Monoprotection of α,ω-Alkanediamines with the N-Benzyloxycarbonyl Group

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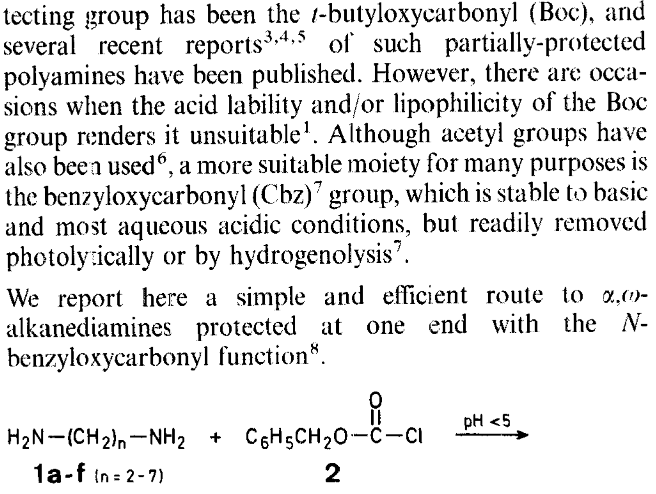
Many syntheses[1,2] of asymmetric compounds based on alkanediamines require that these compounds be available as monoprotected intermediates. The most widely-used protecting group has been the *t*-butyloxycarbonyl (Boc), and several recent reports[3,4,5] of such partially-protected polyamines have been published. However, there are occasions when the acid lability and/or lipophilicity of the Boc group renders it unsuitable[1]. Although acetyl groups have also been used[6], a more suitable moiety for many purposes is the benzyloxycarbonyl (Cbz)[7] group, which is stable to basic and most aqueous acidic conditions, but readily removed photolytically or by hydrogenolysis[7].

We report here a simple and efficient route to α,ω-alkanediamines protected at one end with the N-benzyloxycarbonyl function[8].



$$H_2N-(CH_2)_n-NH_2 + C_6H_5CH_2O-\overset{O}{\overset{\|}{C}}-Cl \xrightarrow{pH<5}$$

1a-f (n = 2-7) **2**

$$C_6H_5CH_2O-\overset{O}{\overset{\|}{C}}-NH-(CH_2)_n-NH_2 +$$

3a-f

$$C_6H_5CH_2O-\overset{O}{\overset{\|}{C}}-NH-(CH_2)_n-\overset{O}{\overset{\|}{C}}-OCH_2C_6H_5$$

4a-f

Table. (N-Benzyloxycarbonyl)-α,ω-alkanediamines **3a-f**

Product No.	n	Yield[a] [%]	m.p. [°C] of 3 · HCl[b]	Molecular Formula[c] of 3 · HCl	
3a	2	71	157-159°	Ref.[8], m.p. 158-159°	
3b	3	57	189.5-190.5	$C_{11}H_{16}N_2O_2 \cdot HCl$	(244.7)
3c	4	49	195-197°	$C_{12}H_{18}N_2O_2 \cdot HCl$	(257.8)
3d	5	47	172-173°	$C_{13}H_{20}N_2O_2 \cdot HCl$	(272.8)
3e	6	34	177-178°	$C_{14}H_{22}N_2O_2 \cdot HCl$	(286.8)
3f	7	29	165-167°	$C_{15}H_{24}N_2O_2 \cdot HCl$	(300.8)

[a] Yield of free amine **3** based on **2**.

[b] Recrystallized from methanol/ethyl acetate.

[c] Satisfactory microanalyses obtained: C ± 0.2, H ± 0.3, N ± 0.1, Cl ± 0.2.

The reaction with diamines **1** is carried out in aqueous solution at pH 3.5-4.5. Measurement of pH is achieved by the addition of bromocresol green as an internal indicator, and benzyl carbonochloridate (**2**) is added dropwise with simultaneous addition of aqueous potassium acetate to buffer the solution; pH control is critical, with large amounts of bis-derivatives **4** being formed if the pH is allowed to rise even momentarily above about 5. The monoamines **3**, obtained in yields of up to 71 % (depending on chain length) are waxes, and were characterized as their hydrochloride salts. All compounds **3a-f** were homogeneous by T.L.C., analyzed correctly, and had ^{1}H-N.M.R. spectra in accord with the assigned structures.

Melting points are uncorrected. Analyses were performed by Dr. A. D. Campbell, University of Otago, New Zealand. Reactions were followed by T. L. C. (silica gel 60, eluted with *n*-butanol/water/acetic acid 5:4:1, top phase) and visualized by U.V. and phosphomolybdic acid.

