Synthesis of water-soluble mono- and ditopic imidazoliums for carbene ligands

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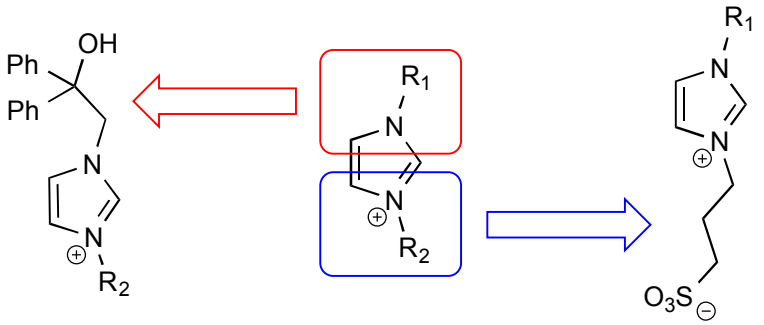
Supporting Information Placeholder



ABSTRACT: Synthesis of ditopic imidazoliums was achieved using a modular step-wise procedure. The procedure itself is amenable to a wide array of functional groups that can be incorporated into the imidazolium architecture. The resulting compounds range from ditopic zwitterions to highly-soluble dicationic aromatics.

Imidazole is a versatile starting material for all manner of chemicals and materials. The fields of Metal-Organic Frameworks (MOFs)[1-3] and ionic liquids (ILs)[4-8] rely upon the imidazole moiety for a number of important structures. Additionally, imidazole is used as a ligand for myriad coordination compounds in the transition,[9-11] main group,[12-14] lanthanide[15,16] and actinide series.[16,17] While a classical coordination mode through one of the nitrogen atoms is useful, the utility of this heterocycle is amplified by the ability to coordinate through the 2-carbon as an *N*-heterocyclic carbene (NHC).[11,18]

In all of these cases, the ability to functionalize the imidazole core allows for a great number of structures and new modes of binding to aid in catalyst activity, solubility, and structural characteristics. The goal of this work is to differentially substitute the nitrogen atoms of the imidazole core toward water-soluble imidazoliums that can also function as carbene-type ligands. Our laboratory's interest in these structures came from the water-soluble catalysis currently being reported by many groups[19-24] and the lanthanide coordination chemistry of Polly Arnold and coworkers.[25-27] Outside of coordination chemistry, we have also found utility in tethering fluorophores to the imidazole core and creating water-soluble dyes for scintillation studies currently being conducted in our laboratory. What follows is the synthetic strategy employed for making various imidazolium derivatives on a scale of tens of grams and installing either a cationic or anionic tail for increased aqueous solubility.

