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A Systematic Review on Synthetic Methods of Symmetric Triazines

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ABSTRACT

Triazines are interesting class of heterocyclic compounds. Various synthetic analogs of symmetric triazines have been prepared and evaluated for many pharmacological activities in different models with desired findings. Some analogs have shown potent pharmacological activity and may be considered as lead molecule for the development of future drugs. This review is an attempt to organize the chemical aspects of 1,3,5 triazine analogs reported till date systematically

Keywords: Substituted 1, 3, 5-triazines,chemical aspects, pharmacological activities.

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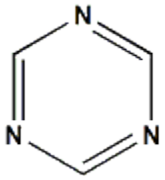
INTRODUCTION

Selection of Lead Moiety and Nucleus Introduction



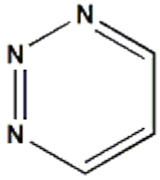
Triazine - IUPAC name: 1, 3, 5-triazine, s-triazine

1, 3,5-triazine, also called s-triazine, is an organic chemical compound with the formula (HCN)3. It is a six-membered heterocyclic aromatic ring. The atoms in triazine rings are analogous to those in benzene rings, which makes triazines aromatic compounds like benzene. One of several isomeric triazines s-triazine and its derivatives are useful in a variety of applications**.**

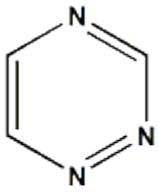
Triazine is the chemical species of six-membered heterocyclic ring compound with three nitrogens replacing carbon-hydrogen units in the benzene ring structure.The carbon-hydrogen units on the benzene ring position of the molecule have been replaced by nitrogens.The triazines are among the oldest known organic nitrogen-containing heterocycles. They can structurally be divided into three types: 1,2,3-triazines (**1**), 1,2,4-triazines (**2**) and 1,3,5-triazines (**3**). Of these three possible triazine isomers, the 1,2,3-triazines are by far the least studied class in comparison with their 1,2,4- and 1,3,5-isomers, because the ring system is the least stable of the three. Only a few papers dealing with 1,2,3-triazines have been published and the number of known compounds of this type is still small[1]. It also appears that no significant use of 1,2,3-triazines has yet been reported. In contrast to 1,2,3-triazines, the 1,2,4-triazines are well known.

Triazines are weak base. Triazines have much weaker resonance energy than benzene, so nucleophilic substitution is preferred than electrophilic substitution. Heterocyclic bearing a symmetrical s-triazines or 1, 3, 5-triazines moieties, represent an interesting class of compounds possessing a wide spectrum of biological activities such as anti-cancer, antiviral, fungicidal, insecticidal, bactericidal, herbicidal and antimicrobial, antimalarial agents. They also find applications as dyes, lubricants and analytical reagents. A large number of 1,2,4-triazines have demonstrated a spectrum of biological activities and have been used for various therapeutic purposes. For example, drug such as lamotrigine (**4**), which has a 1,2,4-triazine in its chemical structure, has been used clinically as an antiepileptic drug, and its mode of action suggests an involvement of sodium channels blockade.[2] 1,3,5-Triazines,also known as symmetric or *s*-triazines, having been known for almost 200 years, are commonly found in biologically active

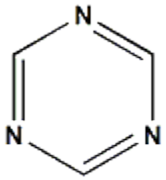
chemical entities. Baker triazines (1,2-dihydro-1,3,5-triazines, **5**) have been thoroughly investigated and found to be potent dihydrofolate reductase inhibitors that exhibit anticancer property[3]. In this review synthesis of several types of 1,3,5-triazines will be described.



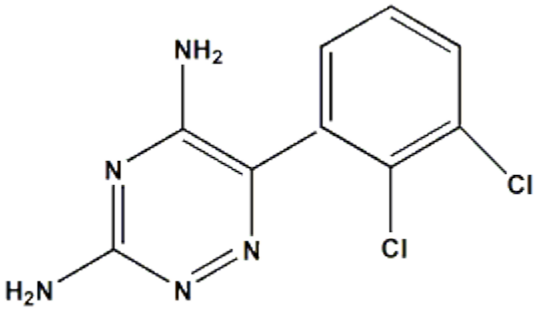
1,2,3-Triazines(1)



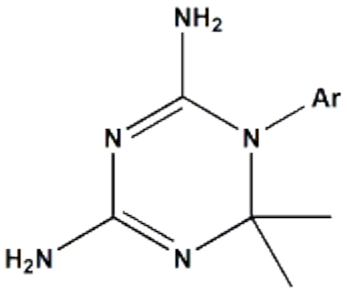
1,2,4-Triazines(2)



1,3,5-Triazines(3)



Lamotrigine(4)

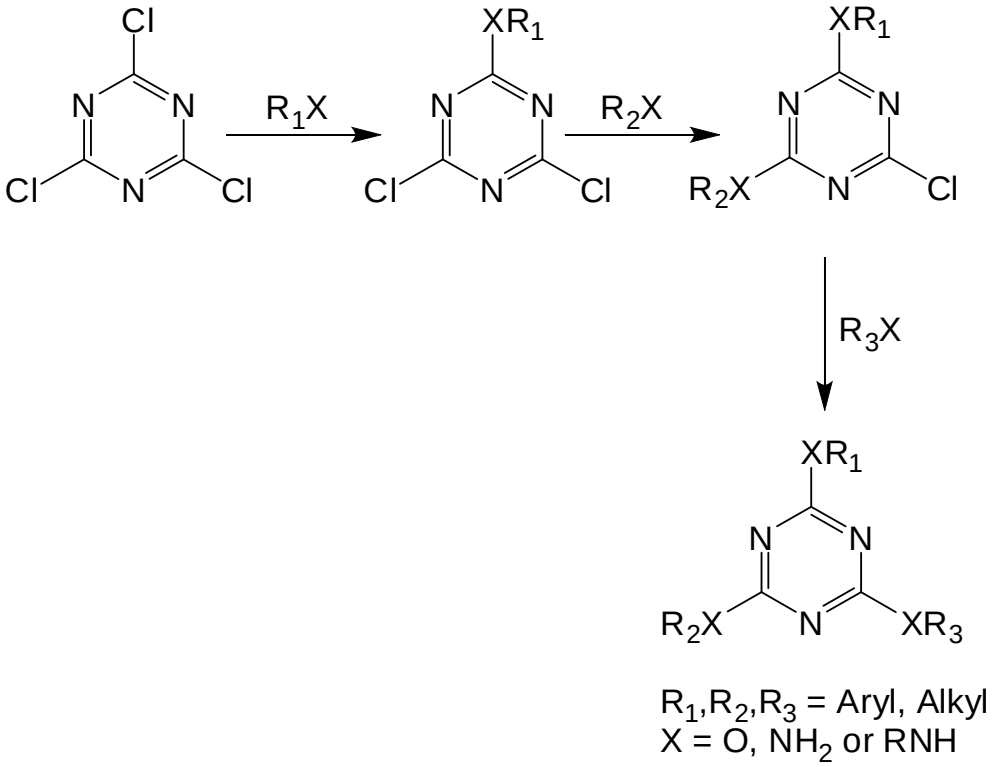


Bakers Triazine(5)

