

Generation of trimethylsulfonium cation from dimethyl sulfoxide and dimethyl sulfate: implications for the synthesis of epoxides from aldehydes and ketones

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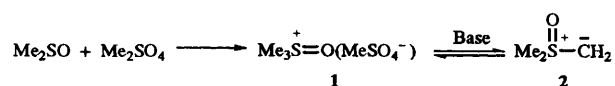
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The reaction between dimethyl sulfoxide (DMSO) and dimethyl sulfate has been monitored qualitatively by ¹H NMR spectroscopy. At reaction temperatures of 20, 50 and 90 °C, the major product is methoxydimethylsulfonium methyl sulfate **5** whereas at 100 °C the major product is trimethylsulfonium methyl sulfate **6** together with minor amounts of methoxydimethylsulfonium methyl sulfate; formaldehyde was qualitatively identified as a product by derivatisation (2,4-dinitrophenylhydrazine). Treatment of the product ensuing from the latter reaction with potassium hydroxide, followed by addition of (separately) benzaldehyde and 1-(2,4-dichlorophenyl)pentan-1-one gave the expected epoxides **4a** and **4b**, respectively.

The mode of alkylation of dimethyl sulfoxide (DMSO) is governed by the degree of 'hard' or 'soft' character of the incipient reactant alkyl cation.¹ For example, methyl iodide reacts with DMSO at 50 °C to give trimethyloxosulfonium iodide [Me₃S⁺=O(I⁻)],^{2a-c} and an analogous product is formed from methyl bromide, albeit in a potentially hazardous synthesis;^{2d} reactions with CH₃X (X = ONO₂, OTs and OBs) give products of *O*-methylation [Me₂S⁺OMe(X⁻)].^{2a} It is believed¹ that *O*-alkylated products are formed under conditions of kinetic control whereas elevated temperatures and long reaction times provide thermodynamically more favourable oxosulfonium salts: for example DMSO reacts with trimethylene sulfone at 20 °C over 48 h to give a product of *O*-alkylation, whereas the *S*-alkylated derivative is formed at higher temperature (85 °C/24 h).³ It should be noted that structural evidence⁴ regarding the outcome of alkylation of DMSO is valuable, because ylides derived from trimethyloxosulfonium salts [e.g. Me₂S⁺(O)C⁻H₂] are of synthetic value for the transformation of aldehydes and ketones into epoxides.⁵

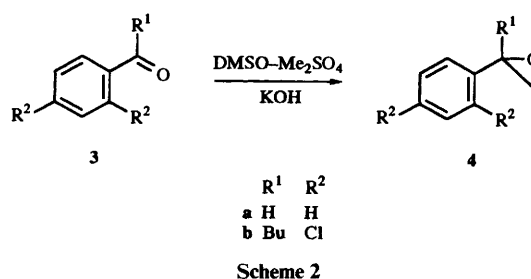
As part of a wider study of epoxidation through sulfur ylides⁶ we wished to evaluate the efficiency of trimethyloxosulfonium methyl sulfate (Me₃S⁺=OMeSO₄⁻) thence the ylide (Me₂S⁺(O)C⁻H₂) in this respect. Epoxidation procedures using ylides derived from trimethylsulfonium methyl sulfate are documented⁷ but there is little information on analogous processes through oxosulfonium methyl sulfates. Zerbes *et al.*⁸ achieved the transformation of ketones (e.g. ArOCH₂COBu^t; Ar = Aryl) into epoxides through an ylide believed to be **2** derived from a salt believed to be **1**; the latter was reported to be obtained by heating DMSO and dimethyl sulfate, preferably in the temperature range 60–110 °C. We have reinvestigated this type of process and confirm its effectiveness, but conclude that the mechanism is more complex than had been assumed⁸ (*cf.* Scheme 1).



