediates (e.g., **26**) tagged with an ion, and these can be more easily purified from the product mixture.

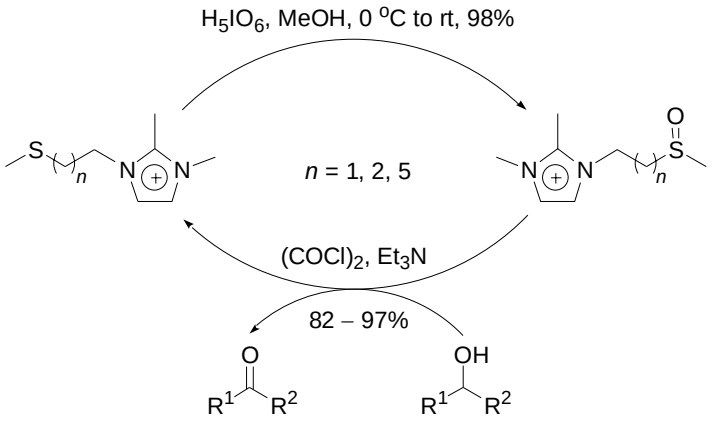
Other ionic liquids with purposed groups have been called task-specific ILs (TSILs). This term was coined by J. H. Davis, Jr. just as IL chemistry was starting to burgeon in the late 1990s, presumably to underscore the possibilities of tuning ILs to a specific purpose. Davis and coworkers introduced ILs based on imidazolium salts appended to ureas, thioureas, or thioethers which were specific to the task of mercury (II) and cadium (II) removal from water.[387, 388] They also prepared ILs based on imidazolium salts appended to amines, which fixed carbon dioxide as an ammonium carbamate.[389] In 2004, Davis reviewed the topic of TSILs.[390] Other authors' ruminations on the requirements for ILs providing an ideal environment for nucleophilic subsitution and Diels–Alder reactions were reviewed in the preceding discussions, and it seems that, if these hypothetical ILs materialized, they would qualify for the TSIL label.



Scheme 21. Handy and coworkers' Diels–Alder and α-tosyloxyation reactions with reagents supported on ILs derived from fructose.[381-385] Conversion of fructose to 4(5)-hydroxymethylimidazole: J. R. Trotter, W. J. Darby, *Org. Synth.* **1944**, *24*, 64; *ibid*. **1955**, *III*, 460. Refs therein: Darby, Lewis, Trotter, *J. Am. Chem. Soc.* **1942**, *64*, 463; Parrod, *Bull. Soc. Chim. Fr.* **1932**, *51* (4), 1424; Weidenhagen, Herrmann, Wegner, *Chem. Ber.* **1937**, *70*, 570.

There is a fine line between the ILs used for ILSS and those called TSILs. The IL specifically designed for nuclephilic substitutions of thiocyanate, [C_4mim][SCN], and [C_4mim][OH] were both called TSILs by the respective authors. The ILs featured in the "Paradigm Confirmed" paper from Earle, Katdare, and Seddon could qualify as TSILs to anyone interested in biasing the reactions of toluene and nitric acid to give chlorotoluene, nitrotoluene,

or benzoic acid. An imidazolium cation supporting an alkyl group terminating in a sulfonyl chloride moiety promoting Beckmann rearrangements was called a TSIL by its inventors.[391] By contrast, Chan and X. He prepared imidazolium salts they used for Swern-type oxidations as shown in Scheme 22 and called this reaction a method in ILSS. They stressed that the reduced thioetheral imidazolium ILs were odorless, and that these could be recovered.[392]



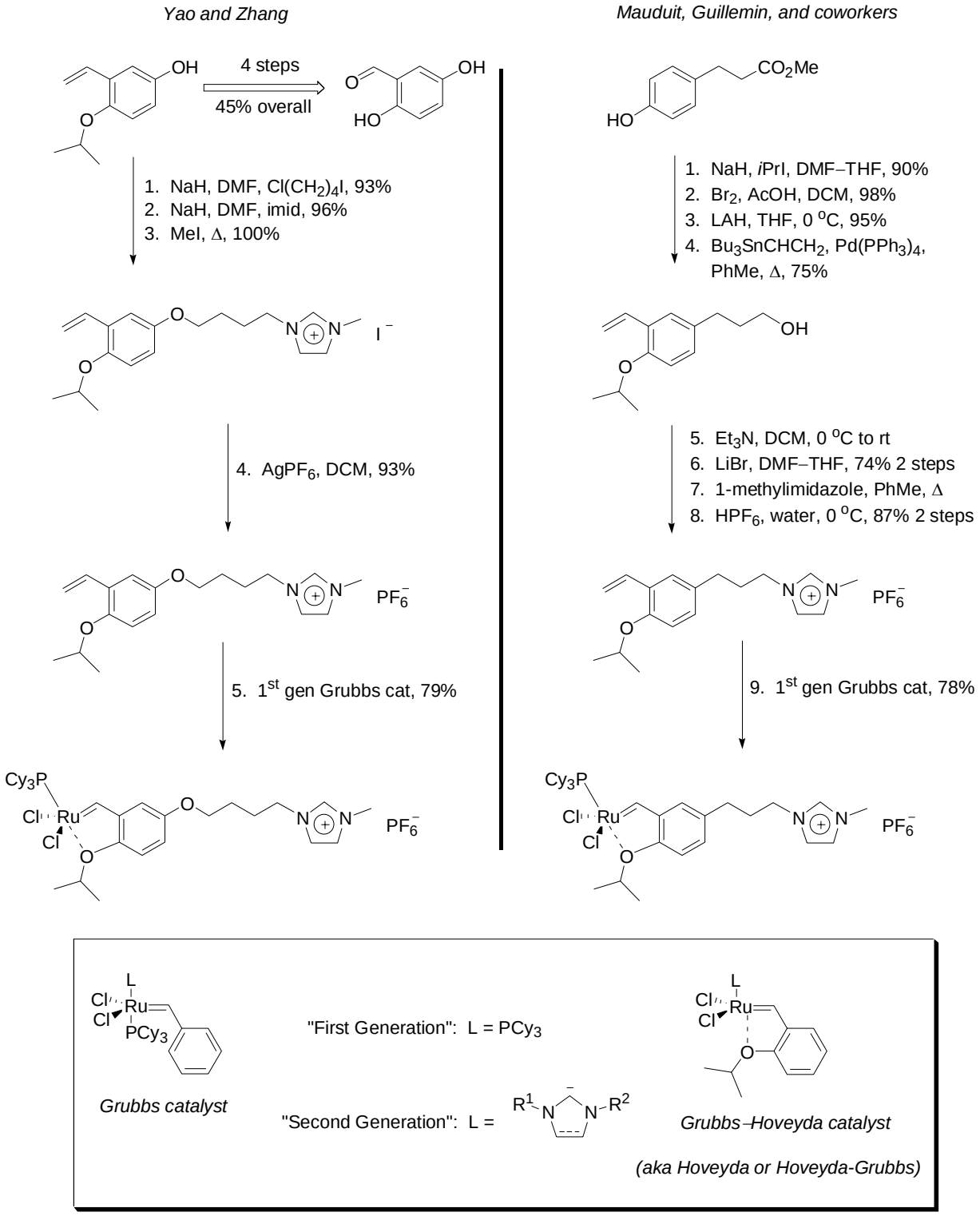
Scheme 22. Chan and He's synthesis of IL supported sulfoxides and their use in Swern-type oxidations.[392] The authors prepared the thioethereal IL in a 92% overall yield from dmim as follows: 1. $Br(CH_2)_{(n+1)}OH$, 60 – 70 °C (n = 1, 2, 5). 2. AgOTf, MeCN, 98% 2 steps. 3. MsCl, Cs_2CO_3, MeCN, 97%. 4. $(H_2N)_2CS$, MeCN, Δ; then aq NaOH; then Me_2SO_4, 99%.

Some of the many ILs with a molecular elaboration or physical property suiting them to a purpose have *also* been called functionalized ILs (lead refs[393, 394]). The only imaginable reason to call certain ILs functionalized instead of task-specific is to avoid implying that their functionalizations could only perform one task. For the most part, the so-called functionalized ILs stop short of carrying reactive moieties. When ILs are called functionalized ILs, some of the

roles they fill include encouraging the formation of nanoparticles, the stabilization of transition metal catalysts, and aiding in the recovery of these catalysts.

The recurrent themes and the potential of designed ILs are epitomized in the following example of imidazolium ILs incorporating the first generation Grubbs–Hoveyda catalyst. These were independently introduced by Q. Yao and Y. Zhang,[395] and by M. Mauduit, J.-C. Guillemin, and coworkers (Scheme 23);[396] both groups have since released the second generation variants of these catalysts.[397, 398] In performing Grubbs metatheses, Yao and Zhang applied their catalysts in 10% $[C_4mim][PF_6]$ in dichloromethane; Mauduit, Guillemin, and coworkers used $[C_4mim][PF_6]$ with no cosolvent with similar results. To recover the adducts, Yao and Zhang removed the cosolvent, recovered their products with ether, and recycled $[C_4mim][PF_6]$ containing their supported catalyst. Mauduit, Guillemin, and coworkers extracted their products directly from the reaction mixture with toluene. The latter group also studied the reaction of their catalyst in $[C_4mim][NTf_2]$, where they found it more difficult to recover the adducts using toluene, and returned to the $[PF_6]$ IL.

In their respective studies, both groups saw a decrease in yield from > 98% down to 50% or less after the first recycle of conventional first generation Grubbs or Grubbs–Hoveyda catalysts. By comparison, the catalysts elaborated as ILs from both groups gave > 98% yields in the first cycle with one exception. The recycled catalysts, with few exceptions, continued to give > 90% yields over several recycles. In the exceptions, yields were still 70 – 80%. Yao and Zhang carried their catalysts through as many as 17 recycles; Mauduit, Guillemin and coworkers carried theirs through as many as 10. It seems the upper limit on recyclability in some cases was the point at which the authors gave up on finding a decrease in activity. Mauduit, Guillemin and



Scheme 23. First and second generation Grubbs and Grubbs–Hoveyda catalysts, and ILs functionalized with them from Yao and Zhang,[395] and from Mauduit, Guillemin, and coworkers.[396]

coworkers also put a number to the efficacy of catalyst retention in $[C_4mim][PF_6]$ based on how much ruthenium leached into the isolate. They quote a benchmark for ruthenium contamination in Grubbs adducts of 200 – 40 ppm following the best current methods of metal removal. Following simple extraction from $[C_4mim][PF_6]$, their adducts retained 22 – 1.2 ppm—i.e., at most, just over half of the minimum left by conventional metal sequestration methods.

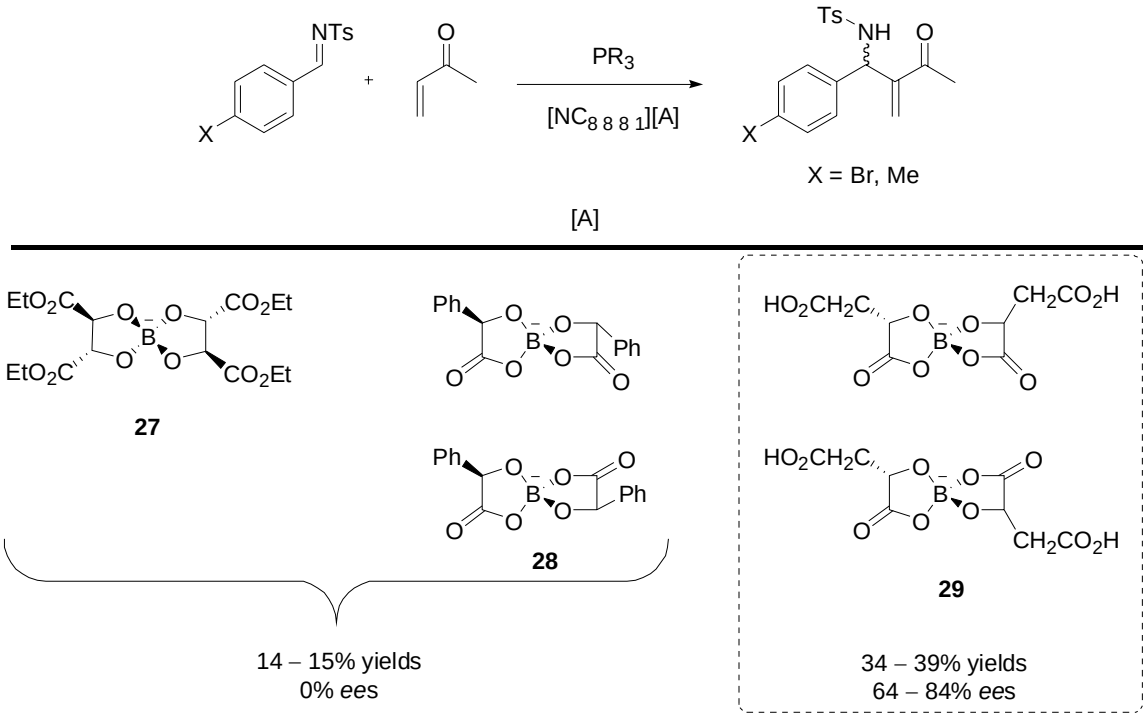
Another leading edge in IL chemistry that would benefit from entirely new routes to ILs is the synthesis of chiral ILs (which are sometimes called CILs, but not here). The structures of known chiral ILs and topics in chirality and asymmetric synthesis as they dovetail with ILs were thoroughly reviewed once each in 2003 and 2004, and twice in 2005.[221-224] The current trend shows that ILs are valuable media for enantioselective catalysis when they facilitate recovery of the metal catalysts so often featured in catalytic asymmetric reactions, and that ILs may amplify the enantioselection imparted by a chiral catalyst if they associate with that catalyst (e.g.[399]). However, there are very few examples of chiral ILs themselves imposing detectable, let alone meaningful enantioselectivities on a reaction. There are so few examples that the brief listing of enantioselection phenomena by chiral ILs that follows is very nearly if not entirely comprehensive. The many examples of chiral ILs that have not found any application (e.g., Handy's nicotine derivatives) are not included here.Some of Howarth and coworkers' studies on the suitability of imidazolium salts as catalysts of the Diels–Alder reaction were attempted in the presence of *N*,*N*'-di-(2*S*)-2-methylbutylimidazolium bromide, which had been introduced by Welton and coworkers one year earlier; it was present in a catalytic amount and gave enantiomeric excesses < 5%.[308] Enantioselective Diels–Alder reactions in a chiral IL applied in solvent quantity were first attempted by Earle, Seddon, and P. B. McCormac in the same 1999 paper from which several of the examples of Diels–Alder reactions in Table 24 were taken.

They introduced [C_4mim][lactate], which did not give any detectable enantioselection in Diels–Alder reactions in it.[311] The conjugate base of such a weak acid was introduced by anion exchange from [C_4mim][Cl] with sodium lactate in acetone.

Wasserscheid and coworkers prepared chiral oxazolinium ILs from amino alcohols derived from amino acids, and chiral ammonium ILs derived from both (–)-ephedrine and (*R*)-2-amino-1-butanol. When one of the ILs derived from (–)-ephedrine was combined with the sodium salt of Mosher's acid in racemic form, the fluorine signals of the α-trifluoromethyl groups in racemic Mosher's acid salt were resolved in the ^{19}F NMR spectrum.[400] D. W. Armstrong and coworkers used some of these ILs in work on photoisomerizations of the Diels–Alder adducts from the reactions of anthracenes and acetylene dicarboxylate, and they added derivatives of (+)- and (–)-menthol, (*R*)-methylbenzylamine, and (2*S*)-(3-cyano-2-hydroxypropyl)trimethylammonium to the library; they achieved enantiomeric excesses up to 12%.[401] G. Vo-Thanh and coworkers added more derivatives to the (–)-ephedrine set with microwave syntheses of them,[402] and found that Diels–Alder reactions of Danishefsky's diene and chiral imines derived from α-methylbenzylamine in these ILs proceeded in up to 60% *de*, which was about twice as high as the diastereomeric excesses recovered with either no IL or an achiral IL.[403] Two years earlier this group had demonstrated the first enantioselective syntheses in ILs using only a chiral IL for enantioselection when they prepared Baylis–Hillman adducts in up to 44% *ee*.[404]

W. Leitner and coworkers examined Baylis–Hillman reactions in chiral ILs following Vo-Thanh and coworkers' precedent, and achieved enantiomeric excesses up to 84% using [$NC_{8\,8\,8\,1}$] ILs paired with asymmetric borate anions (Scheme 24).[405] The borate anions were prepared in > 99% yield by boiling an aqueous solution of boric acid, two equivalents of the

appropriate ligand, and one equivalent sodium hydroxide in an open flask. After the solvent had evaporated, the sodium borate salts derived from mandelic and malic acids (**28** and **29**, respectively) were obtained as diastereomeric mixtures.



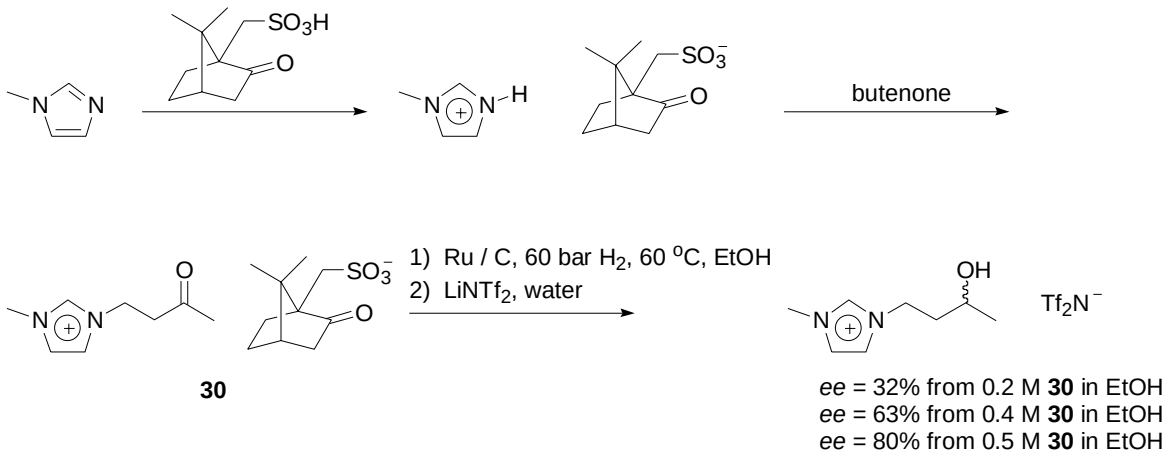
Scheme 24. An enantioselective Baylis–Hillman reaction from Leitner and coworkers providing the highest enantiomeric excess achieved when a chiral IL is the only chiral influence: 84%.[405]

Baylis–Hillman reactions in $[NC_{8\ 8\ 8\ 1}]$[**29**] gave low chemical yields, but the adducts from *N*-tosyl-4-bromo- and -methylbenzaldimine were recovered in enantiomeric excesses up to 84%, which the authors compared to enantiomeric excesses of 94 and 83% for other asymmetric Baylis–Hillman reactions in conventional solvents.[405] *N*-Tosyl-4-nitrobenzaldimine reacted to 10% *ee* under the same conditions. The reactions with $[NC_{8\ 8\ 8\ 1}]$[**27**] and [**28**] proceeded in lower chemical yields with no enantioselection. From this latter observation, the authors

surmised a Brønsted acid was necessary to direct the reaction, but add that the same reactions in tetrahydrofuran or dichloromethane in the presence of [$NC_{8\,8\,8\,1}$][**29**], its antecedent sodium salt, or the parent malic acid gave no enantioselection. In showing as much, they not only demonstrated the first highly enantioselective reaction in a chiral IL with no other source of chiral information, but that it is essential to perform this particular reaction *in* the IL.

Note that the authors performed anion exchanges to the [$NC_{8\,8\,8\,1}$] ILs by adding a solution of sodium **27**, **28**, or **29** in acetone to a solution of [$NC_{8\,8\,8\,1}$][Cl] in acetone. If it is true that these particular salts were freely soluble in acetone, this is a better than average example of anion exchange with an alkali metal in an organic solvent in that it is functionally similar to anion exchange with a heavy metal salt; the precipitation of sodium chloride from genuinely soluble salts would favor exchange to [$NC_{8\,8\,8\,1}$] ILs. Notwithstanding the fact anion exchange between salts freely soluble in acetone should be *more* efficient, these IL formulations surely could have benefited from more purification, but none was described beyond filtration of the sodium chloride precipitate and removal of acetone.

Wasserscheid, P. S. Schulz, and coworkers accomplished an enantioselective hydrogenation *of* a chiral IL with no other source of chiral information (Scheme 25).[406] They took this approach to demonstrate the chirality transfer possible when forcing the association of an achiral substrate and chiral information through ion pairing effects. As expected, the enantioselection of the reaction varied with the concentration of IL **30** in ethanol. They also note that the net change of methylimidazole to an IL like **30** to a chiral alcohol could be adapted to a broader synthetic method for the asymmetric reduction of ketones to chiral alcohols through a chiral auxiliary strategy if the imidazolium aspect could be removed.



Scheme 25. Reduction of a chiral IL by Wasserscheid and coworkers.[406]

Chiral ILs have also been applied to tasks in analytical chemistry. Armstrong and coworkers conceived of [C_4mim][Cl] containing cyclodextrins as chiral stationary phases for gas chromatography in 2001, and found that a few racemic compounds could be resolved by this mixture.[407] In 2004, Armstrong, Welton, and J. Ding reprised this example, showing chiral ILs could also function as a chiral selecting stationary phase in gas chromatography.[408] C. D. Tran and coworkers prepared chiral [NTf_2] ILs from the combination of aqueous solutions of lithium *bis*-triflimide and the commercially available enantiomers of (3-chloro-2-hydroxypropyl)trimethylammonium chloride—the (*S*) enantiomer of which is only ~4 USD / g. They recorded the CD spectrum of each enantiomer, showed these spectra did not change after 15 hours in an oven at 100 – 150 °C, and demonstrated these ILs could function as chiral resolving agents in NMR and in IR spectroscopy.[409]

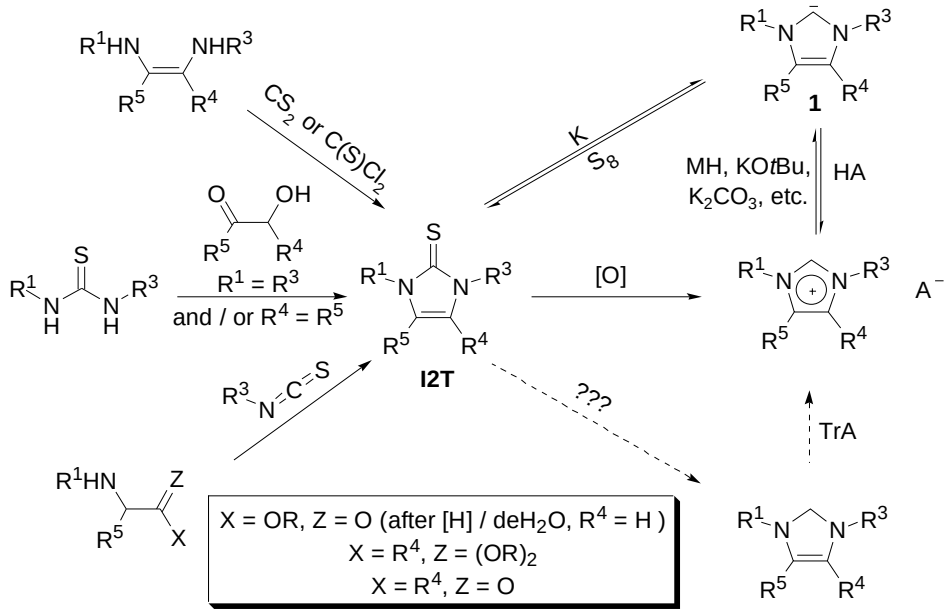
Conventional ILs have many uses, but the immediately preceding examples show new synthetic routes to ILs are necessary. Ionic liquids structurally manipulated for synthetic purposes within a few different paradigms are already known, and there can be no doubt that designed ILs can legitimately improve known synthetic methods. Classic ILs can be extended to

SILP reactions but, regardless of how some of these classes are delineated, the assembly of polymer supported ILs, ILs supporting reagents for ILSS, TSILs, and functionalized ILs demand synthetic effort, as do new chiral ILs. There has not been much attention paid to the development of new and creative syntheses for these new ILs. The current syntheses of designed ILs still revolve around a quaternization and anion exchange approach following the construction of either a required group bearing a leaving group or an elaborate imidazole (or both). If the design, synthesis, and utilization of structurally distinguished ILs is the frontier of IL chemistry, it follows that the development of synthetic methods delivering them is also, and it stands to reason that the value of new methods in the synthesis of ILs can only get greater.

One alternative synthesis of ionic liquids that has not yet been introduced here centers on the preparation and purification of an NHC **1** from an imidazolium salt. Earle and Seddon transformed 1,3-dialkylimidazolium halides to discrete NHCs **1**, which were distilled and then reprotonated to different ILs.[410] Maase and K. Massonne reported a similar process.[411] Ohno and coworkers synthesized [C_2mim] ILs based on natural amino acids. They used an anion exchange resin to convert [C_2mim][Br] to [C_2mim][OH], which was treated with an amino acid to generate the IL and water, the latter of which was removed under vacuum.[358] Circuitous as these routes seem, they are valuable in that they can provide ILs of higher purity and, because they proceed through potent bases in the form of NHCs **1**[144-147] or a hydroxide salt, they can incorporate a large number of anions. Instead of reprotonating NHCs **1** to ILs, they can also be reacted with electrophiles to introduce new functionality at C(2). Examples of such reactions are available in Table 4 and the surrounding text, and Handy and Okelo recently demonstrated the process in the context of IL synthesis.[47] The problem with these alternative IL syntheses is that

they require imidazolium salts be in hand at the outset; they can offer ILs diversified at C(2) or in the anion, but nowhere else.

A conversion of **I2T**s to ILs would be useful (Scheme 26). Provided no halogenated reagents are used, the IL products will be inherently halide free. Ideally, an all-organic reaction would lead to a product mixture with lipophilic impurities that could be washed from the IL product. Imidazole-2-thiones are all the more attractive for conversion to ILs since the method of assembly allows variation of the 1-, 3-, 4-, and 5-substituents,[412, 413] and this adaptability has an obvious bearing on expanding the library of IL cations, including chiral entries. Further, a variety of anions could be introduced depending on the method of **I2T** desulfurization. A reductive desulfurization to the carbene with elemental potassium[141] followed by treatment with acid, or an unprecedented route to the *gem*-diamine followed by oxidation should yield the desired IL. Regarding the latter, similar systems have been ionized with trityl tetrafluoroborate.[414] In this context, the only byproduct would be triphenylmethane and the inorganic contamination possible by other conceivable routes would be avoided. Oxidative desulfurizations of **I2T**s to imidazolium salts with hydrogen peroxide and an acid,[415-418] iron (III) chloride,[419] and nitric acid[420-422] are well known.[413] Dimethyldioxirane can be used,[423] and oxidation of an **I2T** with *m*CPBA in the presence of perchloric acid yields an imidazolium perchlorate directly.[424]



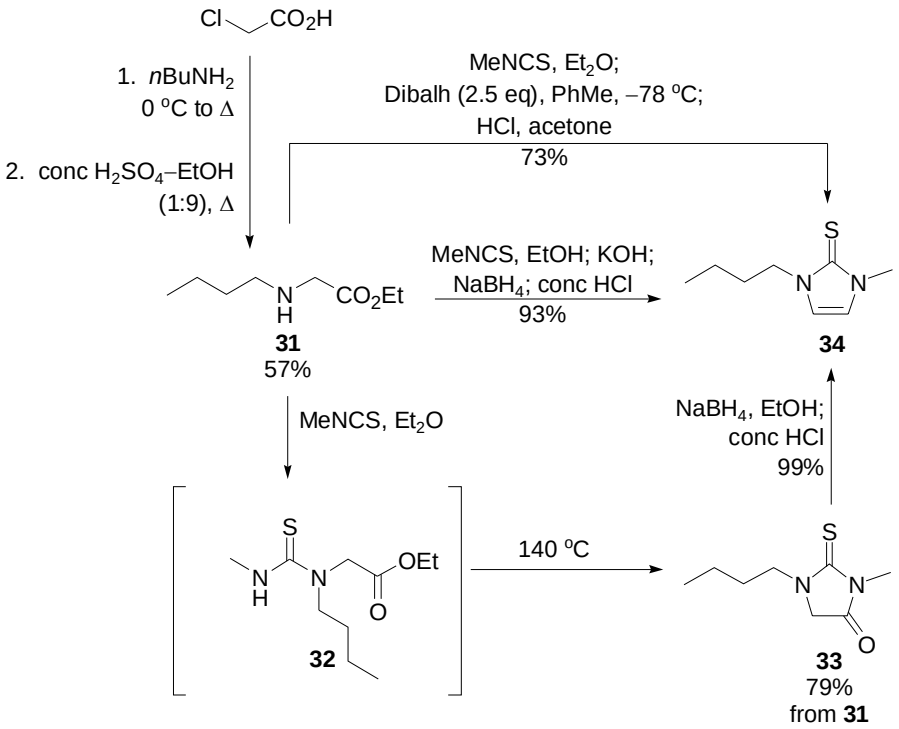
Scheme 26. Known and postulated routes to imidazolium salts through an **I2T**.

The installation of anions which could be exchanged with myriad acids on contact but which are not strong enough bases to raise any concern about populations of NHC **1** would be especially useful. Acetate and benzoate ILs are particularly appealing because the former could be distilled from a new IL product after acidification, and the latter could be removed by extraction with ether. Carboxylate ILs appeared sporadically throughout the preceding text, where they were prepared by the anion exchange of [C_4mim][Cl] and sodium lactate in acetone (to make [C_4mim][lactate]),[311] imidazole quaternizations with dimethyl carbonate ([C_2mim][$MeOCO_2$]),[68] and protonations of [C_2mim][OH][358] and NHCs **1**.[410, 411] Carboxylate ILs have also been made by heavy metal anion exchange (to make [C_2mim][OBz])[425] and microwave promoted anion exchange of [$C_n$mim][Cl]s and ammonium benzoate ([C_2mim], [C_4mim], and [C_6mim][OBz]).[426]

CHAPTER 2

OXIDATIVE DESULFURIZATION OF AZOLE-2-THIONES TO AZOLIUM SALTS WITH BENZOYL PEROXIDE

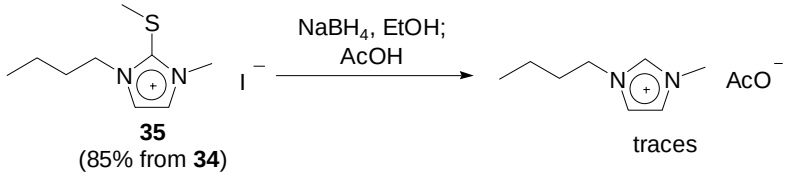
The synthesis of [C_4mim] ILs required 1-butyl-3-methylimidazole-2-thione (**34**), which was pursued using the monoreduction and cyclization of an α-thioureidoester (**32**) with Dibalh as described by J. A. Markwalder and coworkers.[427] The synthesis of ethyl *N*-butylglycinate (**31**) in 71% yield has been reported by the butylamination of ethyl α-bromoacetate in benzene.[428] The reaction of *n*-butylamine with chloroacetic acid and esterification of the residue left after distillation of the amine solvent gave the aminoester in 57% yield (Scheme 27). Following the reaction of **31** with methyl isothiocyanate, two singlets consistent with α protons were found by ^{1}H NMR spectroscopy, suggesting that some 2-thiohydantoin (**33**) had spontaneously formed. It seemed preferable to accomplish the thioureidation, reduction, and cyclization in one pot with excess Dibalh to account for any that may be destroyed by ethanol released in the incidental cyclization of **32** to **33**. 1-Butyl-3-methylimidazole-2-thione (**34**) was isolated in good yield after chromatography. This plan was changed upon finding that **32** completely cyclized to **33** thermally, that **33** was sufficiently electrophilic to undergo sodium borohydride reduction,[429] and that crude **33** could be used. Upon further refinement, it was found that cyclization proceeded more easily with ethanolic potassium hydroxide, which allowed a water-insensitive one pot synthesis of **34** from **31**.



Scheme 27. Syntheses of **34**.

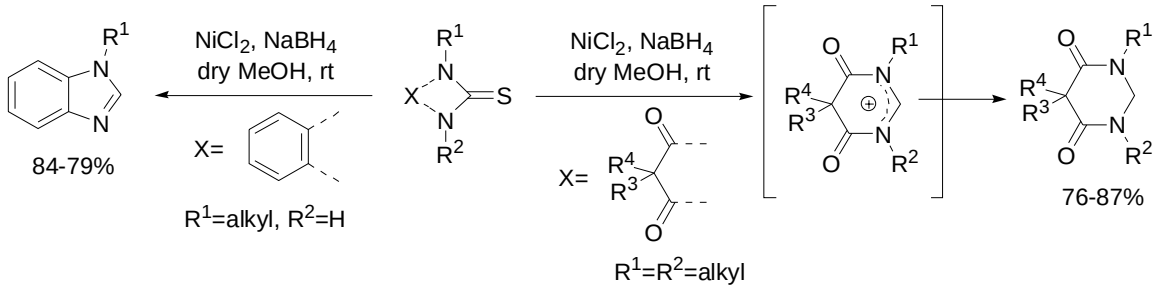
Three reductive desulfurizations of **34** were evaluated without success. Reduction with elemental potassium appeared to proceed as described by Kuhn,[141] but the isolate decomposed without releasing any product by distillation. Acidification of the residue with tetrafluoroboric acid left a brown solution unaffected by Celite, charcoal, silica gel, or aluminum oxide. G. Morel described several desulfurizations of azole-2-thiones, one of which was the reduction of a 2-methylthioimidazolium chloride to the imidazolium chloride with sodium borohydride.[430] After crystalline **35** was reacted with sodium borohydride in ethanol and quenched with acetic acid (Scheme 28), all solvents were distilled and the ^{1}H NMR of the residue revealed the characteristic imidazolium protons at $\delta > 7$ ppm. However, [C_4mim][OAc] could not be adequately purified from the ionic soup of [C_4mim], sodium, iodide, and acetate. Although a

proper IL was not secured by this approach, Morel's conversion of a 2-methylthioimidazolium salt to a crystalline imidazolium chloride could be useful to prepare other ILs in the future.



Scheme 28. Attempted synthesis of [C_4mim][OAc] from **35**.

J. M. Khurana and coworkers described reductive desulfurizations of various thiones with nickel (II) borohydride.[431] Thioureas were exhaustively cleaved to release free amines, whereas monoalkyl benzimidazole-2-thiones were converted to benzimidazoles and 2-thiobarbiturates yielded pyrimidinediones. The last two of these three conversions are shown in Scheme 29. Khurana and coworkers did not report reductions of simple dialkyl **I2T**s, so attempts at the reduction of **34** with nickel (II) borohydride departed from this precedent. However, their 2-thiobarbiturates presumably gave reductive desulfurizations through *N*,*N*'-dialkyl cationic intermediates, and a similar path could have been open for a desulfurization of dialkyl **I2T**s. Thus, it was expected that the reduction of **34** with nickel (II) borohydride would approximate the reduction of 2-thiobarbiturates and give a *gem*-diamine, but it was also conceivable that **34** could reduce to a [C_4mim] product or that the [C_4mim] product could deprotonate to give the carbene. In the event, there was no indication of any of these products in the product mixtures, and **34** was recovered in 28% yield.



Scheme 29. Representative reductive desulfurizations of thiones by Khurana and coworkers.[431]

Oxidative desulfurizations were attempted next. To prepare [C_4mim] carboxylates, hydrogen peroxide and, alternately, acetic or benzoic acid were selected for the process, giving identical results. In a variety of organic solvents (toluene, glyme, *p*-dioxane, di-*n*-butyl ether), a solution of **34** and acid was unresponsive to 30% hydrogen peroxide up to 80 ^{o}C. Even at this temperature a surprisingly large amount of peroxide (ca. 15 eq) was required before the yellow color of **34** was consumed and **34** could not be seen by TLC analysis of the reaction mixture. Following concentration, an immiscible layer could be formed and washed to constant weight with tetrahydrofuran. However, this putative [C_4mim] IL formulation was unacceptable for several reasons, primarily its stability. Upon standing at room temperature, the product, which was initially a very light yellow, darkened and released a precipitate. This decomposition was hastened when the sample was heated for drying, and prevented more thorough characterization.

Assuming residual hydrogen peroxide and acid were responsible for the decomposition, an oxidation of an **I2T** with an organic peroxide that could be washed from the final sample was a logical adaptation. With no precedent using one, benzoyl peroxide seemed appropriate. Compound **34** in toluene resisted oxidation by three equivalents of 75% benzoyl peroxide at 0 ^{o}C, room temperature, and reflux. After the gradual addition of two more equivalents of 75% benzoyl peroxide, however, the yellow color of **34** disappeared and it could no longer be

detected by TLC. Conventional workup and removal of water left an acidic light gold oil which presented only [C_4mim] signals in its ^{1}H NMR spectrum (Figure 8).

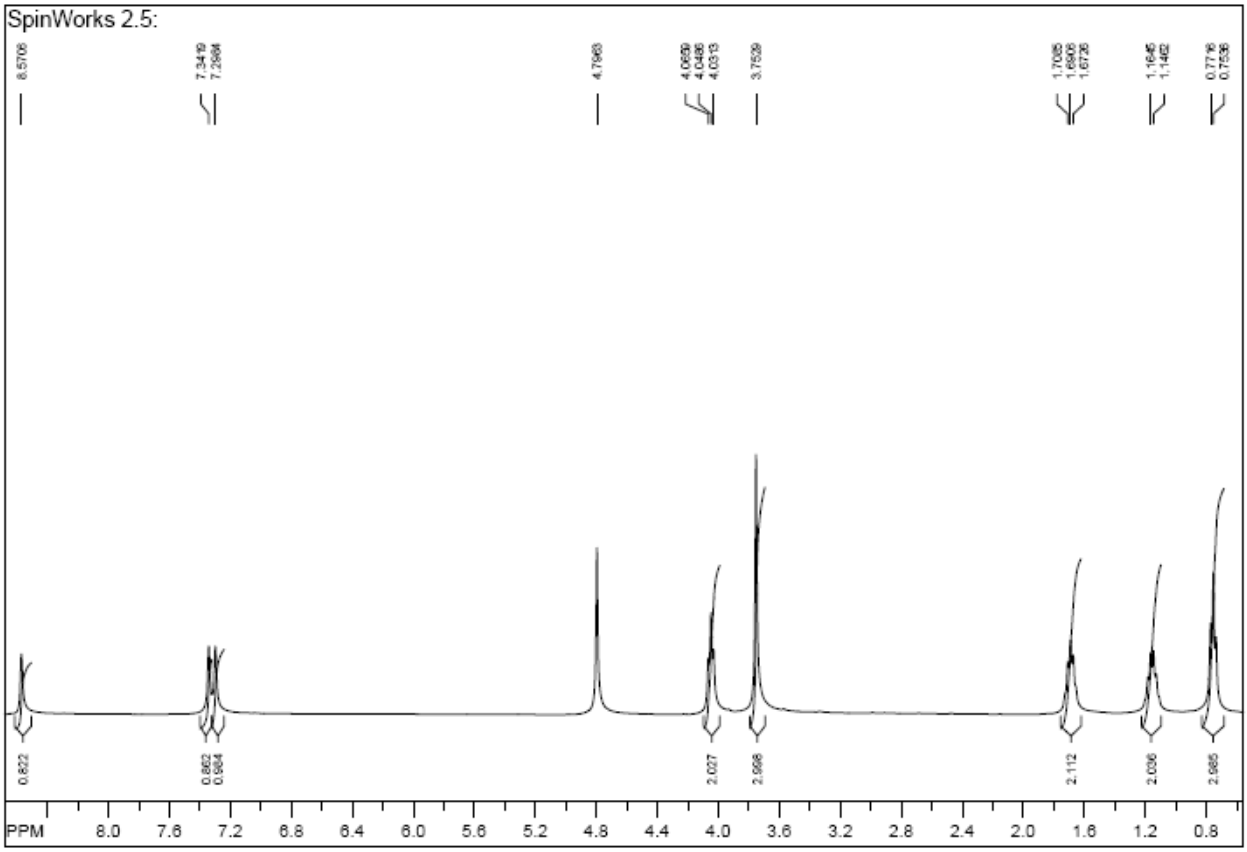
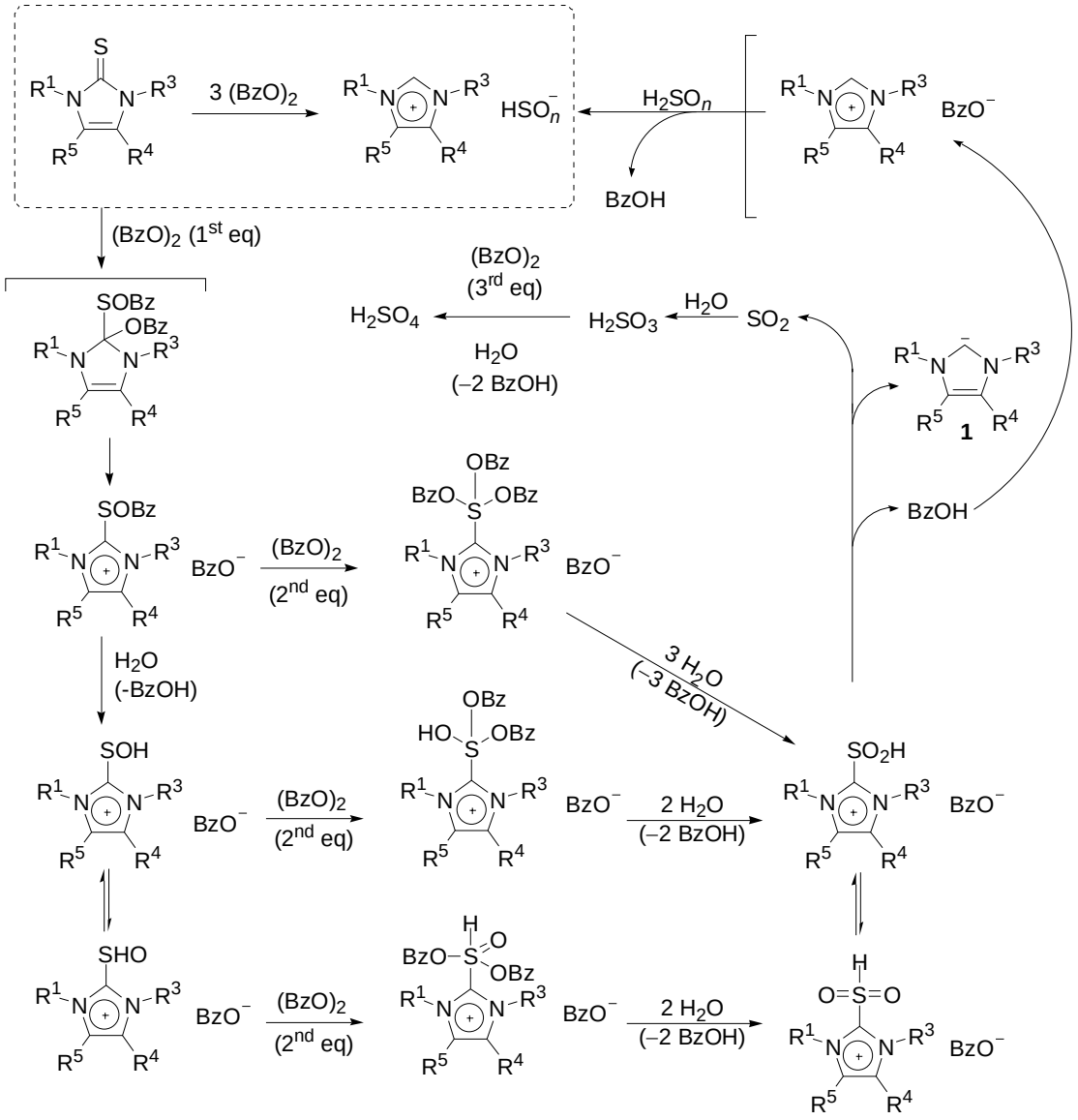


Figure 8. ^{1}H NMR spectrum of the isolate from the first successful oxidation of **34** with 75% $(BzO)_2$. A gold oil was returned after a conventional workup to remove organic soluble impurities followed by the distillation of water. The [C_4mim] cation is visible; the desired [OBz] anion is not.

The last step in the desulfurization likely proceeded via extrusion of sulfur dioxide from an intermediate imidazoliumsulfinic acid like the reaction with hydrogen peroxide.[413] Direct isolation of [C_4mim] as the [OBz] was most likely precluded by hydration of sulfur dioxide to

sulfurous acid, which can be oxidized by benzoyl peroxide to sulfuric acid. Either of these acids would exchange with benzoate to leave the bisulfite or bisulfate, which is a point more easily explained pictorially (Scheme 30). Considering that benzoyl peroxide is commonly employed as a free radical initiator, and that sulfur is known to give many reactions as a radical, a mechanistic rationale leading to the imidazoliumsulfinic acid starting with homolytic scission of benzoyl peroxide and addition of each radical to the thione is more believable than oxygen atom transfer. From there, further oxidation steps, hydrolyses, and collapse of tetrahedral carbon and sulfur intermediates can account for the formation of sulfuric acid and loss of benzoate from the product. This conceptualization also accounts for three of the five equivalents of benzoyl peroxide required by the reaction.

In this reaction, oxidation of sulfite to sulfate species must be nearly quantitative, because selected isolates did not respond to bromine. In a similar reaction, D. W. Karkhanis and L. Field report the isolation of 1,3-dimethylimidazolium bi- and methylsulfates from the oxidation of 1,3-dimethylimidazole-2-thione in methanolic hydrogen peroxide without mention of sulfite species.[417] Through further study, it was found that the addition of **34** to a stirred slurry of benzoyl peroxide in tetrahydrofuran brought the reaction to spontaneous reflux, dissolved benzoyl peroxide, obviated the need to supply heat, and required only 10 mL tetrahydrofuran for the reaction of 10 g 75% benzoyl peroxide with 1 g of **34**, but an anion exchange was necessary. The first attempt at anion exchange was treatment of an aqueous solution of the isolate with two equivalents sodium benzoate (based on the amount of **34** used). The expectation was that this amount of sodium benzoate would simultaneously neutralize bisulfate and supply the desired anion, and that [C_4mim] paired with the softer benzoate could be isolated from the mixture after

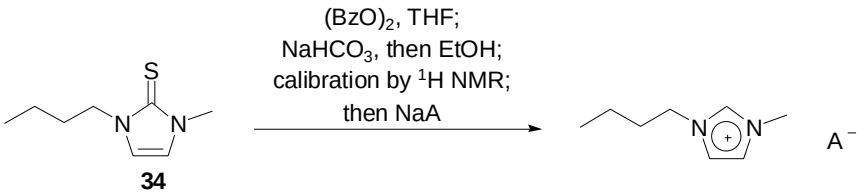


Scheme 30. Putative intermediates in the desulfurization of an **I2T** with $(BzO)_2$, and the mechanistic reason $[C_4mim][OBz]$ was not isolated.

filtration of benzoic acid and removal of water. A solid was isolated. Dupont and coworkers observed the separation of $[C_4mim][BF_4]$ from sufficiently concentrated aqueous potassium chloride,[45] so it seemed reasonable to expect that a $[C_4mim][OBz]$ layer could be forced from the aqueous mother liquor with saturated sodium benzoate. Diethyl ether was added to wash out

benzoic acid formed during the addition of saturated sodium benzoate to the acidic mother liquor, and did indeed reveal two aqueous layers, one rich in IL and another denser layer containing primarily inorganic salts. Unfortunately, the IL product still solidified after extraction with dichloromethane and concentration. It seemed likely these difficulties arose from the need to separate [C_4mim][OBz] from the excess sodium benzoate provided, and that careful application of a stoichiometric amount of sodium benzoate could lead to a more easily purified product.

Solving for the molar amount of [C_4mim] species per gram of solution by ^{1}H NMR prior to the addition of sodium benzoate seemed reasonable. Discoloration and, presumably, decomposition accompanied concentration of aliquots of the initially colorless, aqueous, acidic mother liquor from the benzoyl peroxide oxidation. It was found that sodium bicarbonate and sulfate were insoluble in 2 : 1 ethanol–water. The addition of sodium bicarbonate (1 eq based on **34**) to destroy the putative Brønstead acid byproduct (bisulfate) prior to concentration preserved the sample upon subsequent heating, and following that step with the addition of two volume equivalents of ethanol precipitated the majority of sodium salts. After filtration, an aliquot of the filtrate was concentrated, and spiked with dimethyl sulfoxide. Comparison of the integral of the [C_4mim] methyl proton resonance to the integral of the neatly resolved dimethyl sulfoxide singlet was used to solve for millimoles [C_4mim] species per gram of filtrate. After determination of [C_4mim] concentration with NMR, a stoichiometric amount of sodium benzoate was added to the remaining solution, which was still in 2 : 1 ethanol–water, and a second crop of sodium salts precipitated (Scheme 31, A = OBz).



Scheme 31. General approach to the preparation of [C_4mim] ILs from **5**.

The requirement for ethanol was surprisingly strict; the neutralized mother liquor was unaffected by tetrahydrofuran, *tert*-butyl alcohol, isopropanol, or acetone. While methanol and acetonitrile forced out some sediment, the dry weight of the salt removed by suction filtration was less than that precipitated with ethanol. Note that T. Bach and coworkers reported a similar anion exchange with thiazolium salts using 2 : 1 methanol–water to precipitate inorganic salts.[424] No additional solid was precipitated with more than two volume equivalents ethanol, and neither crop of precipitate gave any signals in the ^{1}H NMR spectrum. The calibration process also provided an estimate of the yield following oxidation, which could vary from 60 to 80%, but was typically > 70%. Concentration of the second filtrate prepared according to Scheme 31 left a suspension in need of further purification, the approach to which is addressed after making an observation on the relevance of this anion exchange to the larger body of IL preparation methodologies.

Recall the criticism of the simplistic view of anion exchange between IL precursors and alkali metals. In the vast majority of current examples of this approach to anion exchange, pure IL cannot be expected by simply washing a mixture of four ions with an organic solvent. The process can only lead to an ionic soup. In this new work alone, this point is borne out by the failure to recover [C_4mim][OBz] from excess sodium benzoate, or [C_4mim][OAc] from the reaction in Scheme 28. These examples should underscore the need to take some meaningful

steps towards the purification of an IL before it is used. At a minimum, washing a large concentrated solution of the IL product mixture in dichloromethane with several tiny portions of water[58] or repetitively cooling and filtering[57] a mixture following anion exchange is necessary. The precipitation of undesired anions as sodium salts from solutions of the product of **I2T** oxidation with benzoyl peroxide is functionally similar to the clean precipitation of heavy metal halides. Like the precipitation of heavy metal halides, precipitation of sodium sulfate and bicarbonate from the appropriate imidazolium and sodium salts in 2 : 1 ethanol–water follows the natural direction of precipitation, where two solutes release one precipitate as opposed to the release of one solute from two precipitates. In a partial survey of sodium salts, it turned out that chlorate, tetrafluoroborate, acetate, chloride, bromide, and trifluoroacetate were all soluble in 2 : 1 ethanol–water, so there was a great deal of latitude in the anion that could be introduced. Most significantly, anions not conveniently available as the acid, such as chlorate, could be supplied.

Note that a preparation of $[C_1mim][ClO_3]$ is introduced later. This material survived concentrations at 60 ^oC before and after it was purified according to the method developed below. There was a detonation in an unoccupied lab several weeks after it was first prepared that was apparently caused by this chlorate. The rack holding it and other samples was destroyed, and the side shield of the fume hood where the samples were stored was crushed through to the wall (Figure 9). The glass shield was approximately one-quarter inch thick. A sample of $[C_4mim][ClO_3]$ was stable for several months, but no one reading this should attempt to reproduce the syntheses of the $[ClO_3]$ ILs.

Figure 9. The glass side shield of a fume hood and an oak rack destroyed by a detonation of $[C_1mim][ClO_3]$.

Unlike anion exchange through the precipitation of heavy metal halides, this method precipitates a mixture of sodium sulfate and bicarbonate of unknown constitution, and the dry weight of the precipitate does not directly indicate the extent of anion exchange. However, the concentration of [C_4mim] species determined in the calibration step could be used to solve the theoretical yield of sodium sulfate and the excess mass of sodium bicarbonate that was supplied prior to calibration. The sum of these masses is the total amount of sodium salt contaminants, and numerous selected precipitates from the anion exchanges described below were dried to constant weight and returned at least 80% of the expected dry mass.

To remove the remaining contaminants, all the normal adsorbents used for the final purifications of ILs were considered. Silica gel chromatography (SGC) in particular appeared suitable for the purification of IL samples prepared according to Scheme 31 because the concentrate from the reaction mixture at the stage of NMR calibration should contain only [C_4mim] and sodium cations paired with sulfate and bicarbonate, and it was immobile on silica gel, even with ethanol as the eluent. The desired combinations of [C_4mim] and supplied anions were expected to be separable from other combinations of ions, although the effect of the desired ILs on the mobility of undesired ions could not be known. Because there are no convenient standards for the assessment of IL purity, one had to be developed to compare the suitability of both different anions to the anion exchange and different approaches to final purification.

Solving for total millimoles [C_4mim] species per gram of sample with a dimethyl sulfoxide spike just as in the calibration step was straightforward. However, with no convenient way to confirm all [C_4mim] species were paired with the intended anion (except for [C_4mim][OBz]), this number could only be used to find the possible range of [C_4mim] content by mass, which is reported as % IL in Table 27. These ranges necessarily start from the

multiplicative product of the millimolecular weight of the lighter (or lightest) reasonable [C_4mim] product (on a per [C_4mim] basis) and millimoles total [C_4mim] species, and run to the multiplicative product of the millimolecular weight of the effectively heavier (or heaviest) reasonable [C_4mim] product. In the reactions reported, [C_4mim]$_2$[SO_4] (MW = 374.50, 187.25 on a per [C_4mim] basis) is the lightest combination of [C_4mim] and an available anion in all cases except the synthesis of [C_4mim][Cl] (MW = 174.67). In that case, the low end of the range is actually the highest possible content of *desired* IL. In all cases, yields are reported on the basis of total *millimoles* [C_4mim] species recovered, *not mass*, and are single numbers *inherently corrected for purity*. The anion exchanges proceeded almost quantitatively (see Experimental Section), so the reported numbers principally reflect the yield of the benzoyl peroxide oxidation. This approximation was used to describe every IL formulation except [C_4mim][OBz], where the integrals of the anion resonances in the ^{1}H NMR spectrum leave little room for [C_4mim] paired with any other anion and IL content is reported as a single number. The maximum IL content of [C_4mim][ClO_3] isolated by Method F actually solves to 101%, which is more believable as cumulative experimental error than as an inherent flaw in the method of analysis. Despite reference to "chromatography", note that the amount of silica gel required was only 5 g silica gel (230 – 400 mesh) per 2 g crude IL in all cases. The products were recovered in bulk elutions of 30 to 50 mL per 2 g crude IL (except in Method C). Based on the dry masses of precipitates described earlier, the content of undesired [C_4mim] should be very low, and the content of desired IL should lie far to the high (low for [C_4mim][Cl]) end of the range, but confirming that suspicion will require new methods of analysis for ILs.

Table 27. Approximate Purities of [C_4mim] ILs prepared according to Scheme 31.[a]

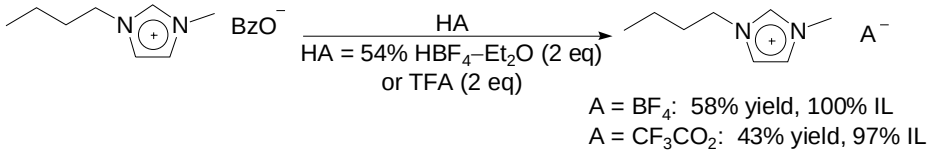
	Method of Purification											
	A		B		C		D		E		F	
A^-	% IL[b]	Yield[c]	% IL[b]	Yield[c]	% IL[b]	Yield[c]	% IL[b]	Yield[c]	% IL[b]	Yield[c]	% IL[b]	Yield[c]
BzO	84	56	70	35	84	30	78	52	98	50	98 96[e]	61[d] 46[d,e]
ClO_3	63–75	41	65–77	25	60–71	37	49–58	38	59–70	32	62–75 85–100[e]	59[d] 58[d,e]
BF_4	68–82	49	75–91	48	62–75	36	47–57	32	65–79	32	65–79	51[d]
AcO	58–61	32	--	--	--	--	48–51	46	53–56	46	--	--
Cl	65–70	37	--	--	--	--	52–56	49	63–68	49	--	--
Br	--	--	--	--	--	--	--	--	--	--	81–95	86[f]
CF_3CO_2	--	--	--	--	--	--	--	--	--	--	62–83	76[f]

[a]Key to methods: A = SGC in EtOH; B = A, then treatment with Celite in DCM; C = SGC with a solvent gradient from Et_2O to THF to EtOH; D = addition of 1 : 1 Et_2O–EtOH, refiltration; E = D then SGC in 1 : 1 Et_2O-EtOH; F = SGC in 1 : 1 Et_2O-EtOH. [b]IL content, as total grams [C_4mim] species per 100 g sample. [c]From **34** in every instance, *corrected for total IL content*. Salts in each column (method) were prepared by anion exchange from the same oxidation mother liquor, except Method F. [d]Yield from **34** following anion exchange from an oxidation proceeding in 62% yield. [e]Purity and yield after a second SGC step in 1 : 1 Et_2O–EtOH. [f]Yield from **34** following anion exchange from an oxidation proceeding in 98% yield.

Elution of the crude isolates over silica gel with ethanol returned [C_4mim][OBz], [BF_4], and [ClO_3] in roughly 40 – 60% yield and 60 – 80% IL content (Method A) as clear light gold, light brown, and brilliant yellow liquids, respectively. Dissolution of these in dichloromethane and treatment with Celite (Method B) gave mixed results. The tetrafluoroborate was purified, the chlorate was essentially unchanged, and the benzoate was actually tainted, though this could be an effect of loss of IL to Celite, which was seen in all cases by decreased yields from **34**. To see if impurities more chromatographically mobile than the ILs could be removed, new isolates were subjected to SGC with a solvent gradient (Method C). Fractions containing IL products were identified by TLC in ethanol, where the IL manifested as a streak from the origin after visualization with PMA (UV_{254} for [C_4mim][OBz]). Aside from the absence of IL product in fractions collected with less polar eluent, there were no discernable differences in any fractions by TLC or in selected fractions by ^{1}H and ^{13}C NMR spectroscopy. When fractions containing IL product were combined, their IL content was no higher than those from Method A. Failure to detect an organic impurity by Method C and the similar IL contents from Methods A – C indicated the major contaminants were inorganic salts and / or silica gel coeluting with IL in ethanol. Fresh isolates were treated with 1 : 1 diethyl ether–ethanol and precipitates formed. When separated from the sediment simply by suction filtration, the dried formulations had lower IL contents than after Method A without exception (Method D, another testament to the difficulty of recouping IL from a mixture of insoluble salts). The ILs were usefully mobile for SGC in 1 : 1 ether–ethanol, and eluting the filtrates from Method D over silica gel with 1 : 1 ether–ethanol (Method E) took the values of IL contents up to levels rivaling those from Method A, except in the case of [C_4mim][OBz], which was significantly purer by this method. New isolates from the oxidation were suspended in 1 : 1 ether–ethanol, loaded on a short column with

their associated precipitates, and recovered with the same solvent system (Method F). Ionic liquids of similar or better IL content than Method E were recovered, and [C_4mim][OBz] was still the purest isolate. The lackluster chloride and acetate were replaced by the bromide and trifluoroacetate to see how softer anions behaved in the emerging method.

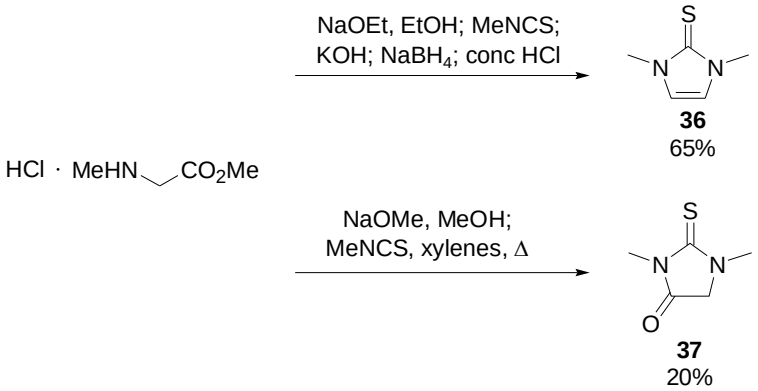
Table 27 demonstrates the ultimate success of the oxidation and anion exchange sequence depends strongly on the supplied anion, which makes acidifications of [C_4mim][OBz] to other ILs all the more necessary. Acidification of [C_4mim][OBz] with aqueous tetrafluoroboric acid followed by chromatography without first removing water was unsuccessful; distillation of water led to decomposition. Treatment of [C_4mim][OBz] with this acid in diethyl ether did not require distillation of water, and gave a solution that could be eluted over silica gel in diethyl ether to two endpoints. First until the issue was not responsive to UV light when spotted on a silica gel plate (signifying the removal of benzoic acid), and second until the issue was not acidic (signifying the removal of excess tetrafluoroboric acid). Colorless [C_4mim][BF_4] was then washed off with 1 : 1 diethyl ether–ethanol; colorless [C_4mim][CF_3CO_2] was similarly obtained as a mobile liquid (Scheme 32). In both cases an excess of the acid was applied to destroy any residual bicarbonate species. Ionic liquid content is reported as a single number since these ILs derive from [C_4mim][OBz], and solves to 101% for [C_4mim][BF_4], which is again attributed to experimental error in what should be a very pure sample.



Scheme 32. Preparation of [C_4mim][BF_4] and [CF_3CO_2] from [OBz].

Treatment of [C_4mim][OBz] with concentrated aqueous hexafluorophosphoric acid did not generate a separate [C_4mim][PF_6] layer, even upon standing for several days. A small amount of very low quality IL separated from saturated aqueous potassium hexafluorophosphate when stirred with aqueous [C_4mim][OBz] for several days; washing the sample with fresh water left only an impure specimen from which no IL was recovered after SGC. The last experiment in the [C_4mim] series was an attempt to convert [C_4mim][OBz] to [OAc]. Percolation of an aqueous solution of [C_4mim][OBz] and an excess of acetic acid with diethyl ether slowly removed benzoic acid; it was necessary to periodically refresh the supply of acetic acid until the returned ether no longer contained benzoic acid. Unfortunately, the IL recovered after removal of water had decomposed and tenaciously retained a large amount of acetic acid.

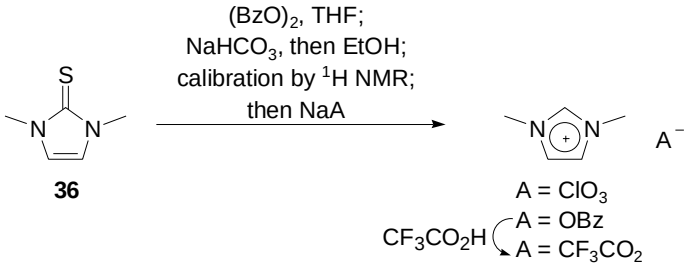
The oxidation and anion exchange protocol thus developed was extended to the synthesis of [C_1mim] ILs. Arduengo and coworkers described the preparation of 1,3-dimethylimidazole-2-thione (**36**) by treating [C_2mim][I] with potassium carbonate and elemental sulfur as exemplified in Schemes 5 and 27.[149] Based on the synthesis of **34**, **36** was made in one pot from methyl sarcosinate hydrochloride after neutralization with fresh sodium ethoxide (Scheme 33). The intermediate hydantoin (**37**) could be isolated in poor yield.



Scheme 33. Syntheses of **36** and **37**.

Compound **36** was much more sensitive to the conditions of oxidation than was **34**. Calibration of the [C_1mim] content following oxidation revealed yields on the order of 30 – 40% unless the temperature was carefully controlled with an ice bath, in which case the yield exceeded 80%. The rest of the process for [C_4mim] IL synthesis (Scheme 31) was extended to [C_1mim] ILs without alteration (Table 28).

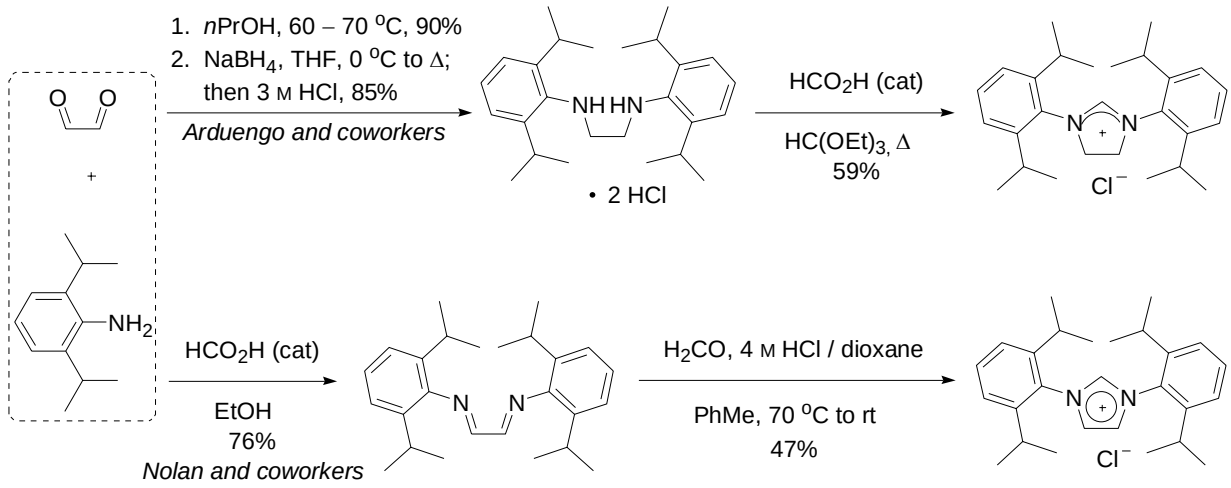
Table 28. Preparation of [C_1mim] ILs from **36**.



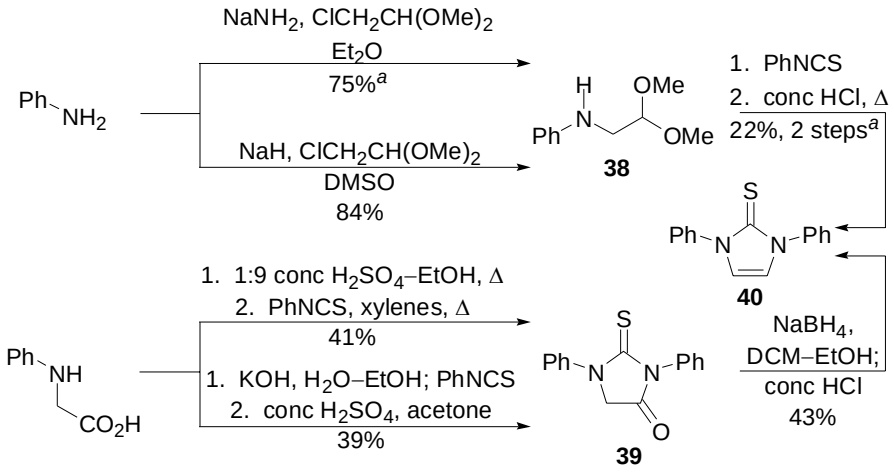
A	% IL[a]	Yield[b]
OBz	77	58
	73[c]	37[c]
ClO_3	68 – 85	60
	70 – 88[c]	41[c]
CF_3CO_2	85[d]	75[d]

[a]IL content, as total grams [C_1mim] species per 100 g sample. [b]From an oxidation of **36** proceeding in 85% yield, *corrected for total IL content*. [c]Yield and % IL after a second chromatographic step. [d]Yield and % IL from once chromatographed [C_1mim][OBz].

1,3-Diphenylimidazolium ([dpim]) salts were also accessible without much adaptation. 1,3-Diarylimidazolium and -inium salts are usually prepared by condensing two equivalents of an aromatic amine with glyoxal or another 1,2-dicarbonyl compound, and condensing the diimine product with formaldehyde, an orthoformate, or an alkyl chloromethyl ether (Scheme 34).[132, 432] Wanzlick and H. J. Schönherr alkylated aniline with chloroacetaldehyde dimethylacetal under the influence of sodium amide in diethyl ether, reacted the product acetal (**38**) with phenylisothiocyanate, and cyclized the intermediate α-thioureidoacetal with acid to make 1,3-diphenylimidazole-2-thione (**40**) in 17% yield over three steps (Scheme 35).[134] In this pursuit of [dpim] salts, **38** was prepared with the same organic reagents, except they were reacted under the influence of sodium hydride in dimethyl sulfoxide. With **38** in hand, however, it could not be converted to **40** using Wanzlick's conditions. Note that Wanzlick and Schönherr also alkylated aniline with chloroacetaldehyde diethylacetal, and carried it through to **40** in 45% total yield, which demonstrates that **39** is not an ideal precursor to **40**. It is odd, however, that no **40** could be recovered from **38** in this context.



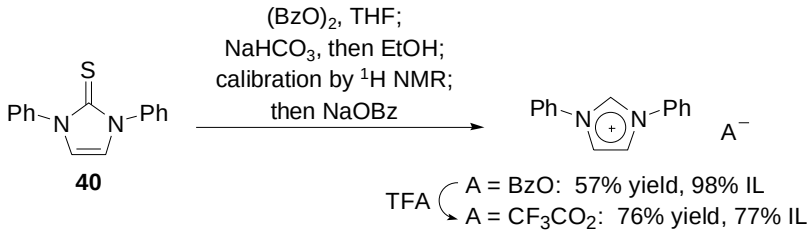
Scheme 34. Representative syntheses of 1,3-diarylimidazolium and -inium salts by Arduengo and coworkers,[132] and by Nolan and coworkers.[432]



Scheme 35. Syntheses of **40**. [a]Conditions and yields for these conversions come from Wanzlick and Schönherr.[134]

Based on the successful syntheses of **34** and **36**, syntheses of **40** from commercial *N*-phenylglycine were attempted. The commercial material arrives in 95% purity as a brown powder with visible heterogeneities, so two approaches were attempted to see if one was better suited to purify the crude reagent by degrees on the way to [dpim] salts. First, *N*-phenylglycine was subjected to a Fischer esterification, and the crude product reacted to **39** with phenyl isothiocyante. Second, based on Johnson and Buchanan's synthesis of 1-methyl-2-thiohydantoin,[433] *N*-phenylglycine was dissolved in aqueous ethanolic potassium hydroxide and acylated with phenyl isothiocyanate. The putative intermediate α-thioureidoacid was precipitated by the addition of aqueous acid, taken up in acetone and dried, then cyclized in low yield by the addition of sulfuric acid, which is likely the result of competitive *S*-alkylation in the acylium intermediate.[434-436] The specimens of **39** secured by either route were indistinguishable by TLC and IR, ^{1}H, and ^{13}C NMR spectroscopy. The melting point of **39** after Fischer esterification was only a few degrees lower and broader than **39** accessed via the α-thioureidoacid. These similarities carried over to **40** following sodium borohydride reduction.

However, [dpim][OBz] prepared from **40** following Fischer esterification contained an impurity that was not sufficiently removed by SGC and four crystallizations, all of which required hot gravity filtrations. On the other hand, **40** prepared from the α-thioureidoacid delivered [dpim][OBz] freed from heterogeneities after silica gel filtration and three crystallizations, only the first of which required a hot gravity filtration (Scheme 36).



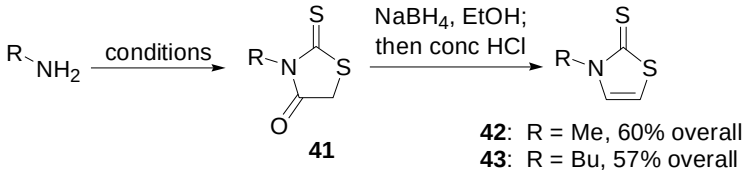
Scheme 36. Syntheses of [dpim] salts.

The final azole-2-thiones converted to azolium salts by this method were thiazole-2-thiones. Virtually all work on thiazolium salts has been on derivatives of 5-(2-hydroxyethyl)-4-methylthiazole, a subunit of vitamin B_1 (thiamin) and popular catalysts for the benzoin and Stetter reactions.[364-366] In the context of IL chemistry, F. Pizzo, L. Vaccaro and coworkers recently prepared a pair of thiazolopyridinium ILs,[437] Davis and K. J. Forrester prepared *N*-butyl-4- and -5-methylthiazolium tetrafluoroborates,[438] M. Deetlefs and Seddon prepared *N*-butyl, -hexyl-, and -octyl-4-methylthiazolium bromides and iodides,[50] and A. C. Gaumont and coworkers have prepared thiazolinium salts derived from the chiral pool.[224] In their paper, Deetlefs and Seddon call their *N*-alkyl-4-methylthiazolium cations "[$C_n$mtz]", and it follows the 4-unsubstituted compounds prepared as follows should be termed "[$C_n$tz]".

Thiazole-2-thiones are classically prepared by alkylating an *N*-alkylthiocarbamate (formed in solution from an amine and carbon disulfide) with an α-halocarbonyl compound, and

cyclizing the substitution product with acid.[439-442] Reactions of the appropriate amine, carbon disulfide, and chloroacetaldehyde delivered crude mixtures of **42** and **43** that did not suitably carry through the oxidation. No reaction took place between the intermediate *N*-alkylthiocarbamates formed in solution and chloroacetaldehyde dimethyl acetal, even in refluxing acetonitrile. Chloroacetic acid readily accepted the *N*-alkylthiocarbamate nucleophiles, however, and the rhodanine intermediates[443, 444] were accessed by a one pot synthesis. Whereas these intermediates resisted bulk purification, **42** and **43** were easily sublimed and distilled, respectively, and purification was deferred until the crude isolates were reduced and dehydrated (Table 29).

Table 29. Syntheses of **42** and **43**.



R	conditions	crude yield **41**
Me, HCl	NaOH (2 eq), water; then CS_2 (1 eq); then aq KO_2CCH_2Cl (1 eq); then conc H_2SO_4	77%
Bu	K_2CO_3 (0.5 eq), CS_2 (1 eq), MeOH; then KO_2CCH_2Cl (1 eq), MeOH; then conc H_2SO_4	94%

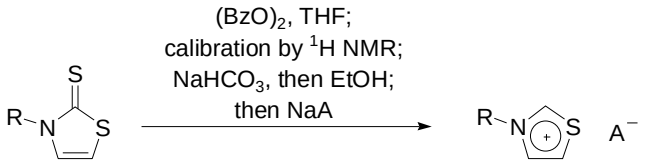
Oxidation of **42** and **43** to their thiazolium salts required some operationally trivial but chemically significant modifications to the existing process. When the aqueous oxidation mother liquor was treated with sodium bicarbonate, then ethanol, and an aliquot of the filtrate was concentrated for ^{1}H NMR calibration, the specimens turned pink and no [C$_n$tz] species were

visible in the spectra. The pK_a values of thiazolium C(2) protons have been reported as 17 to 19 in deuterium oxide[445, 446] and as 12.9 (for vitamin B_1) in methanol.[447] Although these values are several orders of magnitude higher than the pK_a of carbonic acid in water (3.6), the decomposition is likely the result of carbene dimerization, which does not require quantitative conversion of salt to carbene to complete.[448]

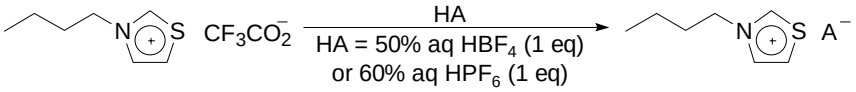
These salts were stable when the acidic mother liquor was concentrated, however, so the method was easily adapted to put the concentration and calibration step before the basification step. After seeing how easily these salts could be destroyed by base, the calibrated [C$_n$tz] content was also used to limit the amount of bicarbonate supplied to one equivalent against putative [C$_n$tz][HSO_4] (Table 30). Successful isolations of azolium benzoates (or other simple carboxylates) seemed unlikely since the pK_a of benzoic acid is 4.2 in water, but for completeness these exchanges were attempted; total [C$_n$tz] species decreased at each measurement from the calibration to each concentration following two SGC steps. Poorly basic anions which were adequate for direct anion exchange in the [C_4mim] series (bromide, tetrafluoroborate, and trifluoroacetate) could be successfully paired with the [C$_n$tz] cation. After purification of the exchanged salts in the usual manner during the early experiments, it was found that, in addition to any inorganic contaminants invisible by ^{1}H and ^{13}C NMR spectroscopy, these crude isolates contained highly colored, comparatively mobile impurities that could be removed by SGC in tetrahydrofuran to a visible endpoint. Thus, following calibration, basification, anion exchange, filtration, and concentration, the [C$_n$tz] salts were slurried in tetrahydrofuran, loaded on a short silica gel column, eluted to a visible endpoint to remove the highly colored impurities, and then the desired salt was collected with 1 : 1 ether–ethanol. Skipping the first chromatography step returned [C$_n$tz] formulations with roughly 50% IL content. Note that the same three anions were

deployed across both oxidized thiazole-2-thiones, but $[C_1tz][CF_3CO_2]$ decomposed upon isolation, and the $[BF_4]$ was lost to the initial tetrahydrofuran eluent. Of course, a formulation of $[C_1tz][BF_4]$ containing around 50% desired IL could be isolated by skipping elution with tetrahydrofuran during SGC. Having seen hot aqueous acid was well tolerated by the thiazolium salts during concentration for calibration, aqueous acids were used to convert $[C_4tz][CF_3CO_2]$ to $[BF_4]$ and $[PF_6]$ (Scheme 37).

Table 30. Synthesis of $[C_1tz]$ and $[C_4tz]$ salts via oxidation and anion exchange.



R	A	% IL	Yield
Me	Br	73 – 89	12
Bu	Br	99 – 100, not more than 9.6% as $[C_4tz][Br]$	26
Bu	BF_4	77 – 92	10
Bu	CF_3CO_2	82 – 100, not more than 72% as $[C_4tz][CF_3CO_2]$	41



A = BF_4: 72% yield, 82 – 99% IL content
A = PF_6: 45% yield, 75 – 100% IL content,
not more than 75% as $[C_4tz][PF_6]$

Scheme 37. Acidification of $[C_4tz][CF_3CO_2]$ to $[BF_4]$ and $[PF_6]$.

The IL contents of $[C_4tz][Br]$, $[CF_3CO_2]$, and $[PF_6]$ had upper bounds of 115, 110, and 112 g IL per 100 g sample, respectively, by the first approximation. These purity approximations seemed too impossibly massive to dismiss as cumulative experimental error, so a second approximation was put into use to report their IL content as the maximum amount of $[C_4tz][Br]$, $[CF_3CO_2]$, and $[PF_6]$. This second approximation relied on several variables (Chart 1). Lower case letters denote millimolar amounts (*m*, *x*, *y*), and capital letters denote absolute masses (M, N) and effective millimolecular masses (A, B). Three simple equations follow naturally from these definitions (Eqs. 9 – 13), but they are not enough to exactly solve four unknowns (*x*, *y*, M, N). If only they were, better approximations of the populations of the heaviest and lightest IL species and of extraneous impurities in all the IL formulations prepared thus far would be possible. Since the minimum value of N is zero, the solutions for *x* or *y* at this value (Eqs. 13) give the maximum value of *x* and minimum value of *y*. The lower bound on IL content is still the maximum mass of the lightest reasonable azolium species (in these instances, $[C_4tz]_2[SO_4]$, MW / 2 = 190.28), which is B*m* at *x* = 0. These corrections return an IL content range and an upper bound on desired IL content, as used in Table 30 and Scheme 37.

m = total mmoles azolium species per 1.0 gram sample

x = total mmoles heavi(er)(est) IL

y = total mmoles light(er)(est) IL

M = total mass azolium species

N = total mass non-IL impurities ≥ 0

A = ((MW heavi(er)(est) IL) / (1000 × [azolium cations] per molecule)) > B

B = ((MW light(er)(est) IL) / (1000 × [azolium cations] per molecule)) < A

Chart 1. Definition of variables used in the second purity approximation for impossibly massive solutions to IL contents.

$$m = x + y \tag{9}$$

$$\mathrm{M} + \mathrm{N} = 1 \tag{10}$$

$$\mathrm{M} = \mathrm{A}x + \mathrm{B}y \tag{11}$$

$$\mathrm{N} = 1 - \mathrm{A}x - \mathrm{B}m + \mathrm{B}x \tag{12x}$$

$$\mathrm{N} = 1 - \mathrm{B}y - \mathrm{A}m + \mathrm{A}y \tag{12y}$$

$$\text{At N} = 0 : \; y_{\min} = (1 - \mathrm{A}m) / (\mathrm{B} - \mathrm{A}) \tag{13x}$$

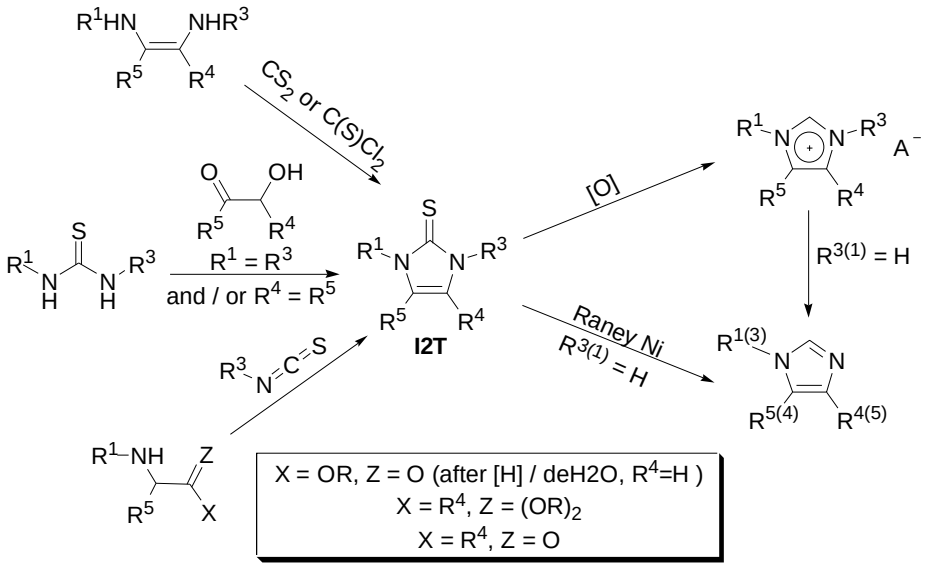
$$\text{At N} = 0 : \; x_{\max} = (1 - \mathrm{B}m) / (\mathrm{A} - \mathrm{B}) \tag{13y}$$

Should the corrections introduced in the [$C_n$tz] series have been applied to the two imidazolium entries solving to > 100% IL content? The overly massive [C_4mim][BF_4] formulation derived from a benzoate with 98% IL content. Although the product is of lower molecular weight, and the specimen of [C_4mim][BF_4] made by acidification could have accumulated extraneous impurities, and consequently returned a *lower* IL content by mass, it is unreasonable to expect the sample would have somehow taken on undesired [C_4mim] salt from somewhere. Hence, [C_4mim] must exist almost entirely as [BF_4] in that formulation, the inflated solution notwithstanding. For [C_4mim][ClO_3], the second approximation puts the maximum [C_4mim][ClO_3] content at 95%.

CHAPTER 3

OXIDATIVE DESULFURIZATION OF 1-ALKYLIMIDAZOLE-2-THIONES TO NEUTRAL IMIDAZOLES WITH BENZOYL PEROXIDE

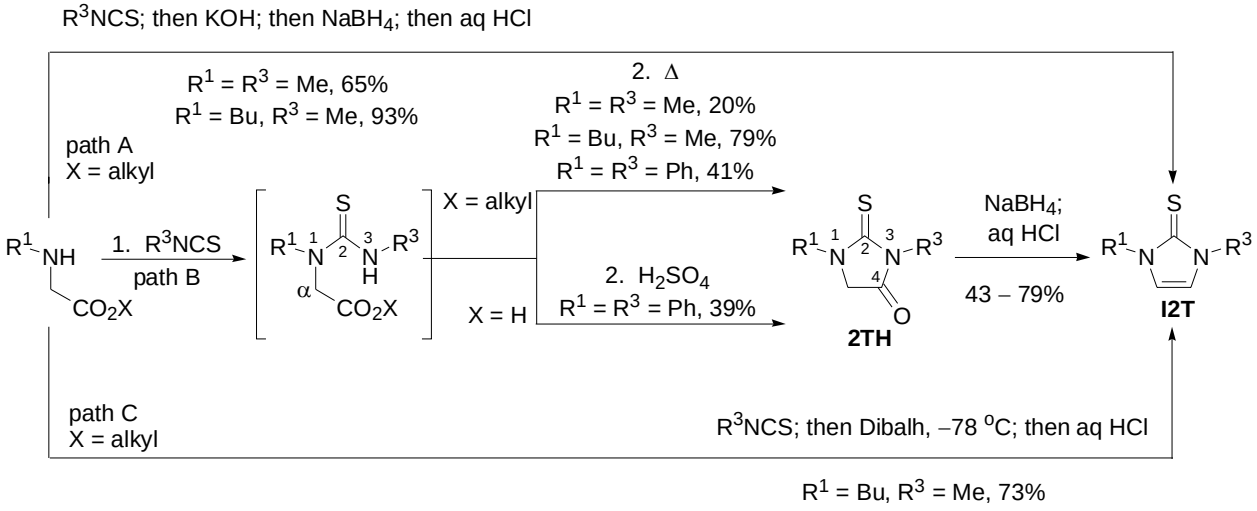
Scheme 26 related simple building blocks to imidazolium salts and NHCs **1** through 1,3-dialkyl **I2T**s. The same oxidative desulfurizations can be considered for the assembly of neutral imidazoles through 1-alkyl instead of 1,3-dialkyl **I2T**s (Scheme 38). Elemental potassium reductively desulfurizes 1,3-dialkyl **I2T**s to NHCs **1**, but it does not give imidazoles from 1-alkyl **I2T**s. Raney nickel does.[412, 413, 449, 450] The significance of the imidazole core in natural products and medicinal chemistry has been the subject of recent reviews.[451-454]



Scheme 38. Scheme 26 revisited: Major routes to imidazoles through **I2T**s.

The methods used to access **I2T**s in the previous chapter are summarized in Scheme 39. Path A recounts the two examples of one pot air- and water-insensitive syntheses of 1,3-dialkyl

I2Ts from aminoesters. Path B starts with the acylation of an α-aminoester or -acid, then splits to show the three examples of thermal cyclizations of α-thioureidoesters (X = alkyl) to 2-thiohydantoins (hereafter called **2TH**s) alongside the one example of an acid catalyzed cyclization of an α-thioureidoacid (X = H, R^1 = R^3 = Ph) to a **2TH**. Path C is the one pot synthesis of an **I2T** from an aminoester using the Dibalh reduction of α-thioureidoesters introduced by Markwalder and coworkers.[427] Each of these routes figured to deliver 1-alkyl **I2T**s for oxidative desulfurization to neutral imidazoles with benzoyl peroxide.



Scheme 39. Syntheses of 1,3-dialkyl **I2T**s used on the way to 1,3-dialkylimidazolium salts.

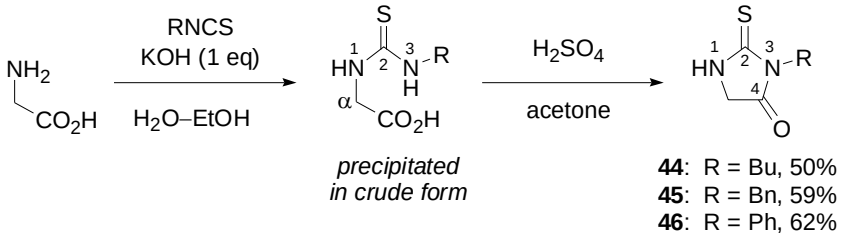
The prospect of an imidazole synthesis by the oxidative desulfurization of an **I2T** furnished by the methods in Scheme 39 is particularly intriguing because this sequence (aminoester or acid → **2TH** → **I2T** → imidazole) is not well known, if at all, even though the newest elementary step is almost 40 years old. There are many examples of imidazole syntheses from **I2T**s, but the thione is commonly prepared by the acylation of an α-aminoketone or α-aminoaldehyde acetal with a thiocyanate, followed by cyclocondensation with acid.[134, 449, 455-457]

No reduction of an intermediate α-thioureidoester or **2TH** is required in that method. Note this entry to an **I2T** and the oxidative desulfurization of it (with nitric acid) dates back at least to W. Marckwald's 1892 report.[458] The classical preparation of **2TH**s is identical in concept to that of **I2T**s; acylation of an α-aminoester or acid with a thiocyanate is followed by cyclization of the intermediate.[429, 433, 459-463] This reaction also traces back at least as far as Marckwald and coworkers.[464] More recently a similar reaction became famous as the basis of the Edman degradation, wherein the unmasked *N*-terminus of a peptide is acylated with a thiocyanate and cyclization at the resultant α-thioureidoamide terminus expels a **2TH** and a peptide shortened by one amino acid residue.[465] There are several examples of alternative **2TH** syntheses, including the reaction of α-isothiocyanantoesters with amines followed by cyclization,[463, 466, 467] condensation of thioureas with 1,2-diones attended by alkyl group transfer under microwave irradiation,[463] and thionation of α-aminoamides.[468] J. E. Scott and G. Henderson reported on the synthesis of **I2T**s from amino acids through **2TH**s, and introduced the metal borohydride reductions for the conversion of **2TH**s to **I2T**s, but they did not desulfurize these to imidazoles.[429]

As applicable as the 1,3-dialkyl **I2T** syntheses in Scheme 39 seemed for preparations of the 1-alkyl **I2T**s necessary for neutral imidazole syntheses, it turned out that only one was suitable. Intermediate α-thioureidoesters prepared by the acylation of ethyl glycinate with butyl-, benzyl-, and phenylisothiocyanates did not convert to **2TH**s under the influence of heat or sodium ethoxide (i.e., Scheme 39, paths A and B, R^1 = H, X = Et, R^3 = Bu, Bn, Ph) or sulfuric acid (which was not previously evaluated for the cyclization of α-thioureidoesters on the way to imidazolium salts). No **I2T** products were isolated when the crude α-thioureidoesters from the reactions of ethyl glycinate and the selected isothiocyanates were freed of protic impurities by a

standard workup and dried under vacuum overnight, then treated with Dibalh followed by acid (i.e., Scheme 39, path C).[427] Note that the α-thioureidoesters that had previously converted to **2TH**s in this work by the application of heat or base were the 1,3-dialkyl variety, whereas those that did not carry through were 3-alkyl.

The **2TH**s were only secured when free glycinate was acylated with isothiocyanates and the crude intermediate α-thioureidoacids were cyclized with sulfuric acid (Scheme 40).[429, 433] As was the case in the synthesis of **40** by acid catalyzed dehydration, these reactions proceeded in moderate yields because of competitive *S*-acylation,[434-436] but this method had the advantages of scaling up nicely for multigram preparations, and chromatography was not necessary. Isolation of **2TH**s **44** – **46** required only the removal of acetone, inundation of the residue with aqueous sodium bicarbonate, and filtration. Presumably, the expected 2-thioamidine byproducts were removed with the mother liquor.



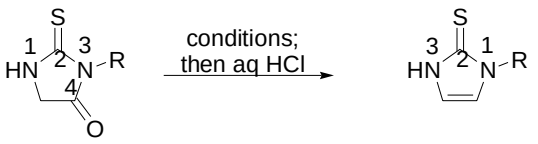
Scheme 40. Synthesis of 3-alkyl **I2T**s (yields are from glycine).

The conditions used to reduce and dehydrate 1,3-dialkyl **2TH**s were not applicable to the conversion of 3-alkyl **2TH**s **44** – **46** to 1-alkyl **I2T**s **47** – **49**. Simply combining **45** and 1.1 equivalents sodium borohydride in ethanol or 3 : 1 glyme–ethanol at room temperature gave an incomplete reaction, and the reagent was still not consumed by 2.2 equivalents sodium

borohydride (Table 31). In TLC analyses of acidified reaction aliquots, the reagent and product spots were joined by a third spot less mobile than either of them. If the reactions were left long enough at room temperature, both reagent and desired product were undetectable by TLC and the least mobile of the three compounds was left. When this product was isolated, it could not be adequately characterized. However, its TLC characteristics are consistent with a 2-thioureidoalcohol, the byproduct expected from ring-chain tautomerism and overreduction as discussed by Scott and Henderson.[429] This overreduction was still observed at 0 °C, but suppressed at –15 to –5 °C. Application of lithium chloride[429, 469, 470] at this temperature forced the reaction to completion. The refinement of these conditions is reported in Table 31 for **45** only, but **44** gave identical results and **46** differed only by reducing and overreducing at lower temperatures. The **2TH**s were not freely soluble in 3 : 1 glyme–ethanol, but disappeared over the course of the reaction. They were only appreciably soluble in pyridine. Since molecular borane liberated during the desired reaction could have been contributing to overreduction, and because pyridine can scavenge borane,[471] it was anticipated that a reaction in pyridine would be ideal. No reaction occurred, even with excess sodium borohydride and lithium chloride at room temperature. Presumably, the **2TH**s were chelated to or deprotonated by pyridine at N(1), and additional electron density at C(4) stifled the reduction.[429]

Desulfurization of the **I2T**s with benzoyl peroxide was straightforward and imidazoles **50** – **52** were obtained after simple workup (Scheme 41). To show the utility of this route, a formal synthesis of three imidazole alkaloids from the sponge *Leucetta* (isonaamine A, and isonaamidines A and C) was undertaken. The total syntheses of these imidazoles were accomplished by S. Ohta and coworkers through imidazole **53**.[472] They commenced with

Table 31. Optimization of the syntheses of **47** – **49**.



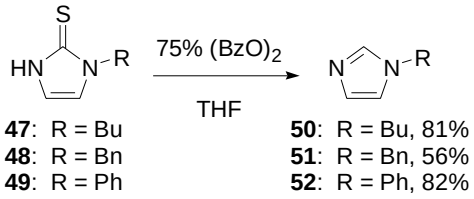
44: R = Bu
45: R = Bn
46: R = Ph

47: R = Bu
48: R = Bn
49: R = Ph

	Conditions					
R	eq $NaBH_4$	eq LiCl	Solvent	T (^oC)	*t* (h)	Result[a]
Bn	1.1	0	EtOH or 3:1 DME–EtOH	rt	16	DNC; OR starts
Bn	2.2	0	EtOH or 3:1 DME–EtOH	rt	16	DNC; OR starts
Bn	2.2	0	EtOH or 3:1 DME–EtOH	0	16	DNC; OR starts
Bn	2.2	0	EtOH or 3:1 DME–EtOH	–15 to –5	16	DNC; no OR
Bn	2.2	0	EtOH or 3:1 DME–EtOH	–20 to –30	16	NR
Bn	1.1	1.1	3 : 1 DME–EtOH	rt	6	C; OR starts
Bn	1.1	1.1	3 : 1 DME–EtOH	0	8	DNC; no OR
Bn	2.2	2.2	3 : 1 DME–EtOH	0	6	C; OR starts
Bn	2.2	2.2	3 : 1 DME–EtOH	–15 to –5	6	C; no OR; 97%
Bu	2.2	2.2	3 : 1 DME–EtOH	–15 to –5	6	C; no OR; 88%
Ph	2.2	2.2	3 : 1 DME–EtOH	–25 to –15	6	C; no OR; 71%
Bu, Bn, or Ph	1.1	0	py	rt	24	NR
Bu, Bn, or Ph	1.1	1.1	py	rt	24	NR
Bu, Bn, or Ph	2.2	2.2	py	rt	24	NR

[a]Abbreviations: DNC = does not complete; OR = overreduction; NR = no reaction; C = completes.

