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Synthesis of 1, 2, 4-triazole, 1, 3, 4-thiadiazole and 1, 3, 4-oxadiazole derivatives of 6-nitrobenzimidazole

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A series of new 5-(6′-nitrobenzimidazole-1-ylmethyl-1,2,4-triazoles **5, 8**, 1,3,4-thiadiazole **9**, and 1, 3, 4-oxadiazole **10** has been synthesized from 6-nitrobenzimidazole I via 1-*N*-(6′-nitrobenzimidazole-1-carbonylmethyl)-4-phenyl-3-thiosemicarbazide **6**. The thiosemicarbazides have been readily obtained from 6-nitrobenzimidazole-1-acetic acid hydrazide **3** in good yield. These compounds have been characterized on the basis of elemental analyses, IR, NMR and MS.

In the past years, the literature is enriched with progressive findings about the synthesis and pharmacological action of fused heterocycles. The benzimidazole nucleus is associated with diverse pharmacological activities such as antibacterial[1,2], insecticidal[3,4] and fungicidal[5] effects. Similarly, certain 1, 2, 4-triazole, thiadiazole and oxadiazole derivatives have also been reported to possess pesticidal potentialities and bactericidal[6,7]. In this work, we focus interest on incorporating thiosemiarbazides, triazoles, thiadiazole and oxadiazole with 6-nitrobenzimidazole in one framework and hope to obtain a few compounds having better antimicrobial activity. Eight new compounds have been synthesized and characterized.

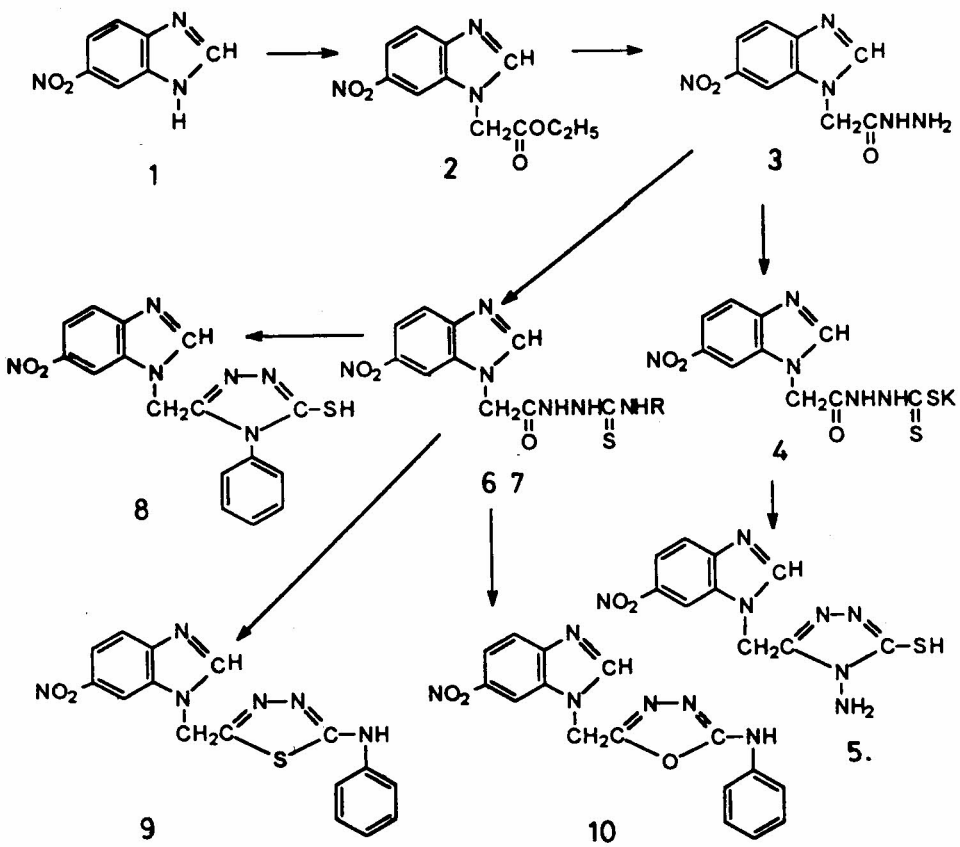
The reaction of 6-nitrobenzimidazole **1** with ethyl chloroacetate in the presence of dry ethyl acetate, anhyd. Potassium carbonate and polyethylene glycol 400, yielded the desired ethyl 6-nitrobenzimidazole-1-acetate which was converted into 6-nitrobenzimidazole-1-acetic acid hydrazide **3** with an excess of 85% hydrazine hydrate under reflux. The precursor **6, 7**, was conveniently synthesized by refluxing acid hydrazide **3** with aryl isothiocyanate in abs. ethanol and DMF for 2 hr. The reaction sequence leading to the formation of 4 different title compounds is outlined in Scheme I.

