Formation and Hydrolysis of Methylthiomethyl Esters

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Summary The synthesis of methylthiomethyl esters is reported; these can be hydrolysed under neutral or acidic conditions, and are useful as protecting groups for carboxylic acids.

IN relation to our current interest in dethioacetalisation,[1] we have studied the use of thiomethyl esters as protecting groups for carboxylic acids. We believed that, following recent work on dethioacetalisation *via* *S*-alkylation,[2] thiomethyl esters (**1**) should be cleaved readily on treatment with methyl iodide in aqueous acetone.

$R^1CO_2CH_2SR^2$ (**1**) $R^1CO_2CH_2S^+(Me)R^2\ I^-$ (**2**)

The thiomethyl esters were synthesised by Mills' procedure.[3] Thus, equimolar (per CO_2H) quantities of the carboxylic acid, Et_3N, and $ClCH_2{\cdot}S{\cdot}Me$ were heated in refluxing MeCN for 24 h. After removal of solvent, the residue was washed with dry benzene, the benzene solution was evaporated, and the desired ester was obtained by vacuum distillation.

TABLE. *Methylthiomethyl esters and their hydrolysis*

Acid	Ester (**1**; R^2 = Me) B.p. (Torr)	Yield (%)	Yield after hydrolysis (%) CF_3CO_2H	$MeI-H_2O$
Benzoic	106—108°(2)	84	98	91
Octanoic	84—88°(0·9)	78	81	96
Adipic	154—156°(0·8)	72	93	62

The stability of the methylthiomethyl esters towards aqueous alkali is comparable to that of ordinary alkyl esters, and they are stable to mild reducing agents such as $NaBH_4$ and Zn–MeOH. The parent carboxylic acid may be regenerated by either of the following non-basic hydrolytic methods. (A) The ester (1 mmol) is treated with CF_3CO_2H (1 ml) for 15 min at room temperature, diluted with water, and extracted with benzene or ether to provide the acid which is purified by recrystallisation or distillation. (B) The ester (2 mmol) is refluxed with MeI (1 ml) and water (1 ml) in acetone (15 ml) for 17 h. After evaporation the residue is worked-up as in method (A). Examples are in the Table.

While the first step of the hydrolysis undoubtedly consists of *S*-methylation, (**1**)→(**2**), the site of subsequent attack by water (acyl *vs.* alkyl) cannot be ascertained. The acid-catalysed reaction may be envisaged as *O*-protonation[4] followed by fragmentation.

The homologous methylthioethyl esters[5] are known compounds, and their hydrolysis involves either *S*-methylation[5] or oxidation to the sulphones[6] followed by, in each case, treatment with alkali (pH 10—11).

All new compounds gave satisfactory analytical data and spectra consistent with the assigned structures.

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