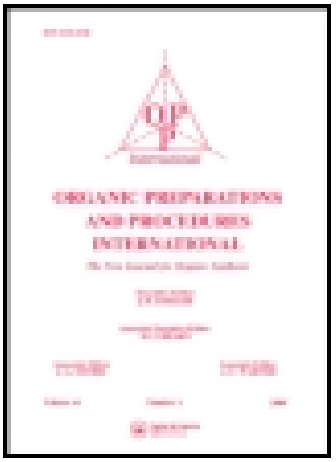

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CONCISE SYNTHESIS OF N-PROTECTED CARBOXYALKYL ETHER AMINES

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CONCISE SYNTHESIS OF *N*-PROTECTED CARBOXYALKYL ETHER AMINES

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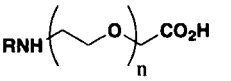
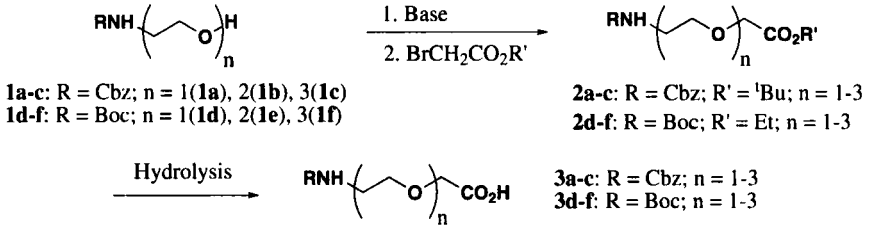
Water soluble poly(ethyleneglycol) (PEG) linkers that tether biomolecules have found widespread applications in medicinal chemistry due to their biocompatibility, amphilicity, low immunogenicity and toxicity.[1-9] Short bifunctional ethyleneglycol linkers provide the desirable properties of PEG and are extremely attractive materials for bioconjugation.[10-13] We present herein a concise synthesis a series of short bifunctional linkers, the *N*-protected carboxyalkyl ether amines (Fig. 1).

Previous efforts for the preparation of these compounds have been limited to either multi-step sequences or specific preparations that are not adaptable to the preparation of a variety of *N*-protected carboxyalkyl ether amines.[14-16] Our approach envisioned *O*-alkylation of the *N*-protected amino alcohols **1a-f** with an alkyl bromoacetate followed by ester hydrolysis to afford the desired compounds (*Scheme 1*). A lack of chemoselective deprotonation in the first step would result in a mixture of products arising from *N*-alkylation, *O*-alkylation and/or both. A brief investigation of the effects of temperature and counter-ion on the alkylation



3a-c: R = Cbz; n = 1-3
3d-f: R = Boc; n = 1-3

Fig. 1



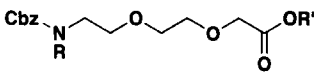
1a-c: R = Cbz; n = 1(**1a**), 2(**1b**), 3(**1c**)
1d-f: R = Boc; n = 1(**1d**), 2(**1e**), 3(**1f**)

2a-c: R = Cbz; R' = ^{t}Bu; n = 1-3
2d-f: R = Boc; R' = Et; n = 1-3

3a-c: R = Cbz; n = 1-3
3d-f: R = Boc; n = 1-3

Scheme 1

of the alcohol **1b**[17] was undertaken. Deprotonation of **1b** at 0° for 30 min followed by alkylation with *tert*-butyl bromoacetate gave ester **2b** in 51% yield.[18] None of the isomeric mono-*N*-alkylated product was observed. By-products **4b, 5b** and **6b** were isolated in 14%, 11% and 5% yield, respectively. Lowering the temperature decreased the yield of **2b** while increasing production of the undesired by-product **4b**;[19] the use of either sodium or lithium *tert*-butoxide resulted in substantially lower yields of **2b**.[19] The optimal reaction conditions resulting from this brief investigation were deprotonation of the *N*-protected amino alcohol by potassium *tert*-butoxide in THF at 0° followed by alkylation with *tert*-butyl bromoacetate.



