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Addition of N-Heterocyclic Carbenes to Imines: Phenoxide Assisted Deprotonation of an Imidazolium Moiety and Generation of Breslow Intermediates Derived from Imines

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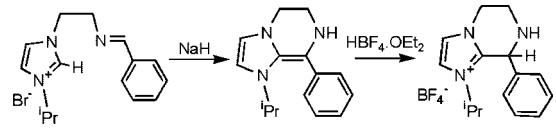
ABSTRACT



Reactions between imidazolium-imine salts and base result in C−C bond formation via intermediate *N*-heterocyclic carbenes. In the presence of a proximal OH moiety, carbene formation occurs via intramolecular deprotonation by phenoxide. For simple imines, a reactive Breslow-type intermediate gives access to new heterocycles with the formation of six- and seven-member rings.

Nucleophilic N-heterocyclic carbenes (NHC's) have been extensively investigated over the past decade principally for application as ancillary ligands to metal-mediated catalysis and as nucleophilic organocatalysts.[1] Stoichiometric reactivity has also been explored, particularly addition to multiple C═X (where X = O, S, C) and to a lesser extent formal insertion into saturated C−H and N−H bonds.[2] Furthermore, there are many useful *N*-heterocyclic compounds derived from NHC precursors such as imidazoles and imidazolium salts that exhibit interesting and useful chemistry in their own right including pharmaceuticals, components in biological systems, and as ionic liquids.[3] Therefore, the discovery of NHC reactivity has potential implications encompassing catalyst design and degradation and functional *N*-heterocycles.

One conspicuous reaction that has not been developed is the addition of NHC's to imines. For traditional carbenes, reaction occurs via initial electrophilic addition of carbene to the imine nitrogen atom giving azomethine ylide intermediates and a range of products that are dependent on the carbene.[4] With respect to NHC's there are now several examples where reactions between imines and aldehydes are catalyzed by an NHC;[5] however, turnover appears to require that the Breslow type intermediate **1** (Figure 1) acts as the nucleophile to the imine.[6]

(1) (a) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, 2006. (b) *N-Heterocyclic Carbenes (NHC) in Transition Metal Catalysis*; Glorius, F., Ed.; Topic in Organometallic Chemistry, Vol. 28; Springer-Verlag: Berlin, 2006.

(2) (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) Kuhn, N.; Steimann, M.; Weyers, G. *Z. Naturforsch.* **1999**, *54*, 427. (c) Lloyd-Jones, G. C.; Alder, R. W.; Owen-Smith, G. J. J. *Chem. Eur. J.* **2006**, *12*, 5361. (d) Frey, G. D.; Lavallo, V.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Science* **2007**, *316*, 439.

(3) (a) Eicher, T.; Hauptnamm, S. *The Chemistry of Heterocycles: Structure, Reactions, Synthesis, and Applications*, 2nd ed.; Wiley-VCH: Weinheim, 2003. For recent examples where metal NHC intermediates are directly implicated in bicyclic heterocycle synthesis see: (b) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202. (c) Wiedemann, S. H.; Lewis, J. C.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2006**, *128*, 2452. (d) Rech, J. C.; Yato, M.; Duckett, D.; Ember, B.; LoGrasso, P. V.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 490. (e) Clement, N. D.; Cavell, K. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3845.

(4) (a) Sasaki, T.; Eguchi, S.; Toi, N. *J. Org. Chem.* **1978**, *43*, 3810. (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.

