Asian Journal of Chemistry Vol. 19, No. 1, (2007), 564–568

Synthesis and Antimicrobial Activity of 3-Arylimino-4-(4′-benzylidene amino phenyl)-5-phenylimino-1,2,4-dithiazolidenes

SHITAL V. GANDHE* and B.N. BERAD

Department of Chemistry, Shri Shivaji Science College, Amravati-444 603, India

A series of 3-arylimino-4-(4′-benzylidene amino phenyl)-5-phenylimino-1,2,4-dithiazolidenes **(5a–f)** have been obtained by the basification of their hydrochlorides **(4a–f)**, which were synthesized by the interaction of N-phenyl-S-chloro-isothiocarbamoyl chloride and 1-(4′-benzylidene amino phenyl)-3-aryl thiocarbamides **(3a–f)**. The latter were synthesized by the condensation of benzaldehyde and different 1-(4′-amino phenyl)-3-aryl thiocarbamides **(2a–f)**. **(2a–f)** were synthesized by refluxing *p*-phenylene diamine and different aryl isothiocyanates **(1a–f)** in $CHCl_3$ medium. Bromination of **(5a–f)** by bromine in glacial acetic acid gave dibromoderivatives. The title compounds were assayed for their antimicrobial activity against gram-positive as well as gram-negative microorganisms.

Key Words: Synthesis, Antimicrobial activity, 3,4,5-Trisubstituted-1,2,4-dithiazolidenes.

INTODUCTION

Synthetic application of N-phenyl-S-chloro isothiocarbamoyl chloride[1–3] has been recently investigated. The reagent has shown to have enough potentiality in the synthesis of nitrogen and sulphur containing 5- and 6-membered heterocyclic compounds. Therefore, the reagent was prepared and its reaction with substituted thiocarbamides has been carried out to give fully substituted 1,2,4-dithiazolidenes.

RESULT AND DISCUSSION

The parent compound *p*-phenylene diamine was refluxed with *o*-tolyl isothiocyanate **(1a)** in chloroform medium for 1.5 h (1 : 1). Chloroform was distilled off and the residue of 1-(4′-amino phenyl)-3-*o*-tolyl thiocarbamide **(2a)** was obtained. **(2a)** was recrystallized from aqueous ethanol (80%), m.p. 160°C. The compound was found to be desulphurizable when boiled with alkaline lead acetate solution. This indicated the presence of >C=S group. **(2a)** was condensed with benzaldehyde using chloroform as solvent for 2 h. The reaction mixture was then cooled and chloroform was distilled off to give the solid 1-(4′-benzylidene amino phenyl)-3-*o*-tolyl thiocarbamide **(3a)**, recrystallized from aqueous ethanol (80%), m.p. 142°C.

(3a) was refluxed with N-phenyl-S-chloro isothiocarbamoyl chloride[4] using chloroform medium for 3.5 h. The evolution of hydrogen chloride gas was tested by moist blue litmus. On cooling the reaction mixture, chloroform was distilled off to give a sticky mass, which on washing with petroleum ether gave a granular solid of 3-*o*-tolylimino-4-(4′-benzylidene amino phenyl)-5-phenylimino-1,2,4-dithiazolidene hydrochloride **(4a)** ($C_{28}H_{22}N_4S_2 \cdot HCl$). This was acidic to litmus. On determination of equivalent weight, it was found to be monohydrochloride. On basification with aqueous ammonia solution this afforded a free base **(5a).** It was recrystallized from aqueous ethanol (60%), m.p. 102°C. It was found to be non-desulphurizable with alkaline lead acetate solution indicating the absence of >C═S group.

The IR spectrum[5, 6] of **(5a)** showed the presence of bonds due to ν(C═N) 1583 cm^{-1}, ν(C—N) 1316 cm^{-1}, ν(C—S) 758 cm^{-1}, ν(S—S) 506 cm^{-1}.

The ^{1}H-NMR spectrum showed the peak at δ 2.15 (3H, —CH,), δ 6.6 (1H, ═CH—), δ 7.07–7.92 (18H, Aromatic).

Therefore, the product has been assigned structure 3-*o*-tolylimino-4(4′-benzylidene amino phenyl)-5-phenylimino-1,2,4-dithiazolidene **(5a).**

The compounds **(5b-f)** were synthesized by extending the reaction of N-phenyl-S-chloro isothiocarbamoyl chloride with **(3b-f)** and related products were isolated in good yield (Table-1).

