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RECENT USES OF 2,4,6-TRICHLORO-1,3,5-TRIAZINES AND ITS DERIVATIVES

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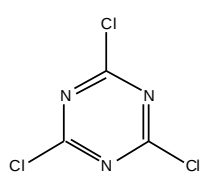
Abstract:-Triazines is the chemical species of six-membered heterocyclic ring compounds with three nitrogens replacing carbon-hydrogen units in the benzene ring structure. The names of the three isomers indicate which of the carbon-hydrogen units on the benzene ring position of the molecule have been replaced by nitrogens, called 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine respectively. Symmetrical 1,3,5-triazine is the most common. Triazines are prepared from cyanic acid amide by trimerization (1,3,5-triazine). Pyridine is the aromatic nitrogen heterocyclic compound having only one nitrogen and diazines are with two nitrogen atoms, triazines having three nitrogen atoms on the benzene ring system. Triazines are weak bases. Triazines have much weaker resonance energy than benzene, so nuceophilic substitution is preferred than electrophilic substitution. 1,3,5-Triazine or s-triazine moiety, represents an interesting class of compounds possessing a wide spectrum of biological activities[1-5] such as antimalarial, antibacterial, antimycobacterial, antifungal, herbicidal, anticancer, antitumoral and antiviral etc.

Keywords: Triazines , carbon-hydrogen , aromatic nitrogen heterocyclic .

INTRODUCTION

1,3,5-Triazines have shown wide spread applications in the pharmaceutical, textile, plastic and rubber industries. They are used as pesticides, dyestuffs, explosives and surface agents. The chemistry of this group of compounds has been studied intensively and has been the subject of many reviews.[6-9]

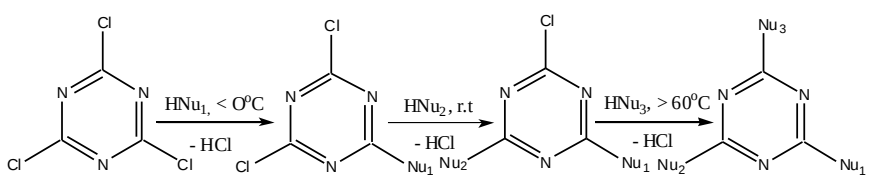


2,4,6-Trichloro-1,3,5-Triazine
OR
Cyanuric chloride (CC)

Fig. 1

All of the s-triazine derivatives that have wide spread practical applications are 2,4,6-mono, di- or tri-substituted, symmetrical and non-symmetrical compounds bearing different substituents. The most important reagent for obtaining these compounds is cyanuric chloride (CC), because of the reactivity of its chlorine atoms towards nucleophiles. It is also important to stress that 2,4,6-trichloro-1,3,5-triazine is an inexpensive, commercially available reagent, which is controlled by temperature making its applications even more attractive.

An empirical rule, based upon observation, is that mono-substitution of chlorine occurs below or at 0°C, di-substitution occurs at room temperature and tri-substitution above 60°C (Scheme 1).



HNu_1, HNu_2, HNu_3= N,O, P, S, F nucleophiles

Scheme: 1

Triazine compounds are often used as the basis for various herbicides such as cyanuric chloride (2,4,6-trichloro-1,3,5-triazine). Chlorine-substituted triazines are also used as reactive dyes. These compounds react through a chlorine group with hydroxyl groups present in cellulose fibres in nucleophilic substitution, the other triazine positions contain chromophores. Mixture of triazines and water are also used to remove H_2S from natural gas.

Most of the reactions of 2,4,6-trichloro-1,3,5-triazine involve the chlorine atoms which are allowed to react selectively (one or more at a time) with nucleophilic reagents. The high reactivity of s-triazine derivatives seems to have maximum resonance stabilization of a charge which can be achieved in the transition state. Even the deactivated mono and disubstituted sometimes even trisubstituted products of 2,4,6-trichloro-1,3,5-triazines show high reactivity towards substitution.

Triazine as Antibacterial Agent

H. R. Bhat *et al.*[10] synthesized a series of novel hybrid 4-amino quinoline-1,3,5-triazine derivatives (fig.2) and subsequently tested against representative gram +ve and gram -ve microorganisms for determination of their antibacterial activity.

