# New System for 'Activation' of Dimethyl Sulphoxide in Pummerer-like Reactions

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*Summary* t-Butyl bromide was found to be a particularly effective 'activator' of dimethyl sulphoxide in reactions with nucleophiles (carboxylic acids, benzyloxycarbonyl *N*-protected amino-acids, and phenols) in the presence of $NaHCO_3$ at room temperature.

IN reactions involving suitable electrophilic 'activators,' dimethyl sulphoxide undergoes the Pummerer rearrangement[1] or other well known reactions with a variety of nucleophiles (carboxylic acids,[2] phenols,[3] amines,[4] alcohols,[5] *etc.*). We have now discovered that t-butyl bromide acts as a particularly effective '$Me_2SO$ activator' in reactions

with nucleophiles under weakly basic conditions. 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 temperatures.[6] In a typical procedure $Bu^tBr$ (10 mmol) was added slowly to a suspension of a carboxylic acid (1 mmol) and $NaHCO_3$ (10 mmol) in $Me_2SO$ (5 ml) at room temperature. The mixture was stirred for 16 h, extracted with $Et_2O$, and the extracts were reduced to a small volume and distilled. The methylthiomethyl esters (**2**) were obtained in quantitative yields, presumably *via* the unstable alkoxysulphonium salt intermediate† (**1**), according to reaction (1). The reaction appears to be general for

$$Me_2SO + Bu^tBr \longrightarrow \underset{(\mathbf{1})}{[Me_2S^+OBu^tBr^-]} \xrightarrow[RCO_2H]{NaHCO_3} \underset{(\mathbf{2})}{RCO_2CH_2SMe} \quad (1)$$

a variety of carboxylic acids; the results are reported in the Table.

The extremely mild conditions allowed the reaction to be extended to Z-*N*-protected amino-acids (tryptophan and phenylalanine), the corresponding methylthiomethyl esters being obtained in very high yields without racemization, thus providing a substantial improvement over methods currently used for the protection of acids[7] and amino-acids[8] in peptide synthesis.

While investigating the mechanism of the reaction, we felt that extension to other nucleophiles should provide information on the effectiveness and the limitations of this hitherto unreported 'activator.' Thus, the reaction of phenol was studied under essentially identical conditions leading in good conversion (75%) into the following products;‡ $MeSCH_2OPh$ (49%), *o*-$MeSCH_2C_6H_4OH$ (31%), *o*-$MeSCH_2C_6H_4OCH_2SMe$ (11%), and *oo'*-$(MeSCH_2)_2C_6H_3OH$ (9%), identified by comparison of their spectral data with those reported.[3] Similarly, *o*-cresol (conversion 55%) gave the corresponding products‡ *o*-$MeC_6H_4OCH_2SMe$ (56%), *o*-$MeSCH_2(o'\text{-}Me)C_6H_3OH$ (40%), and *o*-$MeSCH_2(o'\text{-}Me)C_6H_3OCH_2SMe$ (4%).

TABLE. Synthesis of the methylthiomethyl esters (**2**).[a]

| Acid | % Yield of (**2**) | B.p. ($\theta$/°C) [$p$/mmHg] |
|---|---|---|
| Acetic | 98[c] | 50 [15] |
| Benzoic | 99[c] | 55 [0·1] |
| 3-Methylbutanoic | 96[c] | 40 [0·1] |
| 3-Methylbut-2-enoic | 96[c] | 48 [0·1] |
| Adipic | 98[c,e] | 154—156 [0·8] |
| Cinnamic | 96[c] | Oil |
| Z-*N*-Tryptophan[b] | 93[d] | Solid[f] |
| Z-*N*-Phenylalanine[b] | 90[d] | Oil[g] |

[a] Compounds were identified by their elemental analysis and spectral data. [b] Z = benzyloxycarbonyl. [c] Yields are based on g.l.c. analysis in the presence of an internal standard (benzophenone). [d] Yields are based on the isolated products (preparative t.l.c.). [e] Bis(methylthiomethyl) ester. [f] M.p. 127—128 °C; $[\alpha]_D^{25}$ −23·0° (*c* 1, EtOAc). [g] $[\alpha]_D^{25}$ −22·3° (*c* 1, EtOAc).

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† This hypothesis, still under study, is supported by chemical and spectroscopic evidence.

‡ Relative proportions (in parentheses) were determined by combined spectrometric and g.l.c. analyses, using t-butylphenol as internal standard.

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