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SYNTHESIS AND BIOLOGICAL EVALUATION OF PHARMACOLOGICALLY IMPORTANT [1,2,4] DITHIAZOLIDINES

PRAVIN R. KAWLE[*], PRADIP P. DEOHATE, B. N. BERAD[a] and J. R. CHOUDHARI[b]

PG Department of Chemistry, Shri Radhakisan Laxminarayan Toshniwal College of Science, AKOLA – 444001 (M.S.) INDIA
[a]PG Department of Chemistry, Rashtrasant Tukadoji Maharaj Nagpur University, Fule Campus, NAGPUR – 440033 (M.S.) INDIA
[b]Department of Chemistry, Yashwantrao Chavan Arts and Science College, Manglurpir, WASHIM – 444403 (M.S.) INDIA

ABSTRACT

Series of 4-acridin-9-yl-3-arylimino-5-phenylimino-[1,2,4] dithiazolidines have been synthesised by the interaction of 1-acridin-9-yl-3-aryl thiourea with N-phenyl S-chloro isothiocarbamoyl chloride in refluxing chloroform medium followed by basification with dilute ammonium hydroxide solution. Initially 1-acridin-9-yl-3-aryl thioureas have been prepared by the interaction of 9-amino acridine hydrochloride with N-aryl isothiocyanates. Constitutions of synthesized compounds have been delineated on the basis of chemical transformation, elemental analysis, equivalent weight determination, IR, ^{1}H NMR, ^{13}C NMR, and mass spectral studies. The title compounds were evaluated for their antimicrobial activity against the microorganisms like *S. typhi*, *E. coli*, *B. subtilis* and *S. aureus*.

Key words: Antimicrobial activity, Biological evaluation, Substituted [1,2,4]-dithiazolidines.

INTRODUCTION

Synthesis, structural properties and antimicrobial activities of various [1,2,4]-dithiazolidines have been reported earlier[1-5]. The literature has been enriched with progressive finding about the synthesis of [1,2,4]-dithiazolidines by using reagent N-phenyl-S-chloro isothiocarbamoyl chloride[6-10] and oxidative cyclization using bromine and iodine. [1,2,4]-dithiazolidine have been also found to possess potent anti-tumour, anti-tuberculosis anti-cancer and anti-dibetic properties[11,12]. In view of utility of N-phenyl-S-chloro

[*]Author for correspondence; E-mail: pravink280685@rediffmail.com

isothiocarbamoyl chloride in the synthesis of heterocyclic compounds and as a part of wider programme to provide alternative routes of synthesis[13,14] and now the method for synthesis of substituted 4-acridin-9-yl-3-arylimino-5-phenylimino-[1,2,4]-dithiazolidines is reported.

EXPERIMENTAL

The melting points of all synthesized compounds were recorded using hot paraffin-bath and are uncorrected. Chemicals used were of A.R. grade. ^{1}H NMR, spectra were recorded with TMS as internal standard using $CDCl_3$ and DMSO-d^6 as solvents. IR spectra recorded on Perkin-Elmer spectrophotometer in the range 4000-400 cm^{-1} in Nujol Mull and as KBr pellete. Purity of the compounds was checked on Silica gel-G plates by TLC.

Synthesis of 1-acridin-9-yl-3-phenyl thiourea (2a)

The compound 1-acridin-9-yl-3-phenyl thiourea (2a) was prepared by refluxing the mixture of N-phenyl isothiocyanate (0.01 M) and 9-amino acridine hydrochloride (0.01 M) in alkaline medium using chloroform as a solvent for 1 h. on water bath, a solid mass was obtained. It was crystallized from ethanol and identified as a 1-acridin-9-yl-3-phenyl thiourea. This reaction was extended to synthesize other substituted thioureas using different N-aryl isothiocyanates by reported method.[14]

Synthesis of 4-acridin-9-yl-3,5-bis-phenylimino-[1,2,4]-dithiazolidines (4a)

1-acridin-9-yl-3-phenyl thiourea (0.01 M) (2a) was suspended in chloroform, to this solution of N-phenyl S-chloro isothiocarbamoyl chloride (0.01 M) was added. The reaction mixture was refluxed on water bath for 2h, the evolution of chlorine gas was observed. The chloroform was distilled off, a sticky mass was obtained. It was repeatedly wash with petroleum ether (40-60^{o}C) followed by addition of ethanol, a solid acidic to litmus was isolated. It was crystallized from ethanol (78%) m.p. 186^{o}C and identified as a 4-acridin-9-yl-3,5-bis-phenylimino-[1,2,4]-dithiazolidine hydrochlorides (3a).

