A FACILE SYNTHESIS OF SELECTIVELY PROTECTED LINEAR OLIGOAMINES

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A convenient multi-gram preparative method for the synthesis of linear oligoamines having the terminal primary amino groups unprotected and the central secondary amino functions protected with *tert*-butoxycarbonyl groups is presented. At the same time, simple one-pot preparation of the α,ω-bis(trifluoroacetamide) intermediates **2** has been developed. NMR spectra of the novel selectively protected oligoamines are also discussed.

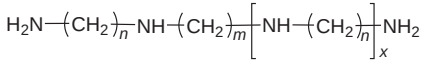
Keywords: Amines; NMR spectroscopy; Protecting groups; Azacrown macrocycles; Polyamines; Building blocks.

Oligo- and polyamines are an important class of organic compounds. Natural linear oligoamines, such as putrescine, spermine, and spermidine are involved in a variety of biological functions[1–4]. Recently, they have received increased attention due to their putative role in the ion channel regulation and cell proliferation[4–6]. Synthetic macrocyclic oligo- and polyamines have been studied as artificial receptors for recognition of both cationic and anionic species[7–10]. Unique properties of metal complexes of oligo- and polyamines have initiated an intensive research on their potential application in medicine, catalysis, electrochemistry and material chemistry.

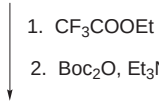
Selectively functionalized linear oligoamines are key intermediates in syntheses of naturally occuring and synthetic polyamine analogues and conjugates. Recently, the methods of selective derivatization of the amino functions of linear oligoamines have been reviewed[4]. In the project leading to novel polyamine macrocyclic ligands, we needed oligoamine precursors, whose terminal primary amino functions are unprotected while the central secondary amino groups are protected with a suitable protecting group. Since our final macrocycles contain the benzylic moiety sensitive to the reductive cleavage, we have chosen the *tert*-butoxycarbonyl (Boc) group for the protection. Following the macrocyclization step, the Boc group can be

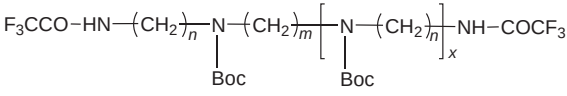
cleanly removed on strong acid treatment under mild conditions leaving the remaining ligand skeleton unaffected.

To introduce the Boc groups selectively to the secondary amino functions of linear oligoamines, the primary amino groups must be temporarily protected. Recently, the trifluoroacetyl group has been shown to be appropriate for this purpose[11–13]. The α,ω-bis(trifluoroacetamide)s are formed exclusively in nearly quantitative yields on the reaction of ethyl trifluoroacetate with linear oligoamines; they are easily cleaved by alkaline hydrolysis, when the Boc group is stable. Therefore, the synthetic pathway shown in Scheme 1 was selected. Previously, the same strategy has been used for the preparation of *tert*-butyl *N*-(4-aminobutyl)-*N*-(3-aminopropyl)-carbamate[12], indicating feasibility of the chosen way. However, the reported synthetic protocol[12] involved two chromatographic separations unsuitable for large-scale preparations.



1





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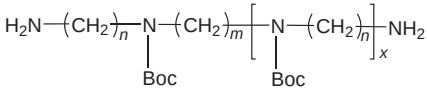

3

In formulae **1**-**3**: **a,** $n = 2$, $m = 2$, $x = 0$ Boc = COO*t*Bu
b, $n = 2$, $m = 2$, $x = 1$
c, $n = 2$, $m = 3$, $x = 1$
d, $n = 3$, $m = 2$, $x = 1$
e, $n = 2$, $m = 2$, $x = 2$

SCHEME 1

Our preliminary experiments confirmed the quantitative formation of the α,ω-bis(trifluoroacetamide)s upon the reaction of ethyl trifluoroacetate with oligoamines **1** at 0 °C in several solvents and also the possibility of introducing the Boc protecting groups to the remaining amino functions of the α,ω-bis(trifluoroacetamide) intermediates. Consequently, the experimental conditions were optimized resulting in a general one-pot procedure for the preparation of the selectively protected oligoamines **2**. A simple final crystallization of **2** is a key operation allowing to run the preparation on a multigram scale. Typically, 20–40 g amount of the compounds **2** was produced in a single batch. The protected oligoamines **2** proved to be stable compounds that can be stored for months. Moreover, pure derivative **2e** was obtained even when technical oligoamine **1e** (Janssen, assay *ca* 85%) was used as a starting material. In this case, yield of the product decreased to 60% compared with 83% in the preparation employing pure amine **1e** (Merck, 95%+).

