

A Facile Preparation of Imidazolium Chlorides

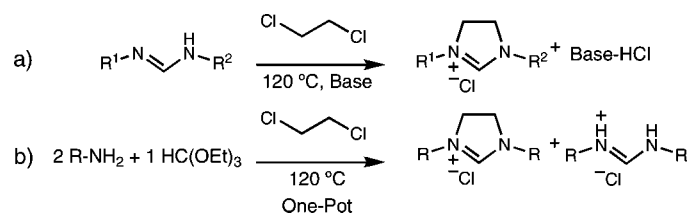
Kevin M. Kuhn and Robert H. Grubbs*

The Arnold and Mabel Beckman Laboratory of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

rhg@caltech.edu

Received March 18, 2008

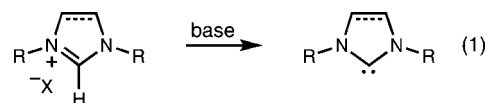
ABSTRACT



A process for the preparation of symmetric and unsymmetric imidazolium chlorides that involves reaction of a formamidine with dichloroethane and a base (a) is described. This method makes it possible to obtain numerous imidazolium chlorides under solvent-free reaction conditions and in excellent yields with purification by simple filtration. Alternatively, symmetric imidazolium chlorides can be prepared directly in moderate yields from substituted anilines by utilizing half of the formamidine intermediate as sacrificial base (b).

Since the first isolation of a stable N-heterocyclic carbene (NHC) by Arduengo,¹ their use as ligands in organometallic complexes has become routine. NHCs, as neutral, two-electron donors with little π -accepting character, have replaced phosphines in a variety of applications.² Particularly, the use of NHCs as ligands in ruthenium-based olefin metathesis has allowed for great gains in both activity and stability.³ There is also increasing interest in the use of NHCs as nucleophilic reagents and organocatalysts, with wide application in reactions such as the benzoin condensation, among others.⁴

NHCs are often prepared in situ via the deprotonation of their corresponding imidazol(in)ium salts (eq 1).⁵ Therefore, facile and high-yielding methods for the synthesis of imidazol(in)ium salts are of great interest.



The synthesis of unsaturated imidazolium salts, previously optimized by Arduengo et al., involves a one-pot procedure from glyoxal, substituted aniline, formaldehyde, and acid starting materials.⁶ Saturated imidazolium salts, however, are prepared from the reaction of triethyl orthoformate with the corresponding diamine.⁷ This approach suffers several

(1) Arduengo, A. J., III; Harlow, R. L.; Kline, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 361–363.

(2) (a) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–91. (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309. (c) Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239–2246. (d) Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev.* **2004**, *248*, 2247–2273. (e) Diez-Gonzalez, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, *251*, 874–883.

(3) (a) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247–2250. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (c) Huang, J. K.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678.

(4) For a review of recent work, see: Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000.

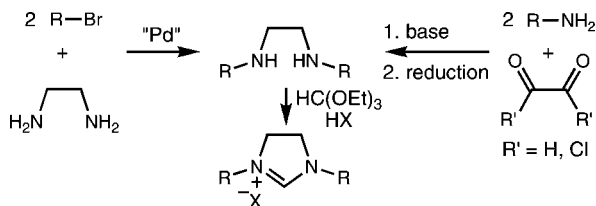
(5) (a) Öfele, K. *J. Organomet. Chem.* **1968**, *12*, P42–P43. (b) Herrmann, W. A.; Köcher, C.; Goossen, L. J.; Artus, G. R. *J. Chem.—Eur. J.* **1996**, *2*, 1627–1636. (c) Méry, D.; Aranzaes, J. R.; Astruc, D. *J. Am. Chem. Soc.* **2006**, *128*, 5602–5603.

(6) Arduengo, A. J., III. Preparation of 1,3-Disubstituted Imidazolium Salts. U.S. Patent No. 5077414, 1991.

(7) Arduengo, A. J., III; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523–14534.