The compound **(5a)** was brominated with bromine in acetic acid. The mixture on shaking for 30 min afforded dibromo derivative **(6a)** (Table-1).

This reation of bromination was extended to other 1,2,4-dithiazolidines **(5b-f)** and corresponding dibromo derivatives **(6b-f)** were isolated in good yield.

The IR spectrum of **(6a)** showed the presence of absorption bands due to ν(C═N, 1580 cm^{-1}), ν(C—N, 1320 cm^{-1}), ν(C—S, 746 cm^{-1}), ν(S—S, 510 cm^{-1}).

The ^{1}H-NMR spectrum showed the peak at δ 2.20 (3H, —CH_3), δ 7.07–7.92 (18H, Aromatic).

Antimicrobial Activity: The title compounds **(5a-f)** were screened for their antimicrobial activity against pathogenic bacteria using cup-plate diffusion method[7, 8] at a concentration of 100 μg/mL in DMF. The micro-organism used included both gram-positive as well as gram-negative strains like *E. coli, B. subtilis, P. vulgaris, Shigella.* Sensitivity plates were seeded with a bacterial inoculum of 1×10^6 CIU/mL and each well (diameter 10 mm) was loaded with test compound solution in DMF. Zones of inhibition were recorded after incubation for 24 h using vernier callipers.

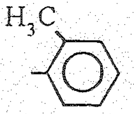
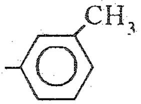
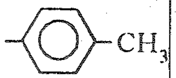
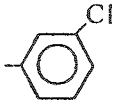
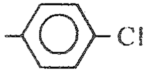
Inhibition zones for different compounds against different micro-organisms indicated that **5b, 5d, 5f** against *B. subtillis,* **5b, 5f** against *E. coli,* **5d** against *S. aureus,* **5a** against *P. vulgaris* are highly active. Most of the compounds are active against these micro-organisms except **5c** against *S. aureus,* **5b** against *P. vulgaris,* **5f** against *Shigella.*

Organism	5a	5b	5c	5d	5e	5f
E. coli	25	30	28	20	17	36
B. subtilis	20	32	18	36	22	31
S. aueeus	27	24	> 12	30	21	17
P. vulgaris	36	> 12	16	18	22	26
Shigella	23	17	21	23	18	> 12

Diameter of inhibition zone in mm: (Concentration 100 mg/mL)'

30 and above	Highly active
20–30 mm	Moderately active
12–20 mm	Active
> 12 mm	Inactive

TABLE-1

Compound	R	Final compounds					Derivatives			
		m.f.	m.p. (°C)	Yield (%)	Analysis (%) Found (Calcd.)		m.p. (°C)	Yield (%)	Analysis (%) Found (Calcd.)	
					N	S			N	S
5a	—C_6H_4—CH_3 (*o*-) 	$C_{28}H_{22}N_4S_2$	102	84	11.69 (11.71)	13.24 (13.28)	124	82	8.72 (8.80)	9.98 (10.06)
5b	—C_6H_5 	$C_{27}H_{20}N_4S_2$	110	69	12.08 (12.06)	13.72 (13.79)	120	75	8.92 (9.00)	10.20 (10.28)
5c	—C_6H_4—CH_3 (*m*-) 	$C_{28}H_{22}N_4S_2$	98	72	11.62 (11.71)	13.26 (13.38)	130	66	8.73 (8.80)	10.09 (10.06)
5d	—C_6H_4—CH_3 (*p*-) 	$C_{28}H_{22}N_4S_2$	86	70	11.73 (11.71)	13.32 (13.38)	135	74	8.78 (8.80)	10.02 (10.06)
5e	—C_6H_4Cl (*m*-) 	$C_{27}H_{19}N_4S_2Cl$	96	62	11.20 (11.23)	12.79 (12.83)	140	69	8.49 (8.53)	9.68 (9.74)
5f	—C_6H_4Cl (*p*-) 	$C_{27}H_{19}N_4S_2Cl$	104	79	11.25 (11.23)	12.75 (12.83)	132	78	8.50 (8.53)	9.75 (9.74)

EXPERIMENTAL

All melting points were recorded using hot paraffin bath and were uncorrected. Infrared spectra were recorded on Perkin-Elmer spectrophotometer in the range 4000–400 cm^{-1} in Nujol Mull and as KBr pellets. PMR spectra were recorded using $CDCl_3$ and DMSO-d^6 as solvents and with TMS as internal standard. Chemicals used were of AR-grade. Purity of the compounds was checked on silica gel G-plates by TLC.

