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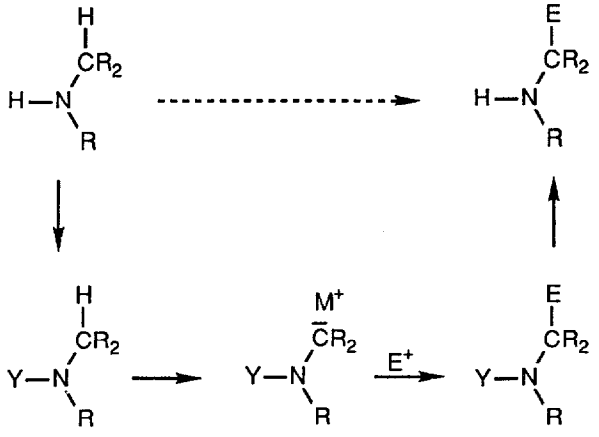
α-LITHIOAMINE SYNTHETIC EQUIVALENTS FROM DIPOLE-STABILIZED CARBANIONS: THE *t*-BOC GROUP AS AN ACTIVATOR FOR α'-LITHIATION OF CARBAMATES

Peter Beak* and Won-Koo Lee
Department of Chemistry, Roger Adams Laboratory
University of Illinois at Urbana-Champaign

Summary: The *t*-Boc group activates the α'-lithiation of piperidinyl and related carbamates to give lithium reagents which add to electrophiles to provide α'-elaborated carbamates.

Elaboration of secondary amines by the sequence of addition of an activating group to nitrogen, α'-lithiation, electrophilic substitution, and removal of the activating group to give the α-substituted amine has become a useful synthetic strategy in recent years. This general methodology is illustrated in Scheme 1 and has been reviewed.[1] Use of the formamidine group as the activating function, discovered by Meyers and coworkers, is a notable example.[2] We have sought a dipole-stabilizing group which would be convenient to use and effective with typical secondary amines. In this communication we wish to report that the well-known *t*-Boc group, which is easily added and removed, can direct α'-lithiation.

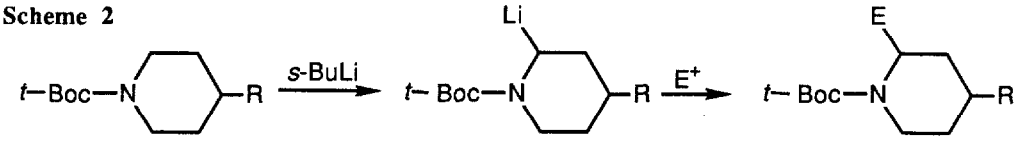
Scheme 1



Y = $(CH_3)_3COCO$

Reactions of piperidine derivatives in the sequence of Scheme 1 provide a severe test of the lithiation and substitution steps of the elaboration sequence.[3] In Scheme 2 and Table I we show that the α'-lithiation and electrophilic substitution of four piperidinyl *t*-butyl carbamates can be achieved by treatment with *s*-butyllithium at -78 °C followed by addition of the electrophile. The first reaction in entry 1 of the table is presented in detail below. The fifth and sixth entries in the table show extensions of this methodology to pyrrolidinyl and perhydroazepinyl carbamates. The dimethyl system is the seventh entry. In the case of the 1,2,3,4-tetrahydroquinolinyl carbamate, shown as the eighth entry, lithiation is "ortho" directed.[4]

Scheme 2



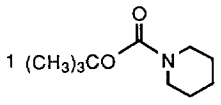
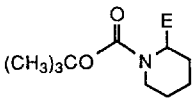
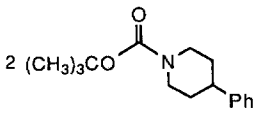
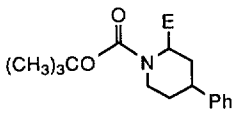
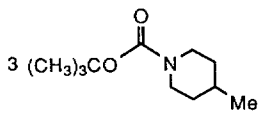
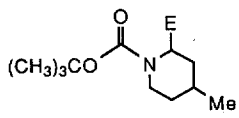
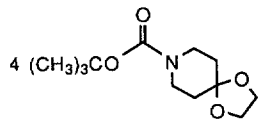
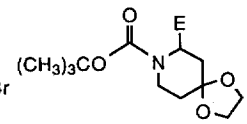
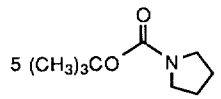
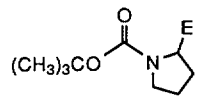
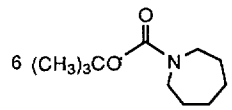
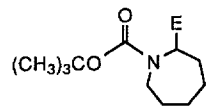
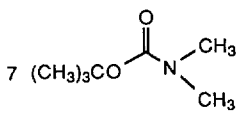
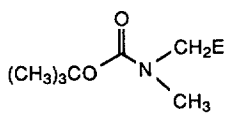
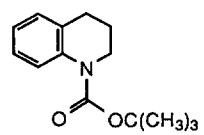
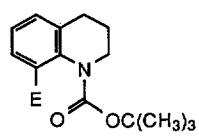
R = H, Ph, CH_3, $(OCH_2)_2$

Carbamates have been used by Seebach, by Pandit, by Macdonald, and by Comins as dipole-stabilizing functions for α'-lithiation-electrophilic substitutions adjacent to nitrogen.[1,5,6] In those cases the carbamates either have been highly stereically hindered or used with amines which have additional activation due to unsaturation. The *t*-butyl carbamates in Table 1 were prepared by standard procedures and this function is readily removed by mild acid treatment. The use of *t*-butyl carbamates of secondary amines to provide α'-lithioamine synthetic equivalents makes this approach to the elaboration of secondary amines quite convenient.

