Synthesis of Some New Heterobicyclic Nitrogen Systems Bearing 7H-1,2,4-Triazolo[1,5-*d*]tetrazol-6-yl Moiety for Biological Interest

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Reaction of 6-mercapto-7H-1,2,4-triazolo[1,5-*d*]tetrazole (**1**) wtih 1,2-phenylenediamine afforded *N*-{7H-1,2,4-triazolo[1,5-*d*]tetrazol-6-yl}-1,2-phenylenediamine which was cyclized to benzimidazolyl-1,2,4-triazolo[1,5-*d*]tetrazoles using various one-carbon cyclizing agents. Also, the treatment of **1** with maleic anhydride or phthalic anhydride gave the corresponding thio derivatives followed by hydrazinolysis to afford the thio heterobicyclic systems. Former structures of the products have been established upon elemental and spectral analyses.

Keywords: 1,2,4-Triazolo[1,5-*d*]tetrazole; Reactions; Cyclization.

INTRODUCTION

In view of the varied biological properties of 1,2,4-triazoles,[1] tetrazoles,[2] benzimdazoles,[3-6] pyridazines,[7] and phthalazines,[8,9] but there is little information in the literature on the synthesis of 1,2,4-triazolotetrazoles,[10-14] although a good deal of work has been carried out on various other fused 1,2,4-triazoles. In light of these findings, the present work describes the synthesis of a variety of heterobicyclic derivatives of biological interest.

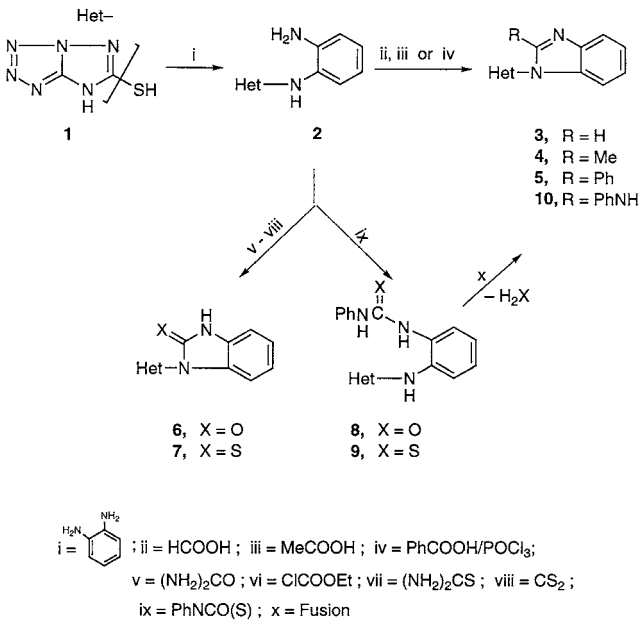
RESULTS AND DISCUSSION

Reaction of 6-mercapto-7H-1,2,4-triazolo[1,5-*d*]tetrazole (**1**) with 1,2-phenylenediamine in the presence of yellow mercury (II) oxide yielded **2** through the loss of hydrogen sulfide. The ^{1}H NMR spectrum of the product **2** revealed NH_2 and NH proton signals. This provided the evidence that the product should be assigned as N-{7H-1,2,4-triazolo[1,5-*d*]-tetrazol-6-yl}-1,2-phenylenediamine (**2**). Compound **2** is the key to prepare our target compounds with different one-carbon cyclizing reagents.

Heating of **2** with formic acid, acetic acid, or benzoic acid in the presence of phosphorus oxychloride directly afforded the corresponding benzimidazolyl-1,2,4-triazolo-[1,5-*d*]tetrazoles (**3-5**), respectively. On the other hand, treatment of compound **2** with urea or ethyl chloroformate in pyridine gave a single product in each case which was identified as **6**.