Similarly other compounds (3b-g) were prepared from (2b-g): 3b (70%) m.p. 188^{o}C; 3c (65%) m.p. 184^{o}C; 3d (72%) m.p. 183^{o}C; 3e (68%) m.p. 232^{o}C; 3f (68%) m.p. 168^{o}C; 3 g (74%) m.p. 238^{o}C.

On basification of (3a) with dilute ammonium hydroxide solution free base (4a) was obtained, it was crystallized from aqueous ethanol, m.p. 170^{o}C. (Found: C, 68.12; H, 3.28; N, 11.28; S, 6.98. Calcd. for $C_{27}H_{18}N_4S_2$: C, 70.12; H, 3.89; N, 12.12; S, 7.14%); ν_{max} 1550 (C = N), 1342 (C-N), 758 (C-S), 483 cm^{-1} (S-S); δ ($CDCl_3$ + DMSO-d6) 7.14-7.46 (10H, m, Ar-H); δ ($CDCl_3$ + DMSO-d6) 124-128 (Ar-C), 38-40 (C-N). Similarly, free base (4b) was

prepared from (3b): (4b), m.p. 158°C (Found: C, 66.91; H, 4.10; N, 11.68; S, 12.40. Calcd. for $C_{28}H_{20}N_4S_2$: C,70.58; H, 4.20; N, 11.76; S,13.44%); ν_{max} 1538 (C = N), 1332 (C-N), 763 (C-S), 458 cm^{-1} (S-S); δ ($CDCl_3$ + DMSO-d6) 6.90-7.41 (9H, m, Ar-H), 2.32 (3H, s, Ar-CH3); δ ($CDCl_3$ + DMSO-d6) 124-128 (Ar-C), 38-40 (C-N). This reaction was extended to synthesize other free bases (4c-g): (4c), m.p. 156°C (Found: C, 70.18; H, 4.15; N, 11.70 S, 13.21. Calcd. for $C_{28}H_{20}N_4S_2$: C,70.58; H, 4.20; N, 11.76; S, 13.44%); (4d), m.p. 178°C (Found: C, 66.13; H, 4.11; N, 10.89; S, 12.55. Calcd. for $C_{28}H_{20}N_4S_2$: C, 70.58; H, 4.20; N, 11.76; S, 13.44%); (4e), m.p. 226°C (Found: C, 64.93; H, 3.32; N, 11.18; S, 13.47. Calcd. for $C_{27}H_{17}N_4S_2Cl$: C, 65.32; H, 3.42; N, 11.29; S, 12.90%); (4f), m.p. 158°C (Found: C, 65.11; H, 3.39; N, 11.20; S, 12.86. Calcd. for $C_{27}H_{17}N_4S_2Cl$: C, 65.32; H, 3.42; N, 11.29; S, 12.90%); (4g), m.p. 226°C (Found: C, 65.28; H, 3.30; N, 11.26; S, 12.73. Calcd. For $C_{27}H_{17}N_4S_2Cl$: C, 65.32; H, 3.42; N, 11.29; S, 12.90%) (**Scheme 1**).

Antimicrobial activity

The synthesized compounds (4a-g) were screened for their antibacterial activity using cup plate diffusion method[17,18]. The bacterial organisms used included both gram-positive as well as gram-negative strains like *S. typhi, E. coli, B. subtilis* and *S. aureus.* Sensitivity plates were seeded with a bacterial innoculum of 1 x 10^6 CIU mL^{-1} and each well (diameter 10 mm) was loaded with 0.1 mL^{-1} of test compound solution (1000 µg mL^{-1}) in dimethyl formamide, so that concentration of each test compound was 100 µg/mL^{-1}. The zones of inhibition were recorded after incubation for 24 h at 37°C, using vernier caliper. Inhibition zone record of the compounds clearly indicated that (4 d) and (4 g) were highly active against *E. coli* and moderately active against *S. aureus* and *B. subtilis.* Majority of the compounds were found inactive against *S. typhi*.