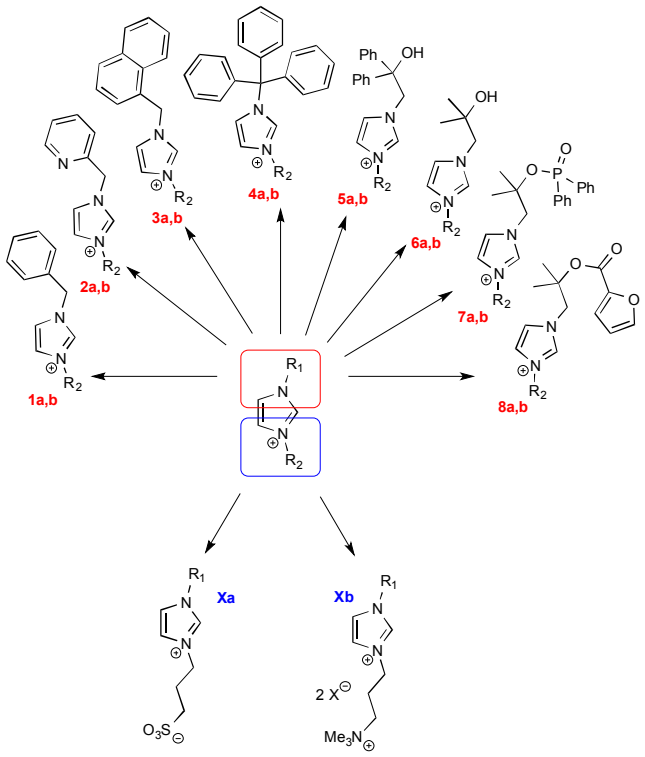
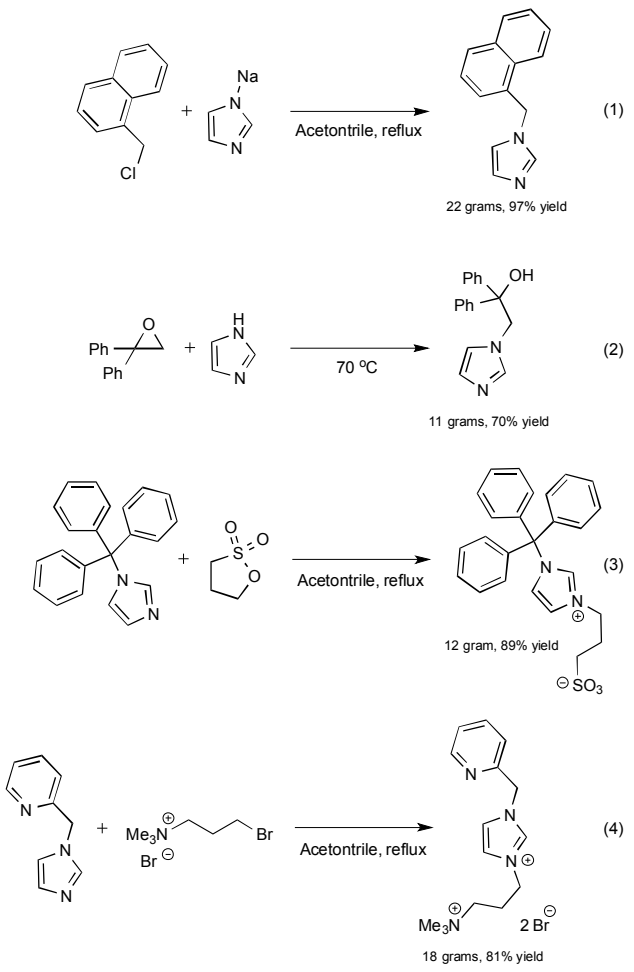


Figure 1. Burst diagram showing the concept of bifunctionality and possible permutations of the chosen moieties.

When possible, a modular two-step synthetic procedure is employed whereby the imidazole is first functionalized with the aryl or binding moiety (group A, Figure 1) followed by the sulfonate or ammonium (group B, Figure 1) to cap the final compound. Figure 1 shows the scope of the imidazoliums we have synthesized. It is a general procedure that others can replicate easily, possibly even with other similar building blocks not reported herein.

Conveniently, the synthesis of these imidazoliums can proceed through addition of different electrophiles in a step-wise fashion to afford the products without risk of oversubstitution. Where possible, the imidazole with a group A moiety substituted at the 1-position was purchased from commercial sources. This was the case for 1-benzylimidazole, 2-((1*H*-imidazol-1-yl)methyl)pyridine, and 1-(1*H*-imidazol-1-yl)-2-methylpropan-2-yl furan-2-carboxylate. The group A substituents can be divided into two general categories: non-coordinating and coordinating.

Scheme 1. Representative syntheses of the group A-substituted imidazole (1,2) and the addition of the ionic tethers to form the final imidazoliums (3,4).



The non-coordinating group A substituents are introduced using the corresponding alkyl chloride with yields in excess of 90%. As an example, the 1-(naphthalen-1-ylmethyl)-1H-imidazole is synthesized by refluxing the alkyl chloride in the presence of sodium imidazolide to avoid the use of an exogenous base (Reaction 1, Scheme 1). After filtration and extraction, 22 grams of an orange oil is obtained (96% yield), and the purity is confirmed by ^{1}H NMR spectroscopy.