N-(Benzyloxycarbonyl)-propane-1, 3-diamine (3b):

Propane-1,3-diamine (**1b**, n = 3; 19.3 g, 0.26 mol) is dissolved in water (50 ml) containing bromocresol green as indicator. Methanesulfonic acid (~ 46 g, 0.48 mol) in water (50 ml) is added until a blue to pale yellow colour transition is just achieved (pH ~ 3.8). The solution is diluted with ethanol (140 ml), vigorously stirred, and treated at 20 °C simultaneously with solutions of benzyl carbonochloridate (**2**; 39.0 g, 0.23 mol) in dimethoxyethane (50 ml) and 50 % w/v aqueous potassium acetate (~ 100 ml). This is best carried out by *alternate dropwise* additions of the solution of **2** and that of potassium acetate, to maintain the pale yellow-green colouration of the indicator; pH control is critical; allowing the pH to rise significantly (to a blue colouration) at *any point* in the reaction results in the formation of large quantities of the bis-benzyloxycarbonyl derivative **4b**. After the additions are complete the mixture is stirred at room temperature for 1 h, and volatiles are removed at low temperature under vacuum. The residue is shaken with water (500 ml) and filtered to remove small quantities of the bis-derivative. The filtrate is washed with benzene (3 × 150 ml), basified with excess 40 % aqueous sodium hydroxide solution, and then extracted with benzene (300 ml). The organic layer is washed once with saturated aqueous sodium chloride (200 ml), dried with sodium sulfate, and evaporated in vacuo to give **3b** as a viscous oil; yield: 27 g (57 % based on **2**); pure enough for most purposes. Treatment of a sample with acetone/hydrochloric acid (1.05 equiv) followed by crystallization of the precipitate from methanol/ethyl acetate gives the hydrochloride of **3b**; m.p. 189.5-190.5 °C.

		C	H	N	Cl
$C_{11}H_{16}N_2O_2 \cdot HCl$	calc.	54.0	7.3	11.5	14.6
(244.7)	found	54.0	7.0	11.5	14.5

N-(Benzyloxycarbonyl)-heptane-1,7-diamine (3f):

Heptane-1,7-diamine (**1f**, n = 7; 13.0 g, 0.10 mol) is dissolved in water (20 ml) containing bromocresol green as indicator. Methanesulfonic acid (~ 19.2 g, 0.20 mol) in water (15 ml) is added until a blue to yellow colour transition is just achieved. The solution is diluted with ethanol (70 ml), vigorously stirred and held at 20 °C while solutions of **2** (15.2 g, 0.089 mol) in dimethoxyethane (25 ml) and 25% w/v aqueous potassium acetate (~ 60 ml) are added dropwise simultaneously at rates which maintain correct reaction pH (yellow-green indicator colouration). The reaction is slower than with **1b**, necessitating that all the **2** is added together with a small portion of the potassium acetate; the remainder of this is then added slowly over 1.5 h. After all the potassium acetate is added, the mixture is stirred at 20 °C for a further 1 h, the volatiles are removed in vacuo, the residue is shaken with water (200 ml), and filtered to remove a quantity of the bis-derivative. The filtrate is washed with benzene (3 × 60 ml), basified with excess 40% aqueous sodium hydroxide solution and then extracted with benzene/petroleum ether (80–100 °C) (1:1, 150 ml). The organic layer is washed once with saturated aqueous sodium chloride (100 ml), dried with sodium sulfate and evaporated in vacuo to give **3f** as a low melting solid; yield: 6.8 g (29%); pure enough for most purposes. The hydrochloride salt crystallizes from methanol/ethyl acetate as colourless prisms; m.p. 165–167 °C.

$C_{15}H_{24}N_2O_2 \cdot HCl$	calc.	C 59.9	H 8.4	N 9.3	Cl 11.8
(300.8)	found	59.7	8.5	9.4	12.0

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[1] G.J. Atwell, W. Leupin, S.J. Twigden, W.A. Denny, *J. Am. Chem. Soc.* **105**, 2913 (1983).

[2] J.B. Hansen, E. Langvad, F. Frandsen, O. Buchardt, *J. Med. Chem.* **26**, 1510 (1983).

[3] G.L. Stahl, R. Walter, C.W. Smith, *J. Org. Chem.* **43**, 2285 (1978).

[4] R. Andruskiewicz et al., *Pol. J. Chem.* **52**, 1167 (1978).

[5] J.B. Hansen, M.C. Nielsen, U. Ehrbahr, and O. Buchardt. *Synthesis* **1982**, 405.

