A Convenient and General Method for the Preparation of *tert*-Butoxycarbonylaminoalkanenitriles and Their Conversion to Mono-*tert*-butoxycarbonylalkanediamines

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A new method is described for the synthesis of *tert*-butoxycarbonylaminoalkanenitriles **3** by dehydration of the corresponding carboxamides **2** (prepared in two steps from aminoalkanoic acids) in the presence of trifluoroacetic anhydride and triethylamine. *N*-Boc-aminoalkanenitriles **3** are easily converted to mono-*N*-Boc-alkanediamines **4** under mild conditions avoiding the cleavage of the *N*-protective group. The monoprotected alkanediamines **4** are useful tools in affinity chromatography.

N-protected aminoalkanenitriles have proven to be versatile intermediates capable of furnishing *N*-protected aminoalkanamidines, aminoalkanimidoesters and aminoalkanethioamides, precursors of aminoalkylthiazoles.[1] Moreover, the catalytic reduction of the nitrile group provides a useful method for the preparation of monoprotected alkanediamines, which have many applications in chemistry and in biochemistry. For example, they can be used as bifunctional reagents in affinity chromatography: only one NH_2 group of a 1-amino-ω-Boc-aminoalkane (Boc = *tert*-butoxycarbonyl) can participate in the coupling with the matrix, the other being subsequently regenerated by mild hydrolysis of the Boc protecting group and then allowed to react with the appropriate ligand.[2,3]

The routes previously described for the preparation of some monoblocked alkanediamines[4,5] suffer from limited scope, are not selective concerning the sites of the protecting group and failed in some cases. They generally consist in introducing the protective group on both amino groups followed by a selective cleavage and rely on the relative solubilities of mono and diprotected alkanediamines. For example, the commercially available N-Boc-1,6-hexanediamine is obtained with difficulty (as its HCl salt) after cautious separation of the corresponding disubstituted by-product[6], whereas monofunctionalization of 1,4-diaminobutane is only effective in acidic medium.[7] The attempted stepwise protection of polyamines such as spermidine serve to demonstrate the identical reactivity of primary amine groups; in order to obtain a polyamine with different protecting groups it is often necessary to successively create the amine groups in question.[8,9]

The sequential method here reported takes in account the preceeding conclusions and has proved to be very general for the preparation of linker diamines of various sizes.

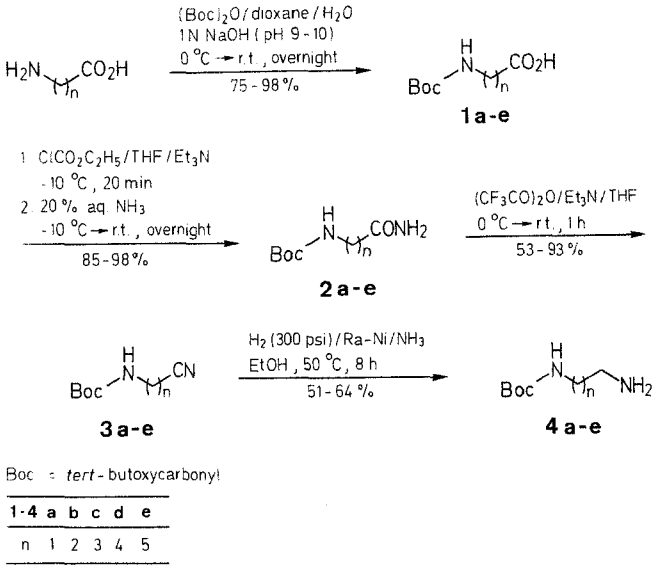

Table 1. Acids **1** and Amides **2** Prepared

Product	1		2	
	Yield (%)	mp (°C)[a] (solvent) or/and bp (°C)/Torr	Yield (%)	mp (°C)[b]
a	87	87–89	90	94
b	88	77–77.5 (hexane/PE)[c] 138–142/0.25	92	154–155
c	96	50–51 (hexane/EtOAc) 78–82/0.2	85	127–127.5
d	75	49–50 (hexane/PE) 160–168/0.8	95	139
e	98	48 (cyclohexane) 162–166/0.25	98	124–124.5

[a] Uncorrected, measured with a Büchi-510 apparatus.
[b] Recrystallized from EtOAc.
[c] PE = petroleum ether.