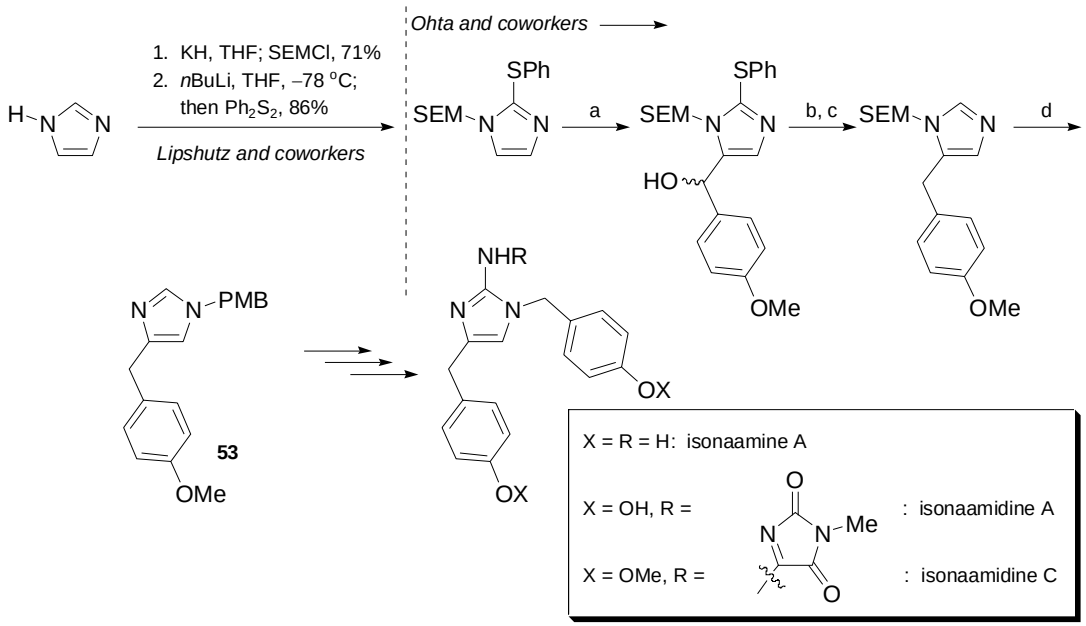
lithiation of 1-SEM-2-phenylthioimidazole, which is available from imidazole in two synthetic steps, both of which require strictly anhydrous conditions (Scheme 42).[473, 474]



47: R = Bu
48: R = Bn
49: R = Ph

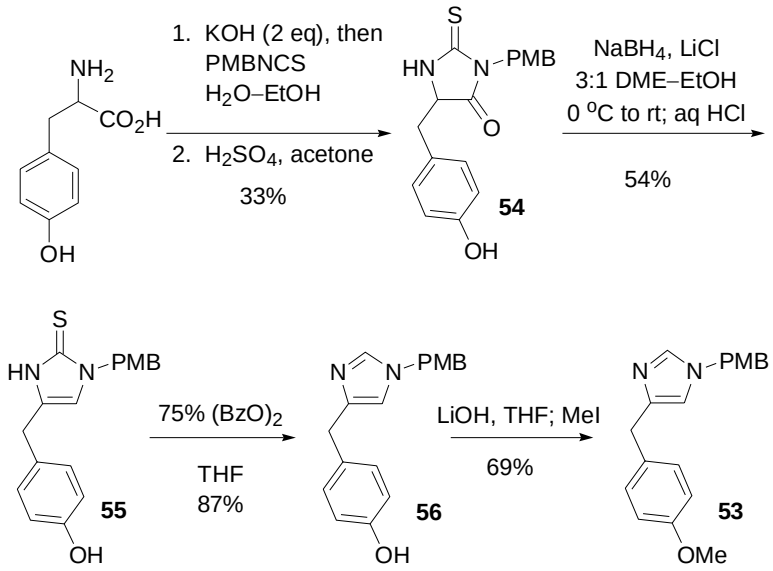
50: R = Bu, 81%
51: R = Bn, 56%
52: R = Ph, 82%

Scheme 41. Oxidative desulfurization of 1-alkyl **I2T**s to neutral imidazoles with benzoyl peroxide.



Scheme 42. Synthesis of 1-SEM-2-phenylthiomidazole by B. H. Lipshutz and coworkers,[473, 474] and its elaboration to **53**, a synthon of isonaamine A and of isonaamidines A and C, by Ohta and coworkers.[472] Reagents and conditions: a) *n*BuLi, *p*-anisaldehyde, THF, 87%. b) Et_3SiH, CF_3COOH, DCM, 100%. c) $NaBH_4$, $NiCl_2 \cdot 6\ H_2O$, THF–MeOH, 95%. d) PMBBr, EtOAc, then 10% aq HCl, 78%.

Based on the synthesis of imidazoles from amino acids developed above, imidazole **53** was expected from conversions of tyrosine (Scheme 43). The necessary isothiocyanate was prepared from *p*-methoxybenzylamine and thiophosgene on a large scale based on a protocol from M. D. Threadgill and coworkers.[475] Following its reaction with tyrosine dianion, cyclization in sulfuric acid and acetone proceeded in low yield, but no chromatography was necessary and the reaction was amenable to the preparation of several grams **54**. Compound **54** was less sensitive to the conditions of reduction than were the model **2TH**s. Indeed, **54** was so sturdy that it was not entirely consumed after several days at room temperature with occasional replenishment of lithium and borohydride salts. Thus, the reduction and dehydration to **55** was accomplished in moderate yield and the first chromatographic purification of this study was necessary. The feature reaction proceeded smoothly and in high yield; like the model imidazoles, isolation of **56** required only a simple workup. Starting from tyrosine required a methylation to deliver **53**. *O*-Methyltyrosine could have been used to complete the synthesis of **53** in four steps instead of five, but the commercial derivative is roughly 100 times as expensive as the parent compound. In deferring methylation, however, the synthesis of **53** concluded with a 69% yield and a chromatographic purification. Note that Ohta and coworkers demethylated both aryl methyl ethers of **53** for their syntheses of isonaamine A and isonaamidine A,[472] so a demethylation of **56** at the PMB ether would be an alternative formal synthesis of two of the three *Leucetta* imidazoles.



Scheme 43. Synthesis of **53** from tyrosine.

CHAPTER 4

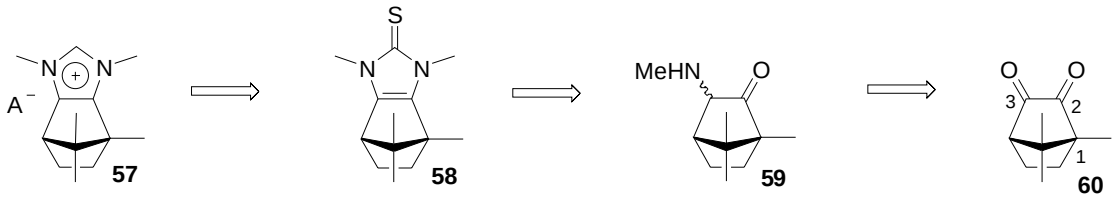
TRANSFORMATIONS ON CAMPHOR NOT PROVIDING A CHIRAL IONIC LIQUID

Cations appearing in chiral salts contained in the preceding references were furnished in some cases by the synthesis of chiral heterocycles and quatnernizing them with simple alkyl groups, and in others by the quaternization of a simple heterocycle with a chiral alkyl halide or equivalent. Certain chiral salts could conceivably be assembled by the condensation of suitable carbonyl compounds with amines in a manner analogous to the synthesis of azolium salts shown in Scheme 34. Bach and coworkers have prepared a chiral thiazolium salt derived from menthone by oxidative desulfurization of it with *m*CPBA.[424] However chirality is introduced to these systems, the components are prepared from the usual chiral pool suspects, primarily terpenes (e.g., menthol, menthone, pinene, citronellol), amines (e.g., nicotine, methylbenzylamine), esters (e.g., ethyl lactate), and amino alcohols (e.g., valinol, ephedrine).

Camphor first appeared as the (1*S*)-10-camphorsulfonate anion in a chiral IL in 2005,[476] and as an *N*-substitutent on imidazolium salts just this year.[477] The chiral IL hydrogenated by Wasserscheid and coworkers (Scheme 25) featured a camphorsulfonate anion. There are many structural examples of camphor fused to a pyridyl ring or bearing it as a substituent that could presumably be quaternized to chiral ILs, but have not been.[478] Derivatives of the parent terpene that are particularly useful in asymmetric synthesis are (2*S*)-(–)-*N*,*N*-dimethylaminoisoborneol ((–)-DAIB), and the Oppolzer sultam (2,10-camphorsultam) and the related oxaziridine.[479-481] Any ILs derived from camphor could be considered for use as chiral solvents, and azolium salts

in particular could also be useful as precursors to NHCs either as ligands or catalysts. It is also possible these salts could function as chiral H–bond catalysts and chiral shift reagents.

The fused camphor imidazolium salt **57** was targeted even though the camphor skeleton is a challenging environment for further derivatization (Scheme 44). Except for reliably condensing with hydroxylamines and hydrazines, the C(2) carbonyl of camphor is difficult to react with nitrogen nucleophiles.[482, 483] By comparison, C(3) of camphorquinone (**60**) is highly electrophilic and this starting material can be prepared in large quantities from the reaction of camphor and selenium dioxide (see Experimental Section).[484] Further, the C(3) carbonyl of **60** is attacked by nucleophiles in vast preference to C(2) even when the nucleophile is one that can react at C(2). For example, **60** is converted to its C(3) monooxime in 20 min at room temperature in the presence of pyridine and hydroxylamine hydrochloride, whereas the condensation of hydroxylamine at C(2) of camphor requires several hours reaction time in boiling ethanol. Although nitrogen nucleophiles preferentially add to C(3) of **60**, reductive amidation is one of the reactions that can be given by camphor C(2).[485-488] Thus, a Leuckart–Wallach reaction followed by hydrolysis to aminoketone **59** seemed possible with the caveat that the reaction temperature and time be kept as low and short as possible to prevent successive Leuckart–Wallach reactions.

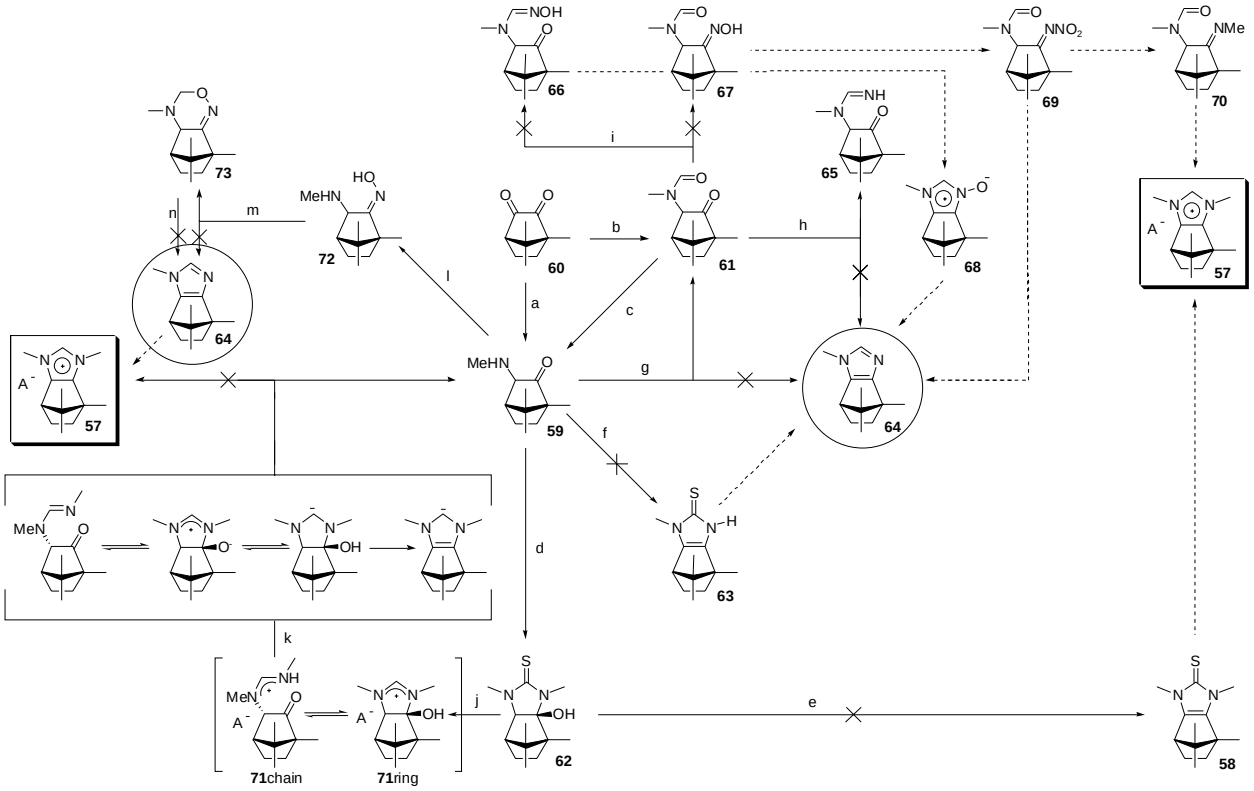


Scheme 44. Retrosynthetic analysis of **57**.

Following a Leuckart–Wallach reaction and hydrolysis with acylation of the aminoketone **59** by methylisothiocyante would yield an intermediate α-thioureido ketone with the nitrogen nucleophile fixed in close proximity to camphor C(2), which was expected to overcome the inertness of the carbonyl and allow condensation to **58**. This plan was setting up for the oxidative desulfurization developed here, but any acquisition of **57** was desirable and other methods were considered alongside the one shown in Scheme 44.

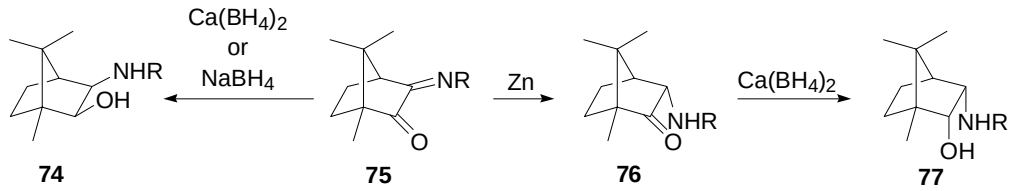
The attempts at the synthesis of **57** from **60** according to this plan are summarized in Scheme 45. Quinone **60** was prepared by a scaled up literature protocol demonstrated to provide optically pure material,[484] and 4-hydroxyimidazolidine-2-thione **62** crystallized to diasteromeric purity as indicated. All other compounds appearing in Scheme 45 were recovered as a mixture of diasteromers (if at all) and were carried through any subsequent conversions as such. Note that *none* of the desired products devoid of stereochemistry at C(2) and C(3) (**57**, **58**, **63**, **64**, **68**) yielded to synthesis, as indicated by the xed or dashed arrows leading to them; the latter signifies reactions that could not be attempted because of a synthetic breakdown upstream.

Reductive amination of **60** to **59** with concentrated aqueous methylamine and formic acid proceeded in low yield (< 30%), but the Leuckart–Wallach reaction of **60** to **61** was accomplished in much better yield (89 – 92% crude), and hydrolysis of it to **59** was preferable to a one step synthesis. Amidoketone **61** was a viscous orange oil which could be distilled from a dark residue in 75% yield, but the ^{1}H and ^{13}C NMR spectra of the distillate were unchanged from the crude isolate. When the distilled material was hydrolyzed in aqueous hydrochloric acid, **59** was recovered in quantitative yield. Crude **61** figured to be just as suitable, and hydrolysis of it returned **59** in 74% yield from **60** following distillation of **59**, which equates to a quantitative yield based on the amount of **61** that would have been expected following distillation.



Scheme 45. Reagents and conditions: a) 40% aq $MeNH_2$, HCO_2H, Δ, < 30%. b) 3 : 1 NMF–HCO_2H, 120 °C, 2 h, 92% crude, 75% distilled. c) 6 M aq HCl, Δ, 100% from distilled **61**, 74% from **60** through crude **61**. d) MeNCS, THF; crystallization from 5 : 1 *n*-heptane–isopropanol, 54%. e) P_2O_5, $CHCl_3$, NR. TsOH, PhMe, < 60 °C, NR; > 60 °C, dec. TfOH in THF, DCM, or acetone, NR. Concentrated aq $HClO_4$–Et_2O, NR. Dry, steady stream HCl in boiling AcOH, NR. f) NH_4NCS, PhMe or EtOH, Δ; yielded a mixture of 4-hydroxyimidazolidine-2-thione intermediates. g) formamide, Δ, 45%. h) NH_4OAc, AcOH, Δ, 78% crude. i) NH_3OHCl; only sm recovered. j) $(BzO)_2$, THF; see text for a description of the result. k) 6 M aq NaOH, Δ; acid quench, 100%. l) NH_3OHCl, water, Δ, 96% crude. m) 37% formalin, 6 M HCl, THF, 76% crude. n) AcOH, or Ac_2O in AcOH, or NaOAc in AcOH, or 85% H_3PO_4, dec.

Insofar as it is relevant to the stereochemical outcome of the Leuckart–Wallach reaction, note that S. E. Denmark and I. Rivera prepared several *cis*-*exo*-3-aminoisoborneols (**74**) from 3-imino derivatives of **60** (**75**, Scheme 46).[489] Other examples in stereocontrol in metal hydride reductions of compounds similar to **75** are the reduction of the 3-monooxime of **60** with lithium aluminum hydride, which yields an intermediate on the way to (–)-DAIB,[490] and the reduction of the same oxime to unsubstituted *cis*-3-aminoisoborneol by M. M. Joullié and coworkers,[491] which was based on J. Ipaktschi's reduction of camphor oxime to isobornylamine with sodium borohydride in the presence of nickel (II) chloride.[492] In each of these cases, the first hydride delivery occurred on the less hindered *re* (β) face, and the preference for hydride delivery to the same face was even greater in the second reduction because there was even more steric bulk on the *si* (α) face following the first reduction. Following Denmark's and Rivera's reductions of compounds **75** to α-alkylamino camphors (**76**) with elemental zinc, however, the new stereocenter could have epimerized after installation, but did not. They exclusively recovered *cis*-*endo*-3-aminoborneols (**77**) following reductions of **76** with calcium borohydride even though hydride delivery in this step could have given a mixture of diastereomers—the isopropylene bridge would direct hydride delivery to the β face while the new amine group would direct hydride delivery to the α face. They did not observe epimerization and did not find a minor diastereomer because their examples featured no alkyl groups smaller than isopropyl.[489] The presence of a large alkamino group disposed the substituted nitrogen to the β face during the first reduction, and stifled epimerization. It also blocked hydride delivery from the β face during the second reduction.



R = *i*Pr, *i*Bu, 3-Am, neopentyl, *t*Bu, Ar

Scheme 46. Syntheses of *cis*-3-aminoisoborneols and -borneols by Denmark and Rivera.

In the case of **61** prepared by reductive amidation here, the resulting diasteromeric mixture of amidoketones **61** and of aminoketones **59** from their hydrolysis may reflect poor stereoselection during hydride delivery in the Leuckart–Wallach step, or may indicate **61** and **59** are epimerizable, or both. A definitive answer to whether diastereoselection in the Leuckart–Wallach reaction or epimerization or both led to the stereochemical compositions of mixtures of **61** and **59** was not pursued because this stereochemistry would have been immaterial in a successful synthesis of **57**, where the stereochemistry at C(3) would have been destroyed in the last stages of the synthesis.

Aminoketone **59** was a mobile, brilliant yellow oil which added readily to methyl isothiocyanate, but it did not proceed to **58** following treatment with a catalytic amount of acid or base. Rather, the reaction stopped at the 4-hydroxyimidazolidine-2-thione **62**, which was characterized by X-ray crystallography (Figure 10). This unforeseen development derailed the rest of the synthesis, especially when it was found that **62** would not release water under increasingly forcing conditions in a separate reaction (Scheme 45, conditions e). The only reaction observed in these attempts was the decomposition of **62** in the presence of warm sulfonic acids (e.g., TsOH and TfOH). This hydrate was so stable that it even withstood dry hydrochloric acid bubbled into a refluxing solution of it in acetic acid, where no conversion was observed after three days.

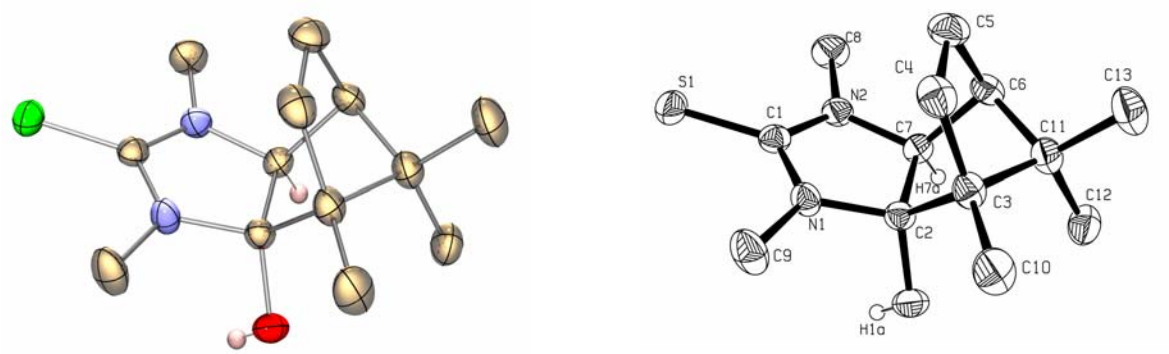


Figure 10. Two X-ray crystal structure representations of 4-hydroxyimidazolidine-2-thione **62**.

After **58** could not be prepared, conversions that could provide imidazole **64** for use in a quaternization reaction were considered, as were those which could deliver **57** by traditional condensation reactions. The conversion of **59** to **63** was attempted first. Refluxing a mixture of ammonium thiocyanate and an aminoketone as either a suspension in toluene or a solution in ethanol are standard methods for the desired acylation and cyclization,[413, 449, 455] but the reaction of **59** again led to a mixture of 4-hydroxyimidazolidine-2-thiones, and this time they could not be separated. The indicator of diasteromeric 4-hydroxyimidazolidine-2-thiones is the appearance of two peaks between δ = 70 and δ = 100 ppm in the ^{13}C NMR spectrum. There were no peaks ascribable to an alkene in the ^{13}C NMR spectrum.

A classical imidazole synthesis is the cyclocondensation of an α-aminoketone and an amide, which is frequently low yielding. T. N. Sorrell and W. E. Allen have provided modern examples of this reaction,[493] and the conversion of **59** to **64** in boiling formamide was attempted. Remarkably, a transamidation took place and **61**, the amidoketone precursor of aminoketone **59**, was recovered in 45% yield. Another incredible but undesirable reaction was found in the attempted conversion of amidoketone **61** to imidazole **64** with ammonium acetate in

boiling acetic acid. Condensation took place at the amide carbonyl, and delivered amidinoketone **65** in 78% crude yield. The structure could be assigned based on the differences in the ^{13}C NMR spectra of it and **61**. Amidoketone **61** showed diasteromeric amide resonances at 160 – 166 ppm and ketone peaks at 212 and 214 ppm. In the product, the amide peaks were replaced by resonances around 171 ppm, which are consistent with the new amidine moiety of **65**, and ketone resonances were still present at 219 and 225 ppm.

Hydroxylamine is one of only a few reagents conveniently and reliably added to camphor C(2). If the reaction of **61** with methylamine gave **65** because C(2) would not accept methylamine, application of hydroxylamine could potentially deliver amidooxime **67**. On the other hand, having seen **61** led to **65** in the previous reaction, it stood to reason that reaction of the former with the still better nucleophile hydroxylamine could give condensation at the same site, the amide carbonyl, and produce hydroxyamidinoketone **66**. Either of these products from the reaction of **61** with hydroxylamine could have been useful because they could have been considered for cyclization to imidazole-*N*-oxide **68**, which likely would have suffered reduction by phosphine reagents to deliver imidazole **64**.[494, 495] A product mixture containing populations of **66** and **67** could have been just as useful if the mixture would homogenize to **68**. For the record, amidooxime **67** would have been the more useful of the pair because it certainly could have been oxidized to amidonitroimine **69** with nitrous acid, which is a known strategy to increase the electrophilicity of camphor C(2) for the preparation of camphorimines.[482, 483] In this case, the amine for transimination would have been methylamine so as to produce **70**, which would have contained all the atoms necessary to prepare **57**, if **70** could be forced to cyclize.

The only tractable isolate following standard reaction workups after several attempted reactions was unreacted starting material. The simple combination of **61** with hydoxylamine

hydrochloride in refluxing ethanol was not productive, and it was not improved by the application of pyridine, triethylamine, solid NaOH, or aqueous KOH. Considering that the expected products **66** or **67** could have spontaneously cyclized to imidazole-*N*-oxide **68**, and that this material may have been lost to a water wash during workup, each of the reaction conditions were reevaluated and, instead of subjecting them to a conventional workup, the reaction mixtures were concentrated and dried under vacuum. The residues were then partitioned between deuteriochloroform and deuterium oxide, and each layer was analyzed by ^{1}H and ^{13}C NMR spectroscopy. In all cases, the resonances of **61** were the only distinguishing marks in spectra collected in deuteriochlorform. No material was visible in spectra taken on the deuterium oxide wash.

Imidazolinium salts can be deprotonated to carbenes just like imidazolium salts, so it seemed certain that the 4-hydroxyimidazolidine-2-thione **62** would undergo oxidative desulfurization with benzoyl peroxide. Indeed it did, but the question was what product resulted, and what should be done with it. Considering the demonstrated hardiness of **62**, it seemed possible that a salt derived from it could have held together as a 4-hydroxyimidazolinium salt. Unfortunately, after oxidation with benzoyl peroxide and standard refinement of the oxidation mother liquor, the ^{13}C NMR spectrum showed that 4-hydroxyimidazolinium salt **71**ring existed in equlibrium with the amidinioketone **71**chain (Figure 11). At a concentration around 120 ppt, the ketone resonance of **71**chain was barely visible, but it was well resolved from the baseline at a dilution of roughly 60 ppt. Only two stages of dilution are shown in Figure 11, but further dilution of the concentrate did not cause the total disappearance of **71**ring.

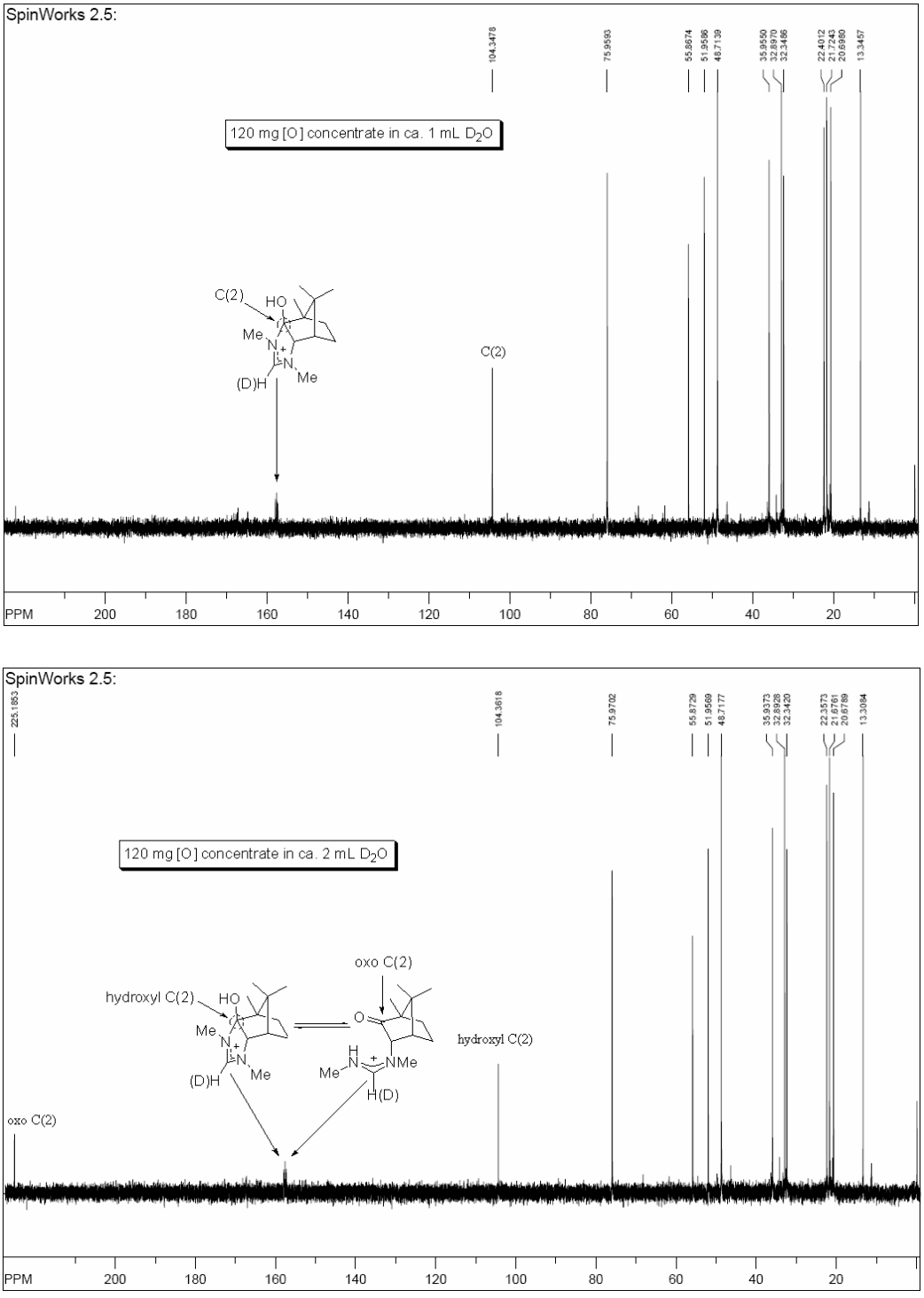


Figure 11. ^{13}C NMR spectroscopy dilution experiments on the product mixture from the benzoyl peroxide oxidation of 4-hydroxyimidazolidine-2-thione **62** shows ring–chain tautomerism in **71**.

The point is arguable, but the mixture of cationic camphor derivatives that is **71** is probably not suitable for any of the purposes conceived for **57**. Although **62** did not dehydrate, there was a chance salts **71** could because they would aromatize to a single compound following loss of water. P. C. Trulove, R. K. Sukumaran, and Osteryoung observed H–D exchange in the NMR spectra of chloroaluminate ILs containing deuterium chloride, and this process is explained by the intermediacy of a dication in a superacidic medium.[79] The prospect of dehydrating salts **71** in acid was not appealing because it was seen in the development of the benzoyl peroxide oxidation of **I2T**s that imidazolium bisulfates produced by the oxidation can decompose on heating. Besides that, salts **71** had not spontaneously dehydrated to **57** in the course of their oxidation by benzoyl peroxide, even though the reaction generates bisulfate and refluxes spontaneously. It was unbelievable that more forcing conditions could lead to anything but decomposition. Hence, the prospect was not appealing, but it was attempted anyway. When a fresh sample of salts **71** was prepared and the mixture was concentrated without first destroying bisulfate, a color change was observed and the ^{13}C NMR spectrum indicated decomposition occurred, but desired product formation did not. The result was the same when

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luxed under dehydrating conditions. Dehydration of salts **71** to a single compound under the influence of base seemed less unlikely. In the hopes that the NHC **1** derived from camphor would prove to be the proverbial thermodynamic well in an equilibrating mixture of it, an amidinoketone, its zwitterionic ring tautomer, and the hydrated NHC **1**, the mixture of salts **71** was refluxed in 6 M aqueous sodium hydroxide. Following acidification of the putative equilibrium mixture, aminoketone **59,** the product of hydrolysis, was recovered in quantitative yield. Note that the ^{1}H and ^{13}C NMR

spectra of this specimen exactly matched the complex spectra provided in the accompanying spectral library (which was taken on a sample of distilled **59**). This circumstance bears out two points. First, it means aminoketone **59** purified by simple distillation is purer than its ^{1}H and ^{13}C NMR spectra would suggest. The sample recovered after the benzoyl peroxide oxidation of **62** came from purified crystalline **62**. It is impossible to believe the same impurities present after the Leuckart–Wallach reaction and hydrolysis would somehow recontaminate **59** that had been, in effect, circuitously purified by way of **62**. Second, this outcome indicates **59** does epimerize, because the sample of **59** inadvertently made from the oxidation and hydrolysis of **62** started from diasteromerically pure material.

Imidazoles are also accessible from the condensation reactions of α-aminooximes and a source of methine.[496] Aminooxime **72** was easily prepared in 96% crude yield by heating an aqueous solution of hydroxylamine hydrochloride and aminoketone **59**, and then easily reacted with 37% formalin in tetrahydrofuran. Unfortunately, the facile reaction given by aminooxime **72** provided oxadiazine **73** in 76% crude yield, and not imidazole **64**. All was still not lost, however. H. Möhrle and coworkers showed that oxadiazines can be dehydrated to imidazoles.[497, 498] Subjecting oxadiazine **73** to each of Möhrle's conditions led to decomposition instead of imidazole **64**, presumably through a rearrangement analogous to those commonly given by camphor compounds under the same conditions (e.g., Beckmann, Wagner–Meerwein).

CHAPTER 5

γ-ADAMANTANE AMINO ACID CHEMISTRY AND THE UNSUITABILITY OF SOME IMIDAZOLIUM IONIC LIQUIDS IN THE PHASE TRANSFER CATALYZED HALOGENATION

> The pronounced lipophilic nature associated with the compact, highly symmetrical architecture of the adamantane molecule invites a study of its influence on characteristics and biological potential of compounds which contain this unique hydrocarbon moiety.
>
> Such a study has now become possible as a result of [P. v. R.] Schleyer's startling discovery of a direct synthesis of adamantane and of [H.] Stetter's extensive exploration of its functional derivatives.[499]

K. Gerzon and coworkers were apparently the first on the scene in designing, synthesizing, and evaluating new drugs containing adamantane. The inset sentences come from their first paper in their series, appearing in 1963—which is six years after Schleyer reported a simple preparation of adamantane,[500] but literature searches have turned up no earlier reports. Gerzon and coworkers do not provide references to either precedented biologically active derivatives or anybody else espousing the potential of the adamantane moiety in medicinal chemistry. Instead, they were working off an idea. The logic behind the development of new medicinal agents incorporating adamantane has not changed significantly, but it has been reinforced by the following results. In these examples of theory and of precedent, note that many other groups could imbue a drug with the same properties. The value of adamantane in particular in these applications is underscored by the fact the bare hydrocarbon gives many useful reactions, and elaborate derivatives of it can be conveniently prepared.[501] The thrust of

the interest in adamantane medicinal agents comes from its size and hydrophobicity, two properties of the hydrocarbon that are not easily delineated in existing examples.

If used to modify a pharmacophore, it is conceivable an adamantane group could protect the biologically active moiety from enzymatic degradation, and that the presence of adamantane could increase the hydrophobicity of a drug covalently bound to it, which could lead to better uptake of a drug by fatty tissue. If the covalently bound drug were one with an affinity for a channel, the active site of an enzyme, or a cellular receptor, the bulky hydrocarbon at the end of a tether could have a few different effects. It could serve to cap the opening of a channel or block the active site of an enzyme; it could either force or limit dissociation of a molecular signal from its receptor, depending on the environment. These are the recurrent themes in the molecular pharmacology of the adamantanes selected for Table 32, which is meant to emphasize the extant literature. Interest in rimantadine (1-(1-adamantyl)ethylamine, appearing in ca. 500 refs, lead ref[502]) has dropped off in the last decade, and it is excluded from Table 32. Some of the so-called IEM molecules are alkammonioadamantanes (ca. 40 refs collectively, lead refs[503-506]) but are excluded from Table 32 to save space. None of the excluded aminoadamantane derivatives undermine the intimation in Table 32 that, as a class, aminoadamantanes exhibit two properties. They can be prophylactic antivirals and they can forestall or even reverse the progression of neurodegenerative disorders, although different derivatives fill each of these roles to vastly different degrees. For example, by most measures, rimantadine is a superior prophylactic antiviral to 1-aminoadamantane, and both are more effective in this role than is memantine. Memantine, however, is the superior drug for Alzheimer's disease.

Table 32. Of the adamantanes of medicinal repute, the largest amount of information is available on these (continued on next page).

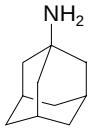
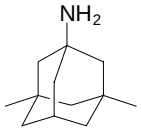
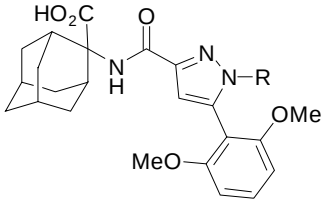
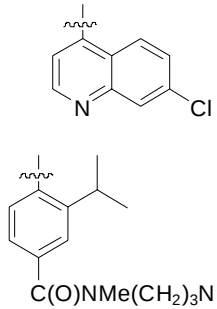
Compound	R	Nomenclature, comments, and lead refs
	--	When it appears in the biological literature, 1-aminoadamantane is more often called amantadine or adamantanamine (with or without another e); trade names Symmetrel and Viregyt. Although the word appears frequently, amantadine is *never* correctly called adamantine because this term comes from the luster scale used by mineralogists. Amantadine appears in ca. 2500 references, 739 of which deal with antiviral properties of the drug—681 of these concern influenza. It has appeared in over 400 refs concerning Parkinson's disease and ca. 40 regarding Alzheimer's disease.[507-514]
	--	1,3-Dimethylaminoadamantane is most commonly called memantine or by its trade name, Namenda. Out of more than 1200 refs on this compound, ca. 400 concern Alzheimer's disease and ca. 150 pertain to Parkinson's disease. Well under 100 refs (37 ± unknown error) deal with any antiviral properties.[514-518]
		The chloroquinoline derivative is called SR48692; the isopropylbenzamide is SR142948A. These names sometimes appear with another S before the name, and with a hyphen or a space between R and the numerals. Together, these derivatives of the α-adamantane amino acid adamantanine account for over 200 refs. They antagonize neurotensin receptors.[519]

Table 32. Of the adamantanes of medicinal repute, the largest amount of information is available on these (continued from last page, continued on next page).

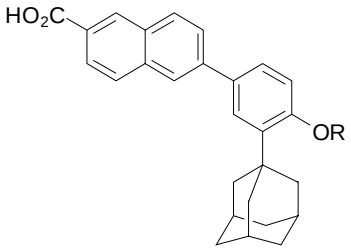
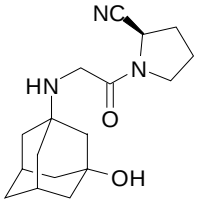
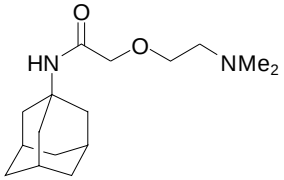
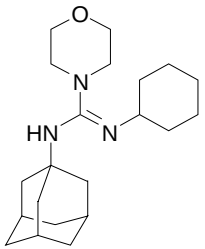
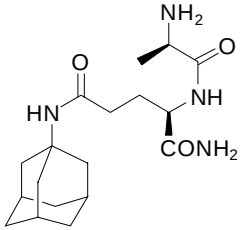
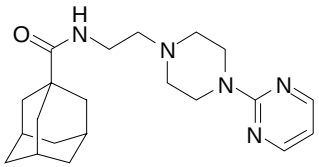
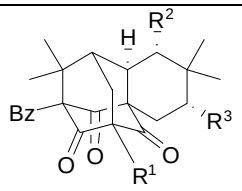
Compound	R	Nomenclature, comments, and lead refs
	H	This synthetic retinoid is called CD437 or AHPN; according to more than 150 refs, it stimulates apoptosis in melanoma, breast cancer, and lung cancer cells.[520-524]
	Me	The methyl ether is called CD271 or adapalene (trade names Differin, Adaferin), and it is an acne treatment appearing in ca. 200 refs.[525-527]
	--	Vildagliptin (LAF237) is also known by the trade name Galvus. Roughly 200 refs describe the drug, and around half of these come from the patent literature. It treats diabetes by inhibiting dipeptidyl peptidase IV.[528]
	--	Tromantidine is active against herpes. Like vildagliptin, it appears in patent documents as much as the scientific literature for a total of ca. 100 refs.[529, 530]

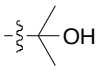
Table 32. Of the adamantanes of medicinal repute, the largest amount of information is available on these (continued from last page).

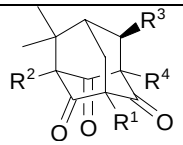
Compound	R	Nomenclature, comments, and lead refs
	--	The simplest name for this guanidine is U37883, but it is often modified with a PN before the U, and with a hyphen between the letters and numerals; an A appears after the last 3 if the reference is using the hydrochloride. It blocks K_{ATP} channels, which could be useful in the treatment of arrhythmia or diuresis, but it appears more often as a tool for mapping K_{ATP} channels in some 60 refs. It can inhibit hair growth, and reverses the effects of minoxidil, which is better known by the trade name Rogaine.[531-535]
	--	The muramyl peptide is AcMur–Ala–D-Glu–NH_2; it is found in bacterial cell walls and elicits an immune response in humans. The compound at left is the original adamantane amide of the glutamic acid side chain of desmuramyl muramyl peptide, which was called adamantylamide dipeptide (AdDP) when created in 1984, and it also stimulates an immune response. Adamantylamide dipeptide and numerous close cousins with different regio- and stereochemistry (and sometimes with inaccurate or bastardized names) appear in over 50 refs.[536]
	--	Adatanserin (WY50324, SEB324) is a mixed agonist / antagonist of serotonin receptors. It agonizes 5-HT_{1A} and antagonizes 5-$HT_{2A/C}$ sites. Out of nearly 40 refs on the compound, less than 10 are from the primary literature. The preponderance of patent over primary literature on adatanserin is unique, even by comparison to other protected adamantane drugs.[537]

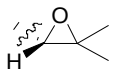
There is no recent and thorough adamantanecentric review of the universe of adamantane derivatives inspired by known pharmacophores. However, even this small treatment of biologically relevant adamantanes would be incomplete without acknowledging the complex natural products with an adamantane nucleus discovered in recent years in extracts of shrubs from the *Hypericum* and *Clusia* genii (Table 33). Closely related heteroadamantanes or bicyclic compounds were isolated alongside these adamantanes.

Table 33. Natural adamantanes.



R^1	R^2	R^3	Name	Refs
geranyl	OH		sampsonione I	[538, 539]
prenyl	H		--	[540]

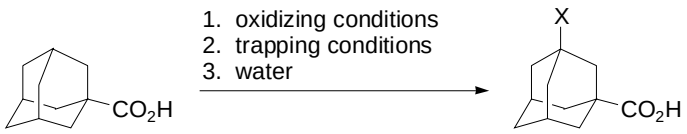


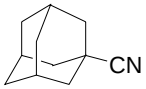
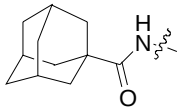
R^1	R^2	R^3	R^4	Name	Refs
geranyl	Bz		prenyl	sampsonione J	[538, 539, 541]
prenyl	Bz		prenyl	28,29-epoxyplukenetione A	[540, 541]
prenyl	Bz	$CHCMe_2$	prenyl	plukenetione A	[541-543]
prenyl	prenyl	$CHCMe_2$	Bz	hyperibone K	[544]

There are two points to take away from the sampsoniones, plukenetiones, and hyperibone in Table 33. The first is that, in the abstract sense, nature uses adamantane, and its incorporation in medicinal agents is not wholly artificial. The other is that adamantanes can be ornate, but they are usually appended to pharmacophores as the 1-amino or 1-carboxy derivatives using the simplest and most readily available admantanes. With the exception of memantine, three bridgehead carbons sit unused in the current examples of biologically relevant adamantanes. This is the case even though installing more functional groups at these positions does not require much more synthetic effort, and even though the adamantane moiety could potentially carry multiple biologically active groups. Among other possibilities, it could be used as a spacer, or it could be designed for the sake of simultaneous presentation of multiple pharmacophores. In another hypothetical situation, one could imagine a biologically active compound which is enzymatically deactivated would be preserved if attached to an adamantane bearing another group which deactivates the offending enzyme.

1-Adamantanecarboxylic acid is commercially available for 1.44 USD / g, and is only a Ritter reaction away from γ-adamantane amide acids (Table 34). Last year, enkephalin analogs containing adamantane amino acids were seen to have some antitumor activity,[545] so the materials below could have inherent medicinal value. At a minimum they are candidates for modules in drug design. The precedent for these reactions was provided by L. N. Butenko and coworkers,[546] who used nitrating solution dried with oleum to prepare the intermediate cation, and acetonitrile to trap it. It is an impressive hydrocarbon functionalization, but the reaction can be accomplished even more easily on a sufficiently large scale (ca. 5 g or more of 1-adamantanecarboxylic acid) because the effect of atmospheric moisture is not as pronounced and there is usually no requirement for oleum.

Table 34. Ritter reactions in the synthesis of γ-adamantane amino acids



Oxidizing conditions		Trapping conditions				
[O]	T (°C)	Nitrile	T (°C)	X	% Yield	Ref
HNO_3–H_2SO_4–oleum	0	MeCN	0	AcNH (**78**)	78	[546]
HNO_3–H_2SO_4	0 → rt	MeCN	0 → rt	AcNH (**78**)	85	--
HNO_3–H_2SO_4	0 → rt	$ClCH_2CN$	0 → rt	$ClCH_2CONH$ (**79**)	85	--
HNO_3–H_2SO_4–oleum	0	Cl_3CCN	0	Cl_3CCONH (**80**)	54 – 65	--
HNO_3–H_2SO_4–oleum	0		0	 **81**	52 – 60	--

In fact, **78** was actually prepared in higher yield without oleum. Further, after the exothermic mixing of nitric and sulfuric acids was accomplished, there was no requirement to carefully control the temperature in reactions free of oleum. The crystal structure of **78** was collected for the first time following its preparation by this adapated method (Figure 12). Butenko and coworkers' method was extended to the direct synthesis of *N*-protected amino acid derivatives **79** and **80**, the former of which had been previously prepared by the Ritter reaction of 1-hydroxy-3-adamantanecarboxylic acid with chloroacetonitrile in concentrated 1 : 1 sulfuric–acetic acids.[547] The reaction to **80** required trichloroacetonitrile, which accepts hydroxylic nucleophiles (e.g., in the Overman rearrangement[548]). For a successful reaction, it was necessary to use Butenko and coworkers' original conditions and exclude environmental

moisture. An adamantane amide (**81**) was prepared by quenching the intermediate cation with 1-adamantanecarbonitrile, which is fairly expensive from commercial sources, but was economically prepared in house from 1-adamantanecarboxylic acid and chlorosulfonylisocyanate. For that preparation, triethylamine[549] was preferable to *N*,*N*-dimethylformamide (the Lohaus method[550]) to decompose the intermediate. This reaction to **81** in over 50% yield was also performed according to Butenko and coworkers' protocol because it was accomplished on a small scale.

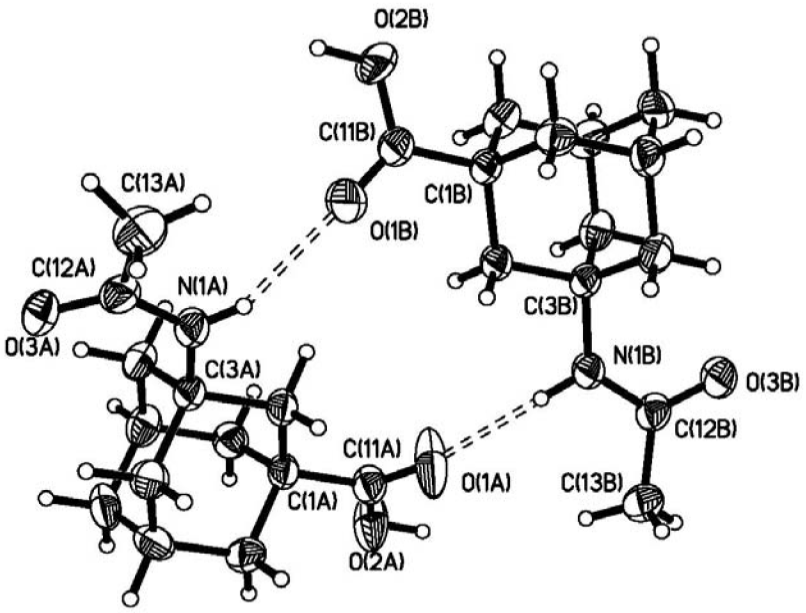
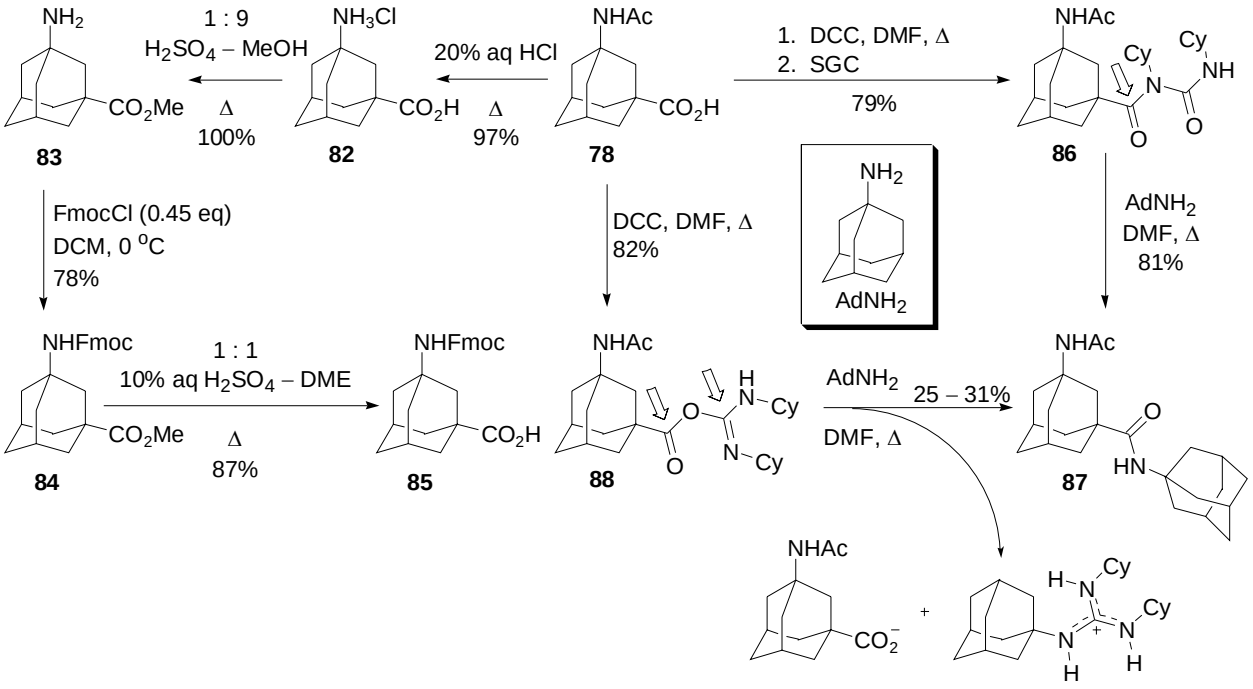


Figure 12. X-ray crystal structure of 1-acetamido-3-adamantanecarboxylic acid **78**.

Archetypal amino acid conversions were evaluated on the γ-adamantane variety using **78** (Scheme 47). The hydrochloride **82** was easily prepared in high yield according to Butenko and coworkers' original method, which consists of hydrolysis, evaporation of aqueous acid, and simple precipitation of the salt by inundation with acetone.[546] In considering protecting groups

for subsequent steps, a great deal of difficulty was anticipated in any attempts at a conventional orthogonal strategy. For example, **82** protected as either the Boc carbamate / methyl ester or the Fmoc carbamate / *tert*-butyl ester would require the introduction of a *tert*-butyl group on a heteroatom near an adamantane. The difficulty of these couplings has proven surmountable elsewhere, however,[551] where the *tert*-butyl esters were prepared in around 90% yield after the free zwitterionic derivative of hydrochloride **82** was refluxed in thionyl chloride and the residue was inundated with *tert*-butyl alcohol following concentration; one example of protection of an adamantanamine with a Boc group proceeded in almost 50% yield.



Scheme 47. Model γ-adamantane amino acid chemistry from **78**.

However, at the time **82** was first in hand, methods to use an Fmoc carbamate and a methyl ester as pseudoorthogonal groups were pursued. Hydrochloride **82** was easily Fischer esterified to methyl ester **83** and *N*-protected as the Fmoc carbamate **84** by the combination of

2.2 equivalents methyl ester **83** relative to Fmoc chloride in cold dichloromethane. Excess **83** that served as the proton scavenger was recovered following an aqueous workup. The standard deprotection of an Fmoc group is treatment with a large excess of 2^{o} amine to free fluorene by a β-elimination, and then to scavenge it as the *N*-(fluorenemethyl)amine so it does not irreversibly alkylate the freed amine of the amino acid. The Fmoc group can be stable to other bases, but there is a limit to what it will tolerate, and it is not compatible with strong inorganic bases like hydroxide and carbonate. Thus, the methyl ester of **84** would survive Fmoc cleavage, but Fmoc would not survive saponification to remove a methyl ester. Selective deprotection of the methyl ester did prove easy, but not mild, and **84** was hydrolyzed to **85** in aqueous sulfuric acid in 87% yield. Milder deprotections of the methyl ester were attempted but were not successful. The reaction of **84** with iodotrimethylsilane formed in solution as described by G. A. Olah and coworkers gave **85** in only 41% yield (100% brsm);[552, 553] the use of various metal iodides in pyridine (to which Fmoc is stable[554]) or other organic solvents[555-559] did not proceed.

To appreciate the model amidations represented in Scheme 47 performed at the carboxylic acid terminus of **78** with DCC, it is important to make clear the chronological order of the appearance of data. Be advised that structures **87** and **88** are not incontrovertibly assigned, but urea **86** was identified by X-ray crystallography (Figure 13), and the structures of **87** and **88** are assigned based on differential spectral and chemical properties from each other and from both **78** and **86**. To assess the suitability of DCC as a coupling agent for adamantane amines and carboxylic acids, **78** and 1-aminoadamantane hydrochloride were refluxed with Hünig's base and DCC in *N*,*N*-dimethylformamide for several days. After the solvent was distilled, the residue was chromatographed over silica gel in neat ethyl acetate to yield what was expected to be **87**. Three carbonyl peaks appeared in the ^{13}C NMR spectrum, however, and the pure isolate was

only identified as **86** after collecting the crystal structure shown in Figure 13. These urea byproducts from DCC couplings are actually very well known.[560, 561] In fact, the ease with which they form and their subsequent inertness is most of the reason other dehydrating agents appear so much more frequently in peptide coupling today than does DCC. However, if the dicyclohexylureic byproduct and its desired coupling partner can withstand the forcing conditions necessary to transfer the acyl group from the urea to the amine, these ureas can give the desired reaction. In the case of these adamantane derivatives, it was possible to prepare a compound assigned structure **87** by refluxing **86** and 1-aminoadamantane in *N*,*N*-dimethylformamide for a week. If the structure assignment is correct, amide **87** was formed in 81% yield; it and **86** are most easily distinguished by their melting points and ^{13}C NMR spectra (see Experimental Section and the included spectral library).

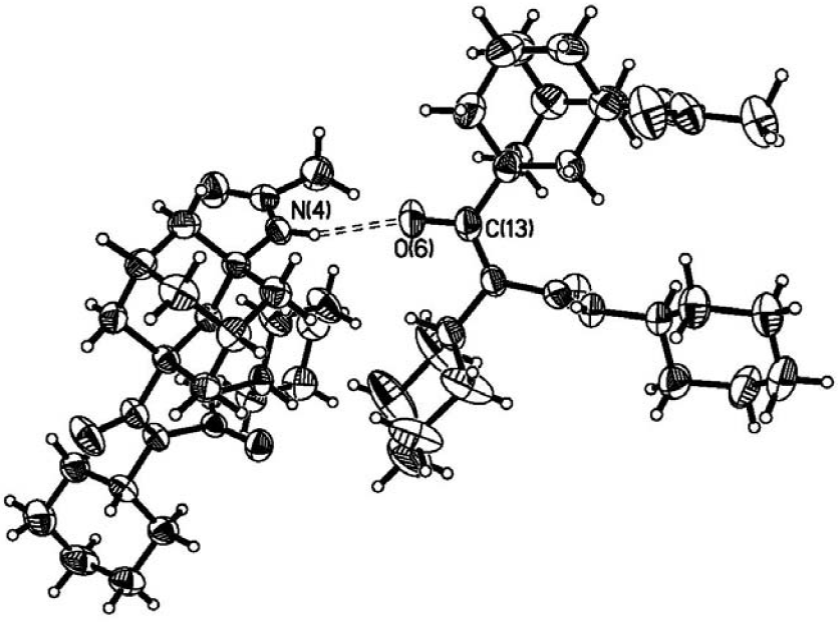


Figure 13. X-ray crystal structure of *N*-(1-acetamido-3-adamantaneacetyl)-*N*,*N*'-dicyclohexylurea, **86**.

The compound assigned structure **88** was found as a white powder that would crash from a sufficiently concentrated mixture of **78** and DCC in hot *N*,*N*-dimethylformamide during attempts to prepare **86** on a large scale. After simply cooling and filtering, this white powder was available in an 82% yield, presuming assigned structure **88** is correct. When this compound was characterized by IR, and ^{1}H and ^{13}C NMR spectroscopy, the spectra were nearly indistinguishable from the positively identified urea **86**, except for the placement of one ^{13}C resonance which came at higher field in the compound assigned structure **88** (Figure 14), which should be expected in exchanging one C=O carbonyl in **86** for a C=N carbonyl in **88**.

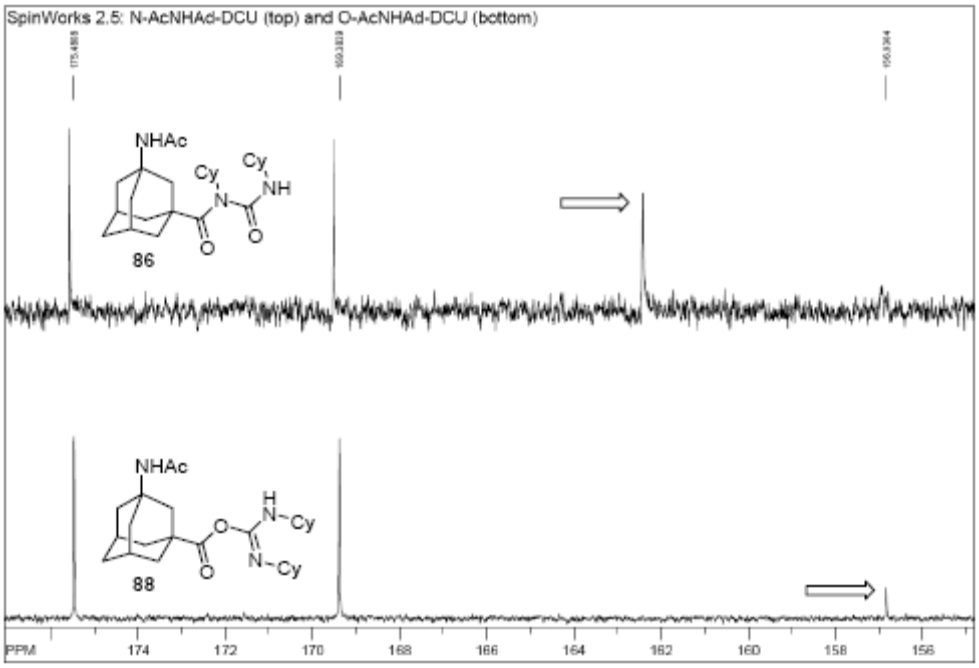


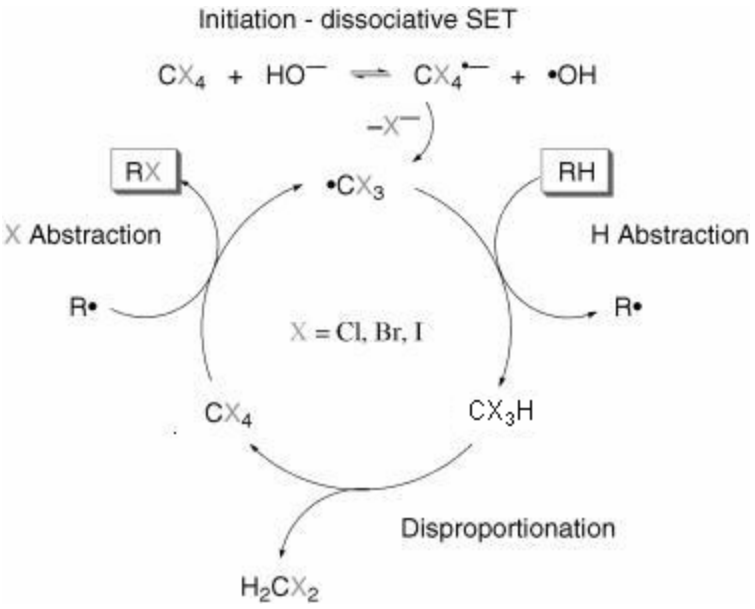
Figure 14. Different carbonyl resonances in the ^{13}C NMR spectra of **86** and the compound assigned structure **88**.

Different isolates could only have resulted because **86** was isolated by a chromatographic purification whereas the compound assigned structure **88** was precipitated. The compound

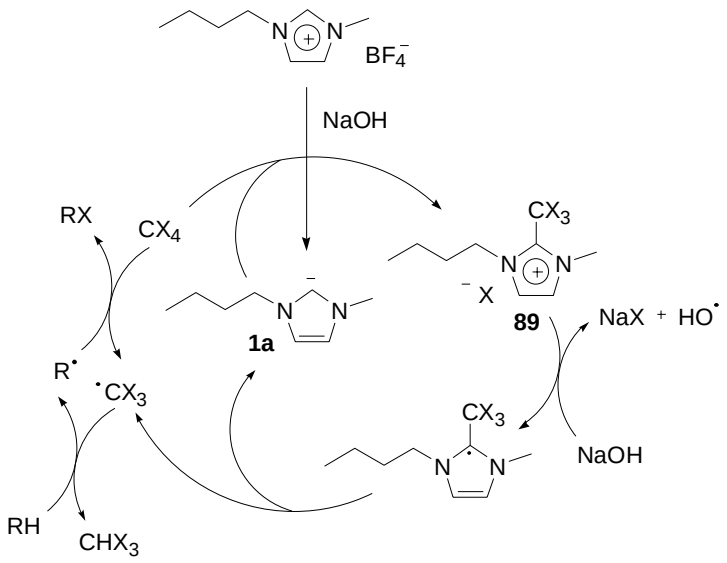
isolated without such treatment required a structure which could isomerize to **86** in the presence of a Lewis acid, and this is another piece of evidence for the assignment of the *O*-acylisoureic structure **88** to the precipitated isolate. Interestingly, the compound assigned structure **88** could be converted to **86** chromatographically, but it could not be converted by refluxing over silica gel in ethyl acetate. The compound assigned structure **88** reacted with 1-aminoadamantane under the same conditions as urea **86**, and it also gave the compound assigned structure **87**, but in about one-third the yield. This result is more evidence that the structural assignments of **87** and **88** are accurate. The difference in preparative yields of the compound assigned structure **87** from urea **86** and from the compound assigned structure **88** can be explained by observing that an *O*-acylisourea has two sites which may reasonably accept an amine nucelophile, whereas a urea only has one; the respective electrophilic carbonyls are labeled with arrows in structures **86** and **88** in Scheme 47. The more electrophilic site of an *O*-acylisourea is the acyl carbonyl, but in this series of adamantane derivatives, it is far more sterically hindered than is the acylisourea carbonyl. Substitution at the latter of these carbonyls would produce a guanidinium carboxylate instead of an amide. On the other hand, an *N*-acylurea like **86** can be reasonably expected to only give an acyl substitution where *N*,*N*'-dicyclohexylurea is expelled, and the reaction of such an acylurea with a nitrogen nucleophile should give an amide as the major product. The observation of these differences in chemical behavior is more evidence in support of the assigned structures **87** and **88**.

γ-Adamantane amino acids and their peptides could be more useful with more functional groups on them, especially since adamantanes programmed for specific medicinal purposes are desired. Halogenated γ-adamantane amino acids would be valuable because adamantyl halides can be alkylated in a method similar to a Sakurai reaction that was described by T. Sasaki and

coworkers.[562, 563] The synthesis of halogenated γ-adamantane amino acids under phase transfer catalyzed conditions (Scheme 48)[564-567] and adapting the halogenation protocol to utilize ILs as phase transfer catalysts were considered at the same time. The thinking behind performing the reaction in an IL was that it would homogenize what had always been a biphasic reaction, and that a homogeneous reaction would be accelerated more than could be expected by simply applying more phase transfer catalyst. Notwithstanding the fact that the reagent being transferred from the aqueous to the organic phase in the phase transfer catalyzed halogenation is sodium hydoxide, which functions as a single electron reducing agent,[568] the first IL considered for the purpose was $[C_4mim][BF_4]$. As should be clear from the foregoing discussion on the outcomes of reactions in ILs in the presence of strong bases, there was a possibility the desired reaction would escape any side reactions of NHC **1**. It was even hypothesized that any NHC **1** formed by the combination of $[C_4mim][BF_4]$ with 50% aqueous sodium hydroxide could have positively influenced the mechanistic course of the reaction (Scheme 49).



Scheme 48. The PTC halogenation of unactivated hydrocarbons.

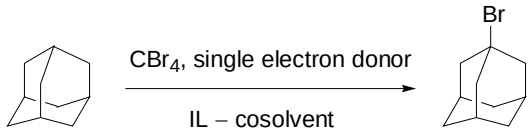


Scheme 49. A purely hypothetical alternative mechanistic basis for alkane halogenation in the presence of [C_4mim][BF_4] deprotonated to NHC **1a**.

Neither positive outcome materialized, however, and the reaction using [C_4mim][BF_4] as a phase transfer catalyst promptly tarred (Table 35, Entry 1) and adamantane was recovered quantitatively. Considering that Ranu and coworkers reported the preparation of [C_4mim][OH] in dichloromethane,[356] it seems unlikely that liberated **1a** reacted with the cosolvent in this case, although it is possible. Carbon tetrabromide was also present, and Begtrup observed that NHCs **1** add to it.[139] This addition is part of the rationale for the hypothetical alkane halogenation process in Scheme 49, but it seems the actual course of the reaction was hydrolysis of **89** to carbon dioxide and **1a**, not single electron reduction and homolytic bond cleavage to produce tribromomethane radical and regenerate **1a**.

Sodium chlorate can also serve as the single electron donor,[569] should not deprotonate [C_4mim], and would be more appropriate for the intended halogenations of elaborate γ-adamantane amino acids. The zero reaction (Table 35, Entry 2) delivered 1-bromoadamantane in

Table 35. Attempts at PTC halogenations in ILs and mixtures.



Entry	eq CBr_4	single electron donor (eq)	IL (eq)	T (^oC)	(co)solvent	% yield
1	1.2	50% aq NaOH	$[C_4mim][BF_4]$ (10)	rt	DCM	0[a]
2	1	$NaClO_3$ (5)	--	80	DCE[b]	60
3	1	--	$[C_4mim][BF_4]$ (5)	80	DCE[b]	0
4	1	$NaClO_3$ (0.1)	$[C_4mim][BF_4]$ (0.1)	80	DCE[b]	0
5	1	$NaClO_3$ (1)	$[C_4mim][BF_4]$ (1)	80	DCE[b]	0
6	1	$NaClO_3$ (5)	$[C_4mim][BF_4]$ (5)	80	DCE[b]	0
7	2	$NaClO_3$ (20)	$[C_4mim][BF_4]$ (20)	80	--	0
8	2	$NaClO_3$ (20)	$[C_4mim][BF_4]$ (10)	80	PhF[c]	0
9	1.5	$[C_4mim][ClO_3]$		rt → 90	PhF[d] DCE[d]	0
10	1.5	$[C_1mim][ClO_3]$		rt	PhF[d] DCE[d]	0

[a]Within seconds of the combination of reagents, vigorous gas evolution occurred, the flask was warm to the touch, and brown flocculent formed. Except for the flask being warm to the touch, all of the same observations were made when the reagents were mixed at 0 ^oC. [b]This was the primary solvent, used in an amount of 5 mL / 1 mmol (0.186 g) adamantane. [c]This reaction was run in a 1 : 1 (v / v) mixture of $[C_4mim][BF_4]$ and PhF. [d]Just enough of this solvent was applied to dissolve adamantane and CBr_4 in the IL.

60% yield; no reaction was observed in the presence of [C_4mim][BF_4] and the absence of a single electron donor (Entry 3). No 1-bromoadamantane was recovered from reactions in the presence of both salts (Entries 4 – 8). Entry 4 could have failed because of the small amount of sodium chlorate supplied, but there was still no yield in Entries 5 or 6, the latter of which was the same as the zero reaction except for the presence of [C_4mim][BF_4]. A large excess of sodium chlorate and IL (Entry 7) was ineffective, and the effect of the latter was undone even when [C_4mim][BF_4] was present in a lower molar amount than sodium chlorate, (Entry 8).

In light of this data, it may not be surprising that [C_4mim][ClO_3] also gave no reaction (Entry 9). On the other hand, the reaction mixtures from entries 4 – 8 were hetereogeneous, so it is conceivable the IL salted out sodium chlorate, and [C_4mim] did not effectively escort chlorate into the organic phase. The reaction mixture from Entry 9, however was homogeneous and there was certainly an excess of chlorate in solution; there was still no yield. The possibility that the butyl group of [C_4mim] in each of these entries was acting as a radical scavenger was considered. It may have done that, but the methyl groups in [C_1mim][ClO_3] should not have, and this IL still caused no desired reaction (Entry 10). The strangest thing about the reactions in Entries 4 – 10 is that, in each of them, a color change was observed, and a separate layer formed, which should indicate a reaction. The separate layer was presumably the appropriate [$C_n$mim][Br], which is not freely soluble in either dichloroethane or fluorobenzene. However, there was no convenient way to confirm this suspicion because the identifying properties of the invested IL and the putative IL cannot be easily resolved. This byproduct could have been formed if the reduction of carbon tetrabromide to tetrabromomethane radical anion and its dissociation to tribromomethane radical and bromide occurred. Why this radical generation may have occurred and not led to desired product is discussed below.

CHAPTER 6

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Imidazole- and thiazole-2-thiones are reliably desulfurized with benzoyl peroxide, and this method should require little adaptation to allow preparations of structurally related targets. The anion exchange following oxidations of either 1,3-dialkyl **I2T**s or thiazole-2-thiones to salts must be carefully regulated, but this task is easily accomplished. This methodology provides inherently halide free salts, and it has turned out that it is best suited to the preparation of imidazolium benzoates. These benzoates were targets when the research program was initiated because it was assumed they could be converted to other salts with acid, but the fact that they are recovered in higher yields and IL contents than products from other anion exchanges is purely coincidental. Of course, [ClO_3] ILs were also accessible in high yields and IL contents following anion exchange, but at least one is explosive, so it is unlikely [ClO_3] ILs will ever be seen again.

Preparations of [C_4mim][BF_4] and of [C_4mim], [C_1mim], and [dpim][CF_3CO_2] demonstrate the viability of the oxidation → anion exchange → acidification sequence. The preparations of **I2T**s in one pot are striking, especially since one of these preparations allows a two step synthesis of [C_1mim][OBz] from commercially available sarcosine methyl ester hydrochloride. Imidazole quaternizations with methyl and ethyl chloride or bromide require an autoclave. Methyl or ethyl iodide can be used for the quaternization, but a productive anion exchange of an imidazolium iodide requires exchange with an alkali or heavy metal salt because iodide is not conveniently exchanged by acids.

The specimens of [C$_n$tz] ILs from this new route were recovered in disappointing yield and, sometimes, low desired IL content. Nonetheless, these entries are also valuable examples because the parent heterocycle for a quaternization reaction is prohibitively expensive—thiazole costs 111 USD / 5 g. The existing alternative is to simply quaternize (4)(5)-methylthiazole to [C$_n$mtz] ILs.

Quaternization / anion exchange syntheses do not allow fine tuning of the structures of ILs or of other azolium salts as does the benzoyl peroxide method. The protocol can also furnish ILs with substituents which are not introducible by a quaternization route, as seen in the synthesis of [dpim] salts, and this feature of the synthesis is the most important. The investment of both capital and effort is much higher for commonly available ILs by this method than by the standard one. However, the synthesis is not difficult or expensive in the absolute sense, and the investments required for certain salts could be much lower by this method even when a suitable alternative exists. For example, Scheme 34 shows representative syntheses of diarylimidazolium and -inium salts. Both routes start with the condensation of two equivalents of an aromatic amine on glyoxal, which means the sequence only leads to products where both aryl substitutents are identical. By the method introduced here, the substitutent on each nitrogen is introduced separately before the thione reagent is assembled, and this method would be preferable for the synthesis of salts differentiated at each nitrogen. On the other hand, Nolan's synthesis provided imidazolium salts in roughly 35% yield from commercial materials and Arduengo's provided imidazolinium salts in roughly 45% yield from commercial compounds. The synthesis of [dpim][OBz] proceeded in a 57% yield from thione **40**, but the thione was prepared in 17% total yield from commercial sources.

The potential for elaborations at C(4)(5) in the final products by this new protocol is augmented by the fact the synthesis commences with an amino acid or ester, either of which can be easily alkylated under conditions of phase transfer catalysis. This manipulation figures to be more convenient than custom syntheses of α-aminoaldehydes or -ketones, especially considering the comparative ease of handling and storage of amino acids and esters instead of the corresponding aldehydes and ketones. By this method, an IL precursor could also be elaborated at C(5) at the **2TH** stage, which is also relevant to the synthesis of imidazoles from amino acids.

The oxidation of **I2T**s to neutral imidazoles is not only adaptable, but operationally facile because, when **2TH**s are prepared by the dehydration of α-thioureido acids, the major byproduct is removed during filtration. There is a large commensurate loss in yield, but final purification is simplified—all solid **2TH**s prepared here were crystallized or reprecipitated—and would be of little concern in a synthetic plan which introduces advanced C(5) substituents at the stage of a simple **2TH**. Another advantage to this synthesis of imidazoles is the chromatographic mobility of the **I2T**s relative to imidazoles. Chromatography was only required in this series of reactions following the incomplete reduction of **54** to **55**, but the retention factors are available from TLC monitoring of the formation of the **I2T**s. Except for the phenolic **I2T 55** made during the formal synthesis of *Leucetta* alkaloids, these compounds had retention factors around 0.5 in 2 : 1 ether – hexanes, which made them far more mobile on silica gel than were the imidazoles they became. For example, phenolic **I2T 55** was chromatographically purified with ethyl acetate as the eluent, whereas methyl ether **53** prepared by desulfurization of **55** and methylation required ethanolic ethyl acetate as the eluent. In this example, the **I2T** moiety was better chromatographically behaved when appended to a phenol than was the corresponding imidazole when appended to a methyl aryl ether.

Thus, if used in the synthesis of a complex imidazole target, it could be expected a chromatographically slow imidazole moiety could be masked as the more mobile **I2T** precursor until the last synthetic stages, and it is noteworthy that **I2T**s are visible at 254 nm. It is probably fair to say oxidation with benzoyl peroxide is the first to make such a strategy possible, because other desulfurization agents (e.g., excess hydrogen peroxide, conc HNO_3, *m*CPBA, DMDO, Raney Ni) could more easily interfere with many functional groups present in an advanced intermediate than could benzoyl peroxide. As far as can be ascertained, these entries to **50** – **53** are also the first complete examples of the amino acid → **2TH** → **I2T** → imidazole sequence, which is also convenient because scrupulously dry glassware, reagents, or solvents were not required at any point.

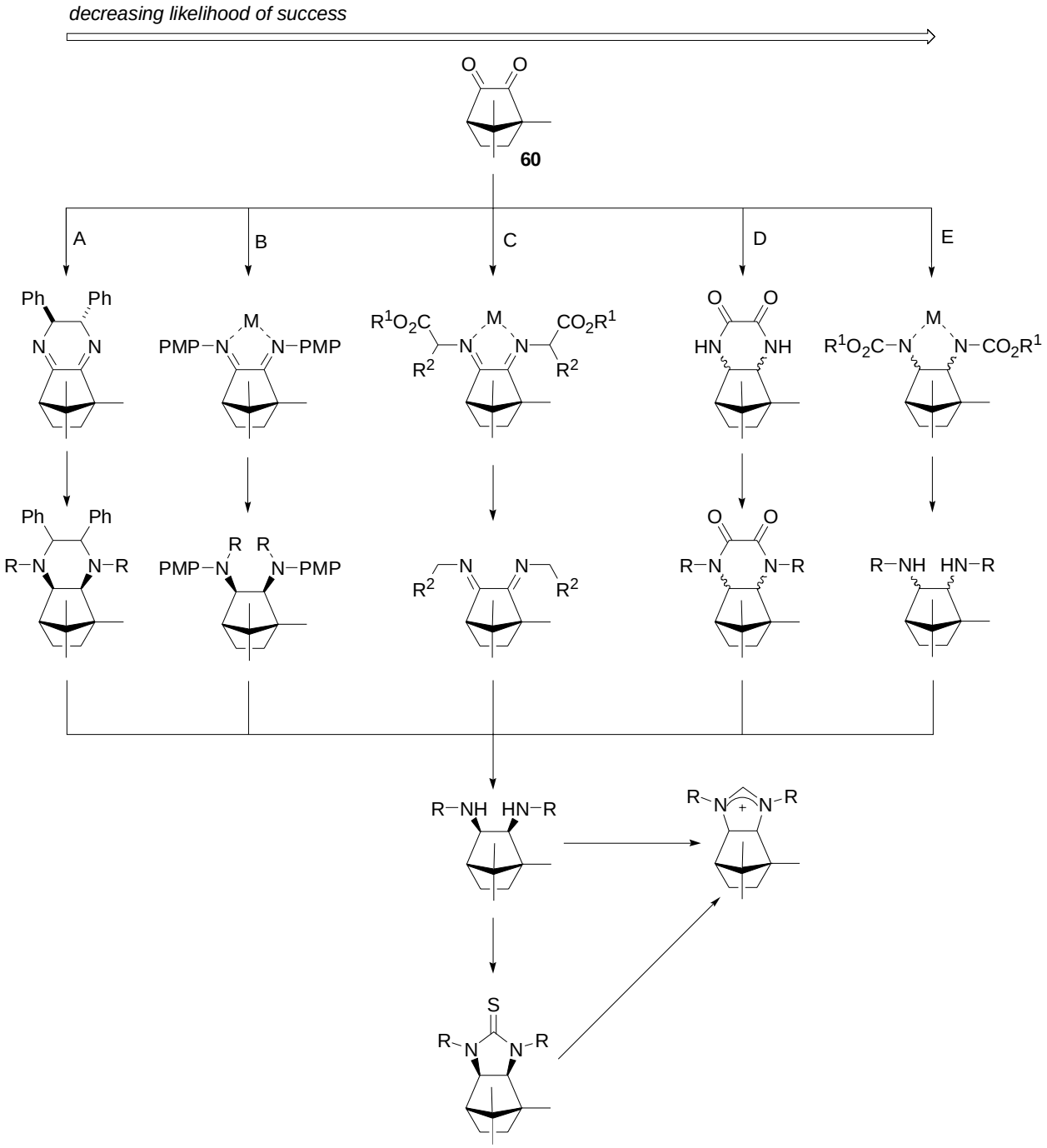
It is unfortunate that a chiral IL derived from camphor could not be accessed. In terms of ILs with chiral cations, many of the current examples rely on hydrolytically unstable derivates of chiral pool molecules (e.g., oxazolinium salts derived from amino alcohols or pinene), or do not confine chiral information near the cationic center (e.g., ephedrine and 2-methylbutyl derivatives), which one would expect must associate with the transition structure of any enantioselective reaction occurring under its direction. Wasserscheid and coworkers' hydrogenation (Scheme 25) demonstrated how valuable strong ion pairing can be to an enantioselective reaction of (and, presumably, in) an IL. An imidazolium cation fused to camphor would have been hydrolytically stable and would have fixed the chiral information in a certain position.

Whether the interest going forward is in showcasing the desulfurization and anion exchange route or simply getting a new chiral IL in hand, the wisest move from here is probably to target an IL derived from a different chiral starting material. However, there are a few

possible reactions on the camphor scaffold worth some consideration for future work (Scheme 50). All these proposals require backing up the synthetic plan to camphorquinone and pursuing an imidazolinium salt by positioning a nitrogen nucleophile near camphor C(2) through some initial reaction at C(3). They are ordered such that the apparent likelihood of a successful reaction decreases from left to right; they are framed as isobornyldiamine syntheses because these diamines should carry through to imidazolinium salts with or without the intermediacy of an imidazolidine-2-thione.

The precedent for route A comes from C. A. Busacca and coworkers, who condensed *rac*-diphenylethylendiamine with camphorquinone, then sequentially reduced the product with sodium borohydride and freed the amine moieties by catalytic hydrogenation.[570] Note that they found it was important to use the chiral diamine because the intermediate derived from the *meso* compound underwent electrocyclic ring opening, but it was not important to apply the chiral diamine in optically enriched form. The synthesis of an isobornyldiamine put forth in Scheme 50 differs only by the inclusion of an *N*-alkylation step, and it is hard to imagine this route would not deliver a suitable chiral IL precursor. Camphordiimines like that appearing in path B are accessible by the reactions of aromatic amines with camphorquinone under the influence of a strongly coordinating metal. Only reactions of aniline are precedented.[571, 572] Path B assumes the same reaction with *p*-anisidine is possible, and this route would afford an isobornyldiamine diprotected with the *p*-methoxyphenyl (PMP) group following reduction, which could be alkylated before deprotection with cerium (IV) ammonium nitrate.

Path C is the first route considered which has no closely related literature precedent, and assumes the organizing effect of a coordinating metal could be used to prepare camphordiimines from aliphatic amines. Applying this aliphatic amine as an aminoester would allow a reaction at

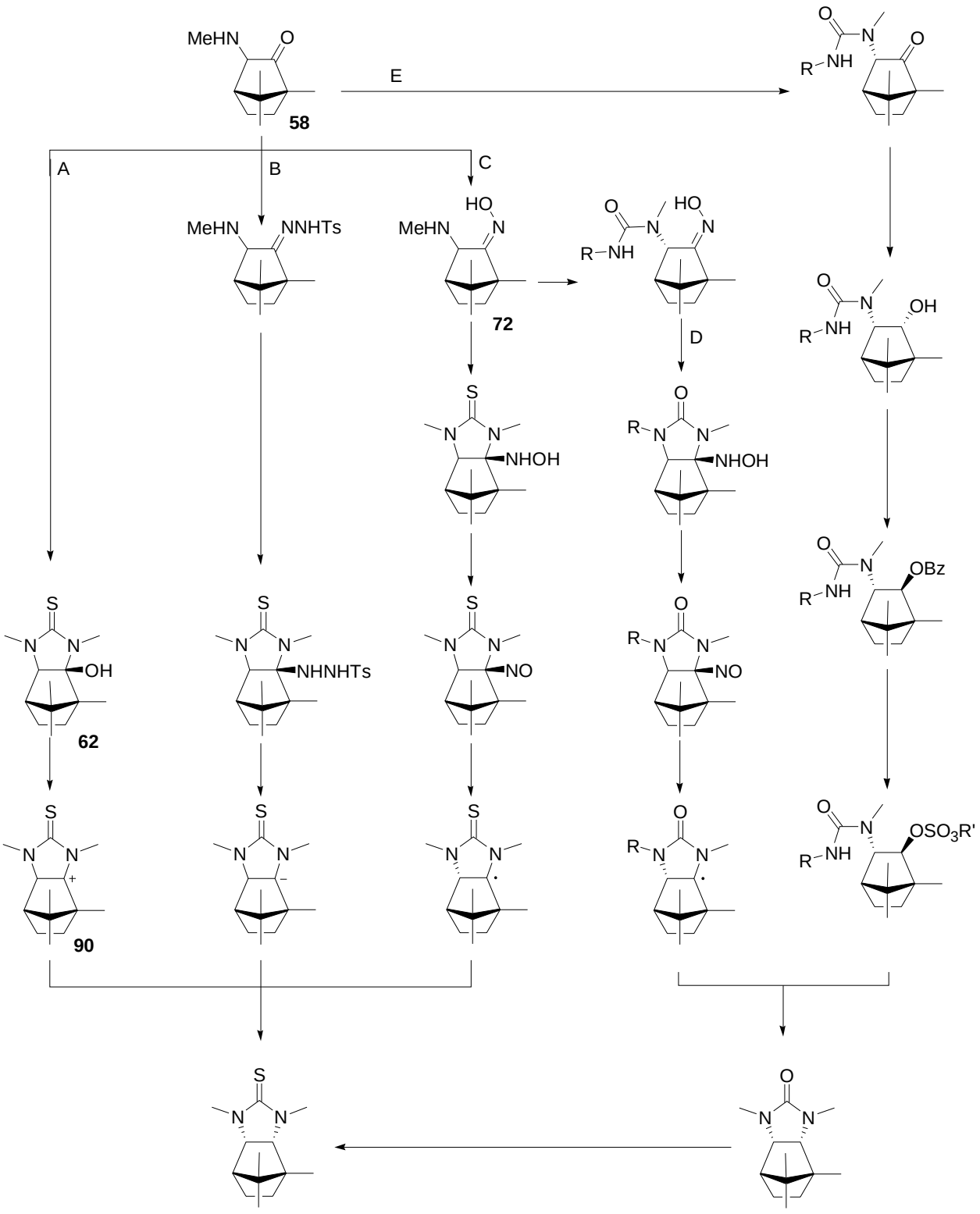


Scheme 50. Conceivable routes to imidazolidine-2-thiones from organized double condensations on camphorquinone (**60**).

the high temperature that is a known requirement for this sort of double condensation. Following saponification, the product should decarboxylate in a manner analogous to enzymatic amino acid decarboxylations accomplished with pyruvate as a cofactor. Path D is based on the concept of tethering a nucleophile near camphor C(2) as in Busacca and coworkers' synthesis of *cis*-3-aminoisobornylamine and as in the accidental synthesis of 4-hydroxyimidazolidine-2-thione **62**. Assuming hydride delivery from formic acid is meaningfully stereoselective in the first place, stereocontrol in a double Leuckart–Wallach reaction of camphorquinone with oxalyl amide would likely be a problem. Path E would require alkyl carbamates which give reductive aminations. Presuming sequential reductive aminations could be accomplished, the rest of the conversions would be straightforward.

The data above should confirm the futility of any more work on imidazolium salts. As for why a revised synthetic plan should start from camphorquinone, if one considers how another degree of saturation could be introduced to the derivatives currently available or to presumably easily available derivatives, the idea stumbles out of the gate (Scheme 51). The infeasability of the tosylhydrazone (path B) and Mitsunobu (path E) routes in Scheme 51 should be self evident. A route proceeding through cation **90** (path A) would be difficult to accomplish because the cation is sterically hindered, and it is hard to believe any of the common hydride transfer agents could get near the cationic site. For the same reason, **62** probably would not undergo Barton-McCombie deoxygenation.

Other routes proceeding through a free radical quench (paths C and D) are intriguing, however. Path C would require a method to oxidize a hydroxylamine while sparing a sulfur atom, and the introduction of free radical centers in the presence of sulfur atoms would likely invite side reactions. Undesirable reactions the sulfur atom would likely give are precluded in



Scheme 51. Conversion of the available camphor derivatives to an imidazoline-2-thione seems unlikely.

path D, which proceeds from the acylation of **72** with an isocyanate instead of an isothiocyanate. This approach seems the most plausible out of the set in Scheme 51, but it seems wiser to pursue the chemistry in Scheme 50, or to select a different terpene for derivatization.

It is difficult to know where to go in the pursuit of a phase transfer catalyzed halogenation in or with ILs. Only [$C_n$mim] ILs were evaluated for the purpose of transferring hydroxide or chlorate into an organic phase, but these ILs clearly cannot tolerate the former under the halogenation conditions, and they appear to have a poisoning effect on the reaction initiated by the latter. The first and most obvious change is to reevaluate the same model phase transfer halogenations in [$C_n$mp] and [PR_4] ILs, which have come into far more widespread use since this program of research was initiated. The [$C_n$mp] ILs should even tolerate 50% aqueous sodium hydroxide, so they could be used in the prototypical PTC method, and could also be assessed with a different single electron donor if desired. The oxophilic [PR_4] ILs may or may not give a side reaction with hydroxide, but should be compatible with chlorate or another single electron donor. Then again, so should have the [$C_n$mim] ILs.

Changing the IL may not lead to success because the problem in the attempted PTC halogenations initiated by chlorate may have been the very presence of IL. The explanation for the failure of these reactions simply cannot be that ILs did not transfer chlorate into the reaction phase. Chlorate can initiate the reaction without any phase transfer catalyst and, more significantly, [ClO_3] ILs miscible with the organic solvents were also used and certainly made chlorate available for a subsequent reaction. Color changes and phase separations were observed in the reactions almost immediately, and these observations suggest the initiation stage of the reaction took place. Yet adamantane was recovered quantitatively. It is possible [$C_n$mim][ClO_3]

or [C_4mim][BF_4] and sodium chlorate actually did *initiate* the reaction, but that tribromomethane radicals combined in preference to abstracting a hydrogen from adamantane.

The mechanistic rationale for this theory runs as follows. Assume [$C_n$mim] cations facilitated dissolution of chlorate in the organic phase (when it was not applied directly as the [$C_n$mim] IL) and single electron transfer to tetrabromomethane. This reduction step is not the type of charge concentrating endeavor which ILs favor, but the overall process is because the formed tetrabromomethane radical anion decomposes to tribromomethyl radical and bromide. Further, the [$C_n$mim] cations should have assisted the decomposition step. The release of [$C_n$mim][Br] as a precipitate followed, which would explain the observation of the formation of a second layer in the reaction mixture. There is no substantial polarity change between the ground state ($Br_3C^{\bullet}$ and adamantane) and the transition structure in the propagation step, and there is certainly no increase in polarity. Hence, the IL would not facilitate hydrogen abstraction and could potentially discourage the propagation step after facilitating the radical formation step. That would leave the tribromomethane radicals no course of reaction but combination. At the time, the prospect of a premature termination was not considered, and no effort was made to find 1,1,1,2,2,2-hexabromoethane as a byproduct. This material would not have stood out during analyses, either, because it is invisible in ^{1}H NMR spectroscopy and should give peaks < 0 ppm in ^{13}C NMR spectroscopy—note that the ^{13}C NMR chemical shift of tetrabromomethane is $\delta = -29.71$. Hence, there is currently no hard data to support such a hypothesis, but there is also no other apparent explanation.

CHAPTER 7

EXPERIMENTAL SECTION

General: Methyl isothiocyanate (97%) was distilled prior to use. All other reagents were used as received from commercial sources. NMR spectra of compounds in the [C_4mim], [dpim], and [$C_n$tz] series were recorded on a Varian Mercury 400; compounds in the [C_1mim] series were analyzed on a Bruker AV400WB. Mass spectra were collected on a Hewlett-Packard 5970 or a Finnegan MAT 311A (both EI). IR spectra were taken in ATR mode on a BioRad Excalibur Series FTS 4000 (Harrick Split Pea or Specac Golden Gate Diamond accessory) or a Bruker Optics IFS 48 (Specac Golden Gate Diamond accessory). HRMS analyses were performed on a Finnigan MAT 95 or a Bruker Daltonics 4.7T FTMS (both EI). Mps were recorded on a MelTemp apparatus or a Büchi SMP-20 and are uncorrected. All chromatographic purifications were performed with 230 – 400 mesh silica gel. Yields of salt products are reported from both the oxidation step and the anion exchange (AE).

The observed ^{1}H NMR coupling constants between C(4) and C(5) protons from azole-2-thiones with C_s symmetry (**34**, **42**, **43**) are small (J = 3 – 4 Hz). This fine structure is obscured by line broadening in at least one ^{1}H NMR signal of most salt formulations derived from these thiones; only [C_1tz] and [C_4tz][Br], and [C_4tz][BF_4] are unaffected. This effect has been discussed in terms of the magnetic properties of nitrogen and sulfur and of H–D exchange in nitrogen heterocycles.[573-576] Since this broadening is observed for the salts but not the thiones, the latter case is probably the dominant factor here. When this distortion is observed, it is designated in the line assignment of the affected peak with an "LB" before the apparent

multiplicity of the affected peak. Three salts ([C_4tz][BF_4] and [Br], and [dpim][OBz]) underwent C(2) H–D exchange too rapidly to see the C(2) proton in ^{1}H NMR; the associated C(2) triplets in ^{13}C NMR spectra were observed.

Ethyl *N*-butylglycinate (31): Over the course of 30 min, chloroacetic acid (100.05 g, 1.06 mol) was cautiously added portionwise to *n*$BuNH_2$ (1.0 L, 740 g, 10.0 mol) cooled with an ice bath. After addition, the ice bath was removed and the mixture was refluxed 4 h, whereupon *n*$BuNH_2$ was removed by distillation. Residual *n*$BuNH_2$ was released by three additions and distillations of EtOH (100 mL ea). The mixture was cautiously acidified with 1 : 9 (v / v) conc H_2SO_4–EtOH (1.0 L), then refluxed 48 h. EtOH (ca. 500 mL) was removed by rotary evaporation, and the remaining solution was poured into Na_2CO_3 (175 g) in water (1.1 L). The mixture was extracted with DCM (3 × 200 mL), and the combined organic layers were washed with water, then brine (1 × 100 mL ea), dried ($MgSO_4$), filtered, and concentrated. Aminoester **31** (96.15 g, 604 mmol, 57%) was distilled from the crude mixture ($bp_{0.23}$ 42 °C, lit[428] $bp_{1.1}$ 52 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14 (q, *J* = 7 Hz, 2 H), 3.33 (s, 2 H), 2.54 (t, *J* = 7 Hz, 2 H), 1.50 (br s, 1 H), 1.44 (quintet, *J* = 7 Hz, 2 H), 1.34 (sextet, *J* = 7 Hz, 2 H), 1.22 (t, *J* = 7 Hz, 3 H), 0.85 (t, *J* = 7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 60.5, 50.9, 49.1, 32.0, 20.2, 14.0, 13.8 ppm.

1-Butyl-3-methyl-2-thiohydantoin (33): Methyl isothiocyanate (44.15 g, 604 mmol) was dissolved in dry Et_2O (50 mL) and added dropwise to freshly distilled **31** (96.15 g, 604 mmol) cooled with an ice bath. The reaction was continued at 0 °C for 10 min after complete addition, then fitted with a simple distillation apparatus for the removal of Et_2O. The thick orange residue was stirred neat and heated 3 d at 140 – 150 °C. The product at this stage was used for the

synthesis of **34** described below, but can be distilled ($bp_{0.55}$ = 126 °C, 79% yield). After one distillation each, compound **33** was the same red hue as **34** made from it. The distillates had similar bps, which probably reflect a common codistilling impurity. Their appearance and bps could be resolved by further purification, but their respective spectroscopic and chromatographic characteristics were unchanged. In this case, distilled **33** (4.63 g) was chromatographed (100 g silica gel, eluent: 2 : 1 Et_2O–pet ether, R_f = 0.6) and redistilled ($bp_{0.15}$ = 86 °C), returning **33** (3.25 g) as a dull yellow oil (70% recovery, 55% yield from **31**). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.01 (s, 2 H), 3.81 (t, *J* = 8 Hz, 2 H), 3.24 (s, 3 H), 1.65 (quintet, *J* = 8 Hz, 2 H), 1.40 (sextet, *J* = 8 Hz, 2 H), 0.97 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.0, 170.6, 51.7, 46.5, 29.0, 28.1, 19.7, 13.6 ppm. MS: *m*/*z* (%) = 186 (100) [M^+], 157 (18) [M^+ – Et], 153 (25) [M^+ – SH], 144 (46) [M^+ – propene], 130 (20) [M^+ – butene]. IR (film): $\tilde{\nu}$ = 3597, 3480, 2958, 2932, 2872, 1744, 1496, 1334 cm^{-1}. HRMS (EI) calcd for $C_8H_{14}N_2OS$: 186.0827, found 186.0822.