4b: R = $CH_2CO_2{}^tBu$; R' = ^tBu
5b: R = H; R' = $(OCH_2CH_2)_2NHCbz$
6b: R = $CH_2CO_2{}^tBu$; R' = $(OCH_2CH_2)_2NHCbz$

The scope of our method was expanded to include other *N*-protected alcohols (*Table 1*) to produce ester precursors of *N*-protected carboxyalkyl ether amines **2b-2f** in 30-65% yield; the Cbz-protected ethanolamine **1a** underwent an internal displacement of a benzyloxy group and afforded none of the desired ester **2a**.[20] *O*-Alkylation of the Boc-protected alcohols gave similar or higher yields than the Cbz-protected alcohols.

Trifluoroacetic acid cleavage of *tert*-butyl esters **2b-c** gave the *N*-protected carboxyalkyl ether amines **3b-c** in 78-87% yields, while saponification of the corresponding ethyl esters **2d-f** with LiOH gave the corresponding acids **3d-f** in 71-75% yields (*Table 1*).

Table 1. Yields of Esters **2b-f** and Acids **3b-f** [a]

Esters	**2b** (51%)	**2c** (45%)	**2d** (30%)	**2e** (65%)	**3f** (45%)
Acids	**3b** (87%)	**3c** (78%)	**3d** (74%)	**3e** (75%)	**3f** (71%)

a) Yields after flash chromatography.

In summary, we have developed a concise synthesis of *N*-protected carboxyalkyl ether amines **3b-f**. Future applications of these hydrophilic linkers will be reported in due course.

EXPERIMENTAL SECTION

^1H and ^{13}C NMR were recorded on a Varian Gemini 2300 Spectrometer. Chemical shifts are reported in parts per million relative to TMS as internal standard and coupling constants (*J*) are in hertz. Electrospray mass spectra were obtained on a PE Sciex API 100 system. FAB HRMS were obtained on a JEOL JMS-SX102A Hybrid Mass Spectrometer. All chemicals, including **1a** and **1d**, were purchased from Aldrich (Milwaukee, WI, USA). Alcohols **1b**,[17] **1e**,[21] and **1f**[21] were synthesized using known literature procedures. All solvents, HPLC grade, were purchased from EM Science (Gibbstown, NJ, USA) and used as received. Thin-layer chromatography was performed using pre-coated Whatman MK6F silica gel plates purchased from Whatman, Inc. (Clifton, NJ, USA). Flash chromatography was performed on Merck grade 60 silica gel (230-400 mesh) which was purchased from EM Science. THF was freshly distilled from a purple solution of sodium and benzophenone.

2-[2-{2-(*N*-Benzyloxycarbonyl)aminoethoxy}ethoxy]ethanol (1c).- 2-[2-{2-Aminoethoxy}ethoxy]ethanol[21] (10.0 g, 53.9 mmol) was treated with *N*-(benzyloxycarbonyloxy)succinimide (17.5 g, 70.1 mmol) as described for the literature syntheses of **1e-f**[21] to afford **1c** as a colorless oil (10.1 g, 67%) after flash chromatography [ethyl acetate (EtOAc) to 5% methanol in EtOAc]. ^1H NMR ($CDCl_3$): δ 7.37-7.31 (m, 5 H), 5.44 (br s, 1 H), 5.11 (s, 2 H), 3.71-3.54 (m, 10 H), 3.43-3.38 (m, 2 H), 2.48 (br s, 1 H). ^{13}C NMR ($CDCl_3$): δ 156.37, 136.42, 128.26 (2C), 127.90, 127.84 (2C), 72.40, 70.10, 70.01, 69.87, 66.39, 61.31, 40.61. FAB HRMS calcd for $C_{14}H_{22}NO_5$: 284.1498. Found: 284.1492.