The first goal of the sequence is a simple procedure for the preparation of aminoalkanenitriles, in which the amino group is protected by the Boc group, which is easily removed under mild conditions.[10] Many methods for the conversion of primary amido group into the corresponding cyano group are known,[11] but they are often characterized by harsh reaction conditions, unusual reagents or difficult work-up procedures incompatible with the acid lability of the Boc group. The procedure here described involved the treatment of commercially available aminoalkanoic acids with di-*tert*-butyl dicarbonate [$(Boc)_2O$][12] to afford *N*-Boc-aminoalkanoic acids **1** which, by reaction with ethyl carbonochloridate and aqueous ammonia[13] gave the

Table 2. Boc-aminoalkanenitriles **3** and Mono-Boc-alkanediamines **4** Prepared

Product	Yield (%)	mp (°C)[a] or/ and bp (°C)/Torr	Molecular Formula[b]	n_D (°C)	IR[c] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[d] δ	MS (70 eV)[e] m/z (M^+)
3a	85	94–96/0.15	$C_7H_{12}N_2O_2$ (156.2)	solid	1700 (C=O), 2240 (C≡N), 3360 (NH)	1.4 (s, 9H, Boc); 4.0–4.05 (d, 2H, CH_2); 5.1–5.3 (m, 1H, NH)	156
3b	93	39–40 92–96/0.4	$C_8H_{14}N_2O_2$ (170.2)	solid	1680 (C=O), 2240 (C≡N), 3330 (NH)	1.4 (s, 9H, Boc); 2.5–2.7 (t, 2H, CH_2CN); 3.3–3.5 (m, 2H, CH_2NH); 5.0–5.4 (m, 1H, NH)	170
3c	88	102–108/0.2	$C_9H_{16}N_2O_2$ (184.2)	solid	1680 (C=O), 2240 (C≡N), 3330 (NH)	1.4 (s, 9H, Boc); 1.7–2.0 (m, 2H, CH_2); 2.2–2.5 (m, 2H, CH_2CN); 3.1–3.3 (m, 2H, CH_2NH); 5.0–5.3 (m, 1H, NH)	184
3d	53	122–124/0.2	$C_{10}H_{18}N_2O_2$ (198.3)	solid	1670 (C=O), 2235 (C≡N), 3320 (NH)	1.3–1.5 (m, 2H, CH_2); 1.4 (s, 9H, Boc); 1.7–2.0 (m, 2H, CH_2CH_2NH); 2.2–2.5 (m, 2H, CH_2CN); 3.0–3.3 (m, 2H, CH_2NH); 4.7–5.0 (m, 1H, NH)	198
3e	75	45–46 126–130/0.3	$C_{11}H_{20}N_2O_2$ (212.3)	solid	1680 (C=O), 2235 (C≡N), 3320 (NH)	1.3–1.8 (m, 6H, $CH_2CH_2CH_2$); 1.4 (s, 9H, Boc); 2.2–2.5 (m, 2H, CH_2CN); 3.0–3.3 (m, 2H, CH_2NH); 4.7–5.0 (m, 1H, NH)	212
4a	51	108–109 79–80/0.3	$C_7H_{16}N_2O_2$ (160.2)	1.4505 (20)	1670 (C=O), 3340 (NH, NH_2)	1.4 (s, 9H, Boc); 1.8 (s, 2H, NH_2); 2.6–2.9 (m, 2H, CH_2NHBoc); 3.0–3.3 (m, 2H, CH_2NH_2); 5.4–5.8 (m, 1H, NH)	160
4b	59	94–96/0.2	$C_8H_{18}N_2O_2$ (174.2)	1.4595 (20.3)	1665 (C=O), 3180–3400 (NH, NH_2)	1.4 (s, 9H, Boc); 1.6 (s, 2H, NH_2); 1.5–1.8 (m, 2H, CH_2); 2.7–2.9 (m, 2H, CH_2NHBoc); 3.0–3.3 (m, 2H, CH_2NH_2); 5.1–5.4 (m, 1H, NH)	174
4c	64	88–89 86–90/0.1	$C_9H_{20}N_2O_2$ (188.3)	1.4608 (20)	1680 (C=O), 3200–3320 (NH, NH_2)	1.3 (s, 2H, NH_2); 1.4 (s, 9H, Boc); 1.4–1.6 (m, 4H, CH_2CH_2); 2.6–2.8 (m, 2H, CH_2NHBoc); 3.0–3.3 (m, 2H, CH_2NH_2); 4.8–5.1 (m, 1H, NH)	188
4d	60	97–98/0.2	$C_{10}H_{22}N_2O_2$ (202.3)	1.4588 (20)	1670 (C=O), 3200–3400 (NH, NH_2)	1.4 (s, 9H, Boc); 1.3–1.6 (m, 6H, $CH_2CH_2CH_2$); 1.8 (s, 2H, NH_2); 2.5–2.8 (m, 2H, CH_2NHBoc); 2.9–3.3 (m, 2H, CH_2NH_2); 4.9–5.2 (m, 1H, NH)	202
4e	63	102.5–103.5 106–110/0.3	$C_{11}H_{24}N_2O_2$ (216.3)	solid	1670 (C=O), 3200–3400 (NH, NH_2)	1.4 (s, 9H, Boc); 1.2–1.8 (m, 8H, $CH_2CH_2CH_2CH_2$); 1.8 (s, 2H, NH_2); 2.5–2.8 (m, 2H, CH_2NHBoc); 3.0–3.3 (m, 2H, CH_2NH_2); 5.3 (s, 1H, NH)	216