1-Butyl-3-methylimidazole-2-thione (34): With DIBALH: Using glassware dried at 180 °C overnight, assembled while hot, and cooled under argon, freshly distilled **31** (2.44 g, 15.3 mmol) was treated with methyl isothiocyanate (1.12 g, 15.3 mmol) as described in the preparation of **33**. After addition was complete, the ice bath was removed and the reaction achieved rt over the course of 30 min, then was cooled to –78 °C for the addition of 20 wt % Dibalh in PhMe (32 mL, 27.5 g, 5.50 g Dibalh, 38.7 mmol). The mixture was stirred for 30 min, the cold bath was removed, and the reaction was quenched and worked up as described by Markwalder and coworkers[427] to yield crude **34** (2.68 g) that was chromatographed (70 g silica gel, eluent: 2 : 1 Et_2O–pet ether, R_f = 0.4) to yield **34** (1.91 g, 11.2 mmol, 73%). One pot preparation from **31**:

Freshly distilled **31** (1.50 g, 9.42 mmol) in EtOH (10 mL) at 0 ^{o}C was treated with methyl isothiocyanate (0.69 g, 9.44 mmol), stirred at 0 ^{o}C for 10 min after complete addition, then allowed to achieve rt over the course of 30 min. After the addition of 85% KOH (0.05 g, 0.80 mmol), analysis by TLC indicated cyclization to intermediate **33** was complete in 30 min, and $NaBH_4$ (0.36 g, 9.42 mmol) in EtOH (15 mL) was added. The solution was stirred 7 h, then quenched with conc aq HCl (5 mL) and stirred 30 min. The slurry was diluted with water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were washed with water and brine (1 × 20 mL ea), dried ($MgSO_4$), filtered, and concentrated to yield yellow **34** (1.49 g, 8.8 mmol, 93%). From **33**: Crude **33** prepared as described above was diluted with EtOH (200 mL) and cautiously treated with $NaBH_4$ (22.84 g, 604 mmol) in EtOH (600 mL). The mixture turned from the deep red color of crude **33** to a bright purple while stirring 7 h, and was then slowly treated with conc aq HCl (200 mL, 2.40 mol), turning an intense yellow while stirring 30 min. The slurry was poured into water (750 mL) containing NaCl (100 g), and shaken with DCM (500 mL). The mixture slowly separated into two layers, and the organic layer was collected. The aq layer was extracted with more DCM (3 × 100 mL), the combined organic layers were washed with water (1 × 100 mL) and repetitively with brine (100 mL) until the recovered volume was approximately equal to the volume invested (requiring at least 3 ×), then dried ($MgSO_4$), filtered and concentrated to leave crude **34** (98.97 g) as an oil that was distilled ($bp_{0.4}$ = 132 ^{o}C) (81.15 g, 477 mmol, 79% from **31**, 99% from **33**). After one distillation each, compound **34** was the same red hue as **33** used to make it. The distillates had similar bps, which probably reflect a common codistilling impurity. Their appearance and bps could be resolved by further purification, but their respective spectroscopic and chromatographic characteristics were unchanged. In this case, distilled **34** (4.38 g) was chromatographed (105 g silica gel, eluent: 2 :

1 Et_2O–pet ether, R_f = 0.4) and redistilled ($bp_{0.15}$ = 77 °C), returning **34** as a brilliant yellow oil (1.68 g, 38% recovery, 30% from **33**). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (d, *J* = 4 Hz, 1 H), 6.83 (d, *J* = 4 Hz, 1 H), 4.03 (t, *J* = 8 Hz, 2 H), 3.60 (s, 3H), 1.75 (quintet, *J* = 8 Hz, 2 H), 1.37 (sextet, *J* = 8 Hz, 2 H), 0.96 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 117.1, 116.0, 46.8, 34.2, 30.1, 18.9, 12.9 ppm. MS: *m*/*z* (%) = 170 (100) [M^+], 141 (33) [M^+ – Et], 137 (77) [M^+ – SH], 128 (43) [M^+ – propene], 114 (72) [M^+ – butene]. IR (film): $\tilde{\nu}$ = 3449, 3095, 2957, 2932, 2872, 1569, 1461, 1413, 1401 cm^{-1}. HRMS (EI) calcd for $C_8H_{14}N_2S$: 170.0878, found 170.0878.

1-Butyl-3-methylimidazole-2-thione methyl iodide (35): A solution of **34** (9.56 g, 56.1 mmol) in DME (100 mL) in an Erlenmeyer flask was treated with MeI (5.5 mL, 12.54 g, 88.3 mmol). A precipitate formed while stirring 30 min at rt, and was dissolved by bringing the mixture to a gentle reflux by direct contact with a hot plate and adding *t*-BuOH (125 mL). The solution was cooled back to rt, frozen at –30 °C overnight, thawed, and filtered to yield **35** (15.70 g, 50.3 mmol, 90%). Mp 110–115 °C. ^{1}H NMR (400 MHz, D_2O): δ = 7.61 (LB s, 1 H), 7.57 (LB s, 1 H), 4.31 (LB t, *J* = 6 Hz, 2 H), 3.94 (s, 3 H), 2.48 (s, 3 H), 1.83 (LB quintet, *J* = 6 Hz, 2 H), 1.34 (LB sextet, *J* = 6 Hz, 2H), 0.91 (t, *J* = 6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 140.8, 124.8, 123.2, 49.3, 35.8, 31.5, 18.9, 17.2, 12.8 ppm.

Oxidation of 34 with $(BzO)_2$: A two-necked flask containing a magnetically stirred slurry of 75% $(BzO)_2$ (190.10 g, MW_{eff} = 322.97, 589 mmol) in THF (200 mL) was cooled in an ice bath, and fitted with an addition funnel containing neat **34** (20.04 g, 118 mmol) and a condenser. The reaction first bubbled and fumed locally as **34** was introduced dropwise, then achieved reflux,

dissolving $(BzO)_2$. The persistent yellow color of **34** disappeared as the oxidation continued. The reaction stood at rt until excess $(BzO)_2$ precipitated. The mixture was filtered, and the filter cake was washed with water (100 mL). The filtrate was diluted with Et_2O (200 mL) and shaken, the aq layer was recovered, washed with DCM (5 × 20 mL), drained onto $NaHCO_3$ (9.86 g, 117 mmol), stirred 15 min, then treated with EtOH (300 mL) and stirred 30 min. The supernatant was recovered by suction filtration into a tared flask, and the filter cake was washed with EtOH (2 × 20 mL). An aliquot (4.5803 g) was removed from the aq EtOH solution (407.67 g), concentrated, spiked with DMSO (0.1018 g, 1.30 mmol), and the entire mixture was taken up in D_2O. When the integral of the neatly resolved C(3) methyl singlet at ca. 4 ppm was set to 3.0, the integral of the neatly resolved DMSO singlet at ca. 2.8 ppm integrated to 9.48 H, corresponding to a $[C_4mim]$ species concentration of 0.8247 mmol / 4.5803 g soln, or 0.1800 mmol $[C_4mim]$ species / g solution (73.4 mmol, 62%).

AE to $[C_4mim][OBz]$: A portion of the calibrated soln from the oxidation of **34** (367.67 g, 66.2 mmol, representing 106 mmol **34**) was treated with NaOBz (9.54 g, 66.2 mmol), stirred 2.5 h, suction filtered, and concentrated. The product and associated sediment were taken up in 1 : 1 Et_2O–EtOH (100 mL) and loaded on silica gel (50 g) packed in 1 : 1 Et_2O-EtOH. The column was drained to level the loaded volume with the top of the column below the insoluble matter. The vessel originally containing the sample was rinsed with fresh 1 : 1 Et_2O–EtOH (100 mL), which was loaded on the column and similarly leveled. The column was washed with fresh 1 : 1 Et_2O–EtOH (400 mL). All column issue was collected in one vessel, concentrated, then dried at 0.2 mm Hg to leave a light gold liquid (17.18 g, 3.78 mmol $[C_4mim][OBz]$ per g; 64.9 mmol, 16.90 g $[C_4mim][OBz]$ total, 98% from AE, 61% from **34**). A portion of this formulation (2.45

g, 9.26 mmol [C_4mim][OBz]) was rechromatographed (5 g silica gel, 10 mL loading and rinsing vol, 40 mL wash vol), returning a light gold liquid (1.88 g, 3.69 mmol [C_4mim][OBz] per g; 6.94 mmol, 1.81 g [C_4mim][OBz] total, 75% recovery, 46% from **5**) after drying under vacuum. ^{1}H NMR (400 MHz, D_2O): δ = 8.36 (s, 1 H), 7.71 (d, *J* = 8 Hz, 2 H), 7.33 (t, *J* = 8 Hz, 1 H), 7.26 (t, *J* = 8 Hz, 2 H), 7.15 (LB s, 1 H), 7.13 (LB s, 1 H), 3.85 (t, *J* = 8 Hz, 2 H), 3.62 (s, 3 H), 1.54 (quintet, *J* = 8 Hz, 2 H), 1.06 (sextet, *J* = 8 Hz, 2 H), 0.74 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 179.1, 140.9, 140.3, 136.1, 133.8, 133.1, 128.2, 126.9, 54.0, 43.7, 36.0, 23.6, 17.6 ppm. IR (film): $\tilde{\nu}$ = 3153, 3061, 2963, 2859, 1597, 1556, 1364 cm^{-1}.

AE to [C_4mim][ClO_3]: A portion of the calibrated soln from the oxidation of **34** (33.35 g, 6.00 mmol, representing 9.65 mmol **34**) was treated with $NaClO_3$ (0.64 g, 6.01 mmol), stirred 2.5 h, suction filtered, concentrated, and purified on silica gel (5 g) like [C_4mim][OBz] with 1 : 1 Et_2O–EtOH (10 mL ea loading, rinsing, and washing vols) to recover a brilliant yellow liquid that was dried under vacuum (1.72 g, 3.33 mmol [C_4mim] salts per g; 5.73 mmol [C_4mim] salts total, 96% from AE, 59% from **34**). A portion of the isolate (1.69 g, 5.63 mmol [C_4mim] salts) was identically rechromatographed and dried under vacuum to return a sample identical in appearance (1.24 g, 4.53 mmol [C_4mim] salts per g; 5.62 mmol [C_4mim] salts total, 100% recovery, 58% from **34**). ^{1}H NMR (400 MHz, D_2O): δ = 8.81 (s, 1 H), 7.57 (LB s, 1 H), 7.52 (LB s, 1 H), 4.26 (t, *J* = 8 Hz, 2 H), 3.97 (s, 3 H), 1.89 (quintet, *J* = 8 Hz, 2 H), 1.38 (sextet, *J* = 8 Hz, 2 H), 0.99 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 140.5, 128.2, 126.9, 53.9, 43.6, 36.0, 23.5, 17.4 ppm.

Acidification of [C_4mim][OBz] to [C_4mim][CF_3CO_2]: Once-chromatographed [C_4mim][OBz] (2.0 g, 7.56 mmol) was treated with neat TFA (1.2 mL, 1.84 g, 16.2 mmol). Before the mixture could cool, it was loaded on silica gel (5 g) packed in Et_2O. The column was washed with Et_2O until the collected wash did not respond to UV light when spotted on a TLC plate and was not acidic (requiring ca. 30 mL). The column was then washed with 1 : 1 Et_2O–EtOH (50 mL), the collected issue was concentrated and dried under vacuum to isolate [C_4mim][CF_3CO_2] (0.82 g, 3.88 mmol [C_4mim][CF_3CO_2] per g; 3.18 mmol, 0.80 g [C_4mim][CF_3CO_2] total, 43%). ^{1}H NMR (400 MHz, D_2O): δ = 8.75 (s, 1 H), 7.48 (LB s, 1 H), 7.44 (LB s, 1 H), 4.17 (t, J = 7.2 Hz, 2 H), 3.89 (s, 3 H), 1.81 (quintet, J = 7.2 Hz, 2 H), 1.29 (sextet, J = 7.2 Hz, 2 H), 0.89 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 166.8 (q, $^2J(^{13}C–^{19}F)$ = 35), 140.5, 128.3, 127.0, 119.8 (q, $^1J(^{13}C–^{19}F)$ = 291 Hz), 54.0, 43.6, 36.0, 23.5, 17.4 ppm. IR (film): $\tilde{\nu}$ = 3157, 3092, 2966, 2865, 1683, 1576, 1197, 1164, 1110 cm^{-1}.

Acidification of [C_4mim][OBz] to [C_4mim][BF_4]: Once-chromatographed [C_4mim][OBz] (2.0 g, 7.56 mmol) was treated with 54 wt % HBF_4–Et_2O (2.1 mL, 1.34 g HBF_4, 15.2 mmol). Before the solution cooled down, it was loaded on silica gel (5 g) packed in Et_2O. The column was eluted with Et_2O until the issue was not UV-responsive when spotted on a TLC plate (requiring ca. 30 mL) and further until pH paper was unaffected (requiring ca. 120 mL more). [C_4mim][BF_4] (0.98 g, 4.48 mmol [C_4mim][BF_4] per g; 4.38 mmol, "0.99g" [C_4mim][BF_4] total, 58% yield) was then washed off with 1 : 1 Et_2O–EtOH (75 mL), concentrated, and dried under vacuum. ^{1}H NMR (400 MHz, D_2O): δ = 8.72 (s, 1H), 7.55 (LB s, 1 H), 7.51 (LB s, 1 H), 4.26 (t, J = 8 Hz, 2 H), 3.97 (s, 3 H), 1.91 (quintet, J = 8 Hz, 2 H), 1.40 (sextet, J = 8 Hz, 2 H), 0.99 (t,

J = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 140.7, 128.3, 127.0, 54.1, 43.6, 36.2, 23.6, 17.5 ppm. IR (film): $\tilde{\nu}$ = 3631, 3567, 3160, 3121, 2964, 2938, 2877, 1046, 1018 cm^{-1}.

1,3-Dimethylimidazole-2-thione (36): Fresh ethanolic NaOEt was prepared by the dissolution of Na (8.90 g, 387 mmol) in EtOH (250 mL). Solid methyl sarcosinate hydrochloride (50 g, 358 mmol) was cautiously added to the solution through a powder funnel, and any residue was washed in with EtOH (ca. 100 mL). The solution was stirred 30 min, cooled to 0 °C, then methyl isothiocyanate (26.2 g, 358 mmol) in EtOH (300 mL) was added, the ice bath was removed, and the reaction was stirred 1 h before the addition of 85% KOH (2.25 g, 34.1 mmol). Solid $NaBH_4$ (13.6 g, 360 mmol) was added 2 h later. Stirring was continued overnight, then conc HCl (150 mL, 1.80 mol) was added. After 30 min, the bright yellow slurry was diluted with water (400 mL) and extracted with DCM (2 × 400 mL, 1 × 200 mL). The combined organic layers were washed with water, then brine (1 × 200 mL ea), dried ($MgSO_4$), filtered and evaporated to leave crude **36** (33.3 g) as a yellow solid which was crystallized twice from EtOH (350 mL) to leave colorless **36** (29.89 g, 233 mmol, 65%). Mp 177 – 179.5 °C (lit[149] = 182–184 °C). The ^{1}H and ^{13}C NMR spectra matched the reference.[149]

1,3-Dimethyl-2-thiohydantoin (37): Fresh methanolic NaOMe was prepared by the dissolution of Na (4.12 g, 179 mmol) in MeOH (50 mL). Solid methyl sarcosinate hydrochloride (25.00 g, 179 mmol) was added and the solution was stirred 30 min, cooled to 0 °C, treated with methyl isothiocyanate (13.10 g, 179 mmol) in xylenes (100 mL), stirred 10 min at 0 °C, and stirred 30 more min after removal of the ice bath. A simple distillation apparatus was installed, MeOH was removed, then a condenser was attached and the reaction was refluxed 3 d. After a hot gravity

filtration, the filtrate was cooled to rt, then to –30 °C. The precipitate was recovered by suction filtration and crystallized thrice from 20:20:1 PhMe–*n*-C_7H_{14}–EtOH to deliver **37** (5.17 g, 35.9 mmol, 20%). Mp 91.5 – 93 °C (lit[429] 92–92.5 °C). ^{1}H (400 MHz, $CDCl_3$): δ = 4.06 (s, 2 H), 3.33 (s, 3 H), 3.21 (s, 3 H) ppm. ^{13}C (100 MHz, $CDCl_3$): δ = 183.4, 170.3, 53.86, 33.9, 28.3 ppm.

Oxidation of 36 with $(BzO)_2$: To oxidize **36** (32.72 g, 255 mmol), a magnetically stirred slurry of 75% $(BzO)_2$ (412.0 g, MW_{eff} = 322.97, 1.28 mol) in THF (250 mL) was first treated with small (ca. 150 mg) portions of **36**, which turned orange and fumed, until the stiff slurry stirred freely, and the flask was warm to the touch, but not hot enough to completely dissolve $(BzO)_2$. Then an ice bath was added, and small portions of **36** were added at a faster rate, stopping for ca. 1 min every time vigorous gas evolution was observed. Complete addition required 30 min, after which time the ice bath was removed and the solution was stirred for 1 h. Unlike the analogous reaction with **34**, excess $(BzO)_2$ did not precipitate, so the stock solution was thinned with Et_2O (400 mL) and water (100 mL). The aq layer was recovered, and the organic layer was washed with water (1 × 50 mL). The combined aq layers were washed with DCM (5 × 40 mL), then drained onto solid $NaHCO_3$ (21.5 g, 256 mmol), stirred 15 min, treated with EtOH (600 mL), stirred 30 min, suction filtered into a tared flask, and the filter cake was washed with EtOH (2 × 50 mL). An aliquot (6.095 g) was removed from the solution (803.395 g), concentrated, spiked with DMSO (0.080 g), and the ^{1}H NMR revealed a concentration of 0.2708 mmol [C_1mim] species / g solution (218 mmol, 85%).

AE to [C_1mim][OBz]: A portion of the calibrated solution from the oxidation of **36** (614.57 g, 166 mmol, representing 195 mmol **36**) was treated with NaOBz (23.98 g, 166 mmol), stirred 2.5 h, suction filtered, and concentrated. The residue was purified on silica gel (65 g) like [C_4mim][OBz] using 1 : 1 Et_2O–EtOH (loading and rinsing vols of 200 mL, 250 mL washing vol). Concentration and drying under vacuum left [C_1mim][OBz] as a clear brown liquid (31.80 g, 3.54 [C_1mim][OBz] mmol per g; 113 mmol, 24.58 g [C_1mim][OBz] total, 68% from AE, 58% from **36**). A portion of the isolate (2.00 g, 7.08 mmol) was rechromatographed over silica gel (5 g) with 1 : 1 Et_2O–EtOH (loading, rinsing, and washing volumes of 25 mL ea). Concentration and drying left a specimen identical in appearance (1.35 g, 3.31 mmol [C_1mim][OBz] per g; 4.47 mmol, 0.98 g [C_1mim][OBz] total, 63% recovery, 37% from **36**). ^{1}H NMR (400 MHz, D_2O): δ = 8.46 (s, 1 H), 7.82 (d, J = 8 Hz, 2 H), 7.50 (t, J = 8 Hz, 1 H), 7.42 (t, J = 8 Hz, 2 H), 7.27 (s, 2 H), 3.76 (s, 6 H) ppm. ^{13}C (100 MHz, D_2O): δ = 176.4, 137.9, 137.5, 132.9, 130.4, 129.9, 125.0, 37.1 ppm. IR (film): $\tilde{\nu}$ = 3381, 3147, 3062, 2960, 2935, 2873, 1596, 1553, 1368 cm^{-1}.

AE to [C_1mim][ClO_3]: A portion of the calibrated solution from the oxidation of **36** (182.73 g, 49.5 mmol, representing 58.0 mmol **36**) was treated with $NaClO_3$ (5.27 g, 49.5 mmol), stirred 2.5 h, suction filtered, and concentrated. The residue was purified on silica gel (20 g) like [C_4mim][OBz] using 1 : 1 Et_2O–EtOH (100 mL loading and rinsing vols, 150 mL fresh vol). Concentration and drying under vacuum left the product (7.32 g, 4.71 mmol [C_1mim] salts per g; 34.5 mmol [C_1mim] salts total, 70% from AE, 59% from **36**). A portion of the isolate (2.042 g, 9.62 mmol) was rechromatographed over silica gel (5 g) with 1 : 1 Et_2O–EtOH (loading, rinsing, and washing volumes of 20 mL ea). Concentration and drying under vacuum left a visually indistinguishable product (1.38 g, 4.85 mmol [C_1mim] salts per g; 6.69 mmol [C_1mim] salts

total, 70% recovery, 41% from **36**). ^{1}H NMR (400 MHz, D_2O): δ = 8.68 (s, 1 H), 7.45 (s, 2 H), 3.92 (s, 6 H) ppm. ^{13}C (100 MHz, D_2O): δ = 138.2, 125.0, 37.2 ppm.

Acidification of [C_1mim][OBz] to [C_1mim][CF_3CO_2]: Once-chromatographed [C_1mim][OBz] (2 g, 7.08 mmol) was treated with neat TFA (2.3 g, 20.2 mmol). Before the mixture could cool, it was loaded on silica gel (5 g) packed in Et_2O, and the column was washed with Et_2O (130 mL) to remove BzOH and excess TFA. The column was washed with 1 : 1 Et_2O–EtOH (60 mL), concentrated and dried under vacuum to return [C_1mim][CF_3CO_2] (1.31 g, 4.07 mmol [C_1mim][CF_3CO_2] per g; 5.33 mmol, 1.12 g [C_1mim][CF_3CO_2] total, 75%). ^{1}H NMR (400 MHz, D_2O): δ = 8.64 (s, 1 H), 7.41 (s, 2 H), 3.89 (s, 6 H) ppm. ^{13}C (100 MHz, D_2O): δ = 163.8 (q, $^{2}J(^{13}C–^{19}F)$ = 35 Hz), 137.9, 125.0, 119.5 (q, $^{1}J(^{13}C–^{19}F)$ = 291 Hz), 37.2 ppm. IR (film): $\tilde{\nu}$ = 3424, 3150, 3095, 2965, 2939, 2878, 1683, 1198, 1166, 1119 cm^{-1}.

Anilinoacetaldehyde dimethyl acetal (38): Using glassware dried at 180 °C overnight, a 2 L three-necked flask was fitted with an argon inlet, a 125 mL pressure equalized addition funnel, and a glass stopper. The apparatus was cooled under a positive pressure of argon before the stopper was removed to load unwashed 60% NaH dispersion in mineral oil (32 g, 800 mmol) through an oven dried, dessicator cooled glass funnel. This funnel was rinsed with anhydrous DMSO (600 mL) and the glass stopper was replaced. The mixture was stirred 30 min at rt, whereupon most NaH had disappeared, and dry, distilled aniline (100 mL, 102 g, 1.10 mol) was introduced dropwise through an addition funnel. As sodium anilide was allowed to form over the course of 2 h at rt, the mixture turned opaque purple. Chloroacetaldehyde dimethyl acetal (83 mL, 91 g, 729 mmol) was then added dropwise through an addition funnel. The mixture was

kept under a positive pressure of argon as stirring continued 24 h after complete addition of the acetal. Slow addition of water (300 mL) followed, then NaOH (80 g) was added and allowed to dissolve before the mixture was saturated with NaCl (ca. 200 g). The mixture was washed with DCM (1 × 300 mL, 2 × 150 mL), and the combined organic extracts were washed with half-saturated NaCl (2 × 100 mL), water (2 × 100 mL), and brine (1 × 100 mL) before drying (Na_2SO_4), concentrating, and distilling ($bp_{0.20}$ 71 – 92.5 ^oC) to yield crude **38** (150.80 g, >100%) as a yellow oil. The crude product was distilled twice more ($bp_{0.2}$ 60 – 61.5 ^oC, lit[134] bp_{14} 156 – 159.5 ^oC) to isolate pure **38** (110.87 g, 612 mmol, 84%) as a colorless oil that quickly yellowed upon standing. Wanzlick and Schönherr did not report NMR spectra of **38**.[134] ^1H NMR (400 MHz, $CDCl_3$): δ =7.12 (t, *J* = 8 Hz, 2 H), 6.66 (t, *J* = 8 Hz, 1 H), 6.57 (d, *J* = 8 Hz, 2 H), 4.48 (t, *J* = 5.5 Hz, 1 H), 3.84 (br s, 1 H), 3.32 (s, 6 H), 3.19 (d, *J* = 5.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.8, 124.1, 112.5, 107.9, 97.4, 48.5, 40.3.

1,3-Diphenyl-2-thiohydantoin (39): Following Fischer esterification: *N*-Phenylglycine (95%, 20.5 g, 129 mmol) was dissolved in a prepared mixture of 98% H_2SO_4 (35 mL) and EtOH (315 mL) and refluxed 24 h, after which most EtOH was removed by rotary evaporation. The residue was cautiously treated with sat aq Na_2CO_3 (400 mL) and extracted with DCM (3 × 100 mL). The combined organic extracts were washed with water and brine (1 × 100 mL ea), dried ($MgSO_4$), filtered and concentrated. The residue (16.17 g, ca. 90 mmol aminoester) was treated with xylenes (200 mL) and phenylisothiocyanate (12.20 g, 90 mmol), and refluxed 60 h. In the course of the reaction a black film separated from a gold solution and deposited on the walls of the reaction flask. The gold solution was then separated from some black particulate matter by hot gravity filtration. The filtrate was cooled to rt, then –30 ^oC, and the resulting precipitate was

collected by suction filtration and washed with pet ether to deliver **39** (14.10 g, 53 mmol, 41% [2 steps]). Mp 214 – 219 °C. Through α-thioureido acid cyclization: *N*-Phenylglycine (95%, 8.45 g, 53.1 mmol) was added to a mixture of 50% aq KOH (6.27 g, 55.9 mmol), EtOH (18 mL) and water (10 mL). After dissolution, EtOH (8 mL) was added, the mixture was cooled to 0 °C, then phenylisothiocyanate (7.56 g, 55.9 mmol) in EtOH (6 mL) was added dropwise through an addition funnel. The funnel was rinsed with EtOH (5 mL), then the ice bath was removed and the reaction stirred 3 h. Following addition of 1 M HCl (200 mL), the mixture was stirred 30 min, cooled to 0 °C, and the intermediate acid was collected by suction filtration. The filter cake was taken up in acetone (400 mL), dried ($MgSO_4$), and filtered. At this point, TLC analysis (eluent: ether) showed a mixture of two compounds, one of which (R_f = 0.9, Et_2O) proved to be **39** and the other (R_f = 0.0 to 0.3) was presumed to be the intermediate acid. The solution was treated with 98% H_2SO_4 (5 mL), and the slower spot disappeared while stirring 3 d at rt. Acetone was removed by rotary evaporation, and the residue was treated with sat aq $NaHCO_3$ (250 mL), stirred 30 min, and filtered. The filter cake was reprecipitated twice from 1.5 : 1 DCE–*i*PrOH to deliver **39** (5.61 g, 20.9 mmol, 39%); the first reprecipitation required a hot gravity filtration. Mp 218 – 220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8 Hz, 2 H), 7.54–7.46 (m, 5 H), 7.37 (m, 3 H), 4.59 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.1, 169.1, 138.0, 133.2, 129.4, 129.3, 129.2, 128.5, 128.0, 125.4, 55.1 ppm. MS: *m*/*z* (%) = 268 (100) [M^+], 239 (21), 105 (39), 77 (23) [Ph^+]. IR (ATR): $\tilde{\nu}$ = 3056, 2939, 1756, 1592, 1453 cm^{-1}.

1,3-Diphenylimidazole-2-thione (40): A solution of **39** (15.22 g, 56.7 mmol) prepared by α-thioureido acid cyclization was brought to vigorous reflux in DCM (200 mL) prior to treatment

with $NaBH_4$ (2.36 g, 62.4 mmol) in EtOH (75 mL). Monitoring the reaction by TLC was difficult because **39** and **40** had identical R_fs in a variety of solvent systems; however, **39** was dark purple when viewed at 254 nm while **40** was a brilliant blue. After 2.5 h at reflux, the solution was cooled to rt, cautiously treated with conc aq HCl (40 mL, 480 mmol), stirred 30 min at rt, then diluted with water (200 mL). The released DCM was collected, and the water was washed with DCM (2 × 100 mL). The combined organic extracts were washed with water, then brine (1 × 100 mL ea), dried ($MgSO_4$), filtered, and concentrated. Crystallization of the residue from EtOH returned **40** (6.21 g, 24.6 mmol, 43%). Mp 156 – 158.5 °C (lit[134] mp 161 °C). Wanzlick and Schönherr's ^{1}H NMR was reported on the τ scale and only resolved aromatic from vinyl protons at 100 MHz.[134] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8 Hz, 4 H), 7.51 (t, *J* = 8 Hz, 4 H), 7.42 (t, *J* = 8 Hz, 2 H), 6.97 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 138.0, 128.9, 128.3, 126.1, 118.6 ppm. MS: *m*/*z* (%) = 252 (76) [M^+], 251 (100) [M^+ – H], 77 (12) [Ph^+]. IR (ATR): $\tilde{\nu}$ = 3175, 3141, 1594, 1493 cm^{-1}.

Oxidation of 40 with $(BzO)_2$: A magnetically stirred slurry of 75% $(BzO)_2$ (31.99 g, MW_{eff} = 322.97, 99.0 mmol) in THF (40 mL) was slowly treated with **40** (5.0 g, 19.8 mmol) in THF (30 mL). Addition of solid instead of dissolved **40** resulted in violent gas evolution. The reaction refluxed, dissolving $(BzO)_2$, and cooled back to rt, precipitating $(BzO)_2$, within 1 h, after which the mixture was diluted with water (25 mL), filtered, and the filter cake was washed with water (25 mL). The first addition of water was necessary because the solid salt product was not freely soluble in the wet THF mother liquor, as evidenced by an obvious dissolution of some of the filter cake in wash water if the first addition of water was neglected. The filtrate was shaken with Et_2O (100 mL), the aq layer was recovered and washed with DCM (5 × 5 mL), and then

drained onto solid $NaHCO_3$ (1.66 g, 19.8 mmol) and stirred 15 min. Additional water (ca. 25 mL) was needed for solubility, and brought the total volume of water to ca. 83 mL (ca. 8 mL from 75% $(BzO)_2$, and 75 mL wash water). Sufficient EtOH (175 mL) was added to precipitate putative Na_2SO_4, and the mixture was suction filtered into a tared flask. An aliquot (2.7861 g) was removed from the solution (212.49 g), concentrated, spiked with DMSO (0.0257 g, 0.329 mmol), and the ^{1}H NMR revealed a concentration of 0.0894 mmol [dpim] species / g solution (19.0 mmol, 96%).

AE to [dpim][OBz]: A portion of the calibrated soln from the oxidation of **40** (208.36 g, 18.6 mmol, representing 19.4 mmol **40**) was treated with NaOBz (2.68 g, 18.6 mmol), stirred 2 h, suction filtered, concentrated, and purified on silica gel (15 g) like [C_4mim][OBz] using 1 : 1 Et_2O–EtOH (50 mL load volume, 20 mL rinse volume, 200 mL wash volume). After removal of the solvents, the solid residue was crystallized from 1.5 : 1 $CHCl_3$–THF, which required a hot gravity filtration to remove a billowy insoluble material. The isolate was recrystallized from *t*BuOH twice, macerated with Et_2O to remove a large mass of *t*BuOH clinging to the salt, suction filtered, and then dried at 0.2 mmHg to return [dpim][OBz] (3.80 g, 2.85 mmol [dpim][OBz] per g; 10.84 mmol, 3.71 g [dpim][OBz] total, 58% from AE, 56% from **40**). Mp 144 – 148 ^{o}C (dec). The C(2) proton was invisible by ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD): δ = 8.20 (s, 2 H), 7.92 (d, J = 8 Hz, 2 H), 7.79 (d, J = 8 Hz, 4 H), 7.62–7.54 (m, 6 H), 7.35 (t, J = 8 Hz, 1 H), 7.29 (t, J = 8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD): δ = 174.1, 138.7, 135.0, ca. 138 (t), 130.83, 130.82, 130.3, 129.5, 127.9, 122.8, 122.4. IR (ATR): $\tilde{\nu}$ = 3472, 3082, 2968, 1592, 1544 cm^{-1}.

Acidification of [dpim][OBz] to [dpim][CF_3CO_2]: A slurry of [dpim][OBz] (0.55 g, 1.57 mmol) in THF (5 mL) was slowly treated with TFA (0.26 mL, 0.40 g, 3.5 mmol), and a clear, colorless solution resulted. THF was removed and the residue was crystallized thrice from toluene and dried at 0.2 mm Hg to deliver [dpim][CF_3CO_2] (0.52 g, 2.32 mmol [dpim][CF_3CO_2] per g; 1.20 mmol, 0.40 g [dpim][CF_3CO_2] total, 76%). Mp 95 – 96 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.35 (s, 1 H), 8.05 (s, 2 H), 7.76 (d, J = 8 Hz, 4 H), 7.57–7.54 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4 (q, $^2J(^{13}C–^{19}F)$ = 37 Hz), 134.4, 133.7, 130.8, 130.6, 122.3, 122.1, 116.0 (q, $^1J(^{13}C–^{19}F)$ = 289 Hz) ppm. IR (ATR): $\tilde{\nu}$ = 3135, 3107, 3081, 1754, 1190, 1127, 1067 cm^{-1}.

3-Methylthiazole-2-thione (42): To a solution of NaOH (26.58 g, 665 mmol) in water (200 mL) was added methylamine hydrochloride (22.51 g, 333 mmol), which was allowed to dissolve before the addition of CS_2 (20 mL, 25.32 g, 333 mmol). Over the course of 2 h, a clear red solution resulted, which was stirred a further 3 h before the addition of a prepared solution of chloroacetic acid (31.43 g, 333 mmol) and K_2CO_3 (23.22 g, 168 mmol) in water (150 mL). The mixture was stirred 5 h, then cautiously treated with conc H_2SO_4 (10 mL, 180 mmol) and stirred overnight. The formed precipitate (50.86 g) was collected by suction filtration, dissolved in DCM (300 mL), washed with water (1 × 50 mL), sat aq $NaHCO_3$ (1 × 100 mL), water (1 × 50 mL), brine (1 × 100 mL), dried ($MgSO_4$), filtered and concentrated to give orange crystals (37.74 g, 256 mmol putative rhodanine intermediate **41**). These crystals were dissolved in EtOH (800 mL), cooled to 0 ^oC, treated with $NaBH_4$ (9.70 g, 256 mmol), stirred 20 min at 0 ^oC before the ice bath was removed, then allowed 40 min to achieve rt. The mixture had turned brown. After the slow addition of conc HCl (125 mL, 1.50 mol), the bright yellow mixture was stirred 30 min,

then concentrated by rotary evaporation at 100 mbar in a 60 ^{o}C water bath until most EtOH had been removed. The mixture was diluted with water (500 mL) and washed with DCM (3 × 100 mL). The combined organic extracts were washed successively with water and brine (1 × 100 mL ea), dried ($MgSO_4$), filtered and concentrated to leave crude, brown **42** (27.64 g) which was sublimed twice at 0.15 mm Hg from a 95 – 100 ^{o}C oil bath to yield **42** (26.36 g, 201 mmol, 60%) as sticky orange crystals. Mp 45 – 47 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, J = 4 Hz, 1 H), 6.65 (d, J = 4 Hz, 1 H), 3.71 (s, 3 H) ppm. ^{13}C (100 MHz, $CDCl_3$): δ = 187.4, 132.3, 110.9, 37.5 ppm. MS: m/z (%) = 131 (100) [M^+], 72 (20) [H_2CNCS^+], 58 (21) [$HCCSH^+$]. IR (ATR): $\tilde{\nu}$ = 3124, 3090, 3050, 1556 cm^{-1}.

Oxidation of 42 with $(BzO)_2$: A stirred slurry of $(BzO)_2$ (184.58 g, MW_{eff} = 322.97, 572 mmol) in THF (250 mL) was treated with solid **42** (15.0 g, 114 mmol) in one portion. After the reaction refluxed under its own power and cooled back to rt, an ice bath was added to force the precipitation of excess $(BzO)_2$, which was removed by suction filtration. The filter cake was washed with water (75 mL), and the filtrate was shaken with Et_2O (250 mL). The aqueous layer was separated and washed with DCM (5 × 15 mL), then recovered in a tared flask. An aliquot (4.1421 g) was removed from the isolated solution (102.75 g), concentrated, spiked with DMSO (0.0483 g), and the ^{1}H NMR in D_2O revealed a concentration of 0.9138 mmol [C_1tz] species / g solution (94 mmol, 82%).

AE to [C_1tz][Br]: A portion of the calibrated soln from the oxidation of **42** (34.71 g, 31.7 mmol, corresponding to 38.5 mmol **42**) was treated with $NaHCO_3$ (2.66 g, 31.7 mmol) and NaBr (3.26 g, 31.7 mmol), stirred 30 min, then treated with EtOH (75 mL) and stirred 2 h. The

precipitate was removed by suction filtration, the filtrate was concentrated by rotary evaporation, and the isolate was purified like [C_4tz][CF_3CO_2] using THF to load the salt and rinse the reaction vessel (15 mL) and to wash (ca. 120 mL) most of the color off the silica gel column (15 g). The column was washed with 1 : 1 EtOH–Et_2O (400 mL), the collected issue was concentrated, and the residue was crystallized twice from 3 : 1 *i*PrOH–THF to deliver [C_1tz][Br] (0.95 g, 4.92 mmol [C_1tz] salts per g; 4.67 mmol [C_1tz] salts total, 15% from AE, 12% from **42**). Mp 51.5 – 56 °C. ^{1}H NMR (400 MHz, D_2O): δ = 10.02 (s, 1 H), 8.44 (d, J = 4 Hz, 1 H), 8.29 (d, J = 4 Hz, 1 H), 4.33 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 159.57 (t), 138.4, 126.2, 41.6. IR (ATR): $\tilde{\nu}$ = 3390, 3069, 2074 cm^{-1}.

3-Butylthiazole-2-thione (43): A mixture of *n*$BuNH_2$ (25 mL, 18.5 g, 253 mmol), K_2CO_3 (17.24 g, 125 mmol), and CS_2 (15 mL, 18.99 g, 249 mmol) in MeOH (300 mL) required ca. 3 h to cleanly dissolve, whereupon a prepared solution of chloroacetic acid (23.90 g, 253 mmol) and K_2CO_3 (17.45 g, 126 mmol) in MeOH (400 mL) was added. KCl precipitated during the reaction was removed by suction filtration every 1.5 h to allow easy stirring of the mixture. After 4.5 h at rt, and three suction filtrations, no more KCl precipitate formed, and the mixture was cautiously acidified with conc H_2SO_4 (30 mL, 540 mmol). The solution was stirred overnight, then most EtOH was removed by rotary evaporation. The mixture was diluted with water (200 mL) and washed with DCM (3 × 100 mL). The combined organic layers were washed with sat aq $NaHCO_3$, then water, then brine (1 × 100 mL ea), dried ($MgSO_4$), filtered and concentrated to leave a yellow oil (44.14 g, 233 mmol putative rhodanine intermediate **41**), which was dissolved in EtOH (200 mL) and cooled to 0 °C. The solution was treated with $NaBH_4$ (8.81 g, 233 mmol), stirred 20 min at 0 °C before the ice bath was removed, then allowed

40 min. to achieve rt. The mixture had turned brown, but during the slow addition of conc HCl (100 mL, 1200 mmol), turned yellow again. The acidified mixture stirred 30 min at rt before it was diluted with water (750 mL) and washed with DCM (3 × 150 mL). The combined organic layers were washed successively with water and brine (1 × 100 mL ea), dried ($MgSO_4$), filtered and concentrated to leave crude **43** (27.69 g), which was distilled ($bp_{0.20}$ 118 – 130 ^oC) to deliver **43** (24.41 g, 141 mmol, 57%) as a bright yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 4 Hz, 1 H), 6.65 (d, *J* = 4 Hz, 1 H), 4.17 (t, *J* = 8 Hz, 2 H), 1.79 (quintet, *J* = 8 Hz, 2 H), 1.41 (sextet, *J* = 8 Hz, 2 H), 0.96 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.0, 131.4, 111.1, 49.6, 30.4, 19.7, 13.6 ppm. MS: *m*/*z* (%) = 173 (90) [M^+], 144 (17) [M^+ – Et], 140 (62) [M^+ – SH], 131 (26) [M^+ – propene], 117 (100) [M^+ – butene]. IR (film): $\tilde{\nu}$ = 3099, 3049, 2956, 2930, 2870, 1548 cm^{-1}.

Oxidation of 43 with $(BzO)_2$: A stirred slurry of 75% $(BzO)_2$ (130.90 g, MW_{eff} = 322.97, 405 mmol) in THF (110 mL) was treated with neat **43** (14.02 g, 80.9 mmol) added through a funnel in one portion. The holding vessel and funnel were rinsed with THF (2 × 10 mL). The reaction cycled from rt to reflux, dissolving $(BzO)_2$, and back to rt, precipitating $(BzO)_2$, in less than 1 h. The precipitate was removed by suction filtration, and the filter cake was washed with water (70 mL). The filtrate was shaken with Et_2O (130 mL), the aq layer was recovered and washed with DCM (5 × 14 mL), then drained into a tared flask. An aliquot (3.1377 g) was removed from the isolated solution (92.31 g), concentrated, and spiked with DMSO (0.0634 g), and the ^1H NMR in D_2O revealed a concentration of 0.4062 mmol [C_4tz] species / g solution (37.5 mmol, 46%).

AE to [C_4tz][CF_3CO_2]: A portion of the calibrated soln from the oxidation of **43** (44.05 g, 17.9 mmol, representing 38.6 mmol **43**) was treated with $NaHCO_3$ (3.01 g, 35.8 mmol), then TFA (2.04 g, 17.9 mmol), and stirred 30 min before the addition of EtOH (100 mL). The mixture was stirred 2 h, suction filtered, and concentrated by rotary evaporation. The crude isolate was slurried in THF (20 mL), loaded on a column of silica gel (20 g) packed in THF, and the loading volume was forced down to the top of the column. The reaction vessel was rinsed with THF (20 mL), which was similarly loaded and forced down. The column was then washed with fresh THF until the issue was nearly colorless (requiring ca. 90 mL). The column was washed with 1 : 1 EtOH–Et_2O (300 mL), the collected issue was concentrated and the residue was dried under vacuum to isolate [C_4tz][CF_3CO_2] (3.68 g, 4.30 mmol [C_4tz] salts per g; 15.8 mmol [C_4tz] salts total, 88% from AE, 41% from **43**). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.03 (s, 1 H), 8.56 (d, J = 3.2, 1 H), 8.36 (LB t, 1 H), 4.68 (t, J = 7.4, 2 H), 1.96 (quintet, J = 7.4, 2 H), 1.35 (sextet, J = 7.4, 2 H), 0.93 (t, J = 7.4, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2 (q, $^2J(^{13}C–^{19}F)$ = 33 Hz), 159.7, 137.2, 126.5, 117.3 (q, $^1J(^{13}C–^{19}F)$ = 294 Hz), 55.5, 32.4, 19.3, 13.2 ppm. IR (film): $\tilde{\nu}$ = 3397, 3056, 2964, 2939, 2878, 1666, 1197, 1164, 1117 cm^{-1}.

AE to [C_4tz][Br]: A portion of the calibrated soln from the oxidation of **43** (14.85 g, 6.03 mmol, corresponding to 13.0 mmol **43**) was treated with $NaHCO_3$ (0.51 g, 6.07 mmol) and NaBr (0.62 g, 6.03 mmol), and stirred 30 min before the addition of EtOH (50 mL). The mixture was stirred 2 h, suction filtered, and concentrated by rotary evaporation. The crude isolate was purified like [C_4tz][CF_3CO_2] using THF to load the salt and rinse the reaction vessel (5 mL) and to wash (ca. 50 mL) most of the color off the silica gel column (3 g). The column was washed with 1 : 1 EtOH–Et_2O (70 mL), the collected issue was concentrated, and the residue was

crystallized twice from 1 : 1 *i*PrOH–THF to recover [C_4tz][Br] (0.65 g, 5.18 mmol [C_4tz] salts per g; 3.37 mmol [C_4tz] salts total, 56% from AE, 26% from **43**). Mp 134 – 135 °C. The C(2) proton was invisible by ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$): δ = 8.62 (d, *J* = 4 Hz, 1 H), 8.38 (d, *J* = 4 Hz, 1 H), 4.70 (t, *J* = 8 Hz, 2 H), 2.01 (quintet, *J* = 8 Hz, 2 H), 1.42 (sextet, *J* = 8 Hz, 2 H), 1.01 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$): δ = ca. 160 (t), 137.7, 127.2, 55.9, 32.8, 19.8, 13.5 ppm. IR (ATR): $\tilde{\nu}$ = 3070, 3010, 2869 cm^{-1}.

AE to [C_4tz][BF_4]: A portion of the calibrated soln from the oxidation of **43** (14.94 g, 6.07 mmol) was treated with $NaHCO_3$ (0.51 g, 6.07 mmol) and $NaBF_4$ (0.67 g, 6.10 mmol), and stirred 30 min before the addition of EtOH (50 mL). The mixture was stirred 2 h, suction filtered, and concentrated by rotary evaporation. The crude isolate was purified like [C_4tz][CF_3CO_2] using THF to load the salt and rinse the reaction vessel (5 mL) and to wash (ca. 40 mL) most of the color off the silica gel column (5 g). The product was washed off with 1 : 1 EtOH–Et_2O (70 mL) to deliver [C_4tz][BF_4] (0.33 g, 4.02 mmol [C_4tz] salts per g; 1.33 mmol [C_4tz] salts total, 22% from AE, 10% from **43**). It was clear from a TLC analysis that a great deal of [C_4tz][BF_4] was lost to the initial THF wash.

Acidification of [C_4tz][CF_3CO_2] to [C_4tz][BF_4]: A solution of [C_4tz][CF_3CO_2] (1.5 g, 6.45 mmol) in water (5 mL) was treated with 50% aq (8.029 M) HBF_4 (0.81 mL, 6.50 mmol), and concentrated by distillation at atmospheric pressure. After distillation, the sample was put under the light vacuum provided by a water aspirator for 1 h, then taken up in DCM (5 mL), loaded on silica gel (4 g) packed in Et_2O, and the column was eluted with Et_2O until the issue was neutral when spotted on pH paper, requiring ca. 80 mL. The column was then eluted with 1 : 1 EtOH–

Et_2O (70 mL), the collected issue was concentrated and the residue was dried under vacuum to isolate $[C_4tz][BF_4]$ (1.17 g, 3.99 mmol $[C_4tz]$ salts per g; 4.67 mmol $[C_4tz]$ salts total, 72%). The C(2) proton was invisible by ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$): δ = 8.43 (d, *J* = 3.5 Hz, 1 H), 8.26 (d, *J* = 3.5 Hz, 1 H), 4.60 (t, *J* = 8 Hz, 2 H), 1.99 (quintet, *J* = 8 Hz, 2 H), 1.39 (sextet, *J* = 8 Hz, 2 H), 0.98 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$): δ = 157.9 (t, $^1J(^{13}C–D)$ = 75 Hz), 137.4, 126.5, 55.8, 32.4, 19.5, 13.2 ppm. IR (film): $\tilde{\nu}$ = 3116, 2964, 2937, 2877, 1025 cm^{-1}.

Acidification of $[C_4tz][CF_3CO_2]$ to $[C_4tz][PF_6]$: A solution of $[C_4tz][CF_3CO_2]$ (1.5 g, 6.03 mmol) in water (5 mL) was treated with 60% aq (6.786 M) HPF_6 (0.89 mL, 6.0 mmol), and concentrated by distillation at atmospheric pressure. After distillation, the sample was put under the light vacuum provided by a water aspirator for 1 h, then was taken up in DCM (5 mL) and loaded on silica gel (4 g) packed in Et_2O. When the column was eluted with Et_2O, the issue never turned acidic when spotted on pH paper, suggesting that HPF_6 does not move on silica gel with ether as eluent. Nevertheless, the column was washed with Et_2O (50 mL). The column was then eluted with 1 : 1 EtOH–Et_2O (70 mL) to return $[C_4tz][PF_6]$ (0.70 g, 3.91 mmol per g; 2.74 mmol total, 45%). The bulk issue was pH-neutral, indicating the IL isolate did not pick up residual HPF_6. ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$): δ = 10.0 (s, 1 H), 8.36 (d, *J* = 2 Hz, 1 H), 8.21 (LB s, 1 H), 4.60 (t, *J* = 8 Hz, 2 H), 1.98 (quintet, *J* = 8 Hz, 2 H), 1.40 (sextet, *J* = 8 Hz, 2 H), 0.99 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C (100 MHz, $CDCl_3/CD_3OD$): δ = ca. 157 (t), 137.5, 126.6, 55.9, 32.4, 19.5, 13.3 ppm. IR (ATR): $\tilde{\nu}$ = 3115, 2964, 2937, 2877, 1029 cm^{-1}.

Quaternization and AE synthesis of [C_4mim][BF_4] from 1-methylimidazole: Distilled 1-methylimidazole (230 mL, 236.9 g, 2.88 mol) was treated with distilled *n*BuCl (360 mL, 316.8 g, 3.42 mol) and refluxed 40 h, then excess *n*BuCl was removed by distillation. Crystals of [C_4mim][Cl] could not be formed, and the mixture was diluted with water (160 mL) and treated with 50% aq HBF_4 (365 mL, 514.7 g, 2.93 mol). The solution was stirred 24 h, then aq HCl was removed by distillation. The residue was taken up in DCM (2.2 L), the ca. 2.8 L solution was split in half, and each half was repeatedly washed with water (15 mL). The separatory funnel was rinsed with fresh water between each wash. After ca. 20 washes per half, the water wash had the same pH as the water invested, and no precipitate formed when $AgNO_3$ was added. Each cloudy and yellow fraction was washed twice more with water,[58] then dried and decolorized by the addition of 20 g Celite-521. Pristine solutions were recovered after Celite was removed by gravity filtration. The halves were recombined, DCM was removed, and the product was magnetically stirred while dried under vacuum 8 h at 100 ^oC to leave [C_4mim][BF_4] (494.05 g, 2.19 mol, 76%). The concentrated product was slightly yellow en masse, but samples up to ca. 20 mL were colorless.

General synthesis of 2-thiohydantoins: Based on the procedure of Johnson and Buchanan,[433] glycine (6.54 g, 87 mmol to make **44**; 5.46 g, 73 mmol to make **45**; 5.86 g, 78 mmol to make **46**) was dissolved in 1 eq 50% aq KOH (9.78 g, 87 mmol to make **44**; 8.16 g, 73 mmol to make **45**; 8.76 g, 78 mmol to make **46**), the soln was thinned with EtOH (1.2 mL per 1 g 50% aq KOH), cooled to 0 ^oC, then treated dropwise with 1 eq of the appropriate isothiocyanate (10.03 g, 87 mmol *n*-butyl- to make **44**; 10.85 g, 73 mmol benzyl- to make **45**; 10.55 g, 78 mmol phenyl- to make **46**) in a vol of EtOH roughly equal to the supplied mass of 50% aq KOH. The reaction

was stirred 3 h, then acidified with 1 M HCl (200 mL ea). The crude α-thioureidoacid was collected by suction filtration, and the filtrate was cooled to 0 °C and refiltered. The combined isolates were taken up in as little acetone as feasible (250 mL to make **44** and **45**, 300 mL to make **46**), dried ($MgSO_4$), gravity filtered, treated with 96 – 98% H_2SO_4 (5 mL ea), and followed to completion by TLC (eluent: Et_2O), where the α-thioureidoacid appeared as a streak from the origin. When the product (R_fs specified below) was the only mobile component in TLC (3 d to make **44** and **46**, 6 d to make **45**), the reaction was stripped of acetone, carefully neutralized with sat aq $NaHCO_3$ (250 mL ea), and suction filtered.

3-Butyl-2-thiohydantoin (44): After two crystallizations from 2 : 1 *n*-C_7H_{16}–toluene where **44** was harvested by simple decantation of the mother liquor, and one more crystallization from PhMe followed by suction filtration, **44** (7.49 g, 43 mmol, 50%) was recovered as colorless crystals (R_f = 0.78, Et_2O). Mp 106.5 – 109 °C (lit[463] mp 109.8 – 110.7 °C). ^{1}H NMR (400 MHz, DMSO–d_6): δ = 10.15 (s, 1 H), 4.12 (s, 2 H), 3.64 (t, *J* = 8 Hz, 2 H), 1.52 (quintet, *J* = 8 Hz, 2 H), 1.27 (sextet, *J* = 8 Hz, 2 H), 0.89 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, DMSO–d_6): δ = 183.3, 172.5, 48.2, 39.6, 29.2, 19.3, 13.4 ppm. IR (ATR): $\tilde{\nu}$ = 3262, 2960, 2926, 2873, 2857, 1708, 1506 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_7H_{12}N_2OS$ [M^+]: 172.06703; found: 172.0666.

3-Benzyl-2-thiohydantoin (45): Crystallization from EtOAc, which required a hot gravity filtration, returned **45** (8.86 g, 43 mmol, 59%) as large amber crystals (R_f = 0.78, Et_2O). Mp 176 – 177 °C (lit.[461] 154 – 156 °C). ^{1}H NMR (400 MHz, DMSO–d_6): δ = 10.31 (s, 1 H), 7.32 – 7.24 (m, 5 H), 4.87 (s, 2 H), 4.20 (s, 2 H) ppm. ^{13}C NMR (100 MHz, DMSO–d_6): δ = 183.1,

172.5, 136.3, 128.2, 127.4, 127.1, 48.4, 43.2 ppm. IR (ATR): $\tilde{\nu}$ = 3268, 2904, 1709, 1507 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{10}H_{10}N_2OS$ [M^+]: 206.05138; found: 206.0509.

3-Phenyl-2-thiohydantoin (46): Crystallization from nitromethane, which required a hot gravity filtration, returned **46** (9.37 g, 49 mmol, 62%) as bright yellow crystals (R_f = 0.62, Et_2O). Mp 248 – 252 °C (dec) (lit[463] 258.3 – 259.7 °C; lit[577] 243 °C). ^1H NMR (400 MHz, DMSO–d_6): δ = 10.40 (s, 1 H), 7.48 (t, *J* = 8 Hz, 2 H), 7.41 (t, *J* = 8 Hz, 1 H), 7.27 (d, *J* = 8 Hz, 2 H), 4.28 (s, 2 H) ppm. ^{13}C NMR (100 MHz, DMSO–d_6): δ = 183.2, 172.0, 133.3, 128.7, 128.5, 128.4, 49.0 ppm. IR (ATR): $\tilde{\nu}$ = 3140, 3000, 2953, 2913, 1758, 1516 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_9H_8N_2OS$ [M^+]: 192.03573; found: 192.0353.

General synthesis of imidazole-2-thiones: A stock soln of 0.50 M LiCl–$NaBH_4$ in 3 : 1 DME–EtOH was prepared by vigorously stirring $NaBH_4$ (7.56 g, 200 mmol) into a fresh soln of LiCl (8.47 g, 200 mmol) in 3 : 1 DME–EtOH (300 mL). The soln was made up to 400 mL total with 3 : 1 DME–EtOH. NaCl formed as a fine precipitate[578] that was smoothly transferred in the necessary volume (128 mL, 64 mmol for **44**; 108 mL, 54 mmol for **45**; 116 mL, 58 mmol for **46**) for reduction of the appropriate **2TH** (5 g, 29 mmol **44**, 26 mmol **45**, 28 mmol **46**). The prepared soln was cooled into the temperature range specified in Table 1 before the **2TH** was added in one portion. The reaction was followed by TLC analysis (eluent: Et_2O) of Et_2O extracts of acidified reaction aliquots. After 6 h, only the **I2T** was visible. The reaction was quenched with conc aq HCl (50 mL), stirred 30 min, diluted with water (50 mL), and washed with DCM (3 × 50 mL). The combined organic extract was washed with water and brine (1 × 50 mL ea), dried ($MgSO_4$), filtered, and concentrated to leave **47** – **49** as specified.

1-Butylimidazole-2-thione (47): Yield 4.35 g (28 mmol, 97%; R_f = 0.44, Et_2O). Mp 80 – 81.5 °C (lit[456] 80 – 81 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.13 (br s, 1 H), 6.74 (d, *J* = 1.6 Hz, 1 H), 6.71 (d, *J* = 1.6 Hz, 1 H), 4.01 (t, *J* = 8 Hz, 2 H), 1.76 (quintet, *J* = 8 Hz, 2 H), 1.38 (sextet, *J* = 8 Hz, 2 H), 0.95 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 117.7, 114.3, 46.6, 31.0, 19.6, 13.5 ppm. MS (EI): *m/z* (%): 156 (100) [M^+], 127 (27) [M^+ – Et], 123 (45) [M^+ – SH], 114 (30) [M^+ – propene], 100 (73) [M^+ – butene]. IR (ATR): $\tilde{\nu}$ = 3092, 2954, 1571 cm^{-1}. HRMS (EI): *m/z* calcd for $C_7H_{12}N_2S$ [M^+]: 156.07212; found: 156.0718.

1-Benzylimidazole-2-thione (48): Yield 4.31 g (23 mmol, 88%; R_f = 0.44, Et_2O). Mp 145 – 148 °C (lit[456] 145 – 146 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.25 (br s, 1 H), 7.36–7.30 (br m, 5 H), 6.72 (d, *J* = 1.8 Hz, 1 H), 6.58 (d, *J* = 1.8 Hz, 1 H), 5.23 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 135.6, 128.8, 128.11, 128.10, 117.7, 114.7, 50.2 ppm. MS (EI): *m/z* (%): 190 (84) [M^+], 157 (28) [M^+ – SH], 91 (100) [Bn^+]. IR (ATR): $\tilde{\nu}$ = 3137, 3084, 3008, 2920, 1573 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{10}H_{10}N_2S$ [M^+]: 190.05647; found: 190.0559.

1-Phenylimidazole-2-thione (49): Yield 3.48 g (20 mmol, 71%; R_f = 0.38, Et_2O). Mp 182 – 183 °C (lit[456] 179 – 180 °C; lit[457] 181 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.45 (br s, 1 H), 7.59 (d, *J* = 8 Hz, 2 H), 7.50 (t, *J* = 8 Hz, 2 H), 7.42 (t, *J* = 8 Hz, 1 H), 6.86 (d, *J* < 2 Hz, 1 H), 6.82 (d, *J* < 2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 137.4, 129.1, 128.4, 125.9, 119.4, 115.1 ppm. MS (EI): *m/z* (%): 176 (69) [M^+], 175 (100) [M^+ – H], 77 (10) [Ph^+]. IR (ATR): $\tilde{\nu}$ = 3071, 3005, 2894, 1574 cm^{-1}. HRMS (EI): *m/z* calcd for $C_9H_8N_2S$ [M^+]: 176.04082; found: 176.0404.

General oxidative desulfurization of imidazole-2-thiones: Solid **I2T** (0.50 g, 3.2 mmol **47**, 2.6 mmol **48**, 2.8 mmol **49**) was added to a stirred slurry of 75% $(BzO)_2$ (MW_{eff} = 322.97; 5.17 g, 16 mmol for **47**; 4.24 g, 13 mmol for **48**; 4.58 g, 14 mmol for **49**) in THF (10 mL), which brought the reaction to spontaneous reflux. After cooling to rt, the reaction was diluted with water (20 mL) and Et_2O (20 mL). The aq layer was collected, the organic layer was washed with water (1 × 10 mL). The combined aq wash was washed with DCM (3 × 10 mL), then treated with 6 M NaOH (2 mL) and stirred until no $(BzO)_2$ was visible by TLC (less than 1 h). The aq soln was washed with Et_2O (3 × 10 mL), the combined organic extract was washed with water and brine (1 × 10 mL ea), dried ($MgSO_4$), filtered, and concentrated to leave **50** – **52** as specified below.

1-Butylimidazole (50): Yield 0.32 g (2.6 mmol, 81%) colorless oil, which was authenticated with commercial 1-butylimidazole by ^1H and ^{13}C NMR, and TLC (R_f = 0.10, Et_2O).

1-Benzylimidazole (51): Yield 0.23 g (1.5 mmol, 56%) colorless crystals, mp 69.5 – 72 ^oC, which were authenticated with commercial 1-benzylimidazole (mp 68 – 70 ^oC) by mp, mmp, ^1H and ^{13}C NMR, and TLC (R_f = 0.10, Et_2O).

1-Phenylimidazole (52): Yield 0.33 g (2.3 mmol, 82%) colorless oil, which was authenticated with commercial 1-phenylimidazole by ^1H and ^{13}C NMR, and TLC (R_f = 0.25, Et_2O).

***p*-Methoxybenzylisothiocyanate (PMBNCS):** The procedurer from Threadgill and coworkers[475] was scaled up for the reaction of 4-methoxybenzylamine (25.92 g, 189 mmol),

$CaCO_3$ (19.44 g, 194 mmol), and $CSCl_2$ (29 mL, 44 g, 383 mmol) in $CHCl_3$ (175 mL) and water (175 mL). The isolate was distilled ($bp_{0.2–0.3}$ 92.5 – 94 °C) to return PMBNCS (30.24 g, 169 mmol, 89%) with spectral properties matching the chromatographed material from the reference.

3-(*p*-Methoxybenzyl)-5-(*p*-hydroxybenzyl)-2-thiohydantoin (54): A mixture of tyrosine (8.14 g, 45 mmol) and 50% aq KOH (10.08 g, 90 mmol) was diluted to a total vol of 50 mL with water and thoroughly dissolved before the addition of EtOH (150 mL). The soln was cooled to 0 °C, then treated dropwise with PMBNCS (8.05 g, 45 mmol) in EtOH (10 mL), stirred 3 h, treated with 1 M HCl (400 mL), stirred 1 h, and frozen at –30 °C overnight. As the mass came back to rt, the aqueous layer separated from an orange solid. The aqueous layer was decanted and the orange solid was concentrated twice from acetone (200 mL ea), redissolved in acetone (300 mL), dried ($MgSO_4$), filtered, and treated with 96 – 98% H_2SO_4 (10 mL). The cyclization required 3 d, whereupon acetone was removed, the residue was treated with sat aq $NaHCO_3$ (500 mL), and the mixture was washed with DCM (3 × 100 mL). The combined organic extract was washed with water and brine (1 × 50 mL ea), dried ($MgSO_4$), filtered and evaporated to leave a dark brown oil (19.98 g) which released crude **54** as yellow crystals upon standing. The dark supernatant was removed by pipette, and the separated material (6.54 g) was recrystallized from *i*PrOH to deliver **54** (5.05 g, 15 mmol, 33%; R_f = 0.78, Et_2O). Mp 163 – 165 °C. ^{1}H NMR (400 MHz, DMSO–d_6): δ = 10.47 (s, 1 H, N*H*), 9.36 (s, 1 H, O*H*), 6.92 (d, *J* = 8 Hz, 2 H, ArH), 6.72 (d, *J* = 8 Hz, 2 H, ArH), 6.64–6.61 (m, 4 H, ArH), 4.62 (s, 2 H, NCH_2C$_6$H$_4$OMe), 4.59 (t, *J* = 4 Hz, 1 H, H-5), 3.70 (s, 3 H, OCH_3), 2.95 (d, *J* = 4 Hz, 2 H, CH_2C$_6$H$_4$OH) ppm. ^{13}C NMR (100 MHz, DMSO–d_6): δ = 182.1, 173.7, 157.9, 156.2, 130.6, 127.7, 127.6, 124.2, 114.9, 113.3, 59.8,

54.8, 42.3, 34.5 ppm. IR (ATR): $\tilde{\nu}$ = 3390, 3207, 3010, 2923, 2845, 1731, 1512 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{18}H_{18}N_2O_3S$ [M^+]: 342.10381; found: 342.1031.

1-(*p*-Methoxybenzyl)-4-(*p*-hydroxybenzyl)imidazole-2-thione (55): 2-Thiohydantoin **54** (2.21 g, 6.5 mmol) was less sensitive to the conditions of reduction than the model compounds, and was added to a soln of $NaBH_4$ (0.54 g, 14 mmol) and LiCl (0.60 g, 14 mmol) in 3 : 1 DME–EtOH (30 mL) at 0 °C. The reaction was allowed to achieve rt overnight. A TLC analysis showed incomplete consumption of **54**, but no overreduction. The reaction was stopped by the addition of conc aq HCl (10 mL). The mixture was stirred 30 min, diluted with water (150 mL), and washed with DCM (3 × 50 mL). The combined organic extracts were washed with water and brine (1 × 20 mL ea), dried ($MgSO_4$), filtered, plugged with 230 – 400 mesh silica gel (3 g), and concentrated. The silica gel plug was loaded on a silica gel column (230 – 400 mesh, 60 g) packed in EtOAc; elution with the same delivered **55** (1.14 g, 3.5 mmol, 54%; R_f = 0.76). Mp 198 – 204 °C. ^{1}H NMR (400 MHz, $CDCl_3$–DMSO–d_6): δ = 11.80 (s, 1 H, N*H*), 8.76 (s, 1 H, O*H*), 7.24 (d, *J* = 8 Hz, 2 H, ArH), 6.97 (d, *J* = 8 Hz, 2 H, ArH), 6.84 (d, *J* = 8 Hz, 2 H, ArH), 6.74 (d, *J* = 8 Hz, 2 H, ArH), 6.17 (s, 1 H, H-5), 5.06 (s, 2 H, NCH_2PhOMe), 3.77 (s, 3 H, OCH_3), 3.60 (s, 2 H, C$H_2C_6H_4$OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$–DMSO–d_6): δ = 160.5, 159.0, 155.9, 129.4, 129.3, 129.1, 128.3, 127.4, 115.3, 113.8, 113.6, 55.0, 49.1, 30.2 ppm. IR (ATR): $\tilde{\nu}$ = 3128, 3069, 3013, 2964, 2924, 1511 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{18}H_{18}N_2O_2S$ [M^+]: 326.10890; found: 326.1090.

1-(*p*-Methoxybenzyl)-4-(*p*-hydroxybenzyl)imidazole (56): Solid **55** (1.0 g, 3.1 mmol) was added in one portion to a slurry of 75% $(BzO)_2$ (4.95 g, 15 mmol) in THF (5 mL). The reaction

came to reflux under its own power, and after cooling back to rt the mixture was diluted with water (20 mL) and ether (20 mL). The aqueous layer was collected, the organic layer was washed with water (1 × 10 mL). The combined aq layers were washed with DCM (3 × 5 mL), then treated with 6 M NaOH (5 mL) and stirred until no $(BzO)_2$ was visible by TLC (less than 1 h). The pH was lowered to 8 with sat aq NH_4Cl (25 mL) before extraction with DCM (3 × 10 mL). The combined organic layers were washed with water and brine (1 × 20 mL ea), dried ($MgSO_4$), filtered, and concentrated to leave **56** (0.79 g, 2.7 mmol, 87%). Mp 131–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD): δ = 7.44 (s, 1 H, ImH), 7.11 (d, *J* = 8 Hz, 2 H, ArH), 7.05 (d, *J* = 8 Hz, 2 H, ArH), 6.87 (d, *J* = 8 Hz, 2 H, ArH), 6.74 (d, *J* = 8 Hz, 2 H, ArH), 6.51 (s, 1 H, ImH), 4.95 (s, 2 H, NC*H*$_2$PhOMe), 4.47 (br s, 1 H, O*H*), 3.79 (s, 3 H, OC*H*$_3$), 3.77 (s, 2 H, C*H*$_2$C$_6$H$_4$OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD): δ = 159.7, 155.3, 142.9, 136.5, 131.0, 129.9, 129.2, 128.2, 116.4, 115.4, 114.5, 55.4, 50.6, 33.8 ppm. MS (EI): *m*/*z* (%): 294 (26) [M^+], 121 (100) [*p*-MeOBn$^+$]. IR (ATR): $\tilde{\nu}$ = 3106, 3034, 2996, 2903, 2829, 2787, 2669, 2580, 1609, 1509 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{18}H_{18}N_2O_2$ [M^+]: 294.13683; found: 294.1367.

1,4-di-(*p*-Methoxybenzyl)imidazole (53): A soln of **56** (0.3053 g, 1.04 mmol) in THF (10 mL) was treated with LiOH monohydrate (0.0447 g, 1.07 mmol) and turned into a fine dispersion while stirring overnight. Addition of MeI (84 μL, 0.19 g, 1.35 mmol) gave a clear soln in 2 h, which was stirred another 4 h before the addition of water (30 mL). The mixture was washed with DCM (3 × 15 mL), the combined organic extract was washed with water and brine (1 × 20 mL ea), dried ($MgSO_4$), filtered and concentrated. After chromatography over 230 – 400 mesh silica gel (20 g) with a solvent gradient (EtOAc → 5:1 EtOAc–EtOH), the crude product (R_f =

0.40, 5:1 EtOAc–EtOH) contained phenol **56**, and was redissolved in Et_2O (50 mL), washed with 3 M NaOH (3 × 25 mL), water and brine (1 × 25 mL ea), dried ($MgSO_4$), filtered, and concentrated to return **53** (0.2200 g, 0.71 mmol, 69%) with ^1H and ^{13}C NMR spectra matching the reference.[472] Mp 83.5 – 86 °C (lit[472] 84 – 85 °C).

Camphorquinone (60): Based on the method of White and coworkers,[484] Ac_2O (140 mL, 151.2 g, 1.48 mol) was added to (1*R*)-(+)-camphor (200.0 g, 1.31 mol). After the addition of SeO_2 (80.0 g, 0.72 mol), the mixture was refluxed for 1 h, cooled to rt, and further SeO_2 (80.0 g) was added. The mixture was returned to reflux for 1.5 h, cooled to rt, and further SeO_2 (80.0 g) was added. After another 3.5 h at reflux, the mixture was cooled to rt for the last addition of SeO_2 (80.0 g), then refluxed a further 8 h. The mixture was removed from heat, cooled to rt, diliuted with PhMe (200 mL), and suction filtered to remove elemental Se. After using PhMe (ca. 1.0 L total) to rinse the reaction vessel, wash the Se filter cake, and aid in the transfer of the filtrate to a distillation flask, the product mixture was stripped of all solvents under increasingly strenuous conditions. Distillation started at 200 mbar from a 60 °C water bath and finished under the highest vacuum afforded by the vacuum pump used (ca. 14 mbar) from a water bath at 80 °C. The residue was taken up in EtOAc (1.8 L) and filtered through Celite-521 (200 g) already wet with EtOAc. The filtrate was washed with 10% aq NaOH (2 × 500 mL) and brine (1 × 200 mL), dried ($MgSO_4$), filtered, and concentrated to leave **60** (174.18 g, 1.05 mol, 80%) as a hard yellow powder with spectral properties matching the reference.[484] Mp 203 – 205 °C (lit[484] 198 – 199 °C, commercial 200 – 203 °C).

α-(*N*-Methylformamido)camphor (61): A solution of 3 : 1 NMF–HCO_2H (400 mL) was added to a flask containing **60** (88.0 g, 530 mmol). The flask was fitted with a reflux condenser routed to an oil bubbler, placed in an oil bath at rt, and heat was applied until a vigorous evolution of gas started, which occurred at an internal temperature of ca. 120 °C. Gas evolution would not cease entirely, but after it had obviously tapered off (in ca. 1 h), the reaction mixture was cautiously poured into sat aq $NaHCO_3$ (1.4 L) with stirring. The mixture was washed with DCM (3 × 200 mL), and the combined organic layers were washed with water (2 × 100 mL), sat aq $NaHCO_3$ (1 × 200 mL), water (1 × 100 mL), and brine (1 × 200 mL), then dried ($MgSO_4$), filtered, and concentrated to leave crude **61** (101.58 g, 485 mmol, 92%) as a viscous orange oil. Crude **61** was used in the next step, but could be distilled ($bp_{0.11–0.125}$ 103 – 113 °C) from a black residue to return **61** with unaltered physical and spectral characteristics in 75% yield from **60**. The complex ^1H and ^{13}C spectra of distilled **61** are included in the accompanying spectral library.

α-Methylaminocamphor (59): Crude **61** (101.58 g) prepared as described above was boiled into 3 M aq HCl (400 mL) over the course of 2 h. The mixture was then cooled to rt and washed with Et_2O (3 × 100 mL). The recovered aq layer was cooled to 0 °C with stirring, then cautiously treated with enough solid NaOH (75 g, 1.69 mol) to destroy all supplied HCl (1.2 mol) and the theoretical yield of HCO_2H (ca. 0.364 mol), and to make the solution strongly basic. The mixture turned cloudy as NaOH was allowed to thoroughly dissolve and the temperature was held at 0 °C. While the mixture was still cold, solid NaCl (50 g) was added and stirring at 0 °C continued 1 h, during which time the amount of NaCl added did not thoroughly dissolve, and after which time DCM (200 mL) was added. After stirring another 30 min, the biphasic supernatant mixture was decanted into a separatory funnel, the organic phase was

recovered, and the NaCl sediment was washed with portions of DCM (3 × 100 mL) which were then used to wash the aq phase. The combined organic layers were washed with brine (1 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to leave crude **59** (80.64 g) which was distilled ($bp_{0.225–0.26}$ 53 – 59.5 °C) to give **59** as a yellow oil (71.32 g, 393 mmol, 74% from **60**). The complex ^1H and ^{13}C NMR spectra of distilled **59** are included in the accompanying spectral library.

4-Hydroxyimidazolidine-2-thione 62: A solution of methyl isothiocyanate (16.40 g, 224 mmol) in THF (20 mL) was added dropwise to a solution of distilled **59** (40.65 g, 224 mmol) in THF (200 mL) at rt and stirred 6 h. After removal of THF, two crystallizations from 5 : 1 *n*-heptane–*i*PrOH returned **62** (30.77 g, 121 mmol, 54%) as large colorless crystals. Mp 187 – 188.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.70 (s, 1 H, O*H*), 4.12 (d, *J* = 4 Hz, 1 H, H-3), 3.05 (s, 6 H, two unresolved NCH_3), 2.03 (br t, 1 H, H-4), 1.49 – 1.38 (br m, 2 H), 1.16 – 1.08 (br m, 4 H), 1.01 (s, 3 H), 0.93 – 0.89 (br m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.1, 72.1, 53.6, 49.4, 47.4, 32.8, 30.6, 30.1, 20.8, 20.2, 19.0, 11.6 ppm. The X-ray crystal structure appears in the text as Figure 10.

α-Methylaminocamphoroxime (72): Distilled **59** (13.99 g, 77.2 mmol) was added to a solution of hydroxylamine hydrochloride (16.09 g, 232 mmol) in water (25 mL) and refluxed 3 h. Stirring was continued after the mixture was removed from heat to prevent solidification. The mixture was basified with 6 M aq NaOH (50 mL) and washed with DCM (3 × 75 mL). The combined organic extracts were washed with water and brine (1 × 75 mL ea), dried ($MgSO_4$), filtered, and concentrated to leave crude **72** (14.53 g, 74.0 mmol, 96%) as a slowly solidifying

colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.70 (d, *J* = 4 Hz, 1 H, H-3), 2.31 (s, 3 H, NC*H*$_3$) 1.98 (br t, 1 H), 1.85 (br t, 1 H), 1.66 (br t, 1 H), 1.51 (br t, 2 H), 0.99 – 0.76 (br m, 11 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.3, 58.9, 50.8, 45.6, 45.0, 33.2, 31.8, 18.1, 18.0, 17.6, 10.4 ppm.

Oxadiazine 73: Oxime **72** (4.94 g, 25.2 mmol) prepared as described above was dissolved in THF (5 mL) and treated with 37% formalin (10 mL, 134.3 mmol H_2CO) and 6 M HCl (1 mL). After 1 h at rt, the mixture was treated with 6 M NaOH (4 mL) and washed with DCM (3 × 15 mL). The combined organic layers were washed with water and brine (1 × 15 mL ea), dried ($MgSO_4$), filtered, and evaporated to leave crude **73** (3.99 g, 19.2 mmol, 76%) as a cloudy oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.30 (d, *J* = 9.8 Hz, 1 H, NC*H*$_2$O), 3.99 (d, *J* = 9.8 Hz, 1 H, NC*H*$_2$O), 2.9 (br s, 1 H, H-3), 2.50 (s, 3 H, NC*H*$_3$), 1.98 (t, *J* = 4 Hz, 1 H, H-4), 1.89 – 1.78 (br m, 2 H), 1.68 – 1.62 (br m, 1 H), 1.41 – 1.35 (br m, 1 H), 1.11 (s, 3 H), 0.99 (s, 3 H), 0.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 180.5, 86.6, 60.7, 53.3, 48.1, 46.2, 42.9, 37.2, 19.9, 19.8, 18.8, 10.0 ppm.

General method I for the Ritter reaction of a sufficiently large quantity of 1-adamantanecarboxylic acid with a nitrile impervious to incidental water: In an adaptation of the original method from Butenko and coworkers,[546] a sufficiently large mass (over ca. 5 g) of 1-adamantanecarboxylic acid (MW = 180.24) in a one necked flask was cooled to 0 ^{o}C and cautiously treated with a volume of conc HNO_3 (68.0 – 70.0%, ρ = 1.400 g / mL, M = 15.3) equal to the mass of 1-adamantanecarboxylic acid, which is to say 2.76 eq HNO_3. Stirring was commenced as soon as feasible during the addition, and when this mixture reattained 0 ^{o}C, a

volume of conc H_2SO_4 equal to six times the volume of conc HNO_3 was cautiously added. The ice bath was replenished as necessary to keep the mixture cold during this addition. After the addition was complete, the mixture was left unperturbed for 4 h, whereupon it was cooled back to 0 ^oC for the addition of 1 eq or a convenient mass or volume close to 1 eq of a nitrile impervious to water. The mixture was left unperturbed a further 4 h after this addition was complete, then the whole mass was poured over ice (1 kg / 100 g 1-adamantanecarboxylic acid invested). The precipitated acetamido adamantanecarboxylic acids were collected by suction filtration and treated as described below.

1-Acetamido-3-adamantanecarboxylic acid (78): Using general method I described above, 1-adamantanecarboxylic acid (100 g, 555 mmol) was oxidized in a mixture of conc HNO_3 (100 mL) and conc H_2SO_4 (600 mL) and the oxidation product was trapped with MeCN (30 mL, 23.6 g, 574 mmol). When the reaction mixture was poured over ice, the quenching step gave a remarkable sequence of color changes from brown → black → dark green → light green → dark blue → light blue before a white precipitate settled from the mixture. Precipitated **78** (111.9 g, 471.2 mmol, 85%) was collected by suction filtration and dried in an oven at 110 ^oC overnight. Mp 240 – 242 ^oC (lit[546] 255 – 256 ^oC; lit[551] 251 ^oC). The ^1H and ^{13}C NMR spectra of **78** were identical to those most recently published.[551] The X-ray crystal structure appears in the text as Figure 12.

1-Chloroacetamido-3-adamantanecarboxylic acid (79): Using general method I described above, 1-adamantanecarboxylic acid (100 g, 555 mmol) was oxidized in a mixture of conc HNO_3 (100 mL) and conc H_2SO_4 (600 mL) and the oxidation product was trapped with

chloroacetonitrile (40 mL, 47.72 g, 632 mmol). After quenching the reaction, **79** (128.19 g, 472 mmol, 85%) was collected by suction filtration and crystallized from acetone. Mp 160 – 162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.35 (br s, 1 H, COO*H*), 6.29 (s, 1 H, N*H*), 3.94 (s, 2 H, C*H*$_2$Cl), 2.34 (br s, 2 H, AdH), 2.17 (s, 2 H, AdH), 2.02 (br d, $J \approx 2$ Hz, 4 H, AdH), 1.87 (br d, $J = 2.4$ Hz, 4 H), 1.67 (br m, 2 H, AdH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 181.1 (C_q), 164.9 (C_q), 52.4 (C_q), 42.7 (CH_2), 42.2 (C_q), 41.8 (CH_2), 40.1 (CH_2), 37.5 (CH_2), 35.0 (CH_2), 28.8 (CH) ppm. MS (EI): *m*/*z* (%): 271 (24) [M^+], 179 (100). IR (ATR): $\tilde{\nu}$ = 3367, 3344, 3078, 3007, 2943, 2911, 2858, 1689, 1646, 1550 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{13}H_{18}ClNO_3$: 271.09752; found: 271.0952.

General method II for the Ritter reaction of a small amount of 1-adamantanecarboxylic acid and / or of a nitrile sensitive to incidental water: These Ritter reactions of 1-adamantanecarboxylic acid required the conditions originally described by Butenko and coworkers.[546] Thus, a quantity of 1-adamantanecarboxylic acid was oxidized in a mixture of 1 : 3 : 4 HNO_3–H_2SO_4–30% oleum based on 2 eq HNO_3 relative to adamantanecarboxylic acid. The reagents were introduced as described in general method I, but especially great care had to be taken to keep the flask cold during the addition of oleum. In the event oleum was added too quickly and charred the mixture, no desired product was found at the end of the reaction. The mixtures containing oleum could also char if they were allowed to attain rt, so it was necessary to keep the mixture at 0 °C for the duration of the reaction after a successful combination of acids. The nitrilium intermediate was still hydrolyzed by simply pouring the mixture over ice, and the desired amidoadamantanes were isolated as described below.

1-Trichloroacetamido-1-adamantanecarboxylic acid (80): Using general method II described above, 1-adamantanecarboxylic acid (13.4 g, 74.3 mmol) was treated successively with conc HNO_3 (10 mL), conc H_2SO_4 (30 mL), and 30% oleum (40 mL). After 4 h at 0 ^oC, trichloroacetonitrile (10.73 g, 74.3 mmol) was added dropwise; after another 4 h at 0 ^oC, the miture was poured over ice (250 g), releasing a gummy precipitate from which **80** (13.62 g, 40.0 mmol, 54%) was recovered as colorless crystals after two crystallizations from acetone. Mp 175.5 – 177 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.39 (br s, 1 H), 2.28 (br t, J < 2 Hz, 2 H), 2.21 (s, 2 H), 2.05 (br m, 4 H), 1.90 (br m, 4 H), 1.69 (br m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182 (C_q), 161 (C_q), 93.1 (C_q, CCl_3), 53.6 (C_q), 42.4 (C_q), 41.3 (CH_2), 39.7 (CH_2), 37.4 (CH_2), 34.9 (CH_2), 28.9 (CH) ppm. MS (EI): *m/z* (%): 222 (5), 179 (100), 161 (5), 133 (14). IR (ATR): $\tilde{\nu}$ = 3410, 3382, 2920, 2865, 2641, 1722, 1689, 1509 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{13}H_{16}Cl_3NO_3$: 339.019578; found: 339.02136.

1-Adamantanecarbonitrile: Using glassware dried at 180 ^oC overnight, an apparatus consisting of a two necked flask fitted with a reflux condenser and an addition funnel was assembled while hot, and cooled under a positive pressure of argon. The flask was charged with 1-adamantanecarboxylic acid (5.44 g, 30.2 mmol), which was dissolved with DCE (50 mL) before a solution of chlorosulfonylisocyanate (6.41 g, 45.3 mmol) in DCE (50 mL) was added through an addition funnel. The solution was refluxed 8 h, then cooled to rt and treated with neat triethylamine (10 mL, 7.26 g, 71.7 mmol), whereupon vigorous gas evolution was observed. The mixture turned brown while stirring overnight, and was washed with 3 M aq HCl (2 × 50 mL), water (2 × 50 mL), 1 M aq NaOH (3 × 25 mL), water and brine (1 × 50 mL ea), dried ($MgSO_4$), filtered, plugged with basic aluminum oxide (5 g) and concentrated. The aluminum oxide plug

was loaded on a column of aluminum oxide (200 g) packed in hexanes. Elution with 19 : 1 hexanes–ether delivered 1-adamantanecarbonitrile (4.58 g, 28.4 mmol, 94%) with ^{1}H and ^{13}C NMR, and IR spectra matching a commercial sample. It was used in the next step without further characterization or purification.

1-Adamantanecarboxamido-3-adamantanecarboxylic acid (81): Using general method II described above, 1-adamantanecarboxylic acid (1.34 g, 7.43 mmol) was treated successively with conc HNO_3 (1 mL), conc H_2SO_4 (3 mL), and 30% oleum (4 mL) and stirred 4 h at 0 ^{o}C, at which time 1-adamantanecarbonitrile (1.22 g, 7.57 mmol) prepared as described above was added as a solution in conc H_2SO_4 (4 mL). After a further 4 h at 0 ^{o}C, the mixture was poured over ice (20 g), and the precipitate was recovered by extraction with DCM (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The isolate was reprecipitated from acetone to yield **81** (1.59 g, 4.45 mmol, 60%). Mp 238 – 244 ^{o}C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.27 (br s, 1 H), 2.20 (br s, 2 H), 2.13 (br s, 2 H), 2.06 – 1.97 (br d, 7 H), 1.89 – 1.80 (br d, 10 H), 1.76 – 1.57 (br m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 184 (C_q), 177.5 (C_q), 51.3 (C_q), 42.3 (C_q), 42.2 (CH_2), 40.9 (C_q), 40.5 (CH_2), 39.3 (CH_2), 37.6 (CH_2), 36.4 (CH_2), 35.2 (CH_2), 30.0 (CH), 28.1 (CH) ppm. MS (EI): *m*/*z* (%): 357 (56) [M^{+}], 221 (4), 179 (13), 135 (100). IR (ATR): $\tilde{\nu}$ = 3402, 3338, 2908, 2852, 2657, 1695, 1636, 1532 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{22}H_{31}NO_3$: 357.230394; found: 357.2321.

1-Aminoadamantane-3-carboxylic acid hydrochloride (82): Following the method of Butenko and coworkers,[546] **78** (10.56 g, 44.5 mmol) was boiled in a mixture of conc aq HCl (100 mL) and water (75 mL) for 15 h. After the distillation of aq HCl, the concentrate was

inundated with acetone and **82** (10.0 g, 43.2 mmol, 97%) was collected by suction filtration. Mp > 300 °C (lit[546] > 300 °C; lit[551] > 300 °C). The ^{1}H and ^{13}C NMR spectra of **82** were identical to those most recently published.[551]

Methyl 1-aminoadamantane-3-carboxylate (83): Hydrochloride **82** (2.76 g, 11.9 mmol) was refluxed in 1 : 9 conc H_2SO_4–MeOH (30 mL) overnight. The mixture was cooled to rt and carefully poured over Na_2CO_3 (10 g, 94 mmol), and the mixture was slurried in water (150 mL) and DCM (15 mL). The organic phase was recovered and the aqueous phase was washed with DCM (3 × 10 mL). The combined organic layers were washed with 6 M NaOH (1 × 10 mL), water (2 × 30 mL), brine (1 × 30 mL), dried ($MgSO_4$), filtered, and concentrated to leave crude **83** (2.68 g, > 100%) as a cloudy oil which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.65 (s, 3 H, OC*H*$_3$), 2.17 (br t, $J \approx 4$ Hz, 2 H), 1.82 – 1.77 (br m, 4 H), 1.70 (s, 2 H), 1.63 – 1.52 (br m, 6 H), 1.26 (br s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.0 (C_q), 51.5 (CH_3), 47.41 (C_q or CH_2), 47.40 (CH_2 or C_q), 45.0 (CH_2), 42.8 (C_q), 37.7 (CH_2), 35.1 (CH_2), 29.3 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 3357, 3286, 2907, 2853, 1730 cm^{-1}.

Methyl *N*-Fmoc-1-amino-3-adamantanecarboxylate (84): A two necked flask flame dried immediately prior to use was fitted with a gas inlet and a rubber septum and cooled under a positive pressure of argon before it was charged with FmocCl (2.47 g, 9.55 mmol) and dry DCM (40 mL). The solution was cooled to 0 °C and the rubber septum was exchanged for a capped pressure equalized addition funnel loaded with **83** (4 g, ca. 19 mmol) in DCM (4 mL); **83** had been dried under vacuum overnight. The solution of **83** was added dropwise over the course of 15 min, the reaction continued at 0 °C for 15 min, and then the ice bath was removed and the

reaction was left a further 1 h before the reaction mixture was poured into iced 3 M aq HCl (160 mL). The organic layer was recovered and the aqueous layer was washed with DCM (2 × 50 mL). Excess **83** was recovered by basifying and extracting the aqueous layer as described in the above preparation of it. The combined organic layers from the preparation of **84** were washed with water and brine (1 × 30 mL ea), dried ($MgSO_4$), and concentrated to reveal a yellow oil. Purification by silica gel chromatography (100 g silica gel, eluent: 1 : 1 Et_2O–hexanes) returned **84** (R_f = 0.4, 3.2 g, 7.42 mmol, 78%). Mp 121 – 122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 8 Hz, 2 H), 7.57 (d, *J* = 8 Hz, 2 H), 7.38 (t, *J* = 8 Hz, 2 H), 7.30 (t, *J* = 8 Hz, 2 H), 4.64 – 4.35 (br d, 2 H), 4.18 (t, *J* = 8 Hz, 1 H), 3.64 (s, 3 H), 2.13 – 1.72 (br m, 14 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.7 (C_q), (*), 144.0 (C_q), 141.3 (C_q), 127.5 (CH), 126.9 (CH), 124.8 (CH), 119.9 (CH), 65.8 (CH_2), 51.8 (CH_3), 50.9 (C_q), 47.3 (CH_2), 42.56 (CH_2 or C_q), 42.52 (C_q or CH_2), 40.7 (CH_2), 37.7 (CH_2), 35.1 (CH_2), 29.0 (CH) ppm. *Denotes a missing carbamate resonance. It is not problematic for the structural assignment that this characteristically weak peak was not resolved from the baseline. The molecular formula was confirmed by HRMS (see below), and two carbonyl absorptions were found in the IR spectrum, which should be confirmation enough. For more confirmation, consider that the only other reasonably isolable compound from this reaction in the quantity recovered would be the 9-fluorenemethylamine (i.e., (9-Fl)CH_2NR_2). These amines are byproducts that can result from the combination of dibenzofulvene and the free amine released following deprotonation of Fmoc and extrusion of CO_2 in solution. This structure, first, would not account for the mass found by HRMS or the absorptions found in the IR spectrum and, second, is itself not accounted for in the ^{13}C NMR spectrum. The ^{13}C resonance of the methylene group of *N*-*tert*-butyl-*N*-(9-fluorenemethyl)amine comes at δ = 46.3 ppm;[579] there are methylene resonances in this region of the ^{13}C NMR

spectrum of **84**, but these are are accounted for by the adamantane moiety. The only other signal in the ^{13}C NMR spectrum from a methylene group is at δ = 65.8 ppm. Based on the placement of the corresponding signal in *N*-*tert*-butyl-*N*-(9-fluorenemethyl)amine, this reaonance is not believable as a signal from an *N*-adamantyl-*N*-(9-fluorenemethyl)amine byproduct. By comparison, it is a typical chemical shift for the ^{13}C resonance of the methylene group of an Fmoc moiety in an Fmoc protected amine, and is in line with the resonances of the same carbon in examples of other γ-adamantane amino acids protected with Fmoc.[551] MS (EI): *m*/*z* (%): 284 (1), 251 (8), 210 (33), 209 (54), 196 (22), 195 (5), 178 (35), 166 (38), 165 (44), 153 (26), 152 (79), 151 (72), 150 (63), 139 (12), 138 (12), 120 (16), 109 (15), 108 (32), 107 (19), 95 (34), 94 (100), 93 (44), 92 (8), 91 (20), 81 (10), 80 (5), 79 (11), 78 (3), 77 (15), 59 (13), 58 (23), 57 (64), 56 (5), 55 (9), 45 (10), 44 (10), 43 (13), 42 (12), 41 (30), 40 (39), 39 (12), 38 (17), 37 (3), 36 (54). IR (ATR): $\tilde{\nu}$ = 3349, 2939, 2913, 2887, 2861, 1736, 1719, 1695, 1523 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{27}H_{29}NO_4$: 431.209659; found: 431.2085.

***N*-Fmoc-1-amino-3-adamantanecarboxylic acid (85):** Ester **84** (0.42 g, 0.97 mmol) was refluxed in 1 : 1 10% aq H_2SO_4–DME (50 mL) until it was no longer visible by TLC (ca. 3 d). Addition of brine (25 mL) and Et_2O (25 mL) separated the homogeneous mixture into two phases. The organic layer was washed with water and brine (1 × 20 mL ea) and was set aside. The aqueous washes of the organic layer recovered from the reaction were added to the aqueous layer recovered from the reaction, and the solution was washed with DCM (3 × 25 mL). The organic layer recovered from the reaction was added to the combined DCM washes, and the solution was washed with water and brine (1 × 30 mL ea), dried ($MgSO_4$), filtered, plugged with silica gel (3 g), and concentrated. The silica gel plug was loaded atop a column of silica gel (50

g) packed in 7 : 3 pentane–THF. Elution with the same returned **85** (R_f = 0.3, 0.354 g, 0.85 mmol, 87%). Mp 188 – 193 °C (lit[551] 193 °C). The material was authenticated by mmp (186 – 192 °C) with a sample (mp 188 – 190 °C) provided by L. Wanka.

***O*-(1-Acetamido-3-adamantaneacetyl)-*N,N'*-dicyclohexylisourea (88):** A solution of **78** (5.75 g, 24.2 mmol) and DCC (5.00 g, 24.2 mmol) in DMF (100 mL) was refluxed 4 d, at which time the reflux condenser was replaced with a simple distillation apparatus and half the volume of DMF was removed. Upon cooling, the compound assigned structure **88** (6.22 g, 14.0 mmol, 57.94%) precipitated and was collected by suction filtration. The filtrate was returned to the heat and half of the remaining volume of DMF was removed. Upon cooling to rt, and then to –30 °C, a second crop of the compound assigned structure **88** (2.60 g, 5.86 mmol, 24.21%; 8.82 g, 19.9 mmol, 82% total) was recovered. Mp 188 – 192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.21 (br t, J < 4 Hz, 2 H), 2.09 (s, 2 H), 2.04 – 2.00 (br d, 2 H), 1.93 – 1.84 (br m, 11 H), 1.78 (d, J = 2.6 Hz, 6 H), 1.72 – 1.58 (br m, 8 H), 1.37 – 1.30 (br m, 4 H), 1.22 – 1.07 (br m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.5 (C_q), 169.4 (C_q), 156.8 (C_q), 52.1 (C_q), 49.0 (CH), 47.7 (CH), 42.6 (CH_2), 42.3 (C_q), 40.6 (CH_2), 38.2 (CH_2), 35.2 (CH_2), 33.8 (CH_2), 33.0 (CH_2), 29.1 (CH), 25.5 (CH_2), 25.4 (CH_2), 24.8 (CH_2), 24.7 (CH_2), 24.4 (CH_3) ppm. MS (EI): *m*/*z* (%): 318 (2), 237 (2), 224 (23), 143 (19), 99 (27), 56 (100), 55 (18), 44 (7), 43 (20), 42 (4), 41 (18), 40 (44). IR (ATR): $\tilde{\nu}$ = 3329, 3060, 2929, 2910, 2851, 2671, 1648, 1629, 1540 cm^{-1}.

