Synthesis and antimicrobial activity of 1,3,5-thiadiazines and their isomerism into 1,3,5-triazines

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A series of 2,6-diphenylimino-4-(substituted)-benzylidene amino-1,3,5-thiadiazines 4a-g have been obtained by the basification of their hydrochlorides 3a-g, which are prepared by interaction of N-phenyl isocyanodichloride and 1-(substituted)-benzylidene amidino-3-phenyl thiocarbamides 2a-g. The latter have been synthesized by the condensation of 1-amidino-3-phenyl thiocarbamide 1 and different aliphatic and aromatic aldehydes. Compounds 4a-g on acylation afford monoacetyl derivatives 5a-g, on reaction with sodium nitrite in acidic medium afforded mononitroso derivatives 6a-g, and on boiling with 5% aqueous ethanolic (1:1) sodium hydroxide solution isomerize into corresponding 1-phenyl-2-phenylimino-4-(substituted)-benzylidene amino-6-thio-1,3,5-triazines 7a-g. The title compounds have been assayed for their antimicrobial activity against gram-positive as well as gram-negative microorganisms.

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1,3,5-Thiadiazines and their rearranged products, 1,3,5-triazines have been shown to possess brightening and fibre finishing properties in textile industry.1,2 Symmetric triazines have also been used as chain lengthening agents in polyurethane polymerization, azodyes and paints, plastic and rubber.3 They are also used as fungicidal,4 insecticidal5 and as medicinal compounds. In view of the utility of these compounds in various fields and as a part of wider programme to provide alternative routes for the synthesis of various 5 and 6 membered heterocyclic compounds, now the method for the synthesis of 1,3,5-thiadiazines and their rearrangement to 1,3,5-triazines is reported.

Results and Discussion

The parent compound 1-amidino-3-phenyl thiocarbamide1,8 1 was prepared by refluxing the mixture of guanidine nitrate (0.01 mole), phenylisothiocyanate (0.01 mole) and sodium hydroxide (0.01 mole) in ethanolic medium for 2 hr. This was transformed into 1-(substituted) benzylidene amidino-3-phenyl thiocarbamides 2a-g by condensing with different aliphatic and aromatic aldehydes in refluxing chloroform medium. Compounds 1 and 2a-g were found to be desulphurizable when boiled with alkaline lead acetate solution.

Compounds 2a-g were then reacted with N-phenyl isocyanodichloride5 in boiling chloroform for 3 hr. The evolution of hydrogen chloride gas was clearly noticed as tested with moist blue litmus paper. Cooling the reaction mixture and distilling off chloroform afforded sticky masses, which on washing with petroleum ether gave granular solids. These were acidic to litmus and on titrimetric analysis identified as monohydrochlorides of 2,6-diphenylimino-4-(substituted)-benzylidene amino-1,3,5-thiadiazines 3a-g. These on basification with aqueous ammonia solution afforded free bases 4a-g. Compounds 4a-g on acylation with acetic anhydride and glacial acetic acid yielded monoacetyl derivatives 5a-g, on reaction with sodium nitrite in acidic medium yielded mononitroso derivatives 6a-g and on boiling with aqueous ethanolic (1:1) sodium hydroxide solution isomerized into corresponding 1-phenyl-2-phenylimino-4-(substituted) benzylidene amino-6-thio-1,3,5-triazines 7a-g (Scheme I).

Antimicrobial activity

The title compounds 4a-g were screened for their antibacterial activity using cup plate diffusion method.10,11 The bacterial organisms 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 1×10^5 CIU/mL and each well (diameter 10mm) was loaded with 0.1 mL of test compound solution (1000 μg/mL) in DMF. So that concentration of each test compound was 100μg/mL. The zones of inhibition were recorded after incubation for 24 hr using Vernier caliper. Inhibition zone record of the compounds clearly indicated that 4c and 4e were highly active against S. typhi and B. subtilis and moderately active against E. coli. Majority of the compounds were found inactive against S. aureus and A. aerogenes.
Screening of the title compounds for antifungal activity using paper disc method\textsuperscript{12,13} showed that 4d and 4f were highly active against \textit{A. niger}, whereas other compounds showed low to moderate activity. The zones of inhibition were recorded after incubation for 48 hr at 37°C.

