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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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Contents

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

Keywords: 2,4,6-Trichloro-1,3,5-triazine; 2-Chloro-4,6-dimethoxy-s-triazine; Functional group transformations.
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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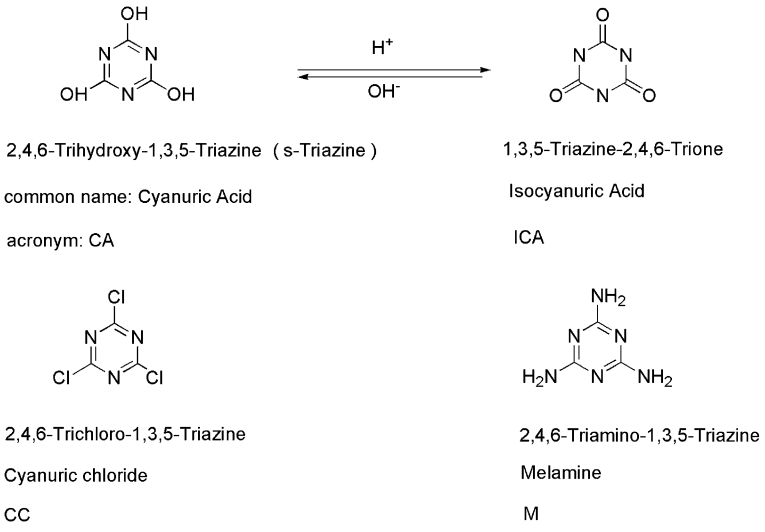


Figure 1.

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)

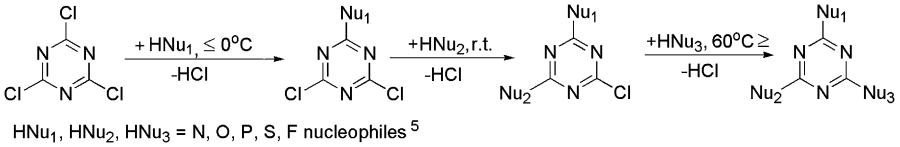
The ease of displacement of chlorine atoms in cyanuric chloride by various nucleophiles, in the presence of a hydrochloride acceptor (usually sodium carbonate, bicarbonate, hydroxide or tertiary amines), makes this reagent useful for the preparation of mono-, di- and tri-substituted 1,3,5-triazines.[2] 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.

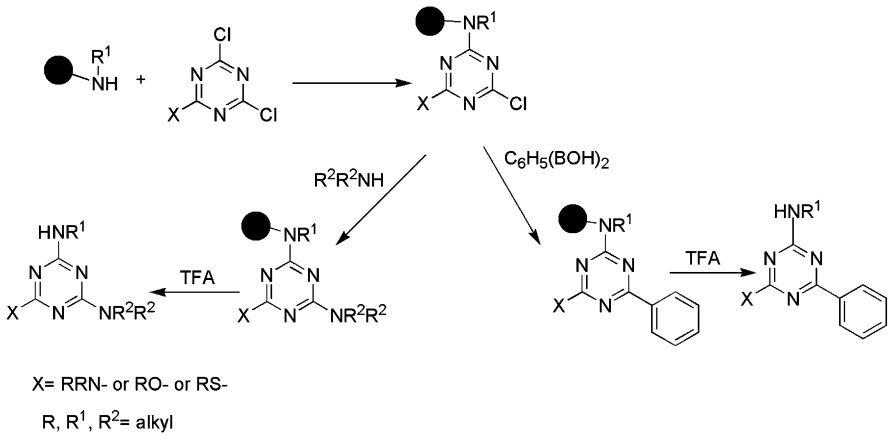
A new orthogonal method for solid-phase synthesis of 2,4,6-trisubstituted 1,3,5-triazine was developed by Chang et al.[9,10] They attached a primary amine to an aldehyde resin by reductive amination. This was then reacted with separately prepared mono-substituted dichloro-*s*-triazine. The trisubstituted 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).

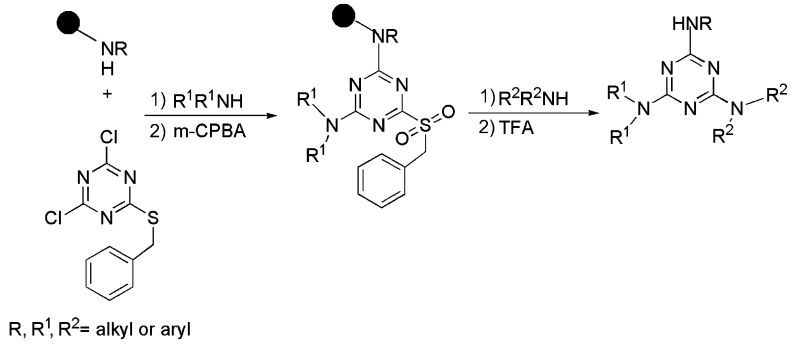
To avoid harsh conditions in the substitution of the last chlorine atom by an amino group Simanek et al.[12] treated chlorotriazine with either triphenylmethylamine and diphenylmethylamine or 2,4-dimethoxybenzylamine. The substitution was accomplished in 5–15 min using microwave technique. The acid labile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



Scheme 1.



Scheme 2.



Scheme 3.

3. Applications of CC in synthesis of substituted *s*-triazines

Falorni et al.[13] synthesized tri-functionalized orthogonally protected templates **1** (Fig. 2) in a one-pot procedure, which was used in a liquid-phase parallel synthesis.

By reacting CC with 3 equiv of *p*-hydroxybenzaldehyde, Tahmassebi and Sasaki[14] obtained, a triangular- 'tripod' in a single step **2** (Fig. 2). It was used for the imprinting of a silica surface[14] or for linking to N-terminus peptides by reductive amination to assemble three-helix bundle proteins.[15] A linear template- 'dipod' **3** was also synthesized using a 2,4-dichloro-6-methoxy-1,3,5-triazine with 2 equiv of aldehyde, instead of CC.[16]

Gustafson,[17] for the first time, incorporated a triazine ring in carbohydrates, peptides, aminimides, and α-ketoamides by the selective derivatization of CC in a one-pot procedure using automated parrallel solution synthesis, e.g., **4** (Fig. 2).

Recently, the synthesis of a novel disubstituted exocyclic triazylamino nucleoside **5** (Fig. 3) library was reported using a stepwise amination of CC on a semiautomated synthesizer.[18,19] The natural mimic nucleosides were obtained as potential antitumor and antiviral agents.

