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A Modular Synthesis of Highly Substituted Imidazolium Salts

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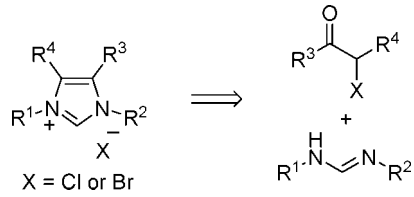
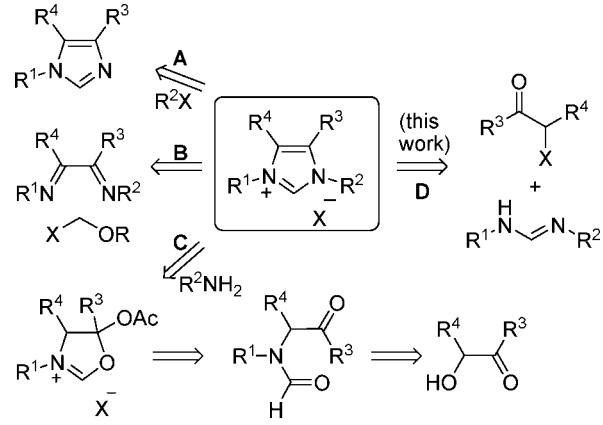
ABSTRACT



A versatile and modular one-pot method for the preparation of differently substituted symmetrical and unsymmetrical imidazolium salts is reported, and 19 examples are given. In the key step, readily available formamidines and α-halo ketones are coupled to give imidazolinium salts 3, followed by imidazolium salt formation by acylation-induced elimination. For many substitution patterns of the imidazolium salt products, this efficient strategy compares favorably with well-known processes in terms of yield, ease of synthesis, and robustness.

N-Heterocyclic carbenes (NHCs) have found widespread applications as ligands in organometallic chemistry and transition metal catalysis[1] and as organocatalysts themselves.[2] Of the different kinds of NHCs, imidazolylidenes are especially popular,[3] and the most common way of preparation is the deprotonation of the corresponding imidazolium salts. Therefore, efficient methods for the formation of 2-unsubstituted imidazolium salts with different substitution patterns are highly desirable. Until recently, the two standard routes for the formation of imidazolium salts were the alkylation of imidazoles (Scheme 1, **A**) and the alkylation/cyclization of 1,2-bisimines (Scheme 1, **B**).[4] However, these approaches are limited and generally do not allow the facile formation

Scheme 1. Most Important Routes to Imidazolium Salts



[§] These two authors have contributed equally to this work.

(1) (a) Arduengo, A. J., III. *Acc. Chem. Res.* **1999**, *32*, 913. (b) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (c) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (d) Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239. (e) Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev.* **2004**, *248*, 2247. (f) Diez-Gonzalez, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, *251*, 874. (g) Nolan, S. P., Ed. *N-Heterocyclic Carbenes in Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (h) Glorius, F., Ed. *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Springer: Berlin, 2007. (i) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2768.

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(3) Imidazolylidenes are the only class of NHCs that plays a significant role in transition-metal catalysis *and* in organocatalysis. A *Web of Science* search on 23.12.2008 for the topics "imidazolium", "imidazolinium", "triazolium", and "thiazolium" resulted in 3846, 168, 398, and 634 hits, respectively. Moreover, searching for these azolium salts in addition to the two topics "carbene" and "catalysis" resulted in 211, 24, 17, and 25 hits, respectively.

