2-Chloro-*N*-methylbenzothiazolium Trifluoromethanesulphonate: an Efficient Condensing Agent for the Preparation of Thiol Esters and Amides

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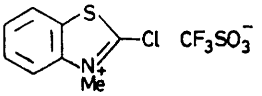
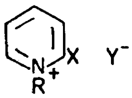
Summary 2-Chloro-*N*-methylbenzothiazolium trifluoromethanesulphonate is readily prepared and handled, and effects the formation of thiol esters and amides in excellent yields under mild non-acidic conditions.

IN connection with total syntheses of naturally occurring macrocyclic lactones[1] and lactams,[2] it was desirable to find improved methods whereby various functional groups could be protected and also macrocyclic rings constructed. The title compound (I) serves these purposes efficiently and we have used it for some time[3] to prepare thiol esters,[4] thus indirectly *O*-esters,[5] and amides[6] as well as lactones and lactams. The recent appearance of reports[7] concerning the use of a pyridinium salt (II) for similar purposes has prompted us to summarize our results at this stage.



(I)



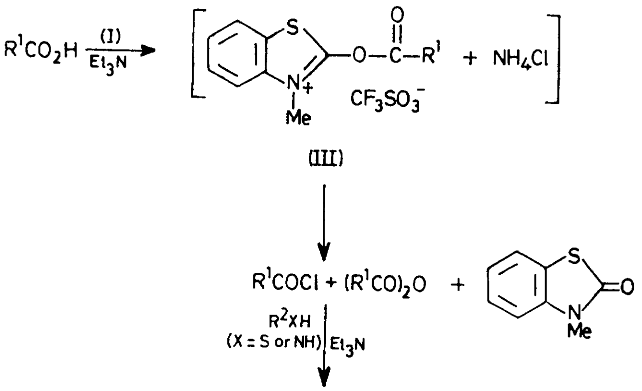
(II)

TABLE. Isolated yields (%) of R^{1}COXR^2 prepared from R^{1}CO$_2$H and R^{2}XH with reagent (I).

R^{1}CO$_2$H	R^{2}XH			
	n-C$_6$H$_{13}$-SH	PhSH	PhCH-(NH$_2$)Me	PhNH$_2$
C$_6$H$_{11}$CO$_2$H	85	91	90[a]	87
PhCO$_2$H	75	80	82[b]	62
n-C$_7$H$_{15}$CO$_2$H	92	90	93	82

[a] Heating to reflux was not required. [b] At room temperature for 1 h.

A single general procedure applies to the preparation of both thiol esters and amides. Thus, a mixture of a carboxylic acid (1 equiv.) and triethylamine (1 equiv.) is added to a 0·1 M acetonitrile solution of (I) (1 equiv.) at 0 °C with stirring. After 10 min a mixture of a thiol or an amine (1 equiv.) and triethylamine (1 equiv.) is added all at once. The solution is maintained at room temperature for 30 min followed by heating at reflux. Within 30 min the reaction is normally complete (see Table) and the product is isolated in the usual manner. The Table illustrates a few typical examples to demonstrate the general applicability of this method.



SCHEME

Preliminary experiments (i.r. and g.l.c.) have shown that (I) reacts exothermally with the carboxylic acid in the presence of triethylamine to form *N*-methylbenzothiazolidone and the acid chloride (Scheme), a part of which is converted into the corresponding acid anhydride (10—30%).† As is well known, the reaction of acid anhydrides with R^{2}XH

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† It is possible that the acid anhydride has formed from the intermediate (III).

proceeds more slowly than that of acid chlorides, therefore heating is recommended for completion of the reaction (*vide supra*). The carboxylic acid produced in this reaction appears to be recycled, at least in part, to raise the yield of the overall reaction. *O*-Esters have also been prepared in this way but, because of the lower nucleophilicity of the hydroxy group compared with that of thiols and amines, the second step (in particular with the acid anhydride) requires prolonged reaction time in order to obtain good yields (*e.g.*, when both R^1 and R^2 are secondary). The reaction course delineated above clearly shows that the oxygen affinity of the immonium group is in a sense similar to that of the phosphonium salt,[8] and indicates that this method could be improved further.

Reagent (I) is prepared from commercially available 2-chlorobenzothiazole and methyl trifluoromethanesulphonate and is a non-hygroscopic, crystalline compound, m.p. 130 °C. which requires no special precautions in handling.

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[2] V. Prelog and W. Oppolzer, *Helv. Chim. Acta*, 1973, **56**, 2279; K. L. Rinehart, Jr., *Accounts Chem. Res.*, 1972, **5**, 57.

[3] First discussed at the University of Chicago, 13th October, 1975.

[4] *Cf.* S. Masamune, S. Kamata, J. Diakur, Y. Sugihara, and G. S. Bates, *Canad. J. Chem.*, 1975, **53**, 3693.

[5] S. Masamune, S. Kamata, and W. Schilling, *J. Amer. Chem. Soc.*, 1975, **97**, 3515.

[6] See, for instance, 'Amino-acids, Peptides, and Proteins,' Specialist Periodical Reports, The Chemical Society, Vol. 1, 1969—Vol. 6, 1975.

[7] T. Mukaiyama, *Angew. Chem. Internat. Edn.*, 1976, **15**, 94. The properties of (II) and related compounds have been studied extensively by Balli and his coworkers: H. Balli and F. Kersting, *Annalen*, 1961, **647**, 1; H. Balli and D. Schelz, *Helv. Chim. Acta*, 1970, **53**, 1903.

[8] For the utilization of this principle in similar reactions, see J. G. Calzada and J. Hooz, *Org. Synth.*, 1974, **54**, 63, and references quoted therein.