***N*-(1-Acetamido-3-adamantaneacetyl)-*N,N'*-dicyclohexylurea (86):** A quantity of the compound assigned structure **88** was eluted over silica gel in ethyl acetate to deliver **86** in 96% yield. Mp 192.5 – 195 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.20 (br t, J < 4 Hz, 2 H), 2.09 (s, 2

H), 2.03 – 2.00 (br d, 3 H), 1.94 – 1.84 (br m, 11 H), 1.78 (d, *J* = 2.6 Hz, 5 H), 1.70 – 1.59 (br m, 8 H), 1.39 – 1.29 (br m, 4 H), 1.22 – 1.05 (br m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.6 (C_q), 169.5 (C_q), 162.2 (C_q), 52.2 (C_q), 48.9 (CH), 47.8 (CH), 42.5 (CH_2), 42.3 (C_q), 40.6 (CH_2), 38.2 (CH_2), 35.3 (CH_2), 33.8 (CH_2), 33.0 (CH_2), 29.1 (CH), 25.54 (CH_2), 25.46 (CH_2), 24.83 (CH_2), 24.79 (CH_2), 24.4 (CH_3) ppm. MS (EI): *m*/*z* (%): 318 (1), 237 (3), 224 (21), 179 (5), 143 (17), 99 (27), 98 (19), 73 (12), 70 (11), 67 (5), 61 (26), 56 (100), 55 (21), 44 (11), 43 (16), 42 (7), 41 (16), 40 (40). IR (ATR): $\tilde{\nu}$ = 3314, 3066, 2931, 2852, 2666, 1676, 1649, 1630, 1544 cm^{-1}. The X-ray crystal structure appears in the text as Figure 13.

(1-Acetamido-3-adamantanecarboxamido)adamantane (87): For 1 week in refluxing DMF were reacted urea **86** (6.62 g, 14.9 mmol) prepared as described above and 1-aminoadamantane (2.27 g, 15.0 mmol) prepared separately from commercial 1-aminoadamantane hydrochloride by a standard workup. Following removal of DMF under reduced pressure, the residue was reprecipitated from acetone to return the compound assigned structure **87** (4.46 g, 12.5 mmol, 84%). Mp 207 – 208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.21 (br s, 2 H), 2.09 (s, 2 H), 2.04 – 1.85 (br m, 11 H), 1.79 (br d, *J* = 2 Hz, 5 H), 1.71 – 1.59 (br m, 7 H), 1.40 – 1.30 (br m, 3 H), 1.22 – 1.05 (4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.5, 169.1, 52.2, 47.8, 42.6, 42.3, 40.7, 38.2, 35.2, 33.1, 29.1, 25.5, 24.8, 24.5 ppm. MS (EI): *m*/*z* (%): 318 (16), 276 (7), 237 (16), 224 (19), 192 (8), 178 (10), 143 (17), 100 (8), 99 (35), 98 (23), 94 (31), 70 (10), 61 (21), 57 (12), 56 (100), 55 (23), 45 (14), 44 (7), 43 (17), 41 (20), 40 (34). IR (ATR): $\tilde{\nu}$ = 3329, 3059, 2930, 2910, 2856, 2672, 1648, 1629, 1537 cm^{-1}.

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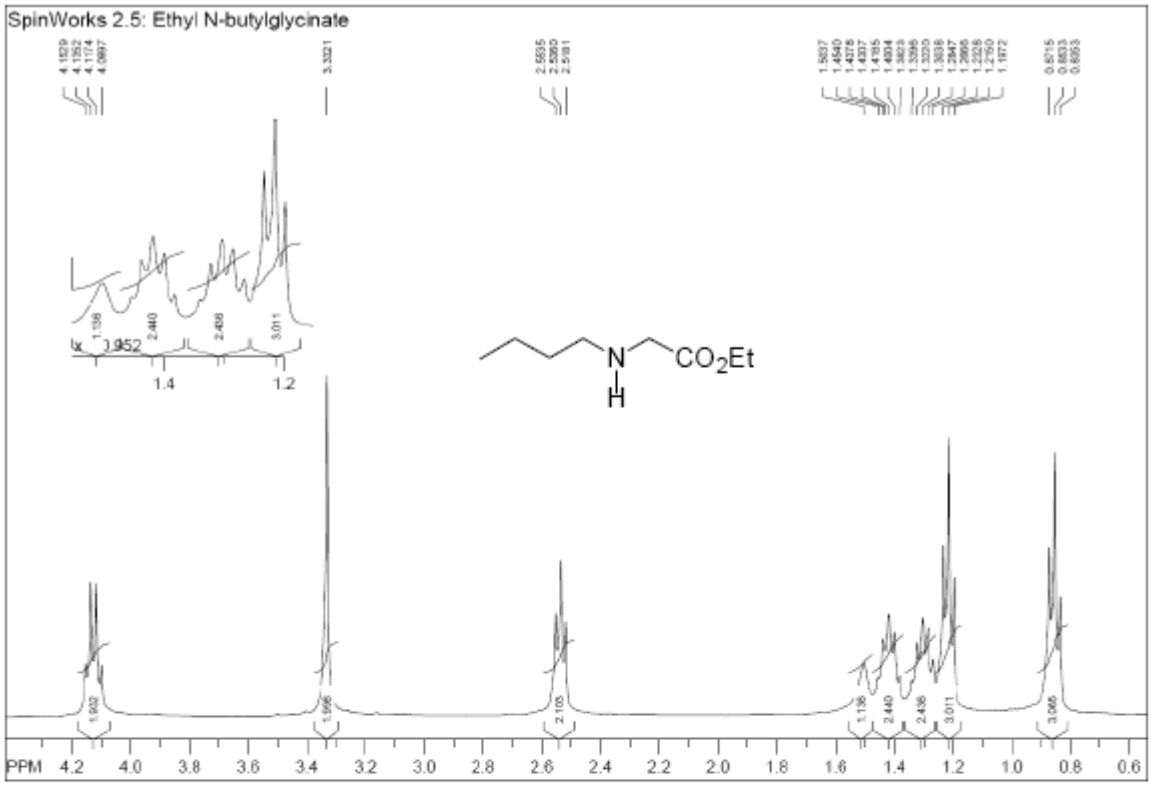
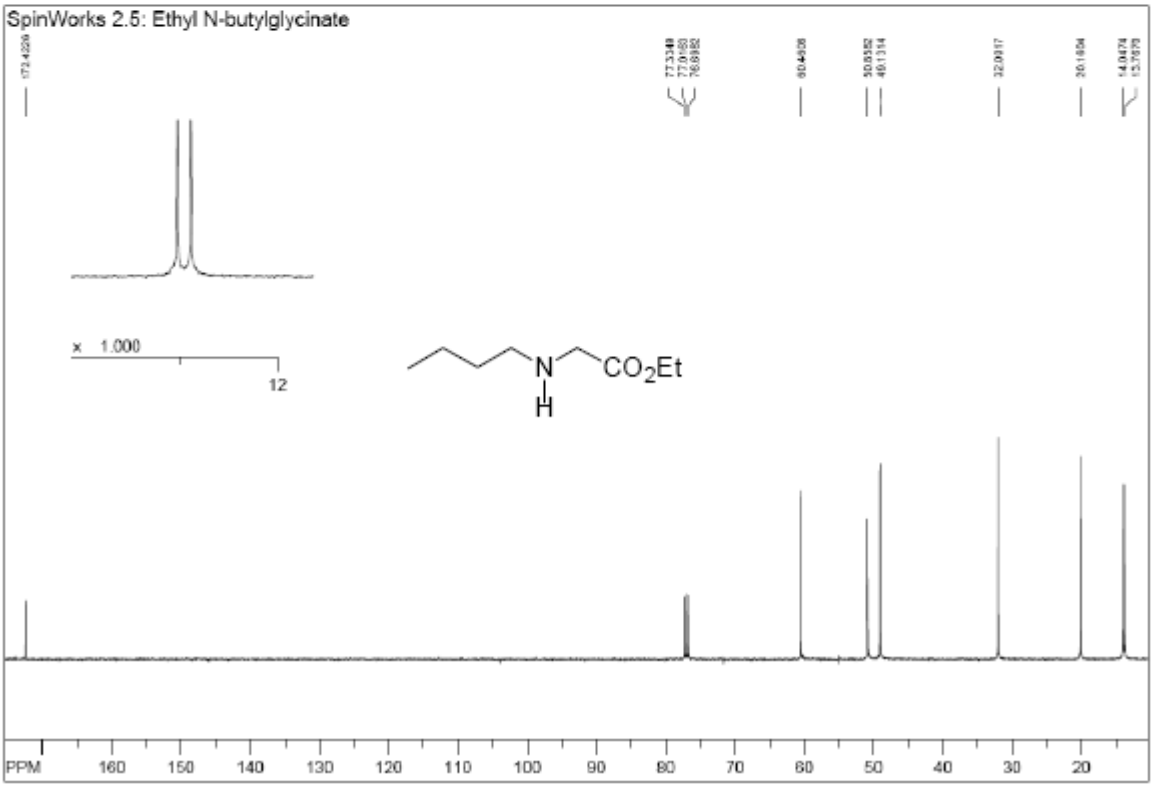
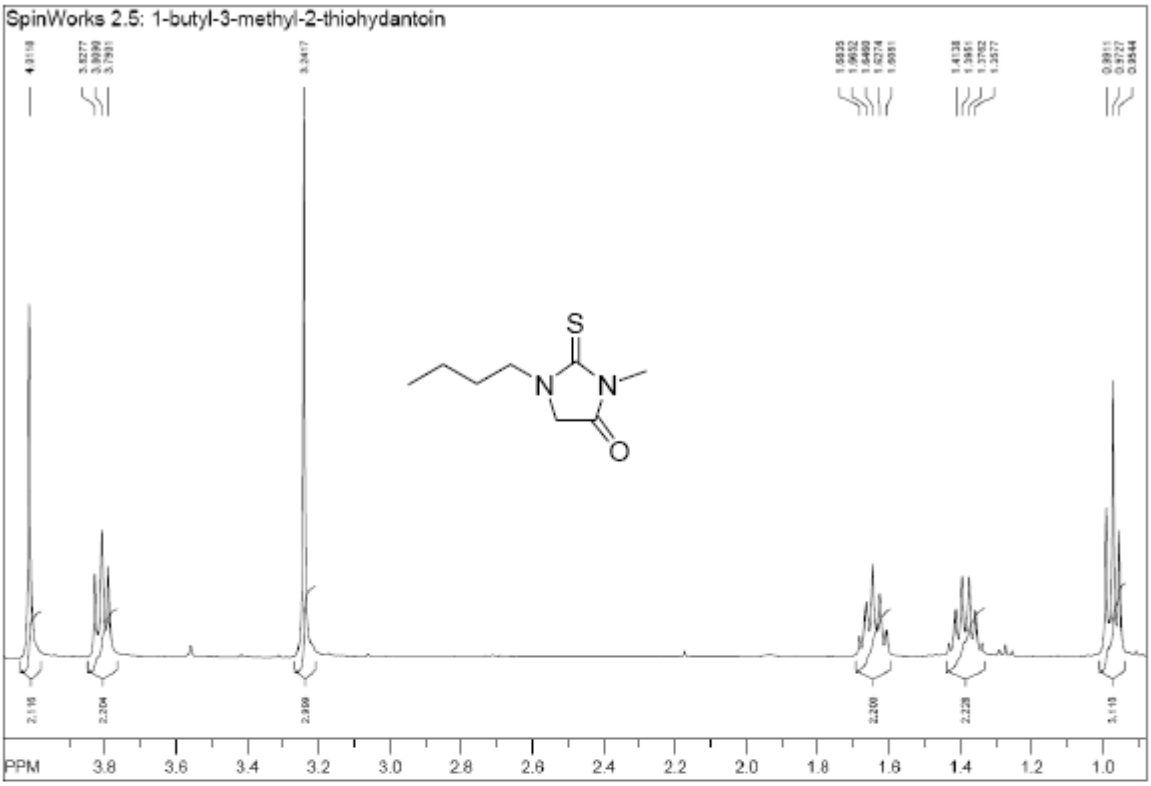
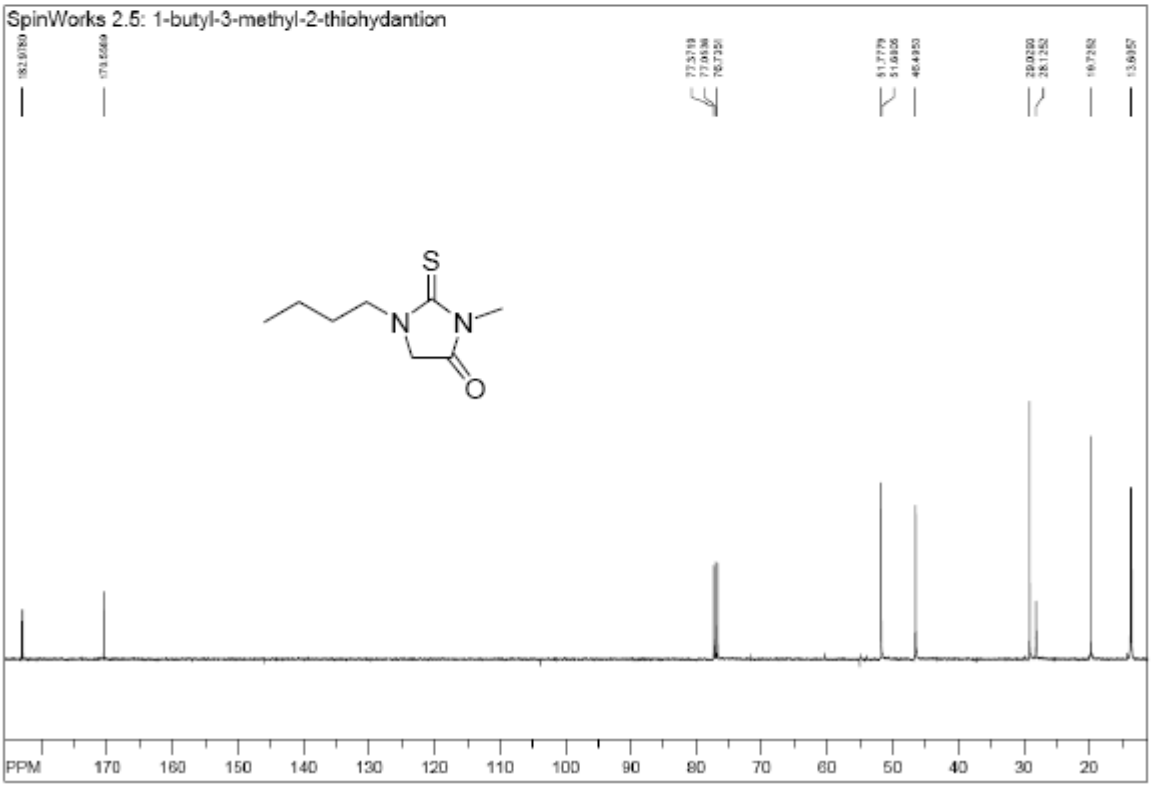
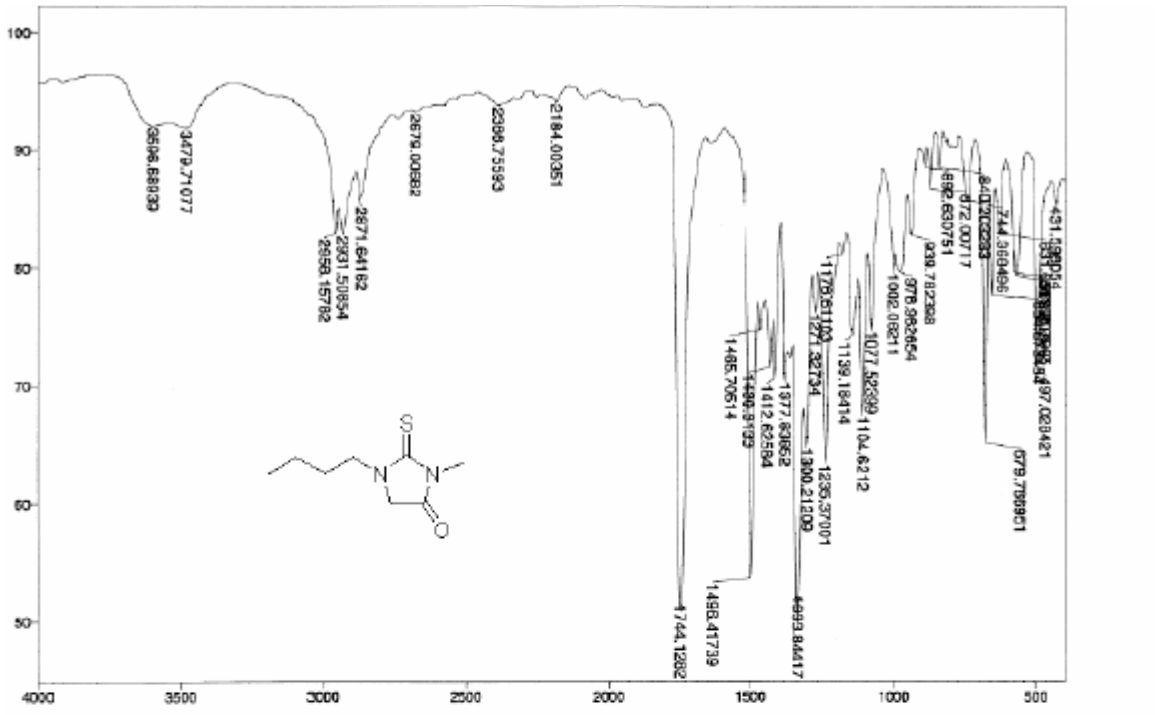
APPENDIX: LIBRARY OF ^{1}H AND ^{13}C NMR, IR, AND MASS SPECTRA

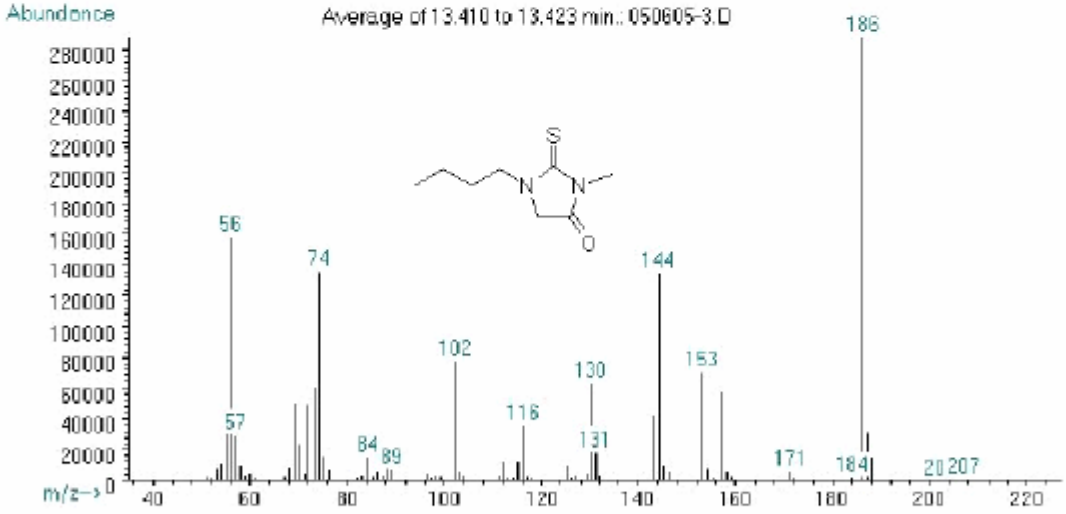

SpinWorks 2.5: Ethyl N-butylglycinate
N
H
CO2Et
PPM

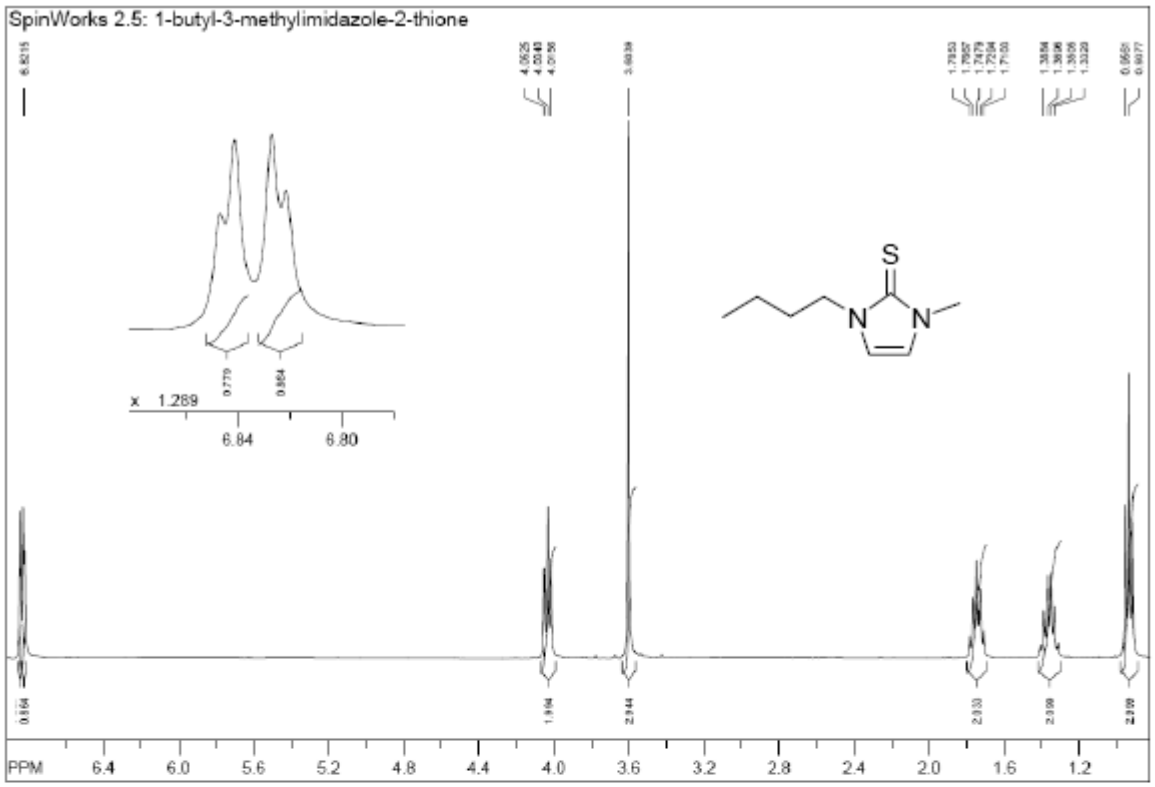

SpinWorks 2.5: Ethyl N-butylglycinate
N
H
CO2Et
PPM

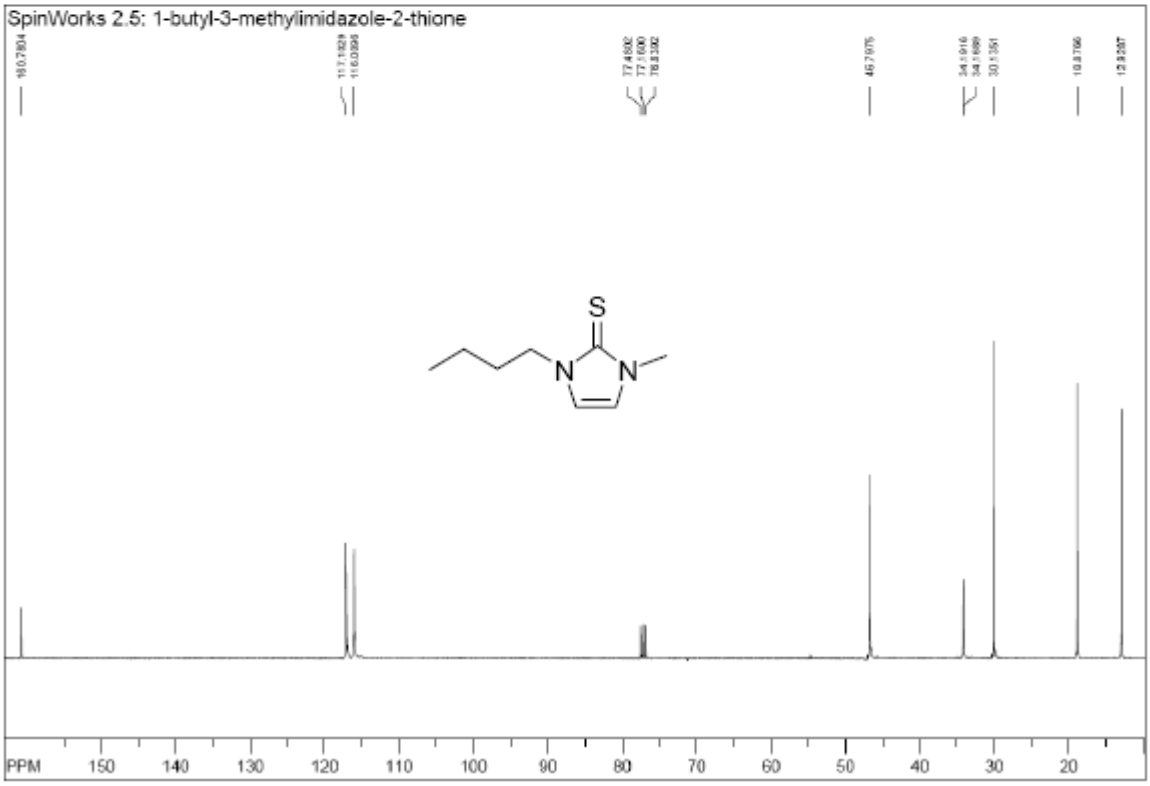

SpinWorks 2.5: 1-butyl-3-methyl-2-thiohydantoin
S
N
N
O
PPM
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0

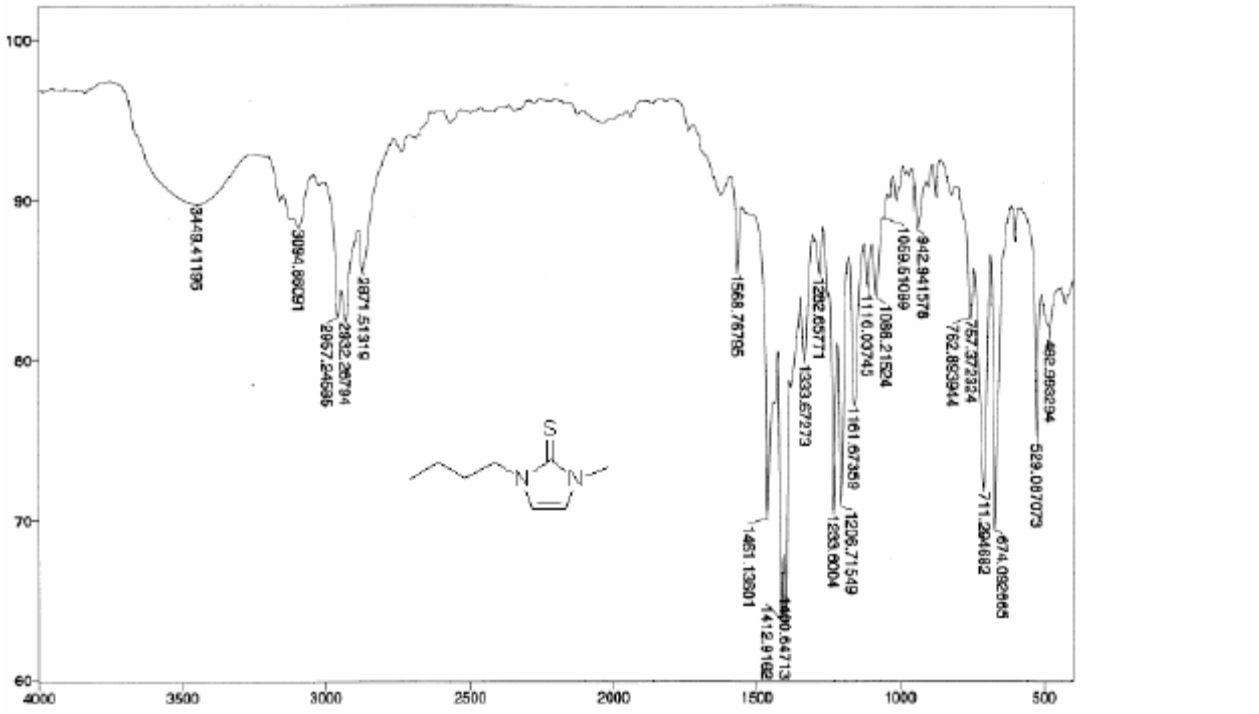

SpinWorks 2.5: 1-butyl-3-methyl-2-thiohydantion
S
N
N
O
PPM
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

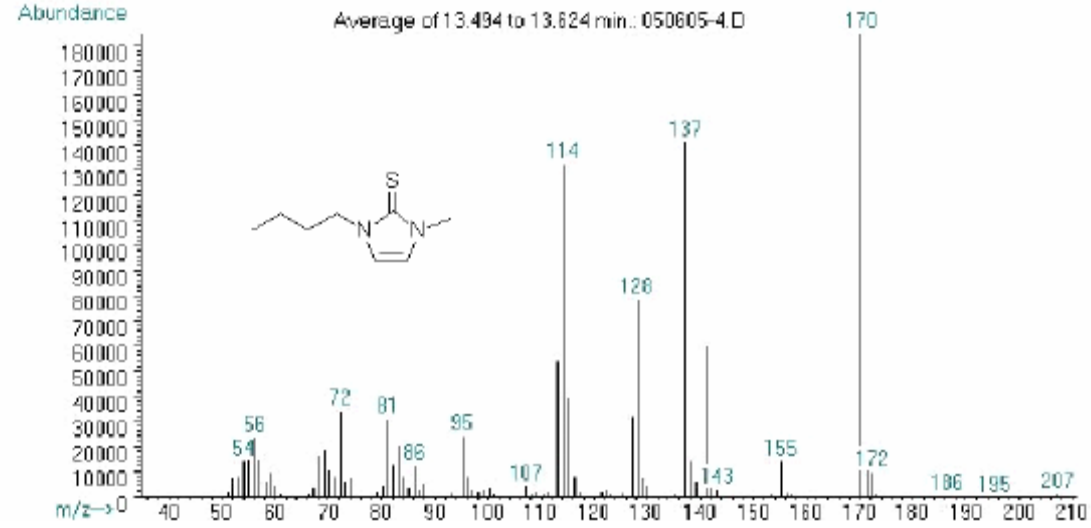

3586.68939
3479.71077
2871.64162
2931.50854
2958.15762
2679.00382
2586.75593
2184.00351
1744.1282
1498.41739
1485.70514
1412.62584
1377.83662
1300.21209
1235.37001
1139.18414
1104.6212
1027.52389
1002.08211
978.982654
939.782368
892.630751
872.00717
744.366496
679.759951
4993.84417

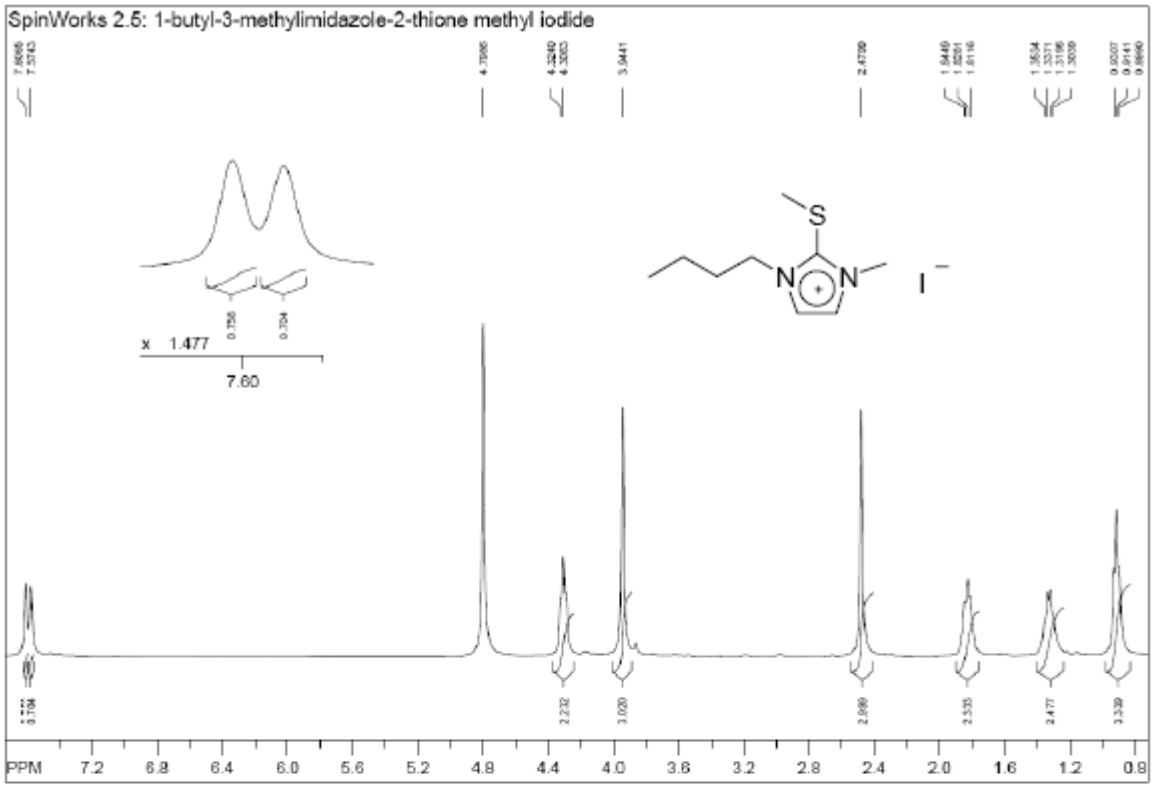

Abundance
Average of 13.410 to 13.423 min.: 050605-3.D
m/z-->
186
144
74
56
102
153
130
116
57
131
84
89
171
184
207

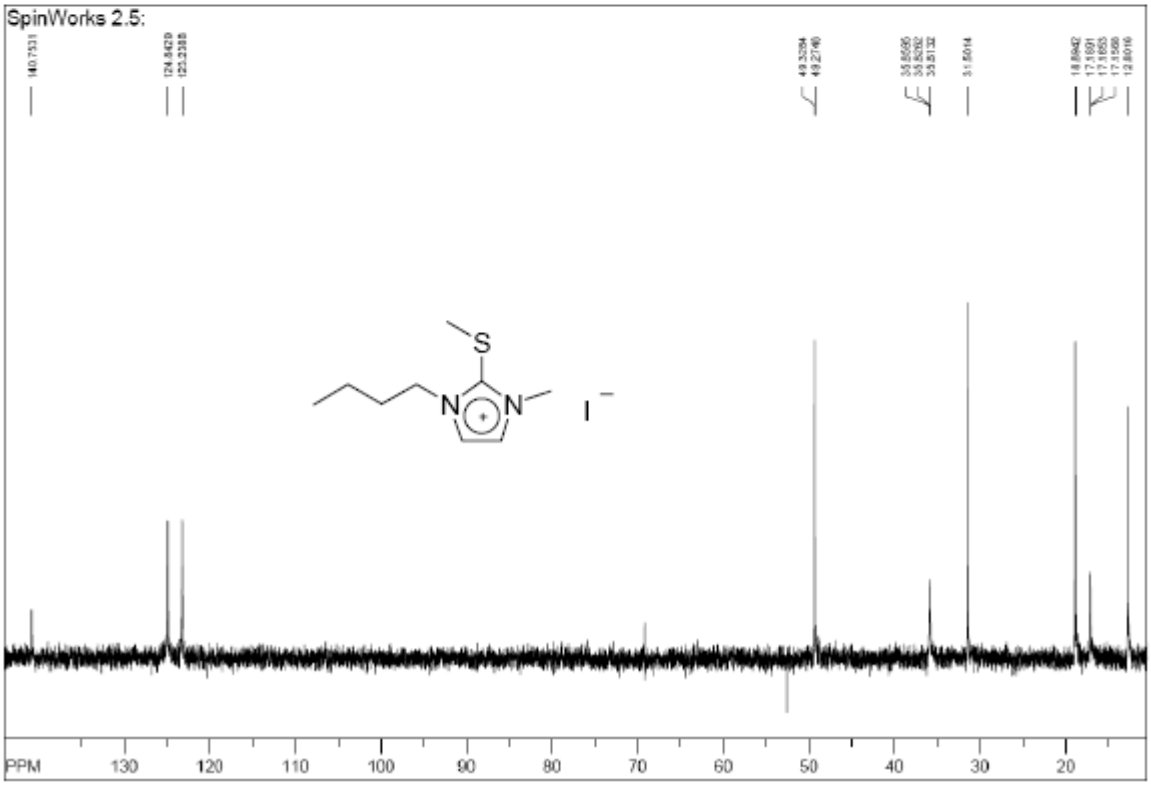

SpinWorks 2.5: 1-butyl-3-methylimidazole-2-thione
S
N
N
x 1.289
6.84
6.80
PPM
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2

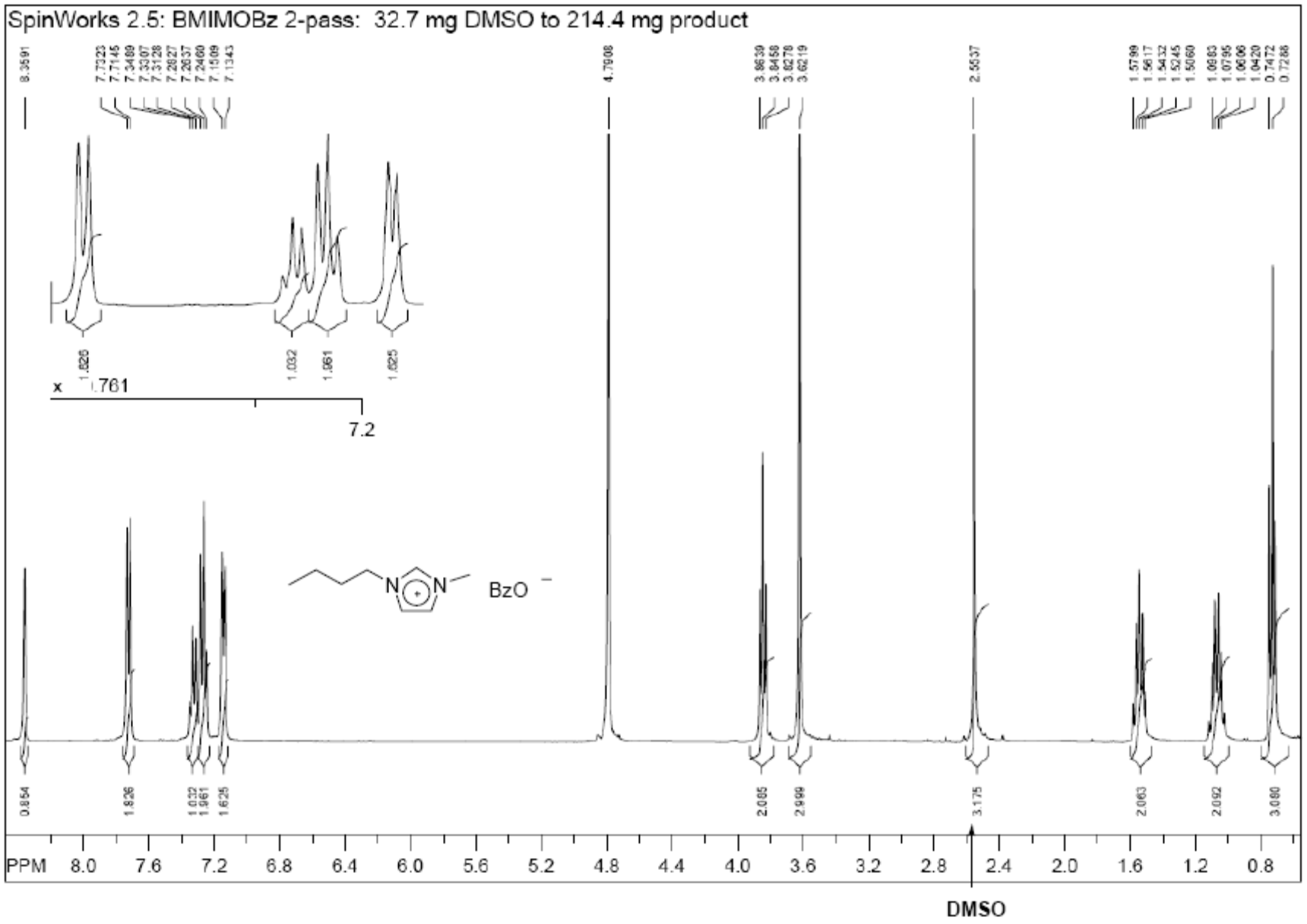

SpinWorks 2.5: 1-butyl-3-methylimidazole-2-thione
S
N
N
PPM
150
140
130
120
110
100
90
80
70
60
50
40
30
20

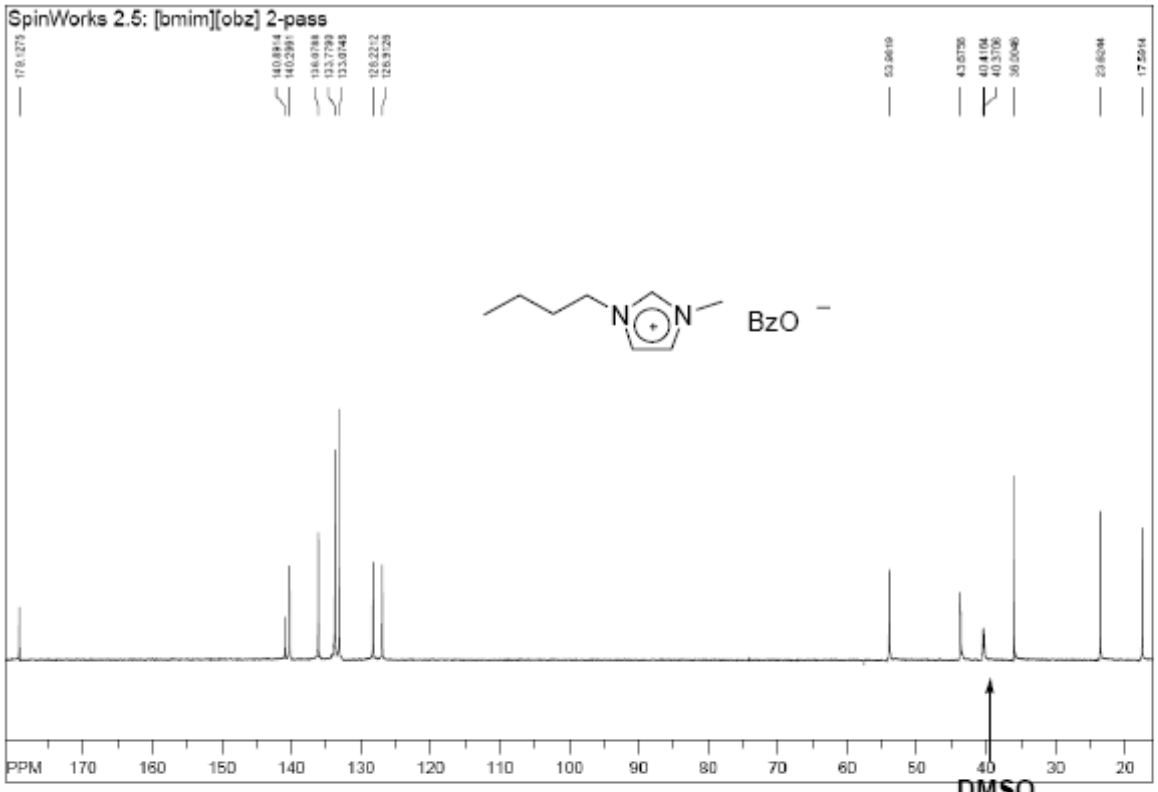

100
90
80
70
60
4000
3500
3000
2500
2000
1500
1000
500
3419.41195
3094.66091
2957.24586
2871.51319
1568.78795
1461.13901
1333.67273
1282.65771
1206.71549
1161.67359
1116.00745
1086.21524
1059.51089
942.941578
762.863944
711.264682
674.092865
529.067073
S
N
N

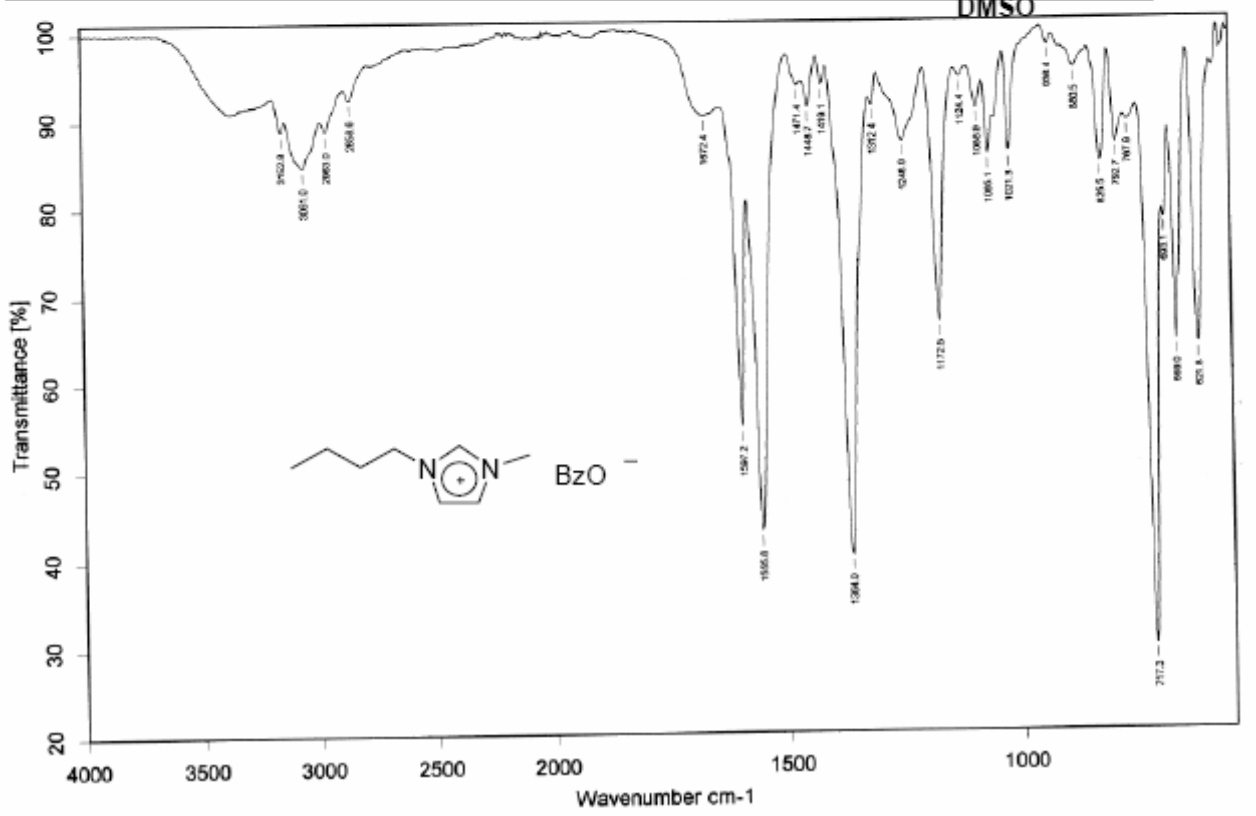

Abundance
Average of 13.484 to 13.624 min.: 050605-4.D
180000
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
m/z→
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
170
137
114
126
72
81
56
54
95
88
107
143
155
172
186
195
207
S
N
N

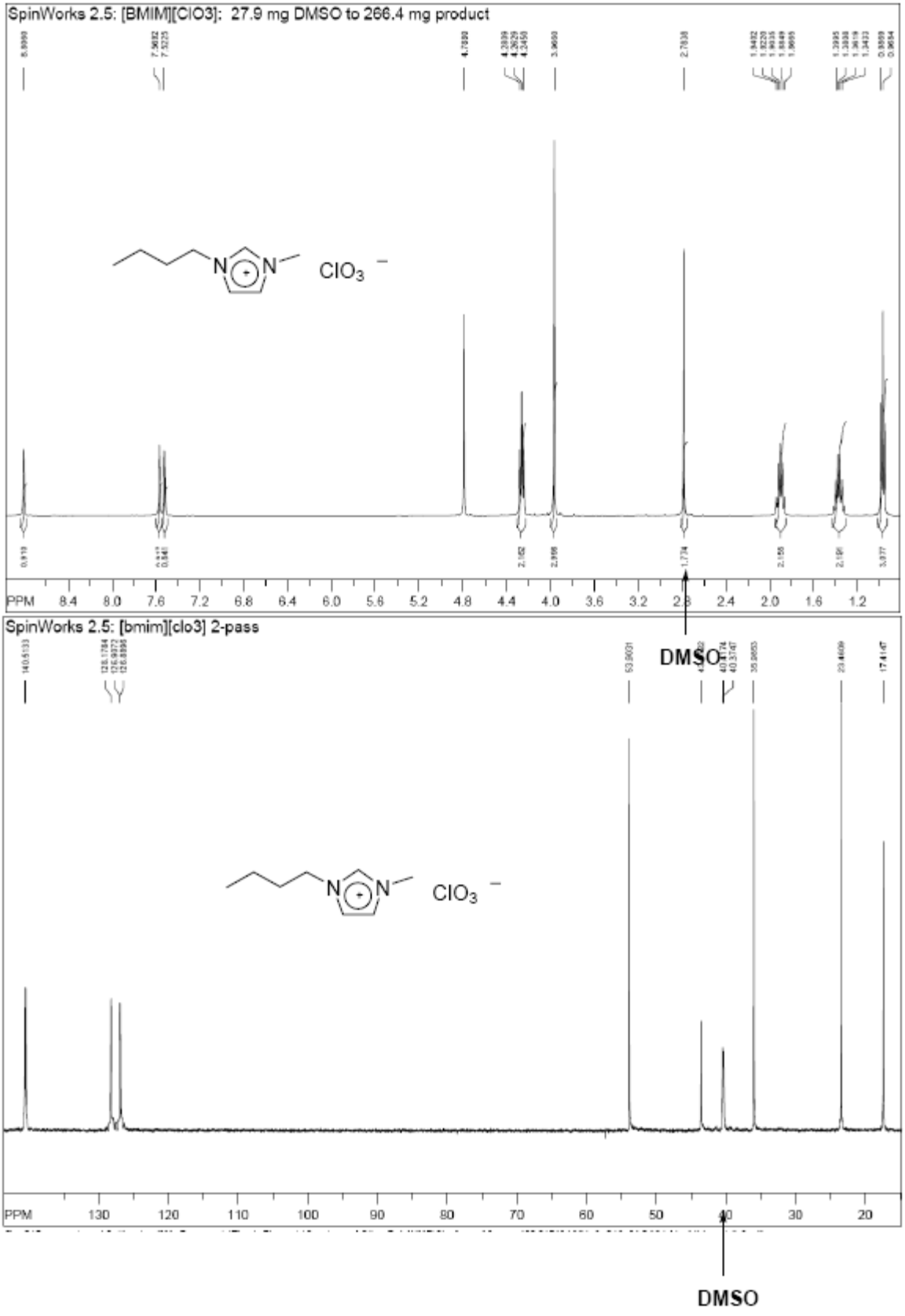

SpinWorks 2.5: 1-butyl-3-methylimidazole-2-thione methyl iodide
x 1.477
7.60
PPM

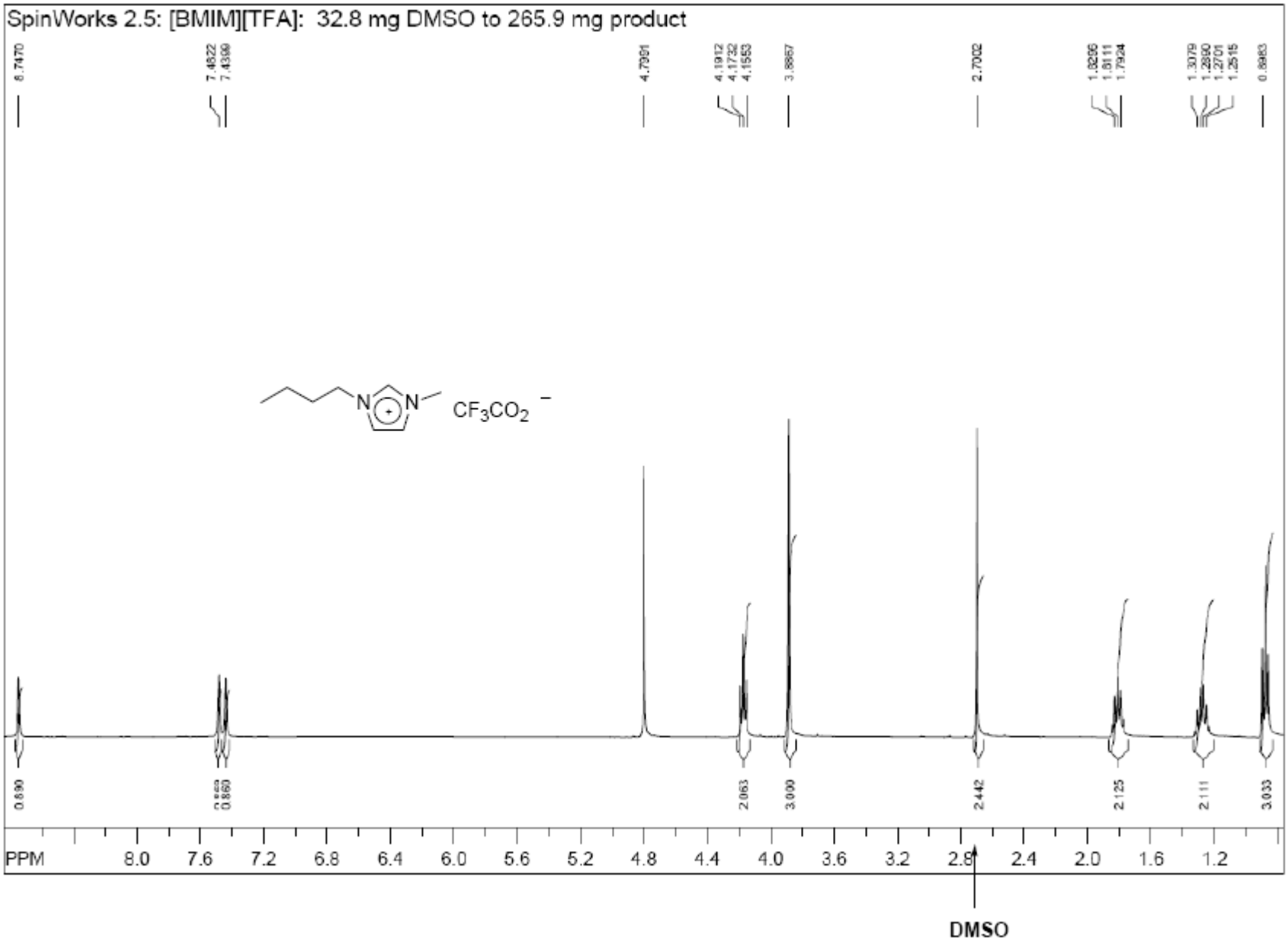

SpinWorks 2.5:
PPM

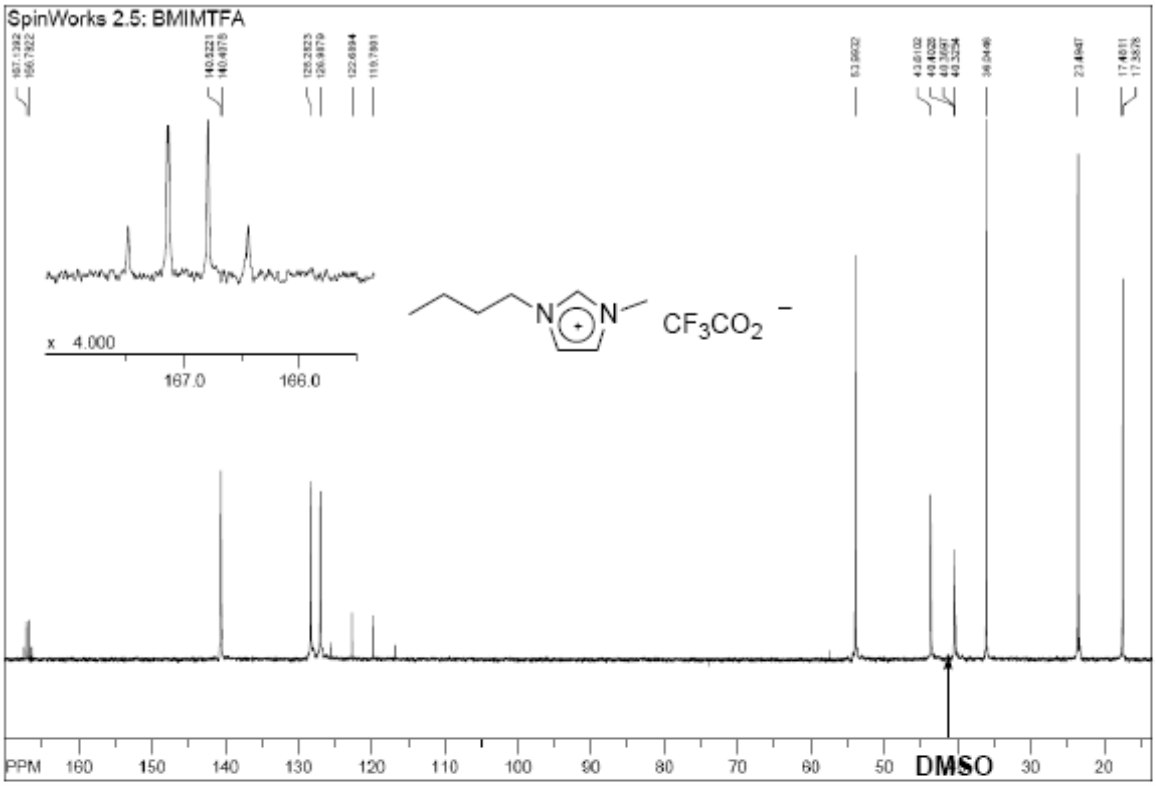

SpinWorks 2.5: BMIMOBz 2-pass: 32.7 mg DMSO to 214.4 mg product
8.3591
7.7323
7.7145
7.3489
7.3307
7.3128
7.2827
7.2637
7.2460
7.1509
7.1343
4.7908
3.8639
3.8458
3.8278
3.8219
2.5537
1.5799
1.5617
1.5432
1.5245
1.5060
1.0983
1.0795
1.0606
1.0420
0.7472
0.7288
1.826
1.032
1.961
1.625
x 1.761
7.2
BzO
0.854
1.826
1.032
1.961
1.625
2.085
2.999
3.175
2.063
2.092
3.080
PPM 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8
DMSO

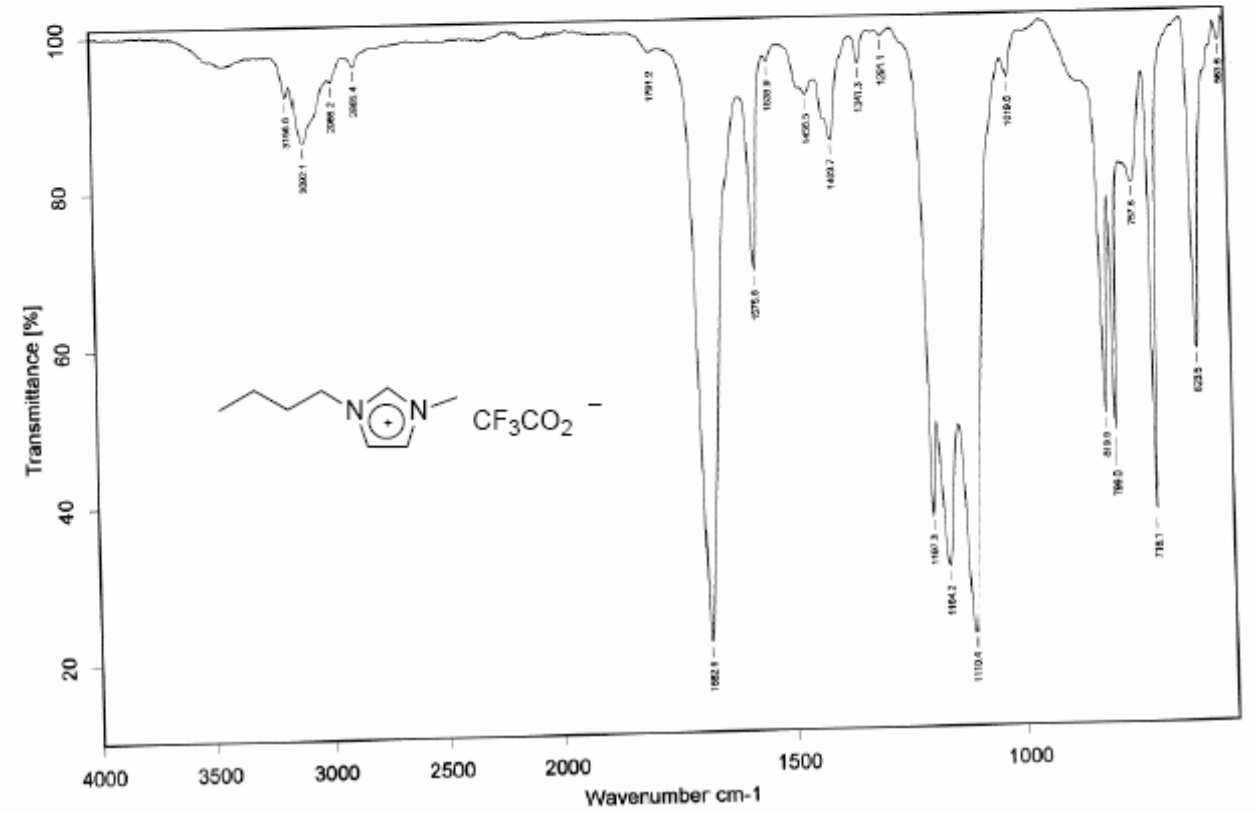

SpinWorks 2.5: [bmim][obz] 2-pass
N
N
BzO
PPM 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
DMSO

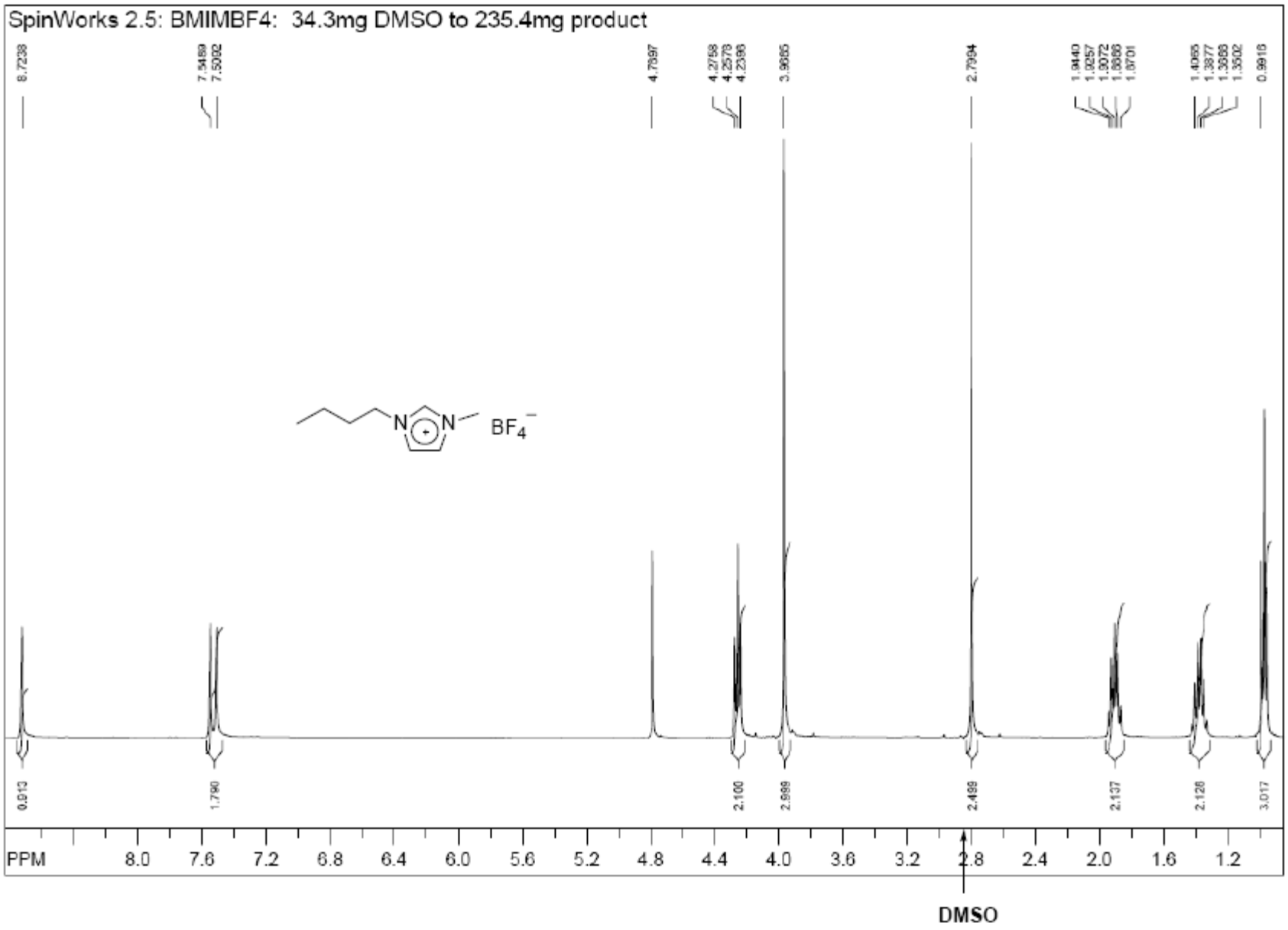

Transmittance [%]
100 90 80 70 60 50 40 30 20
4000 3500 3000 2500 2000 1500 1000
Wavenumber cm-1
N
N
BzO

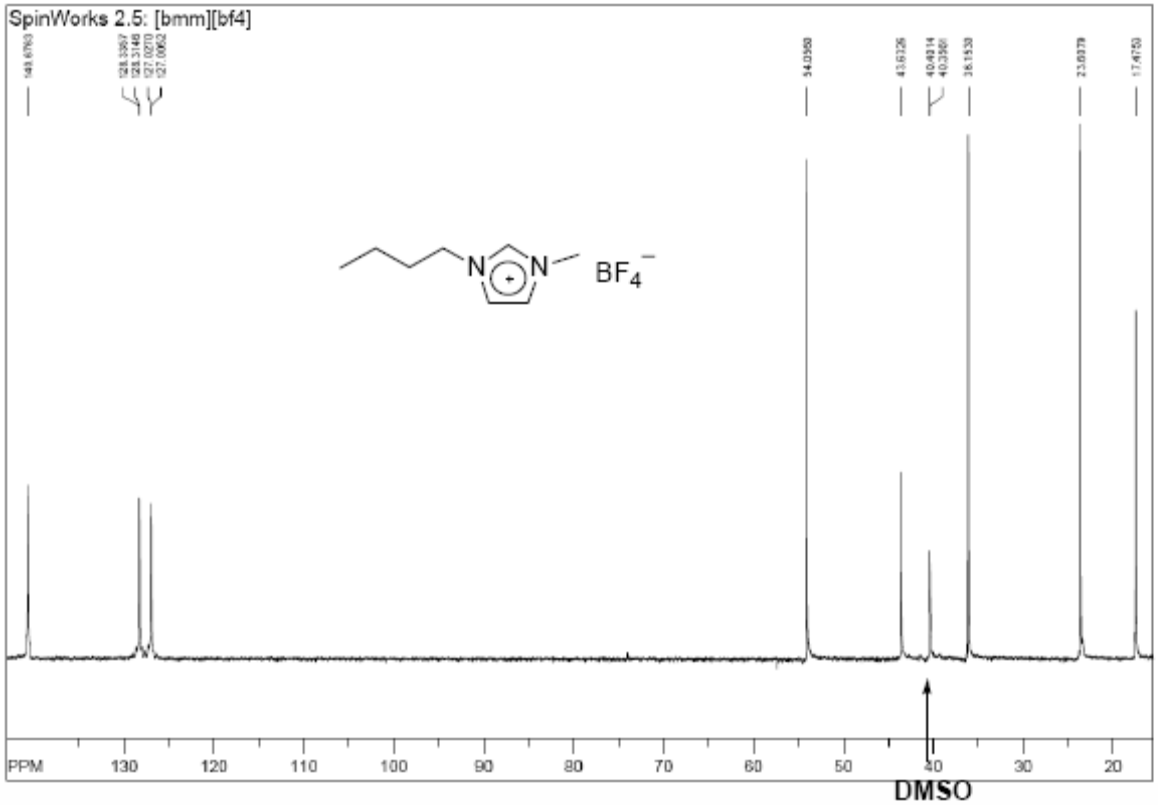

SpinWorks 2.5: [BMIM][ClO3]: 27.9 mg DMSO to 266.4 mg product
PPM 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2
DMSO
SpinWorks 2.5: [bmim][clo3] 2-pass
PPM 130 120 110 100 90 80 70 60 50 40 30 20
DMSO

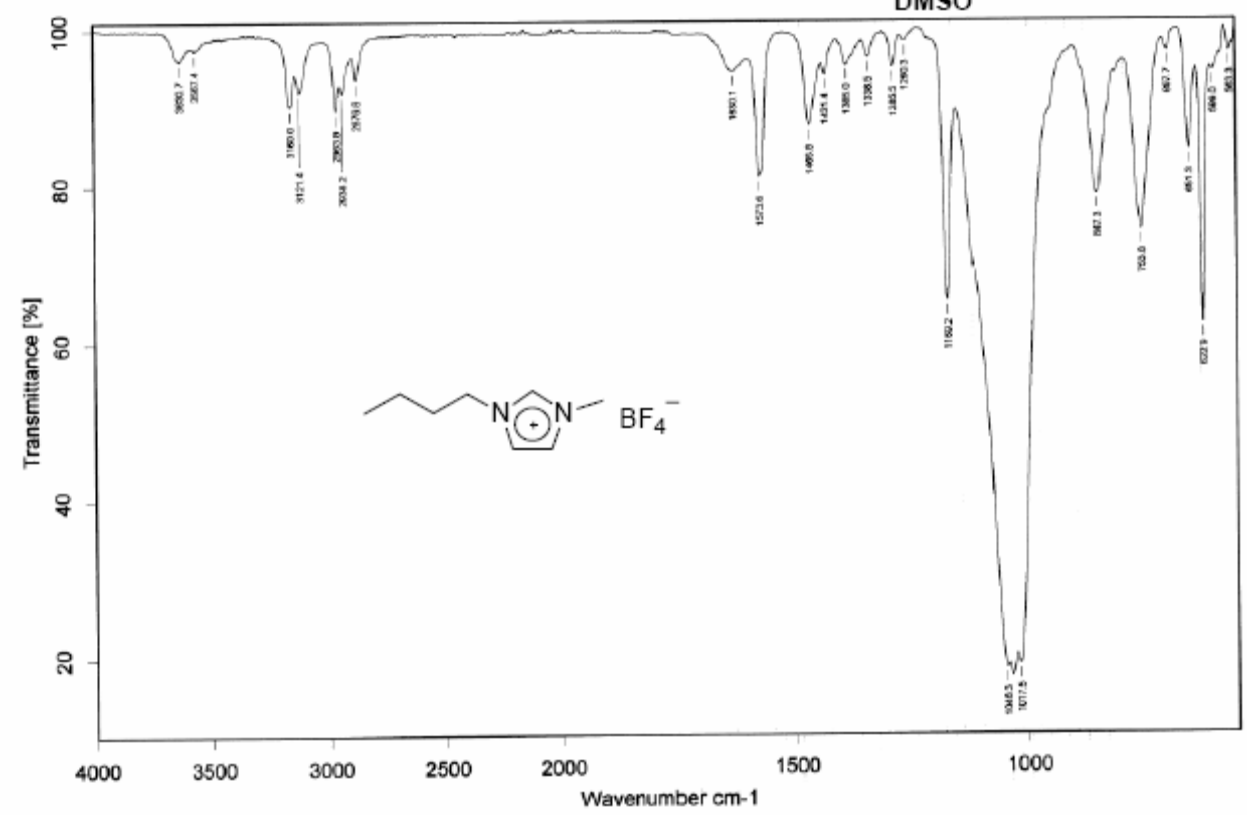

SpinWorks 2.5: [BMIM][TFA]: 32.8 mg DMSO to 265.9 mg product
8.7470
7.4522
7.4399
4.7991
4.1912
4.1732
4.1553
3.8857
2.7002
1.8296
1.8111
1.7924
1.3079
1.2890
1.2701
1.2515
0.9483
0.890
2.063
3.000
2.442
2.125
2.111
3.033
PPM
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
DMSO

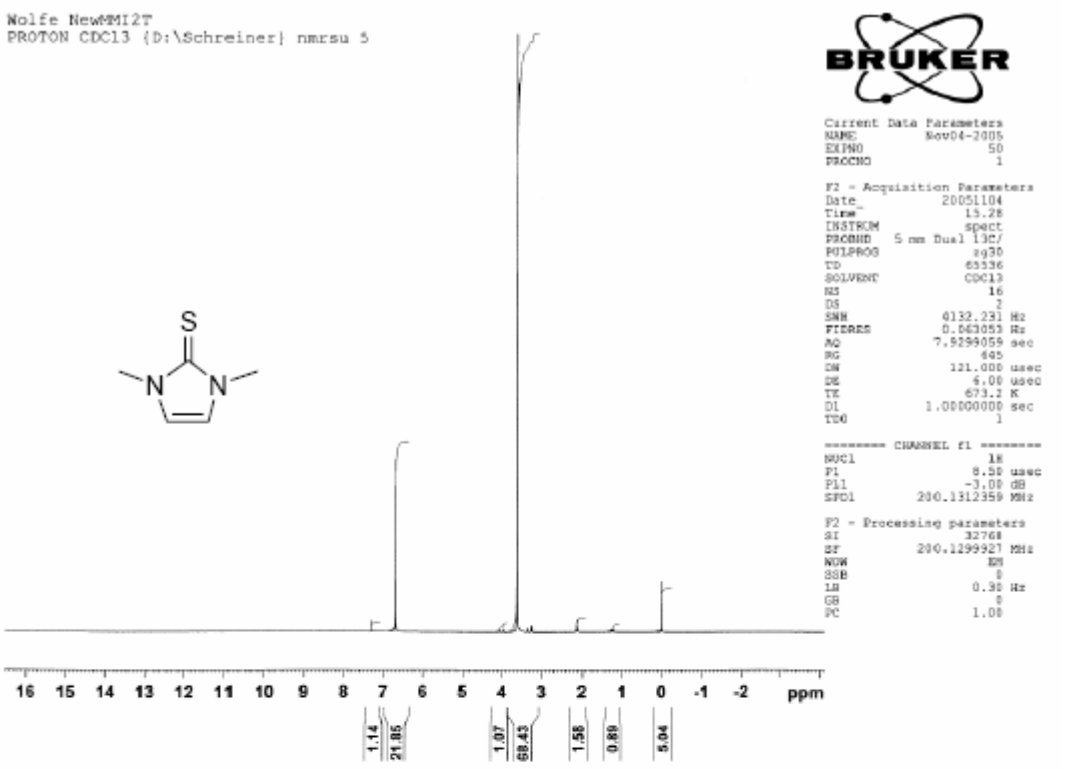

SpinWorks 2.5: BMIMTFA
x 4.000
167.0
166.0
DMSO
PPM 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
CF3CO2 −


Transmittance [%]
100
80
60
40
20
4000
3500
3000
2500
2000
1500
1000
Waverumber cm-1
CF3CO2 −


SpinWorks 2.5: BMIMBF4: 34.3mg DMSO to 235.4mg product
8.7238
7.5489
7.5092
4.7697
4.2758
4.2578
4.2396
3.9665
2.7934
1.9449
1.9257
1.9072
1.8886
1.8701
1.4055
1.3877
1.3688
1.3502
0.9916
N
N
BF4−
0.913
1.790
2.100
2.999
2.499
2.137
2.126
3.017
PPM
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
DMSO


SpinWorks 2.5: [bmm][bf4]
PPM
130
120
110
100
90
80
70
60
50
40
30
20
DMSO
BF4−


Transmittance [%]
100
80
60
40
20
4000
3500
3000
2500
2000
1500
1000
Wavenumber cm-1
BF4−

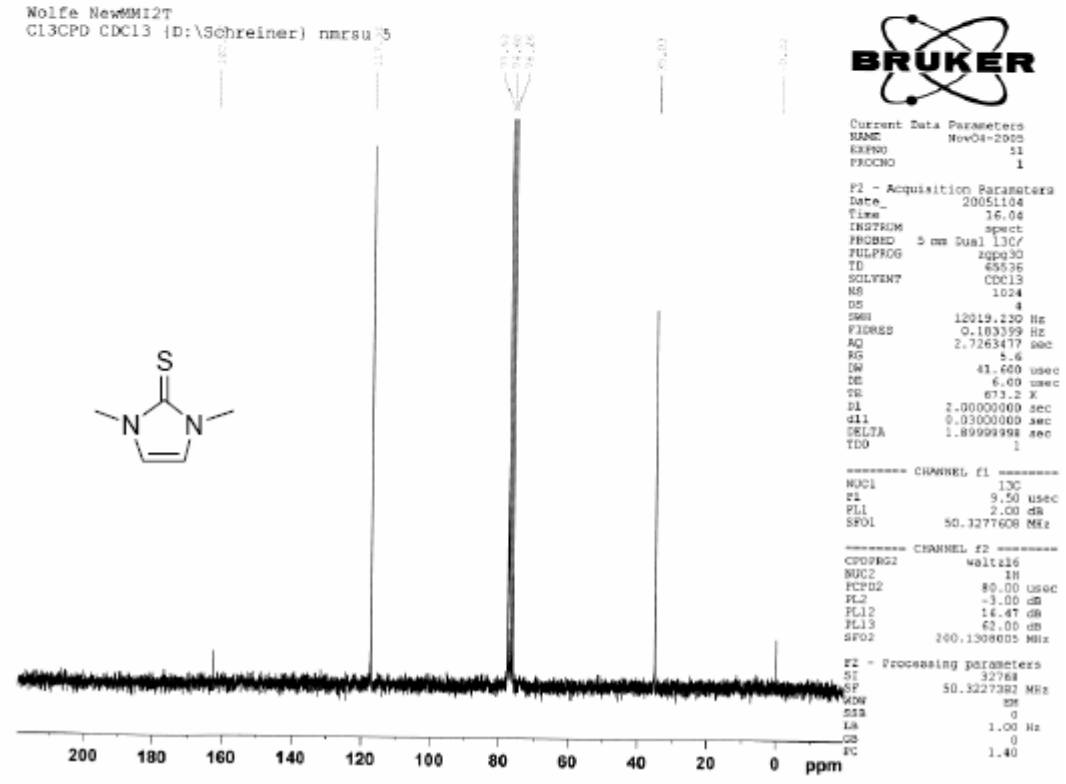


Current Data Parameters
NAME Nov04-2005
EXPNO 50
PROCNO 1

F2 - Acquisition Parameters
Date_ 20051104
Time 15.28
INSTRM spect
PROBHD 5 mm Dual 13C/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 6132.231 Hz
FIDRES 0.063053 Hz
AQ 7.9299059 sec
RG 645
DW 121.000 usec
DE 6.00 usec
TE 673.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 8.50 usec
PL1 -3.00 dB
SFO1 200.1312359 MHz

F2 - Processing parameters
SI 32768
SF 200.1299927 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



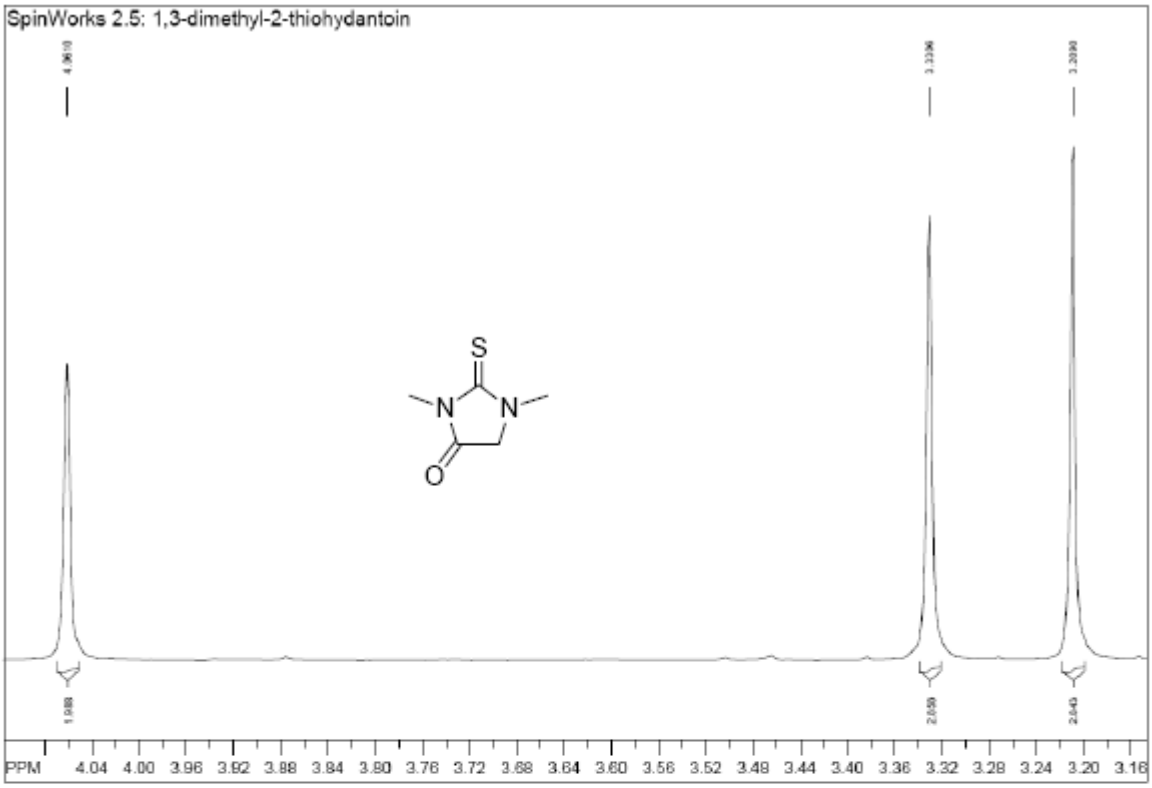
Current Data Parameters
NAME Nov04-2005
EXPNO 51
PROCNO 1

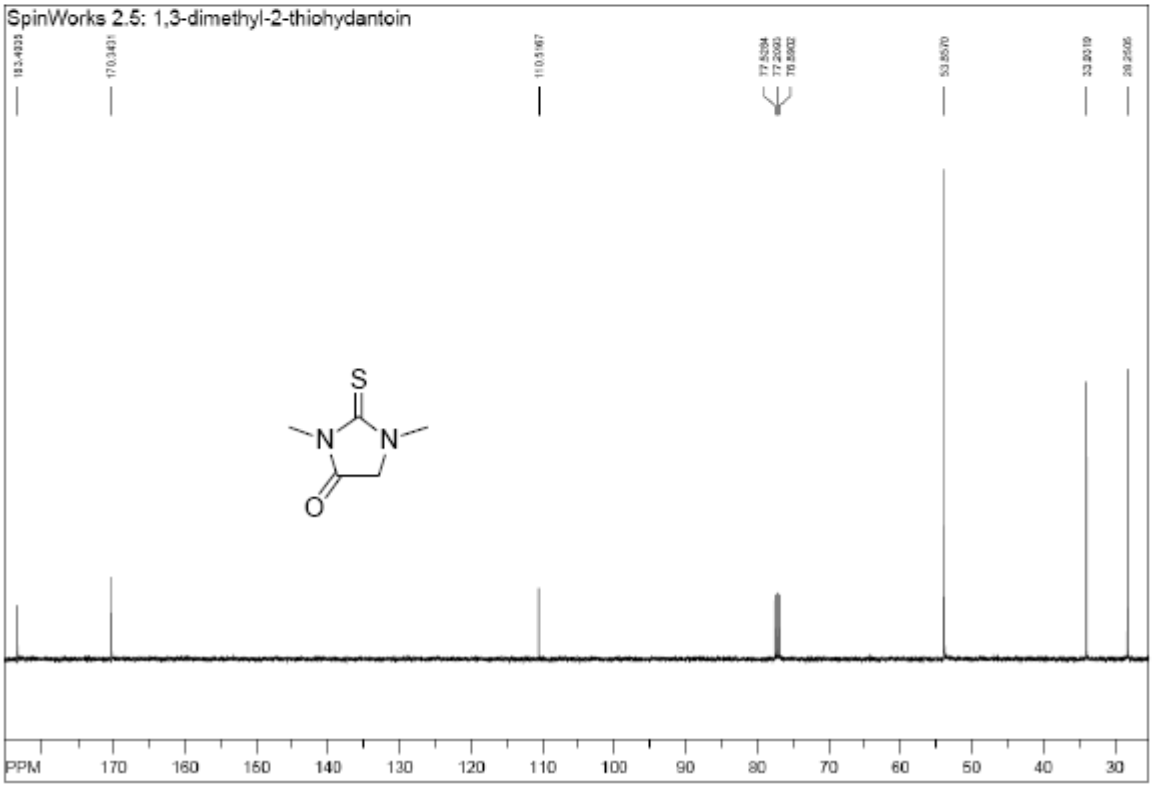
F2 - Acquisition Parameters
Date_ 20051104
Time 16.04
INSTRM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 5.6
DW 41.600 usec
DE 6.00 usec
TE 673.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

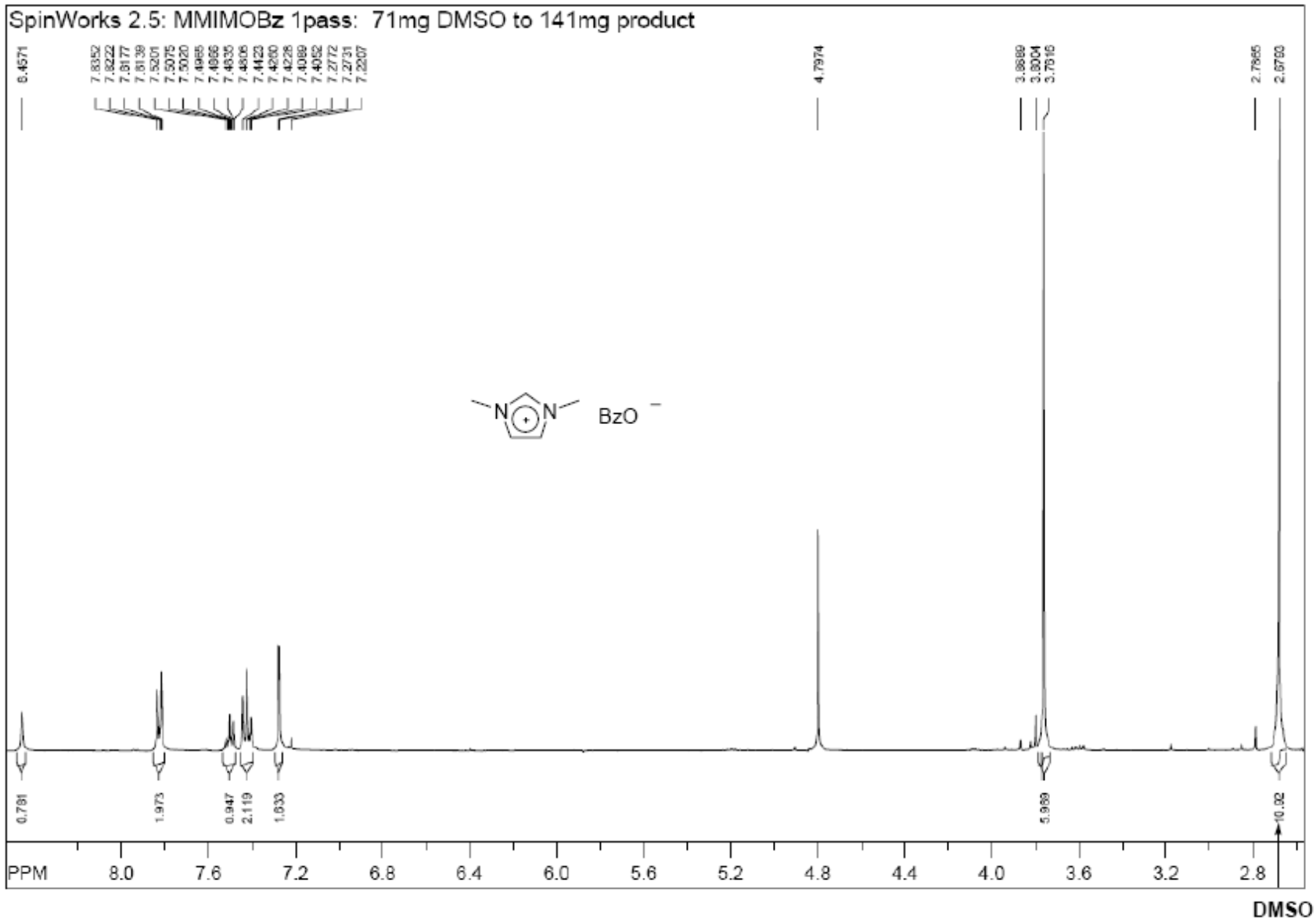
======== CHANNEL f1 ========
NUC1 13C
P1 9.50 usec
PL1 2.00 dB
SFO1 50.3277608 MHz

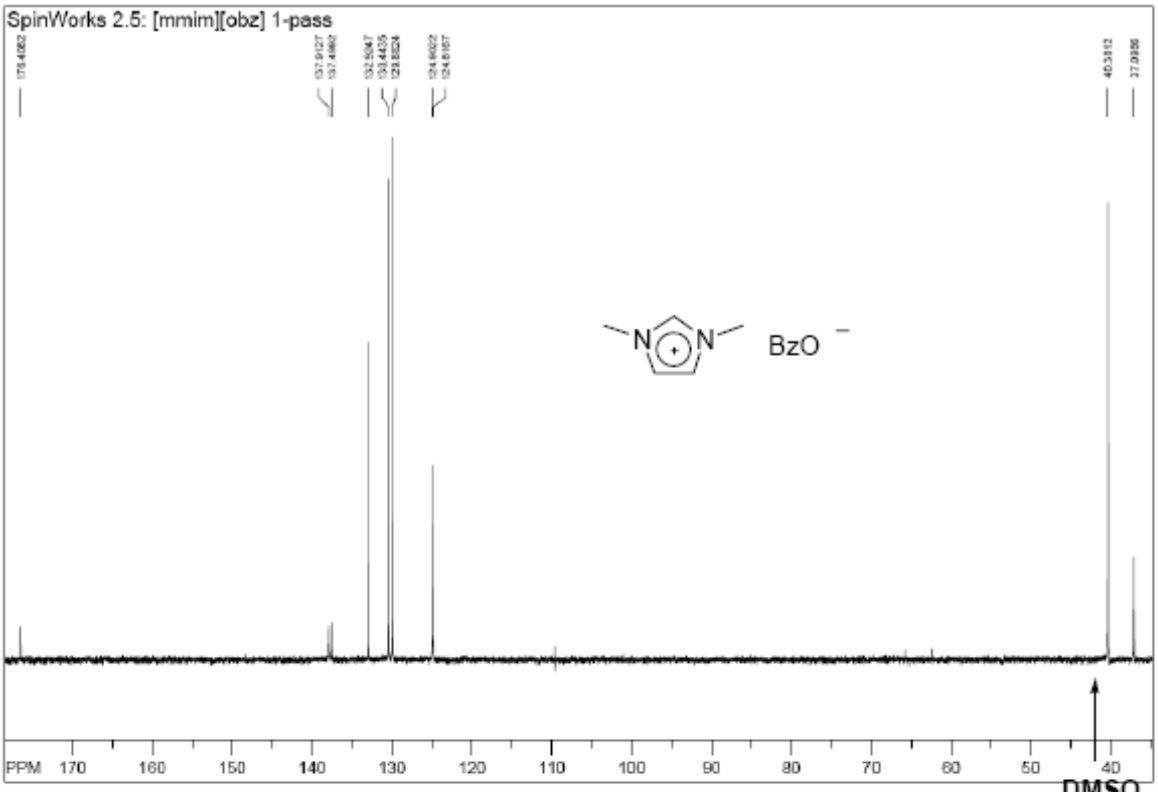
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 16.47 dB
PL13 62.00 dB
SFO2 200.1300005 MHz

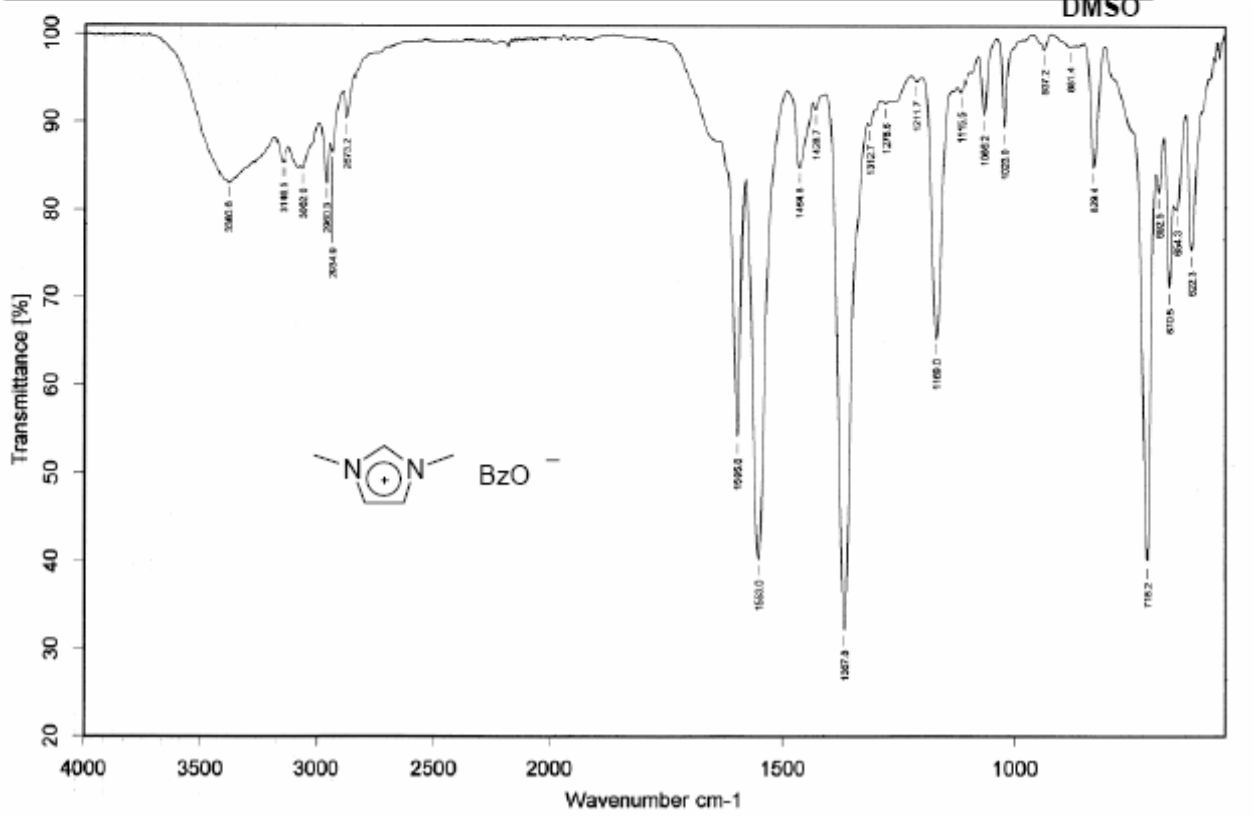
F2 - Processing parameters
SI 32768
SF 50.3227382 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

