Reaction of Phenols with t-Butyl Bromide–Dimethyl Sulphoxide. Methylthiomethylation *versus* Bromination

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t-Butyl bromide-activated dimethyl sulphoxide reacts with phenols to give either methylthiomethylation or bromination products. Several equilibria are shown to be simultaneously present in the system; however, by appropriate choice of several parameters (basicity, temperature, and reactant ratio) it is possible to drive the reaction selectively in one direction. A general discussion on the mechanism of these reactions is given.

Recently we have reported [1,2] a Pummerer-type reaction of acids and *N*-protected amino acids with dimethyl sulphoxide (Me_2SO) and t-butyl bromide (TBB) in the presence of a base. It was, therefore, of interest to ascertain whether other nucleophiles, produced *in situ* from acid substrates under basic conditions, react with the same reagent system. In this paper we report the results of studies on the reaction of phenols with the TBB–Me_2SO system under basic or neutral conditions.

Acid-catalysed reactions of phenols with dimethyl sulphoxide and dicyclohexylcarbodi-imide have already been extensively studied.[3,4] The principal products obtained were phenols substituted in one or both of the available *ortho*-positions by methylthiomethyl (MTM) groups, along with compounds containing the 1,3-benzoxathian ring system. Conversion into *o*-MTMphenols was also accomplished in the presence of pyridine–sulphur trioxide,[5] acetic anhydride,[6] and *N*-chlorosuccinimide [7] with dimethyl sulphoxide or halogenosulphonium halides.[7]

Results and Discussion

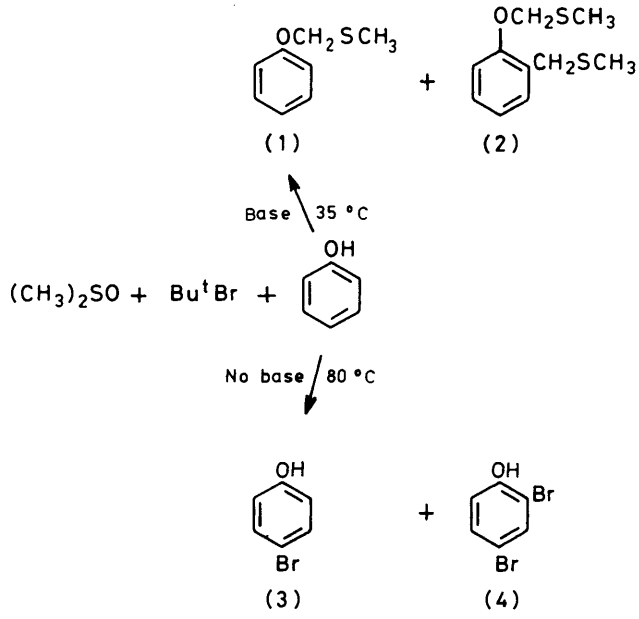
The reaction of phenol (10 mmol) with dimethyl sulphoxide (50 ml) and t-butyl bromide (100 mmol) in the presence of a base (K_2CO_3, 100 mmol) at 35 °C afforded methylthiomethyl phenyl ether (1) (84% yield) and methylthiomethyl 2-(methylthiomethyl)phenyl ether (2) (16% yield), along with traces of the mono- and di-*ortho*-substituted phenols.

In the absence of the base, the reaction took a completely different course and yielded 4-bromophenol (3) and 2,4-dibromophenol (4) (with relative yields of 75 and 23% at 80 °C) (see Scheme 1).

In a previous ^1H n.m.r. study [2] on the reaction mechanism of Me_2SO with TBB, we had already observed that the system could behave as a brominating reagent of isobutene formed *in situ* by elimination of HBr from t-butyl bromide.† We now discuss the discriminating factors and the mechanistic details of these reactions.

Methylthiomethylation.—We suggest that Me_2SO reacts with TBB to form an initial t-butoxysulphonium bromide intermediate (5) which, in the presence of phenol under basic conditions, undergoes nucleophilic substitution to yield the aryloxysulphonium bromide (6), already proposed as the key intermediate in the acid-catalysed reactions of phenols with activated Me_2SO.[3,4,7]

In the presence of a base, intermediate (6) can be converted into the sulphur-stabilised ylide (7) which, on principle, could simultaneously undergo a [1,2]-sigmatropic (Stevens [9]) rearrangement to give the methylthiomethyl phenyl ether (1), and a [2,3]-sigmatropic (Sommelet–Hauser [10]) rearrangement to yield 2-(methylthiomethyl)phenol (8), further converted into the corresponding MTMether (2) (Scheme 2).



