t-Butyl Bromide–Dimethyl Sulphoxide Reactions. Pummerer-like Reaction with Carboxylic Acids and *N*-Protected Amino-acids

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t-Butyl bromide-activated dimethyl sulphoxide reacted with carboxylic acids and differently *N*-protected amino-acids in the presence of a base ($NaHCO_3$ or Et_3N). High to quantitative yields of methylthiomethyl (MTM) esters were obtained in all cases without interference by other functional groups or racemization. The mechanism of the reaction is discussed on the basis of the products formed, of spectral data, and of other miscellaneous experiments.

THE chemistry of dimethyl sulphoxide (Me_2SO) has been studied for many years.[1] Much is known about its nucleophilic properties towards a number of electrophilic reagents, which bring about oxidations, Pummerer rearrangements, and other reactions. All the numerous Me_2SO activators are strong electron-accepting reagents such as acetic [2] and trifluoroacetic [3] anhydrides, phosphorus pentaoxide,[4] dicyclohexylcarbodi-imide/acid,[5] oxalyl chloride,[6] and others.

Quite unexpectedly, we have found that a ' masked electrophile ' such as t-butyl bromide (TBB) can act as a particularly effective Me_2SO-activator at room temperature, under weakly basic conditions, leading in reactions with carboxylic acids to a Pummerer-type reaction.[7] This is surprising, since it is generally accepted that alkyl bromides are inert to Me_2SO in the absence of metal-ion assisting agents even at high temperature.[8] It is also notable that this is the first case of a Pummerer-type reaction carried out under basic conditions. In the present paper we report the results obtained by reacting the TBB–Me_2SO system with a variety of carboxylic acids and *N*-protected amino-acids. The reaction mechanism is discussed on the basis of the products formed, of spectral data, and of other miscellaneous experiments.

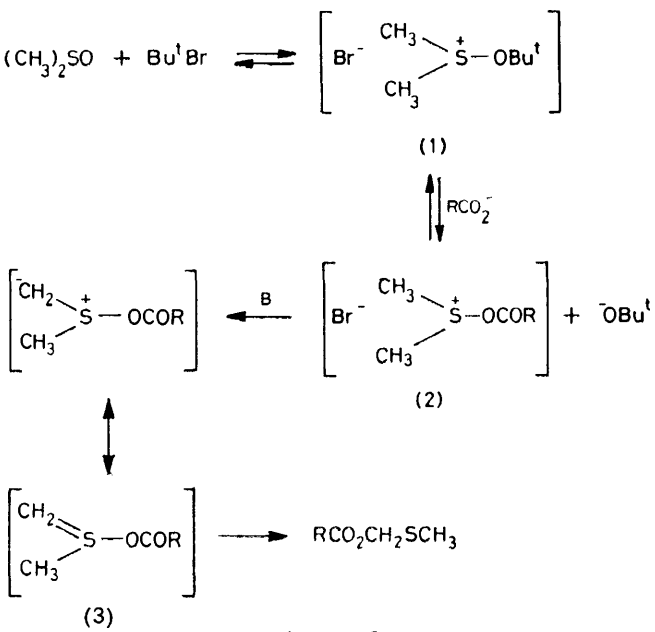
RESULTS AND DISCUSSION

The reaction conditions are very specific, so that slight changes in the ratio of the reactants increase the heterogeneity of the system and dramatically depress the reaction. In a typical run, TBB (10 mmol) in Me_2SO (5 ml) was added dropwise to a suspension of carboxylic acid or *N*-protected amino-acid (1 mmol) in Me_2SO (5 ml) in the presence (excess) of a weak base B (sodium hydrogencarbonate or triethylamine) at room temperature.

$$RCO_2H \xrightarrow[Me_2SO\text{–}TBB]{B} RCO_2CH_2SMe$$

The formation of MTM esters has also been demonstrated by Onodera,[4b] following reactions of carboxylic acids with Me_2SO activated by phosphorus pentaoxide, at 70 °C and by Lerch and Moffatt [5b] with Me_2SO activated by dicyclohexylcarbodi-imide under acid catalysis. In both cases they were considered as the products of a Pummerer-type rearrangement.[9] In view of the similarities of these reactions with our procedure, we propose the mechanism outlined in Scheme 1.