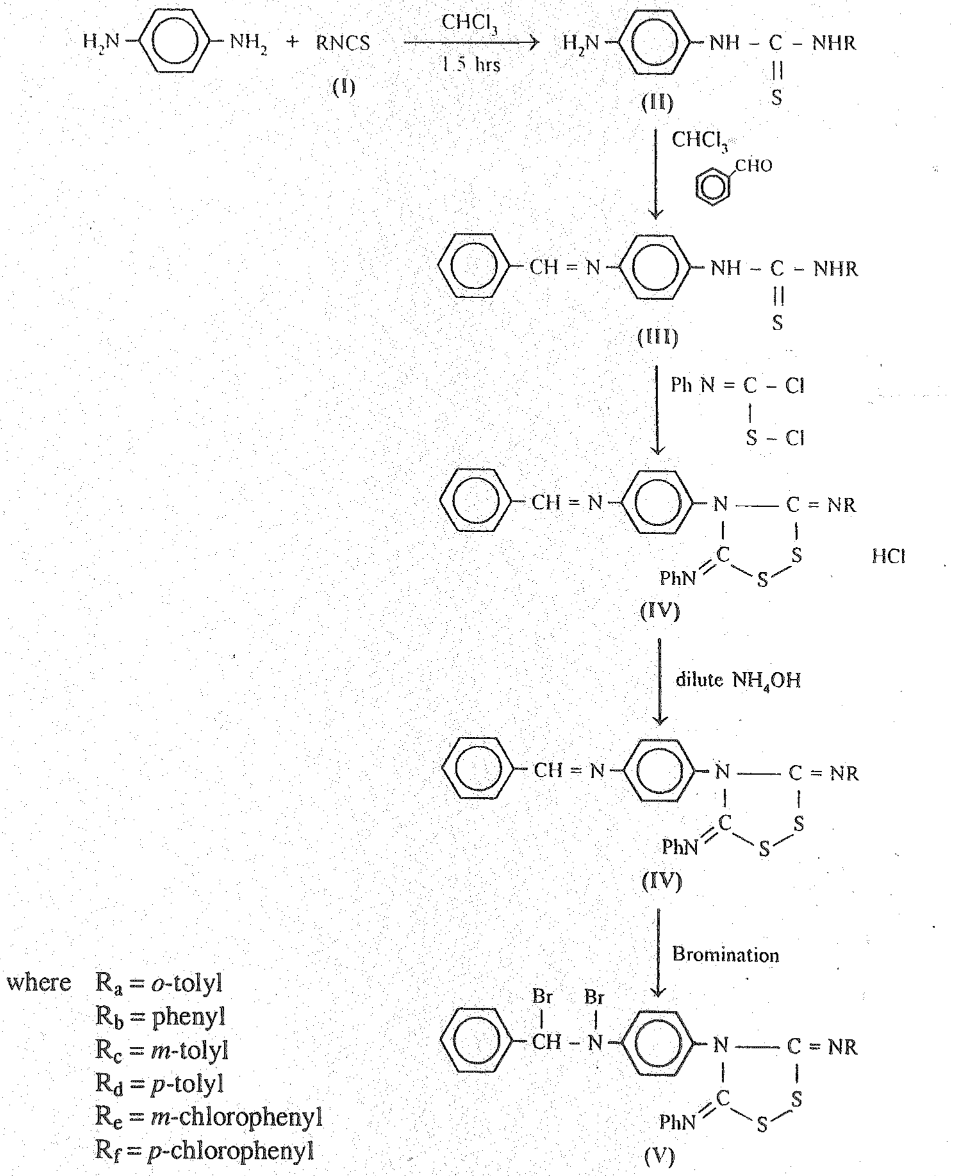
Synthesis of 1-(4′-amino phenyl)-3-*o*-tolyl thiocarbamide (2a): Phenylene diamine (0.01 mol) and *o*-tolyl isothiocyanate **(2a)** (0.01 mol) were refluxed using 15 mL chloroform as a solvent for 1.5 h. The reaction mixture was cooled and chloroform was distilled off. The solid **(2a)** was recrystallized from aqueous ethanol (80%), m.p. 160°C. Analysis (%): Found: C 65.24, H 5.72, N 16.20, S 12.39. Calcd. for $C_{14}H_{15}N_3S$: C 65.36, H 5.83, N 16.34, S 12.45.

