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Regioselective *N*-Methyl Carbon Lithiation of *N*-Boc-Methylalkylamines. Expedient Synthesis of Unsymmetrical Amines

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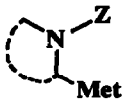
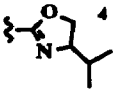
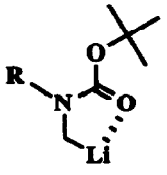
Abstract: The regioselective lithiation and functionalization at the *N*-methyl group of N-*t*-Boc-N-methylalkylamines **3** and **5** are shown with a variety of electrophiles to give products **4** and **6**, respectively, thus providing a convenient methodology for the elaboration of unsymmetrical amines.

α-Lithioamine synthetic equivalents, based on the dipole-stabilized carbanion concept, have evolved as useful species for the development of new synthetic methodology for amine elaboration.[1] From the currently known amine derivatives **1a-d**, the *N*-*t*-butyloxycarbonyl (Boc)[2] (**1a**), *N*-*t*-butyl-formamidine[3] (**1b**) and *N*-benzyl-oxazolidinone functionalities[4] have emerged as the most useful directing groups, possessing the dual properties of strong activation and ease of removal.[5,6] In this Letter, we report the highly regioselective primary over secondary deprotonation in an unsymmetrical acyclic *N*-Boc amine (**2**), affording a new method for branched amine synthesis.[7,8]



1

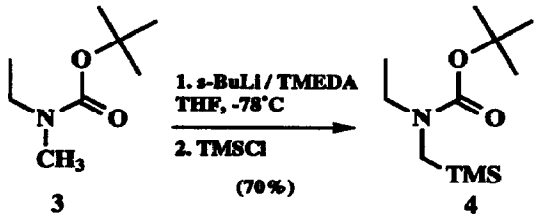
a: Met = Li; Z = CO_2t-Bu [1,2]
b: Met = Li; Z = CH=Nt-Bu [3]
c: Met = Li; Z =  [4]
d: Met = SnR_3; Z = CO_2t-Bu. [5]



2

a: R = $CH(Me)_2$
b: R = CH_3
c: R = C_2H_5

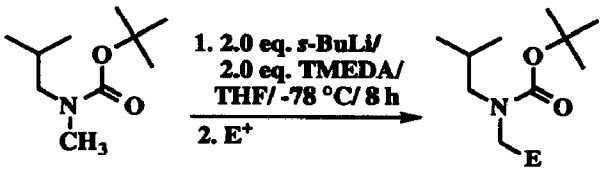
A preliminary experiment, metalation and TMSCl quench of *N*-Boc-*N*-ethylmethylamine (**3**) to give exclusively product **4** in 70% yield, provided a prototypical case which suggested the potential generality of the selective *N*-methyl lithiation process.



3 4

In order to develop this methodology for the construction of biologically active compounds, we examined the lithiation of *N*-Boc-*N*-isobutylmethylamine (**5**).[9] Thus metalation (*s*-BuLi/TMEDA/THF/-78°C) of **5** followed by deuteration led to regiospecific formation of **6a**. This result is consistent with observations of secondary over tertiary substitution in unsymmetrical cyclic cases.[2] The use of a variety of other electrophiles furnished the corresponding adducts **6b-l** in good yields (**Table**).

Table. Regiospecific Synthesis of *N*-Boc-*N*-isobutylalkylamines (6)



5 6

Entry	Conditions[a]	E^+	Product	Yield, %[c]
1	A[b]	D_2O	**6a** D	83[d]
2	A	MeI	**6b** Me	81
3	A	BuI	**6c** Bu	70
4	A	$H_2C{=}CHCH_2Br$	**6d** $CH_2CH{=}CH_2$	72
5	A	$PhCH_2Br$	**6e** CH_2Ph	66
6	B	$(CH_3)_2CHCHO$	**6f** $CH(OH)CH(CH_3)_2$	74
7	B	PhCHO	**6g** CH(OH)Ph	57
8	B	$3\text{-}(MeO)C_6H_4CHO$	**6h** $CH(OH)C_6H_4\text{-}3(OMe)$	70
9	B	$4\text{-}(MeO)C_6H_4CHO$	**6i** CH(OH)Ph-4(OMe)	53
10	B	2-PyCHO	**6j** CH(OH)-2-Py	49
11	A	TMSCl	**6k** TMS	81
12	A	Me_3SnCl	**6l** $SnMe_3$	71

