Selective Synthesis of Carbamate Protected Polyamines Using Alkyl Phenyl Carbonates

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Abstract: Utilising alkyl phenyl carbonates, an economical, practical and versatile method for selective Boc, Cbz and Alloc protection of polyamines has been developed. This method allows Boc, Cbz and Alloc protection of primary amines in the presence of secondary amines by reaction of the polyamines with the alkyl phenyl carbonates. Also, this method allows mono carbamate protection of simple symmetrical aliphatic α,ω-alkanediamines in high yields with respect to the diamine. Finally, the method allows selective carbamate protection of a primary amine located on a primary carbon in the presence of a primary amine located on a secondary or a tertiary carbon in excellent yields.

Key words: protecting groups, amines, regioselectivity, chemoselectivity, carbonates

Aliphatic polyamines are a class of compounds with a variety of interesting functions. These range from being part of toxins in spiders and wasps, through neurotransmission in humans and fruit-ripening in plants, to ligands in inorganic chemistry.[1–4] Also, they have proved useful as linkers and building blocks in supramolecular architectures.[5]

A problem often encountered in the synthesis, or in the synthetic use of polyamines, is selective protection of the amino groups. This synthetic challenge has been dealt with in a number of ways[6] and elegant multi-step synthetic procedures have been developed to strategically incorporate protection groups in polyamines.[7,8]

Alkyl phenyl carbonates have only found limited use as acylating agents in formation of carbamates in spite of the number of reports in the literature.[9–18] The kinetics of the reaction between alkyl aryl carbonates and primary and secondary amines have been investigated previously, and it has clearly been shown that secondary amines react much slower than primary amines.[19,20]

This result inspired the work presented herein, where a selective method for carbamate protection of polyamines using alkyl phenyl carbonates is developed.

The alkyl phenyl carbonates investigated in this study were *tert*-butyl phenyl carbonate (**1**),[21] benzyl phenyl carbonate (**2**)[22] and allyl phenyl carbonate (**3**)[23] introducing the Boc (*tert*-butoxycarbonyl), Cbz (benzyloxycarbonyl) and Alloc (allyloxycarbonyl) protecting groups, respectively (Figure 1).

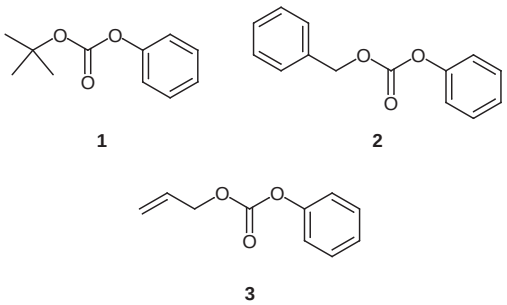

Figure 1

tert-Butyl phenyl carbonate (**1**) is commercially available. Benzyl phenyl carbonate (**2**) and allyl phenyl carbonate (**3**) were prepared by a slight modification of the published method for benzyl phenyl carbonate by reaction between phenyl chloroformate and the respective alcohol (benzyl alcohol and allyl alcohol) in the presence of pyridine. The three carbonates are stable, easy handled and can be stored refrigerated without noticeable decomposition (a problem often encountered with the alkyl chloroformates).[24]

Recently, a selective method for Boc and Cbz protection of primary amino groups in polyamines based on *O*-alkyl *O′*-(*N*-succinimidyl) carbonates was published.[25] However the selectivity of the method relies on performing the reactions at –40 °C. Furthermore, selectivity for reaction on primary amino groups over secondary amino groups has been shown with the commercially available reagent, 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), also at low temperatures.[26]

The two natural polyamines spermidine (**4**) and spermine (**5**), and the two symmetrical triamines diethylenetriamine (**6**) and dipropylenetriamine (**7**) were chosen as the polyamines for this study, all containing both primary and secondary amino moieties. We found the reaction between the polyamines and the alkyl phenyl carbonates afforded chemoselective carbamate protection of the primary amino groups in high yields (Scheme 1).

Performing the reactions at room temperature in CH_2Cl_2 (or in DMF) using 1.1 equivalent alkyl phenyl carbonate per primary amino group gave the chemoselective carbamate protected polyamines after aqueous workup. The prepared compounds and the obtained yields are presented in Table 1 (protected amines **15**–**26**).

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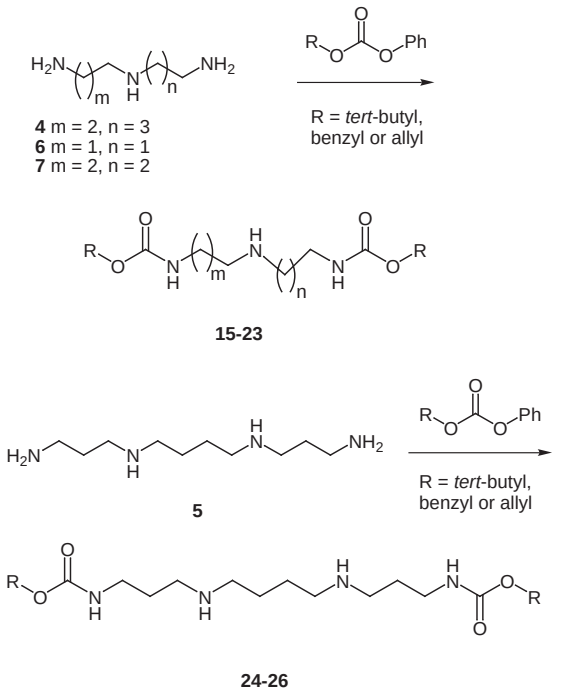