Experimental Section

Elemental analysis were carried out on a Carlo Erba 1106 elemental analysis instrument. IR spectra were obtained on a Nicolet FT-IR 170 SX spectrometer (KBr disks), ^{1}H NMR spectra on a Bruker FT-Ac80 spectrometer, mass spectra on a HP 5899A spectrometer and ^{13}C NMR spectra on Bruker AM-400 spectrometer. Melting points were taken on a Kofler melting point apparatus and uncorrected.

Ethyl 6-nitrobenzimidazole-1-acetate 2—To a mixture of 4.08 g (25 mmole) 6-nitrobenzimidazole **1**, 4 mL polyethylene glycol 400 and 8 g anhyd. K_2CO_3 in 200 mL dry ethyl acetate was added 3 mL ethyl chloroacetate and it was agitated for 5 hr. The inorganic solids were filtered and the solvent was washed with cold water three times. Organic layer was separated and was pure enough for next reaction (65%), m.p. 96-98°.

6-Nitrobenzimidazole-1-acetic acid hydrazide[8] 3. To a solution of 2.49 g (0.01 mole) compound **2** dissolved in 50 mL abs. ethanol was added 1.5 mL 85% hydrazine hydrate and it was refluxed for 2 hr. The reaction solution was cooled and the product filtered, washed with cold water and ethanol and recrystallized from DMSO-ethanol, yield 92%, m.p. 192-94° (Found: C, 46.10; H, 3.75; N, 29.20. Calcd. For $C_9H_9N_5O_3$: C, 45.96; H, 3.83; N, 29.79%). IR: 3036 (ν_{C-H} aryl), 3296, 3170 (ν_{N-H}) 1618 (ν_{C-N}), 1663($\nu_{C=O}$), 1340 (ν_{NO_2} sym), 1532 (asym); NMR: 9.45 (1H, b, NH), 7.6-8.6 (4H, m, $C_7H_4N_3O_2$), 5.06(2H, s, CH_2), 4.40(2H, b, NH_2); MS: 235 (M^+, 45.0), 40(100%),



