Bridgehead nitrogen heterocyclic system: Facile synthesis and bioactivity of \( s \)-triazolo[3,4-\( b \)] [1,3,4] thiadiazoles, \( s \)-triazolo[3,4-\( b \)] [1,3,4] thiadiazines and related heterocycles

Jag Mohan

Department of Chemistry, Maharshi Dayanand University, Rohtak 124001, India
e-mail: get_manika@rediffmail.com

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The reaction of 3-\( p \)-hydroxyphenyl-1-4-amino-5-mercapto-s-triazole 1 with various reagents to afford a variety of novel polycyclic heterocyclic systems is described. The products are characterized on the basis of elemental analyses and spectral data. The antibacterial and antifungal activity of some of the compounds have also been evaluated.

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In continuation of our earlier work\(^1\) on the synthesis of condensed bridgehead nitrogen heterocyclic systems, we report herein the synthesis of \( s \)-triazolo-thiadiazole and \( s \)-triazolo-thiadiazine derived from 3-\( p \)-hydroxyphenyl-1-4-amino-5-mercapto-s-triazole 1 and the biological activity associated with them. The reaction of 1 with chloroacetic acid in the presence of sodium acetate furnished 2 in 65% yield. Similarly the reaction of 1 with \( \alpha \) -bromoketone in the presence of potassium carbonate gave 3 in 82% yield. It is also found that the reaction of 1 with benzoin afforded a polycyclic adduct 4 in 73% yield. In the same way while the reaction of 1 with 2,3-dichloroquinoline produced the product 5, the reaction with carbon disulphide gave 6. Compound 1 was also found to react with \( p \)-chlorobenzoic acid to give 7 (Scheme I). The structures of compounds 2-6 have been established on the basis of their IR and \( ^1 \)H NMR spectral data.

**Antimicrobial Activity**

The compounds 2, 3 (R=Br), 5 and 6 were evaluated for their antimicrobial activity against gram-positive \textit{Staphylococcus aureus}, gram-negative \textit{Escherichia coli} and \textit{Pseudomonas aeruginosa} and the fungus \textit{Candida albicans} by neat samples and serial plate dilution method\(^6\).

The minimum inhibitory concentration (MIC) of the compounds 2 and 3 was found to be 1000 \( \mu \)g/mL against \textit{E. coli} and \textit{P. aeruginosa}. Compounds 5 and 6 showed activity against \textit{P. aeruginosa} and \textit{C. albicans}; when tested as neat samples.

**Experimental Section**

TLC was run on silica gel G plates using acetone-benzene (1:3) as irrigant. Melting points are uncorrected. IR (KBr) and \( ^1 \)H NMR spectra (chemical shifts in \( \delta \), ppm) were recorded on Hitachi 215 and Varian VXR-200 MHz spectrometers, respectively.

**3-\( p \)-Hydroxyphenyl-4-amino-5-mercapto-s-triazole 1.** This was prepared from \( p \)-hydroxybenzoyl hydrazide following the method of Reid et al.\(^8\) in 75% yield, m.p. 257\(^\circ\) (lit.\(^7\) m.p. 257\(^\circ\)).

**3-\( p \)-Hydroxyphenyl-5\( H \)-6,7-dihydro-s-triazolo-[3,4-\( b \)] [1,3,4] thiadiazin-6-one 2.** A mixture of 1 (1.04 g, 0.005 mole), chloroacetic acid (0.47 g, 0.005 mole) and anhyd. sodium acetate (0.41 g, 0.005 mole) in absolute alcohol (50 mL) was heated under reflux for 6 hr and cooled in ice. The solid thus separated was filtered, washed thoroughly with water and crystallized from methanol to give white shining crystals, m.p. >250\(^\circ\)C, yield 65\% (Found: C, 48.29; H, 3.45; N, 22.25; S, 13.02. C\(_{10}\)H\(_8\)N\(_4\)SO\(_2\) requires C, 49.61; H, 2.84; N, 14.47; S, 8.26%); IR: 835, 840 (\( \nu \)C=O); 3300-3500 (broad band) (N-H stretching), 1620 (C=N), 1695 (C=O), 3040 (aromatic C-H stretching); 3300-3500 (broad band) (N-H stretching), 1510 (C-N stretching), 1400 (C=O), 1230 (C=N), 1160 (C-O), 1110 (C=O), 1060 (C=O), 970 (C-O). 1H NMR (DMSO-\( d_6 \)) 8.1 (2H, d, J=9Hz, C\(_2\)'-H & C\(_6\)'-H) 8.1 (2H, d, J=9Hz, C\(_2\)'-H & C\(_6\)'-H).

**5\( \text{b} \)-Bromophenyl]-3-p-hydroxyphenyl-7\( \text{H} \)-s-triazolo[3,4-\( b \)] [1,3,4] thiadiazine 3a (Ar=p-Br-C\(_6\)H\(_4\)).** A mixture of 1 (2.14 g, 0.005 mole) and \( p \)-bromophenacylbromide (1.39 g, 0.005 mole) in absolute ethanol (40 mL) was heated under reflux for 5 hr, cooled and neutralised with aqueous potassium carbonate solution. The solid thus separated was filtered, washed thoroughly with water and crystallized from ethanol as pale yellow crystals, m.p. 220\(^\circ\)C, yield 1.56 g (82\%) (Found: C, 49.83; H, 2.65; N, 14.62; S, 8.13. C\(_9\)H\(_8\)N\(_4\)S requires C, 49.61; H, 2.84; N, 14.47; S, 8.26%); IR: 835, 840...
NOTES

(1,4-disubstituted benzene rings), 1520 (C-N stretching), 1610, 1620 (C=N), 3040 (aromatic C-H stretching), 3140 (O-H stretching); 1H NMR (DMSO-d6): 1.50 (1H, s, OH), 4.35 (2H, s, SCH2), 7.2-8.4 (8H, m, aromatic protons). Compounds 3b and 3c were prepared in similar way and their physical data are as follows:

3b (Ar=p-NO2-C6H4): m.p. 205°C; yield 62.5% (Found: C, 54.46; H, 3.23; S, 9.21. C16H11N5O3S requires C, 54.39; H, 3.11; S, 9.06%).

