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Unexpected Ring Expansion of an Enantiopure Imidazoline Carbene Ligand

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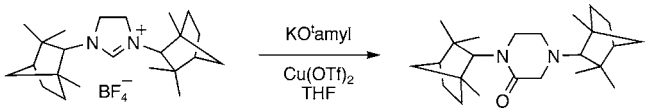
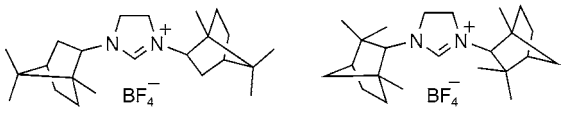
ABSTRACT



We report an unexpected ring expansion reaction of an enantiopure fenchone-derived imidazolinium salt during attempts to form copper complexes of the corresponding imidazoline carbene ligand. A *N*,*N*′-difenchyl piperazinone was formed in low yield together with the difenchyl-substituted five-membered urea.

Recently, saturated and unsaturated imidazolium salts have attracted considerable interest since the discovery that they are precursors to N-heterocyclic carbenes, an important class of ligands for coordination chemistry and catalysis.[1]

Saba and co-workers[2] reported an efficient method for the synthesis of imidazolinium, pyrimidinium, and diazepinium salts by reaction of ortho esters with 1,4-, 1,5-, or 1,6-diamines, respectively, and an ammonium salt such as tetrafluoroborate. Hartwig and co-workers[3] have reported the synthesis of the enantiopure chiral imidazolinium tetrafluoroborate salt **1** (Figure 1) from camphor and employed the corresponding carbene ligand in palladium-catalyzed enantioselective formation of oxindoles. We have synthesized the corresponding fenchyl derivative **2** (Figure 1), by a different route and have been studying this compound as a ligand precursor in synthesis.



1 2

Figure 1. Structures of camphor and fenchone-derived imidazolinium salts; enantiopure carbene ligand precursors.

Imidazol-2-ylidene ligands derived from fenchone have not been reported, and we thought that the steric bulk of the fenchone group would contribute to the carbene's kinetic stability by protecting the reactive center from attack, as postulated by Arduengo[4] in the synthesis of the adamantyl carbene derivatives. In addition, the increased bulk of the chiral groups may increase the enantiocontrol in asymmetric reactions. To this end, the synthesis shown in Scheme 1 was carried out.

Reaction of commercially available fenchone **3** with hydroxylamine hydrochloride, in the presence of pyridine, gave the oxime **4** which, on treatment with aqueous sodium nitrite in the presence of acid, formed the fenchone nitroimine **5**. Reaction with half of a molar equivalent of ethylenediamine led to the diimine **6** in essentially quantitative yield. Reduction gave the desired diamine **7** selectively and in high yield. Cyclization using the methodology of Saba and co-workers[2] employing triethyl orthoformate afforded the imidazolinium salt **2**. This route could allow different backbones or substituted backbones to be introduced to modify the imidazoline carbene ligand.

Treatment of the imidazolinium salt **2** with a base should afford the carbene ligand **8** (Scheme 2) which, on reaction

(1) For reviews, see: (a) Herrmann, W. A. *Angew. Chem., Int. Ed*. **2002**, *41*, 1290. (b) Jafapour, L.; Nolan, S. P. *Adv. Organomet. Chem*. **2001**, *46*, 181. (c) Bourrissou, D.; Guerret, O.; Gabbai, F. P.; Betrand, G. *Chem. Rev*. **2000**, *100*, 39.

(2) Saba, S.; Brescia, A. M.; Kaloustian, M. K. *Tetrahedron Lett*. **1991**, *32*, 5031.