Upon alkaline hydrolysis of **2**, the trifluoroacetyl protecting groups were removed giving diamines **3** in nearly quantitative yields. Thus, a simple and highly efficient synthetic procedure leading to the Boc-protected oligoamines **3** has been developed. The selectively protected oligoamines **3** can serve as useful building blocks in preparations of polyamine macrocycles as well as molecules of biological interest.

The room-temperature ^{1}H and ^{13}C NMR spectra of compounds **2a**–**2e** and **3a**–**3e** show in general doubling and/or different extent of line-broadening of most of their signals in $CDCl_3$ and DMSO solution. Increasing temperature (50 °C) leads to coalescence of doubled signals and sharpening of others. The observed dynamic effects have obviously their origin in: (i) formation of seven- or eight-membered rings by intramolecular H-bondings between NH proton of trifluoroacetamido group (in **2a**–**2e**) or amino group (in **3a**–**3e**) and C=O oxygen of *tert*-butoxycarbonyl group; (ii) hindered rotation around tertiary amide bonds N–CO of N-Boc groups leading to slow or medium rates of interconversion between *cis* and *trans* isomers in solution (secondary amide bonds NH–CO in trifluoroacetamido groups are known to exist in solution exclusively as *trans* isomers); (iii) hindered rotation about single bonds of the oligoamine backbone due to the presence of bulky substituents (Boc and $COCF_3$). The character of the spectra does not allow to study these effects in detail. ^{1}H and ^{13}C NMR data of compounds **2a**–**2e** and **3a**–**3e** (at 50 °C), summarized in Tables I and II, confirm the presence of all the structural fragments and symmetry of the molecules.

EXPERIMENTAL

NMR spectra were measured on a Varian UNITY-500 spectrometer (^{1}H at 499.9 MHz, ^{13}C at 125.7 MHz) in $CDCl_3$ with TMS as an internal reference. Mass spectra were recorded on a ZAB EQ (VG Analytical) instrument using the FAB technique (Xe, 8 kV, matrix: thioglycerol–glycerol 3:1). Oligoamine **1c** was prepared according to a literature procedure[14]; other chemicals were obtained from Aldrich or Merck and were used without further purification. Dichloromethane was freshly distilled from CaH_2.

General Procedure for Synthesis of **2**

To a solution of oligoamine **1** in dichloromethane (0.5 M, 1 equiv.) cooled in an ice bath, a solution of ethyl trifluoroacetate in dichloromethane (2 M, 2.1 equiv.) was added dropwise at 0–5 °C. The mixture was stirred at 0–5 °C for another 30 min, then heated to room tem-

TABLE I
^{1}H NMR data of compounds **2a**–**2e** and **3a**–**3e** in $CDCl_3$ (50 °C)

Compound	N–$(CH_2)_2$–N	N–$(CH_2)_3$–N	NH or NH_2	*t*-Bu
2a	3.49 um (8 H)	–	7.53 b (1 H); 7.41 b (1 H)	1.46 s (9 H)
2b	3.30–3.56 um (12 H)	–	8.80 b (1 H); 7.65 b (1 H)	1.44 s (18 H)
2c	3.47 um (8 H)	3.21 t (4 H), *J* = 7.2 1.76 p (2 H), *J* = 7.2	7.78 b (2 H)	1.46 s (18 H)
2d	3.30 um (4 H)	3.30 um (8 H) 1.74 um (4 H)	7.92 b (2 H)	1.46 s (18 H)
2e	3.47 um (8 H) 3.33 um (8 H)	–	7.94 b (1 H) 7.80 b (1 H)	1.46 s (9 H) 1.45 s (18 H)
3a	3.28 t (4 H), *J* = 6.6 2.84 t (4 H), *J* = 6.6	–	1.19 bs (4 H)	1.46 s (9 H)
3b	3.34 b (4 H) 3.26 bt (4 H), *J* = 6.6 2.83 t (4 H), *J* = 6.6	–	1.21 bs (4 H)	1.46 s (18 H)
3c	2.83 t (4 H), *J* = 6.6 3.25 t (4 H), *J* = 6.6	3.22 t (4 H), *J* = 7.5 1.78 m (2 H	1.34 bs (4 H)	1.46 s (18 H)
3d	3.29 b (4 H)	2.69 t (4 H), *J* = 6.8 1.65 p (4 H), *J* = 6.8 3.29 b (4 H))	1.42 bs (4 H)	1.46 s (18 H)
3e	3.26 b (8 H) 3.18 bt (4 H), *J* = 6.5 2.75 t (4 H), *J* = 6.5	–	≈1.40 bs (4 H)	1.392 s (9 H) 1.388 s (18 H)