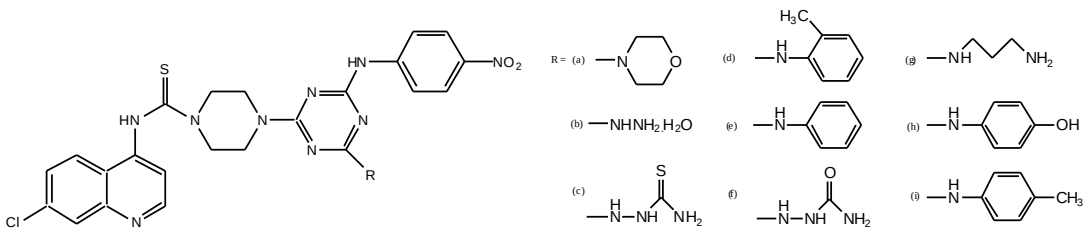


Fig. 2

Triazine as Antifungal Agent

V. Milata, et al.[11] studied synthesis and antifungal efficacy of 1,3,5-triazines. Their biological activity against wood-destroying fungi *Serpula lacrymans, Coniophora puteana* and *Trametes versicolor* was tested by the impregnated filter paper method. S. lacrymans occurred as the most sensitive fungus (from the 3 fungi) in the presence of triazines. Triazines having three imidazole or three 4,5-diphenylimidazole groups (fig.3) were a slightly more effective than others. However, their efficacy in comparison with the commercial fungicides Tebuconazole and IPBC was insufficient.

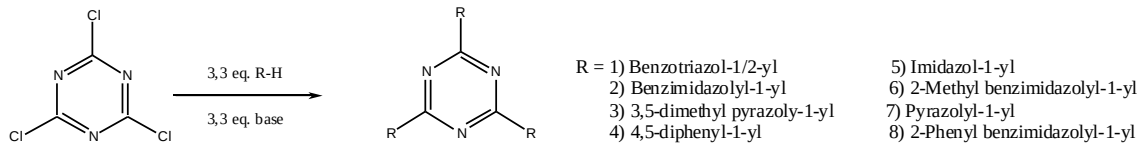
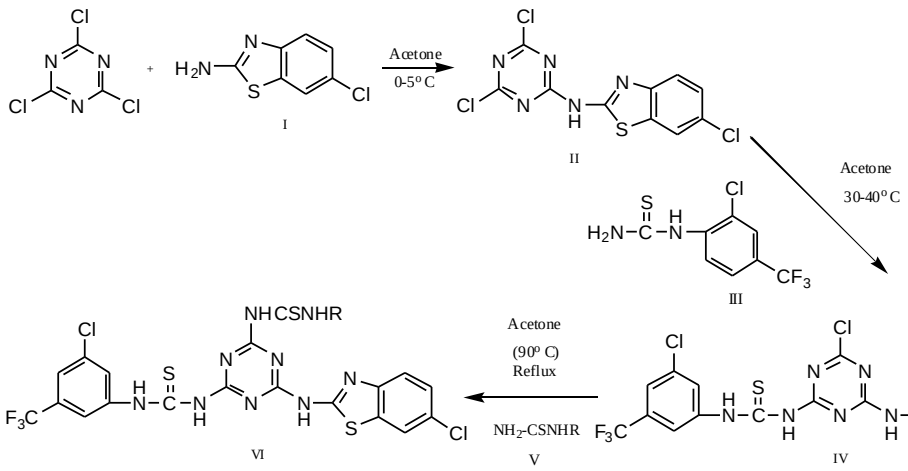


Fig.3

V. Sareen *et al.*[12] synthesized 2-(6-chlorobenzothiazol-2'-yl amino)-4-(2-chloro-4-trifluoro methyl phenyl thioureido)-6-(substituted thioureido)-1,3,5-triazine. These compounds were evaluated for their antifungal activity and shown promising results.



R = 4-FC_6H_4, 2-FC_6H_4, 2-NO_2-C_6H_4, 2-$OCH_3C_6H_4$, 4-Cl C_6H_4, CH2=CH-CH2, C_6H_5, NH_2

Scheme: 2

Triazine as Antimicrobial Agent

Several compounds N^2-(aryl)-N^4, N^6-bis (1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4,6-triamines were prepared.[13] All newly synthesized compounds had been tested for their antimicrobial activities against gram +ve and gram -ve bacteria.

Microwave-assisted procedure is described for the synthesis of a library of s-triazinyl piperazines and piperidines having 4-aminobenzonitrile and 8-hydroxyquinoline moieties.14 The newly synthesized analogs (fig.4) were assayed for efficacy against some human pathogenic bacterial and fungal strains, i.e., three gram -ve bacteria (*K. pneumoniae, S. typhi, P. vulgaris*), one gram +ve bacteria (*B. cereus*) and two fungal species (*A. clavatus, A. fumigatus*) with an intent to develop a novel class of antimicrobial agents. The results of bioassay showed that some of the newly synthesized s-triazines emerged as lead molecules with excellent MIC (mg/mL) values against the full array of bacterial and fungal pathogens comparable to the common antibiotics.