\textbf{Experimental Section}

The melting points of all synthesized compounds were recorded using hot paraffin-bath and are uncorrected. Chemicals used were of AR grade. \textsuperscript{1}H NMR spectra were recorded with TMS as internal standared using CDCl\textsubscript{3}, and DMSO-\textit{d}\textsubscript{6}, as solvents. IR
spectra were recorded on Perkin-Elmer spectrophotometer in the range 4000-400 cm⁻¹ in Nujol mull and as KBr pellet. Purity of the compounds was checked on silica gel-G plates by TLC.

Parent compound 1-amidino-3-phenyl thiocarbamide 1 was prepared by refluxing the mixture of guanidine nitrate (0.01mole), phenyl isothiocyanate (0.01mole) and sodium hydroxide (0.01mole) in ethanolic medium for 2 hr.

**Synthesis of 1-(4′-methoxy)-benzylidene amidino-3-phenyl thiocarbamide 2a.** A mixture of 1-amidino-3-phenyl thiocarbamide 1 (0.01mole) and 4'-methoxy benzaldehyde (0.01mole) in chloroform (10mL) was refluxed for 2.5 hr. Then chloroform was distilled off and granular solid mass was obtained. It was crystallised from ethanol and identified as 1-(4′-methoxy)-benzylidene amidino-3-phenyl thiocarbamide 2a, (78%), m.p. 192°C.

Similarly, other thiocarbamides, 2b-g were obtained using different aliphatic and aromatic aldehydes.

**Synthesis of 2,6-diphenylimino-4-(4′-methoxy)-benzylidene amino-1,3,5-thiadiazine 4a.** 1-(4′-methoxy)benzylidene amidino-3-phenyl thiocarbamide 2a, (0.01 mole) was suspended in chloroform (15 mL). To this a solution of isocyanodichloride (0.01mole) in chloroform was added. The reaction mixture was refluxed on water bath for 2 hr. 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, crystallised from ethanol (80%), m.p. 210°C and identified as monohydrochloride of 2,6-diphenylimino-4-(4′-methoxy) benzylidene amino-1,3,5-thiadiazine 3a.

Similarly, other compounds, 3b-g were prepared from 2b-g; 3b (82%), m.p. 178°C, 3c (78%), m.p. 212°C, 3d (79%), m.p. 132°C, 3e (75%), m.p. 248°C, 3f (82%), m.p. 208°C, 3g (76%), m.p.228°C.

On basification of 3a with dilute ammonia solution a free base 4a was obtained, it was crystallised from aqueous ethanol, m.p.190°C (Found: C, 66.48; H, 4.42; N, 16.90; S, 7.64. Caled for C₁₉H₁₇N₅O₂S: C, 66.82; H, 4.60; N, 16.94; S, 7.74%); IR: 1605 (C=O), 1291 (C-N), 1227 (N-N), 843 (1,4-disubstituted benzene ring), 693 cm⁻¹ (C-S) 613; 1H NMR (CDCl₃+DMSO-d₆): 10.67 (1H, s, NH), 8.79 (1H, s, CH=N), 7.04-7.72 (14H, m, Ar-H), 3.95 (3H, s, O-CH₃); 4b, m.p.155°C (Found: C, 67.53; H, 5.14; N, 19.68; S, 7.45. Caled for C₂₃H₂₀N₅S: C, 67.60; H, 5.16; N, 19.71; S, 7.51%); 4c, m.p.198°C (Found: C, 63.13; H, 3.82; N, 16.78; S, 7.61. Caled for C₂₄H₂₁N₅SCl: C, 63.23; H, 3.83; N, 16.76; S, 7.66%); 4d, m.p.128°C (Found: C, 64.21; H, 4.21; N, 16.22; S, 7.44. Caled for C₂₄H₂₁O₂N₅S: C, 64.33; H, 4.42; N, 16.31; S, 7.45%); 4e, m.p. 195°C (Found: C, 68.81; H, 4.44; N, 18.29; S, 8.31. Caled for C₂₅H₂₂N₅S: C, 68.92; H, 4.43; N, 18.27; S, 8.35%); 4f, m.p.182°C (Found: C, 65.65; H, 4.80; N, 20.11; S, 9.18. Caled for C₂₆H₂₃N₅S: C, 65.70; H, 4.89; N, 20.17; S, 9.22%); 4g, m.p. 206°C (Found: C, 63.51; H, 4.52; N, 21.75; S, 9.89. Caled for C₂₇H₂₄N₅S: C, 63.55; H, 4.67; N, 21.80; S, 9.96%).