Likewise, thiourea or carbon disulfide also reacted with **2** to furnish the same product **7**. All attempts directly towards the isolation of the intermediates were unsuccessful. Subsequent reaction of **2** with phenyl isocyanate or its sulfur analog resulted in the formation of the isoable intermediates **8** and **9**. However, heating of **8** or **9** above their melting points gave a single product which was found to be compound **10** through the loss of water or hydrogen sulfide (Scheme I).

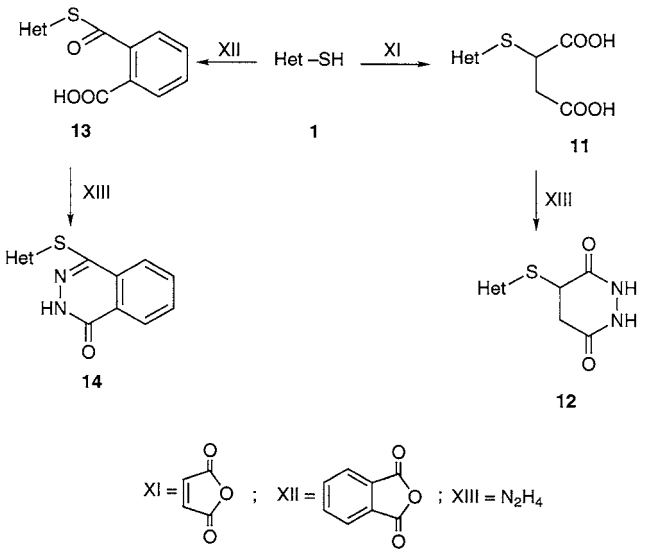
Scheme I



Furthermore, the reaction of **1** with maleic anhydride or phthalic anhydride resulted in the formation of the thio derivatives **11** and **13** which showed IR absorptions characteristic

of NH, OH, and carbonyl groups. Cyclization of either **11** or **13** by heating with hyrazine hydrate furnished products which showed NH and CON absorptions in the IR region. Accordingly, the products were assigned the thio-pyridazinyl and phthalazinyl structures **12** and **14** (Scheme II).

Scheme II



EXPERIMENTAL SECTION

Melting points were determined in open capillaries using a MEL-TEMP II melting apparatus and are uncorrected. The infrared spectra (IR) were recorded on a Perkin-Elmer FT Paragon 1000 and Pye-Unicam SP3-300 spectrometers. ^{1}H NMR spectra were scanned on a Varian Mercury VXR-3000 spectrometer using tetramethylsilane (TMS) as an internal standard. MS were recorded on a Shimadzu GCMs-QP 1000EX mass spectrometer at 70 ev. Microanalyses were carried out at the Microanalytical Unit, Cairo University, Egypt.

N-{7H-1,2,4-Triazolo[1,5-*d*]tetrazol-6-yl}-1,2-phenylenediamine (2)

A mixture of 6-mercapto-7H-1,2,4-triazolo[1,5-*d*]tetrazole[15] **1** (1.0 g, 7.04 mmol), 1,2-phenylenediamine (0.76 g, 7.03 mmol), yellow mercury (II) oxide (1.53 g, 7.06 mmol), and ethanol (15 mL) was heated on a water-bath for 4 h. After cooling the inorganic material was filtered and the filtrate was evaporated, then the separated crystalline product was collected by filtration, dried, and crystallized from ethanol to give **2** (0.99 g; 65%, yield) mp 270 °C, IR (KBr, ν/cm^{-1}): 3343 (NH_2), 3244 (NH), 1620 (C=N); ^{1}H NMR (DMSO-d_6, δ/ppm) 12.10, 11.80 (2s, 1H each, 2NH), 7.40, 7.15 (m, 4H, ArH), 4.50 (s, 2H, NH_2). Anal. calcd for $C_8H_8N_8$: C, 44.4; H, 3.7; N, 51.9; Found: C, 44.1; H, 3.4; N, 60.2.