SYNTHETIC ROUTES FOR PREPARATION OF TRIAZINES

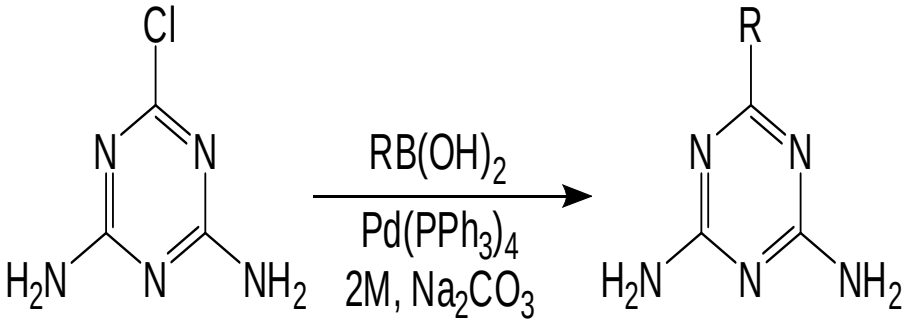
The synthesis of 1,3,5-triazines can be achieved with various different synthetic strategies using different starting materials. The possible synthetic routes of different types of 1,3,5-triazines such as fully unsaturated 1,3,5-triazines, dihydro-1,3,5-triazines and fused 1,3,5-triazines are reviewed as follows:

The nucleophilic displacement of chlorine from cyanuric chloride is the first method considered for the preparation of fully unsaturated 1,3,5-triazine derivatives. The three chloro substituents may be replaced sequentially depending upon the temperature of the reaction, and it is this property that makes cyanuric chloride so valuable in the synthesis of differently substituted 1,3,5-triazines (Scheme 1) [4].



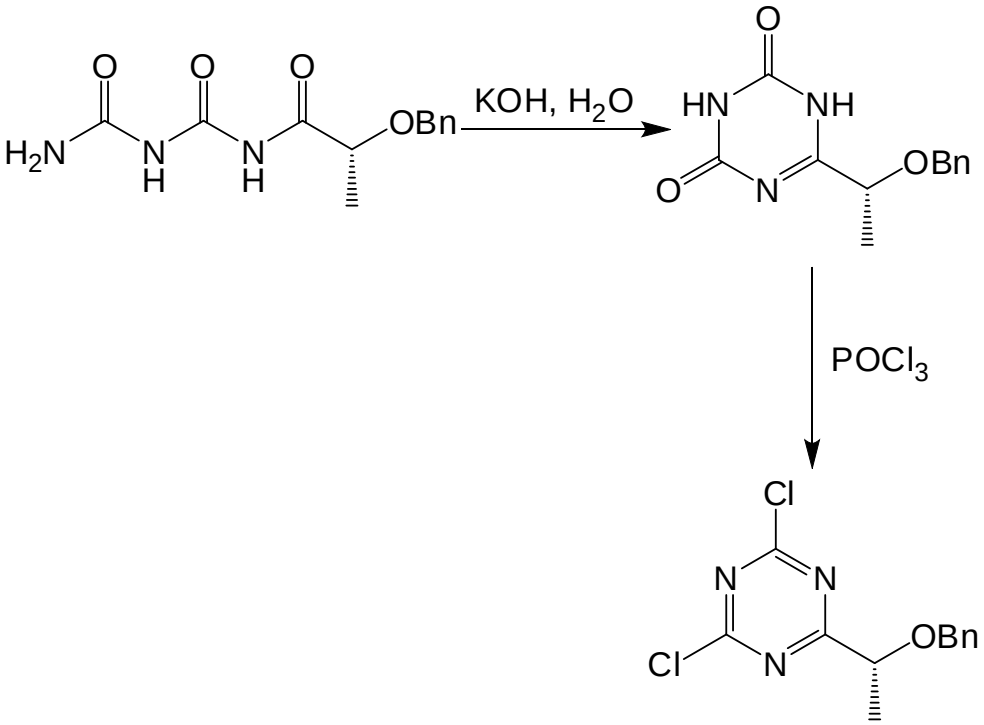
Scheme 1

The high yielding synthesis of 1,3,5-triazines was carried out *via* palladium-catalyzed Suzuki cross-coupling reactions of commercial available 6-chloro-2,4-diaminotriazine and aryl boronic acids (Scheme 2) [5].



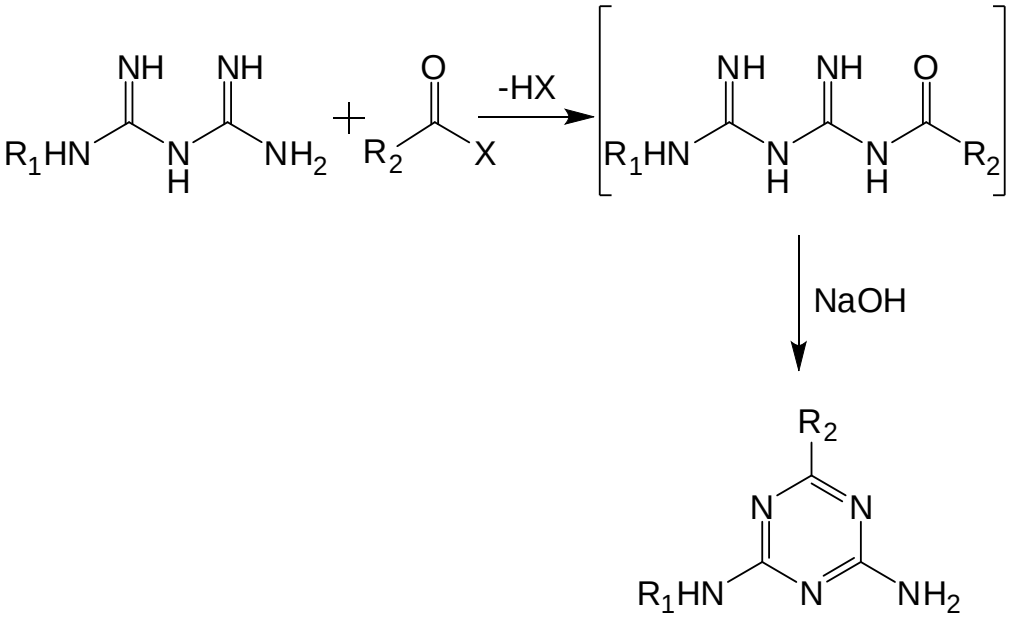
Scheme 2

(*R*)-2-Benzyloxy-N-ureidocarbonyl-propionamide was cyclized under basic condition to form 1,3,5-triazine-dione, which was then heated with phosphorous oxychloride to obtain the dichloro-1,3,5-triazine (Scheme 3) [6].



