Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 1791–1793

BIOORGANIC &
MEDICINAL
CHEMISTRY
LETTERS

Modification of the Swern Oxidation: Use of a Recyclable, Polystyrene Bound Sulfoxide

Derek C. Cole,* Joseph R. Stock and Jo Anne Kappel

Chemical Sciences, Wyeth Research, 401 N. Middletown Rd., Pearl River, NY 10965, USA

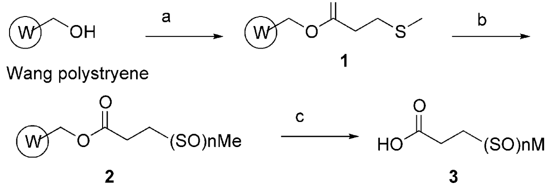
Received 3 December 2001; accepted 23 April 2002

Abstract—A method has been developed for the oxidation of sulfides to sulfoxides on polystyrene resin. The polystyrene bound sulfoxide may be used in Swern oxidation reactions, and the used reagent may be regenerated by oxidation with *tert*-butylhydrogen peroxide. © 2002 Elsevier Science Ltd. All rights reserved.

The Swern oxidation of primary and secondary alcohols to aldehydes and ketones, using oxalyl chloride to activate the dimethyl sulfoxide (DMSO), is a very common reaction in organic synthesis.[1] Unfortunately, the reaction produces the unpleasant-smelling, volatile byproduct, dimethyl sulfide (bp 37 °C). Vederas et al. have shown that DMSO may be replaced with 6-(methylsulfinyl)hexanoic acid in Swern oxidation reactions.[2] This modification generates the non-volatile 6-(methylsulfanyl)hexanoic acid, which is easily removed from the reaction by base extraction. The 6-(methylsulfinyl)-hexanoic acid was also attached to chloromethyl polystyrene resin (Merrifield resin) to form a polymer bound reagent. More recently Vederas has attached the 6-(methylsulfinyl)hexanoic acid to a soluble poly(ethylene glycol) (PEG) support.[3] After use in the Swern reaction the PEG-bound reagent is readily recycled by sodium periodate oxidation, with no loss in activity.

The polystyrene bound sulfoxide developed by Vederas et al. was found to lose its activity (92–78%) on regeneration by sodium periodate oxidation. It was suggested that this was due to cross-linking of the polystyrene backbone by the oxalyl chloride. We have investigated the oxidation of polystyrene bound sulfides to sulfoxides and found sodium periodate to be an inefficient oxidation reagent, which leads to incomplete reaction. We suggest the inefficient oxidation is due to the poor swelling capacity of polystyrene in the polar solvents (ethanol/water mix) used in the sodium periodate oxidation.

In order to find conditions for oxidation of polystyrene bound sulfides to sulfoxides, we attached 3-methylsulfanyl propionic acid[4] to Wang polystyrene resin and subjected it to various oxidation conditions as shown in Scheme 1. The oxidized resins **2** were then cleaved with trifluoroacetic acid (TFA) to liberate the free acids **3**, which were analyzed by NMR to determine the extent of oxidation. Conditions including hydrogen peroxide and sodium periodate gave mixtures of sulfide and sulfoxide. *meta*-Chloroperbenzoic acid (*m*CPBA) has been reported to oxidize sulfides to sulfoxides on polystyrene resin, but the ratio must be carefully controlled as excess *m*CPBA leads to over oxidation to the sulfone.[5] *tert*-Butyl hydrogen peroxide (*t*BHP) in the presence of catalytic amount of *para*-toluene sulfonic acid (*p*TSA) gives efficient oxidation of sulfides to the sulfoxides with no observed sulfone.