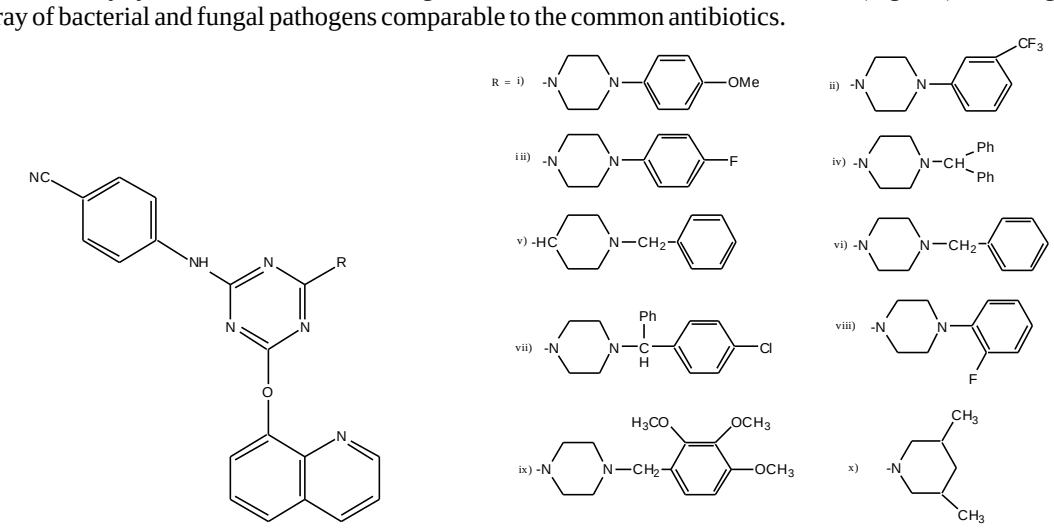
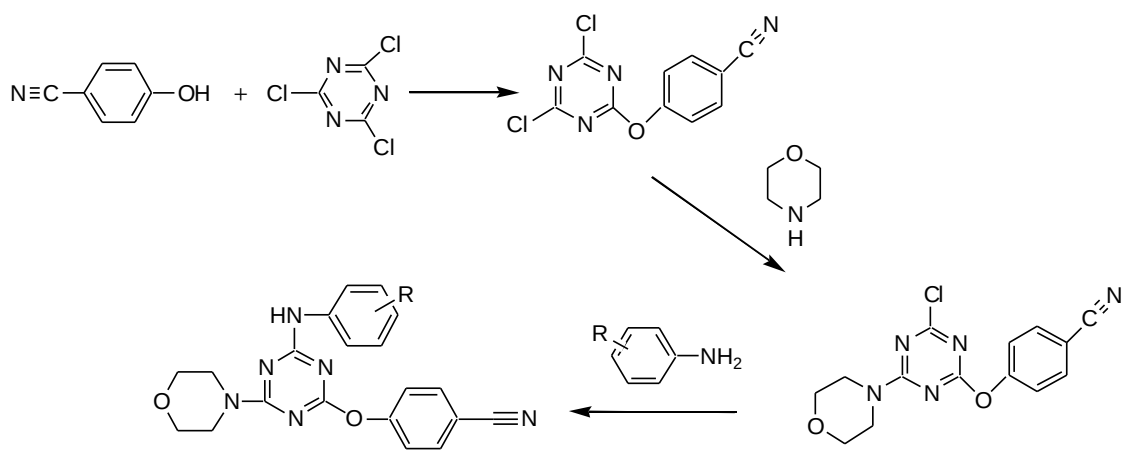


Fig. 4

Synthesis, structural elucidation and antimicrobial screening of s-triazinyl substituted aryl amine derivatives was studied.[15,16] These compounds (fig.5) show microbial activity against gram -ve bacteria and gram +ve bacteria and two fungal species. The compounds were tested using agar cup method for antimicrobial and anti fungal activity using *E. Coli, P. Aeruginosa, S. Aureus, S. Pyogenus (bacteria) C. Albicans, A. Niger and A. Claycus (fungi).*

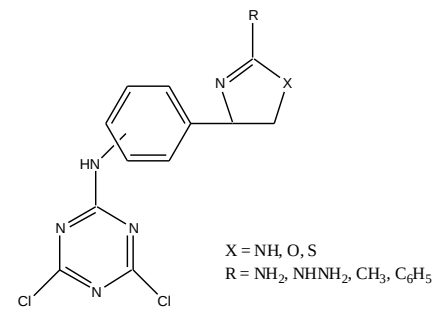


R = a) 4-CH_3, b) 4-F, c) 3-Cl-4-F, d) H, e) 4-OCH_3,
f) 4-Cl, g) 3-CH_3, h) 3-Cl, i) 3-Br j) 3-OCH_3,