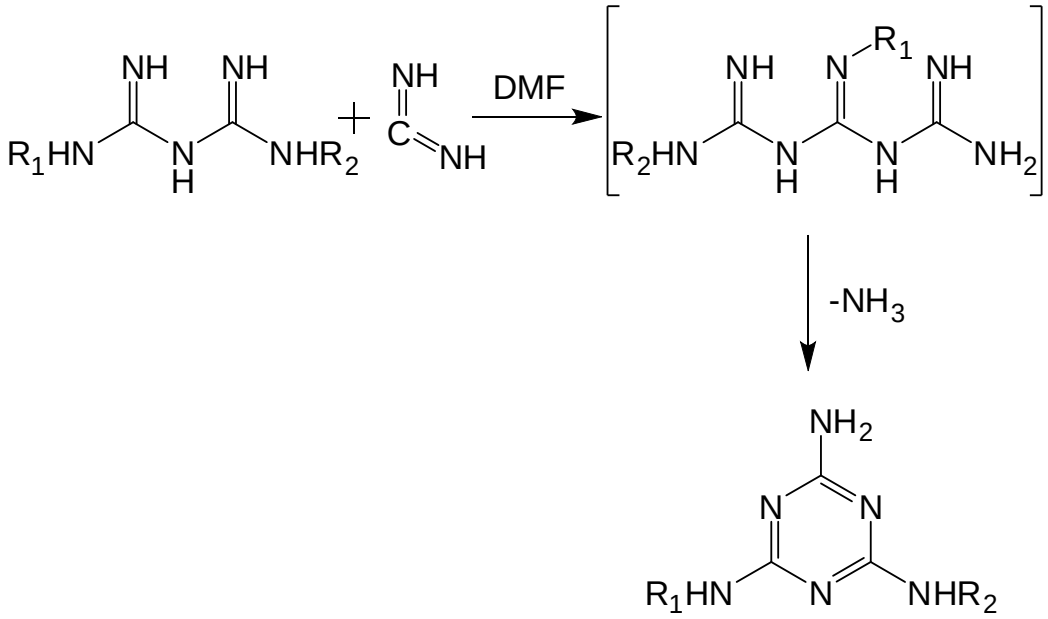
Scheme 3

Biguanide react with a variety of carboxylic acid derivatives in basic or neutral conditions to produce a wide range of 6-aryl or alkyl substituted-2,4-diamino-1,3,5-triazines (Scheme 4) [7].



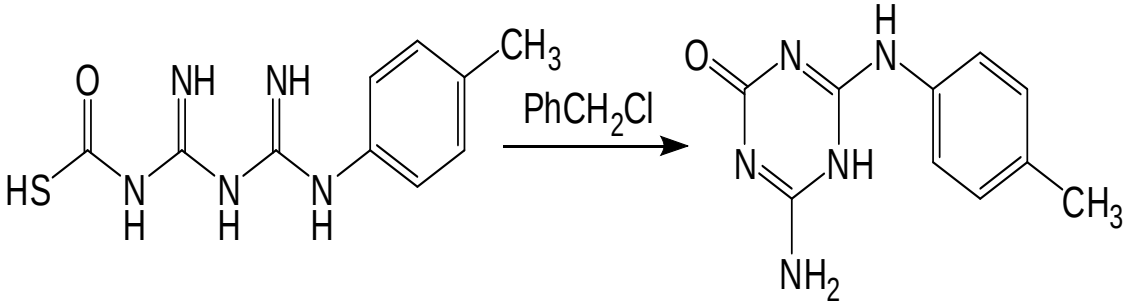
Scheme 4

Biguanides react with carbodiimides to form melamine derivatives in 60-70% yields (Scheme 5) [8].



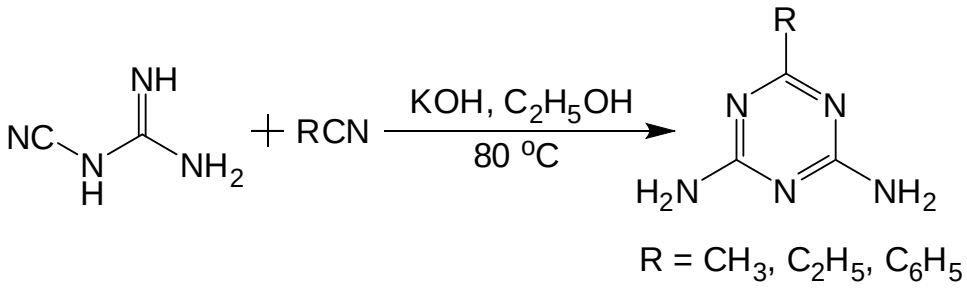
Scheme 5

Using thiocarbamic substituted biguanide derivative as a starting material, targeted 4-amino-6-*p*-tolylamino-5H-1,3,5-triazin-2-one was synthesized by the treatment of benzylchloride and with the elimination of benzyl mercaptan (Scheme 6) [9].



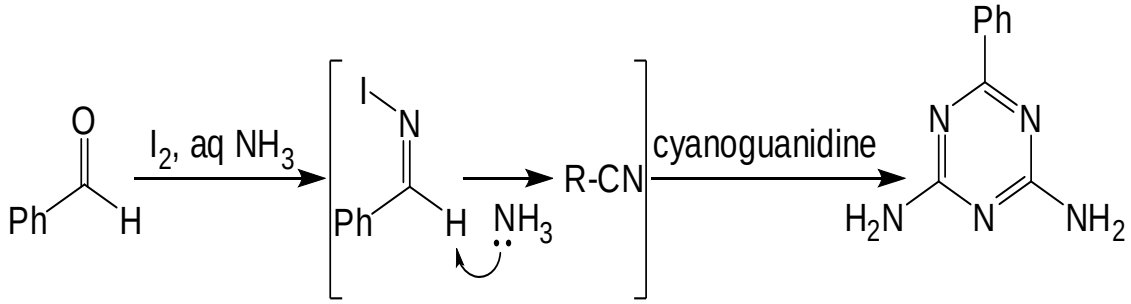
Scheme 6

Nitrile is the most commonly used two-atom fragment to condense with cyanogunidine in the synthesis of 6-substituted-2,4-diamino-1,3,5-triazines. The condensation is catalyzed by potassium hydroxide and subjected to temperature between 82°C and 150°C for 1.5-44 h which is dependent on the nitriles used (Scheme 7) [10].



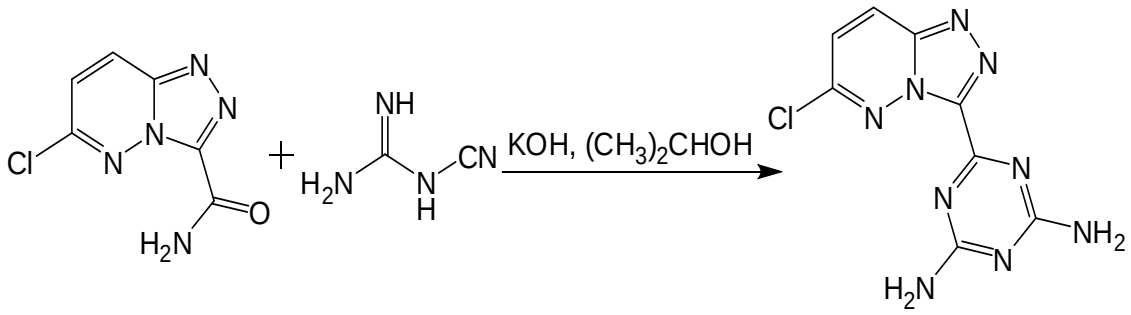
Scheme 7

As shown in Scheme 4.8, benzonitrile, which was produced *in situ* from the reaction of benzaldehyde with I_2/aq NH_3, was treated with cyanoguanidine (1.1 equiv) and KOH (2.2 equiv) at refluxing temperature for 24 h to obtain 2,6-diamino-4-phenyl-1,3,5-triazine with 78% yield [11].