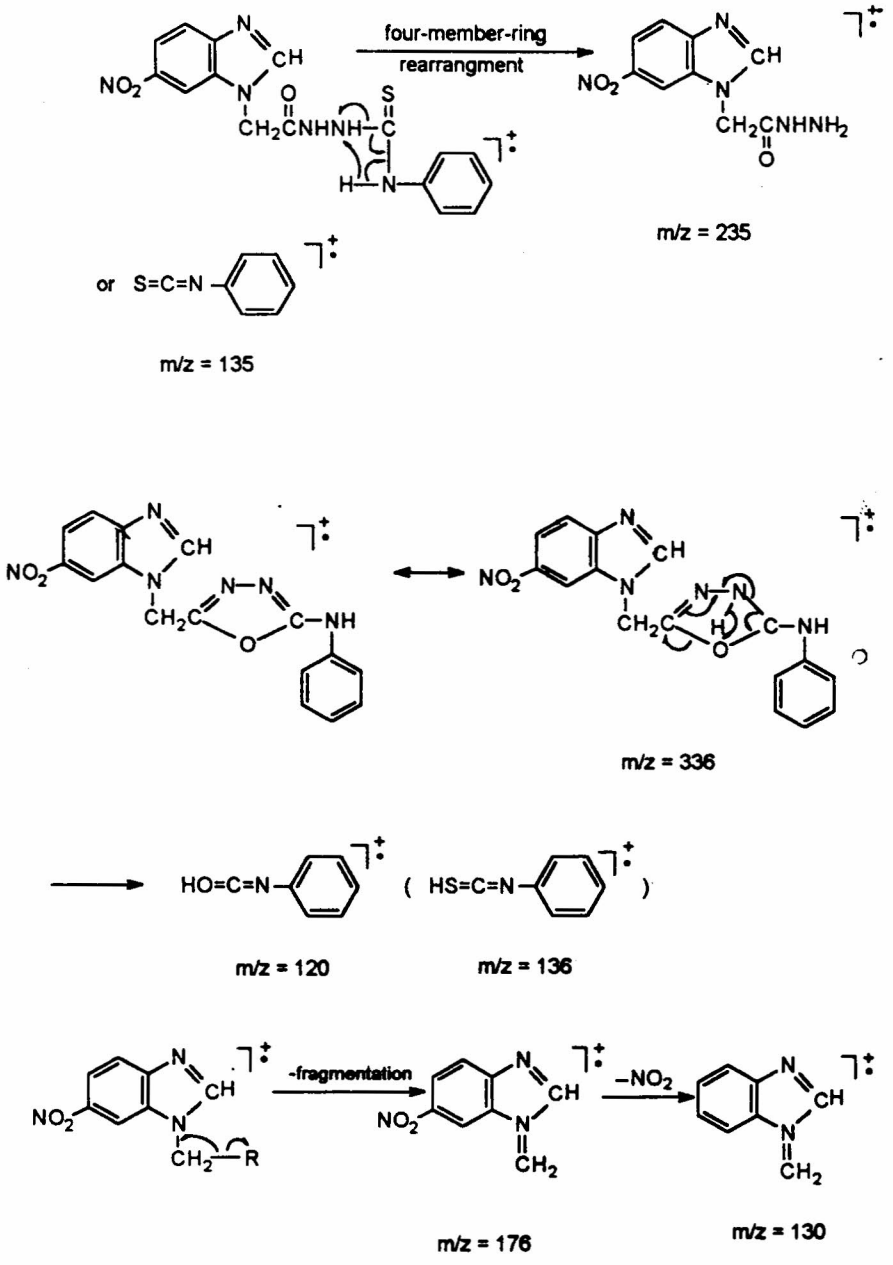
Scheme I

76 (22.0), 103(11.0), 130(45.0), 176(27.0), 219(1.0).

5-(6′-Nitrobenzimidazole-1-ylmethyl)-3-mercapto-4-amino-1, 2, 4-triazole[9] 5. To a solution of 0.84 g (0.015 mole) KOH, 100 mL abs. ethanol and 2.35 g (0.01 mole) compound **3** was added 1.14 g (0.015 mole) carbon disulfide and the contents agitated at room temperature for 16 hr. It was then diluted with 50 mL dry ether, and the precipitated solid filtered, washed with dry ether, and then dried over anhyd. $CaCl_2$. The salt **4**, prepared as described above, were obtained in nearly quantitative yield 99%, m.p. 268-70°; IR: 3050, 2966 (ν_{C-H} aryl), 3219, 3100 (ν_{N-H}), 1609 (ν_{C-N}), 1710($\nu_{C=O}$), 1207(ν_{C-S}), 1343(ν_{NO_2} asym); NMR: 7.3-8.5 (4H, m, $C_7H_4N_3O_2$), 5.28(2H, s, CH_2).

A suspension of (1.75 g, 5 mmole) of potassium salt **4** IV, 10 mmole 85% hydrazine hydrate, and 1 mL water was refluxed with stirring for 2 hr. The colour of the reaction mixture changed to light green and it was then diluted with ice cold water (20 mL) and neutralized with dil. HCl to *p*H 5. The precipitate obtained was filtered, washed with cold water and purified by KOH and dil. HCl, yield 63%), m.p. 252-53° (Found: C, 40.91; H, 3.16; N, 33.10. Calcd. for $C_{10}H_9N_7O_2S$: C, 41.24; H, 3.09: N, 33.68%); IR: 3043, 2991 (ν_{C-H} aryl), 3333 (ν_{N-H}), 1592 (ν_{C-N}), 1200 (ν_{C-S}), 2589 (ν_{S-H}), 1335 (ν_{NO_2} sym), 1518 (ν_{NO_2} asym); NMR : 13.67 (1H, b, SH), 7.6-8.6 (4H, m, $C_7H_4N_3O_2$), 5.66 (2H, s, CH_2), 3.5(2H, b, NH_2); MS: 291(M^+ 39.0), 40(100%), 76(10.0). 130 (14.0), 164(23.0), 277(5.0).