Synthesis of 1-(4′-benzylidene amino phenyl)-3-*o*-tolyl thiocarbamide (3a): Benzaldehyde (0.01 mol) and 1-(4′-amino phenyl)-3-*o*-tolyl thiocarbamide **(2a)** (0.01 mol) were condensed using chloroform as a solvent for 2 h on a water bath. The reaction mixture was cooled and chloroform was distilled off when solid **(3a)** was isolated; it was recrystallized from aqueous ethanol (80%), m.p. 142°C. Analysis (%): Found: C 72.92, H 5.42, N 12.02, S 9.16. Calcd. for $C_{21}H_{19}N_3S$: C 73.04, H 5.50, N 12.17, S 9.27.

Synthesis of 3-*o*-tolylimino-4-(4′-benzylidene amino phenyl)-5-phenylimino-1,2,4-dithiazolidene (5a): The mixture of 1-(4′-benzylidene amino phenyl)-3-*o*-tolyl thiocarbamide **(3a)** (0.01 mol) and N-phenyl-S-chloro isothiocarbamoyl chloride (0.01 mol) was refluxed in chloroform as solvent for *ca.* 3.5 h. Evolution of hydrogen chloride gas was noticed. The reaction mixture was cooled and chloroform was distilled off when a sticky mass was obtained which was washed several times with petroleum ether (60–80°C) to give a granular solid of 3-*o*-tolylimino-4-(4′-benzylidene amino phenyl)-5-phenylimino-1,2,4-dithiazolidene hydrochloride **(4a).** It was acidic to litmus. On determination of equivalent weight it was found to be monohydrochloride. On basification with aqueous ammonia solution it afforded free base **(5a)**. It was recrystallized from aqueous ethanol (60%), m.p. 102°C. Analysis (%): Found: C 70.14, H 4.56, N 11.69, S 13.24. Calcd. for $C_{28}H_{22}N_4S_2$: C 70.29, H 4.60, N 11.71, S 13.38.

Synthesis of dibromo derivative of 3-*o*-tolylimino-4-(4′-benzylidene amino phenyl)-5-phenylimino-1,2,4-dithiazolidene (6a): The 3-*o*-tolylimino-4-(4′-benzylidene amino phenyl)-5-phenylimino-1,2,4-dithiazolidene **(5a)** (0.01 mol) was brominated with bromine in glacial acetic acid (0.01 mol). The reaction was carried out by shaking the reaction mixture for 1/2 h. The reaction mixture was poured on a little crushed ice to get a granular yellowish solid which was recrystallized from aqueous ethanol (80%), m.p. 124°C. Analysis (%): Found: C 52.75, H 3.39, N 8.72, S 9.98. Calcd. for $C_{28}H_{22}N_4S_2Br_2$: C 52.83, H 3.45, N 8.80, S 10.06.

The formation of products **2, 3, 4, 5** and **6** can be shown as given in reaction **Scheme-I**.



where R_a = *o*-tolyl
R_b = phenyl
R_c = *m*-tolyl
R_d = *p*-tolyl
R_e = *m*-chlorophenyl
R_f = *p*-chlorophenyl

Scheme-1

REFERENCES

1. M.G. Paranjpe and A.S. Mahajan, *Indian J. Chem.*, **10**, 1138 (1972).
2. C.S. Bhaskar, N.N. Vidhale and B.N. Berad, *Asian J. Chem.*, **14**, 162 (2002).
3. V.K. Verma, *Indian J. Chem.*, **1**, 116 (1963).
4. G. Ottmann and H. Hooks, *J. Org. Chem.*, **31**, 838 (1966).
5. N.B. Colthup, L.H. Daly and S.E. Wiberly, Introduction to Infrared and Raman Spectroscopy, Academic Press, New York (1964).
6. R.M. Silverstein and G.C. Bassler, Spectroscopic Identification of Organic Compounds, John Wiley, Inc., New York (1967).
7. A.L. Barry, The Antimicrobial Suseptibility Test: Principle and Practices, Ullus Lea & Febiger, Philadelphia, Pa, USA, p. 180.
8. F. Cavanagh, Analytical Microbiology, Academic Press, New York, p. 126 (1963).

(*Received*: 19 December 2005; *Accepted*: 30 June 2006) AJC-4978