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A Facile Preparation of Imidazolinium Chlorides

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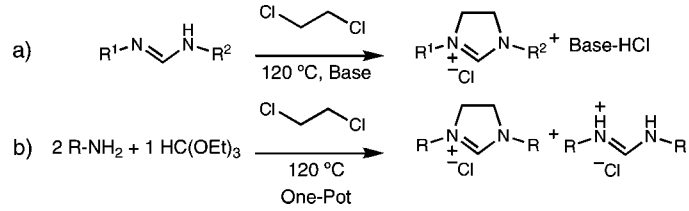
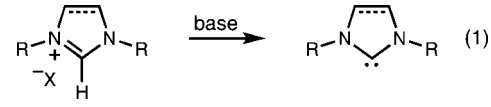
ABSTRACT



A process for the preparation of symmetric and unsymmetric imidazolinium chlorides that involves reaction of a formamidine with dichloroethane and a base (a) is described. This method makes it possible to obtain numerous imidazolinium chlorides under solvent-free reaction conditions and in excellent yields with purification by simple filtration. Alternatively, symmetric imidazolinium 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 imidazolinium 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.

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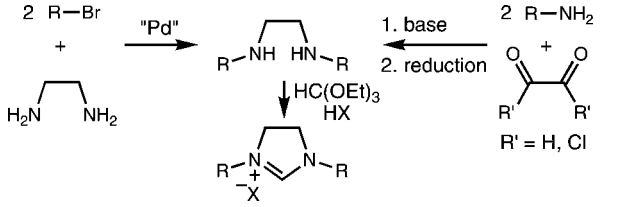
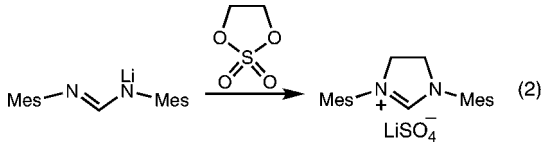
drawbacks: the preparation of the diamine generally includes either a palladium C−N coupling or a condensation and reduction sequence (Scheme 1);[8] moreover, purification of

Scheme 1. Common Syntheses of Imidazolinium Salts



the unstable diamine sometimes requires careful chromatography. Unsymmetric imidazolinium 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 imidazolinium salts from the addition of "di-electrophiles" to lithiated formamidines.[10] For example, 1,3-dimesitylimidazolinium lithium sulfate was prepared in high yield with 1,3,2-dioxathiolane-2,2-dioxide as the dielectrophile (eq 2).



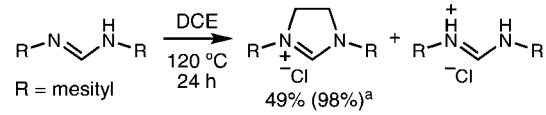
(2)

Following Bertrand's report, we reasoned that imidazolinium 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 imidazolinium chlorides because they are generally prepared in a one-step solvent-free reaction from materials already utilized in imidazolinium salt synthesis, namely anilines and triethylorthoformate.

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

Our preliminary efforts focused on the preparation of 1,3-dimesitylimidazolinium 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-dimesitylimidazolinium 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 sacrifical 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 imidazolinium 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 imidazolinium chlorides were prepared in good yields (entries 5 and 6). Our synthesis of 1-(2,6-difluorophenyl)-3-(mesityl)imidazolinium 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 subsituents 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-

(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.; Guilard, R. *Eur. J. Org. Chem.* **2005**, 261–280.

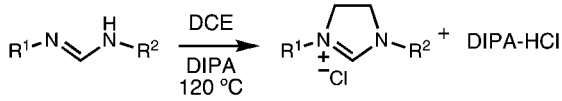
(9) (a) Vougioukalakis, G. C.; Grubbs, R. H. *Organometallics* **2007**, *26*, 2469–2472. (b) Winkelmann, O.; Linder, D.; Lacuor, J.; Näther, C.; Lüning, U. *Eur. J. Org. Chem.* **2007**, *22*, 3687–3697.

(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.

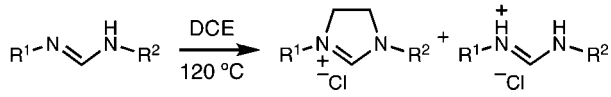
(11) Dains, F. B.; Malleis, O. O.; Meyer, J. T. *J. Am. Chem. Soc.* **1913**, *35*, 970–976.

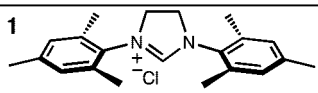
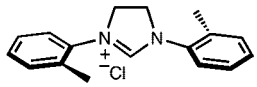
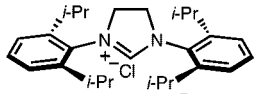
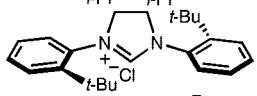
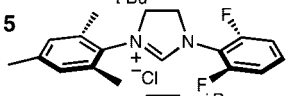
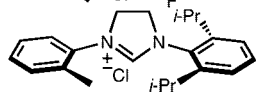
Table 1. Preparation of 1,3 Diarylimidazolinium Chlorides from Formamidines

Method A



Method B

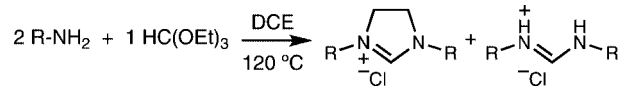


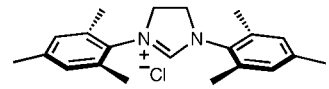
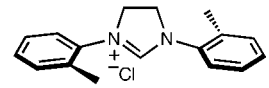
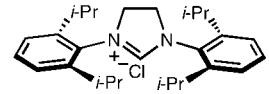
entry	product	time (h)	A yield (%)[a]	B yield (%)[a,b]
1		24	92	49 (98)
2		24	43[c]	48 (96)
3		36	91	46 (92)
4		168[d]	42	19 (38)
5		36	75	41 (82)
6		24	80	43 (86)

[a] Isolated yield of the desired imidazolinium 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 formamidine as base. [d] While neither reaction had reached 100% conversion, the reactions were stopped after 7 days.

zolinium chlorides from substituted anilines (Table 2). The formamidine, as base and intermediate, is formed in situ, and the cyclization then proceeds as normal. Regrettably, replacement of the sacrificial formamidine 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 formamidine hydrochloride could be successful on the large scale. In our studies, 1,3-dimesitylimidazolinium

Table 2. Preparation of 1,3 Diarylimidizolinium 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 imidazolinium 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 imidazolinium chlorides from formamidines in excellent yields. Because the formamidine precursors and imidazolinium 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 imidazolinium 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 imidazolinium chlorides (entries 1−6, Table 1). This material is available free of charge via the Internet at http://pubs.acs.org.

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