Scheme 1 Mechanism suggested earlier for the formation of epoxides from carbonyl compounds using the DMSO–Me₂SO₄ system⁸

Results and discussion

In the present work, sulfonium salts **5**^{4a} and **6**^{7b} were prepared by literature procedures, and trimethyloxosulfonium methyl sulfate **1** was synthesised by ruthenium tetroxide-promoted



oxidation of trimethylsulfonium methyl sulfate by adaptation of the method of Heather.⁹ With these salts to hand, definitive ¹H NMR assignments could be compiled, and the thermal reaction of DMSO and dimethyl sulfate could be qualitatively monitored. The following observations were made (see Tables 1 and 2).

(a) In separate reactions of DMSO and Me₂SO₄ at 22 and 50 °C, the only detectable product is methoxydimethylsulfonium methyl sulfate **5**; when this reaction is carried out at 90 °C for several hours, the major product is trimethylsulfonium methyl sulfate **6** (see Table 1). (b) When a DMSO–Me₂SO₄ mixture is heated incrementally in the range 20–100 °C, a rapid increase in the concentration of trimethylsulfonium methyl sulfate **6** is observed at 100 °C with a short hold time (1 h) (see Table 2).

These results suggested that dimethylsulfonium methylide (Me₂S⁺C⁻H₂) would be generated by base treatment of thermally pre-cycled DMSO–Me₂SO₄ mixtures (e.g. 90 °C/4 h); subsequent addition of an aldehyde or ketone would then result in oxirane formation. On the other hand, pre-treatment of DMSO–Me₂SO₄ mixtures below *ca.* 90 °C would generate methoxydimethylsulfonium methyl sulfate **5** as the major product and this would not be expected to act as a precursor for ylide generation and oxirane synthesis.

Epoxidation experiments were then conducted in the present

Table 1 ^1H NMR investigation^a of separate reactions of dimethyl sulfoxide and dimethyl sulfate at 22, 50 and 90 °C

Temp ($T/^\circ\text{C}$)	Time (t/h)	^1H NMR integration ratio						
		Me_2SO 2.5 ppm	Me_3S^+ 2.9 ppm	$\text{Me}_2\text{S}^+\text{OMe}$ 3.35 ppm	MeSO_4^- 3.45 ppm	$\text{Me}_3\text{S}^+\text{O}$ 3.85 ppm	Me_2SO_4 4.0 ppm	$\text{Me}_2\text{S}^+\text{OMe}$ 4.04 ppm
22	1	2.2	<i>b</i>	0.8	1.0	<i>b</i>	1.2	0.9
	4	1.0	<i>b</i>	1.5	1.0	<i>b</i>	1.5	1.0
	24	0.3	<i>b</i>	1.9	1.0	<i>b</i>	0.1	1.0
50	1	0.2	<i>b</i>	1.7	1.0	0.2	0.2	1.0
	4	0.1	<i>b</i>	2.0	1.0	<i>b</i>	0.1	1.0
	24	<i>b</i>	<i>b</i>	2.2	1.0	0.3	0.2	1.2
90	1	0.2	0.1	1.6	1.0	0.1	0.1	0.8
	4	0.1	3.0	<i>b</i>	1.0	0.4	<i>b</i>	<i>b</i>
	24	0.1	3.0	<i>b</i>	1.0	0.3	<i>b</i>	<i>b</i>

^a See Experimental section for reaction conditions. ^b No observable resonance.

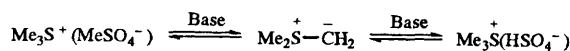
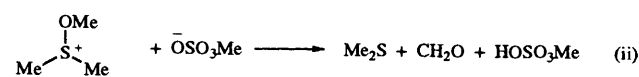
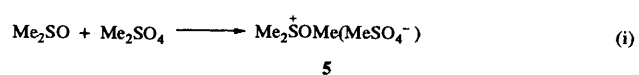
Table 2 ^1H NMR investigation^a of the reaction of dimethyl sulfoxide and dimethyl sulfate through the temperature range 20–100 °C