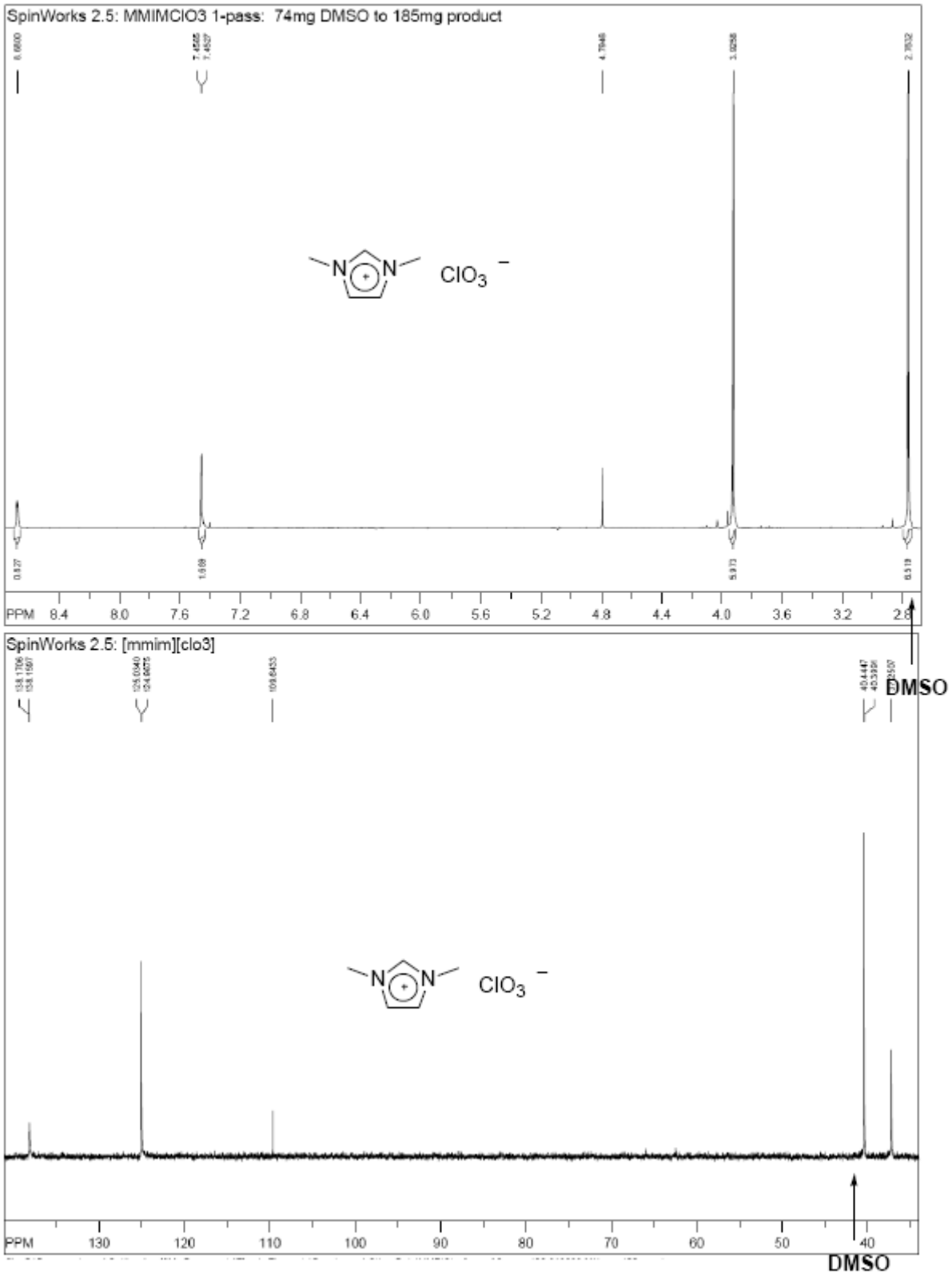

SpinWorks 2.5: 1,3-dimethyl-2-thiohydantoin
S
N
N
O
PPM
4.04 4.00 3.96 3.92 3.88 3.84 3.80 3.76 3.72 3.68 3.64 3.60 3.56 3.52 3.48 3.44 3.40 3.36 3.32 3.28 3.24 3.20 3.16

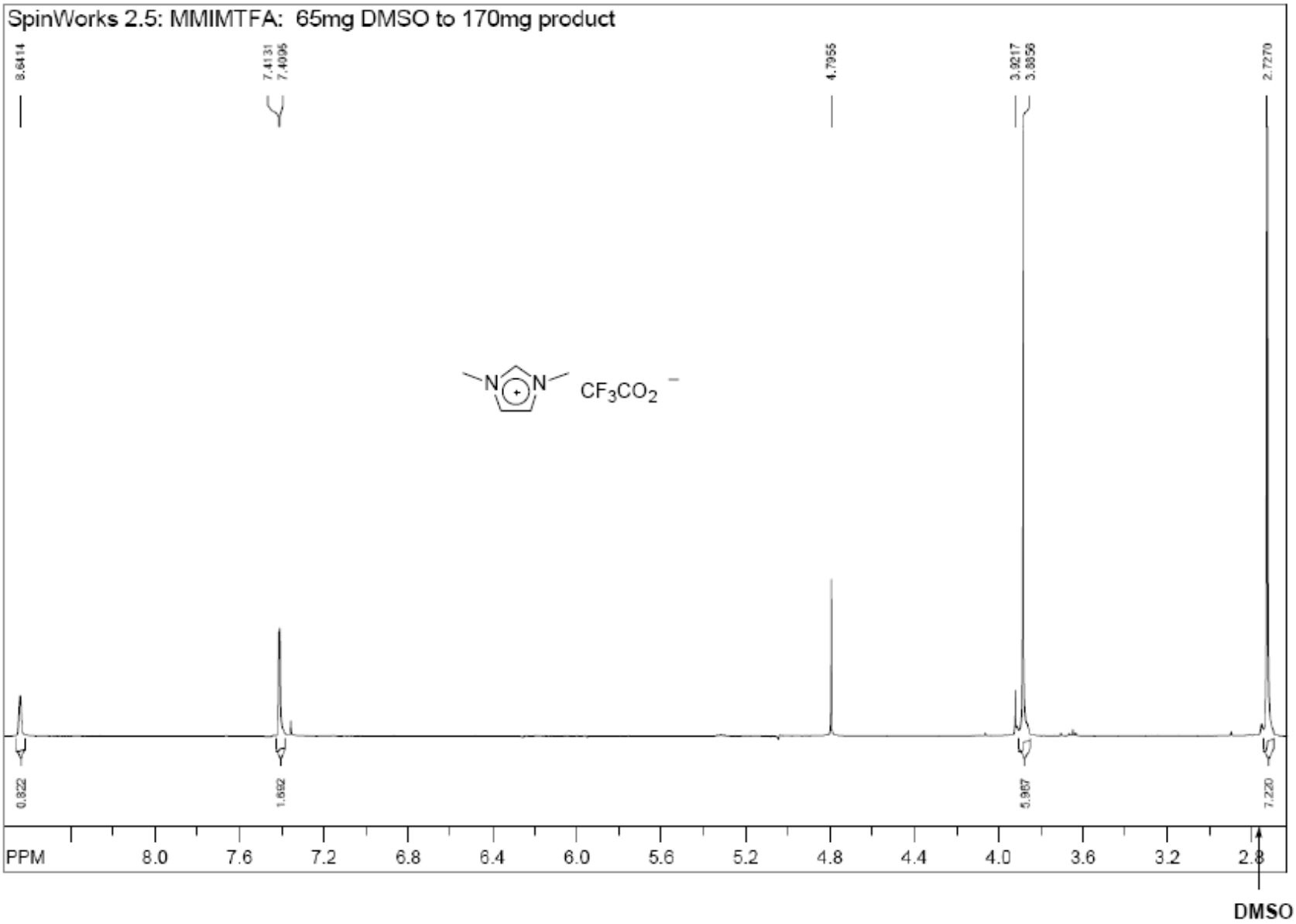

SpinWorks 2.5: 1,3-dimethyl-2-thiohydantoin
S
N
N
O
PPM
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30

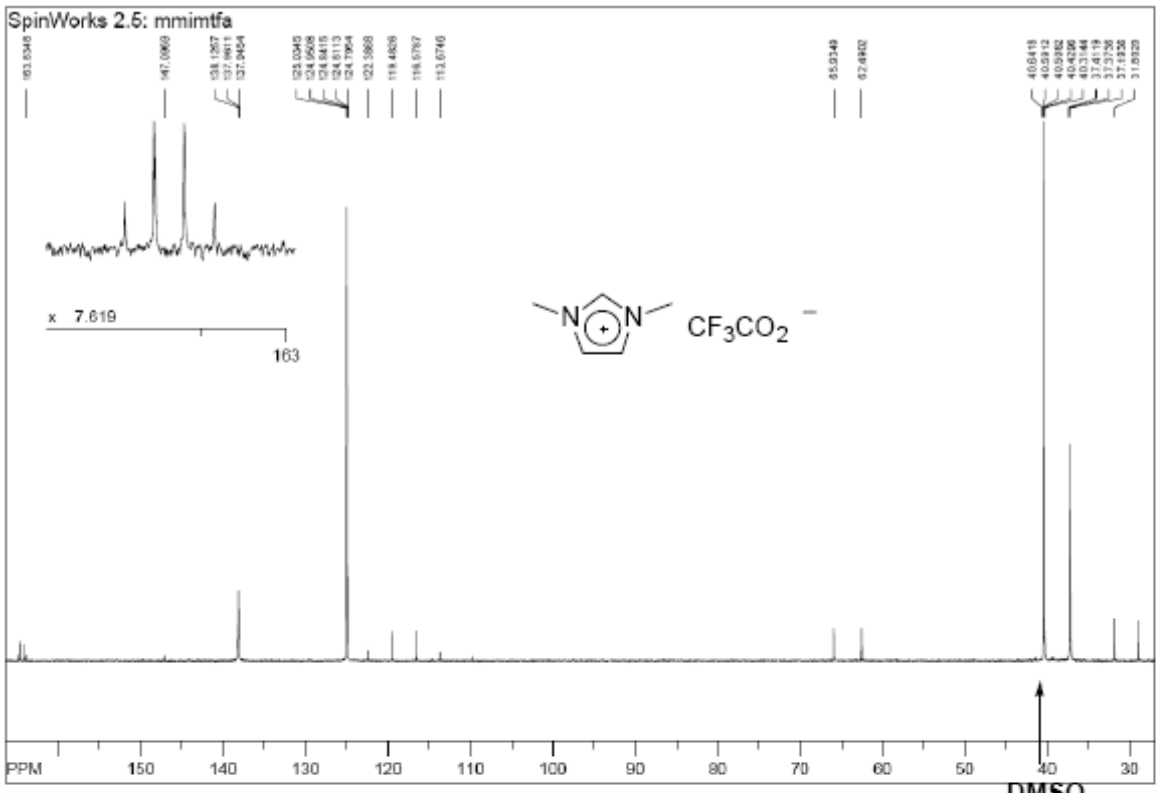

SpinWorks 2.5: MMIMOBz 1pass: 71mg DMSO to 141mg product
8.4571
7.8352
7.8222
7.8177
7.8139
7.5201
7.5075
7.5020
7.4985
7.4866
7.4830
7.4806
7.4423
7.4280
7.4228
7.4089
7.4052
7.2772
7.2731
7.2207
4.7974
3.8689
3.8004
3.7616
2.7885
2.6793
BzO
0.781
1.973
0.947
2.119
1.833
5.959
10.00
PPM
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
DMSO

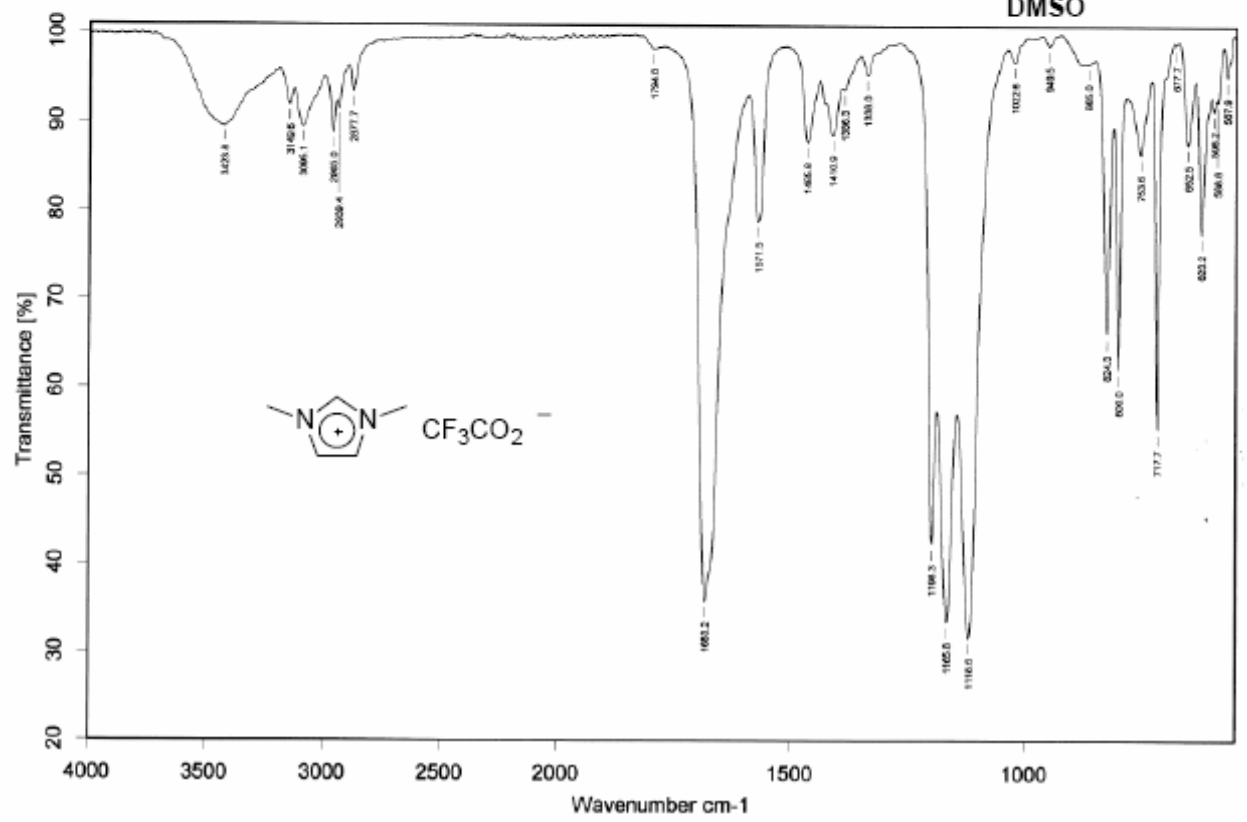

SpinWorks 2.5: [mmim][obz] 1-pass
PPM 170 160 150 140 130 120 110 100 90 80 70 60 50 40
DMSO
BzO ⁻

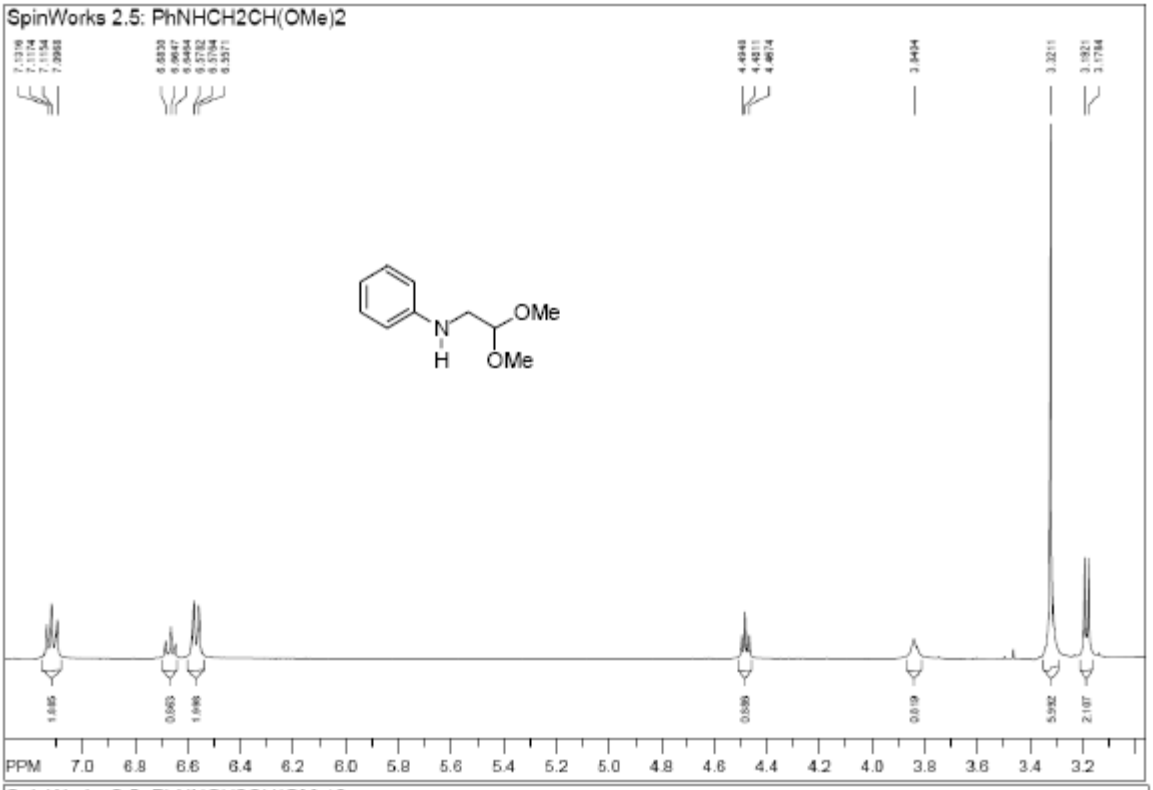

Transmittance [%]
Wavenumber cm-1
4000 3500 3000 2500 2000 1500 1000
BzO ⁻

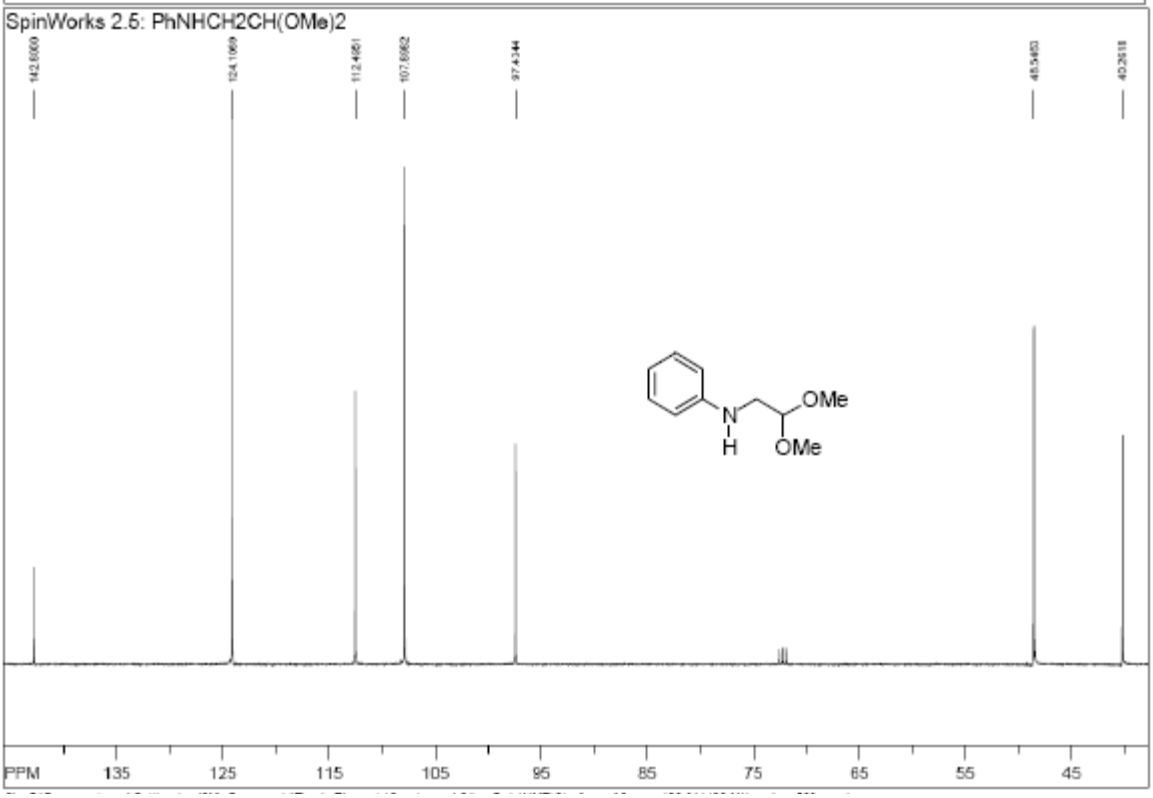

SpinWorks 2.5: MMIMClO3 1-pass: 74mg DMSO to 185mg product
PPM 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8
DMSO
SpinWorks 2.5: [mmim][clo3]
PPM 130 120 110 100 90 80 70 60 50 40
DMSO

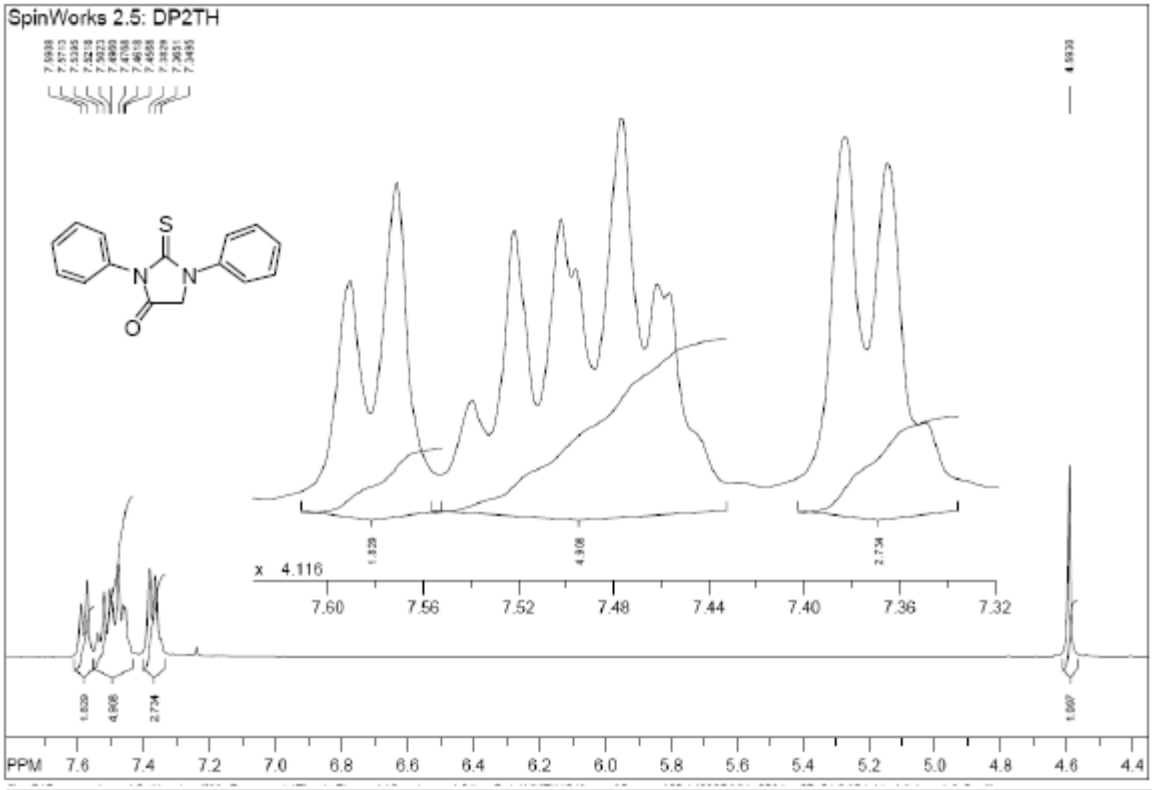

SpinWorks 2.5: MMIMTFA: 65mg DMSO to 170mg product
8.6414
7.4131
7.4096
4.7955
3.9217
3.8856
2.7270
N
N
$CF_3CO_2^-$
0.822
1.692
5.957
7.220
PPM
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
DMSO

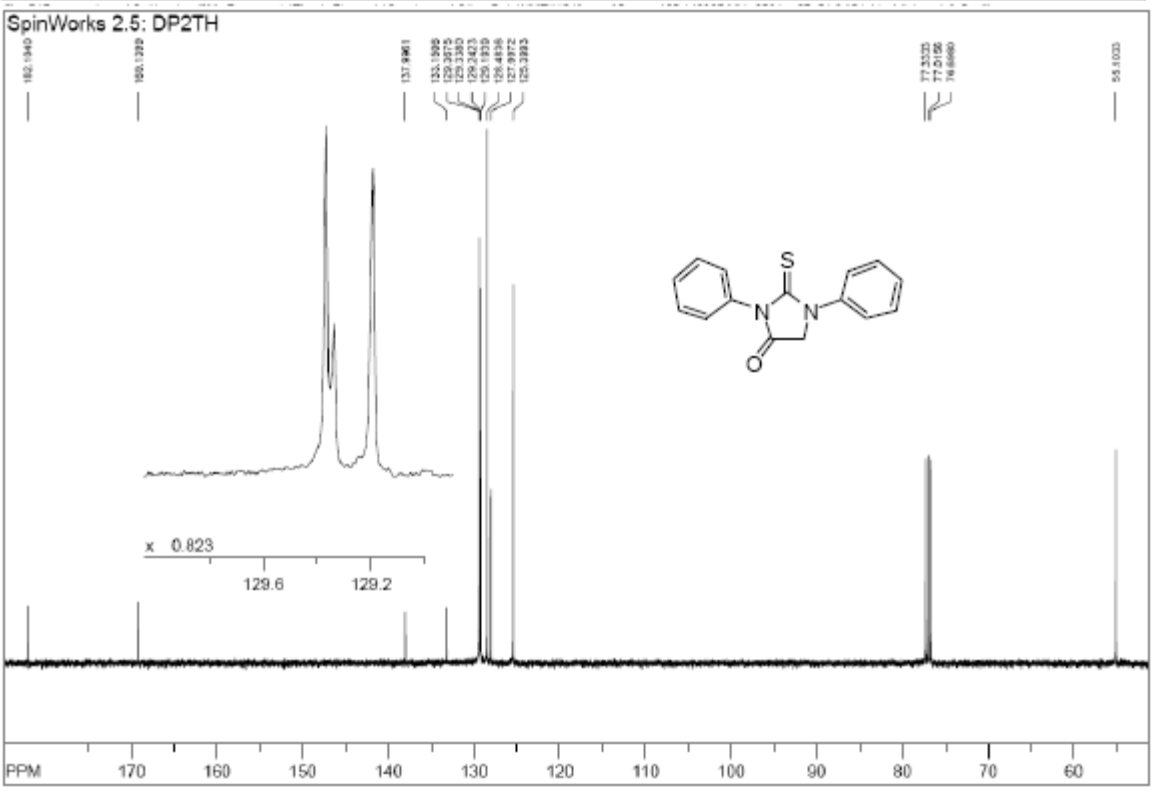

SpinWorks 2.5: mmimtfa
x 7.619
163
PPM
150
140
130
120
110
100
90
80
70
60
50
40
30
DMSO
CF3CO2 −

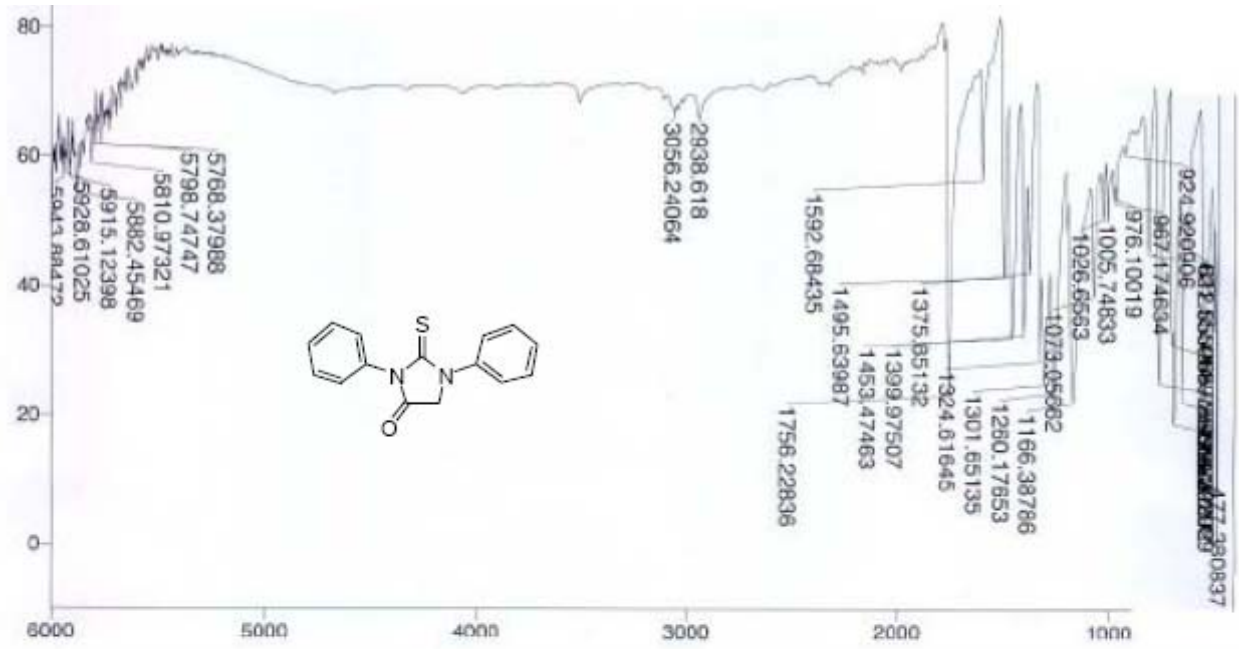

Transmittance [%]
Wavenumber cm-1
4000
3500
3000
2500
2000
1500
1000
CF3CO2 −

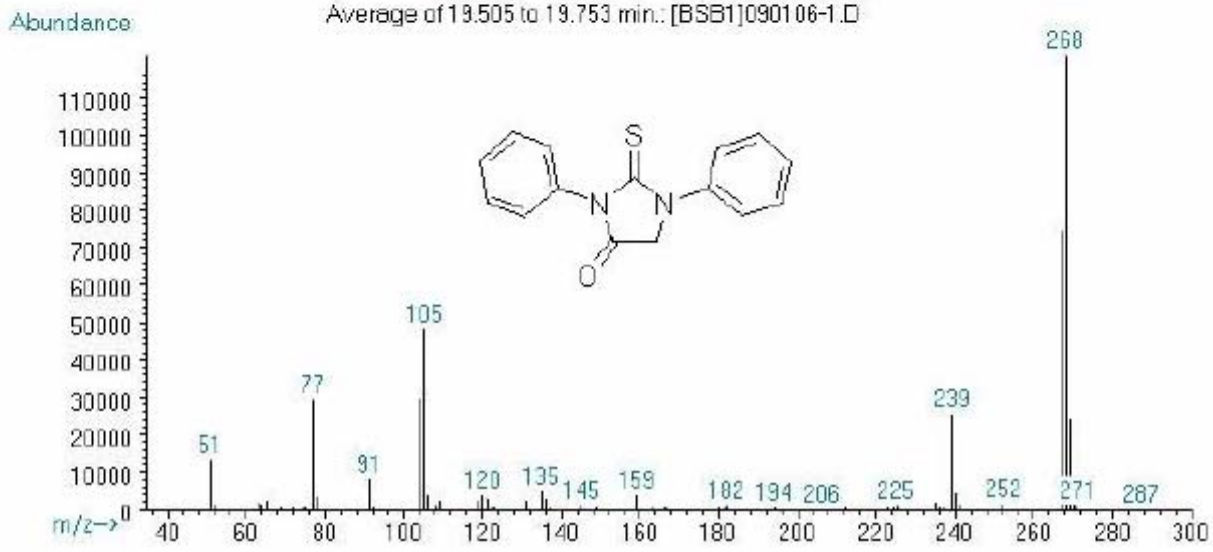

SpinWorks 2.5: PhNHCH2CH(OMe)2
OMe
N
H
OMe
PPM

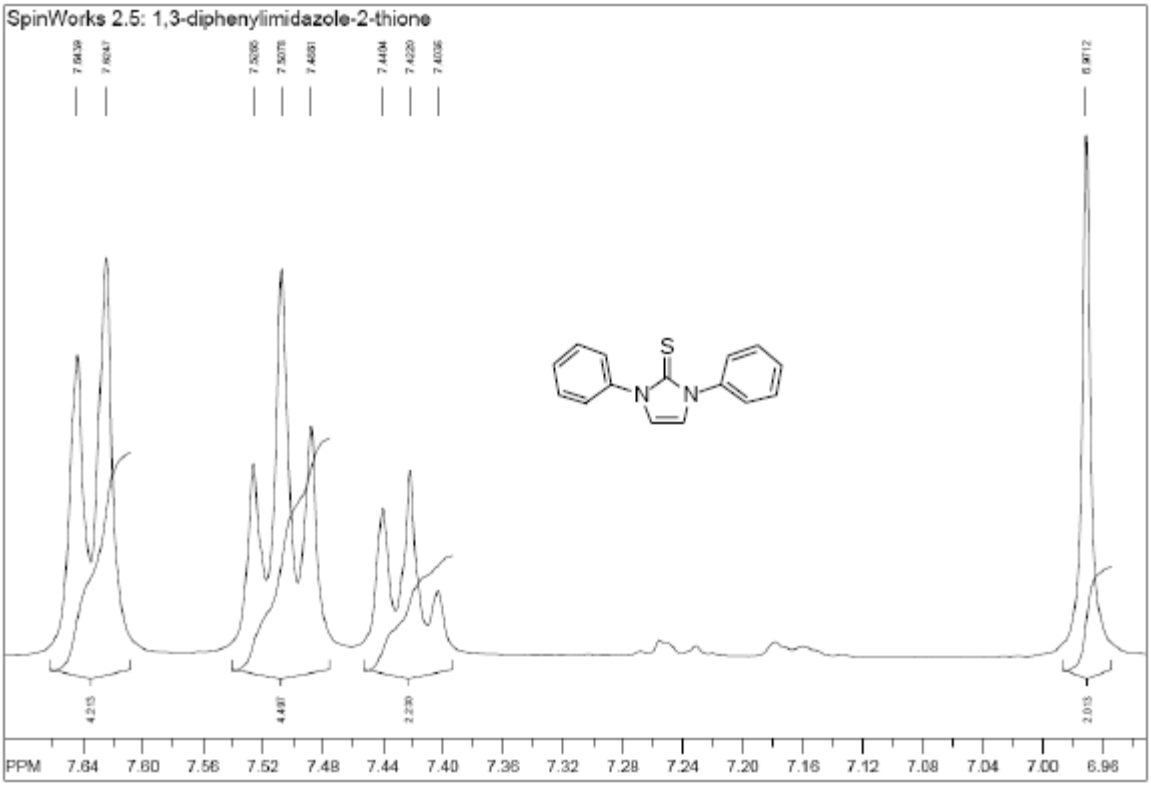

SpinWorks 2.5: PhNHCH2CH(OMe)2
142.8609
124.1069
112.4051
107.6982
97.4344
48.5463
40.2618
OMe
N
H
OMe
PPM

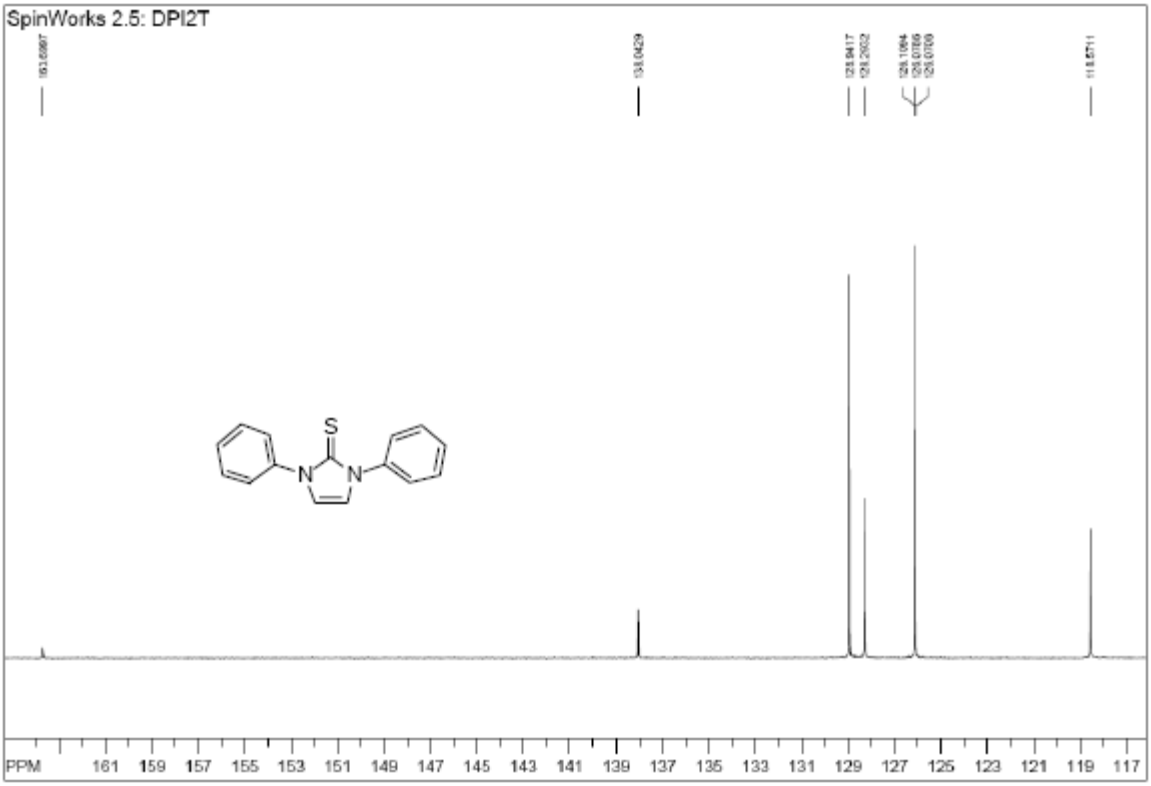

SpinWorks 2.5: DP2TH
S
N
N
O
x 4.116
7.60
7.56
7.52
7.48
7.44
7.40
7.36
7.32
PPM 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4

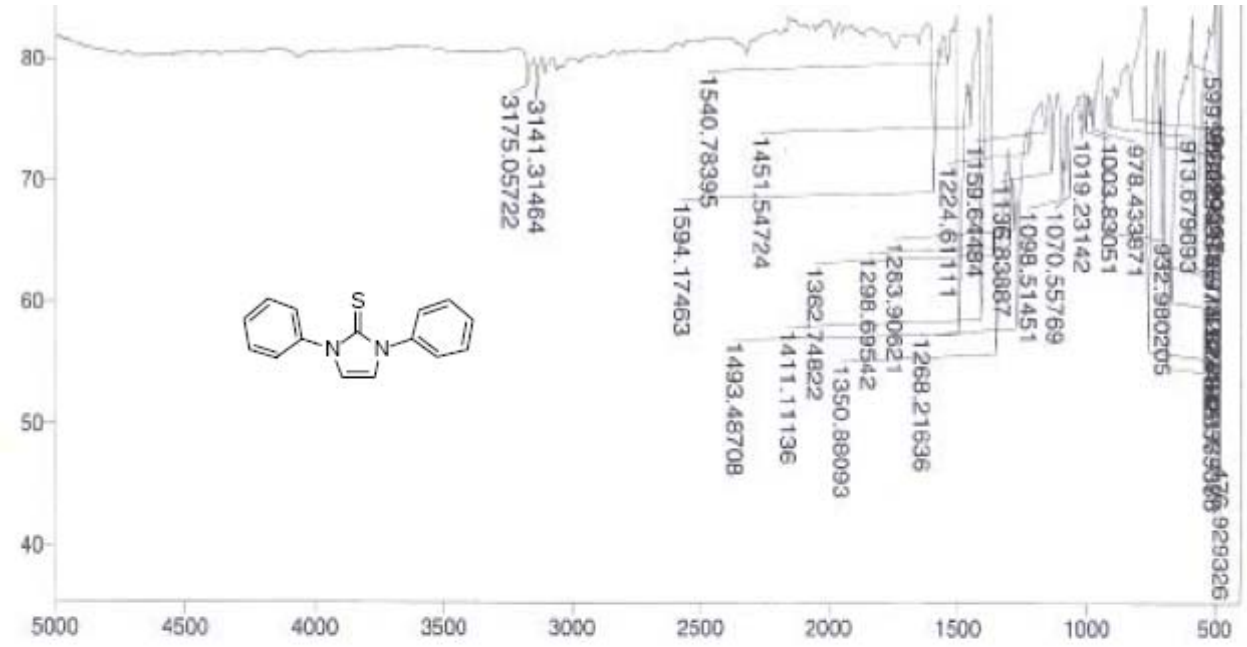

SpinWorks 2.5: DP2TH
S
N
N
O
x 0.823
129.6
129.2
PPM 170 160 150 140 130 120 110 100 90 80 70 60

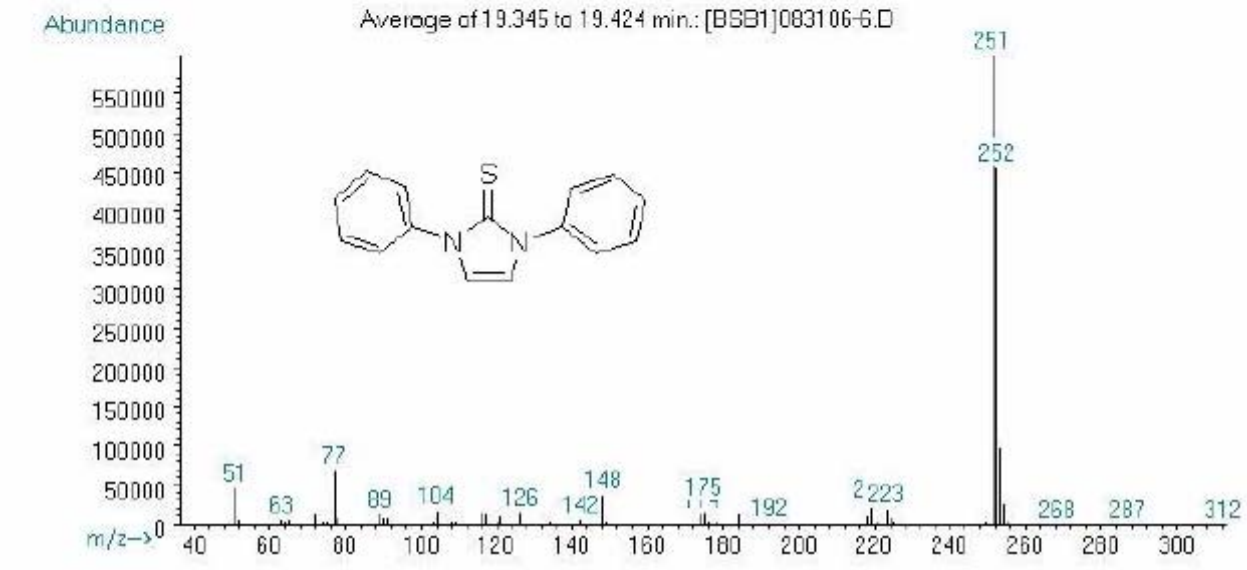

80
60
40
20
0
6000
5000
4000
3000
2000
1000
5768.37988
5798.74747
5810.97321
5915.12398
5882.45469
5928.61025
3056.24064
2938.618
1592.68435
1495.63987
1375.85132
1399.97507
1453.47463
1324.61645
1301.65135
1280.17653
1166.38786
1073.05682
1026.6563
1005.74633
976.10019
924.92906
1756.22836

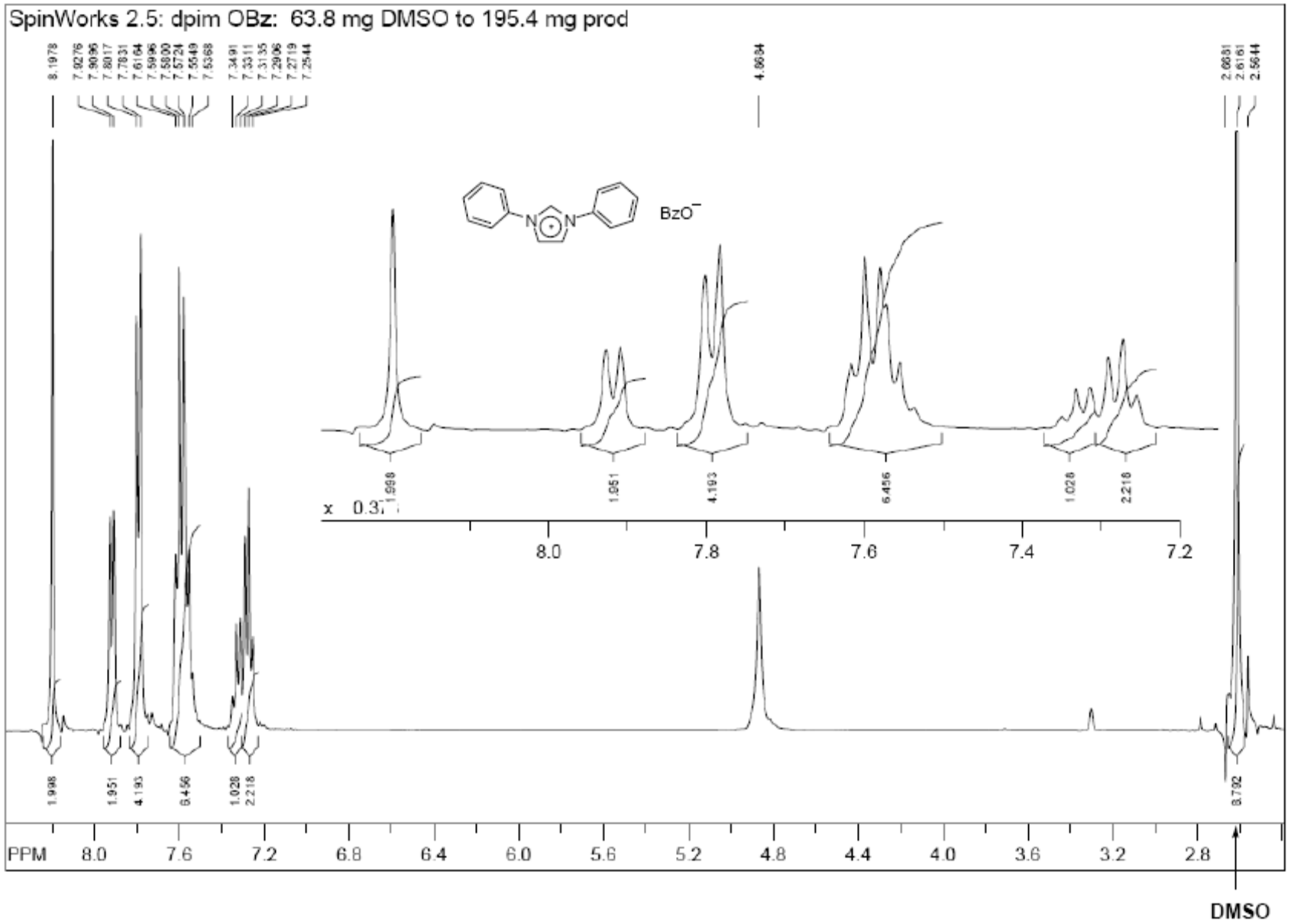

Abundance
Average of 19.505 to 19.753 min.: [BSB1]090106-1.D
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
m/z-->
40
60
80
100
120
140
160
180
200
220
240
260
280
300
268
105
77
239
51
91
120
135
145
159
182
194
206
225
252
271
287

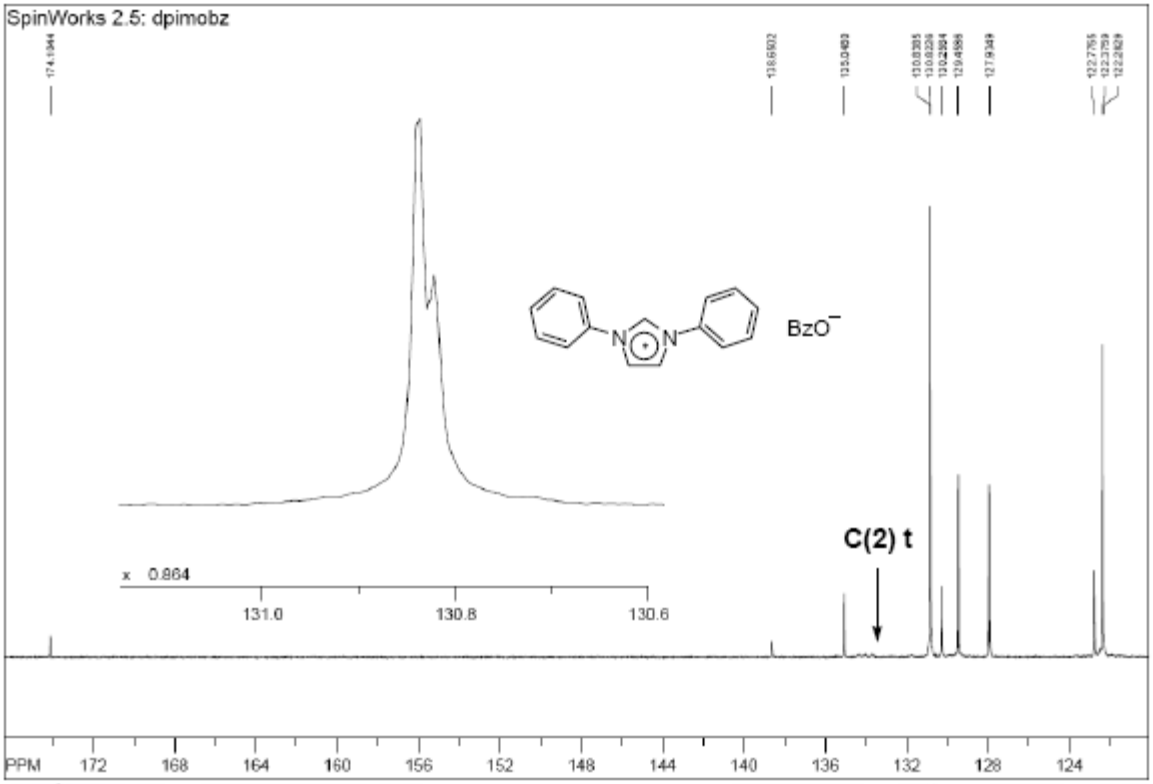

SpinWorks 2.5: 1,3-diphenylimidazole-2-thione
7.6439
7.6647
7.5285
7.5078
7.4591
7.4494
7.4220
7.4036
6.9712
4.215
4.497
2.239
2.013
S
N
N
PPM 7.64 7.60 7.56 7.52 7.48 7.44 7.40 7.36 7.32 7.28 7.24 7.20 7.16 7.12 7.08 7.04 7.00 6.96

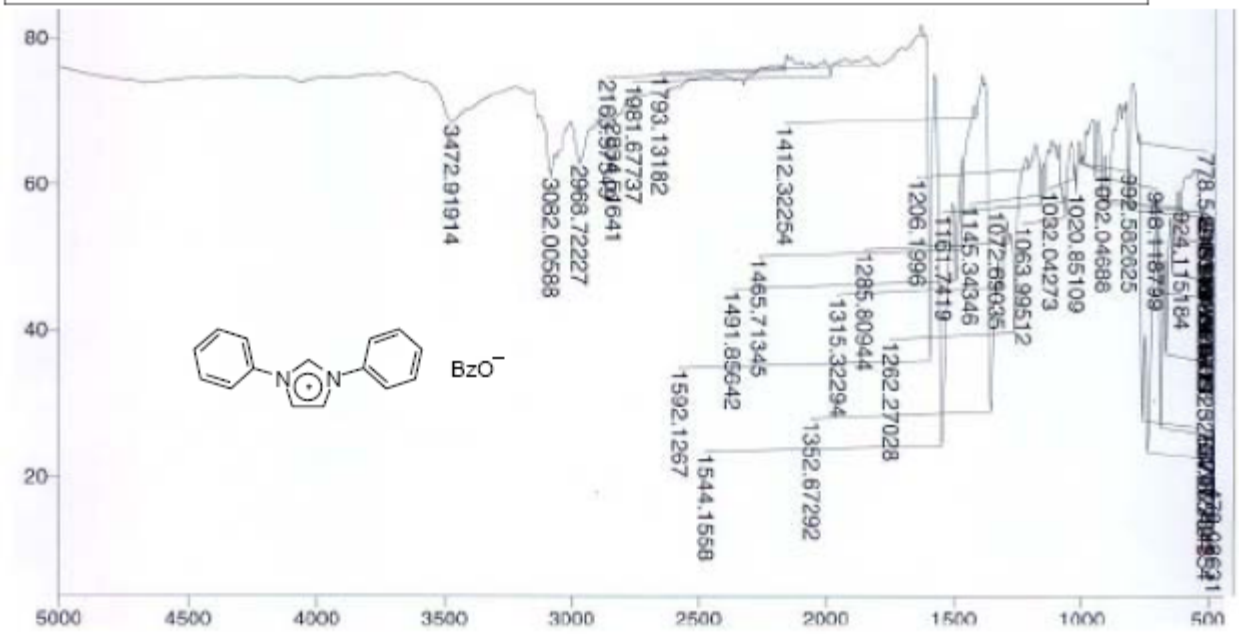

SpinWorks 2.5: DPI2T
153.6997
138.0429
128.9417
128.2602
126.1084
126.0789
126.0709
118.5711
S
N
N
PPM 161 159 157 155 153 151 149 147 145 143 141 139 137 135 133 131 129 127 125 123 121 119 117

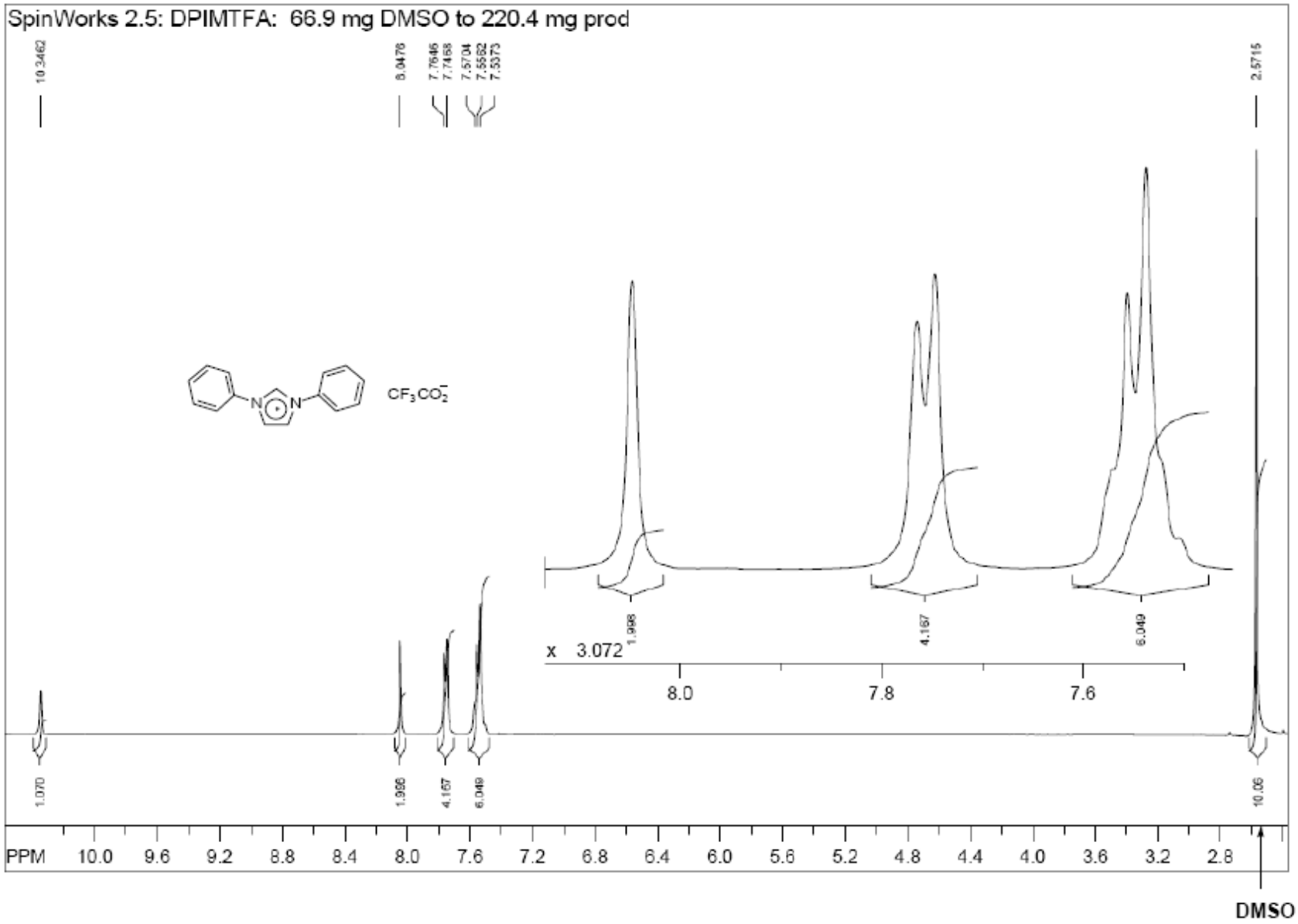

3175.05722
3141.31464
1540.78395
1594.17463
1451.54724
1493.48708
1411.11136
1362.74822
1298.69542
1263.90621
1350.88093
1268.21636
1224.61111
1159.64484
1196.83887
1098.51451
1070.55769
1019.23142
1003.83051
978.433671
932.980205
913.679093

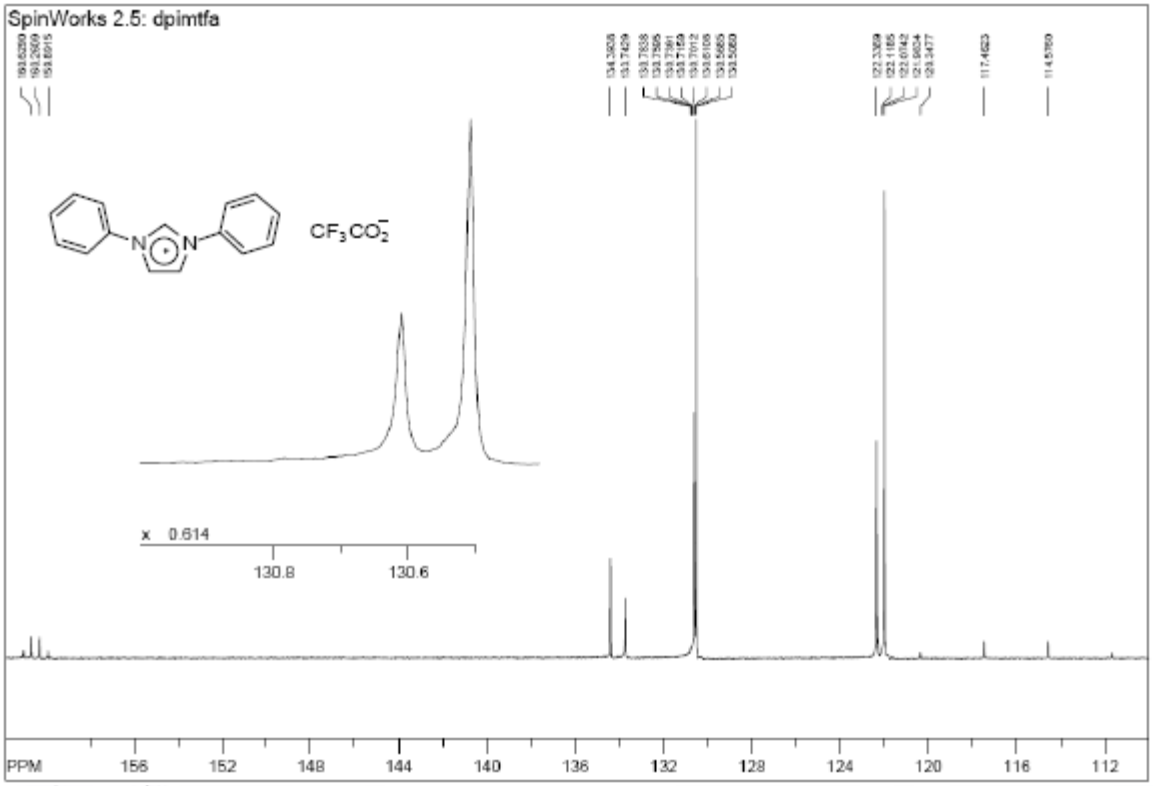

Abundance
Average of 19.345 to 19.424 min.: [BSB1]083106-6.D
m/z-->
251
252
77
51
63
89
104
126
142
148
175
192
223
268
287
312

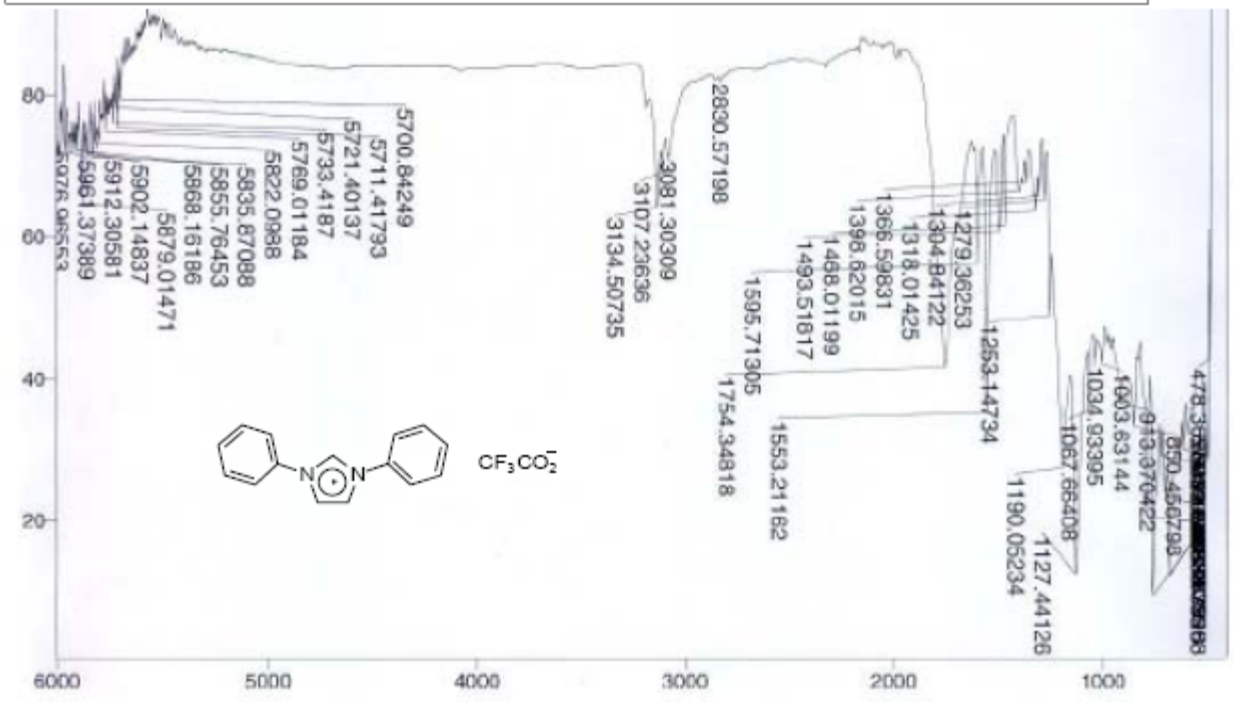

SpinWorks 2.5: dpim OBz: 63.8 mg DMSO to 195.4 mg prod
BzO⁻
PPM
DMSO

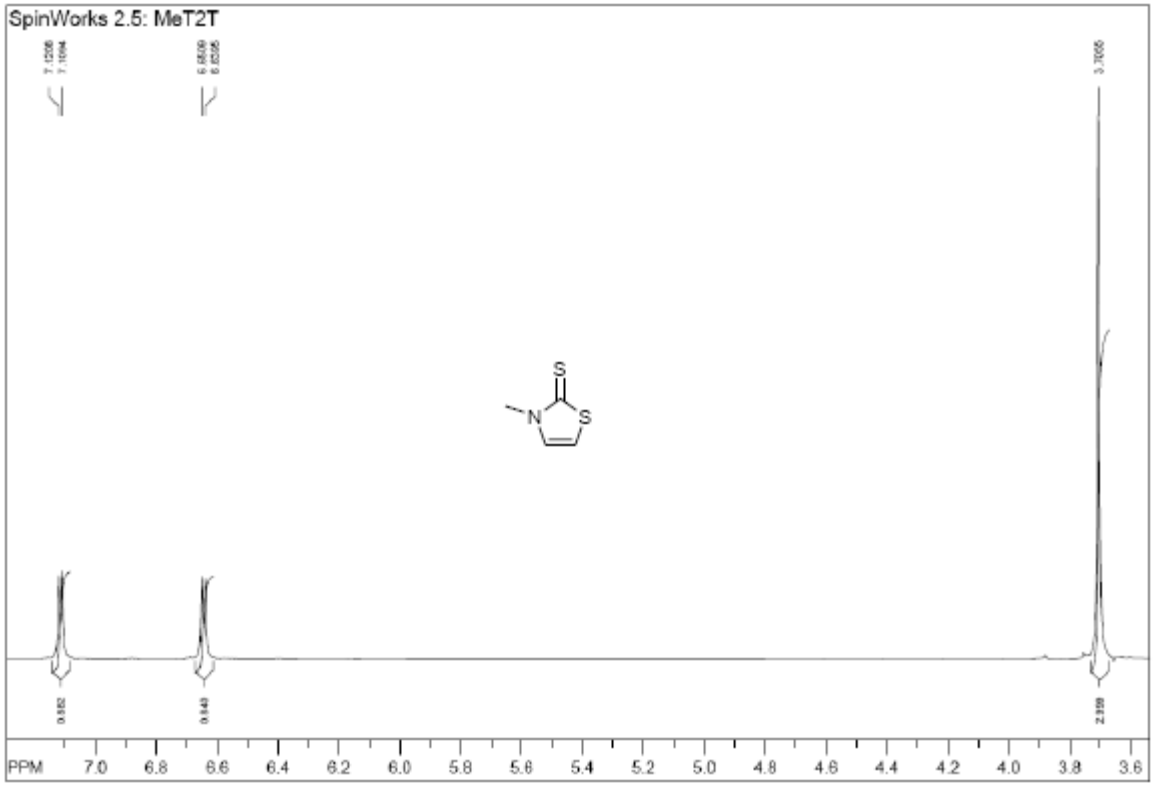

SpinWorks 2.5: dpimobz
BzO⁻
C(2) t
x 0.864
131.0
130.8
130.6
PPM 172 168 164 160 156 152 148 144 140 136 132 128 124

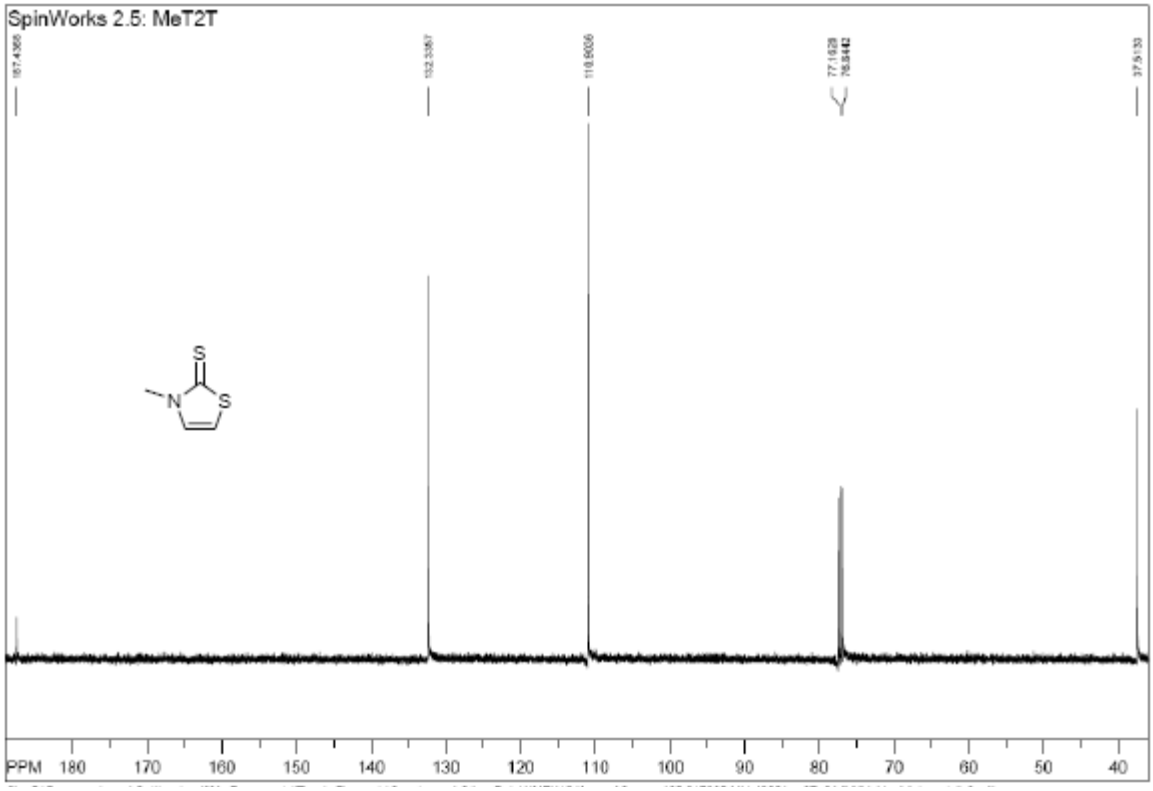

BzO⁻
3472.91914
3032.00588
2968.72227
1793.13182
1981.67737
1412.32254
1206.1996
1161.7419
1145.34346
1072.69035
1063.99512
1032.04273
1020.85109
992.502625
924.115184
1491.85642
1465.71345
1315.32294
1285.80944
1262.27028
1592.1267
1544.1558
1352.67292
80
60
40
20
5000 4500 4000 3500 3000 2500 2000 1500 1000 500

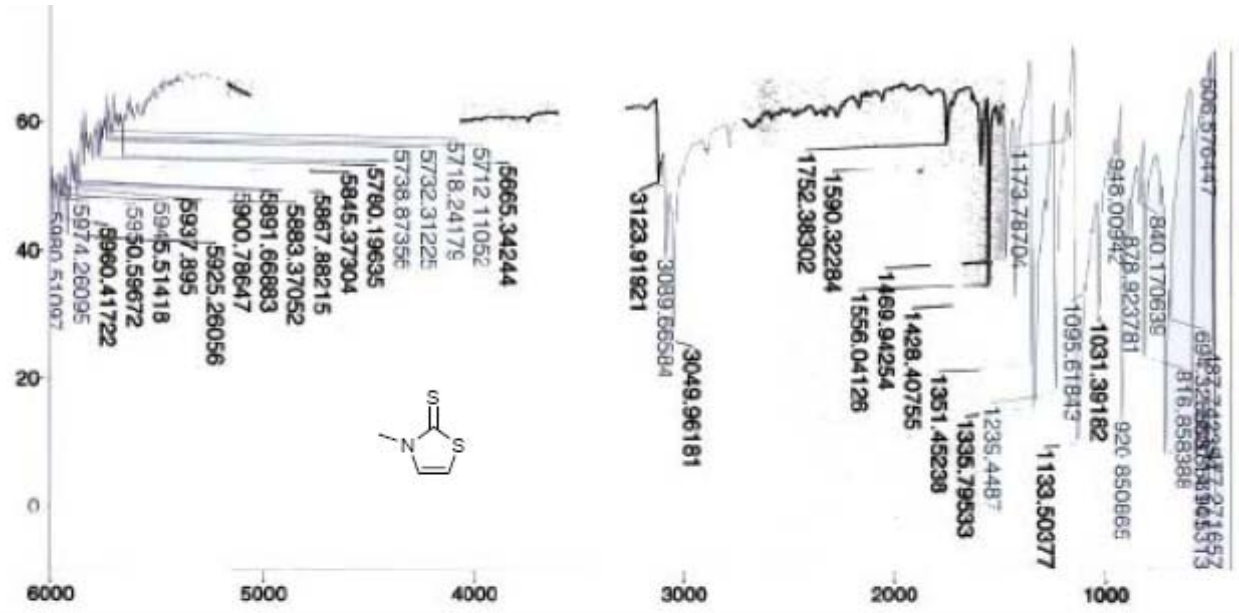

SpinWorks 2.5: DPIMTFA: 66.9 mg DMSO to 220.4 mg prod
10.3462
8.0476
7.7646
7.7458
7.5704
7.5552
7.5373
2.5715
$CF_3CO_2^-$
x 3.072
1.998
4.167
6.049
8.0
7.8
7.6
1.070
1.996
4.167
6.049
10.00
PPM 10.0 9.6 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8
DMSO

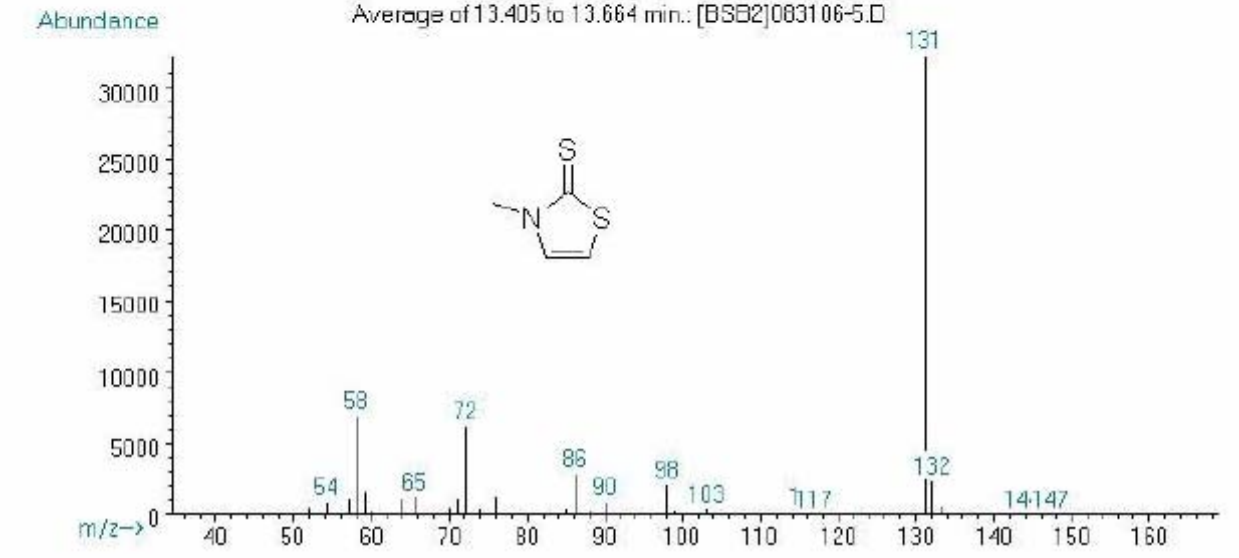

SpinWorks 2.5: dpimtfa
$CF_3CO_2^-$
x 0.614
130.8
130.6
PPM
156
152
148
144
140
136
132
128
124
120
116
112

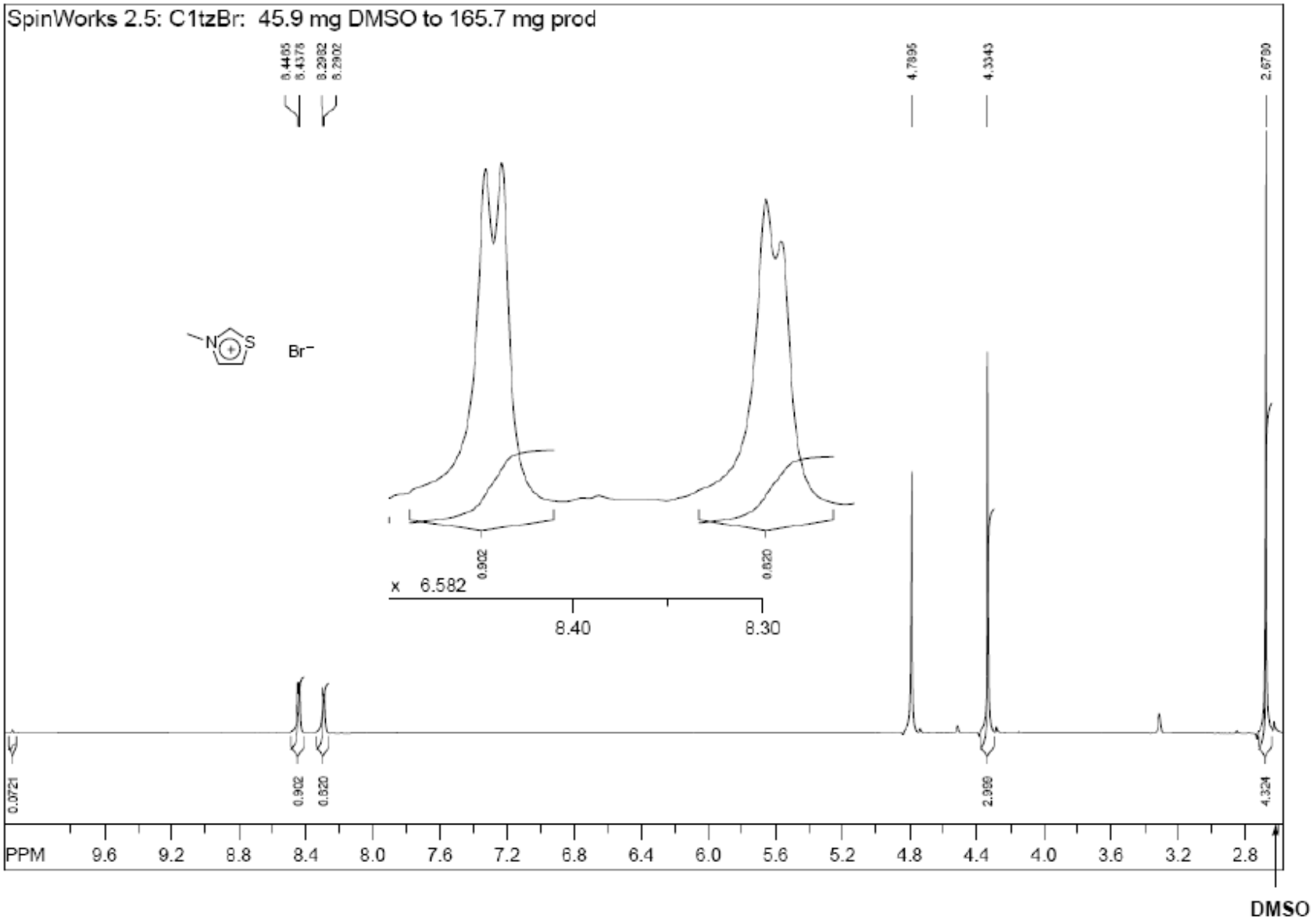

5700.84249
5711.41793
5721.40137
5733.4187
5769.01184
5822.0988
5835.87088
5855.76453
5868.16186
5879.01471
5902.14837
5912.30581
5961.37389
3081.30309
3107.23636
3134.50735
2830.57198
1366.59831
1398.62015
1468.01199
1493.51617
1505.71305
1754.34818
1553.21162
1279.36253
1304.84122
1318.01425
1253.14734
1034.93395
1003.63144
913.37642
1067.66408
1190.05234
1127.44126
$CF_3CO_2^-$
80
60
40
20
6000
5000
4000
3000
2000
1000

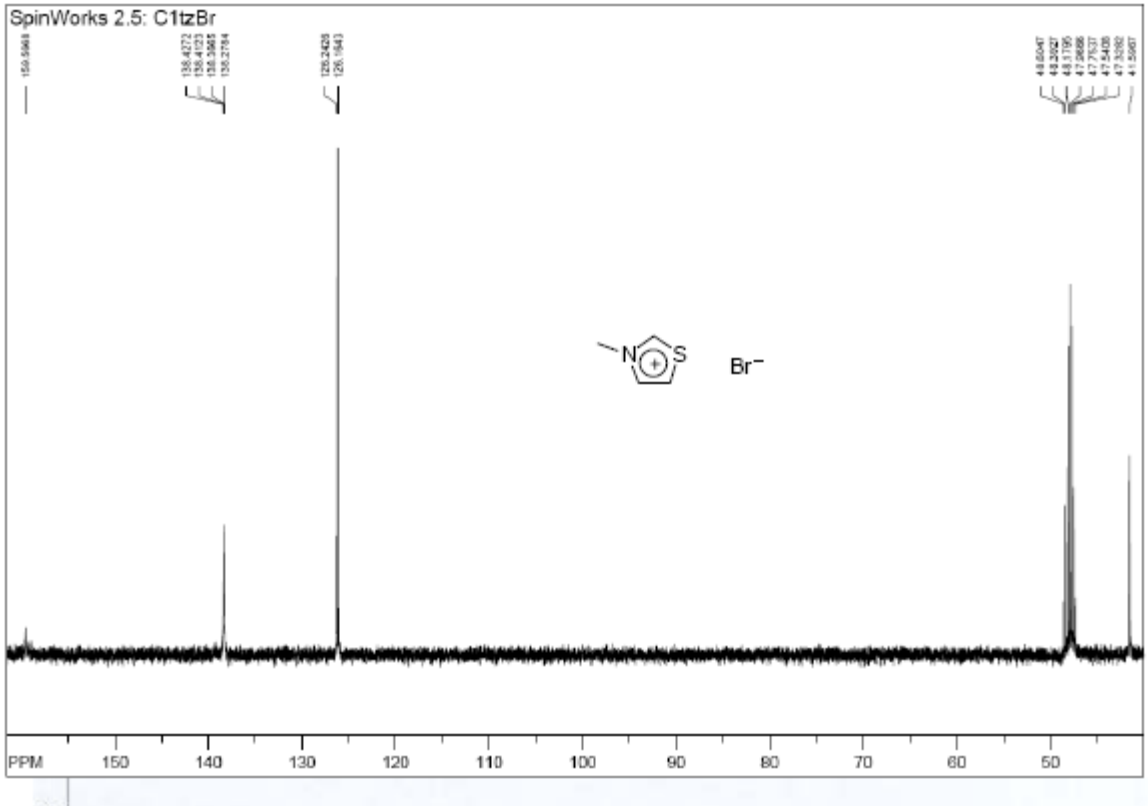

SpinWorks 2.5: MeT2T
PPM 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6

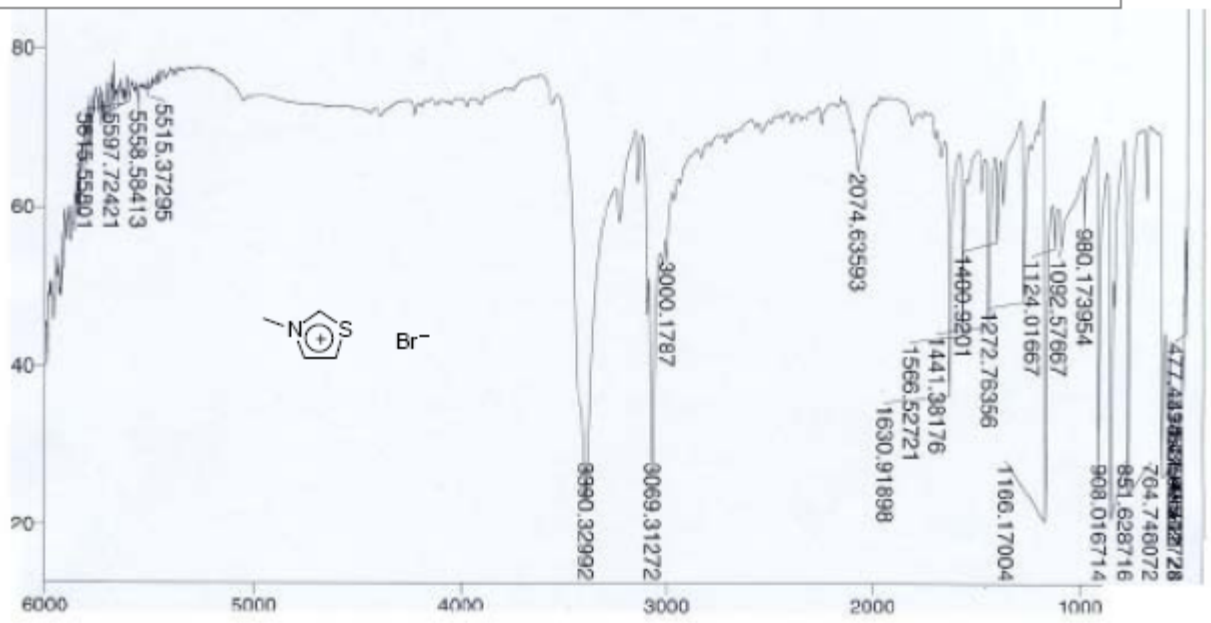

SpinWorks 2.5: MeT2T
PPM 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40

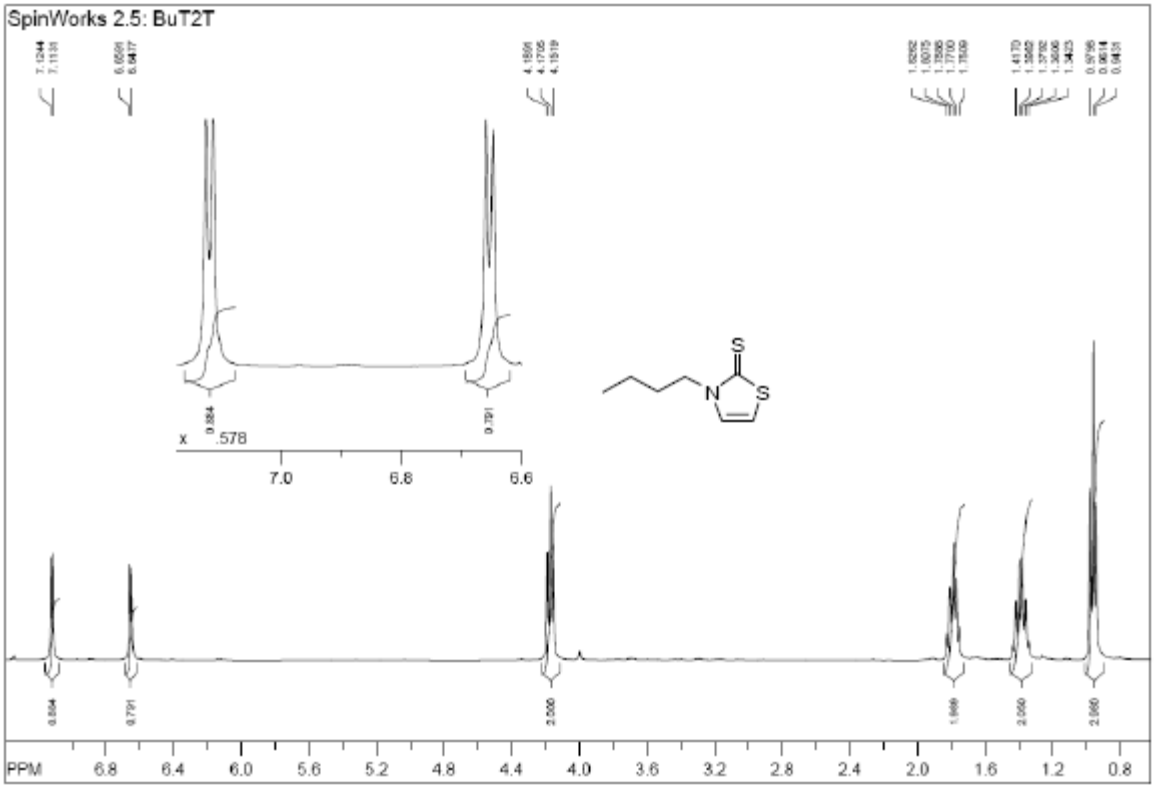

5665.34244
5712.11052
5718.24179
5732.31225
5738.87356
5780.19635
5845.37304
5867.88215
5883.37052
5891.66883
5900.78647
5925.26056
5937.895
5945.51418
5950.59672
5960.41722
5974.26095
3123.91921
3039.66584
3049.96181
1752.38302
1590.32284
1556.04126
1469.94254
1428.40755
1351.45239
1335.79533
1235.4487
1173.78704
1133.50377
1095.61819
1031.39182
948.00942
928.923781
920.850665
840.170639
816.858388
506.570447

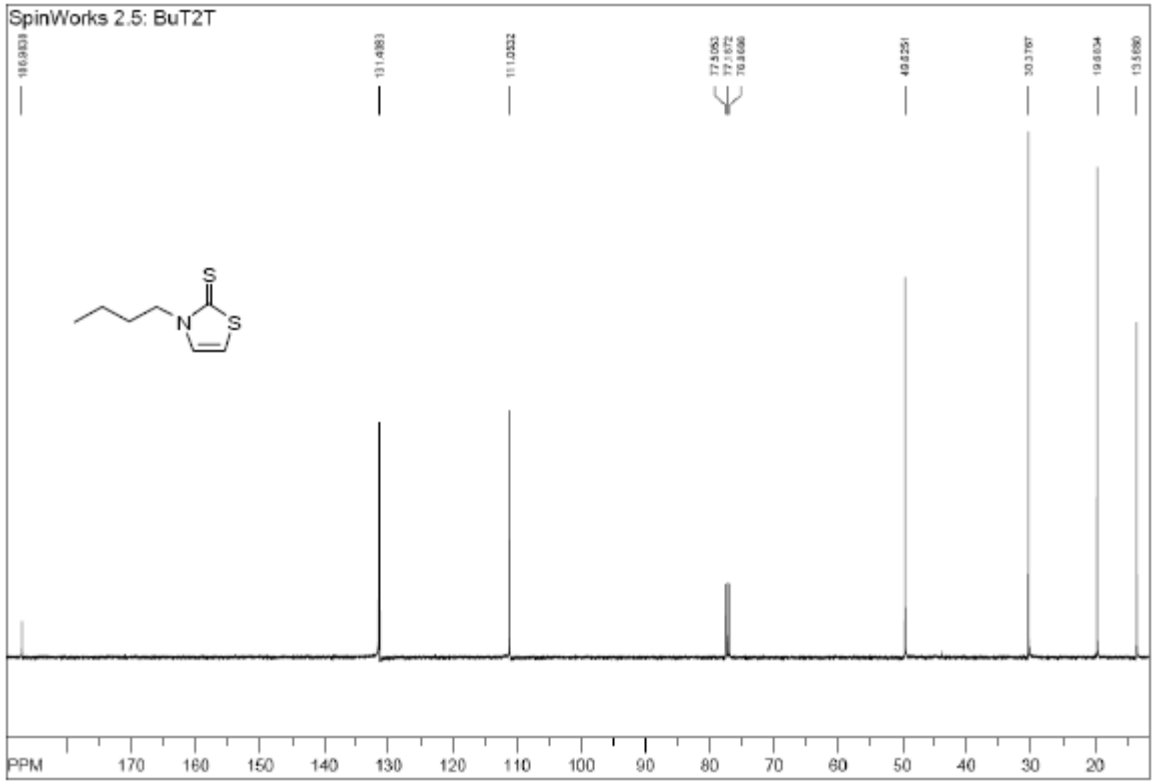

Abundance
Average of 13.405 to 13.664 min.: [BSB2]083106-5.D
m/z->
131
132
58
72
54
65
86
90
98
103
117
141
147

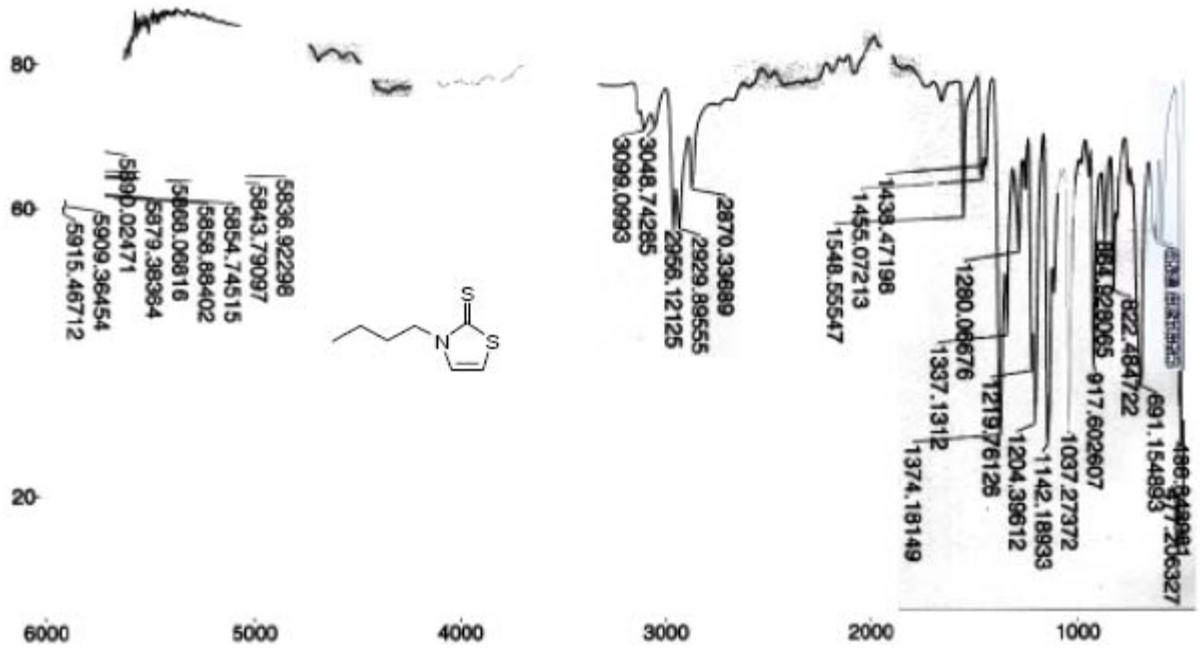

SpinWorks 2.5: C1tzBr: 45.9 mg DMSO to 165.7 mg prod
8.4465
8.4376
8.2932
8.2902
4.7895
4.3343
2.6790
Br⁻
x 6.582
8.40
8.30
0.902
0.820
0.0721
0.902
0.820
2.999
4.324
PPM
9.6
9.2
8.8
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
DMSO

