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Heterocyclic systems containing bridgehead nitrogen atom: Synthesis and evaluation of bio-activity of thiazolo[3,2-*b*]-*s*-triazoles and isomeric thiazolo[2,3-c]-*s*-triazoles

Parvin Kumar, Jag Mohan & J K Makrandi*

Department of Chemistry, Maharshi Dayanand University, Rohtak 124001, India
E-mail: jkmakrandi@gmail.com

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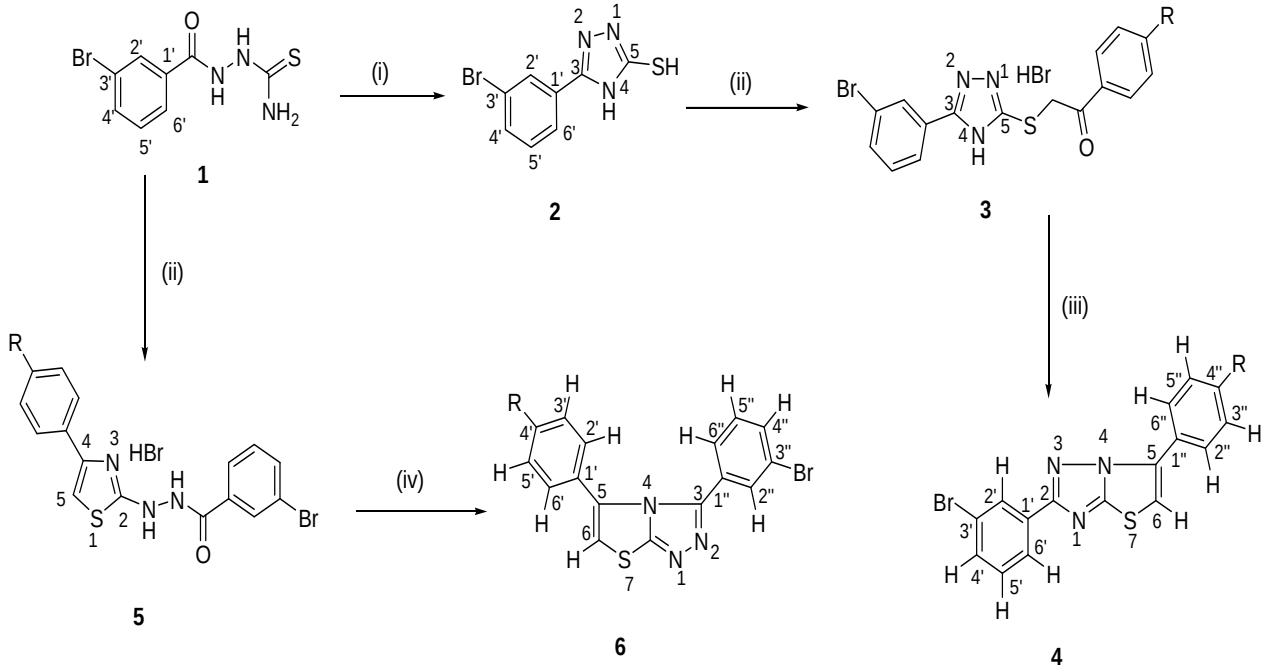
Synthesis of 2-(3'-bromophenyl)-5-(*p*-bromophenyl) thiazolo[3,2-*b*]-*s*-triazoles **4** has been achieved starting from the appropriate 5-mercapto-3-(3'-bromo phenyl)-*s*-triazole **2**. Compound **2** on condensation with α-haloketones gives the ketones **3** which on cyclization with PPA afford 5-(*p*-bromophenyl)-2-(3'-bromophenyl)thiazolo[3,2-*b*]-*s*-triazoles **4** and not the isomeric thiazolo[2,3-*c*]-*s*-triazoles **6**. This has been established by an unequivocal synthesis of **6** through $POCl_3$ cyclization of 3'-bromobenzoylhydrazino-4-*p*-bromophenyl-thiazole hydrobromide **5**. The diuretic, antibacterial and antifungal activities of some of the compounds have also been evaluated.