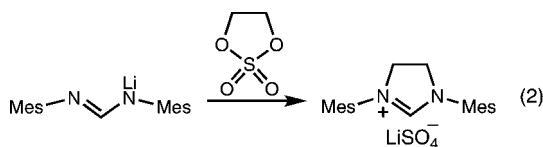
drawbacks: the preparation of the diamine generally includes either a palladium C–N coupling or a condensation and reduction sequence (Scheme 1);⁸ moreover, purification of

Scheme 1. Common Syntheses of Imidazolium Salts



the unstable diamine sometimes requires careful chromatography. Unsymmetric imidazolium salts are especially challenging synthetic targets due to the introduction of the differing substituents.⁹

Recently, Bertrand et al. developed an alternative retrosynthetic disconnection and prepared a range of five-, six-, and seven-membered imidazolium salts from the addition of “di-electrophiles” to lithiated formamidines.¹⁰ For example, 1,3-dimesitylimidazolium lithium sulfate was prepared in high yield with 1,3,2-dioxathiolane-2,2-dioxide as the dielectrophile (eq 2).



Following Bertrand's report, we reasoned that imidazolium chlorides could be more easily prepared directly from the reaction of formamidines with dichloroethane (DCE) in the presence of a base. Formamidines are ideal precursors for the preparation of imidazolium chlorides because they are generally prepared in a one-step solvent-free reaction from materials already utilized in imidazolium salt synthesis, namely anilines and triethylorthoformate.

Herein, we report this new synthetic strategy for the preparation of imidazolium chlorides under solvent-free reaction conditions and in excellent yields with purification by simple filtration. This strategy also allows for the preparation of symmetric imidazolium chlorides in a one-step, three-component procedure directly from substituted anilines.

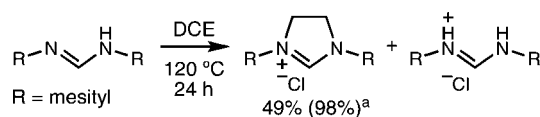
(8) (a) For recent examples, see: Ritter, T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 11788–11789. (b) Stylianides, N.; Danopoulos, A. A.; Pugh, D.; Hancock, F.; Zanotti-Gerosa, A. *Organometallics* **2007**, *26*, 5627–5635. (c) Courchay, F. C.; Sworen, J. C.; Ghiviriga, I.; Abboud, A.; Wagener, K. B. *Organometallics* **2006**, *25*, 6074–6086. (d) Beletskaya, I. P.; Bessmertnykh, A. G.; Averin, A. D.; Denat, F.; Guillard, R. *Eur. J. Org. Chem.* **2005**, 261–280.

(9) (a) Vougioukalakis, G. C.; Grubbs, R. H. *Organometallics* **2007**, *26*, 2469–2472. (b) Winkelmann, O.; Linder, D.; Lacuor, J.; Näther, C.; Lüning, U. *Eur. J. Org. Chem.* **2007**, *22*, 3687–3697.

(10) (a) Jazzar, R.; Liang, H.; Donnadieu, B.; Bertrand, G. *J. Organomet. Chem.* **2006**, *691*, 3201–3205. (b) Jazzar, R.; Bourg, J.-B.; Dewhurst, R. D.; Donnadieu, B.; Bertrand, G. *J. Org. Chem.* **2007**, *72*, 3492–3499.

Our preliminary efforts focused on the preparation of 1,3-dimesitylimidazolium chloride from *N,N'*-bis(mesityl)formamidine. The formamidine can act as both substrate and sacrificial base in the reaction. After optimization, the reaction led to nearly quantitative, reproducible yields of pure 1,3-dimesitylimidazolium chloride (Scheme 2) *N,N'*-bis-

Scheme 2



^a Yield in parentheses based on a 50% theoretical yield with half of the substrate considered as a sacrificial base.

(mesityl)formamidine hydrochloride could also be isolated and easily reverted to the formamidine for future use by solvation in pyridine and precipitation into water.¹¹

Numerous bases were screened to find an effective replacement for the sacrificial formamidine. Only diisopropylethylamine (DIPA) was shown to perform well in the reaction. Bases such as pyridine and triethylamine were too nucleophilic and reacted preferentially with dichloroethane. Strong bases such as sodium hydride deprotonated the final product.

The two methods were both successful in preparing a series of other imidazolium chlorides starting from a variety of anilines (Table 1). In all cases, reactions were completed neat in 10–20 equiv of dichloroethane and a slight excess of base. Products were easily purified by removal of excess dichloroethane, trituration in acetone or hot toluene, and filtration.

