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NOTE

Synthesis of novel benzo-1,2,5-thiadiazines, their antimicrobial activity and isomerization into benzo-1,2,4-triazines

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Benzo[*c*]-6-aryl/alkylimino-l,2,5-thiadiazines (4a-g) have been obtained by the basification of benzo[*c*]-6-aryl/alkylimino-1,2,5-thiadiazine dihydroiodides (3a-g). The latter were synthesized by the oxidative cyclisation of substituted l-aryl/alkyl-3-(2′-aminophenyl)thiocarbamides (2a-g) by ethanolic iodine. Compounds (4a-g) on acylation with acetic anhydride and glacial acetic acid in 1 : 2 ratio afforded 2,5-diacetyl derivatives (5a-g), on reaction with sodium nitrite in 1 : 2 ratio in acidic medium afforded 2,5-dinitroso derivatives (6a-g) and on boiling with aqueous ethanolic sodium hydroxide solution isomerized into corresponding benzo-l,2,4-triazines (7a-g). The title compounds were assayed for their antimicrobial activity against gram-positive and gram-negative micro-organisms.

Benzothiadiazines have been reported to possess significant β-blocking and hypotensive activity[1]. Various 1,2,4- and 1,3,5-benzothiadiazines have been earlier reported in literature[2]. There seems to be scanty work on the synthesis of benzo-l,2,5-thiadiazines. In the present communication we are reporting the synthesis of novel benzo-1,2,5-thiadiazines, their antimicrobial activity and isomerization into benzo-l,2,4-triazines.

Results and discussion

The parent compounds 1-aryl/alkyl-3-(2′-aminophenyl) thiocarbamides (**2a-g**) were prepared by refluxing the mixture of *o*-phenylenediamine (0.01 mol) and aryl/alkyl isothiocyanates (0.01 mol) (**la-g**) in carbon tetrachloride. These were transformed into benzo[*c*]-6-aryl/alkylimino-1,2,5-thiadiazine dihydroiodides (**3a-g**) by the oxidative cyclisation using ethanolic iodine and basified with dilute ammonium hydroxide solution to afford the respective free bases, benzo[*c*]-6-aryl/alkylimino-1,2,5-thiadiazines (**4a-g**).

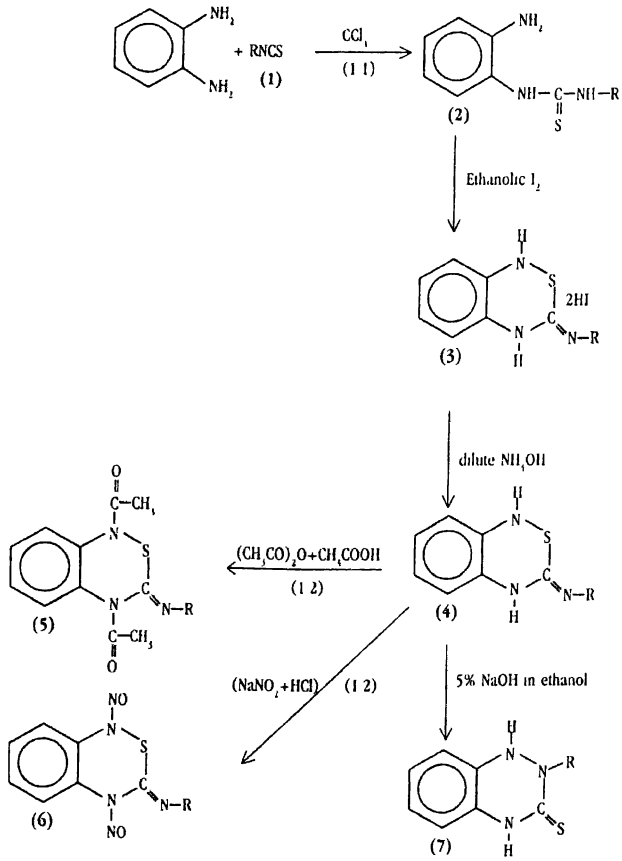
Compounds (**4a-g**) on acylation with acetic anhydride and glacial acetic acid in 1 : 2 ratio afforded 2,5-diacetyl derivatives (**5a-g**), on reaction with sodium nitrite in 1 : 2 ratio in acidic medium afforded 2,5-dinitroso derivatives (**6a-g**) and on boiling with aqueous ethanolic sodium hydroxide solution isomerized into corresponding benzo-l ,2,4-triazines (**7a-g**).

