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Note

Chemoselective reduction of carbamates by $LiAlH_4$†

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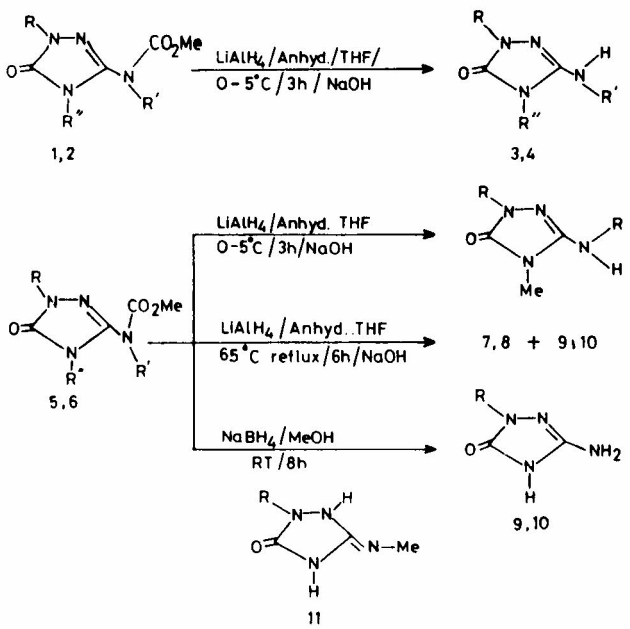
LAH reductions of 5-methoxycarbonylamino-5-methyl or 5-*H*-2-substituted-2,4-dihydro-3*H*-1,2,4-triazole-3-ones lead to chemoselective reduction of carbamates to furnish the corresponding N-methyl derivatives.

Reduction of esters, aldehydes, ketones and other carbonyl group by lithium aluminium hydride (LAH) is a well established method[1-4] and a few reports[5-7] also exist for its use to reduce carbamates to N-methyl derivatives. Our studies on the metal hydride reductions of 5-methoxycarbonyl-amino-5-methyl or 5*H*-2-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-ones have revealed the possibility of chemoselective reduction of carbamates by LAH. The details of the study are presented here.



Compd. No.	R	R′	R″
1,3	Ph	Me	H
2,4	Ph	Me	Me
5,7,9	Ph	H	H
6,8,10	pBrC$_6$H$_4$	H	H

Compounds **1** and **2** prepared by the method reported earlier[8], react with LAH to furnish two N-methylated products **3** and **4**[9]. The PMR spectrum of **3** revealed the presence of N-methyl protons at C-5 as a doublet at δ 2.92 and NH proton at position-4 at δ 11.35. Deuterium exchange converts this doublet into a singlet, thus lending support for the presence of methyl group on the primary amino residue at position-5 in compound **3**. The protons of the N-methyl group in compound **4** appeared at δ 3.01 as a doublet while the other N-methyl protons at position-4 as a singlet at 3.19. LAH reductions of compounds **5** and **6** at lower temperature yielded products **7** and **8** respectively. The appearance of characteristic signal of the N-methyl protons at δ 3.23 as a singlet and the disappearance of the signal at δ 10.80 indicated its presence at position-4 in compounds **7** and **8**. The other alternative structure **11** was ruled out since this will be tautomeric with **3**. It, therefore, appears that during LAH reduction, the carbamate group, possibly after the initial hydride attack migrates to position N-4, which after subsequent hydride attack leads to compounds **7** and **8**. The LAH reduction of compounds **5** and **6** at higher temperature furnish compounds **9** and **10** besides **7** and **8**. The structures of compounds **9** and **10** have been authenticated by comparing them with the compounds prepared by the unambiguous route of synthesis[9,10]. Unlike LAH, $NaBH_4$ reductions of compounds **5** and **6** exclusively yielded products **9** and **10** respectively. The formation of compounds **7** and **8** is interesting since monomethylated derivatives or **5** and **6** are difficult to obtain. Thus, it may be concluded that besides providing an example for the chemoselective reduction of carbamates, the present study also provides an access to synthesize the N-methyl derivatives of 1,2,4-trihydro and 2,4-dihydro-3*H*-1,2,4-triazole-3-one.