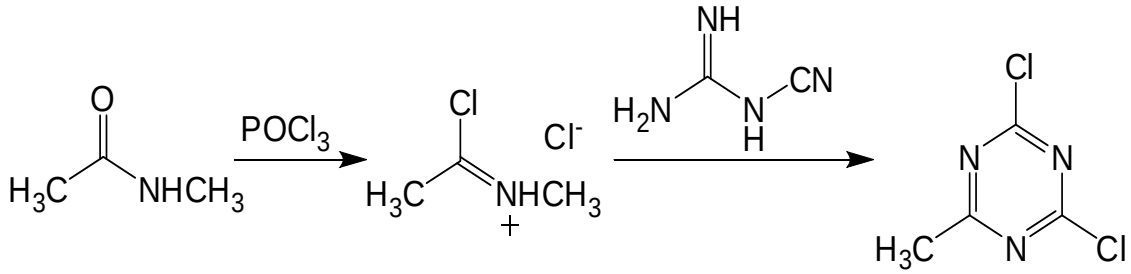
Scheme 8

Starting from 1,2,4-triazolo[4,3-b]pyridazine-3-carboxamide, a heterocyclic substituted-2,4-diamino-1,3,5-triazine was synthesized in the presence of potassium hydroxide in isopropyl alcohol (Scheme 9) [12].



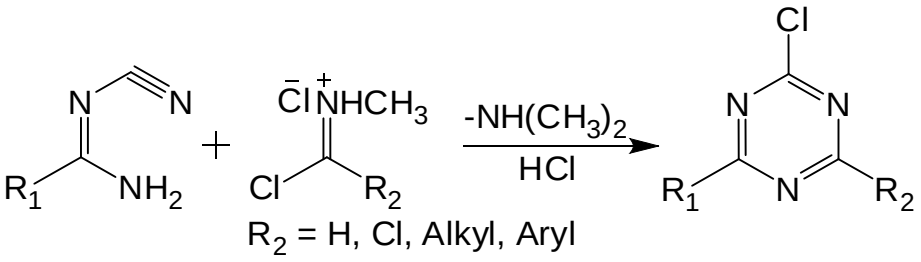
Scheme 9

Dichloro-1,3,5-triazines can be synthesized from the cyclocondensation reaction between cyanoguanidine and chloromethyleneiminium salts (Scheme 10) [13].



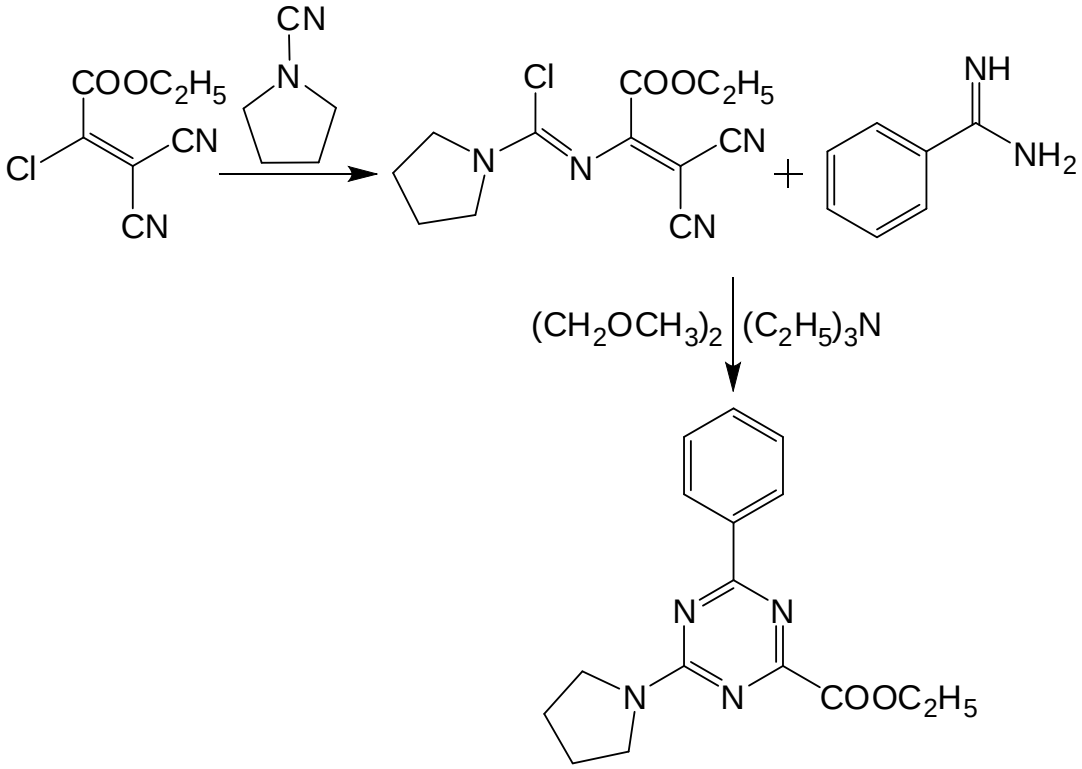
Scheme 10

As illustrated in Scheme 4.11, the synthesis of aryl- and alkyl-substituted 1,3,5-triazines may readily be achieved by the condensation of *N*-cyanoamidines with chloromethyleneiminium salts [14].



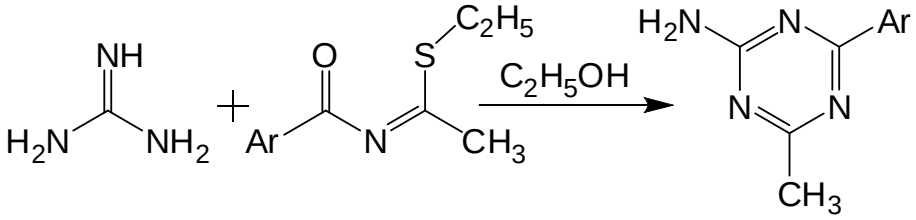
Scheme 11

Addition reaction of ethyl 2-chloro-3,3-dicyanoacrylate with pyrrolidino nitrile gives 49-63% intermediate. In the presence of triethylamine, this intermediate reacts with the bisnucleophilic amidine $H_2NPhC=NH$ to give 1,3,5-triazines in 64-82% yield (Scheme 12) [15].



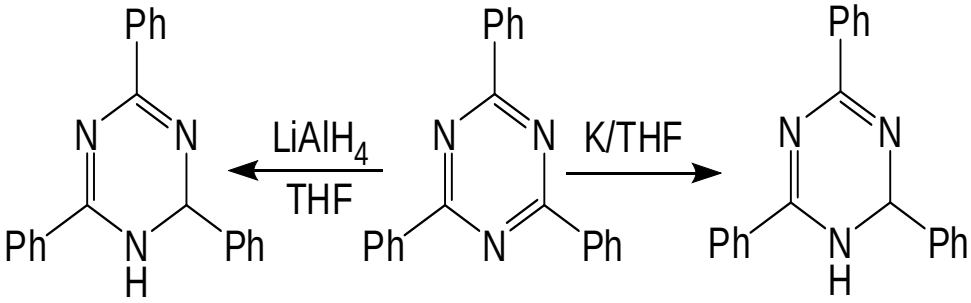
Scheme 12

The reaction of the N-aroylthioimidates with guanidine in ethanol gives 1,3,5-triazines in 60-93% yield. It provides one of the few methods to synthesize monoamino-1,3,5-triazines with different alkyl or aryl substitutions (Scheme 13) [16].