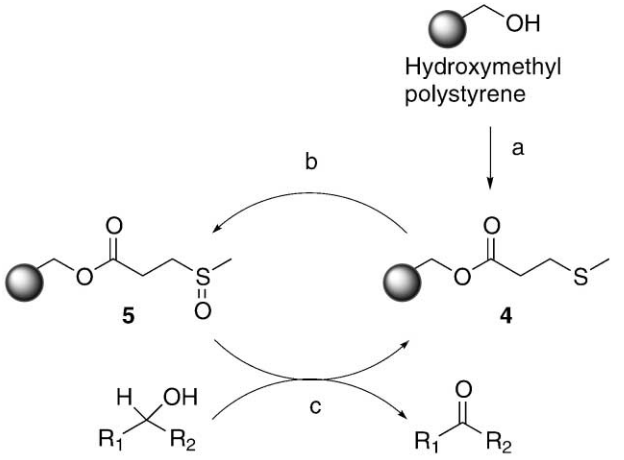


Scheme 1. Reagents and conditions: (a) 3-(methylthio) propionic acid, DMAP, 1,3-diisopropylcarbodiimide (DIC); (b) oxidation method (see Table 1); (c) TFA/DCM (1:1).

---

*Corresponding author. Fax: + 1-845-602-5561; e-mail: coledc@wyeth.com

PII: S0960-894X(02)00281-0



Scheme 2. Reagents and conditions: (a) 3-(methylthio) propionic acid, DMAP, DIC; (b) 70% *t*BHP, *p*TSA, DCM; (c) $(COCl)_2$, Et_3N, DCM.

Table 1. Oxidation of polystyrene bound sulfide

Oxidation method[a]	Reagent	% Sulfide[b]	% Sulfoxide[b]	% Sulfone[b]
A	H_2O_2	33	66	0
B	*m*CPBA, 1 equiv	5	60	35
C	*m*CPBA 2 equiv	0	Trace	100
D	$NaIO_4$	33	66	0
E	*t*BHP	23	77	0
F	*t*BHP, *p*TSA	0	100	0

[a] Oxidation method: (A) 30% hydrogen peroxide (10 equiv) in MeOH; (B) *m*CPBA (1 equiv) in DCM; (C) *m*CPBA (2 equiv) in DCM; (D) sodium periodate (10 equiv) in EtOH/water; (E) 70% *t*BHP (10 equiv) in DCM; (F) 70% *t*BHP (10 equiv) with *p*TSA (1.5 equiv) in DCM.

[b] Percentages were calculated by integration of the CH_3 peak of the cleaved products in the proton NMR spectrum ($CDCl_3$) ($RSCH_3$ 2.14 ppm; $RSOCH_3$ 2.74 ppm; RSO_2CH_3 2.99 ppm).

Having shown that polystyrene bound sulfides are efficiently oxidized to sulfoxides with 70% *t*BHP in the presence of *p*TSA, the next step was to prepare a polystyrene bound sulfoxide for use in the Swern oxidation. Thus, as shown in Scheme 2, 3-methylsulfanyl propionic acid was attached to hydroxymethyl polystyrene resin. The resin bound sulfide **4** was then oxidized to the sulfoxide **5**.

The sulfoxide reagent **5** was used to oxidize several test alcohols under the standard conditions described below. HPLC analysis[6] of the reaction mixtures showed complete conversion to the aldehyde or ketone with no trace of alcohol remaining. The isolated yields of aldehydes and ketones after flash chromatography are shown in Table 2.

To test the recyclability of the polystyrene bound reagent **5**, α-methyl-2-naphthylenemethanol was oxidized to 2′-acetonaphthone using the standard conditions. After the reaction the reduced resin was washed and re-oxidized using *t*BHP and *p*TSA. The resin was then reused to oxidize α-methyl-2-naphthylenemethanol. Again HPLC analysis indicated complete conversion to the ketone, which was obtained in 71% isolated yield.

In conclusion, an inexpensive, readily synthesized, recyclable, polystyrene bound sulfoxide reagent has been developed which may be used in place of DMSO in Swern oxidations. The reagent is easily removed by filtration and can be recycled and reused.

