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Development of New Linkers for the Formation of Aliphatic C-H Bonds on Polymeric Supports

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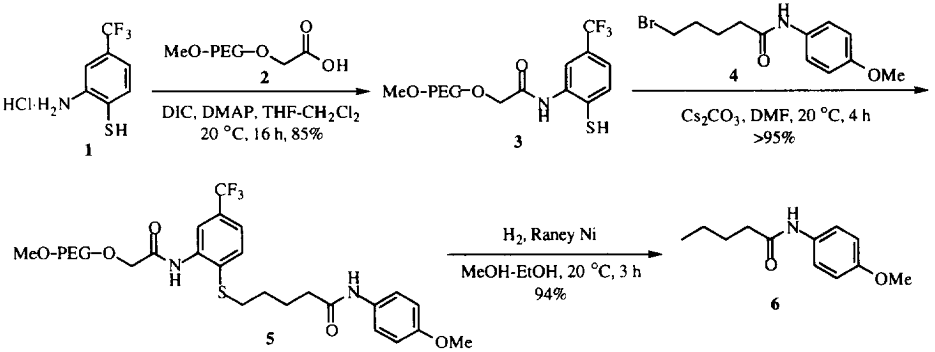
Abstract: *Two polymeric linkers, **8** and **11**, were prepared in high yields. Attachment of an alkyl group to these linkers was facile, and their cleavage from the MeO-PEG polymer support was accomplished by desulfurization using Raney nickel to yield the new carbon-hydrogen bond product **6**. The protocol reported herein allows efficient preparation of new polymeric linkers as well as their possible application to combinatorial libraries.* © 1997 Published by Elsevier Science Ltd.

The first reports on the preparation of non-peptide small molecule libraries were published several years ago.[1] Since then combinatorial chemists have focused on the development of new technologies as related to the polymer supported synthesis of small molecules for medicinal purposes, and, in particular, methodologies for new carriers of molecular scaffolds.[2] In this pursuit, a variety of polymeric linkers have been developed with the common theme of convenient attachment and later removal of the non-peptide molecule of interest from the polymeric support.[3]

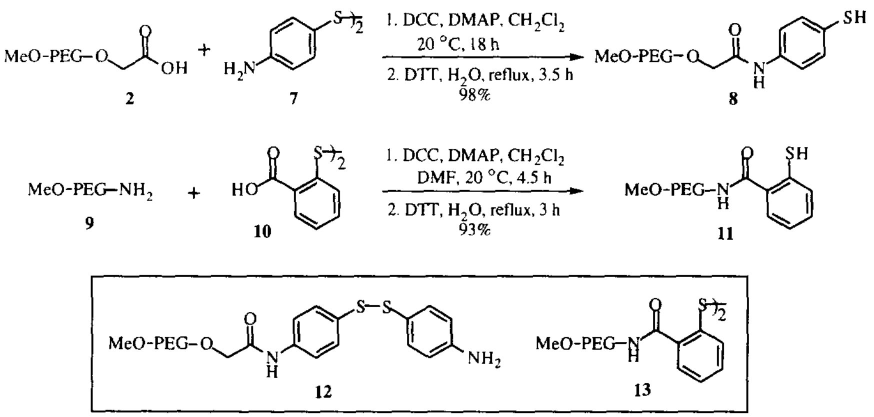
Scheme I



It has been suggested that linkers which would allow efficient formation of molecules containing carbon-hydrogen bonds would be of great significance for diverse application to non-peptide library syntheses.[2] From this standpoint, an aliphatic carbon-hydrogen bond would be a highly desirable functionality if it could be strategically placed on, and later recovered from a polymeric support. Although there have been several examples of carbon-hydrogen bond formation after detachment from polymeric tethers, these have been limited to benzylic, aromatic and aldehyde C-H bonds.[4] In this regard, we have sought a versatile linkage for the generation of an aliphatic carbon-hydrogen bond *via* its cleavage from the soluble homopolymer, polyethylene glycol monomethyl ether (MeO-PEG),[5] the first example of such we recently described (*cf.* Scheme I).[6] Herein we report our continued effort to find a more efficient polymeric linker that will allow the facile attachment and release of organic molecules containing a carbon-hydrogen bond.