[a] Uncorrected, measured with a Büchi-510 apparatus.
[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.17, N ±0.30.
[c] Recorded on a Perkin-Elmer 297 spectrophotometer.
[d] Recorded on a Brucker WP 80 SY spectrometer.
[e] Molecular ion peaks observed in the CI/NH_3 (**3**) or EI (**4**) mass spectra, recorded on a Ribermag R10-10 spectrometer.

corresponding *N*-Boc-aminoalkanamides **2**. Dehydration of the carboxamides was accomplished by trifluoroacetic anhydride in the presence of an excess of triethylamine.

The N-Boc-aminoalkanenitriles **3** thus obtained in a good yield were then submitted to a catalytic hydrogenation under mild conditions such that the Boc protecting group was not cleaved. Use of Raney nickel at 50 °C and 300 psi of hydrogen for 8 h gave the expected mono-protected alkanediamines **4** in excellent yield.

3-(*tert*-Butoxycarbonylamino)propanoic Acid (1b); Typical Procedure:
A mixture of di-*tert*-butyl dicarbonate (6 g, 27.5 mmol) in dioxane/water (2:1, 80 mL) is added dropwise to a stirred solution of β-alanine (2.2 g, 25 mmol) in dioxane/water (2:1, 80 mL) at 0 °C at such a rate that the pH is maintained at 9–10 (pH meter) by careful addition of 1 N aq. NaOH. The mixture is allowed to warm to room temperature and the pH is checked periodically and maintained at 9.0, if necessary, by the addition of further 1 N aq. NaOH. Stirring is continued overnight, then the solvent is evaporated. The residual oil is taken up in water and the solution extracted with Et_2O (3 × 35 mL). The aqueous phase is acidified with citric acid (to pH 3) and extracted with EtOAc. The organic layer is dried (Na_2SO_4) and solvent is evaporated. The residual oil is purified by distillation under reduced pressure and crystallized from hexane/petroleum ether (7:1); yield: 4.2 g (88%): mp 77–77.5 °C; bp 138–142 °C/0.25 Torr (see Table 1).

IR (KBr): ν = 1665–1690 cm^{-1} (br, C=O).

3-(*tert*-Butoxycarbonylamino)propanamide (2b); Typical Procedure:
A mixture of 3-Boc-aminopropanoic acid (**1b**; 4.2 g, 22 mmol) in THF (50 mL) and Et_3N (3.1 mL, 22 mmol) is cooled to −10 °C. Ice-cooled $ClCO_2Et$ (2.1 mL, 22 mmol) is added dropwise and stirring is continued for 20 min at −10 °C. A 20% NH_3 solution (4.7 mL, 55 mmol) is then added, and the heterogeneous mixture is allowed to gradually warm to room temperature and stirred overnight. The crude product obtained by evaporation under reduced pressure is extracted several times with boiling EtOAc (3 × 30 mL). The pure material crystallizes from the EtOAc on standing; yield: 3.8 g (92%); mp 154–155 °C (see Table 1).

IR (KBr): ν = 1630 (m, C=O), 1665 (m, C=O), 3330 cm^{-1} (br, NH).

3-(*tert*-Butoxycarbonylamino)propionitrile (3b); Typical Procedure:
Et_3N (4.9 mL, 35 mmol) is added to 3-Boc-aminopropanamide (**2b**; 3.0 g, 16 mmol) dissolved in anhydrous THF (10 mL). The stirred solution is cooled in an ice bath and trifluoroacetic anhydride (2.5 mL, 17.5 mmol) is added dropwise. The mixture is allowed to reach room temperature, and after 1 h the reaction is quenched with water (10 mL).

The residue obtained after evaporation of the organic phase is extracted with ether (3 × 50 mL); the extract is washed successively with 0.1 N aq. HCl and 0.1 N aq. NaOH. The organic layer is dried (Na_2SO_4) and concentrated. The resulting oil is purified by distillation under reduced pressure and slowly crystallizes (see Table 2).

4-(*tert*-Butoxycarbonylamino)-1-butylamine (4c); Typical Procedure:
A high pressure autoclave is charged with a solution of 3-Boc-aminobutyronitrile (**3c**; 2.4 g, 14.1 mmol) in EtOH (50 mL) saturated with NH_3, Raney Ni (0.5 g) and H_2 at a pressure of 300 psi. The mixture is stirred at 50 °C for 8 h. After filtration of the catalyst, the filtrate is evaporated to dryness. The crude oil is purified by distillation under reduced pressure (see Table 2).

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