Preparation of a Water-soluble Acylating Agent: Benzoylation of Acids, Amines, and Phenols with 2-Benzoylthio-1-methylpyridinium Chloride in Aqueous Phase

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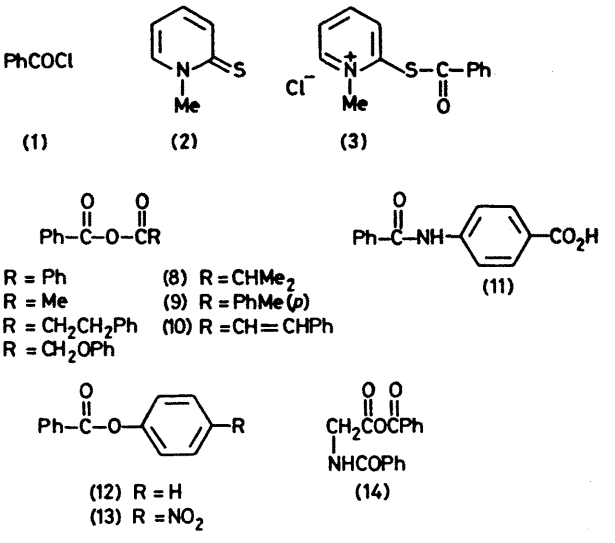
Summary 2-Benzoylthio-1-methylpyridinium chloride, prepared from benzoyl chloride and 1-methyl-2(1*H*)-pyridothione, is found to act as an acylating agent in aqueous phase.

ESTERS of thiocarboxylic acids are generally much more reactive than the corresponding carboxylic acid esters and frequently serve as acylating agents in biological reactions, *e.g.*, acetyl-CoA.[1] Furthermore, their hydrophilic or hydrophobic nature often plays an important role, not only in biochemical reactions, but also in synthetic methods involving, *e.g.* phase transfer catalysis.[2] We therefore attempted to synthesize and characterize a reactive, water-soluble thioester. We now report that a 2-benzoylthio-1-methylpyridinium salt acts as a water-soluble acylating agent; the pyridinium group should not only activate the thioester but also make the compounds water-soluble.

Treatment of 1-methyl-2(1*H*)-pyridothione (**2**) with benzoyl chloride (**1**) in refluxing acetonitrile for 2 h afforded 2-benzoylthio-1-methylpyridinium chloride (**3**) as a highly hygroscopic precipitate. Its n.m.r. spectrum in $CDCl_3$ showed that it exists in equilibrium with the starting materials (**1**) and (**2**), in a ratio of *ca.* 1:4. Compound (**3**), however, was stable in D_2O, at least for 1 h, strongly suggesting that it might act as a benzoylating agent in an aqueous layer. In fact, gradual addition of 1N NaOH to an aqueous solution containing a crude precipitate of (**3**) gave benzoic anhydride in 37% yield after silica gel column chromatography. This reaction presumably involves initial hydrolysis of (**3**) followed by nucleophilic attack of the benzoic acid thus formed on (**3**).



When (**1**) and (**2**) were mixed in chloroform–water, the salt (**3**) formed was selectively extracted into the aqueous layer, as shown by n.m.r. spectroscopy. This led to a more convenient 'one-pot' procedure; without isolation of (**3**), direct addition of NaOH to a chloroform–water solution of (**1**) and (**2**) afforded benzoic anhydride in 76% yield. Under the same conditions but in the absence of (**2**), the hydrolysis product, benzoic acid, was the major product together with small amounts of benzoic anhydride and the

starting material (**1**). In the procedure using compound (**2**) 0·3 equiv. of (**2**) could be used with only a slight decrease in the yield of benzoic anhydride; however, a further decrease in the amount of (**2**) caused an increase in the yield of benzoic acid.

Unsymmetric acid anhydrides were also prepared by this procedure. Sodium acetate was added to a chloroform–water solution of (**1**) and (**2**) to give acetic benzoic anhydride (**5**) in 88% yield as estimated from n.m.r. spectroscopy. Formation of acetanilide (59%) by addition of aniline to the crude product proved that (**5**) had been generated. Similar reactions of (**3**) with 3-phenylpropanoic acid, phenoxyacetic acid, isobutyric acid, *p*-toluic acid, and cinnamic acid in the presence of an equimolar amount of sodium hydrogen carbonate or sodium hydroxide afforded the corresponding mixed acid anhydride (**6**)—(**10**) in 82, 79, 61, 91, and 66% yields, respectively, as estimated from n.m.r. spectroscopy. Addition of aniline to the crude products (**6**)—(**9**) gave the corresponding anilides in 62, 63, 21, and 23%† yields, respectively.

When (**3**) was similarly treated with trifluoroacetic acid, only the hydrolysis product was detected. This is reasonable because benzoic trifluoroacetic anhydride was readily hydrolysed by stirring in benzene–water solution.

Benzoylation of *p*-aminobenzoic acid, phenol, and *p*-nitrophenol with (**3**) occurred smoothly to give the corresponding benzoylated products (**11**)—(**13**) in 75, 83, and 81% yields, respectively. Similar treatment of glycine gave the *NO*-dibenzoylated product (**14**), which was converted into *N*-benzoylglycine during column chromatography or recrystallization.

Although attempts to prepare a pyridinium salt from (**2**) and acetyl chloride have failed so far, we expect that various kinds of salts can be prepared by changing the counter-ion and/or 1-substituent.

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† Treatment of the crude products (**5**), (**8**), and (**9**), with aniline gave benzanilide in 6, 26, and 55% yields, respectively.

[1] *E.g.*, I. S. Kleiner and J. M. Orten, 'Biochemistry,' 7th edn., C. V. Mosby, Saint Louis, 1966, p. 385.
[2] *E.g.*, E. V. Dehmlow, *Angew. Chem. Internat. Edn.*, 1977, **16**, 493.