General Procedure for the *O*-Alkylation of *N*-Protected Amino Alcohols 1a-f.- A 1.0 M solution of K-O^{t}Bu in tetrahydrofuran (20 mmol) was added to an ice water cooled solution of *N*-carbamate protected alcohol (20 mmol) in dry THF (80 mL). After 30 min, neat ester (24 mmol) was added, stirred for 3 h 0-7° and then at room temperature for 15 h. Water (20 mL) was added and the mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (100 mL) and water (100 mL) and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4, decanted and concentrated *in vacuo* to afford an oil which was purified by flash chromatography as indicated.

***tert*-Butyl 2-[2-(*N*-benzyloxycarbonyl)aminoethoxy]ethoxyacetate (2b).**- Obtained by the *O*-alkylation of **1b** with *tert*-butyl bromoacetate followed by purification of the crude residue using 30% EtOAc/hexanes (R_f = 0.23) to afford 3.66 g (51%) of **2b** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.40-7.28 (m, 5 H), 5.38 (br s, 1 H), 5.11 (s, 2 H), 4.01 (s, 2 H), 3.72-3.63 (m, 4 H), 3.59 (t, *J* = 5.1 Hz, 2 H), 3.44-3.39 (m, 2 H), 1.47 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ 169.54, 156.47, 136.61, 128.43 (2C), 128.03, 127.98 (2C), 81.64, 70.66, 70.24, 70.09, 68.89, 66.56, 40.85, 28.04 (3C). MS (ESI) *m/z*: 354.4 [$C_{18}H_{27}NO_6$+H$^+$].

Anal. Calcd for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.28; H, 7.58; N, 3.90

Analytical Data for by-products **4b, 5b and 6b** - Esters **4b**, **5b** and **6b** were isolated from the *O*-alkylation reaction of alcohol **1b**. Diester **4b** (1.34 g, 14%) [30% EtOAc/hexanes; R_f = 0.36] ^{1}H NMR ($CDCl_3$; mixture of rotamers): δ 7.36-7.28 (m, 5 H), 5.16-5.11 (m, 2 H), 4.03-3.99 (m, 4 H), 3.69-3.52 (m, 8 H), 1.48-1.38 (m, 18 H). ^{13}C NMR [major rotamer] ($CDCl_3$): δ 168.98, 156.01, 136.46, 128.30 (2C), 127.92 (2C), 127.82 (2C), 81.49, 81.36, 70.57, 70.36, 70.14, 68.93, 67.18, 50.76, 48.46, 28.04 (3C), 27.91 (3C). FAB HRMS calcd for $C_{24}H_{39}NO_8$: 468.2597. Found: 468.2603. Diester **5b** (0.57 g, 11%) (80% EtOAc/hexanes; R_f = 0.34) ^{1}H NMR ($CDCl_3$): δ 7.37-7.33 (m, 10 H), 5.41 (br s, 1 H), 5.23 (br s, 1 H), 5.10 (s, 4 H), 4.28-4.00 (m, 3 H), 3.73-3.36 (m, 15 H). FAB HRMS calcd for $C_{26}H_{36}N_2O_9$: 519.2343. Found: 519.2353. Ester **6b** (0.304 g, 5%) (80% EtOAc/hexanes; R_f = 0.54) ^{1}H NMR ($CDCl_3$): δ 7.36-7.32 (m, 10 H), 5.16-5.08 (m, 4 H), 4.30-4.23 (m, 2 H), 4.15-4.11 (m, 2 H), 4.02-3.94 (m, 2 H), 3.71-3.37 (m, 14 H), 1.48-1.37 (m, 9 H). FAB HRMS calcd for $C_{32}H_{46}N_2O_{11}$: 633.3023. Found: 633.2997.

