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Modification of the Swern Oxidation: Use of a Soluble Polymer-Bound, Recyclable, and Odorless Sulfoxide

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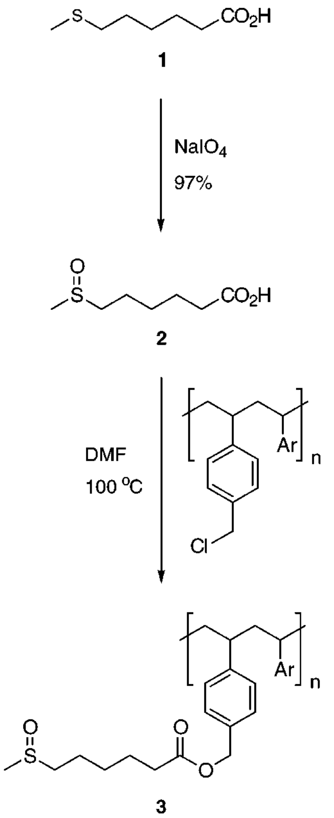
The Swern procedure, using oxalyl chloride activation of dimethyl sulfoxide (DMSO), is one of the most widely used methods of oxidizing primary and secondary alcohols to aldehydes and ketones.[1] Although very effective, this process produces the unpleasant-smelling, volatile (bp 37 °C) byproduct, dimethyl sulfide. We have previously reported the use of 6-(methylsulfinyl)hexanoic acid (**2**) as an efficient substitute for DMSO in Swern oxidation reactions.[2] This modification generates the nonvolatile sulfide **1**, which is easily separable from the reaction mixture by extraction or filtration through silica gel. Also described was preliminary work on the attachment of **2** to commercial chloromethyl polystyrene beads (Merrifield resin) to form a polymer-bound reagent **3** (Scheme 1). The present study expands on these investigations and reports the attachment of **2** to soluble poly(ethylene glycol) (PEG) supports to form polymer-bound reagents that can be easily removed from the reaction mixture by precipitation and filtration. After use in the Swern procedure, the PEG-bound reagent can be readily recycled by periodate oxidation, with no observable loss of oxidation capacity.

Initial studies on supports to bear the sulfoxide functionality necessary for Swern oxidation focused on insoluble solid-phase polymers such as Merrifield resin. Use of a 2-fold excess of polymer-supported sulfoxide **3** in the Swern process quantitatively oxidizes *endo*-borneol to camphor, with no residual acohol remaining. However, after regeneration by sodium metaperiodate oxidation,[3] the oxidation capacity of the polymer-bound reagent is reduced from 92% to 78%. This may be due to cross-linking of the polystyrene backbone by reaction with oxalyl chloride. Clearly, if the reagent is to be recyclable, the polymer-support must be inert to the reaction conditions for both the Swern oxidation and periodate regeneration of the sulfoxide functionality. A rapidly expanding area of polymer-supported chemistry is the use of soluble scaffolds.[4] These have the advantage of forming a homogeneous phase in the reaction medium, but having polymeric properties that simplify product separation and reagent recovery. One of the most versatile and widely used polymer supports for such liquid-phase synthesis is poly(ethylene glycol) (PEG).[5] PEG is soluble in a wide-range of organic solvents and water, thereby facilitating homogeneous reaction, but is insoluble in hexane, diethyl ether, and *tert*-butyl methyl ether.[6] It is therefore easily separated from the reaction mixture by precipitation and filtration.

Scheme 1



When choosing a polymer for liquid-phase synthesis a compromise must be made between loading capacity and solubility. PEG is commercially available in a range of molecular weights up to 20 000; those between 2 000 and 20 000 are crystalline with loading capacities between 1 and 0.1 mmol/g, whereas the lower molecular weight PEG's exist as liquids at room temperature. A number of different size PEG's (with hydroxyl functionalities at both ends) and MeO-PEG's (with the polyether terminated by a methoxy group at one end and a free hydroxyl at the other) were investigated in an attempt to optimize the reaction conditions and loading capacity. Reagent **2** is easily coupled to PEG in the presence of DCC and DMAP.[7] The reduced sulfide acid **1** can be similarly coupled and subsequently oxidized to the sulfoxide **5** with sodium metaperiodate (Scheme 2).[3] Although they have higher loading capacities, the low molecular weight (below 2 000) liquid polymers present problems with