The temperature dependent reactivity of CC was exploited for the synthesis of different kinds of calix[*n*]arens,[20,21] e.g., **6** and **7** (Fig. 3), as well as macrocycles containing triazine moeties linked by diamines,[22] e.g., **8** (Fig. 3). Because of the presence of many hydrogen bond donors and acceptors these compounds exhibit very promising binding properties. CC was also used to link a calix[4]arene to a carbohydrate natural polymer.[23]

By stepwise amination of CC with 5-(4-aminophenyl)-10,15,20-triphenylporphyrin, Carofiglio et al.[24] synthesized

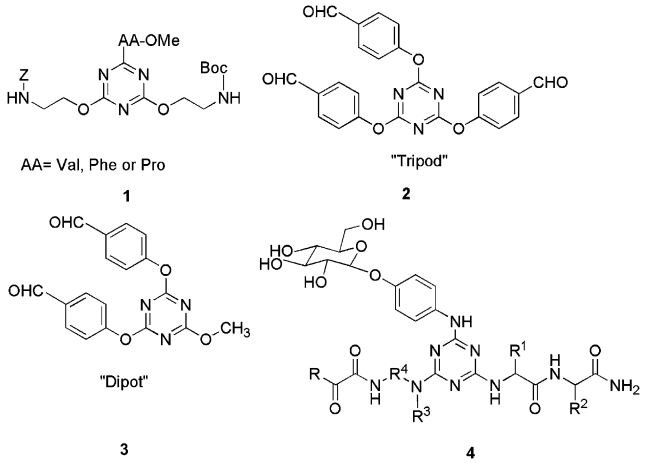


Figure 2.

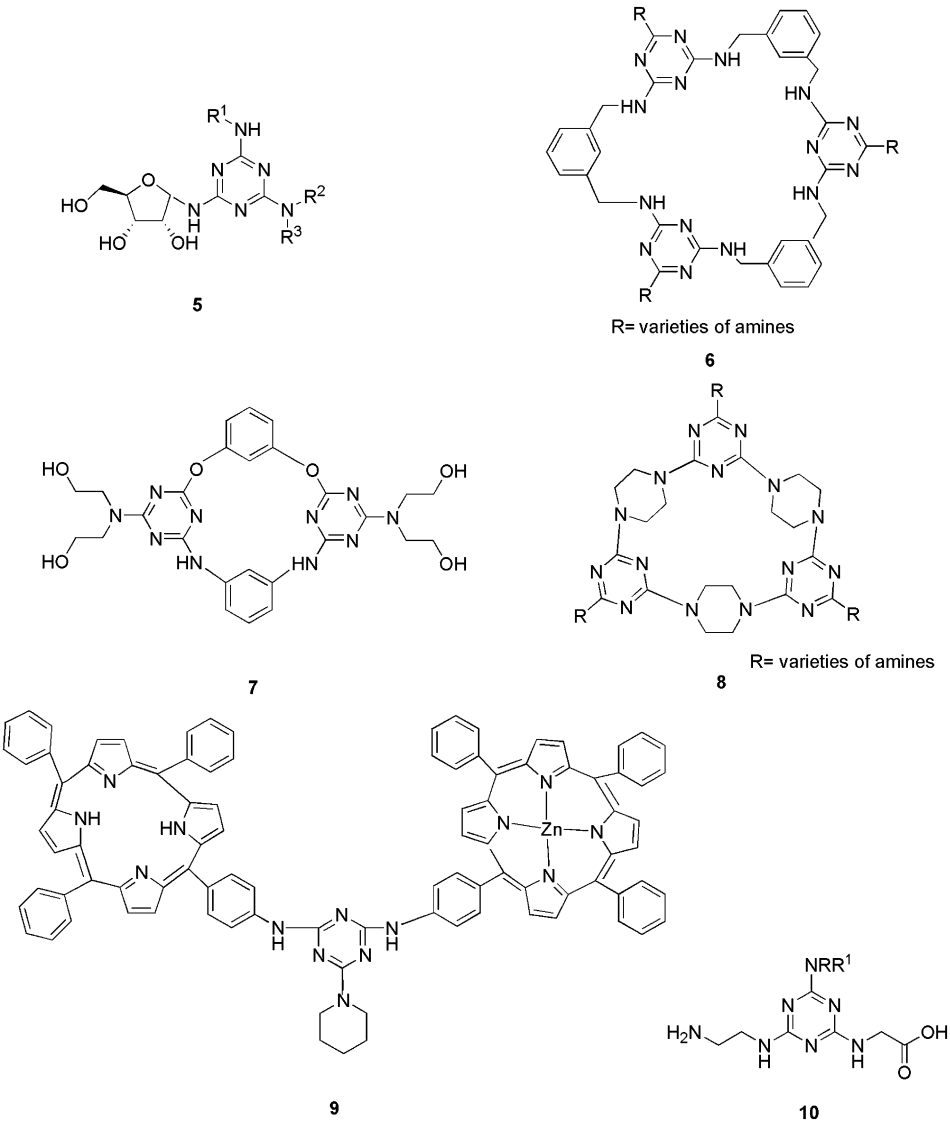


Figure 3.

porphyrin-dyads. Similarly amination with aminoporphyrin produced Zn(II) complex metaloporphyrin dyads like **9** (Fig. 3). CC was also used for obtaining porphyrin oligomers.[25] These compounds have found various applications like mimicking the selectivity and reactivity of enzymes, and as material for optoelectronics.

Zerkowski[26] utilized triazinyl amino acid **10** (Fig. 3) as building block for unnatural peptide analogs, which were obtained from CC by nucleophilic substitution with diamines and amino acid esters. The third chlorine in the triazine ring can be used for incorporation of other functionalities, or for attachment to a solid-phase resin. Several macrocyclic pseudopeptides were synthesized using these derivatives.

Recently, different *o*-carboranyl derivatives of 1,3,5-triazine were synthesized from CC as tumor targeting agents for boron neutron capture therapy (BNCT). One, two or three *o*-carboranyl residues were incorporated into *s*-triazine.[27–29] The remaining chlorine atoms were substituted by various amines[27,28] or acids,[29] e.g., **11** and **12** (Fig. 4).

A new Sharpless asymmetric ligand was synthesized using CC, quinine, and 4-bromoaniline[30] **13** (Fig. 4). This new catalyst is inexpensive, and gives a good yield and enantioselectivity in the dihydroxylation of alkenes.

