Intramolecular Cyclizations of α-Lithioamine Synthetic Equivalents: Convenient Syntheses of 3-, 5-, and 6-Membered-Ring Heterocyclic Nitrogen Compounds and Elaborations of 3-Membered Ring Systems

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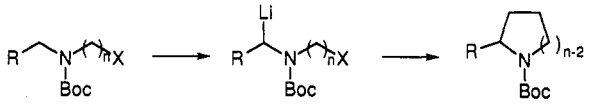
Summary: A lithiation–intramolecular cyclization reaction of *N*-Boc chloroalkyl secondary amines is reported to provide the 2-aryl-substituted pyrrolidine and piperidines **6**, **7**, **9**, and **11** and a series of 2-azabicyclo[3.1.0] derivatives **14–25**, including cyclopropane derivatives of proline and of the indolizidine–pyrrolizidine alkaloid ring system. Lithiation–substitutions of *N*-Boc-*N*-ethylcyclopropylamine to give **27–29** and lithiation–silylations of *N*-Boc aziridines to give **31–33** also are reported.

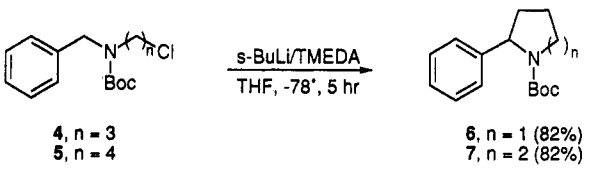
Saturated heterocyclic nitrogen compounds generally have been prepared by reactions which involve ring construction by carbon nitrogen bond formations in nucleophilic reactions of amines, by cycloadditions, or by rearrangements.[1] The recent development of α-lithioamine synthetic equivalents from *N*-Boc-amines offers a convenient alternative in which a carbanionic center adjacent to nitrogen can be used for ring and carbon–carbon bond formation.[2] The key steps are illustrated for the conversion of **1** *via* **2** to **3**. The use of α-lithioamine



1 **2** **3**

synthetic equivalents to form carbon–carbon bonds with subsequent formation of the heterocycle by displacement by nitrogen has been reported by Meyers and Marra to prepare 2-aryl-*N*-methylpiperidines and -pyrrolidines from formamidines and by Fraser and co-workers to prepare 2-phenyl-*N*-benzyl-piperidine from nitrosopiperidine.[3,4] In this paper, we provide methodology for syntheses of 3-, 5-, and 6-membered saturated nitrogen heterocycles by the methodology generalized for the formation of **3** from **1**. We have also found that when a cyclopropyl ring is formed by this approach, subsequent lithiation and substitution become facile and extensions of that result in substitutions of *N*-Boc-cyclopropylamine and *N*-Boc-aziridine are reported.

Syntheses of 2-phenyl-*N*-Boc-pyrrolidine (**6**) and 2-phenyl-*N*-Boc-piperidine (**7**) illustrate the methodology. Treatments of **4** and **5**, respectively, with *s*-BuLi/TMEDA in THF at −78 °C for 5 h provide the products in the yields indicated.

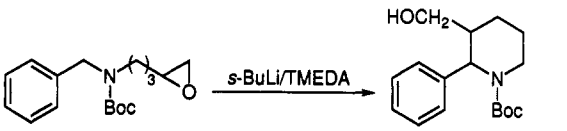


4, n = 3
5, n = 4

6, n = 1 (82%)
7, n = 2 (82%)

A demonstration of the methodology for alkaloid synthesis is provided by the conversion of *N*-Boc-(3-pyridyl)methylamine **8** to *N*-Boc-anabasine (**9**). It is

8 **9** (56%)

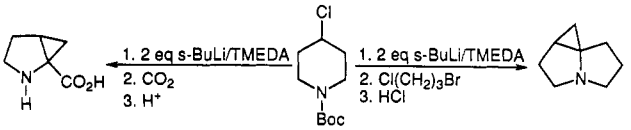


10 **11** (41%)

notable that the pyridine ring is stable to the organolithium reagents under the conditions needed to effect the α′-lithiation and displacement. It is also interesting that **8** could be prepared by reaction of the *N*-Boc-amine with 1-bromo-4-chlorobutane without interference from the nucleophilic pyridene nitrogen. The methodology can be used to open an epoxide ring and provides 2-phenyl-3-(hydroxymethyl)piperidine as a mixture of diastereomers as shown for the synthesis of **11** from **10**. The epoxide **9** was prepared by reaction of the corresponding olefin with *m*-chloroperbenzoic acid.

A more novel use of the methodology is the formation of 2-azabicyclo[3.1.0]hexane systems. The parent compound **13** was readily formed by treatment on *N*-Boc-4-chloropiperidine (**12**) with *s*-BuLi/TMEDA for 8 h at −78 °C. The cyclopropyl proton adjacent to nitrogen in **13** is available for deprotonation and electrophilic substitution as shown by the fact that treatment of **12** with 2.2 equiv of *s*-BuLi/TMEDA followed by the electrophiles shown in Table 1 gave the bicyclic products **14–23** in the yields indicated.