Fig. 5

Triazine as Antimitotic Agent

D. Karunakaram *et al.*[17] studied anti mitotic activity of some newly synthesized s-triazine derivatives. A variety of s-triazine derivatives 4,6-dichloro-N-(3-substituted phenyl)-1,3,5-triazin-2-amine derivatives (B1 to B6) and 4,6-dichloro-N-(4-substituted phenyl)-1,3,5-triazin-2-amine derivatives (C1 to C6)- were prepared by reacting cyanuric chloride with amine substituted acetophenone and bromination of the ketone. The newly synthesized compounds (fig.6) were evaluated for anti mitotic activity and were found to have minimum activity compared to standard. All the compounds showed dose dependant activity.

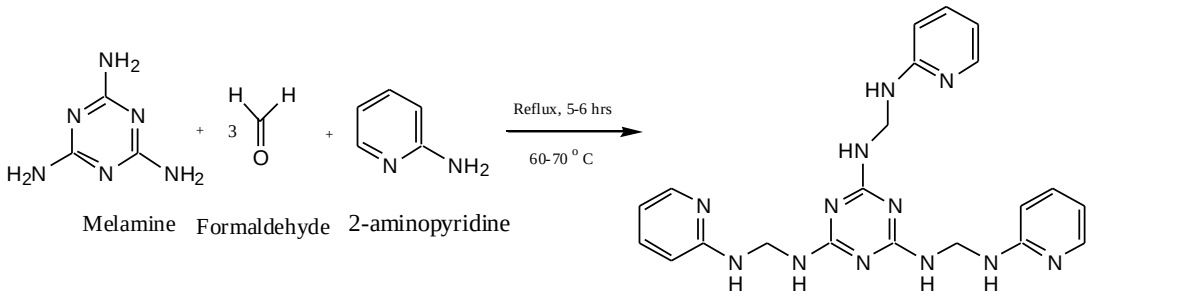


4,6-dichloro-N-(3 or 4-substituted phenyl)-1,3,5-triazine-2-amine

Fig. 6

Triazine as Anticorrosion Agent

C. Verma et al.18 synthesized N^2, N^4, N^6-tris (Pyridin-2-ylamino) methyl)-1,3,5-triazine-2,4,6-triamine by modified method using ultrasonication technique. Its molecule possesses effective corrosion inhibition property on corrosion of mild steel in 1 M Hydrochloric acid medium. The adsorption of inhibitor on the mild steel surface obeys Langmuir adsorption isotherm.



N^2, N^4, N^6,-tris [(pyridin-2-ylamino)methyl]-1,3,5-triazine-2,4,6-triamine

Scheme 3: Synthetic route of N^2, N^4, N^6-tris((Pyridin-2-ylamino)methyl)-1,3,5-triazine-2,4,6-triamine

Triazine as micellar mimic properties

Synthesis and micellar mimic properties of bile acid trimers was studied.[19] Two fan-shaped bile acid (fig.7) trimers have been synthesized via CuI-catalyzed azide-alkyne cycloaddition (CuAAC) 'click chemistry', and their extraction experiments of cresol red sodium (CR) and pyrene were investigated in the polar and non-polar solvents (fig.10), respectively. The transmission electron microscopy (TEM) results showed that the homogenous hollow capsules formed with the diameter size range of 40-70 nm in a solution of water and acetone. Thus the amphiphilicity of two fan-shaped bile acid trimers (fig.8 & 9) might be used as the promising candidate in biological and drug delivery applications.

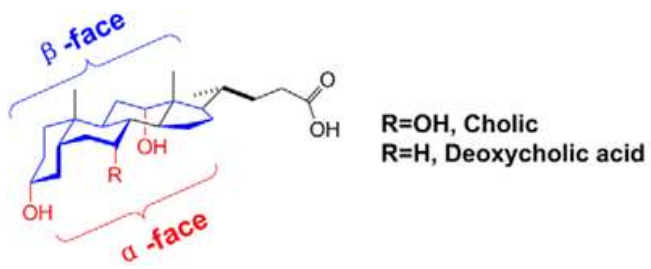


Fig. 7: Structure of bile acids (cholic acid and deoxycholic acid).