1-*N*- (6′-Nitrobenzimidazole-1-carbonylmethyl)-4-aryl-3-thiosemicarbazide 6, 7. A solution containing 0.75 g (3 mmole) compound **3** and appropriate isothiocyanate (3 mmole) in ethanol (50 mL) and DMF (4 mL) was heated under reflux for 2 hr. The separated product was filtered,



Scheme II

washed with ethanol and recrystallized from DMSO-ethanol. Compound **6** yield, 90%, m.p. 198-99° (Found: C, 52.81; H, 3.80; N, 22.34. Calcd. for $C_{16}H_{14}N_6O_3S$: C, 51.89; H, 3.78; N, 22.70%); IR: 3002, 2990 ($\nu_{C\text{-}N}$ aryl), 3225, 3163, 3105 ($\nu_{N\text{-}H}$), 1619 ($\nu_{C\text{-}N}$), 1725 ($\nu_{C\text{-}O}$), 1202 ($\nu_{C\text{-}S}$), 1337 (ν_{NO_2} sym), 1526 (ν_{NO_2} asym); ^{1}H NMR; 10.56 (1H, b, N^1H), 9.81(1H, b, N^2H), 9.75(1H, b, N^4H), 7.1-8.6(9H, m, C_6H_5, $C_7H_4N_3O_2$), 5.20(2H, s, CH_2); ^{13}C NMR: a, 125.4; b, 128.2; c, 142.4; d, 138.9; e, 149.0; f, 46.0; g, 181.2; h, 166.1; i, 142.9; j, 111.5; k, 118.1; l, 115.7. ms: 370 (M^+ 0.04), 77 (72.5), 93(35.5), 130(26.7), 135(100%), 163(2.4), 176(18.5), 177(17.8), 235(19.3), 277(2.4), 352(0.4). Compound **7** (90%), m.p. 158-60° (Found: C, 57.21; H, 3.72; N, 20.18 (Calcd. For

$C_{20}H_{16}N_6O_3S$: C, 57.14; H, 3.81; N, 20.00%); IR: 3067, 2990 (ν_{C-H} aryl), 3260, 3177, 3104 (ν_{N-H}), 1618(ν_{C-N}), 1703($\nu_{C=O}$), 1207(ν_{C-S}), 1338 (ν_{NO_2} sym), 1531(ν_{NO_2} asym); NMR: 10.63 (1H, b, N^1H), 9.94(1H, b, N^2H), 9.72(1H, b, N^4H), 7.3-8.6(11H, m, $C_{10}H_7$, $C_7H_4N_3O_2$), 5.20(2H, s, CH_2). ms: 420(M^+ 0.02), 77(18.5), 127(22.3), 130(18.0), 143(17.6), 176(20.4), 185(82.4), 235(15.8%).

5-(6′-Nitrobenzimidazole-1-ylmethyl)-4-phenyl-3-mercapto-1, 2, 4-triazole[10] 8. A suspension of the thiosemicarbazide[6] (1.85 g, 5 mmole) in ethanol (30 mL) was dissolved in aq. NaOH (3 mL, 4 *N*) and gently refluxed for 1 hr. The resulting clear solution was treated with decolourising charcoal, cooled and filtered. The filtrate was adjusted to *p*H 5-6 with dil. Acetic acid and the precipitated pale yellow solid filtered, washed with water, dried and recrystallized from methanol, yield 87%, m.p. 282-84° (Found: C, 54.50; H, 3.50; N, 23.82. Calcd. for:$C_{16}H_{12}N_6O_2S$: C, 54.55; H, 3.41; N, 23.86%); IR: 3029, 2910 (ν_{C-H} aryl), 1592 (ν_{C-H}), 1203 (ν_{C-S}), 2589(ν_{S-H}), 1346 (ν_{NO_2} sym), 1521 (ν_{NO_2} asym); NMR: 13.93 (1H, b, SH), 5.62(2H, s, CH_2), 7.47-8.57(9H, m, $C_7H_4N_3O_2$, C_6H_5); MS: 352(M^+ 62.5), 77(38.2), 92(11.2), 117(8.0), 176 (9.3), 190(9.2), 335(2.5%).

