

Efficient use of trimethylsulfonium methylsulfate as a reagent for the epoxidation of carbonyl-containing compounds

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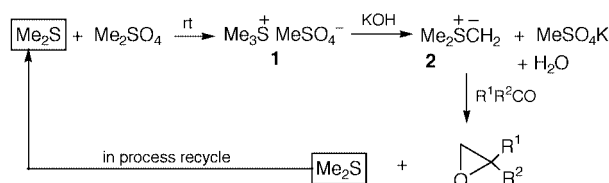
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A process for the efficient conversion of trimethylsulfonium methylsulfate into dimethylsulfonium methanide, thence epoxides, has been devised. Thus dimethyl sulfate and dimethyl sulfide are caused to react in the presence of either a mineral acid or an organic acid. The anion of trimethylsulfonium methyl sulfate is converted by the acid into methyl hydrogen sulfate, which in turn reacts with excess dimethyl sulfide to form trimethylsulfonium hydrogen sulfate. The outcome is that both methyl groups of dimethyl sulfate are converted into the desired trimethylsulfonium salt, thence dimethylsulfonium methanide; the process is mediated by low boiling dimethyl sulfide which can be recycled, and the by-product (K_2SO_4) is more easily disposed of than potassium methyl sulfate.

Introduction

Trimethylsulfonium methyl sulfate (**1**)^{1,2} is an inexpensive, efficient precursor of dimethylsulfonium methanide (**2**), a valuable reactive intermediate for the transformation of aldehydes and ketones into epoxides³ (see Scheme 1). Generation of the ylide

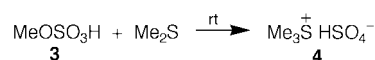


Scheme 1

2 from the salt **1** can be effected under homogeneous or phase transfer conditions;² an important feature of the latter method is that it is not necessary to add a phase transfer catalyst.

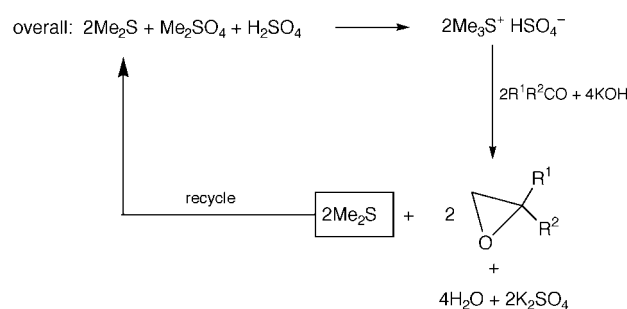
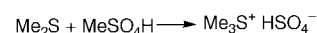
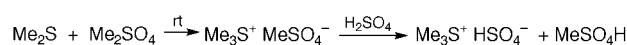
The use of dimethyl sulfate as a methylating agent for dimethyl sulfide has important advantages compared with alkyl halides: thus the products do not contain corrosive chloride ions, and the process does not involve the use of gaseous starting materials (e.g. $MeCl$, $MeBr$). Dimethyl sulfate is also less expensive than the corresponding methyl halides but it has one serious drawback — generally only *one* of the two methyl groups available is utilised in epoxide formation. This is effectively a yield loss of 50% and the effluent loading is higher, containing one equivalent of an alkali methyl sulfate salt per mole of dimethyl sulfate used. The aim of the present study was to devise an efficient process for using *both* methyl groups of dimethyl sulfate for epoxidation through ylides derived from sulfonium species.

We have reported earlier⁴ that methyl hydrogen sulfate (**3**)⁵ methylates dimethyl sulfide at ambient temperature to produce trimethylsulfonium hydrogen sulfate (**4**) (Scheme 2). This led to



Scheme 2

the questions: could the methyl sulfate anion in trimethylsulfonium methyl sulfate be converted *in situ* into methyl hydrogen sulfate, and would this react with a further equivalent of dimethyl sulfide *in situ*? If this could be achieved, a method of utilizing both methyl groups from dimethyl sulfate would be available. This would result in the formation of two equivalents of trimethylsulfonium cation thence two equivalents of dimethylsulfonium methanide on treatment with base; overall, two equivalents of epoxide would ensue from one equivalent of dimethyl sulfate. An illustration of how sulfuric acid could be used for achieving efficient conversion to epoxide is shown in Scheme 3 from which it should be noted that the epoxidation



Scheme 3

by-product would be dimethyl sulfide (bp 38 °C) which can be contained and recycled using standard industrial process technology.

