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Archives of Applied Science Research, 2012, 4 (2):805-808
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-508X
CODEN (USA) AASRC9

Synthesis of novel derivatives containing s-triazine moiety as potential antibacterial agents

K. N. Sarmah*, N. K. Sarmah[3], K. B. Kurmi[1] and Talha V. Patel[2]

Department of Chemistry, Shree Jayendrapuri Arts & Science College, Bharuch, Gujarat, India

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ABSTRACT

Some novel compounds are synthesized using the substitution of chlorine in 2,4,6-trichloro-s-triazine by some moieties having structural as well as biological importance like imidazole, benzimidazole and what not which are anti infective agents. In this manner six novel compounds are prepared and they are subjected to antibacterial screening prior to this the synthesized compounds are duly characterized by spectral analysis. These compounds reveal substantive antibacterial activities against some randomly chosen both gram +ve & gram-ve bacteria. The promising results are in support of the fact that the compounds are worth to be optimized for some novel drugs in future. The newly synthesized compounds were characterized using IR, ^{1}H-NMR.

Keywords: - Benzimidazole, Substituted thiourea, Cyanuric chloride and Antimicrobial activity.

INTRODUCTION

S-Triazine derivatives represent an important class of compounds due to their potential to be biologically active. They are known to be anti-protozoals[1], anticancer agents[2], estrogen receptor modulators[3], antimalarials[4], cyclin-dependent kinase modulators[5], and antimicrobials[6]. Cyanuric chloride, an inexpensive, easily available reagent, of low toxicity and less corrosive than other similar reactants, has been widely used in organic reactions[7]. 1,3,5-triazines (or s-triazines) are a class of compounds well known for a long time and still continue the object of considerable interest mainly due to their application in different fields, including the production of herbicides and polymer photostabilizers[8] . Some 1,3,5-triazines display important biological properties; for example hexamethylmelamine (HMM, (a) & 2-amino-4-morphlino-s-triazine (b) are used clinically due to their antitumor properties to treat lung, breast and ovarian cancer, respectively[9]. The diverse biological activities observed for different molecule containing the 1,3,5-triazine unit have been further explored in order to discover other new potential molecules through the synthesis of libraries by combinatorial approaches[10]. Certain 1, 3, 5-triazine derivatives are also used as chiral stationary phases, for example, the chiral solvating agent(c) for the determination of enantiometric excess by NMR spectroscopy[11] and determination of absolute configuration by circular dichroism[12]. Urea[13] and thiourea[14] of different aryl amines are associated with a wide range of pharmacological activities. Substituted s-triazine derivatives shows tubercular[15], diuretic[16], antiviral[17] and antifungal[18] activities too. In this paper we present the syntheses, characterization and in-vitro antibacterial activity of the tri-substituted-1,3,5-triazine derivatives. The structure of these compounds have been confirmed from spectral analysis like FTIR, ^{1}H NMR (400 MHz) and elemental analysis.