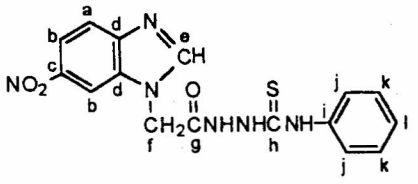
5- (6′-Nitrobenzimidazole-1-ylmethyl) -2-phenylamino-1, 3, 4-thiadiazole[11] 9. Compound **6** (0.37 g, 1 mmole) was dissolved with cooling in conc H_2SO_4. (4 mL) and stirred well. The solution was left at room temperature for 2 hr, and poured over crushed ice. It was filtered and the residue was washed with water, recrystallized from DMSO-H_2O yield (74%, m.p. 240-42° (Found: C, 54.58; H, 3.38; N, 23.76. Calcd. for $C_{16}H_{12}N_6O_2S$: C, 54.5; H, 3.41; N, 23.86%); IR: 3030, 2952 (ν_{C-N} aryl), 3240(ν_{N-H}), 1602(ν_{C-N}), 1342(ν_{NO_2} sym), 1519(ν_{NO_2} asym). NMR: 10.30 (1H, b, NH),, 6.8-8.8(9H, m, $C_7H_4N_3O_2$, C_6H_5), 5.98 (2H, s, CH_2). ms; 352(M^+ 56.0), 40(100%),77 (41.0), 118 (12.0), 136 (24.0), 150 (10.0), 190 (57.0).

5-(6′-Nitrobenzimidazole-ylmethyl)-2-phenylamino-1, 3, 4-oxadiazole 10. A suspension of 0.37 g (1 mmole) compound **6** in ethanol (15 mL) was dissolved in cold aq. NaOH (5 mL, 4 *N*) at 0°C. To this clear solution, iodine in aq. KI (5%) was added gradually with stirring till the colour of iodine persisted at room temperature. The reaction mixture was heated under rerflux for 3 hr, cooled and poured into ice water. The precipitated solid was filtered, washed with water and recrystallized from methanol-ethanol. M.p. 225-27°, yield 71%, m.p. 225-27° (Found: C, 57.10; H, 3.50; N, 24.86. Calcd. for $C_{16}H_{12}N_6O_3$: C, 57.14; H, 3.57; N, 25.00%); IR: 3050, 2973 (ν_{C-H} aryl), 3212 (ν_{N-H}), 1620 (ν_{C-N}), 1332 (ν_{NO_2} sym), 1524(ν_{NO_2} asym); NMR: 10.51 (1H, b, NH), 6.87-8.74(9H, m, $C_7H_4N_3O_2$, C_6H_5), 5.92(2H, s, CH_2). ms: 336 (M^+ 100%), 118(24.8), 120(53.7), 130(27.4), 174(76.0), 177 (8.5).

Infrared spectra. The infrared spectra of compounds **3** and **4** showed two bands at 3100-3300 cm^{-1} due to ν_{NH} vibrations. The strong bands at 1663 and 1710 cm^{-1} were assigned to the stretching vibrations of carbonyl groups, respectively. The compounds **6** and **7** showed three bands around at 3240, 3170 and 3100 cm^{-1} due to ν_{N-H} vibrations respectively. The strong bands at 1725 and 1703 cm^{-1} were attributed to the stretching vibrations of carbonyl groups, respectively. The presence of bands of compounds **5, 8** around 1200 and 2589 cm^{-1} due to $\nu_{C=S}$ and ν_{S-H}, respectively, indicated their presence in thione-form as well as in thiol-form in a tautomeric mixture. All the compounds showed symmetric stretching and asymmetric stretching vibrations of (ν_{NO_2} at 1370-1330 cm^{-1} and 1530-1500 cm^{-1}, respectively.

NMR spectra. The DMSO-d_6 peak at 2.49 ppm (proton spectra) and the DMSO-d_6 central peak at 39.50 ppm were used as internal standards. The ^1H NMR spectra of the compounds were obtained in DMSO-d_6 (compound **4** in D_2O). In order to confirm the position of alkylating reaction of 6-nitrobenzimidazole, the ^{13}C NMR spectrum and DEPT-135° spectrum of the compound **6** were obtained and the presence of six quaternary carbon atoms indicated substituted position on N-atom (as shown in Scheme II).

Mass spectra. The aromatic compounds usually have strong molecular ion peak (CI) but the molecular ion peak of aryl thiosemicarbazides are weak owing to the C–N bond between N^2H and –C–easy to break, so two strong fragment peaks are observed, e.g. compound **6** exhibits fragment peaks at m/z 135(100.0%) and m/z 235 (19.3%). The main peaks of compounds are given in



Scheme III

Experimental Section. The mechanism of splitting of a few fragment can be explained as the following: m/z 235 and 135 (compound **6**); m/z 120 (53.7%) and 136 (24%) (compound **9, 10**); m/z 176 and 130 (compound **3, 5, 6, 8** and **10**).

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