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An Efficient Synthesis of Imidazolinium Salts Using Vinyl Sulfonium Salts

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ABSTRACT

The synthesis of imidazolinium salts from the reaction of formamidines and (2-bromoethyl)diphenylsulfonium triflate is described. A variety of symmetrical and unsymmetrical imidazolinium triflate salts were synthesized in high yield in short reaction times under mild conditions. Aromatic and aliphatic N-substituents work well. The reaction is proposed to proceed via generation of a vinyl sulfonium salt intermediate from the bromoethylsulfonium triflate.

The use of N-Heterocyclic Carbenes (NHCs) as ligands and as organocatalysts has become widespread since the first report of the isolation of a stable NHC by Arduengo.[1] Imidazolium and imidazolinium salts are commonly used as precursors to NHCs; thus synthetic methods to access these heterocycles are important.[2−8]

Scheme 1 shows the three bond disconnections most commonly applied in the synthesis of these heterocycles.

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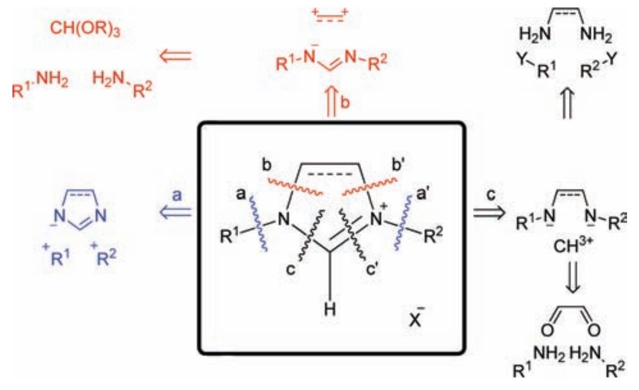
Disconnection 'a' can be an S_N2 displacement of a leaving group by nitrogen or a metal-catalyzed C−N bond formation.[5] Disconnection 'c' is typically the reaction of a diamine with an orthoformate and a source of HX.[5,6] The required diamine is typically formed either by a reductive amination with glyoxal or by alkylation of the diamine. Disconnection 'b' corresponds to a reaction between what is formally an ethyl dication and a formamidine.[7,8] The formamidine can, in turn, be generated from the reaction of an amine with an orthoformate. α-Halocarbonyl compounds have often been used to form the ethyl bridge. However, more recently the use of 'dielectrophiles' such as dihaloethanes has been described.[7,8] In particular, Kuhn and Grubbs have described a two-step synthesis of imidazolinium salts.[7] Anilines were reacted with ethyl orthoformate to yield formamidines, which were heated at 120 °C in dichloroethane in a sealed tube to give symmetrical and unsymmetrical imidazolinium salts in good yields. This method worked well with electron-rich anilines, but anilines bearing very bulky groups or electron-withdrawing groups did not work well. Nonetheless the simplicity of this method makes it attractive.

Scheme 1. Approaches to the Synthesis of Imidazolinium Salts



Although there are a range of methods for the synthesis of imidazolinium salts, there are drawbacks and/or limitations in substrate scope in all cases. Thus, in many cases, extra reduction steps are required due to the oxidation state of the starting materials and these limit the functional groups that can be tolerated.[5,6a−6c,6e−6i] In addition, the synthesis of nonsymmetrical salts ($R^1 \neq R^2$) would be challenging with some methods.[6a−d,i]

Recently, it has been shown that vinylsulfonium salt **2** and the more stable bromoethylsulfonium salt **1** are both highly effective in annulation reactions, e.g., in the synthesis of morpholines and oxazepines.[9,10] Herein, we describe the application of these salts in a simple and rapid method for the synthesis of imidazolinium salts.

Scheme 2 shows our proposed reaction pathway based on analogous reactions with amino alcohols. Thus, treatment of bromoethylsulfonium salt **1** with base leads to the formation of vinylsulfonium salt **2** in situ.[11] The vinylsulfonium salt **2** is an excellent electrophile and should react rapidly with **3** to form sulfur ylide **4**. Following proton transfer to unmask a second electrophilic center, an intramolecular nucleophilic attack would be expected to displace Ph_2S to give the desired imidazolinium triflate salt **5**.