TABLE II
^{13}C NMR data of compounds **2a**–**2e** and **3a**–**3e** in $CDCl_3$ (50 °C)

Compound	$N–(CH_2)_2–N$	$N–(CH_2)_3–N$	$CO–CF_3$	$CO–O–C(CH_3)_3$
2a	39.81 (2 C) 46.73 (2 C)	–	≈158.5 (2 C) vb 115.86 (2 C) q, ^1J(C,F) = 288.1	157.10 (1 C) 82.14 (1 C) 28.13 (3 C)
2b	40.10 (2 C) 46.10 (2 C) 50.20 (2 C)	–	157.73 (2 C) q, ^2J(C,F) = 37.1 116.00 (2 C) q, ^1J(C,F) = 292.2	156.80 (2 C) 81.50 (2 C) 28.26 (6 C)
2c	45.94 (4 C)	40.52 (2 C) 28.30 (1 C)	157.73 (2 C) q, ^2J(C,F) = 38.1 115.91 (2 C) q, ^1J(C,F) = 287.1	≈157.2 (2 C) 81.17 (2 C) 28.30 (6 C)
2d	45.04 (2 C)	35.76 (2 C) 26.99 (2 C) 43.74 (2 C)	157.30 (2 C) q, ^2J(C,F) = 36.1 115.95 (2 C) q, ^1J(C,F) = 285.2	156.57 (2 C) 81.00 (2 C) 28.29 (6 C)
2e	40.40 (2 C) 45.76 (2 C) 45.96 (4 C)	–	157.58 (2 C) q, ^2J(C,F) = 36.8 115.79 (2 C) q, ^2J(C,F) = 288.1	155.50 (3 C) 81.10 (2 C) 80.54 (1 C) 28.18 (6 C) 28.32 (3 C)
3a	40.79 (2 C) 50.77 (2 C)	–	–	156.03 (1 C) 79.60 (1 C) 28.38 (3 C)
3b	40.88 (2 C) 51.10 (2 C) 45.98 (2 C)	–	–	155.66 (2 C) 79.68 (2 C) 28.43 (6 C)
3c	40.71 (2 C) 50.19 (2 C)	45.35 (2 C) 29.62 (1 C)	–	155.67 (2 C) 79.54 (2 C) 28.40 (6 C)
3d	45.22 (2 C)	39.20 (2 C) 32.20 (2 C) 45.22 (2 C)	–	155.34 (2 C) 79.41 (2 C) 28.31 (6 C)
3e	40.77 (2 C) 50.77 (2 C) 45.78 (4 C)	–	–	155.61 (2 C) 155.22 (1 C) 79.63 (2 C) 79.75 (1 C) 28.40 (6 C) 28.38 (3 C)

perature and stirred for additional 1 h. Triethylamine (2.1 equiv.) was added followed by dropwise addition of a solution of di-*tert*-butyl dicarbonate in dichloromethane (2 M, 2.1 equiv.). The reaction mixture was stirred at room temperature for 5 h, then transferred to a separatory funnel and washed twice with aqueous $NaHCO_3$ and water. The dichloromethane solution was dried over K_2CO_3 and, upon removal of the drying agent, its volume was reduced to 1/3. The same volume of hexane was added and the mixture was left standing in a refrigerator for 3 h. The white microcrystalline product was isolated by filtration, washed with hexane and dried.

tert-Butyl N,N-bis[2-(trifluoroacetamido)ethyl]carbamate (**2a**). Yield 87%, m.p. 113–115 °C. For $C_{13}H_{19}F_6N_3O_4$ (395.3) calculated: 39.50% C, 4.84% H, 28.84% F, 10.63% N; found: 39.54% C, 4.89% H, 28.94% F, 10.72% N. FAB-MS, *m/z*: 396 ($[M + H]^+$).

N,N′-(Ethylenebis{[(tert-butoxycarbonyl)imino]ethylene})bis(trifluoroacetamide) (**2b**). Yield 90%, m.p. 158–159 °C. For $C_{20}H_{32}F_6N_4O_6$ (538.5) calculated: 44.61% C, 5.99% H, 21.17% F, 10.40% N; found: 44.67% C, 6.08% H, 21.02% F, 10.50% N. FAB-MS, *m/z*: 539 ($[M + H]^+$).

