

Lithiation of *N*-Boc-2-methyltetrahydro-1,3-oxazine: A Synthetic Equivalent for 1-Lithio-3-hydroxy-1-propylamine

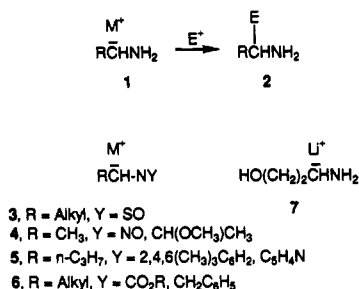
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Received October 19, 1992

Summary: A α -metallo amine synthetic equivalent of an unactivated primary amine, 1-lithio-3-hydroxy-1-propylamine (7) is provided by the lithiation of *N*-Boc-2-methyltetrahydro-1,3-oxazine (8) to give 9 which on reaction with electrophiles and hydrolysis gives derivatives of 1-substituted 3-hydroxy-1-propylamines 10–24.

The synthetic development of unactivated α -metallo amine equivalents for primary amines has been limited.^{1,2} Four such equivalents have been reported for conversions of derivatives of 1 to derivatives of 2. A metalation-allylation sequence of *N*-sulfinylamines which proceeds via 3 was communicated by Schell. Saavedra has reported lithiation and methylation of the nitroso derivative 4.⁴ A lithiation-alkylation sequence which involves 5, an imine derivative of 2,4,6-(trimethylphenyl)-2-pyridylketimine, has been communicated by Hornback.⁵ More recently, tin-lithium exchanges of carbamates of α' -amido stannanes to give 6 which undergoes reaction with a variety of electrophiles have been reported by Pearson and Lindbeck.⁶ We wish to report a lithiation-electrophilic substitution-hydrolysis sequence which proceeds via the synthetic equivalent 7 and provides derivatives of 1-substituted-3-hydroxy-1-propylamines.



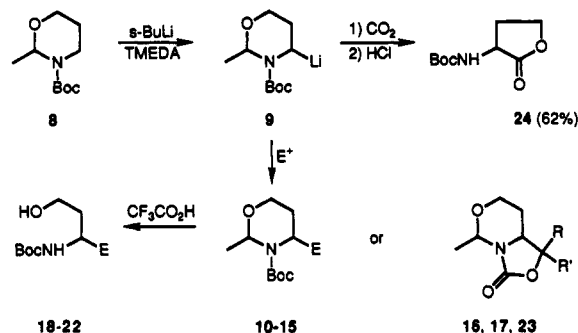
Treatment of *N*-Boc-2-methyltetrahydro-1,3-oxazine (8) with 2.5 equiv of *s*-BuLi/TMEDA at -78°C gives 9 which undergoes reactions with electrophiles to provide the products 10–17 and 23 in the yields indicated in the

Table I. Products from the Lithiation-Substitution-Hydrolysis of *N*-Boc-2-methyltetrahydro-1,3-oxazine (8)

compd	E	%	compd	E	%
10	Si(CH ₃) ₃	85	18	Si(CH ₃) ₃	89
11	CH ₃	80	19	CH ₃	86
12	CH ₂ C ₆ H ₅	55	20	CH ₂ C ₆ H ₅	85
13	<i>n</i> -C ₄ H ₉	52	21	<i>n</i> -C ₄ H ₉	83
14	Sn(<i>n</i> -C ₄ H ₉) ₃	57	22	Sn(<i>n</i> -C ₄ H ₉) ₃	84
15	CO ₂ CH ₃	62	24		62
16	R = R' = C ₆ H ₅	64			
17	R = H, R' = C ₆ H ₅	60			
23 ^a	R = R' = (CH ₂) ₄	80			

^a From 14.

reaction scheme and in Table I. In THF, lithiation times of 5 h are adequate while reactions in Et₂O require 8 h for satisfactory yields. Products 12–14 and 17 are mixtures of diastereoisomers.⁷ The product 23 was obtained by tin-lithium exchange of 14 followed by reaction with cyclohexanone. The lactone 24 could be obtained directly from 9 by reaction with carbon dioxide followed by treatment with aqueous HCl as well as by treatment of 15 with the same acid. The conversions of 10–14 to the *N*-Boc-1-substituted-3-hydroxypropylamines 18–22 were achieved by treatment of the substituted oxazines with trifluoroacetic acid in THF at 0 – 25°C for 4–5 h. The preparations of 15 and 24 illustrate the use of this methodology for the synthesis of an amino acid derivative.