Experimental

Preparation of 2-Trimethylsilylpiperidinyl-*t*-butylcarbamate. A solution of piperidinyl-*t*-butylcarbamate (126 mg, 0.68 mmol) in 1.40 mL of ether was cooled to -78 °C and treated with TMEDA (174 mg, 1.50 mmol) followed by *s*-BuLi (1.50 M, 0.54 mL, 0.82 mmol). The mixture was stirred for 3.5 h and treated with chlorotrimethylsilane (89 mg, 0.82 mmol) then slowly warmed to room temperature and diluted with 2 mL of water. The mixture was extracted with ether (5 mL x 5) and the combined extracts were dried over K_2CO_3. The extracts were concentrated to give the crude product, which was purified by column chromatography with 10% EtOAc/hexane as eluent to give 164 mg (94%) of the oily product. ^{1}H NMR ($CDCl_3$) δ 4.25-3.50 (br, 2H), 3.00-2.50 (br, 1H), 1.68-1.34 (m, 6H), 1.43 (s, 9H), 0.06 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 154.7, 78.6, 45.2, 41.7, 28.4, 25.8, 23.5, 22.5, -0.8. MS m/e (relative intensity) 200 (M^+-57, 57), 186 (100), 156 (93), 128 (45), 84 (56), 73 (95), 57 (62). Anal Calcd for $C_{13}H_{27}NO_2Si$: C, 60.65; H, 10.57; N, 5.44. Found: C, 60.62; H, 10.58; N, 5.48.

Table I. Lithiation/Substitution of *t*-Butyl Carbamates.

Entry	Substrate	Electrophile	Product	E	Yield (%)[a]
1		Me_3SiCl Bu_3SnCl Ph CHO PhSSPh Me_2SO_4		Me_3Si Bu_3Sn Ph CHOH SPh Me	94 100 68 61 53
2		Me_3SiCl MeI $CH_2{=}CHCH_2Br$		Me_3Si Me $CH_2CH{=}CH_2$	99 83 77
3		MeI		Me	41
4		Me_3SiCl MeI $CH_2{=}CHCH_2Br$		Me_3Si Me $CH_2CH{=}CH_2$	59 74 69
5		Me_3SiCl Bu_3SnCl		Me_3Si Bu_3Sn	81 25
6		Me_3SiCl Bu_3SnCl		Me_3Si Bu_3Sn	61 45
7		Me_3SiCl MeI DMF EtI		Me_3Si Me CHO Et	70 62 53 81
8		Me_3SiCl MeI $BrCH_2CH_2CH_2Cl$		Me_3Si Me $(CH_2)_3Cl$	82 78 60

a. Yields are calculated after purification. b. Metalating agent is *s*-BuLi / TMEDA except for entry 7 where *s*-BuLi was used.

Acknowledgement. We are grateful to the National Institute of Health-Institute of General Medicine for support of this work.

References and Notes

1. P. Beak, W. J. Zajdel, D.B. Reitz, *Chem. Revs.* 1984, *84*, 471.

2. Although achiral formamidines derived from unactivated secondary amines can be used, most attention has been given to chiral formamidines in which the α' hydrogen is also activated by unsaturation. A.I. Meyers; P.D. Edwards; W.F. Rieker; T.R. Bailey, *J. Am. Chem. Soc.* 1984, *106*, 3270; A.I. Meyers, D.A. Dickman, T.R. Bailey, *ibid* 1985, *107*, 7974: A.I. Meyers, P.D. Edwards, T.R. Bailey, G.E. Jadgmann, Jr., *J. Org. Chem.* 1985, *50*, 1019: R.E. Gawley, G. Hart, M. Goicoechea-Pappas, A.L. Smith. *J. Org. Chem.* 1986, *51*, 3076.

3. P. Beak and W.J. Zajdel, *J. Am. Chem. Soc.* 1984, *106*, 1010.

4. M.P. Sibi and V. Snieckus, *J. Org. Chem*, 1983, *48*, 1935; J.E. Macdonald and G.S. Poindexter, *Tetrahedron Lett.* 1987, 1851; A. Godard, J.M. Jacquelin, G. Queguiner *J. Organometallic Chem.* 1988, *354*, 273.

5. T. Hassel, D. Seebach, *Angew. Chem. Int. Ed.* 1978, *17*, 274; T. Hassel, D. Seebach, *Helv. Chim. Acta.* 1987, *61*, 2237; J.C. Armande, U.K. Pandit *Tetrahedron Lett.* 1977, 897; T.L. Macdonald, *J. Org. Chem.* 1980, *45*, 193; D.L. Comins and M.A. Weglarz, *J. Org. Chem.* 1988, *52*, 4437.

6. A remarkable α'-lithiation at a methyl group of a lithio dithiocarbamate has recently been reported by Ahlbrecht: H. Ahlbrecht and D. Kornetzky, *Syntheses* 1988, 775. This reaction could be attributed to a complex-induced proximity effect: P. Beak and A.I. Meyers, *Accts. Chem. Res.* 1986, *19*, 356.

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