NCRISET-2017 e-ISSN: 2456-3463
International Journal Of Innovations In Engineering And Science, Vol. 2, No.6, 2017
www.ijies.net

Synthesis And Biological Importance Of -1,3,5-Thiadiazines As Antibacterial And Antifungal Agents

Kavita. M. Heda[1]

[1]Department of Chemistry,Shri R. L. T. College of Science,Akola – 444001(M.S.) India

E-mail: kavitaheda25@gmail.com

Abstract:- *Variety of 3-Aryl-4-S-benzyl-6-p-tolylimino-2-phenylimino-2,3-dihydro-1,3,5- thiadiazines were synthesized by the interaction of phenyl isocyanodichloride with various 1-Aryl-5-p-tolyl-2-S-benzyl-2,4- isodithiobiuretes respectively in refluxing chloroform medium and were screened for their antibacterial and antifungal activities against some selected pathogenic organisms like Escherichia coli, Proteus vulgaris, Staphylococcus aureus, Salmonella typhimurium, Klebsiella pneumonie, Psudomonas aeruginosa, Aspergillus Niger and Candida albicance. These compounds show appreciable activity towards these microorganisms.*

The identities of these newly synthesized -1,3,5-thiadiazines have been established on the basis of elemental analysis, IR, [1]HNMR and MASS spectral studies.

The literature survey reveals that the heterocyclic compounds having 1, 3, 5-thiadiazines nucleus enhanced pharmaceutical, medicinal, agricultural and industrial values. The high synthetic versatility exhibited by the isothiocyanate moiety has allowed its use as a building block in the preparation of a variety of derivatives. In carbohydrates, the strong electrophilicity shown by isothiocyanates, together with the possibility of undergoing cyclization reaction has made it possible to access a broad spectrum of heterocyclic compounds, of either synthetic or pharmaceutical interest.

Key words: Phenyl isocyanodichloride, 2,4- isodithiobiuretes, 1,3,5-thiadiazines, Antimicrobial activity

Introduction

1, 3, 5-thiadiazines and their rearranged product 1, 3, 5-triazines have been shown to possess brightening and fiber finishing properties in textile industry[1,2], symmetric triazines have also been used as chain lengthing agents in polyurethane, polymerization[3],azodye, paints, plastic and rubber[4]. They are also used as fungicidal[5], insecticidal[6], and as medicinal compounds. The literature survey reveals that the heterocyclic compounds having 1, 3, 5-thiadiazines nucleus enhanced pharmaceutical, medicinal, agricultural and industrial values.

The chemistry of heterocyclic compounds continues to explore the field of carbohydrate chemistry. Literature survey also revealed that the heterocyclic derivatives of sugar possess antimicrobial[7-9], and antitumor activity[10-12]. Thiadiazines and their derivativs acts as antifibrinolytic [13], cardiotonic[14], anesthetic, cardiovascular and hypometabolic agents[15]. It is also used as fungicidal[16] , insecticidal[17] as well as medicinal compounds.

Results and discussion

Several 3-Aryl-4-*S*-benzyl-6-*p*-tolylimino-2-phenylimino-2,3-dihydro-[1,3,5] thiadiazine [Hydrochloride] (3a-j) have been synthesized by the interaction of 1-Aryl-5-*p*-tolyl-2-*S*-benzyl-2,4-isodithiobiurets (2a-j) and phenyl isocyanodichloride (1). To the chloroform suspension of Phenyl isothiocyanate chlorinated on chlorination assembly .This chlorinated solution was added to 1-Aryl-5-*p*-tolyl-2-*S*-benzyl-2,4-isodithiobiuret in chloroform medium . Then the reaction mixture was reflux for 3 hrs. and a sticky mass obtained as a residue was triturated several times with petroleum ether (60-80^{o}C).. A product will separate out.

The IR spectra of products shows bands due to Ar-H, N-H, C=N, C-N, C-S stretching and ^{1}HNMR spectra of products distinctly displayed signals due to aromatic protons and aliphatic Protons. The Mass spectrum of product was also observed. The identities of these newly synthesized compounds have been established on the basis of usual chemical transformations and also IR, ^{1}H NMR and Mass spectral studies[18-20].

METHOLOGY

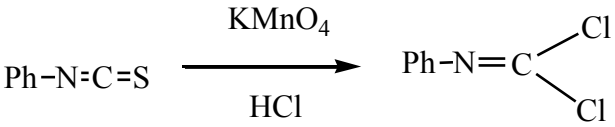
General Methods

All chemicals were research grade. Melting points determined are uncorrected. IR spectra were recorded in KBr on a FT-IR Perkin-Elmer RXI(4000-450cm^{-1}) spectrophotometer. ^{1}H NMR measurements were performed on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in $CDCl_3$ solution with TMS as internal reference. The Mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap Mass spectrometer. Thin layer chromatography (TLC) was performed on silica Gel G and spots were visualized by iodine vapour. The compounds were screened for their antibacterial and antifungal activities by the disc diffusion assay method[21]. The compounds describe in this paper were first time synthesized by the multistep reaction protocol.
The required phenyl isocyanodichloride[22] was prepared by known procedure (Scheme 1). 1-Aryl-5-p-tolyl-2-S-benzyl-2,4-isodithiobiurets, was prepared by the interaction of 1-Aryl-S-benzyl isothiocarbamide and *p*-tolyl isothiocyanate (Scheme 2).