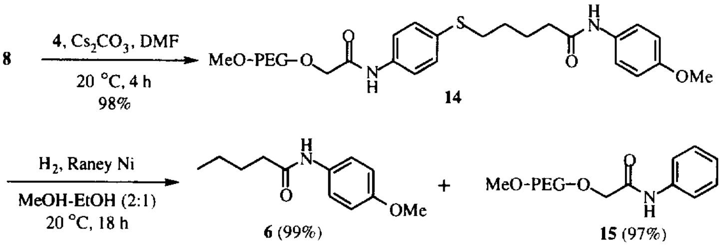
As depicted in Scheme I, the polymeric linker **3** was attached to bromide **4** to afford the alkyl group bearing polymer **5**. In turn, cleavage from the polymeric linker under desulfurization conditions provided the desired molecule **6** with a new carbon-hydrogen bond. This exemplary methodology exhibited the facile points of incorporation and cleavage of a small molecular scaffold. Nevertheless, the synthesis of the polymeric linker **3** was rather arduous, mainly due to the concomitant formation of the corresponding thioester as well as a tendency of the starting material **1** to dimerize *via* air oxidation.[7] In order to avert these shortcomings, aromatic disulfides[7] with various substitution patterns were examined, among which two representative cases are shown in Scheme II.

Scheme II



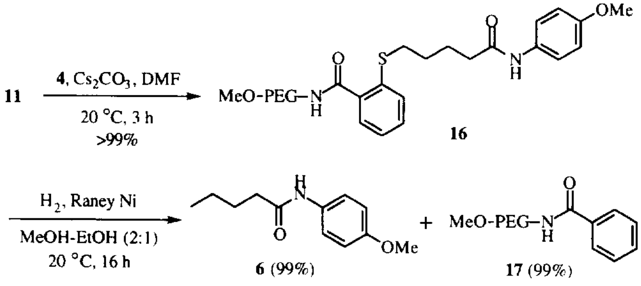
Similar to the previous route, polyethylene glycol monomethyl ether carboxylic acid **2** was used as the polymeric backbone. Commercially available 4-aminophenyl disulfide **7** was coupled with MeO-PEG acid **2** under standard DCC coupling conditions to furnish a mixture of dimer and monomer, with the monomer **12** as the predominant species. This mixture was exposed to dithiothreitol (Cleland's reagent),[8] giving clean reduction of all species and exclusively yielding the polymeric linker **8**.[9] Switching the functionalities embedded in the coupling partners, MeO-PEG amine **9** and 2,2'-dithiosalicylic acid **10** were reacted to afford a mixture of dimer and monomer, however, the dimer **13** was now the major product. This mixture was subjected to reduction using Cleland's reagent, leading to the preparation of thiol **11**. The feasibility of small molecule attachment and later cleavage of these polymeric linkers was investigated utilizing a similar strategy as shown in Scheme I.

Scheme III



Linker **8** was alkylated with bromide **4** in the presence of cesium carbonate to generate MeO-PEG sulfide **14** in 98% yield (Scheme III). Subsequently, functional group cleavage was accomplished under desulfurization conditions using Raney nickel.[10] By employing precipitation techniques with Et_2O (*cf.* experimental section), desulfurized MeO-PEG **15** was filtered as a powder, whereas the desired alkyl molecule **6** with a new carbon-hydrogen bond was obtained quantitatively in a spectroscopically pure form simply by concentrating the filtrate.

Scheme IV



As illustrated in Scheme IV, attachment of bromide **4** to MeO-PEG thiol **11** proceeded smoothly to deliver the alkylated MeO-PEG **16**. This in turn underwent desulfurization, resulting in the quantitative liberation of the desired small molecule **6** in the solution phase, which was separated from the precipitated MeO-PEG **17**. With both linkers (**8** and **11**), excellent mass balance was observed in both the attachment and cleavage reactions. In addition, the high coupling efficiency observed should make this methodology adaptable to numerous applications.

In conclusion, we have described the syntheses of two new polymeric linkers that should allow for the facile attachment and cleavage of a small molecule/molecular scaffold containing aliphatic carbon-hydrogen bonds. These polymeric linking units should be of general interest based on the following: 1) They were easily prepared from commercially available starting materials. 2) They are not prone to the previous oxidation problems as seen with linker **3**. Moreover, the successful alkylation with a non-activated bromide[11] implies that these linkers maybe useful for the incorporation/synthesis of various kinds of small molecules, constituting a new arena of combinatorial techniques. The further application of these polymeric linkers to a variety of alkyl groups is now under study, and will be reported in due course.