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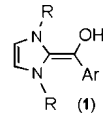
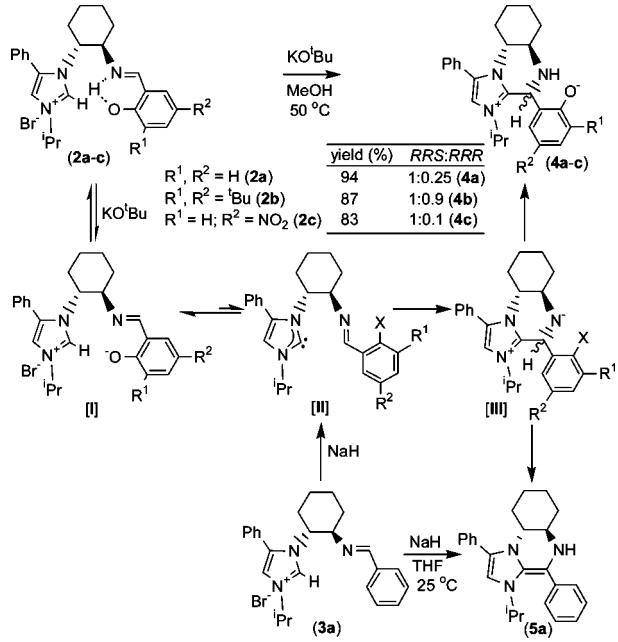


Figure 1. Breslow-type intermediate.

Herein, we describe the intramolecular reaction between NHC's and imines to give Breslow-type intermediates that provides access to new classes of heterocycles containing six- and seven-member rings. In cases where a proximal phenoxide group is present on the imine moiety, kinetic evidence suggests that reaction proceeds via internal deprotonation of an imidazolium moiety by phenoxide, followed by subsequent addition of NHC to imine. The use of chiral imidazolium-imine salts has also allowed stereochemical phenomena to be investigated.

Initial work focused on compounds **2a**−**c** and **3a** (Scheme 1) that represent precursors to chiral NHC-imine ligand

Scheme 1. Proposed Mechanism for the Formation of Betaine (**4a**−**c**) and Breslow Type (**5a**) Compounds



complexes which can be prepared without the need to isolate free NHC-imine compounds.[7] Indeed initial deprotonation attempts did not lead to the formation of free NHC-imine derivatives as judged by NMR spectroscopy. However, reports describing hydrogen-bonding interactions between imidazolium and phenoxide moieties[8] and the possibility of using **2a**−**c** as hydrogen-bonding organocatalysts[9] prompted us to investigate the deprotonation of **2a**−**c**.

Reaction between **2a**−**c** and 1 equiv of KOMe in an NMR tube showed, in the ^{1}H NMR spectra the generation of product signals with commensurate loss of the imine C*H* signal. Preparative scale reactions allowed the isolation and characterization of compounds **4a**−**c** (Scheme 1) where NMR spectroscopy ultimately confirmed the presence of signals corresponding to two diastereoisomers *RRR* and *RRS* that are differentiated by configuration at the new stereogenic center.

The molecular structures of (*RRR*)-**4b** (Supporting Information) and (*RRS*)-**4c** (Figure 2) have been determined by single

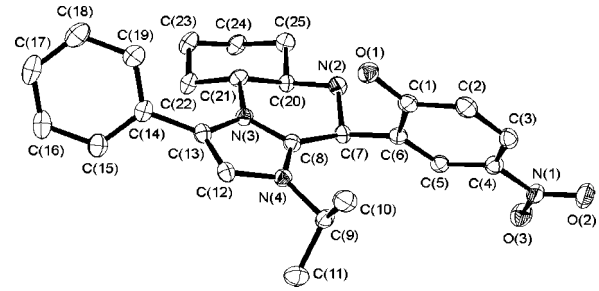


Figure 2. Molecular structure of *RRS*-**4c**. Thermal ellipsoids are at 50% probability and hydrogen atoms have been removed for clarity.

crystal X-ray diffraction confirming the proposed formulations. Interestingly, there is no indication of *intra* or *inter*molecular hydrogen bonding between phenoxide (O^-) and amine N(H) groups, which contrasts with the hydrogen bonding observed between imine-*N* and phenol-O*H* in the precursors.[10]