***tert*-Butyl 2-[2-{2-(*N*-benzyloxycarbonyl)aminoethoxy}ethoxy]ethoxyacetate (2c).**- Obtained by the *O*-alkylation of **1c** with *tert*-butyl bromoacetate followed by purification of the crude residue using 50% EtOAc/hexanes (R_f = 0.23) to afford 3.56 g (45%) of **2c** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.37-7.30 (m, 5 H), 5.38 (br s, 1 H), 5.10 (s, 2 H), 3.99 (s, 2 H), 3.68-3.60 (m, 8 H), 3.58-3.54 (m, 2 H), 3.42-3.37 (m, 2 H), 1.47 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ 169.47, 156.39, 136.49, 128.28, 127.88, 127.84, 81.43, 70.43, 70.30, 70.29, 69.99, 69.86, 68.74, 66.37, 40.10, 28.23 (3C). MS (ESI) *m/z*: 398.3 [$C_{20}H_{31}NO_7$+H]$^+$.

Anal. Calcd for $C_{20}H_{31}NO_7$: C, 60.44; H, 7.86; N, 3.52. Found: C, 60.25; H, 8.03; N, 3.38

Ethyl 2-(*N*-*tert*-butoxycarbonyl)aminoethoxyacetate (2d).- Obtained by the *O*-alkylation of **1d** with ethyl bromoacetate followed by purification of the crude residue using 20% EtOAc/hexanes (R_f =

0.26) to afford 1.46 g (30%) of **2d** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 5.16 (br s, 1 H), 4.23 (q, *J* = 7.0 Hz, 2 H), 4.09 (s, 2 H), 3.62 (t, *J* = 5.1 Hz, 2 H), 3.38-3.33 (m, 2 H), 1.45 (s, 9 H), 1.30 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 170.86, 156.44, 79.68, 71.26, 68.74, 61.42, 40.82, 28.82 (3C), 14.59. MS (ESI) *m/z*: 248.2 $[C_{11}H_{21}NO_5+H]^+$.

Anal. Calcd for $C_{11}H_{21}NO_5$: C, 53.43; H, 8.56; N, 5.66. Found: C, 53.19; H, 8.57; N, 5.38

Ethyl 2-[2-(*N*-*tert*-butoxycarbonyl)aminoethoxy]ethoxyacetate (2e).- Obtained by the *O*-alkylation of **1e** with ethyl bromoacetate followed by purification of the crude residue using 50% EtOAc/hexanes (R_f = 0.26) to afford 3.79 g (65%) of **2e** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 4.23 (q, *J* = 6.9 Hz, 2 H), 4.14 (s, 2 H), 3.74-3.65 (m, 4 H), 3.55 (t, *J* = 4.8 Hz, 2 H), 3.35-3.30 (m, 2 H), 1.45 (s, 9 H), 1.29 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 170.38, 155.97, 79.15, 70.86, 70.32, 70.28, 68.66, 60.84, 40.34, 28.38 (3C), 14.17. MS (ESI) *m/z*: 292.2 $[C_{13}H_{25}NO_6+H]^+$.

Anal. Calcd for $C_{13}H_{25}NO_6$: C, 53.59; H, 8.65; N, 4.81. Found: C, 53.27; H, 8.66; N, 4.75

Ethyl 2-[2-{2-(*N*-*tert*-butoxycarbonyl)aminoethoxy}ethoxy]ethoxyacetate (2f).- Obtained by the *O*-alkylation of **1f** with ethyl bromoacetate followed by purification of the crude residue using 50% EtOAc/hexanes (R_f = 0.26) to afford 3.79 g (45%) of **2f** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 5.06 (br s, 1 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 4.16 (s, 2 H), 3.77-3.53 (m, 10 H), 3.34-3.29 (m, 2 H), 1.44 (s, 9 H), 1.29 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 170.85, 156.45, 79.51, 71.24, 70.99, 70.90, 70.67, 70.57, 69.06, 61.24, 40.74, 28.81 (3C), 14.59. MS (ESI) *m/z*: 398.3 $[C_{15}H_{29}NO_7+H]^+$.