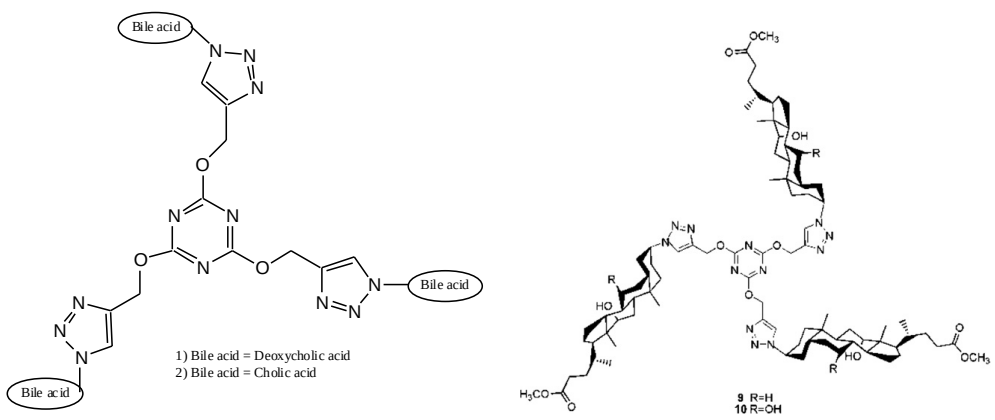


Fig.8 & 9: Structure of two fan-shaped molecules containing three bile acid units.

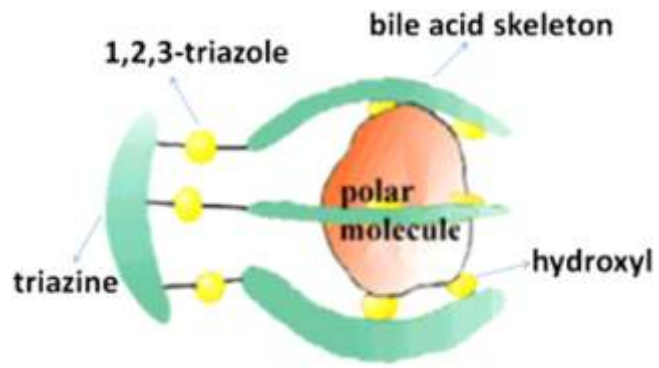
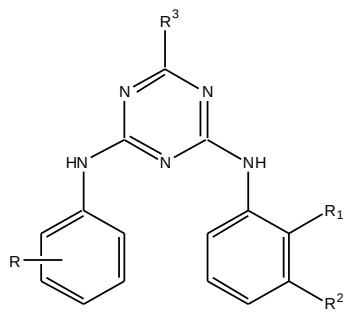


Fig.10: Assumption mode of the trimer's amphiphilic conformation in non-polar solvent systems

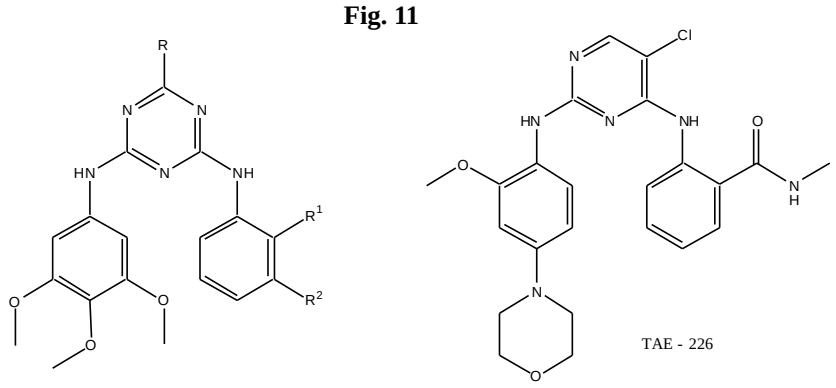
Triazine as FAK (focal adhesion kinase) inhibitor

D. Pascal *et al.*[20] reported that the synthesis of novel diarylamino-1,3,5-triazine derivatives (fig.11) as FAK (focal adhesion kinase) inhibitors and the evaluation of their anti-angiogenic activity on HUVEC cells. Compound I revealed that the mode of interaction with the FAK kinase domain is highly similar to that observed in the complex of TAE-226 (fig.12).



