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Condensed Bridgehead Nitrogen Heterocyclic System: Microwave Assisted Synthesis and Bioactivity of s-Triazolo[3,4-b][1,3,4]thiadiazoles, s-Triazolo[3,4-b][1,3,4]thiadiazines and s-Triazolo [3',4':2,3]thiadiazino[5,6-b]quinoxaline

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N-[3-(4-Amino-5-mercapto-4H-[1,2,3]triazol-3-yl)-4,5,6,7-tetrahydro-benzo[b] thiophen-2-yl]benzamide (1) on condensation with chloroacetic acid, α-haloketone and benzoin furnishes [1,2,4]triazolo[3,4-b][1,3,4]thiadiazine derivatives (2), (3) and (4) respectively, while condensation with 2,3-dichloroquinoxaline, carbon disulphide, aromatic carboxylic acid and aromatic carboxaldehydes yield the cyclic products, [1,2,4] triazolo[3,4-b][1,3,4]thiadiazole derivatives (5), (6), (7), (8) respectively. The compounds have been characterized on the basis of elemental analysis and spectral data. The antibacterial, antifungal and antitubercular activities of the compounds have also been evaluated.

Key Words: Nitrogen, Heterocyclic compounds, Quinoxaline.

INTRODUCTION

1,2,3-Triazolo[3,4-b][1,3,4]thiadiazine and 1,2,3 triazolo-[3,4-b][1,3,4]thiadiazole have been reported to have important biological activities[1,2] *viz.* antibacterial, antifungal, analgesic and antiinflammatory. Microwave assisted reactions[3] using dry media[4] have attracted much interest because of the simplicity in operation, greater selectivity and rapid synthesis of variety of heterocyclic compounds[5]. Keeping this in view, it was thought worthwhile to develop rapid syntheses of title compounds under solvent free conditions using microwave irradiation.

EXPERIMENTAL

The melting points were recorded on electrothermal apparatus and are uncorrected. IR Spectra were recorded in KBr on a Perkin-Elmer 983; ^{1}H NMR spectra on a Bruker Avance 300 MHz instrument using $CDCl_3$ as solvent (chemical shifts in δ' ppm) using TMS as internal standard; mass spectra on a Finning LCQ mass spectrometer. Microwave irradiation was carried out in Padmini Essentia oven, Model Brownie at 2450 MHz. Elemental analysis were performed on a Heracus CHN-Rapid analyzer. The purity of the compounds was checked on silica gel coated Al plates (Merck).

N-[3-(4-Amino-5-mercapto-4*H*-[1,2,3]triazol-3-yl)-4,5,6,7-tetrahydro-benzo[b] thiophen-2-yl]benzamide (1]): It was synthesized by green route as per reported method[6,7] IR (cm^{-1}): 1530 ν(C-N stretching), 1610 ν(C=N), 2640 ν(S-H stretching), 3140, 3340 ν(N-H stretching); ^{1}H NMR ($CDCl_3$): δ 1.62 (d, 4H, protons of two methylene groups in cyclohexane ring), 2.0 (s, 2H, NH_2), 2.02 (s, 3H, CH_3), 2.55 (d, 4H, protons of two methylene groups in cyclohexane ring), 3.0 (s, 1H, Ar, SH), 8.0 (s, 1H, NH).

N-[3-(6-Oxo-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)-4,5,6,7-tetrahydro-benzo[b]-thiophen-2-yl]benzamide (2): A solution of **1** (0.01 mol), chloroacetic acid (0.01 mol) and freshly prepared fused sodium acetate (0.01 mol) was prepared. Acidic alumina (aluminium oxide, acidic, Brockmann I, ~150 mesh, 58 Å CAMAG 506-C-I, Surface area 155 m^2/g. pH = 6.0) was added to the above solution at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina-bath[8] and irradiated for 40-80 s. The mixture was cooled and then product was extracted with dry methanol and poured onto crushed ice. The solid thus separated was filtered, washed thoroughly with water and recrystallized from aqueous ethanol; IR (cm^{-1}): 1540 ν(C-N stretching), 1630 ν(C=N), 1670 ν(C=O); ^{1}H NMR ($CDCl_3$): δ 1.62 (d, 4H, protons of two methylene groups in cyclohexane ring),, 2.55 (d, 4H, protons of two methylene groups in cyclohexane ring), 3.82 (s, 2H, methylene group in thiadiazine), 6.3-6.9 (m, 5H, ArH), 8.0 (s, 2H, NH).