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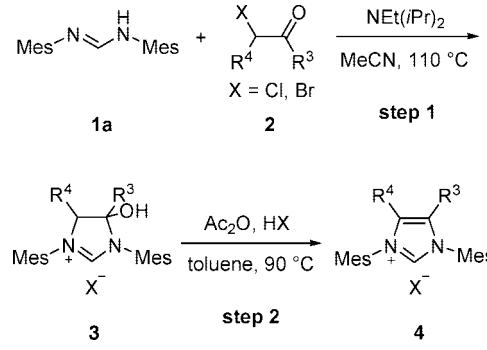
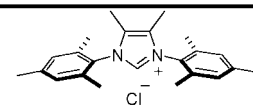
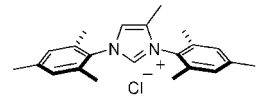
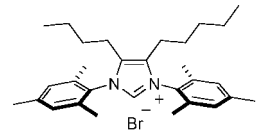
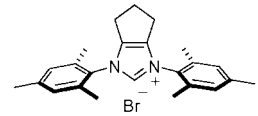
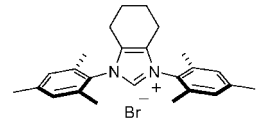
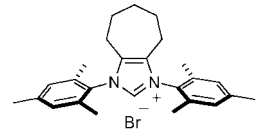
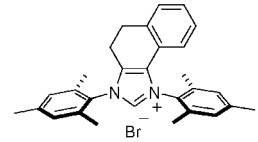
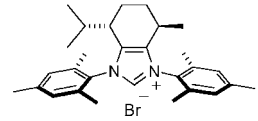
of differently 1,3-diaryl-substituted or 4,5-disubstituted imidazolium salts.[5] The situation changed with a procedure recently developed by Fürstner et al. (Scheme 1, **C**).[6] This latter method provides a variety of imidazolium salts with different substitution patterns, for example, differently 1,3-diaryl-substituted ones. However, the step count is quite high, and the linear nature of this sequence/route decelerates the rapid synthesis of a series of related imidazolium salts.

Recently, Bertrand et al. reported a new retrosynthetic disconnection of imidazolidinium salts and prepared them by an alkylation of lithiated formamidines.[7] Subsequently, Grubbs et al. developed a powerful method for the synthesis of saturated imidazolinium salts by coupling of formamidines with 1,2-dichloroethane.[8,9] In addition, Bielawski et al. formed a quinone-annulated imidazolium salt from 2,3-dichloro-1,4-naphthoquinone and *N*,*N*′-dimesitylformamidine.[10] On the basis of our continuous interest in the synthesis, structure, and catalytic activity of metal−NHC complexes[11] and of NHCs as organocatalysts,[12] these reports inspired us to evaluate a new approach to imidazolium salts: the formation of highly and differently substituted unsaturated imidazolium salts by coupling of formamidines with readily available α-halo ketones, followed by an acylation-induced elimination. Because of a lack of synthetic methods, almost all imidazolylidenes applied in catalysis are 4,5-unsubstituted ones. Therefore, we were especially intrigued by the possibility to rapidly form 4,5-dialkyl-substituted NHC precursors, enabling the investigation of their electronic and catalytic properties. Here we report the realization of this efficient and versatile approach toward imidazolium salts.

As coupling partners of the formamidines, α-halogenated ketones were chosen since they are commercially available or easily prepared, for example, by α-bromination of the corresponding ketones. In addition, the carbonyl group increases the reactivity of the halide for substitution reactions,

Table 1. Synthesis of Various IMes Derivatives[a]



entry	imidazolium salt	product	time [h] step1;2	yield[b] [%]
1		**4a**	20;14	89
2		**4b**	20;14	70
3		**4c**	20;17	85
4		**4d**	21;18	77
5		**4e**	20;17	72
6		**4f**	84;23	47
7		**4g**	21;14	94
8[c]		**4h**	148;41	11

[a] Reaction conditions. Step 1: **1a** (3 mmol), **2** (6 mmol), $NEt(iPr)_2$ (3.6 mmol), MeCN (6 mL). Step 2: Ac_2O (9 mmol), HCl or HBr (4.5 mmol), toluene (7.6 mL). [b] Isolated yield of the desired IMes derivative. [c] Due to the slow reaction in the first step, another portion of α-bromoketone (5.41 mmol) was added after 125 h.