MATERIALS AND METHODS

General

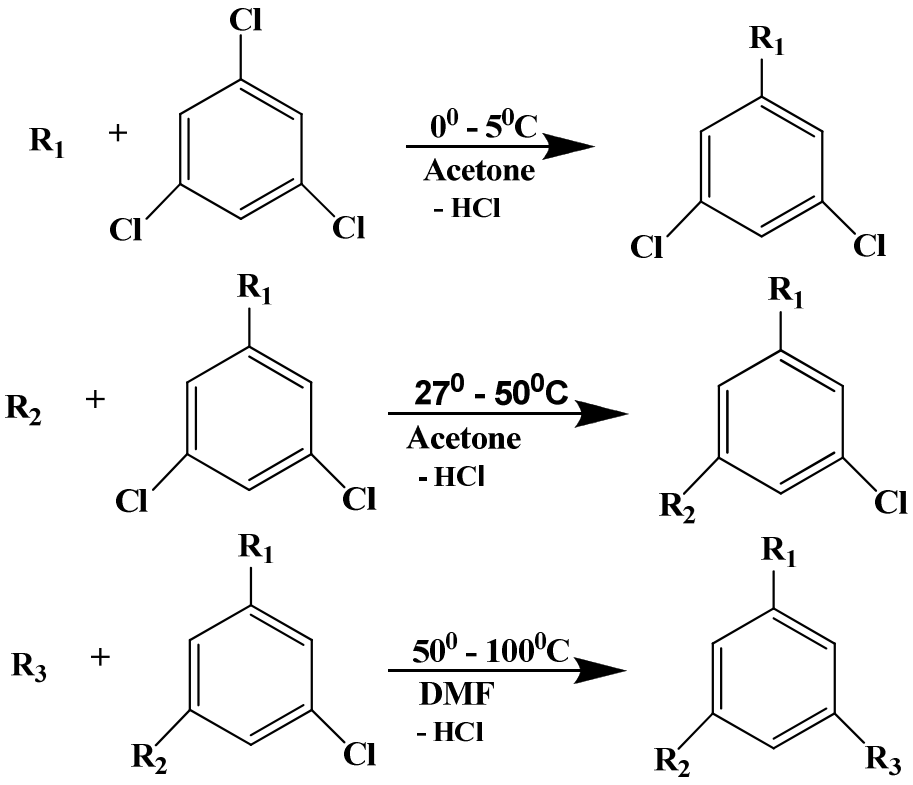
All the melting points were taken in open capillaries tube and are uncorrected. The purity of compounds was checked routinely by TLC (0.5 mm thickness)Using silica gel – G coated Al – plates (Merck) and spots were

visualized by exposing the dry plates in iodine vapours. IR spectra were recorded on FTIR spectrophotometer using KBr technique.^{1}H NMR spectra on a Varian 400 FT MHz NMR instrument at using $CDCl_3$ as solvent and TMS as internal reference..

The triazines described were synthesized starting from cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) and different nucleophiles . The chlorine atoms of cyanuric chloride can be replaced successively by substituted or non–substituted different amino groups. The nucleophiles can selectively displace the different chlorines by controlling the reaction temperature[19].

In general, the first chlorine can be displaced while the temperature is maintained at 0-5^{0}C, the second between 27-50^{0}C and the third substitution happens at reflux temperature. Other important factors that have to be considered for the preparation of the different derivatives are the nature of the reactive group and the order of entry of the group. .When different amino groups are introduced , the less reactive one is introduced before the more reactive one. The reactions, in most cases, are carried out in aqueous suspensions, since the products precipitate from solution, simplifying their isolation[20]. To increase the reactivity and the yield, the cyanuric chloride is previously dissolved in acetone and then poured into ice-water to get a very fine suspension. The reaction of cyanuric chloride with different amines gives 2-sustituted-4,6-dichloro-1,3,5-triazines[21-22]. The 2,4-disubstituted-6-chloro-1,3,5-triazines are obtained by reaction of a further amine with the 2-substituted-4,6-dichloro-1,3,5-triazine in the presence of base. The displacement of the last chlorine is carried out at reflux temperature affording the product in good yields .The product had a low solubility in most organic solvents, except DMSO. However, purification was achieved by recrystallization from methanol-water solution. The elegance of this method lies in its simplicity in use and handling to achieve the desired target.

Synthesis



WHERE R_1 ,R_2 and R_3 are given in below table.