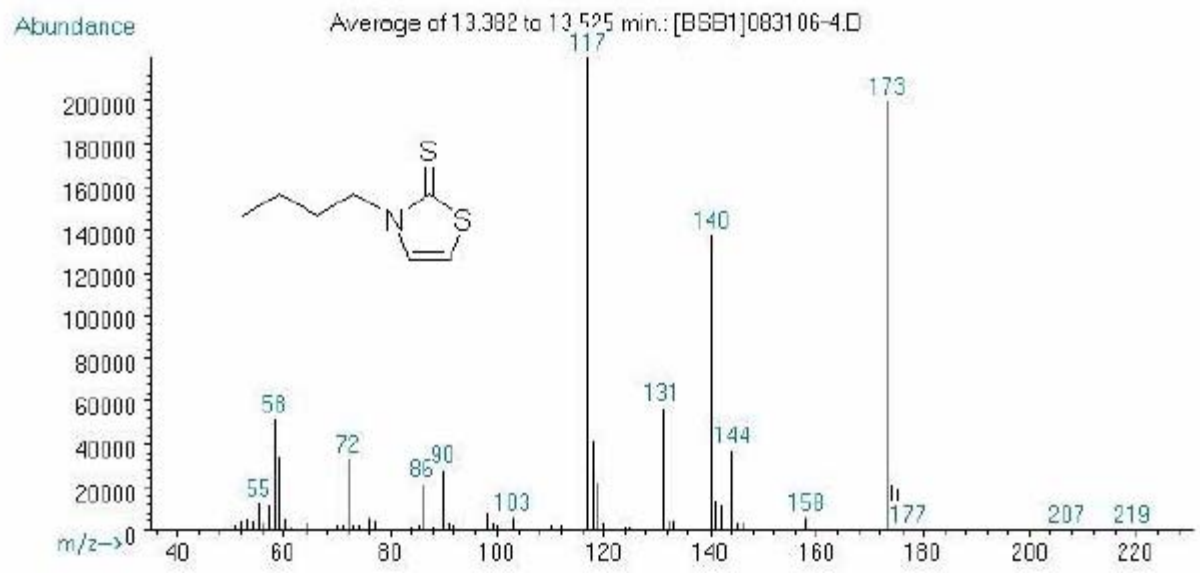

SpinWorks 2.5: C1tzBr
PPM
150
140
130
120
110
100
90
80
70
60
50
Br⁻

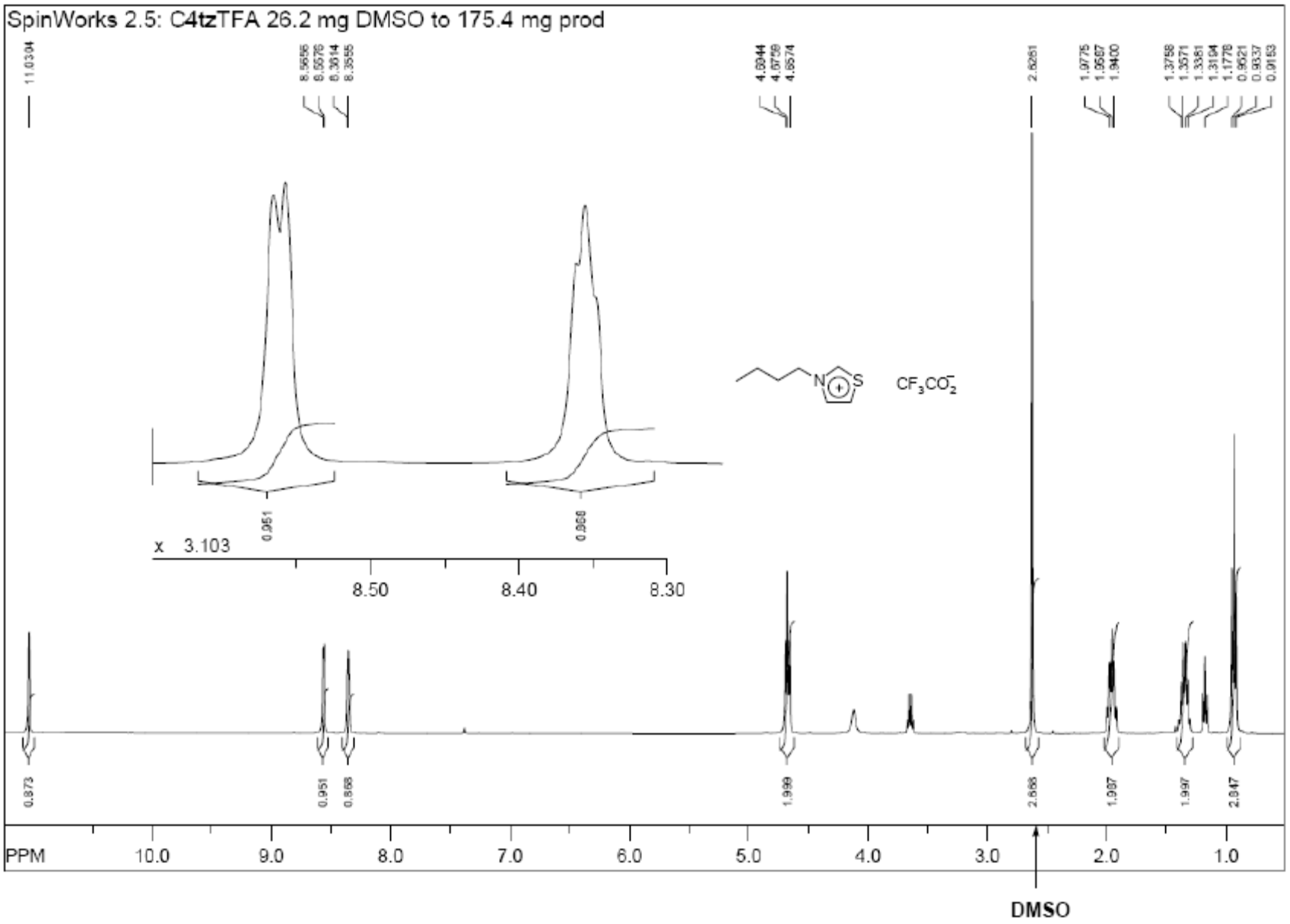

80
60
40
20
6000
5000
4000
3000
2000
1000
5515.37295
5558.58413
5597.72421
2074.63593
3000.1787
3069.31272
3990.32992
1630.91898
1566.52721
1441.38176
1400.9201
1272.76356
1166.17004
1124.01667
1092.57667
980.173954
908.016714
851.628716
764.746072
Br⁻

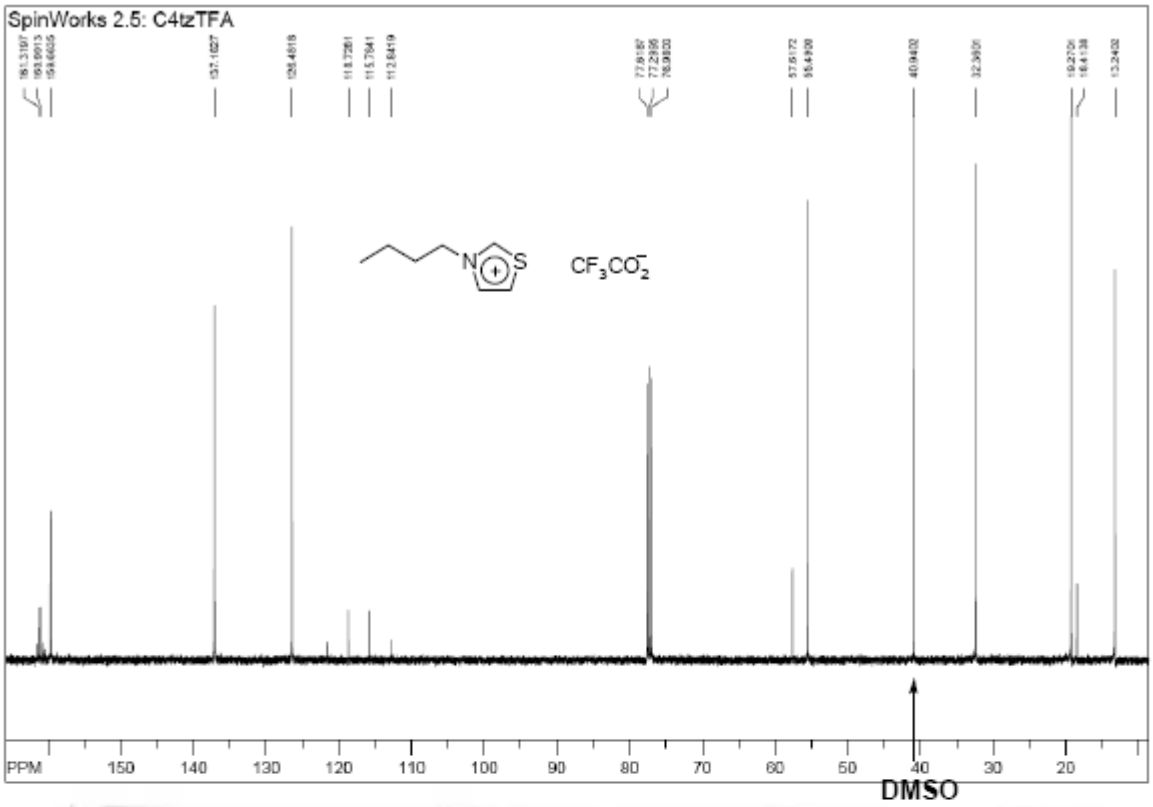

SpinWorks 2.5: BuT2T
PPM
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8

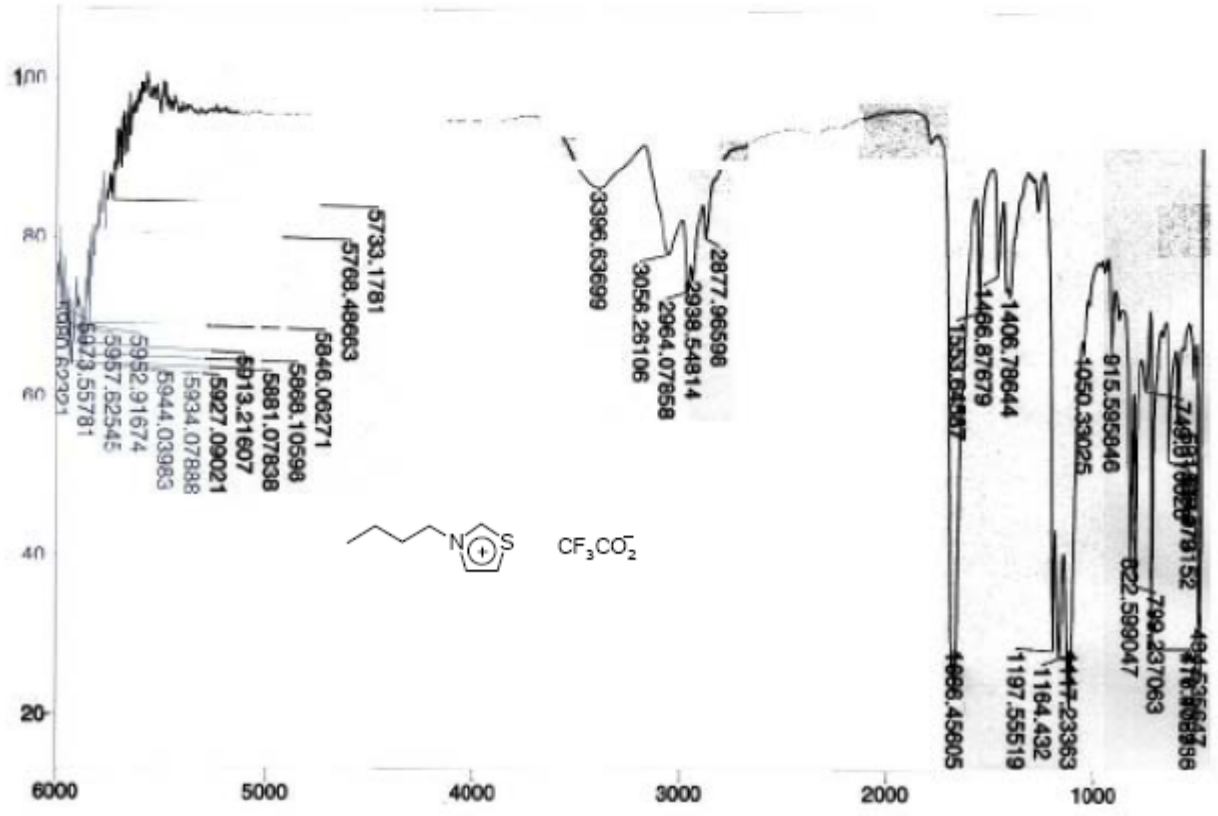

SpinWorks 2.5: BuT2T
PPM
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

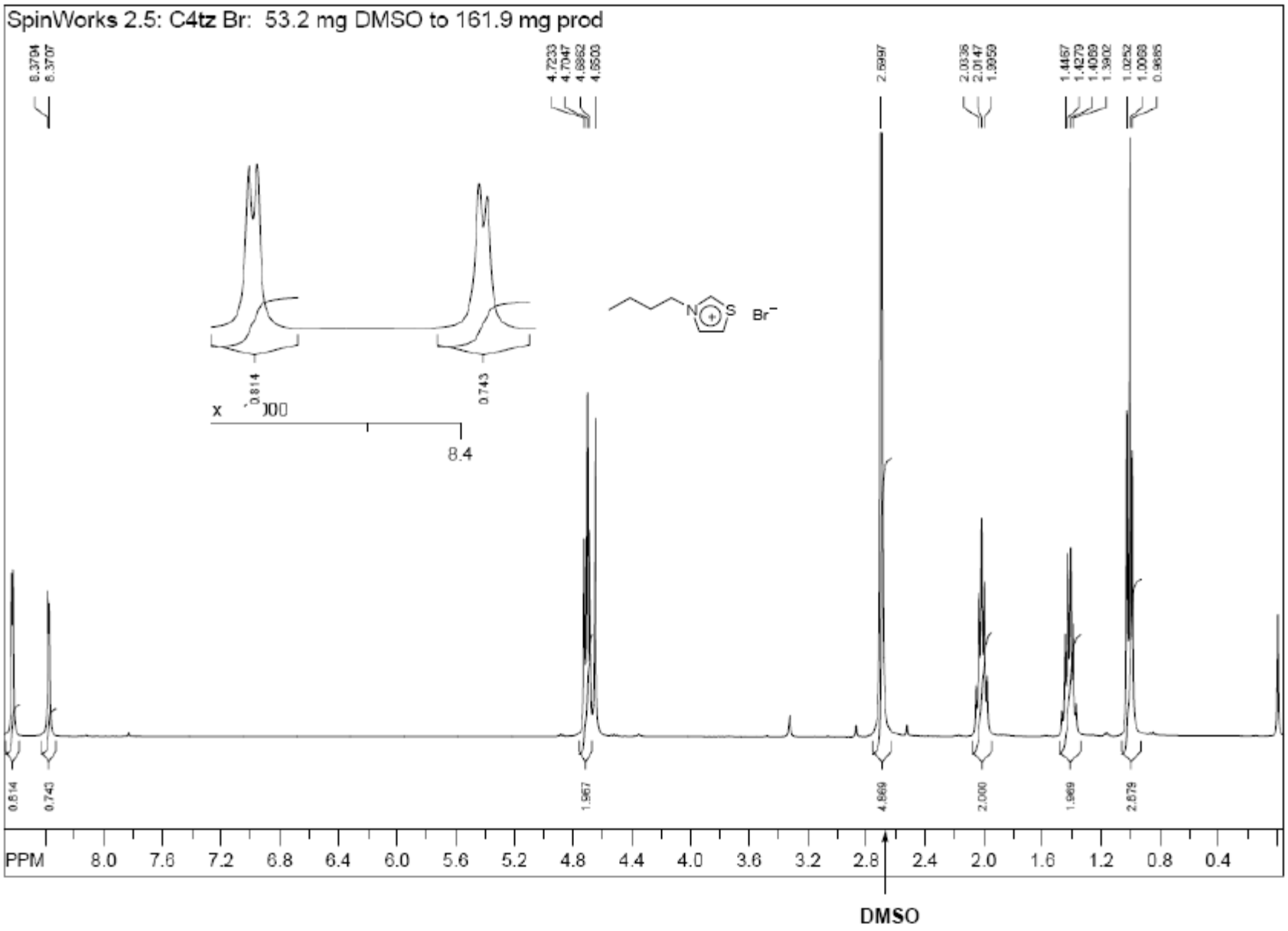

80
60
20
6000
5000
4000
3000
2000
1000
5915.46712
5909.36454
5879.38384
5858.88402
5854.74515
5843.79097
5836.92296
3099.0993
3048.74285
2956.12125
2929.89555
2870.33689
1548.55547
1455.07213
1438.47198
1374.18149
1337.1312
1280.06676
1219.76126
1204.39612
1142.18933
1037.27372
917.602607
822.484722
691.154893

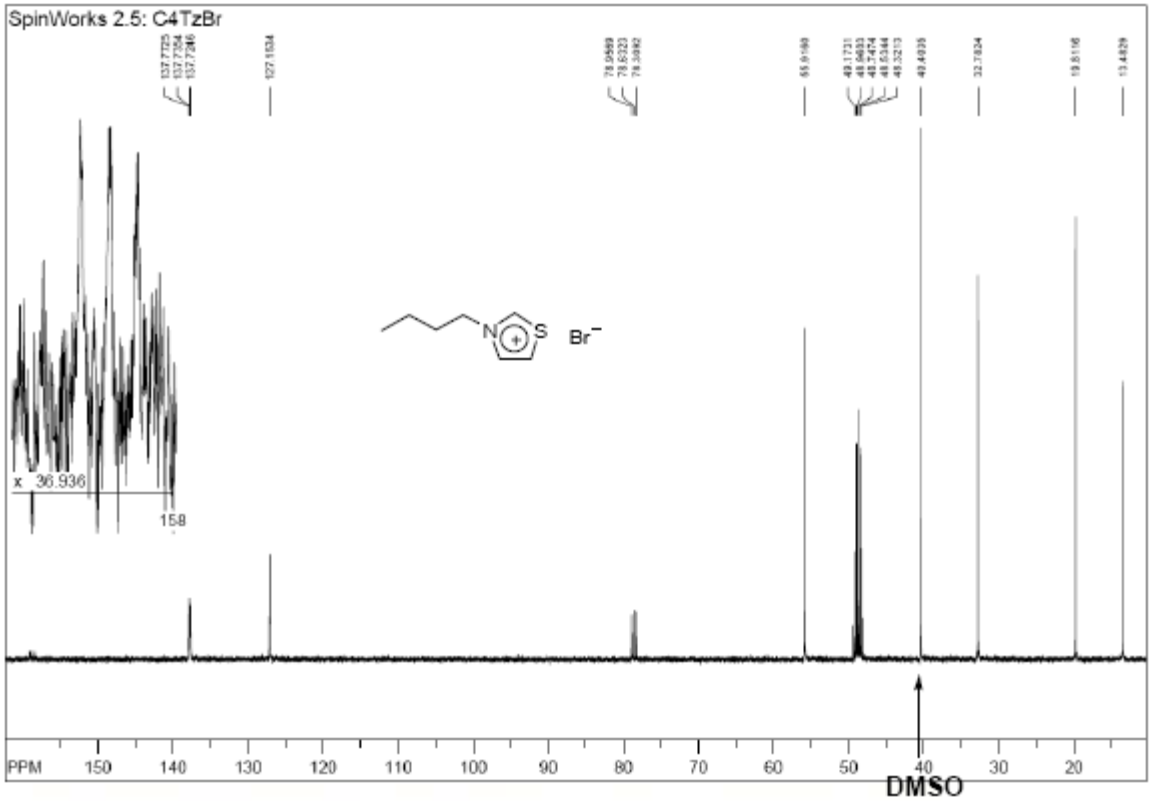

Abundance
Average of 13.382 to 13.525 min.: [BSB1]083106-4.D
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
m/z-->
40
60
80
100
120
140
160
180
200
220
117
173
140
131
58
144
72
86
90
55
103
158
177
207
219

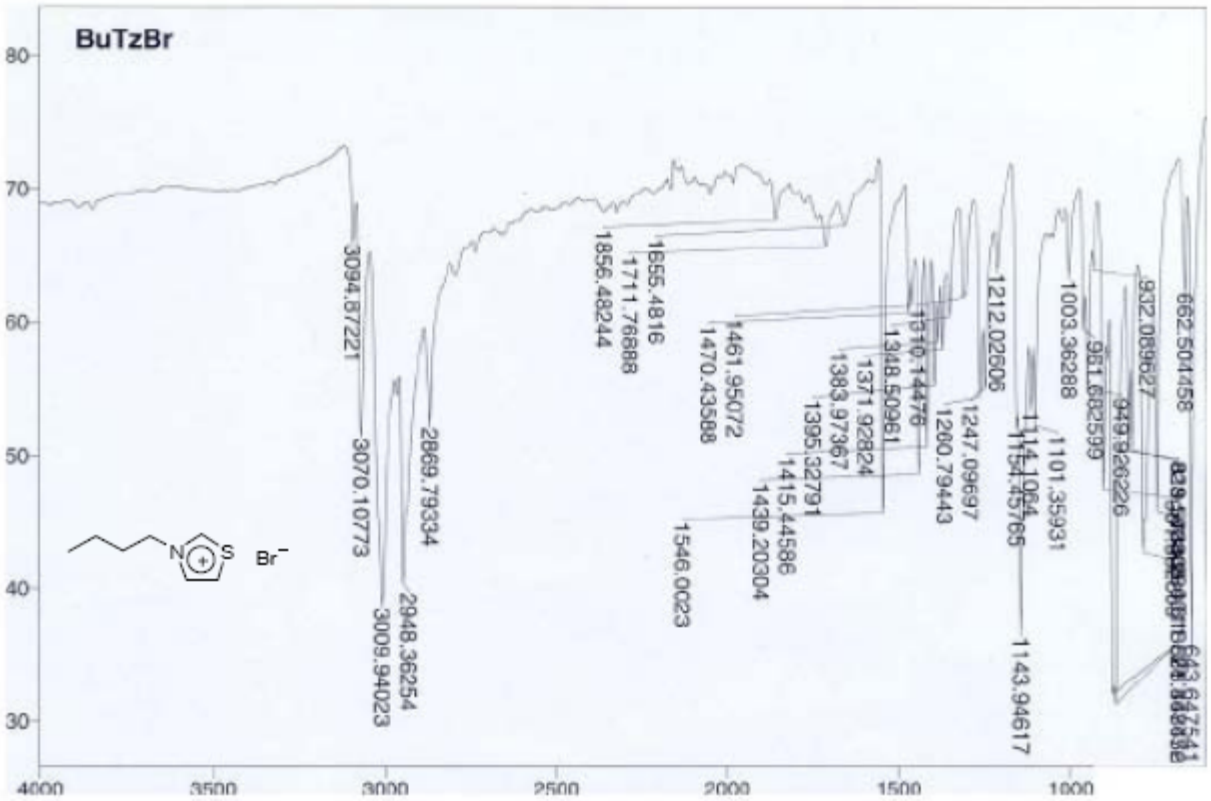

SpinWorks 2.5: C4tzTFA 26.2 mg DMSO to 175.4 mg prod
11.0394
8.5656
8.5576
8.3514
8.3455
4.6044
4.5756
4.5574
2.6261
1.9775
1.9587
1.9400
1.3758
1.3571
1.3381
1.3194
1.1776
0.9521
0.9337
0.9153
0.951
0.868
x 3.103
8.50
8.40
8.30
$CF_3CO_2^-$
0.873
0.951
0.868
1.999
2.668
1.987
1.997
2.947
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
DMSO

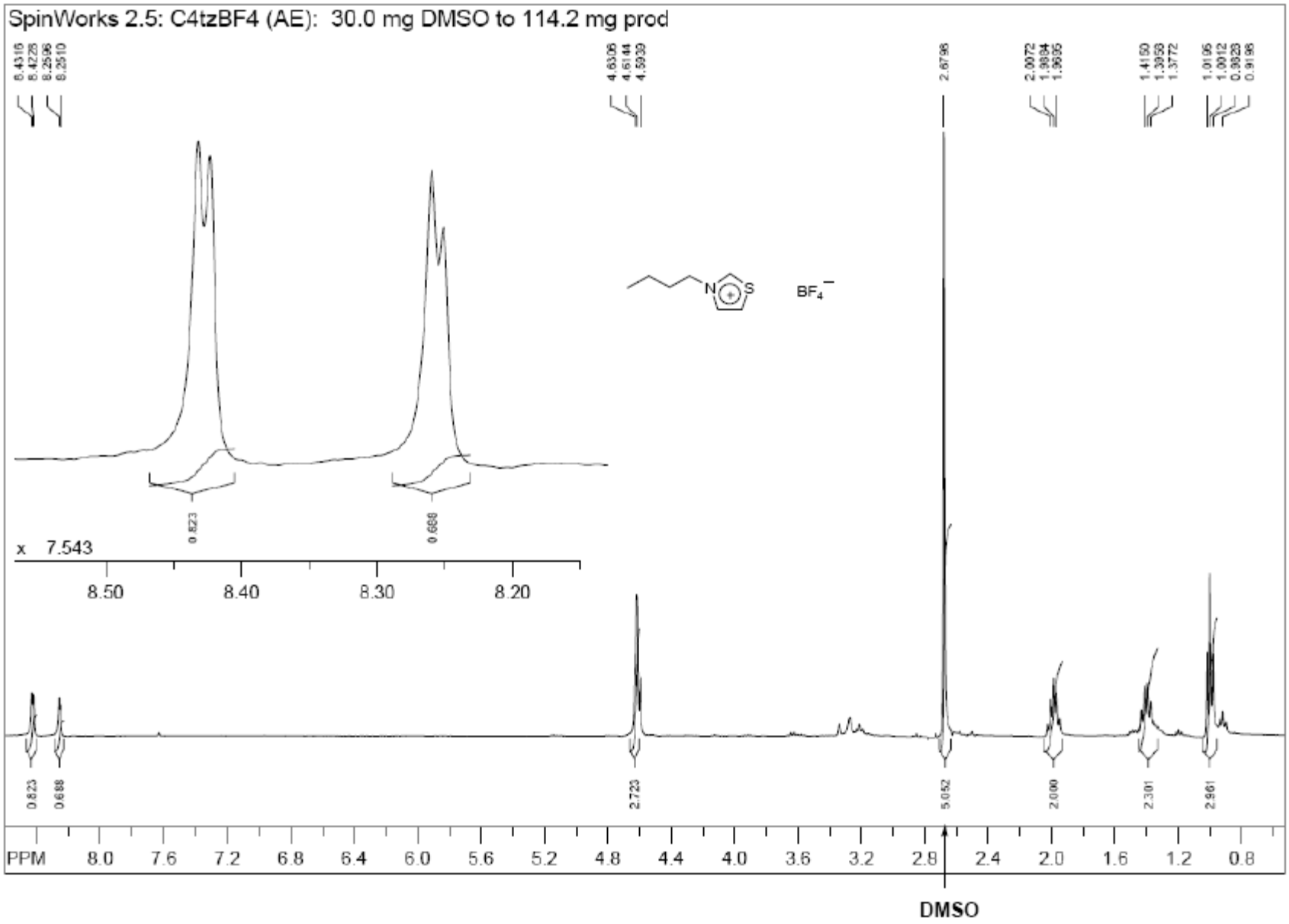

SpinWorks 2.5: C4tzTFA
PPM
150
140
130
120
110
100
90
80
70
60
50
40
30
20
DMSO
CF3CO2-

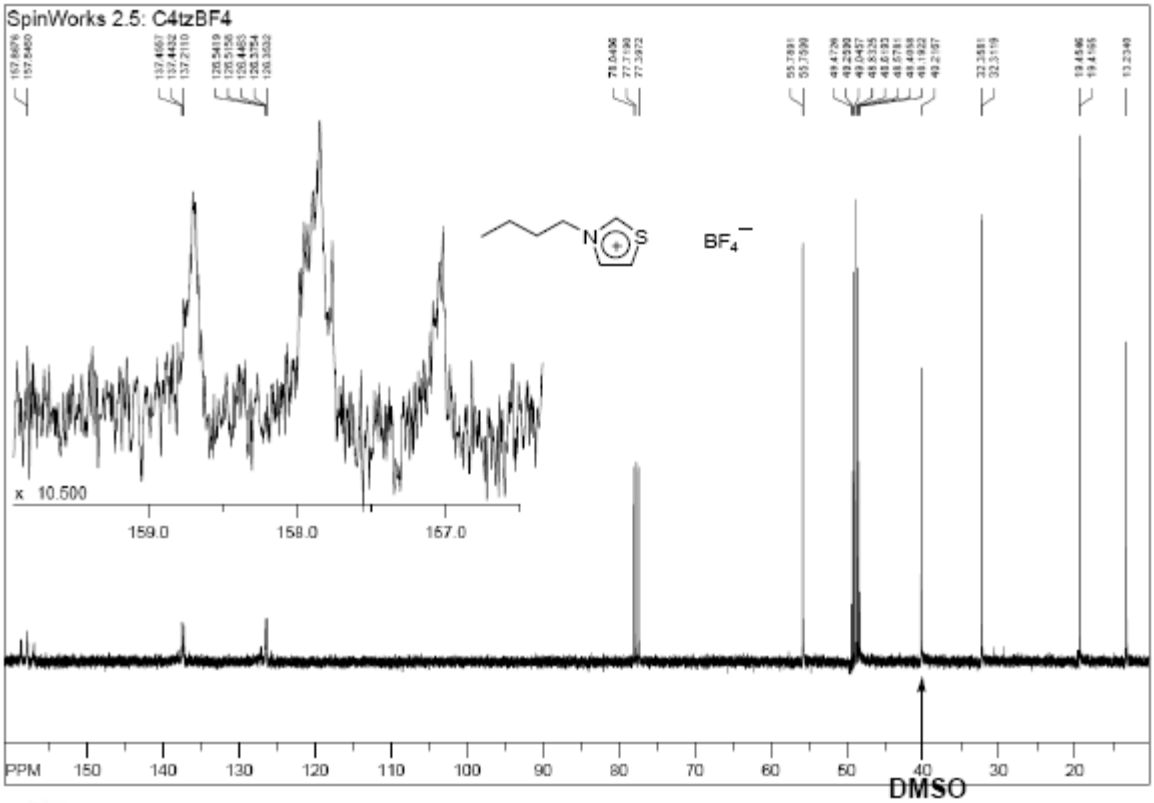

100
80
60
40
20
6000
5000
4000
3000
2000
1000
5733.1781
5768.48663
5846.06271
5868.10598
5881.07838
5913.21607
5927.09021
5934.07888
5944.03983
5952.91674
5957.62545
5973.55781
3396.63699
3056.26106
2964.07658
2938.54814
2877.96598
1553.62587
1466.87679
1406.78644
1197.55519
1164.432
1050.33025
915.595846
822.599047
799.237063
CF3CO2-

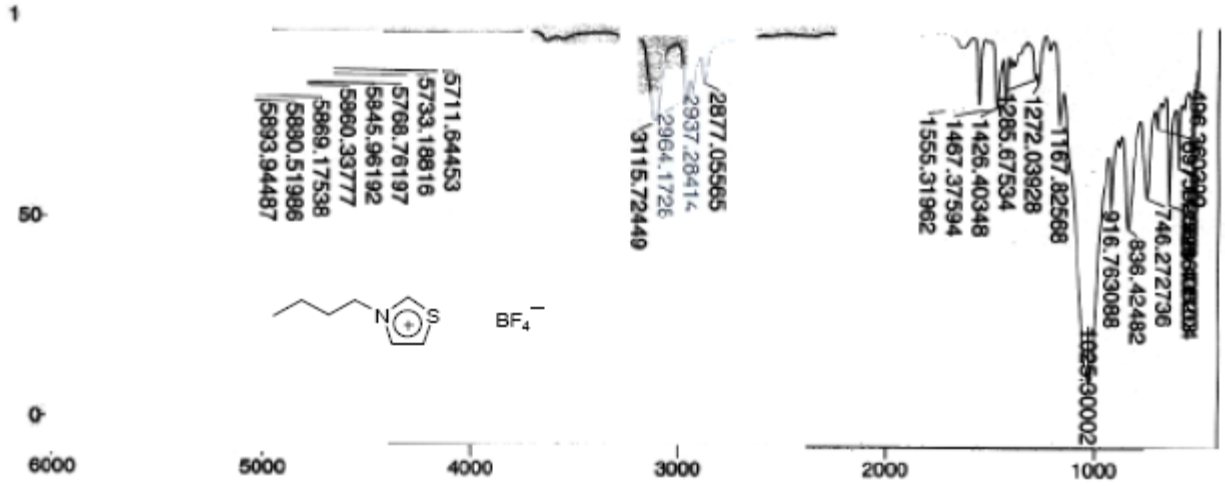

SpinWorks 2.5: C4tz Br: 53.2 mg DMSO to 161.9 mg prod
8.3794
8.3707
4.7233
4.7047
4.6862
4.6503
2.6997
2.0336
2.0147
1.9959
1.4457
1.4279
1.4089
1.3902
1.0252
1.0068
0.9885
0.814
0.743
8.4
Br⁻
0.814
0.743
1.967
4.969
2.000
1.969
2.679
PPM
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
DMSO

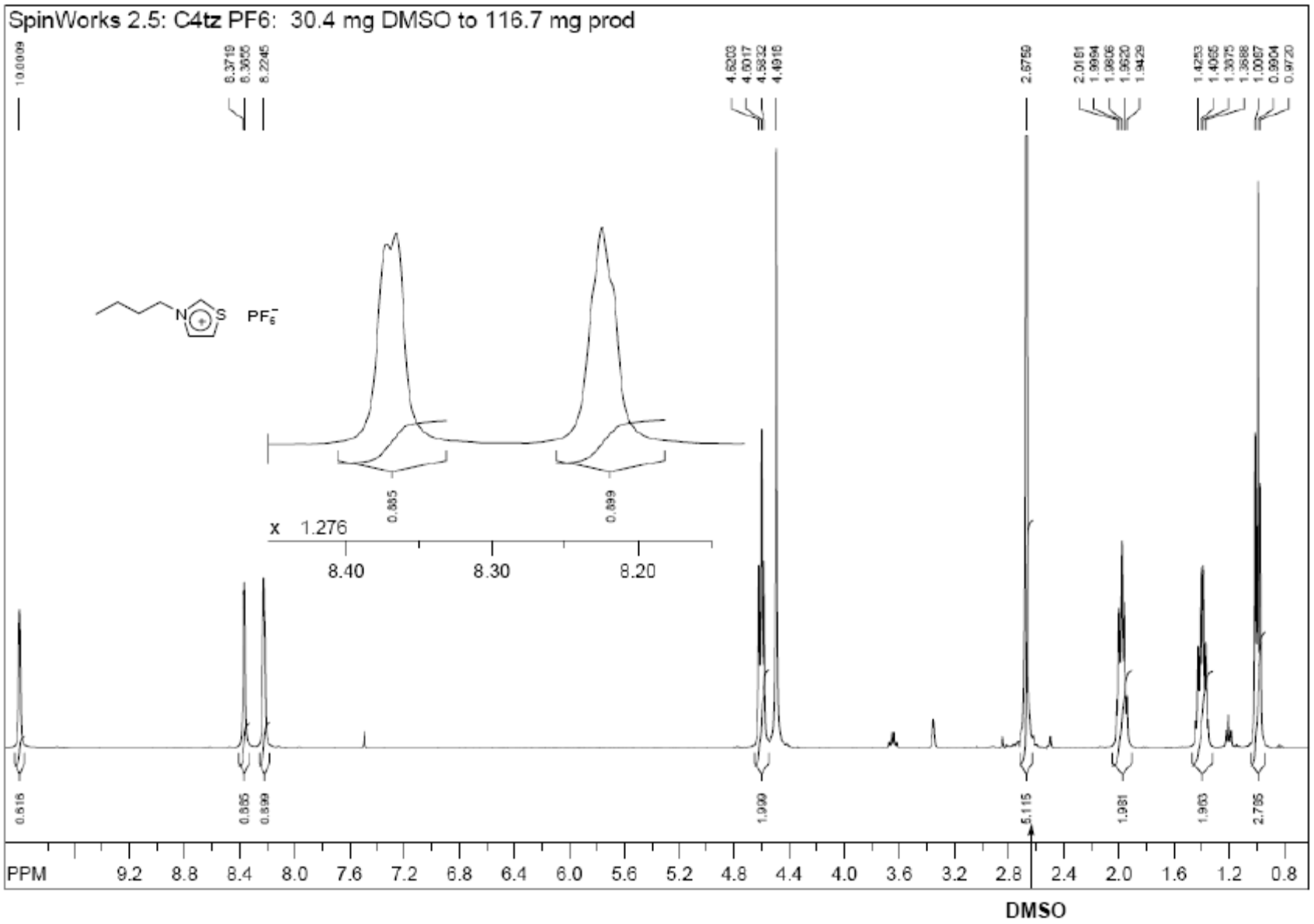

SpinWorks 2.5: C4TzBr
x 36.936
158
Br⁻
PPM
150
140
130
120
110
100
90
80
70
60
50
40
30
20
DMSO

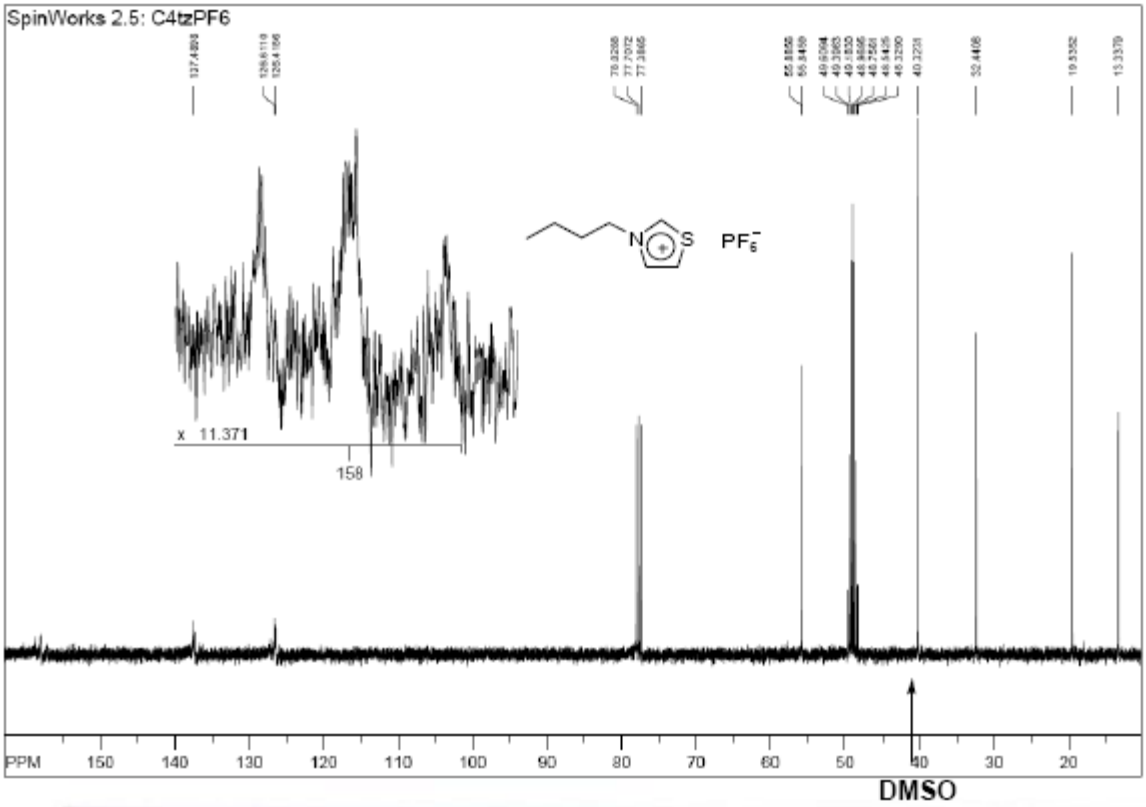

BuTzBr
Br⁻
3094.87221
3070.10773
3009.94023
2948.36254
2869.79334
1856.48244
1711.76888
1655.4816
1546.0023
1470.43588
1461.95072
1439.20304
1415.44586
1395.32791
1383.97367
1371.92824
1348.50961
1310.14476
1260.79443
1247.09697
1212.02606
1154.45765
1143.94617
1101.35931
1003.36288
961.682599
932.089627
662.504158

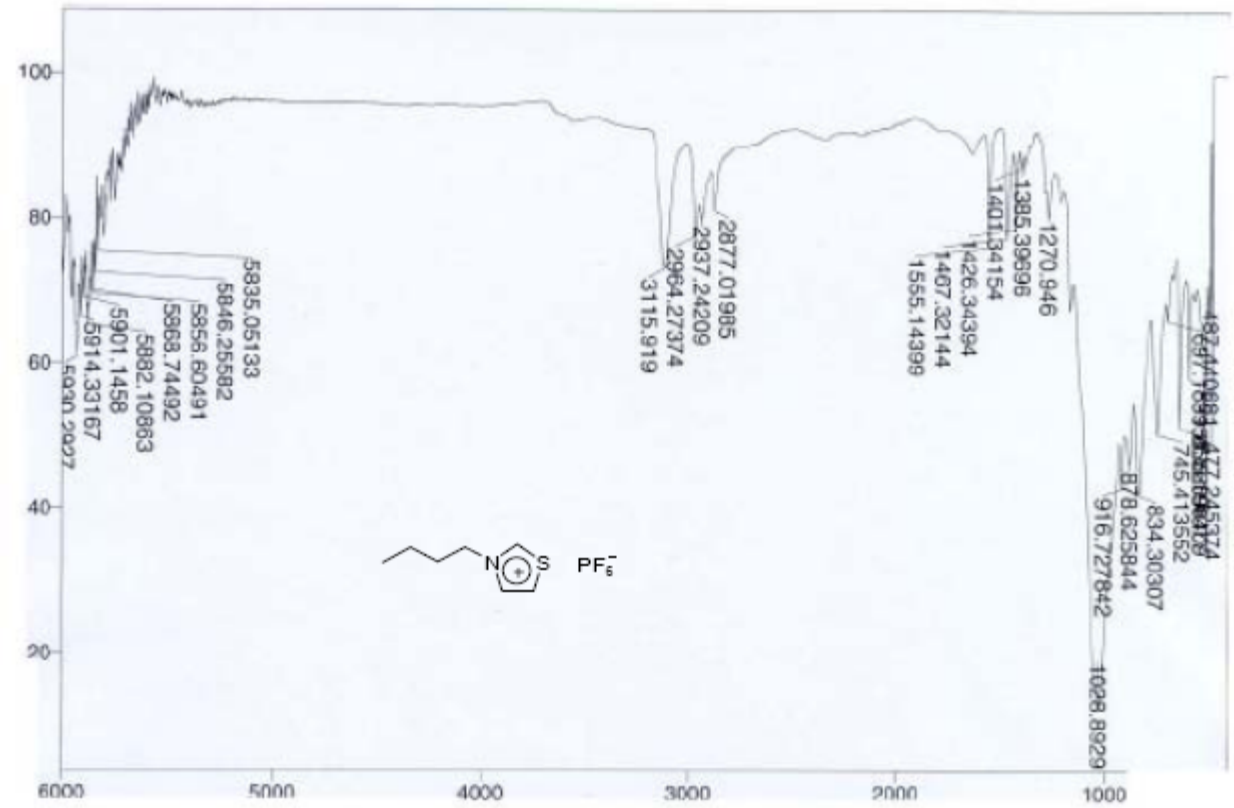

SpinWorks 2.5: C4tzBF4 (AE): 30.0 mg DMSO to 114.2 mg prod
8.4316
8.4226
8.2596
8.2510
4.6306
4.6144
4.5939
2.6796
2.0072
1.9894
1.9635
1.4150
1.3953
1.3772
1.0196
1.0012
0.9829
0.9196
N
S
BF4−
0.823
0.688
x 7.543
8.50
8.40
8.30
8.20
0.823
0.688
2.723
5.052
2.000
2.301
2.961
PPM
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
DMSO


SpinWorks 2.5: C4tzBF4
x 10.500
159.0
158.0
157.0
PPM
DMSO
BF4


5711.64453
5733.18816
5768.76197
5845.96192
5860.33777
5869.17538
5880.51986
5893.94487
2877.05565
2937.28414
3115.72449
1555.31962
1467.37594
1426.40348
1285.67534
1272.03928
1167.82568
916.763088
836.42482
746.272736
6000
5000
4000
3000
2000
1000
BF4


SpinWorks 2.5: C4tz PF6: 30.4 mg DMSO to 116.7 mg prod
10.0000
8.3719
8.3655
8.2245
4.6203
4.6017
4.5832
4.4916
2.6759
2.0161
1.9994
1.9806
1.9620
1.9429
1.4253
1.4066
1.3875
1.3688
1.0067
0.9904
0.9720
PF6-
0.885
0.899
x 1.276
8.40
8.30
8.20
0.616
0.885
0.899
1.000
5.115
1.981
1.963
2.785
PPM
9.2
8.8
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
DMSO


SpinWorks 2.5: C4bzPF6
x 11.371
158
PPM
DMSO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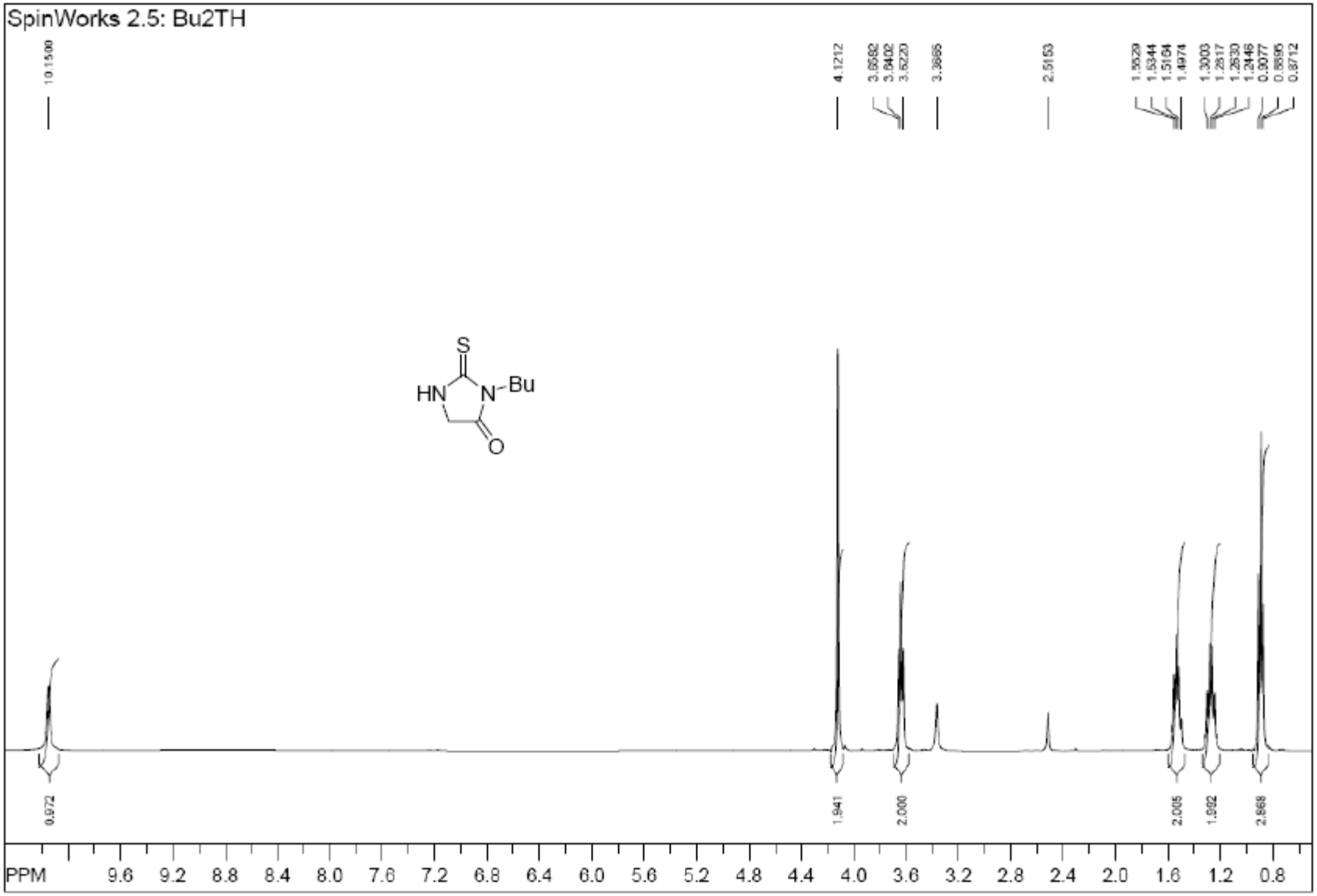
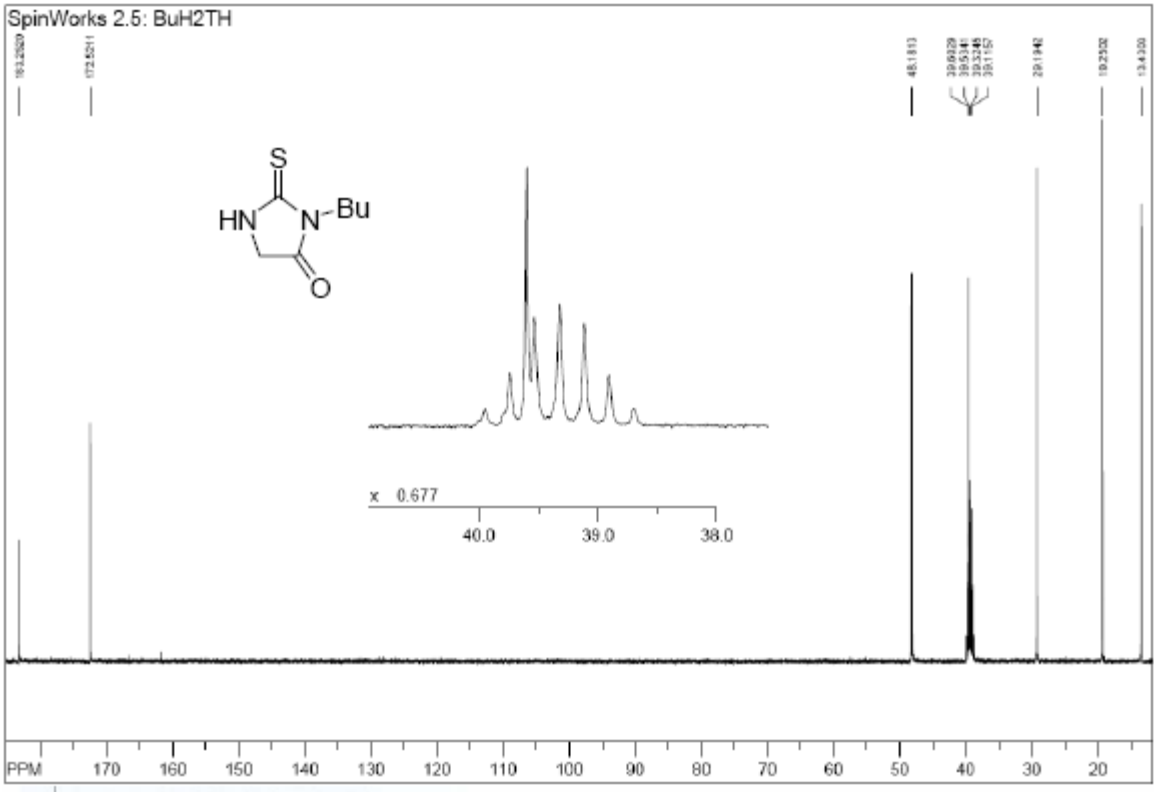
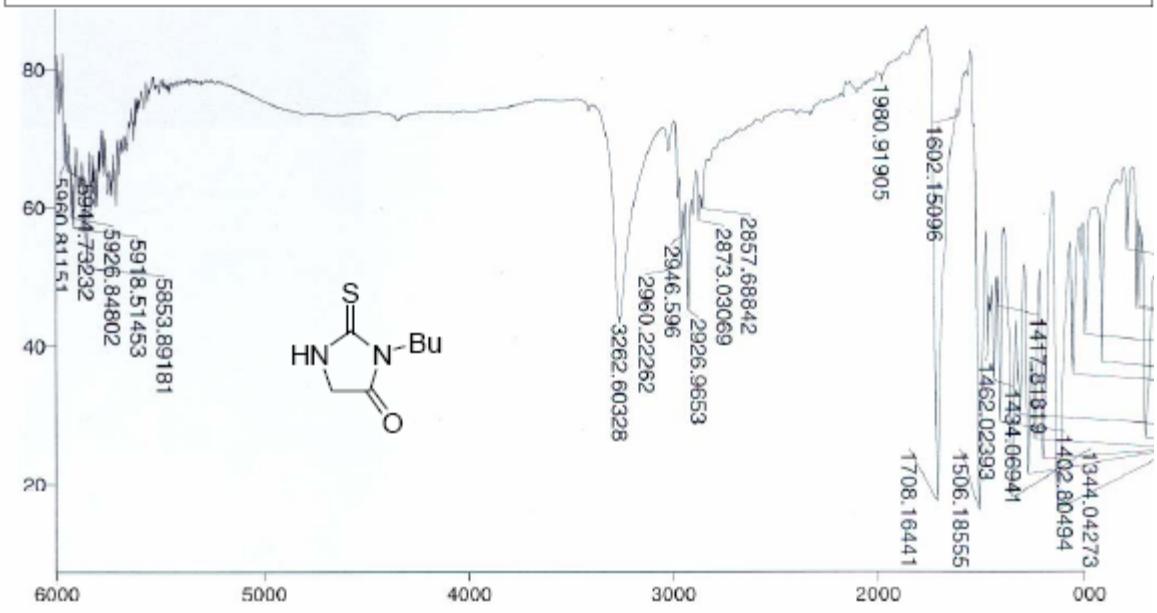
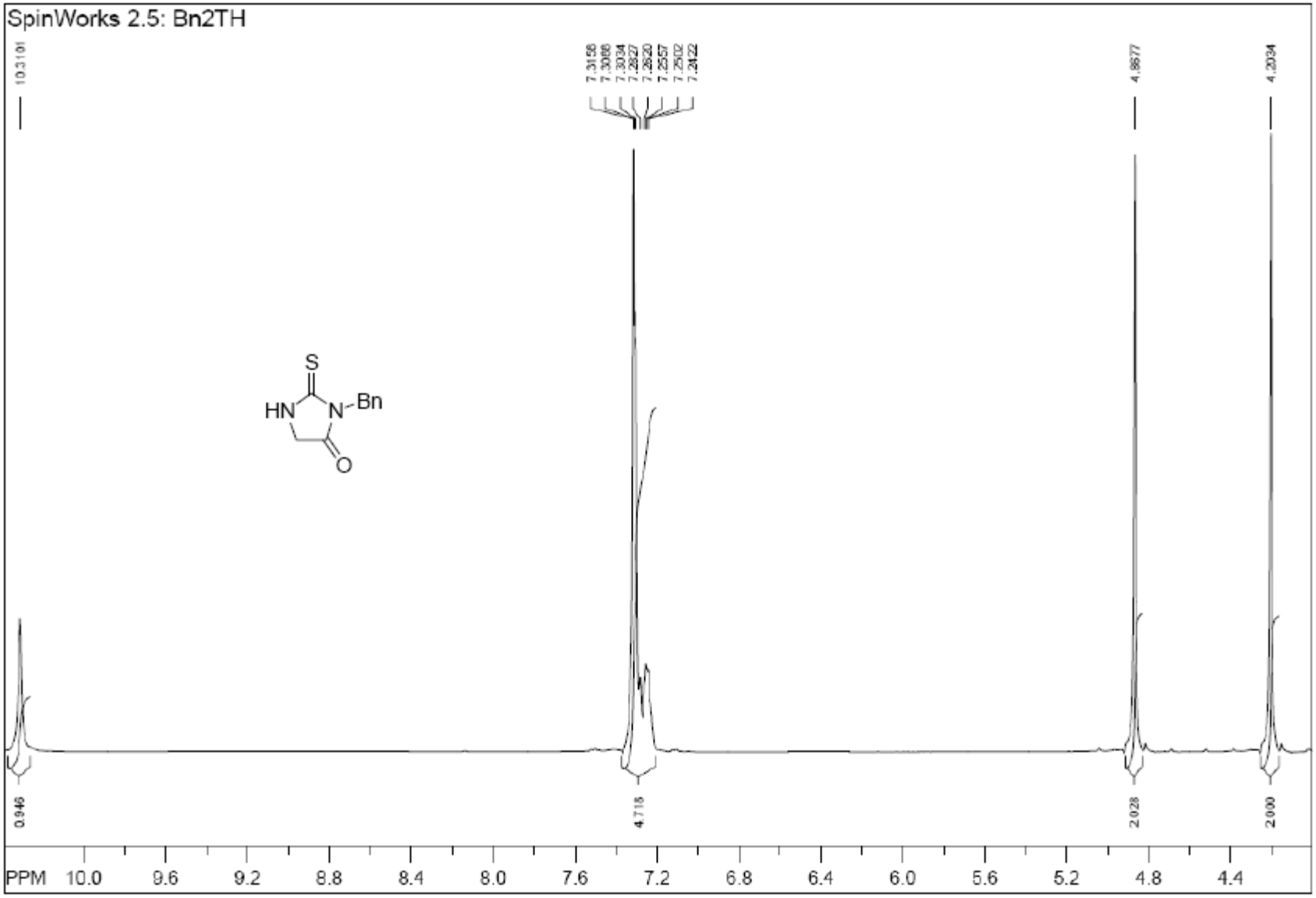
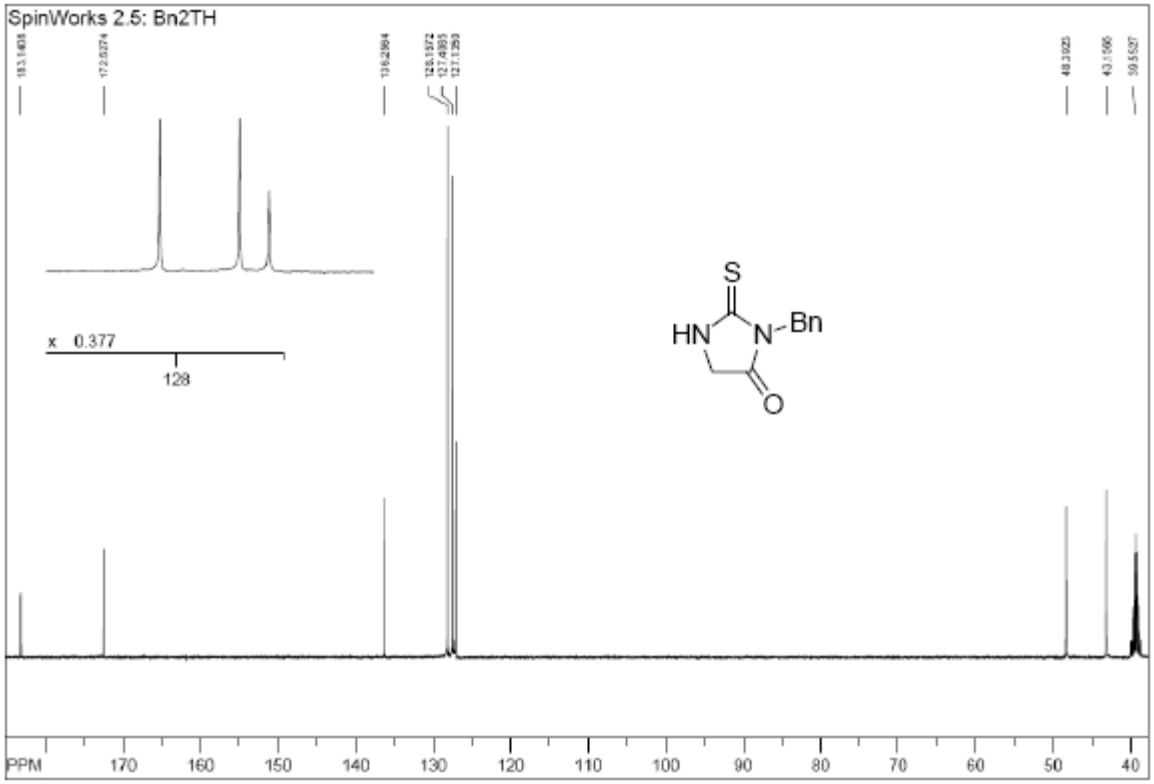
5846.25582
5856.60491
5868.74492
5882.10663
5901.1458
5914.33167
3115.919
2964.27374
2937.24209
2877.01985
1555.14399
1426.34394
1407.32144
1401.34154
1385.39998
1270.946
1028.8929
916.727842
878.625844
834.30307
745.413552

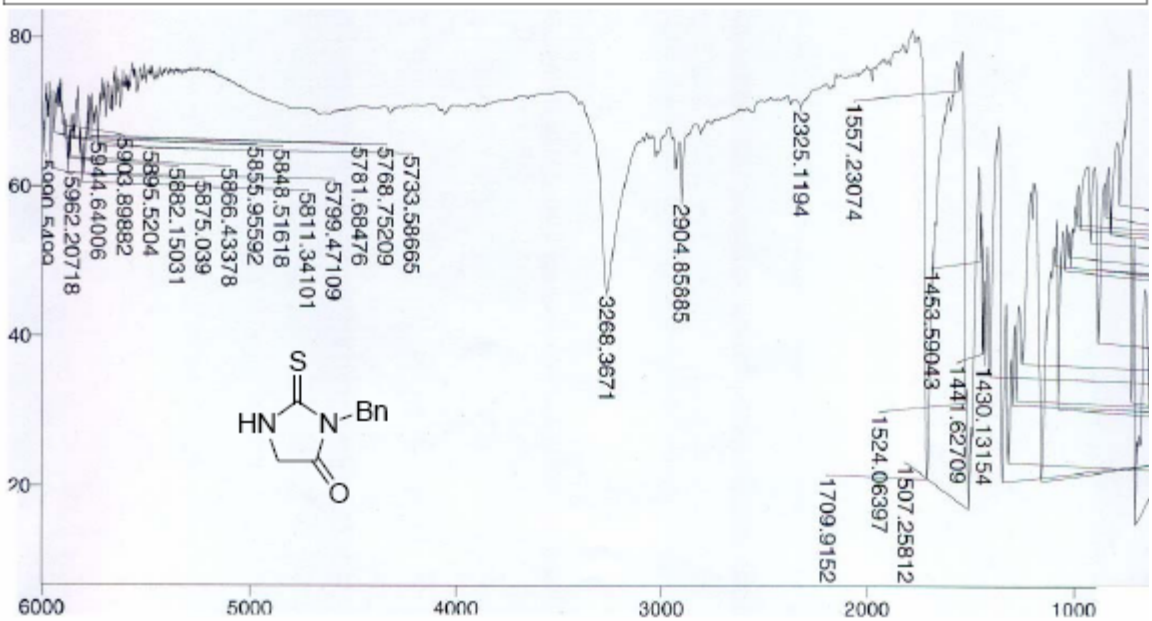

SpinWorks 2.5: Bu2TH
10.1500
4.1212
3.6582
3.6402
3.6220
3.3685
2.5153
1.5529
1.5344
1.5164
1.4974
1.3003
1.2817
1.2630
1.2446
0.9077
0.8896
0.8712
S
HN
N
Bu
O
0.972
1.941
2.000
2.005
1.992
2.868
PPM
9.6
9.2
8.8
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8

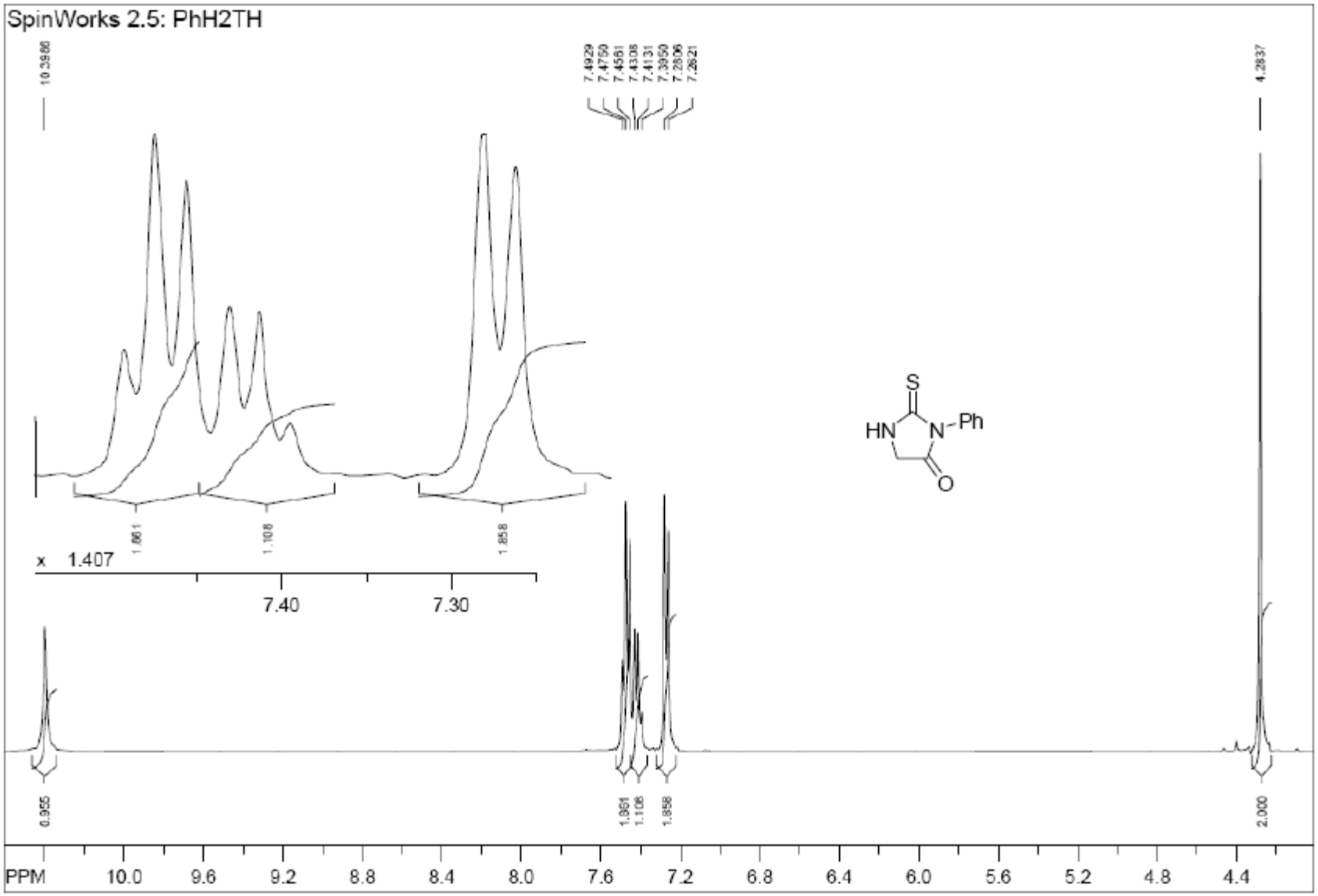

SpinWorks 2.5: BuH2TH
S
HN
N-Bu
O
x 0.677
40.0
39.0
38.0
PPM
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

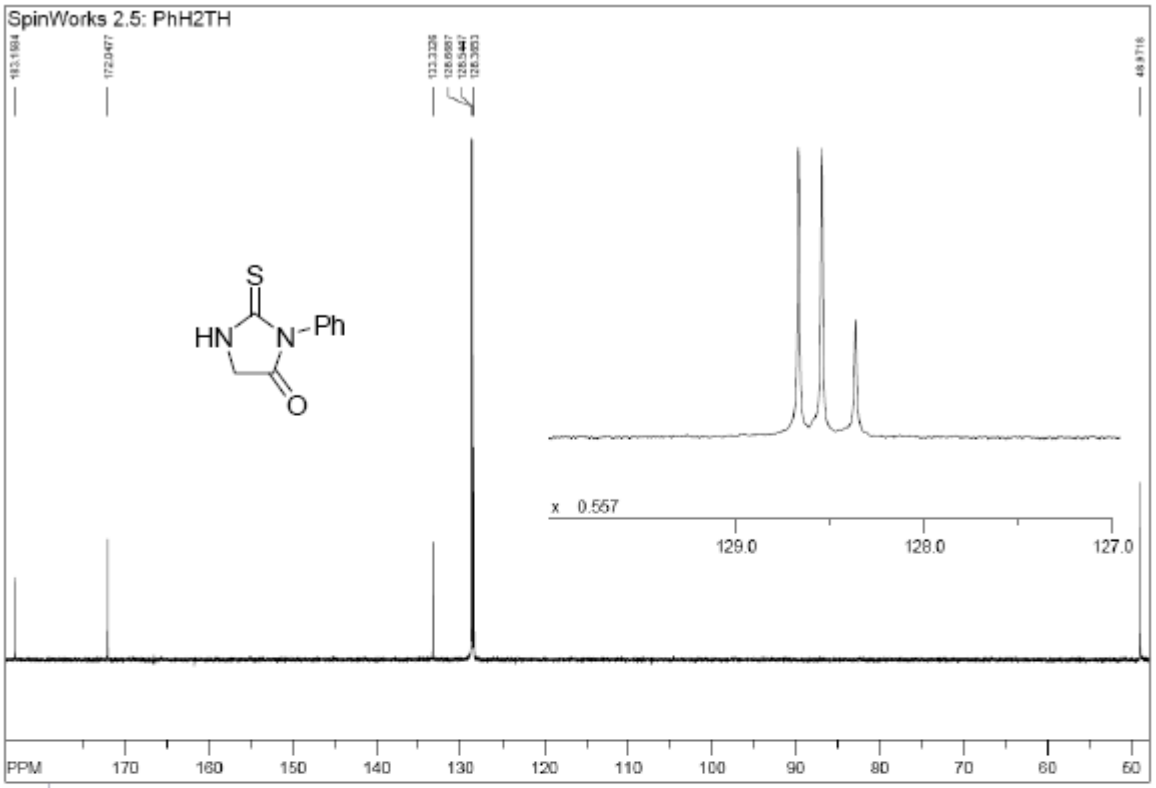

80
60
40
20
S
HN
N-Bu
O
5960.81151
5944.73232
5926.84802
5918.51453
5853.89181
3262.60328
2960.22262
2946.596
2926.9653
2873.03069
2857.68842
1980.91905
1708.16441
1602.15096
1506.18555
1462.02393
1434.06941
1417.81819
1402.80494
1344.04273
6000
5000
4000
3000
2000
000

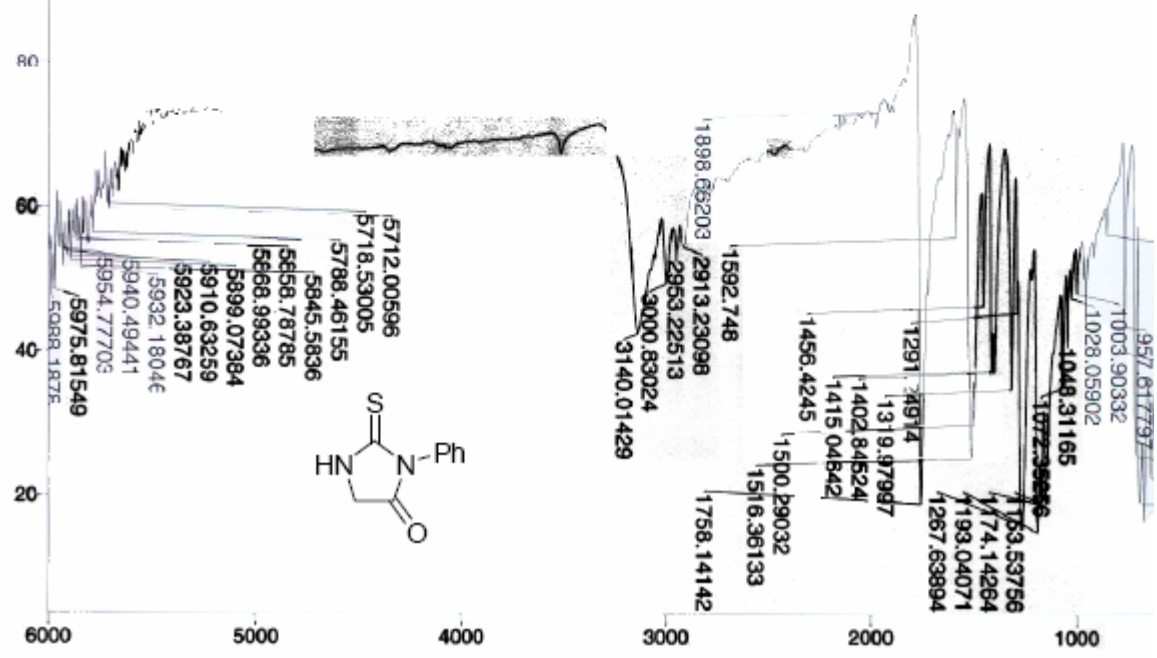

SpinWorks 2.5: Bn2TH
10.3101
7.3158
7.3066
7.3034
7.2827
7.2620
7.2557
7.2502
7.2422
4.8677
4.2034
S
HN
N
Bn
O
0.946
4.716
2.028
2.000
PPM 10.0 9.6 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4


SpinWorks 2.5: Bn2TH
x 0.377
128
S
HN
N
Bn
O
PPM
170
160
150
140
130
120
110
100
90
80
70
60
50
40


80
60
40
20
6000
5000
4000
3000
2000
1000
5962.20718
5944.64006
5903.89882
5895.5204
5882.15031
5875.039
5866.43378
5855.95592
5848.51618
5811.34101
5799.47109
5781.68476
5768.75209
5733.58665
3268.3671
2904.85885
2325.1194
1557.23074
1453.59043
1441.62709
1430.13154
1524.06397
1507.25812
1709.9152
S
HN
N
Bn
O


SpinWorks 2.5: PhH2TH
10.3986
7.4929
7.4750
7.4561
7.4308
7.4131
7.3959
7.2806
7.2621
4.2837
S
HN
N
Ph
O
1.861
1.106
1.858
x 1.407
7.40
7.30
0.955
1.861
1.106
1.858
2.000
PPM
10.0
9.6
9.2
8.8
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4


SpinWorks 2.5: PhH2TH
S
HN
N
Ph
O
x 0.567
129.0
128.0
127.0
PPM
170
160
150
140
130
120
110
100
90
80
70
60
50


80
60
40
20
6000
5000
4000
3000
2000
1000
5975.81549
5954.77703
5940.49441
5932.18046
5923.38767
5910.63259
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5868.99336
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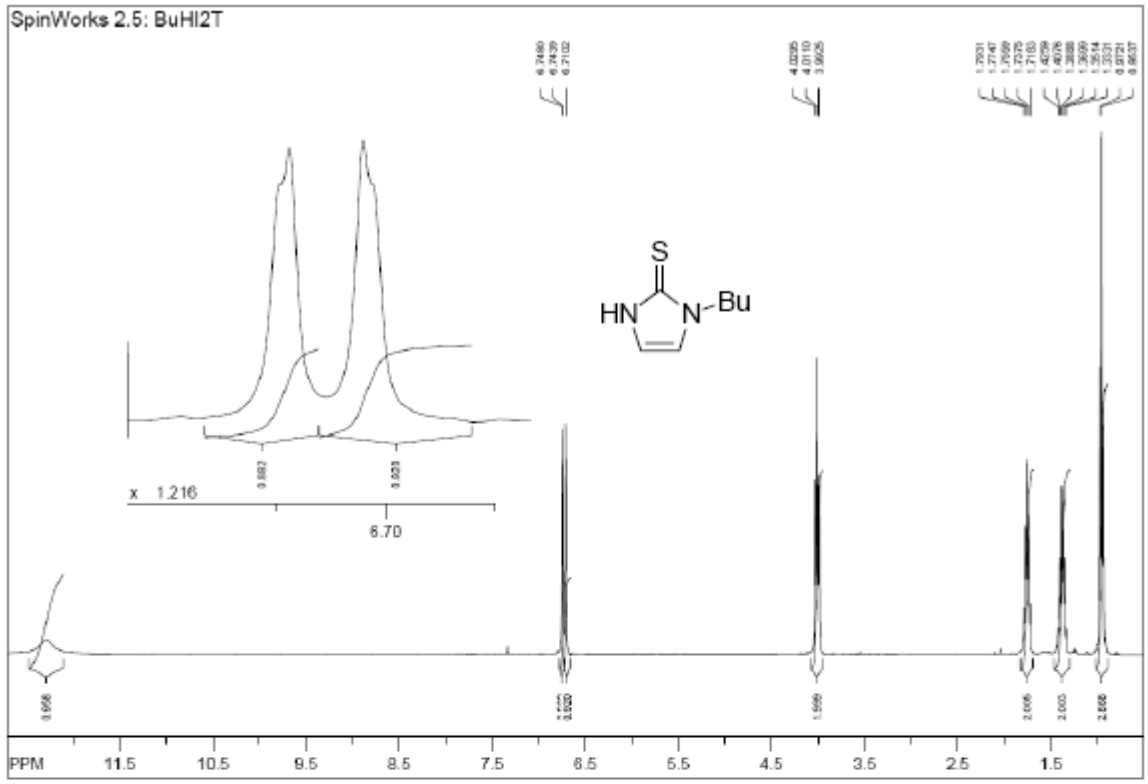
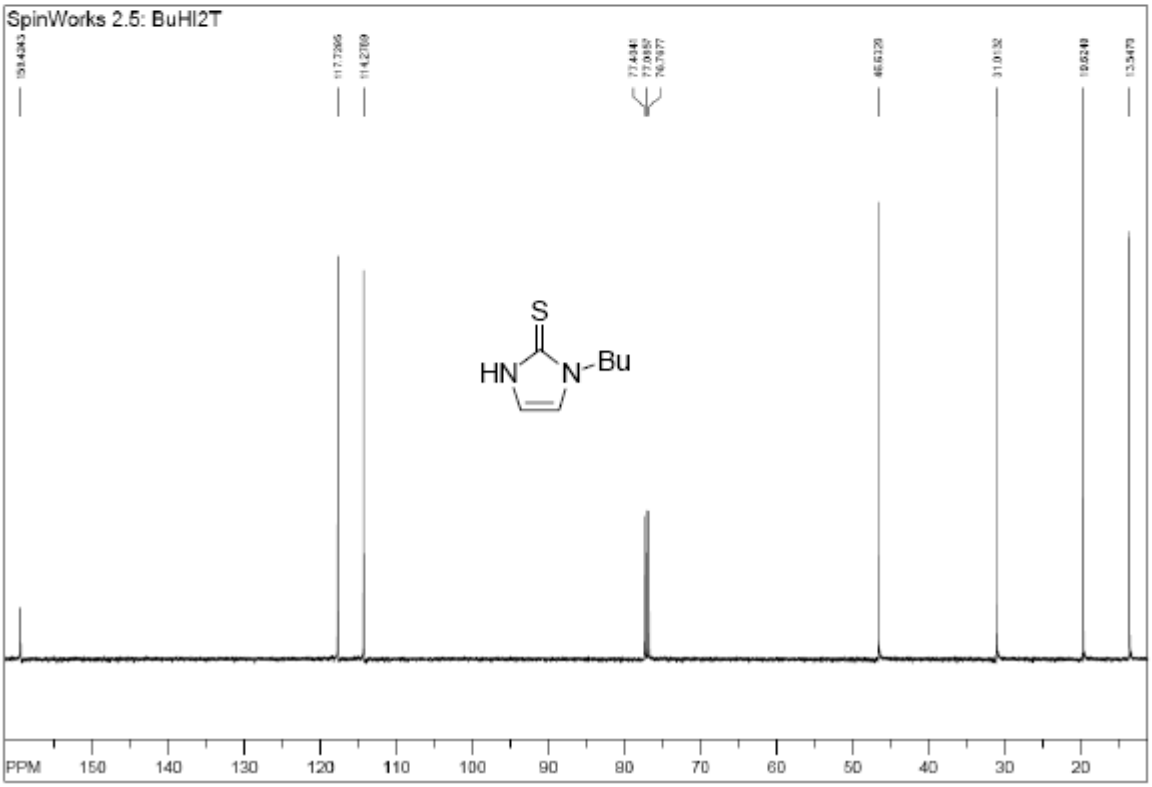
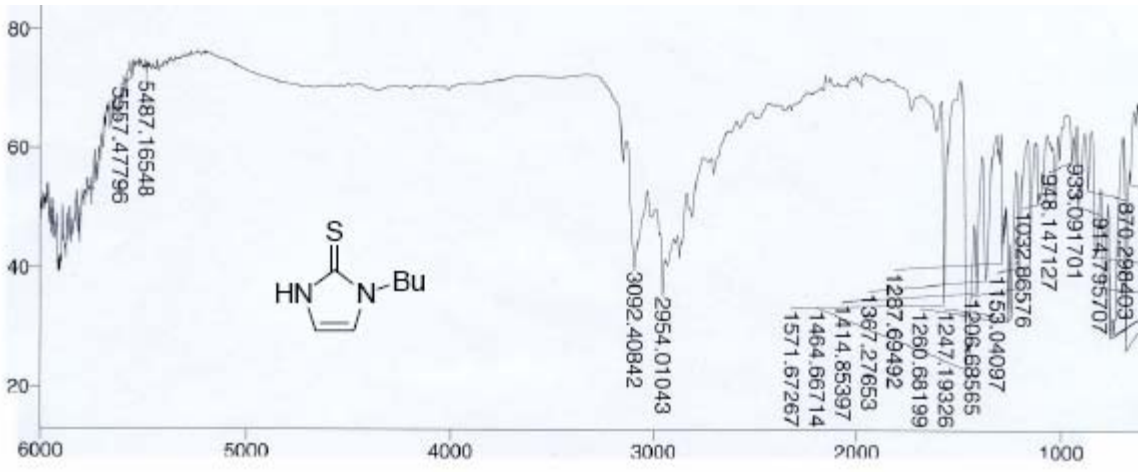
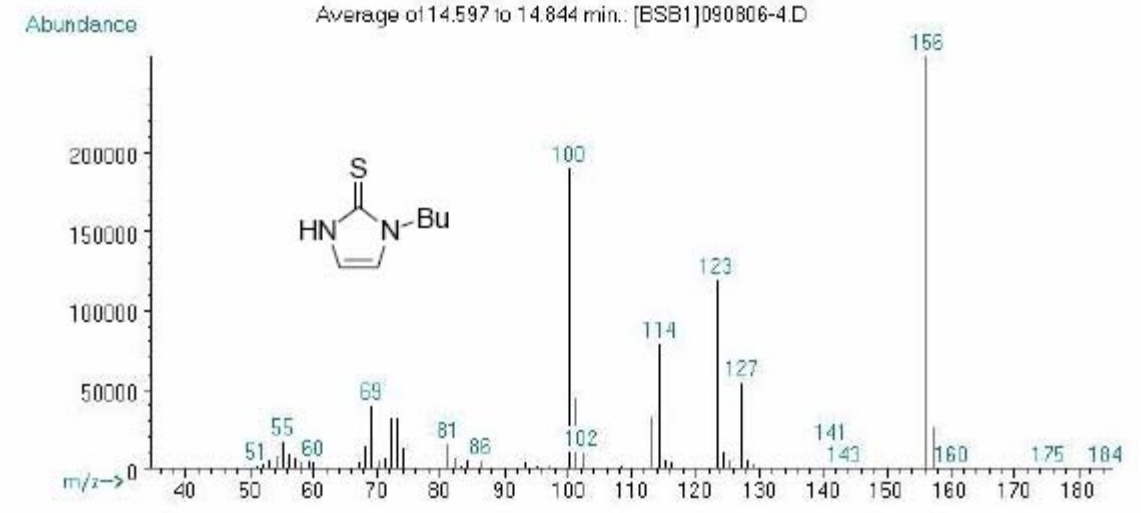
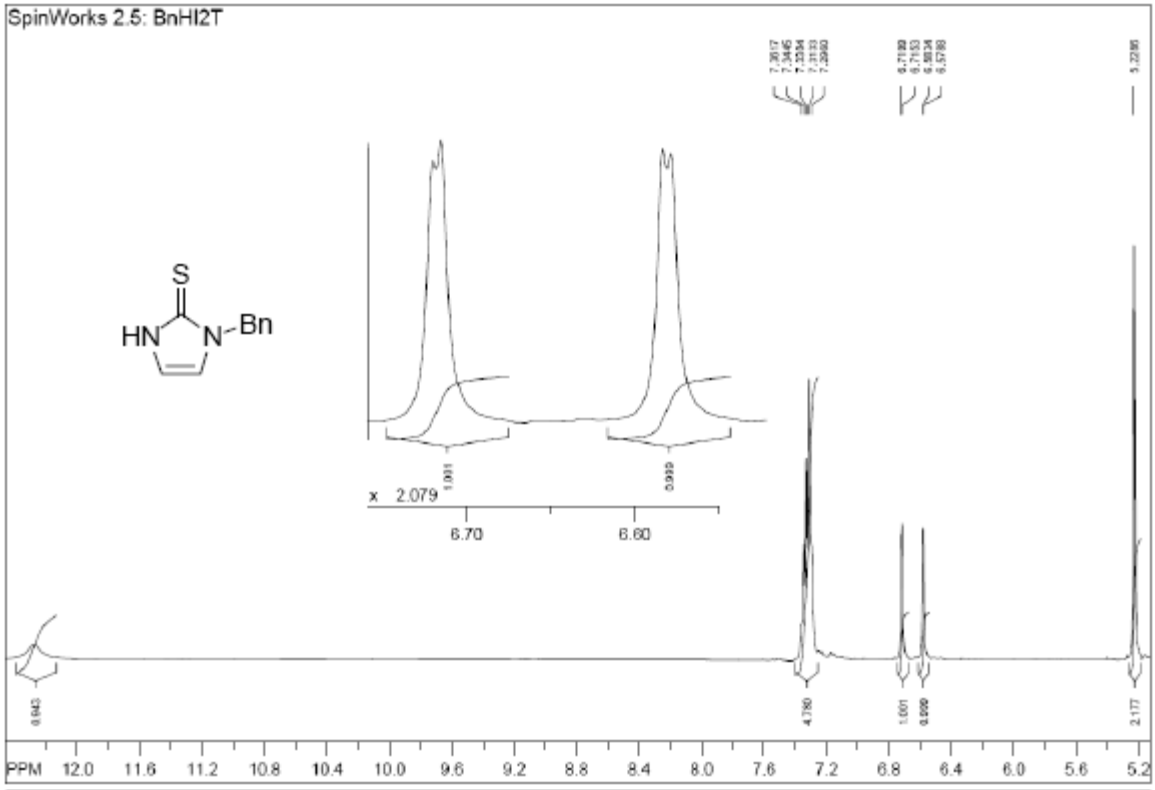
5845.58836
5788.46155
5718.53005
5712.00596
3140.01429
3000.83024
2953.22513
2913.23098
1898.65203
1592.746
1456.4245
1516.36133
1500.29032
1758.14142
1267.63894
1193.04071
1174.14264
1048.31165
1028.05902
1003.90332
957.617797
HN
N
Ph
O

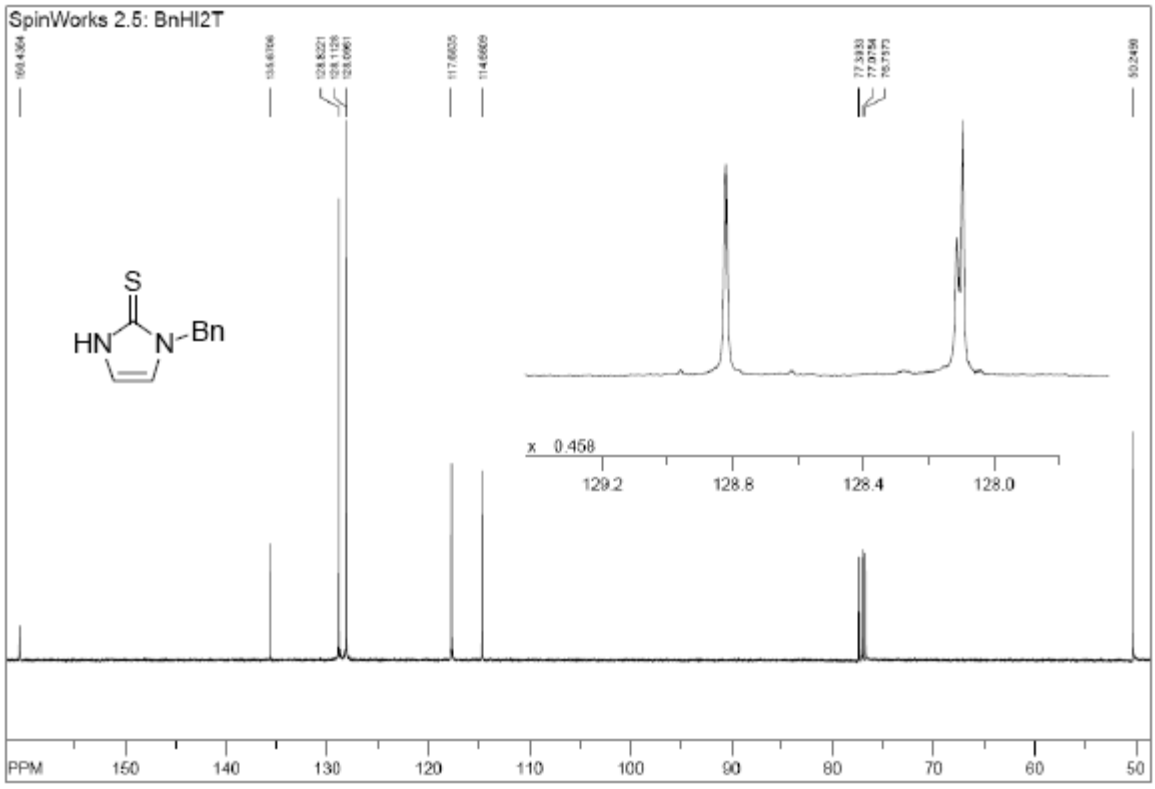

SpinWorks 2.5: BuHI2T
S
HN
N
Bu
x 1.216
6.70
PPM
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5

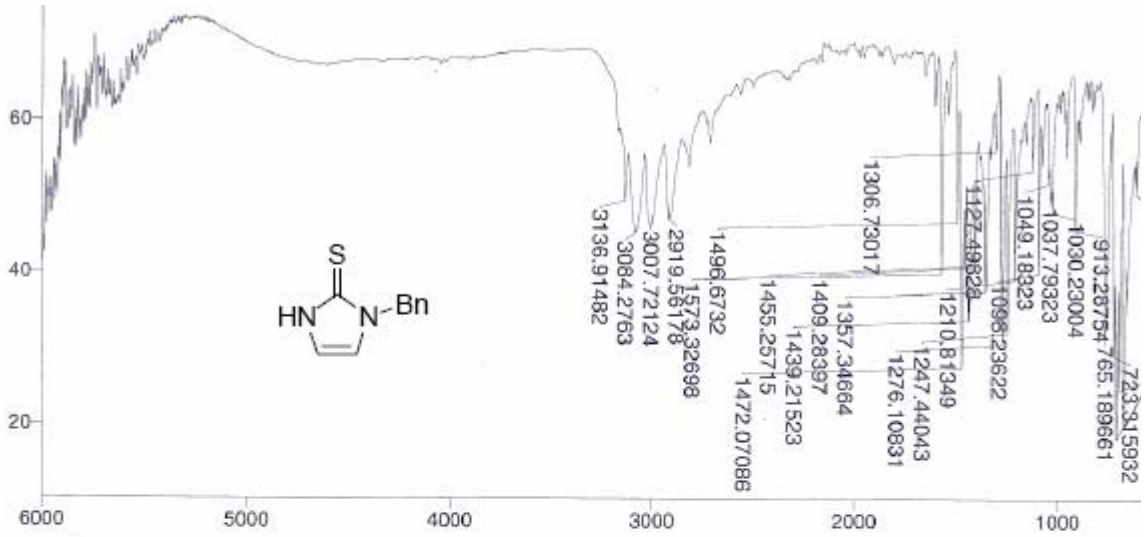

SpinWorks 2.5: BuHI2T
S
HN
N
Bu
PPM
150
140
130
120
110
100
90
80
70
60
50
40
30
20

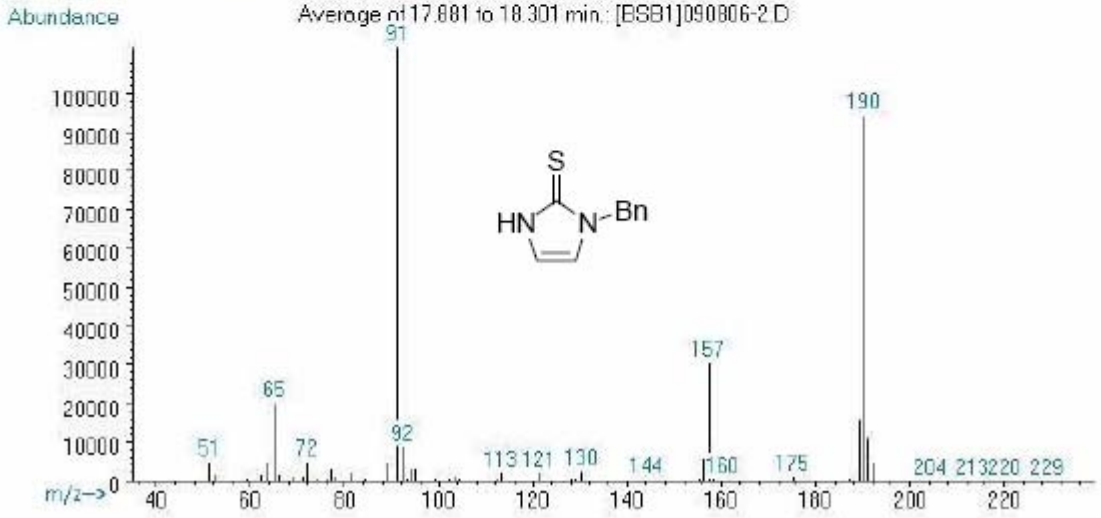

80
60
40
20
6000
5000
4000
3000
2000
1000
5487.16548
5567.47796
3092.40842
2954.01043
1571.67267
1464.66714
1414.85397
1367.27653
1287.69492
1260.68199
1247.19326
1206.68565
1153.04097
1032.86576
948.147127
933.091701
914.795707
870.266493
S
HN
N
Bu

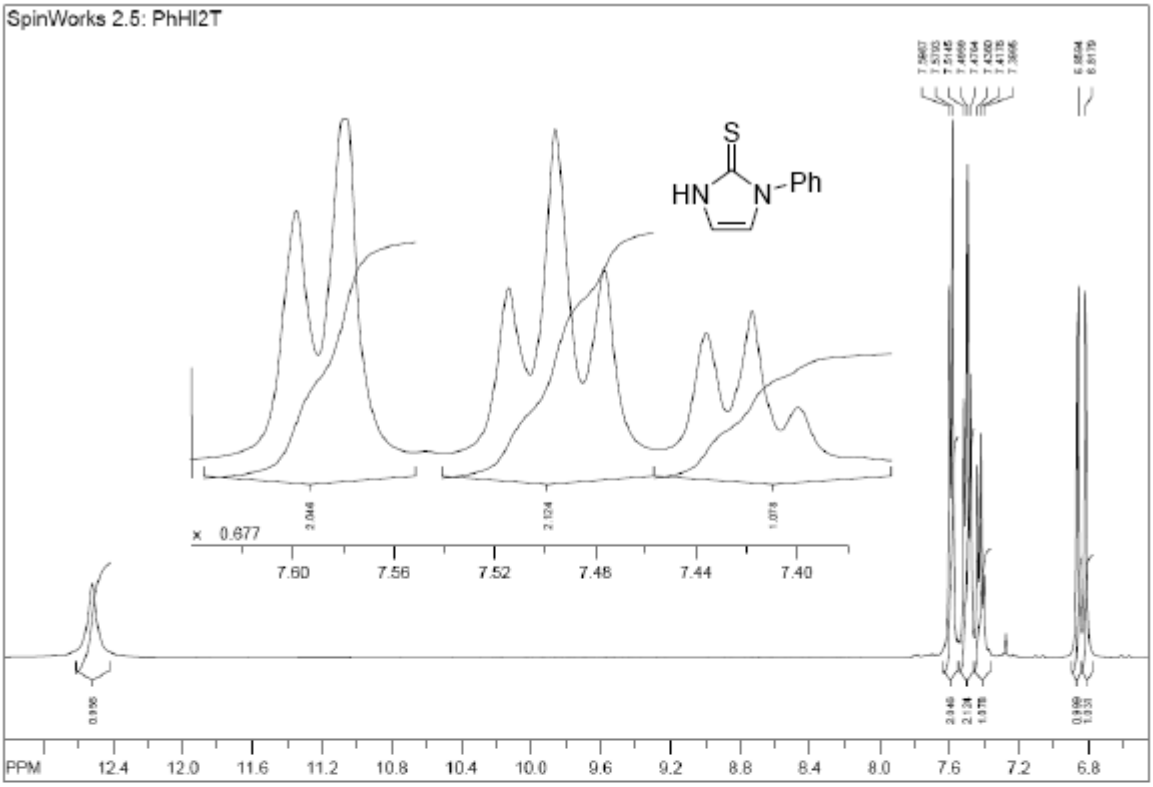

Abundance
Average of 14.597 to 14.844 min.: [BSB1]090806-4.D
200000
150000
100000
50000
0
m/z-->
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
156
100
123
114
127
69
55
51
60
81
86
102
141
143
160
175
184
S
HN
N
Bu