Scheme 1

The three different protection groups introduced on the primary amino groups are orthogonal, which means that they can respectively be removed, under different conditions,[6] and this strategy therefore opens synthetic pathways, for manipulation of the secondary amino groups present in the polyamines. In general the Boc protection group can be removed under acidic conditions, the Cbz protection group can be removed by catalytic hydrogenation and the Alloc protection group can be removed by treatment with Pd. Both Adamczyk[25] and Phanstiel[26] have used this strategy in their synthetic work. Other orthogonal protection groups for amines and general conditions for their removal has been described elsewhere, and an excellent selection is available.[6]

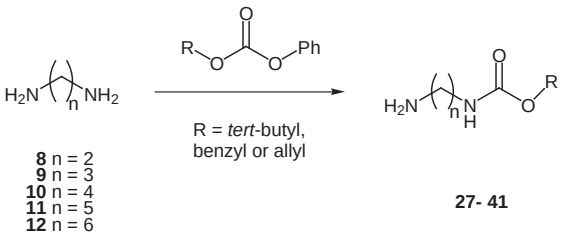
The usefulness of mono carbamate protected α,ω-alkanediamines is evident from many applications in synthetic procedures[7] and by the numerous ways they have been prepared.[6]

The most common direct method (one pot) for the preparation of the mono Boc protected α,ω-diamines has been developed by Krapcho and co-workers where di-*tert*-butyl dicarbonate is reacted with an excess (6–7 equiv) of the α,ω-alkanediamine.[27,28] This method gives high yields with respect to the di-*tert*-butyl dicarbonate, but low yields with respect to the α,ω-diamine. Moreover the procedure requires slow addition of the di-*tert*-butyl dicarbonate at 0 °C which, in our experience, can cause problems with respect to crystallisation of the di-*tert*-butyl dicarbonate during the addition period.

The mono Cbz carbamate protected α,ω-alkanediamines have been prepared by slow addition of benzyl chloroformate to an excess of the α,ω-diamines in a buffered solution by Denny and co-workers.[29] This method gives good yields with respect to the benzyl chloroformate, but it suffers from difficulties in controlling the pH in the reaction mixture. Dibenzyl carbonate has also been used for this purpose,[30] but like the Boc protection with di-*tert*-butyl dicarbonate this requires a large excess of the diamine.

A general method to selectively introduce the Alloc protection group once on α,ω-diamines has not, to the best of our knowledge, been developed. The preparation of some of the compounds has been reported previously, though generally in low yields.[31–34]

We found that reacting the α,ω-diamines **8**–**12** with one equivalent of alkyl phenyl carbonate (Scheme 2) in ethanol at room temperature (with the *tert*-butyl phenyl carbonate reflux was necessary) afforded the mono carbamate protected diamine in good to high yields (protected amines **27**–**41** in the Table).



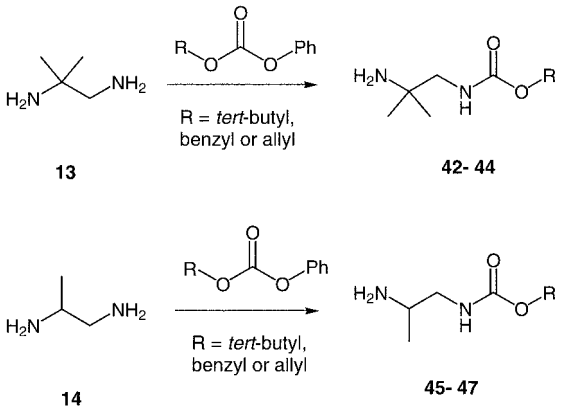
Scheme 2

Small amounts of bis alkyloxycarbonyl α,ω-alkanediamines and unreacted α,ω-alkanediamine are easily removed during the aqueous workup. As evident from the results, selectivity for mono protection decreases with the length of the alkane chain, and when sufficiently long (5 methylene groups) there was no longer selectivity for mono protection (yields were approximately 50%).

Scaling up this process showed to be amenable as the mono protection of 1,2-ethanediamine was carried out on a large scale (0.33 mol).

The selectivity in the introduction of the three protection groups was further tested by reaction with unsymmetrical aliphatic diamines. Selectivity towards reaction with primary amines located on a primary carbon in the presence of a primary amine located on either a secondary or a tertiary carbon was studied by reaction of the alkyl phenyl carbonates with the two diamines, 2-methyl-1,2-propanediamine (**13**) and 1,2-propanediamine (**14**) (Scheme 3). Both of these diamines were successfully mono carbamate protected on the primary amino groups located on the primary carbon atom in high yields with the three carbonates (protected amines **42**–**47** in the Table 1). This remarkable selectivity has only been reported on few occasions previously, also using mixed carbonates.[25,35] Much to our surprise these highly selective reactions preceded best when two equivalents of alkyl phenyl carbonate were used.

In summary, this paper describes a highly selective, versatile and practical method for carbamate protection of

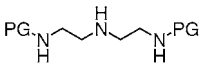
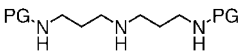
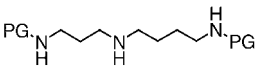
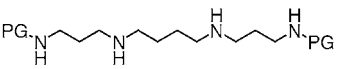
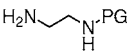
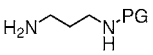
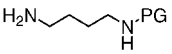
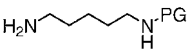
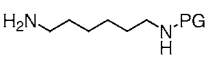
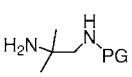
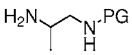


Scheme 3

aliphatic polyamines using alkyl phenyl carbonates as the acylating agent.