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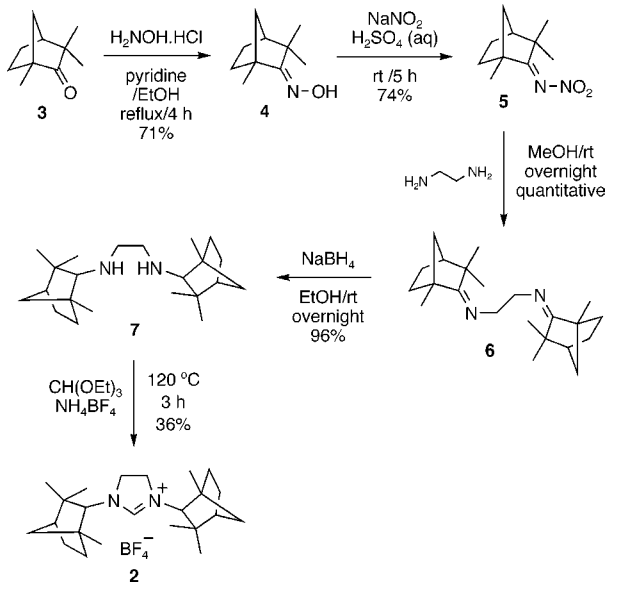
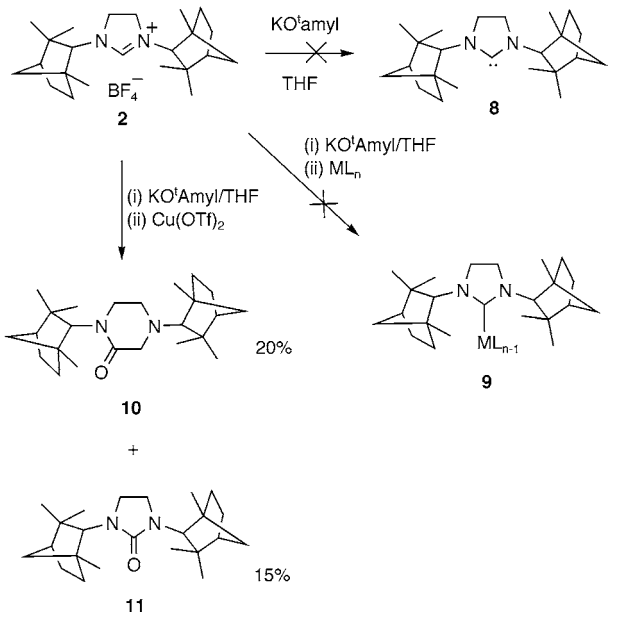
Scheme 1. Synthesis of the Difenchylimidazolinium Tetrafluoroborate Carbene Ligand Precursor



with a metal complex, should give the corresponding carbene−metal complex **9**.

Imidazolylidine and imidazolinylidine complexes have been isolated from a number of metals. Recently, several copper complexes[5] with N-heterocyclic carbene ligands have been isolated and their structures determined. Copper complexes have been reported as catalysts for several reactions including conjugate reduction[6] and addition.[7] We were interested in preparing copper complexes of the new chiral fenchyl ligands as catalysts in synthesis and studied the

Scheme 2. Reaction of the Difenchylimidazolinium Salt with Base and Cuprous Triflate Forming Piperazinone **10** and Urea **11**

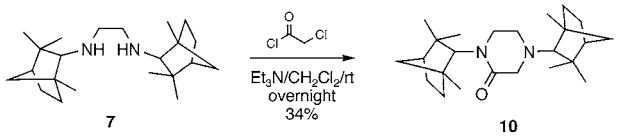


reaction of the imidazolinium salt **2** with copper salts. Here, we report an unexpected ring expansion reaction of the imidazolinium ring in **2** on treatment with base and copper(II) triflate which occurred during attempts to prepare copper complexes.

Our strategy for employing the new fenchyl imidazoline ligand involved the generation of the active carbenes from the corresponding imidazolinium salt **2** by treatment with a suitable base, generally potassium-*tert*-butoxide, potassium-*tert*-amylate, or lithium-*tert*-butoxide. The required transition-metal salt was then added to the generated carbene solution in the hope that the imidazol-2-ylidene would substitute one or two ligands to form the corresponding novel mono- or bis-substituted transition-metal complexes.

Reaction of difenchyl imidazolinium tetrafluoroborate salt **2**, potassium-*tert*-amylate, and copper(II) triflate did, however, afford the unexpected ring expanded piperazin-2-one **10** and the urea derivative **11**, rather than a copper complex, as shown in Scheme 2. The two products were separated by

Scheme 3. Unambiguous Synthesis of Piperazinone **10** by Reaction of Diamine **7** with Chloroacetyl Chloride



chromatography and further purified by recrystallization to give colorless crystals, which were identified by single-crystal X-ray diffraction, as shown in Figures 2 and 3.

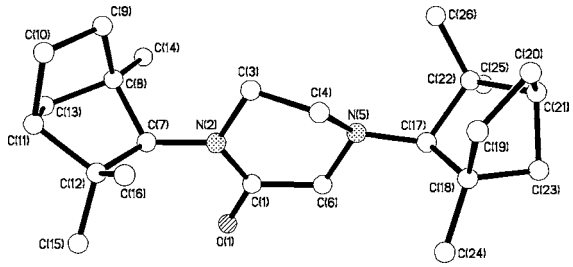


Figure 2. X-ray crystal structure of the unexpected ring expansion product, piperazinone **10**.

To further confirm the structure of the unexpected piperazin-2-one product **10**, it was synthesized by an unambiguous route (Scheme 3). The diamine **7** was reacted with chloro-

(5) (a) Tulloch, A. A. D.; Danopoulos, A. A.; Kleinhenz, S.; Light, M. E.; Hursthouse, M. B.; Eastham, G. *Organometallics* **2001**, *20*, 2027. (b) Arnold, P. L.; Scarisbrick, A. C.; Blake, A. J.; Wilson, C. *Chem. Commun.* **2001**, 2340.

(6) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417.