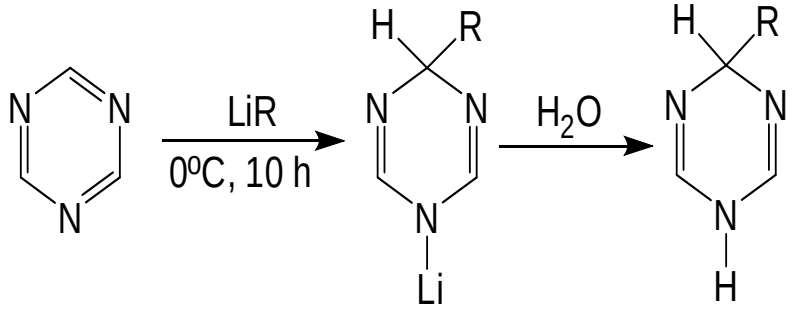
Scheme 13

The known reactions involve preparation of 2,4,6-triphenyl-1,2-dihydro-1,3,5 triazine from the reductions on 2,4,6-triphenyl-1,3,5-triazines using lithium aluminum hydride or by treatment with potassium in THF followed by hydrolysis (Scheme 14) [17].



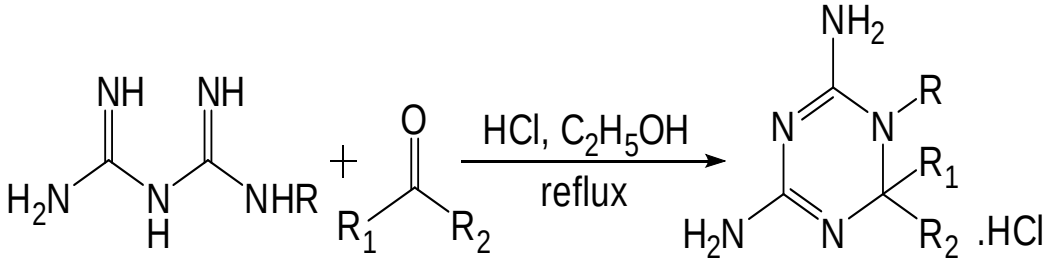
Scheme 14

Boesveld *et al.* have reported a series of addition products of mono substituted 1,4-dihydro-1,3,5-triazines, synthesized from the treatment of 1,3,5-triazine with an alkyllithium LiR [R=Me, n-Bu, t-Bu, Ph, CH_2TMS, $CH(TMS)_2$ or $Si(TMS)_3(THF)_3$] upon hydrolysis (Scheme 15) [18].



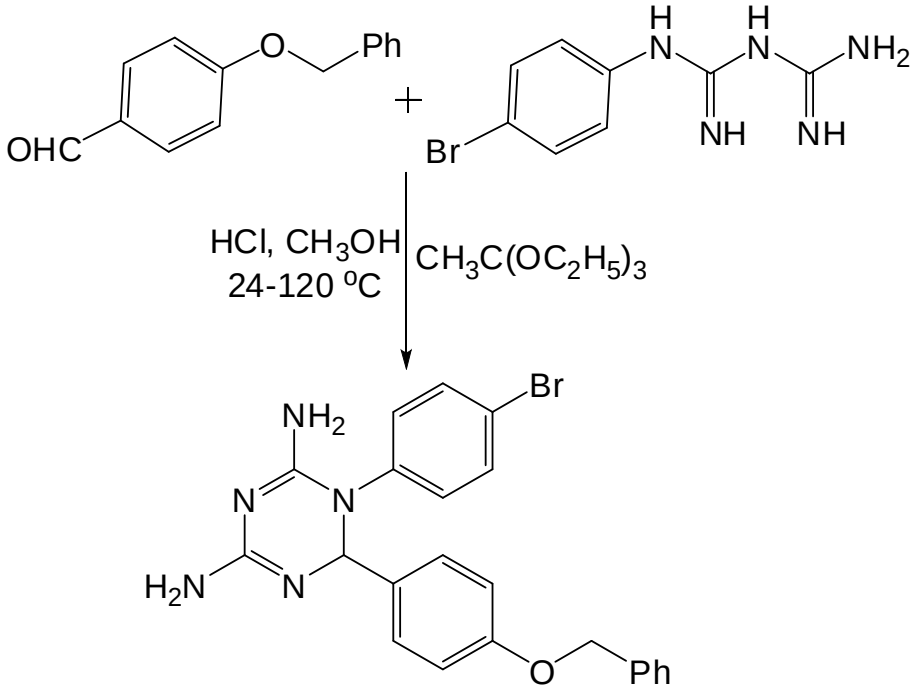
Scheme 15.

Various biguanides have been reported to react with aldehyde or ketone to give the corresponding 1,2-dihydro-1,3,5-triazines (Scheme 16) [19].



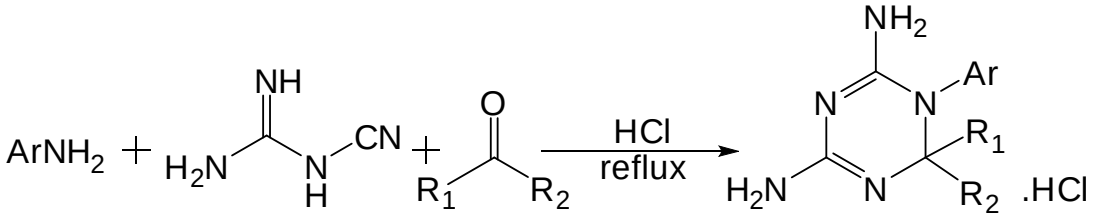
Scheme 16

An efficient synthesis of 1-aryl-4,6-diamino-1,2-dihydro-1,3,5-triazines using triethyl-orthoacetate as a water scavenger has also been reported in good yield from an acid-catalyzed reaction between corresponding arylbiguanide hydrochlorides and carbonyl compounds (Scheme 17) [20].



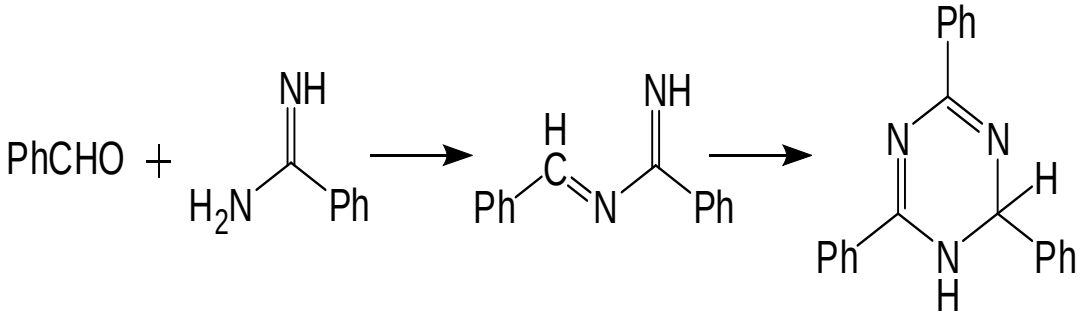
Scheme 17

Dicyanamide can be used as a starting material to prepare 1,2-dihydro-1,3,5-triazines. It can react with molecular equivalent of the aryl amine or its acid salt plus one equivalent of acid and a ketone or an aldehyde with the loss of one molecule of water to give the 1,2-dihydro-1,3,5-triazine nucleus (Scheme 18) [21].