Unless otherwise stated, all starting materials were obtained from commercial suppliers and used as received. Solvents were HPLC grade and were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz NMR (Varian) apparatus (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) or on a 400 MHz NMR (Bruker) apparatus (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Proton chemical shifts are reported in ppm downfield from tetramethylsilane (TMS) and carbon chemical shifts in ppm downfield of TMS using the resonance of the deuterated solvent as internal standard. Mps were measured on a Büchi B-140 apparatus and are uncorrected. Elemental analysis was performed by Mrs Karin Linthoe. Fast-atom bombardment (FAB) mass spectra were recorded on a Jeol JMS-HX 110A Tandem Mass Spectrometer in the positive ion mode using *m*-nitrobenzylalcohol (*m*-NBA) as the matrix.

Table 1 Selective Protection of Polyamines with Alkyl Phenyl Carbonates

Amine		Protected Amine[a]	Yield[b] (%)
6		**15** PG = Boc	61
		16 PG = Cbz	72
		17 PG = Alloc	52
7		**18** PG = Boc	73
		19 PG = Cbz	77
		20 PG = Alloc	73
4		**21** PG = Boc	78
		22 PG = Cbz	71
		23 PG = Alloc	89
5		**24** PG = Boc	86
		25 PG = Cbz	67
		26 PG = Alloc	98
8		**27** PG = Boc	65
		28 PG = Cbz	64
		29 PG = Alloc	67
9		**30** PG = Boc	68
		31 PG = Cbz	72
		32 PG = Alloc	86
10		**33** PG = Boc	63
		34 PG = Cbz	63
		35 PG = Alloc	77
11		**36** PG = Boc	50
		37 PG = Cbz	56
		38 PG = Alloc	51
12		**39** PG = Boc	49
		40 PG = Cbz	48
		41 PG = Alloc	46
13		**42** PG = Boc	91
		43 PG = Cbz	97
		44 PG = Alloc	96
14		**45** PG = Boc	70
		46 PG = Cbz	69
		47 PG = Alloc	75

[a] PG = Protection Group: Boc = Me_3COCO, Cbz = $PhCH_2OCO$, Alloc = CH_2CHCH_2OCO.
[b] Yields are based on the polyamine.

HRMS were recorded on a Micromass Q-TOF apparatus using electrospray ionisation (ESI) technique.

Benzyl Phenyl Carbonate (2)
To a mixture of benzyl alcohol (108.0 g, 1.0 mol), pyridine (100 mL) and CH_2Cl_2 (175 mL) in a 500 mL 3-necked flask equipped with a condenser, mechanical stirring and an addition funnel was added phenyl chloroformate (156.0 g, 1.0 mol) over a period of 1 h. The reaction mixture was stirred for an additional 3 h, and H_2O (250 mL) was added. The ether phase was washed with aq H_2SO_4 (2 M; 2 × 250 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was distilled in vacuum to give **2**.

Yield: 180.2 g (79%); colourless oil; bp 146–150 °C/0.2 mmHg (127–131 °C/0.1 mmHg).

^{1}H NMR ($CDCl_3$): δ = 5.37 (s, 2 H), 7.18–7.48 (m, 10 H).

Allyl Phenyl Carbonate (3)
Preparation by the procedure described for benzyl phenyl carbonate.

Yield 159.5 g (90 %); colourless oil; bp 75–78 °C/0.2 mmHg.

^{1}H NMR ($CDCl_3$): δ = 4.8 (d, 2 H, *J* = 5.7 Hz), 5.31–5.48 (m, 2 H), 5.94–6.10 (m, 1 H), 7.22–7.46 (m, 5 H).

Carbamate Protection of Polyamines with Alkyl Phenyl Carbonates; General Procedure
To a solution of the polyamine (0.05 mol) in DMF (50 mL) or CH_2Cl_2 (100 mL) was added the appropriate alkyl phenyl carbonate (1.1 equiv per primary amino group). The reaction mixture was stirred overnight at r.t. and poured into a phosphate buffer (2 L; 0.025 M K_2HPO_4 and 0.025 M NaH_2PO_4). The pH was adjusted to 3 with aq H_2SO_4 (2 M), and the mixture was extracted with CH_2Cl_2 (2 × 250 mL). The aq phase was made strongly alkaline with aq NaOH (9 M), and extracted with CH_2Cl_2 (3 × 250 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. The residual solvents were removed by drying the protected amines at 0.1 mmHg at 40 °C.

In case of the Cbz protected amines **16** and **19**, the corresponding hydrochlorides were found to insoluble in H_2O, and could be formed simply by addition of aq HCl (2 M) to the crude amines. The hydrochlorides thus obtained were crystallised from EtOH to give the analytically pure salts **16**·HCl and **19**·HCl.

In case of the natural polyamines **4** and **5** the reactions were carried out on a 5–10 mmol scale.

[2-(2-*tert*-Butoxycarbonylaminoethylamino)ethyl]carbamic Acid *tert*-Butyl Ester (15)
This was synthesised according to the general procedure from diethylenetriamine using DMF as the solvent [and a catalytic amount of Et_3N (5 mL)].

Yield: 9.3 g (61%); white solid; mp 73–75 °C.

^{1}H NMR ($CDCl_3$): δ = 1.36 (s, 18 H), 1.86 (br s, 1 H), 2.64 (t, 2 H, *J* = 6 Hz), 3.13 (q, 2 H, *J* = 6 Hz), 5.12 (br s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 28.2, 40.1, 48.6, 78.9, 156.0.

