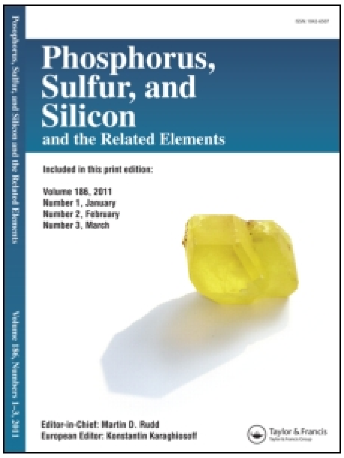

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BICYCLIC COMPOUNDS DERIVED FROM 4-AMINO-3-MERCAPTO-1,2,4-TRIAZOLES: FACILE ROUTES TO 1,2,4-TRIAZOLO [3,4-b][1,3,4]THIADIAZOLES AND 1,2,4-TRIAZOLO[3,4-b][1,3,4]THIADIAZINES

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Treatment of 5-substituted-4-amino-3-mercapto-1,2,4-triazoles (**1**), with triethyl ortho-formate or acetyl chloride gave the corresponding triazolo[3,4-b]thiadiazoles (**2**) and (**3**), respectively. Reaction of (**1**) with phenacyl bromide, DMAD and DEAD afforded the corresponding thiazolo[3,4-b][1,3,4] thiadiazines (**4**), (**5**) and (**6**), respectively. Reaction of (**1**) with propargyl bromide in the presence of sodium methoxide gave the corresponding sulfide (**7**) which upon treatment with LiH gave the corresponding 1,2,4-triazolo[3,4-b][1,3,4]thiadiazine (**8**). Reaction of (**1**) with 2,4-dinitrochlorobenzene gave substituted 5H-1,2,4-triazolo[3,4-b][1,3,4]benzothiadiazine (**9**).

Keywords: Triazoles; Facile route; Thiadiazines; Thiadiazoles; dimethyl acetylenedicarboxylate

1,2,4-triazolo[3,4-b][[1,3,4]thiadiazoles and 1,2,4-triazolo[3,4-b][1,3,4] thiadiazines constitute two classes of compounds interesting from view points of chemical reactivity[1–5] and biological activity. Antibacterial[6–8] and antiinflamatory activity[9] as well as interesting CNS depressing activity[10] has been reported for certain of the derivatives. Some 6-substituted-3-(pyridine-4-yl)-1,2,4-triazolo[3,4-b][1,3,4] thiadiazoles exhibit moderate antimalarial and antitumor activity[11].

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In continuation of our work on the synthesis of bridgehead nitrogen heterocycles[12] synthesis of some new 1,2,4-triazolo[3,4-b][1,3,4] thiadiazoles and 1,2,4-triazolo[3,4-b][1,3,4] thiadiazines have been accomplished and presented in this communication.

In 1966 Potts and co-workers[13] reported the preparation of different derivatives of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles by ring closure of 5-substituted triazoles using suitable acyl chlorides in the presence of phosphoryl chloride. Most recently similar compounds were prepared by ring closure of (**1**) with carboxylic acid in the presence of phosphoryl chloride[1].

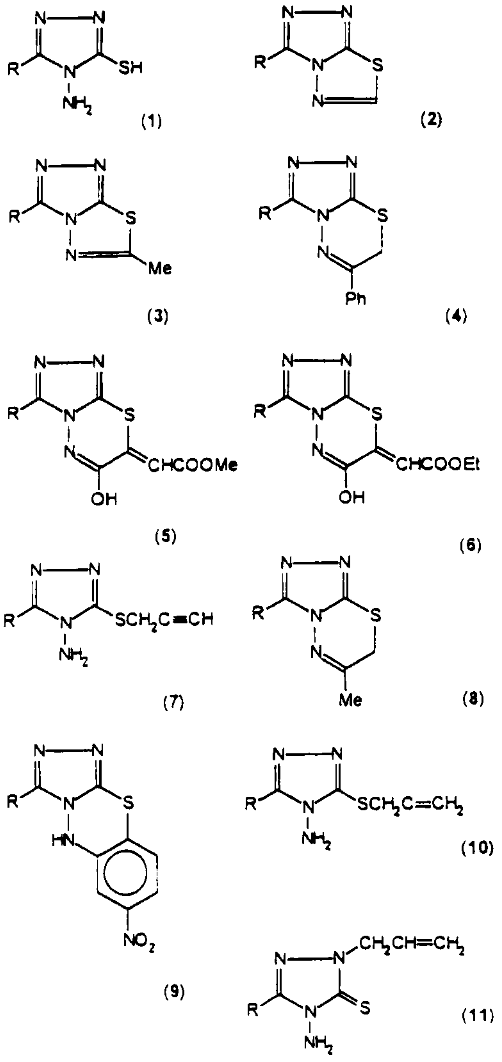
Interestingly we found that 1,2,4-triazolo[3,4-b][1,3,4] thiadiazoles (**2**, R=Me and **3**, R=Me) can be readily made by reaction of (**1**, R=Me) with ethyl orthoformate in the presence of triethylamine or acetyl chloride in the presence of pyridine.