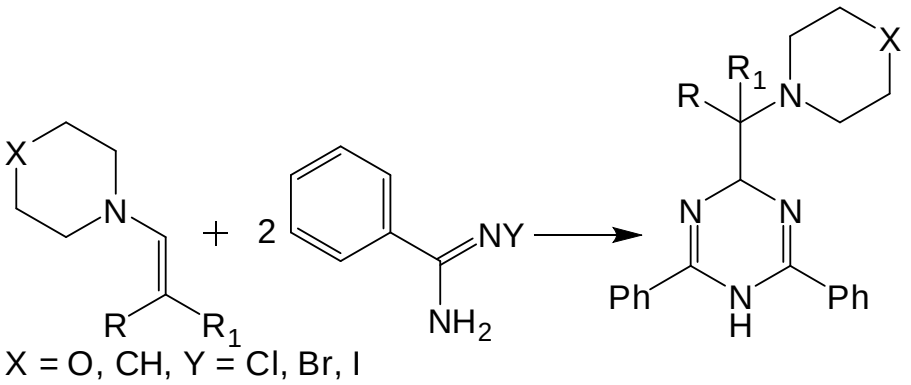
Scheme 18

Condensation of benzaldehyde with benzamidine gives 2,4,6-triphenyl-1,2- dihydro-1,3,5-triazine (Scheme 19) [22].



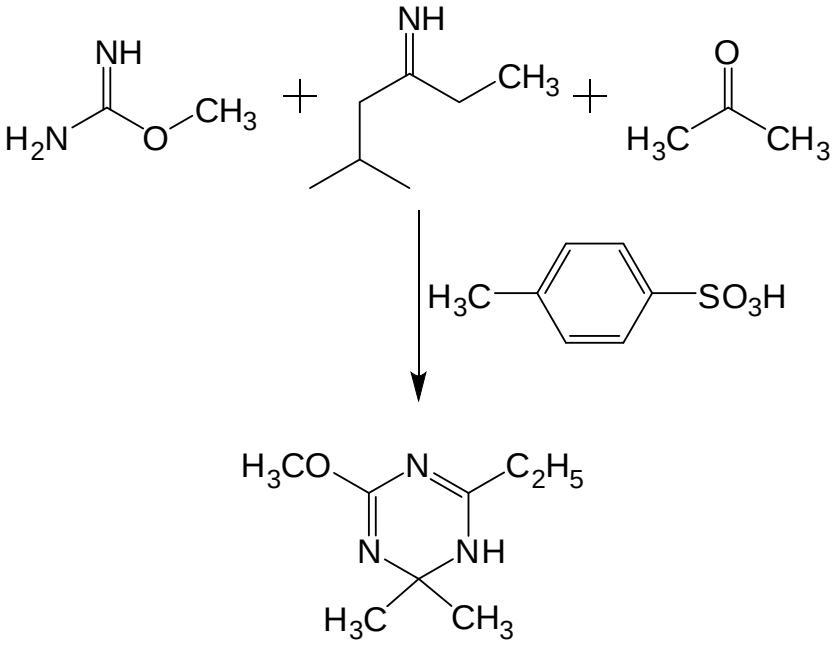
Scheme 19

The reaction of N-haloamidines with enamines derived from aldehydes forms 1,4-dihydro-1,3,5-triazines (Scheme 20) [23].



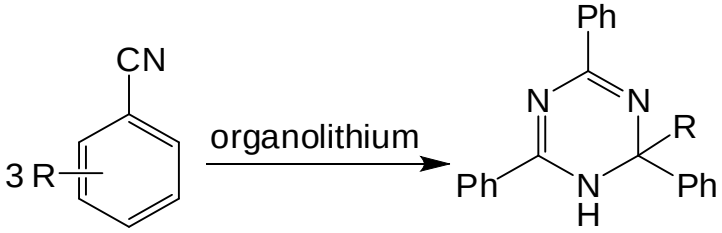
Scheme 20

A three-component condensation of isopropylpropionimidate with *O*-methylisourea tosylate in the presence of acetone gives 39.4% of 1,2-dihydro-1,3,5-triazine (Scheme 21) [24].



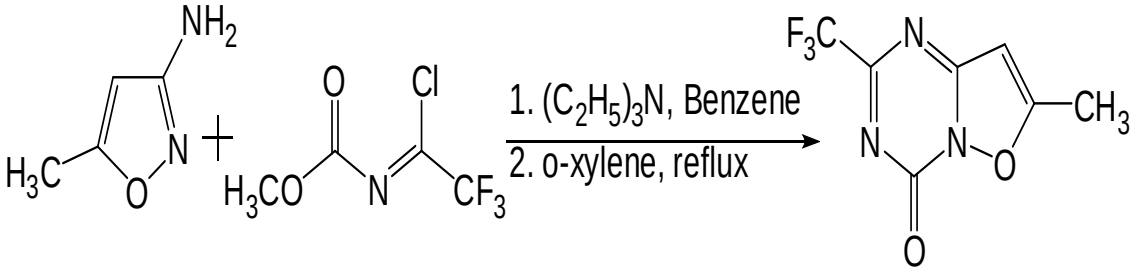
Scheme 21

Cook *et al*. obtained 2,2,4,6-tetraphenyl-1,2-dihydro-1,3,5-triazines as the sole product and succeeded in preparing a series of 1,2-dihydro-1,3,5-triazines (Scheme 22) [25].



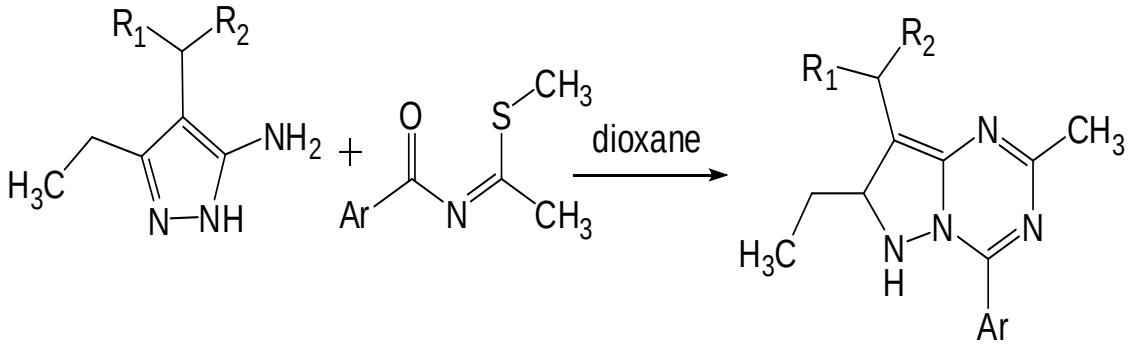
Scheme 22

2-Trihalomethyl-4H-isoxazolo [2,3-a]-1,3,5-triazin-4-ones have been synthesized by cyclization of 3-amino-5-methylisoxazole with N-(1-chloro-2,2,2-trihaloethylidene)-*O*-methyl-urethanes (Scheme 23) [26].



