Unexpected Reactions of Push–Pull N-Heterocyclic Carbene Derived from *N*-(4-Methoxyphenyl)-*N*-(4-nitrophenyl)-imidazolium Chloride

Zhi-Qiang Zhu,[a] Ming-Yue Jiang,[b] Jin-Hong Lin,[a] Cheng-Pan Zhang,[a] Xiao-Chun Hang,[a] Chang-Ge Zheng,[b] Qing-Yun Chen,[a] Ji-Chang Xiao*[a]

[a] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
345 Lingling Road, Shanghai 200032, P. R. of China
Fax +86(21)64166128; E-mail: jchxiao@mail.sioc.ac.cn

[b] School of Chemical and Material Engineering, Southern Yantze University, 1800 Lihu Road, Wuxi 214122, P. R. of China

Received 5 May 2009

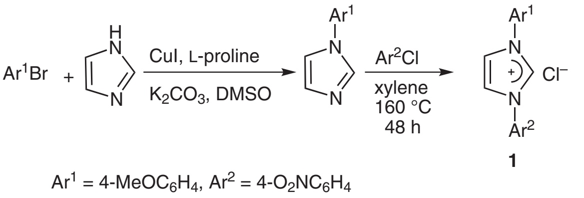
Abstract: A new precursor of N-heterocyclic carbene bearing push–pull substituents has been synthesized by the quaternization of 1-(4-methoxyphenyl)-imidazole. Unexpected reactions between the carbene generated in situ and aromatic aldehydes or acrylates were observed resulting in the formation of imidazole derivatives.

Key words: N-heterocyclic carbenes, nucleophilic addition, aromatic substitution, rearrangements

Significant achievements have been made during the past decades in the area of N-heterocyclic carbenes (NHC) for the important roles they played in coordination chemistry and organocatalysis.[1] Compared with traditional phosphine ligands and metallic catalysts, NHC are often more economical and environmentally friendly. They have been widely used in olefin metathesis (second-generation Grubbs metathesis catalyst),[2] Heck reaction,[3] benzoin condensation,[4] Stetter reaction,[5] transesterification,[6] and other reactions.[7] Besides, NHC also participate as nucleophilic reactants towards a variety of electrophilic species leading to novel molecular frameworks.[8] Very recently, Nair and Ma have reported the application of NHC in multicomponent reactions.[9] It could be expected that the exploration of the structure and chemical reactivity of NHC will definitely have fascinating prospects. Substituents on the N-atoms of NHC have strong influence on their properties. Since the isolation of the first stable NHC by Arduengo,[10] it is recognized that the steric shielding of the carbene carbon by means of the sterically demanding adamantyl groups is an important factor affecting the stability of NHC. Much attention has been paid on the steric factors of the substituents thereafter.[11] Interestingly, NHC with different electron-donating or -withdrawing substituents on the nitrogen atoms have not been much studied.

NHC are most frequently prepared via deprotonation of the corresponding azolium salts which can be readily synthesized.[1f] For example, symmetrically N,N′-disubstituted imidazolium salts can be easily obtained from the multicomponent condensation of primary amines, glyoxal and formaldehyde,[12] while the quaternization of N-substituted imidazoles usually resulted in the formation of unsymmetrically N,N′-disubstituted imidazolium salts. However, the direct quaternization of N-aryl substituted imidazoles with other aryl halides are difficult or even impossible.[13] We and others have recently described the synthesis of several imidazolium-based ionic salts with donor–acceptor substituents and investigated their applications as second-order nonlinear materials.[14] These results prompted us to extend our research to the possible applications of the imidazolium salts bearing push–pull substituents as NHC precursors.

For simplicity, the methoxy and the nitro group were chosen as a push–pull combination of substituents on N-hetereocyclic carbene to be synthesized. The imidazolium salt was prepared according to our previous work.[14] Coupling reaction of imidazole and 1-bromo-4-methoxybenzene afforded the N-arylated product 1-(4-methoxyphenyl)-imidazole. Subsequent quaternization with aryl halides presented challenges in terms of chemical reactivity, which is different from the quaternization with 1-chloro-2,4-dinitrobenzene. Higher temperature and prolonged reaction time were required for the quaternization to occur (Scheme 1). The corresponding imidazolium salt **1** was obtained in 18% yield after heating at 160 °C for 48 hours.