TBB–Me_2SO Reaction Products.—We suggest that the first intermediate along the reaction co-ordinate is the t-butoxysulphonium bromide (1) which may be a more

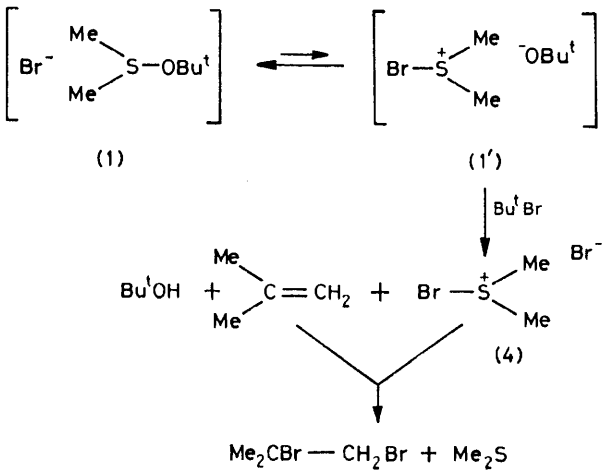


SCHEME 1

or less tight ion pair, and may or may not give rise to a t-butoxybromosulphurane.[10]

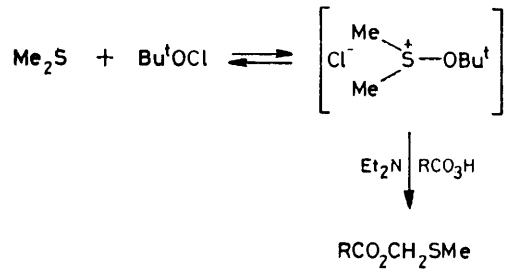
Intermediate (1) could not be detected by ^1H n.m.r. in a solution of Me_2SO and TBB at room temperature. Unlike solutions of BF_3, P_4O_{10}, SO_3 or concentrated sulphuric acid in Me_2SO, the only signals observed in solution of TBB were those attributable to the starting materials.

However, upon heating at 45 °C, the signals corresponding to the reactants slowly disappear and new signals due to t-butyl alcohol, dimethyl sulphide and 1,2-dibromo-2-methylpropane appear. These compounds can be derived from intermediate (1), according to the mechanism shown in Scheme 2. The results are consistent when using $[^2H_6]Me_2SO$. Signals corresponding to Me_2SO and to Me_2S are absent, and no isotopic effect is detected.



SCHEME 2

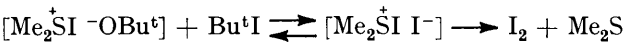
Intermediate (1) is the analogue of that proposed [10,11] for the reaction of sulphides with t-butyl hypochlorite, which was characterized as the corresponding hexachloroantimonate by ^{1}H n.m.r.[12] Indeed, from the reaction of dimethyl sulphide and t-butyl hypochlorite with benzoic acid in the presence of Et_3N, we obtained the corresponding MTM esters.



We conclude that: (*a*) Me_2SO reacts, though slowly, with TBB under mild conditions; (*b*) the initial reaction is an equilibrium which highly favours reactants and the small amount of intermediate (1) formed cannot be detected by ordinary n.m.r. monitoring. In the presence of nucleophiles (RCO_2^- in our case), the intermediate is drained off towards the formation of products.

However, we cannot exclude that the acyloxysulphonium intermediate (2) might arise from the bromosulphonium bromide (4) by nucleophilic displacement by RCO_2^-. The reaction is feasible, as demonstrated by the following experiment: bromosulphonium bromide (4), obtained from dimethyl sulphide and bromine in CCl_4,[13] by reaction with benzoic acid followed by addition of Et_3N, afforded methylthiomethyl benzoate.