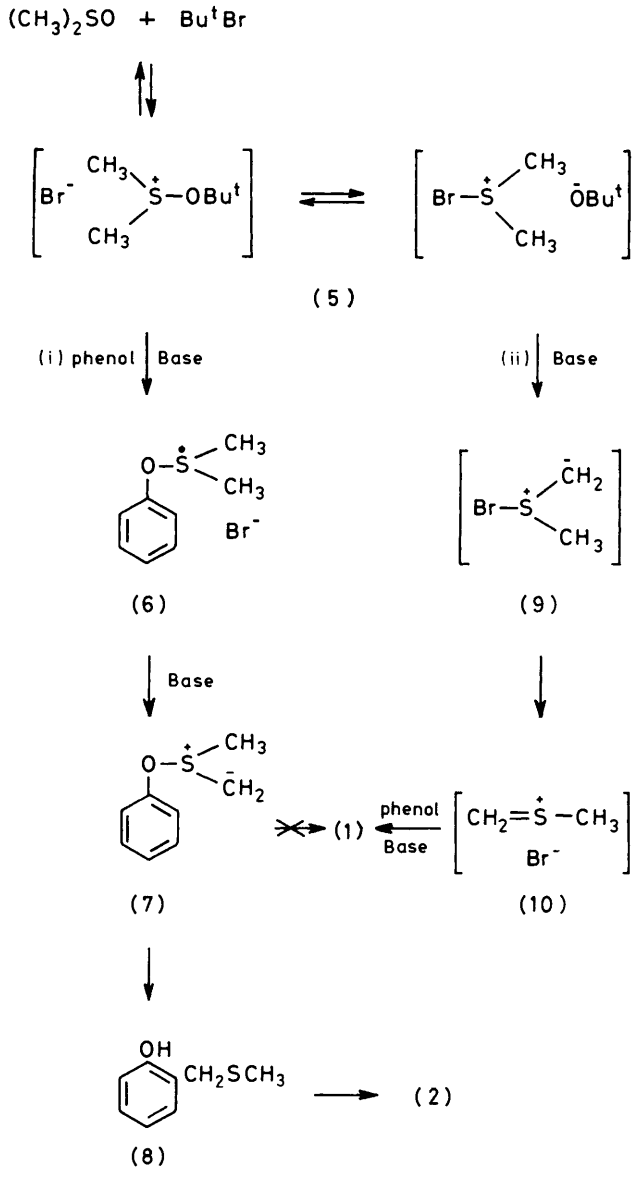
Scheme 1.

An alternative possibility for the formation of the ether would be a stepwise ionic or radical dissociation–recombination sequence, involving an intermediate ion- or radical-pair which could collapse to the *O*-alkylated product.

Other groups have reported CIDNP effects with other Stevens rearrangements involving sulphur ylides.[11] In our hands, an attempted study [12] of the reaction mechanism failed to detect any CIDNP effect.

The reaction turned out to be very sensitive to both the nature and the strength of the base. While, in the reaction with carboxylic acids,[2] weak bases such as $NaHCO_3$ and Et_3N were found to be most effective for the conversion into MTM esters (quantitative yields in the isolated products), with phenol, on the other hand, the reactivity increased with the base strength and in the order $Li_2CO_3 < Na_2CO_3 \leq K_2CO_3$ (Table 1). This could be accounted for by the weaker acidity of phenol and by the different degree of association of the ion pairs ($ArO^- M^+$) formed in the reaction mixture.[13] Quite surprisingly, when preformed metal phenoxides were allowed to react with the TBB–Me_2SO system, the methylthiomethylation reaction was strongly depressed in favour of the competitive

† The peculiar brominating properties of DMSO–TBB have been successively confirmed and synthetically applied to other bromine scavengers such as alkenes, alkynes, and indoles (ref. 8).



Scheme 2.

elimination of t-butyl bromide. It is not, therefore, phenoxide ion itself but a more complex species (metal- and/or proton-co-ordinated phenoxide) which is the effective nucleophile in the methylthiomethylation reaction.

