SYNTHESIS OF NEW NON-SYMMETRIC SUBSTITUTED TRIAZINES AND TRIAZINE DERIVATIVES BY SN AR REACTION MECHANISM

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Abstract
Attempts were made to carry out the laboratory synthesis of non-symmetric mono- and di- substituted 1,3,5-triazines containing amine and ether group by the action of electron donating substituent on 2,4,6-trichloro-1,3,5-triazines by aromatic nucleophilic substitution reaction mechanism(S_NAr reaction) by temperature controlled. The introduction of amino group (-NH-) and ether (-O-) linker bridge shows more promising antibacterial activity. Yield of newly synthesized compounds were quite well and their structures were confirmed by using IR, ^{1}H NMR and Mass spectral data.
***Key words:*cyanuric chloride, 2,4,6-trichloro-1,3,5-triazines and its derivatives,1-naphthol, spectral data.**

INTRODUCTION:

S-triazine is a six member heterocyclic compound having a chemical formula $C_3N_3Cl_3$. All the 2,4,6 - mono, di- or tri- substituted S-triazine derivatives have wide practical applications. 2,4,6-trichloro S-triazine derivatives prepared by replacement of one chlorine atom at 0-5^{0}C, second one at 60-80^{0}C.[1]Cynuric chloride is an inexpensive, commercially available reagent and is useful for the preparation of variety of S-triazine derivatives. S-triazinederivatives have received considerable attention because of their potent biological activity, for example in medicinal chemistry as anticancer, antiplasmodial and also use for the development of the treatment of diabetes, epilepsy, inflammation and analgesic.[2-4]Some of organic molecules containing S-triazine moiety have been extensively used as therapeutic agents such as Sulfasymazine, Irsoglandin, Troclosene K12 and Prometrynetc.[5] During last few years the potential of S-triazine derivatives in agrochemical and medicinal properties have been subjected to investigation. Literature survey reveals that amino substituted S-triazine derivatives and thio substituted S-triazine derivatives are associated with number of pronounced antibacterial activities against gram positive (B.subtilis, B. sphaericus, S. aureusetc) and gram negative organism (E. coli, K. aerogenes, P. aeruginosa) etc.[7-9]The present work focused on stepwise design and optimization of functional groups selected to reduce the RW pharmaceutical properties based on 1,3,5-triazines as template. The results provide some insight into the structure-function relationship of these agents.[10]Here we report on the preparation of a series of new 2,4,6-trisubstituted-1,3,5-triazines via sequential substitution of the three chlorine of cyanuric chloride by N-, O- and S- centered nucleophiles.[12]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.[14]Globally, researchers are trying to synthesize new drugs with better pharmacokinetic and pharmacodynamics properties with fewer adverse effects.[16-18]In this work we prepared various 1,3,5-triazine derivatives by replacing one, two or three chlorine by different nucleophiles including aromatic amines, phenols and thiols by nucleophilic substitution reaction in the presence of a hydrochloride acceptor usually sodium carbonate, bicarbonate, hydroxide or tertiary amines.

MATERIAL AND METHOD:

Solvents and reagents were purchased from Sigma-Aldrich and Merck. Unless otherwise stated, the normal workup from organic solvent involved drying over Na_2SO_4. Progress of the reaction was monitored by thin-layer chromatography (TLC) using aluminum sheets coated with silica gel F254 (Merck) and suitable solvent systems. Spots were visualized by a Spectroline UV Lamp (254 or 365 nm) or I_2 vapor.The IR spectra were recorded (KBr discs) on a Perkin Elmer 1650 FT-IR instrument. NMR spectra were recorded on a BrukerAvance II 400 MH_Z NMR spectrometer (SAIF Punjab University Chandigarh) using DMSO as a solvent and TMS as an internal standard with 1H resonant frequency of 400 MH_Z.Chemical shifts are reported in parts per million (ppm) and are referenced relative to residual solvent (e.g. $CHCl_3$, $CDCl_3$, DMSO). Melting points were obtained in open capillary tubes using a MEL-Temp II melting point apparatus and uncorrected. Mass spectra (MS) were recorded on a Perkin-Elmer Q-Mass 910 instrument by using electron impact (EI) at 70 eV.

GENERAL PROCEDUREOFSYNTHESIS

Synthesis of 4,6-dichloro-N-(2,5-dimethylphenyl)-1,3,5-triazin-2-amine.