The carbon nitride was synthesized by heating CC and sodium azide in benzene at 220 °C, which forms high quality nanotubes **14** (Fig. 4), by self-assembly.[31]

A fluorous derivative of a radical 2,2,6,6-tetramethyl piperidine-1-oxyl (TEMPO) was synthesized using CC **15** (Fig. 4), which is efficient, selective, and an easily recoverable catalyst for oxidation of alcohols.[32]

N^{α}-dichlorotriazinyl-arginylalkyl-amide monohydrochlorides, e.g., **16** (Fig. 4) were synthesized as new surfactants for application as antimicrobial and antihelminthic agents

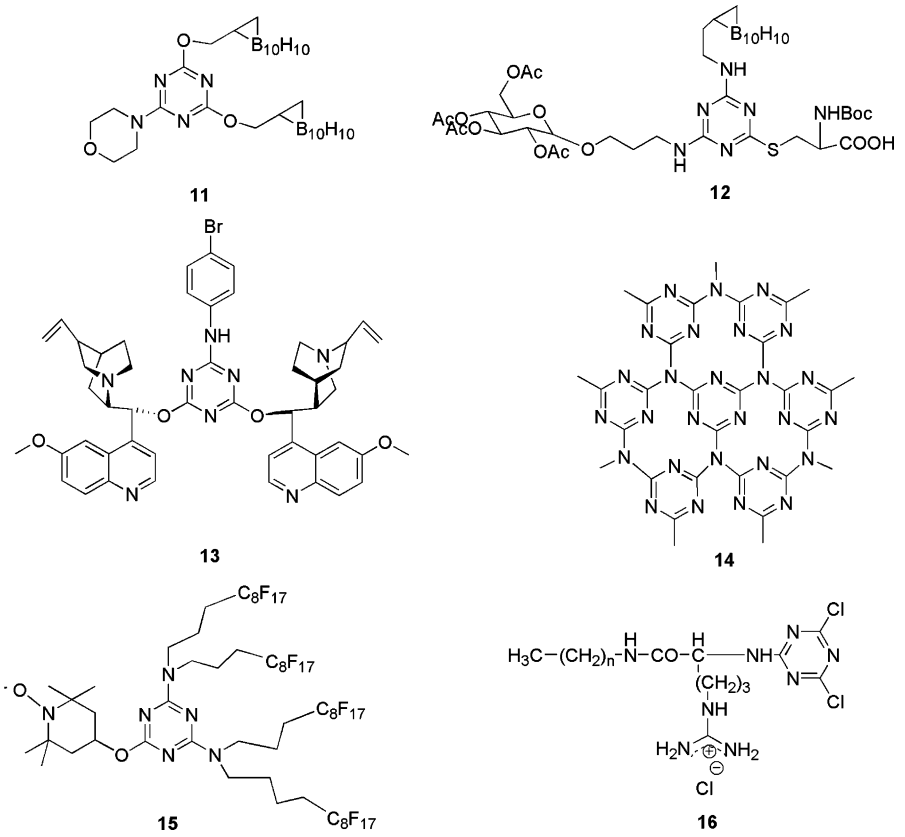


Figure 4.

for wool and cotton, to protect these material from degradation.[33]

4. CC in dendrimers synthesis and supramolecular complexes

Controlling the reaction temperature of CC with different diamines allowed Simanek's group[34–40] and Lai et al.[41] to synthesize dendrimers, e.g., **17** (Fig. 5), even without employing protection and deprotection processes. They have potential applications in medicine as vehicles for drug delivery, and in the area of electro- and optomaterials.

Triazine derivatives, such as cyanuric or isocyanuric acids and melamines (obtained from CC), can act as both hydrogen bond donors and acceptors. The hydrogen-bonding networks that form between them are responsible for forming supramolecular, well defined and stable aggregates. These aggregates were first described by Lehn[42] and by Whitesides.[43] The noncovalently bonded assemblies can exist in different forms, e.g., as a cyclic rosette **18** (Fig. 5), and have been the subject of many structural studies[44–53] and reviews.[54–56] The Reinhoudt group[46,52,56,57] combined synthesized calix[4] arene dimelamine with cyanuric or barbituric acid, and studied the aggregates formed between them.

5. Cyanuric chloride in functional group transformation

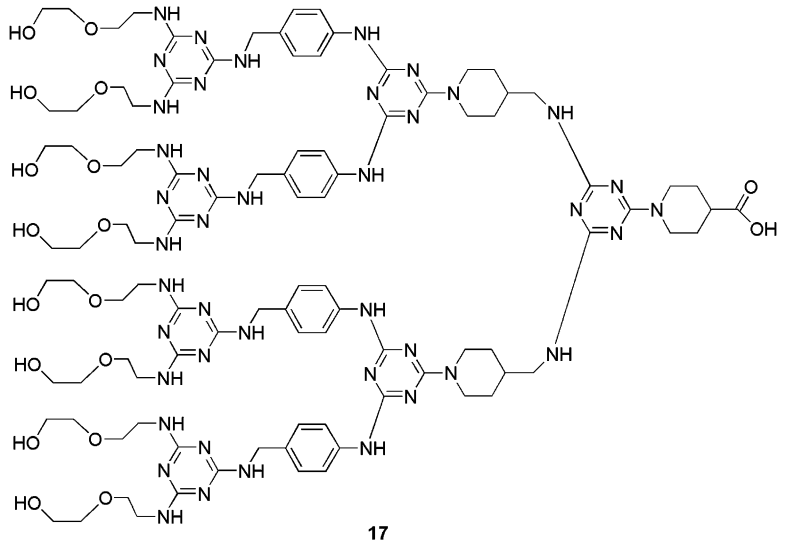
In spite of the enormous number of publications devoted to functional group transformation,[58] there is still a need for mild methods that exhibit selectivity among functional groups, especially in the case of polyfunctional derivatives. In the older literature, one can find examples of applications of 2,4,6-trichloro-1,3,5-triazine in synthesis.[59–66] Recently there has been a considerable growth of interest in the use of cyanuric chloride and its derivatives in organic synthesis.

Cyanuric chloride is often used for activation of carboxylic acids in various transformations. There is disagreement about the initial product of the reaction of carboxylic acids with CC. Some claim that the product is acid chloride,[59,61–63,67] which was isolated and characterized in some cases. Others[68–72] argue that the acylated *s*-triazine is an intermediate, but there is a lack of direct proof of its formation.[73]

Falorni[68] reported that carboxylic acids, including *N*-protected amino acids, can be activated with CC and subsequently reduced to their corresponding alcohols with sodium borohydride in water (Scheme 4). This method is particularly suitable for the reduction of *N*-*Z*, *N*-Boc, and *N*-Fmoc amino acids, and results in high yields without racemization. The authors suggest that 2-acyloxy-4,6-dichloro-1,3,5-triazine is formed as an intermediate.