Keywords: α-Haloketones, PPA, $POCl_3$, diuretic, antibacterial, antifungal

Yale and Piala[1] have reported that *s*-triazole systems, *i.e.* 5-(*p*-aminophenyl)-*s*-triazolo-3-thiol, exhibit diuretic and natriuretic activity in rats when administered intraperitoneally. Moreover, the compounds containing a thiadiazine nucleus (*i.e.* chlorothiazide and hydrochlorothiazide) are used as diuretics.

In continuation of the earlier work on the synthesis of biologically active condensed bridgehead nitrogen heterocyclic systems[2-10], this paper reports the synthesis of 5-*p*-bromophenyl-2-(3'-bromophenyl) thiazolo[3,2-*b*]-*s*-triazoles **4** and the isomeric 5-*p*-bromophenyl-3-(3'-bromo-phenyl)thiazolo[2,3-*c*]-*s*-triazoles **6** (**Scheme I**) and the biological activity associated with them.

5-Mercapto-3-(3'-bromophenyl)-*s*-triazole **2** when heated with *α*-haloketones in absolute ethanol gave uncyclized ketones **3** which underwent PPA cyclization giving thiazolo[3,2-*b*]-*s*-triazoles **4** and not thiazolo[2,3-*c*]-*s*-triazoles **6**. The ketones **3**, being unsymmetrical, on PPA cyclization is expected to give thiazolo[3,2-*b*]-*s*-triazoles **4** or thiazolo[2,3-*c*]-*s*-triazoles **6** or both, depending on the mode of



Scheme I — (i) NaOH; (ii) *p*-R-C_6H_4-$COCH_2Br$; (iii) PPA, aq K_2CO_3; (iv) $POCl_3$, aq K_2CO_3

cyclization. The ketone **3**, however, on cyclization gave only one product (TLC). The ^{1}H NMR spectral data of the cyclized product was not of much help in deciding its structure (**4** or **6**). Hence **6** were synthesized by an unequivocal method. Condensation of 1-(3'-bromobenzoyl)-3-thio-semicarbazide **1** with α-haloketones yielded 2-(3'-bromobenzoyl)hydrazino-4-substituted thiazole hydrobromides **5** which on $POCl_3$ cyclization gave 3-(3'-bromophenyl) -5-substituted phenyl thiazolo[2, 3-*c*]-*s*-triazoles **6**.

The compound **6** was not identical with the cyclized product obtained from **2** with α-haloketones followed by cyclization of ketone **3** with PPA. This suggests that the cyclized products obtained from **3** should have the structures **4**. The structures **3-6** have been supported by IR and ^{1}H NMR spectral data. Compounds **3** and **5** exhibit a band in the region 1670-1700 cm^{-1} (C=O) whereas absence of this band in the IR spectra of **4** and **6** indicates the absence of a carbonyl group, thereby suggesting their cyclic structures. The signals at δ 8.05 (1H, s, C_6-H) and 8.08 (1H, s, C_6-H) in ^{1}H NMR spectra of **4a** and **6a** respectively corroborated the cyclic structures of these compounds.

Antimicrobial Activity

The compounds **4** and **6** were evaluated for their antimicrobial activity against gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* bacteria and the fungus *Candida albicans* by using neat samples and by serial plate dilution method[11].

The compounds **4** and **6** were found to be active against *Pseudomonas aeruginosa* and *C. albicans* when tested as neat samples and may be useful for local application in the form of powder or ointment. Further investigations to study the toxicity following local application are yet to be completed.

