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Syntheses of Alkylated Malonates on a Traceless Linker Derived Soluble Polymer Support

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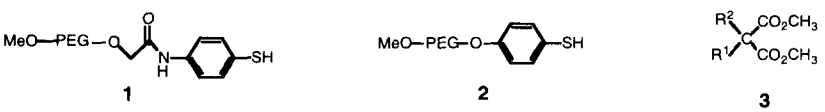
Abstract: A new traceless soluble polymeric linker and a corresponding alkylating strategy has been developed. Dimethyl malonate was alkylated with a variety of polymeric halides and these resulting polymer bound malonates underwent further alkylation with additional monoalkyl halides. The methodology described should provide access to libraries of dialkyl malonates.

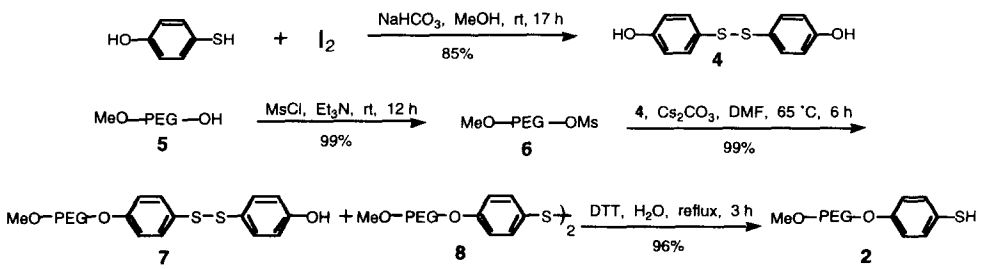
Recently, our efforts have been devoted to the development and application of a traceless linker that is stable to a variety of chemical reaction conditions and ultimately can undergo chemical transformation forming a new C-H bond upon cleavage. Although we have previously reported[1] several traceless soluble polymeric linkers among which **1** has shown promise (Figure I), the functionality between the polymer and the linker, (i.e., an amide bond), is still susceptible to alteration by a variety of reagents. In addition, the starting poly(ethylene glycol) (PEG) polymer is expensive,[2] which also limits its potential use on a large scale. Generally speaking, amides can tolerate a variety of reaction conditions, but they still cannot survive reagents like $LiAlH_4$, strong bases, acids or nucleophiles at elevated temperatures. Moreover, primary and secondary amides are also capable of reacting with electrophiles, such as acyl and mesyl chlorides. Therefore, it is crucial to develop a more versatile traceless linker that can be applied to multi-step synthetic processes. Ethers are extremely unreactive, even under harsh conditions as mentioned (*vide supra*); based on this and the inherent limitations found in **1**, we replaced the amide bond of **1** with an ether moiety. Thus, a new traceless polymeric linker (**2**) was designed (Figure I), and its versatility is demonstrated through the synthesis of dialkyl malonates.

Figure I



The synthesis of **2** is depicted in Scheme I. The very inexpensive PEG polymer, poly(ethylene glycol) methyl ether[3] (**5**) was chosen as the starting material. Mesylation of **5** with mesyl chloride (6 eq) in anhydrous CH_2Cl_2 in the presence of Et_3N (18 eq) at room temperature under argon for 12 h afforded **6** in 99% yield.[4]

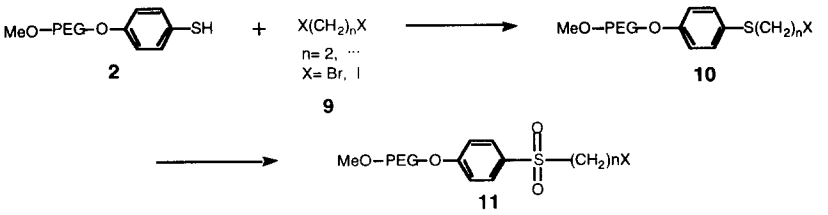
Scheme I



The disulfide **4**, to be used as the ether tether was obtained by oxidation of 4-hydroxythiophenol with I_2 (0.51 eq) in absolute MeOH in the presence of $NaHCO_3$ (2.8 eq) at room temperature for 17 h in 85% yield. Treatment of **6** with disulfide **4** (3 eq) in anhydrous DMF in the presence of anhydrous Cs_2CO_3 (4 eq) at 65 °C under argon for 6 h furnished, after work-up with Amberlite® IR-120(plus) ion-exchange resin/MeOH,[5] a mixture of **7** and **8** in 99% yield. Reduction of this mixture with DTT (10 eq) in H_2O at gentle reflux under argon for 3 h gave after work-up[6] the new polymeric linker **2** in 96% yield.