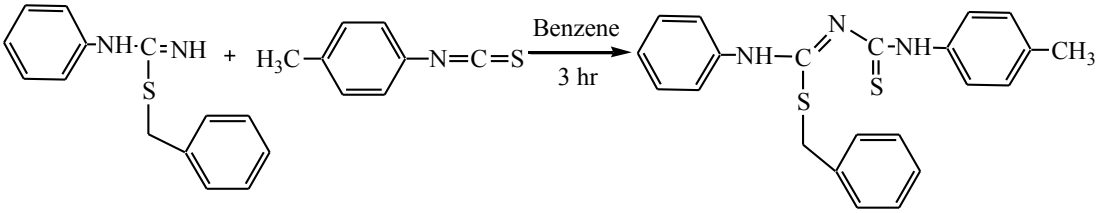
1]Synthesis of 3-Aryl-4-S-benzyl-6-p-tolylimino-2-phenylimino-2,3-dihydro-[1,3,5] thiadiazine[Hydrochloride] (Scheme 3)

3-Aryl-4-*S*-benzyl-6-*p*-tolylimino-2-phenylimino-2,3-dihydro-[1,3,5] thiadiazine[Hydrochloride] was prepared by the interaction of 1-Aryl-5-*p*-tolyl-2-*S*-benzyl-2,4-isodithiobiurets and phenyl isocyanodichloride in chloroform medium. A chloroform solution of Phenyl isocyanodichloride was mixed with the chloroform solution of 1-Aryl-5-*p*-tolyl-2-*S*-benzyl-2,4-isodithiobiuret. Then the reaction mixture was reflux on boiling water bath for 3 hr during which evolution of HCl was noticed. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was brought to room temperature and the solvent removed under reduced pressure to obtain residue. This residue was triturated several times with petroleum ether (60-80^{o}C) to afford a pale yellow solid.

Scheme 1-

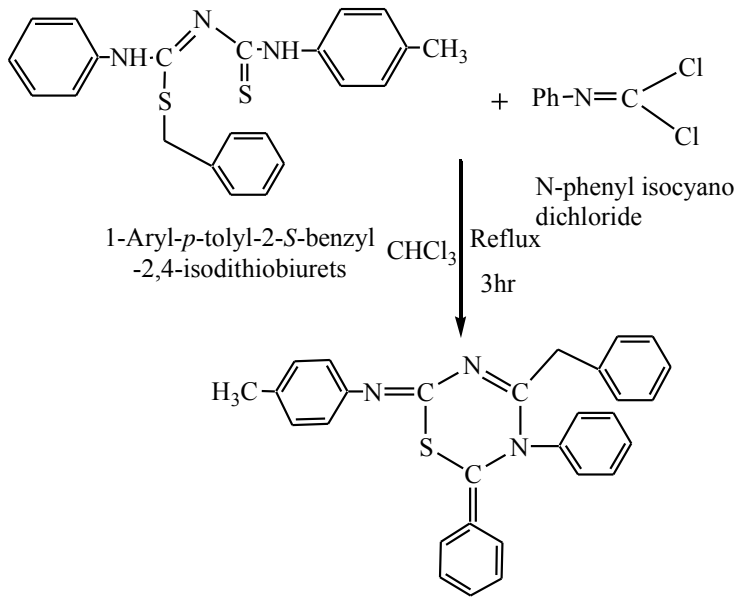


Scheme 2-



1-Aryl-*5*-*p*-tolyl-2-*S*-benzyl-2,4-isodithiobiurets

Scheme 3-



3-Aryl-4-*S*-benzyl-6-*p*-tolylimino-2-phenylimino-2,3-dihydro-1,3,5-thiadiazine

[hydrochloride]

Where, R= (a) Phenyl, (b) *o*-Cl-phenyl, (c) *m*-Cl-phenyl, (d) *p*-Cl-phenyl, (e) *o*-NO_2-phenyl, (f) *m*-NO_2-phenyl, (g) *p*-NO_2-phenyl

3a: IR (KBr):υ 3201 (Ar-H), 2877 (Ali-H), 1523 (C=N), 1450 (C-C), 1323 (C-N), 694 (C-S). H NMR (δ in ppm, $CDCl_3$): δ 7.63 - 6.91 (19H, m, Ar. H), δ 4.27- 2.26 (5H, m, Ali. H) Mass (m/z): 490 (M^+), 477, 387, 300, 91; Anal. Calcd for $C_{29}H_{24}N_4S_2$,: C, 70.73; H, 4.87; N, 11.38; S, 13.00; Found: C, 70.70; H, 4.85; N, 11.40; S, 13.04.

On the basis of all above facts the product with m. p. 98°C was assigned the structure 3-Phenyl-4-*S*-benzyl-6-*p*-tolylimino-2-phenylimino 2,3-dihydro- [1,3,5] thiadiazine [Hydrochloride]

When the reaction of phenyl isocyanodichloride was extended to several other 1-Aryl-5-*p*-tolyl-2-*S*-benzyl-2,4-isodithiobiurets corresponding 3-Aryl-4-*S*-benzyl-6-*p*-tolylimino-2-phenylimino 2,3-dihydro- [1,3,5] thiadiazine [Hydrochloride] has been synthesized.

3c: IR (KBr):υ 3030 (Ar-H), 2872 (Ali-H), 1566 (C=N), 1475 (C-C), 1267(C-N), 792 (C-S). H NMR (δ in ppm, $CDCl_3$): δ 7.62-7.21 (18H, m, Ar. H), δ 4.57- 2.38 (5H, m, Ali. H) Mass (m/z): 526 (M^+), 425, 403, 91; Anal. Calcd for $C_{29}H_{23}N_4S_2Cl$,: C, 66.09; H, 4.36; N, 10.63; S, 12.15; Found: C, 66.05; H, 4.33; N, 10.67; S, 12.18.

3g: IR (KBr):υ 3062 (Ar-H), 2895 (Ali-H), 1504 (C=N), 1481 (C-C), 1303(C-N), 754(C-S). H NMR (δ in ppm, $CDCl_3$): δ8.08-6.56 (18H, m, Ar. H), δ4.42- 1.59 (5H, m, Ali. H) Mass (m/z): 537 (M^+), 490, 462, 404, 390, 91; Anal. Calcd for $C_{29}H_{23}N_5S_2O_2$,: C, 64.80; H, 4.28; N, 13.03; S, 11.91; Found: C, 64.85; H, 4.25; N, 13.08; S, 11.95;.

Table -1: Physical data for characterization of compounds (3a-g)

Compd	Yield %	R_f	M.P. ^{0}C	Analysis (%): Found (calcd)	
				N	S
3a	80.00	0.67	98	11.40(11.38)	13.04(13.00)

3b	69.00	0.75	125	10.59 (10.63)	12.10 (12.15)
3c	80.00	0.58	143	10.67(10.63)	12.18(12.15)
3d	78.00	0.55	102	10.68 (10.63)	12.13 (12.15)
3e	65.00	0.65	130	13.05(13.03)	11.93 (11.91)
3f	70.00	0.48	135	13.00 (13.03)	11.88 (11.91)
3g	68.90	0.51	121	13.08 (13.03)	11.95 (11.91)

C and H analysis was found satisfactory in all cases.

Antimicrobial activity:

All the compounds have been screened for both; antimicrobial and antifungal activity by using disc diffusion assay. For this, sterial filter paper disc (6 mm) impregnated with fixed doses of compounds was placed on pre-innoculated surface. The disc bearing plates were incubated at 37^{o}C for 24 h. After incubation, zone diameter were measured. The compounds were taken at a concentration or 1 mg/mL using dimethyl sulphoxide as a solvent. Amikacin (100 µg/mL) was used as standard for antibacterial and fluconazole (100µg/mL) as a standard for antifungal activity. The compound were screened for antibacterial activity against *Eschrichia coli, Proteus vulgaris, Staphylococcus aureus, Salmonella typhi,* and *Psudomonas aeruginosa* in nutrient agar medium and for, antifungal activity against *Aspergillus niger* and *Candida albicance* in potato dextrose agar medium. It has been observed that all the compounds showed good activity against both; bacteria and fungi.

Compound	*E. coli*	*S. aureus*	*P. vulgaris*	*P. aeruginosa*	*S. typhi*	*A. niger*	*C. albicance*
1(3a)	17	16	20	19	18	19	20
2(3b)	10	15	15	12	20	20	21
3(3c)	18	14	19	17	15	17	19
4(3d)	14	19	--	18	19	20	19
5(3e)	16	19	17	14	18	20	21
6(3f)	11	08	19	15	16	21	--
7(3g)	18	16	16	16	--	20	18
Amikacin	18	21	23	19	20		
Fluconazole						24	24

Sample	**Disc content**	**Resistant**	**Intermediate**	**Sensitive**
Amikacin	100ug/ml	≤ 15 mm	16-20 mm	≥ 21 mm
Fluconazole	100ug/ml	≤ 15 mm	16-20 mm	≥ 21 mm

Acknowledgement

Authors are thankful to SAIF, CDRI Chandigarh for providing the spectral data. Authors are also thankful to Dr. Rupali Mantri (M. D. Microbiology), Assistant Professor, G. M. C., Akola for her help in doing antimicrobial activity and also Dr. V. D. Nanoty for encouragement and necessary facilities.

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