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NOTE

Synthesis and Antimicrobial Activity of 2-Phenylimino-3-amido-5-aryl/alkylimino-1,3,4-thiadiazolidines

MANISHA AJMIRE* and B.N. BERAD
Department of Chemistry, Shri Shivaji Science College, Amravati-444 603, India.

Several 2-phenylimino-3-amido-5-aryl/alkylimino-1,3,4-thiadiazolidines (**4a–g**) have been synthesized by the interaction of 1-aryl-2-thio-bis-urea (**2a**) and phenylimino cyanodichloride (**1**) in refluxing chloroform medium followed by basification of resulting compound (**3a–g**). The compounds (**2a–g**) have been prepared by the condensation of aryl/alkyl isothiocyanates and semicarbazide. The compounds (**4a–g**) on acetylation afforded monoacetyl derivatives. The synthesized compounds were assayed for their antimicrobial activity against gram +ve and gram –ve microorganisms.

Key Words: Synthesis, Antimicrobial activity, 1,3,4-Thiadiazolidine.

For the synthesis of 1,3,4-thiadiazolidine and cyclization and other routes have been employed earlier[1–6]. Thiadiazoles are of vital importance as drugs. These compounds possess diverse range of physiological activities[7–12] explore the new route for the synthesis of heterocyclic compounds. In the present paper, the synthesis and antimicrobial activity of 2-phenyl-imino-3-amido-5-aryl/alkyl-imino-1,3,4-thiadiazolidines have been reported.

All melting points were recorded using hot paraffin bath and are uncorrected. Chemicals used were of AR grade. IR-spectra (4000–400 cm^{-1}) were recorded on Perkin-Elmer spectrophotometer 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 compound was checked on silica gel-G plates by TLC.

Synthesis of 1-phenyl-2-thio-bis urea (2a): Semicarbazide (0.01 mol), phenyl isothiocyanate (0.01 mol) and chloroform (10 mL) were refluxed for 2 h. On distilling off chloroform a solid residue was obtained; it was washed with petroleum ether. It was recrystallized from ethanol to get a colourless crystalline solid (**2a**), yield 83%, m.p. 180°C.

The above reaction was extended to synthesize compounds (**2b–g**) crystallized from ethanol: **b** (85%) m.p. 110°C; **c** (74%), m.p. 122°C; **d** (87%), m.p. 160°C; **e** (78%), m.p. 174°C; **f** (81%), m.p. 170°C; **g** (69%), m.p. 115°C.

Synthesis of 2-(4-chloro phenylimino)-3-amido-5-aryl/alkylimino-1,3,4-

thiadiazolidine (5a): 1-Aryl-2-thio-bis urea (0.01 mol) was suspended in chloroform (20 mL); to this solution phenylimino cyanodichloride (0.01 mol) in chloroform was added. The reaction mixture was then refluxed on a water bath for 3 h. The evolution of hydrogen chloride gas was observed. After cooling the reaction mixture, the chloroform was distilled off when a sticky mass was obtained. It was repeatedly washed with petroleum ether (60–80°C) followed by addition of ethanol; a colourless solid acidic to litmus was isolated; it was recrystallized from ethanol, m.p. 140°C. On basification of 2-(4-chloro phenylimino)-3-amido-5-aryl/alkylimino-1,3,4-thiadiazolidine hydrochloride with dilute ammonium hydroxide solution, a faint yellow coloured free base (**5a**) was obtained. It was crystallized from aqueous ethanol.