Temp. ($T/^\circ\text{C}$), Time (t/h)	^1H NMR integration ratio						
	Me_2SO 2.5 ppm	Me_3S^+ 2.9 ppm	$\text{Me}_2\text{S}^+\text{OMe}$ 3.35 ppm	MeSO_4^- 3.45 ppm	$\text{Me}_3\text{S}^+\text{O}$ 3.85 ppm	Me_2SO_4 4.0 ppm	$\text{Me}_2\text{S}^+\text{OMe}$ 4.04 ppm
20, 1	4.8	<i>b</i>	0.5	1.0	<i>b</i>	2.8	0.9
50, 1	0.3	<i>b</i>	2.1	1.0	<i>b</i>	0.3	1.0
90, 1	0.2	<i>b</i>	1.8	1.0	<i>b</i>	0.2	0.9
100, 1	0.4	1.7	0.2	1.0	0.4	0.1	0.1

^a See Experimental section for reaction conditions. ^b No observable resonance.

work on benzaldehyde and (separately) 1-(2,4-dichlorophenyl)pentan-1-one **3b** using pre-synthesised trimethylsulfonium methyl sulfate^{7b} **6** as a 'model' system. The epoxides **4a** and **4b** were formed in 79 and 83% yields, respectively, after generation of dimethylsulfonium methylide with an excess of potassium hydroxide. The DMSO–dimethyl sulfate epoxidation method, as reported,⁸ was then evaluated for comparison: the reagents were heated for 24 h at 100 °C and the product was cooled before treatment with potassium hydroxide. Yields of epoxides were in the range 44–82% depending on the molar ratios of the reactants.

We have not yet adduced definitive evidence for the mechanism of formation of trimethylsulfonium methyl sulfate **6** from the thermal reaction of DMSO and dimethyl sulfate, although we have trapped formaldehyde qualitatively as a by-product in epoxidations. A possible mechanism (Scheme 3) could involve initial formation of methoxydimethylsulfonium methyl sulfate **5** (step i) followed by its thermal decomposition (step ii) in a manner akin to the Kornblum oxidation of methanol. The final step (iii) could involve generation of trimethylsulfonium methyl sulfate **6** through nucleophilic attack of dimethyl sulfide on the sulfonium salt **5**. Our qualitative ^1H NMR results indicate a build up in $[\text{MeSO}_4]^-$ during the course of the reaction (Tables 1, 2) but we cannot exclude alternative pathways to trimethylsulfonium salt formation (see *e.g.* step iv in Scheme 3).⁶ Thus we have shown by ^1H NMR analysis that the reaction of methoxydimethylsulfonium methyl sulfate (**5**; 1 mol equiv.) and dimethyl sulfide (1 mol equiv.) in DMSO at 20 °C gives trimethylsulfonium methyl sulfate **6** in >90% yield after 24 h; similarly, when (**5**; 1 mol equiv.) is treated with dimethyl sulfide in acetonitrile solvent under the same conditions, the salt **6** is formed in addition to the expected stoichiometric amount of DMSO. The salt **6** is also formed almost quantitatively (^1H NMR) when MeHSO_4 ¹⁰ is caused to react with dimethyl sulfide at 35–40 °C for 2 h. A wider study of the influence of reagent stoichiometry is required before the detailed mechanism of trimethylsulfonium salt formation can be understood.



Scheme 3 Modified mechanisms for ylide formation through the DMSO– Me_2SO_4 system (this work)

Experimental

Preparation of trimethylsulfonium methyl sulfate **6**

This hygroscopic salt was prepared by a literature procedure^{7b} in quantitative yield, mp 92–94 °C (lit.,⁹ 100–104 °C); $\delta_{\text{H}}([\text{}^2\text{H}_6\text{]-DMSO-DSS}^\dagger)$ 2.9 [s, 9 H, $(\text{CH}_3)_3\text{S}^+$] and 3.55 (s, 3 H, CH_3SO_4^-); note that the ^1H NMR resonances for this salt are incorrectly assigned in ref. 7b.

