Asian Journal of Chemistry Vol. 16, No. 1 (2004), 255–260

Synthesis of Some Novel 1,2,4-Dithiazolidines and Their Antibacterial and Antifungal Activity

PRADIP P. DEOHATE*, JYOTI P. DEOHATE and B.N. BERAD
Department of Chemistry
Shri Shivaji Science College, Amravati-444 603, India

3-Naphthylimino-4-aryl/alkyl-5-phenylimino-1,2,4-dithiazolidines (**Va–g**) have been obtained by the basification of 3-naphthylimino-4-aryl/alkyl-5-phenylimino-1,2,4-dithiazolidine hydrochlorides (**IVa–g**). The latter were synthesized by the interaction of N-phenyl-S-chloro isothiocarbamoyl chloride (**III**) and 1-naphthyl-3-aryl/alkyl thiocarbamides (**IIa–g**), which were prepared initially by the condensation of aryl/alkyl isothiocyanates (**Ia–g**) and 1-naphthylamine. The title compounds were assayed for their antibacterial and antifungal activity against gram-positive as well as gram-negative microorganisms such as *E. coli*, *S. aureus*, *S. typhi*, *B. subtilis*, *A. aerogenes* and *A. niger*.

Key Words: 1,2,4-Dithiazolidines, Antibacterial, Antifungal.

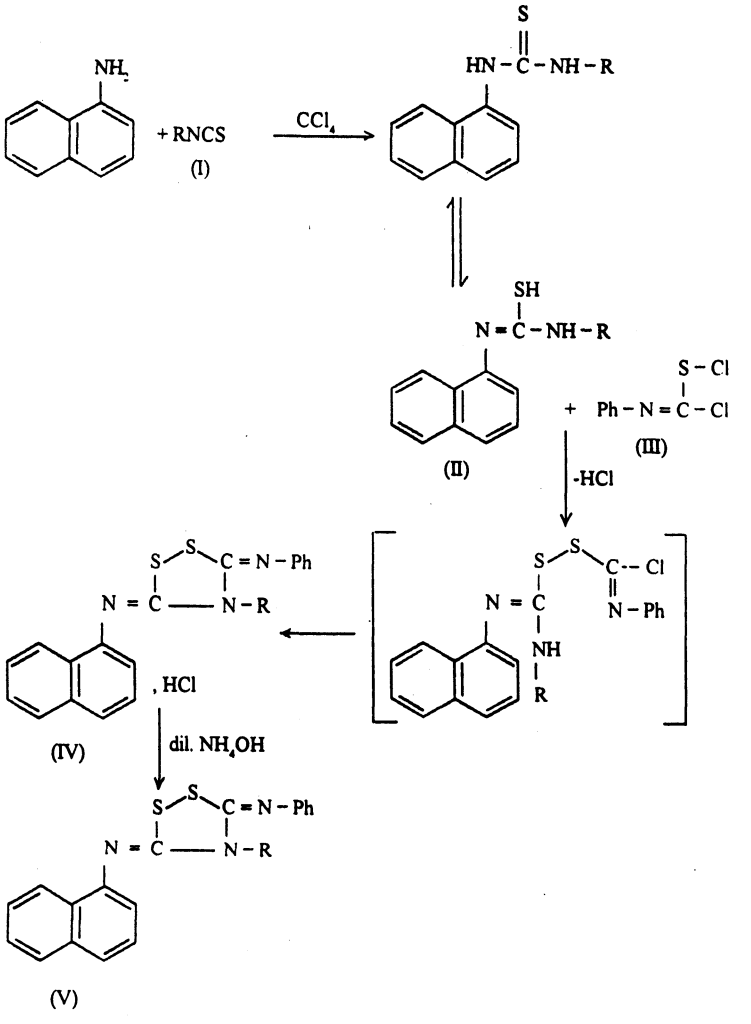
INTRODUCTION

Synthesis of various 1,2,4-dithiazolidines have been reported earlier[1–6]. Recently the synthetic applications of N-phenyl-S-chloro isothiocarbamoyl chloride have been investigated[7–9]. The reagent has been shown to have enough potentiality in the synthesis of nitrogen and sulphur containing 5 and 6 membered heterocylic compounds. So with the aim to extend the application of N-phenyl-S-chloro isothiocarbamoyl chloride in the synthesis of naphthyl substituted 1,2,4-dithiazolidines, its reaction has been carried out with naphthyl substituted thiocarbamides to yield the desired 1,2,4-dithiazolidines and assayed for their antibacterial and antifungal activity.

EXPERIMENTAL

The melting points were recorded using hot paraffin bath and uncorrected. Chemicals used were of AR grade. IR spectra were recorded on Perkin-Elmer spectrometer in the range 4000–400 cm^{-1} in Nujol mull and as KBr pellets. PMR spectra were recorded with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvents. Purity of the compounds was checked on silica gel-G plates by TLC.