Diuretic testing in rats

Burn's method[12], as recorded by Heller[13], was used. Albino rats of both sexes, weighing between 150-200 g were used. For determining the diuretic activity, groups of eight rats were used and the animals were fasted overnight but allowed water *ad lib*. Test compounds were administered in volumes of 10% alcohol lead which amounted to 5% of the body weight of rats. The control group was given the solvent only. Four rats were placed together in the metabolic cages, resting on a glass funnel. Cross over tests were performed after 48 hr. Urine volumes were measured after intervals of every 30 min for a maximum duration of 5 hr. The diuresis was calculated by comparing the urine volumes of control and experimental groups. The compounds **4** and **6** were tested for diuretic activity against the dose 50 mg, 100 mg and 1 g/kg of body weight and found to possess no appreciable diuretic activity at these concentrations.

Experimental Section

TLC was run on silica gel G plates using acetone-benzene (1:3) as eluent. Melting points are uncorrected. IR (KBr, cm^{-1}) and ^{1}H NMR spectra (δ, ppm downfield from TMS) were recorded on Hitachi-215 and Varian VXR-300 MHz spectrometers respectively.

1- (3'-Bromobenzoyl)-3-thiosemicarbazide, 1

This was prepared by the reaction of *m*-bromobenzoyl hydrazide with potassium thiocynate, under acidic conditions, according to the method of Dhaka *et al*[14] in 70% yield, m.p. 190°C. Found: C, 35.19; H, 3.00; N, 15.50; S, 11.81. $C_8H_8BrN_3OS$ requires C, 35.04; H, 2.92; N, 15.33; S, 11.68%.

5-Mercapto-3-*m*-bromophenyl-*s*-triazole, 2

1-(*m*-Bromobenzoyl)-3-thiosemicarbazide **1** (10 g) in 8% NaOH (100 mL) was heated under reflux for 4 hr. The reaction mixture was cooled to RT and acidified with dil. acetic acid. The product separated was filtered, washed well with water and purified by recrystallization from ethanol as shiny crystals. m.p. > 240°C, yield 8 g (85.63%). Found: C, 37.35; H, 2.28; N, 16.53; S, 12.64. $C_8H_6BrN_3S$ requires C, 37.50; H, 2.34; N, 16.41; S, 12.5%. IR (KBr): 710, 765, 870 (1, 3-disubstituted benzene ring), 1610 (C=N), 2620 (S-H stretching), 3050 (aromatic C-H stretching), 3220 cm^{-1} (N-H).

5-*p*-Bromobenzoylmethylmercapto-3-*m*-bromophenyl-*s*-triazole hydrobromide, 3a (R= Br)

A mixture of compound **2** (1.28 g, 0.005 mole), *p*-bromophenacyl bromide (1.39 g, 0.005 mole) in absolute ethanol (70 mL) was heated under reflux for 6 hr. The reaction mixture was cooled to RT and the solid thus separated was filtered, washed well with water and purified by recrystallization from methanol, m.p. 168°C, yield 1.35 g (50.56%). Found: C, 36.09; H, 2.33; N, 7.68; S, 5.83. $C_{16}H_{12}Br_3N_3OS$ requires C, 35.95; H, 2.25; N, 7.87; S, 5.99%. IR (KBr): 695, 778, 818, 893 (1, 3 and 1, 4-disubstituted benzene rings), 1520 (C–N stretching), 1600, 1620 (C=C and C=N), 1690 (C=O), 3283 cm^{-1} (N-H stretching).

A similar procedure was adopted for the synthesis of compounds **3b** (R=Cl) yield (53%), m.p. 189°C. Found: C, 39.35; H, 2.51; N, 8.69; S, 6.41. $C_{16}H_{12}Br_2ClN_3OS$ requires C, 39.22; H, 2.45; N, 8.58; S, 6.54%.