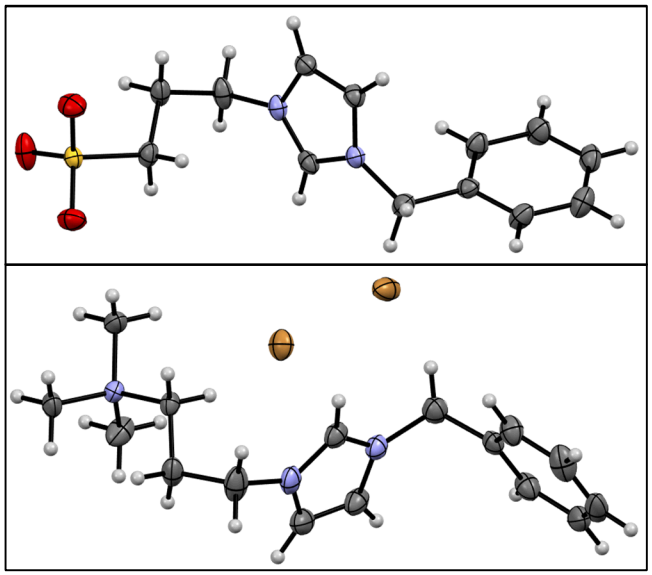


Figure 2. X-ray crystal structure determinations of imidazoliums 1a (top) and 1b (bottom). Ellipsoids are at 50% probability level.

To synthesize the imidazoles with a coordinating group, a procedure was borrowed from Arnold and coworkers using oxiranes as the electrophile of choice.[28] In keeping with the desire to avoid exogenous base, the oxirane allows for the use of 1H-imidazole without needing a base since the proton transfers from the imidazole nitrogen to form the alcohol after ring-opening of the epoxide. Both 2,2-dimethyloxirane and 2,2-diphenyloxirane were employed to generate the resulting starting alcohols **5** and **6**, respectively. As an example, 2-(1H-imidazol-1-yl)-1,1-diphenylethanol was synthesized by melting the imidazole in the presence of 2,2-diphenyloxirane at 70 °C (Reaction 2, Scheme 1). After extraction with hot ethanol, crystallization, and filtration, the product was obtained as a white crystalline solid (11 grams, 71% yield).

These alcohols provide another useful point for further functionalization. Esterification reactions are simple to implement here, and one variant that is useful in our laboratory is the 2-furanyl ester. Installing a diphenyl phosphoryl moiety is facilitated by the use of the corresponding phosphoryl chloride. In these cases, the products are taken directly on to the group B functionalization step since purification is most convenient at the final stage.