With polymer **2** we sought to develop alkylating strategies for alcohols, phenols, thiophenols, primary / secondary amines, and carbonyl compounds so that the syntheses of a variety of molecules could be carried out on the PEG polymer support. As illustrated in Scheme II, alkylation of **2** using symmetric dihalide **9** should lead to the halogenated sulfide **10** which then may serve as a polymeric alkylating agent. In cases of syntheses involving sulfur substituents and other oxidatively sensitive molecules, **10,** could be converted to the halogenated sulfone **11** prior to the next synthetic transformation.

Scheme II

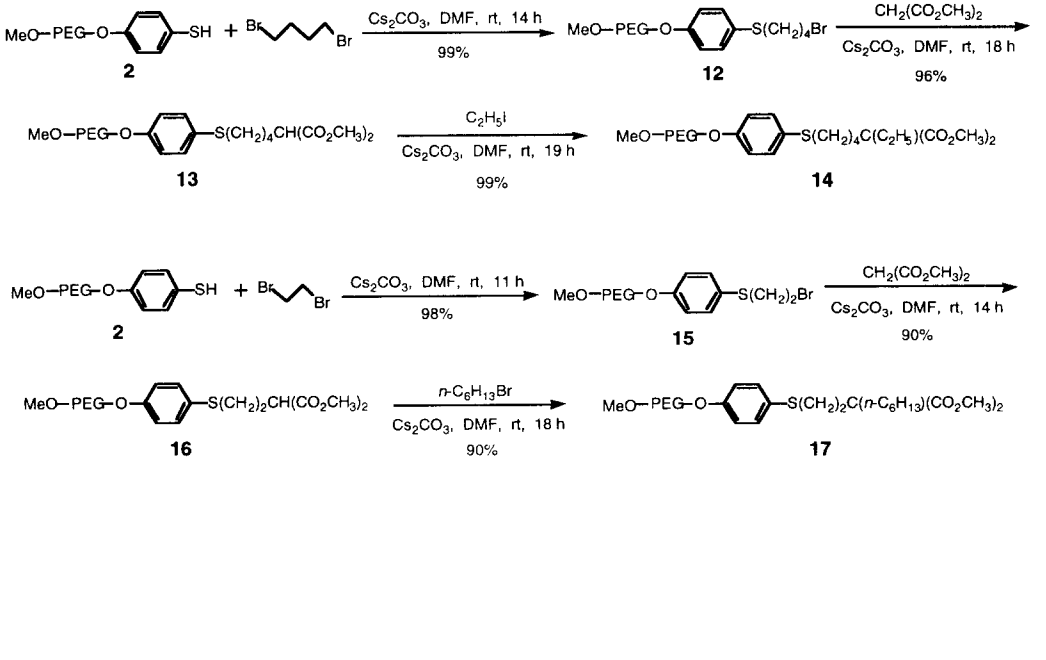


2 **9** **10** **11**

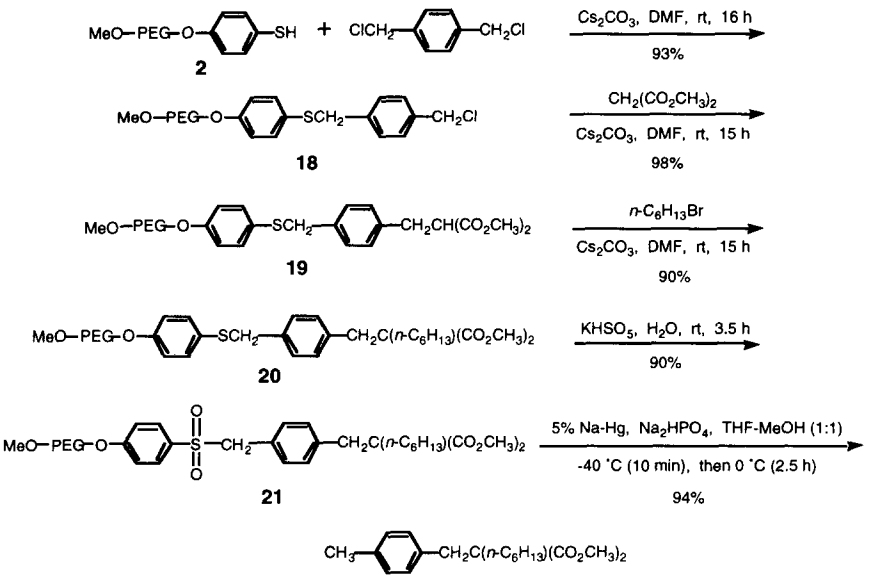
Considering the versatility of 1,3-dicarbonyl compounds in organic and drug synthesis,[7] we envisioned the incorporation of malonate into the polymer via alkylation with **10** or **11**. This transformation should result in a facile access to numerous malonate molecules, i.e., **3** (Figure I). Moreover, malonate is an ideal molecule for diversification, this being accomplished by varying the two substituents, R^1 and R^2, and by later transformation of the diester functional group (Figure 1). This sequence of events should in principle provide a wide range of building blocks for library construction. We have investigated the alkylation of **2** with several dihalides to give **10**, the alkylation of malonate with **10,** and the further alkylation of the resulting polymeric malonates with alkyl halides.

As outlined in Scheme III, treatment of **2** with 1,4-dibromobutane (30 eq) in anhydrous DMF in the presence of anhydrous Cs_2CO_3 (3 eq) at room temperature under argon for 14 h delivered, after work-up,the

Scheme III



2 **12** **13** **14** **15** **16** **17**