Results and discussion

It was demonstrated at the outset that no reaction occurred between trimethylsulfonium methyl sulfate and an excess of dimethyl sulfide (1.5 mol equiv.) after 7 h at 35 °C; thus no change was apparent in the integrated ¹H NMR singlet resonances at $\delta = 3.0$ (Me_3S^+) and 3.55 ppm ($MeSO_4^-$), respectively. In contrast, when concentrated sulfuric acid (0.5 mol equiv.) was added to the above mixture, an exothermic reaction occurred,

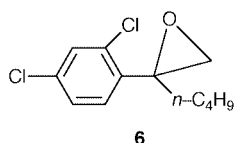
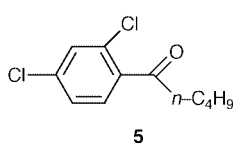
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Table 1 Reaction of trimethylsulfonium methyl sulfate^a and dimethyl sulfide^a with mineral acids and Amberlyst resin

Acid	Acid–MeSO ₄ [−] (mol. equiv.–mol. equiv.)	Time/h	Temp./°C	¹ H NMR integration ratio (CH ₃) ₃ S ⁺ :CH ₃ SO ₄ [−]	% Reaction
HCl (36%)	1	6	40	29:1 ^c	~80%
H ₃ PO ₄ (85%)	1.5	6	40	5.7:1	25%
PhSO ₃ H	4	6	35–40	No peak for CH ₃ SO ₄ [−]	100%
Amberlyst	^b	6	35–40	4:1	~20%

^a Trimethylsulfonium methyl sulfate (1.0 equiv.) and dimethyl sulfide (2.0 equiv.). ^b For a polymer supported acid, the mole equivalent cannot be calculated. ^c Mixture used in subsequent epoxidation reaction.

and ¹H NMR analysis indicated a 30% conversion to trimethylsulfonium hydrogen sulfate and methyl hydrogen sulfate after 48 h at room temperature. The reaction of Me₃S⁺MeSO₄[−]–Me₂S–concentrated H₂SO₄ was then repeated (40 °C, 6 h) with a molar ratio of 1:1.5:2, respectively. After 6 h at 40 °C and standing at room temperature, the product consisted of two layers with the lower layer at pH zero; ¹H NMR analysis of this layer indicated an almost quantitative conversion to trimethylsulfonium hydrogen sulfate. The latter was then used for epoxidation using our procedure described earlier:⁶ 1-(2,4-dichlorophenyl)pentan-1-one (**5**) [1 mol equiv.], potassium



hydroxide (5 equiv.) and trimethylsulfonium cation (1.05 equiv.) were allowed to react in *tert*-butyl alcohol at room temperature to afford the epoxide **6** in 73% yield. The use of hydrochloric, phosphoric, benzene sulfonic acid and a strong cation exchange resin (Amberlyst 15) was then evaluated in respect of the pre-epoxidation step as described above (see Table 1).

The use of hydrochloric acid showed a significant rise in the (CH₃)₃S⁺:CH₃SO₄[−] ratio but phosphoric acid showed only a slight increase under the same conditions. Benzenesulfonic acid, using a four-fold molar excess, resulted in complete conversion, with no methyl sulfate anion remaining. The use of Amberlyst 15 resulted in a slight increase in the ratio to 4:1, but the resin absorbed the liquid and the reaction mixture became very viscous. Further work would be required to optimise the quantity of Amberlyst 15 required.

The reaction mixture produced from the use of hydrochloric acid was also used for epoxidation as described above. Two equivalents of 1-(2,4-dichlorophenyl)pentan-1-one (**5**) were used per equivalent of trimethylsulfonium methyl sulfate and the product epoxide **6** was isolated in 54% yield. This yield could be improved by allowing the reaction of trimethylsulfonium methyl sulfate and dimethyl sulfide to go to completion, either by allowing a longer reaction time, by increasing the temperature or by adding a larger excess of hydrochloric acid. It may be noted that the mixture produced from this reaction will contain the trimethylsulfonium cation with two different counter ions (Cl[−] and HSO₄[−]).

Conclusions

A new, efficient epoxidation method has been devised based on dimethyl sulfate (1 equiv.) and dimethyl sulfide (2 equiv.) to produce trimethylsulfonium cation (2 equiv.), utilizing both methyl groups present in dimethyl sulfate. Sulfuric acid is used to generate methyl hydrogen sulfate as an intermediate, but other acids, *e.g.* hydrochloric acid, can also fulfil the same role.

Experimental

¹H NMR spectra were recorded on a Bruker WP-SY (80 MHz)

spectrometer; chemical shifts are quoted in ppm downfield from tetramethylsilane and 3-(trimethylsilyl)propanesulfonic acid, sodium salt (DSS), and coupling constants are in Hertz. Amberlyst 15 was purchased from Aldrich.

1-(2,4-Dichlorophenyl)pentan-1-one (**5**)⁷ and 2-butyl-2-(2,4-dichlorophenyl)oxirane (**6**)⁸

Compounds **5** and **6** were prepared by known methods. NMR spectral data are as follows: Compound **5** δ_H (CDCl₃–TMS) 0.75–1.9 (m, 7H, (CH₂)₂CH₃), 2.87 (t, 2H, CH₂), 7.15–7.5 (m, 3H, aromatic H).

Compound **6** δ_H (CDCl₃–TMS) 0.5–2.4 (m, 9H, (CH₂)₃CH₃), 2.6–3.0 (m, 2H, CH₂O), 7.0–7.5 (m, 3H, aromatic H).

