Mono-Protected Diamines. N^{α}-*tert*-Butoxycarbonyl α,ω-Alkanediamine Hydrochlorides from Amino alcohols.

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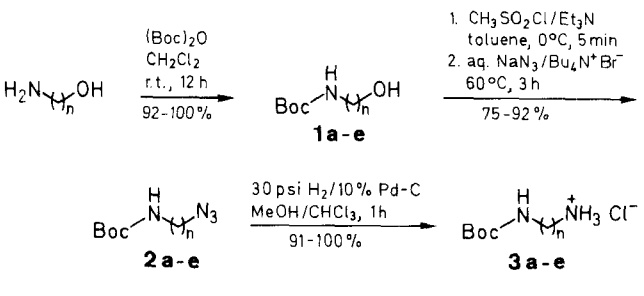
N^{α}-*tert*-Butoxycarbonyl α,ω-alkanediamine hydrochlorides **3a–e** are prepared from the amino alcohols in yields of 66–87%. Reaction of the free amine with di-*tert*-butyl dicarbonate gives the *N*-*tert*-Butoxycarbonylamino alcohol **1a–e**. One-pot conversion to the azide **2a–e** via the mesylate under phase-transfer conditions followed by hydrogenolysis in the presence of chloroform yields the title compounds.

N^{α}-*tert*-Butoxycarbonyl α,ω-alkanediamines are one type of differentially protected homobifunctional reagents that have great utility in many biochemical applications. Included in these are the linking of small organic molecules (haptens) to proteins to form immunogenic or enzyme conjugates; the linking of small organic molecules (haptens) to fluorescent labels forming tracers important in the development and performance of immunodiagnostic tests; the covalent attachment of proteins to solid supports in the preparation of affinity columns.[1] While many α,ω-alkanediamines are commercially available, we have found that some published methods developed to mono-protect them are often difficult to reproduce, especially on the higher homologs.[2–4] Mechanistic studies indicate that high dilution, a large excess of the diamine, and deactivated acylating reagents are often necessary to minimize the yield of the di-protected species.[5] An alternate approach is the *N*-protection of a bifunctional amine, followed by the conversion of the other functional group to an unprotected amine. ω-Bromoamides have been converted to the corresponding monoacylated diamines via the azide.[6] More recently a scheme has been reported using α,ω-alkaneamino carboxamides, in which the carboxamide is converted to the amine via dehydration to the nitrile and subsequent hydrogenation (Raney Nickel, 300 psi).[7] While yields were acceptable, many labs may not be equiped to perform high-pressure hydrogenations.



1-3	a	b	c	d	e
n	2	3	4	5	6

ω-Amino alcohols are readily available and easily converted to N^{α}-*tert*-butoxycarbonyl α,ω-alkanediamine hydrochlorides, which are stable, crystalline solids that may be deprotected under mild conditions.[8]

ω-Amino alcohols are *N*-protected upon reaction with di-*tert*-butyldicarbonate in dichloromethane at room temperature giving the *N*-*tert*-butoxycarbonylamino alcohols **1a–e** after simple aqueous workup. The hydroxyl group is converted in less than 5 minutes at 0 °C to the mesylate quantitatively (as observed on thin layer chromatography: silica gel, ethyl acetate/hexanes, 1:1) with methanesulfonyl chloride in toluene in the presence of triethylamine as the acid scavenger. The intermediate mesylate is not isolated, but converted directly to the azide upon the addition of an aqueous solution of sodium azide and a catalytic amount (10 mole%) of the phase transfer-catalyst, tetrabutylammonium bromide. The reaction proceeds slowly at room temperature, but with heating at 60 °C for 3 hours the hitherto unreported azide **2a–e** can be isolated by a simple aqueous workup. Conversion to the stable amine hydrochloride **3a–e** is accomplished by hydrogenolysis over 10% palladium on carbon (30 psi) in the presence of a small amount of chloroform which serves as the hydrogen chloride source.[9]

All reagents were purchased from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin and were used without further purification. Solvents employed were of reagent or HPLC grade and were used as received. ^{1}H-NMR spectra were recorded at 200 MHz on a Chemagnetics A-200 spectrometer. IR spectra were recorded on a Perkin-Elmer 298 IR spectrometer. Chemical ionization mass spectra were recorded on either a Hewlett-Packard 5985 or Nermag R30-10. Melting points are uncorrected and were taken on a Thomas-Hoover Uni-melt capillary melting point apparatus. Elemental Analyses were performed by Galbraith Laboratories, Knoxville, Tennesee.

6-(*N*-*tert*-Butoxycarbonylamino)-1-hexanol (1e); Typical Procedure:
6-Amino-1-hexanol (10 g, 85.3 mmol) is dissolved in CH_2Cl_2 (50 mL) in a 250 mL round-bottom flask equiped with a magnetic stirrer and a pressure equalizing addition funnel. Di-*tert*-butyl dicarbonate (20 g, 92 mmol) in CH_2Cl_2 (50 mL) is added dropwise over 30 min. After stirring for 12 h, the solution is diluted with Et_2O (100 mL) and washed with phosphate buffer (0.5 M, pH 5.4, 2 × 50 mL), sat. $NaHCO_3$ (50 mL), brine (50 mL) and dried ($MgSO_4$), then evaporated to give **1e** as an oil that solidifies on refrigeration, yield: 18.5 g (100%). (See Table 1.)