Experimental Section

General Procedure. Infrared (**IR**) spectra were recorded on a Nicolet 510 FT-IR spectrometer and absorption maxima are reported in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (**^{1}H NMR**) spectra were recorded on a 300 MHz (Bruker AM-300) spectrometer. Carbon nuclear magnetic resonance (**^{13}C NMR**) spectra were recorded at 75 MHz on a Bruker AM-300 spectrometer. Chemical shifts for proton and carbon resonances are reported in ppm (δ) relative to tetramethylsilane. Mass spectral data were provided by Dr. G. Siudzak of the Scripps Research Institute Mass Spectrometry facilities.

PEG materials are readily available from Shearwater polymers, Inc. The MeO-PEG used in this study had an average molecular weight of 5,000. Commercial grade solvents were used without further purification unless specified. THF was distilled from sodium benzophenone ketyl before use, and CH_2Cl_2 was distilled from calcium hydride.

Preparation of bromide 4. Under a nitrogen atmosphere, *p*-anisidine (2.2 g, 18 mmol) and triethylamine (3.2 mL, 23 mmol) were dissolved in dry THF (100 mL) at 20 °C. With vigorous stirring, 5-bromovaleryl chloride (2.0 mL, 15 mmol) was added dropwise. After the resulting heavy suspension was stirred at 20 °C for 3.5 hours, the reaction was quenched by adding water (50 mL). The heterogeneous solution was extracted with EtOAc, then the combined organic portions were washed with 1 N HCl (50 mL), water (30 mL) and brine (50 mL) successively. The clear solution was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and solidified by adding hexanes (120 mL) slowly. The resultant precipitate was filtered, rinsed with hexanes (2 x 20 mL) and dried *in vacuo* to afford the desired bromide **4** as a purplish gray powder (3.9 g, 14 mmol, 91%): **IR** (neat film) 836, 1301, 1516, 1548, 1598, 1657, 2866, 2998, 3053, 3308 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.82-2.02 (m, 4 H), 2.38 (t, J = 7.2 Hz, 2 H), 3.44 (t, J = 6.2 Hz, 2 H), 3.79 (s, 3 H), 6.85 (d, J = 9.0 Hz, 2 H), 7.20 (br s, N$\underline{H}$), 7.40 (d, J = 9.0 Hz, 2 H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 24.31, 32.23, 33.47, 36.43, 55.65, 114.26, 122.11, 131.04, 156.58, 170.83; **HRMS** calcd for $C_{12}H_{16}BrNO_2$ (M^+ + H; ^{79}Br) 286.0443, found 286.0446.

Preparation of MeO-PEG thiol 8. In dry CH_2Cl_2 (15 mL) were dissolved polyethylene glycol monomethyl ether carboxylic acid **2** (1.0 g, 0.20 mmol), 4-aminophenyl disulfide **7** (100 mg, 0.40 mmol), 4-dimethylaminopyridine (10 mg, 0.081 mmol) and 1,3-dicyclohexylcarbodiimide (100 mg, 0.48 mmol). After the reaction was stirred at 20 °C for 18 hours under N_2, the resulting yellow suspension was triturated with

Et_2O (150 mL) and filtered. The filtered precipitate was successively washed with EtOH (3 x 20 mL) and Et_2O (2 x 20 mL). The solid was collected and dried *in vacuo* to give a mixture of monomeric and dimeric amides as a pale yellow solid (1.0 g, 0.19 mmol, 96%).

The mixture of disulfide (200 mg, 0.038 mmol) and dithiothreitol (45 mg, 0.29 mmol) was dissolved in water (2 mL) at 20 °C. Under an atmosphere of nitrogen, the clear solution was heated to reflux for 3.5 hours, then cooled to room temperature. After methanol (2 mL) was added, the solution was transferred to a 500 mL flask. The reaction vessel was rinsed with methanol (2 x 1.5 mL), and the combined solutions were treated with Et_2O (350 mL). The resulting precipitate was filtered and rinsed with Et_2O (2 x 25 mL), then dried *in vacuo* to afford the desired MeO-PEG thiol **8** as a white powder (200 mg, 0.039 mmol, >99%): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.36 (s, 3 H), 3.37-3.78 (m, PEG), 4.08 (s, 2 H), 7.24 (d, J = 8.6 Hz, 2 H), 7.51 (d, J = 8.6 Hz, 2 H), 8.81 (br s, N$\underline{H}$).