Reaction of trimethylsulfonium methyl sulfate, dimethyl sulfide and sulfuric acid

Dimethyl sulfide (3.60 g, 0.058 mol) was added to a solution of trimethylsulfonium methyl sulfate (5.97 g, 0.029 mol) in water (0.5 ml). 98% Sulfuric acid (5.8 g, 0.058 mol) was added dropwise to the stirred mixture which was then heated to 40 °C and stirred for 6 h. The product was held unagitated for 16 h after which it consisted of two layers with a large lower aqueous layer of pH = 0. A sample of this layer was removed for ¹H NMR analysis. δ_H (DMSO-*d*₆–DSS) 2.1 (s, 1H, (CH₃)₂S), 3.0 (s, 13H, (CH₃)₃S⁺), 3.5 (s, 0.1H, CH₃SO₄[−]).

Epoxidation of 1-(2,4-dichlorophenyl)pentan-1-one (**5**) using the reaction mixture from above

To the above reaction mixture containing trimethylsulfonium cation (assumed 0.058 mol) was added *tert*-butyl alcohol (4.10 g, 0.055 mol) and 1-(2,4-dichlorophenyl)pentan-1-one (13.38 g, 0.055 mol). This mixture was stirred and potassium hydroxide (15.4 g, 0.275 mol) was added in portions. The colour of the mixture changed quickly to yellow and an exotherm was observed; cooling with an ice bath was applied. Half of the potassium hydroxide was added and the mixture was stirred for 1 h, then the remainder was added over 20 min. The mixture was very viscous but became less so during the 3 h stirring period. The mixture was held unagitated over 2 days. Samples were removed periodically for gas chromatographic analysis (Shimadzu GC-9A instrument with a Shimadzu C-R3A Chromatopac Integrator). The column was of fused silica (2 m × 3 mm) with 5% OV17 stationary phase; the oven temperature was 180 °C. Samples (~0.5 ml) were added to a mixture of dichloromethane (~1 ml) and water (~1 ml) and shaken. The lower dichloromethane layer (1 μl) was injected, showing retention times for 1-(2,4-dichlorophenyl)pentan-1-one (**5**) and the epoxide **6** = 8.4 and 7.7 min, respectively.

The progress of reaction was monitored by GC % areas for ketone **5** and epoxide **6** at the following times: end of KOH addition (1 h, 20 min; ratio of **5**:**6** = 86:13), 3 h (**5**:**6** = 25:68) and 48 h (**5**:**6** = 9:89); the yield of **6** after 48 h was 73%.

To the bulk reaction mixture was added water (50 cm³) and the solvents were then evaporated by distillation, up to a column head temperature of 55 °C. Water (*ca.* 250 cm³) was added and the lower organic layer was separated and washed

with water (50 cm³) to afford the crude epoxide **6** (10.55 g); a further batch (0.6 g) of epoxide **6** was isolated through extraction of the aqueous washings with dichloromethane (total yield = 73% from GC analysis).

Reaction of trimethylsulfonium methyl sulfate and dimethyl sulfide in the presence of other acids (HCl, H₃PO₄, PhSO₃H, Amberlyst 15)

Dimethyl sulfide was added to dimethyl sulfate and the acid was then added slowly (see Table 1 for mol ratios); water (0.8 ml for a 88 mmol amount of Me₂S) was used as an additive for the reaction with PhSO₃H. The mixtures were heated up to 40 °C and progress monitored by ¹H NMR analysis. The reaction with Amberlyst 15 was carried out as follows: dimethyl sulfide (3.90 g, 0.064 mol) was added to a solution of trimethylsulfonium methyl sulfate (6.12 g, 0.032 mol) in water (0.6 ml). Amberlyst 15 (6.90 g) was added but the mixture was very viscous. A second aliquot of dimethyl sulfide (5 ml) was added, the mixture was stirred at 35–40 °C for 6 h and then held overnight at room temperature. Water (5 ml) was added and samples were removed for ¹H NMR analysis. The ketone **5** was epoxid-

ised by the standard method (see above) using the product of the hydrochloric acid reaction described above. The yield of epoxide **6** was 54%.

References

- 1 T. Kutsuma, I. Nagayama, T. Okazaki, T. Sakamoto and S. Akaboshi, *Heterocycles*, 1977, **8**, 397.
- 2 P. Mosset and R. Greé, *Synth. Commun.*, 1985, **15**, 749.
- 3 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, **84**, 3782; E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.
- 4 J. Forrester, R. V. H. Jones, P. N. Preston and E. S. C. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2289.
- 5 I. Rusev and D. Chochkova, *Khim. Ind. (Sofia)*, 1986 **58**, 445 (*Chem. Abstr.*, **107**, 115953).
- 6 J. Forrester, R. V. H. Jones, P. N. Preston and E. S. C. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1937.
- 7 M. Ueda, Y. Seino and J. Sugiyama, *Polym. J. (Tokyo)*, 1993, **25**, 1319.
- 8 G. R. Davies and A. G. Williams, Eur. Pat. Appl EP 93562 (1983); (*Chem. Abstr.*, **100**, 58802).

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