Address for correspondence: Pradip P. Deohate, Sant Krupa, Prakash Colony, Morshi-444 905, Dist. Amravati, India.



where **(Ia)–(Va)** : R = *p*-tolyl, **(Ib)–(Vb)** : R = *o*-tolyl, **(Ic)–(Vc)** : R = *m*-tolyl, **(Id)–(Vd)** : R = phenyl, **(Ie)–(Ve)** : R = *o*-chlorophenyl, **(If)–(Vf)** : R = *p*-chlorophenyl, **(Ia)–(Vg)** : R = *t*-butyl.

Synthesis of 1-naphthyl-3-*p*-tolyl thiocarbamide (IIa)

A mixture of 1-naphthylamine (0.01 mol) and *p*-tolyl isothiocyanate (0.01 mol) **(Ia)** in carbon tetrachloride (20 mL) was refluxed for 1.5 h. The reaction mixture was cooled and the solid residue obtained was crystallized from ethanol (75%), m.p. 172°C. (Found: C, 73.18; H, 5.11; N, 9.62; S, 10.62. Calcd. for $C_{18}H_{16}N_2S$: C, 73.97; H, 5.47; N, 9.58; S, 10.95%). This reaction was extended to synthesize compounds **(IIb–g)** using other aryl/alkyl isothiocyanates **(Ib–g).**

Synthesis of 3-naphthylimino-4-*p*-tolyl-5-phenylimino-1,2,4-dithiazolidine (Va)

1-Naphthyl-3-*p*-tolyl thiocarbamide (0.01 mol) **(IIa)** was suspended in chlo-

roform (15 mL). To this a solution of N-phenyl-S-chloro isothiocarbamoyl chloride (0.01 mol) **(III)** in chloroform was added. The reaction mixture was refluxed on a water bath for 2.0 h. The evolution of hydrogen chloride gas was observed. Then chloroform was distilled off, a sticky mass was obtained. It was repeatedly washed with petroleum ether (60–80°C) followed by addition of ethanol; a solid acidic to litmus was isolated. It was crystallized from ethanol (70%), m.p. 169°C and identified as monohydrochloride of 3-naphthylimino-4-*p*-tolyl-5-phenylimino-1,2,4-dithiazolidine **(IVa).**

On basification with dilute ammonia solution a free base **(Va)** was obtained and crystallized from aqueous ethanol, m.p. 97°C. (Found: C, 69.92; H, 4.31; N, 9.20; S, 14.93. Calcd. for $C_{25}H_{19}N_3S_2$: C, 70.58; H, 4.47; N, 9.88; S, 15.05%). On extending the above reaction to other 1-naphthyl-3-aryl/alkyl thiocarbamides **(IIb–g)** the related 1,2,4-dithiazolidines **(Vb–g)** were isolated in good yield. (Table-1).

The title compounds **(Va–g)** were screened for their antibacterial activity against microorganisms *E. coli, S. aureus, S. typhi, B. subtilis, A. aerogenes* and antifungal activity against *A. niger.*

RESULTS AND DISCUSSION

Initially 1-naphthylamine was reacted with *p*-tolyl isothiocyanate **(Ia)** in carbon tetrachloride medium for 1.5 h. On cooling the reaction mixture and distilling off carbon tetrachloride the solid residue of 1-naphthyl-3-*p*-tolyl thiocarbamide **(IIa)** was obtained. It was washed with petroleum ether (60–80°C) and recrystallized from ethanol (75%), m.p. 172°C. The compound was found to be desulphurizable when boiled with alkaline lead acetate solution indicating presence of >C=S group.

The other 1-naphthyl-3-aryl/alkyl thiocarbamides **(IIb–g)** were prepared by extending this reaction to other aryl/alkyl isothiocyanates: **IIb** (78%), m.p. 174°C; **IIc** (69%), m.p. 150°C; **IId** (75%), m.p. 166°C; **IIe** (79%), m.p. 168°C; **IIf** (72%), m.p. 160°C; **IIg** (65%), m.p. 102°C.

The 1-naphthyl-3-*p*-tolyl thiocarbamide **(IIa)** was then reacted with N-phenyl-S-chloro isothiocarbamoyl chloride[7–9] **(III)** in boiling chloroform for 2 h. The evolution of hydrogen chloride gas was clearly noticed and tested with moist blue litmus paper. Cooling the reaction mixture and distilling off chloroform afforded a sticky mass, which on washing with petroleum ether gave a granular solid. It was crystallized from ethanol (70%), m.p. 169°C. It was acidic to litmus. On determination of equivalent weight it was found to be monohydrochloride **(IVa).** This on basification with aqueous ammonia solution afforded a free base **(Va),** crystallized from aqueous ethanol, m.p. 97°C.