Preparation of trimethyloxosulfonium methyl sulfate **1**

This compound was prepared by adaptation of a literature procedure.⁹ Ruthenium dioxide hydrate (0.156 g, 1.2 mmol) was

[†] DSS = Sodium 4,4-dimethyl-4-silapentane-1-sulfonate.

added to a stirred solution of trimethylsulfonium methyl sulfate (12.34 g, 66 mmol) in water (42 cm³). Sodium periodate (14.31 g, 0.67 mol) was added in portions to the stirred mixture over a period of 2 h and stirring was continued at room temperature for 2.5 h. The thick slurry of sodium iodate was filtered through a pad of 'Celite' filter aid. The filtrates were concentrated under reduced pressure to give the impure title salt as a crude black solid (15.8 g).

A portion of this solid (14.8 g) was extracted for 3 days with hot acetone in a Soxhlet extractor. On cooling of the solvent, a white solid was precipitated. This solid was dried in a vacuum desiccator to give the hygroscopic title compound (1.31 g), mp 139–140 °C; $\delta_{\text{H}}(\text{D}_2\text{O}-\text{DSS})$ 3.73 (s, 3 H, CH_3SO_4^-), 3.85 [s, 9 H, $(\text{CH}_3)_3\text{S}^+\text{O}$]; $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$ 3000 (CH), 1500 and 1000 (S=O); m/z (FAB, low resolution: consider $\text{Me}_3\text{S}^+\text{OMeSO}_4^-$ as M^+X^-) 93 (M^+) and 297 (M_2^+X^-); FAB (high resolution) 297.0479 (Calc. for M_2^+X^- : 297.0500), 314.9915 (Calc. for M^+X_2^- : 314.9878). It proved impossible to obtain satisfactory data from elemental analysis (C, H, S) but the Na content was low (<0.025%) (from inductively coupled plasma spectroscopy).

Preparation of methoxydimethylsulfonium methyl sulfate 5

Dimethyl sulfoxide (30.0 g, 0.38 mol) was added to dimethyl sulfate (47.0 g, 0.38 mol) and the mixture stirred at room temperature for 24 h. The mixture was then held unagitated for 2 days at room temperature during which time it solidified to give the colourless, hygroscopic title compound (75 g, 97%); $\delta_{\text{H}}([{}^2\text{H}_6]-\text{DMSO}-\text{DSS})$ 3.35 (s, 6 H, CH_3S), 3.45 (s, 3 H, CH_3SO_4^-) and 4.03 (s, 3 H, OCH_3); the sample was contaminated with a trace of dimethyl sulfate (δ 4.0).

¹H NMR Investigation of the reaction of dimethyl sulfoxide and dimethyl sulfate

Dimethyl sulfoxide (3.12 g, 0.05 mol) and dimethyl sulfate (5.03 g, 0.04 mol) were stirred at 22 °C for 24 h, samples being removed after 1, 4, and 24 h for ¹H NMR analysis. This procedure was then repeated at 50 and 90 °C (see Table 1).

In a separate experiment, a mixture of dimethyl sulfoxide (3.12 g, 0.04 mol) and dimethyl sulfate (5.03 g, 0.04 mol) was stirred whilst the temperature was increased at hourly intervals in stages: 20→50→90→100 °C. Samples were removed for ¹H NMR analysis at the end of each 1 h period (see Table 2).