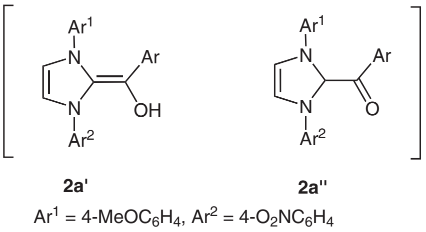


Scheme 1 Synthesis of NHC precursor **1**

With the imidazolium salt **1** in hand, we then explored its application as a NHC precursor in organic synthesis. It is well known that the condensation of benzaldehyde to benzoin can be catalyzed by most NHC.[4] The benzoin condensation was therefore investigated using the NHC with donor–acceptor substituents generated in situ from **1**. A mixture of **1**, K_3PO_4, and 3,4-dichlorobenzaldehyde in dried ethyl acetate was stirred at room temperature for 8 hours. After usual workup, to our surprise, no expected benzoin product could be detected. Only one unknown compound was isolated.

SYNLETT 2009, No. 14, pp 2305–2308
Advanced online publication: 07.08.2009
DOI: 10.1055/s-0029-1217813; Art ID: W06709ST

The mass spectrum and ^{1}H NMR of the unknown product suggested the formation of an adduct between the NHC and 3,4-dichlorobenzaldehyde. Its structure was then considered to be **2a′** or **2a″** (Scheme 2). However, no characteristic absorption peak of hydroxyl or carbonyl group was observed in its IR spectrum. Fortunately, single crystals of the unknown compound suitable for X-ray crystallography were obtained. Then the structure was unambiguously assigned to be *p*-nitrophenyl group migrated product (see Supporting Information).[15] The NHC here did not act as a catalyst, but instead, act as a reactant in the reaction.

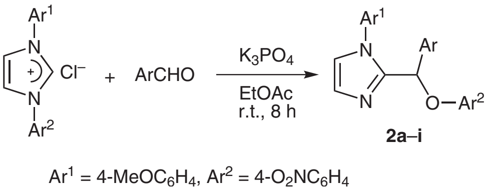


Scheme 2 Possible product from the reaction of **1** with 3,4-dichlorobenzaldehyde

Similar results were also obtained when other aromatic aldehydes with electron-withdrawing or -donating group on the phenyl ring were used as substrates. The yields were not significantly changed while varying the substituents on the aromatic aldehydes, indicating good functional-group tolerance of the reaction (Table 1).

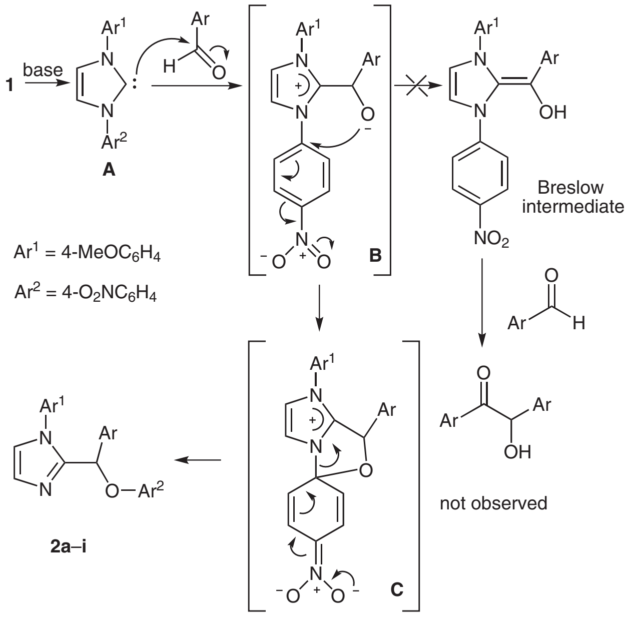
A plausible mechanism for this unexpected reaction is proposed as outlined in Scheme 3. The nucleophilic NHC **A** generated from **1** in the presence of base attacked the carbonyl carbon to give the intermediate **B**. The presence of nitro group in **B** might hamper its further rearrangement to a Breslow intermediate.[16] Thus no benzoin product was observed. The intermediate **B** then undergoes an intramolecular nucleophilic attack to give the cyclized intermediate **C**, which rearranged subsequently to afford imidazole derivatives **2a–d**. The formation of **2a–d** could also be regarded as an intramolecular nucleophilic aromatic substitution of **B**, which might be resulted from the electronically push–pull effect of the substituents, showing its large difference in chemical reactivity from the other common NHC.