bromosulfide **12**[8] in 99% yield. Alkylation of dimethyl malonate (8 eq) with **12** in anhydrous DMF in the presence of anhydrous Cs_2CO_3 (8 eq) at room temperature under argon for 18 h afforded the diester **13**[9] in 96% yield. Further alkylation of **13** with iodoethane (10 eq) under similar reaction conditions (Cs_2CO_3(6 eq)/DMF) was accomplished to give **14** in 99% yield. The PEG-linker **2** could also be treated with 1,2-dibromoethane providing **15** in 98% yield. Encouragingly, alkylation of dimethyl malonate with **15** under the optimized conditions (Cs_2CO_3/DMF) proceeded to furnish **16** in 90% yield. Considering that bromosulfide **15** might undergo elimination under the alkylating conditions to form a thermodynamically favored vinyl thiol ether instead of the desired substitution product **16**, we were quite pleased with the result.

To further examine the reactivity of these polymeric malonates diester **16** was treated with 1-bromohexane, Cs_2CO_3 and DMF. Gratifyingly, the reaction proceeded to produce **17** in 90% yield. For the construction of libraries, R^1 and R^2 should represent a plethora of structures, therefore, we decided to exploit the possibility of alkylation of **2** with symmetric aromatic ring-containing dihalides. The benzyl chloride, α,α'-dichloro-p-xylene was used for the alkylation of **2**, and the chlorosulfide **18** was obtained in 93% yield. Treatment of **18** with dimethyl malonate, Cs_2CO_3 and DMF provided the diester **19** in 98% yield. Further alkylation of **19** with 1-bromohexane gave **20** in 90% yield. To confirm the structures of the final alkylated products, compound **20** was selected for cleavage. Oxidation of **20** with $KHSO_5$[1c] (4 eq) in H_2O at room temperature for 3.5 h furnished sulfone **21** in 90% yield. Reductive cleavage of **21** with 5% Na-Hg[1c] in THF-MeOH (1:1) at low temperature gave the desired product **22** in 94% yield.