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Scheme 2

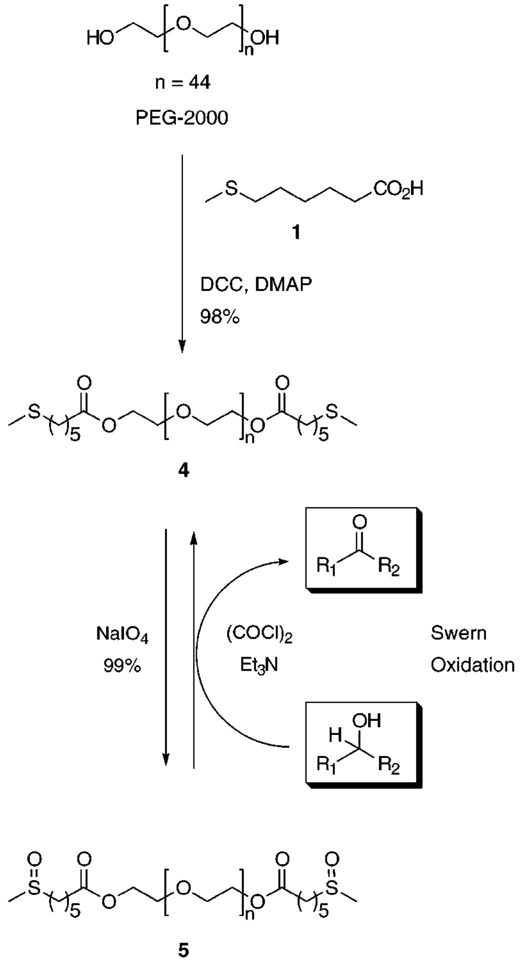

Table 1. Oxidation of Alcohols with Modified Swern Procedure

alcohol	isolated R_1R_2CO yield (%) with PEG-sulfoxide (**5**)	isolated R_1R_2CO yield (%) with sulfoxide acid (**2**)	lit. yield (%)[a]
endo-borneol	91	90	98
3,5-dimethoxybenzyl alcohol	94	94	–
n-dodecanol	99	92	99
cinnamyl alcohol	94	93	98
benzoin	99	94	95
cholesterol	94	–	95
sec-phenethyl alcohol	99	–	98

[a] See ref 1a.

separation after completion of the reaction. The higher molecular weight (above 5 000) polymers have significantly lower loading capacities and therefore large amounts of material are required for stoichiometric oxidation reactions. The optimum size was determined to be 2 000. At this molecular weight the polymer is solid at room temperature and therefore can be easily precipitated from the reaction mixture. The loading capacity of PEG is twice that of MeO-PEG, and, therefore, since no differences in synthesis or reactivity between the mono- and bifunctional polymers were observed, PEG-2000 was used to study the oxidation capacity and recyclability of the reagent.

As was found for the polystyrene-supported reagent,[2] if a stoichiometric amount of the PEG-supported reagent **5** is used to oxidize *endo*-borneol, a small amount (approximately 4%) of the alcohol remains unchanged. However, use of 1 mol equiv of the bifunctional reagent in the Swern process results in quantitative oxidation of *endo*-borneol to camphor, with no residual alcohol remaining. To examine the scope of this soluble polymer-supported sulfoxide reagent **5**, a number of alcohols were tested using optimal conditions for complete oxidation (Table 1). In a typical procedure, a dichloromethane solution of **5** (1.0 equiv [2 oxidizing equiv]) is treated at −50 to −60 °C with oxalyl chloride (1.5 equiv) followed by a solution of the alcohol (1.0 equiv), and after 45 min, excess triethylamine (6 equiv). The solution is then kept at −45 °C for 2.5 h before being warmed to room temperature. Workup involves concentration of the reaction mixture to approximately 10 mL, addition of diethyl ether (approximately 100 mL) to precipitate the polymer (cooling to −20 °C for 10 min accelerates precipitation), and filtration. The filtrate is concentrated to give the oxidized product, which typically contains a trace of polymer contamination (1%). This can be easily removed by passing an ethereal suspension through a pad of silica. The solid polymer reagent, which is a 1:1 mixture of the sulfide and sulfoxide, is contaminated with triethylammonium hydrochloride. Although this does not affect the subsequent periodate oxidation, it can be removed by washing a dichloromethane solution with water. In each case an essentially quantitative oxidation of alcohol to aldehyde or ketone was observed by ^1H NMR spectrometry. The yields of isolated product, after removal of the polymer contamination, compare favorably with those of the original Swern reaction.[1a]

To test the recyclability of the PEG-supported sulfoxide **5**, *endo*-borneol was oxidized under limiting conditions, using a slight excess of sulfoxide (1.2 oxidizing equiv) and oxalyl chloride (1.1 equiv). After the Swern reaction, the recovered PEG-supported sulfide **4** was oxidized with sodium metaperiodate to regenerate the PEG-supported sulfoxide **5** in a 91% recovered yield. This regenerated sulfoxide can be used again to transform *endo*-borneol to camphor and shows no loss of oxidation capacity. Five such oxidation/regeneration cycles with a single batch of **5** could be repeated with no observable reduction in oxidation capability.

In conclusion, a recyclable, soluble polymer-supported sulfoxide has been developed that can be used in place of DMSO in Swern oxidation procedures with no loss of efficiency. The reagent greatly simplifies the reaction workup and does not produce any of the unpleasant byproducts (e.g. dimethyl sulfide) produced by use of DMSO. It can be repeatedly recycled and reused without diminishing its effectiveness, and thus has potential for application in combinatorial chemistry.