Rayle and Fellmeth[70] successfully used CC for the preparation of amides, and claim that 2,4,6-triacyloxy-1,3,5-triazine is an intermediate (Scheme 5).

A new route in the synthesis of diazo ketones was reported by the Forbes group.[71] Aryl carboxylic acids were activated by CC, and reacted with diazomethane (Scheme 6) to diazocarbonyl compounds with moderate yields. Unfortunately,



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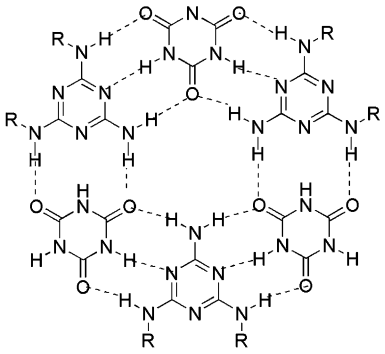

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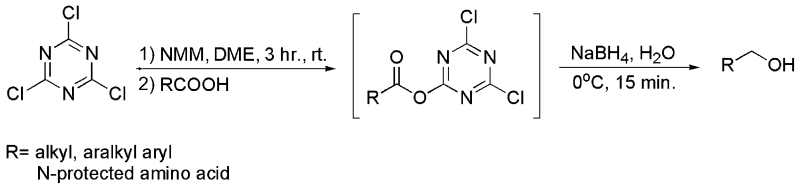
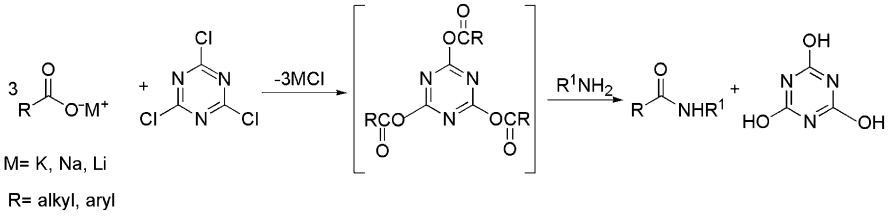
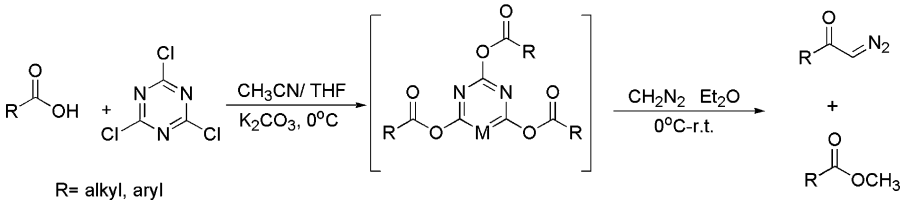
Figure 5.



Scheme 4.



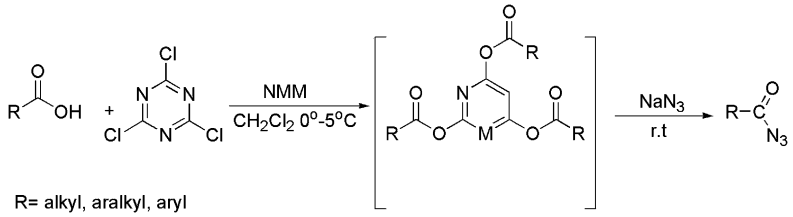
Scheme 5.



Scheme 6.

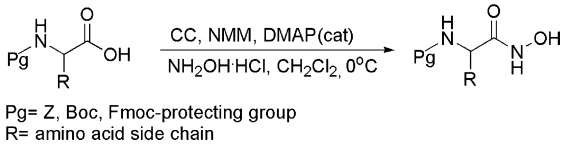
during this reaction a significant amount of methyl esters were formed as a by-product. This reaction was carried out in water, in a one-pot procedure, which is an advantage over other methods.

Bandgar and Pandit[72] applied CC for synthesis of acyl azides directly from carboxylic acids (Scheme 7). Various aryl, heteroaryl, alkylaryl, and alkyl carboxylic acyl azides were obtained under mild conditions with high yields.



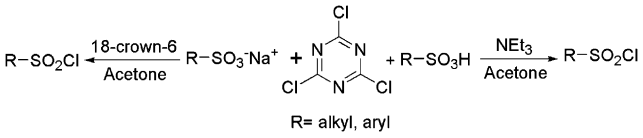
Scheme 7.

Recently, Giacomelli[74] reported a mild and simple one-step method for the preparation of hydroxamic acids. The carboxylic acid or *N*-protected α-amino acid was treated with CC in the presence of NMM followed by hydroxylamine hydrochloride (Scheme 8). Even though the reaction took 6–12 h, the purity and yields were high and no significant racemization was observed. No *O*-acyl or di and triacylated products were formed. Also, hydroxamic acids of *N*-protected dipeptides were obtained by this method.



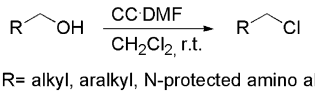
Scheme 8.

2,4,6-Trichloro-1,3,5-triazine was applied as a chlorinating agent for the preparation of sulfonyl chlorides from sulfonic acids under neutral conditions.[75] CC, sulfonic acids, and triethylamine or CC, sodium sulfonates, and catalytic amounts of 18-crown-6 acetone, after heating under reflux gave, good to excellent yields of alkyl and aryl sulfonyl chlorides (Scheme 9).



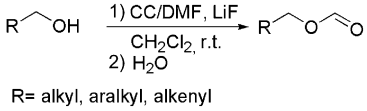
Scheme 9.

Although Sandler[60] used CC for the preparation of alkyl chlorides from their corresponding alcohols, Giacomelli[76] elegantly improved the reaction by using CC and a dimethylformamid adduct[77] for chlorination (Scheme 10). Also, alkyl bromides were obtained by addition of sodium bromide to the CC/DMF adduct. The method was very mild, efficient, and chemoselective. *N*-protected-β-aminochlorides were obtained from their corresponding amino alcohols as well as chloroalcohols from diols.



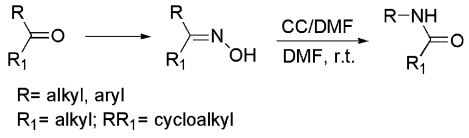
Scheme 10.

