Asian Journal of Chemistry Vol. 16, No. 2 (2004), 773–778

Novel Benzo-1,3,6-Thiadiazepines; Synthesis, Antimicrobial Activity and Isomerization into Benzo-1,3,5-Triazepines

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

Benzo-(4,5-d)- 2-phenylimino - 7-aryl/alkylimino - 1,3,6-thiadiazepines (**IVa–g**) have been obtained by the basification of benzo-(4,5-d)-2-phenylimino-7-aryl/alkylimino-1,3,6-thiadiazepine hydrochlorides (**IIIa–g**). The latter were synthesized by the interaction of N-phenyl isocyano dichloride and 1-aryl/alkyl-3-(2′–amino)phenyl thiocarbamides (**IIa–g**), which were prepared initially by the condensation of aryl/alkyl isothiocyanates (**Ia–g**) and *o*-phenylenediamine. Compounds (**IVa–g**) on acylation with acetic anhydride and glacial acetic acid in 1 : 2 ratio afforded 3,6-diacetyl derivatives (**Va–g**) and on boiling with aqueous ethanolic sodium hydroxide solution isomerized into corresponding benzo-1,3,5-triazepines (**VIa–g**) The title compounds were assayed for their antimicrobial 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: Benzo-1,3,6-thiadiazepines, Synthesis, Antimicrobial, Isomerization, Benzo-1,3,5-triazepines.

INTRODUCTION

Synthesis of a few 1,2,5-benzothiadiazepines have been reported earlier in literature[1–3]. Pyrrallo-benzothiadiazepines have been shown to possess anti-HIV-1 and anti-HIV-1RT inhibitory activity comparable to nevirapine[4, 5]. There seems to be scanty work on the synthesis of benzo-1,3,6-thiadiazepines. The synthetic applications of N-phenyl isocyanodichloride[6] have been investigated earlier and shown to have enough potential in the synthesis of nitrogen and sulphur containing heterocyclic compounds.[7] Thus with the aim to synthesize benzo-1,3,6-thiadiazepines reaction of N-phenyl isocyanodichloride has been carried out with different 1-aryl/alkyl-3-(2-amino)phenyl thiocarbamides. These benzo-1,3,6-thiadiazepines were screened for their antimicrobial activity and isomerized into benzo-1,3,5-triazepines.

EXPERIMENTAL

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

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

Synthesis of 1-*p*-tolyl-3-(2′-amino)phenyl thiocarbamide (IIa)

A mixture of *o*-phenylenediamine (0.01 mol) and *p*-tolyl isothiocyanate (0.01 mol) (**Ia**) in carbon tetrachloride (15 mL) was refluxed for 2.0 h. The reaction mixture was cooled and the solid residue obtained was crystallized from ethanol (82%), m.p. 158°C. (Found: C, 65.16; H, 5.71; N, 16.41; S, 12.21. Calcd. For $C_{14}H_{15}N_3S$: C,65.36; H, 5.83; N, 16.34; S, 12.45%). This reaction was extended to synthesize other compounds (**IIb–g**) using other aryl/alkyl isothiocyanates (**I b–g**).

Synthesis of benzo-(4,5-d)-2-phenylimino-7-*p*-tolylimino-1,3,6-thiadiazepine (IVa)

1-*p*-tolyl-3-(2′-amino)phenylthiocarbamide (0.01 mol) (**IIa**) was suspended in chloroform (15 mL). To this a solution of N-phenyl isocyanodichloride[6] (0.01 mol) in chloroform was added. The reaction mixture was refluxed on water bath for 2.0 h. The evolution of hydrogen chloride gas was observed. The chloroform was distilled off and 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 crystallised from ethanol (70%), m.p. 194°C and identified as monohydrochloride of benzo-(4,5-d)-2-phenylimino-7-*p*-tolylimino-1,3,6-thiadiazepine (**IIIa**).