MS (FAB): *m*/*z* = 304.2 (MH^+).

[2-(2-Benzyloxycarbonylaminoethylamino)ethyl]carbamic Acid Benzyl Ester (16)
Synthesised according to the general procedure from diethylenetriamine using CH_2Cl_2 as the solvent.

Yield: 13.5 g (72%); white solid; mp 73–75 °C.

^{1}H NMR ($CDCl_3$): δ = 1.25 (br s, 1 H), 2.73 (s, 4 H), 3.25 (s, 4 H), 5.08 (s, 4 H), 5.19 (br s, 2 H), 7.33 (s, 10 H).

^{13}C NMR ($CDCl_3$): δ = 40.3, 48.4, 66.4, 127.8, 128.0, 128.2, 136.3, 156.5.

MS (FAB): *m*/*z* = 372.1 (MH^+).

16·HCl

White crystals; mp 202–204 °C.

^{1}H NMR (DMSO-d_6): δ = 3.00 (t, 4 H, *J* = 6 Hz), 3.36 (q, 4 H, *J* = 6 Hz), 5.04 (s, 4 H), 7.28–7.36 (m, 10 H), 7.53 (t, 2 H, *J* = 6 Hz), 9.25 (br s, 2 H).

^{13}C NMR (DMSO-d_6): δ = 36.9, 46.5, 65.6, 127.8, 127.9, 128.4, 136.9, 156.2.

Anal. Calcd for $C_{20}H_{26}N_3O_4Cl$: C, 58.89; H, 6.42; N, 10.30; Cl, 8.69. Found: C, 58.99; H, 6.24; N, 10.29; Cl, 8.56.

[2-(2-Allyloxycarbonylaminoethylamino)ethyl]carbamic Acid Allyl Ester (17)
Synthesised according to the general procedure from diethylenetriamine using CH_2Cl_2 as the solvent.

Yield: 7.0 g (52%); white solid; mp 55–57 °C.

^{1}H NMR ($CDCl_3$): δ =1.32 (br s, 1 H), 2.64 (t, 4 H, *J* = 6 Hz), 3.17 (q, 4 H, *J* = 6 Hz), 4.45 (d, 4 H, *J* = 5 Hz), 5.10–5.23 (m, 4 H), 5.61 (br s, 2 H), 5.72–5.89 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 40.3, 48.3, 65.1, 117.2, 132.7, 156.3.

MS (FAB): *m*/*z* = 272 (MH^+).

Anal. Calcd for $C_{12}H_{21}N_3O_4$: C, 53.12; H, 7.80; N, 15.49. Found: C, 52.96; H, 8.00; N, 15.50.

[3-(3-*tert*-Butoxycarbonylaminopropylamino)propyl]carbamic Acid *tert*-Butyl Ester (18)
This compound was synthesised according to the general procedure from dipropylenetriamine using DMF as the solvent.

Yield: 12.1 g (73%); white solid; mp 67–69 °C.

^{1}H NMR ($CDCl_3$): δ = 1.43 (s, 18 H), 1.63 (quint, 4 H), 2.64 (t, 4 H, *J* = 6 Hz), 3.19 (q, 4 H), 5.20 (br s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 28.3, 29.7, 38.9, 47.3, 156.0.

MS (FAB): *m*/*z* = 332.1 (MH^+).

[3-(3-Benzyloxycarbonylaminopropylamino)propyl]carbamic Acid Benzyl Ester (19)
Synthesised according to the general procedure from dipropylenetriamine using CH_2Cl_2 as the solvent.

Yield: 17.0 g (77%); white waxy solid; mp 56–58 °C.

^{1}H NMR ($CDCl_3$): δ = 1.22 (br s, 1 H), 1.63 (t, 4 H, *J* = 6 Hz), 2.62 (t, 4 H, *J* = 6 Hz), 3.18–3.25 (m, 4 H), 5.05 (s, 4 H) 5.53 (br s, 2 H), 7.30 (s, 10 H).

^{13}C NMR ($CDCl_3$): δ = 29.3, 39.1, 47.0, 66.1, 127.6, 127.9, 128.1, 136.5, 156.3.

MS (FAB): *m*/*z* = 400.2 (MH^+).

19·HCl

White crystals; mp 208–210 °C.

^{1}H NMR (DMSO-d_6): δ = 1.68–1.79 (m, 4 H), 2.84 (t, 4 H, *J* = 7 Hz), 3.08 (q, 4 H, *J* = 6 Hz), 5.01 (s, 4 H), 7.35 (m, 10 H), 8.96 (br s, 2 H).

^{13}C NMR (DMSO-d_6): δ = 26.2, 37.6, 44.6, 65.4, 127.8, 127.9, 128.2, 128.4, 137.2, 156.3.

Anal. Calcd for $C_{22}H_{30}N_3ClO_4$: C, 60.61; H, 6.94; N, 9.63; Cl, 8.13. Found: C, 60.71; H, 6.91; N, 9.46; Cl, 8.00.

[3-(3-Allyloxycarbonylaminopropylamino)propyl]carbamic Acid Allyl Ester (20)
Synthesised according to the general procedure from dipropylenetriamine using CH_2Cl_2 as the solvent.

Yield: 11.0 g (73%); white solid; mp 52–54 °C.