Table 1: Various Substituted compound

Compounds	R_1	R_2	R_3
1a	Dicyclohexylamine	N-methyl piperazine	-Cl
1b	Dicyclohexylamine	Monoethanolamine	-Cl
2a	Benzimidazole	2-chlorophenylthiourea	2-chloroaniline
2b	Benzimidazole	4-chlorophenylthiourea	4-chloroaniline
2c	Benzimidazole	4-fluorophenylthiourea	4-fluoroaniline
2d	Benzimidazole	3-methylphenylthiourea	3-methylaniline

Table 2 : Physical and Analytical Data

Comp No.	M.P (^{0}C)	Yield (%)	M.F. (M_f)	Calcd.(%) / Observed (%) C H N	IR(in KBr) (wavenumber in cm^{-1})	1H NMR I n $CDCl_3$ (δ,ppm)
1a.	166-167	68.70	$C_{20}H_{33}N_6Cl$	61.14 8.40 21.40 60.92 5.10 21.25	504.4 (Ar-Cl) 1619(C=N 1327(C-N)	1.031.83(m,10H) 2.75 (s,3H –CH_3) 2.93-3.79(m,4H) 4.07-4.57(m,4H)
1b.	153-155	68.35	$C_{17}H_{28}N_5OCl$	57.70 7.92 19.80 57.45 6.82 19.34	501.5(Ar-Cl) 1578(C=N) 1340(C-N) 3259(-OH) 1530 (-NH-)	1.02-1.36(m,10H) 1.57 -1.66(t,3H) 4.21 (-OH) 3.79-3.81(t,3H)
2a.	143-145	72	$C_{23}H_{16}N_8SCl_2$	54.43 22.09 3.1 54.22 22.02 3.11	496.2(Ar-Cl) 1340(C-N) 1676.8(C=N) 1410(C=S)	7.10-7.85(m,12H Ar-H) 3.7214 aryl NH 8.5865(long) 2NH
2b.	138-140	71	$C_{23}H_{16}N_8SCl_2$	54.43 22.09 3.15 54.08 21.94 3.10	500.1(Ar-Cl) 1342(C-N) 1674(C=N) 1412(C=S)	7.05-7.80(m,12HAr H) 3.7938(arylNH) 8.6074(2NH)
2c.	146-148	68.50	$C_{23}H_{16}N_8SF_2$	53.90 3.12 21.87 53.86 2.98 21.44	1187.6(Ar-F) 1346(C-N) 1668(C=N) 1415(C=S)	6.95-7.75 (m,12 H,Ar-H) 8.9236 (2 NH) 3.9174(aryl NH)
2d.	168-170	71.32	$C_{25}H_{22}N_8S$	64.19 4.42 23.88 64.37 4.72 24.03	1350 (C-N) 1671(C=N) 1526(-NH-) 1350(C=S)	3.9125(aryl NH) 8.2159(2 NH) 7.15-7.88 (m,12H,Ar-H)

Antibacterial screening :

The in-vitro antibacterial activities of the above synthesized compounds are done against Gram +ve strains and against Gram –ve strains using agar cup method. The zone of inhibition was measured in mm. All the compounds reported in Table-2 are tested at 2mg/ml concentration under similarly controlled condition of experiments carried out by using Chloramphenicol (50µg/ml) as a standard for a comparison.

Table 3 : In-vitro antibacterial activity of trisubstituted-s-triazines. Zone of inhibition in mm(Concentration: 50 µg/ml)

Compound	E-coli	S-typhae	B.Subtilis
1a	08	07	10
1b	12	25	37
2a	10	19	No-inhibition
2b	10	18	No-inhibition
2c	No-inhibition	17	11
2d	12	20	44
(Standard drug) Chloramphenicol (50µg/ml)	18	24	20

RESULTS AND DISCUSSION

From the zone of inhibition of different compounds, It is obvious that the compound 2d is the strongest of all. Comparing 1a & 1b another conclusion can be made that the replacement of chlorine in cyanuric chloride by aliphatic amine as substituent, produces more effective result than the hetero cyclo-alkyl group. Another fact, which is evident from the above result is that compound 2d is having more structural relevance along with the stereo electronic factor so far activity is concerned. The thiourea and benzimidazole moieties create structural crowding and various allosteric sites. On the other hand all three groups are providing sufficient electronic pressure to make it more active.