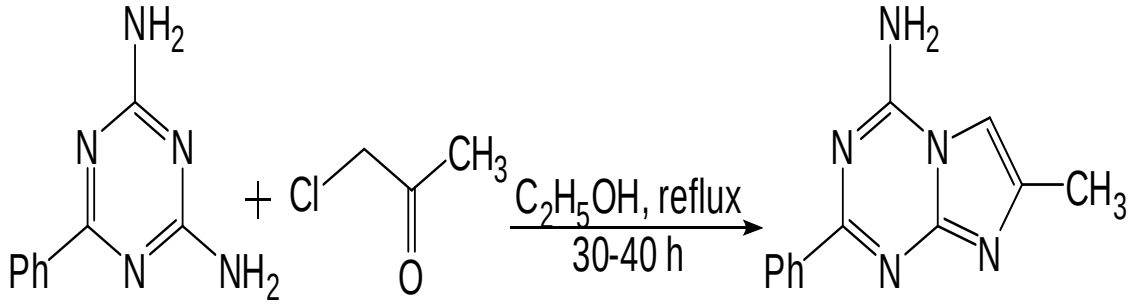
Scheme 23

The pyrazolo-[1,5-a]-1,3,5-triazines have been prepared in a convergent fashion by the coupling of 3-aminopyrazole with aroyl thioimidates (Scheme 24) [27].



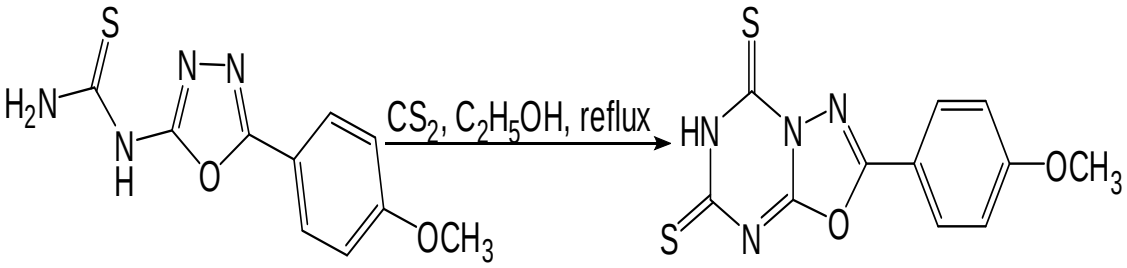
Scheme 24

The synthesis of 7-substituted-2-phenylimidazo[1,2-a]-1,3,5-triazine-4-yl-amines also employs similar strategy by cyclization of 2,4-diamino-1,3,5-triazine in refluxing ethanol with 2-chloroacetone (Scheme 25) [28].



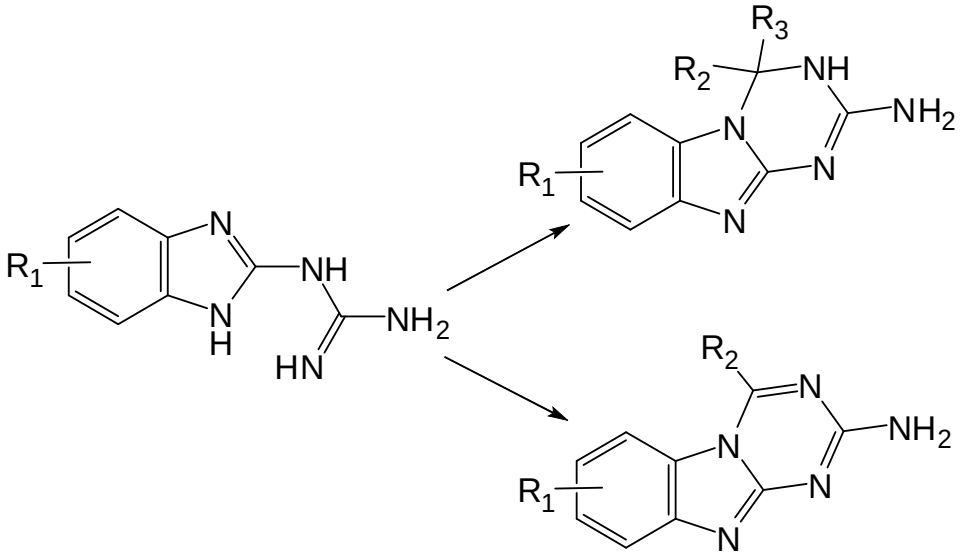
Scheme 25

N^1-(5-Aryl-1,3,4-oxadiazolo-2-yl)-ureas on cyclocondensation with CS_2/KOH afforded 2-aryl-1,3,4-oxadiazole[3,2-a]-1,3,5-triazine-5,7-(6H) dithione nucleo bases (Scheme 26) [29].



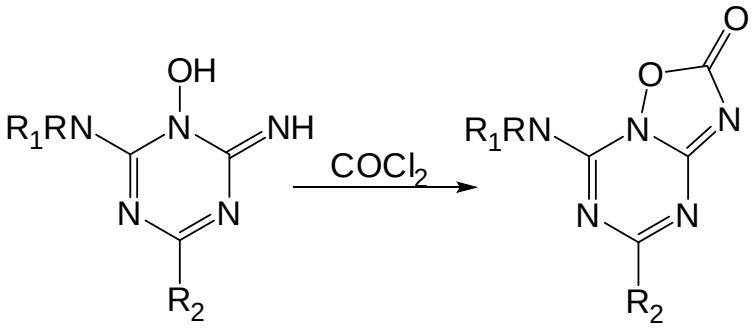
Scheme 26

2-Amino-1,3,5-triazino[1,2-a]benzimidazoles were obtained by a ring annelation from 2-guanidinobenzimidazoles (Scheme 27) [30].



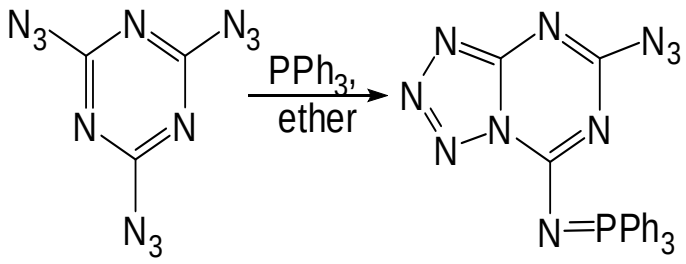
Scheme 27

Oxadiazolo-1,3,5-triazinederivatives which showed antihypertensive and vasodilating activity, have been prepared by cyclocondensation of 2,4-diamino-6-(diallylamino)-1,3,5-triazin-3-oxide with $COCl_2$ (Scheme 28) [31].



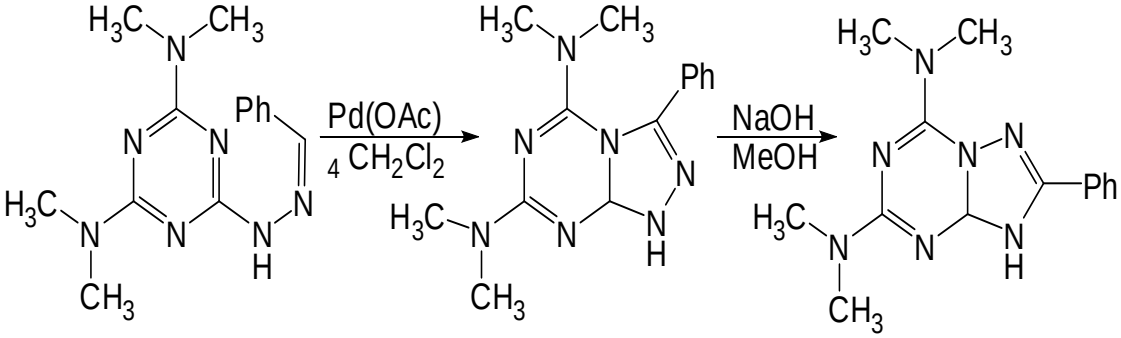
Scheme 28

2-Triphenylphosphanimino-4-azidotetrazolo[5,1-a]-1,3,5-triazine has been obtained by reaction of 2,4,6-triazido-1,3,5-triazine with one equivalent of triphenylphosphine (Scheme 29) [32].