N,N′-(Propane-1,3-diylbis{[(tert-butoxycarbonyl)imino]ethylene})bis(trifluoroacetamide) (**2c**). Yield 89%, m.p. 143–145 °C. For $C_{21}H_{34}F_6N_4O_6$ (552.5) calculated: 45.65% C, 6.20% H, 20.63% F, 10.14% N; found: 45.59% C, 6.48% H, 20.78% F, 10.13% N. FAB-MS, *m/z*: 553 ($[M + H]^+$).

N,N′-(Ethylenebis{[(tert-butoxycarbonyl)imino]propane-1,3-diyl})bis(trifluoroacetamide) (**2d**). Yield 91%, m.p. 108–110 °C. For $C_{22}H_{36}F_6N_4O_6$ (566.5) calculated: 46.64% C, 6.40% H, 20.12% F, 9.89% N; found: 46.48% C, 6.62% H, 20.27% F, 9.87% N. FAB-MS, *m/z*: 567 ($[M + H]^+$).

N,N′-([(tert-Butoxycarbonyl)imino]bis{ethylene[(tert-butoxycarbonyl)imino]ethylene})-bis(trifluoroacetamide) (**2e**). Yield 83%, m.p. 127–129 °C. For $C_{27}H_{45}F_6N_5O_8$ (681.7) calculated: 47.57% C, 6.65% H, 16.72% F, 10.27% N; found: 47.20% C, 6.59% H, 17.00% F, 10.19% N. FAB-MS, *m/z*: 682 ($[M + H]^+$).

General Procedure for Synthesis of **3**

To a solution of **2** in ethanol (0.2 M, 1 equiv.), an aqueous solution of NaOH (3 M, 10–15 equiv.) was added. The mixture was stirred at room temperature for 6 h. Ethanol was evaporated and the residue was extracted with three portions of dichloromethane. The extracts were combined and dried over K_2CO_3. Upon the dichloromethane removal and drying *in vacuo*, product **3** was obtained as a colourless viscous liquid.

tert-Butyl N,N-bis(2-aminoethyl)carbamate (**3a**). Yield 72%. For $C_9H_{21}N_3O_2$ (203.3) calculated: 53.18% C, 10.41% H, 20.67% N; found: 52.86% C, 10.67% H, 19.94% N. FAB-HRMS, *m/z*: 204.1698 (for $[M + H]^+$ calculated: 204.1712).

2,2′-{Ethylenebis[(tert-butoxycarbonyl)imino]}diethan-1-amine (**3b**). Yield 84% (white solid), m.p. 73–75 °C. For $C_{16}H_{34}N_4O_4$ (346.5) calculated: 55.47% C, 9.89% H, 16.17% N; found: 54.97% C, 9.95% H, 15.91% N. FAB-HRMS, *m/z*: 347.2642 (for $[M + H]^+$ calculated: 347.2658).

2,2′-{Propane-1,3-diylbis[(tert-butoxycarbonyl)imino]}diethan-1-amine (**3c**). Yield 91%. For $C_{17}H_{36}N_4O_4$ (360.5) calculated: 56.64% C, 10.07% H, 15.54% N; found: 55.58% C, 9.95% H, 15.37% N. FAB-HRMS, *m/z:* 361.2824 (for $[M + H]^+$ calculated: 361.2815).

3,3′-{Ethylenebis[(tert-butoxycarbonyl)imino]}dipropan-1-amine (**3d**). Yield 93%. For $C_{18}H_{38}N_4O_4$ (374.5) calculated: 57.73% C, 10.23% H, 14.96% N; found: 56.87% C, 10.21% H, 14.71% N. FAB-HRMS, *m/z:* 375.2998 (for $[M + H]^+$ calculated: 375.2971).

2,2′-([(tert-Butoxycarbonyl)imino]bis{ethylene[(tert-butoxycarbonyl)imino]})diethan-1-amine (**3e**). Yield 93%. For $C_{23}H_{47}N_5O_6$ (489.6) calculated: 56.42% C, 9.67% H, 14.30% N; found: 55.83% C, 9.46% H, 14.18% N. FAB-HRMS, *m/z*: 490.3605 (for $[M + H]^+$ calculated: 490.3605).

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