Conversion of benzaldehyde and 1-(2,4-dichlorophenyl)pentan-1-one 3b into the oxiranes 4a and 4b, respectively

(a) Through authentic trimethylsulfonium methyl sulfate 6. 1-(2,4-Dichlorophenyl)pentan-1-one **3b** (4.70 g, 0.02 mol) and potassium hydroxide (1.9 g, 0.034 mol) were added to trimethylsulfonium methyl sulfate (3.76 g, 0.02 mol), dichloromethane (10 cm³), *tert*-butyl alcohol (1 cm³) and water (0.4 cm³); the mixture was stirred at room temperature for 12 h after which a further aliquot of KOH (0.85 g, 0.15 mol) was

added to it. The mixture was then heated under reflux for 3 h after which it was poured into water (20 cm³). The aqueous layer was separated and extracted with dichloromethane (2 × 50 cm³). The combined organic layer and extracts were dried (MgSO_4) and evaporated under reduced pressure to leave a yellow oil (5.1 g). This was analysed by gas chromatography (DB 17 stationary phase on fused silica, injection temp. 250 °C) in respect of molar responses of authentic 2-butyl-2-(2,4-dichlorophenyl)oxirane **4b** (t_{R} 2.2 min). The yield of epoxide was 83%.

A similar procedure was used to prepare the epoxide **4a** (79%) from benzaldehyde.

(b) Through trimethylsulfonium methyl sulfate formed from dimethyl sulfoxide and dimethyl sulfate. Dimethyl sulfate (2.52 g, 0.02 mol) and dimethyl sulfoxide (1.56 g, 0.02 mol) were heated at 100 °C for 24 h after which the mixture was cooled to room temperature. 1-(2,4-Dichlorophenyl)pentan-1-one **3b** (4.7 g, 0.02 mol), potassium hydroxide (2.75 g, 0.05 mol), dichloromethane (10 cm³), *tert*-butyl alcohol (1 cm³) and water (0.4 cm³) were added to the mixture which was then heated under reflux for 7 h; the oxirane **4b** was formed in 63% yield as estimated in part (a) above. The yield of epoxide was increased to 82% by conducting the experiment with a molar ratio of ketone:DMSO:Me₂SO₄:KOH of 1:2:2:2.5

A similar procedure was used to prepare the epoxide **4a** (52%) from benzaldehyde; the yield decreased to 44% by alteration of the stoichiometry as outlined above.

References

- 1 D. Martin and H. Hauthal, *Dimethyl Sulphoxide*, Van Nostrand, 1975, p 302.
- 2 (a) S. G. Smith and S. Winstein, *Tetrahedron*, 1958, **3**, 31; (b) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1957; (c) R. Kuhn and H. Trischmann, *Liebigs Ann. Chem.*, 1958, **611**, 117; (d) *Chem. Br.*, 1973, **9**, 523.
- 3 G. Natus and E. J. Goethals, *Bull. Soc. Chem. Belg.*, 1965, **74**, 450.
- 4 See e.g. (a) K. Torssell, *Acta Chem. Scand.*, 1967, **21**, 1; (b) M. Kobayashi, K. Kamiyama, H. Minato, Y. Oishi, Y. Takada and Y. Hattori, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 3703.
- 5 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.
- 6 J. Forrester, R. V. H. Jones, P. N. Preston and E. S. C. Simpson, *J. Chem. Soc., Perkin Trans 1*, 1993, 1937.
- 7 T. Kutsuma, I. Nagayama, T. Okazaki, T. Sakamoto and S. Akaboshi, *Heterocycles*, 1977, **8**, 397; (b) P. Mosset and R. Gré, *Synth. Commun.*, 1985, **15**, 749.
- 8 R. Zerbes, W. S. Linke, K.-H. Mohrmann and W. Reiser (to Bayer A.-G) G. P., DE 3, 315, 524 A1 (1984) (*Chem. Abstr.*, **102**, 78708).
- 9 J. B. Heather (to Stauffer Chemical Co.), USP 4,625, 065 (1986) (*Chem. Abstr.*, **106**, 155583).
- 10 I. Rusev and D. Chochkova, *Khim. Ind. (Sofia)*, 1986, **58**, 445.

Paper S/02510I

Received 19th April 1995

Accepted 2nd June 1995