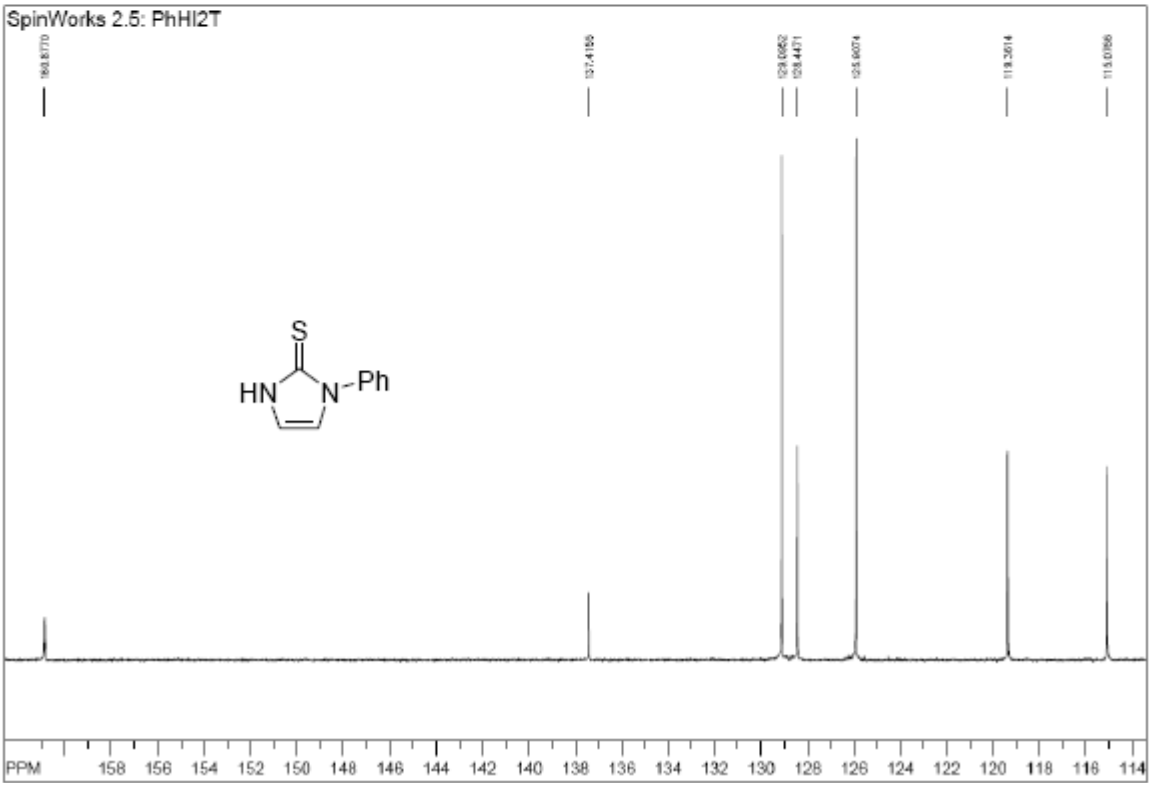

SpinWorks 2.5: BnHI2T
S
HN
N
Bn
x 2.079
6.70
6.60
PPM 12.0 11.6 11.2 10.8 10.4 10.0 9.6 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2

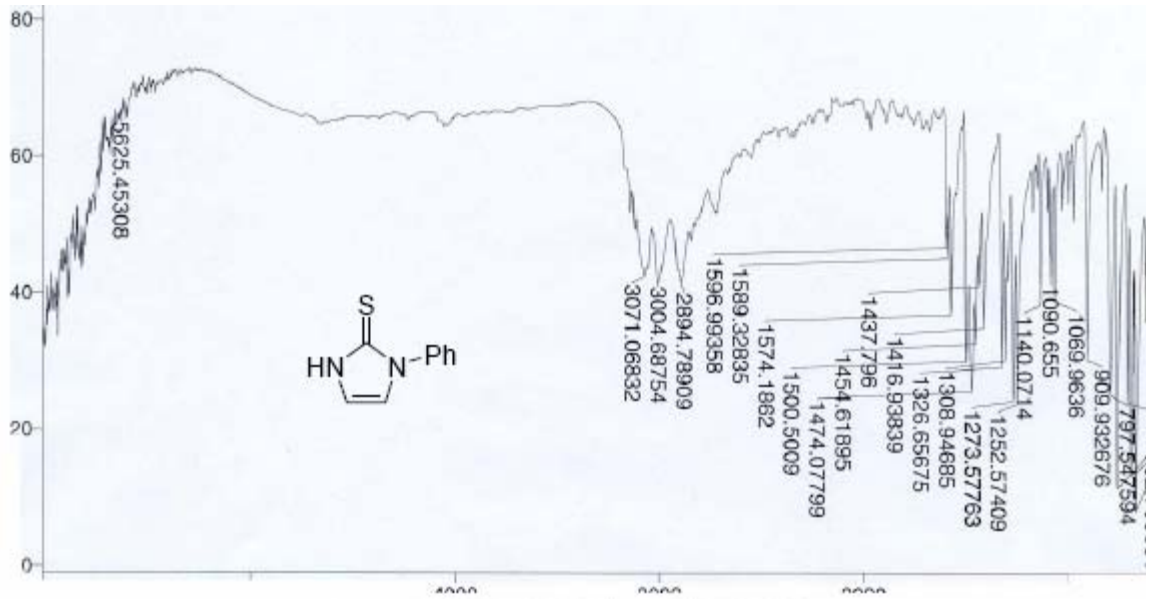

SpinWorks 2.5: BnHI2T
S
HN
N
Bn
x 0.458
129.2
128.8
128.4
128.0
PPM 150 140 130 120 110 100 90 80 70 60 50

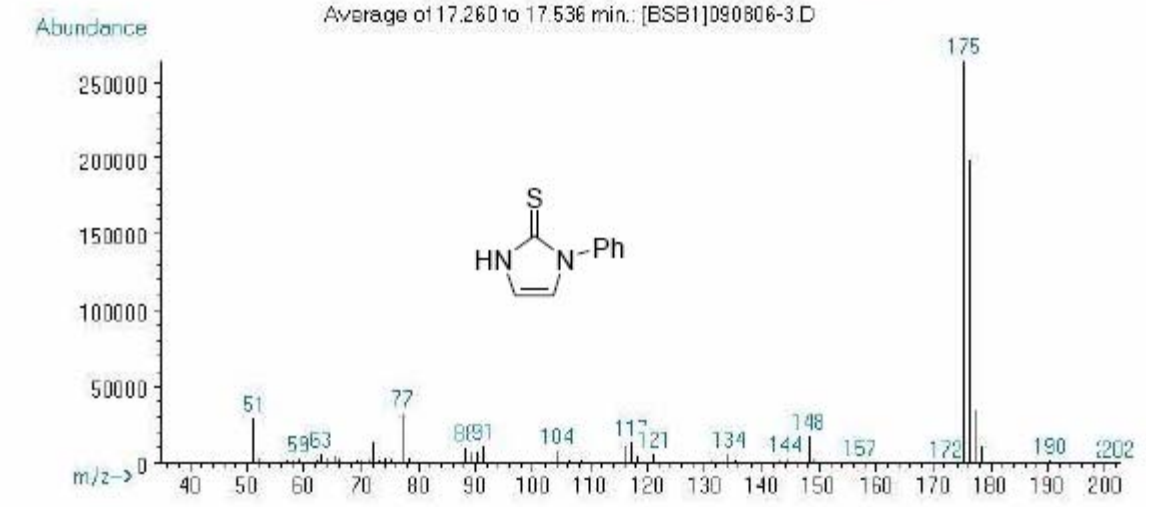

S
HN
N-Bn
3136.91482
3084.2763
3007.72124
2919.58178
1573.32698
1496.6732
1472.07086
1455.25715
1439.21523
1409.28397
1357.34664
1306.73017
1276.10631
1247.44043
1210.81349
1127.49629
1098.23622
1049.18323
1037.79323
1030.23004
913.28754
765.18966
723.45932

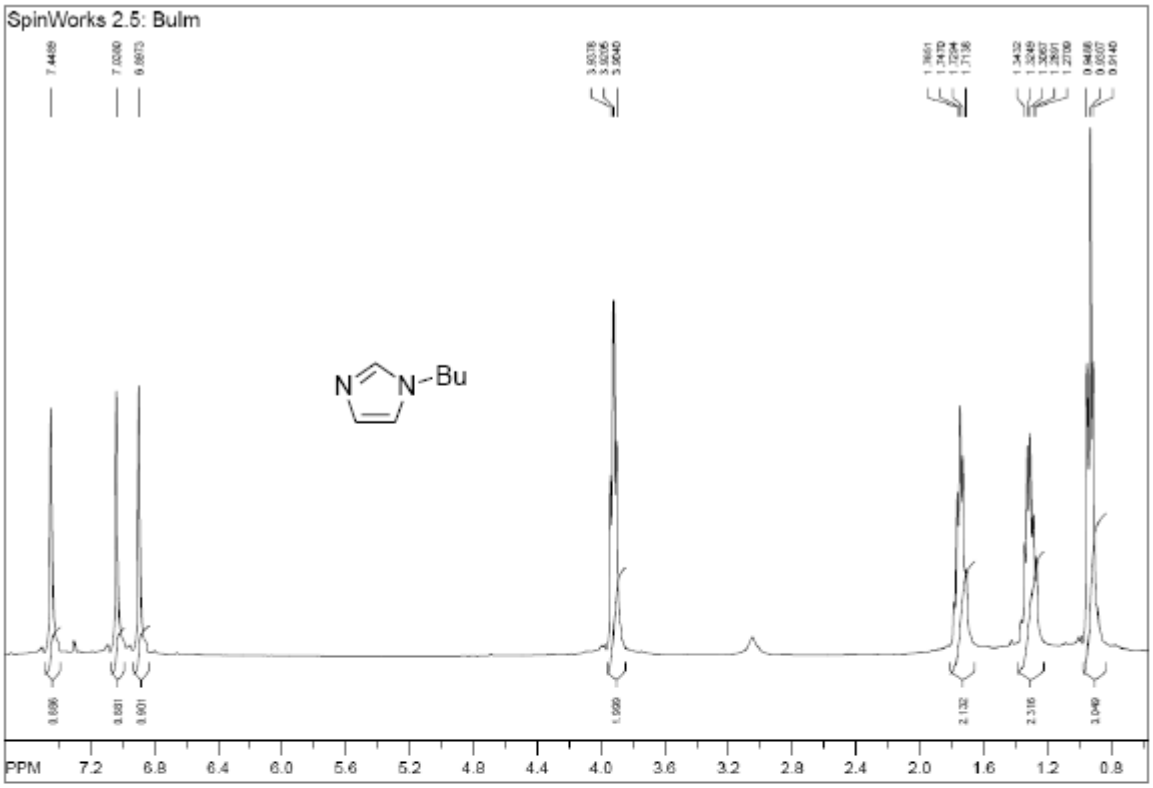

Abundance
Average of 17.681 to 18.301 min.: [BSB1]090806-2.D
S
HN
N-Bn
91
190
157
65
92
51
72
113 121 130
144
160
175
204 213220 229
m/z-->

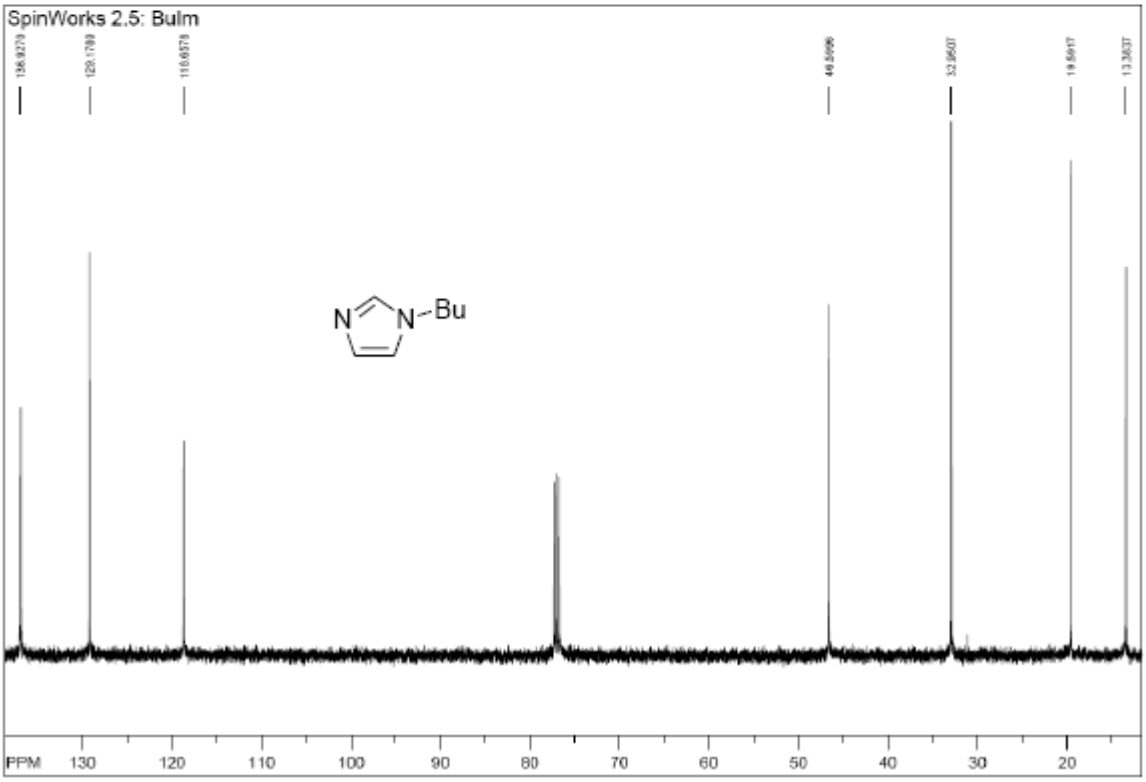

SpinWorks 2.5: PhHI2T
S
HN
N
Ph
x 0.677
7.60
7.56
7.52
7.48
7.44
7.40
PPM
12.4
12.0
11.6
11.2
10.8
10.4
10.0
9.6
9.2
8.8
8.4
8.0
7.6
7.2
6.8

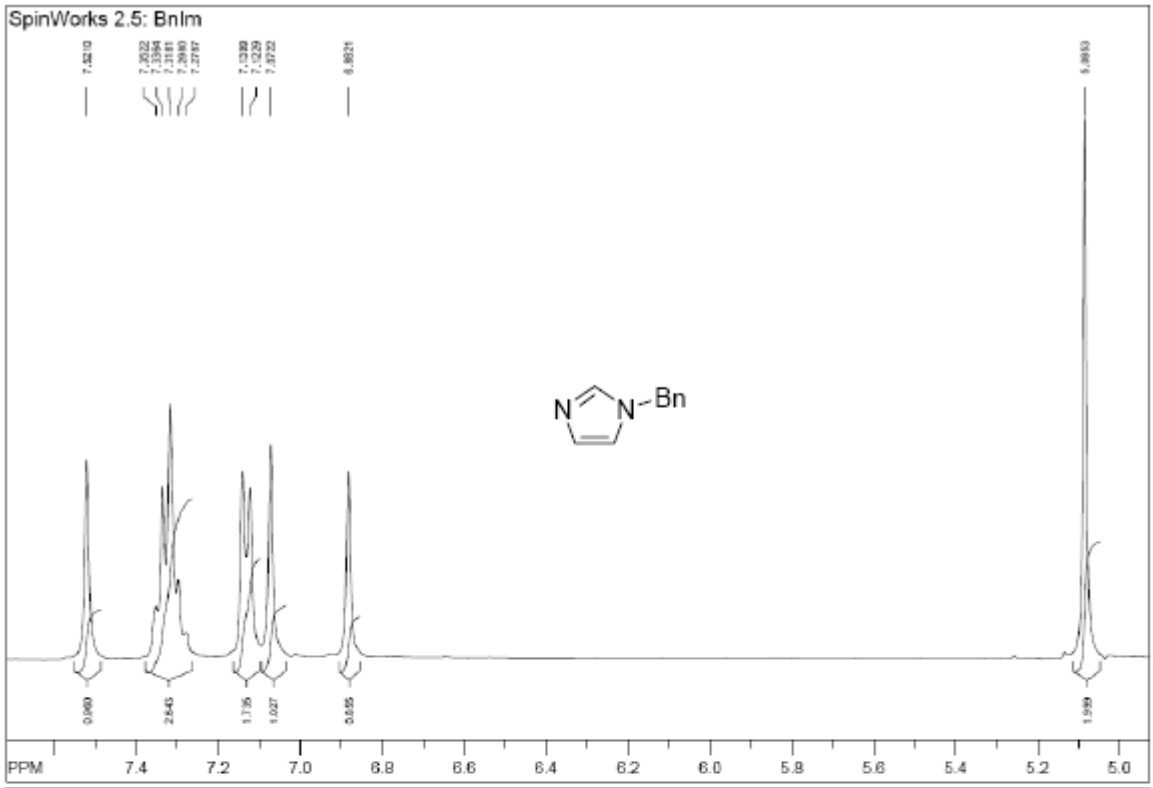

SpinWorks 2.5: PhHI2T
163.8770
137.4159
129.6952
128.4471
125.6074
118.3614
115.0766
S
HN
N
Ph
PPM
158
156
154
152
150
148
146
144
142
140
138
136
134
132
130
128
126
124
122
120
118
116
114

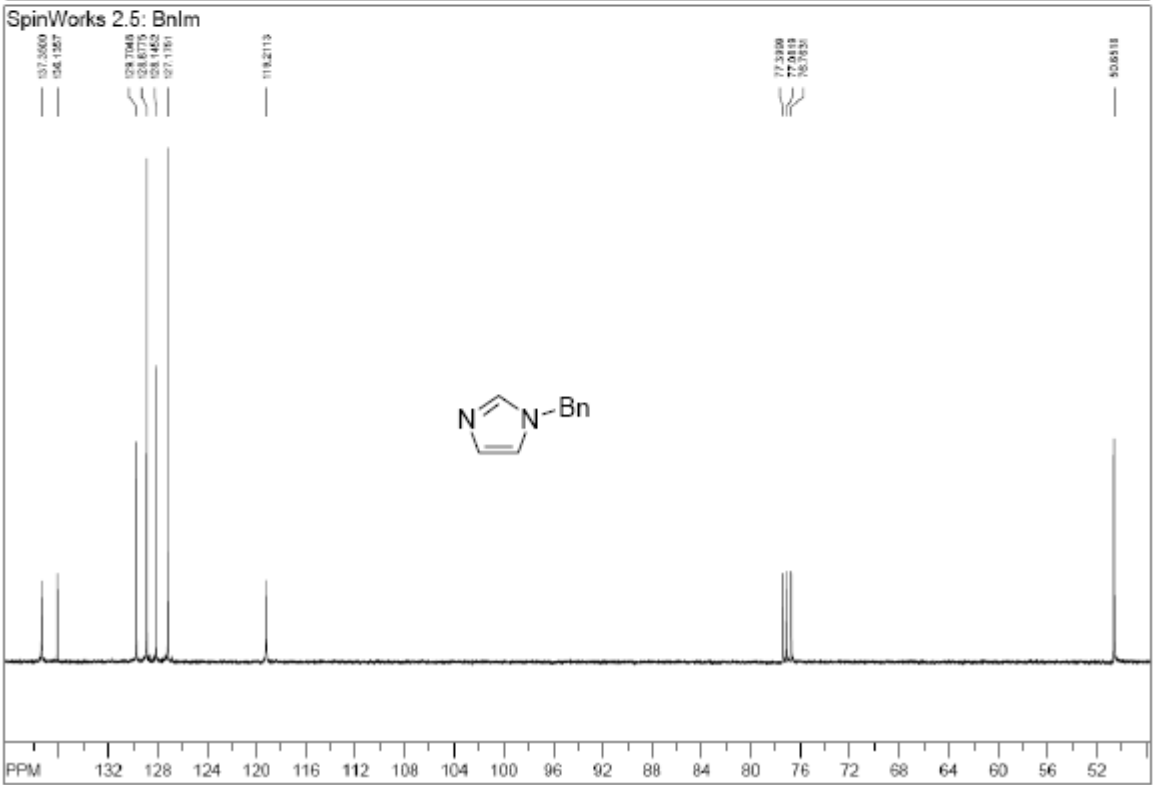

80
60
40
20
0
5625.45308
3071.06832
3004.68754
2894.78909
1596.99358
1589.32835
1574.1862
1500.5009
1474.07799
1454.61895
1437.796
1416.93839
1326.65675
1308.94685
1273.57763
1252.57409
1140.0714
1090.655
1069.9636
909.932676
797.547594
S
HN
N
Ph

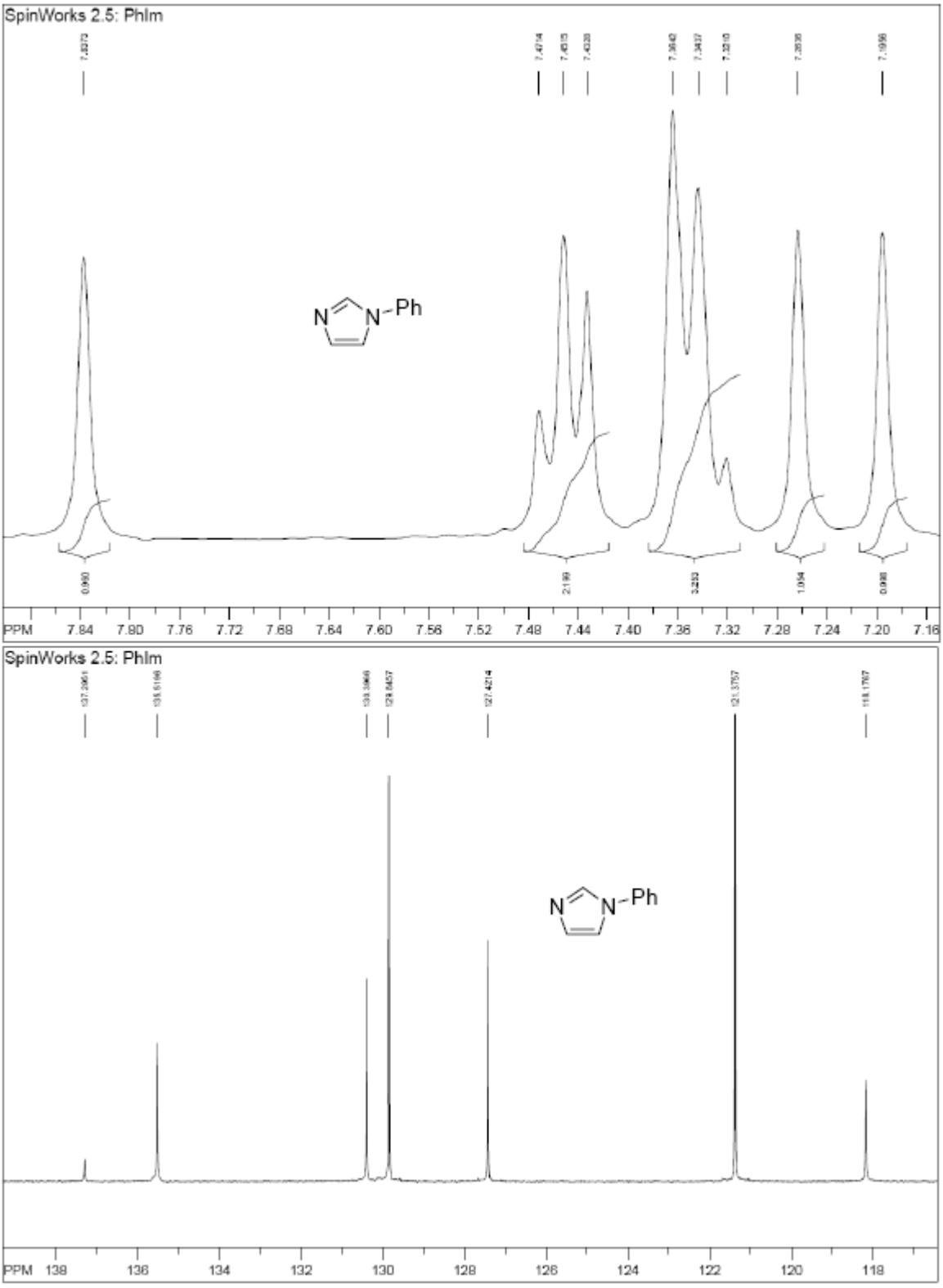

Average of 17.260 to 17.536 min.: [BSB1]090806-3.D
Abundance
250000
200000
150000
100000
50000
0
m/z-->
40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200
51
59
63
77
89
91
104
117
121
134
144
148
157
172
175
190
202
S
HN
N
Ph

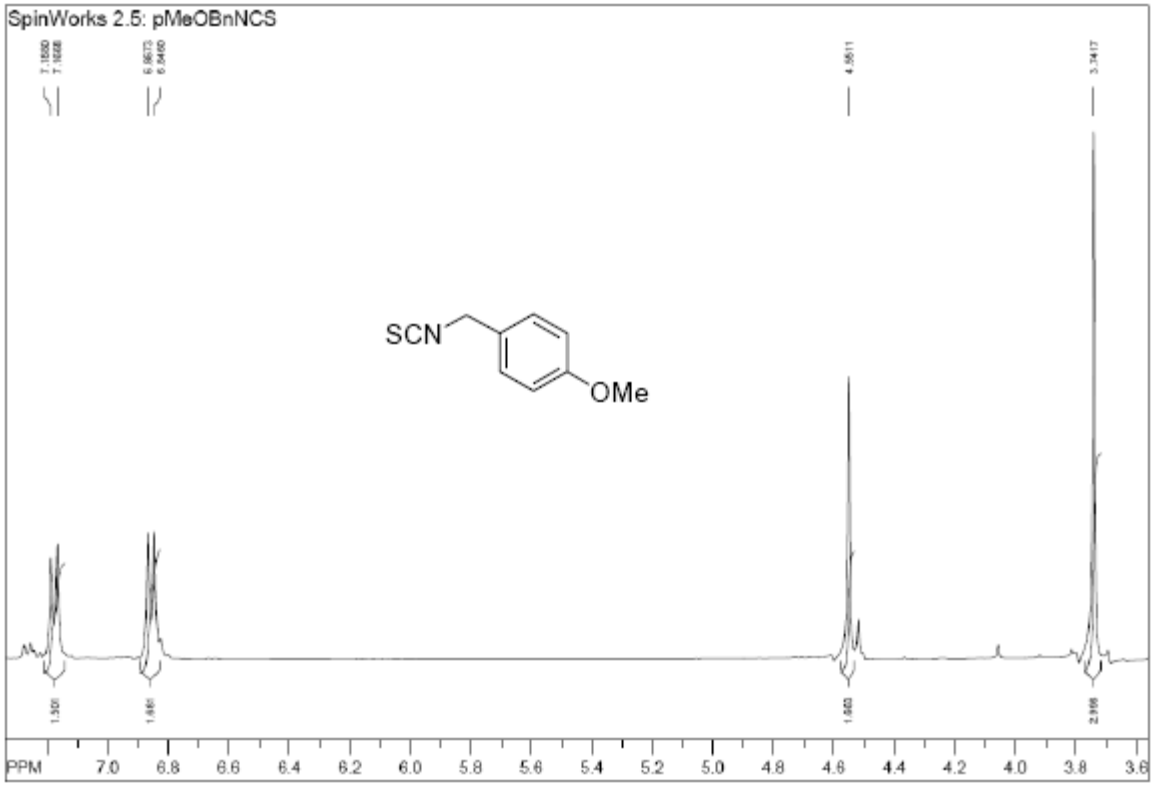

SpinWorks 2.5: Bulm
N
N
Bu
PPM
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8

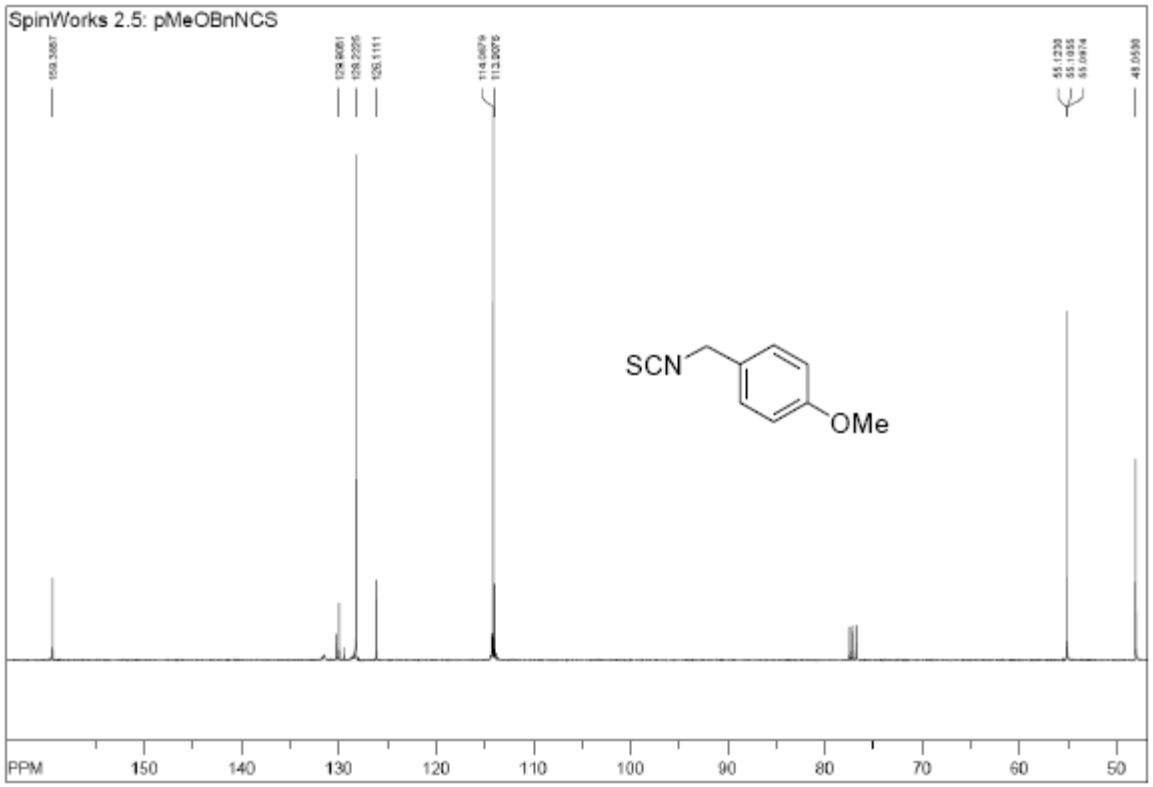

SpinWorks 2.5: Bulm
N
N
Bu
PPM
130
120
110
100
90
80
70
60
50
40
30
20

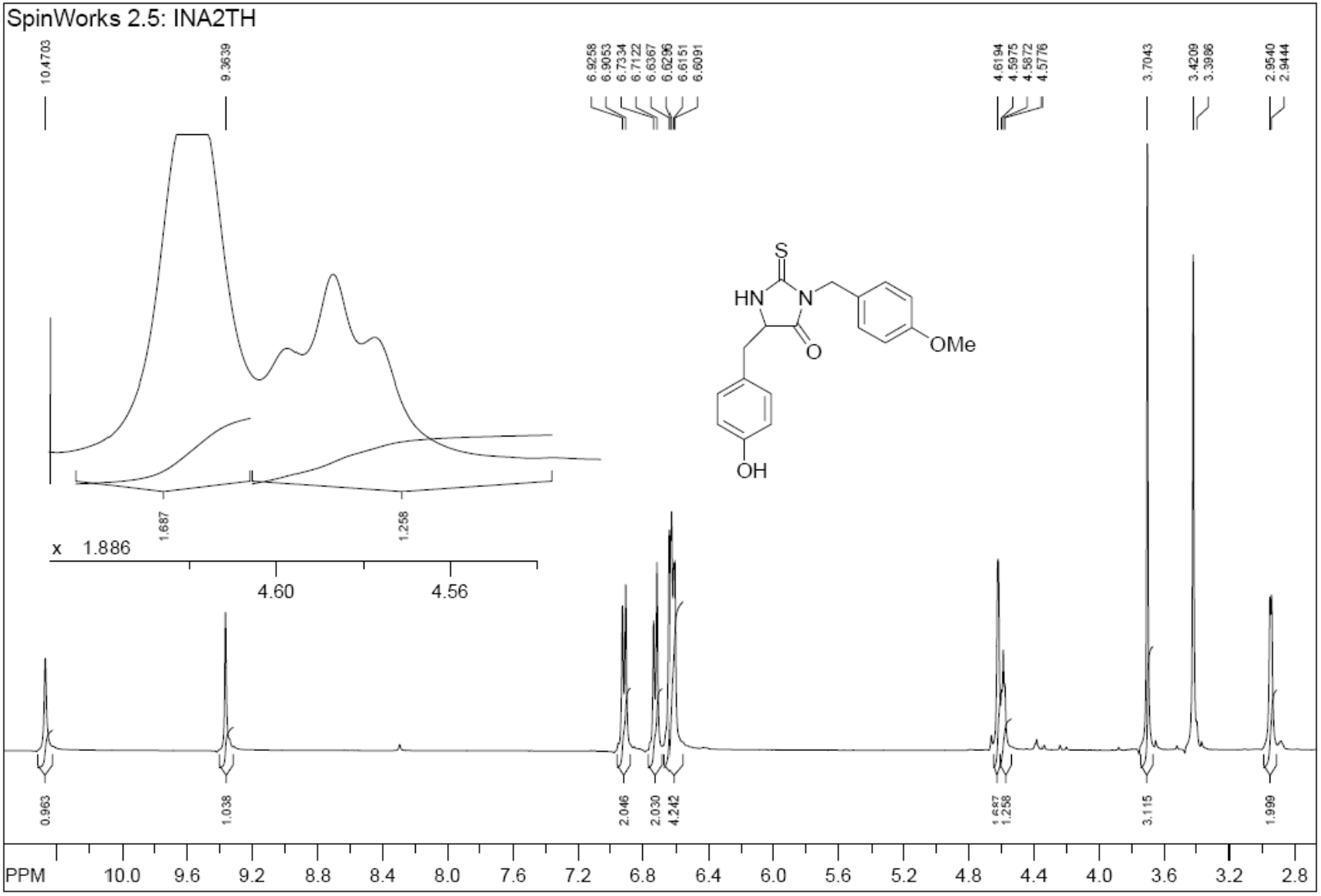

SpinWorks 2.5: BnIm
7.5870
7.3394
7.3181
7.2960
7.2797
7.1399
7.1239
7.0722
6.8821
5.4853
0.969
2.643
1.735
1.027
0.855
1.999
N
N
Bn
PPM
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0

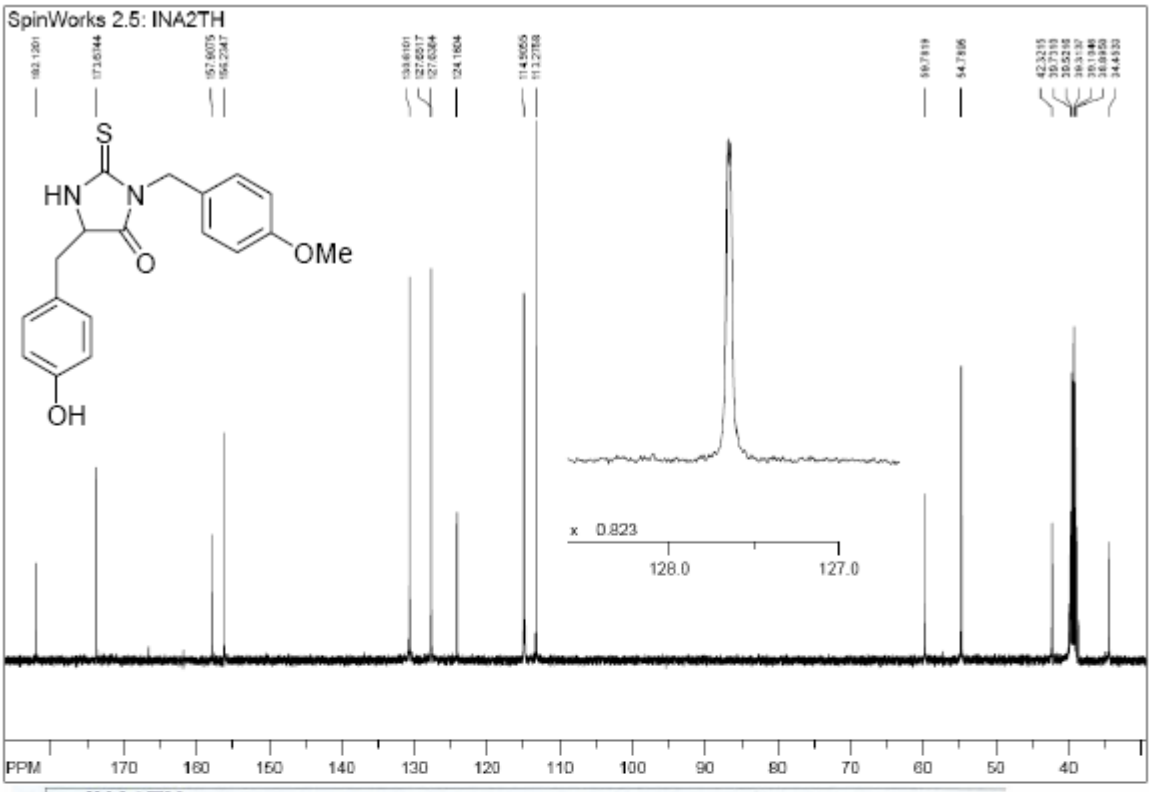

SpinWorks 2.5: BnIm
137.3569
128.7045
128.6775
128.1462
127.1161
118.2113
77.3399
77.0819
76.7653
50.6518
N
N
Bn
PPM
132
128
124
120
116
112
108
104
100
96
92
88
84
80
76
72
68
64
60
56
52

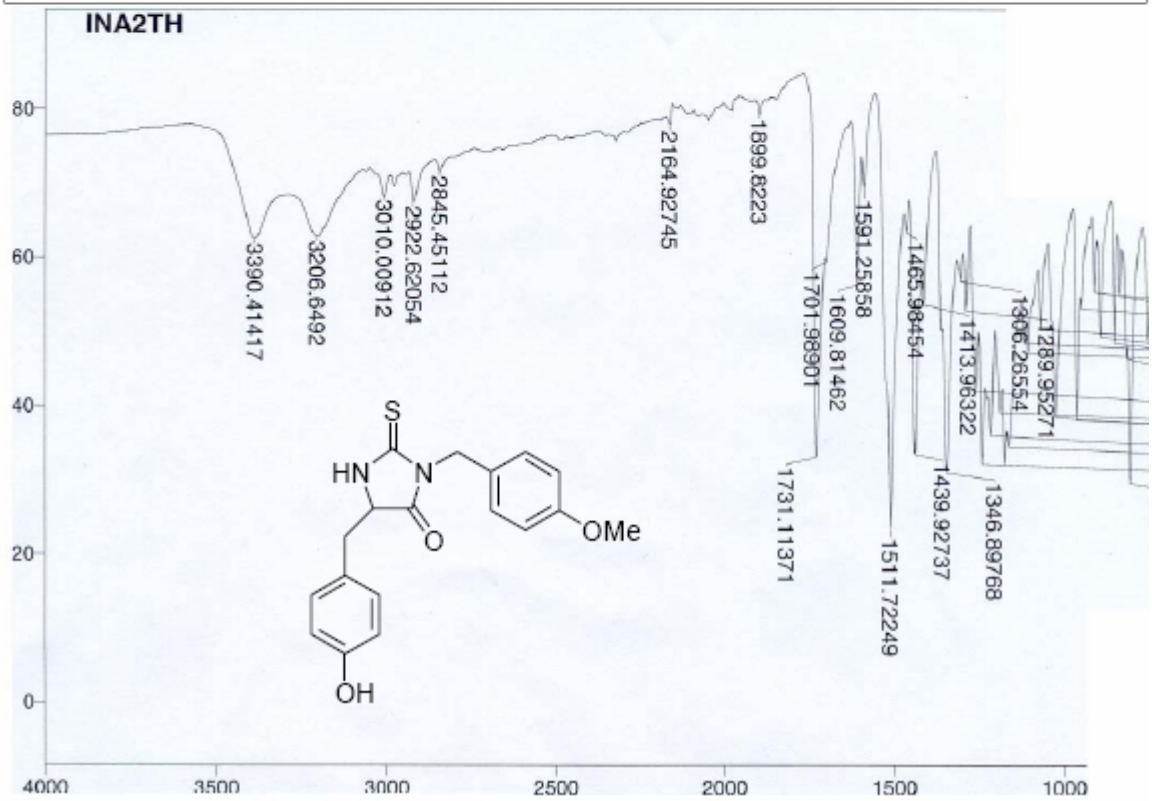

SpinWorks 2.5: PhIm
7.8379
7.4794
7.4515
7.4238
7.3642
7.3437
7.3215
7.2835
7.1998
N
N-Ph
0.990
2.199
3.253
1.054
0.998
PPM 7.84 7.80 7.76 7.72 7.68 7.64 7.60 7.56 7.52 7.48 7.44 7.40 7.36 7.32 7.28 7.24 7.20 7.16
SpinWorks 2.5: PhIm
137.2961
135.5199
129.8457
127.4214
121.3757
118.1767
N
N-Ph
PPM 138 136 134 132 130 128 126 124 122 120 118

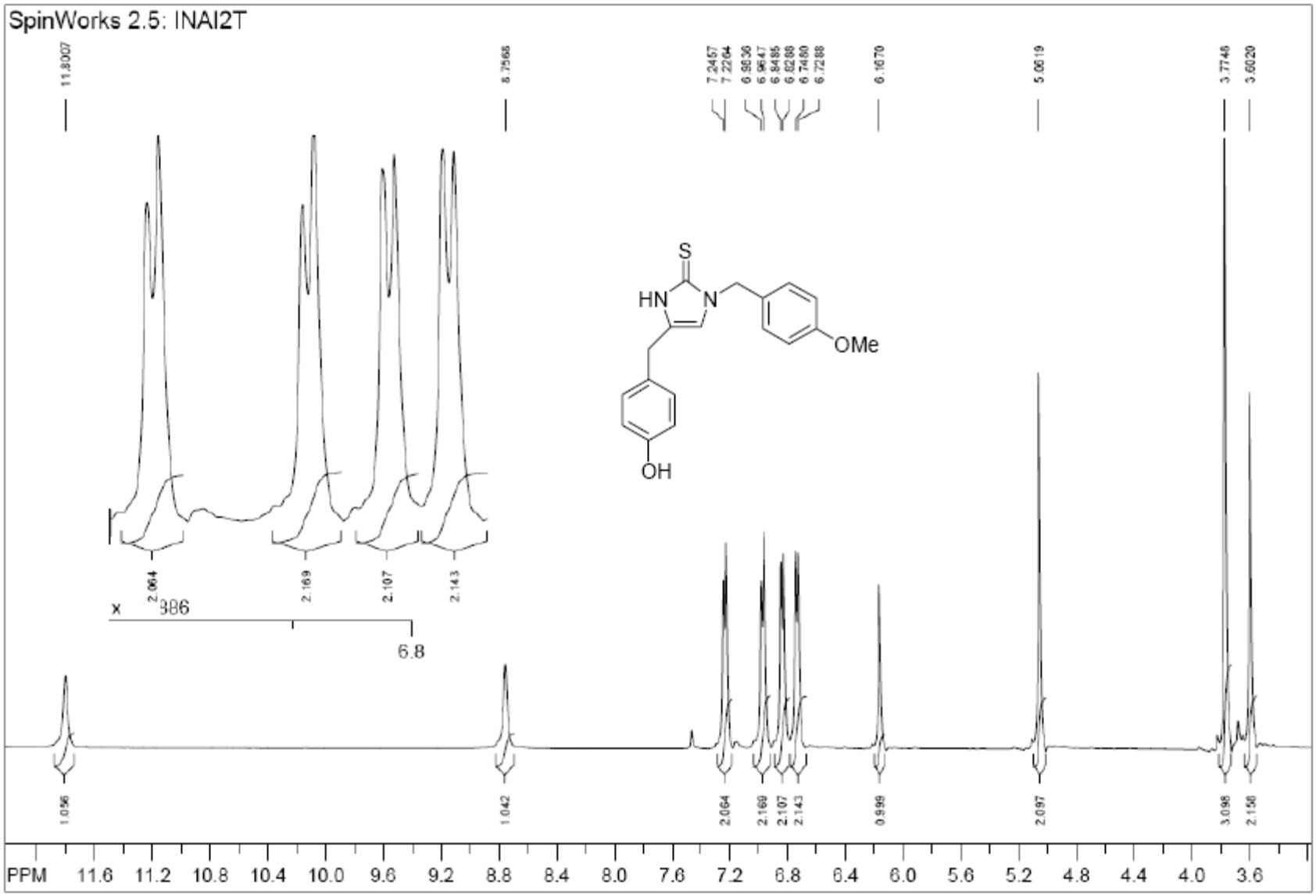

SpinWorks 2.5: pMeOBnNCS
SCN
OMe
PPM

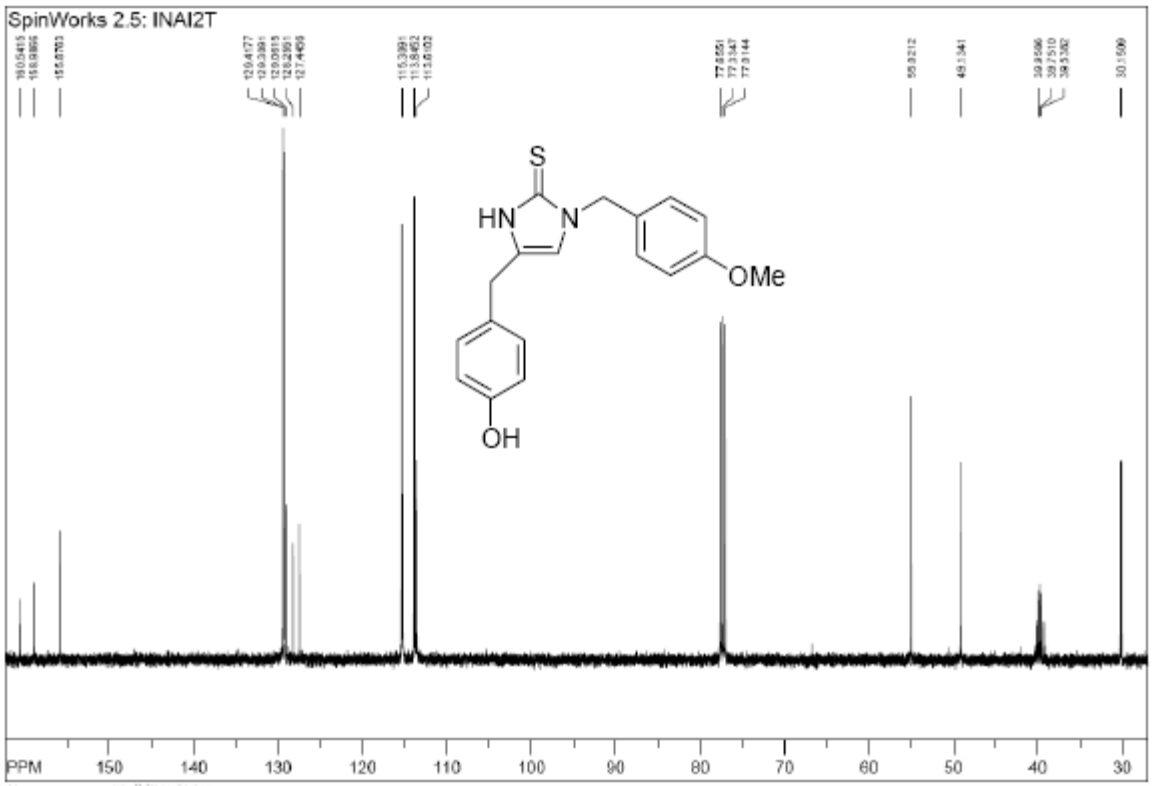

SpinWorks 2.5: pMeOBnNCS
SCN
OMe
PPM

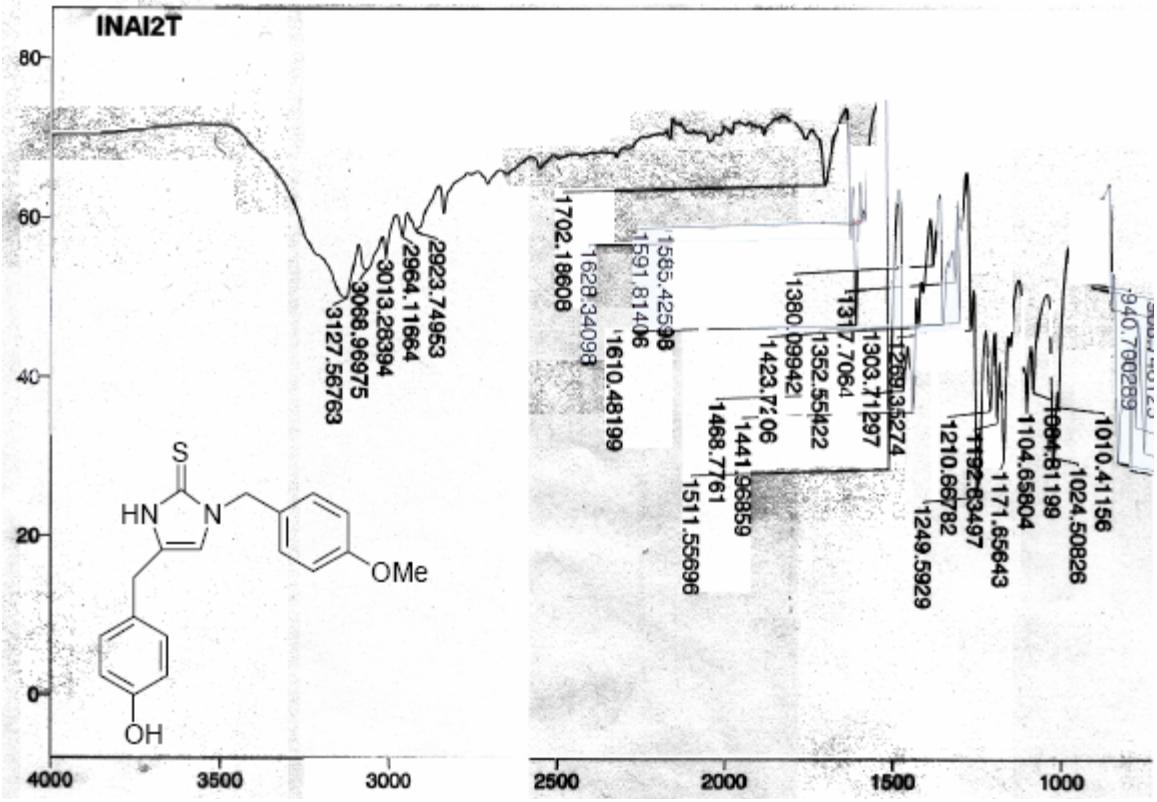

SpinWorks 2.5: INA2TH
10.4703
9.3639
6.9258
6.9053
6.7334
6.7122
6.6367
6.6296
6.6151
6.6091
4.6194
4.5975
4.5872
4.5776
3.7043
3.4209
3.3986
2.9540
2.9444
S
HN
N
O
OMe
OH
1.687
1.258
x 1.886
4.60
4.56
0.963
1.038
2.046
2.030
4.242
1.687
1.258
3.115
1.999
PPM
10.0
9.6
9.2
8.8
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8

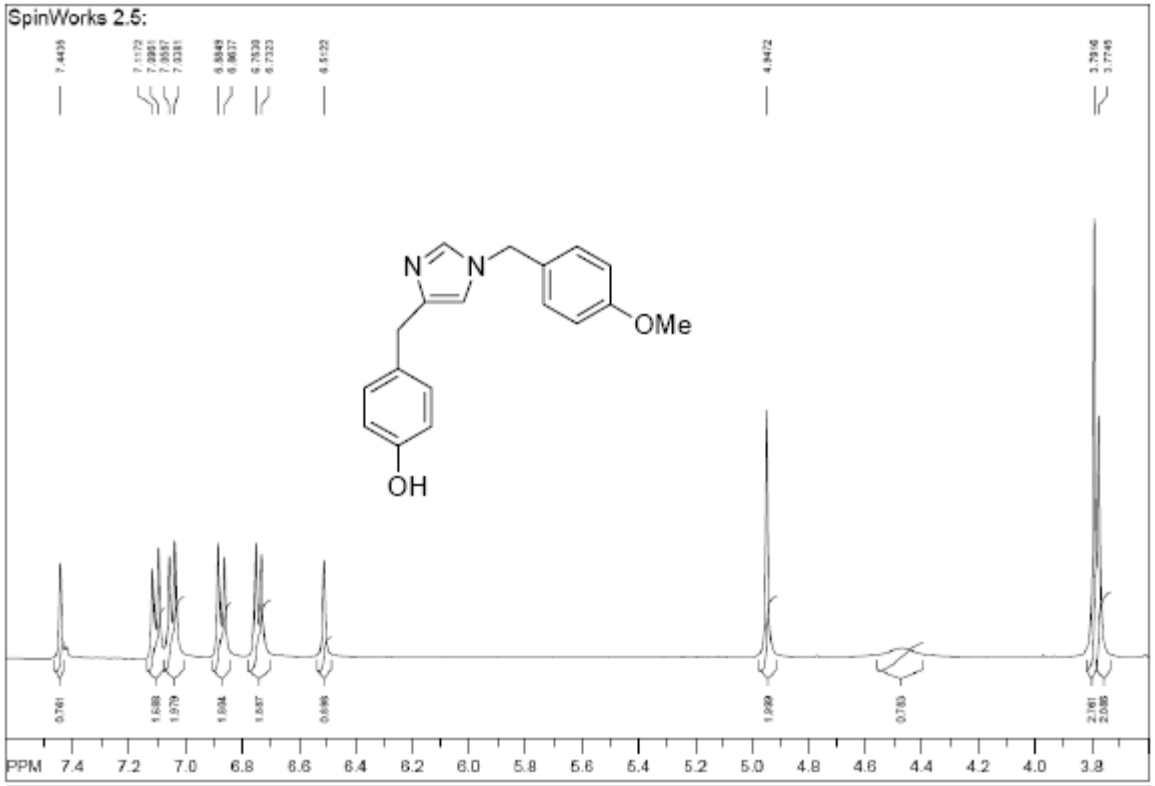

SpinWorks 2.5: INA2TH
S
HN
N
O
OMe
OH
x 0.823
128.0
127.0
PPM
170
160
150
140
130
120
110
100
90
80
70
60
50
40

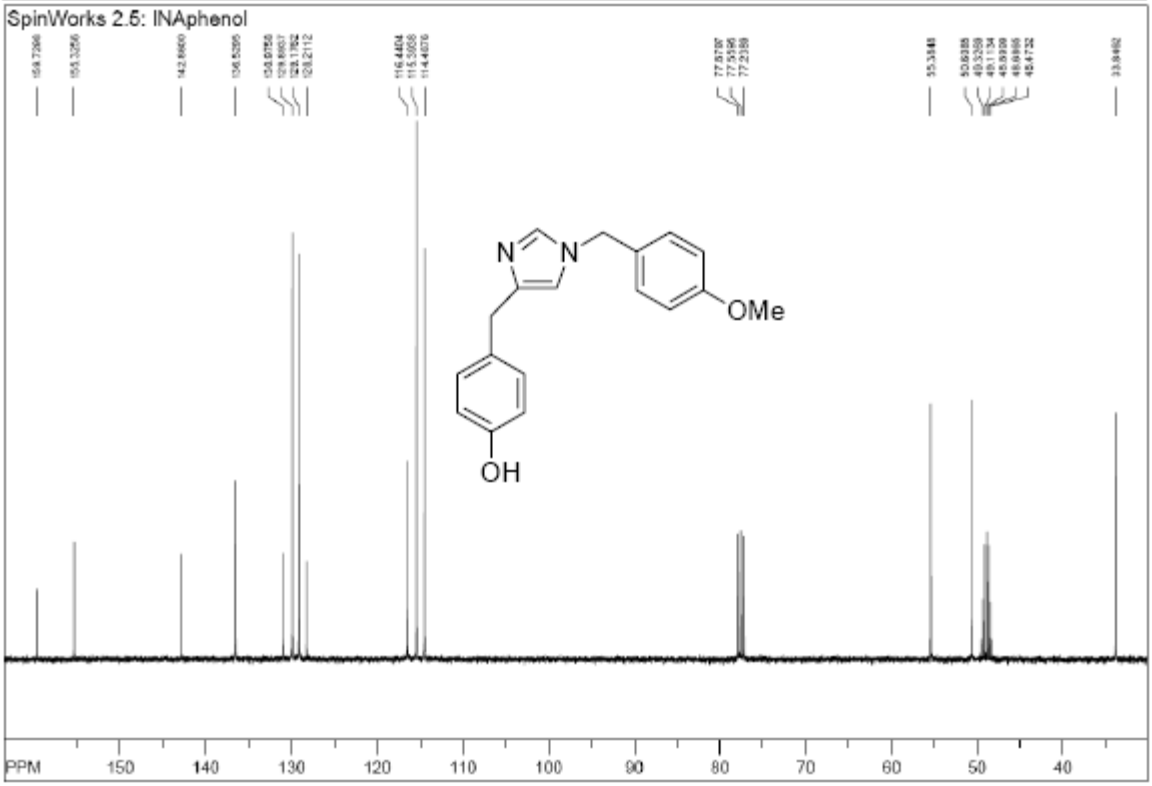

INA2TH
3390.41417
3206.6492
3010.00912
2922.62054
2845.45112
2164.92745
1899.8223
1731.11371
1701.98901
1609.81462
1591.25858
1511.72249
1465.98454
1439.92737
1413.96322
1346.89768
1306.26554
1289.95271
S
HN
N
O
OMe
OH
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000

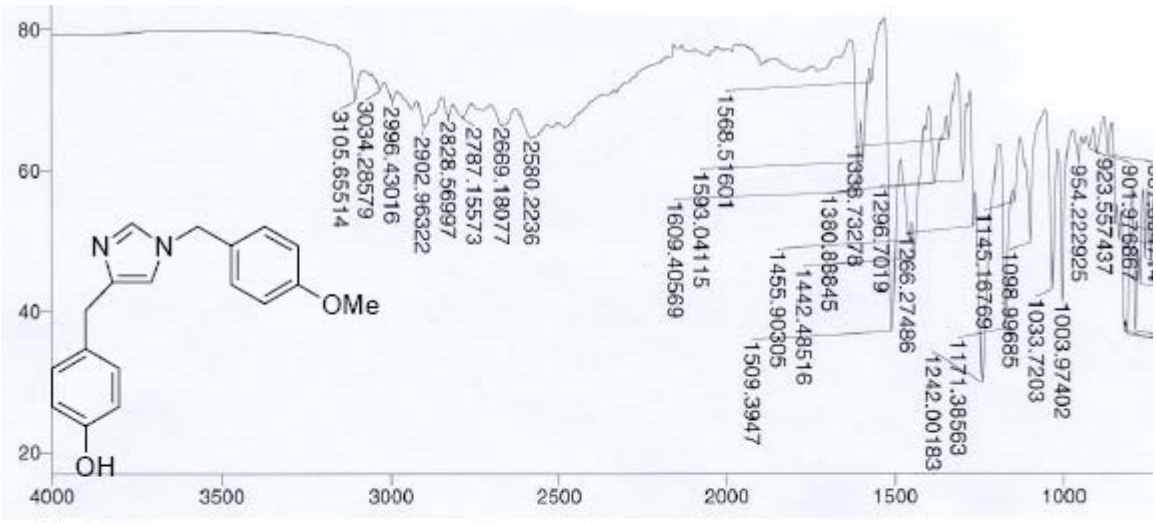

SpinWorks 2.5: INAI2T
11.8007
8.7568
7.2457
7.2264
6.9836
6.9647
6.8485
6.8268
6.7460
6.7288
6.1670
5.0619
3.7748
3.6020
S
HN
N
OMe
OH
2.064
2.169
2.107
2.143
x 386
6.8
1.056
1.042
2.064
2.169
2.107
2.143
0.999
2.097
3.098
2.156
PPM 11.6 11.2 10.8 10.4 10.0 9.6 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6

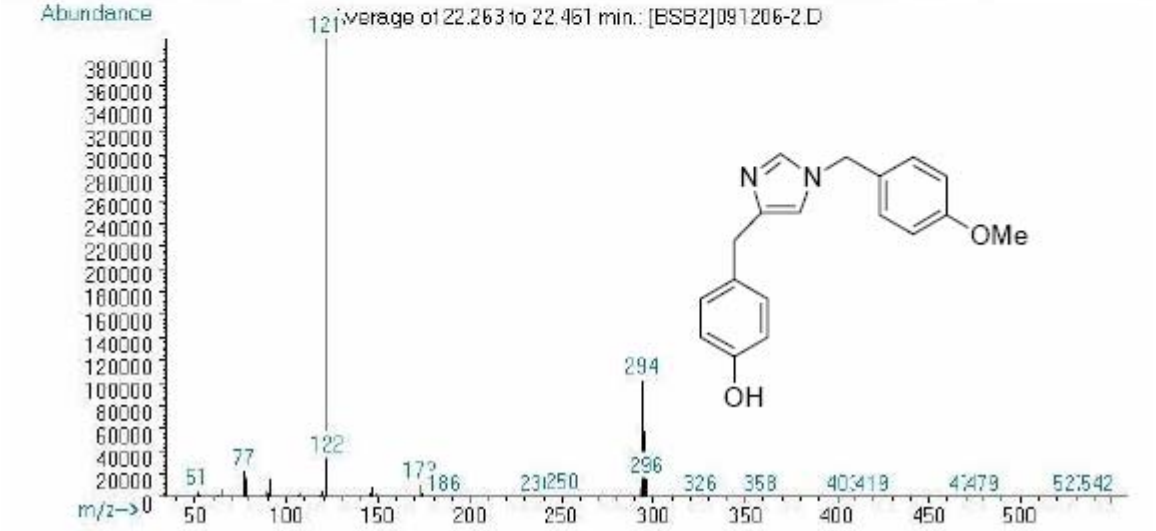

SpinWorks 2.5: INAI2T
S
HN
N
OMe
OH
PPM
150
140
130
120
110
100
90
80
70
60
50
40
30

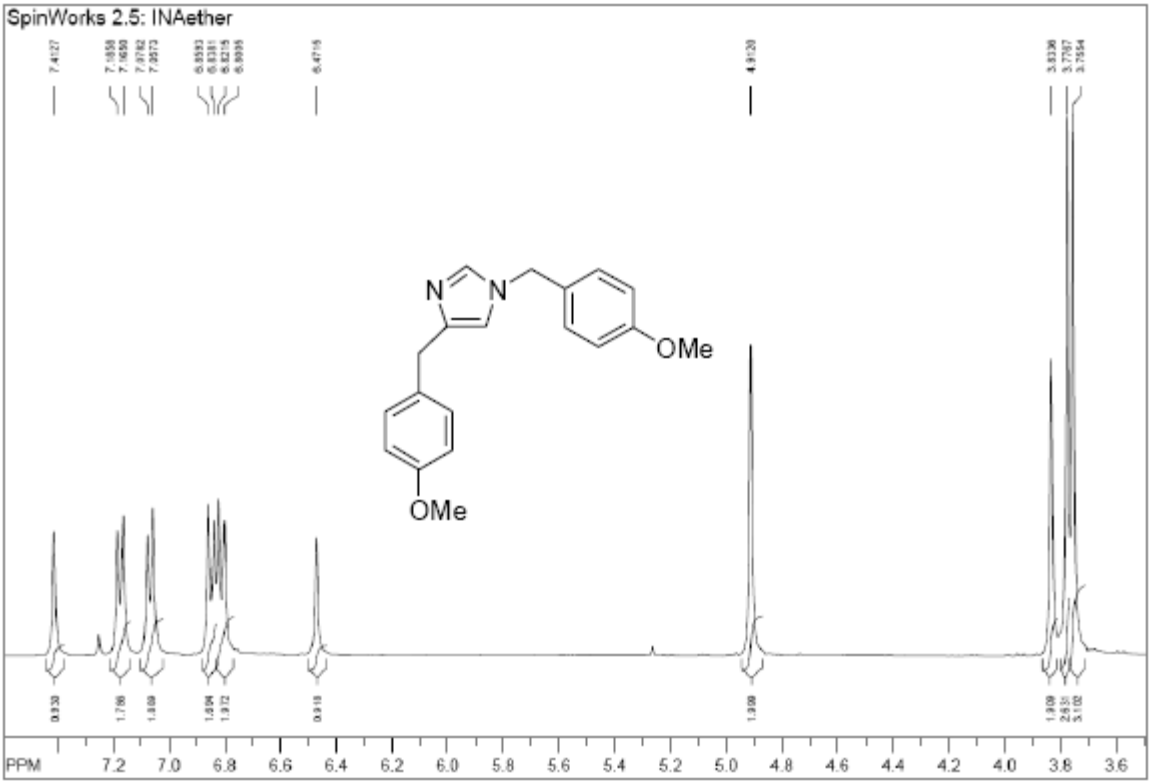

INAI2T
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
3127.58763
3068.96975
3013.28394
2964.11664
2923.74953
1702.18608
1628.34098
1591.81406
1585.42598
1610.48199
1380.09942
1352.55422
1317.7064
1303.71297
1423.7206
1441.96859
1468.7761
1511.55696
1249.5929
1210.66782
1171.65643
1104.65804
1024.50828
1010.41156
940.760269
S
HN
N
OMe
OH

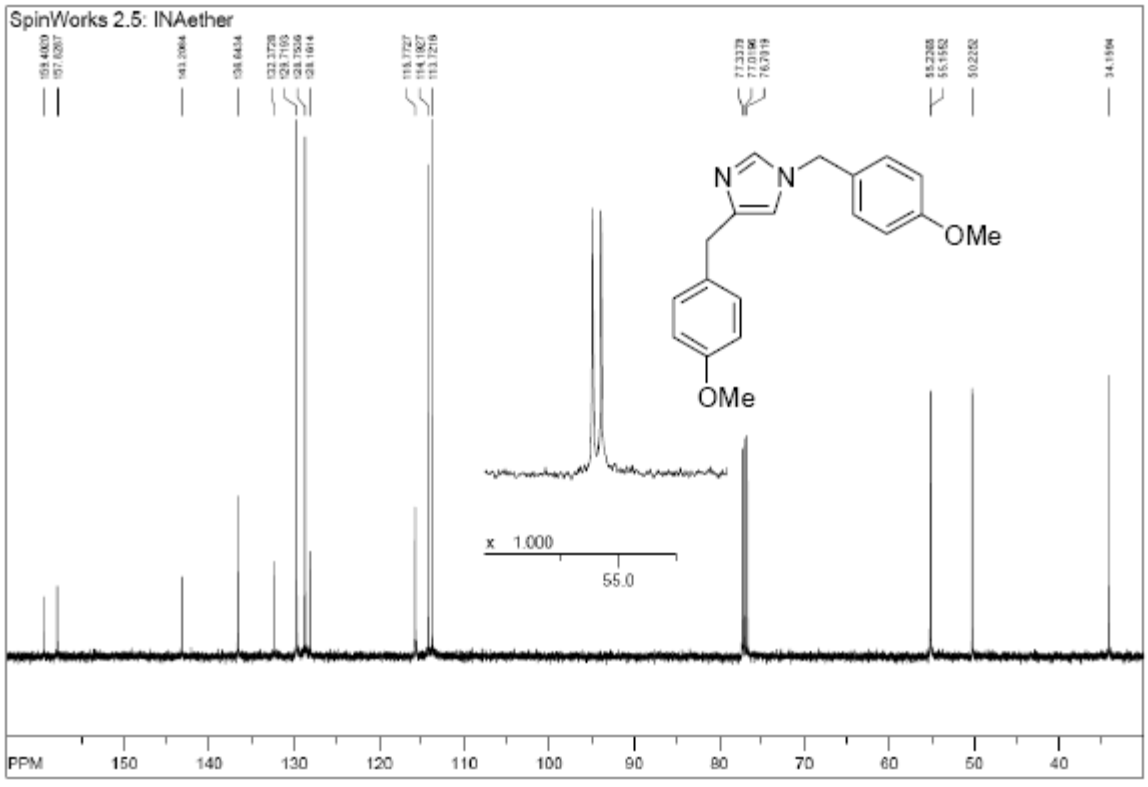

SpinWorks 2.5:
N
N
OMe
OH
PPM 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8

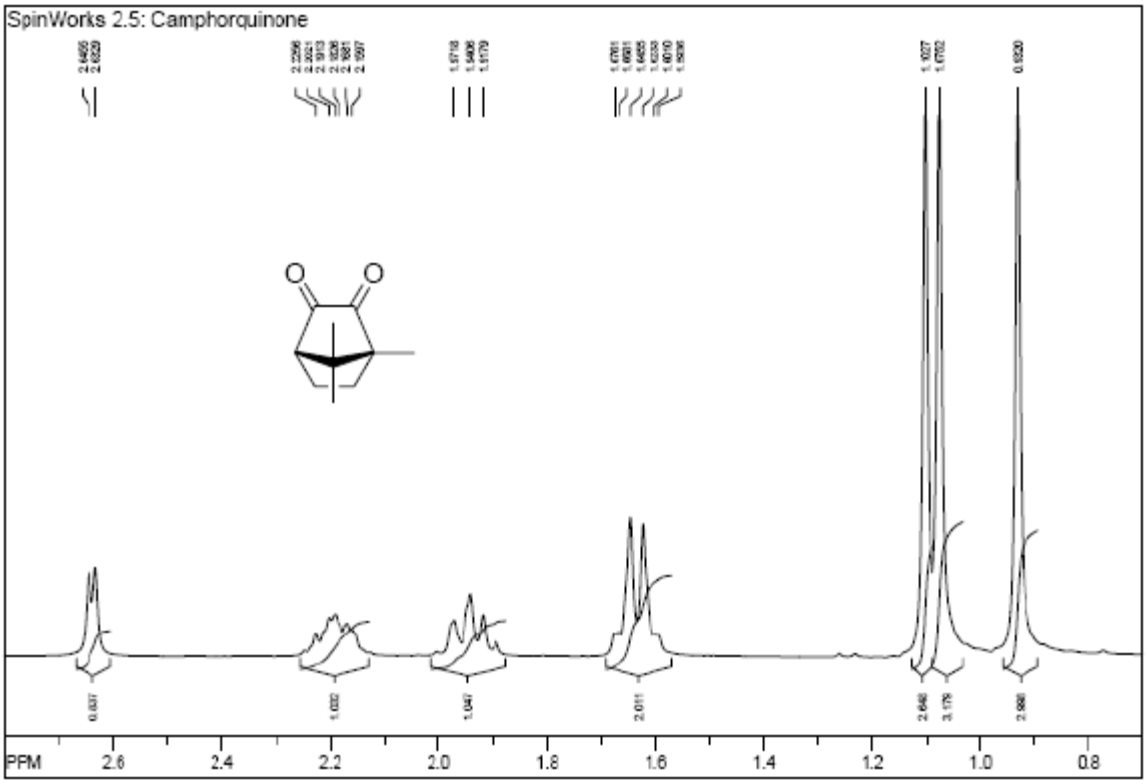

SpinWorks 2.5: INAphenol
N
N
OMe
OH
PPM 150 140 130 120 110 100 90 80 70 60 50 40

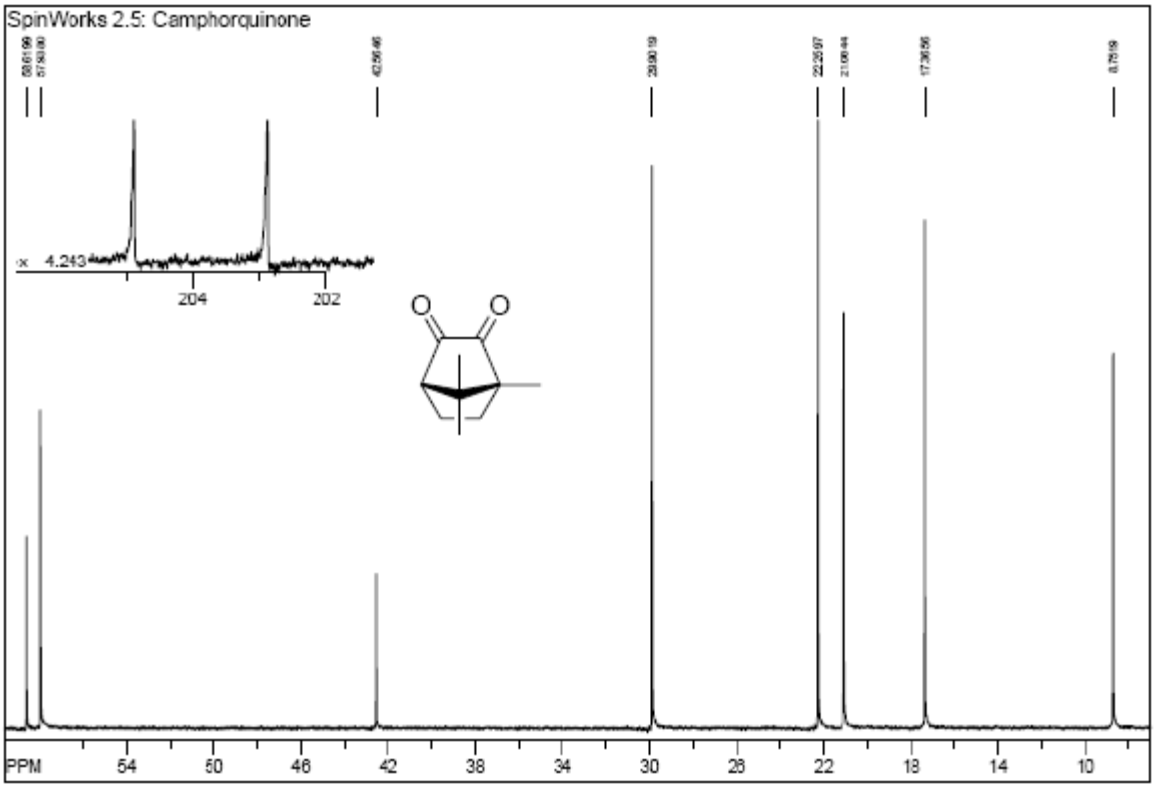

80
60
40
20
4000
3500
3000
2500
2000
1500
1000
3105.65514
3034.28579
2996.43016
2902.96322
2828.56997
2787.15573
2669.18077
2580.2236
1568.51601
1593.04115
1609.40569
1338.73278
1296.7019
1380.88845
1455.90305
1442.48516
1509.3947
1266.27486
1242.00183
1145.16769
1171.38563
1098.99685
1033.7203
1003.97402
954.222925
923.557437
901.976867
N
N
OMe
OH

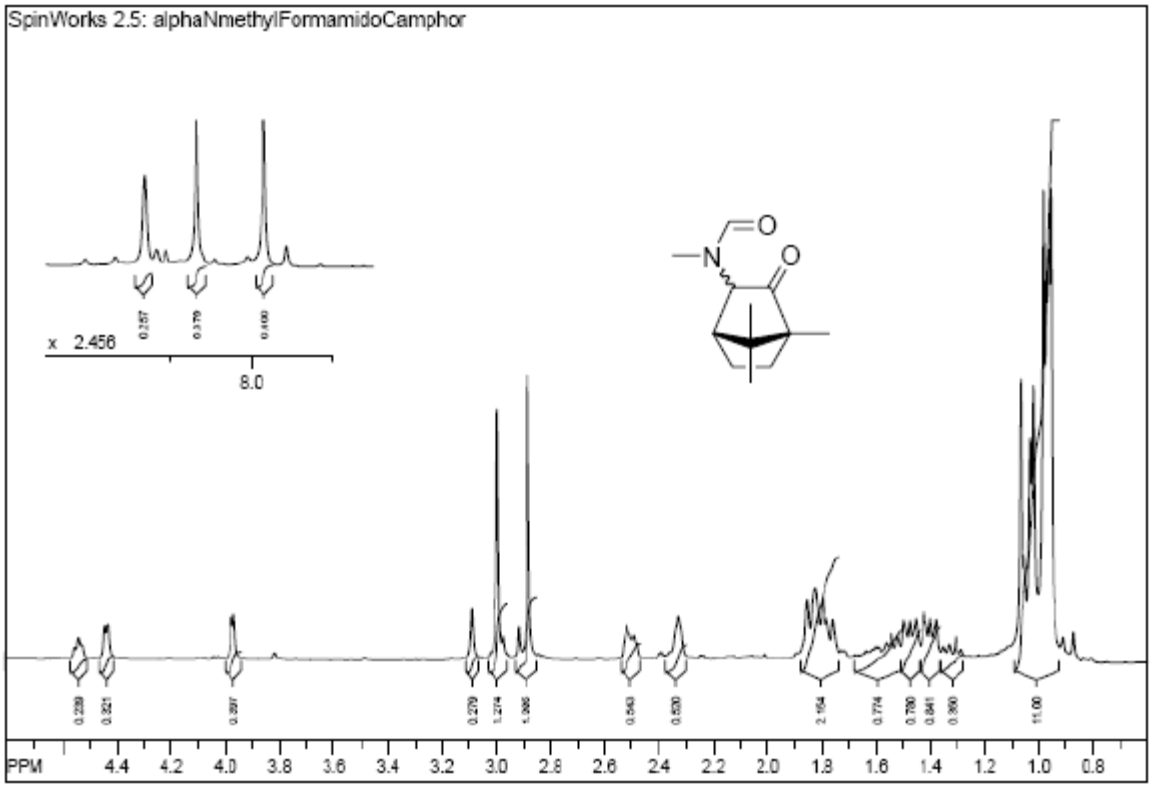

Abundance
Average of 22.263 to 22.461 min.: [BSB2]091206-2.D
380000
360000
340000
320000
300000
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
m/z-->0
50
100
150
200
250
300
350
400
450
500
121
294
122
77
51
173
186
231
250
296
326
358
403
419
479
525
542
N
N
OMe
OH

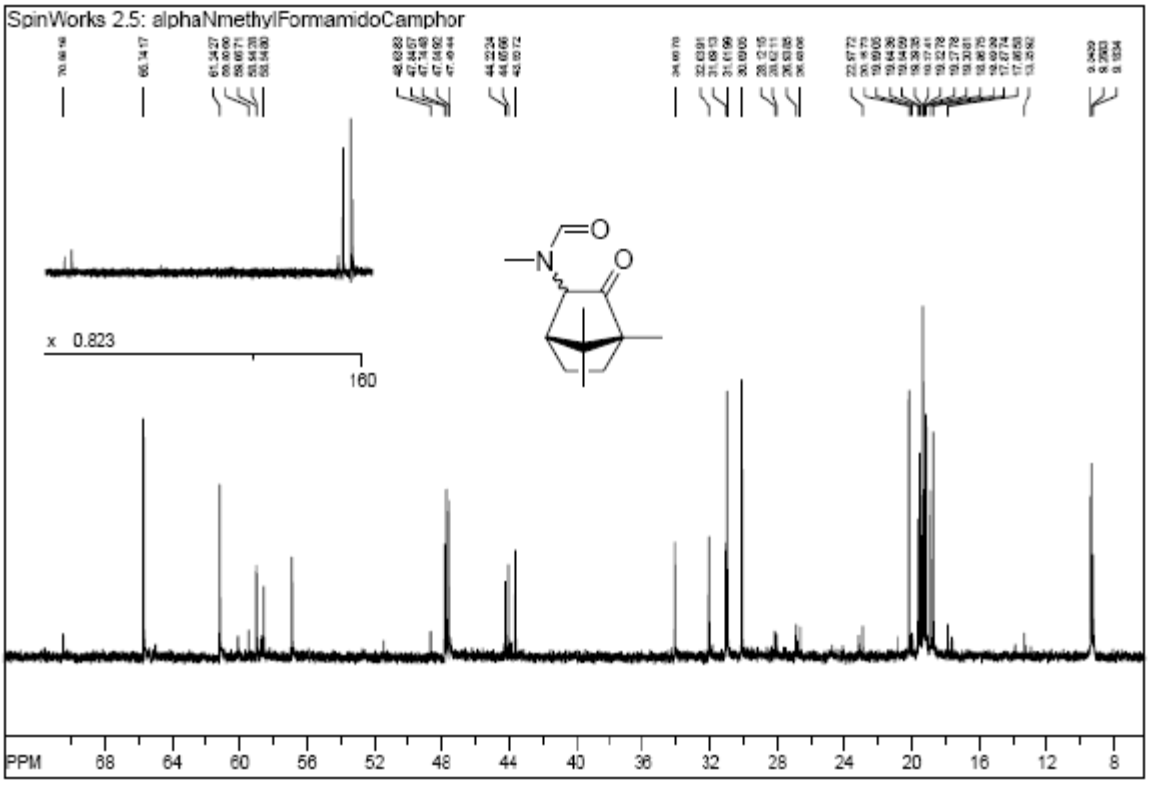

SpinWorks 2.5: INAether
N
N
OMe
OMe
PPM
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6

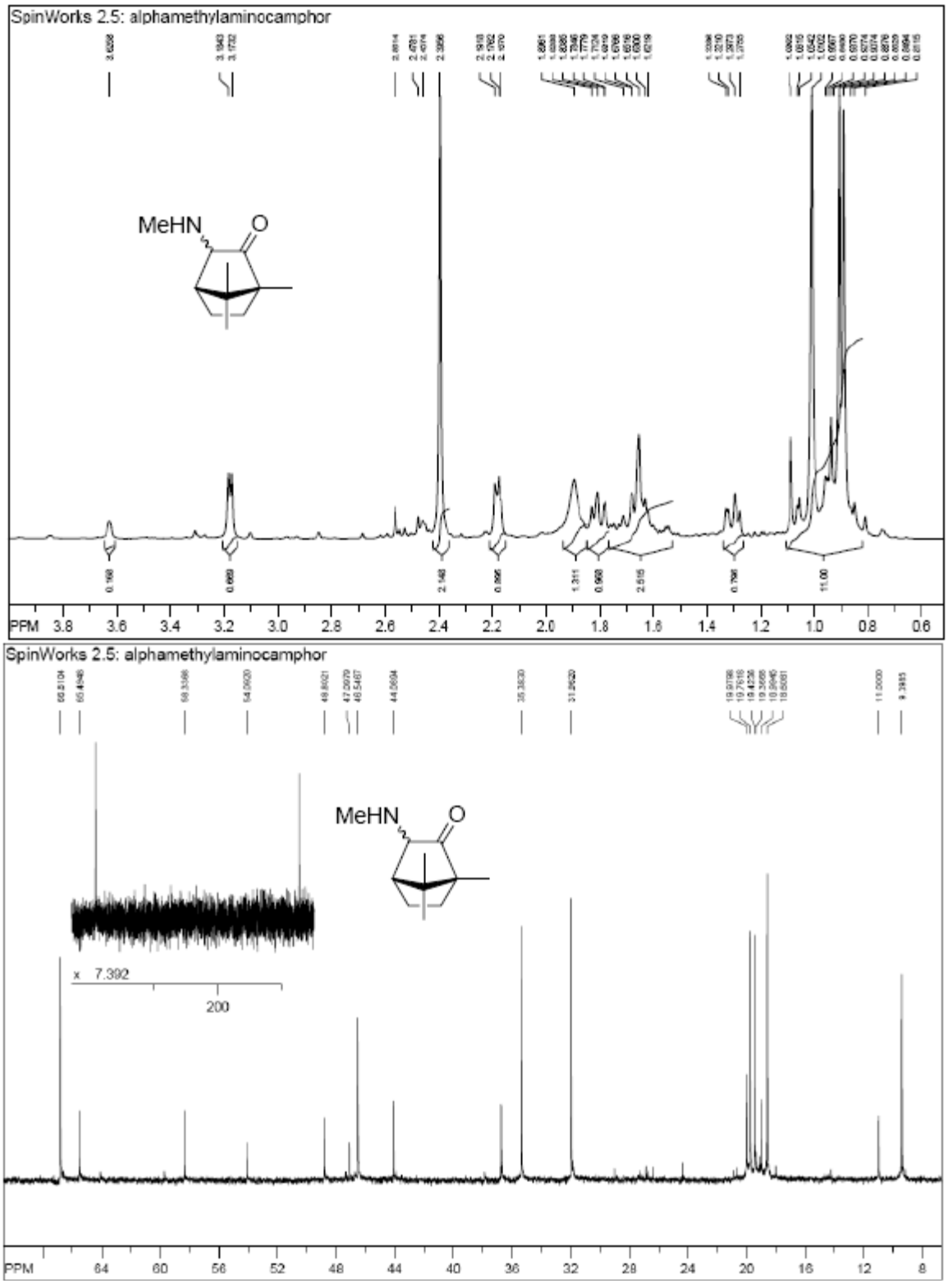

SpinWorks 2.5: INAether
N
N
OMe
OMe
x 1.000
55.0
PPM
150
140
130
120
110
100
90
80
70
60
50
40

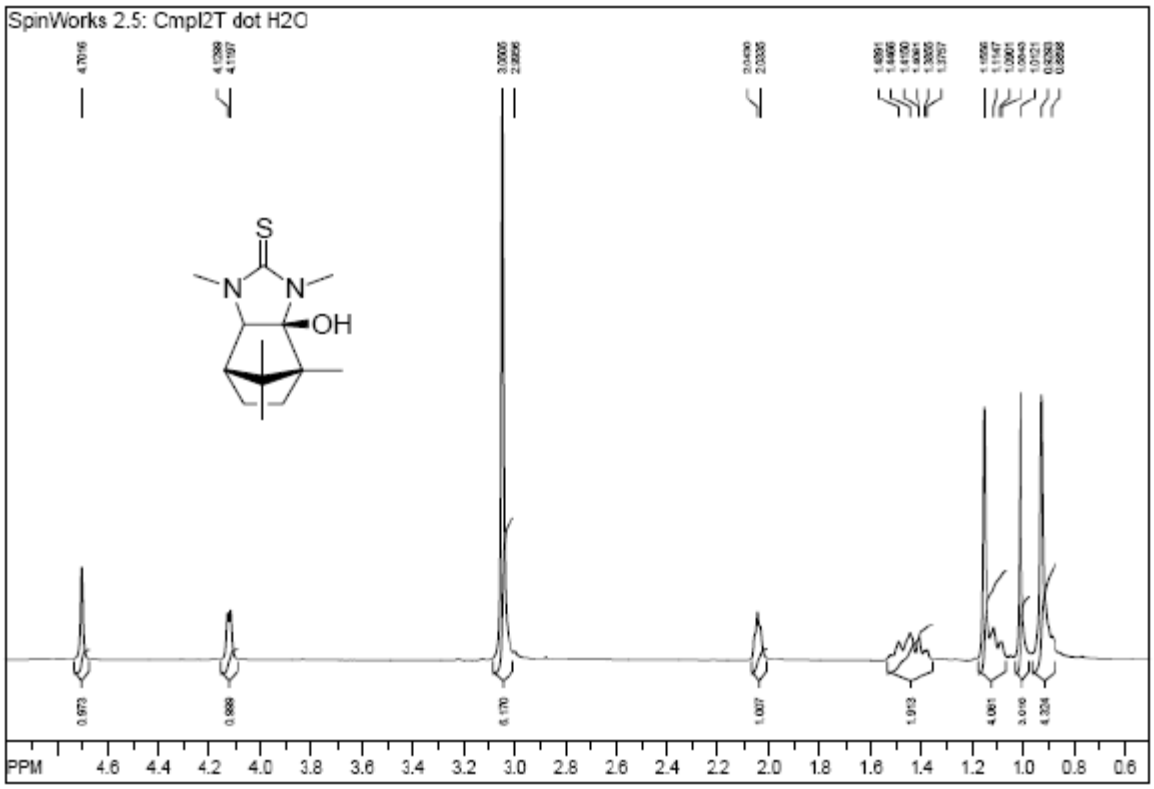

SpinWorks 2.5: Camphorquinone
PPM
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8

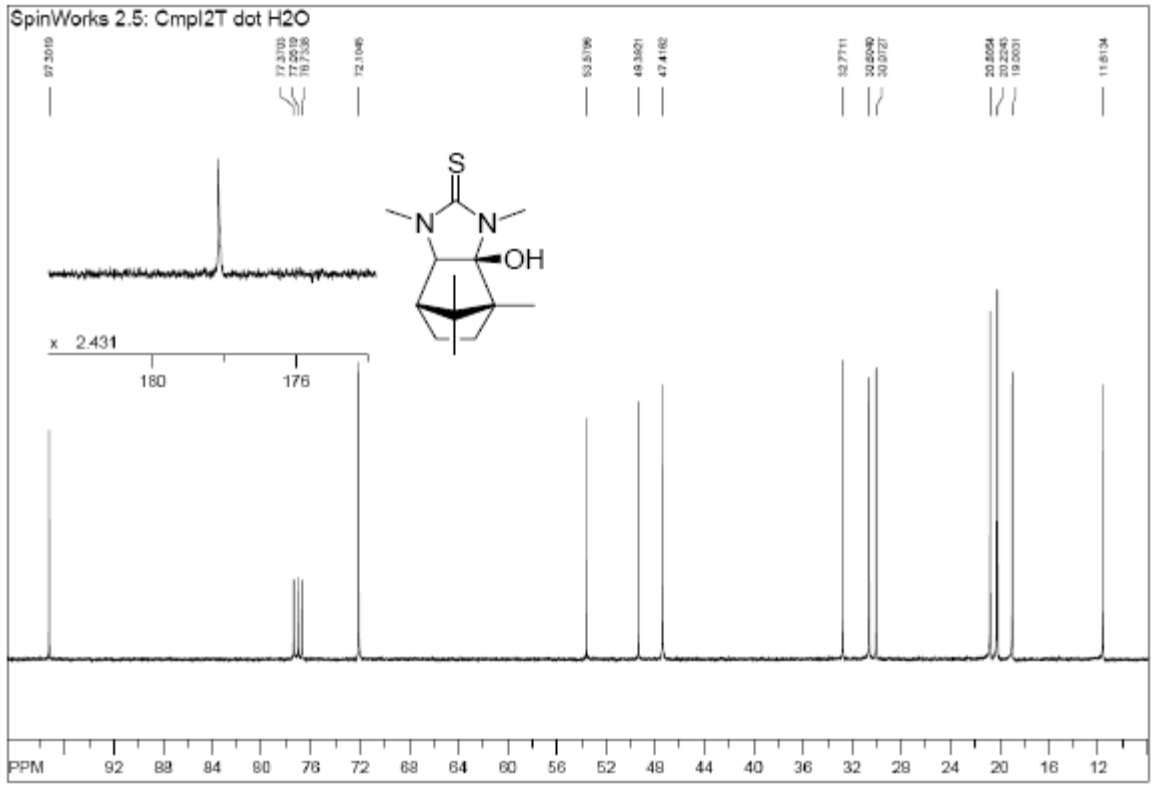

SpinWorks 2.5: Camphorquinone
4.243
204
202
PPM
54
50
46
42
38
34
30
26
22
18
14
10

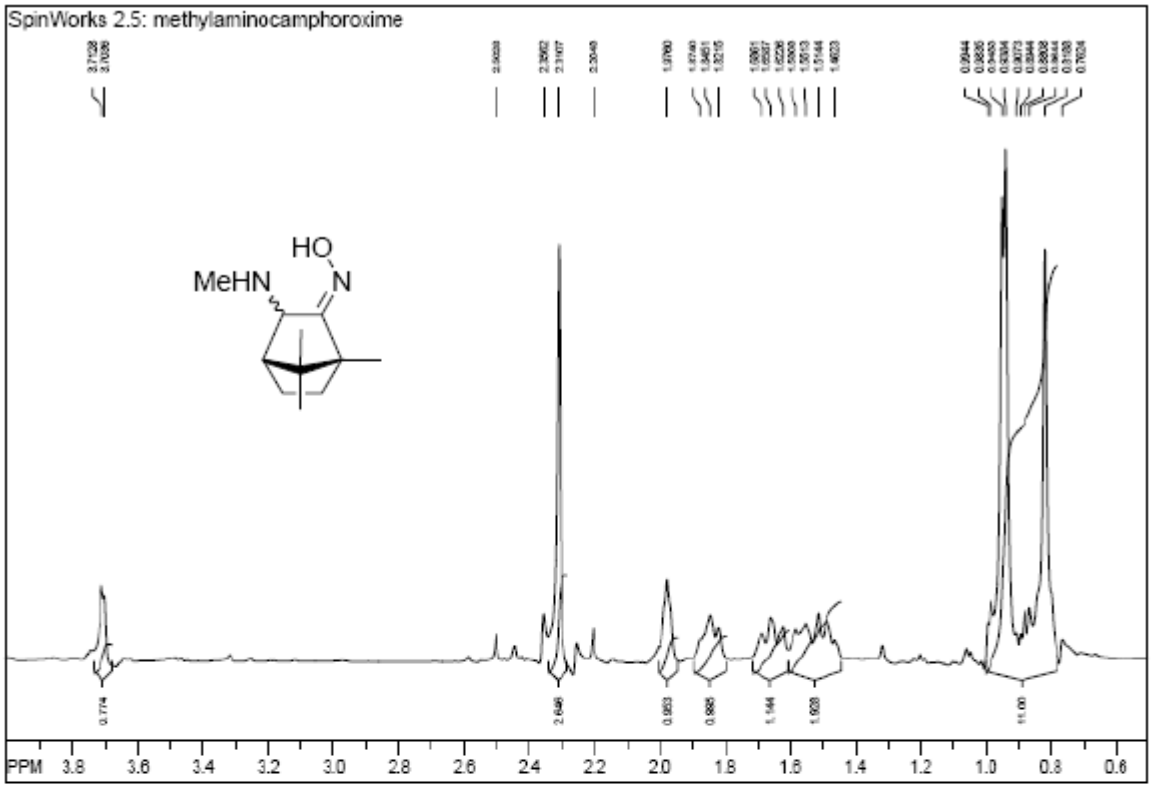

SpinWorks 2.5: alphaNmethylFormamidoCamphor
x 2.456
8.0
PPM
4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8