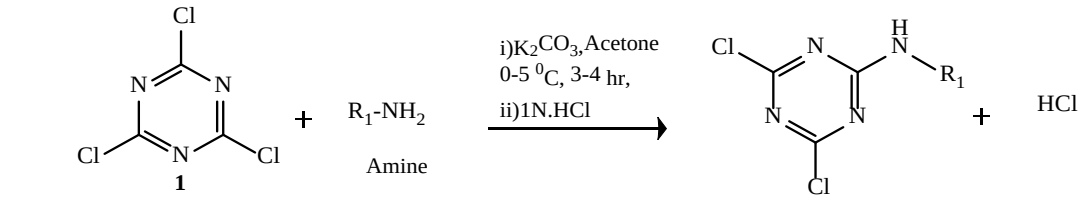
Solution of cyanuric chloride (2 g, 0.01 mole) was prepared by dissolving it in acetone (20 ml). To this solution added 2,5-dimethyl aniline (1.35 ml, 0.01 mole) and potassium carbonate (4.4 g, 0.03 mole). This mixture was vigorously stirred for 3 h at 0–5 °C and poured over the crushed ice when solid product was precipitated out. Crude product was filtered, washed with water. Further product was taken in small amount of water and neutralized with 1N HCl and filtered out. Product was crystallized from ethanol.

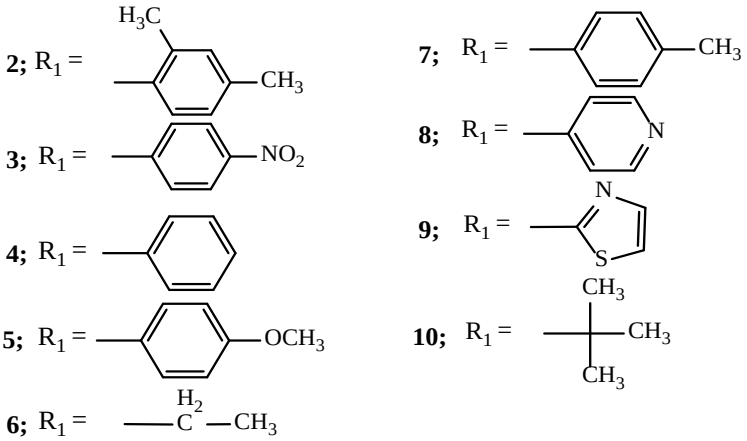
Synthesis of 4-chloro-N-(2,5-dimethylphenyl)-6-(naphthalen-1-yloxy)-1,3,5-triazin-2-amine.

Solution of 4,6-dichloro-N-(2,5-dimethylphenyl)-1,3,5-triazin-2-amine (3 g, 0.01 mole) was prepared it in tetrahydro furan (10 ml). To this solution added potassium carbonate (4.59 g 0.03 mole) and solution of 1-naphthol (1.59 g 0.01 mole) in tetrahydro furan.This mixture was vigorously stirred at 60 ^{0}C for 6 hr. The solution was neutralized by 1N HCl and precipitate formed was filtered out and washed with water and crystallized from ethanol.