Scheme 2. Proposed Mechanism for the Synthesis of Imidazolinium Salts 3

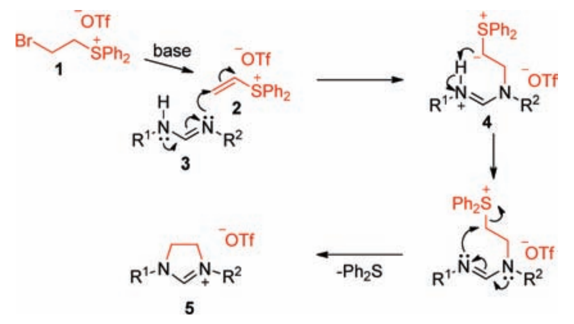


Table 1 shows the results of the initial screening of reaction conditions using mesityl-substituted formamidine **3a** as a model substrate. The use of Hünig's base (iPr$_2$EtN) and acetonitrile gave rise to high yields of imidazolinium salt **5a** in just 2.5 h at room temperature. The product could be isolated without recourse to chromatography; washing with Et_2O and water to remove Ph_2S and diisopropylethylammonium bromide gave analytically pure triflate salt **5a**. We note that the intermediacy of a vinylsulfonium salt in the reaction is supported by the following observations: (i) direct use of vinylsulfonium salt **2** gave similar yields; (ii) the use of 2-bromoethyl triflate instead of **1** gave much lower yields under the optimized conditions.

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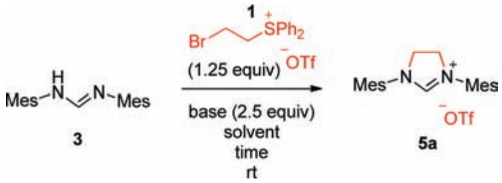
(11) Salt **1** is a commercially available stable crystalline salt and is preferred to vinylsulfonium salt **2** for ease of handling.

Table 1. Optimization of the Annulation Procedure



entry	base	solvent	time (h)	yield (%)[a]
1	DBU	CH_2Cl_2	16	30
2	NaH	CH_2Cl_2	16	56
3	*i*Pr_2EtN	CH_2Cl_2	16	58
4	*i*Pr_2EtN	THF	7	78
5	*i*Pr_2EtN	$CF_3C_6H_5$	3	88
6	*i*Pr_2EtN	EtOAc	3	90
7	*i*Pr_2EtN	MeCN	2.5	91

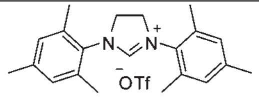
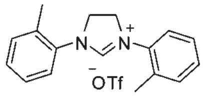
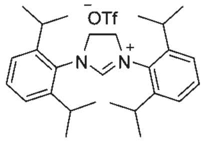
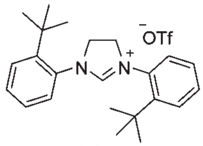
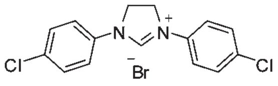
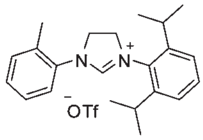
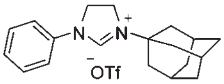
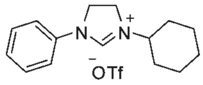
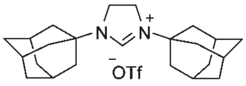
[a] Isolated yield.

Having found suitable reaction conditions, the reaction scope was explored (Table 2). The *N*-aryl symmetrical formamidines **5b**–**e** all gave high yields in less than 4 h in refluxing acetonitrile. Particularly of note is the fact that bulky formamidines gave high yields in short reaction times (entries 3, 4, 9). This scope compares favorably to the method of Grubbs[7] (after 7 days in refluxing dichloroethane, the reaction to make **5d** had reached 60% conversion).