Another aspect which deserves attention is the *O*- : *C*-alkylation ratio obtained with the different bases. As reported in Table 1, the *O*- : *C*-alkylation ratio increases with the base strength (compare the entries with $NaHCO_3$ and Na_2CO_3), and also with the dissociation of the eventual ion pairs (Li < Na < K). In an important study [14] of solvation and ion-pairing effects on the rearrangement of the dibenzyl sulphide carbanion, it was concluded that the more dissociated species leads to the Sommelet rearrangement while the less dissociated species (contact ion pair) leads only to the Stevens rearrangement. Therefore, our results cannot be interpreted as if both *O*- and *C*-alkylated products would derive from the same ylide intermediate (7), Moreover, had intermediate (7) been able to give rise to a dissociation–recombination mechanism,*

* In no case was a *para*-substituted phenol ever isolated.

Table 1. Reaction of phenol with the TBB–Me_2SO system in the presence of various bases [a]

Base	Conversion (%)	Products (%) *O*-MTM (1)	*C*-MTM (2)	*C*-MTM (8)
Et_3N	100	56	35 [b]	9
Pr^iNH	81	49	37 [b]	14
$NaHCO_3$	79	55	28 [b]	17
Li_2CO_3	30	57		43
Na_2CO_3	100	76	24 [c]	
K_2CO_3	100	84	16 [c]	

[a] TBB : Me_2SO : phenol : base = 10 : 70 : 1 : 10 mol : mol; at 35 °C for 24 h (an excess of DMSO was added to solubilize inorganic bases). [b] Includes traces of MTM 2,6-bis(MTM)phenyl ether. [c] Compound (2) only.

Table 2. Reaction of substituted phenols with the TBB–Me_2SO system in the presence of Et_3N [a]

Substrate	Conversion (%)	Products (%) *O*-MTM	*C*-MTM	*C*-MTM (12)
4-Nitrophenol	100	100 [b]		
2-Methylphenol	100	66	34 [b,c]	
2,6-Dimethylphenol	100	49		51 [d]
2,4,6-Trimethylphenol	100	48		52 [d]

[a] TBB : Me_2SO : substituted phenol : Et_3N 10 : 70 : 1 : 10 at 35 °C for 24 h. [b] Spectroscopic data agreed well with those reported in the literature.[7] [c] The figure includes 2-methyl-6-MTMphenol [4] (20% yield) and MTM 2-methyl-6-MTMphenyl ether (14% yield). [d] Spectroscopic data agreed well with those reported in the literature.[4]

the necessarily intimate ion pair $[ArO^- \ CH_2{=}\overset{+}{S}CH_3]$ should be insensitive towards other interactions with metal ions.

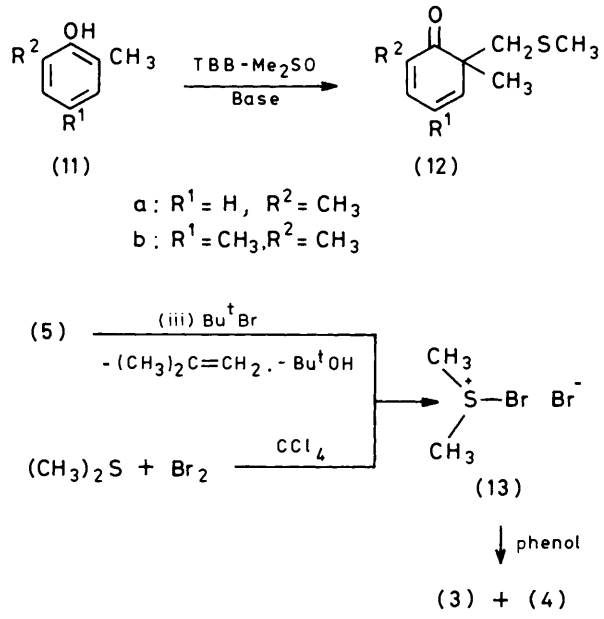
A more likely route to *O*-methylthiomethylation would involve hydrogen abstraction from the first intermediate formed, (5), to give the ylide (9), which then produces the methylmethylenesulphonium ion (10), able to react with the metal phenoxide species (Scheme 2). Ample precedent for a similar mechanistic speculation exists in the work by Vilsmaier and Sprügel,[15] which has lately been confirmed by Gassman.[7] In agreement with the latter author, the less nucleophilic 4-nitrophenol produced exclusively *O*-methylthiomethylation products, whereas the increasingly nucleophilic 2-methyl-, 2,6-dimethyl- (11a), and 2,4,6-trimethylphenol (11b) led to increased *C*-alkylation (see Table 2), allowing the isolation of the dienones (12).†

Direct involvement of the phenolic OH group in the *C*-methylmethylation pathway was further established by the inertness of anisole under the experimental conditions.