6-(Benzimidazol-1-yl)-7H-1,2,4-triazolo[1,5-*d*]tetrazole (3)

A mixture of **2** (1.0 g, 4.63 mmol) and formic acid (10 mL) was heated under reflux for 6 h then left to cool down at room temperature, and the separated crystalline product was collected by filtration and dried then recrystallized from ethanol to give **3** (0.79 g; 75.5% yield), mp 210 °C; IR (KBr, ν/cm^{-1}): 3059 (NH), 1602 (C=N); ^{1}H NMR (DMSO-d_6, δ/ppm) 12.10 (s, 1H, NH), 8.60 (s, 1H, benzimidazole ring H), 7.50-7.00 (m, 4H, ArH). Anal. calcd for $C_9H_6N_8$: C, 47.8; H, 2.7; N, 49.6; Found: C, 48.01; H, 3.0; N, 49.2.

6-(2-Methylbenzimidazol-1-yl)-7H-1,2,4-triazolo[1,5-*d*]tetrazole (4)

A mixture of **2** (1.0 g, 4.63 mmol) in acetic acid (10 mL) was heated under reflux for 4 h and then evaporated to dryness. The obtained residue was crystallized from ethanol to give **4** (0.71 g; 64% yield); mp 190 °C; IR (KBr, ν/cm^{-1}): 3081 (NH), 1620 (C=N); ^{1}H NMR (DMSO-d_6, δ/ppm) 12.60 (s, 1H, NH), 8.00-7.00 (m, 4H, ArH), 2.30 (s, 3H, CH_3). Anal. calcd for $C_{10}H_8N_8$: C, 50.0; H, 3.3; N, 46.7; Found: C, 49.6; H, 3.5; N, 47.1.

6-(2-Phenylbenzimidazol-1-yl)-7H-1,2,4-triazolo[1,5-*d*]tetrazole (5)

A mixture of **2** (1.0 g, 4.63 mmol) and benzoic acid (0.57 g, 4.63 mmol) in phosphorus oxychloride (5 mL) was heated under reflux for 3 h. The reaction mixture was poured onto ice-water and treated with sodium bicarbonate. The separated product was collected by filtration, washed with water, and crystallized from ethanol to give **5** (0.81 g; 58% yield), mp 220 °C; IR (KBr, ν/cm^{-1}): 3060 (NH), 1621 (C=N); ^{1}H NMR (DMSO-d_6, δ/ppm) 12.80 (s, 1H, NH), 8.00-7.00 (m, 9H, ArH); MS: *m/z* 303 (9%, M+1). Anal. calcd for $C_{15}H_{10}N_8$: C, 59.6; H, 3.3; N, 37.1; Found: C, 60.0; H, 3.6; N, 36.8.

6-(2-Oxobenzimidazol-1-yl)-7H-1,2,4-triazolo[1,5-*d*]tetrazole (6)

Method (A). A mixture of **2** (1.0 g, 4.63 mmol) and urea (0.28 g, 4.63 mmol) was heated at 150 °C for 1.5 h. The obtained residue was crystallized from ethanol to give **6** (0.72 g; 64% yield), mp 200 °C; IR (KBr, ν/cm^{-1}): 3329 (NH), 1675 (CON), 1626 (C=N); ^{1}H NMR (DMSO-d_6, δ/ppm) 12.80, 11.82 (2s, 1H each, 2NH), 8.00-7.00 (m, 4H, ArH). Anal.

calcd for $C_9H_6N_8O$: C, 44.6; H, 2.5; N, 46.3; Found: C, 45.0; H, 2.9; N, 46.7.

Method (B). A solution of **2** (1.0 g, 4.63 mmol) in pyridine (2 mL) was treated with ethyl chloroformate (10 mL) and the mixture was heated at reflux for 4 h. The reaction mixture was poured onto ice-water and the formed product was collected by filtration, washed with water, and crystallized from ethanol to give **6** (0.62 g; 55% yield).