**Synthesis of 2,6-diphenylimino-3-acetyl-4-(4′-methoxy)-benzylidene amino-1,3,5-thiadiazine 5a.** A mixture of 2,6-diphenylimino-4-(4′-methoxy) benzylidene amino-1,3,5-thiadiazine 4a, (0.01mole) and acetic anhydride (0.01mole) in glacial acetic acid (10mL) was refluxed for 2 hr. The reaction mixture was cooled and poured in a little crushed ice with water, a whitish solid precipitated was crystallised from warm water with ethanol to give 5a, (78%), m.p. 204°C (Found: C, 65.91; H, 4.50; N, 15.34; S, 6.98. Caled for C₂₃H₂₁N₅O₂S: C, 65.93; H, 4.61; N, 15.38; S, 7.03%); IR: 1681 (C=O), 1591 (C=N), 1280 (C-N), 688 cm⁻¹ (C-S); 1H NMR (CDCl₃+DMSO-d₆): 8.71 (1H, s, CH=N), 6.91-7.68 (14H, m, Ar-H), 3.93 (3H, s, O-CH₃), 2.13 (3H, s, CO-CH₃); 5b (75%), m.p. 168°C, 5c (80%), m.p. 214°C, 5d (81%), m.p.144°C, 5e (78%), m.p.172°C, 5f (75%), m.p.202°C, 5g (70%), m.p.228°C.