On basification with dilute ammonia solution a free base (**IVa**) was obtained and crystallised from aqueous ethanol, m.p. 184°C. (Found : C,69.98 ; H, 4.94; N, 15.68; S, 8.87. Calcd. for $C_{21}H_{18}N_4S$: C, 70.39; H, 5.02; N, 15.64; S, 8.93%). On extending the above reaction to other 1-aryl/alkyl-3-(2′-amino)phenyl thiocarbamides (**IIb–g**) the related 1,3,6-thiadiazepines (**IVb–g**) were isolated in good yield (Table-1).

Synthesis of benzo-(4,5-d)-3,6-diacetyl-2-phenylimino-7-*p*-tolylimino-1,3,6-thiadiazepine (Va)

A mixture of benzo-(4,5-d)-2-phenylimino-7-*p*-tolylimino-1,3,6-thiadiazepine (**IVa**); (0.01 mol) and acetic anhydride (0.02 mol) in glacial acetic acid (10 mL) was refluxed for 1.5 h. The reaction mixture was cooled and poured in a little crushed ice with water. A yellowish white solid powder was precipitated (**Va**) and crystallised from aqueous ethanol (72%), m.p. 198°C. (Found: C, 67.77; H, 4.74; N, 12.71; S, 7.19. Calcd. For $C_{25}H_{22}N_4O_2S$: C,67.87; H, 4.97; N, 12.66; S, 7.23%).

Similarly other diacetyl derivatives (**Vb–g**) were isolated in good yield (Table-1).

Isomerization: Synthesis of benzo-(6,7-f)-2-phenylimino-3-*p*-tolyl-4-thio-1,3,5-triazepine (VIa)

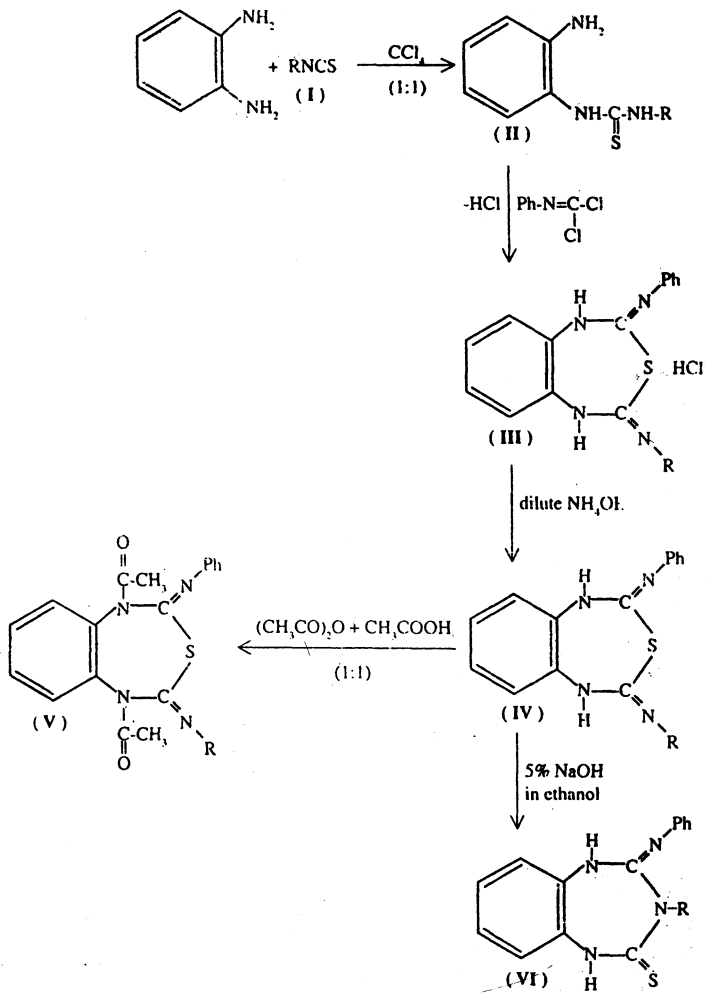
Benzo-(4.5-d)-2-phenylimino-7-*p*-tolylimino-1,3,6-thiadiazepine (**IVa**) was boiled for 1 h with 5% aqueous ethanolic (1 : 1) sodium hydroxide solution and the solid obtained after cooling the reaction mixture was crystallized from ethanol to give **VIa** (68%), m.p. 171°C. (Found: C, 70.14; H, 5.06; N, 15.59; S, 8.91. Calcd. For $C_{21}H_{18}N_4S$: C, 70.39; H, 5.02; N, 15.64, S, 8.93%). It was found to be desulphurizable when boiled with alkaline lead acetate solution indicating presence of —NH—C=S linkage.