^{1}H NMR ($CDCl_3$): δ = 1.24 (br s, 1 H), 1.60 (quint, 4 H), 2.59 (t, 4 H, *J* = 7 Hz), 3.20 (q, 4 H, *J* = 6 Hz), 4.49 (d, 4 H, *J* = 5 Hz), 5.08–5.23 (m, 4 H), 5.60 (br s, 2 H), 5.73–5.89 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 29.3, 39.1, 47.1, 65.0, 117.1, 132.8, 156.1.

MS (FAB): *m*/*z* = 300.2 (MH^+).

Anal. Calcd for $C_{14}H_{25}N_3O_4$: C, 56.17; H, 8.42; N, 14.04. Found: C, 56.16; H, 8.24; N, 14.06.

***N*^{1},*N*^{8}-Bis(*tert*-butoxycarbonyl)spermidine (21)**
This compound was synthesised according to the general procedure from spermidine (1.08 g, 7.40 mmol) using DMF as the solvent.

Yield: 2.00 g (78%); white solid; mp 70–72 °C.

^{1}H NMR ($CDCl_3$): δ = 1.20–1.30 (br s, 1 H), 1.42 (s, 18 H), 1.52 (m, 4 H), 1.63 (quint, 2 H, *J* = 7.0 Hz), 2.59 (t, 2 H, *J* = 6.4 Hz), 2.65 (t, 2 H, *J* = 6.4 Hz), 3.11 (q, 2 H, *J* = 5.9 Hz), 3.19 (q, 2 H, *J* = 6.4 Hz), 4.82 (br s, 1 H), 5.20 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 26.9, 27.7, 28.4, 29.5, 38.9, 40.3, 47.4, 49.2, 79.0, 156.0, 156.2.

MS (FAB): *m*/*z* = 346.3 (MH^+).

***N*^{1},*N*^{8}-Bis(benzyloxycarbonyl)spermidine (22)[6]**
This compound was synthesised according to the general procedure from spermidine (1.12 g, 7.72 mmol) using DMF as the solvent.

Yield: 2.27 g (71%); white solid; mp 78–80 °C.

^{1}H NMR ($CDCl_3$): δ = 1.48–1.60 (m, 5 H), 1.65 (m, 2 H), 2.59 (t, 2 H, *J* = 6.4 Hz), 2.62 (t, 2 H, *J* = 6.4 Hz), 3.18 (q, 2 H, *J* = 6.4 Hz), 3.26 (q, 2 H, *J* = 6.4 Hz), 5.09 (s, 4 H), 5.20 (br s, 1 H), 5.52 (br s, 1 H), 7.25–7.45 (m, 10 H).

^{13}C NMR ($CDCl_3$): δ = 27.1, 27.8, 29.6, 39.7, 41.0, 47.5, 49.3, 66.7, 128.2, 128.6, 129.6, 136.7, 136.8, 156.7.

MS (FAB): *m*/*z* = 414.3 (MH^+).

***N*^{1},*N*^{8}-Bis(allyloxycarbonyl)spermidine (23)**
Synthesised according to the general procedure from spermidine (1.16 g, 7.97 mmol) using CH_2Cl_2 as the solvent.

Yield: 2.23 g (89%); white solid; mp 41–43 °C.

^{1}H NMR ($CDCl_3$): δ = 1.00–1.20 (br s, 1 H), 1.53 (m, 4 H), 1.66 (quint, 2 H, *J* = 6.6 Hz), 2.60 (t, 2 H, *J* = 6.6 Hz), 2.68 (t, 2 H, *J* = 6.2 Hz), 3.18 (q, 2 H, *J* = 6.2 Hz), 3.27 (q, 2 H, *J* = 6.2 Hz), 4.54 (d, 4 H, *J* = 5.5 Hz), 5.19 (dd, 2 H, *J* = 1.5, 10.3 Hz), 5.29 (dd, 2 H, *J* = 1.5, 17.2 Hz), 5.57 (br s, 2 H), 5.91 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 27.2, 27.7, 29.4, 39.8, 40.8, 47.7, 49.2, 65.3, 117.4, 133.0, 156.2.

MS (FAB): *m*/*z* = 314.3 (MH^+).

Anal. Calcd for $C_{14}H_{25}N_3O_4$: C, 57.49; H, 8.67; N, 13.41. Found: C, 57.29; H, 8.67; N, 13.33.

***N*^{1},*N*^{8}-Bis(*tert*-butoxycarbonyl)spermine (24)**
Synthesised according to the general procedure from spermine (1.06 g, 5.25 mmol) using DMF as the solvent.

Yield: 1.89 g (86 %); white solid.

^{1}H NMR ($CDCl_3$): δ = 1.40 (s, 18 H), 1.52 (m, 4 H), 1.63 (quint, 4 H, *J* = 6.6 Hz), 1.93 (br s, 2 H), 2.59 (m, 4 H), 2.65 (t, 4 H, *J* = 6.6 Hz), 3.17 (q, 4 H, *J* = 5.8 Hz), 5.19 (br s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 27.8, 28.6, 29.8, 39.1, 47.4, 49.6, 79.1, 156.3.

MS (FAB): *m*/*z* = 403.4 (MH^+).

***N*^{1},*N*^{8}-Bis(benzyloxycarbonyl)spermine (25)**
This compound was synthesised according to the general procedure from spermine (1.64 g, 8.12 mmol) using CH_2Cl_2 as the solvent.

Yield: 2.57 g (67 %); white solid; mp 72–75 °C.

^{1}H NMR ($CDCl_3$): δ = 1.21 (br s, 2 H), 1.49 (m, 4 H), 1.64 (quint, 4 H, *J* = 6.4 Hz), 2.58 (m, 4 H), 2.65 (t, 4 H, *J* = 6.4 Hz), 3.27 (q, 4 H, *J* = 5.5 Hz), 5.09 (s, 4 H), 5.68 (br s, 2 H), 7.30–7.38 (m, 10 H).