I

Fig. 11



TAE - 226

2-(3,4,5-trimethoxyphenylamino)-1,3,5-triazine derivatives compared to TAE - 226

R = Cl, H, $NHCH_3$, CH_3, CF_3

R^2 = H, $NHSO_2$,

R^3 = 2,4-dimethoxy, 2-OCH_3-4-morpholine, 3,4-dimethoxy-5-$(CH_2)_2CONH_2$, 4-CH_2NH_2

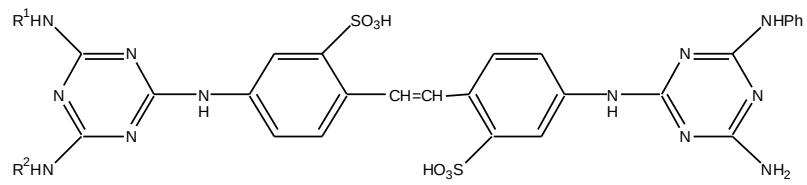
R^1 = H, $NHSO_2CH_3$, $NHCOCH_3$, $NHCOOCH_3$, $NHCON(CH_3)_2$, $CONHCH_3$, $CONHCH(CH_3)_2$, $CONHCH(CH_3)_2$, $CONHCH(CH_2CH_3)_2$, $CONHCH(CH_2CH_2)_2$, $CONH(CH_2)_2OH$, CO_2CH_3,$CONH(CH_2)_2N(CH_3)_2$

Fig. 12

Triazine as Fluorescent brighteners

The synthesis and properties of asymmetrically substituted 4,4'-Bis(1,3,5-triazin-6-yl) diaminostilbene-2,2'-disulfonic acid derivatives as fluorescent brighteners[II] were studied.21,22 Newly synthesized compounds a and b contain m-(sodium sulfo)anilino group and c and d (fig.14) contain N-(sodium carboxymethyl)amino group. These compounds showed almost the same value of whiteness as CI 86 (fig.13). These high whiteness can be obtained by using a substituent that can form a hydrogen bond with the OH group of cotton fiber.

Fig. 13: The structure of CI 86.



Compound - (a-d)

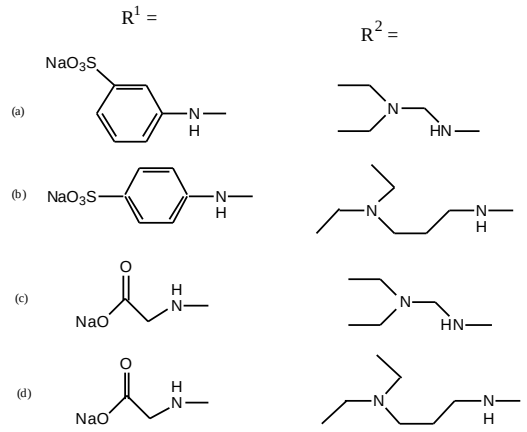


Fig. 14 (a-d)

Triazine as a structure sorbent for chromatography

Y. V. Patrushev *et al.*[23] reported the use of triazine polymer as a structurized sorbent for chromatography. In this work, the first time the possibility to use as chromatographic sorbent a new material based on microporous triazine polymer of regular structure PAF-6 (fig.15 &16) whose synthesis and properties have been described elsewhere.24

This polymer has a narrow pore size distribution with an average pore diameter of 11.8 Å and shows high thermal stability. These properties make it attractive for gas chromatography. The formation of a two dimensional structure on triazine basis allows the preparation of chromatographic sorbent with a regular system of pores of the same size. This structure, in contrast to microporous sorbents based on divinylbenzene, enables one to unify diffusion processes in pores and thus increase the separation efficiency.

A novel 2D porous organic framework based on the nucleophilic substitution of cyanuric chloride has been designed and synthesized successfully, which possesses an ordered structure, permanent porosity and drug release ability towards ibuprofen.

