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Synthesis of acyl azides from carboxylic acids using cyanuric chloride

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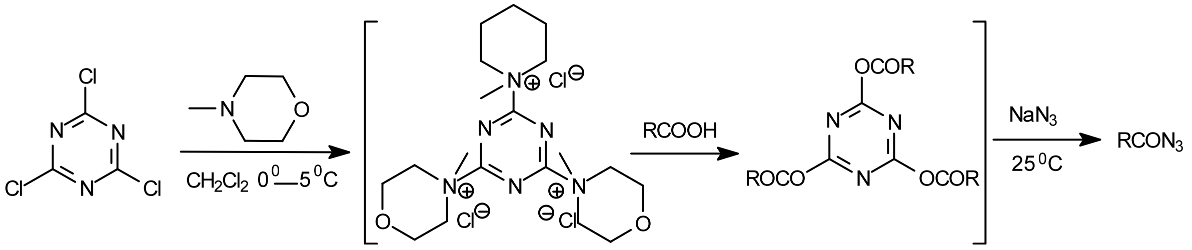
Abstract—A mild, efficient and general method for the preparation of acyl azides from carboxylic acids and sodium azide using cyanuric chloride is described. © 2002 Published by Elsevier Science Ltd.

Acyl azides are valuable synthetic intermediates in organic chemistry.[1] They are useful for the preparation of amides and heterocyclic compounds. They undergo facile thermal rearrangement to isocyanates from which amines, urethanes, thiourethanes, ketenimines, carbodiimides and ureas can be conveniently prepared. Acyl azides are usually prepared from acid derivatives such as acid halides and acyl hydrazides.[1,2] Preparations of acyl azides include the reactions of acyl chlorides with azide ions in a mixture of water and water-miscible organic solvents. If the reaction is performed in organic solvents without the addition of water, the reaction has to be carried out at a higher temperature which leads to Curtius rearrangement of the acyl azide. The reaction has also been carried out under milder conditions by using 'activated' sodium azide,[3] lithium azide,[4] the readily soluble but hazardous hydrazoic acid and by means of special reagents such as tetramethylguanidinium or tetraalkylammonium azides.[5] The transformation of aroyl chlorides into aroyl azides has also been performed at 0°C in dichloromethane in the presence of a catalytic amount of zinc iodide.[6] However, acid chlorides or other highly reactive carboxylic acid derivatives are not always at hand and there is continued interest in the development of methods for the direct transformation of carboxylic acids or other readily available starting materials into acyl azides.

The combinations of chromic anhydride–trimethylsilyl azide[7] and triazidochlorosilane-activated manganese dioxide[8] have been reported for the preparation of acyl azides from aldehydes. There are a few reports on the direct conversion of carboxylic acids to acyl azides by using acid activators such as ethyl chloroformate,[9] diphenylphosphoryl azide (DDPA),[10] phenyldichlorophosphate,[11] $SOCl_2$–DMF[12] and NCS–Ph_3P.[13] More recently, acyl azides have been prepared from carboxylic acids under mild conditions using triphosgene [bis(trichloromethyl)carbonate] as an acid activator.[14]

Over the last few years there has been a considerable growth in interest in the use of cyanuric chloride or its 4,6-dimethoxy derivative, 2-chloro-4,6-dimethoxy-1,3,5-triazine in organic synthesis.[15] Carboxylic acids can be



Scheme 1.

Keywords: carboxylic acid; acyl azide; cyanuric chloride; sodium azide.

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Table 1. Synthesis of acyl azides from carboxylic acids using cyanuric chloride

Entry	Carboxylic acid	Acyl azide	Yield[a,b] (%)	Mp (°C) [lit.][14]
1	Benzoic acid	Benzoyl azide	86	Oil
2	2-Hydroxybenzoic acid	2-Hydroxybenzoyl azide	83	Oil
3	4-Hydroxybenzoic acid	4-Hydroxybenzoyl azide	94	Oil
4	2-Chlorobenzoic acid	2-Chlorobenzoyl azide	91	61 [62–64]
5	4-Chlorobenzoic acid	4-Chlorobenzoyl azide	93	38 [39–42]
6	4-Nitrobenzoic acid	4-Nitrobenzoyl azide	84	71 [68–69]
7	3,5-Dinitrobenzoic acid	3,5-Dinitrobenzoyl azide	71	69 [69–70]
8	Nicotinic acid	Nicotinoyl azide	73	Oil
9	2,4-Dichlorophenoxyacetic acid	2,4-Dichlorophenoxyacetyl azide	92	Oil
10	Phenylacetic acid	Phenylacetyl azide	80	Oil
11	β-Naphthylacetic acid	β-Naphthylacetyl azide	81	78
12	Cinnamic acid	Cinnamoyl azide	84	80 [82–84]
13	Hexanoic acid	Hexanoyl azide	94	Oil
14	Octanoic acid	Octanoyl azide	91	Oil
15	Nonanoic acid	Nonanoyl azide	93	Oil
16	Decanoic acid	Decanoyl azide	94	Oil

[a] Yields of pure isolated products.

[b] Products were characterized by physical constants, IR, ^{1}H NMR, MS spectroscopic data and elemental analyses.

activated with cyanuric chloride and subsequently reduced to the corresponding alcohols with $NaBH_4$ in water.[16] We now report the use of cyanuric chloride for the direct conversion of carboxylic acids to acyl azides (Scheme 1).

Various aryl, heteroaryl, alkylaryl and alkyl carboxylic acids on reaction with cyanuric chloride in the presence of sodium azide and *N*-methylmorpholine undergo smooth conversion to the corresponding acyl azides in excellent yields (Table 1). It is important to note that cyanuric chloride is a safe and inexpensive reagent in comparison to the recently reported use of hazardous and expensive triphosgene.[14]

In conclusion, this method was found to be a very mild, efficient and general procedure for the conversion of carboxylic acids to the corresponding acyl azides without Curtius rearrangement leading to an isocyanate.

General procedure for the synthesis of acyl azides: To a solution of cyanuric chloride (5 mmol) in dichloromethane (30 ml), *N*-methylmorpholine (15 mmol) was added at 0°C–5°C with continuous stirring. A white suspension was formed to which a solution of the carboxylic acid (15 mmol) in dichloromethane (10 ml) was added and the stirring was continued at the same temperature for 3 h. The mixture was filtered through Celite and to this filtrate, NaN_3 (15 mmol) added and the stirring was continued for 3 h at room temperature. After completion of the reaction (TLC), the mixture was washed with a saturated solution of $NaHCO_3$ (3×10 ml) and then with water (3×10 ml). The organic layer was dried with anhydrous Na_2SO_4, passed through short a silica-gel column, and the solvent removed under reduced pressure to give the pure acyl azide.

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