^{13}C NMR ($CDCl_3$): δ = 27.9, 29.6, 40.2, 48.0, 49.8, 66.6, 128.1, 128.6, 136.9, 156.6.

MS (FAB): *m*/*z* = 471.4 (MH^+).

***N*^{1},*N*^{8}-Bis(allyloxycarbonyl)spermine (26)**
This compound was synthesised according to the general procedure from spermine (1.64 g, 8.12 mmol) using CH_2Cl_2 as the solvent.

Yield: 2.93 g (98 %); white solid; mp 39–41 °C.

^{1}H NMR ($CDCl_3$): δ = 1.47 (quint, 4 H, *J* = 3.3 Hz), 1.53 (br s, 2 H), 1.61 (quint, 4 H, *J* = 6.6 Hz), 2.55 (t, 4 H, *J* = 5.9 Hz), 2.63 (t, 4 H, *J* = 6.6 Hz), 3.21 (d, 4 H, *J* = 4.4 Hz), 4.49 (d, 4 H, *J* = 5.1 Hz), 5.13 (dd, 2 H, *J* = 1.1, 10.3 Hz), 5.23 (dd, 2 H, *J* = 1.1, 17.2 Hz), 5.72 (br s, 2 H), 5.86 (m, 2 H, *J* = 5.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 27.6, 29.4, 39.8, 47.7, 49.5, 65.1, 117.2, 133.0, 156.2.

MS (FAB): *m*/*z* = 371.3 (MH^+).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{35}N_4O_4$ (MH^+): 371.2658; found: 371.2630.

Mono Carbamate Protection of Aliphatic Diamines; General Procedure
Alkyl phenyl carbonate (5.0 mmol) (in the cases of the unsymmetrical diamines 10 mmol of alkyl phenyl carbonate was used) was added to a stirring solution of diamine (5.0 mmol) in absolute EtOH (20 mL). The reaction mixture was stirred over night at r.t. (reflux in the case of *tert*-butyl phenyl carbonate) followed by removal of the volatiles in vacuo. H_2O (25 mL) was added and the pH adjusted to 3 by addition of aq HCl (2 M) followed by extraction with CH_2Cl_2 (2 × 50 mL). The aq phase was then made strongly alkaline by addition of aq NaOH (2 M) and extracted with CH_2Cl_2 (3 × 80 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo to afford the desired products.

(2-Aminoethyl)carbamic Acid *tert*-Butyl Ester (27)
From 1,2-ethanediamine (33.3 mmol).

Yield: 3.44 g (65%); colourless oil.

Scale Up
tert-Butyl phenyl carbonate (20.0 g, 0.33 mol) was added to a stirring solution of 1,2-ethanediamine (64.62 g, 0.33 mol) in absolute EtOH (200 mL). The reaction mixture was refluxed overnight (keeping the temperature of the oil bath at a maximum of 80 °C) followed by removal of the volatiles in vacuo. H_2O (300 mL) was added and the pH adjusted to 3 by addition of aq HCl (2 M) followed by extraction with CH_2Cl_2 (4 × 500 mL). The aq phase was then made strongly alkaline by addition of aq NaOH (2 M) and extracted with CH_2Cl_2 (5 × 500 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo to afford **27**.

Yield: 34.6 g (65%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.43 [br s, 11 H, $(CH_3)_3$ and NH_2], 2.78 (t, 2 H, *J* = 5.9 Hz), 3.15 (q, 2 H, *J* = 5.9 Hz), 4.96 (br s, 1 H, NHCO).

^{13}C NMR ($CDCl_3$): δ = 28.3, 41.5, 42.6, 79.2, 156.1.

MS (FAB): *m*/*z* = 161.1 (MH^+).

(2-Aminoethyl)carbamic Acid Benzyl Ester (28)
From 1,2-ethanediamine (5 mmol).

Yield: 0.62 g (64%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.38 (br s, 2 H), 2.76–2.85 (m, 2 H), 3.19–3.36 (m, 2 H), 5.10 (s, 2 H), 5.24 (br s, 1 H), 7.31–7.37 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 41.5, 43.6, 66.5, 127.9, 128.0, 128.4, 136.4, 156.5.

MS (FAB): *m*/*z* = 195.1 (MH^+).

(2-Aminoethyl)carbamic Acid Allyl Ester (29)
From 1,2-ethanediamine (5 mmol).

Yield: 0.48 g (67%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 2.04 (br s, 2 H), 2.81 (t, 2 H, *J* = 5.8 Hz), 3.22 (m, 2 H), 4.53 (d, 2 H, *J* = 5.5 Hz), 5.15–5.31 (m, 2 H), 5.45 (br s, 1 H), 5.82–5.97 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 41.4, 43.2, 65.3, 117.4, 132.8, 156.4.

MS (FAB): *m*/*z* = 145.0 (MH^+).

(3-Aminopropyl)carbamic Acid *tert*-Butyl Ester (30)
From 1,3-propanediamine (13.5 mmol).

Yield: 1.61 g (68%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.40 (s, 9 H), 1.55–1.65 (m, 2 H), 2.26 (br s, 2 H), 2.74 (t, 2 H, *J* = 6.4 Hz), 3.13–3.20 (m, 2 H), 5.08 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 28.2, 32.7, 38.1, 39.2, 78.8, 156.0.

MS (FAB): *m*/*z* = 175.1 (MH^+).