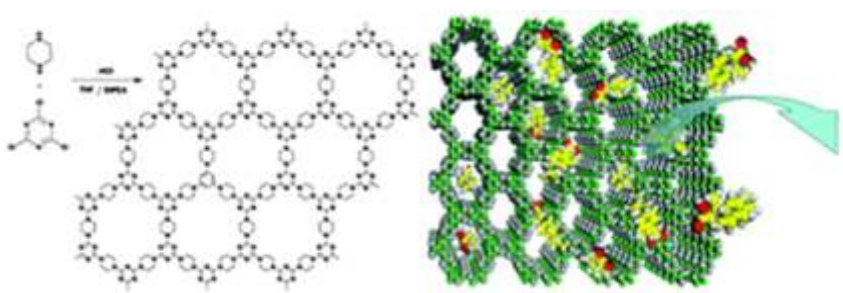


Fig. 15

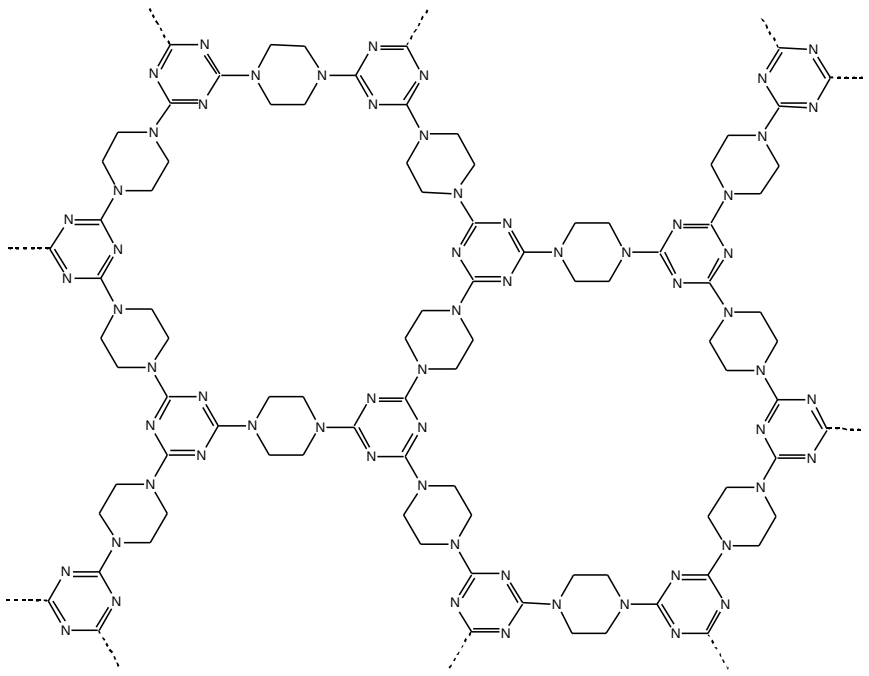


Fig. 16

Triazine as polymeric nanofilm by electrochemical poly-merization technique on aluminium surface.

F. Wang *et al.*[25] prepared 6-diallylamino-1,3,5-triazine-2,4-dithiol functional nanofilm (fig.17) by electrochemical polymerization technique on aluminium surface.

The functional polymeric nanofilm of 6-diallylamino-1,3,5-triazine-2,4-dithiol monosodium (DAN) was successfully prepared by cyclic voltammetry and galvanostatic technique in $NaNO_2$ supporting electrolyte on pure aluminium surface. Based on results of cyclic voltammetry and X-ray photoelectron spectroscopy (XPS), the mechanism of electrochemical polymerization was speculated, which indicated that the radical polymerization took place during the electrochemical polymerization process. The poly (6-diallylamino-1,3,5-triazine-2,4-dithiol) (PDA) functional nanofilm was also investigated by means of FT-IR spectra. The result also showed that the structure of polymeric nanofilm was consisted of Al_2O_3 and PDA. And the optimal electrochemical polymerization time of DAN at current density of 0.2 mA/cm^2 at 298 K in $NaNO_2$ solution is 6 min. It is expected that electrochemical polymerization technique will bring the direct joining between aluminium and rubber in the process of curing with the formed polymeric nanofilm.

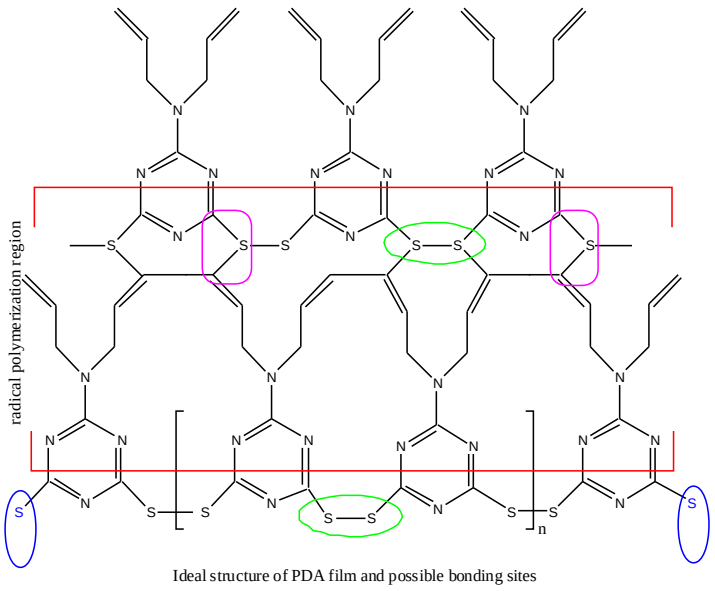


Fig. 17

Triazine as catalyst:

i) The Fischer indole synthesis

The Fischer indole synthesis using 2,4,6-trichloro-1,3,5-triazine (TCT) catalyst was carried out by S. Eranna *et al*.[26] Under these conditions several functional groups such as ester, cyano, sulfone, amides, and ethers are tolerated. By this method, many functional analysis pure indoles were prepared easily without the need of purification (fig.18 & 19).