In conclusion, a versatile traceless polymeric linker **2** has been synthesized starting from a very inexpensive PEG polymer. This soluble polymer was successfully alkylated using symmetric dihalides, while these formed polymeric halides have been gainfully utilized in the highly efficient alkylation with dimethyl malonates. In addition, a series of efficacious work-up techniques for the PEG polymer have been established. We believe that the new polymeric linker **2** is capable of tolerating a variety of reaction conditions, therefore, it could play an interesting role in multi-step synthesis and library construction. Moreover, the successful incorporation of dimethyl malonate into the PEG polymer will allow introduction of diversity at several stages, i.e., R^1 and R^2 as well as additional transformations of the diester functional group. Currently, we are developing alternative alkylating strategies using unsymmetric alkylating agents, and exploring the possibility of alkylation of the malonate moiety using secondary alkylating agents in order to expand upon the R^1 and R^2 repertoire.

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REFERENCES AND NOTES

1. (a) Jung, K. W.; Zhao, X.; Janda, K. D. *Tetrahedron Lett.* **1996**, *37*, 6491. (b) Jung, K. W.; Zhao, X.; Janda, K. D. *Tetrahedron* **1997**, *53*, 6645. (c) Zhao, X.; Jung, K. W.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 977.
2. Available from Shearwater Polymers, $300/5g.
3. Available from Aldrich, $55.50/500g.
4. The generated by-product, $Et_3N{\cdot}HCl$ was removed by washing ether-precipitated **6** with 2-propanol. In general, the recommended volume of ether for complete precipitation of the PEG polymer is 250-300 mL of ether per gram of polymer. The purity of **6**, and all PEG-bound materials was determined by ^{1}H-NMR spectroscopy. Compound **6**, ^{1}H-NMR (500 MHz, $CDCL_3$): δ 3.08 (s, 3 H), 3.37 (s, 3 H), 3.47-3.79 (m, PEG), 4.37 (t, J=4.5 Hz, 2 H).
5. The work-up procedure is as follows:
   After the reaction mixture was cooled to room temperature, absolute MeOH was added followed by Amberlite® IR-120(plus) ion-exchange resin (excess, acidifying the cesium salt of **7**). Stirring was continued for an additional 3 h. The resin was removed by filtration, the filtrate evaporated to dryness, and redissolved in CH_2Cl_2, filtered through celite and washed with CH_2Cl_2. The combined filtrate/washings were concentrated to a small volume, and triturated with anhydrous Et_2O. The resulting white solid was filtered, washed with ether and dried *in vacuo*.
6. The work-up procedure is as follows:
   After cooling to room temperature, the reaction mixture was co-evaporated with MeOH, and then redissolved in MeOH, and triturated with anhydrous Et_2O. The resulting white solid was filtered, washed with ether and dried *in vacuo*.
7. *The Organic Chemistry of Drug Synthesis*; Lednicer, D.; Mitscher, L. A.; Eds.; John Wiley and Sons, New York, Vol. 1, **1977** and Vol. 2, **1980**.
8. The work-up procedure is as follows:
   The reaction mixture was evaporated to dryness, redissolved in CH_2Cl_2, filtered through celite and washed with CH_2Cl_2. The combined filtrate/washings were concentrated to a small volume and triturated with anhydrous Et_2O. The resulting white solid was filtered, washed with ether and dried *in vacuo*. ^{1}H-NMR (250 MHz, $CDCL_3$): δ 1.71 (m, 2 H), 1.98 (m, 2 H), 2.83 (t, J=5.8 Hz, 2 H), 3.37 (s, 3 H), 3.45-3.96 (m, PEG and $C\underline{H}_2Br$), 4.11 (t, J=5.0 Hz, 2 H), 6.85 (d, J=8.8 Hz, 2 H), 7.32 (d, J=8.8 Hz, 2 H).
9. ^{1}H-NMR (250 MHz, $CDCL_3$): δ 1.43 (m, 2 H), 1.59 (m, 2 H), 1.89 (m, 2 H), 2.79 (t, J=5.6 Hz, 2 H), 3.37 (s, 3 H), 3.46-3.96 (m, PEG and $C\underline{H}(CO_2C\underline{H}_3)_2$), 4.10 (t, J=5.3 Hz, 2 H), 6.84 (d, J=8.8 Hz, 2 H), 7.30 (d, J=8.8 Hz, 2 H).

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