Preparation of MeO-PEG thiol 11. Under a N_2 atmosphere, polyethylene glycol monomethyl ether amine **9** (2.0 g, 0.40 mmol), 2,2'-dithiosalicylic acid **10** (330 mg, 1.08 mmol), 4-dimethylaminopyridine (10 mg, 0.081 mmol) and 1,3-dicyclohexylcarbodiimide (290 mg, 1.41 mmol) were dissolved in anhydrous dimethylformamide (10 mL). After dry CH_2Cl_2 (10 mL) was added, the resulting orange colored solution with heavy white precipitate was stirred at 20 °C for 4.5 hours. The reaction mixture was filtered through Celite® and rinsed with CH_2Cl_2 (25 mL). Subsequently, the clear filtrate was triturated by adding Et_2O (250 mL), and the resulting precipitate was filtered. The solid was successively washed with EtOH (3 x 25 mL) and Et_2O (2 x 25 mL), then dried *in vacuo* to provide a mixture of monomeric and dimeric amides as a pale yellow powder (2.0 g, 0.39 mmol, 98%).

The mixture of disulfides (400 mg, 0.078 mmol) and dithiothreitol (90 mg, 0.58 mmol) were dissolved in water (3 mL) at 20 °C. Under an atmosphere of nitrogen, the yellow solution was heated to reflux for 3 hours, then cooled to room temperature. The reaction solution was poured into a 500 mL flask and the reaction vessel was rinsed with methanol (3 x 2 mL). After the combined solutions were treated with Et_2O (200 mL), the resulting precipitate was filtered and rinsed with Et_2O (2 x 20 mL), then dried *in vacuo* to furnish MeO-PEG thiol **11** as a pale green powder (380 mg, 0.074 mmol, 95%): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.36 (s, 3 H), 3.37-3.86 (m, PEG), 7.10-7.58 (m, 3 H and N$\underline{H}$), 7.76 (d, J = 8.6 Hz, 1 H).

Alkylation of MeO-PEG thiol 8. Under N_2, the polymeric linker MeO-PEG thiol **8** (135 mg, 0.026 mmol), bromide **4** (85 mg, 0.30 mmol) and cesium carbonate (85 mg, 0.26 mmol) were mixed in anhydrous dimethylfomamide (3.5 mL) at 20 °C. The clear solution with some residual particles of cesium carbonate was stirred vigorously at 20 °C for 4 hours, then filtered and rinsed with CH_2Cl_2 (3 mL). After the clear filtrate was triturated by adding Et_2O (100 mL), the resulting white precipitate was filtered and rinsed with Et_2O (20 mL). The solid was collected and dried *in vacuo* to yield the alkyl group bearing MeO-PEG **14** as a white powder (137 mg, 0.026 mmol, 98%): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.69 (m, 2 H), 1.83 (m, 2 H), 2.33 (t, J = 9.0 Hz, 2 H), 2.90 (t, J = 7.2 Hz, 2 H), 3.37 (s, 3 H), 3.39-3.88 (m, PEG), 4.10 (s, 2 H), 6.82 (d, J = 9.0 Hz, 2 H), 7.31 (d, J = 8.6 Hz, 2 H), 7.43 (d, J = 9.0 Hz, 2 H), 7.55 (d, J = 8.6 Hz, 2 H), 8.88 (br s, N$\underline{H}$).

Cleavage of alkylated MeO-PEG 14. Into a pressure bottle were placed MeO-PEG sulfide **14** (130 mg, 0.024 mmol), activated Raney® nickel (50% slurry in water; 10 mg, 0.085 mmol) and absolute methanol (3 mL). The mixture was shaken for a minute and absolute ethanol (1.5 mL) was added. Under a 34 psi hydrogen atmosphere, the black suspension was shaken vigorously for 18 hours, then filtered through Celite® and rinsed with CH_2Cl_2 (20 mL). The clear filtrate was concentrated *in vacuo* and dissolved again in CH_2Cl_2 (10 mL). After the solution was solidified by adding Et_2O (100 mL), the resulting precipitate was filtered and rinsed with Et_2O (20 mL). The filtered solid was collected and dried *in vacuo* to give the desulfurized MeO-PEG **15** as a white powder (120 mg, 0.024 mmol, 97%), while the residual filtrate was concentrated *in vacuo* to afford the desired alkyl product **6** in a spectroscopically pure form (5 mg, 0.024 mmol, 99%).