(3-Aminopropyl)carbamic Acid Benzyl Ester (31)
From 1,3-propanediamine (5 mmol).

Yield: 0.75 g (72%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.52 (br s, 2 H), 1.62 (quint, 2 H, *J* = 6.4 Hz), 2.75 (t, 2 H, *J* = 6.4 Hz), 3.27 (q, 2 H), 5.09 (s, 2 H), 5.33 (br s, 1 H), 7.30–7.36 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 32.9, 39.1, 39.6, 66.5, 127.8, 127.9, 128.3, 136.6, 156.4.

MS (FAB): *m*/*z* = 209.1 (MH^+).

(3-Aminopropyl)carbamic Acid Allyl Ester (32)
From 1,3-propanediamine (5 mmol).

Yield: 0.68 g (86%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.62 (quint, 2 H, *J* = 6.4 Hz), 1.91 (br s, 2 H), 2.76 (t, 2 H, *J* = 6.4 Hz), 3.25 (q, 2 H), 4.52 (d, 2 H, *J* = 4.69 Hz), 5.14–5.30 (m, 2 H), 5.48 (br s, 1 H), 5.81–5.97 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 32.5, 38.8, 39.4, 65.2, 117.3, 132.9, 156.3.

MS (FAB): *m*/*z* = 159.0 (MH^+).

Anal. Calcd for $C_{14}H_{25}N_3O_4$: C, 53.15; H, 8.92; N, 17.71. Found: C, 53.37; H, 9.08; N, 18.01.

(4-Aminobutyl)carbamic Acid *tert*-Butyl Ester (33)
From 1,4-butanediamine (5 mmol).

Yield: 0.59 g (63%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.37 (s, 9 H), 1.41–1.46 (m, 4 H), 1.90 (br s, 2 H), 2.63–2.68 (m, 2 H), 3.01–3,10 (m, 2 H), 4.85 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 27.2, 28.2, 30.3, 40.2, 41.4, 78.8, 155.8.

MS (FAB): *m*/*z* = 189.0 (MH^+).

(4-Aminobutyl)carbamic Acid Benzyl Ester (34)
From 1,4-butanediamine (5 mmol).

Yield: 0.70 g (63%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.42–1.58 (m, 6 H), 2.67–2.75 (m, 2 H), 3.15–3.25 (m, 2 H), 5.03 (br s, 1 H), 5.09 (s, 2 H), 7.29–7.39 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 27.3, 30.6, 40.8, 41.6, 66.5, 127.9, 128.0, 128.4, 136.5, 156.3.

MS (FAB): *m*/*z* = 223.0 (MH^+).

(4-Aminobutyl)carbamic Acid Allyl Ester (35)
From 1,4-butanediamine (5 mmol).

Yield: 0.66 g (77%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.46–1.55 (m, 4 H), 2.00 (br s, 2 H), 2.68–2.74 (m, 2 H), 3.13–3.20 (m, 2 H), 4.53 (d, 2 H, *J* = 4.4 Hz), 5.14 (br s, 1 H), 5.15–5.31 (m, 2 H), 5.82–5.96 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 27.2, 30.2, 40.7, 41.4, 65.2, 117.3, 132.9, 156.1.

MS (FAB): *m*/*z* = 173.0 (MH^+).

Anal. Calcd for $C_{14}H_{25}N_3O_4$: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.70; H, 9.57; N, 16.58.

(5-Aminopentyl)carbamic Acid *tert*-Butyl Ester (36)
From 1,5-pentanediamine (5 mmol).

Yield: 0.52 g (50%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.36–1.43 (s, 9 H), 1.44–1.53 (m, 6 H), 2.70 (t, 2 H, *J* = 6.2 Hz), 3.00–3.11 (m, 2 H), 3.74 (br s, 2 H), 4.80 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 23.8, 28.3, 29.6, 31.7, 40.3, 41.1, 78.8, 155.9.

MS (FAB): *m*/*z* = 203.0 (MH^+).

(5-Aminopentyl)carbamic Acid Benzyl Ester (37)
From 1,5-pentanediamine (5 mmol).

Yield: 0.66 g (56%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.27–1.37 (m, 2 H), 1.38–1.52 (m, 4 H), 1.80 (br s, 2 H), 2.66 (t, 2 H, *J* = 6.4 Hz), 3.11–3.20 (m, 2 H), 5.06 (s, 2 H), 7.30–7.35 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 23.8, 29.6, 32.8, 40.7, 41.6, 66.3, 127.8, 127.8, 128.3, 136.5, 156.3.

MS (FAB): *m*/*z* = 237.1 (MH^+).

(5-Aminopentyl)carbamic Acid Allyl Ester (38)[3]
From 1,5-pentanediamine (5 mmol).

Yield: 0.47 g (51%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.31–1.41 (m, 2 H), 1.44–1.55 (m, 4 H), 2.71 (t, 2 H, *J* = 5.3 Hz), 2.99 (br s, 2 H), 3.13 (q, 2 H), 4.53 (d, 2 H, *J* = 5.3 Hz), 4.99 (br s, 1 H), 5.15–5.32 (m, 2 H), 5.82–5.97 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 23.8, 29.6, 32.1, 40.7, 41.4, 65.3, 117.4, 132.9, 156.2.

MS (FAB): *m*/*z* = 187.1 (MH^+).

(6-Aminohexyl)carbamic Acid *tert*-Butyl Ester (39)
From 1,6-hexanediamine (15.5 mmol).