The CC/DMF complex was also used for selective protection of primary alcohols by a formyl residue[78] (Scheme 11). Phenols, along with 2°, 3° benzylic, allylic, and propargylic alcohols did not react in the given conditions. *N*-protected β-amino alcohols were also converted to *O*-formates with some exceptions.



Scheme 11.

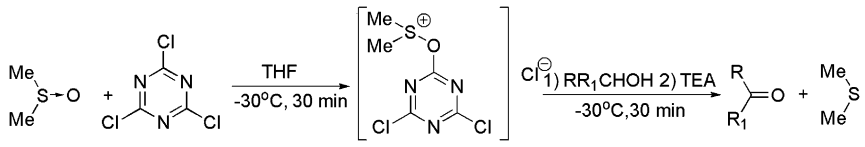
Ketoxime, upon treatment with the CC/DMF complex in dimethylformamide at room temperature, underwent the Beckmann rearrangement[79] with high yields and purity (Scheme 12). In the case of cyclic ketones, lactams were obtained in high yields. Aldoximes gave nitriles under the same conditions. Recently, other authors[80] performed a Beckmann rearrangement in acetonitrile using an acidic cocatalyst besides CC.



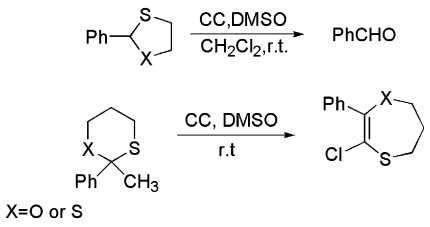
Scheme 12.

Cyanuric chloride catalyzes the oxidation of different types of thiols to disulfides using dimethylsulfoxide, resulting in high yields and purity.[81] De Luca et al.[82] used CC for activation of DMSO in the Swern oxidation (Scheme 13). A variety of aldehydes, ketones, and *N*-protected amino aldehydes were prepared with high yields.

Karimi[83] reported efficient deprotection of a variety of 1,3-dithioacetals and 1,3-oxathiolanes to their corresponding carbonyl compounds using CC. The reaction conditions were mild and time short, and the isolated products were pure and of high yields. 1,3-Oxathioacetals and 1,3 dithioacetals of enolizable ketones gave ring enlargement product derivatives, for example, see Scheme 14.

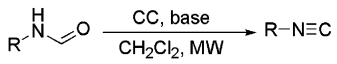


Scheme 13.



Scheme 14.

A very mild method for the conversion of formamides to isonitriles using CC in the presence of a base was recently published by Porcheddu et al.[84] They postulate that the reaction proceeds through the formation of an *O*-acylated intermediate (Scheme 15).



Scheme 15.

Using microwave irradiation (MW), alkyl, cyclic, acyclic benzylic and aromatic, and optically active isonitriles were obtained in a matter of minutes with high yields.

6. Cyanuric chloride in solid-phase synthesis

Solid-phase synthesis, since it's discovery by Merifield,[85] is now routinely used in automated synthesizers.[86] Cyanuric chloride also found applications in solid-supported strategy.

Masala and Tadei[69] loaded CC on different types of amino functionalized resins. These new reagents were used for activation of carboxylic acids to give amides and dipeptides (Scheme 16). A series of aliphatic and aromatic carboxylic acids, and primary and secondary amines, gave amides with good yields.

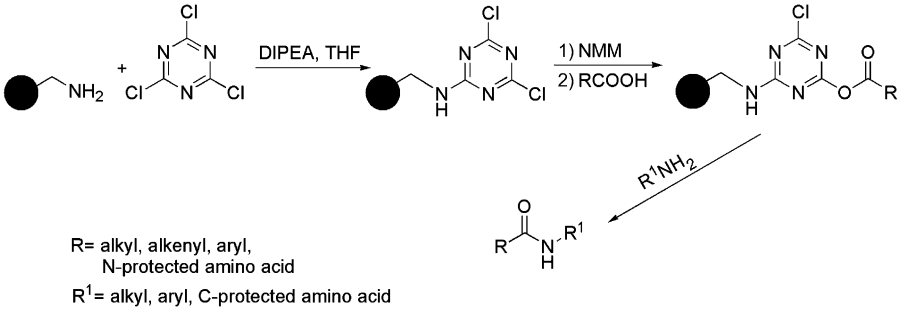
A new resin supported chlorinating reagent, based on CC, has been developed by Luo and co-workers.[67] Cyanuric chloride, loaded on a modified Wang resin, was used for the preparation of acyl chlorides (Scheme 17). The acyl chlorides were not isolated, but were converted to their benzylamides or esters. The yields were good, but chiral amino acids were racemized.

Polyethylene glycol (MeO–PEG–OH) was reacted with CC to give PEG-dichlorotriazine,[87] which was used as a soluble electrophilic scavenger that removes alcohols, thiols, triphenylphosphine, and phosphine oxide from the reaction mixture by selective precipitation and filtration (Scheme 18).

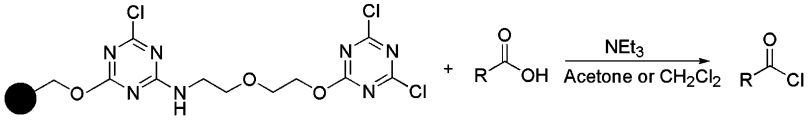
Marsh[88] loaded resins with *s*-triazine dendrimers, which have been used as proton and nucleophile scavengers **18** and **19**, respectively (Fig. 6) in the purification of combinatorially derived products.