Table 1 Reaction of NHC Precursor **1** with Aromatic Aldehydes



Entry	Ar	Product	Yield (%)[a]
1	3,4-$Cl_2C_6H_3$	**2a**	81
2	4-MeC_6H_4	**2b**	69
3	Ph	**2c**	78
4	3-$O_2NC_6H_4$	**2d**	73
5	4-FC_6H_4	**2e**	83
6	4-ClC_6H_4	**2f**	79
7	4-BrC_6H_4	**2g**	75
8	3-BrC_6H_4	**2h**	68
9	3,5-$(OMe)_2C_6H_3$	**2i**	72

[a] Isolated yields.

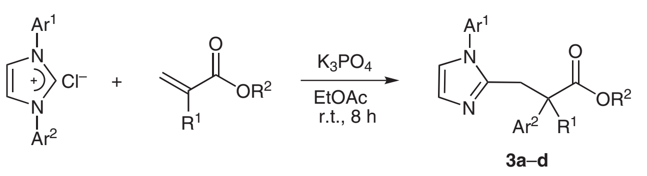


Scheme 3 Proposed mechanism

Considerable interest has been attracted in using NHC as nucleophilic reagents.[8] Enders et al. found that reaction of NHC 1,3,4-triphenyl-4,5-dihydro-l,2,4-triazol-5-ylidene with α,β-unsaturated carbonyl compound ethyl maleate produced methylenetriazoline rather than cyclopropane derivatives.[8a] To gain more insight into the reactivity of the NHC bearing push–pull substituents, we explored its reaction with α,β-unsaturated carbonyl compounds.

Under the same conditions as described above, the reaction of the NHC generated in situ from **1** with methacrylate proceeded smoothly to deliver the product **3a** in 79% yield (Table 2), which was fully characterized by spectroscopic analysis, ESI-HRMS, and IR. The structure of **3a** was further confirmed by single-crystal X-ray diffraction analysis (see Supporting Information).[15] The reaction was found to be applicable to a variety of other acrylates, giving the corresponding products **3b–d** in good yields. It can be seen that the reaction is very sensitive to the steric hindrance of the α,β-unsaturated carbonyl compounds. The presence of β-methyl group of the acrylates decreased the yield of **3d** remarkably (entry 4). Nevertheless, 89% yield of **3d** can be obtained by increasing the reaction time and temperature (entry 5).

Table 2 Reaction of NHC Precursor **1** with Acrylates



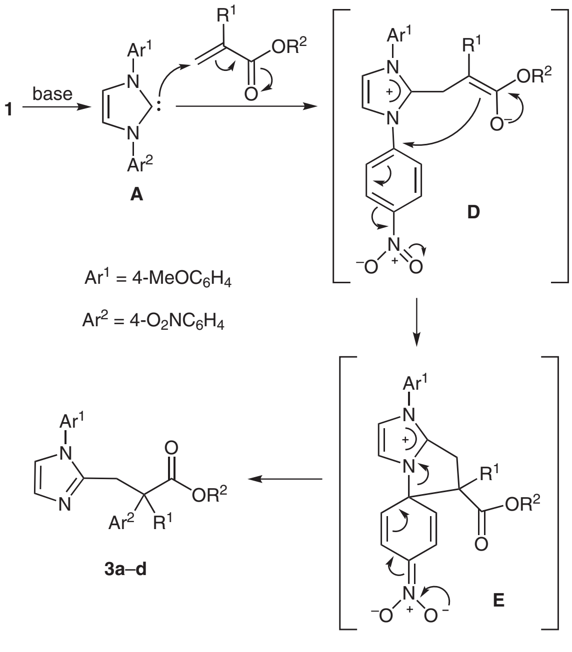
Ar^1 = 4-MeOC_6H_4, Ar^2 = 4-$O_2NC_6H_4$

Entry	R^1	R^2	Product	Yield (%)[a]
1	H	Me	**3a**	79
2	H	Et	**3b**	82
3	H	*t*-Bu	**3c**	58
4	Me	Me	**3d**	11
5	Me	Me	**3d**	89[b]

[a] Isolated yields.

[b] At 65 °C for 13 h.