Anal. Calcd for $C_{15}H_{29}NO_7$: C, 53.72; H, 8.72; N, 4.18. Found: C, 53.46; H, 8.55; N, 3.94

General Procedure for the Trifluoroacetic Acid Cleavage of *tert*-Butyl Esters 2b and 2c.- Trifluoroacetic acid (6 mL) was added to a 0° solution of the ester (5 mmol) in dichloromethane (6 mL). After completion of addition, the reaction mixture was warmed to room temperature by removing the cooling bath and stirring for 3 h. The reaction mixture was concentrated *in vacuo* and the residue dissolved in EtOAc (100 mL), washed with 1N NaOH (5 x 40 mL) and the aqueous layer extracted with EtOAc (40 mL). The aqueous layer was acidified (pH 1) with conc. HCl and extracted with EtOAc (3 x 50 mL). The organic extracts were combined, dried over Na_2SO_4, decanted and concentrated *in vacuo*. The residue was purified by flash chromatography and the products were isolated after diluting and concentrating *in vacuo* successively with methanol/toluene (1/1, 3 × 40 mL), followed by methanol (40 mL), followed by EtOAc (40 mL) and finally with chloroform (40 mL) to remove acetic acid completely. The resultant residue was dissolved in water (100 mL) and lyophilized to afford the desired pure products.

2-[2-(*N*-Benzyloxycarbonyl)aminoethoxy]ethoxyacetic Acid (3b).- (2.17 g, 87%) [90/10 EtOAc/1% acetic acid in methanol; (R_f = 0.29)]. ^{1}H NMR ($CDCl_3$): δ 7.37-7.31 (m, 5 H), 5.21 (br s, 1 H), 5.11 (s, 2 H), 4.14 (s, 2 H), 3.76-3.73 (m, 2 H), 3.67-3.59 (m, 4 H), 3.45-3.39 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 173.34, 156.64, 136.37, 128.39 (4C), 127.95, 70.70, 70.03, 69.94, 68.25, 66.64, 40.62. MS (ESI) *m/z*: 298.2 $[C_{14}H_{19}NO_6+H]^+$.

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.76. Found: C, 56.49; H, 6.53; N, 4.55

2-[2-{2-(*N*-Benzyloxycarbonyl)aminoethoxy}ethoxy]ethoxyacetic Acid (3c).- (1.32 g, 78%) [90/10 EtOAc/1% acetic acid in methanol; (R_f = 0.28)]. ^{1}H NMR ($CDCl_3$): δ 7.38-7.32 (m, 5 H), 5.40 (br s, 1 H), 5.10 (s, 2 H), 4.11 (s, 2 H), 3.74-3.54 (m, 10 H), 3.43-3.38 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 172.65, 156.59, 136.51, 128.45, 128.06, 128.04, 71.14, 70.40, 70.14, 70.03, 69.93, 68.62, 66.65, 40.76. MS (ESI) *m/z*: 342.3 [$C_{16}H_{23}NO_7$+H$^+$].

Anal. Calcd for $C_{16}H_{23}NO_7$: C, 56.30; H, 6.79; N, 4.10 Found: C, 56.53; H, 6.85; N, 4.14

General Procedure for the Lithium Hydroxide Hydrolysis of Ethyl Esters 2d-f.- Lithium hydroxide monohydrate (2.2 eq.) was added to a solution of the ethyl ester (5 mmol) in dioxane (22 mL). Water was added until a clear yellow solution was obtained and after 1.5 h, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in water (50 mL), washed with EtOAc (50 mL) and then made acidic to pH 1 with conc. HCl. The acidic solution was extracted with EtOAc (4 × 40 mL) and the combined organic extracts were dried over Na_2SO_4, decanted and concentrated *in vacuo* to afford a residue which was purified by flash chromatography. Pure products were isolated after removal of acetic acid and subsequent lyophilization as described above.