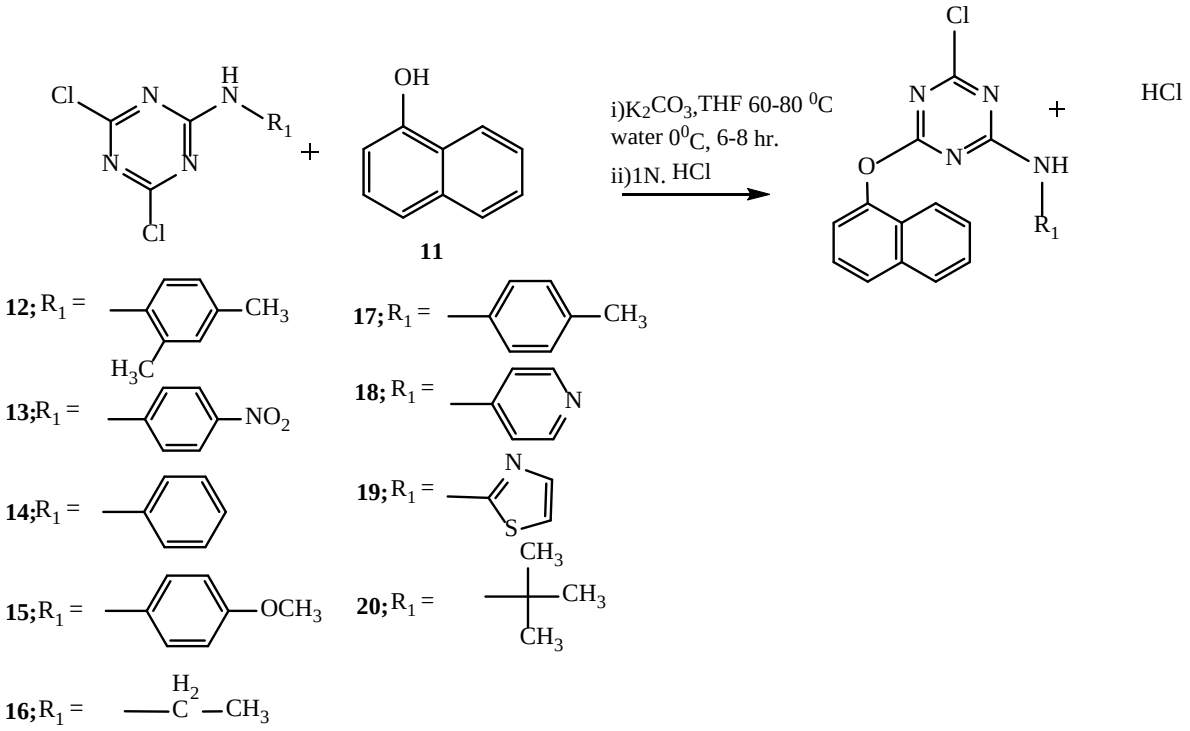
Experimental section.

Scheme 1





Scheme 2



RESULT AND DISCUSSION:

The target compounds and respective intermediates were synthesized as outline in scheme. The first step consist of the nucleophilic substitution of first chlorine atom of cyanuric chloride by 2,5-dimethyl aniline to give 4,6-dichloro-N-(2,5-dimethylphenyl)-1,3,5-triazin-2-amine with an efficient yield. Appearance of IR absorption peak at 3270 cm^{-1} shows the attachment of 2^0 amine group.The intermediate 4-chloro-N-(2,5-dimethylphenyl)-6-(naphthalen-1-yloxy)-1,3,5-triazin-2-amine obtained by reaction with 1-naphthol. It displayed absorption band at 1112 cm^{-1} which showed the presence of C–O– linkage. Melting points were determined in an open capillary tube and are uncorrected.

Table No:1

Sr.No.	Amines	Compound	Yield	Colour
1	2,5-Dimethyl aniline	**2**	93 %	White
2	4-Nitro aniline	**3**	75 %	Yellow
3	Aniline	**4**	70%	White
5	p-Anisidine	**5**	79 %	Gray
6	Ethyl amine	**6**	68 %	Brown
7	p-Toluidine	**7**	82 %	White
8	4-Aminopyridine	**8**	73 %	Yellow
9	2-Aminothiazole	**9**	66 %	Yellow
10	tert- Butyl amine	**10**	89 %	White

1. 4-Chloro-N-(2,5-dimethylphenyl)-6-(naphthalene-1-yloxy)-1,3,5-triazine-2-amine.(12)

Colourless solid was obtained, m.p.135 ^{0}C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$): δ 8.18(s,1H,NH), δ 7.99 (dd,1Hz,J=8.5,J=2.3Hz,Ar-H), δ 7.72 (d,1H,J=8.5Hz,Ar-H), δ 7.29 (d,1H,J=2.5Hz, Ar-H), δ 6.65-7.80 (m,Ar-H), δ 2.30 (s,3H,Ar-CH_3), IR (cm^{-1}) : 3350.40(NH, amine), 3310.27, 3123.1, 1652.35, 1342.3, 1263, 1060 (C-O), 1020, 905, 850.1 MS (m/z) at 377.30 (M+),379.30 (M+2), 380.30 (M+3).