1-Azido-6-(*tert*-butoxycarbonylamino)hexane (2e); Typical Procedure:
To a solution of **1e** (1 g, 4.6 mmol) and triethylamine (640 µL, 4.6 mmol) in toluene (20 mL), which has been cooled to 0 °C in an ice bath, is added methanesulfonyl chloride (355 µL, 4.6 mmol) under nitrogen. After stirring for 5 min, tetrabutylammonium bromide (140 mg, 0.46 mmol) and a solution of NaN_3 (2.5 g, 38.5 mmol) in water (10 mL) is added. The reaction is heated to 60 °C for 3 h. The reaction is then allowed to cool to r.t., diluted with Et_2O (100 mL) and washed with phosphate buffer (0.5 M, pH 5.4, 20 mL), brine (20 mL) and dried ($MgSO_4$), then evaporated to give **2e** as an oil, yield: 1.02 g (92%). (See Table 2.)

[*Caution:* Sodium azide forms explosive salts with other metals. The excess azide should be decomposed after the workup by reaction with nitrous acid, before flushing down the sink.[12]]

Table 1. α-*tert*-Butoxycarbonylamino-ω-alkanols **1a–e** Prepared

Product	Yield (%)	Molecular Formula[a,b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ	MS (DCI/NH_3)[d] m/z
1a	92	$C_7H_{15}NO_3$ (161.2)	1.46 (s, 9H, Boc), 3.24–3.33 (q, 2H, BocNHC$\underline{H}_2$), 3.65–3.73 (q, 2H, C$\underline{H}_2$OH), 5.1–5.3 (br, 1H, BocN$\underline{H}$)	162 $(M+H)^+$, 179 $(M+NH_4)^+$
1b[10]	100	$C_8H_{17}NO_3$ (175.2)	1.44 (s, 9H, Boc), 1.60–1.76 (m, 2H, C$\underline{H}_2$), 3.21–3.31 (q, 2H, BocNHC$\underline{H}_2$), 3.63–3.68 (t, 2H, C$\underline{H}_2$OH), 4.96–5.13 (br, 1H, BocN$\underline{H}$)	176 $(M+H)^+$, 193 $(M+NH_4)^+$
1c	98	$C_9H_{19}NO_3$ (189.3)	1.44 (s, 9H, Boc), 1.57–1.62 (m, 4H, (C$\underline{H}_2$)$_2$), 3.11–3.20 (q, 2H, BocNHC$\underline{H}_2$), 3.63–3.72 (q, 2H, C$\underline{H}_2$OH), 4.52–4.69 (br, 1H, BocN$\underline{H}$)	190 $(M+H)^+$, 207 $(M+NH_4)^+$
1d[10]	100	$C_{10}H_{21}NO_3$ (203.3)	1.44 (s, 9H, Boc), 1.32–1.63 (m, 6H, (C$\underline{H}_2$)$_3$), 3.08–3.17 (q, 2H, BocNHC$\underline{H}_2$), 3.60–3.69 (q, 2H, C$\underline{H}_2$OH), 4.32–4.56 (br, 1H, BocN$\underline{H}$)	204 $(M+H)^+$, 221 $(M+NH_4)^+$
1e[11]	100	$C_{11}H_{23}NO_3$ (217.3)	1.46 (s, 9H, Boc), 1.12–1.60 (m, 8H, (C$\underline{H}_2$)$_4$), 3.0–3.13 (q, 2H, BocNHC$\underline{H}_2$), 3.53–3.63 (t, 2H, C$\underline{H}_2$OH), 4.53–4.68 (br, 1H, BocN$\underline{H}$)	218 $(M+H)^+$, 235 $(M+NH_4)^+$

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.26, N ±0.22 except for **1b**, N +0.45.
[b] Compounds **1a–1e** are oils at r.t.
[c] Performed on a Chemagnetics A-200 NMR.
[d] Performed on an HP 5985 or Nermag R30-10.