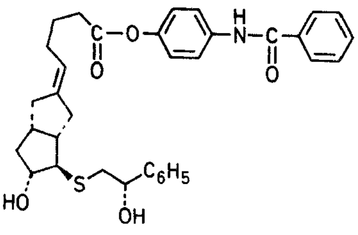
[6] P.W. Erhardt et al., *J. Med. Chem.* **26**, 1109 (1983).

[7] L.F. Fieser, M. Fieser, *Reagents for Organic Synthesis*, Vol. 1, John Wiley & Sons, New York, 1967, 109.

[8] P.L. Barker, P.L. Gendler, H. Rapaport, *J. Org. Chem.* **46**, 2455 (1981) reported the synthesis of *N*-(benzyloxycarbonyl)-ethane-1,2-diamine, without experimental details.
See also: T.S. Moore, M. Boyle, V.M. Thorne, *J. Chem. Soc.* **1929**, 39.

R.F. Newton, S.M. Roberts, R.J.K. Taylor, *Synthesis* **1984** (6), 449–478:

The structure of compound **305** (p. 475) should be:



305 (EMD 46335)

H. Sard, R.P. Duffley, L.R. Robertson, R.K. Razdan, *Synthesis* **1984** (6), 506–509:

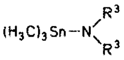
The fourth sentence in the paragraph above Scheme A (p. 507) should read:
This racemic compound could be preferentially enriched by a single recrystallization from ethanol as the (–)-dibenzoyl-L-tartrate salt **5a** (96% yield).

C.K. Ghosh, N. Tewari, A. Bhattacharya, *Synthesis* **1984** (7), 614–615:

Compounds **2a–d** should be named as 3-ethoxy-10-oxo-4,4a-dihydro-3*H*,10*H*-pyrano[4,3-*b*][1]benzopyrans.

Abstract 6925, *Synthesis* **1984** (7), 624:

The structure of reagent **5** should be:



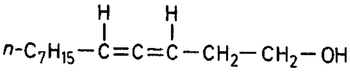
(5)

M. Sato, N. Katsumata, S. Ebine, *Synthesis* **1984** (8), 685:

The title compound should be named 4,5-Dihydrobenzocyclobutene-4,5-dione.

R.E. Doolittle, *Synthesis* **1984** (9), 730–732:

The structure of product **3** (p. 730) should be:

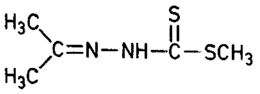


$$n\text{-}C_7H_{15}-\overset{H}{\overset{|}{C}}=C=\overset{H}{\overset{|}{C}}-CH_2-CH_2-OH$$

3

Y. Nakayama, Y. Sanemitsu, *Synthesis* **1984** (9), 771–772:

The structure of compound **6** (p. 772) should be:



6

I. Reichelt, H.-U. Reissig, *Synthesis* **1984** (9), 786–787:

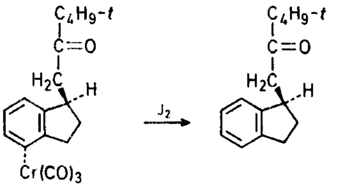
The title compounds **2** should be named as 3-oxo-2,3,4,5-tetrahydropyridazines

M. Tirant, T.D. Smith, *Synthesis* **1984** (10), 833–834

The names for products **2a** and **3a** should be bis[2-hydroxybenzylidenehydrazino] sulfide and 2-hydroxyethyl 2-hydroxybenzylidenehydrazino sulfide, respectively.

Abstract 6971, *Synthesis* **1984** (10), 892:

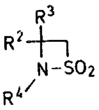
The structures of products **4** and **5** should be:



4 **5**

Abstract 6976, *Synthesis* **1984** (10), 894:

The structure of product **8** should be:



8

E.A. Mistryukov, I.K. Korshevetz, *Synthesis* **1984** (11), 947–949:

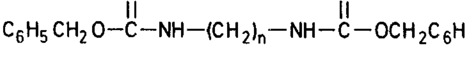
Compound **10** should be named as 1-(1-cyclohexenyl)-3-diethylaminopropyne.

Z. Arnold, V. Kral, G.V. Kryshtal, L.A. Yanovskaya, *Synthesis* **1984** (11), 974–976:

The title compounds **5** should be named as 3-substituted 2,2-diethoxycarbonyl-4-formyl-2,3-dihydrofurans.

G.J. Atwell, W.A. Denny, *Synthesis* **1984** (12), 1032–1033:

The structure of products **4a–f** (p. 1032) should be:



$$C_6H_5CH_2O-\overset{O}{\overset{\|}{C}}-NH-(CH_2)_n-NH-\overset{O}{\overset{\|}{C}}-OCH_2C_6H_5$$

4a-f

R.G. McR. Wright, *Synthesis* **1984** (12), 1058–1061:

Formula **8** should be replaced by: