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Synthesis and Antimicrobial Activity of Substituted Thiazolo-S-Triazin

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ABSTRACT

A few 3-thio-4 aryl/alkyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines (V) have been synthesized by interaction of N-phenyl isocyanodichloride (III) and 1-(4-phenylthiazol-2yl)-3-aryl/alkyl thiocarbamide (II). The latter in turn have been prepared by the interaction of 2-amino-4-phenylthiazole and aryl/alkyl isothiocyanates (I). These compounds were screened for their antimicrobial activity. The identities of these new S-triazines have been established on the basis of usual chemical transformation IR and PMR studies.

Keywords: Synthesis of Thiazolo-S-triazines, 1, 3, 5-triazines, Antimicrobial activity.

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INTRODUCTION

An assessment of literature regarding 1, 3, 5-traizines are prepared by different routes. N-phenyl-S-chloro isothiocarbamoyl chloride [1-3] and N-phenyl isocyanodichloride [4-8] have been shown to have applications in synthesis of several 1, 3, 5-traizines derivatives [9-12]. Therefore, it appeared sufficiently interesting to prepare different S-triazines as a part of fused ring system, involving interaction of N-phenyl isocyanodichloride and 1-(4-phenylthiazol-2yl)-3-aryl/alkyl thiocarbamide (II). These thiocarbamides and S-triazines were screened for their antimicrobial activities against *S-aureus, E-coli, A-aerogenes, P-vulgris*.

The required 2-amino-4-phenylthiazole was prepared by earlier known procedure [13, 14]. The interaction of 2-amino-4-phenylthiazole and p-tolyl isothiocyanate(Ia) in chloroform medium for 2 hours afforded thiocarbamide(IIa). 1-(4-phenylthiazol-2yl)-3-p-tolyl thiocarbamide (IIa) and N-phenyl isocyanodichloride (III) were refluxed in chloroform medium. The evolution of hydrochloric acid gas was observed. The reaction mixture after processing gave 3-thio-4-p-tolyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines (Va). The identities of thiocarbamide and S-triazine have been established on the basis of usual chemical transformation IR, PMR spectral studies.

MATERIALS AND METHODS

Experimental

All the reagents used in this synthesis were of analytical grade and used without further purification. The melting points were determined in open capillaries and are uncorrected. The infrared spectrum was recorded on PerkinElmer instrument. ^{1}H NMR spectra was recorded in DMSO/$CDCl_3$ using TMS as an internal standard. The chemical shifts are expressed in δ ppm.

Synthesis of 2-amino-4-phenyl thiazol

Acetophenone (12ml), thiourea (15.2gm), iodine (25gm) and 60ml distilled water was refluxed for four hours. The reaction was observed by using TLC. After completion of the reaction, the reaction mixture was cool and poured on crushed ice to get solid, basify the solid with sodium hydroxide flakes, filter and crystallized from ethanol: water(70%) gave golden colored fibers of 2-amino-4-phenyl thiazol, melting point 125^{O}C. (Found:C,61.26; H,4.40; N,45.60; S,17.99% $C_9H_8N_2S$ requires C,61.36; H,4.54; N,45.90; S,18.18%).

Synthesis of 1-(4-phenylthiazole-2yl)-3-aryl/alkyl thiocarbamide

Formation of 1-(4-phenylthiazole-2yl)-3-p-tolyl thiocarbamide (IIa)

2-amino-4-phenylthiazole (0.01mole), p-tolyl isothiocyanate (0.01mole) and chloroform (20ml) as a medium was taken in a round bottom flask fitted with reflux condenser. The resulting mixture refluxed for two hours under water bath. The progress of the reaction was

monitored by TLC. After completion of reaction, mixture cooled to room temperature, the solvent was evaporated under reduced pressure and the crude product 1-(4-phenylthiazole-2yl)-3-p-tolyl thiocarbamide (IIa) was washed several times with petroleum ether (60-80^{O}) and re-crystallized form ethanol, melting point 150^{O}C (Found: C, 62.69; H, 4.56; N, 12.93; S, 19.70% $C_{17}H_{15}N_3S_2$ requires C, 62.76; H, 4.61; N, 12.92; S, 19.69%

The main absorption bands observed in IR spectrum of the product are listed below

ν(N-H)3300, ν(C=N)1590, ν(C=S)1325, ν(C-S)750.

The PMR spectrum of the product also clearly indicated the presence of aromatic protons at (δ 6.7ppm) and N-H proton at (δ 6.2ppm), Ar-CH3 protons at (δ 3.0ppm).

Preparation of 3-thio-4-p-tolyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines(Va)

In round bottom flask chloroform suspension of 1-(4-phenylthiazol-2yl)-3-p-tolyl thiocarbamide (IIa) was added gradually a chloroformed solution of N-isocynodichloride (III) and the reaction mixture were refluxed over a boiling water bath for 2 hours. Evolution of HCl was noticed. The reaction progress of reaction was observed by TLC. After completion of the reaction, reaction mixture was cooled at room temperature. The solvent was evaporated under reduced pressure, resultant semisolid was separated. It was washed several times with petroleum ether (60-80^{O}) folled by ethanol, afforded a solid 3-thio-4-p-tolyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines hydrochloride (IVa). It was acidic nature and was de-sulphurizable when boiled with alkaline plumbite solution. On determination of equivalent weight, it was found to be monohydrochloride. On basification with dilute ammonia solution a stable free base that is 3-thio-4-p-tolyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines(Va) was obtained. It was crystallized with aqueous ethanol (70%), melting point 90 ^{O}C (Found: C, 67.61; H, 4.09; N, 13.00; S, 14.90%, $C_{24}H_{18}N_4S_2$ requires C, 67.60; H, 4.22; N, 13.14; S, 15.02%).

The main absorption bands observed in Infrared spectrum [15-16] of the product 3-thio-4-p-tolyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines(Va) ν(C=N)1610, ν(C=S)1350, ν(C-N)1310, ν(C-S)700.

The PMR spectrum [17] of the product also clearly indicated the presence of aromatic protons at (δ7-8ppm) and Ar-CH_3 at (δ 2.7ppm).

RESULT AND DISCUSSION

The thiocarbamides (IIa-IIg) have been isolated in good yield, (Table-1).

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Table 1: Formation of 1-(4-phenylthiazol-2yl)-3-aryl/alkyl thiocarbamide (II)
Reagents: 2-amino-4-phenylthiazole and aryl/alkyl isothiocyanates (I)

Aryl/alkyl isocynodichloride (I)	1-(4-phenylthiazol-2yl)-3-aryl/alkyl thiocarbamide (II)	Yield %	M. P. ^{O}C	Found (Calculated) %	
				N%	S%
p-tolyl isocyanodichloride (Ia)	1-(4-phenylthiazol-2yl)- p-tolyl thiocarbamide (IIa)	70	150	12.93 (12.92)	19.70 (19.69)
o-tolyl isocyanodichloride (Ib)	1-(4-phenylthiazol-2yl)- o-tolyl thiocarbamide (IIb)	73	138	12.70 (12.92)	19.60 (19.69)
m-tolyl isocyanodichloride (Ic)	1-(4-phenylthiazol-2yl)- m-tolyl thiocarbamide (IIc)	70	152	12.78 (12.92)	19.55 (19.69)
phenyl isocyanodichloride (Id)	1-(4-phenylthiazol-2yl)-phenyl thiocarbamide (IId)	66	148	13.35 (13.50)	20.40 (20.57)
o-chloro phenyl isocyanodichloride (Ie)	1-(4-phenylthiazol-2yl)-o-chlorophenyl thiocarbamide (IIe)	90	140	12.00 (12.16)	18.39 (18.52)
p-chloro phenyl isocyanodichloride (If)	1-(4-phenylthiazol-2yl)-p-chlorophenyl thiocarbamide (IIf)	85	180	12.06 (12.16)	18.35 (18.52)
t-butyl isocyanodichloride (Ig)	1-(4-phenylthiazol-2yl)-t-butyl thiocarbamide (IIg)	80	140	14.31 (14.43)	21.88 (21.99)

Table 2: Formation of 3-thio-4 aryl/alkyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines (V)
Reagents: 1-(4-phenylthiazol-2yl)-3-aryl/alkyl thiocarbamide (II) and N-phenyl isocyanodichloride (III)

1-(4-phenylthiazol-2yl)-3-aryl/alkyl thiocarbamide (II)	3-thio-4 aryl/alkyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines Hydrochlorode (IV)	Yield %	M. P. ^{O}C	Eq. weight Found (Calc.)	3-thio-4 aryl/alkyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines (V)	M. P. ^{O}C
1-(4-phenylthiazol-2yl)- p-tolyl thiocarbamide (IIa)	3-thio-4 - p-tolyl -5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines Hydrochlorode (IVa)	85	100	468.00 (462.5)	3-thio-4 - p-tolyl -5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines (Va)	90
1-(4-phenylthiazol-2yl)- o-tolyl thiocarbamide (IIb)	3-thio-4- o-tolyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines Hydrochlorode (IVb)	85	115	472.00 (462.50)	3-thio-4- o-tolyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines (Vb)	100
1-(4-phenylthiazol-2yl)- m-tolyl thiocarbamide (IIc)	3-thio-4 - m-tolyl -5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines Hydrochlorode (IVc)	60	130	466.50 (462.50)	3-thio-4 - m-tolyl -5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines (Vc)	105
1-(4-phenylthiazol-2yl)-phenyl thiocarbamide (IId)	3-thio-4 -phenyl -5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines	70	118	445.75 (448.50)	3-thio-4 -phenyl -5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-	110

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	Hydrochlorode (IVd)				triazines (Vd)	
1-(4-phenylthiazol-2yl)-o-chlorophenyl thiocarbamide (IIe)	3-thio-4 -o-chlorophenyl -5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines Hydrochlorode (IVe)	75	110	490.00 (481.50)	3-thio-4 -o-chlorophenyl -5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines (Ve)	102
1-(4-phenylthiazol-2yl)-p-chlorophenyl thiocarbamide (IIf)	3-thio-4 -p-chlorophenyl -5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines Hydrochlorode (IVf)	75	115	489.00 (481.50)	3-thio-4 -p-chlorophenyl -5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines (Vf)	140
1-(4-phenylthiazol-2yl)-t-butyl thiocarbamide (IIg)	3-thio-4 -t-butyl -5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines Hydrochlorode (IVg)	55	140	421.00 (425.50)	3-thio-4 -t-butyl -5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines (Vg)	120

Table 3: Antimicrobial activity of 3-thio-4 aryl/alkyl-5-phenylimino-6-phenylthiazolo-(2, 3-b) -1, 3, 5-triazines (V)

Organisms	3-thio-4 aryl/alkyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines (V)						
	(V a)	(V b)	(V c)	(V d)	(V e)	(V f)	(V g)
S.aureus	+	-	-	-	+++	++	+++
E.coli	+++	+++	-	++	+++	-	+++
A.aerogenes	+++	-	-	-	+++	+++	+++
P.vulgris	+++	+++	-	-	-	-	++

(-) => Inactive (less than 12mm), (+) => Weakly Active (12-16 mm), (++) => Moderately Active (17-20 mm)
(+++) => Highly Active (21-37 mm)

Table 4: Antimicrobial activity of 1-(4-phenylthiazol-2yl)-3-aryl/alkyl thiocarbamide (II)

Organisms	1-(4-phenylthiazol-2yl)-3-aryl/alkyl thiocarbamides (II)						
	(IIa)	(IIb)	(IIc)	(IId)	(IIe)	(IIf)	(IIg)
S.aureus	++	+++	+++	-	+++	+++	+++
E.coli	-	+++	-	-	+++	+++	+
A.aerogenes	+++	+++	++	-	+++	++	++
P.vulgris	-	-	+++	-	-	+++	+++

The reaction of 1-(4-phenylthiazol-2yl)-3-p-tolyl thiocarbamide (IIa) and N-isocynodichloride (III) in equimolar proportion were carried out in chloroform medium for 2 hours. The evolution of hydrochloric acid gas was observed. On distilling off chloroform afforded sticky mass, which on washing with several times with petroleum ether (60-80^{O}) followed by little amount of ethanol gave granular solid 3-thio-4-p-tolyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines hydrochloride(IVa). It was acidic to litmus. On determination of equivalent weight it was found to be mono-hydrochloride. On basification with aqueous ammonia solution gave free base. 3-thio-4-p-tolyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines (Va). It was crystallized from aqueous ethanol (70%), m. p. 90^{O}C. The compound was found to be desulphurizable when boiled with alkaline plumbite solution. On the basis of elemental analysis of the 3-thio-4-p-tolyl-5-phenylimino-6-phenylthiazolo-(2, 3-b)-1, 3, 5-triazines(Va), the molecular formula was found to be $C_{24}H_{18}N_4S_2$.

The reaction of N-phenyl isocyanodichloride (III) was capable of extension to several other 1-(4-phenylthiazol-2yl)-3-aryl/alkyl thiocarbamides (IIb-IIg) and related 1, 3, 5-triazines (Vb-Vg) have been isolated in good yield, (Table-2).

Antimicrobial Activity

All synthesized compounds i.e. thiocarbamides (IIa-IIg) [18-22] and S-triazines (Va-Vg) [23, 24] have been screened for antimicrobial activity by using well method. The plates were incubated at 37^{O}C for 24 hours. Inhibition zones read after incubation is over for bacterial strains. The compounds were taken at a concentration of 1mg/ml using DMSO as a solvent. The compounds were screened for their antimicrobial activity against various pathogenic bacteria such as *S-aureus, E-coli, A-aerogenes,* and *P-vulgris* in nutrient agar medium. It has been observed that most of the compounds show good activities like compound IIa-IIc and IIe-IIg were moderately active against S-aureus. Compound IIb,IIe and IIf were highly active against E-coli. IIa, IIb and IIe were greatly active and IIc, IIg, IIf were moderately active against A-aerogenes while the compound IIc, IIg, IIf were very much active against the organisms P-valgaris.

The observations indicated that the compound IIb and IIe showed high antimicrobial activity with test organism except *P-valgaris.* And the compound IIf also showed elevated activity against all the organisms (Table-3).