6-(2-Thioxobenzimidazol-1-yl)-7H-1,2,4-triazolo[1,5-*d*]tetrazole (7)

Method (A). A mixture of **2** (1.0 g, 4.63 mmol) and thiourea (0.35 g, 4.63 mmol) was heated at 200 °C for 2 h. The solid remaining was crystallized from ethanol to give **6** (0.80 g; 67% yield), m.p: 190 °C; IR (KBr, ν/cm^{-1}): 3387 (NH), 1620 (C=N); ^{1}H NMR (DMSO-d_6, δ/ppm) 12.80, 11.73 (2s, 1H each, 2NH), 8.08-7.22 (m, 4H, ArH). Anal. calcd for $C_9H_6N_8S$: C, 41.9; H, 2.3; N, 43.4; Found: C, 42.3; H, 2.7; N, 42.9.

Method (B). A solution of **2** (1.0 g, 4.63 mmol) in pyridine (2 mL) was treated with carbon disulfide (5 mL) and the mixture was heated under reflux for 4 h and then evaporated, and the formed residue was crystallized from ethanol to give **7** (0.69 g; 58% yield).

2-(3′-Phenylurea)-*N*-{7H-1,2,4-triazolo[1,5-*d*]tetrazol-6-yl}-aniline (8)

A solution of **2** (1.0 g, 4.63 mmol) in ethanol (15 mL) was treated with phenyl isocyanate (0.55 g, 4.63 mmol) and the reaction mixture was refluxed for 2 h then allowed to cool down to room temperature, and the product which separated was filtered off then recrystallized from ethanol to give **8** (0.81 g; 52% yield), mp 270 °C; IR (KBr, ν/cm^{-1}): 3299 (NH), 1685 (CON), 1625 (C=N); ^{1}H NMR (DMSO-d_6, δ/ppm) 12.80 (s, 1H, NH), 10.91 (s, 3H, 3NH), 8.02-7.22 (m, 9H, ArH). Anal. calcd for $C_{15}H_{13}N_9O$: C, 53.7; H, 3.9; N, 37.6; Found: C, 54.2; H, 4.3; N, 37.1.

2-(3′-Phenylthiourea)-*N*-{7H-1,2,4-triazolo[1,5-*d*]tetrazol-6-yl}aniline (9)

A solution of **2** (1.0 g, 4.63 mmol) in ethanol (15 mL) was treated with phenyl isothiocyanate (0.63 g, 4.63 mmol); the reaction mixture was refluxed for 1.5 h. After cooling, the solidified material was crystallized from ethanol to give **9** (0.91 g; 56% yield), mp 250 °C; IR (KBr, ν/cm^{-1}): 3371 (NH), 1624 (C=N); ^{1}H NMR (DMSO-d_6, δ/ppm) 12.80 (s, 1H, NH), 10.81 (s, 3H, 3NH), 8.00-7.03 (m, 9H, ArH). Anal. calcd for $C_{15}H_{13}N_9S$: C, 51.3; H, 3.7; N, 35.9; Found: C, 51.8; H, 4.0; N, 36.4.

6-(2-Phenylaminobenzimidazol-1-yl)-7H-1,2,4-triazolo[1,5-*d*]tetrazole (10)

Method (A). Compound **8** (1.0 g, 2.99 mmol) was heated at 275 °C in an oil bath for 1 h. The obtained residue was crystallized from ethanol to give **10** (0.61 g; 64% yield), mp 210 °C; IR (KBr, ν/cm^{-1}): 3371 (NH), 1605 (C=N); ^{1}H NMR (DMSO-d_6, δ/ppm) 12.80, 10.90 (2s, 1H each, 2NH), 8.00-7.00 (m, 9H, ArH); MS: *m/z* 317 (6%, M). Anal. calcd for $C_{15}H_{11}N_9$: C, 56.8; H, 3.5; N, 39.8; Found: C, 57.1; H, 3.9; N, 40.1.

Method (B). Compound **9** (1.0 g, 2.85 mmol) was heated at 260 °C in an oil bath for 1 h. The obtained mass was crystallized from ethanol to give **10** (0.61 g; 67% yield).