7. 2-Chloro-4,6-dimethoxy-1,3,5-triazine in functional group transformation

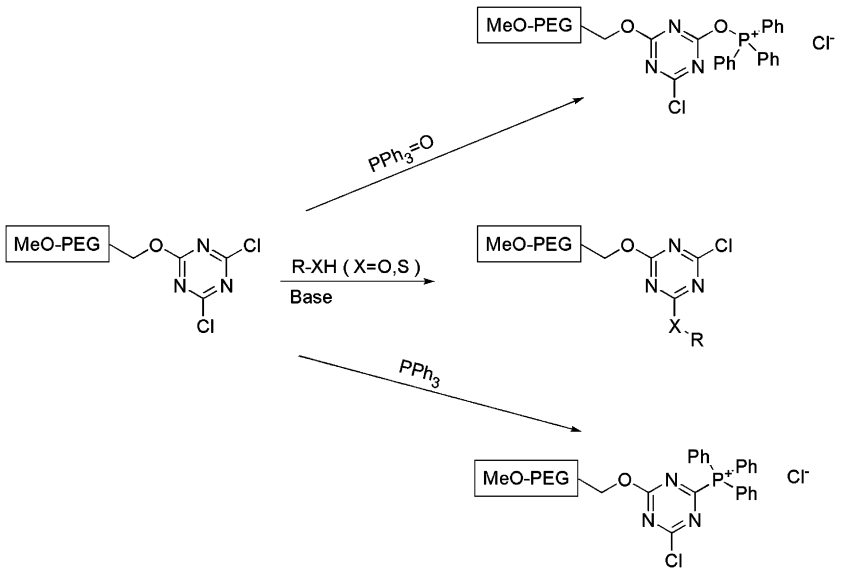
2-Chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) was recently found to have wide applications as a condensing reagent in peptide chemistry.[73] It is commercially available, but can also be easily synthesized.[7,89] Activation of carboxylic acids by means of CDMT is a multi-step process, and was elegantly and thoroughly examined by Kaminski.[73,90,91] It depends upon the specific reaction conditions, such as the order of addition of reagents.[92] The reaction



Scheme 16.



Scheme 17.



Scheme 18.

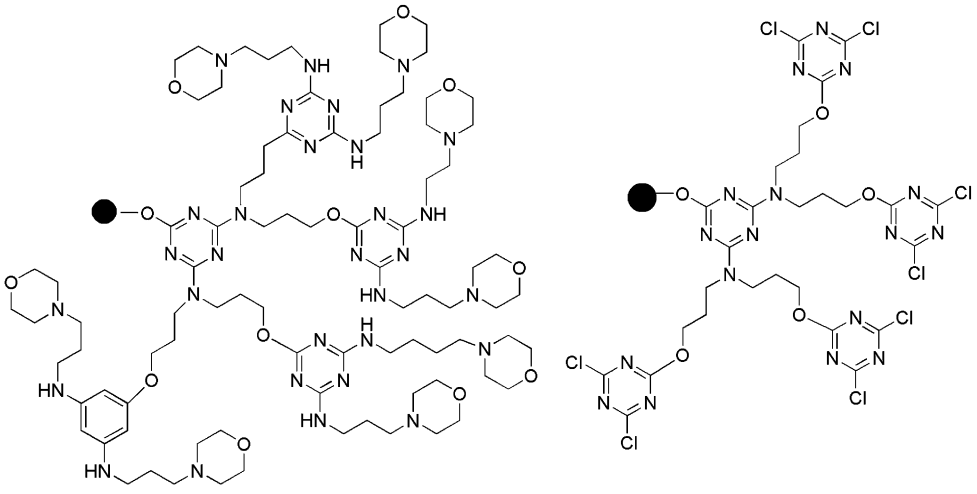


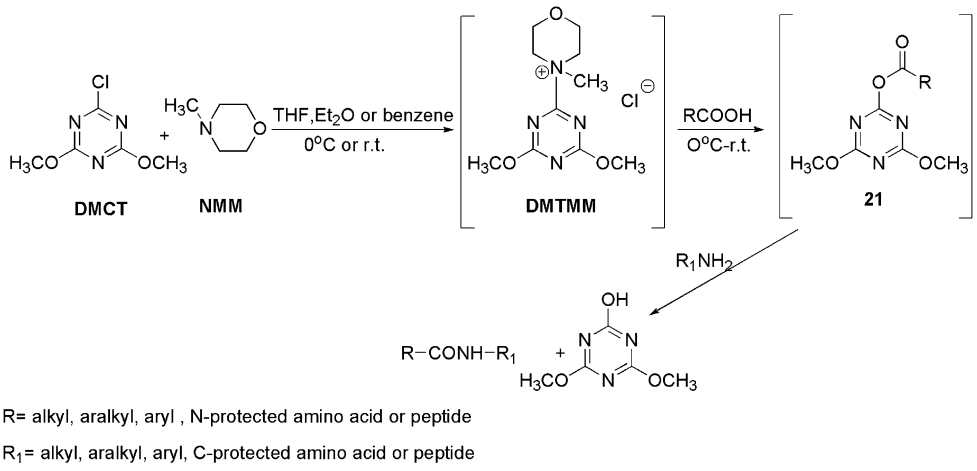
Figure 6.

requires the presence of a tertiary amine, usually *N*-methylmorpholine (NMM). In standard procedure, the first step was reacting CDMT with NMM to form 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM), and then the carboxylic acid was added in the next step generating an active ester **21** (Scheme 19), which subsequently gave with an amine the desired product.

No significant racemization was observed during the synthesis of peptides. Optical purity was found to be more that 99.5%.[73] Another sequence of addition of reagents, e.g., mixing CDMT with carboxylic acid and NMM, stirring for 1 h, then adding amino acid ester, lead to significant racemization via formation of azlactone.[92] Another protocol was suggested by Garrett et al.[92] The reaction was provided in a one-pot, one-step procedure, i.e., they mixed CDMT with acid and amine reagents and then NMM to the reaction medium. No significant loss of configuration was observed, and the reaction was finish faster. When chiral tertiary amines such as strychnine, brucine or sparteine were used instead of NMM, using CDMT in coupling of racemic *N*-protected amino acid with amino components, the reaction proceeds enantioselectively.[91]

4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride was isolated and fully characterized.[90,93] It is a stable compound that can be stored in the solid state at room temperature for up to a month or for several months in the refrigerator, without detectable decomposition. This reagent combined with carboxylic acid gave an active ester **21** (Scheme 19), and was used as condensing reagent for synthesis of esters and amides.[94–96]

Taddei[97] reported the application of DMTMM to the solid-phase synthesis of peptides. The yields and purity of the products were high.



Scheme 19.

Recently, Kaminski et al.[98] introduced 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate as a more stable reagent than the corresponding DMTMM chloride. The new coupling reagent was used in ester and peptide synthesis, in solution, and in solid-phase synthesis.

DMTMM **21** (Scheme 20) can be generated by different protocols mentioned above. This active ester, without isolation was used for many transformation of carboxylic group.