Antimicrobial activity :

The title compounds (**4a-g**) were screened for their antibacterial activity using cup plate diffusion method[3]. The bacterial organisms used in the present investigation were isolated from human being with characteristic infections and diseases. The isolates were pathogenic. The pathogens used included both gram-positive and 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^{-1} and each well (diameter 10 mm) was loaded with 0.1 ml of test compound solution (1000 μg ml^{-1}) in dimethylformamide. So that concentration of each test compounds was 100 μg ml^{-1}. The zones of inhibition were recorded after incubation for 24 h using vernier caliper. Inhibition zone record of the compounds clearly indicates that **4d** and **4f** were highly active against *S. aureus* and *B. subtilis*. Almost all compounds showed low to moderate activity against *A. aerogenes* and majority of the compounds were found inactive against *E. coli* and *S. typhi*.

Sreening of the title compounds for antifungal activity using paper disc method[4] showed that **4c** and **4f** were highly active against *A. niger*, whereas other compounds showed low to moderate activity. The zones of inhibition were recorded after incubation for 48 h at 37°.

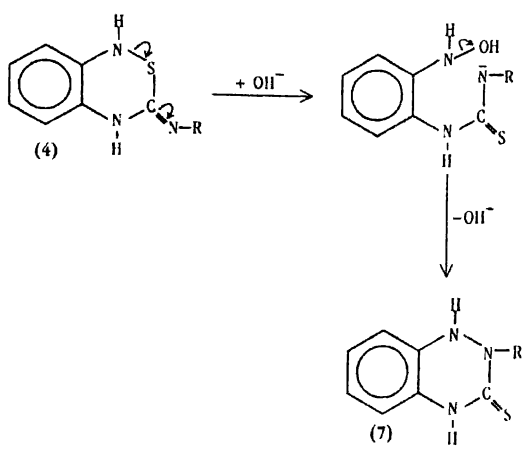
In present findings, the antibacterial and antifungal activity can not directly related to the structure. In antibacterial screening compounds with *p*-chlorophenyl and *m*-tolyl substituents on nitrogen atom are found to be highly active against micro-organisms *S. aureus* and *B. subtilis* whereas in antifungul screening compounds with *p*-chlorophenyl and *o*-tolyl substituents are found to be highly active against micro-organism *A. niger* and other compounds showed low to moderate activity.



Scheme 1

		R		R
where,	**1-6a**	Phenyl	**1-6e**	*o*-Chlorophenyl
	1-6b	*p*-Tolyl	**1-6f**	*p*-Chlorophenyl
	1-6c	*o*-Tolyl	**1-6g**	*t*-Butyl
	1-6d	*m*-Tolyl		

Transformation of benzo-1,2,5-thiadiazines (**4**) to benzo-1,2,4-triazines (**7**) takes place by the mechanism as below[7]



Experimental

All melting points were recorded using hot paraffin bath and are uncorrected. Chemicals used were of A.R. grade. IR spectra (4000–400 cm^{-1}) were recorded on Perkin-Elmer spectrophotometer in nujol mull and as KBr pelletes. 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.

The compound 1-phenyl-3-(2′-aminophenyl)thiocarbamide (**2a**) was prepared by refluxing the mixture of *o*-phenylenediamine (0.01 mol) and phenyl isothiocyanate (**la**) (0.01 mol) in carbon tetrachloride (20 ml) for 1.5 h by the reported method[5]. This reaction was then extended to synthesize the compounds (**2b-g**) using different aryl/alkyl isothiocyanates (**1b-g**).

Synthesis of benzo[c]-6-phenylimino-l,2,5-thiadiazine (**4a**) :

A paste of 1-phenyl-3-(2′-aminophenyl)thiocarbamide (**2a**) was prepared in ethanol and ethanolic iodine solution was added drop by drop to the paste with constant stirring. The colour of iodine initially disappeared. The addition was continued till violet colour of iodine persisted. The mixture was left overnight at RT and the separated solid; benzo[*c*]-6-phenylimino-1,2,5-thiadiazine dihydroiodide (**3a**), which was acidic to litmus was crystallised from ethanol (83%), m.p. 152°. Similarly, other compounds **3b-g** were obtained from **2b-g** : **3b** (85%), m.p. 151°; **c** (74%), m.p. 158°, **d** (87%), m.p. 146°; **e** (78%), m.p. 87°; **f** (81%), m.p. 164°; **g** (69%), m.p. 115°.