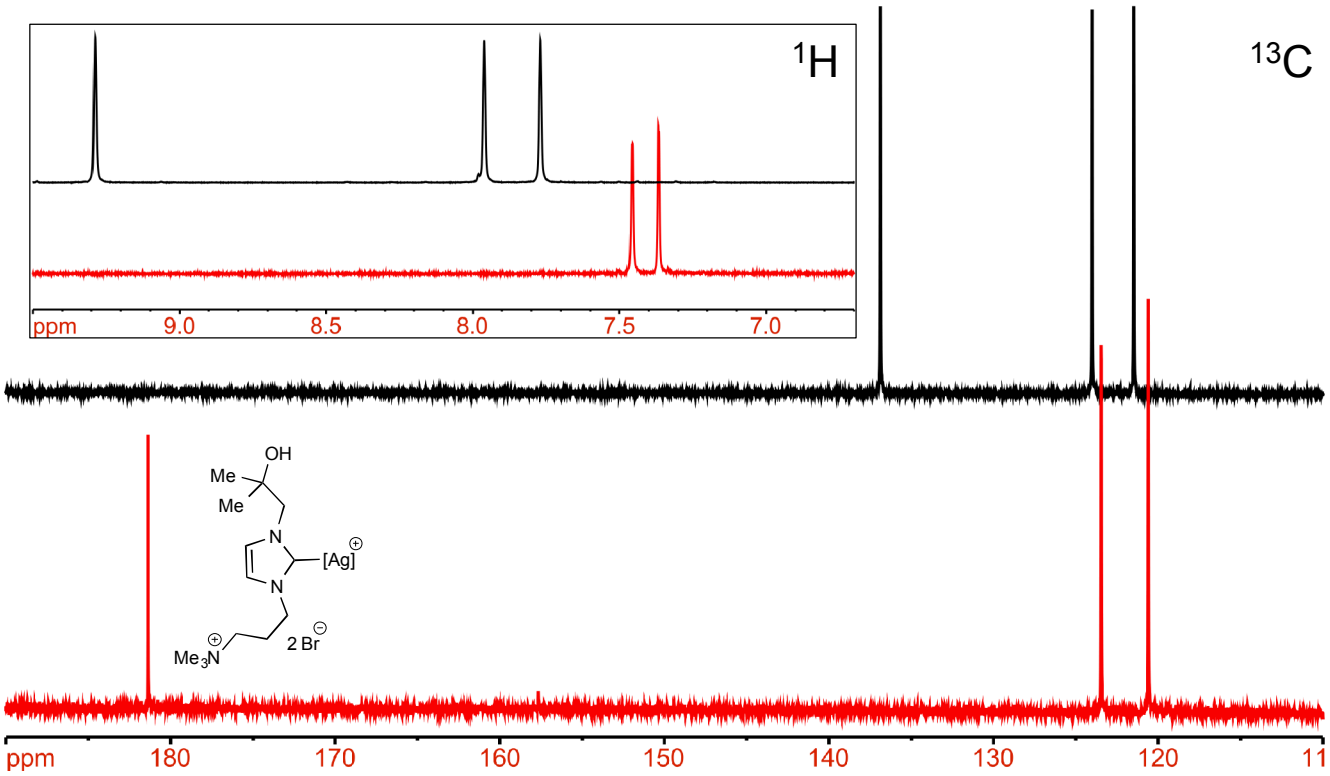


Figure 3. NMR spectra of 6b before (black trace) and after (red trace) treatment with silver(I) oxide.

With the group A substituents installed, both the cationic and anionic tethers can be attached to the unfunctionalized nitrogen of the imidazole to form the final imidazolium. In the case of the anionic sulfonate, the compound is a zwitterion with no additional counterion. The cationic ammoniums necessitate two equivalents of the counterion, bromides in these preparations, to counterbalance the imidazolium and ammonium ions, which improves the water solubility. A representative procedure for the sulfonate synthesis starts with the group A-substituted imidazole, 1-tritylimidazole, treated with 1.2 equivalents of 1,2-oxathiolane 2,2-dioxide in acetonitrile (Reaction 3, Scheme 1). The reaction mixture is refluxed over the course of 72 hours with precipitation of the salt. The product, 3-(1-trityl-1*H*-imidazol-3-ium-3-yl)propane-1-sulfonate is collected by filtration, washed with acetonitrile and acetone, and dried under vacuum to afford 12.4 grams of white solid in 89% yield. A 6-membered cyclic sultone is also available, but the reaction rate is considerably slower using this moiety and was deemed not worth exploring further. The ammonium of choice came in the form of (3-bromopropyl)trimethylammonium bromide to match the 3-carbon tether of the sulfonates. Just as the 4-carbon, 6-membered ring sultone did not result in high yields of product, the 4-carbon ammonium also gave lower yields and less pure reaction mixtures. It is not clear why this is the case, and the reaction scope was kept at the 3-carbon tether. The 2-pyridyl-substituted imidazole is alkylated using a substoichiometric amount (0.9 equivalents) of the ammonium in acetonitrile and refluxing the reaction mixture for 72 hours (Reaction 4, Scheme 1). The solid product, **2b** (18 grams, 81% yield), is then filtered off after allowing the reaction mixture to cool to room temperature, washing with acetonitrile and acetone, and drying under vacuum. Both of these procedures are performed with anhydrous solvents to prevent products from becoming oils.

Aqueous catalysis is an inspiration for this work, and we found that the majority of these compounds are soluble in aqueous media. As a general rule, the ammonium salts were by far more soluble and could even dissolve in polar organics such as ethanol, methanol, dimethylsulfoxide, and sparingly into solvents like acetonitrile and acetone. Differences in substitution did not significantly alter the observed behavior. The sulfonate salts showed the most variation in solubility as the substituents were varied. The highly arylated compounds such as **3a**, **4a**, and **5a** are nearly insoluble in water and characterization could only be obtained using dimethylsulfoxide.

