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Recent applications of 2,4,6-trichloro-1,3,5-triazine and its derivatives in organic synthesis

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1. Introduction

1,3,5-Triazine derivatives have been known for a long period of time. They have found widespread applications in the pharmaceutical, textile, plastic, and rubber industries, and are used as pesticides, dyestuffs, optical bleaches, explosives, and surface active agents. The chemistry of this group of compounds has been studied intensively and has been the subject of many reviews.[1–6]

Development of valuable methods for the preparation of many substances is still a challenge. The main issues in modern synthetic organic chemistry are selectivity, mildness, improvement of efficiency, and the avoidance of toxic reagents and by-products. From this point of view, considerable attention has been devoted to the development of new 1,3,5-triazine derivatives as reagents in organic synthesis.

Because common, nonsystematic nomenclature is prevalent in the chemical literature of triazine, it is important to briefly review the systematic and common names of some important derivatives, which are shown in Figure 1.

All of the *s*-triazine derivatives that have wide practical applications are 2,4,6-mono, di- or tri-substituted, symmetrical and nonsymmetrical compounds bearing different substituents. The most important reagent for obtaining these compounds is cyanuric chloride (CC), because of the

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Abbreviations: CA, cyanuric acid; ICA, isocyanuric acid; CC, cyanuric chloride; TCICA, trichloroisocyanuric acid; M, melamine; BNCT, boron neutron capture therapy; TEMPO, 2,2,6,6-tetramethyl piperidine-1-oxyl; Z, benzyloxycarbonyl; Boc, *tert*-butoxycarbonyl; Fmoc, 9-fluorenylmethoxycarbonyl; NMM, 4-methylmorpholine; DMF, dimethylformamid; MW, microwave irradiation; DMSO, dimethylsulfoxide; PEG, polyethylene glycol; CDMT, 2-chloro-4,6-dimethoxy-1,3,5-triazine; DMTMM, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride; ^{F}CDMT, 2-chloro-4,6-bis[(heptadecafluorononyl)oxy]-1,3,5-triazine; CF, 2,4,6-trifluoro-1,3,5-triazine; Trt, trityl; THF, tetrahydrofuran; TEA, triethylamine; Py, pyridine; *m*-CPBA, *meta*-chloroperbenzoic acid; DME, 1,2-dimethoxyethane; DIPEA, diisopropylethylamine.

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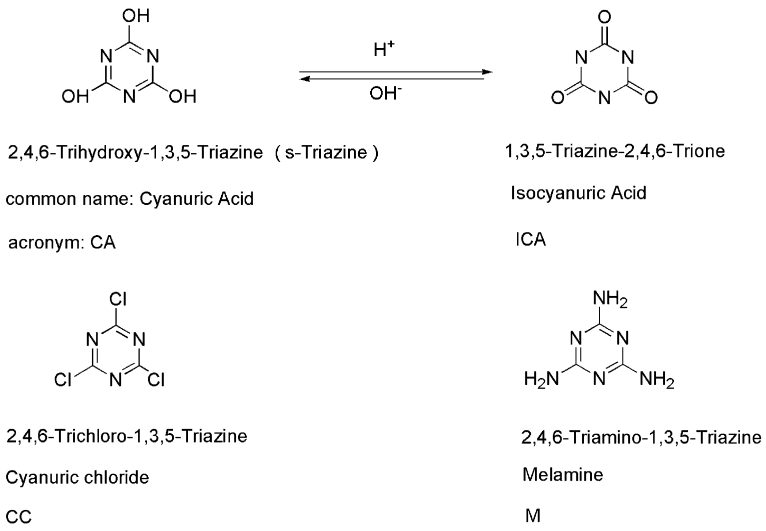


Figure 1.

reactivity of its chlorine atoms toward nucleophiles. It is also important to stress that CC is commercially available and a very inexpensive reagent, which makes its applications even more attractive. In this review, the synthesis of new 2,4,6-derivatives of 1,3,5-triazine together with novel applications of cyanuric chloride and its derivatives, in a variety of synthetic transformations, will be presented. Because of the large volume of work in this area, only the most relevant recently published applications will be presented.

2. 2,4,6-Trichloro-1,3,5-triazine (CC)

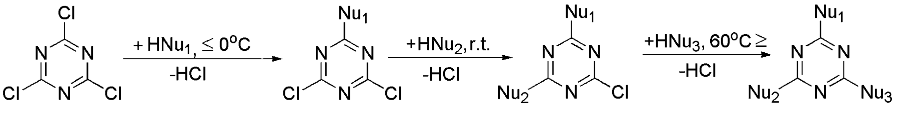
The ease of displacement of chlorine atoms in cyanuric chloride by various nucleophiles, in the presence of a hydrochloride acceptor (usually sodium carbonate, bicarbonate, hydroxide or tertiary amines), makes this reagent useful for the preparation of mono-, di- and tri-substituted 1,3,5-triazines.[2] The substitution of chlorine can be controlled by temperature to run in a stepwise manner. An empirical rule, based upon observation, is that mono-substitution of chlorine occurs below or at 0 °C, di-substitution at room temperature and tri-substitution above 60 °C (Scheme 1).

The substitution pattern also depends on the structure of the nucleophile, its basic strength and steric factors, the substituent already present in the *s*-triazine ring and the nature of solvent used. Therefore the empirical rule given above is just a rough guideline, and there are many variations from these conditions. By controlling the temperature, time, and optimization of variables, such as solvent and base, the substitution of chlorine in CC with different substituents can be accomplished in one pot, if the correct order of addition of nucleophiles is followed (e.g., O-nucleophiles followed by N-nucleophiles). For example, Menicagli [7,8] achieved nearly quantitave yields of both symmetric and nonsymmetric mono-, di- and tri-substituted alkoxy and amino 1,3,5-triazines by nucleophilic substitution of CC in one pot in the presence of a catalytic amount of 18-crown-6.

A new orthogonal method for solid-phase synthesis of 2,4,6-trisubstituted 1,3,5-triazine was developed by Chang et al.[9,10] They attached a primary amine to an aldehyde resin by reductive amination. This was then reacted with separately prepared mono-substituted dichloro-*s*-triazine. The trisubstituted derivatives were obtained by nucleophilic reaction with an amine,[9] or by a Suzuki coupling reaction with phenylboronic acid.[9] Cleavage of the resin gave the trisubstituted product (Scheme 2) with high purity. Unfortunately, the authors did not report the yields of this reaction.[9,10]

An interesting strategy based on sulfones was presented by the same authors.[11] Separately synthesized 2-benzylsulfanyl-2,6-dichloro-1,3,5-triazine was reacted with amine bonded to the resin. After substitution of the third chlorine atom with a primary or secondary amine, the thioether was oxidized to benzyl sulfone generating a good leaving group. Reaction with another amine and cleavage of the resin gave the trisubstituted *s*-triazine (Scheme 3).

To avoid harsh conditions in the substitution of the last chlorine atom by an amino group Simanek et al.[12] treated chlorotriazine with either triphenylmethylamine and diphenylmethylamine or 2,4-dimethoxybenzylamine. The substitution was accomplished in 5–15 min using microwave technique. The acid labile benzylic groups were removed by trifluoroacetic acid giving the product with high yield.



HNu_1, HNu_2, HNu_3 = N, O, P, S, F nucleophiles[5]

Scheme 1.