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ESTERIFICATION OF STERICALLY HINDERED CARBOXYLIC ACIDS USING DIMETHYL SULPHATE

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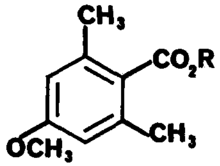
A recent report outlines the use of triethyloxonium fluoroborate for the esterification of sterically hindered carboxylic acids.[1] In connection with another problem we required ester (1b) which we planned to obtain by esterification of the corresponding sterically hindered 2,6-dimethylbenzoic acid (1a). The results of this proposal prompt us to report an alternative procedure for the esterification of hindered benzoic acids which proceeds in essentially quantitative yield.

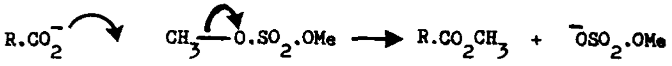


(1)

a R=H : b R=CH_3

Sterically hindered carboxylic acids like (1a) are well known to present difficulties during attempted esterification, and early procedures for overcoming these difficulties have been recently summarised.[1] Esterification of (1a)[2] *via* the acid chloride ($SOCl_2$/pyridine; then dry MeOH) gave (1b) in ~ 65% yield but this procedure (cf ref. 3) was tedious and involved a very sensitive acid chloride intermediate. Esterification by pyrolysis of the tetramethylammonium salt of (1a) was also examined, but this procedure gave (1b) in only ~ 55% yield.

Dimethyl sulphate (DMS) is a well known methylating reagent which is frequently chosen for O-methylation of phenols and alcohols,[4] but it is seldom considered for esterifications of carboxylic acids. Although this method of esterification is known,[5] it is a much neglected synthetic method. This is surprising because esterification using DMS would appear to be one of the most efficient methods of synthesising esters, and of course, is particularly useful where an acidic medium is to be avoided. In addition, since the reaction is envisaged as a hydrolysis of DMS by the carboxylate anion:-



$$R.CO_2^- \quad CH_3{-}O.SO_2.OMe \longrightarrow R.CO_2CH_3 + {}^-OSO_2.OMe$$

the method should not be subject to serious steric limitations with hindered benzoic acids because the reaction centre is two atoms removed from the ring, and it should therefore be applicable to esterification of (1a).[6] Indeed this was found to be the case, and the overall efficiency and simplicity of this esterification procedure prompts this report.

Esterification using DMS is subject to the side reactions involving hydrolysis of the DMS by the basic medium and hydrolysis of the ester once it is formed. We investigated several base - solvent mixtures to avoid these side reactions and optimise yields in the case of conversion (1a)→(1b) and a summary of these results is included:- (% base in solvent, yield): 10% NaOH in H_2O-MeOH (1:5); 65%: 20% KOH in H_2O; 70%: 5% NaOMe in DMF; 54%: 20% Na_2CO_3 in H_2O; 60%. By employing a method whereby 1.1 mole of concentrated ($\sim$25%) aqueous NaOH was added at room temperature to a well stirred mixture of (1a) (1 mole) and DMS (1.1 mole) in dioxan solution, followed by a terminal reflux for 0.5 hr., we consistently obtained yields of $>$ 95% for the conversion (1a)→(1b). In other experiments where a dry acetone solution of (1a) and DMS was boiled under reflux for 3 hr., in the presence of anhydrous K_2CO_3 (10% excess)[7] once again high ($>$95%) yields of pure (1b), m.p. 56° (Lit.,[3] m.p. 56.5°), ν_{max}(Nujol) 1730 cm^{-1}. τ($CDCl_3$) 3.43 (2H), 6.16 (OMe), 6.30 (OMe), 7.71 (2x:CMe), could be obtained. These two procedures for esterification of (1a) were found to be of general application, and were used to esterify other carboxylic acids, including the hindered molecules mesitoic acid and triphenylacetic acid, in equally high yields. In the light of these observations, and the special application to hindered molecules, the use of DMS as an esterification reagent would appear to warrant more general consideration in the future than it has enjoyed in the past.

References

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6. A combination of DMS and dicyclohexylethylamine has been employed by F.H. Stodola, *J. Org. Chem.*, 29, 2490 (1964) for the esterification of 2,3,5,6-tetramethylbenzoic acid on milligram scale but this experiment did not reflect the synthetic potentiality of this method of esterification of hindered carboxylic acids.
7. Anhydrous K_2CO_3 has also been recommended for O-methylation of phenols by DMS which are sensitive to strong bases (see ref. 4).