The intent of this work is to functionalize imidazoliums quickly and easily using a modular, two-step process. In our laboratory, the compounds serve several purposes, but one major thrust came in the form of coordination chemistry. A wide array of lanthanide carbene complexes have been reported by Arnold recently, and that inspired our interest in water soluble variants. Only preliminary work has been done to date, but the following show some utility for how these imidazoliums could be used as precursors to carbene complexes. The following is provided as an example of the types of chemistry available, but these specific results are preliminary and found to not be general for the entire series of imidazoliums reported here.

Silver reagents are commonly used to generate NHCs for transmetallation to form other metal complexes.[29,30] The reported imidazoliums are candidates for this type of

methodology, and Figure 3 shows 1H and 13C NMR spectra of **6b** before and after treatment with silver(I) oxide in dimethylsulfoxide at 80 °C. This silver oxide method is not general across the entire series of compounds. However, imidazolium **5b** with its cationic tether is likely more amenable to the formation of the carbene due to the chelation of the pendant alcohol. The analogous sulfonate imidazolium did not yield a clean NMR spectrum possible because the sulfonate could interfere in the coordination to silver.

Several other authors have reported the use of lanthanide trisamides as convenient synthons for lanthanide complexes.[26,31-33] The cerium variant is the choice in our laboratory because the single, unpaired *f*-electron present in the *f*-orbital manifold allows for fluorescence in the 400-500 nm region of the visible spectrum.[32] The addition of one equivalent of the cerium trisamide to one equivalent of phenyl-substituted imidazolium with the sulfonate tether at -35 °C yields the sulfonato-coordinated complex **9** without deprotonation of the imidazolium. The X-ray crystal structure was obtained from the solid upon recrystallization from cold toluene (Figure 4). The compound is temperature sensitive and will decompose if allowed to warm to room temperature. Unfortunately, the decomposition leads to a mixture of many products that could not be purified or separated.

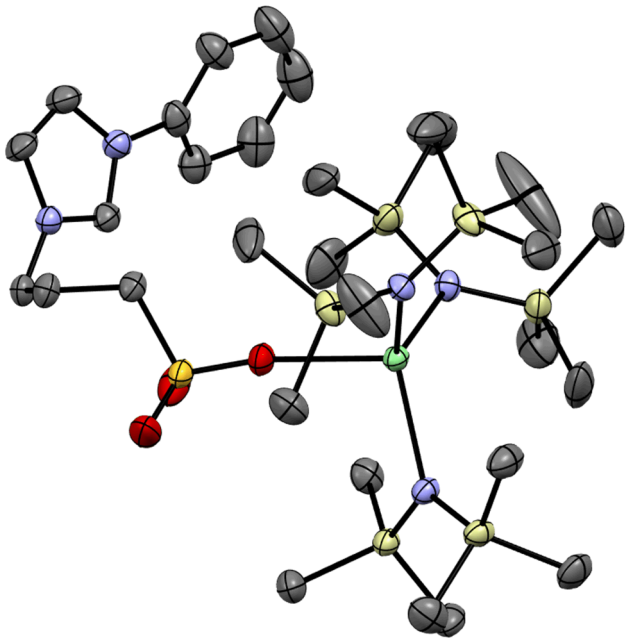


Figure 4. X-ray crystal structure determination of Cerium complex 9. Ellipsoids are shown at 50% probability level.

In summary, we have developed a method for doubly-substituting imidazole toward water-soluble imidazoliums useful as ligands or as a general platform for solubility purposes. The step-wise preparation is robust enough to be scaled to tens of grams for each of the imidazoliums listed. Solubility in water, dimethylsulfoxide, and polar organics is as expected. Finally, two examples of the imidazoliums used as ligands is reported.

ASSOCIATED CONTENT

Supporting Information

Supplementary materials include experimental procedures and spectroscopic data for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally. (match statement to author names with a symbol)

Notes

Any additional relevant notes should be placed here.

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