The method was readily extended to the use of symmetrical formamidines bearing aliphatic N-substituents (reported to be problem substrates for the Grubbs method), and especially important are the unsymmetrical formamidines[12] bearing both an aromatic and an aliphatic N-substituent (entries 7, 8) or two different aromatic groups (entry 6).

In almost all cases, elemental analyses of the products were consistent with analytically pure triflate salts being obtained.[13,14] Interestingly, in the case of **5e** the bromide salt was isolated with ca. 10% of the triflate salt as a 'contaminant'.

Table 2. Synthesis of Imidazolinium Salts Using Bromoethylsulfonium Salt **1**

entry	product	time (h)	yield (%)[a]
1	 **5a**	2.5 (1)	91[b] (89)[c]
2	 **5b**	1.25	95
3	 **5c**	1.5	90
4	 **5d**	3	90
5	 **5e**	4	71[d]
6	 **5f**	1.5	80
7	 **5g**	2.5	85
8	 **5h**	2	72
9	 **5i**	2.5	71

[a] Isolated yield. [b] rt. [c] With vinylsulfonium triflate **2** instead of **1**, at reflux. [d] With 10–13% triflate counterion as contaminant.

In the case of symmetrically substituted salts there is no need to preform the formamidine; a one-pot synthesis from the requisite amine is possible. Thus, triethylorthoformate and the amine can be reacted to form a formamidine; after in

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(12) For example, Grubbs has recently reported an *N*-aryl, *N*-alkyl *N*-heterocyclic carbene (NHC) ruthenium metathesis catalyst which was highly selective for the kinetic ethenolysis of methyl oleate at low catalyst loading (500 ppm): Thomas, R. M.; Keitz, B. K.; Champagne, T. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *asap*, DOI: 10.1021/ja200246e.

(13) For examples where the counterion is important in transition-metal-catalyzed reactions, see: (a) Adam, W.; Roschmann, K. J.; Saha-Möller, C. R. *Eur. J. Org. Chem.* **2000**, 3519–3521. (b) Collman, J. P.; Zeng, L.; Brauman, J. I. *Inorg. Chem.* **2004**, *43*, 2672–2679. (c) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagn, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066–10067. (d) Drent, E.; van Broekhoven, J. A. M.; Doyle, M. J. *J. Organomet. Chem.* **1991**, *417*, 235–251. (e) Evans, L. A.; Fey, N.; Harvey, J. N.; Hose, D.; Lloyd-Jones, G. C.; Murray, P.; Orpen, A. G.; Osborne, R.; Owen-Smith, G. J. J.; Purdie, M. *J. Am. Chem. Soc.* **2008**, *130*, 14471–14473. (f) Clark, T. P.; Landis, C. R. *J. Am. Chem. Soc.* **2003**, *125*, 11792–11793. (g) Antoniotti, S.; Dalla, V.; Duñach, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 7860–7888.

(14) There are limits to how well elemental analysis can distinguish between the bromide and the triflate salt. While the results were entirely consistent with the triflate salts for **5a**–**d**,**f**–**i**, contamination with up to ca. 10% bromide instead of triflate would still give satisfactory analyses. The exact limit is dependent on the molecular weight of the imidazolinium part.

Scheme 3. One-Pot Synthesis of Imidazolinium Triflates from Amines and Bromoethylsulfonium Triflate **1**

vacuo drying and addition of solvent, base, and bromoethylsulfonium salt **1** to the reaction vessel, the imidazolinium salts **5a,i** were isolated in excellent yields (Scheme 3).

In conclusion, we have demonstrated that the synthesis of imidazolinium salts can be achieved in high yields and short reaction times using a simple, mild procedure. The method is applicable to the synthesis of symmetrical and unsymmetrical imidazolinium salts bearing aromatic or aliphatic groups. A one-pot procedure from commercially available materials has been shown to be effective for symmetrical imidazolinium triflate salts. Of particular note are the excellent results that can be obtained with sterically hindered amines.

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Supporting Information Available. Synthesis and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.