Bromination.—Whenever the base is not present, phenol is too weak a nucleophile to react with intermediate (5), which may, instead, give rise to bromodimethylsulphonium bromide (13), which may be the source of positive bromine.[2,8]

Intermediate (13), prepared independently [16] from dimethyl

† Compounds (12a and b) have also been isolated by Moffatt [4a] and Pfitzner [4b] under different conditions. Compound (12a) is converted into the 4-MTMphenol and (12b) into the 3-MTMphenol by treatment with acid or simply by t.l.c. on silica gel.



Scheme 3.

sulphide and bromine in CCl_4, when isolated and treated with phenol in Me_2SO at room temperature afforded the brominated products (3) and (4) (Scheme 3).

Nevertheless, at low temperature and after addition of a base, exclusive *ortho*-methylthiomethylation of phenol was obtained, thus confirming Gassman's results with halogenosulphonium halides.[7]

The yield and percentage conversion of phenol into either methylthiomethyl- or bromo-derivatives were dependent also on the Me_2SO : TBB ratio. An excess of Me_2SO (5 : 1) was required to achieve methylthiomethylation, whereas an excess of TBB (1 : 2) favoured bromination.

A final distinctive parameter varied in this study of the reaction conditions was the temperature: 35 °C was sufficient for methylthiomethylation, whereas heating at 80 °C was required for bromination, thus signifying that a pathway of higher activation energy is involved in the latter process.

Anisole was poorly brominated under our conditions. It is conceivable that the brominating species, the bromosulphonium bromide (13), is slowly released in the TBB–Me_2SO system and that isobutene, produced in the reaction itself (iii in Scheme 3), competes successfully with the less nucleophilic anisole for positive bromine (Br^+). In fact, if using previously prepared compound (13), the reaction is very fast and leads to 4-bromoanisole in quantitative yield.

Conclusions.—The TBB–Me_2SO system reacts with phenols along at least three different pathways: the first intermediate, the alkoxysulphonium bromide (5) may undergo: (i) nucleophilic attack by a phenoxide species to give an aryloxysulphonium bromide intermediate (6) (Scheme 2); (ii) removal of a proton to form a sulphur-stabilised ylide (9) (Scheme 2); or (iii) nucleophilic substitution by a bromide ion to give the bromosulphonium bromide (13) together with isobutene and t-butyl alcohol (Scheme 3). By accurate control of several parameters (basicity, temperature, reactant ratio) it is possible to drive the reaction selectively in one direction. The nature and the association state of the nucleophiles present in the reaction determine the final selection between substitution on phenol, paths (i) + (ii), or elimination of HBr from t-butyl bromide, reaction (iii), as well as *O*- (ii) *versus* *C*-alkylation (i).

By appropriate choice of the reaction conditions (K_2CO_3; 35 °C; Me_2SO : TBB 5 : 1), it is also possible to develop a method of synthetic utility for the protection of phenols as methylthiomethyl ethers.[17]

Experimental

M.p.s were determined on a Büchi apparatus and are uncorrected. U.v. spectra were measured with a Cary 14 spectrophotometer. I.r. spectra of solids (KBr) and liquids (film) were recorded on a Perkin-Elmer model 437 spectrophotometer. ^1H N.m.r. spectra were obtained on a Varian EM 360 or a XL 100 spectrometer with tetramethylsilane as internal standard. Mass spectra were obtained using a Varian MAT CH 5 spectrometer at 70 eV. T.l.c. plates, for both analytical and preparative work, used Merck Kieselgel PF_{254} as adsorbent; the appropriate solvent mixtures are given in the text. G.l.c. was performed on a Varian Aerograph 1400. Commercial grade Me_2SO and Bu^{t}Br were used without any purification or drying procedures.