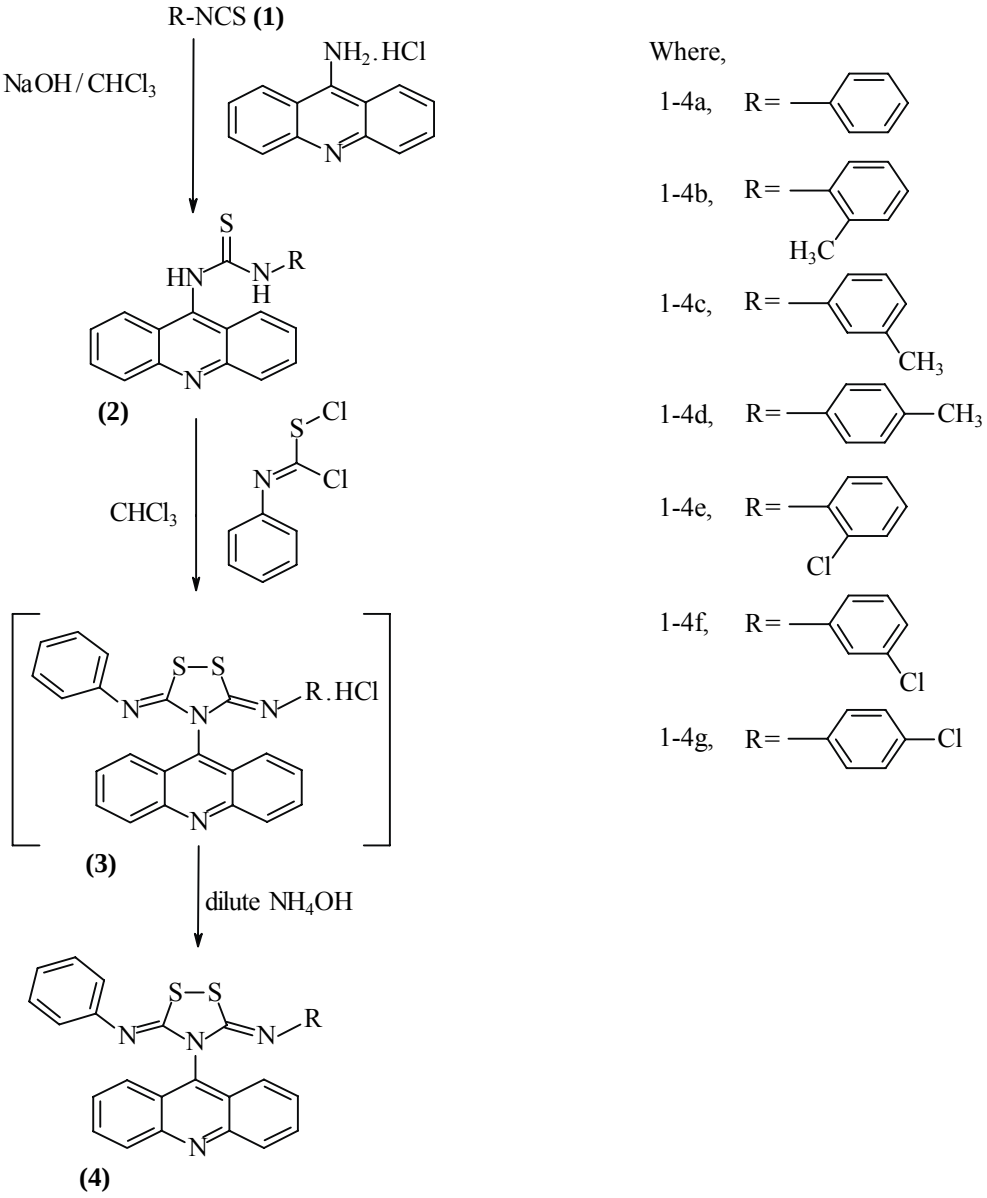
To determine minimum inhibitory concentration (MIC), the serial dilution technique[19] was followed using nutrient broth medium. The MIC values of compounds (4d) and (4g) were determined against *E. coli* and *S. aureus* which were found to be 75 and 70 µg/mL^{-1}, respectively[20].