N-3-(6-Methyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazin-3-yl)-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl]-benzamide (3): Solution of **1** (0.01 mol) and *p*-bromophen acyl bromide (0.01 mol) was added to acidic alumina at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina-bath and irradiated for 40-80 s. The mixture was cooled and then product was extracted with dry methanol and neutralized with aqueous potassium carbonate. The solid thus separated was filtered, washed thoroughly with water and recrystallized from ethanol; IR (cm^{-1}): 835 ν(1,4-disubstituted benzene ring), 1530 ν(C-N stretching), 1620 ν(C=N), 3030 ν(aromatic C-H stretching); ^{1}H NMR ($CDCl_3$): δ 0.9 (s, 3H, CH_3 on thiadiazine), 1.62 (d, 4H, protons of two methylene groups in cyclohexane ring), 2.55 (d, 4H, protons of two methylene groups in cyclohexane ring), 3.0 (s, 2H, methylene group in thiadiazine), 6.3-6.9 (m, 5H, ArH), 8.0 (s, 1H, NH).

N-[3-(6,7-Diphenyl-5*H*-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazin-3-yl)-4,5,6,7-tetrahydro benzo[b] thiophen-2-yl]-benzamide (4): A solution of **1** (0.01 mol), benzoin (0.01 mol) and 2 N KOH solution was prepared. Acidic alumina was added to the above solution at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina-bath and irradiated for 40-80 s. The mixture was cooled and then product was extracted with acetone and was evaporated to dryness. The solid thus separated was washed thoroughly with water and recrystallized from ethanol; IR (cm^{-1}): 715, 755 ν(monosubstituted benzene ring), 1600, 1620 ν(C=C), 1665 ν(C=N), 3040 ν(aromatic C-H stretching), 3410 ν(N-H stretching); ^{1}H NMR ($CDCl_3$): δ 1.62 (d, 4H, protons of two methylene groups in cyclohexane ring), 2.0 (s, 1H, NH), 2.55 (d, 4H, protons of two methylene groups in cyclohexane ring), 6.7-7.42 (m, 15H, ArH), 8.0 (s, 1H, NH).

N-[3-(4H-11-thia-1,2,3a,4,5,10-hexaaza-cyclopenta[b]-anthracen-3-yl)-4,5,6,7-tetra hydro-benzo[b]thiophen-2-yl]benzamide (5): Solution of **1** (0.01 mol), 2,3-dichloro quinoxaline (0.01 mol) and fused sodium acetate (0.02 mol) was added to acidic alumina at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina-bath and irradiated for 40-80 s. The mixture was cooled and then product was extracted with dry methanol, concentrated and cooled. The solid thus separated was filtered, washed thoroughly with water and recrystallized from ethanol; IR (cm^{-1}): 740 ν(1,4-disubstituted benzene ring), 1520 ν(C-N stretching), 1610 ν(C=C), 1660 ν(C=N), 3050 ν(aromatic C-H stretching) ; ^{1}H NMR ($CDCl_3$): δ 1.62 (d, 4H, protons of two methylene groups in cyclohexane ring), 2.55 (d, 4H, protons of two methylene groups in cyclohexane ring), 4.0 (s, 1H, NH), 6.9-7.8 (m, 9H, ArH) 8.0 (s, 1H, NH).