Determination of reaction rates by ^{1}H NMR spectroscopy in d$_4$-methanol using KOMe as base was prompted by the significantly slower synthesis of **4c**. It should be noted that most imidazolium deprotonation reactions for NHC synthesis are conducted as heterogeneous mixtures whereas **2a**−**c** exhibit excellent solubility allowing kinetic data to be acquired. At the concentrations studied, the formation of **4a** ($k_2 = 40.3 \pm 6 \times 10^{-2}$ M^{-1}s^{-1}) and **4b** ($16.2 \pm 7 \times 10^{-2}$ M^{-1}s^{-1}) proceed according to a second order rate law that is first order in both KOMe and **2a**/**b**. However, for **4c** ($k_1 = 0.565 \pm 4 \times 10^{-2}$ s^{-1}) the reaction is pseudo first order overall with respect to **2c**. It is also clear that during reaction slow epimerisation of the new stereogenic center of **4a** and **4b** is occurring and that the kinetic product is the *RRS* diastereoisomer. Furthermore, on heating to 80 °C in the absence of base, **4a**−**c** exhibit H/D exchange in d$_4$-methanol at the new stereogenic center.

(5) (a) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131. (b) Li, G. Q.; Dai, L. X.; You, S. L. *Chem. Commun.* **2007**, 852. (c) He, L.; Jian, T. Y.; Ye, S. *J. Org. Chem.* **2007**, *72*, 7466. (d) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334. (e) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418. (f) Zhang, Y. R.; He, L.; Wu, X.; Shao, P. L.; Ye, S. *Org. Lett.* **2008**, *10*, 277.

(6) Reversible reactions between an NHC and activated *N*-tosylarylimines have been described in refs 5a and 5c.

(7) (a) Bonnet, L. G.; Douthwaite, R. E.; Kariuki, B. M. *Organometallics* **2003**, *22*, 4187. (b) Dyson, G.; Frison, J. C.; Simonovic, S.; Whitwood, A. C.; Douthwaite, R. E. *Organometallics* **2008**, *27*, 281.

(8) Cowan, J. A.; Clyburne, J. A. C.; Davidson, M. G.; Harris, R. L. W.; Howard, J. A. K.; Kupper, P.; Leech, M. A.; Richards, S. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 1432.

(9) (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.

(10) Dudek, G. O. *J. Am. Chem. Soc.* **1963**, *85*, 694.

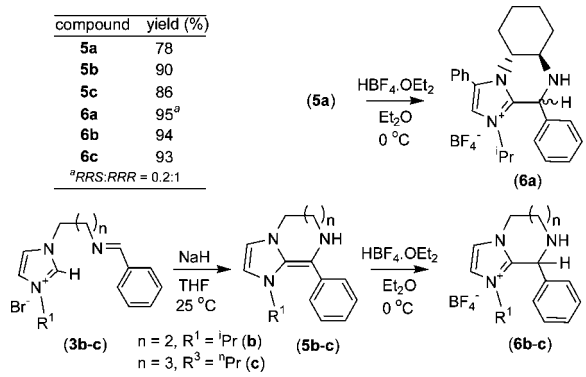
These data are consistent with the mechanism shown in scheme 1. The pK_a values of imidazolium NC(*H*)N (*ca.* 19−25)[11] and iminophenol O*H* (*ca.* 8−10) suggest initial deprotonation of **2a-c** occurs at the phenol to give (**I**) which is in equilibrium with an NHC-imine (**II**).[12] Subsequent cyclization of **II** to an imidazolium amide (**III**)[13] followed by formal proton migration gives (**4a**−**c**). Pre-equilibrium between **2a**−**b** and **Ia**−**b** accounts for KOMe appearing in the rate equation for these substrates, whereas for **2c** the equilibrium is significantly weighted toward **Ic**. The rate-limiting step for **4a**−**b** is initial deprotonation, where presumably the bulky tBu substituents of **Ib** cause a reduction in rate relative to **Ia**. However, for **4c** *intra*molecular deprotonation (**I** to **II**) is rate-limiting because the markedly lower basicity[14] of the phenoxide moiety in **Ic**.