The IR spectrum of **(Va)** showed the presence of ν(C=N) (1609 cm^{-1}), ν(C—N) (1305 cm^{-1}), ν(C—S) (769 cm^{-1}), ν(S—S) (467 cm^{-1}), ν(1,4-disubstituted benzene ring) (824 cm^{-1})[10, 11]. The PMR spectra of the product showed peaks due to Ar—CH_3 (δ 2.3 ppm, s, 3H) and Ar—H (δ 7.05–8.60, m, 16H). On the basis of all the above facts the compound **(Va)** has been assigned the structure 3-naphthyl imino-4-*p*-tolyl-5-phenylimino-1,2,4-dithiazolidine. The other com-

TABLE-1
SYNTHESIS OF 3-NAPHTHYLIMINO-4-ARYL/ALKYL-5-PHENYLIMINO-1,2,4-DITHIAZOLIDINES (Va–g)

Reactants: 1-Naphthyl-3-aryl/alkyl thiocarbamides (IIa–g) (0.01 mol) and N-phenyl-S-chloroisothiocarbamoyl chloride (III) (0.01 mol)

1-Naphthyl-3-aryl/alkyl thiocarbamides (II)	3-Naphthylimino-4-aryl/alkyl-5-phenylimino-1,2,4-dithiazolidines hydrochlorides (IV)	Yield (%)	m.p. (°C)	Eq. wt. found (calcd.)	3-Naphthylimino-4-aryl/alkyl-5-phenylimino-1,2,4-dithiazolidines (free base) (V)	m.p. (°C)	% Analysis found (calcd.) (N)	% Analysis found (calcd.) (S)
1-Naphthyl-3-*p*-tolyl... **(IIa)**	1-Naphthylimino-4-*p*-tolyl... (IVa)	70	169	493.00 (497.14)	3-Naphthylimino-4-*p*-tolyl... **(Va)**	97	9.76 (9.88)	14.98 (15.05)
1-Naphthyl-3-*o*-tolyl... **(IIb)**	1-Naphthylimino-4-*o*-tolyl... (IVb)	65	194	506.00 (511.16)	3-Naphthylimino-4-*o*-tolyl... **(Vb)**	129	9.81 (9.88)	14.96 (15.05)
1-Naphthyl-3-*m*-tolyl... **(IIc)**	3-Naphthylimino-4-*m*-tolyl... (IVc)	69	104	508.00 (511.16)	3-Naphthylimino-4-*m*-tolyl... **(Vc)**	92	9.84 (9.88)	15.01 (15.05)
1-Naphthyl-3-phenyl... **(IId)**	3-Naphthylimino-4-phenyl... (IVd)	72	108	509.00 (511.16)	3-Naphthylimino-4-phenyl,.. **(Vd)**	87	10.18 (10.21)	15.51 (15.57)
1-Naphthyl-3-*o*-Cl-phenyl... **(IIe)**	3-Naphthylimino-4-*o*-Cl-phenyl... (IVe)	64	162	527.00 (531.58)	3-Naphthylimino-4-*o*-Cl-phenyl... **(Ve)**	118	9.36 (9.42)	14.28 (14.36)
1-Naphthyl-3-*p*-Cl-phenyl... **(IIf)**	3-Naphthylimino-4-*p*-Cl-phenyl... (IVf)	74	160	524.00 (531.58)	3-Naphthylimino-4-*p*-Cl-phenyl... **(Vf)**	104	9.33 (9.42)	14.30 (14.36)
1-Naphthyl-3-*t*-butyl... **(IIg)**	3-Naphthylimino-4-*t*-butyl... (IVg)	65	228	476.00 (477.15)	3-Naphthylimino-4-*t*-butyl... **(Vg)**	144	10.71 (10.74)	16.31 (16.36)

pounds **(Vb–g)** were prepared by extending the above reaction to other 1-naphthyl-3-aryl/alkyl thiocarbamides and isolated in good yield (Table-1).

TABLE-2
ANTIBACTERIAL ACTIVITY OF 3-NAPHTHYLIMINO-4-ARYL/ALKYL-5-PHENYLIMINO-1,2,4-DITHIAZOLIDINES **(Va–g)**

(Diameter of inhibition zone in mm; Concentration 100 μg/mL)

Organism	3-Naphthylimino-4-aryl/alkyl-5-phenylimino-1,2,4-dithazolidines (V)						
	Va	**Vb**	**Vc**	**Vd**	**Ve**	**Vf**	**Vg**
E. coli	+++	+++	++	–	+	–	+++
S. aureus	+++	++	+++	+	+	+	+++
S. typhi	–	+	–	–	–	–	+
B. subtilis	–	+	+	++	+++	+	–
A. aerogenes	++	+++	+++	–	+	+	+++

(–) = inactive (12 mm and less),
(+) = weakly active (13–16 mm),
(++) = moderately active (17–20 mm),
(+++) = highly active (21 mm and above).