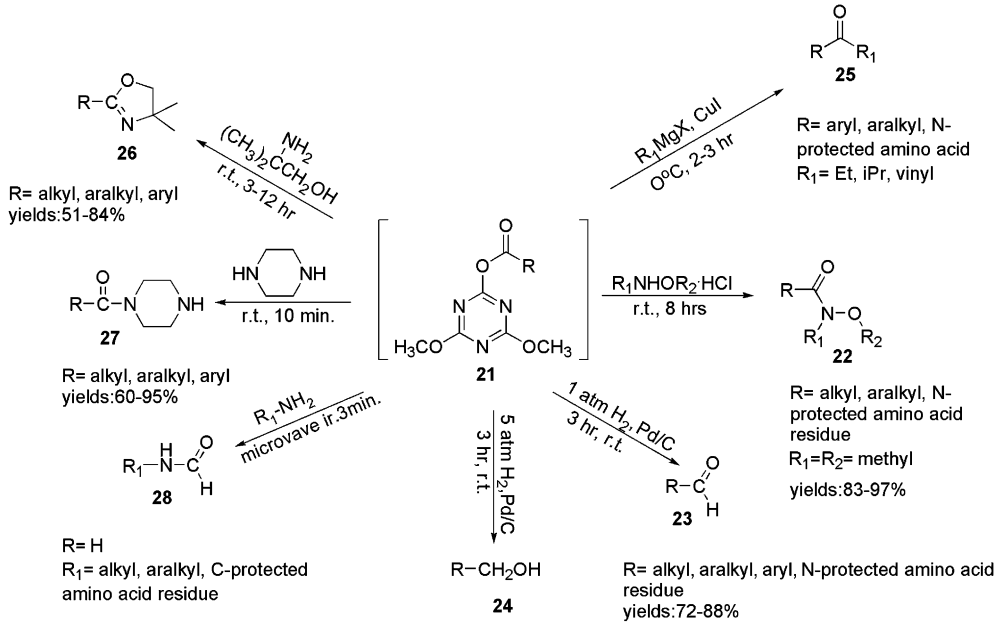
Giacomelli et al.[99] prepared it using CDMT and applied it to the synthesis of *N*-methoxy-*N*-methylamides, commonly named Weinreb amides **22** (Scheme 20), a useful precursor to ketones.[100] A variety of these compounds were obtained quantitatively from carboxylic acids, and *N*-protected amino acids with high yields and purity. DMTMM was also used for this purpose, but the yields of Weinreb amides were lower.

It was reported that active ester **21** (Scheme 20), prepared from DMTMM was reduced by hydrogen and Pt/C as the catalyst to the corresponding aldehyde **23** (Scheme 20) in good yields.[101] Required optimization of the solvent, hydrogen pressure, temperature, and time of reduction are disadvantages to this method. Higher hydrogen pressure (5 atm) gave alcohols.

Activated esters of aromatic carboxylic acid, and *N*-Boc or *N*-*Z* protected α-amino acids were converted to ketones **25** (Scheme 20) or α-amino ketones by Grignard reagent in the presence of stoichiometric amounts of CuI.[102]

Bandar and Pandit[103] reported the synthesis of 2-oxazolines **26** (Scheme 20) from acyloxy triazine. The active ester was reacted at room temperature with 2-amino-2-methyl-1-propanol giving the desired product with good yields.

The same conditions, were used for the selective preparation of monoacylated piperazine derivatives **27** (Scheme 20) with good yields.[104] Monoacylation of symmetrical diamines often becomes problematic due to competitive bisacylation.



Scheme 20.

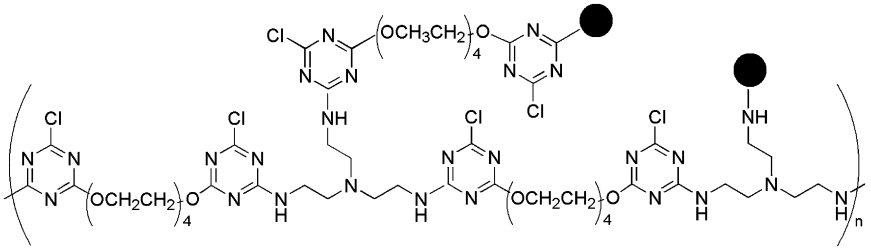
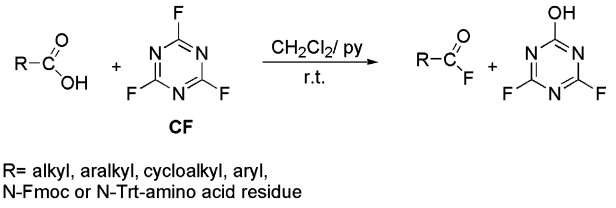


Figure 7.

Recently, active ester **21** of formic acid was used for the formylation of amines and α-amino acid esters **28** (Scheme 20).[105] The reaction was conducted under reflux in methylene chloride, or under microwave irradiation to reduce the reaction time from hours to a few minutes. The yields were high, the products pure and no significant racemization of the chiral centers was observed.

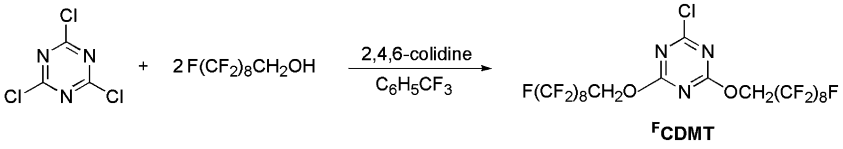
Based on the reactivity of CC, Kunishima et al.[106] published preliminary data about a new immobilized dehydrocondensing reagent in a polymerized form (Fig. 7). This polymer reacts with carboxylic acids, in the presence of a NMM like CDMT or DMTMM, giving active esters, which with amines, gave amides in good yields.



Scheme 22.

8. Applications of other derivatives of *s*-triazine in organic synthesis

Markowicz and Dembinski developed a fluorous 2-chloro-4,6-bis-[(heptadecafluorononyl)oxy]-1,3,5-triazine (^{F}CDMT), an analog of CDMT, as a new coupling reagent in peptide synthesis.[107] It was prepared from CC and heptadecafluorononan-1-ol (Scheme 21), and fully characterized. It is believed that the mechanism of activation of a carboxylic acid by ^{F}CDMT is similar to that of CDMT (Scheme 19). The advantage of this method lies in nonaqueous and non-acidic isolation protocol. The fluorous by-product is insoluble in organic solvents. Extraction by chloroform or ethyl acetate gave, after filtration, di and tripeptides in excellent yields.



Scheme 21.

2,4,6-Trifluoro-1,3,5-triazine CF (Scheme 22), with the common name of cyanuric fluoride, was prepared from CC.[108] It easily converts carboxylic acids as well as *N*-Fmoc and *N*-Trt amino acids, to the corresponding fluorides, which in turn gave excellent yields in both solution and solid-phase peptide synthesis.[109,110] The fluorides were especially useful in the incorporation of sterically hindered amino acids without loss of configuration.