(7) (a) Guillen, F.; Winn, C. L.; Alexakis, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2083. (b) Pytowicz, J.; Roland, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2087.

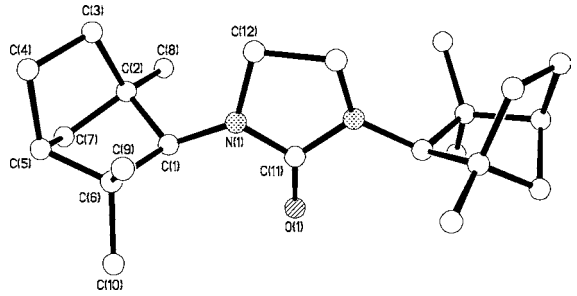
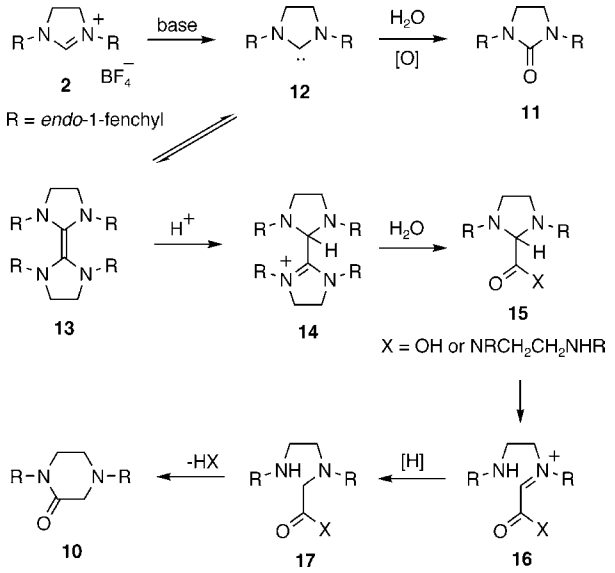


Figure 3. X-ray crystal structure of cyclic urea **11**.

acetyl chloride, in the presence of triethylamine, in dichloromethane. The piperazin-2-one **10** was obtained in low yield by this method but had essentially identical ^{1}H and ^{13}C NMR spectra to the material isolated from the reaction with copper(II) triflate. The ^{1}H NMR and ^{13}C NMR spectra were complex most likely because of hindered rotation about the C−N bonds. Analysis by IR spectroscopy showed the lactam carbonyl signal at 1649 cm^{-1}, and the ^{13}C NMR spectrum showed the carbonyl carbon at 169.6 ppm. The urea **11** was also synthesized by reaction of diamine **7** with triphosgene.

Scheme 4. Possible Mechanism Accounting for the Formation of Piperazinone **10** and Urea **11**



The formation of the urea derivative **11** (Scheme 4) most likely occurs by addition of water to the carbene **12** to form the corresponding hemi-orthoamide which is then oxidized to the stable urea **11**.

The formation of the piperazinone **10** is less easy to account for, and the source of the extra carbon atom in the ring is not obvious. A possible mechanism for the formation of this compound is suggested in Scheme 4. In the presence of potassium-*tert*-amylate, the imidazolinium salt **2** could be deprotonated to afford the carbene **12**. Dimerizaton of the carbene via the Wanzlich equilibrium[8] could give compound **13**, although this might be considered unlikely because of the bulky substituents on nitrogen. Protonation of the double bond in the dimer **13** could have occurred next, during workup or by the presence of adventitious water during the reaction, to form the imidazolinium salt **14**. Hydrolysis of this salt could afford the imidazolidine-2-carboxylic acid or amide **15**, which could ring open to afford the iminium salt **16**. Reduction of the iminium ion **16** could have occurred next, although it is not clear what the reducing agent is. A molecule of **14**, **15**, or the hydrated form of carbene **12** might have acted as a hydride transfer agent, with the latter being oxidized to the urea **11**. Copper may also have been involved in the redox process. None of the piperazinone **10** was isolated in experiments involving treatment of **2** with palladium compounds. Cyclization of compound **17** to form the lactam could occur finally, with elimination of water or an amine, to give the piperazin-2-one **10**. Alternatively, migration of an aminal nitrogen in **14** to the amidinium carbon could have occurred to form the six-membered ring.

In conclusion, we have reported a route to imidazolinium salts bearing bulky fenchyl substituents and identified an unexpected ring expansion reaction to form a disubstituted piperazinone. This reaction indicates imidazolinylidine carbene ligands may not be completely inert under certain reaction conditions. Further work on the use of the fenchyl carbene ligand and the mechanism of the ring expansion is in progress.

Acknowledgment. We thank Loughborough University for financial support.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of isolated and synthetic piperazinone **10**; reaction procedure in which **10** was isolated; method for unambiguous synthesis of **10**; and characterization data for compound **10**. Crystal data for compounds **10** and **11** in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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