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Experimental Section

M.ps were determined on an electrothermal apparatus and are uncorrected. IR spectra: in KBr were recorded on Perkin-Elmer 881 spectrophotometer, ^{1}H NMR and ^{13}C on Bruker WM 400 MHz spectrometer using TMS as standard and EI mass on JEOL-JMS-D-300 spectrometer. Elemental analyses were done on Carlo-Erba-EA 1108 elemental analyzer. Reactions were monitored by TLC on silica gel 60 (E. Merck) of 0.25 mm thickness. Column chromatography was carried on Merck silica gel (70-230 mesh). Room temperature mentioned varies between 25-28°C.

5-Amino-4-methyl-2-phenyl and 4-bromo phenyl-1,2,4-trihydro-3*H*-1,2,4-triazole-3-one (7,8): Procedure A (at lower temp.) To a solution of compound **5,6** (2 mmole) in dry THF (20 mL) was added powdered $LiAlH_4$ (4 mmol) in portions at 0-5°C and the reaction mixture was stirred at room temperature for 3 h. THF was removed *in vacuo*, followed by the addition of 5-10 mL of saturated aq. solution of KOH and finally extracted with EtOAc (3×26 mL). Usual work-up of the organic layer furnished an oily residue which was purified by column chromatography $CHCl_3$:MeOH (97:3; v/v) as eluant to yield **7,8**.

7: Yield 65% (0.248g), m.p. 221°C (MeOH) (Found: C, 56.56; H, 5.51; N, 29.28. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.29; N, 29.45%); IR: 1658 (C=O), 3311 (NH_2); ^{1}H ($CDCl_3$): δ 3.23 (s, 3H, NCH_3), 3.94 (br, 2H, NH_2), 7.13 (m, 1H, ArH), 7.41 (m, 2H, ArH), 7.90 (d, 2H, *J*=7 Hz, ArH); ^{13}C NMR ($CDCl_3$): δ 27.76 (NMe), 117.40 (Ar), 123.02 (Ar), 128.05 (Ar), 136.81 (Ar), 142.45 (C=N), 153.63 (C=O); MS: m/z (%) 191 (23) [M^+], 148 (40).

8: Yield 62% (0.323g), m.p. 204°C (MeOH) (Found: C, 41.92; H, 3.18; N, 20.37. Calcd for $C_9H_9BrN_4O$: C, 40.18; H, 3.37; N, 20.82%); IR: 1654 (C=O), 3321 (NH_2); ^{1}H ($CDCl_3$): δ 3.31 (s, 3H, NCH_3), 3.81 (br, 2H, NH_2), 7.51 (d, 2H, J=7 Hz, ArH), 7.80 (d, 2H, *J*=7 Hz, ArH); MS: m/z 269 (33) [M^+], 255 (42).

5-Amino-2-phenyl and 3-bromophenyl-2,4-dihydro-3$\widehat{H}$-1,2,4-triazole-3-one (9,10). To a solution of compound **5,6** (2 mmol) in MeOH (15 mL) was added $NaBH_4$ (10 mmol) in portions under stirring and continued at room temperature for 8 h. Excess of solvent was removed *in vacuo*, resultant residue was diluted with water (25 mL) and extracted with EtOAc (3×20 mL). Usual work-up of the organic layer furnished an oil which was purified by column chromatography $CHCl_3$:MeOH (92:8 v/v) as eluant to yield **9**[10] (45%) and **10**[9] (42%).

Procedure B (7,8 and 9,10[9,10]) (at elevated temp.). To a solution of compound **5,6** (2 mmol) in dry THF (20 mL) was added $LiAlH_4$ (4 mmol) in portions and was stirred at 65°C for 6 h. Usual work-up procedure was followed as in procedure **A** and the residue thus obtained was purified by column chromatography using $CHCl_3$:MeOH (97:3 v/v) as eluant to give **7** (42%) and **8** (41%). Further elution with $CHCl_3$:MeOH (92:8 v/v) yielded **9**[10] (44%) and **10**[9] (42.5%).

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