Data for **6**: **IR** (neat film) 828, 1301, 1514, 1545, 1601, 1649, 2870, 2905, 2930, 3004, 3052, 3317 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 3 H), 1.38 (m, 2 H), 1.68 (m, 2 H), 2.32 (t, J = 7.4 Hz, 2 H), 3.77 (s, 3 H), 6.83 (d, J = 8.9 Hz, 2 H), 7.40 (d, J = 8.9 Hz, 2 H), 7.37-7.42 (br m, N$\underline{H}$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 14.00, 22.58, 27.97, 37.46, 55.62, 114.22, 122.00, 131.26, 156.46, 171.69; **HRMS** calcd for $C_{12}H_{17}NO_2$ (M^+ + H) 208.1338, found 208.1341.

Data for **15**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.37 (s, 3 H), 3.40-3.88 (m, PEG), 4.11 (s, 2 H), 7.11 (t, J = 8.4 Hz, 1 H), 7.32 (t, J = 8.4 Hz, 2 H), 7.60 (d, J = 8.4 Hz, 2 H), 8.83 (br s, N$\underline{H}$).

Alkylation of MeO-PEG thiol 11. At 20 °C, MeO-PEG thiol **11** (200 mg, 0.039 mmol), bromide **4** (130 mg, 0.45 mmol) and cesium carbonate (130 mg, 0.40 mmol) were mixed in anhydrous dimethylfomamide (5 mL) under N_2. After the resulting pale brown mixture was stirred vigorously at 20 °C for 3 hours, the residual solid was removed by filtration through Celite® followed by rinsing with CH_2Cl_2 (2 x 5 mL). The clear filtrate was treated with Et_2O (150 mL), and the resulting white precipitate was filtered and rinsed with Et_2O (2 x 10 mL). The solid was collected and dried *in vacuo* to deliver alkylated MeO-PEG **16** as a white powder (210 mg, 0.039 mmol, >99%): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.65 (m, 2 H), 1.83 (m, 2 H), 2.35 (t, J = 7.2 Hz, 2 H), 2.93 (t, J = 6.8 Hz, 2 H), 3.37 (s, 3 H), 3.38-3.88 (m, PEG), 6.81 (d, J = 9.0 Hz, 2 H), 7.13-7.52 (m, 6 H), 8.42 (br s, N$\underline{H}$).

Cleavage of alkylated MeO-PEG 16. In absolute methanol (3 mL) was dissolved MeO-PEG sulfide **16** (130 mg, 0.024 mmol). Activated Raney® nickel (50% slurry in water; 10 mg, 0.085 mmol) and absolute ethanol (1.5 mL) were added. The resulting black suspension was shaken vigorously for 16 hours under a 34 psi atmosphere of hydrogen, then filtered through Celite® and rinsed with CH_2Cl_2 (20 mL). The clear filtrate was concentrated *in vacuo* and dissolved again in CH_2Cl_2 (10 mL). After the solution was triturated by adding Et_2O (100 mL), the precipitate was filtered and rinsed with Et_2O (10 mL). The filtered solid was collected and dried *in vacuo* to furnish desulfurized MeO-PEG **17** as a white solid (130 mg, 0.025 mmol, 99%). On the other hand, the filtrate was concentrated *in vacuo* to secure alkyl product **6** in a spectroscopically pure form (5 mg, 0.024 mmol, 99%).

Data for **17**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.37 (s, 3 H), 3.38-3.86 (m, PEG), 7.00 (br s, N$\underline{H}$), 7.33-7.51 (m, 4 H), 7.82 (dd, J = 8.0, 1.4 Hz, 1 H).

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9. Linker **8** was extremely resistant to air oxidation, while **11** was slightly prone to oxidation (less than 5% over 3-4 weeks).

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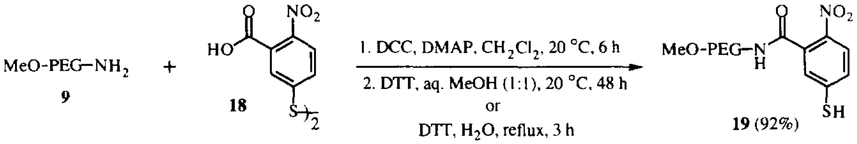
11. All investigated disulfides were not appropriate for alkylation to take place. For example, MeO-PEG thiol **19** was prepared utilizing similar methods described (*vide supra*), however, alkylation did not take place presumably due to the electron deficiency of this thiol nucleophile.



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