which should be beneficial for the desired coupling with formamidines. Our study commenced with the reaction of *N*,*N*′-dimesitylformamidine and commercially available 3-chlorobutan-2-one (Table 1, entry 1). By means of an extensive screening of solvents, temperature, and additives, the suitable reaction conditions were identified. For the initial coupling

(4) (a) Arduengo, A. J., III. Preparation of 1,3-Disubstituted Imidazolium Salts. U.S. Patent No. 5077414, 1991. (b) Arduengo, A. J., III; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523. For a mild but powerful alternative, see: (c) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704.

(5) For a notable exception, see: Kison, C.; Opatz, T. *Synthesis* **2006**, 3727.

(6) (a) Fürstner, A.; Alcarazo, M.; César, V.; Lehmann, C. W. *Chem. Commun.* **2006**, 2176. (b) Fürstner, A.; Alcarazo, M.; César, V.; Krause, H. *Org. Synth.* **2008**, *85*, 34.

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

(8) Kuhn, K. M.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 2075.

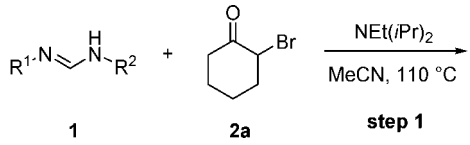
(9) See also: Iglesias, M.; Beetstra, D. J.; Knight, J. C.; Ooi, L.-L.; Stasch, A.; Coles, S.; Male, L.; Hursthouse, M. B.; Cavell, K. J.; Dervisi, A.; Fallis, I. A. *Organometallics* **2008**, *27*, 3279.

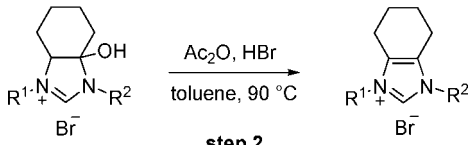
(10) Sanderson, M. D.; Kamplain, J. W.; Bielawski, C. W. *J. Am. Chem. Soc.* **2006**, *128*, 16514.

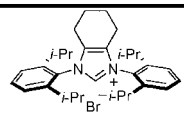
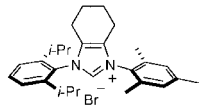
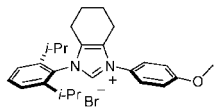
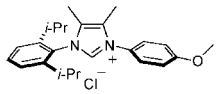
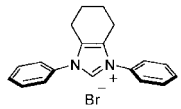
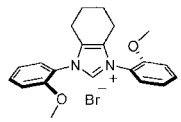
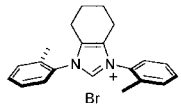
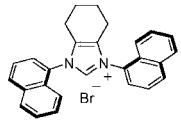
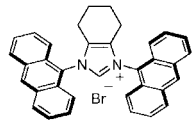
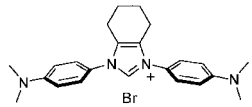
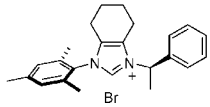
(11) (a) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523. (b) Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925. (c) Burstein, C.; Lehmann, C. W.; Glorius, F. *Tetrahedron* **2005**, *61*, 6207. (d) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195. (e) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690. See also ref. 4b.

(12) (a) Hirano, K.; Piel, I.; Glorius, F. *Adv. Synth. Catal.* **2008**, *350*, 984. (b) Glorius, F.; Hirano, K. *Ernst Schering Found. Symp. Proc.* **2008**, *2*, 159. (c) Tewes, F.; Schlecker, A.; Harms, K.; Glorius, F. *J. Organomet. Chem.* **2007**, *692*, 4593. (d) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. *Synthesis* **2006**, 2418. (e) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205.