On basification of benzo[*c*]-6-phenylimino-1,2,5-thiadiazine dihydroiodide (**3a**) with dilute ammonium hydroxide solution a faint yellow coloured free base (**4a**) was obtained, it was crystallised from aqueous ethanol, m.p. 141° (Found : C, 64.19; H, 4.48; N, 17.33; S, 13.16. Calcd. for $C_{13}H_{11}N_3S$: C, 64.73; H, 4.56; N,17.42; S, 13.27%); ν_{max} 3390 and 3450 (NH), 1614 (C=N) 1334 (C–N), 751 (1,2-disubstituted benzene ring), 697 cm^{-1} (C–S)[6]; δ ($CDCl_3$ + DMSO-d_6) 9.22 (1H, s, NH), 8.89 (1H, s, NH), 7.15–7.53 (9H, m, Ar-H). Similarly, free **4b** was prepared from **3b** : **4b**, m.p. 145° (Found : C, 65.72; H, 5.03; N, 16.41; S,12.49. Calcd. for $C_{14}H_{13}N_3S$: C, 65.88; H, 5.09; N, 16.47; S, 12.54%); ν_{max} 3443 and 3345 (NH), 1657 (C=N), 1311 (C–N), 853 (1,4-disubstituted benzene ring), 750 (1,2-di-substituted benzene ring), 716 cm^{-1} (C–S); δ ($CDCl_3$ +DMSO-d_6) 7.71 (1H, s, NH), 7.58 (1H, s, NH), 6.78–7.43 (8H, m, Ar-H), 2.16 (3H, s, Ar-CH_3). This reaction was extended to synthesize free bases, **4c-g** : **4c**, m.p. 150° (Found : C, 65.67; H, 5.01; N, 16.32; S, 12.68. Calcd. for $C_{14}H_{13}N_3S$: C, 65.88; H, 5.09; N, 16.47; S, 12.54%); **d**, m.p. 141° (Found : C,

65.45; H, 4.98; N, 16.29; S, 12.44. Calcd. for $C_{14}H_{13}N_3S$: C, 65.88; H, 5.09; N, 16.47; S, 12.54%); **e**, m.p. 81° (Found : C, 56.10; H, 3.52; N, 15.27; S, 11.71. Calcd. for $C_{13}H_{10}N_3SCl$: C, 56.62; H, 3.62; N, 15.24; S,11.61%); **f**, m.p. 159° (Found : C, 56.52; H, 3.40; N,15.16; S, 11.58. Calcd. for $C_{13}H_{10}N_3SCl$: C, 56.62 ; H, 3.62 ; N, 15.24; S, 11.61%); **g**, m.p. 108° (Found : C, 59.28; H, 6.64 ; N, 19.09; S, 14.32. Calcd. for $C_{11}H_{15}N_3S$: C, 59.72; H, 6.78; N, 19.00; S, 14.47%).

Synthesis of benzo[c]-2,5-diacetyl-6-phenylimino-l,2,5-thiadiazine (**5a**) :

A mixture of benzo[*c*]-6-phenylimino-1,2,5-thiadiazine (**4a**) (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 white solid powder was precipitated (**5a**) and crystallised from warm water with a little ethanol (80%), m.p. 265° (Found : C, 61.74; H, 4.52; N, 12.79; S, 9.86. Calcd. for $C_{17}H_{15}N_3O_2S$: C, 62.76; H, 4.61; N, 12.92; S, 9.84%); ν_{max} 1690 (C=O), 1635 (C=N), 1295 (C–N), 751 (1,2-disubstituted benzene ring), 719 cm^{-1} (C–S). This reaction was extended to synthesize other diacetyl derivatives, **5b-g** : **5b** (72%), 230° d ; **c** (78%), 186°; **d** (85%), 183°; **e** (80%), 206°; **f** (75%), 184°; **g** (70%), 180°.

Synthesis of benzo[c]-2,5-dinitroso-6-phenylimino-1,2,5-thiadiazin (**6a**) :

A solution of benzo[*c*]-6-phenylimino-1,2,5-thiadiazine (**4a**) (0.01 mol) in 10 ml of ethanol was cooled below 5° and a solution of sodium nitrite (0.02 mol) in 2.5 ml of concentrated hydrochloric acid and 2.5 ml of water was added to it. A greenish yellow solid (**6a**)was precipitated out and crystallised from rectified spirit (78%), m.p. 92° (Found : C, 51.89; H, 2.98; N, 22.98; S, 10.39. Calcd. for $C_{13}H_9H_5O_2S$: C, 52.17; H, 3.01; N, 23.41; S, 10.70%); ν_{max} 1654 (C=N), 1617 (N=O), 1318 (C–N), 1208 (N–N), 744 (1,2-disubstituted benzene ring), 724 cm^{-1} (C–S). This reaction was extended to synthesize other dinitroso derivatives (yield 70–85%), **6b-g** : **6b**, 78°; **c**, 88°, **d**, 76°; **e**, 68°; **f**, 109°; **g**, 94°.