Table 2. ω-Azido-α-*tert*-butoxycarbonylaminoalkanes **2a–e** Prepared

Product	Yield (%)	Molecular Formula[a,b]	IR[b] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ	MS (DCI/NH_3) m/z
2a	75	$C_7H_{14}N_4O_2$ (186.2)	2080 (N_3), 1680 (CO)	1.46 (s, 9H, Boc), 3.26–3.34 (q, 2H, BocNHC$\underline{H}_2$), 3.39–3.45 (t, 2H, C$\underline{H}_2$N$_3$), 5.1–5.3 (br, 1H, BocN$\underline{H}$)	187 $(M+H)^+$, 204 $(M+NH_4)^+$
2b	80	$C_8H_{16}N_4O_2$ (200.2)	2080 (N_3), 1680 (CO)	1.44 (s, 9H, Boc), 1.70–1.83 (m, 2H, C$\underline{H}_2$), 3.16–3.26 (q, 2H, C$\underline{H}_2$N$_3$), 3.32–3.39 (t, 2H, BocNHC$\underline{H}_2$), 4.56–4.72 (br, 1H, BocN$\underline{H}$)	201 $(M+H)^+$, 218 $(M+NH_4)^+$
2c	90	$C_9H_{18}N_4O_2$ (214.3)	2080 (N_3) 1680 (CO)	1.44 (s, 9H, Boc), 1.28–1.68 (m, 4H, (C$\underline{H}_2$)$_2$), 3.11–3.20 (q, 2H, BocNHC$\underline{H}_2$), 3.28–3.34 (t, 2H, CH$_2$N$_3$), 4.52–4.68 (br, 1H, BocN$\underline{H}$)	215 $(M+H)^+$, 232 $(M+NH_4)^+$
2d	80	$C_{10}H_{20}N_4O_2$ (228.3)	2080 (N_3), 1680 (CO)	1.46 (s, 9H, Boc), 1.32–1.68 (m, 6H, (C$\underline{H}_2$)$_3$), 3.07–3.17 (q, 2H, BocNHC$\underline{H}_2$), 3.24–3.31 (t, 2H, C$\underline{H}_2$N$_3$), 4.40–4.6 (br, 1H, BocN$\underline{H}$)	229 $(M+H)^+$, 246 $(M+NH_4)^+$
2e	92	$C_{11}H_{22}N_4O_2$ (242.3)	2080 (N_3), 1680 (CO)	1.43 (s, 9H, Boc), 1.28–1.64 (m, 8H, (C$\underline{H}_2$)$_4$), 2.96–3.12 (q, 2H, BocNHC$\underline{H}_2$), 3.16–3.26 (t, 2H, C$\underline{H}_2$N$_3$), 4.49–4.64 (br, 1H, BocN$\underline{H}$)	243 $(M+H)^+$, 260 $(M+NH_4)^+$

[a] Satisfactory microanalyses obtained: C ±0.26, H ±0.15, N ±0.39 except for **2a**, C +0.35, H +0.23, N −0.47.
[b] Compounds **2a–2e** are oils at r.t.
[c] Neat samples were recorded on a Perkin-Elmer Model 298 IR.

Table 3. N^{α}-*tert*-Butoxycarbonyl-α,ω-alkanediamine Hydrochlorides **3a–e** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)	^{1}H-NMR (CD_3OD/TMS) δ	MS (DCI/NH_3) m/z
3a	96	115–117	$C_7H_{17}ClN_2O_2$ (196.7)	1.46 (s, 9H, Boc), 2.96–3.02 (t, 2H, C$\underline{H}_2$NH$_3^+$), 3.28–3.34 (t, 2H, BocNHC$\underline{H}_2$)	161 $(M+H)^+$
3b	99	149–152	$C_8H_{19}ClN_2O_2$ (210.7)	1.46 (s, 9H, Boc), 1.75–1.89 (m, 2H, C$\underline{H}_2$), 2.92–2.99 (t, 2H, C$\underline{H}_2$NH$_3^+$), 3.13–3.19 (t, 2H, BocNHC$\underline{H}_2$)	175 $(M+H)^+$
3c	100	147–148	155–156[2]	1.44 (s, 9H, Boc), 1.28–1.76 (m, 4H, (C$\underline{H}_2$)$_2$), 2.90–2.97 (t, 2H, C$\underline{H}_2$NH$_3^+$), 3.05–3.11 (t, 2H, BocNHC$\underline{H}_2$)	189 $(M+H)^+$
3d	95	102–105	$C_{10}H_{23}ClN_2O_2$ (238.8)	1.43 (s, 9H, Boc), 1.28–1.72 (m, 6H, (C$\underline{H}_2$)$_3$), 2.88–2.95 (t, 2H, C$\underline{H}_2$NH$_3^+$), 3.01–3.08 (t, 2H, BocNHC$\underline{H}_2$)	203 $(M+H)^+$
3e	91	156–158	153–154[2]	1.43 (s, 9H, Boc), 1.24–1.72 (m, 6H, (C$\underline{H}_2$)$_4$), 2.80–2.95 (t, 2H, C$\underline{H}_2$NH$_3^+$), 2.96–3.06 (q, 2H, BocNHC$\underline{H}_2$)	217 $(M+H)^+$

[a] Satisfactory microanalyses obtained: C ±0.17, H ±0.28, N ±0.31.

***N*-*tert*-Butoxycarbonyl-1,6-hexanediamine Hydrochloride [(6-*tert*-Butoxycarbonylaminohexyl)ammonium Chloride] 3e; Typical Procedure:**

Compound **2e** (1.02 g, 4.2 mmol) is dissolved in MeOH (50 mL) and $CHCl_3$ (1 mL). This solution is hydrogenated over 10% Pd-C (100 mg) at 30 psi hydrogen in a Parr Hydrogenation apparatus for 1 h. The catalyst is separated by filtration though Celite; the Celite washed with additional MeOH (50 mL); and the combined filtrate evaporated. The solid residue is triturated with Et_2O (50 mL) and filtered to give **3e**, yield: 830 mg (91%). (See Table 3.)

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