The reactivity of the halide Me_3CX is strictly related to the ability of the halide X^- to act as leaving group. Thus, only with t-butyl bromide does the reaction take place; with the chloride it is too slow to be observed, and with the iodide the equilibrium is shifted towards the



formation of molecular iodine, which precipitates as crystals from the solution.

The presence of base is essential to the reaction, and it performs, in fact, two important tasks: the ionization of the carboxylic acid, and the removal of the proton from the methyl group of intermediate (2) to form the ylide (3). Therefore weak bases such as $NaHCO_3$ and Et_3N are suitable, whereas stronger bases such as Na_2CO_3, depress the reaction in favour of elimination of the t-alkyl halide.

Methylthiomethylation of Carboxylic Acids and N-Protected Amino-acids.—The method was successfully applied to a wide range of variously functionalized carboxylic acids, without interference by other functional groups. Unsaturated acids (both αβ and ω) give selective methylthiomethylation without bromination of the π-bond (see Table 1).

TABLE 1

Synthesis of methylthiomethyl esters of acids *

Acid	Yield (%) [a]	B.p. (°C/mmHg)
Acetic	95	50 (15) [b]
Benzoic	98	55 (0.1) [c]
3-Methylbutanoic	95	40 (0.1)
3-Methylbut-2-enoic	95	48 (0.1)
Adipic [d]	97	154—156 (0.8)
Cinnamic	95	oil [e]
Undec-10-enoic	90	oil [e]
(*R*,*S*)-Mandelic	80	oil [e]

[a] Yields are based on isolated products. [b] Lit.,[9b] 48.5 (12). [c] Lit.,[9b] 97.5 (0.5). [d] Bis-MTM ester. [e] Product decomposes on heating.

* Physical and spectroscopic data are deposited as SUP 23107.

TABLE 2

Synthesis of methylthiomethyl esters of *N*-protected amino-acids *

N-Protected amino-acid	Yield (%) [a]	M.p. (°C)	$[\alpha]_{589}^{25}$ (*c* 1, EtOH)
Z-L-Trp-OH [b]	94	127—128	−23.0 [c]
Z-L-Ser-OH [d]	88	64	−20.4
Z-L-Ala-OH [e]	98	oil	−60.6
Z-L-Phe-OH [f]	95	oil	−28.8 [c]
BOC-L-Phe-OH [g]	90	oil	−26.1
NPS-L-Phe-OH [h]	85	oil	−21.0
FOR-L-Phe-OH [i]	80	oil	−12.4
PHT-L-Phe-OH [j]	90	52	−169.4
TFA-L-Phe-OH [k]	80	63	−39.0

[a] Yields are based on isolated products. [b] Z = Benzyloxycarbonyl, trp = tryptophan. [c] EtOAc. [d] Ser = serine. [e] Ala = alanine. [f] Phe = phenylalanine. [g] BOC = t-butoxycarbonyl. [h] NPS = *o*-nitrophenylsulphenyl. [i] FOR = formyl. [j] PHT = phthalyl. [k] TFA = trifluoroacetyl.

* Physical and spectroscopic data are deposited as SUP 23107.

The method is seen also to be very convenient with *N*-protected amino-acids, whereas it fails with free amino-acids. Thus, we have prepared MTM esters of *N*-protected amino-acids (tryptophan, phenylalanine, serine, and alanine) in very good yields and without racemization, as verified by the selective removal of the MTM group by $HgCl_2$-assisted hydrolysis (see Table 2).[14] The selective removal of the *N*-protecting group is in progress. MTM esters have not as yet been proposed for the protection of the carboxy-groups of amino-acids, whereas the analogous β-methylthioethyl esters have been satisfactorily used in peptide synthesis.[15]

We conclude that the possibility of performing Pummerer-type reactions under basic conditions increases the importance of the reaction from a synthetic point of view. In fact, it is possible to promote formation of nucleophiles from several acid substrates (organic acids, phenols, enols, *etc.*) particularly reactive towards activated Me_2SO. This is possible because t-butyl bromide is sufficiently electrophilic to activate Me_2SO, but at the same time is unreactive towards other nucleophiles.