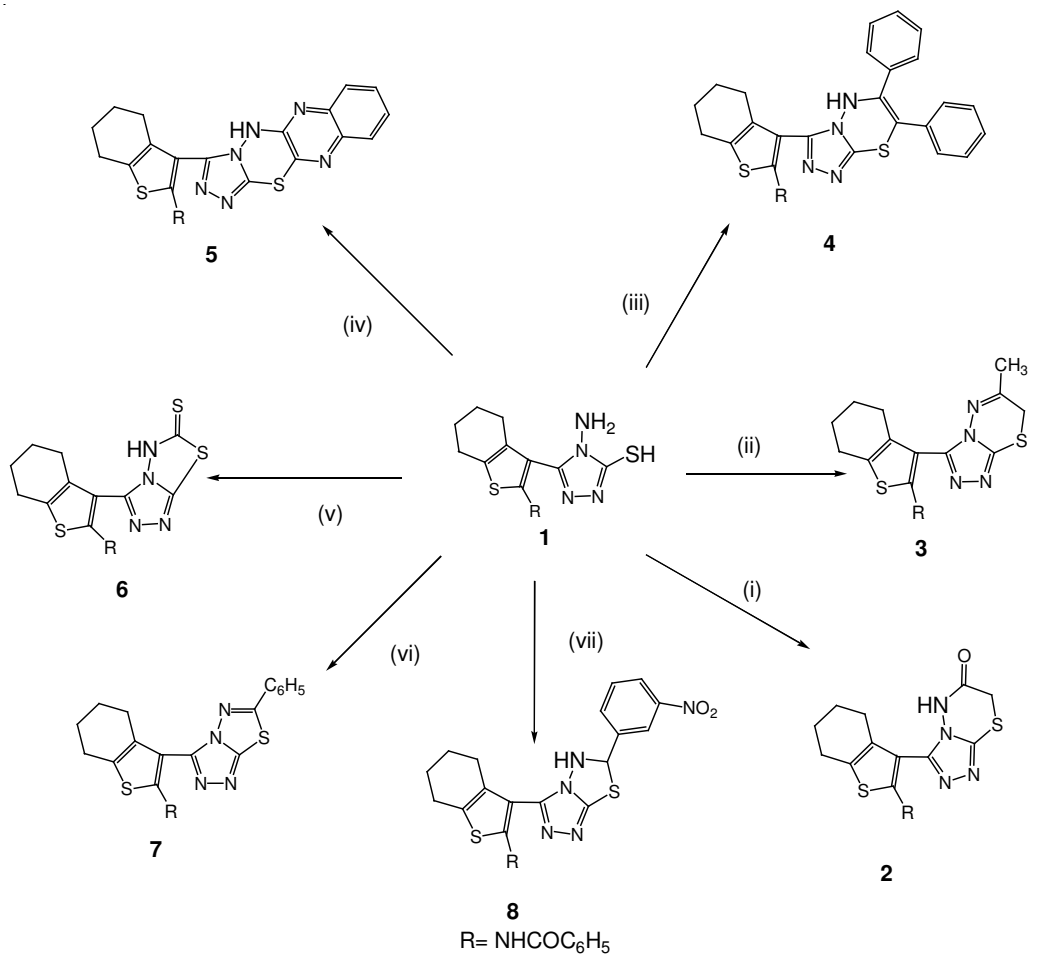
N-[3-(6-Thioxo-5,6-dihydro-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)-4,5,6,7-tetrahydro-benzo[b]-thiophen-2-yl]benzamide (6): Carbon disulphide (0.015 mol) was added dropwise with constant stirring to the solution of **1** (0.01 mol) in methanolic KOH solution. Acidic alumina was added to the above solution at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina-bath and irradiated for 40-80 s. The mixture was cooled and then product was extracted with dry methanol, which was then poured onto ice and acidified with dil. HCl. The solid thus separated was filtered, washed thoroughly with water and recrystallized from aqueous ethanol; IR (cm^{-1}): 1130 ν(CS), 1520 ν(C-N stretching), 1600 ν(C=C), 1665 ν(C=N), 3050 ν(aromatic C-H stretching); ^{1}H NMR ($CDCl_3$): δ 1.62 (d, 4H, protons of two methylene groups in cyclohexane ring), 2.0 (s, 1H, NH), 2.55 (d, 4H, protons of two methylene groups in cyclohexane ring), 6.3-6.9 (m, 5H, ArH), 8.0 (s, 1H, NH).

N-[3-(6-Phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)-4,5,6,7-tetrahydrobenzo [b]thiophen-2-yl]benzamide (7): A solution of **1** (0.01 mol) and *p*-toluic acid (0.01 mol) in $POCl_3$ (5 mL) was prepared. Acidic alumina was added to the above solution at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina-bath and irradiated for 40-80 s. The mixture was cooled and then poured onto ice and neutralized with aqueous potassium carbonate solution. The solid thus separated was filtered, washed thoroughly with water and recrystallized from hexane; IR (cm^{-1}); 830 ν(1,4-disubstituted benzene ring), 1520 ν(C-N stretching), 1600 ν(C=C), 1620 ν(C=N), 3060 ν(aromatic C-H stretching); ^{1}H NMR ($CDCl_3$): δ 1.62 (d, 4H, protons of two methylene groups in cyclohexane ring), 2.55 (d, 4H, protons of two methylene groups in cyclohexane ring), 6.9-7.48 (m, 9H, ArH), 8.0 (s, 1H, NH).