2-{7H-1,2,4-Triazolo[1,5-*d*]tetrazole-6-yl}thiosuccinic acid (11)

A mixture of **1** (1.0 g, 7.04 mmol) and maleic anhydride (0.69 g, 7.04 mmol) was heated in an oil bath at 190 °C for 30 min and then allowed to attain ambient temperature; the solidified material was crystallized from ethanol to give **11** (1.02 g; 56% yield), mp 250 °C; IR (KBr, ν/cm^{-1}): 3423 (OH), 2088 (NH), 1745 (acid-carbonyl, COOH), 1620 (C=N); ^{1}H NMR (DMSO-d_6, δ/ppm) 12.80 (s, 1H, NH), 6.02 (t, 1H, CH), 4.11 (d, 2H, CH_2), 3.51 (s, 2H, 2OH). Anal. calcd for $C_6H_6N_6O_4S$: C, 27.9; H, 2.3; N, 32.6; Found: C, 28.3; H, 2.7; N, 33.1.

4-{7H-1,2,4-Triazolo[1,5-*d*-tetrazol-6-yl}thio-1,2,4,5-tetrahydropyridazine-3,6-dione (12)

A mixture of **11** (1.0 g, 3.88 mmol) and hydrazine hydrate (0.19 g, 3.88 mmol) was heated under reflux for 2 h and then allowed to attain ambient temperature. The product which separated was filtered, washed, and crystallized from ethanol to give **12** (0.59 g; 60% yield), mp 185 °C; IR (KBr, ν/cm^{-1}): 3032 (NH), 1686 (CON), 1578 (C=N); ^{1}H NMR (DMSO-d_6, δ/ppm) 12.80 (s, 1H, NH), 10.12 (s, 2H, 2NH), 6.11 (t, 1H, CH), 4.22 (d, 2H, CH_2). Anal. calcd for $C_6H_6N_8O_2S$: C, 28.4; H, 2.4; N, 44.1; Found: C, 28.09; H, 2.9; N, 44.4.

6-Thio(2-carbobenzoic acid)-7H-1,2,4-triazolo[1,5-*d*]tetrazole (13)

A mixture of **1** (1.0 g, 7.04 mmol) and phthalic anhydride (1.04 g, 7.04 mmol) was heated in an oil bath at 190 °C for 30 min and then allowed to attain ambient temperature; the obtained residue was crystallized from ethanol to give **13** (1.33 g; 65% yield), mp 210 °C; IR (KBr, ν/cm^{-1}): 3286 (OH),

2985 (NH), 1760, 1718 (C=O), 1613 (C=N); ^{1}H NMR (DMSO-d_6, δ/ppm) 12.78 (s, 1H, NH), 8.02-7.00 (m, 4H, ArH), 3.60 (s, 1H, OH). Anal. calcd for $C_{10}H_6N_6O_3S$: C, 41.4; H, 2.1; N, 29.0; Found: C, 42.09; H, 1.8; N, 29.5.

1-{7H-1,2,4-Triazolo[1,5-*d*]tetrazol-6-yl}thiophthalazin-4-one (14)

A mixture of **13** (1.0 g, 3.45 mmol) and hydrazine hydrate (0.17 g, 3.45 mmol) was heated under reflux for 1.5 h. The reaction mixture was allowed to attain ambient temperature, and the product which separated was filtered and crystallized from ethanol to give **14** (0.69 g; 70% yield), mp 185 °C; IR (KBr, ν/cm^{-1}): 3055 (NH), 1674 (CON), 1612 (C=N); ^{1}H NMR (DMSO-d_6, δ/ppm) 12.78 (s, 1H, NH), 10.89 (s, 1H, NH), 8.00-6.87 (m, 4H, ArH). Anal. calcd for $C_{10}H_6N_8OS$: C, 42.0; H, 2.1; N, 39.2; Found: C, 42.5; H, 2.5; N, 39.7.

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