Table 2. Synthesis of Various 1,3-Disubstituted Imidazolium Salts[a]





entry	imidazolium salt	product	time [h] step1;2	yield[b] [%]
1		**4i**	142;26	82
2			144;24	76[c]
3		**4j**	21;9	66
4		**4k**	26;20	51
5[d]		**4l**	50;17	89
6		**4m**	26;26	69
7		**4n**	31;-	24
8		**4o**	21;25	88
9		**4p**	29;16	30
10		**4q**	24;9	40
11		**4r**	21;9	56
12		**4s**	21;9	41

[a] Reaction conditions. Step 1: **1** (3 mmol), **2a** (6 mmol), $NEt(iPr)_2$ (3.6 mmol), MeCN (6 mL). Step 2: Ac_2O (9 mmol), HCl or HBr (4.5 mmol), toluene (7.6 mL); [b] Isolated yield of the desired IMes derivative. [c] Reaction run on larger scale (10 mmol scale of **1**). [d] 3-Chlorobutanone used instead of 2-bromocyclohexanone (**2a**).

reaction, polar aprotic solvents like acetonitrile (MeCN) and dimethylformamide (DMF) proved to be better suited than unpolar or polar protic solvents like toluene, dioxane, or ethanol, though product formation was observed in each case. An increase of the reaction temperature resulted in a shorter reaction time with the best results obtained at 110 °C. Nitrile solvents with higher boiling points like propionitrile and isobutyronitrile led to longer reaction times at 110 °C compared to MeCN and caused an increased formation of side products at temperatures above 110 °C.

Several bases have been screened as additives to increase reaction rate and yield. Notably, and in agreement with the results obtained by Grubbs et al.,[8] diisopropylethylamine ($NEt(iPr)_2$) was found to be optimal. Inorganic bases like K_2CO_3 and NaOAc did not affect the reaction time much, perhaps due to their low solubility in MeCN. In addition, stronger bases like NaH caused formation of many side products.

MeCN did not prove to be a suitable solvent for the elimination step. Therefore, after completion of the first step, MeCN was evaporated in vacuo and toluene was added. The sequence was completed by acylation using acetic anhydride and elimination of acetic acid in the presence of hydrochloric acid in toluene at 90 °C.[6]

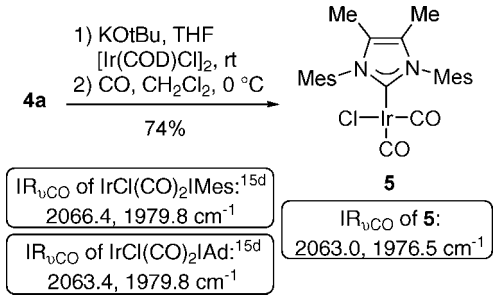
Following this method, the reaction of *N*,*N*′-dimesitylformamidine and commercially available 3-chlorobutan-2-one proceeded smoothly to produce the hydroxyimidazolidinium chloride by substitution of the chloride and intramolecular cyclization. Subsequent dehydration using Ac_2O gave the desired imidazolium salt in 89% overall yield (Table 1, entry 1). In addition, using these optimized conditions, differently substituted α-halogenated ketones were employed while keeping the same mesitylamine derived formamidine (Table 1). Our new method proved to be compatible with many different α-halogenated ketones and led to various literature known as well as novel IMes-derivatives with varying 4- and 5-substituents in good to excellent overall yields. Acyclic (entries 1−3), cyclic (entries 4−8), as well as aromatic ketones of different chain length and ring size were successfully converted into the imidazolium salts. Especially noteworthy is the formation of (−)-menthone-derived imidazolium salt **4h**, which could prove useful for applications in asymmetric catalysis.

Finally, the generality of this method was further examined using various symmetrical and unsymmetrical formamidines with 2-bromocyclohexanone or 3-chloro-2-butanone (Table 2). Notably, most formamidines performed very well and led to new symmetrical and unsymmetrical imidazolium salts in good yields. The synthesis of larger gram quantities proceeds smoothly (Table 2, entry 2). In a few cases (entries 7, 9, and 10), lower yields were obtained; however, the ease of synthesis still renders these results useful. Only the sterically very demanding *N*,*N*-bis(2-*tert*-butylphenyl)formamidine did not provide significant amounts of the desired product (not shown).