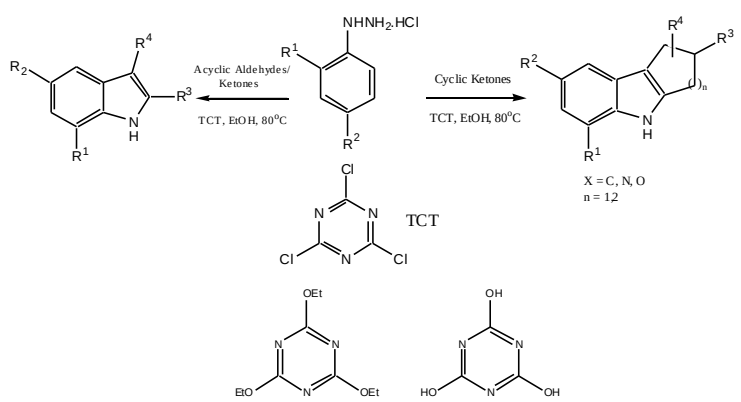
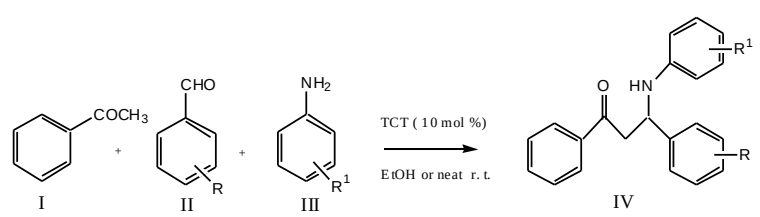


Fig.18 & 19

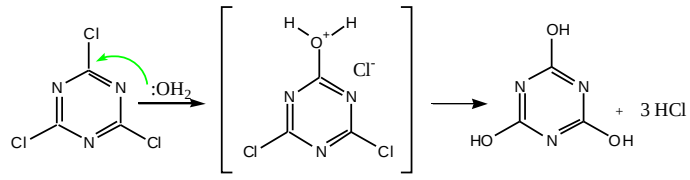
ii) One-pot Mannich-type reaction

F. Nemati *et al.*[27] reported 2,4,6-trichloro-1,3,5-triazine (TCT)-catalyzed one-pot Mannich-type reaction: three component synthesis of β-amino carbonyl compounds. Three-component Mannich-type reaction of acetophenone, aromatic aldehydes and aromatic amines is catalyzed by 2,4,6 trichloro-1,3,5-triazine (fig.20) at ambient temperature in EtOH and solvent-free conditions to give various ß-amino ketones in high yields.



R = H, 4-Me, 4-OMe, 4-Cl, 4-Br. R^1 = H, 4-Me, 4-Br, 3-NO_2, 4-NO_2.

The Mannich Reaction using TCT



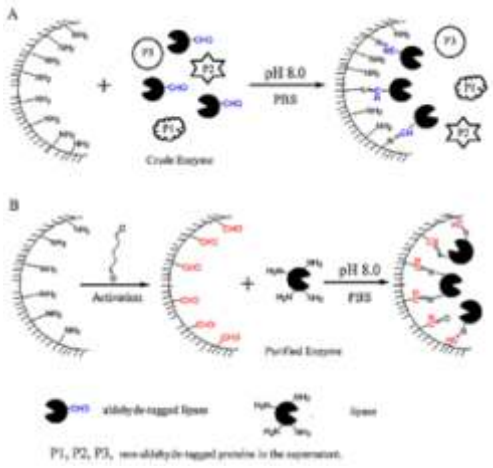
The reaction of TCT with H_2O to release HCl

Fig. 20

iii) R. H. Tale *et al*.[28] reported silica-supported 2,4,6-trichloro-1,3,5-triazine (Silica-TCT), environmentally benign, mild and efficient catalyst for the synthesis of 1,4-dihydropyridines under solvent-free conditions . Use of Silica-TCT catalyst gives several advantages in terms of simple reaction procedure, no need of organic solvent, mild reaction conditions giving quantative yield of desired product.

Triazine as genetically encoded aldehyde tag

A convenient one-step purification and immobilization of lipase using a genetically encoded aldehyde tag.[29] To avoid the unwanted and random covalent linkage between the cross-linker and enzyme's active site in covalent immobilization, a genetically encoded "aldehyde tag" was introduced into recombinant lipase and applied for the one-step purification and covalent immobilization of this enzyme.



Scheme 4: The preparation of the immobilized lipase using the aldehyde tag (IL-AT, A) and the immolized lipase using glutraraldehyde (IL-GA, B). P1, P2, P3 represent the non- aldehyde tagged lipase in the supernatant

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