General Procedure for Oxidation Using Polystyrene Bound Sulfoxide Resin

The polystyrene bound sulfoxide reagent **5** (2 equiv) was suspended in DCM and cooled to −50 to −60 °C. Oxalyl chloride (2 equiv of a 2 M solution in DCM) was added dropwise, followed after 15 min by a solution of alcohol (1 equiv) in DCM. After stirring for 30 min, triethylamine (6 equiv) was added and the mixture allowed to warm to −40 °C for 2 h, then filtered and washed with DCM. The filtrate was concentrated and the residue purified by flash chromatography over silica gel with ethyl acetate and hexanes.

Table 2. Isolated yields of aldehydes and ketones after oxidation with polystyrene bound sulfoxide reagent

Alcohol	Isolated yield (%)
3-Benzyloxybenzyl alcohol	71
Anisoin	80
α-Methyl-2-naphthylenemethanol	82

Sulfide Oxidation Study on Wang Polystyrene Resin

A suspension of Wang Resin (PL-Wang resin, 1.7 mmol/g 150–300 μM, from Polymer Laboratories), 3-(methylthio) propionic acid (5 equiv) and DMAP (1 equiv) in DCM/DMF (1:1) was treated with DIC (5 equiv) and shaken overnight. The material was washed with DMF/water (10:1) (50 mL), DMF (50 mL), DCM (50 mL), MeOH (50 mL) and DCM (3×50 mL). The material was then dried under vacuum.

The sulfide resin **1** was suspended in the appropriate solvent and the reagents indicated in Table 1 added. The mixture was shaken at room temperature overnight, then washed as above and dried under vacuum.

The oxidized resin **2** was treated with DCM/TFA for 30 min, then filtered and the filtrate concentrated. The residue was analyzed by NMR to determine the extent of oxidation.

Preparation of the Polystyrene Bound Swern Reagent

A suspension of hydroxymethyl polystyrene (PL-HMS, 2.0 mmol/g 150–300 μm, from Polymer Laboratories) (10 g, 20 mmol), 3-(methylthio) propionic acid (10.4 mL, 5 equiv) and DMAP (2.44 g, 1 equiv) in DCM/DMF (1:1) was treated with DIC (15.7 mL, 5 equiv) and shaken overnight. The material was washed as above and dried under vacuum. A total of 12 g of white resin was obtained: IR (microscope) 1736 (C=O), 1145 (C–O) cm^{-1}. Percent sulfur calculated based on 100% conversion: 5.32. Found: 5.81.

To a suspension of **4** (11.6 g, 19.3 mmol) in DCM was added 70% *t*-butylhydroperoxide (27.7 mL, 10 equiv) and *para*-toluenesulfonic acid (5.7 g, 1.5 equiv) and the mixture shaken overnight. The material was washed as above then dried under vacuum. A total of 12 g of white resin was obtained: IR (microscope) 1734 (C=O), 1176 (C–O), 1051 (S=O) cm^{-1}. Percent sulfur calculated based on 100% conversion: 5.18. Found: 5.15.

Acknowledgements

The authors would like to acknowledge the help of Andrew Schork for single bead IR and Frank E. Koehn for solid phase NMR.

References and Notes

1. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
2. Liu, Y.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 7856.
3. Harris, J. M.; Liu, Y.; Chai, S.; Andrews, M. D.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2407.
4. 3-(Methylthio) propionic acid from Lancaster (100 g, $114) or TCI-US (500 g, $173).
5. Delpiccolo, C. M. L.; Mata, E. G. *Tetrahedron: Asymmetry* **1999**, *10*, 3893.
6. HPLC conditions: Agilent 1100 HPLC; Waters Xterra™ C_{18} 3.5 μM, 2.1×30 mm column; Solvent A: 0.02% formic acid/water; Solvent B: 0.02% formic acid/acetonitrile; Solvent gradient: Time 0: 90% A; 3.5 min 90% B; 5 min 90% B; Flow rate: 1 mL/min; Detection 215 and 254 nm DAD.