S-triazines (Va-Vg) were screened for their antimicrobial activity. Most of the compounds showed high activity against the different organisms. On observation (Ve) and (Vg) showed high activity and compound (Vf) was moderately active. The compound (Va), (Vb), (Ve), (Vg) were highly active and (Vd) was moderately active against the organism *E.coil*. Against A. aerogenes compounds (Va), (Ve), (Vg), (Vf) showed elevated activity while against *P. vulgaris* compounds (Va), (Vb) showed high activity. On observation of the results, the compounds (Ve) and (Vg) showed measurable activity against the entire organism.

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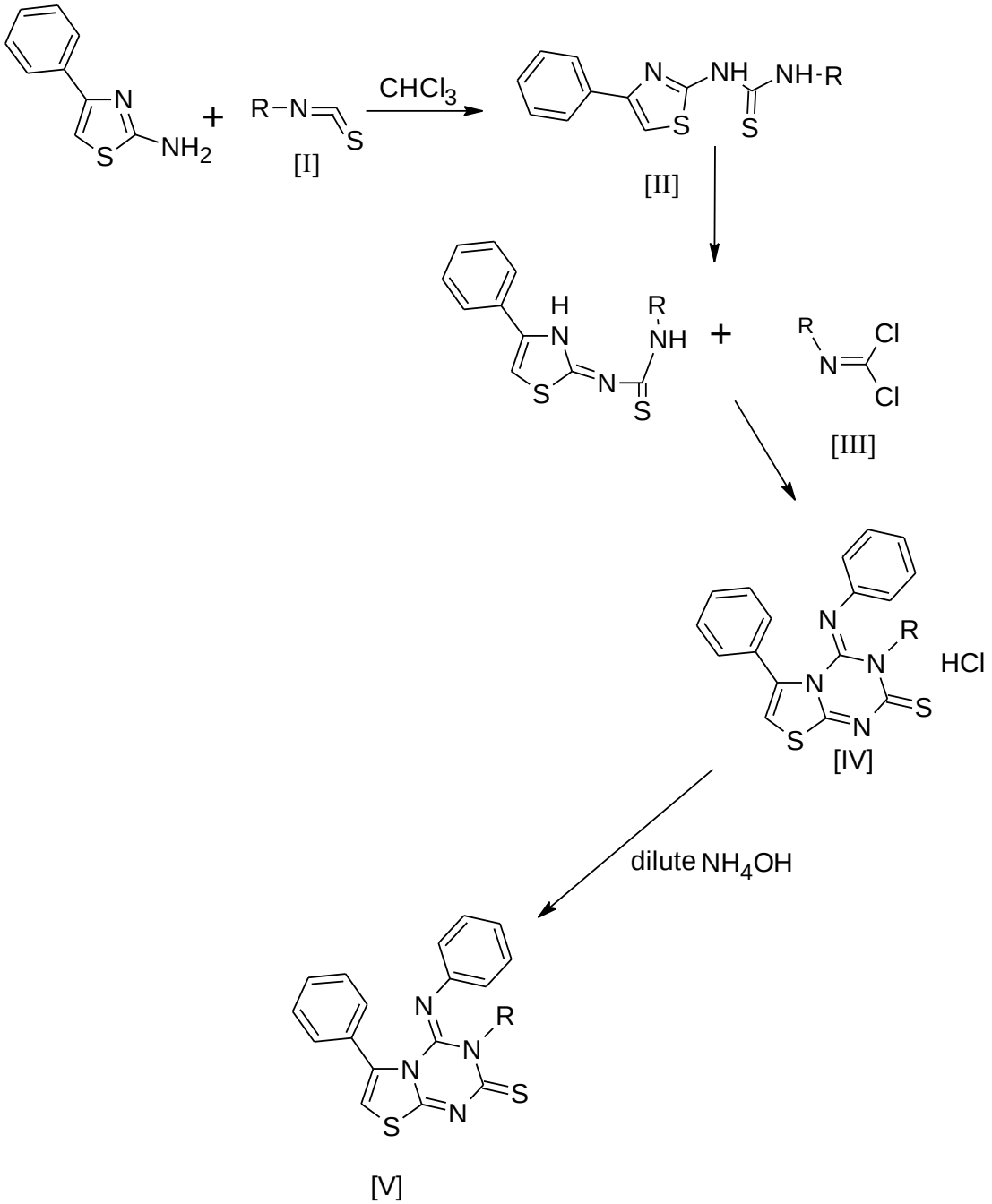
Formations of the compound I, II, III, IV, V are shown in the following reaction scheme



Where R= [I,II,III,IV,V]

a= p-tolyl, b= o-tolyl, c= m-tolyl, d= phenyl,

e= o-cl-phenyl, f= p-cl-phenyl & g= t-butyl

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