Given the observation of formal nucleophilic addition of putative NHC to the phenol-imines of **2a**−**c**, deprotonation of **3a** and additional simple achiral analogues **3b**−**c** (Scheme 2) was investigated. Reaction in alcohols gave intractable

Scheme 2

compound	yield (%)
5a	78
5b	90
5c	86
6a	95[a]
6b	94
6c	93

[a] *RRS*:*RRR* = 0.2:1



products; however, reaction between a mixture of **3a** and 1 equiv of NaH in THF at 25 °C gives a red solution of the enamine **5a** (Scheme 1). Compound **5a** has been characterized spectroscopically and isolated as an air and moisture sensitive oil that is soluble in saturated hydrocarbons. Distinctive NMR data include the ^{13}C signals attributable to the alkenic carbons at 95.1 (N*C*C) and 142.0 ppm (N*C*N) respectively. Poor solubility of **3a** in solvents compatible with deprotonation prevented a kinetic study. However, a modified mechanism (Scheme 1) similar to that for **4a**−**c** is consistent with the formation of **5a** where an NHC-imine (**II**) is accessed directly via deprotonation of the imidazolium moiety followed by nucleophilic addition of NHC to imine giving (**III**) and subsequent formal 1,2-H migration.

(11) (a) Magill, A. M.; Cavell, K. J.; Yates, B. F. *J. Am. Chem. Soc.* **2004**, *126*, 8717. (b) Chu, Y.; Deng, H.; Cheng, J. P. *J. Org. Chem.* **2007**, *72*, 7790.

(12) For a structurally characterized phenoxide-imidazolium adduct and discussion of proton location, see ref 8.

(13) A related imidazolium-amide has been characterized for an *N*-tosylarylimine in ref 5c.

(14) pK_a's of related phenols: phenol (9.99), 4-tert-butylphenol (10.23), and 4-nitrophenol (7.15); from *Lange's Handbook of Chemistry*, 14th ed; McGraw-Hill: New York, 1992; Table 8.8.

Of more general significance, synthesis of **5b**−**c** (Scheme 2) shows that cyclization is not limited to a constrained cyclohexyl ring or C_2 linker and is compatible with a simple imidazolium moiety. Although single crystals of **5a**−**c** have yet to be grown, dioxygen and water stable derivatives can be prepared by protonation to give compounds **6a**−**c** (Scheme 2), where protonation of **5a** gives the diastereoisomers (*RRR*:*RRS*) which exhibit the opposite excess to **4a**−**c**. Additionally, in contrast to **4a**−**c**, H/D exchange in d_4-methanol is not observed at the new stereogenic center of **6a** indicating that for **4a**−**c**, exchange, and potentially epimerisation, are assisted by the proximal phenoxy-imine moiety. A single crystal diffraction study of **6b** (Figure 3) has been determined confirming the

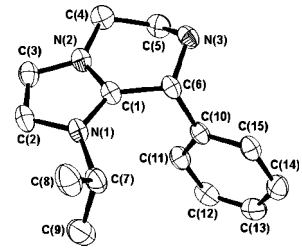


Figure 3. Molecular structure of **6b**. Thermal ellipsoids are at 50% probability and hydrogen atoms and anion have been removed for clarity.

proposed formulation. New signals for the protonated carbon atom in **6a**−**c** are observed at *ca* 5.8 and 56 ppm in the ^{1}H and ^{13}C NMR, respectively.

In summary, unactivated imines undergo base-induced intramolecular cyclization with NHCs to give Breslow-type intermediates such as **5a**−**c**. These compounds are likely to exhibit nucleophilic reactivity beyond the simple protonation described here, providing simple access to new heterocyclic compounds. Nucleophilic reactivity of NHC toward an imine has also been demonstrated via intramolecular deprotonation of imidazolium by proximal phenoxide. Reaction occurs despite the pK_a differences between solvent (MeOH), acid (imidazolium), and base (phenoxide) and is reminiscent of some enzymatic processes, perhaps suggesting a motif for functional NHC organocatalysts. Future work will explore the scope of NHC-imine cyclization with respect to other azolium moieties and the reactivity of compounds of class **5**.

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Supporting Information Available: Preparation and characterizing data of all compounds, kinetic data for **4a**−**c** and crystallographic data of **4a**, **4c** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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