Similarly other compounds (**VIb–g**) were prepared by isomerization (Table-1).

TABLE 1
PHYSICAL DATA AND ELEMENTAL ANALYSIS OF THE COMPOUNDS (IV), (V) AND (VI)

Compd.	R	m.f.	m.p. (°C)	Yield (%)	Elemental analysis found (Calcd.) %	
					N	S
IVa	*p*-tolyl	$C_{21}H_{18}N_4S$	184	70	15.68 (15.64)	8.87 (8.93)
IVb	*o*-tolyl	$C_{21}H_{18}N_4S$	104	74	15.63 (15.64)	8.89 (8.93)
IVc	*m*-tolyl	$C_{21}H_{18}N_4S$	101	69	15.69 (15.64)	8.91 (8.93)
IVd	phenyl	$C_{20}H_{16}N_4S$	118	82	16.21 (16.27)	9.37 (9.30)
IVe	*o*-chlorophenyl	$C_{20}H_{15}N_4SCl$	214	78	14.70 (14.81)	8.39 (8.46)
IVf	*p*-chlorophenyl	$C_{20}H_{15}N_4SCl$	162	77	14.78 (14.81)	8.51 (8.46)
IVg	*t*-butyl	$C_{18}H_{20}N_4S$	102	66	17.24 (17.28)	9.77 (9.87)
Va	*p*-tolyl	$C_{25}H_{22}N_4O_2S$	198	72	12.71 (12.66)	7.19 (7.23)
Vb	*o*-tolyl	$C_{25}H_{22}N_4O_2S$	202	68	12.68 (12.66)	7.26 (7.23)
Vc	*m*-tolyl	$C_{25}H_{22}N_4O_2S$	262(d)	74	12.58 (12.66)	7.18 (7.23)
Vd	phenyl	$C_{24}H_{20}N_4O_2S$	155	81	12.98 (13.08)	7.36 (7.47)
Ve	*o*-chlorophenyl	$C_{24}H_{19}N_4O_2SCl$	227	76	12.04 (12.12)	6.89 (6.92)
Vf	*p*-chlorophenyl	$C_{24}H_{19}N_4O_2SCl$	178	72	12.10 (12.12)	6.85 (6.92)
Vg	*t*-butyl	$C_{22}H_{24}N_4O_2S$	167	69	13.69 (13.72)	7.76 (7.84)
VIa	*p*-tolyl	$C_{21}H_{18}N_4S$	171	68	15.59 (15.64)	8.91 (8.93)
VIb	*o*-tolyl	$C_{21}H_{18}N_4S$	98	71	15.63 (15.64)	8.87 (8.93)
VIc	*m*-tolyl	$C_{21}H_{18}N_4S$	95	66	15.63 (15.64)	8.90 (8.93)
VId	phenyl	$C_{20}H_{16}N_4S$	107	79	16.25 (16.27)	9.23 (9.30)
VIe	*o*-chlorophenyl	$C_{20}H_{15}N_4SCl$	197	74	14.78 (14.81)	8.37 (8.46)
VIf	*p*-chlorophenyl	$C_{20}H_{15}N_4SCl$	136	78	14.74 (14.81)	8.41 (8.46)
VIg	*t*-butyl	$C_{18}H_{20}N_4S$	98	68	17.23 (17.28)	9.77 (9.87)