TABLE-3
ANTIFUNGAL ACTIVITY OF 3-NAPHTHYLIMINO-4-ARYL/ALKYL-5-PHENYLIMINO-1,2,4-DITHIAZOLIDINES **(Va–g)**

(Diameter of inhibition zone in mm)

Organism	3-Naphthylimino-4-aryl/alkyl-5-phenylimino-1,2,4-dithiazolidines (V)							
	Concentration	**Va**	**Vb**	**Vc**	**Vd**	**Ve**	**Vf**	**Vg**
A. niger	1%	++	–	+++	–	++	+++	+
	2%	+	+	+++	–	+++	+++	++

(–) = inactive (12 mm and less),
(+) = weakly active (11–15 mm),
(++) = moderately active (16–20 mm),
(+++) = highly active (21 mm and above).

Antibacterial Activity

The title compounds **(Va–g)** were screened for their antibacterial activity against pathogenic bacteria using cup-plate method[12, 13] at a concentration of 100 μg/mL in D.M.F. The microorganisms used included both gram-positive as well as gram-negative strains like *E. coli, S. aureus, S. typhi, B. subtilis* and *A. aerogenes.* Sensitivity plates were seeded with a bacterial inoculum of 1×10^6 CIU/mL. Each well (cup) was of a diameter 10 mm. The zones of inhibition were recorded after incubation for 24 h using vernier caliper (Table-2).

Compounds **(Va), (Vb), (Vc)** and **(Vg)** showed much more activity against the organisms *E. coli, A. aureus* and *A. aerogenes.* Compound **(Ve)** showed enhanced activity against *B. subtilis.* Other compounds also showed measurable activity against all organisms except. *S. typhi.*

Antifungal Activity

The title compounds **(Va–g)** were screened for their antifungal activity using paper disc method.[14, 15] Paper discs used were of 6 mm diameter which were

soaked in 1 and 2 per cent solutions of the compounds in DMF The tested fungus was *A. niger.* The zones of inhibition were recorded after incubation for 48 h at 37°C (Table-3).

Compounds **(Vc)** and **(Vf)** showed high activity against *A. niger,* whereas other compounds showed considerable activity.

ACKNOWLEDGEMENTS

The authors are very much thankful to Prof. V.G. Bhamburkar, Principal, Shri Shivaji Science College, Amravati for providing necessary facilities and Mr. Arun Ingle, for rendering his help in antimicrobial screening of compounds.

REFERENCES

1. V.K. Verma, *Indian J. Chem.*, **1**, 116 (1963).
2. R. Singh, V.K. Verma and C.V. Agrawal, *J. Indian Chem. Soc.*, **52**, 444 (1975).
3. R. Singh and V.K. Verma, *Indian J. Chem.*, **15B**, 192 (1997).
4. Slomczynska Urszula and Barany George, *J. Herterocylic Chem.*, **21**, 241 (1984).
5. B.N. Singh, *Acta Cienc. Indica (Chem.)*, **24C**, 113 (1998).
6. N.K. Khandelwal, B.N. Berad and M.G. Paranjpe, *J. Indian Chem. Soc.*, **64**, 321 (1987).
7. G. Ottman and H. Hook, *J. Org. Chem.*, **31**, 838 (1966).
8. M.G. Paranjpe and A.S. Mahajan, *Indian J. Chem.*, **10**, 1138 (1972).
9. C.S. Bhaskar, N.N. Vidhale and B.N. Berad, *Asian J. Chem.*, **14**, 162 (2002).
10. N.B. Colthup, L.H. Daly and S.E. Wiberly, Introduction to Infrared and Raman Spectroscopy, Academic Press, New York (1964).
11. R.M. Silverstein, G.C. Bassler and T.C. Morrill, Spectrometric Indentification of Organic Compounds, 4th Edn., John Wiley & Sons, New York (1981).
12. A.L. Barry, in: Illus (Ed.), The Antimicrobial Susceptibility Test: Principle and Practices, Lea and Febiger, Philadephia, Pa., U.S.A., p. 180.
13. F. Cavanagh, Analytical Microbiology, Academic Press, New York, p. 126 (1963).
14. C. Jasper, J.C. Maruzzella and P.A. Henry, *J. Am. Pharm. Assoc.*, 471 (1958).
15. R. Ananthanarayan and G.K. Jagram Pancka, Text Book of Microbiology, 4th Edn., Orient Longmans (1990).

(*Received*: 21 April 2003; *Accepted*: 24 September 2003) AJC-3175