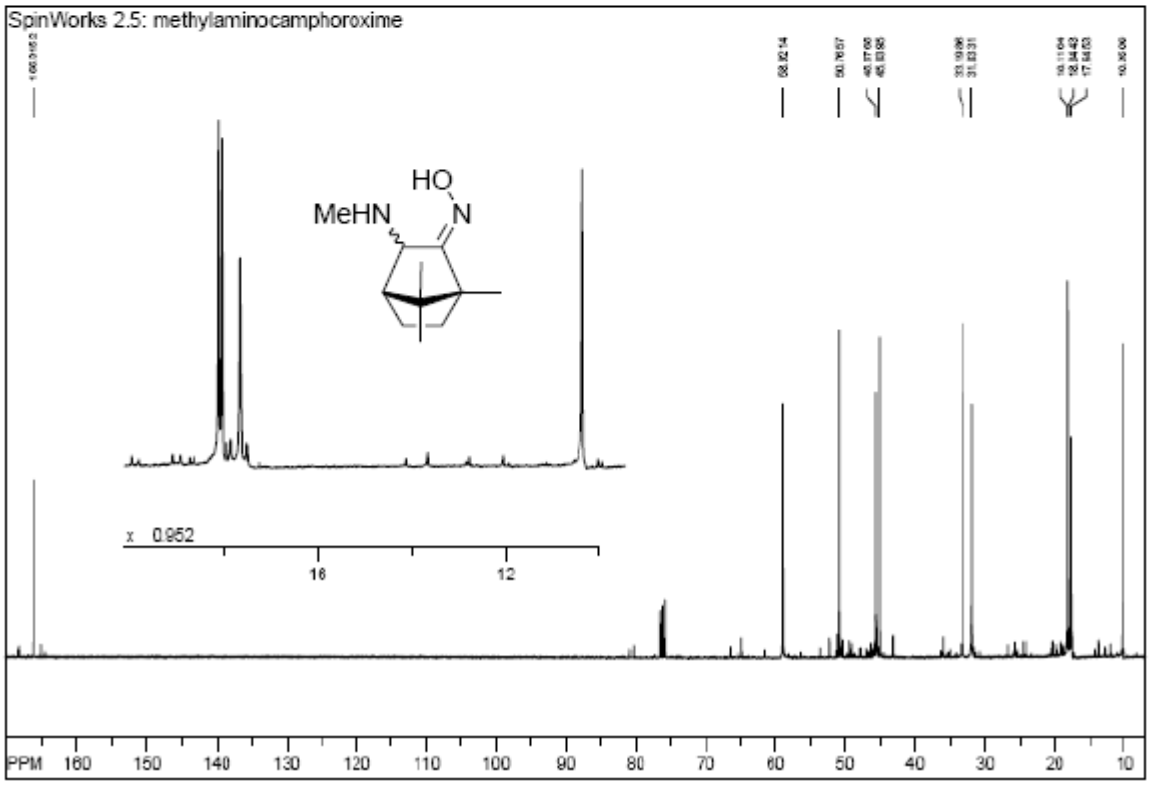

SpinWorks 2.5: alphaNmethylFormamidoCamphor
x 0.823
160
PPM
68 64 60 56 52 48 44 40 36 32 28 24 20 16 12 8

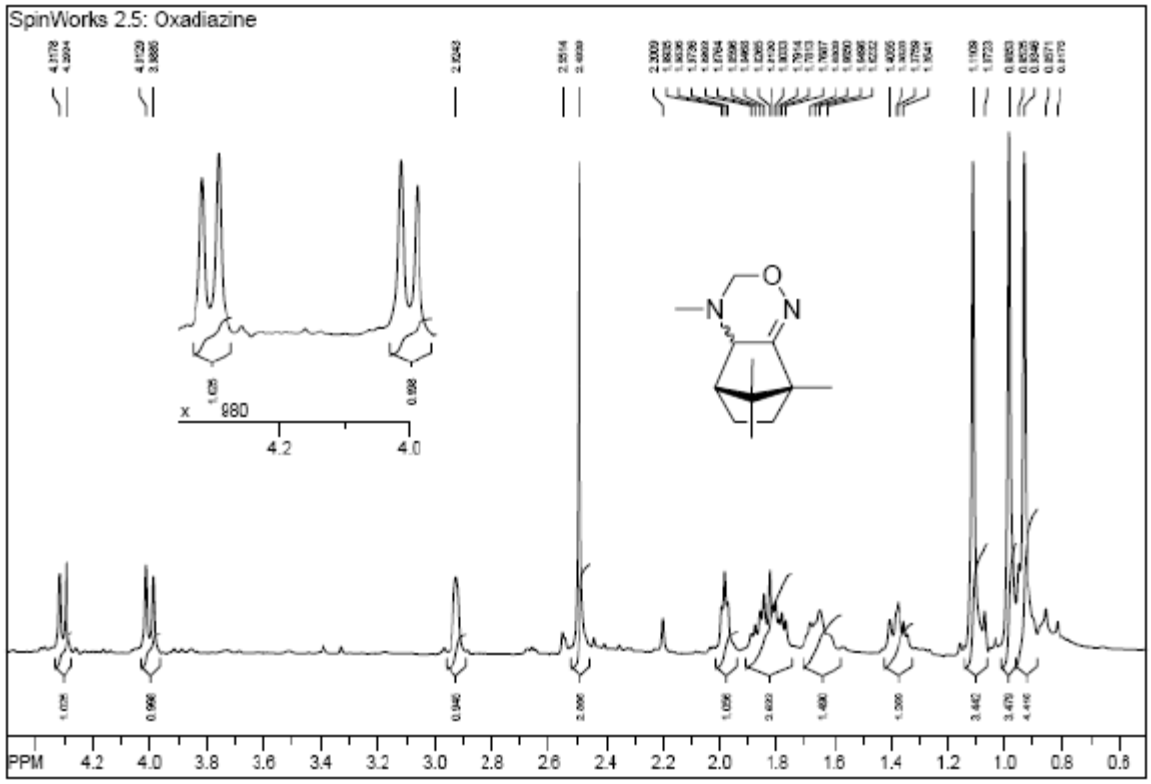

SpinWorks 2.5: alphamethylaminocamphor
MeHN
O
PPM 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
SpinWorks 2.5: alphamethylaminocamphor
MeHN
O
x 7.392
200
PPM 64 60 56 52 48 44 40 36 32 28 24 20 16 12 8

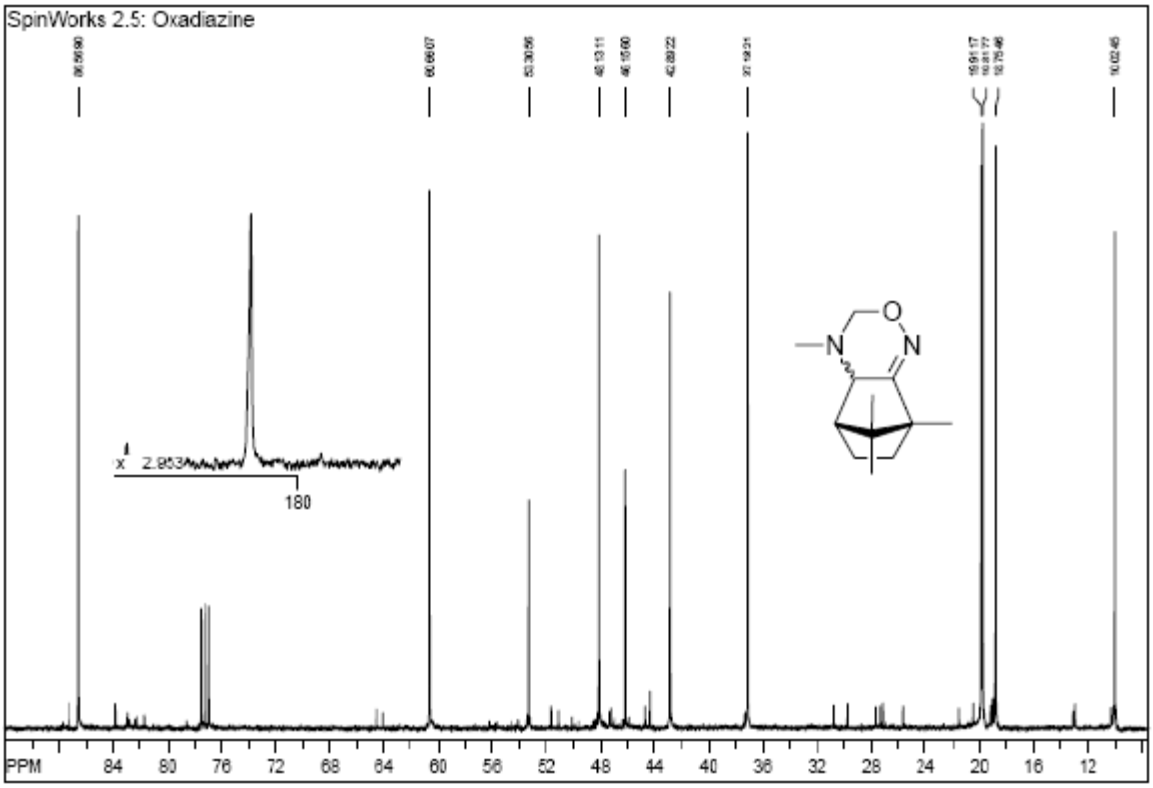

SpinWorks 2.5: CmpI2T dot H2O
S
N
N
OH
PPM
4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6

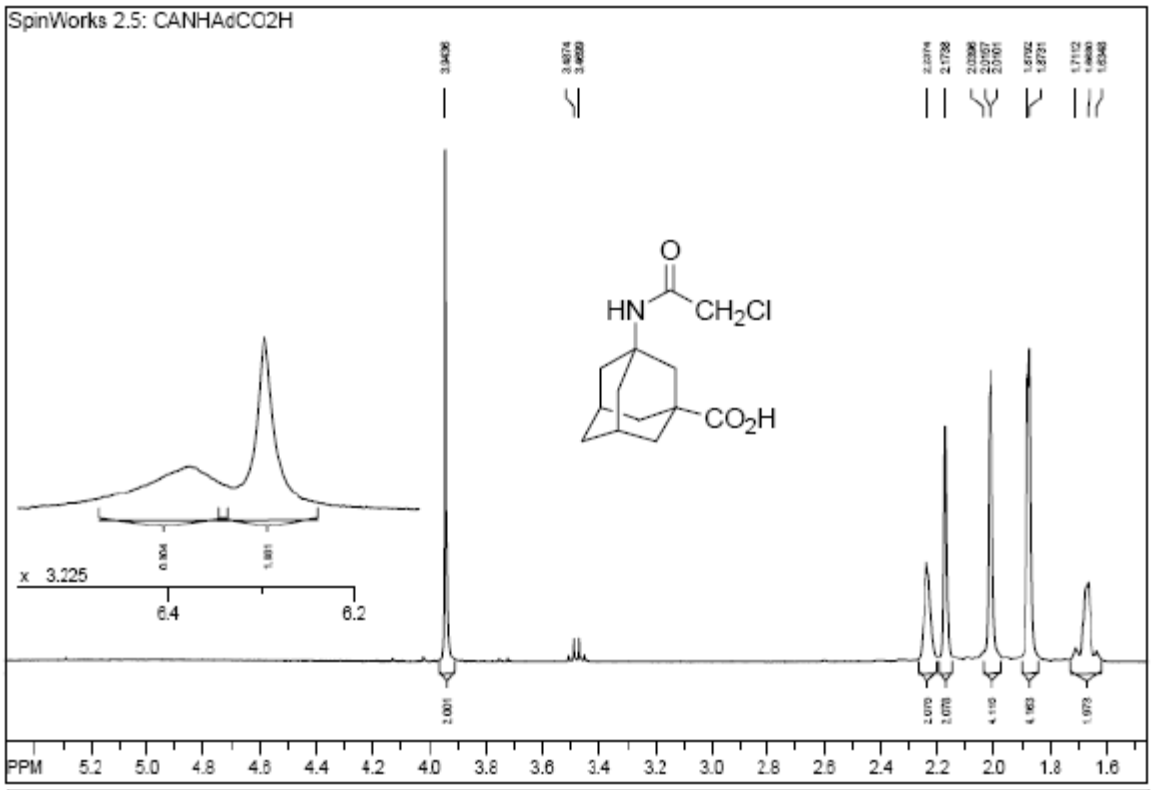

SpinWorks 2.5: CmpI2T dot H2O
S
N
N
OH
x 2.431
180
176
PPM
92 88 84 80 76 72 68 64 60 56 52 48 44 40 36 32 28 24 20 16 12

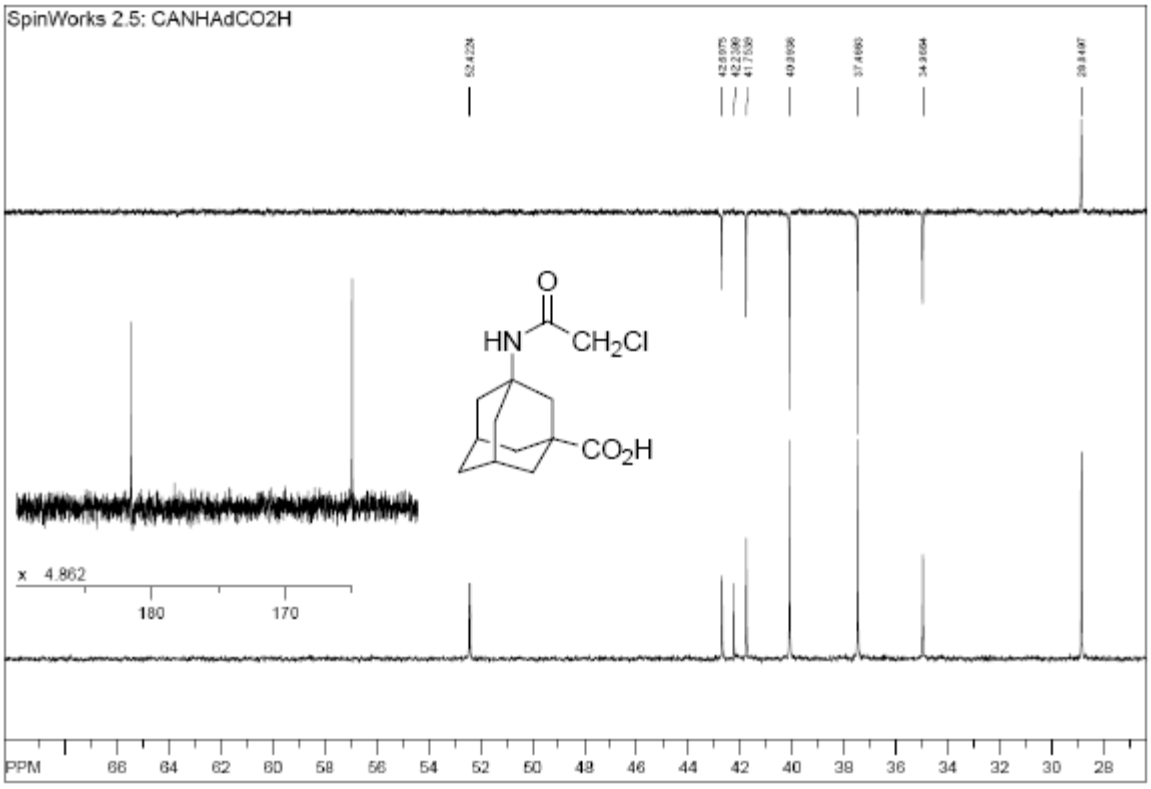

SpinWorks 2.5: methylaminocamphoroxime
HO
N
MeHN
PPM 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6

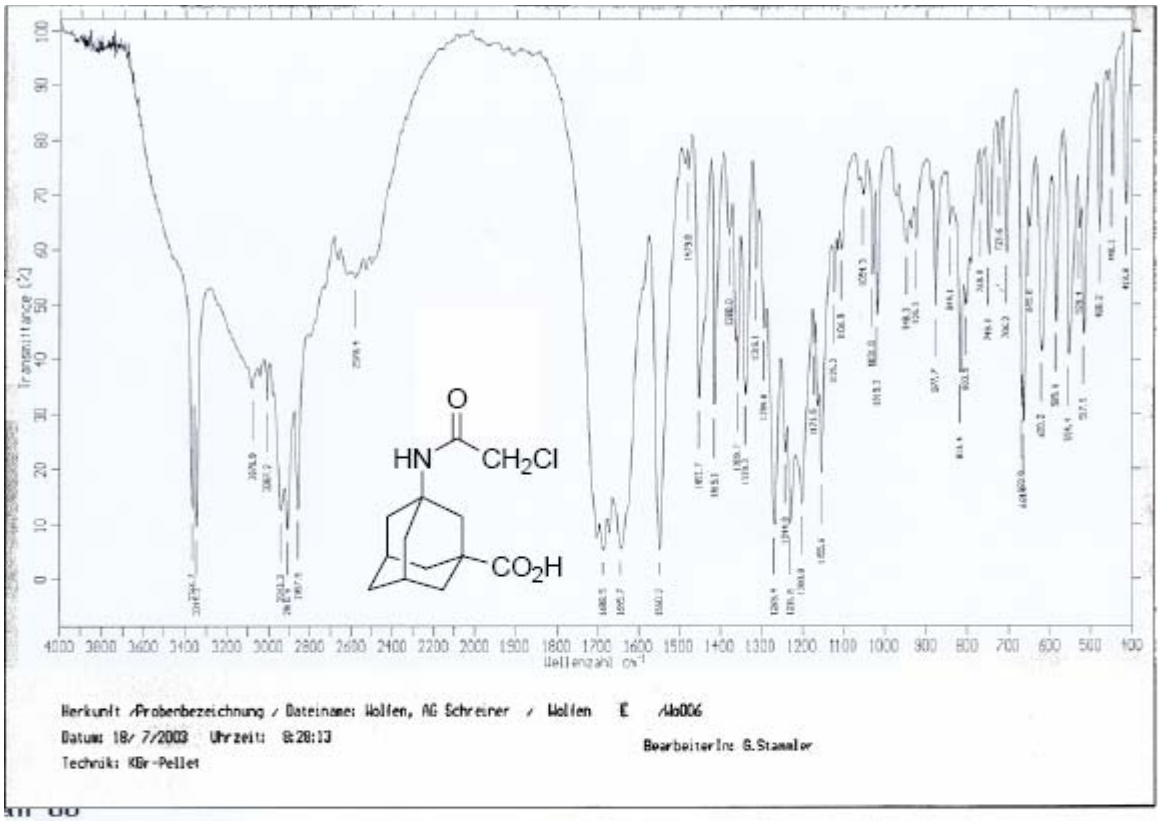

SpinWorks 2.5: methylaminocamphoroxime
HO
N
MeHN
x 0.952
16
12
PPM 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

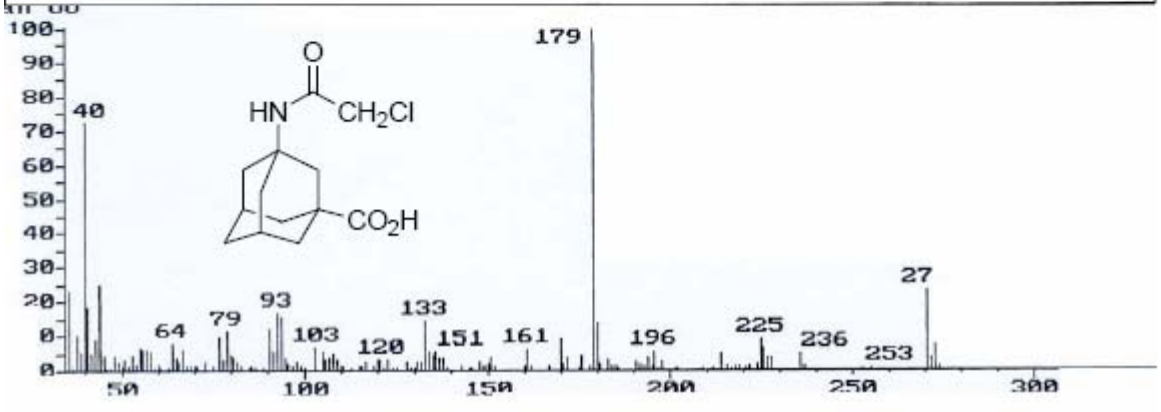

SpinWorks 2.5: Oxadiazine
PPM

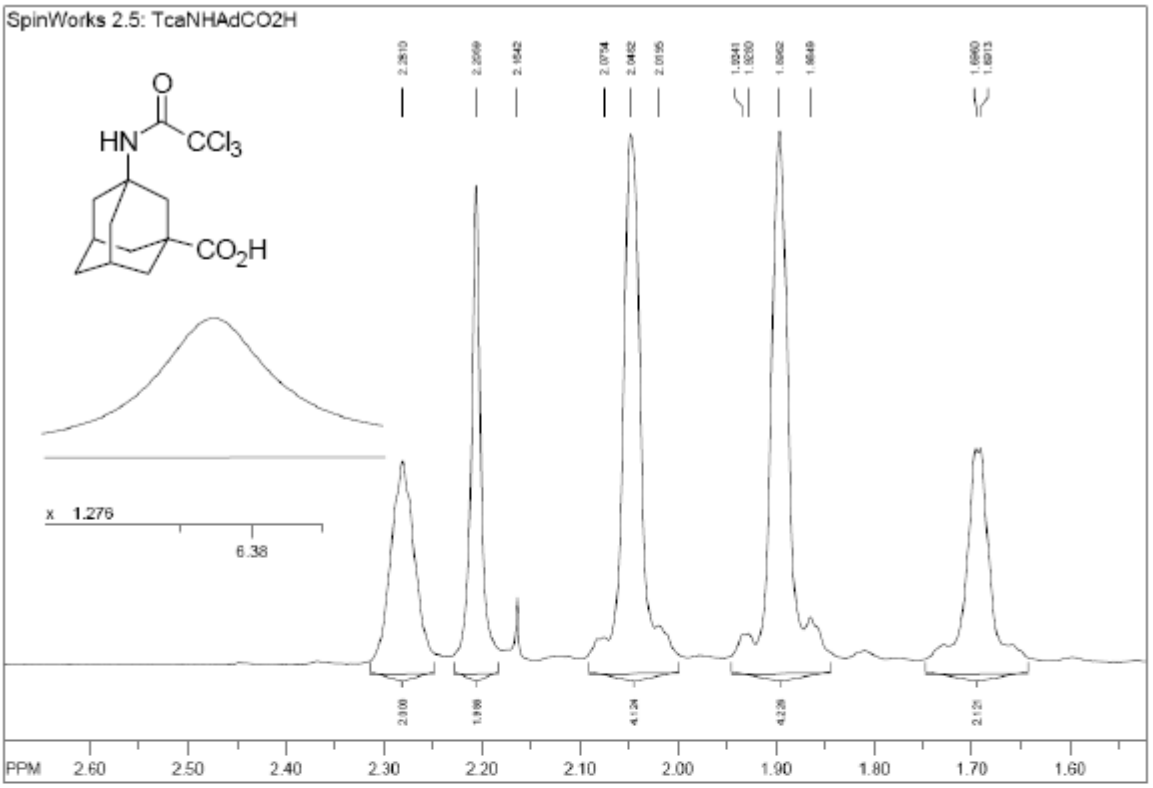

SpinWorks 2.5: Oxadiazine
PPM

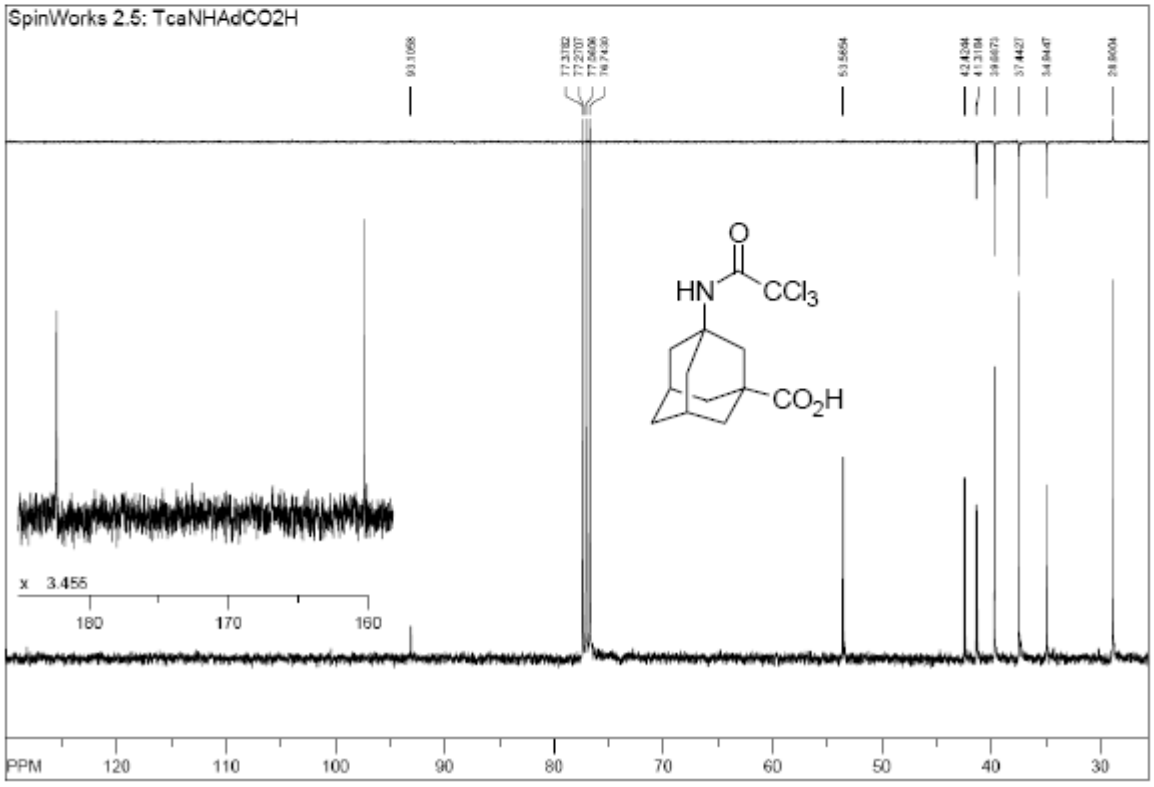

SpinWorks 2.5: CANHAdCO2H
O
HN
CH2Cl
CO2H
x 3.225
6.4
6.2
PPM

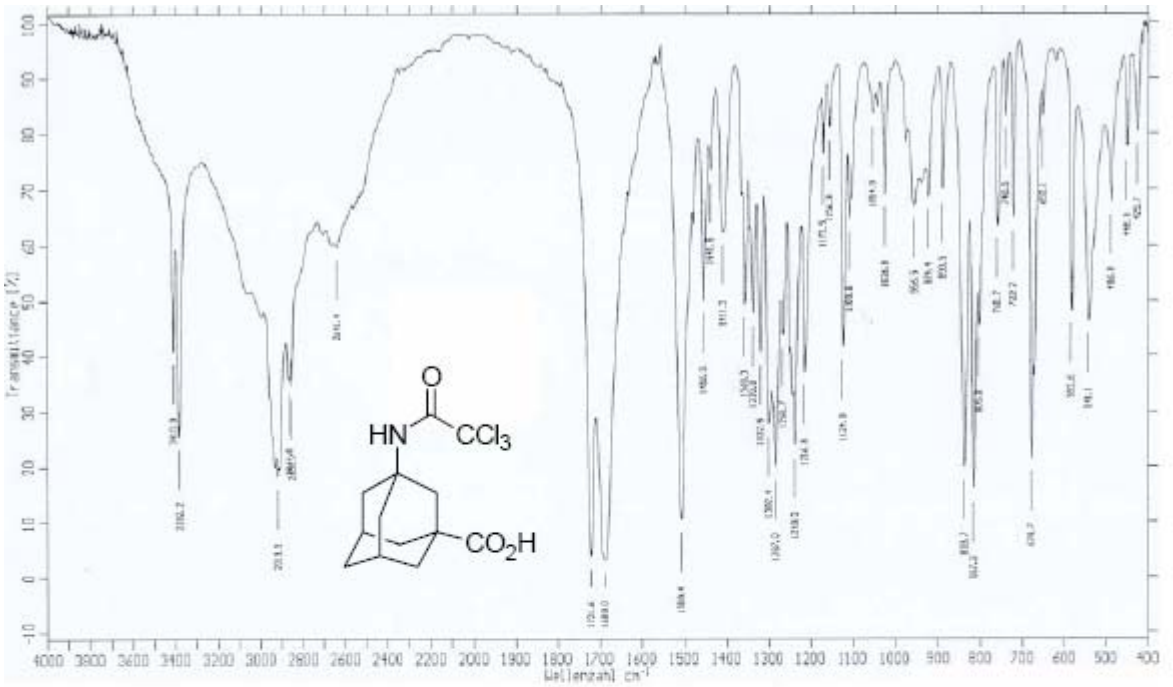

SpinWorks 2.5: CANHAdCO2H
O
HN
CH2Cl
CO2H
x 4.862
180
170
PPM


Transmittance (%)
Wellenzahl cm-1
HN
O
CH2Cl
CO2H
Herkunft /Probenbezeichnung / Dateiname: Wolfen, AG Schreiner / Wolfen E /Wo006
Datum: 18/ 7/2003 Uhrzeit: 8:28:13
Bearbeiter in: G.Stammler
Technik: KBr-Pellet

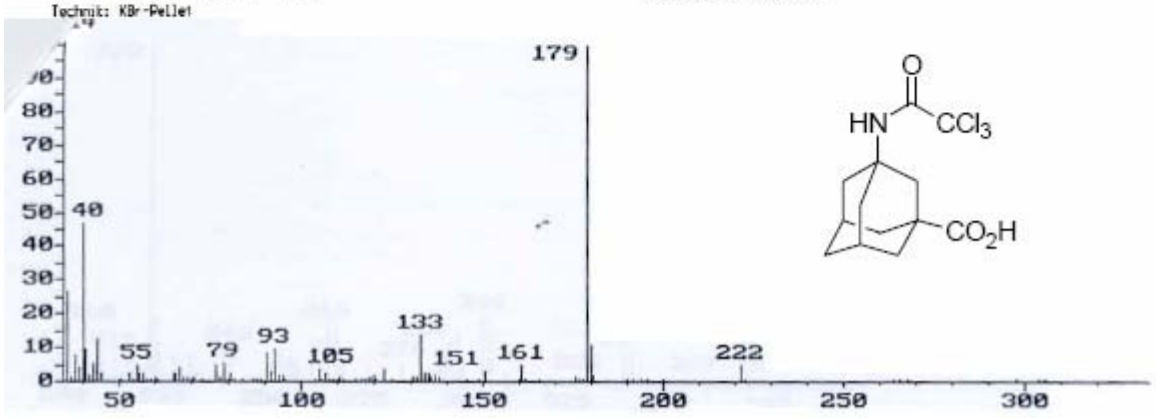

HN
O
CH2Cl
CO2H
179
40
27
93
133
64
79
103
120
151
161
196
225
236
253

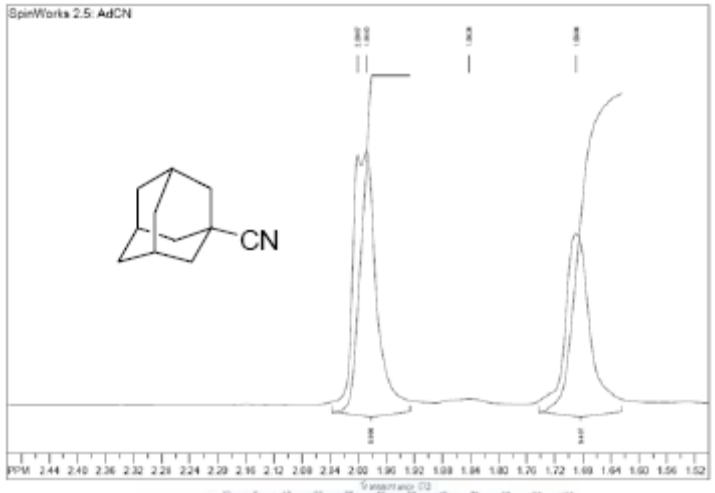

SpinWorks 2.5: TcaNHAdCO2H
HN
O
CCl3
CO2H
x 1.276
6.38
PPM 2.60 2.50 2.40 2.30 2.20 2.10 2.00 1.90 1.80 1.70 1.60

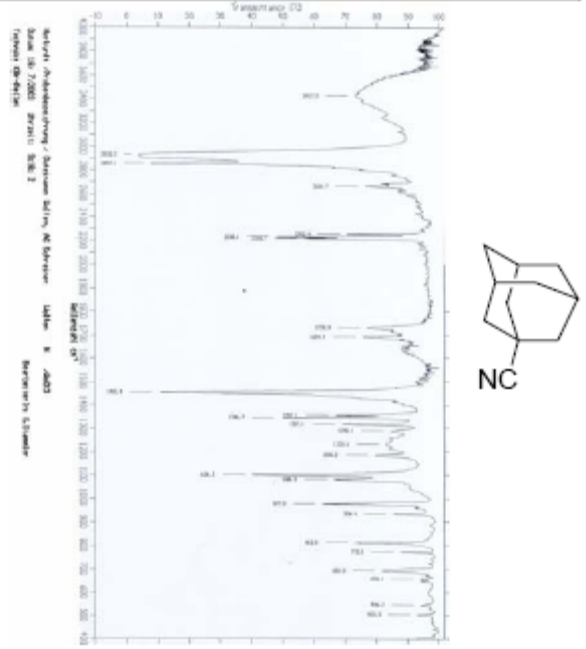

SpinWorks 2.5: TcaNHAdCO2H
HN
O
CCl3
CO2H
x 3.455
180 170 160
PPM 120 110 100 90 80 70 60 50 40 30

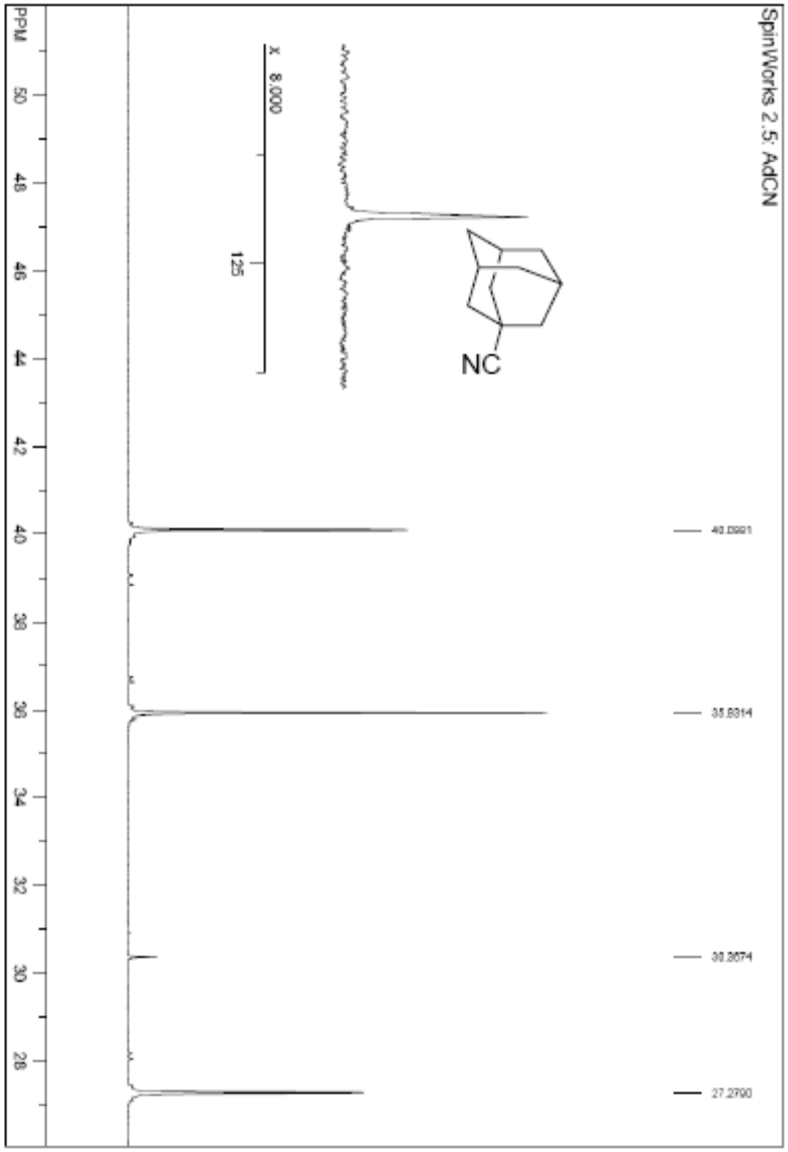


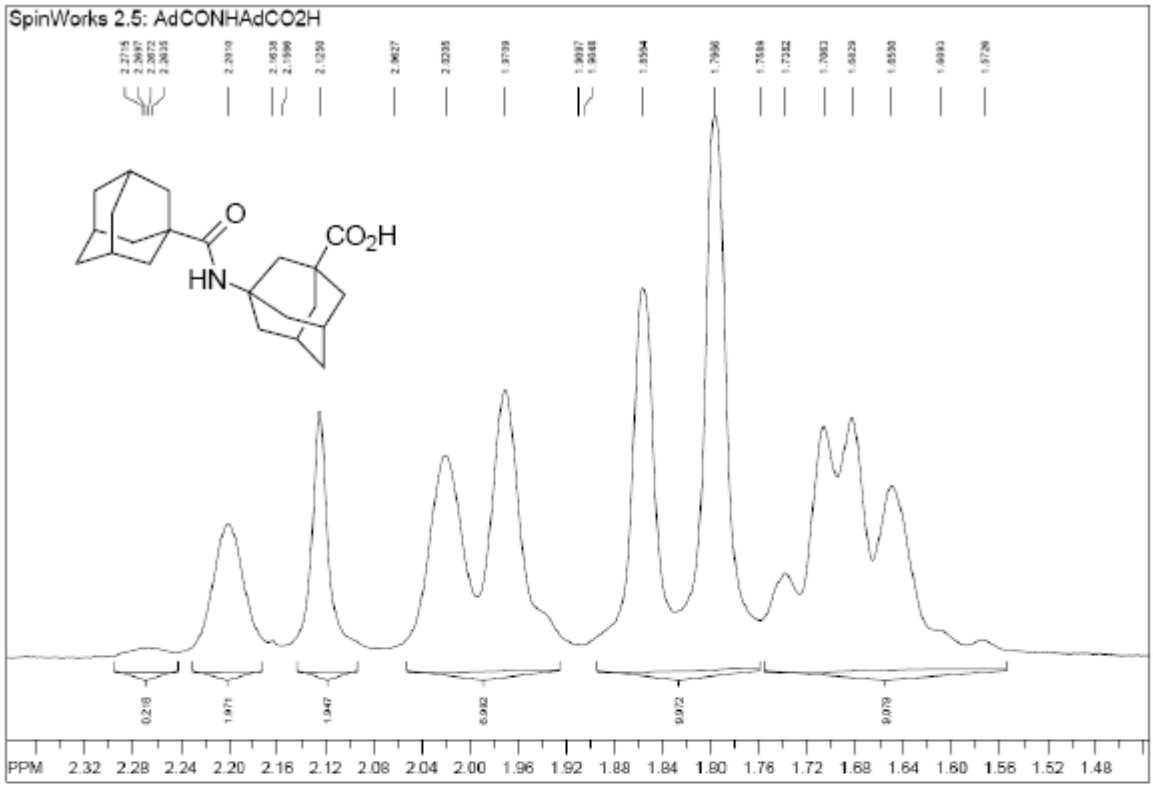
Herkunft /Probenbezeichnung Dateiname: Wolfen, AG Schreiner Wolfen IC /Wo004
Datum: 18/ 7/2003 Uhrzeit: 8:14:34
Technik: KBr-Pellet
Bearbeiter(in: G.Stammler

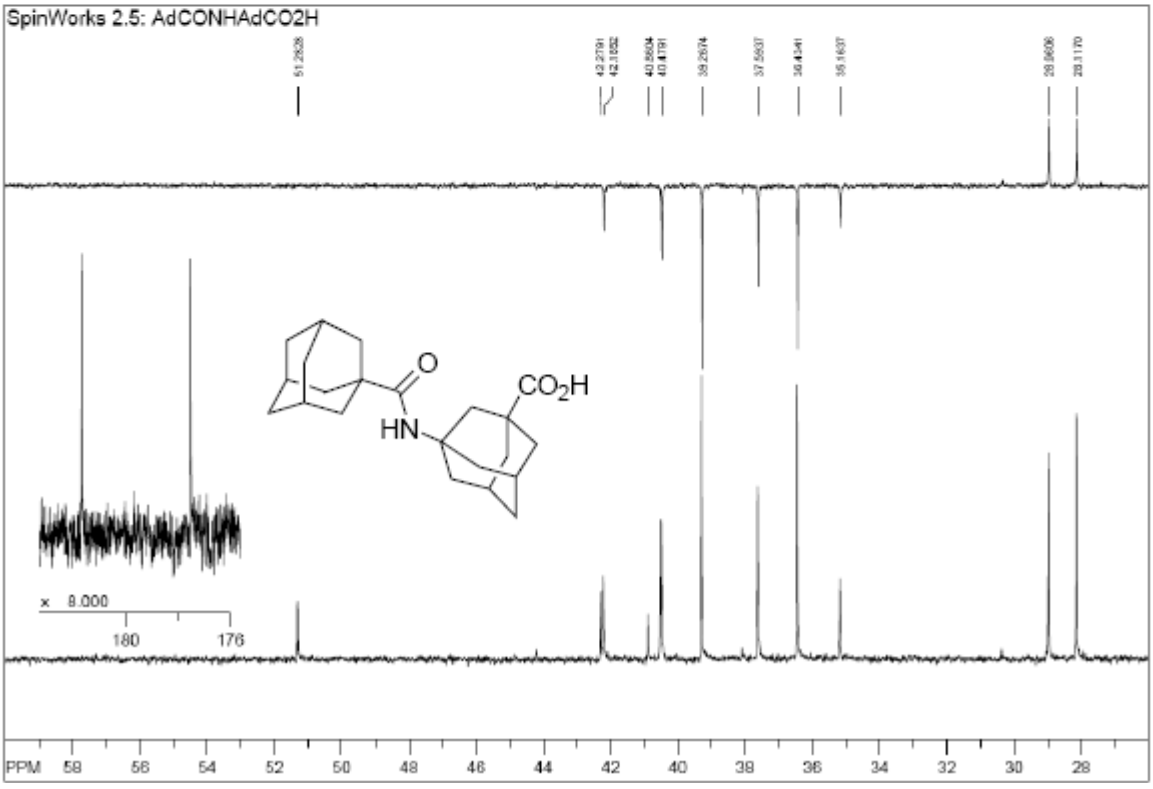


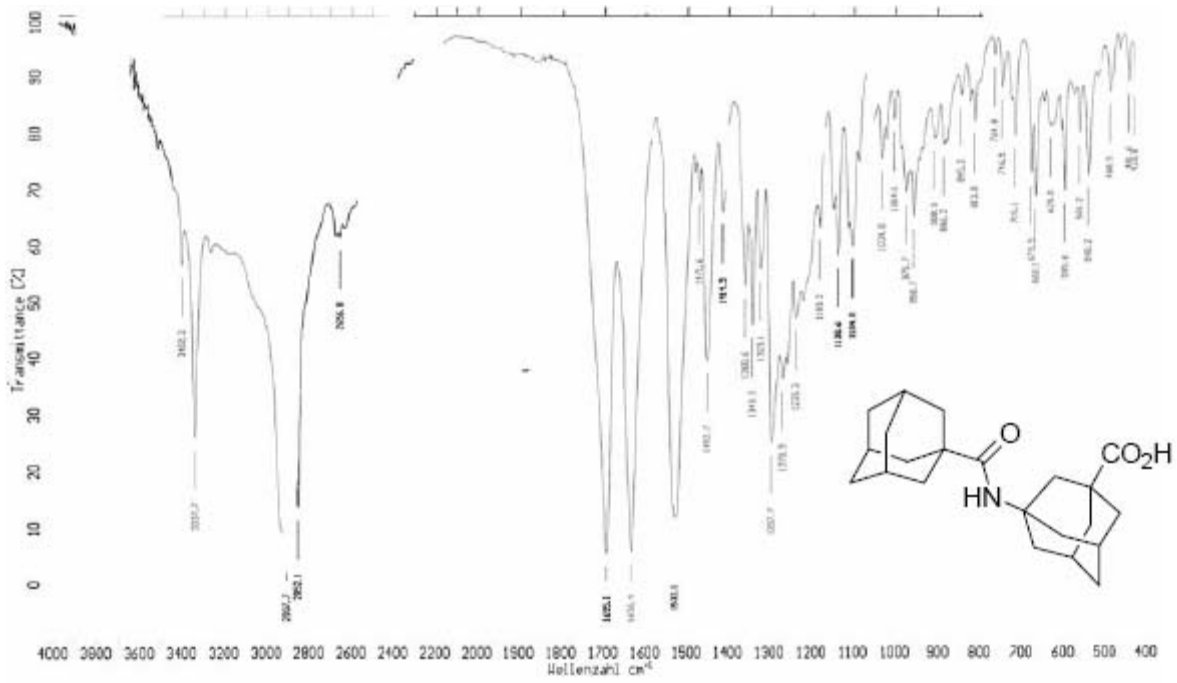

SpinWorks 2.5: AdCN
CN

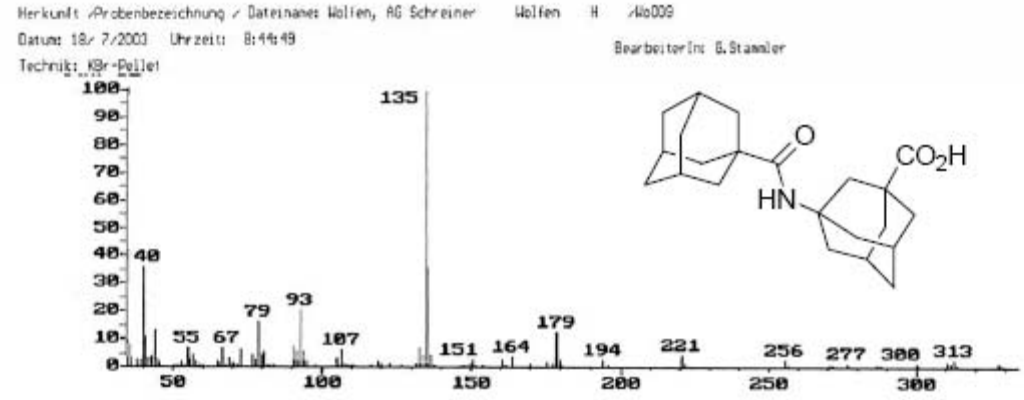

NC

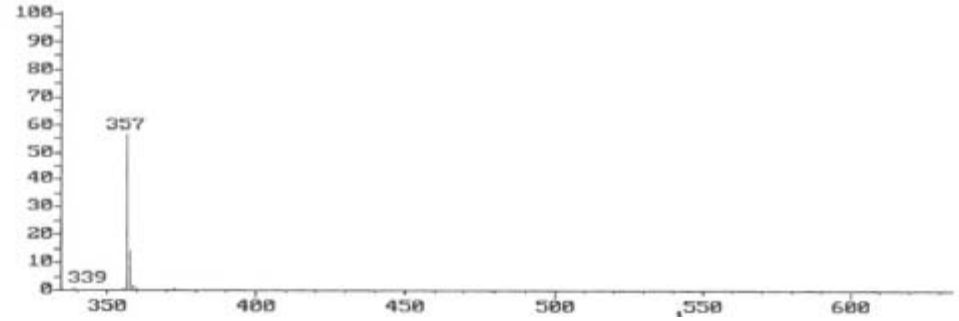

SpinWorks 2.5: AdCN
PPM
x 8.000
125
NC
40.0991
35.8914
30.3074
27.2790

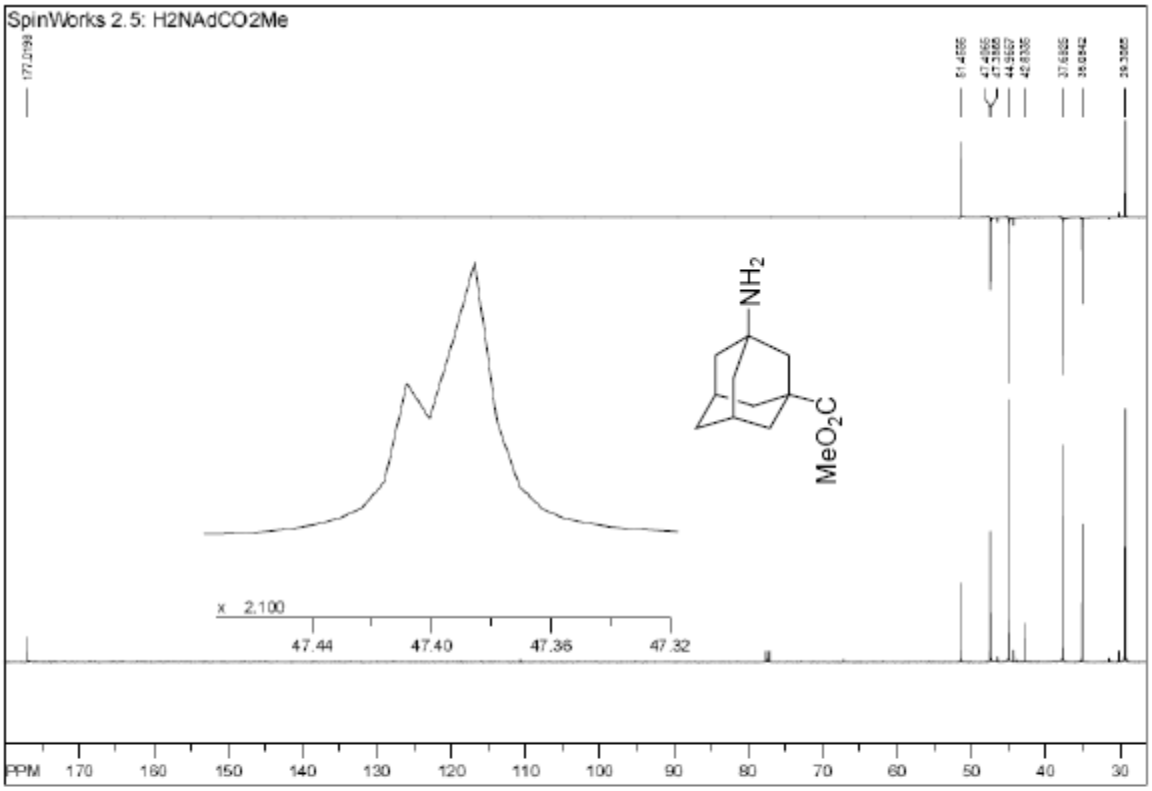

SpinWorks 2.5: AdCONHAdCO2H
O
HN
CO2H
PPM 2.32 2.28 2.24 2.20 2.16 2.12 2.08 2.04 2.00 1.96 1.92 1.88 1.84 1.80 1.76 1.72 1.68 1.64 1.60 1.56 1.52 1.48

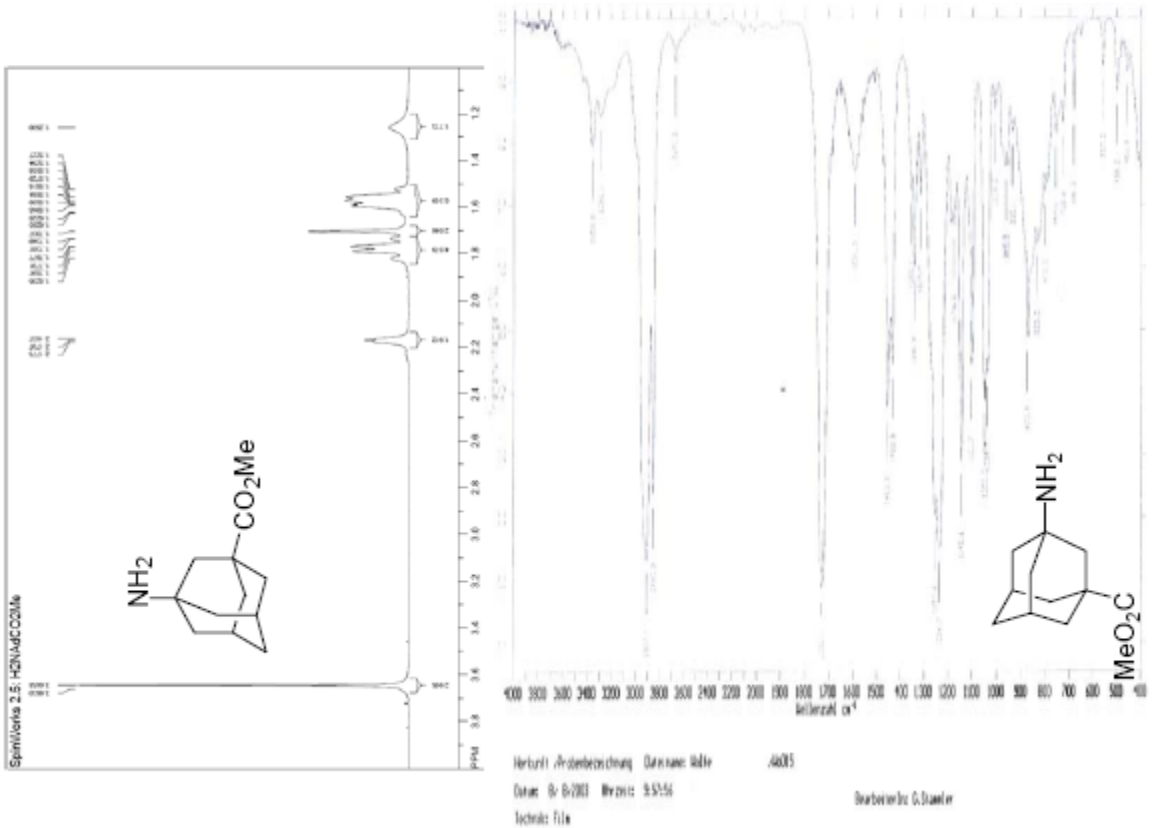

SpinWorks 2.5: AdCONHAdCO2H
O
HN
CO2H
x 8.000
180
176
PPM 58 56 54 52 50 48 46 44 42 40 38 36 34 32 30 28

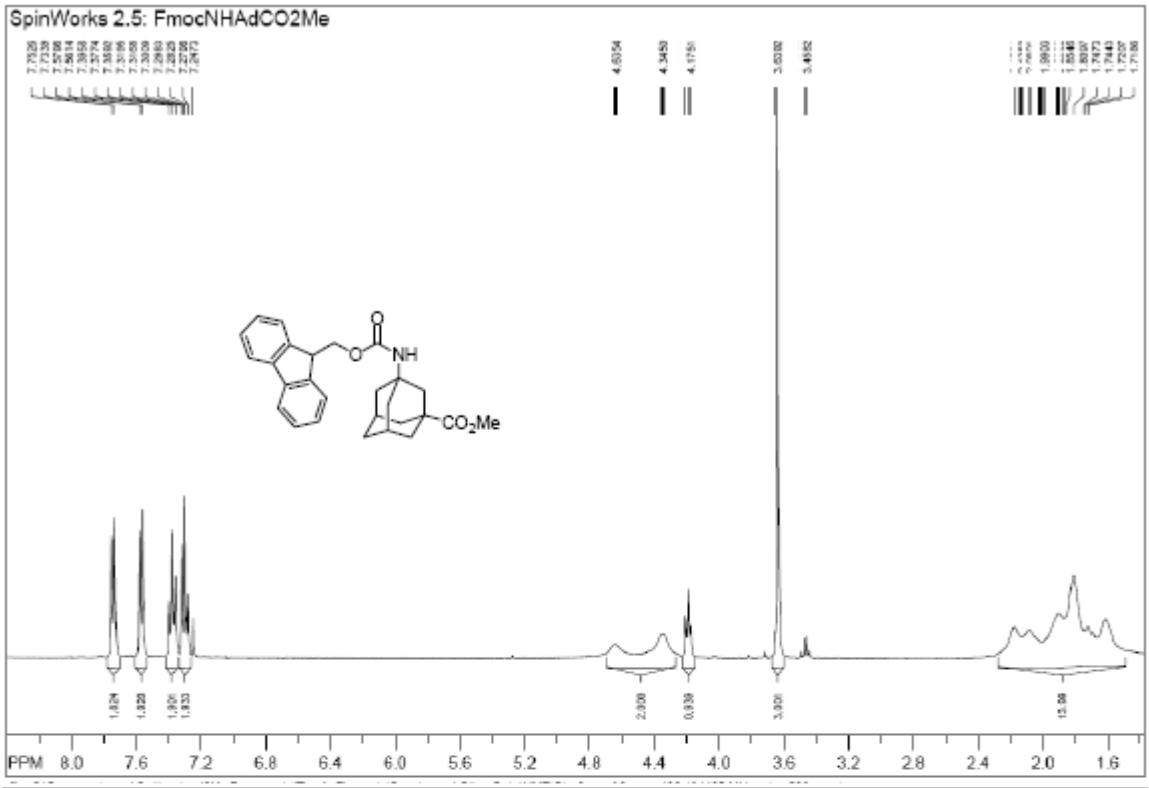

Transmittance [%]
Wellenzahl cm-1
4000 3800 3600 3400 3200 3000 2800 2600 2400 2200 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400
O
HN
CO2H

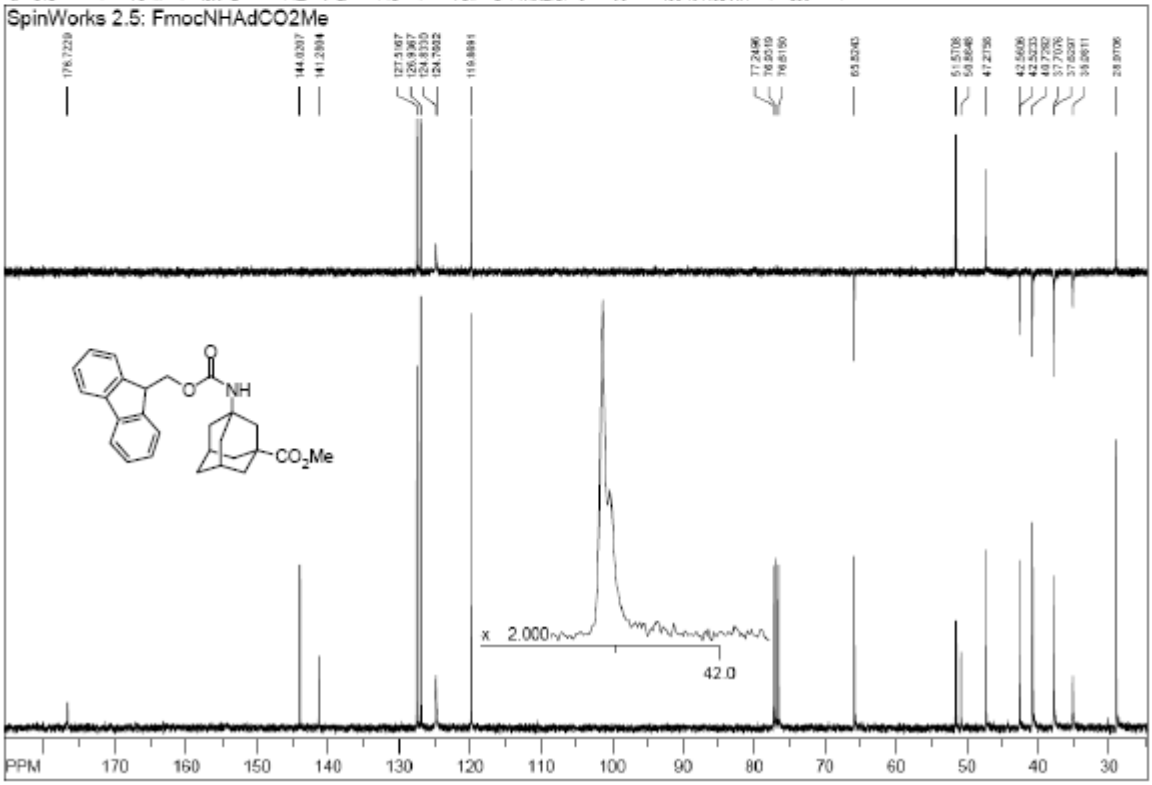

Herkunft /Probenbezeichnung / Dateiname: Wolfen, AG Schreiner Wolfen H /Wo009
Datum: 18/ 7/2003 Uhrzeit: 8:44:49
Bearbeiter(in): G.Stammler
Technik: KBr-Pellet
135
40
79
93
55
67
107
151
164
179
194
221
256
277
300
313
O
HN
CO2H

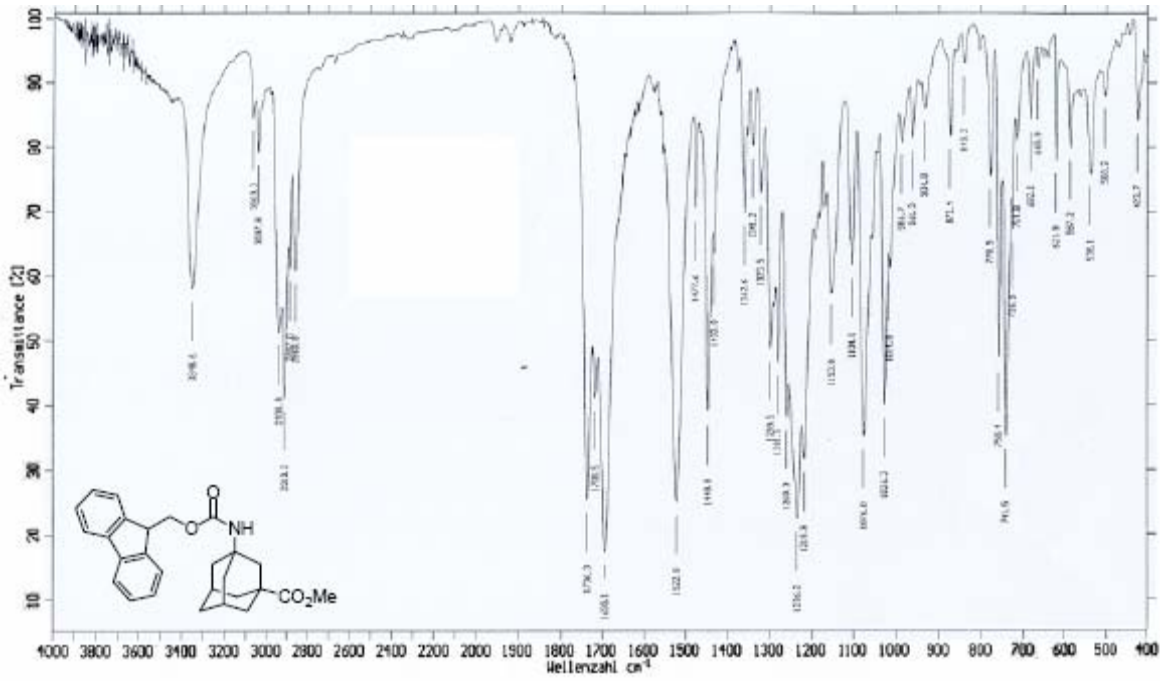

357
339

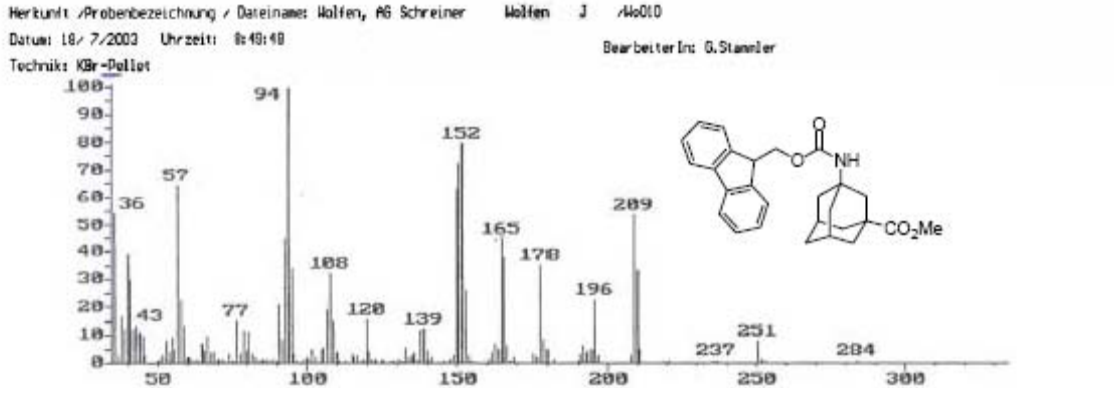

SpinWorks 2.5: H2NAdCO2Me
NH2
MeO2C
x 2.100
47.44
47.40
47.36
47.32
PPM 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30

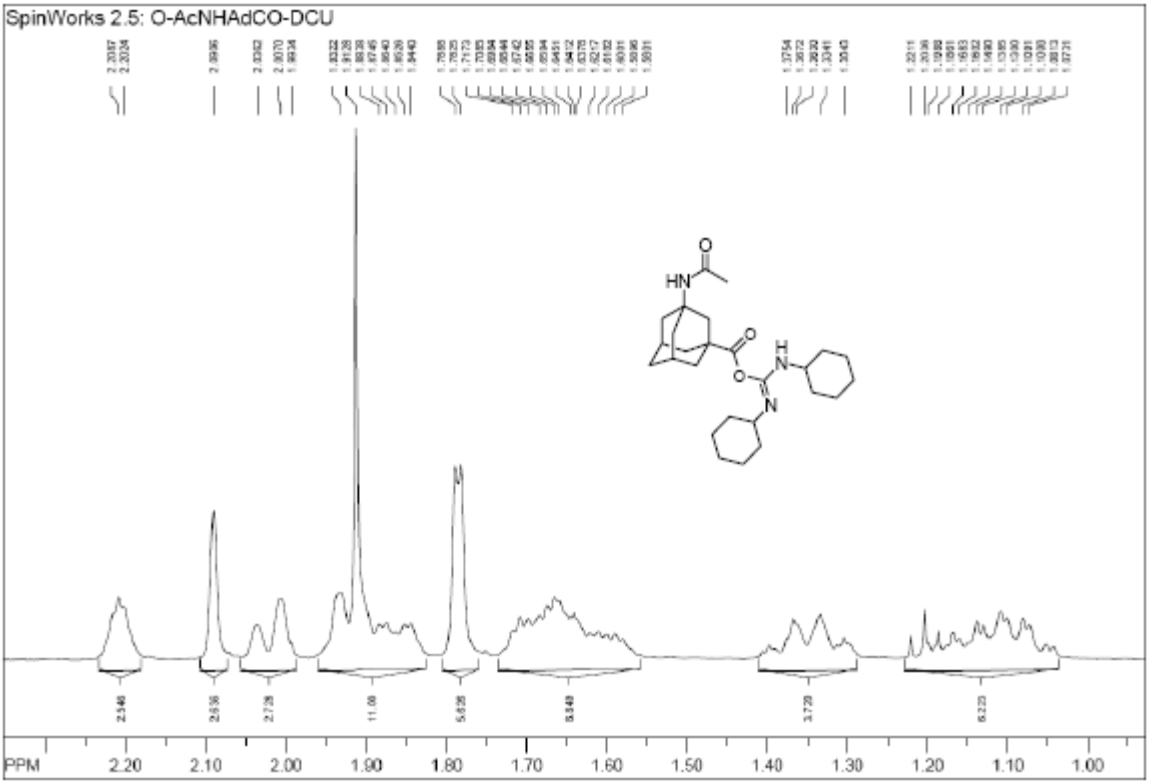

SpinWorks 2.5: H2NAdCO2Me
NH2
CO2Me
NH2
MeO2C

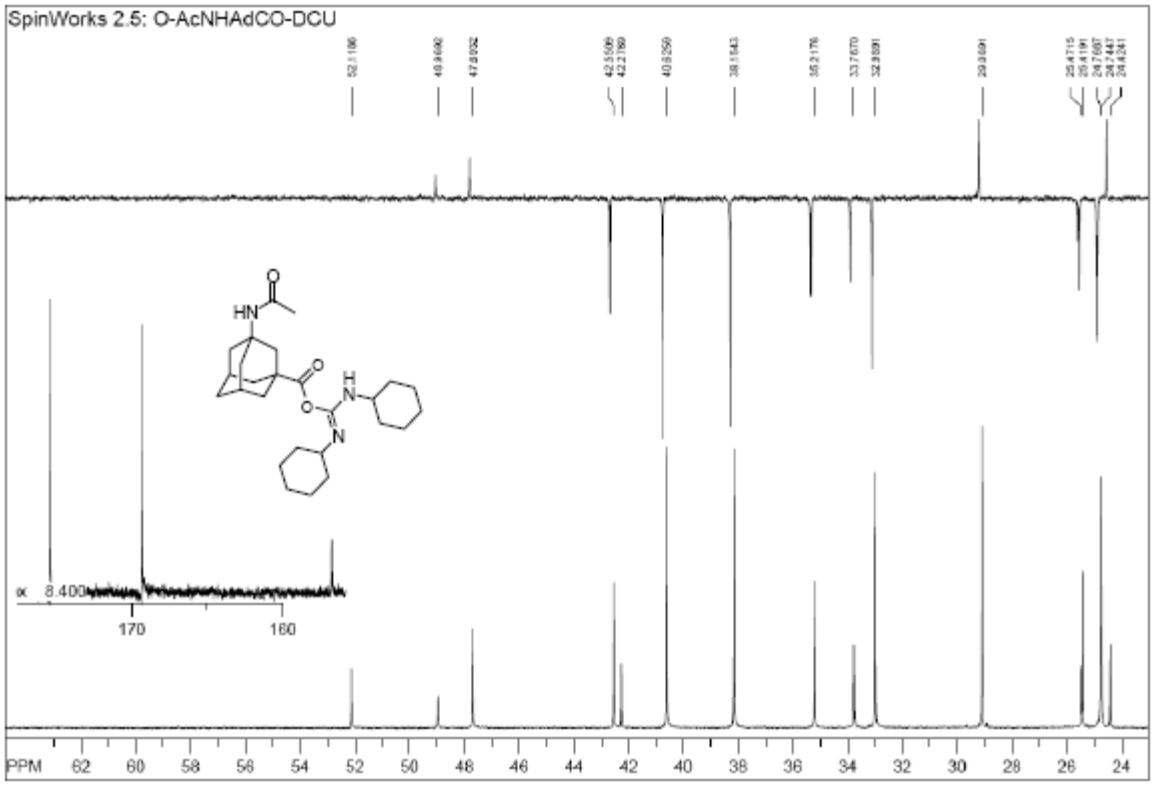

SpinWorks 2.5: FmocNHAdCO2Me
NH
CO2Me
PPM 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6


SpinWorks 2.5: FmocNHAdCO2Me
NH
CO2Me
x 2.000
42.0
PPM 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30


Transmittance [%]
Wellenzahl cm-1
NH
CO2Me


Herkunft /Probenbezeichnung / Dateiname: Wolfen, AG Schreiner Wolfen J /Ao010
Datum: 18/ 7/2003 Uhrzeit: 8:49:48
Bearbeiter in: G.Stammler
Technik: KBr-Pellet
NH
CO2Me


SpinWorks 2.5: O-AcNHAdCO-DCU
PPM
2.20
2.10
2.00
1.90
1.80
1.70
1.60
1.50
1.40
1.30
1.20
1.10
1.00


SpinWorks 2.5: O-AcNHAdCO-DCU
PPM
62
60
58
56
54
52
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38
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32
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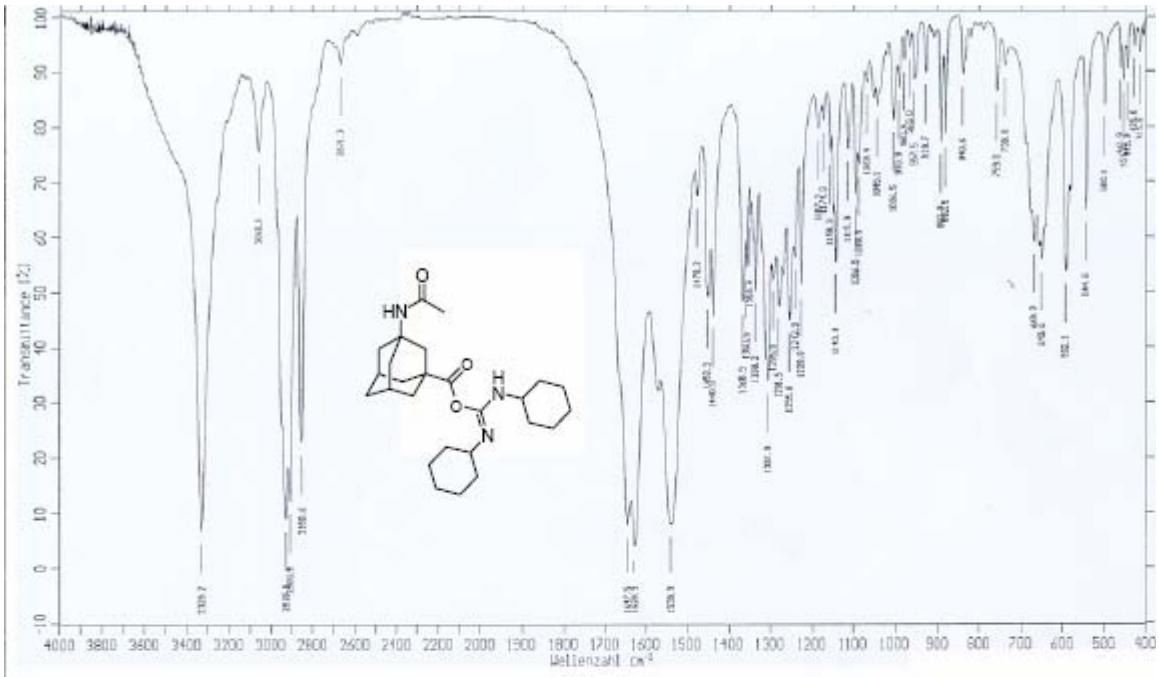
28
26
24

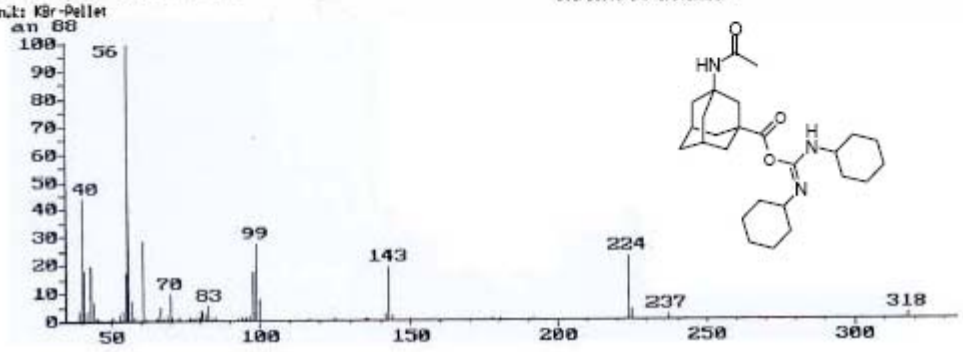


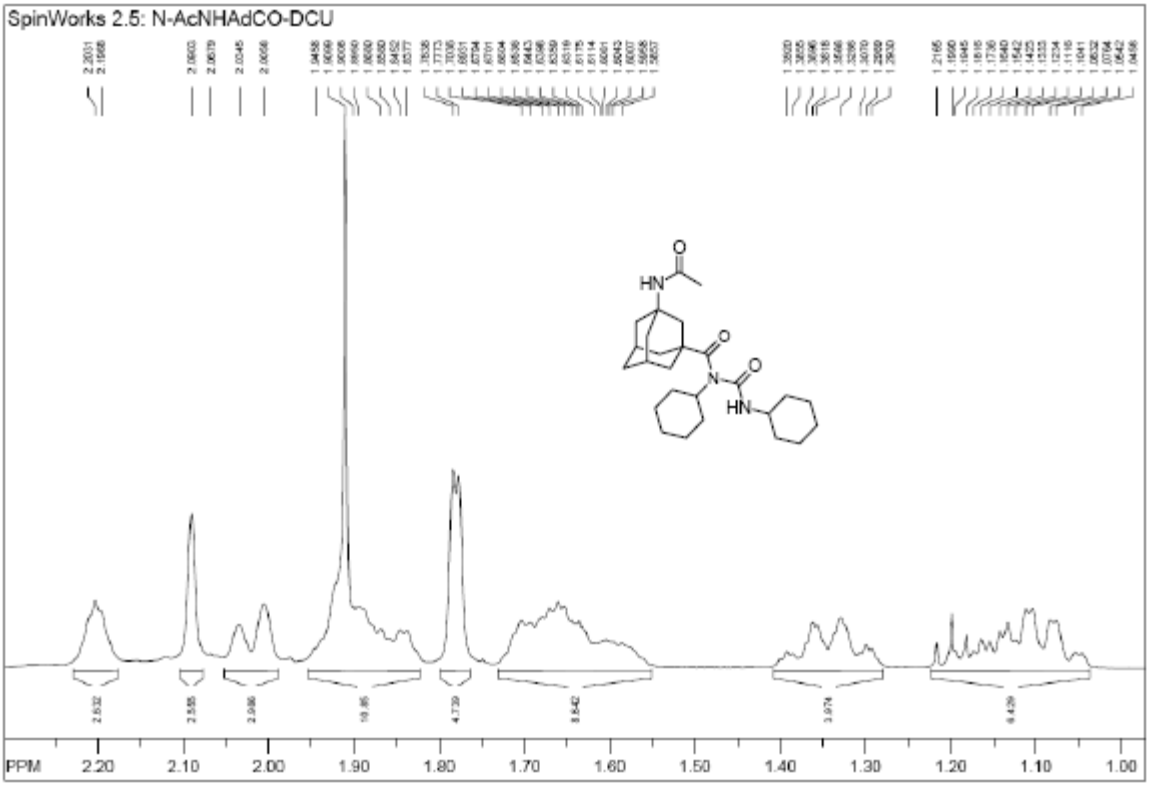
Herkunft /Probenbezeichnung / Dateiname: Wolfen, AG Schreiner / Wolfen A /Wa002

Datum: 18/ 7/2003 Uhrzeit: 8: 2:28

Bearbeiter/in: G.Stammler

Technik: KBr-Pellet

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PPM
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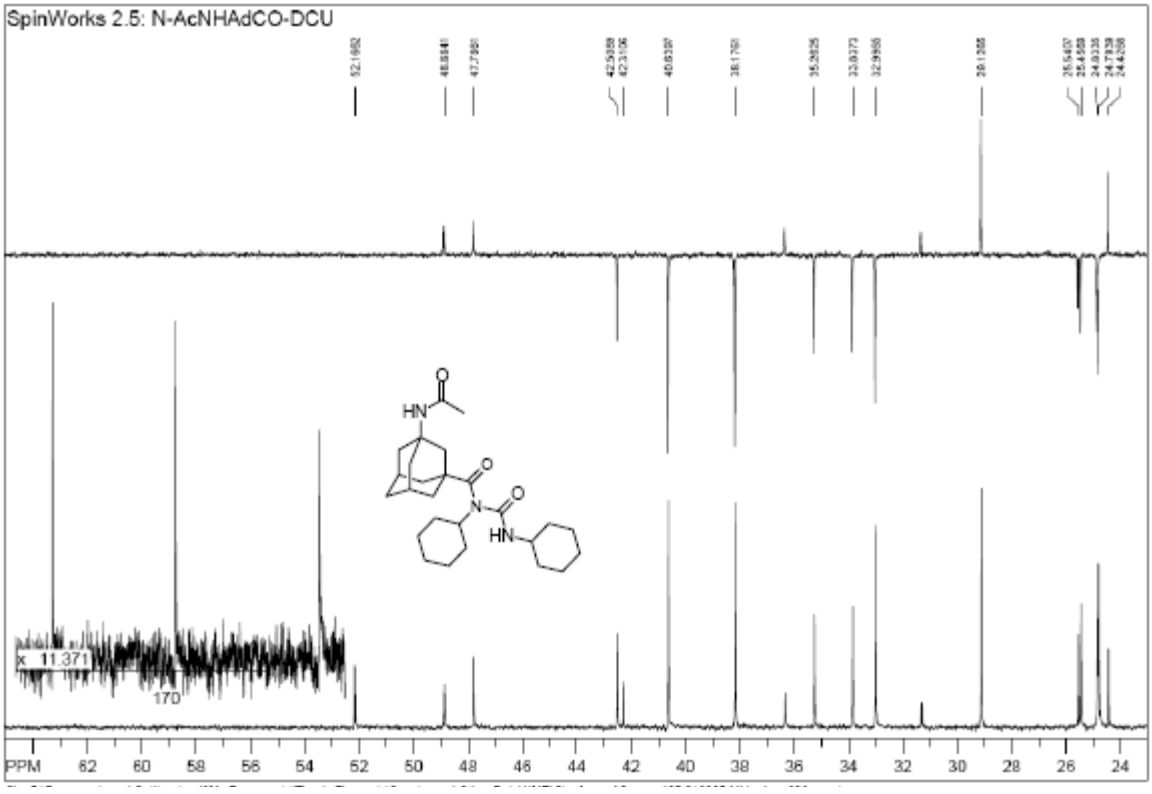
2.10
2.00
1.90
1.80
1.70
1.60
1.50
1.40
1.30
1.20
1.10
1.00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x 11.371
17D
PPM
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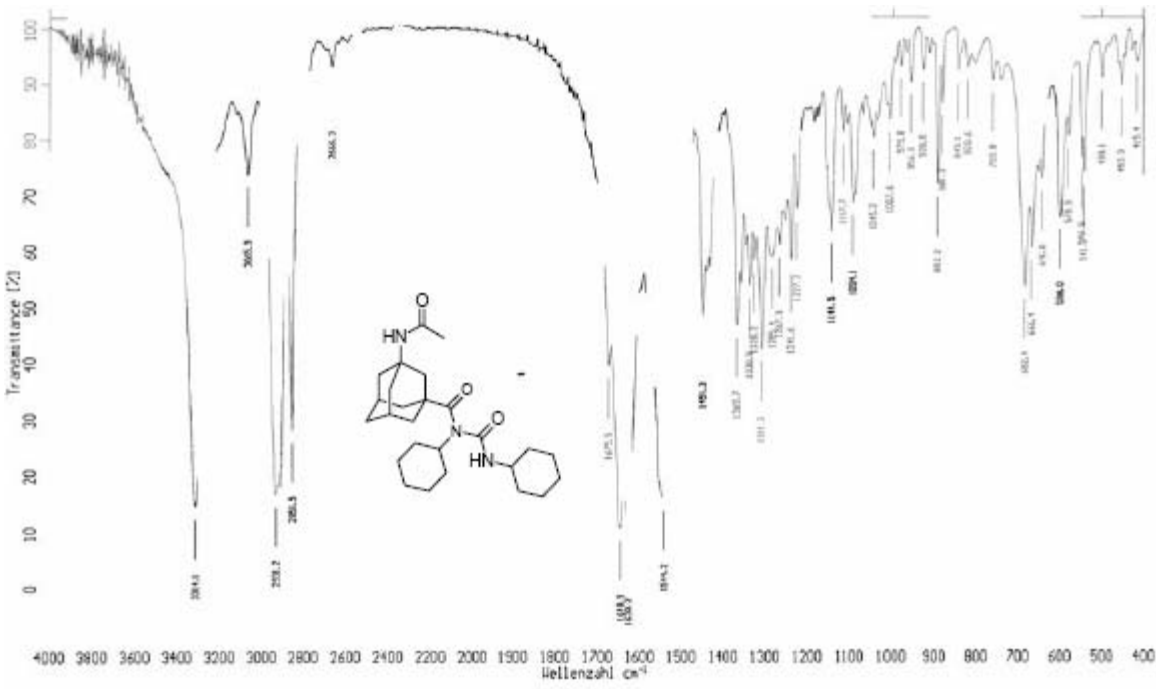
Transmittance [%]
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HN
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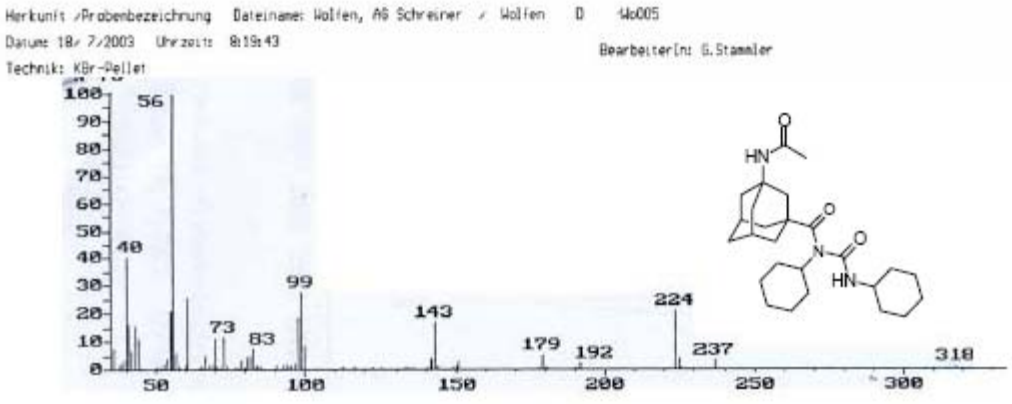
HN


Herkunft /Probenbezeichnung Dateiname: Wolfen, AG Schreiner / Wolfen D 4k005
Datum: 18/ 7/2003 Uhrzeit: 8:19:43
Bearbeiter(in): G.Stammler
Technik: KBr-Pellet
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318
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150
200
250
300
HN
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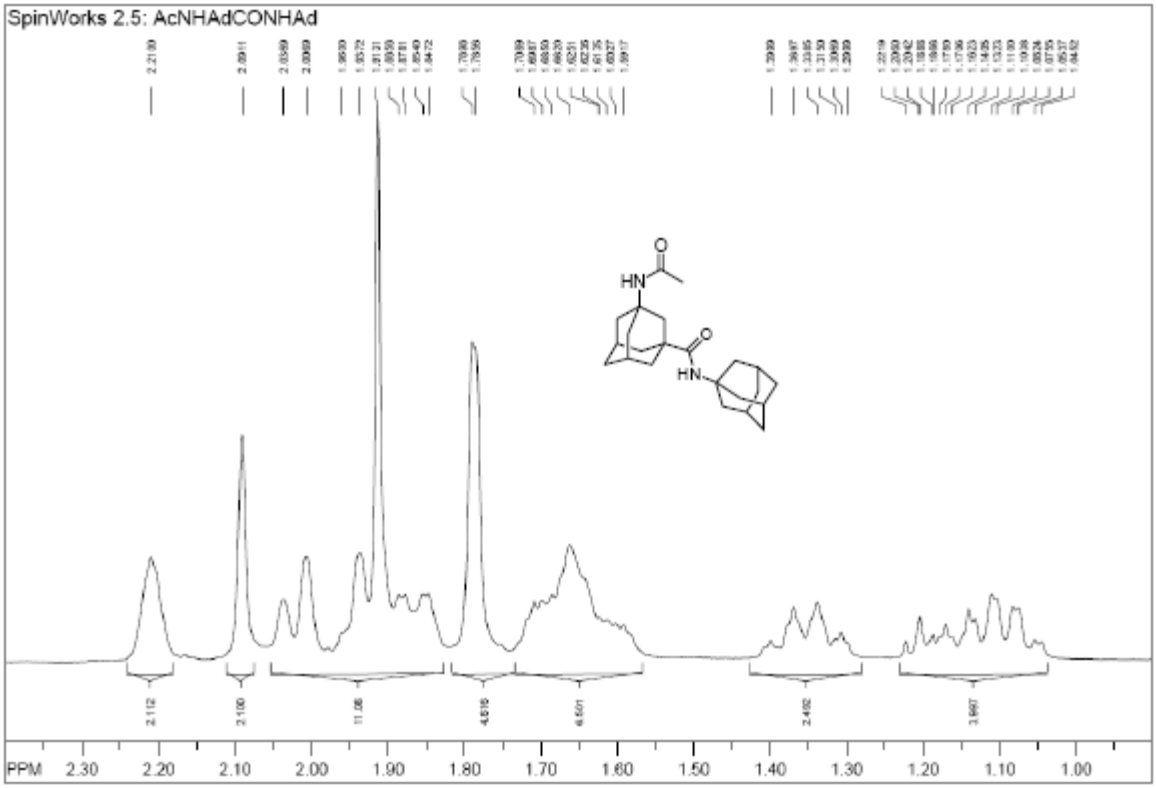
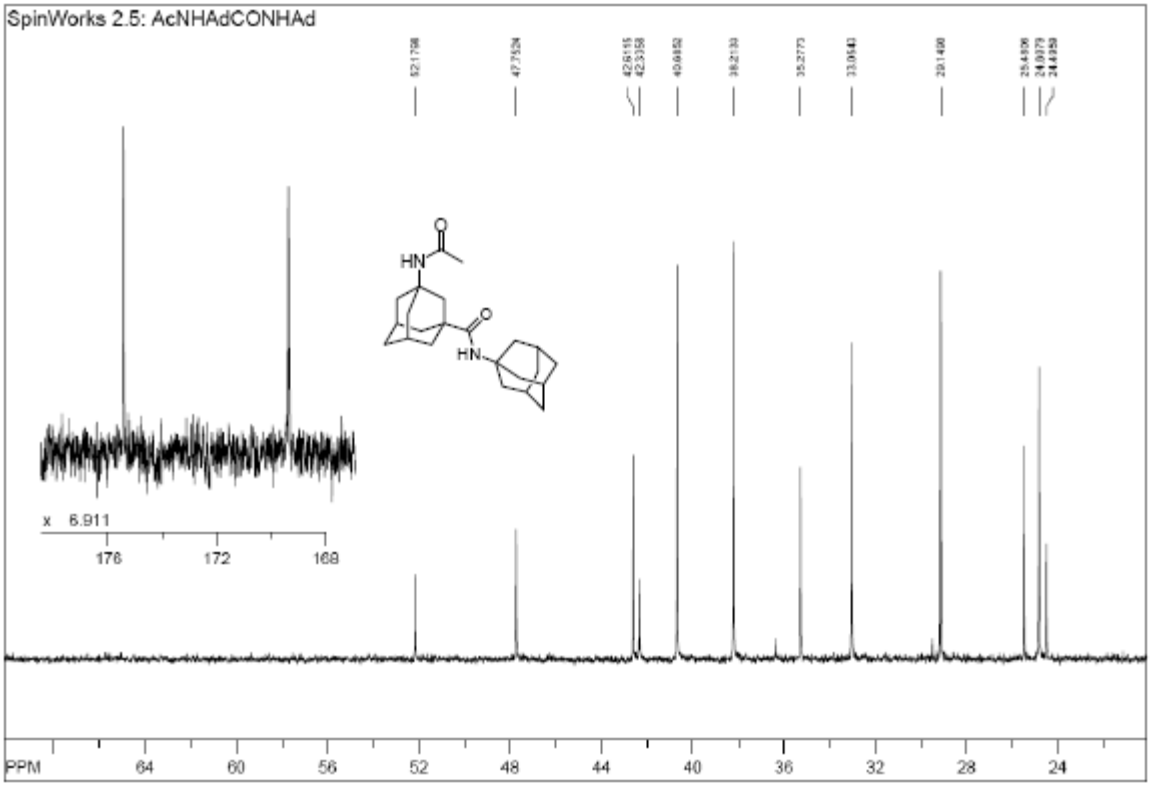
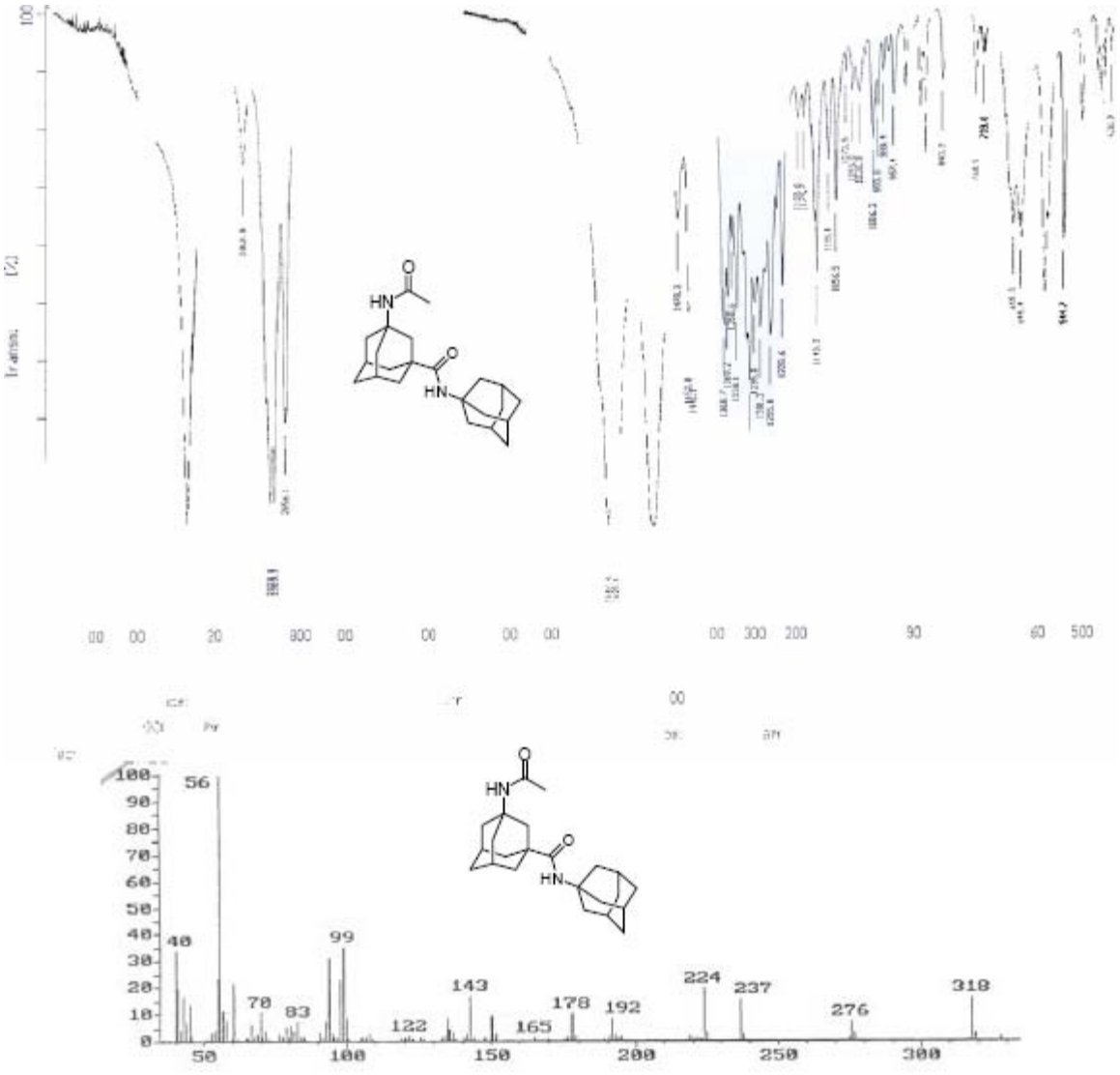
N
HN


SpinWorks 2.5: AcNHAdCONHAd
HN
O
HN
O
PPM 2.30 2.20 2.10 2.00 1.90 1.80 1.70 1.60 1.50 1.40 1.30 1.20 1.10 1.00


SpinWorks 2.5: AcNHAdCONHAd
HN
O
HN
O
x 6.911
176 172 168
PPM 64 60 56 52 48 44 40 36 32 28 24


HN
O
HN
O
100
90
80
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20
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99
70
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143
165
178
192
224
237
276
318
50
100
150
200
250
300