Reaction of (**1**, R=Ph) with phenacyl bromide in refluxing EtOH afforded 3,6-diphenyl-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine (**4**) in good yield.

Acetylenic esters have proven to be very versatile reagents for heterocyclization and many diverse products can be prepared from the addition of these compounds to nitrogen and sulphur containing heterocycles[14]. Although the reaction of (**1**, R=Me) with dimethyl acetylenedicarboxylate (DMAD), to give the adduct (**5**) derived from initial attack by sulphur has been reported in brief[15] we could support the result with firm spectroscopic data and establish the generality of the method by using diethyl acetylenedicarboxylate (DEAD) to give the adduct (**6**).

Compound (**1**, R=Ph) was condensed with propargyl bromide in the presence of sodium methoxide to afford the corresponding propargylsulfide (**7**, R=Me). The latter was cyclized to the corresponding 7H-1,2,4-triazolo[3,4-b][1,3,4] thiadiazine (**8**) by an interesting attack of the amino group to the acetylenic moiety followed by isomerization to convert the methylene moiety to a methyl group. This phenomenon has been already reported by our group[12a,b,c,d,l,16a,b].

We have recently reported on the usefulness of 3,6-dinitro-2-chloropyridine as a bident electrophile[17]. Armed with this experience, compound (**1**, R=Me) was caused to react with 2,4-dinitrochlorobenzene in DMF in the presence of triethylamine to afford 3-methyl-8-nitro-5H-1,2,4-triazolo[3,4-b][1,3,4] benzothiadiazine (**9**). Finally (**1**, R=Me) was condensed with allyl bromide in the presence of sodium methoxide to obtain the corresponding allylsulfide (**10**, R=Me). Attempted cyclization of the latter



SCHEME I

failed in acidic and basic media. However, attempted cyclization of (**10**, R=Me) using $PdCl_2$ led to a 3,3 sigmatropic shift to give (**11**, R=Me). This phenomenon has been reported previously[18].

EXPERIMENTAL SECTION

The melting points are uncorrected and were obtained by a Kofler Heizbank Rechart type 7841 melting point apparatus. IR spectra were obtained on a 4300 Shimadzu spectrometer. The ^{1}HNMR spectra were recorded on a Varian 60 and Bruker AC 100 unless otherwise stated, using TMS as internal reference and mass spectra scanned on a Varian CH-7 instrument at 70 eV.

3-Methyl-1,2,4-triazolo[3,4-b][1,3,4] thiadiazole (2, R=Me)

Compound (1, R=Me) (0.13 g, 1 mmol), triethylortho formate (0.4 ml, 2 mmol) and triethylamine (3 drops) were dissolved in absolute ethanol (10 ml). The reaction mixture was refluxed for 16 hrs. The solvent was evaporated to dryness under reduced pressure. The crude product was directly subjected to column chromatography using $CHCl_3$ as eluent to afford the title compound, m.p. 134–6°C; yield 28%; ^{1}HNMR ($CDCl_3$), 2.7 (s, 3H, Me), 8.6 (s, 1H, CH of thiazole ring); FTIR, 3200, 1620, 1490, 1300, 1280, 1210 cm^{-1}: MS m/z, M$^+$ 140.

3,6-Dimethyl-1,2,4-triazolo[3,4-b][1,3,4] thiadiazole (3, R=Me)

Compound (1, R=Me) (0.26 g, 2 mmol) and acetyl chloride (0.15 ml, 2 mmol) were refluxed in pyridine (5 ml) for 8 hrs. The solvent was evaporated to dryness under reduced pressure. The crude product was directly subjected to column chromatography using $CHCl_3$:MeOH 98:2 to afford the title compound, m.p. 105–7°C; yield 43%; ^{1}HNMR ($CDCl_3$), 2.6 (s, 3H, Me), 2.7 (s, 3H, Me); FTIR, 2990, 1650, 1430, 1300 cm^{-1}; MS m/z, M$^+$ 154.