In summary, the organolithium reagent 9 is a conveniently produced α -lithio amine synthetic equivalent of 7. In view of the limited availability of α -lithio amine synthetic equivalents of primary amines, conversions of the products 18–22 to other primary amines by elaboration at C-3, and the induction of asymmetry at C-1 are of further interest.^{8,9}

(7) The preliminary assignment is based on the fact that a mixture is indicated by NMR spectra, conversions give single compounds on partial hydrolysis, and we have not observed amide rotational isomers in related systems. This assignment and the conversion of 14 to 23 will be discussed in a full report.

(8) For recent studies of highly enantioenriched species analogous to 6 see: Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* 1991, 113, 8546. Chong, J. M.; Park, S. B. *J. Org. Chem.* 1992, 57, 2220.

(9) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* 1991, 113, 9708.

(1) Unactivated α -lithioamine synthetic equivalent are defined as those of structure 1 which bear substituents R that are not capable of providing substantial stabilization for the carbanion. α -Lithio amine derivatives which are based on methyl, benzylic, and allylic amines are more well-known.^{2a}

(2) (a) For summaries of α -lithioamine synthetic equivalents mainly for secondary amines see: Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* 1984, 84, 471–532. Meyers, A. I. *Aldrichim. Acta* 1985, 18, 59. Gawley, R. E.; Rein, K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, England, 1991; Vol. 1, Chapter 2.1; Vol. 3, Chapter 1.2. (b) For sequences related to this report see: Beak, P.; Lee, W. K. *J. Org. Chem.* 1990, 55, 2578. Pfammatter, E.; Seebach, D. *Liebigs Ann. Chem.* 1991, 1323. Fujii, K.; Usami, Y.; Kiry, Y.; Node, M. *Synthesis* 1992, 852.

(3) Schell, F. M.; Carter, J. P.; Wiaux-Zamar, C. *J. Am. Chem. Soc.* 1978, 100, 2894.

(4) Saavedra, J. E. *J. Org. Chem.* 1983, 38, 2388.

(5) Hornback, J. M.; Murugaveri, B. *Tetrahedron Lett* 1989, 30, 5853.

(6) Pearson, W. H.; Lindbeck, A. C. *J. Org. Chem.* 1989, 54, 5650.

General Procedure for the Synthesis of 4-Substituted *N*-Boc-2-methyltetrahydro-1,3-oxazines. A 0.25 M solution of TMEDA (145 mg, 5 mL, 1.25 mmol) in THF was cooled to $-78\text{ }^{\circ}\text{C}$ and treated with *s*-BuLi (1.25 M, 1 mL, 1.25 mmol). The mixture was stirred for 30 min at $-78\text{ }^{\circ}\text{C}$, and a precooled 0.25 M solution of **8** (101 mg, 0.5 mmol) in THF was added. The resulting mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 5 h before a precooled 0.5 M solution of electrophile (1.5 mmol) in THF was added. The resulting reaction mixture was allowed to slowly warm to room temperature and then stirred for 3 h. The mixture was dissolved in 10 mL of water and extracted with ethyl ether (20 mL \times 3) and the combined extracts were dried

over anhydrous MgSO_4 . The extracts were concentrated to give the product which was purified by flash column chromatography with ethyl acetate/hexane as eluent.

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

Supplementary Material Available: Experimental procedures and spectral data for all new compounds (5 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.