[a]A: 2.0 equiv *s*-BuLi/ 2.0 equiv TMEDA/ THF/ -78°C/ 8 h; 1.5 equiv E^+ 22°C. B: 2.0 equiv *s*-BuLi/ 2.0 equiv. TMEDA/ THF/ -78°C/ 8 h; 3.0 equiv E^+ -78°C. [b]Reaction quenched after 6.5 h; [c]Yields of isolated materials. [d]87% d_1 incorporation by ^{13}C NMR.

Alkyl, allylic, and benzylic substitution (entries 2-5) as well as hydroxyalkylation (entries 6-10) may be achieved. Reactions of aromatic aldehydes (entries 7-10) provide a direct route into substituted

phenethylamines,[10] including a pyridyl analogue (entry 10), which may be of pharmacological significance.[11] Silicon and tin electrophiles are also readily introduced (entries 11 and 12).

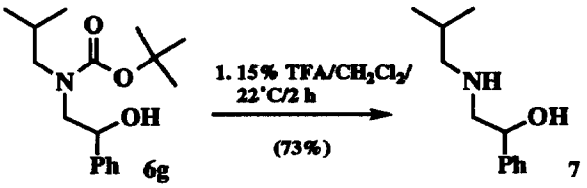
In summary, lithiation of *N*-Boc-*N*-methylalkylamines is highly regioselective for deprotonation at the *N*-methyl group. The intermediate organolithium reagent adds normally to a variety of electrophiles to provide elaborated *N*-Boc amines in synthetically useful yields.[12] These results may find utility as a general and convenient methodology for the construction of unsymmetrical amines.[13,14,15]

Acknowledgement. We wish to thank Drs. John Talley and Dan Getman (G.D. Searle) for their interest and suggestions.

References and Footnotes

1. For summaries of this methodology, see Beak, P.; Zajdel, W.J.; Reitz, D.B. *Chem. Rev.* **1984**, *84*, 471.; Gawley, R.E.; Rein, K. *Comprehensive Organic Chemistry;* Trost, B., Ed.; Pergamon Press: Oxford, England; **1991**; Vol. 1, p 459; Vol. 3, p 65.; Hart, D.J. In *Alkaloids; Chemical and Biological Perspectives*; Pelletier, S.W., Ed.; John Wiley and Sons, Inc.: New York, **1988**, *6*, 227. For a recent application, see Pandey, G.; Lakshmaiah, G. *Tetrahedron Lett.* **1993**, *34*, 4861.
2. (a) Beak, P.; Lee, W.K. *J. Org. Chem.* **1993**, *58*, 1109; (b) Beak, P.; Yum, E.K. *J. Org. Chem.* **1993**, *58*, 823 and references therein.
3. (a) Meyers, A.I.; Milot, G. *J. Org. Chem.* **1993**, *58*, 6638; (b) Meyers, A.I.; Milot, G. *J. Am. Chem. Soc.* **1993**, *115*, 6652 and references therein.
4. Gawley, R.E.; Rein, K.; Chemburkar, S. *J. Org. Chem.* **1989**, *54*, 3002.
5. Direct enantioselective formation of a configurationally stable α-lithioamine synthetic equivalent from *N*-Boc pyrrolidine has been reported: Kerrick, P.T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708.
6. Indirect formation of configurationally stable α-lithioamine equivalents via tin-lithio exchange provides a complementary method: (a) Pearson, W.H.; Lindbeck, A.C.; Kampf, J.W. *J. Am. Chem. Soc.* **1993**, *115*, 2622; (b) Burchat, A.F.; Chong, J.M.; Park, S.B. *Tetrahedron Lett.* **1993**, *34*, 51; (c) Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515.
7. Although this methodology has been widely applied to cyclic and acyclic *N*-Boc systems,[1,2] its use to functionalize unsymmetrical *acyclic*, non-benzylic amines has not been explored.
8. Radical-mediated reactions provide an alternate focus for developing new synthetic methods for amines: (a) Snieckus, V.; Cuevas, J. -C.; Sloan, C.P.; Liu; H.; Curran, D.P. *J. Am. Chem. Soc.* **1990**, *112*, 896; (b) Murakami, M.; Hayashi, M.; Ito; Y. *J. Org. Chem.* **1992**, *57*, 793; (c) Dieter, R. K.; Alexander, C. W. *Synlett* **1993**, 407.
9. Prepared in quantitative yield from the reaction of $(Boc)_2O$ and isobutylmethylamine available from Pflatz Bauer Inc.
10. In these cases, a -78°C quench with HOAc in THF (1:10) was imperative to obtain good yields of products. In contrast to previous observations on *N*-Boc piperidines,[2a] cyclic carbamates were not formed.
11. Busacca, C.A.; Johnson, R.E.; Swestock, J. *J. Org. Chem.* **1993**, *58*, 3299 and references therein.

