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Soluble Polymer Synthesis: An Improved Traceless Linker Methodology for Aliphatic C-H Bond Formation

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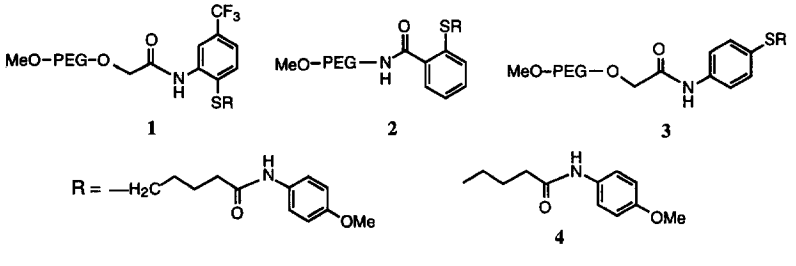
Abstract: *A traceless linker was developed on a soluble polymer support. The methodology allows for the facile attachment of molecules possessing an alkyl halide appendage. The coupled molecule can be further functionalized before subsequent cleavage via a two-step oxidation-reduction sequence. This sequence allows for the synthesis of molecules containing no trace of the linker and the formation of a new C-H bond.*

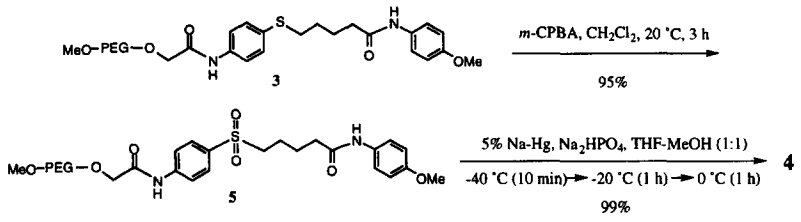
The advent of combinatorial chemistry has led to a revival of polymer supported synthesis.[2] Crucial to this endeavor has been the utilization of linkers allowing facile attachment, functionalization, and release of the molecule of interest. Previously, we reported[3] upon several traceless[4] liquid phase[5] polymeric linkers, their alkylation with a non-peptidic molecule and cleavage of the tethered alkyl group to liberate **4** with no trace of the linker and a new C-H bond (Figure I). Although the cleavage was accomplished either by homolysis under radical conditions (Bu_3SnH, AIBN) or by desulfurization using Raney nickel, both methods have limitations. Using radical conditions the reaction proceeded very slowly, and the percent conversion of the starting material was poor. Furthermore, the generated molecule **4** was difficult to purify from other reaction products. In contrast, desulfurization of these soluble polymeric linker sulfides (**1**, **2** and **3**) by hydrogenolysis using Raney nickel proceeded smoothly. However, the application of this method is still somewhat limited since the synthesized molecule cannot contain reduction-sensitive functional groups, such as sulfur substituents, alkenes, alkynes and epoxides, which cannot survive such conditions. Therefore, it was important to develop a complimentary but broader based methodology for aliphatic C-H bond formation on a polymeric support.

Figure I



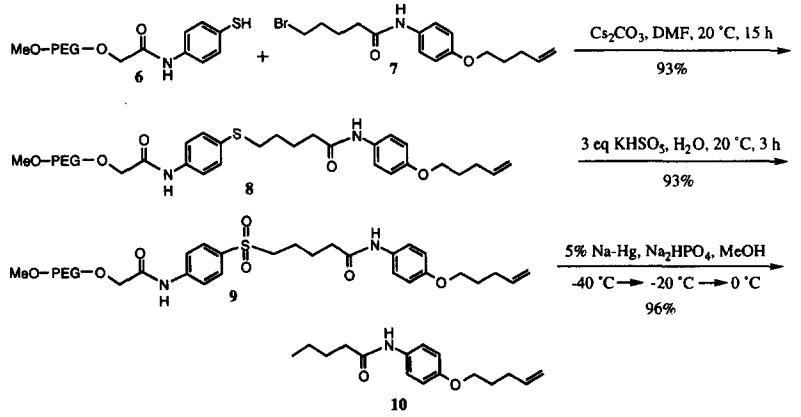
It is well known that Na/Hg is a potent reducing agent for the C-S bond of an aliphatic sulfone. Yet this reagent will not affect a variety of reducible functional groups.[6] Based on this, we switched to a cleavage strategy wherein the polymeric linker sulfide is first oxidized to the corresponding sulfone, which then may undergo reduction with Na/Hg. As depicted in Scheme I, treatment of sulfide **3** with *m*-CPBA (4 eq) in anhydrous CH_2Cl_2 at 20 °C for 3 h afforded sulfone **5** in 95% yield. The sulfone **5** was then treated with 5% Na/Hg in 1:1 THF-MeOH at low temperature under argon to give the desired product **4** in 99% yield.