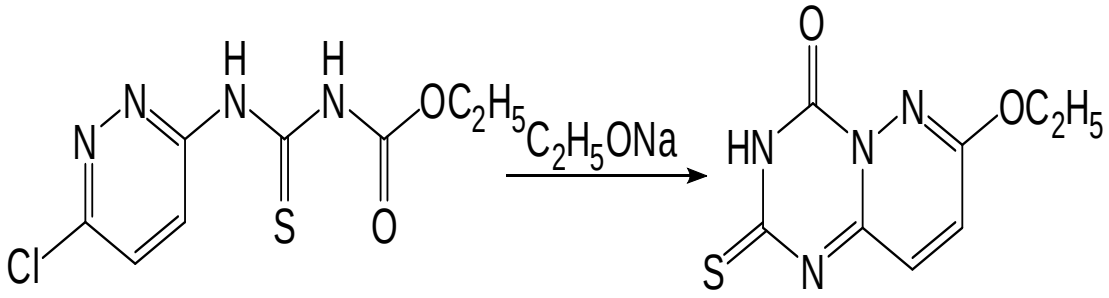
Scheme 29

4-Diamino-6-hydrazone-1,3,5-triazines can be cyclized to 1,2,4-triazolo[4,3-a]-1,3,5-triazines with $Pb(OAc)_4$ in CH_2Cl_2. The product 1,2,4-triazolo[4,3-a]-1,3,5-triazines can be rearranged to 1,2,4-triazolo[1,5-a]-1,3,5-triazines in MeOH-NaOH (Scheme 30) [33].



Scheme 30

N-Carbethoxy-N′-(6′-chloropyridazinyl-3′) thiourea which is upon heating in the presence of sodium ethoxide afforded the compound 7-ethoxy-2-thioxopyridazino[2,3-a]-1,3,5-triazin-4(3H)-one (Scheme 31) [34].



Scheme 31

CONCLUSION

1,3,5-triazine is one of the oldest heterocyclic compound available. Because of its low cost and ease of availability, it emphasizes the sight of researcher for novel synthesis. Some dyes, lubricants and reagents derived from 1,3,5-triazine are already available in market. The present review paper showed that s-triazine synthesis. As 1,3,5-triazine show nucleophilic substitution reaction a series of compound has been synthesized by using chemical reaction of 2,4,6-trisubstituted-1,3,5-

triazines with various nucleophilic reagents like primary and secondary amine. These newly synthesized compound exhibit wide spectrum biological activity such as analgesic and anti-inflammatory, antifungal, antibacterial, histamine blockers, antitubercular and antioxidant. By using same approach series of compounds can be synthesized, characterize and evaluate for desire pharmacological activity with high potency and low toxicity.

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REFERENCES

1. Ohsawa A.; Arai H.; Ohnishi H.; Igeta H. J. Chem. Soc., Chem. Commun., 1981,1174.
2. Leach M. J.; Baxter M. G.; Critchley M. A. E. Epilepsia. 1991, 32 (Suppl. 2), S4.
3. Blaney J. M.; Hansch C.; Silipo C.; Vittoria A. Chem. Rev. 1984, 84, 333-407.
4. [Katritzky A. R.; Rees C. W. Comp. Heterocycl. Chem. 1984, 3, 457.
5. Cooke G.; Augier de Cremiers H.; Rotello V. M.; Tarbit B.; Vanderstraeten P. E. Tetrahedron, 2001, 57, 2787.
6. Mylari B.L.; Withbroe G. J.; Beebe D. A.; Brackett N. S.; Conn E. L.; Coutcher J. B.; Oates P. J.; Zembrowski W. J. Bioorg. Med. Chem. 2003, 11, 4179.
7. Thurston J. T.; Schaefer F. C.; Dudley J. R; Holm-Hansen D. Illuminati G. J. Am. Chem. Soc. 1951, 73, 2992.
8. Kurzer F.; Pitchfork E.D. J. Chem. Soc. 1964, 3459.
9. Parnandiwar J. M. Indian. J. Chem., Section B, 1978, 16B (6), 535.
10. Bartholomew D. Comp. Heterocycl. Chem. 1996, 6, 575.
11. Shie J; Fang J. J. Org. Chem. 2003, 68, 1158.
12. Kosary J.; Kasztreiner E.; Rabloczky G.; Kurthy M. Euro. J. Med. Chem. 1989, 24(1), 97.
13. Chiang G. C. (E. I. du Pont de Nemours and Co.); US Pat. 5095113 (1992)
14. Harris R. L. N. Aus. J. Chem. 1981, 34, 623.
15. Gustafson G.R.; Baldino C.M.; O'Donnel M.E. Sheldon A.; Tarsa R.J.; Vern C.J.; Coffen D.L. Tetrahedron, 1998, 54, 4051.
16. Lin Y. I.; Fields T. L.; Lee V. J.; Lang S. A., Jr. J. Heterocycl. Chem. 1982, 19, 613.
17. Nyquist H. L. J. Org. Chem. 1966, 31, 784.

18. Boesveld W. M.; Hitchcock P. B.; Lappert M. F. J. Chem. Soc., Perkin Trans. 1, 2001, 1103.
19. Modest E. J.; Levine P. J. Org. Chem. 1956, 21, 14.
20. Saesaengseerung N.; Vilaivan T.; Thebtaranonth Y. Syn. Comm. 2002, 32, 2089.
21. Modest E. J. J. Org. Chem. 1956, 21, 1.
22. [Cherkasov V. M.; Kapran N. A.; Zavatzkii V. N. Khim. Geterotsikl. Soedin., 1969, 350.
23. Citerio L.; Pocar D.; Stardi R.; Gioia B. Tetrahedron. 1979, 35, 69.
24. Bader H. J. Org. Chem. 1965, 30, 930.
25. Anker R. M.; Cook A. H. J. Chem. Soc. 1941, 323.
26. Vovk M. V.; Bolbut A. V.; Dorokhov V. I. Chem. Heterocycl. Comp. 2004, 40, 496.
27. Gilligan P. J.; Folmer B. K.; Hartz R. A.; Koch S.; Nanda K. K.; Andreuski S.; Fitzgerald L.; Miller K.; Marshall W. J. Bioorg. Med. Chem. 2003, 11(18), 4093.
28. Novellino E.; Abignente E.; Cosimelli B.; Greco G.; Iadanza M.; Laneri S.; Lavecchia A.; Rimoli M. G. J. Med. Chem. 2002, 45, 5030.
29. Chauhan D.; Chauhan J. S.; Singh J.; Bajpai S. K.; Joshi M. N. Indian J. Chem. 2003, 42B(1), 215.
30. Dolzhenko A. V.; Chui W. K. J. Heterocycl. Chem., 2006, 43 (1), 95.
31. Muller J. C.; Ramuz H. Eur. Pat. Appl. EP 7643 19800206, 61 pp.
32. Kessenich E.; Polborn K.; Schulz A. Inorg. Chem. 2001, 40, 1102.
33. Langdon S..; Simmonds R. J.; Stevens M. F. G. J. Chem. Soc., Perkin Trans. 1984, 5, 993.
34. Zupan M.; Stanovnik B.; Tisler M. J Org. Chem. 1972, 37(19), 2960.