Notably, two challenging unsymmetrical imidazolium chlorides were prepared in good yields (entries 5 and 6). Our synthesis of 1-(2,6-difluorophenyl)-3-(mesityl)imidazolium chloride (entry 5), prepared here in two steps and a 65% overall yield, is a marked improvement over its previous four-step synthesis.^{9a} This method should allow for the properties and applications of unsymmetrical NHCs to be further explored.

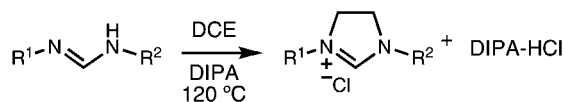
In our ongoing efforts, we have found several substrate limitations. As steric bulk at the *N*-aryl ortho positions is increased, the steric hindrance decreases reaction rate, and longer reaction times are necessary. This is exemplified by the reaction of *N,N'*-bis(2-tert-butylphenyl)formamidine, which only reached 60% conversion after 7 days (entry 4A). Highly electron-withdrawing *N*-aryl substituents also hinder the reaction; the reaction of *N,N'*-bis(2,6-trifluoromethylphenyl)formamidine was unsuccessful. Finally, reaction of a dialkyl formamidine, *N,N'*-bis(cyclohexyl)formamidine, gave only poor yields of the desired product, most likely due to the increased basicity of dialkyl formamidines.

Further efforts focused on a one-step, three-component synthesis of commonly utilized symmetric 1,3-diarylimidi-

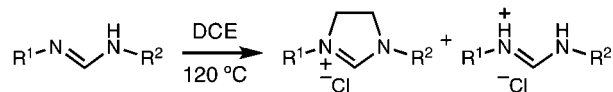
(11) Dains, F. B.; Malleis, O. O.; Meyer, J. T. *J. Am. Chem. Soc.* **1913**, *35*, 970–976.

Table 1. Preparation of 1,3 Diarylimidazolium Chlorides from Formamidines

Method A



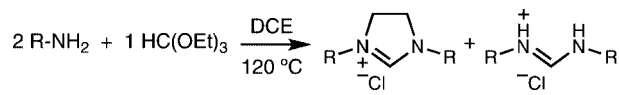
Method B



entry	product	time (h)	A yield (%) ^a	B yield (%) ^{a,b}
1		24	92	49 (98)
2		24	43 ^c	48 (96)
3		36	91	46 (92)
4		168 ^d	42	19 (38)
5		36	75	41 (82)
6		24	80	43 (86)

^a Isolated yield of the desired imidazolium chloride. ^b Yield in parentheses based on a 50% theoretical yield with half of the substrate considered as a sacrificial base. ^c A suitable non-nucleophilic base could not be found to replace the formamide as base. ^d While neither reaction had reached 100% conversion, the reactions were stopped after 7 days.

zolium chlorides from substituted anilines (Table 2). The formamide, as base and intermediate, is formed in situ, and the cyclization then proceeds as normal. Regrettably, replacement of the sacrificial formamide with diisopropylethylamine hindered the initial reaction and resulted in very limited product formation. While yields are lower than the two-step procedure, reaction optimization, and recycling of the formamide hydrochloride could be successful on the large scale. In our studies, 1,3-dimesitylimidazolium

Table 2. Preparation of 1,3 Diarylimidazolium Chlorides from Substituted Anilines in One-Step

entry	product	time (h)	yield (%) ^{a,b}
1		24	45 (90)
2		24	26 (52)
3		36	42 (84)

^a Isolated yield of the desired imidazolium chloride. ^b Yield in parentheses based on a 50% theoretical yield with half of the substrate considered as a sacrificial base.

chloride has been prepared on a 20 g scale without loss in yield or ease of purification.

In conclusion, we have devised a new synthetic strategy for the preparation of symmetric and unsymmetric imidazolium chlorides from formamidines in excellent yields. Because the formamide precursors and imidazolium products are both formed in solvent-free conditions and purified by simple trituration and filtration, this approach is more straightforward as well as more atom-economical than the previously available methods. We have also demonstrated that symmetric imidazolium chlorides can be prepared directly in moderate yields from substituted anilines. We believe these experimentally convenient procedures will find wide application as N-heterocyclic carbenes become even more common as ligands and organocatalysts.

Acknowledgment. We gratefully acknowledge financial support from NIH Grant No. GM31332 to R.H.G.

Supporting Information Available: Full experimental details for all new procedures and characterization data for formamidines (entries 1–6, Table 1) and imidazolium chlorides (entries 1–6, Table 1). This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL800628A