5a (Found: C, 52.01; H, 3.11; N, 20.10; S, 9.06; Calcd. for $C_{15}H_{12}N_5OSCl$: C, 52.02; H, 3.47; N, 20.26; S, 9.26%); ν_{max} 3390 and 3450 ν(—NH), 1614 ν(C═N), 1334 ν(C—N), 750 ν(distributed benzene ring). The PMR is δ($CDCl_3$ + DMSO-d_6) 6.0 (1H, s, NH); 9.6–10.0 (2H, m, Co—NH_2 proton); 7.2–7.6 (5H, m, Ar—H). **5b** was prepared from **4b. 4b**, m.p. 142°C (Found: C, 57.43; H, 4.10; N, 22.23; S, 10.11; Calcd. for $C_{15}H_{13}N_5OS$: C, 57.87; H, 4.18; N, 22.50; S, 10.28%). This reaction was extended to synthesize free bases, **5c–g; 5c**, m.p. 149°C (Found: C, 58.91; H, 4.20; N, 21.02; S, 9.50; Calcd. for $C_{16}H_{15}N_5OS$: C, 59.07; H, 4.61; N, 21.53; S, 9.84%). **5d**, m.p. 202°C (Found: C, 58.80; H, 4.30; N, 20.93; S, 9.50; Calcd. for $C_{16}H_{15}N_5OS$: C, 59.07; H, 4.61; N, 21.53; S, 9.84%). **5e**, m.p. 55°C (Found: C, 58.87; H, 4.25; N, 21.32; S, 9.47; Calcd. for $C_{16}H_{15}N_5OS$: C, 59.07; H, 4.61; N, 21.53; S, 9.84%). **5f**, m.p. 90°C (Found: C, 51.87; H, 3.10; N, 21.95; S, 9.10; Calcd. for $C_{15}H_{12}N_5OSCl$: C, 52.02; H, 3.47; N, 20.26; S, 9.26%). **5g**, m.p. 108°C (Found: C, 53.11; H, 3.30; N, 23.70; S, 10.42; Calcd. for $C_{13}H_{17}N_5OS$: C, 53.60; H, 3.84; N, 24.05; S, 10.99%).

Synthesis of 2-(4-chloro phenylimino)-3-amido-4-acetyl-5-aryl/alkyl imino-1,3,4-thiadiazolidine (6a): A mixture of 2-(4-chloro phenylimio)-3-amido-5-aryl/alkylimino-1,3,4-thiadiazolidine (0.01 mole), acetic anhydride (0.01 mole) and glacial acetic acid (10 mL) was refluxed for 1 h. After refluxing the mixture was poured over a little crushed ice. The granular solid was separated; it was recrystallized from ethanol (80%), m.p. 192°C. (Found: C, 52.22; H, 3.20; N, 17.80; S, 8.06; Calcd. for $C_{17}H_{14}N_5O_2S$: C, 52.57; H, 3.60; N, 18.04; S, 8.24%); IR (KBr, cm^{-1}): 3390 and 3450 ν(—NH), 1601 ν(C═N), 1308 ν(C—N), 1678 ν(C═O), 750 ν(distributed benzene ring). This reaction was extended to synthesize other acetyl derivatives (**6b–g**).

1-Aryl-2-thio-bis urea were prepared by the interaction of semicarbazide and aryl/alkyl isothiocyanates while the phenylimino cyanodichloride was prepared by excessive chlorination of phenyl isothiocyanates. The interaction of 1-aryl-2-thio-bis urea and a phenylimino cyanodichloride in refluxing chloroform medium for 3 h proceeded with the evolution of hydrogen chloride gas. After completion of the reaction and distilling off the solvent the granular solids (**3a–g**) were

isolated. These were acidic to litmus and on determination of equivalent weights by titrimetric analysis were found to be monohydrochlorides. The compounds (**3a–g**) on basification with aqueous ammonia solution gave bases (**4a–g**). The possible alternative structures (**5a–g**) were discarded for these compounds on the basis of the presence of —$CONH_2$ group which cannot be explained by structures (**5a–g**). The compounds (**4a–g**) on acetylation with acetic acid produced monoacetyl derivatives (**6a–g**).

Antimicrobial activity: The title compounds (**4a–g**) were screened for their antimicrobial activity using cup-plate diffusion method[13]. The bacterial organisms used in the present investigation were isolated from human beings 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, P. vulgaris, B. subtilis, Shigella.*

Sensitivity plates were seeded with a bacterial inoculum of 1×10^6 (1 μg/mL) and each well diameter (10 mm) was loaded with 0.1 mL of test compound solution (1000 μg/mL) in DMF, so that the concentration of each test compound was 100 μg/mL. The zones of inhibition were recorded after incubation for 24 h using vernier calliper. Inhibition zones of the compound clearly indicate that compound (**4b**) is having moderate to high activity. It is highly active against *S. aureus*. All the compounds are having high activity against *S. aureus* and most of them are inactive against *B. subtilis*. These compounds showed moderate activity against *E. coli* and *Shigella.*

In the present findings, the antibacterial activity cannot be directly related to the structure. In bacterial screening, compounds with *p*-tolyl, *m*-chloro and *p*-chloro substituents on nitrogen atoms are found to be highly active against the micro-organisms *S. aureus* and *P. vulgaris*.

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