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CYANURIC CHLORIDE : A USEFUL REAGENT FOR CONVERTING CARBOXYLIC ACIDS INTO CHLORIDES, ESTERS, AMIDES AND PEPTIDES[1]

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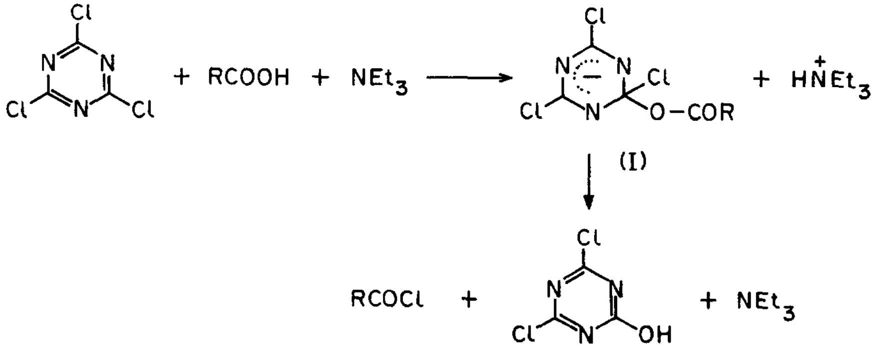
Recent examples of the sustained interest in reagents for the conversion of carboxylic acids to chlorides, esters, amides and peptides are: (a) 2,4,6-trinitrofluorobenzene for the preparation of amides and esters;[2] (b) isocyanides for peptide synthesis;[3] (c) oxalyl chloride and a catalytic amount of DMF for the conversion of carboxylic acids to chlorides via the t-butyldimethylsilyl esters;[4] and (d) esterification of carboxylic acids in the presence of DCC and a catalytic amount of a 4-dialkylaminopyridine[5]. Another useful reagent for these purposes is cyanuric chloride (CC), readily available as an intermediate for the manufacture of reactive dyes, fluorescent brightening agents and agricultural pesticides.

Senier recorded in 1886 the preparation of acetyl and benzoyl chlorides by heating the sodium salts with cyanuric chloride at 100° for 8 hours[6]. Refluxing CC with a large excess of glacial acetic acid has been suggested as a method for the preparation of cyanuric acid, acetyl chloride being simultaneously formed[7]. In the method now described the reaction is carried out at room temperature and CC separates as an insoluble product; the solution containing the acid chloride and any unconverted acid can be used directly for further reactions.



When CC in acetone is treated with 1-2 mols of a carboxylic acid and

1-2 mols of triethylamine (TEA), the acid chloride is rapidly formed, presumably via the σ adduct (I) resulting from a nucleophilic attack of $RCOO^-$ on CC. CC is converted into insoluble dichlorohydroxy- or chlorodihydroxy-s-triazine,[8] which have also been characterized as the corresponding dianilino or monoanilino derivatives.[9]

The general procedure is to add TEA (0.02 mole) to a solution of the carboxylic acid (0.02 mole; 0.01 mole of a dicarboxylic acid) and CC (0.01 mole) in acetone (20 ml or minimum volume required for a clear solution) at 20-30°. After stirring for 3 hours when no CC remains in solution, acetone is removed under reduced pressure and the acid chloride taken up in carbon tetrachloride. Alternatively, when the desired product is an ester or amide, the alcohol, phenol or amine (0.02 mole) is added to the reaction mixture, which is then stirred for 2 hours. The triazine derivative is filtered off and the acetone solution worked up as usual.

Three dipeptides were prepared from (1) Z-glycine, (2) Z-L-valine and (3) Boc-L-valine. After treatment with CC and TEA, glycine ethyl ester hydrochloride is added as a suspension in acetone (10 ml) and TEA (0.04 mole) The reaction mixture is added to ice-water and extracted with chloroform. The dipeptide, recovered from the chloroform solution after the removal of unconverted acid and amine, is then crystallized.[14,15,16] The three peptides and Z-glycine trichlorophenyl ester were characterized by their NMR and mass spectra in addition to their mps.

The yields recorded in the Table are of the isolated products after purification by acid and alkaline washing, when they were chromatographically homogeneous and had mps about 5° lower than the literature values, but before crystallization; the recovery of unreacted acid was not taken into account. A simple routine procedure using the regenerated TEA was followed for the preparation of esters and amides, and no attempt was made to optimise conditions for maximum yields.

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TABLE
Acids converted to chlorides, amides or esters

Acid	Amine, phenol or alcohol	Product[10]	Yield %
Acetic	Aniline	Anilide	84
	p-Aminophenol	p-Hydroxyacetanilide +	55 +
		p-acetoxyacetanilide	35
Trifluoracetic	Aniline	Anilide[11]	64
	L-Valine	N-trifluoracetyl-L-valine[12]	50
Oxalic	Aniline	Anilide	52
Malonic		Chloride or anilide	0
Succinic	Aniline	Anilide	55
Z-glycine	2,4,5-Trichlorophenol	Trichlorophenyl ester[13]	41
Z-glycine	Gly-OEt	Z-Gly-Gly-OEt[14]	40
Z-L-valine	Gly-OEt	Z-L-Val-Gly-OEt[15]	45
Boc-L-valine	Gly-OEt	Boc-L-Val-Gly-OEt[16]	38
Phenylacetic	Aniline	Anilide	86
Benzoic		Chloride	81
	Aniline	Anilide	87
	o-Phenylenediamine	N,N-Dibenzoyl-o-phenylenediamine	68
	o-Aminophenol	N,O-Dibenzoyl-o-aminophenol	73
	Methanol	Methyl benzoate	82
p-Nitrobenzoic		Chloride	58
Cinnamic	Aniline	Anilide	93
Aspirin	Methanol	Methyl ester	45
3-Hydroxy-2-naphthoic	Aniline	Anilide[17]	61

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11 E.J. Bourne *et al.*, *J. Chem. Soc.*, 4014 (1952), prepared this compound by treatment of aniline with trifluoroacetic anhydride.

12 C.A. Panetta, *Org. Synth*. *56*, 122 (1977), has described the "trifluoroacetylation of amines and amino acids under neutral, mild conditions: *N*-trifluoroacetanilide and *N*-trifluoroacetyl-L-tyrosine" by the action of 1,1,1-trichloro-3,3,3-trifluoroacetone in DMSO at 25-35°. Panetta has also discussed the disadvantages of the usual procedure using trifluoroacetic anhydride. In the present work a minor modification in our general procedure was to add L-valine in DMSO (10 ml); the product was worked up as described by Panetta.

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17 Separation through carbon tetrachloride before adding aniline showed that the reaction mixture contained the acid, chloride and depside; cf. E.N. Abrahart, *J. Chem. Soc.*, 424 (1938); R.V. Bhat, R.B. Forster and K. Venkataraman, *J. Soc. Dyers Col.*, *56*, 166 (1940). The anilide, which is sparingly soluble in acetone, was taken up in 2N sodium hydroxide.

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