Syntheses of compounds incorporating the 2-azabicyclo-[3.1.0] ring system in structures which are closely related to families of natural products are demonstrated by the preparations of **24** and **25**. Lithiation cyclization–lithiation



24 (53%) **12** **25** (28%)

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(1) McKillop, A.; Boulton, A. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Eds.; Pergamon Press; Oxford, England, 1984; Vol. 2, p 67. Bird, C. W.; Cheeseman, G. W. H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Eds.; Pergamon Press: Oxford, England, 1984; Vol. 4, p 89. Gilchrist, T. L. *Heterocyclic Chemistry*, 2nd ed.; John Wiley: London, 1992.

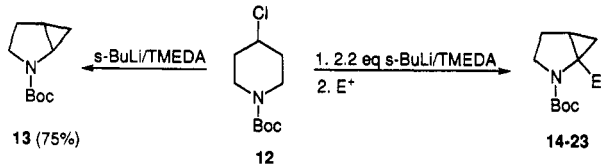
(2) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109 and references cited therein.

(3) Meyers, A. I.; Marra, J. M. *Tetrahedron Lett.* **1985**, *26*, 5863.

(4) Fraser, R. R.; Boussard, G.; Postescu, I. D.; Whiting, J. J.; Wigfield, Y. Y. *Can. J. Chem.* **1973**, *51*, 1109. Attempts to close the ring by carbon–carbon ring formation were not successful with the nitrosoamine.

0022-3263/94/1959-0276$04.50/0

Table 1. Syntheses of 1-Substituted *N*-Boc-2-azabicyclo[3.1.0]hexanes 14–23 from 12

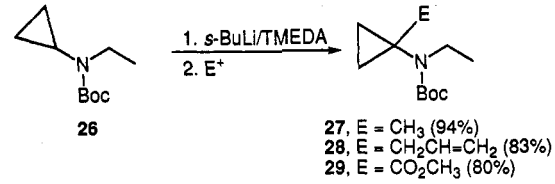


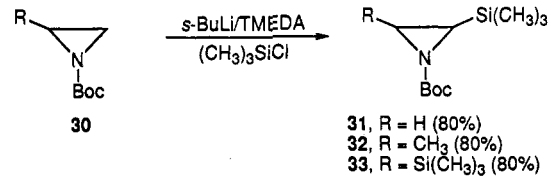
electrophile	product, E	yield (%)
$(CH_3)_3SiCl$	14, $Si(CH_3)_3$	62
CH_2=$CHCH_2Br$	15, CH_2CH=CH_2	58
$C_6H_5CH_2Br$	16, $CH_2C_6H_5$	72
n-C_4H_9I	17, n-C_4H_9	35
CH_3I	18, CH_3	36
$(C_6H_5)_2C$=O	19, $C(OH)(C_6H_5)_2$	65
$(CH_3)_2C$=O	20, $C(OH)(CH_3)_2$	64
p-ClC_6H_4CHO	21, CH(OH)pCl-C_6H_4[a]	45
$(CH_2)_5CO$	22, $C(OH)(CH_2)_5$	46
$(n\text{-}C_4H_9)_3SnCl$	23, $Sn(n\text{-}C_4H_9)_3$	70

[a] A diastereomeric mixture.

of **12** followed by reaction with carbon dioxide and hydrolysis gave **24**, an interesting amino acid which combines the structural features of proline and aminocyclopropanecarboxylic acid.[5] A similar sequence with 1-bromo-3-chloropropane as the electrophile, followed by hydrolysis of the Boc group and cyclization, gave **25**, a cyclopropyl derivative related to the indolizidine and pyrrolizidine alkaloids.[6] These compounds were isolated as their hydrochloride salts.

The facile lithiation of **13** prompted preliminary exploration of the lithiations of other 3-membered ring systems.[7,8] Treatment of *N*-Boc-*N*-ethylcyclopropylamine (**26**) with *s*-BuLi followed by reactions with electrophiles





gave **27–29** in good yields. The lithiations of **13** and **26** provide the first cases in which formation of a dipole-stabilized carbanion occurs by deprotonation of an unstabilized formal tertiary position of a carbamate in the presence of an available secondary position. This is a special situation attributable to the relatively high acidity of the cyclopropyl hydrogen. Extension to the *N*-Boc-aziridines **30** was successful only if the electrophile, trimethylsilyl chloride, was present during the lithiation as shown for the preparations of **31–33**.

The present work provides methodology for the convenient preparation of a variety of nitrogen heterocycles by a lithiation–intramolecular cyclization sequence and elaboration of products. The yields have not yet been optimized, and further development of this approach for the synthesis and elaboration of a variety of heterocyclic amines seems warranted.

Acknowledgment. We are grateful to the National Institutes of Health for support of this work.

Supplementary Material Available: Experimental details for the syntheses of **4–33** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(5) Switzer, F. L.; Van Halbeek, H.; Holt, E. M.; Stammer, C. H. *Tetrahedron* **1989**, *45*, 6091. Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231. Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796.

(6) For reviews, see: indolizidine alkaloids: Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, p 183. Pyrrolizidine alkaloids: Warren, F. L. In *The Alkaloids*; Manske, R. H. F., Ed; Academic Press: New York, **1970**; Vol. 12, p 246.

(7) Lithiation–silylation of *N*-methylmethyleneaziridine has been reported and shown to give an enantioenriched product in the presence of a chiral ligand. Quast, H.; Weise-Vélez, C. A. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 213.

(8) For preparations of lithiated aziridines by tin–lithium exchange, see: Vedejs, E.; Moss, W. O. *J. Am. Chem. Soc.* **1993**, *115*, 1607.