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A SIMPLE METHOD OF PROTECTING A SECONDARY AMINE WITH tert BUTYLOXYCARBONYL (BOC) IN THE PRESENCE OF A PRIMARY AMINE

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Abstract: A simple method for chemically differentiating primary and secondary amines is described in which the primary amine is condensed with benzaldehyde to form an imine leaving the secondary amine available to be protected with BOC. The imine is then hydrolyzed to provide the free primary amine.

In the course of our work, it became necessary to differentiate the primary and secondary amine sites of compounds such as 1. Although compounds in which a secondary amine was protected (with BOC) in the presence of a primary amine have been prepared, elaborate synthetic schemes¹ were required. Differentiating by using low temperature to form the secondary butyloxycarbonyl(BOC) amine was problematic and at best involved a chromatography and a low yield. A succinct method was devised in which the parent diamine was condensed with benzaldehyde to form the imine of the primary amine,

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Substrate	Product	% Yield
	$BOCN - CH_2NH_2$	92
CH₃NH(CH₂)₄NH₂ 2	BOCCH ₃ N(CH ₂) ₄ NH ₂ 7	61
CH ₃ NH(CH ₂) ₂	BOC(CH ₃)N(CH ₂) ₂ -NH ₂ 8	72

Table

leaving the secondary amine untouched. The secondary amine was then treated with BOC anhydride to form the N-BOC derivative. The solvent (toluene) was then removed in vacuo and the residue was hydrolyzed with 1 N KHSO4 at room temperature. When this reaction was complete, the mixture was extracted with ether to remove debris from the BOC reaction, benzaldehyde, and other unwanted materials. Basification with sodium hydroxide while protecting with argon or nitrogen, and saturation with sodium chloride followed by extraction gave the desired amine.

Table 1 shows the results when the sequence was applied to other amines. The products from this sequence have been extremely clean and ready to use directly. Compound 3^2 , a weak primary aromatic amine and a strong secondary amine, was included to present a more difficult challenge to the sequence of differentiation. This compound worked well and required about twice as much time to condense and hydrolyze.



Experimental

General: ¹H NMR spectra were taken on a Varian XL-300 NMR. Compounds 1 and the precursor to 3 were obtained from Aldrich. Compound 2 was obtained from Maybridge. These amines are hygroscopic and readily absorb carbon dioxide from the air forming solid carbonates. These problems can be avoided by protecting them in an inert atmosphere as soon as the amines are released with base.

Compound 6: Benzaldehyde (21.2g.,0.2mol) was added all at once with stirring to a solution of 4-aminomethylpiperidine (22.8g.,0.2mol) dissolved in toluene (250mL). The mixture was refluxed (3 hr) under argon with a Dean-Stark trap attached and 3.6 mL. of water was collected. The reaction was cooled to room temperature and BOC anhydride (48 g.,0.22 mol) was added in divided portions with stirring. After stirring overnight, the solvent was evaporated in vacuo, and the residue was stirred vigorously with aqueous 1N KHSO4 (220 mL) at room temperature until tlc showed the reaction to be complete (approx. 4 hours). The mixture was extracted with ether (3X200 mL) and then the aqueous layer was made strongly basic with NaOH. The aqueous layer was saturated with NaCl, and the product extracted with chloroform (1x100mL then 3X50mL). The combined extracts were dried (MgSO4), filtered, and the solvent evaporated to leave 39.5g. of pure oily 6. (92%). ¹H NMR (CDCL₃)(300MHz): δ 1.14(2H, d,d, J=7Hz,J=4.5Hz),1.45(9H, s), 1.6(1H, m),1.74(2H.bd. J=12.8Hz) 2.68(4H, m), 3.65(2H, bs), 4.12(2H, bm)

Compound 7:¹H NMR (CDCl₃) (300MHz): δ1.45(13H, bm), 1.92(2H, bs), 2.73(2H, t, J=6.84Hz), 2.84(3H, s), 3.21(2H, t, J=6.74Hz).

Compound $8: {}^{1}H$ NMR (DMSO-d₆) (300 MHz): δ 1.33(9H, s), 2.51 (1H,d. J=6.2Hz), 2.55(1H, d, J=7.3Hz), 2.71(3H, s), 3.25((2H, t, J=7.6Hz), 3.32 (1H, s), 4.85(2H, s), 6.49(2H, d, J=1.1Hz), 6.82(2H, d, J=1.6Hz).

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2) This amine was made by preparing the methyl urethane of the aliphatic amine at low temperature (MeOCOCI, Et3N,THF -78°C) then reduction with Red-Al (Red-Al, Ether, RT, 24hr.). The product amine (3) could have been chemically differentiated successfully at very low temperature but it serves as a challenging example done in this way.

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