1,3,5-Trichloro-2,4,6-trioxo-*s*-triazine, with the commonly used name-trichloroisocyanuric acid (TCICA), is produced on a large scale for household and industry use, but has found less applications in organic synthesis. As a *N*-chloramine it was used mostly as a chlorination and oxidation agent, and was the subject of a review where references to it's different applications can be found.[111]

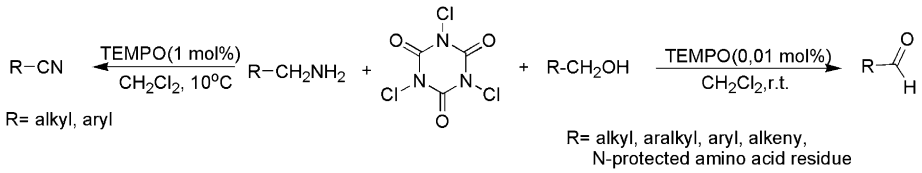
Giacomelli applied TCICA for oxidation of primary alcohols, and *N*-protected-β-amino alcohols to aldehydes (Scheme 23).[112] The reaction was fast (15–20 min), yields high, and no overoxidation to carboxylic acids was detected. The secondary alcohols can be oxidized to ketones, but the reaction requires more than 6 h for completion. Because of this, primary alcohols can be selectively oxidized in the presence of secondary alcohols.

Very recently other authors[113] found that TCICA in the presence of catalytic amount of potassium bromide and wet silica gel selectively oxidized benzylic and secondary alcohols.

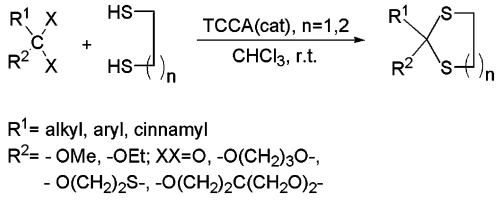
It was reported that TCICA, in the presence of free radical TEMPO, converts primary amines to their corresponding nitriles in mild conditions and with high yields (Scheme 23).[114]

Frouzabadi et al.[115] published that TCICA is an efficient catalyst for the thioacetalization of aldehydes, and the transthioacetalization of *O*,*O*- and *S*,*O*-acetals (Scheme 24). The reaction was run at room temperature and was very selective in the presence of ketones.

Zolfigol et al. recently used TCICA to oxidize 1,3,5-trisubstituted pyrazolines to their corresponding pyrazoles (Scheme 25).[116] The reaction was run at room temperature

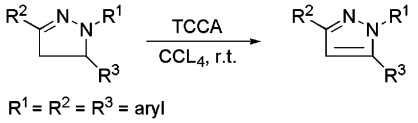


Scheme 23.



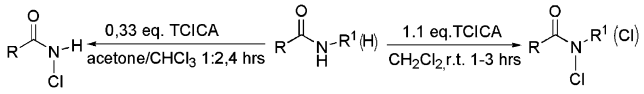
Scheme 24.

in carbon tetrachloride, or under solvent free conditions. In both cases the yields were good.



Scheme 25.

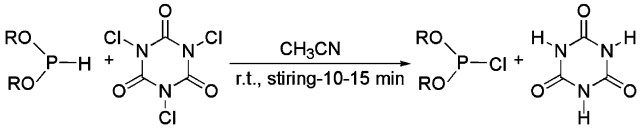
Trichloroisocyanuric acid was also applied for *N*-chlorination of amides, lactams, and carbamates as intermediates in organic synthesis.[117] Primary amides gave *N*-mono or *N*,*N*-dichloroamides, depending on the ratio of reagents and the reaction conditions (Scheme 26). Chlorination of amino acid carbamates does not need the protection of the carboxylic function.



Scheme 26.

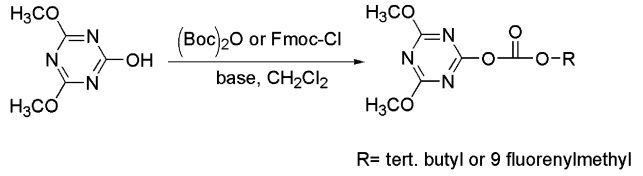
Carboxylic acids can be converted to acid chlorides by a reaction with TCICA in the presence of triphenylphosphine under mild conditions.[118] The acid chlorides were not isolated, but reaction with amines or alcohols afforded corresponding amides or esters (Scheme 27).

A very mild method for obtaining dialkyl chlorophosphates, by stirring TCICA with dialkyl phosphites in acetonitrile at room temperature was published (Scheme 28).[119] The reaction was finished in 10–15 min, giving products in excellent yields.



Scheme 28.

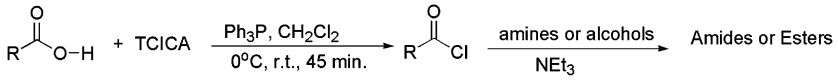
Kunishima et al.[120] very recently reported synthesis of new reagents for introduction of Boc and Fmoc protective groups into amines. By reaction of 4,6-dimethoxy-1,3,5-triazin-2-ol (obtained from CC) with di-*tert*-butyl dicarbonate or with 9-fluorenylmethyl chloroformate, they obtained *tert*-butyl 2,4-dimethoxy-1,3,5-triazinyl carbonate or 9-fluorenylmethyl 4,6-dimethoxy-1,3,5-triazinyl carbonate, respectively (Scheme 29). Both are stable nonirritating compounds, which allowed the introduction of Boc or Fmoc group into amines and amino acids in the range of minutes, without detectable side reactions.



Scheme 29.

9. Conclusion

This paper has reviewed recently published applications of 2,4,6-trichloro-1,3,5-triazine, and its related derivatives in organic synthesis. Increased interest in CC lies in the different reactivities of chlorine atoms, which are easily controlled by temperature. It allows sequential introduction of various substituents into a *s*-triazine ring using a one-pot procedure. These reagents also found applications in solid-phase synthesis by a combinatorial approach, as a template for peptides, for synthesis of dendrimers and noncovalently bonded supramolecular aggregates. Carboxylic acid's activation by CC or DMCT was used in many chemical transformations, and can be a valid alternative to other methods so as to avoid the use of toxic or expensive reagents. Sometimes the reactions needed hours to be completed, but these procedures have advantages over older methods in terms of yields, mildness, and green chemistry.



Scheme 27.

Further applications of cyanuric chloride and its derivatives can be expected.

Acknowledgements

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Biographical sketch

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