Isomerization : Synthesis of benzo[c]-2-phenyl-3-thio-1,2,3,4-tetrahydro-1,2,4-triazine (**7a**) :

Benzo[*c*]-6-phenylimino-1,2,5-thiadiazine (**4a**) was boiled for 1 h with 5% aqueous ethanolic (1 : 1) sodium hydroxide solution and the solid obtained after cooling the reaction mixture was crystallised from ethanol to give **7a** (68%), m.p. 192° (Found : C, 63.71; H, 4.52; N, 17.23; S, 13.18. Calcd. for $C_{13}H_{11}N_3S$: C, 64.73; H, 4.56; N, 17.42; S, 13.27%); ν_{max} 3416 (NH), 1632 (C=N), 1269 (C–N), 1238 (C=S), 749 (1,2-disubstituted benzene ring). It was found to be desulphurizable when boiled with alkaline lead acetate solution indicating -NH-C=S linkage. Similarly other compounds **7b-g**, were prepared by isomerizaion : **6b** (61%), m.p. 181° (Found : C, 64.89; H, 5.02 ; N, 16.37; S, 12.18. Calcd. for $C_{14}H_{13}N_3S$: C, 65.88 ; H, 5.09; N, 16.47; S, 12.54%); **c** (71%), m.p. 162° (Found : C, 65.34; H, 4.98; N, 16.23; S, 12.61. Calcd. for $C_{14}H_{13}N_3S$: C, 65.88; H, 5.09; N, 16.47; S, 12.54 %); **d** (65%), m.p. 131° (Found : C, 65.14; H, 5.11; N, 16.31; S, 12.34. Calcd. for $C_{14}H_{13}N_3S$: C, 65.88; H, 5.09; N, 16.47; S, 12.54%); **e** (82%), m.p. 201–204° (Found : C, 56.19; H, 3.67; N, 15.27; S, 11.27. Calcd. for $C_{13}H_{10}N_3SCl$: C, 56.62; H, 3.62; N, 15.24; S, 11.61%); **f** (70%), m.p. 192° (Found : C, 56.01; H, 3.41; N, 15.21; S, 11.39. Calcd. for $C_{13}H_{10}N_3SCl$: C, 56.62; H, 3.62; N, 15.24; S, 11.61%); **g** (68%), m.p. 148–151° (Found : C, 59.89; H, 6.61 ; N, 18.85 ; S, 14.44. Calcd. for $C_{11}H_{15}N_3S$: C, 59.72; H, 6.78; N, 19.00; S, 14.47%).

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References

1. Bhar Ahmed, A. A. Siddiqui and Manoj Agrawal, *Indian J. Pharmacol.*, 1999, **31**, 33.
2. Y. Girad, J. Atkinson and J. Rokach, *J Chem. Soc.*, 1979, 1043; D. K. Bates, K. A. Tafel and J. P. Xu, *J Heterocyclic Communications*, 1996, **2**, 115; Hong Shan Dong, Kun Wei, Qing Lian Wang and Bin Quan, *J. Chinese Chem. Soc.*, 2000, **47**, 3; Yoshio Imai, Amane Mochizuki and Masa-aki Kakimato, *Synthesis*, 1983, 851; I. Zivkovic, D. M. Thompson, M. Bertolino, D. Uzunov, M. Dibella, E. Costa and A. Guidotti, *Pure Appl. Chem.*, 2002, **74**, 1957.
3. A. L. Barry, "The Antimicrobial Suspectibility Test : Principle and Practices", eds. Illus lea and Fibiger, Philadephia, Pa., U.S.A., 180.
4. R. Ananthanarayan and G. K. Jagram Pancka, "Text Book of Microbiology", 4th. ed., Orient Longmans, 1990.
5. B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, "Vogel's Text Book of Practical Oraganic Chemistry", 5th. ed.
6. N. B. Colthup, L. H. Daly and S. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy", Academic Press, New York, 1964; R. M. Silverstein, G. C. Bassler and T. C. Morrill, "Spectrometric Identification of Organic Compounds", 4th. ed., John Wiely & Sons, New York, 1981.
7. C. J. Cavallito, C. M. Martini and F. C. Nachod, *J. Am. Chem. Soc.*, 1951, **73**, 2354.