General Procedure for Methylthiomethylation.—To a suspension of the appropriate phenol (10 mmol) and base (100 mmol) in Me_2SO (25 ml) was slowly added a solution of Bu^{t}Br (100 mmol) in Me_2SO (25 ml) during 2—3 h at 35 °C. The mixture was stirred for 24 h at 35—40 °C then acidified with HCl (pH 1—2) and extracted with Et_2O three times. The combined extracts were washed with water, dried over Na_2SO_4, and reduced to small volume. Products were separated on preparative silica gel plates with different mixtures (hexane or hexane–ethyl acetate) and characterised.

The previously known methylthiomethylated derivatives of the phenols were identical in all respects with those described in the literature.[3,4,17]

The following compounds have not previously been reported. *Methylthiomethyl 2-(methylthiomethyl)phenyl ether* (2), (Found: C, 56.0; H, 6.6; S, 29.85 .$C_{10}H_{14}OS_2$ requires C, 56.03; H, 6.58; S, 29.92%), *m/z* (%) 214 (16), 153 (19), 108 (96), 91 (16), and 61 (100); δ_H ($CDCl_3$) 2.08 (3 H, s, SCH_3), 2.30 (3 H, s, SCH_3), 3.75 (2 H, s, CH_2SAr), 5.23 (2 H, s, OCH_2S), and 6.80—7.40 (4 H, m, ArH); *methylthiomethyl 2-methylphenyl ether* (Found: C, 64.2; H, 7.2; S, 19.0. $C_9H_{12}OS$ requires C, 64.24; H, 7.19, S, 19.06%), *m/z* (%) 168 (16), 107 (5), 91 (21), and 61 (100); δ_H ($CDCl_3$) 2.20 (3 H, s, SCH_3), 2.23 (3 H, s, CH_3Ar), 5.07 (2 H, s, CH_2S), and 6.60—7.23 (3 H, m, ArH); *methylthiomethyl 2,6-dimethylphenyl ether* (Found: C, 65.85; H, 7.7; S, 17.5. $C_{10}H_{14}OS$ requires C, 65.89; H, 7.74; S, 17.59%), *m/z* (%) 182 (44), 135 (27), 122 (24), 91 (83), and 61 (100); δ_H ($CDCl_3$) 2.30 (total, 9 H, s, SCH_3 and 2 × CH_3), 4.90 (2 H, s, CH_2S), and 6.98 (3 H, s, ArH); *methylthiomethyl 2,4,6-trimethylphenyl ether* (Found: C, 67.25; H, 8.25; S, 16.3. $C_{11}H_{16}OS$ requires C, 67.30; H, 8.22; S, 16.34%), *m/z* (%) 196 (42), 149 (14), 136 (31), and 91 (100); δ_H ($CDCl_3$) 2.10—2.30 (total 12 H, m, SCH_3 and 3 × CH_3), 4.90 (2 H, s, CH_2S), and 6.80 (2 H, s, ArH).

General Procedure for Bromination.—A mixture of the phenol (10 mmol), Me_2SO (25 mmol), and Bu^{t}Br (50 mmol) was stirred at 80 °C. After 2 h the mixture was cooled to room temperature, acidified with aqueous HCl (pH 1—2), and extracted with Et_2O three times. The combined extracts were washed with water, dried over Na_2SO_4, and reduced to small volume. Products were isolated on preparative silica gel plates by development with hexane–ethyl acetate (9 : 1).

Reaction of Dimethyl Sulphide with Bromine and Phenol.—Bromine (33 mmol) was added dropwise during 40 min to a vigorously stirred, ice-cooled solution of dimethyl sulphide (33

mmol) in CCl_4 (30 ml). Yellowish crystals of bromodimethylsulphonium bromide were formed instantaneously. Two separate reactions were then performed on the sulphonium salt. (*a*) To a suspension of the sulphonium salt in CCl_4 was added a solution of phenol (30 mmol) in CCl_4: 4-bromophenol (95% yield) and 2,4-dibromophenol (5% yield) were immediately formed. (*b*) To the suspension of bromodimethylsulphonium bromide in CCl_4, cooled to −60 °C, were added in turn solid phenol (30 mmol) and Et_3N (33 mmol, dropwise) and the mixture, after being stirred for 1 h at −60 °C, was allowed to warm up to room temperature. It was then acidified with aqueous HCl (pH 1—2) and extracted with Et_2O three times. The combined extracts were washed with water, dried over Na_2SO_4, and reduced to small volume. 2-(Methylthiomethyl)-phenol was exclusively obtained (55% yield).

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