Experimental Procedures

General. Most common procedures and instrumentation have been previously described.[8] Cross-linked (divinyl benzene) chloromethylated polystyrene resin (4.15 mequiv/g, Bio-Beads S−X1) was obtained from Bio-Rad Laboratories (Mississauga, ON). Poly(ethylene glycol) was obtained from Aldrich Chemical Co. Inc. Solvents were dried and distilled prior to use according to standard procedures.[9]

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6-(Methylthio)hexanoic Acid (1) and **6-(Methylsulfinyl)-hexanoic Acid (2)** were synthesized as described previously.[2]

Poly(ethylene glycol) Bis(6-(Methylthio)hexanoate) (4). A solution of PEG-2000 (10.0 g, 5.0 mmol), sulfide acid **1** (2.80 g, 17.5 mmol), and DMAP (0.21 g, 1.7 mmol) in dichloromethane (50 mL) was treated with DCC (3.60 g, 17.5 mmol) and stirred overnight. The white urea precipitate was removed by filtration through Celite and washed with CH_2Cl_2. The filtrate was concentrated to ~15 mL, and diethyl ether (150 mL) was added with vigorous stirring to precipitate the polymer. The precipitation was enhanced by stirring in an ice bath for 2 h. The precipitate was removed by filtration, washed with diethyl ether, and dried in vacuo to give 11.17 g (98%) of polymer-bound sulfide **4** as a white solid: IR (CH_2Cl_2 cast) 1733 (m), 1113 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.21 (t, 2H, $J = 4.8$ Hz), 3.64 (s, 88H), 2.48 (t, 2H, $J = 7.3$ Hz), 2.33 (t, 2H, $J = 7.4$ Hz), 2.08 (s, 3H), 1.63 (m, 4H), 1.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.44, 70.45, 69.06, 63.30, 33.90, 28.65, 28.09, 24.37, 15.39.

Poly(ethylene glycol) Bis(6-(Methylsulfinyl)hexanoate) (5). A solution of **4** (10.5 g, 4.6 mmol) in methanol (80 mL) and water (20 mL) at 0 °C was treated with 0.50 M sodium metaperiodate (19.4 mL, 9.7 mmol) overnight, during which time a white precipitate formed. The methanol was removed in vacuo below 10 °C, and the residue was extracted with CH_2Cl_2 (5 × 50 mL). Combined extracts were dried (Na_2SO_4) and evaporated to give 10.6 g (99%) of polymer-bound sulfoxide **5** as a white solid: IR (CH_2Cl_2) 1732 (m), 1114 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.20 (t, 2H, $J = 4.7$ Hz), 3.61 (s, 88H), 2.66 (m, 2H), 2.53 (s, 3H), 2.33 (t, 2H, $J = 7.3$ Hz), 1.76 (m, 2H), 1.65 (m, 2H), 1.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.08, 70.37, 68.93, 63.30, 54.17, 38.44, 33.56, 27.99, 24.20, 22.09.

General Procedure for the Modified Swern Oxidation. A solution of **5** (1.74 g, 0.75 mmol) in dichloromethane (30 mL) is cooled to −50 to −60 °C, oxalyl chloride (0.098 mL, 1.125 mmol) is added dropwise, followed after 15 min by a solution of the alcohol (0.75 mmol) in CH_2Cl_2 (5 mL). The mixture is stirred for 45 min, triethylamine (0.63 mL, 4.5 mmol) is added, and the solution is kept at −45 °C for 2.5 h before warming to room temperature. Workup involves concentration of the reaction mixture to approximately 10 mL, followed by addition of diethyl ether (100 mL) to precipitate the polymer. The precipitation is accelerated by cooling to −20 °C for 10 min. After filtration the filtrate is concentrated in vacuo to give the oxidized product, which typically contains a trace of polymer contamination (1%). This is easily removed by passing an ethereal suspension through a pad of silica. The solid polymer reagent, which is a 1:1 mixture of the sulfide and sulfoxide, is contaminated with triethylammonium hydrochloride. Although this does not affect the subsequent periodate oxidation, it can be removed by washing a dichloromethane solution with water to give recovered polymer-bound reagent in a 98% yield. The product was analyzed by ^1H NMR spectrometry, which showed complete oxidation with no trace of alcohol. All the carbonyl products obtained from the Swern oxidation were characterized by comparing chromatographic and/or spectral properties (^1H NMR, IR, MS) with the authentic samples or literature.

In experiments to determine the recyclabilty of the PEG-bound sulfoxide, limiting conditions were used. Thus, 1 equiv of *endo*-borneol was used for the reaction with 0.6 equiv of polymer-supported sulfoxide **5** and 1.1 equiv of oxalyl chloride: 96% of the alcohol was oxidized to give camphor with 4% left unchanged. The polymer-bound reagent recovered was a 6:1 mixture of sulfide:sulfoxide. It was reoxidized by the above procedure for periodate oxidation, giving a 91% recovery of PEG-bound sulfoxide **5**.

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Additions and Corrections

Vol. 62, 1997

Matthias Köck* and Jochen Junker. How Many NOE Restraints Are Necessary for a Reliable Determination of the Relative Configuration of an Organic Compound: Application to a Model System.

Page 8614. The configuration of compound **1** is correctly designated as 1*R*,6*R*,8*R*,11*R*,12*S*,16*R* in the text. The centers 6, 8, 11, and 12 should be switched in the 2D drawing of **1**.

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