2-(*N-tert*-Butoxycarbonyl)aminoethoxyacetic Acid (3d).- Obtained 0.785 g of a thick clear oil as a mixture of rotamers (74%) [90/10 EtOAc/1% acetic acid in methanol; (R_f = 0.29)]. ^{1}H NMR: δ 5.11 (br s, 1 H), 4.14 (br s, 2 H), 3.64 (t, *J* = 5.1 Hz, 2 H), 3.42-3.30 (m, 2 H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 173.65, 156.35, 79.55, 70.56, 67.76, 40.18, 28.19 (3C). MS (ESI) *m/z*: 220.2 [$C_9H_{17}NO_5$+H]$^+$.

Anal. Calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.28; H, 7.69; N, 6.64

2-[2-(*N-tert*-Butoxycarbonyl)aminoethoxy]ethoxyacetic Acid (3e).- Obtained 0.983 g of a thick pale yellow oil as a mixture of rotamers (75%) [80/20 EtOAc/2% acetic acid in methanol; (R_f = 0.29)]. ^{1}H NMR ($CDCl_3$): δ 5.07 (br s, 1 H), 4.16 (s, 2 H), 3.77-3.73 (m, 2 H), 3.68-3.65 (m, 2 H), 3.59-3.56 (m, 2 H), 3.40-3.21 (m, 2 H), 1.45 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ 173.32, 156.18, 79.37, 70.62, 70.19, 69.95, 68.35, 40.12, 28.23 (3C). MS (ESI) *m/z*: 264.2 [$C_{11}H_{21}NO_6$+H]$^+$.

Anal. Calcd for $C_{11}H_{21}NO_6$: C, 50.18; H, 8.04; N, 5.32. Found: C, 50.03; H, 7.99; N, 5.30

2-[2-{2-(*N-tert*-Butoxycarbonyl)aminoethoxy}ethoxy]ethoxyacetic Acid (3f).- Obtained 1.084 g of a thick clear oil as a mixture of rotamers (71%) [80/20 EtOAc/2% acetic acid in methanol; (R_f = 0.29)]. ^{1}H NMR ($CDCl_3$): δ 5.20 (br s, 1 H), 4.15 (s, 2 H), 3.75-3.52 (m, 10 H), 3.30 (br s, 2 H), 1.43 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ 172.86, 156.15, 79.19, 70.57, 70.17, 70.12, 70.03, 69.78, 68.33, 40.06, 28.19 (3C). MS (ESI) *m/z*: 308.2 [$C_{13}H_{25}NO_7$+H]$^+$.

Anal. Calcd for $C_{13}H_{25}NO_7$: C, 50.80; H, 8.20; N, 4.56. Found: C, 50.89; H, 8.17; N, 4.28

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18. The newly formed methylenic carbon appears at δ 68.89 ppm (assigned using HETCOR) and *not* at ~ δ 43 ppm confirms the structure of **2b**. The methylenic carbon of *N*-(*tert*-butoxycarbonyl)-glycine *tert*-butyl ester in $CDCl_3$ resonates at δ 43.03 ppm.

19. Lower reaction temperatures, -78 or –40°, resulted in a lower yield of **2b**, 41% and 42% respectively, while **4b** was produced in higher yields, 19% and 22% respectively. Room temperature deprotonation and alkylation afforded only 21% of **2b**, 14% of **4b** and many other unidentified by-products. Changing the counterion to either sodium or lithium drastically reduced the yield of **2b**, 21% and 17%, respectively. No other reaction solvents were investigated, however, attempted alkylation of the intermediate alkoxide with the lithium or potassium salt of bromoacetic acid only afforded the desired acid in <10% yield.

20. An oxazolidinone is obtained as a result of an internal displacement of benzyloxy group followed by *N*-alkylation with *tert*-butyl bromoacetate.

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