3c (Ar=C6H5): m.p. 130°C; yield 66% (Found: C, 62.14; H, 3.96; N, 18.32; S, 10.25. C16H12N4OS requires C, 62.33; H, 3.89; N, 18.18; S, 10.38%).

3-p-Hydroxyphenyl-6, 7-diphenyl-5H-s-triazolo[3,4-b][1,3,4]thiadiazine 4. A mixture of 1 (1.04 g, 0.005 mole) and benzoin (1.06 g, 0.005 mole) in ethanol (50 mL) was heated to get a clear solution and to the hot solution was added 2N KOH (1.0 mL). The resulting mixture was refluxed with constant stirring for about half an hour. The yellow precipitate thus separated out was filtered, washed with water and crystallized from ethanol to give yellow crystals, m.p. 61°C, yield 1.4 g (73%) (Found: C, 68.89; H, 4.03; N, 14.64; S, 8.21. C22H16N4SO requires C, 68.75; H, 4.18; N, 14.58; S, 8.33%; IR: 710, 750, 840 (monosubstituted and 1,4-disubstituted benzene rings), 1610, 1625 (C=C and C=N), 3050 (aromatic C-H stretching), 3420 (O-H stretching); 1H NMR (CDCl3): 4.5 (1H, brs, OH group), 7.0-8.2 (14H, m, Ar-H).

3-p-Hydroxyphenyl-5H-s-triazolo[3',4':2,3][1,3,4]-thiadiazino[5,6-b] quinoxaline 5. A mixture of 1 (1.04 g, 0.005 mole), 2,3-dichloroquinoxaline (1.0 g, 0.005 mole) and fused sodium acetate (0.82 g, 0.01 mole) in anhyd. ethanol (40 mL) was refluxed on a steam-bath for 5 hr, cooled and the resulting solid washed with water and crystallized from ethanol as yellow crystals, m.p. 120°C, yield 30% (Found: C, 57.39; H, 3.08; N, 25.32; S, 9.69. C16H10N6SO requires C, 57.48; H, 2.99; N, 25.14; S, 9.58%; IR: 750, 850 (1,2 and 1,4-disubstituted benzene rings), 1515, (C-N stretching), 1610, 1625 (C=C and C=N), 3030 (aromatic C-H stretching), 3300, 3240 broad (N-H and O-H stretching); 1H NMR (CDCl3): 1.2 (1H, s, NH), 1.6 (1H, s, OH), 7.6-8.1 (8H, m, Ar-H); MS: m/z 334 [M]+.

Scheme I
3-p-Hydroxyphenyl-s-triazolo[3,4-b][1,3,4]thiadiazole-6(5H)-thione 6. Carbon disulphide (0.5 mL) was added dropwise with constant stirring to a solution of 1 (1.04 g, 0.005 mole) in pyridine (10 mL). After the addition was over the mixture was heated with stirring on oil-bath for 6 hr at 100°C. Pyridine was removed in vacuo and residue was dissolved in benzene and treated with hexane. The solid thus obtained was filtered and crystallised from ethanol to give yellow crystals, m.p. 257°C, yield 0.6 g (48%) (Found: C, 52.12; H, 2.52; N, 22.22; S, 12.93. C9H6N4S2O requires C, 51.92; H, 2.40; N, 22.40; S, 12.8%); IR: 820 (1,4-disubstituted benzene ring), 1200 (C=S), 1510 (C-N stretching), 1620 (C=N), 3040 (aromatic C-H stretching), 3180 (N-H stretching), 3300 (O-H stretching bonded); 1H NMR (DMSO-d6): 5.45 (1H, bs, OH group), 6.99 (2H, d, J=9Hz, C2′-H AND C6′-H), 7.99 (2H, d, J=9Hz, C3′-H AND C5′-H).

3-p-Hydroxyphenyl-6-(p-chlorophenyl)-s-triazolo[3,4-b][1,3,4]thiadiazole 7. A mixture of 1 (1.04 g, 0.005 mole), and p-chlorobenzoic acid (0.78 g, 0.005 mole) in POCl3 (10 mL) was heated on an oil-bath at 120°C for 1 hr. The reaction mixture was cooled, poured into ice and neutralised with aqueous potassium carbonate solution. The solid thus separated was filtered, washed thoroughly with water and crystallised from ethanol to give colourless crystals, m.p. 160°C, yield 1.1 g (67.07%) (Found: C, 54.56; H, 2.61; N, 17.23; S, 9.86. C15H9N4SOCl requires C, 54.79; H, 2.73; N, 17.04; S, 9.74%); IR: 830, 840 (1,4-disubstituted benzene rings), 1520 (C=N stretching), 1600, 1620 (C=C AND C=N), 3040 (aromatic C-H stretching); MS: m/z 328.5 (M+).

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