12. (a) *Representative procedure:* To a stirred solution of TMEDA (2.0 mmol) in anhydrous THF (5mL) was added dropwise *sec*-BuLi (2.0 mmol, 1.82 mL of a 1.1 M solution) at -78°C, under nitrogen, giving a bright yellow colour. After 30 min, a pre-cooled solution of **1** (1.0 mmol) in anhydrous THF (3 mL) was added dropwise by cannula over 5 min. After 8 h at -78°C, a pre-cooled solution of freshly distilled benzaldehyde (3.50 mmol) in THF (3 mL) was added dropwise by cannula over 5 min. The colourless solution was stirred at -78°C for 1 h and then quenched with a solution of acetic acid (0.5 mL) in THF (5 mL), after warming to room temperature over 1 h, the solution was diluted with saturated $NaHCO_3$ solution (20 mL), and extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed sequentially with saturated $NaHCO_3$ solution (2 x 20 mL), water (2 x 20 mL), brine (20 mL), dried (Na_2SO_4), and evaporated *in vacuo*. Purification by flash chromatography using hexane/ethyl acetate mixtures as eluant gave 200 mg (68%) of *N*-t-butyloxycarbonyl-*N*-isobutyl-2-hydroxy-2-phenylethylamine (**2g**) as a colourless oil, ^1H NMR ($CDCl_3$, 250 MHz) δ 7.22-7.34 (5H, m, ArH), 4.88-4.93 (1H, m, C<u>H</u>(OH)), 3.95 (1H, bs, O<u>H</u>, ex. D_2O), 3.47-3.67 (1H, m, NC<u>H</u> 2CH(OH)), 3.18-3.46 (1H, m, NC<u>H</u>2CH(OH)), 2.79-3.15 (2H, m, NC<u>H</u>2CHCH3), 1.84 (1H, m, C<u>H</u>CH3), 1.46 (9H, s, t-C4H9), 0.83 and 0.84 (d and d, J= 6.62 and 6.63, CH(CH3)2).
13. To demonstrate facile deprotection to phenethylamines, compound **6g** was treated with TFA to give **7** in 73% yield.



14. All new compounds show spectroscopic (^1H and ^{13}C NMR, HRMS) and analytical properties in accordance with their assigned structures.
15. Support from NSERC Canada via Research and Industrial Research Chair awards (VS) and National Science Foundation and National Institutes of Health (PB) is gratefully acknowledged.

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