3,6-Diphenyl-7H-1,2,4-triazolo[3,4-b][1,3,4] thiadiazine (4, R=Ph)

Compound (1, R=Ph) (0.3 g, 1.6 mmol) and phenacyl bromide (0.32 g, 1.6 mmol) were refluxed in ethanol (10 ml) for 5 hrs. To this mixture a solution of potassium carbonate was added. The precipitate was filtered and crystallized from EtOH to afford the title compound, m.p. 163–4°C; yield

50%; ^{1}HNMR ($CDCl_3$), 4.3 (s, 2H, CH_2), 7.65–8.55 (m, 10H, 2Ph); FTIR (KBr disc) 3100, 3000, 2900, 1460 cm^{-1}; MS m/z, M^+ 292.

3-Methyl-6-hydroxy-7-carbomethoxy methylene-1,2,4-triazolo[3,4-b][1,3,4] thiadiazine(5, R=Me)

Compound (1, R=Me) (0.13 g, 1 mmol), dimethyl acetylenedicarboxylate (0.14 g, 1 mmol) and glacial acetic acid (3 drops) were refluxed in CH_3CN-MeOH (10 ml-5 ml) for 3 hrs. The reaction mixture was cooled to room temperature and the precipitate was filtered and crystallized from MeOH to give the title compound, m.p. 262–4°C; yield 54%; ^{1}HNMR (d_6-DMSO), 2.4 (s, 3H, Me), 3.7 (s, 3H, -OMe), 6.8 (s, 1H =CH); FTIR (KBr disc) 3400, 1690 cm^{-1}; MS m/z, M^+273.

3-Methyl-6-hydroxy-7-carboethoxymethylene-1,2,4-TRIAZOLO [3,4-b][1,3,4] thiadiazine (6, R=Me)

This compound was synthesized according to the above procedure using DEAD, m.p. 271–3°C; yield 49%; ^{1}HNMR (d_6-DMSO), 1.25 (t, 3H, Me), 2.35 (s, 3H, Me), 4.25 (q, 2H, CH_2), 6.85 (s, 1H, =CH); FTIR (KBr disc) 3400, 3010, 1690 cm^{-1}; MS m/z, M^+ 253.

4-Amino-3-propargylmercapto-5-phenyl-1,2,4-triazole (7, R=Ph)

Compound (1, R=Ph) (1 g, 5 mmol) was dissolved in a solution of sodium methoxide in methanol (prepared from 0.12 g (5 mmol) sodium in 20 ml methanol). To this solution propargyl bromide (0.47 ml from 80% solution in toluene) was added at room temperature. The reaction mixture was stirred for 30 min at ambient temperature and water (40 ml) was added; the precipitate was filtered, washed and crystallized from water to afford the title compound, m.p. 121–2°C; yield 62%; ^{1}HNMR (d_6-DMSO), 3.2 (s, 1H, =CH), 4.0 (s, 2H, CH_2), 5.8 (s, 2H, NH_2 broad exchangeable with D_2O). 7.1–8.1 (m, 5H, Ph); FTIR (KBr disc) 3300, 3250, 3120 cm^{-1}; MS m/z, M^+ 230.

3-Phenyl-6-methyl-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine (8, R=Ph)

Compound (**7**, R=Ph) (0.87 mmol) and lithium hydride (0.02 g, 2.5 mmol) were refluxed in dimethylsulfoxide for 5 min. The reaction mixture was cooled to room temperature, water (10 ml) was added and the mixture extracted with $CHCl_3$ (3x20 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The crude product was directly subjected to column chromatography using $CHCl_3$:MeOH 98:2 to afford the title compound, m.p. 159–60°C; yield 60%; ^{1}HNMR ($CDCl_3$), 2.5 (s, 3H, Me), 3.6(s, 2H, CH_2), 7.4–7.7 (m, 3H of Ph), 7.9–8.3 (m, 2H of Ph); FTIR, 3050, 2900, 1460 cm^{-1}; MS m/z, M^+ 230.

3-Methyl-8-nitro-5H-1,2,4-triazolo[3,4-b][1,3,4]benzothiadiazine (9, R=Me)

Compound (**1**, R=Me) (0.13 g, 1 mmol), 2,4-dinitro-chlorobenzene (0.2 g, 1 mmol) in DMF (5 ml) were refluxed for 4 hrs. The mixture was cooled to room temperature and water (5 ml) was added. The precipitate was filtered, dried and crystallized from CH_3CN to afford the title compound, m.p. 197–8°C; yield 63%; ^{1}HNMR (d_6-DMSO), 2.4 (s, 3H, Me), 7.3, 8.4, 8.9 (s, 3H, C_6H_3); FTIR, 3300, 1590, 1330 cm^{-1}; MS m/z, M^+ 248.

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