Synthesis and antimicrobial activity of 1,2,4-triazoles

K. D. Patel, B. D. Mistry* and K. R. Desai

Department of Chemistry, B. K. M. Science College, Valsad-396-001, India

Manuscript received 11 September 2001, revised 3 June 2002, accepted 8 August 2002

3-(2',4',6'-Trichlorophenoxyethyl)-4-(4'-methoxyphenyl)-5-aryl-1,2,4-triazoles (4a-j) and 3-(2',4',6'-trichlorophenoxyethyl)-4-(N-benzylidenylamino)-5-mercapto-1,2,4-triazoles (7a-j) have been synthesized, and their antimicrobial activities studied.

Compounds containing 1,2,4-triazole nucleus^{1,2}, hydrazine and N-benzylidene derivatives³ possess various biological activities. Prompted by these observations we undertook synthesis of some triazoles (4a-j, 7a-j) and evaluation of their antibacterial activities.

3-(2',4',6'-Trichlorophenoxyethyl)-4-(4'-methoxyphenyl)-5-aryl-1,2,4-triazoles (4a-j) were obtained by the condensation of 2-(2',4',6'-trichlorophenoxyethyl)-5-aryl-1,3,4-oxadiazoles (3) with 4-methoxyaniline which were prepared from 2,4,6-trichlorophenoxyacetyl hydrazide (2) and aromatic acids using POCl₃ as cyclizing agent. Com-

pound 2 was reacted with CS₂ in presence of KOH in ethanol to yield 3-(2',4',6'-trichlorophenoxyethyl)-5-mercapto-1,3,4-oxadiazole (5), which on reaction with hydrazine hydrate yielded 3-(2',4',6'-trichlorophenoxyethyl)-4-amino-5-mercapto-1,2,4-triazole (6). 3-(2',4',6'-Trichlorophenoxyethyl)-4-(N-benzylidenylamino)-5-mercapto-1,2,4-triazoles (7a-j) were synthesized by condensing 6 with different aromatic aldehydes.

Compounds 4a-j and 7a-j were evaluated for antibacterial activity against *E. coli*, *S. aureus*, *S. typhi* and *B. subtilis* using DMSO as solvent by cup-plate technique⁴.

Compounds 4a, b, c and h and 7a-i showed mild activity against *S. aureus* at 2000 mcg/ml concentration. Compounds 4b, 7i and 7j showed mild activity against *E. coli* in the same concentration. Compounds 4a, b, c, d, f and 7b, e, g were moderately active against *B. subtilis* at in the same concentration. Compounds 7a, c, d, e, g, h, j showed mild activity against *S. typhi* at 2000 mcg/ml concentration.

Experimental

All m.ps. were taken in open capillary tubes and are uncorrected. IR spectra (KBr) were recorded on a Shimadzu-460 spectrophotometer, ¹H NMR spectra on Perkin-Elmer R-32 spectrometer with TMS as the internal standard and mass spectra on a Jeol D-300 instrument.

Ethyl 2,4,6-trichlorophenoxyacetate (1): A mixture of 2,4,6-trichlorophenol (0.01 mol) and ethyl chloroacetate (0.01 mol) was refluxed in dry acetone in presence of anhyd. K₂CO₃ (0.01 mol) for 6 h and then poured onto crushed ice. Liquid product obtained was isolated by ether extraction, (80%), b.p. 197°; $\nu_{\max}$ 1745 (C=O), 1050 and 1260 (C-O-C-), 860-880 (tetra-sub. benzene), 800 cm⁻¹ (C-Cl); δ (DMSO), 2.95 (2H, OCH₂), 1.49 (3H, CH₃), 4.12 (2H, CH₂), 7.51 (2H, ArH), 9.82 (1H, NH).

2,4,6-Trichlorophenoxyacetylhydrazide (2): A mixture of 1 (0.01 mol) and hydrazine hydrate (0.04 mol) in absolute alcohol was refluxed for 5 h. The solution was then

Scheme-1

poured onto crushed ice. The separated solid was crystallized from ethanol. (74%), m.p. 155°; $\nu_{\max}$ 3300–3100 (NH–NH₂), 1650 (CONH), 1055 and 1256 (–C–O–C–), 800–900 (tetra-sub. benzene), 805 cm⁻¹ (C–Cl); δ (DMSO) 3.15 (2H, CH₂), 4.65–5.25 (2H, NH₂), 9.79 (1H, NH).

2-(2',4',6'-Trichlorophenoxyethyl)-5-aryl-1,3,4-oxadiazole (3) : A mixture of 2 (0.01 mol) and an aromatic acid (0.01 mol.) in POCl₃ (5 ml) was refluxed for 5–6 h. The contents were then cooled and poured onto crushed ice and neutralized with NaHCO₃ solution. The resulting solid was dried and crystallized from ethanol : $\nu_{\max}$ 1520 (C=N), 1045 and 1260 (–C–O–C–), 830–895 (tetra-sub. benzene), 810 cm⁻¹ (C–Cl); δ (DMSO) 3.30 (2H, CH₂), 7.50 (2H, ArH).