5-*p*-Bromophenylthiazolo[3, 2-*b*]-2-*m*-bromophenyl-*s*-triazole, 4a (R=Br)

A mixture of **3a** (1.0 g), P_2O_5 (4.0 g) and H_3PO_4 (3.0 mL) was heated under reflux in an oil bath at 150°C for about 3 hr. The reaction mixture was cooled, poured into ice cold water and neutralized with aq. K_2CO_3 solution. The solid thus obtained was purified by recrystallization from ethanol, m.p. 180°C, yield 0.4 g (49.08%). Found: C, 44.00; H, 2.00; N, 9.77; S, 7.49. $C_{16}H_9Br_2N_3S$ requires C, 44.14; H, 2.07; N, 9.65; S, 7.36%. IR (KBr): 700, 778, 819, 889 (1, 3 and 1, 4-disubstituted benzene rings), 1570, 1600 (C=C and C=N), 3089 cm^{-1}(aromatic C-H stretching); ^{1}H NMR (DMSO-d_6): δ 8.05(1H, s, C_6-H), 7.48-8.26 (8H, m, aromatic protons).

A similar procedure was adopted for the synthesis of compounds **4b** (R=Cl) yield (43.86%), m.p. 131°C. Found: C, 49.30; H, 2.36; N, 10.84; S, 8.02. $C_{16}H_9BrClN_3S$ requires C, 49.17; H, 2.30; N, 10.76; S, 8.19%.

2-(*m*-Bromobenzoyl)hydrazino-4-*p*-bromophenylthiazole hydrobromide, 5a (R= Br)

A mixture of compound **1** (1.37 g, 0.005 mole), *p*-bromophenacyl bromide (1.39 g, 0.005 mole) in absolute ethanol (70 mL) was heated under reflux for 5 hr. The reaction mixture was cooled and the solid obtained was purified by recrystallization from ethanol, m.p. 139°C, yield 1.50 g (56.18%). Found: C, 36.10; H, 2.33; N, 7.99; S, 5.82. $C_{16}H_{12}Br_3N_3OS$ requires C, 35.95; H, 2.25; N, 7.87; S, 5.99%. IR (KBr): 674, 734, 827, 909, (1, 3 and 1, 4-disubstituted benzene rings), 1515 (C-N stretching), 1680 (C=O group), 3183, 3255 cm^{-1} (N-H stretching).

A similar procedure was adopted for the synthesis of compounds **5b** (R=Cl), yield (61.22%), m.p. 178°C. Found: C, 39.38; H, 2.53; N, 8.41; S, 6.43. $C_{16}H_{12}Br_2ClN_3SO$ requires C, 39.22; H, 2.45; N, 8.58; S, 6.54%.

5-*p*-Bromophenyl-3-*m*-bromophenylthiazolo[2, 3-*c*]-*s*-triazole, 6a (R=Br)

Compound **5a** (1.0 g) in $POCl_3$ (8 mL) was heated under reflux in an oil bath for 3 hr at 120°-130°C. The reaction mixture was cooled, poured into ice-cold water and neutralized with aq. K_2CO_3 solution. The solid thus separated was washed well with water and purified by recrystallization from ethanol, yield 0.35 g (42.94%), m.p. 203°C. Found: C, 44.00; H, 2.00; N, 9.77; S, 7.49. $C_{16}H_9Br_2N_3S$ requires C, 44.14; H, 2.07; N, 9.65; S, 7.36%. IR (KBr): 700, 775, 835, 875 (1, 3 and 1, 4-disubstituted benzene rings), 1580, 1600 (C=C and C=N), 3089 cm^{-1} (aromatic C-H stretching); ^{1}H NMR (DMSO-d_6): δ 7.15-7.9(8H, m, aromatic protons), 8.08 (1H, s, C_6-H).

A similar procedure was adopted for the synthesis of compounds **6b** (R=Cl) yield (50.13%), m.p. 198°C. Found: C, 49.35; H, 2.38; N, 10.90; S, 7.98. $C_{16}H_9BrClN_3S$ requires C, 49.17; H, 2.30; N, 10.76; S, 8.19%.

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