RESULTS AND DISCUSSION

The compounds 1-acridin-9-yl-3-aryl thioureas (2a-g) were prepared by interaction of N-aryl isothiocyanates with 9-amino acridine in alkaline medium for 2 h using chloroform as a solvent.

Compounds (2a-g) were then reacted with N-phenyl-S-chloro isothiocarbamoyl chloride in boiling chloroform for 2 h. 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 4-acridin-9-yl-3-arylimino-5-phenylimino-[1,2,4]-dithiazolidine hydrochlorides (3a-g). These on basification with aqueous ammonium hydroxide solution afforded free bases (4a-g), respectively.



Scheme 1

The synthesized compounds (4a-g) were screened for their antibacterial activity using cup plate diffusion method. The bacterial organisms used were *S. typhi*, *E. coli*, *B. subtilis* and *S. aureus*. Inhibition zone record of the compounds indicated that (4 d) and (4 g) were highly active against *E. coli* and moderately active against *S. aureus*. Majority of the compounds were found inactive against *S. typhi* and *B. subtilis*. The MIC values of compounds (4 d) and (4 g) were determined against *E. coli* and *S. aureus*, which were found to be 75 and 70 $\mu g/mL^{-1}$, respectively.

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REFERENCES

1. S. Urszula and B. George, J. Hetero. Chem., **21**, 241 (1984).
2. N. K. Khandelwal, B. N. Berad and M. G. Paranjpe, J. Indian Chem. Soc., **64**, 321 (1987).
3. P. P. Deohate, J. P. Deohate and B. N. Berad, Asian J. Chem., **16(1)**, 255 (2004).
4. M. K. Burghate and B. N. Berad, Asian J. Chem., **19(5)**, 3601 (2007).
5. R. T. Jadhav and M. G. Paranjpe, J. Indian Chem. Soc., **59**, 1004 (1982).
6. S. K. Rai, K. Srivastava and V. K. Verma, Indian J. Chem., **20B**, 521 (1981).
7. P. P. Deohate and B. N. Berad, Chemistry an Indian J., **1(6)**, 447-449 (2004).
8. M. G. Dhonde, D. V. Tale and S. P. Deshmukh, Indian J. Chem., **45B**, 829-829 (2006).
9. A. J. Barany, R. P. Hammer, R. B. Merrifield and G. Barany, J. Am Chem. Soc., **127**, 508-509 (2005).
10. P. Manna, R. Singh, K. K. Narang and S. K. Manna, Indian J. Chem., **44B**, 1880 (2005).
11. R. M. Kharate, P. P. Deohate and B. N. Berad, Int. J. Chem. Sci., **7(4)**, 2843-2848 (2009).
12. P. T. Agrawal and S. P. Deshmukh, J. Indian Chem. Soc., **86**, 645-648 (2009).
13. P. T. Agrawal and S. P. Deshmukh, Int. J. Chem. Sci., **8(2),** 969-972 (2010).

14. S. K. Deshmukh, P. T. Agrawal and S. P. Deshmukh, Int. J. Chem. Soc., **88**, 1759-1762 (2011).

15. B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, Vogel's Textbook of Practical Org. Chem., Longman, U.K. (2006).

16. N. B. Colthup, L. H. Daly and S. E. Wiberly, Introduction to Infrared and Raman Spectroscopy, Academic Press, New York (1964).

17. R. M. Silverstein, G. C. Bassler and T. C. Morril, Spectrometric Identification of Organic Compounds, 4th Ed., John Wiley and Sons, New York (1981).

18. A. L. Barry, the Antimicrobial Suspectibility Test: Principle and Practices, Illus Lea and Fibiger, Philadephia Eds., PA., U.S.A. (1976) p. 180.

19. F. Cavanagh, Ed., Analytical Microbiology, Academic Press, New York (1963) p. 126.

20. C. Nishina, N. Enoki, S. Tawata and A. Mori, K. Kobayashi and M. Fukushima, Agric. Bio. Chem., **51**, 13 (1987).

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