N-[3-(6-(3-Nitrophenyl)-5,6-dihydro-[1,2,4]triazolo-[3,4-b][1,3,4]thiadiazol-3-yl)-4,5,6,7-tetrahydro-benzo[b]-thiophen-2-yl]benzamide (8): A solution of **1** (0.01 mol) and *m*-nitrobenzaldehyde (0.01 mol) was prepared. Acidic alumina was added to the above solution at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina-bath and irradiated for 40-80 s. The mixture was cooled and then product was extracted with dry toluene, concentrated and cooled. The solid thus separated was filtered, washed thoroughly with water and recrystallized from ethanol; IR (cm^{-1}): 1350, 1540 ν(NO_2), 1520 ν(C-N stretching), 1600 ν(C=C), 1620 ν(C=N), 3070 ν(aromatic C-H stretching); ^{1}H NMR ($CDCl_3$): δ 1.62 (d, 4H, protons of two methylene groups in cyclohexane ring), 2.0 (s, 1H, NH), 2.55 (d, 4H, protons of two methylene groups in cyclohexane ring), 4.95 (s, 1H, CH group in thiadiazole), 7.0-7.9 (m, 9H, ArH), 8.0 (s, 1H, NH).

RESULTS AND DISCUSSION

The synthesis entails the union of two biologically active nuclei, *viz.* triazole and thiadiazole and also triazoles and thiadiazine. Earlier thiadiazoles and thiadiazines were synthesized in 6-7 h[9], while on solid support under microwave; the reaction was completed within 40-80 s. with improved yield. The reaction of N-[3-(4-amino-5-mercapto-4*H*-[1,2,3]triazol-3-yl)-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl] benzamide (**1**) with chloroacetic acid, α-haloketone, benzoin and 2,3-dichloro-quinoxaline gave [1,2,4]triazolo[3,4-b][1,3,4]thiadiazine derivatives **2**, **3**, **4** and [1,2,]4]triazolo[3,4-b][1,3,4]-thiadiazole (**5**), respectively in good yield. The reaction of (**1**) with carbon disulphide in the presence of alc. KOH, aromatic carboxylic acid in the presence of $POCl_3$ and aromatic carboxaldehyde in the presence of *p*-toluene sulphonic acid yielded the expected products [1,2,4]triazolo[3,4-b][1,3,4]-thiadiazole derivatives **6**, **7**, **8**, respectively (**Scheme-I**). The structures **2-8** have been established on the basis of their ^{1}H NMR, IR and physical data (Table-1).



(i) $ClCH_2COOH$,NaOAc (ii) CH_3COCH_2Br, K_2CO_3(iii) $C_6H_5CHOHCOC_6H_5$, KOH
(iv) 2,3-Dichloroquinoxaline, NaOAc (v) CS_2, KOH (vi) C_6H_5COOH, $POCl_3$(vii) 2 $NO_2C_6H_5$

Scheme-I

TABLE-1
PHYSICAL DATA OF COMPOUNDS **1-8**

Compd.	m.p. (ºC)	m.w.	Yield (%)	Elemental analysis (%): Found (calcd.)	
				C	N
1	194-198	357	85	54.96 (54.91)	18.85 (18.89)
2	203-207	411	81	55.45 (55.40)	17.01 (17.05)
3	209-213	409	82	58.65 (58.69)	17.10 (17.16)
4	168-172	547	79	67.98 (67.93)	12.78 (12.73)
5	252-256	483	90	60.10 (60.16)	19.62 (19.68)
6	229-233	401	86	52.27 (52.23)	16.93 (16.98)
7	207-211	421	85	62.99 (62.95)	15.30 (15.35)
8	229-232	466	87	57.12 (57.17)	16.65 (16.62)

Antimicrobial activity: All the compounds were screened for antibacterial activity against *S. aureus* and *E. coli* by paper disc technique[10]. The concentration of the test compound used was 100 µg. Gentamycin was used as standard. Compounds **2**, **6** and **8** displayed maximum activity against *S. aureus* and *E. coli*. Compounds **4** and **7** showed moderate activity against *S. aureus* but were inactive against *E. coli*. All the other compounds were inactive against both the organisms. The antifungal activity of all the compounds was evaluated against *C. albicans* using the same technique. Nystatin was used as standard. Compounds **2**, **6** and **8** showed highest activity against *C. albicans* and compounds **4** and **7** showed moderate activity while others were inactive against the test organism.

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