To the best of our knowledge, all imidazolium salts formed in the course of this study are new compounds.[13] Therefore, with these highly substituted NHC precursors in hand, most of them 4,5-disubstituted, we were eager to determine the influence

4,5-dialkyl substitution has on the electronic properties. Many different methods for the determination of the electronic properties of NHC ligands in transition-metal complexes have been applied.[14] The most widely accepted methodology, however, is the IR-spectroscopic analysis of the CO stretching frequencies of $(L)Ni(CO)_3$, $(L)Rh(CO)_2Cl$, $(L)Ir(CO)_2Cl$, or related complexes.[15,16] A lot of reference data exist for $(NHC)Ir(CO)_2Cl$ complexes,[15d] and thus, the corresponding iridium complex of carbene precursor **4a** was prepared in high yield following standard methods (Scheme 2).

Scheme 2. Formation of Iridium Complex **5**



It has to be noted that for reasons of comparability the IR spectra have to be measured in CH_2Cl_2 solution (Scheme 2). Comparison of the IR ν_{CO} data obtained for **5** with the one reported for the corresponding iridium complex of IMes[15d] suggests that the NHC derived from **4a** is significantly more electron rich than the 4,5-unsubstituted IMes. Moreover, this system even surpasses IAd[15d] in its electron richness. It seems that the 4,5-dialkyl substitution has a distinct influence on the carbene's electronic properties.

In summary, we have developed an efficient and versatile method for the one-pot synthesis of various highly substituted imidazolium salts. Compared to existing methods, the method described allows the realization of new substitution patterns and/or significantly increases the simplicity and robustness of the synthetic access. In addition, the rather strong influence of 4,5-dialkyl substitution on the NHC's electronic properties renders them more electron rich than the corresponding 4,5-unsubstituted NHCs. Consequently, this convenient method should prove useful for the synthesis of differently substituted NHCs for applications in transition-metal catalysis and in organocatalysis. The preparation, investigation, and application of otherwise difficult to make imidazolium salts are underway. The synthesis of chiral NHC precursors like **4h** by use of chiral α-halogenated ketones and chiral amines is attractive, and this will be reported in due course.

Acknowledgment. We are grateful to Mrs. Karin Gottschalk (WWU) for skillful technical assistance. Generous financial support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the Deutsche Akademische Austauschdienst (fellowship for K.H.), and the Alexander von Humboldt Foundation (fellowship for C.W.) is gratefully acknowledged. The research of F.G. was supported by the Alfried Krupp Prize for Young University Teachers of the Alfried Krupp von Bohlen and Halbach Foundation.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) However, for the bromide of **4a**, see: (a) Enthaler, S.; Jackstell, R.; Hagemann, B.; Junge, K.; Erre, G.; Beller, M. *J. Organomet. Chem.* **2006**, *691*, 4652. (b) Grotevendt, A.; Bartolome, M.; Nielsen, D. J.; Spannenberg, A.; Jackstell, R.; Cavell, K. J.; Oro, L. A.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 9203.

(14) See for example: (a) Magill, A. M.; Cavell, K. J.; Yates, B. F. *J. Am. Chem. Soc.* **2004**, *126*, 8717. (b) Huang, J.; Schwarz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 2370. (c) Luo, L.; Nolan, S. P. *Organometallics* **1994**, *13*, 4781.

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(16) An excellent discussion of NHC donor abilities can be found in the Supporting Information of this publication: Fürstner, A.; Alcazaro, M.; Krause, H.; Lehmann, C. W. *J. Am. Chem. Soc.* **2007**, *129*, 12676.