The formation of **3a–d** was much similar to the above reaction (Scheme 4). The NHC **A** formed first by the deprotonation of **1**. Conjugated addition of carbene **A** to acrylate afforded the zwitterion **D**. Subsequent intramolecular nucleophilic aromatic substitution gave the product **3a–d**.



Scheme 4 Proposed mechanism

In conclusion, we have synthesized a novel N,N′-diaryl-substituted imidazolium salt bearing push–pull substituents. As a new NHC precursor, unexpected but interesting reactions with aromatic aldehydes or acrylates gave rise to imidazole derivatives. Possible mechanisms are proposed involving an intramolecular nucleophilic aromatic substitution. The presence of push–pull substituents in imidazolium salts have important effects on the reactivity of the resulting NHC and changed the subsequent reaction pathway, demonstrating much difference from the commonly used NHC. It can be expected that the reactions presented here will provide useful clues to the development of new NHC. Further work is currently underway on the synthesis and reaction of NHC bearing new combinations of push–pull substituents.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank the Chinese Academy of Sciences (Hundreds of Talents Program) and the National Natural Science Foundation (20772147) for financial support.

References and Notes

(1) For recent reviews, see: (a) Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290. (b) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 5130. (c) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 2768. (d) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988. (e) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (f) Hahn, F. E.; Jahnke, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3122.

(2) (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (b) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1277. (c) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (d) BouzBouz, S.; Boulard, L.; Cossy, J. *Org. Lett.* **2007**, *9*, 3765. (e) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441.

(3) (a) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046. (b) Fiddy, S. G.; Evans, J.; Neisius, T.; Newton, M. A.; Tsoureas, N.; Tulloch, A. A. D.; Danopoulos, A. A. *Chem. Eur. J.* **2007**, *13*, 3652.

(4) (a) Enders, D.; Kallfass, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 1743. (b) Ma, Y.; Wei, S.; Wu, J.; Yang, F.; Liu, B.; Lan, J.; Yang, S.; You, J. *Adv. Synth. Catal.* **2008**, *350*, 2645.

(5) (a) Ciganek, E. *Synthesis* **1995**, 1311. (b) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314. (c) Christmann, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2632. (d) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552.

(6) (a) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583. (b) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587. (c) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971. (d) Singh, R.; Nolan, S. P. *Chem. Commun.* **2005**, 5456. (e) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347. (f) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453.

(7) (a) Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 1472. (b) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798. (c) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418. (d) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2740.

(8) (a) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1021. (b) Enders, D.; Breuer, K.; Raabe, J.; Runsink, J.; Teles, J. H. *Liebigs. Ann.* **1996**, 2019. (c) Kuhn, N.; Weyers, G.; Henkel, G. *Chem. Commun.* **1997**, 627. (d) Rigby, J. H.; Wang, Z. *Org. Lett.* **2002**, *4*, 4289. (e) Rigby, J. H.; Wang, Z. *Org. Lett.* **2003**, *5*, 263. (f) Duong, H. A.; Tekavec, T. N.; Arif, A. M.; Louie, J. *Chem. Commun.* **2004**, 112.

(9) (a) Nair, V.; Bindu, S.; Sreekumar, V.; Rath, N. P. *Org. Lett.* **2003**, *5*, 665. (b) Ma, C.; Yang, Y. *Org. Lett.* **2005**, *7*, 1343. (c) Nair, V.; Sreekumar, V.; Bindu, S.; Suresh, E. *Org. Lett.* **2005**, *7*, 2297. (d) Ma, C.; Ding, H.; Zhang, Y.; Bian, M.; Yao, W. *J. Org. Chem.* **2008**, *73*, 578.

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

(11) Kündig, E. P.; Seidel, T. M.; Jia, Y.; Bernardinelli, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 8484.

(12) (a) Herrmann, W. A.; Köcher, C.; Gooßen, L. J.; Artus, G. R. J. *Chem. Eur. J.* **1996**, *2*, 1627. (b) Böhm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 1602.

(13) Fürstner, A.; Alcarazo, M.; César, V.; Lehmann, C. W. *Chem. Commun.* **2006**, 2176.

(14) Zhu, Z.-Q.; Xiang, S.; Chen, Q.-Y.; Chen, C.; Zeng, Z.; Cui, Y.-P.; Xiao, J.-C. *Chem. Commun.* **2008**, 5016.

(15) CCDC 690599 and CCDC 690600 contain the supplementary crystallographic data for compounds **2a** and **3a**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(16) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.