Scheme I



Although *m*-CPBA gives excellent yields for the oxidation of sulfides to sulfones, this reagent is chemically limited as olefins and ketones can also undergo oxidation to epoxides and esters, respectively under such conditions. Therefore, a highly chemoselective oxidizing agent is required. Trost and Curran have reported[7] that potassium hydrogen persulfate ($KHSO_5$) in aqueous methanol is a convenient and chemoselective reagent for the oxidation of sulfides to sulfones even in the presence of other common functional groups, such as alkenes and ketones. Indeed, when sulfide **8**, obtained by alkylation of **6** with bromide **7**[8] in anhydrous DMF in the presence of Cs_2CO_3, was examined, a satisfactory result was observed, as outlined in Scheme II.

Scheme II

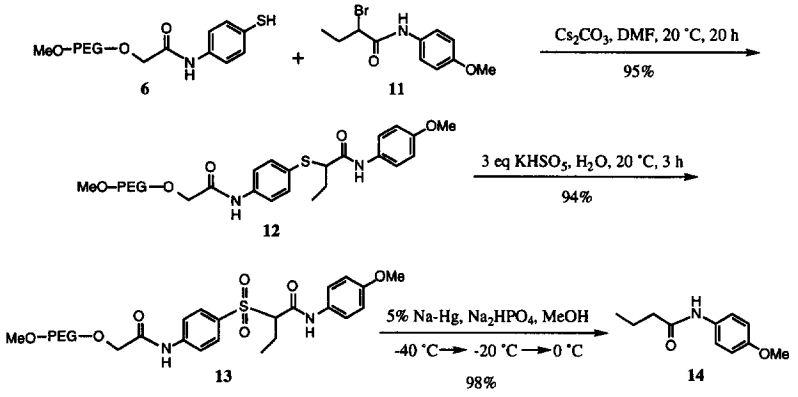


In a typical experimental procedure, a solution of **8** (230 mg, 0.043 mmol) and oxone[9] (40 mg, 0.065 mmol, containing 0.13 mmol $KHSO_5$) in H_2O (2 mL) was stirred at 20 °C for 3 h. The mixture was co-

evaporated with MeOH, and then redissolved in MeOH (5 mL) with the precipitation of inorganic salts. Upon the addition of CH_2Cl_2 (20 mL), the resulting mixture was filtered through celite, and washed with CH_2Cl_2. The combined filtrate and washings were concentrated, redissolved in CH_2Cl_2 (5 mL), and then triturated with anhydrous Et_2O (200 mL). The resulting white solid was filtered, washed with Et_2O, and dried *in vacuo* to give **9** (93%). The sulfone **9** was subjected to reduction with Na/Hg; to a stirred mixture of 5% Na/Hg (805 mg), Na_2HPO_4 (100 mg, 0.70 mmol) and absolute MeOH (2 mL) at -40 °C under argon was added dropwise a solution of **9** (191 mg, 0.035 mmol) in absolute MeOH (2 mL). The resulting mixture was stirred at -40 °C for 10 min, and then at -20 °C for 1 h, finally at 0 °C for 40 min wherein CH_2Cl_2 (30 mL) was added. This mixture was filtered through celite, and washed with CH_2Cl_2. The combined filtrate and washings were concentrated, redissolved in CH_2Cl_2 (5 mL), and triturated with anhydrous Et_2O (200 mL). The resulting suspension was filtered, and washed with ether. The combined filtrate and washings were evaporated to dryness, redissolved in Et_2O (25 mL), and filtered through cotton. The filtrate was concentrated, and dried *in vacuo* to give **10** (8.8 mg, 96%).

In order to further investigate the generality of the methodology, compound **12**, with a β-amidosulfide structural unit, was examined for oxidation and subsequent reduction, as illustrated in Scheme III. As expected, the alkylation of **6** with bromide **11**[10] in anhydrous DMF in the presence of Cs_2CO_3 was achieved in high yield. Surprisingly, oxidation of the sulfide **12** with *m*-CPBA was complicated. Interestingly, the use of $KHSO_5$ led to a clean oxidation reaction, and the sulfone **13** was isolated in 94% yield. Similarly, as seen with **5** and **9**, the reductive cleavage of **13** with Na/Hg provided **14** in excellent yield.

Scheme III



In conclusion, the oxidation of the liquid phase polymeric linker sulfide with *m*-CPBA or $KHSO_5$ and subsequent reductive cleavage of the produced traceless sulfone linker with Na/Hg proves to be a versatile and efficient method for the formation of molecules with a new C-H bond. We believe this methodology should play an important role in the construction of future combinatorial libraries.

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7. Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.
8. Bromide **7** was obtained by alkylation of 4-aminophenol with 5-bromo-1-pentene in anhydrous DMF in the presence of Cs_2CO_3 and subsequent condensation of the alkylated product with 5-bromovaleryl chloride.
9. Potassium hydrogen persulfate, available under the trade name oxone, is a mixture containing 2 moles $KHSO_5$, 1 mole K_2SO_4 and 1 mole $KHSO_4$.
10. Bromide **11** was prepared by condensation of *p*-anisidine with (±)-2-bromobutyryl bromide.

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