**Synthesis of 2,6-diphenylimino-3-nitroso-4-(4′-methoxy)-benzylidene amino-1,3,5-thiadiazine 6a.** A solution of 2,6-diphenylimino-4-(4′-methoxy) benzylidene amino-1,3,5-thiadiazine 4a, (0.01mole) in 10 mL of ethanol was cooled below 5°C and a solution of sodium nitrite (0.01mole) in 2 mL of water was added to it. A greenish yellow solid 6a was precipitated out and crystallised from aqueous ethanol (80%), m.p. 102°C (Found: C, 62.31; H, 3.97; N, 18.93; S, 7.18. Caled for C₂₅H₂₃N₅O₃S: C, 62.44; H, 4.07; N, 19.00; S, 7.23%); IR: 1637 (C=N), 1585 (N=O), 1295 (C-N), 1222 (N-N), 845 (1,4-disubstituted benzene ring), 691 cm⁻¹ (C-S); 6b (71%), m.p. 95°C, 6c (78%), m.p.98°C, 6d (77%), m.p.88°C, 6e (68%), m.p.92°C, 6f (76%), m.p. 102°C, 6g (70%), m.p. 89°C.
Isomerization: Synthesis of 1-phenyl-2-phenylimino-4-(4′-methoxy) benzylideneamino-6-thio-1,3,5-triazine 7a. 2,6-Diphenylimino-4-(4′-methoxy) benzylideneamino-1,3,5-thiadiazine 4a was boiled for 1.5 hr 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 (72%), m.p. 155°C (Found: C, 66.79; H, 4.57; N, 16.86; S, 7.71. Calcd for C23H19N5OS: C, 66.82; H, 4.60; N, 16.94; S, 7.74%); IR: 3440 (NH), 1610 (C=N), 1288 (C-N), 1248 (C=S), 845 cm⁻¹ (1,4-disubstituted benzene ring); MS: m/z 382 (M⁺-OCH₃), 336 (M⁺-Ph), 306 (M⁺-PhOCH₃), 304 (M⁺-Ph-S), 278 (M⁺-PhNCS), 103 (PhNCS⁺), 77 (Ph⁺); 7b (65%), m.p. 148°C (Found: C, 67.47; H, 4.60; N, 16.94; S, 7.74%); MS: m/z 382 (M⁺-OCH₃), 336 (M⁺-Ph), 306 (M⁺-PhOCH₃), 304 (M⁺-Ph-S), 278 (M⁺-PhNCS), 103 (PhNCS⁺), 77 (Ph⁺). It was found to be desulphurizable when boiled with alkaline lead acetate solution indicating -NH-C=S linkage; 7b (65%), m.p. 148°C (Found: C, 67.47; H, 4.60; N, 16.94; S, 7.74%); MS: m/z 382 (M⁺-OCH₃), 336 (M⁺-Ph), 306 (M⁺-PhOCH₃), 304 (M⁺-Ph-S), 278 (M⁺-PhNCS), 103 (PhNCS⁺), 77 (Ph⁺). 7c (69%), m.p.165°C (Found: C, 63.19; H, 3.73; N, 16.71; S, 7.64. Calcd for C22H18N5SCl: C, 63.23; H, 3.83; N, 16.76; S, 7.66%); MS: m/z 340 (M⁺-Ph), 308 (M⁺-Ph-S), 306 (M⁺-PhCl), 282 (M⁺-PhNCS), 103 (PhNCS⁺), 77 (Ph⁺); 7d (72%), m.p.124°C (Found: C, 64.31; H, 4.41; N, 16.32; S, 7.33. Calcd for C23H19N5O2S: C, 64.33; H, 4.42; N, 16.31; S, 7.45%); MS: m/z 398 (M⁺-OCH₃), 352 (M⁺-Ph), 320 (M⁺-Ph-S), 294 (M⁺-PhNCS), 103 (PhNCS⁺), 77 (Ph⁺); 7e (79%), m.p.188°C (Found: C, 68.93; H, 4.45; N, 18.23; S, 8.33. Calcd for C22H17N5S: C, 68.92; H, 4.43; N, 18.27; S, 8.35%); MS: m/z 383 (M⁺), 306 (M⁺-Ph), 274 (M⁺-Ph-S), 248 (M⁺-PhNCS), 229 (M⁺-2Ph), 103 (PhNCS⁺), 77 (Ph⁺); 7f (73%), m.p.172°C (Found: C, 65.35; H, 4.86; N, 20.14; S, 9.21. Calcd for C19H17N5S: C, 65.73; H, 4.89; N, 20.17; S, 9.22%); MS: m/z 332 (M⁺-CH₃), 270 (M⁺-Ph), 238 (M⁺-Ph-S), 212 (M⁺-PhNCS), 103 (PhNCS⁺), 77 (Ph⁺); 7g (68%), m.p.178°C (Found: C, 63.45; H, 4.59; N, 21.73; S, 9.91. Calcd for C17H15N5S: C, 63.55; H, 4.67; N, 21.80; S, 9.96%); MS: m/z 321 (M⁺), 306 (M⁺-CH₃), 244 (M⁺-Ph), 212 (M⁺-Ph-S), 186 (M⁺-PhNCS), 103 (PhNCS⁺), 77 (Ph⁺).

Transformation of 1,3,5-thiadiazines 4a-g to 1,3,5-triazines 7a-g takes place by the mechanism as given in Scheme II.

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References