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



Scheme-1

I–VIa: R = *p*-tolyl; **I-VIb:** R = *o*-tolyl; **I–VIc:** R = *m*-tolyl; **I–VId:** R = phenyl
I–VIe: R = *o*-chlorophenyl; **I-VIf:** R = *p*-chlorophenyl; **I–VIg:** R = *t*-butyl

RESULTS AND DISCUSSION

Initially *o*-phenylenediamine was reacted with *p*-tolyl isothiocyanate (**Ia**) in carbon tetrachloride medium for 2.0 h. On cooling the reaction mixture and distilling off carbon tetrachloride the solid residue of 1-*p*-tolyl-3-(2′-amino)phenyl thiocarbamide (**IIa**) was obtained. It was washed with petroleum ether (60–80°C) and recrystallised from ethanol (82%), m.p. 158°C. The compound was found to be desulphurizable when boiled with alkaline lead acetate solution indicating presence of >C=S group. The other 1-aryl/alkyl-3-(2′-amino)phenyl thiocarbamides (**IIb–g**), were prepared by extending this reaction to other aryl/alkyl isothiocyanates

The 1-*p*-tolyl-3-(2′-amino)phenyl thiocarbamide (**IIa**) was then reacted with

N-phenyl isocyanodichloride in boiling chloroform for 2.0 h. The evolution of hydrogen chloride gas was clearly noticed and tested with moist blue litmus paper. On cooling the reaction mixture and distilling off chloroform afforded a sticky mass, which on washing with petroleum ether gave a granular solid. It was crystallised from ethanol (70%), m.p. 194°C. It was acidic to litmus. On determination of equivalent weight it was found to be monohydrochloride (**IIIa**). This on basification with aqueous ammonia solution afforded a free base (**IVa**), crystallised from aqueous ethanol, m.p. 184°C.

The IR spectrum of (**IVa**) showed the presence of ν(N–H) (3334 cm^{-1}) ν(C=N) (1596 cm^{-1}), ν(C—N) (1311 cm^{-1}), ν(C—S) (692 cm^{-1}), ν(1,4-disubstituted benzene ring) (812 cm^{-1}), ν(1,2-disubstituted benzene ring) (748 cm^{-1})[8,9]. The ^{1}H-NMR spectra of the product showed peaks due to $ArCH_3$ (δ 2.37 ppm, s, 3H), Ar—H (δ 6.93–8.06, m, 13H) and NH (δ 9.40, s, 2H). On the basis of the above facts the compound (**IVa**) has been assigned the structure benzo-(4,5-d)-2-phenylimino-7-*p*-tolylimino-1,3,6-thiadiazepine. The other compounds (**IVb–g**) were prepared by extending the above reaction to other 1-aryl/alkyl-3-(2′-amino)phenyl thiocarbamides (**IIb–g**) and isolated in good yield.

Compound (**IVa**) was acetylated using acetic anhydride and glacial acetic acid in 1 : 2 ratio to give benzo-(4,5-d)-3,6-diacetyl-2-phenylimino-7-*p*-tolylimino-1,3,6-thiadiazepine (**Va**) (72%), m.p. 198°C; I.R.: ν(C=O) (1675 cm^{-1}), ν(C=N) (1637 cm^{-1}), ν(C–N) (1339 cm^{-1}), ν(C–S) (691 cm^{-1}), ν(1,4-disubstituted benzene ring) (813 cm^{-1}), ν(1,2-disubstituted benzene ring) (749 cm^{-1}); ^{1}H-NMR: Ar—CH_3 (δ 2.5 ppm, s, 3H). —CO—CH_3 (δ 2.06 and 2.25, s, 6H) and Ar—H (δ 6.96-7.90, m, 13H). Similarly other diacetyl derivatives (**Vb–g**) were prepared.