2. 4-Chloro-6-(naphthalene-3-yloxy)-N-(4-nitrophenyl)-1,3,5-triazine-2-amine.(13)

Yellow colour solid was obtained,m.p. 155-158 ^{0}C.^{1}H NMR δ ppm (400 MHz, $CDCl_3$): δ 8.03 (s,1H,Ar-NH),δ8.01(dd,2H,J=8.5Hz),δ7.5(m,2H,J=8.2Hz ,J=2.5Hz),δ7.4(dd,2H,J=8.3Hz,J=2.5Hz), δ7.32-7.81 (m,4H,Ar-H), IR (cm^{-1}) : 3409.40, 3060.27 (NH,amine), 1553.1, 652.35, 1225.3, 1363, 1160, 874, 805, 758.1 MS (m/z) at 392.09 (M+),394.09 (M+2), 395.10 (M+3).

3. 4-Chloro-N-ethyl-6-(naphthalene-1-yloxy)-1,3,5-triazine-2-amine.(16)

Dark browncolour solid was obtained, m.p.160 ^{0}C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$):δ 7.4 (dd,1H,J=8.1,Ar-H)δ 7.76 (dd,1H,J=8.3Hz,Ar-H), δ 7.9 (t,NH),δ7.26-7.91 (m, Ar-H),δ 3.47 (t,NH), δ 1.19 (t,3H,CH_3), δ 3.47 (q,2H,CH_2), IR (cm^{-1}) : 3346.00, 3230.87, 3223.01, 1553.35, 1440.6, 1356, 1248, 1120, 859, 850.3 MS (m/z) at 301.20 (M+),303.20 (M+2).

4. 4-Chloro-6-(naphthalene-1-yloxy)-N-p-tolyl-1,3,5-triazine-2-amine.(17)

Brown colour solid was obtained, m.p.155^{0}C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$):δ 7.95 (dd,2H,J=8.2,J=2.6,Ar-H), δ 6.88-7.12(dd,2H,J=8.5,J=2.2,Ar-H), δ 6.75-7.91(m,7H,Ar-H), δ 2.27 (s,3H,Ar-CH_3), IR (cm^{-1}) : 3452.50, 3341.75, 3255.02, 1655.85, 1523.82, 1460, 1342.08, 1223, 869, 854.3 MS (m/z) at 363.3 (M+), 365.3 (M+2), 366.3(M+3).

5. N-tert-butyl-4-chloro-6-(naphthalene-1-yloxy)-1,3,5,-triazine-2-amine.(20)

White colour solid was obtained, m.p.135^{0}C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$):δ 7.08-8.27 (m, Ar-H),δ3.34 (s,1H,NH), δ 1.33-1.67 (s,9H,CH_3), IR (cm^{-1}) : 3460.00, 3335.42, 3263.12, 1452.28, 1420.83, 1345, 1152, 1108, 975, 825.3 MS (m/z) at 333.01 (M+),334 (M+1).

6. 4-Chloro-6-(naphthalene-1-yloxy)-N-o-tolyl-1,3,5-triazin-2-amine.

Light purple colour solid was obtained, m.p.148^{0}C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$): δ 6.85-8.26 (m,Ar-H),δ7.43 (dd,1H,J=7.8,J=2.2)δ 2.55 (s,CH_3), IR (cm^{-1}) : 3486.16, 3365.70, 3298.52, 1826.52, 1562.29, 1458, 1356, 1193, 894, 883 MS (m/z) at 362.81 (M+).

CONCLUSION:

In summary we have successfully exploited the Silica-TCT as an inexpensive and readily available catalyst for synthesis of substituted triazine derivatives. The present work is basically focused on the development of novel s-triazine derivatives with wide therapeutic windows. The interest of organic chemists in 2,4,6-trichloro-1,3,5-triazineas a starting material is due to the temperature dependent reactivity of three chlorine atoms that allow a sequential introduction of various substituents. This article describe a simple method for synthesis of 4,6-dichloro-N-(alkyl phenyl)-1,3,5-triazin-2-amine.The compound was confirmed by the spectral analyses. The sequential replacement of three chlorine atoms on cyanuric chloride with different nucleophile provides the synthesis of a variety of substituted s-triazine molecules. In light of its operational simplicity and efficiency, this reliable method is expected to have a broad utility due to the scope of applications of the s-triazines. Antimicrobial activities of the newly synthesized compounds were investigated. The majority of the compounds came out with promising activity against a wide range of pathogenic bacteria, fungi and mycobacteria. 2,4,6-Trichloro-1,3,5-triazine (TCT) was found to be inexpensive easily available, easy to handle and dramatic generality for various aliphatic or aromatic amines undergoes smooth N-substituted triazines.

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