3-(2',4',6'-Trichlorophenoxyethyl)-4-(4'-methoxyphenyl)-5-aryl-1,2,4-triazole (4a) : A mixture of 3a (0.01 mol) and 4-methoxyaniline (0.01 mol) in dry pyridine (10 ml) was refluxed for 6–8 h. It was then cooled and poured onto crushed ice and acidified with dil. HCl. The resulting solid was washed with cold water, dried and crystallized from ethanol to get 4a (62%), m.p. 90°; $\nu_{\max}$ 3080–3030 (=CH), 1600–1580 (C=C), 1515–1505 (C=N), 1450 (CH def. CH₂), 1245 (–C–O–C–), 850–900 (tetra-sub. benzene), 810 cm⁻¹ (C–Cl); δ (DMSO) 3.73 (3H, Ar-OCH₃), 3.38 (2H, Ar-OCH₂-Ar), 5.29 (1H, Ar-OH), 6.64 (4H, ArH), 7.41–7.82 (4H, ArH), 7.53 (2H, ArH); m/z 375, 362, 354, 266, 197, 199, 201, 165, 167, 137, 122, 123, 124, 109 (base peak), 96, 98, 80.

Similarly, other compounds were prepared (yields 45–70%) : 4b, m.p. 105°; c, 130°; d, 240°; e, 180°; f, 165°; g, 155°; h, 60°; i, 185°; j, 85°.

2-(2',4',6'-Trichlorophenoxyethyl)-5-mercapto-1,3,4-oxadiazole (5) : To a solution of 2 (0.01 mol) in ethanol (20 ml), KOH (0.5 g) in water (5 ml) and CS₂ (0.03 mol) were added. The reaction mixture was refluxed till evolution of H₂S ceased. Thereafter, it was cooled, diluted with cold water (30 ml) and acidified with gl. acetic acid. The solid separated was washed with water and crystallized from ethanol, (70%), m.p. 170°; $\nu_{\max}$ 1525 (C=N), 1050 and 1260 (–C–O–C–), 840–860 (tetra-sub. benzene), 810 cm⁻¹ (C–Cl); δ (DMSO) 3.32 (2H, CH₂), 2.50 (1H, Ar-SH).

3-(2',4',6'-Trichlorophenoxyethyl)-4-amino-5-mercapto-

1,2,4-triazole (6) : A mixture of 5 (0.01 mol) and hydrazine hydrate (0.015 mol) in dry pyridine (15 ml) was refluxed for 2 h. The reaction mixture was then neutralized with dil. HCl under cooling. The solid obtained was crystallized from DMF, (72%), m.p. 108°; $\nu_{\max}$ 3225 (NH₂), 2575 (SH), 1570 (C=N), 1045 and 1250 (–C–O–C–), 830–880 (tetra-sub. benzene), 810 cm⁻¹ (C–Cl); δ (DMSO) 2.52 (1H, SH) 3.33 (2H, CH₂), 5.72 (2H, NH₂).

3-(2',4',6'-Trichlorophenoxyethyl)-4-(N-benzylidiny-amino)-5-mercapto-1,2,4-triazole (7a) : A solution of 6 (0.01 mol) in glacial acetic acid (20 ml) and benzaldehyde (0.01 mol) was refluxed for 20 min. The reaction mixture was then cooled, diluted with water and the resulting solid was washed with water and crystallized from ethanol, (70%), m.p. 148°; $\nu_{\max}$ 3080–3030 (=C–H), 2565 (SH), 1670–1680 (C=N), 1600–1500 (C=C), 1450–1460 (C–H def. CH₂), 1380 (–C–H–), 840–850 (tetra-sub. benzene), 790–810 cm⁻¹ (C–Cl); δ (DMSO) 2.50 (1H, Ar-SH), 3.34 (2H, Ar-OCH₂-Ar), 5.06 (1H, –N=CH-Ar), 7.52 (2H, ArH), 7.73 (2H, ArH), 7.86–8.31 (4H, ArH); m/z 428, 374, 376, 338, 340, 218 (base peak), 220, 195, 197, 199, 201, 196, 198, 200, 202, 181, 182, 120, 121. Similarly, other compounds were prepared (yields 68–88%) : 7b, m.p. 180°; c, 130°; d, 175°; e, 155°; f, 240°; g, 170°; h, 150°; i, 120°; j, 160°.

Acknowledgement

The authors are thankful to Head, Department of Chemistry, South Gujarat University, Surat, to the authorities of B.K.M. Science College, Valsad and C.N.P.F. Arts and D.N. Science College, Dabhoi. for facilities and also to I.I.T., Mumbai and C.D.R.I., Lucknow, for spectral data.

References

1. U. V. Laddi, S. R. Desai, V. S. Somannavar, R. S. Bennur and S. C. Bennur, *Indian J. Chem., Sect. B*, 1998, 37, 461; R. Iqbal, N. H. Rana, N. Ahmad, K. Zamani, S. Ebrahim and N. Iqbal, *Indian J. Chem., Sect. B*, 1998, 37, 506.
2. A. K. Sen Gupta and K. Hajela, *J. Indian Chem. Soc.*, 1981, 58, 690.
3. A. L. Barry, "The Antimicrobial Susceptibility Test, Principle and Practices", 4th. ed., ELBS, London, 1976.