Compound (**IVa**) was isomerized into benzo-(6,7-f)-2-phenylimino-3-*p*-tolyl-4-thio-1,3,5-triazepine (**VIa**) by boiling with aqueous ethanolic (1 : 1) sodium hydroxide (68%), m.p. 171°C; IR: ν(NH) (3305 cm^{-1}). ν(C=N) (1610 cm^{-1}), ν(C=S) (1310 cm^{-1}), ν(C—N) (1290 cm^{-1}), ν(1,4-disubstituted benzene ring) (820 cm^{-1}), ν(1,2-disubstituted benzene ring) (750 cm^{-1}). Similarly other compounds (**IVb–g**) were isomerized into corresponding 1,3,5-triazepines.(**VIb–g**)

Antimicrobial Activity

The title compounds (**IVa–g**) were screened for their antibacterial activity against pathogenic bacteria using cup plate method[10,11] at a concentration of 100 μg/mL in dimethyl formamide. 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 diameter 10 mm. The zones of inhibition were recorded after incubation for 24 h using vernier caliper.

Compounds (**IVb**), (**IVd**) and (**IVg**) showed much more activity against the organisms *E. coli*, *S. aureus* and *A. aerogenes*. Compound (**IVa**) showed enhanced activity against *B. subtilis*. Other compounds also showed low to moderate activity against all organisms except *S. typhi*.

The title compounds (**IVa–g**) were also screened for their antifungal activity using paper disc method[12,13]. Paper discs used were of 6 mm diameter which were soaked in 1 and 2 per cent solutions of the compounds in dimethyl formamide. The tested fungus was *A. niger*. The zones of inhibition were recorded after incubation for 48 h at 37°C.

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

ACKNOWLEDGEMENT

The authors are thankful to Prof. V.G. Bhamburkar, Principal, Shri Shivaji Science College, Amravati, for providing necessary facilities.

REFERENCES

1. M. Artico, R. Silvestri, G. Stefancich, *Synthetic Communications*, **22**, 1433 (1992).
2. G. Stefancich, R. Silvestri, E. Pagnozzi, M. Artico, *J. Heterocyclic Chem.*, **31**, 867 (1994).
3. ———, *J. Heterocyclic Chem.*, **31**, 1033 (1994).
4. M. Artico, R. Silvestri, E. Pagnozzi, G. Stefaneich, S. Massa, A.G. Loi, M. Putzolu, S. Corrias, M.G. Spiga, P. Lacolla, *Bioorganic Medicinal Chem.*, **4**, 837 (1996).
5. R. Silvestri, M. Artico, E. Pagnozzi, C.S. Massa, P. Lacolla, A.G. Loi, M.G. Spiga, S. Corrias. D. Lichino, *Farmaco*, **51**, 425 (1996).
6. G.M. Dyson and Harington, *J. Chem. Soc.*, 191 (1940).
7. C.S. Bhaskar and B.N. Berad, *Asian J. Chem.*, **14**, 679 (2002).
8. N.B. Colthup, L.H. Daly and S.E. Wiberly, Introduction to Infrared and Raman Spectroscopy, Academic Press, New York (1964).
9. R.M. Silverstein, G.C. Bassler and T.C. Morrill, Spectrometric Identification of Organic Compounds, 4th Edn., John Wiely & Sons, New York (1981).
10. A.L. Barry, in: Illus (Ed.), The Antimicrobial Suspectibility Test: Principle and Practices, Lea & Febiger, Philadephia, Pa., U.S.A., 180.
11. F. Cavanagh, Analytical Microbiology, Academic Press, New York, p.126 (1963).
12. C. Jasper, J.C. Maruzzella and P.A. Fleury, *J. Am. Pharm. Assoc.*, 471 (1958).
13. R. Ananthanarayan and G.K. Jagram Pancka, Text Book of Microbiology, 4th Edn., Orient Longman (1990).

(*Received*: 24 June 2003; *Accepted*: 04 December 2003) AJC-3266