Yield: 1.63 g (49%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.26–1.32 (m, 4 H), 1.37–1.44 (m, 13 H), 2.14 (br s, 2 H), 2.65 (t, 2 H, *J* = 7.0 Hz), 3.05 (q, 2 H), 4.66 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 26.3, 26.4, 28.2, 29.8, 33.0, 40.3, 41.7, 78.8, 155.8.

MS (FAB): *m*/*z* = 217.1 (MH^+).

(6-Aminohexyl)carbamic Acid Benzyl Ester (40)
From 1,6-hexanediamine (5 mmol).

Yield: 0.60 g (48%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.28–1.35 (m, 4 H), 1.38–1.51 (m, 4 H), 1.67 (br s, 2 H), 2.66 (t, 2 H, *J* = 6.4 Hz), 3.17 (q, 2 H), 4.95 (br s, 1 H), 5.07 (s, 2 H), 7.31–7.37 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 26.3, 26.4, 29.8, 33.3, 40.8, 41.8, 66.4, 127.9, 127.9, 128.3, 136.5, 156.2.

MS (FAB): *m*/*z* = 251.0.

(6-Aminohexyl)carbamic Acid Allyl Ester (41)[2]
From 1,6-hexanediamine (5 mmol).

Yield: 0.46 g (46%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.32–1.38 (m, 4 H), 1.46–1.56 (m, 4 H), 2.73–2.81 (m, 2 H), 3.17 (q, 2 H), 3.59 (br s, 2 H), 4.55 (d, 2 H, *J* = 5.3 Hz), 4.85 (br s, 1 H), 5.18–5.33 (m, 2 H), 5.85–5.98 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 26.2, 26.2, 29.7, 31.8, 40.7, 41.3, 65.3, 117.4, 132.9, 156.2.

MS (FAB): *m*/*z* = 201.0.

(2-Amino-2-methylpropylcarbamic Acid *tert*-Butyl Ester (42)
From 2-methyl-1,2-propanediamine (17.2 mmol).

Yield: 2.97 g (91%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.09 (s, 6 H), 1.43 (s, 9 H), 1.48 (br s, 2 H), 3.00 (d, 2 H, *J* = 6.4 Hz), 4.97 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 28.0, 28.3, 50.3, 52.0, 79.0, 156.3.

MS (FAB): *m*/*z* = 189.1 (MH^+).

(2-Amino-2-methylpropyl)carbamic Acid Benzyl Ester (43)
From 2-methyl-1,2-propanediamine (5 mmol).

Yield: 1.08 g (97%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.10 (s, 6 H), 1.97 (br s, 2 H), 3.08 (d, 2 H, *J* = 6.4 Hz), 5.10 (s, 2 H), 5.42 (t, 1 H, *J* = 6.4 Hz), 7.33–7.37 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 27.8, 50.3, 52.1, 66.6, 127.9, 127.9, 128.3, 136,4, 156.8.

MS (FAB): *m*/*z* = 223.1 (MH^+).

(2-Amino-2-methylpropyl)carbamic Acid Allyl Ester (44)
From 2-methyl-1,2-propanediamine (5 mmol).

Yield: 0.83 g (96%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.08 (s, 6 H), 1.56 (br s, 2 H), 3.04 (d, 2 H, *J* = 6.4 Hz), 4.6 (d, 2 H), 5.15–5.32 (m, 2 H), 5.33 (br s, 1 H), 5.83–5.97 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 28.0, 50.0, 52.3, 65.4, 117.4, 132.8, 156.7.

MS (FAB): *m*/*z* = 173.0 (MH^+).

Anal. Calcd for $C_{14}H_{25}N_3O_4$: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.57; H, 9.23; N, 16.43.

(2-Aminopropyl)carbamic Acid *tert*-Butyl Ester (45)[5]
From 1,2-propanediamine (18.8 mmol).

Yield: 2.30 g (70%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.10 (d, 3 H, J = 6.0 Hz), 1.42 (s, 9 H), 2.77 (br s, 2 H), 2.88–2.97 (m, 1 H), 3.03–3.10 (m, 1 H), 3.11–3.22 (m, 1 H), 5.17 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 21.2, 28.2, 47.2, 47.7, 79.1, 156.2.

MS (FAB): *m*/*z* = 175.0 (MH^+).

(2-Aminopropyl)carbamic Acid Benzyl Ester (46)
From 1,2-propanediamine (5 mmol).

Yield: 0.72 g (69%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.05 (d, 3 H, J = 6.4 Hz), 1.69 (br s, 2 H), 2.87–3.04 (m, 2 H), 3.14–3.24 (m, 1 H), 5.08 (s, 2 H), 5.50 (br s, 1 H), 7.28–7.37 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 21.1, 46.6, 48.5, 66.4, 127.8, 127.9, 128.3, 136.4, 156.5.

MS (FAB): *m*/*z* = 209.0 (MH^+).

(2-Aminopropyl)carbamic Acid Allyl Ester (47)
From 1,2-propanediamine (5 mmol).

Yield: 0.59 g (75%); colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.08 (d, 3 H, *J* = 5.9 Hz), 2.92–3.24 (m, 5 H, CH, CH_2 and NH_2), 4.53 (d, 2 H, *J* = 5.3 Hz), 5.71 (br s, 1 H), 5.81–5.96 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 20.4, 46.7, 47.9, 65.4, 117.4, 132.8, 156.5.

MS (FAB): *m*/*z* = 159.0 (MH^+).

Anal. Calcd for $C_{14}H_{25}N_3O_4$: C, 53.15; H, 8.92; N, 17.71. Found: C, 53.35; H, 8.98; N, 17.51.

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