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. Optical rotations were measured on a Rudolph Research polarimeter III. T.l.c. plates were used for both analytical and preparative work using Merck Kieselgel PF_{254} and appropriate solvent mixtures. G.l.c. was performed on a Varian Aerograph 1400. Commercial grade Me_2SO and t-BuBr were used without any purification or drying procedure. Physical and spectroscopic data for the MTM esters of acids and *N*-protected amino-acids are deposited as Supplementary Publication No. SUP 23107 (4 pp.).*

Dimethyl Sulphoxide–t-Butyl Bromide Decomposition Products.—Dimethyl sulphoxide (2 mmol) and t-butyl bromide (4 mmol) were placed in an n.m.r. tube in the presence of $SiMe_4$ at room temperature. The spectrum shows two singlets at δ 2.55 and 1.80 (Me_2SO and Bu^tBr). After 4 days, very weak signals began to appear, which, upon heating at 45 °C, slowly increased, while those due to the reactants decreased. The decomposition process is complete within 4 days at 45 °C. The chemical shifts of the products were as follows: t-butyl alcohol (δ 1.22 and 1.30), dimethyl sulphide (δ 2.05), 1,2-dibromo-2-methylpropane (δ 1.82 and 3.85), bromohydrin (δ 1.33 and 3.36, traces), isobutene (δ 1.7 and 4.6, traces), and water (δ 4.00). They were assigned by comparison with authentic samples. Products were also identified by g.l.c./m.s. on a Carbowax–Bentone 5% column, isothermal at 60 °C (for 5 min) and temperature programmed up to 170 °C (20 °C min^{-1}).

Reaction of Dimethyl Sulphide with t-Butyl Hypochlorite and Benzoic Acid.—Dimethyl sulphide (10 mmol) in $CHCl_3$ (10 ml) was reacted with t-butyl hypochlorite (10 mmol) at −50 °C for 30 min. Benzoic acid (10 mmol) in $CHCl_3$ (5 ml) was added and allowed to react for 30 min at −50 °C, then Et_3N was added and the mixture was allowed to warm up slowly to room temperature. It was then evaporated to small bulk and separated by t.l.c. by eluting with hexane–AcOEt (8 : 2). The MTM benzoate ester was obtained in a 65% yield.

Reaction of Dimethyl Sulphide with Bromine and Benzoic Acid.—Bromine (1.8 ml, 33 mmol) was added dropwise during 40 min to a vigorously stirred, ice-cooled solution of dimethyl sulphide (2.43 ml, 33 mmol) in CCl_4 (30 ml). Yellowish crystals were formed instantaneously. To the reaction mixture, cooled to −25 °C (liquid nitrogen in CCl_4) solid benzoic acid (1.22 g, 10 mmol) was added. After stirring for 1 h at −25 °C, Et_3N (20 mmol) was added and the mixture was allowed to warm up to room temperature. It was then extracted with H_2O–AcOEt, and MTM benzoate was obtained in 80% yield.

General Procedure for the Preparation of MTM Esters of Carboxylic Acids and N-Protected Amino-acids.—To a suspension of carboxylic acid or *N*-protected amino-acid (1 mmol) and $NaHCO_3$ (10 mmol) in Me_2SO (5 ml) a solution of Bu^tBr (10 mmol) in Me_2SO (5 ml) was added slowly (2—3 h) at room temperature (25—30 °C). The mixture was stirred for 24 h and finally extracted with Et_2O (3×). The combined ethereal extracts were washed twice with H_2O, dried over $MgSO_4$, and reduced to small volume. Products were purified on a silica gel column eluting with hexane, and subsequently distilled or crystallized.

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* For details see Notice to Authors No. 7, *J. Chem. Soc., Perkin Trans. 1*, 1980, Index issue.

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