Acknowledgement

The authors would like to thanks to the department of Chemistry, Shree Jayendrapuri Arts & Science College, Bharuch, for providing necessary infrastructure to carry out the syntheses & thanks are also due to the Department of Micro-Biology for antibacterial screening. We are also grateful to S.A.I.F. Division, Punjab University, Chandigarh for getting different spectra on subsidized payment.

REFERENCES

[1] Balini, A., Bueno, G.J., Stewart, M.L., Yardley, V., Brun, R., Barrett,P.M.**2005**. *J. Med. Chem*. 48, 5570–5579.

[2] Menicagli, R., Samaritani, S., Signore, G., Vaglini, F., Via, L.D., **2004**. *J. Med. Chem*. 47,4649–4652
[3] Henke, B.R., Consler, T.G., Go, N., Hale, R.L., Hohman, **2002**. *J. Med. Chem*. 45, 5492–5505.
[4] Agarwal, A., Srivastava, K., Puri, S.K., Chauhan, P.M.S., **2005**. *Bioorg. Med. Chem. Lett.* 15, 531–533.
[5] Kuo, G.H., DeAngelis, A., Emanuel, S., Wang, A., Zhang, Y., Connolly, **2005**. *J. Med. Chem*. 48, 4535–4546.
[6] Koc, Z.E., Bingol, H., Saf, A.O., Torlak, E., Coskum, A., **2010**. *J. Hazard. Mater*. 183, 251–255.
[7] Wei Lin Li [a,]*, Qiu Yan Luo [b], Fu Lin Yan [a] Elsevier *Chinese Chemical Letters* 22 **2011**,811–814
[8] Hollink E.; Simanck, E. E., Bergbreiter, **2005,**D. E. *Tetrahedron Lett.*, 46, (2005-2008).
[9] Hedayatullah, M; Lion, C.; Slimane, A. B.; Nachawati, I.**1999,** *Heterocycles*, 51, 1891- 1896,
[10] Khersonsky, S. M., Jung, D.-W.; Kang, T.-W.; Walsh et.wl.**2003,** *J. Am. Chem. Soc.*, 125, 11804-11805.
[11] Iuliano, A.; Lecci, c.; Salvadori, P.**2003,** *Tetrahedron: Asymmetry* 14, 1345-135.
[12] Iuliano, A.; Voir, I.; Salvadori, P. **1999,**J. *Org. Chem.* 16, 5754- 5756.
[13] *Organic Synthesis coll;* 5, 52 **1963**.
[14] Toyoma chemical Industry co. Ltd., **1966,***Chem.. Abstr.*, 64, 11231.
[15] Bahadur, S., et al. **1983,***J. Indian Chem. Soc.*, 60, 168.
[16] Mehta D. J. and Sheth V. K., **1962,** *Arch. Inten. Pharmatodyn*, 138, 480.
[17] Lespagnol, A.; **1975,***Chimie des medicaments, Techniqu et Documentation*, paris, 3,313.
[18] Ghaib, A.; Menager, S.; Verite, P.; Lafont, O.**2002,** *IL Farmaco.*, 57, 109.
[19] Goi, M. **1960,**Reactivities of cyanuric chloride derivatives. I. Displacement reaction of substituted 2,4-bis (anilino-6-chloro)-s- triazines with benzylamine. Yuki Gosei Kaguku Kyokaishi 18, 327-331.
[20] Goi, M. **1960,**Reactivities of Cyanuric chloride derivatives. II. Displacement reactions of 2- chloro-4-substituted 6-anilino-s-triazines with benzylamine. Yuki Gosei Kaguku Kyokaishi,18, 332-336.
[21] Diels, O.**1899,** Zur Kenntnis der cyanurverbindungen. *Ber. Dtsch.Chem..Ges.*,32, 691-702.
[22] Koopman H., J.D. *Chem. pays-Bas*, **77**, 235-240.