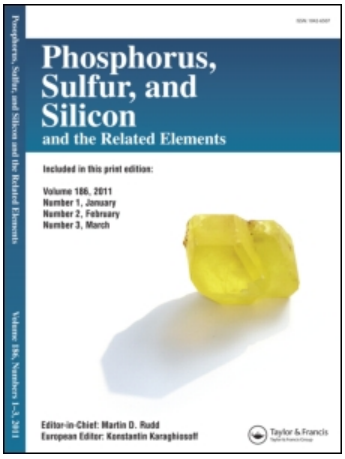

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SYNTHESIS OF A NOVEL HETEROCYCLIC SYSTEM: 4H-[1,2,4]TRIAZINO[4,5-b][1,3] THIADIAZINE

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SYNTHESIS OF A NOVEL HETEROCYCLIC SYSTEM: 4H-[1,2,4]TRIAZINO[4,5-b][1,3] THIADIAZINE

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Cyclocondensation of 6-methyl-4-amino-1,2,4-triazine-5-thione-3-one **3** with propargyl bromide provides a novel heterocyclic system5H-[1,2,4]triazino[4,5-b][1,3] thiadiazine.

Keywords: Triazino-thiadiazine; synthesis; structure

INTRODUCTION

2-Phenylnaphthalene type ring system is reported to exhibit a wide spectrum of biological activity including antitumor activity.[1]. These naphthalene type ring systems can either be carbocyclic or heterocyclic with nitrogen, oxygen or sulfur atoms placed at suitable positions[1], i.e. quinazolines are well known for their pharmacological activity[2].

We are interested in the chemistry of heterocyclic compounds containing nitrogen and sulfur atoms[3]. As a part of a research program on synthesis of heterocyclic compounds containing nitrogen and sulfur and with a view of extending the synthetic utility of propargyl bromide[4] we have prepared a

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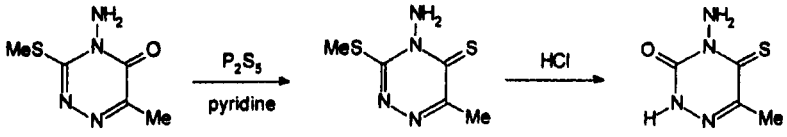
4-amino-5-thioxo-1,2,4-triazin-3-one and investigated the reaction of the latter with propargyl bromide to synthesis a novel heterocyclic system.

4-Amino-3-methylthio-1,2,4-triazin-3-one[5] **1** was first treated with P_2S_5 in dry pyridine to afford 4-amino-6-methyl-3-methylthio-1,2,4-triazin-5-thione **2**. Methylthio group at the 3 position was then selectively hydrolysed in acidic media to afford 4-amino-6-methyl-1,2,4-triazine-5-thion-3-one **3** (Scheme 1)



1 **2** **3**

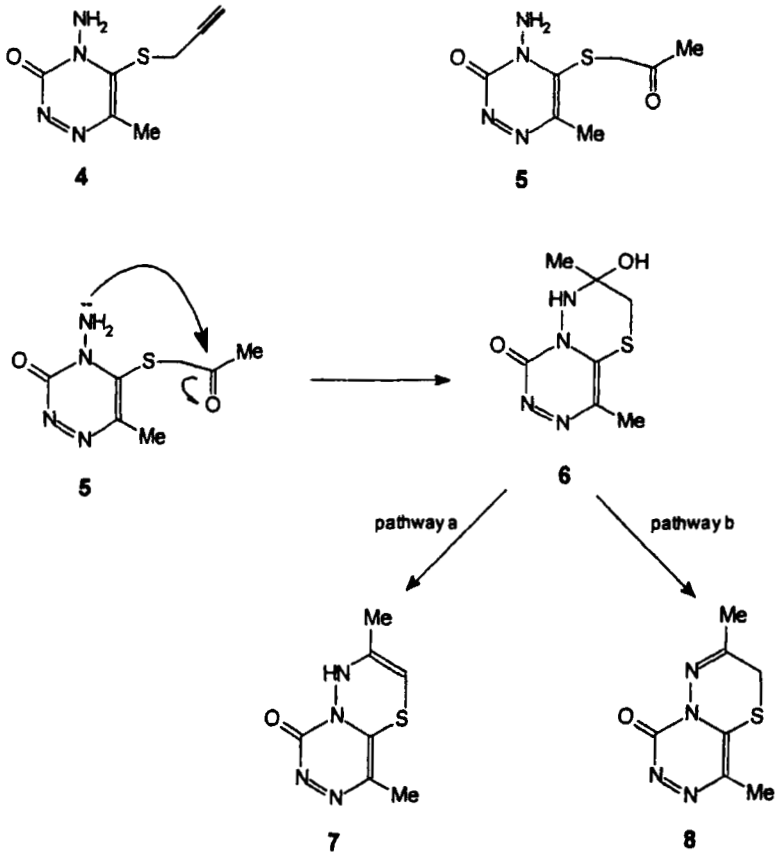
SCHEME 1

Compound **3** was condensed with propargyl bromide to afford the corresponding 5-propargylthio derivative **4**. We have recently described the use of conc. sulfuric acid for cyclization of variety of propargylthio compounds to synthesize fused thiazoles[6]. Armed with these experiences, compound **4** was treated with conc. sulfuric acid, followed by aqueous work up. The resulting compound was identified as **5** instead of the expected cyclized product **6**. The same result can be obtained by the reaction of **3** with chloroacetone. Compound **5** was cyclized by treatment with aqueous sodium carbonate. Depending on the mode of dehydration of the intermediate **6** two tautomers are possible i.e. 5H-1,2,4-triazino[5,4-b][1,3] thiadiazine **7** and 7H-1,2,4-triazino[5,4-b][1,3] thiadiazine **8** (Scheme 2). However after careful examination and comparison of the NMR spectrum of the dehydration product, it became clear that only structure **7** (pathway a) fits the data.

The ^{1}NMR spectrum of the dehydration product showed a vinyl signal at δ 5.75 and no evidence for allylic a proton.

EXPERIMENTAL SECTION

Mps were determined on a Reichert apparatus and are uncorrected. IR spectra were recorded on a Shimatzu spectrometer as KBr disc. ^{1}HNMR



SCHEME 2

spectra were recorded on a Bruker (100 MHz) instrument. Mass spectra were obtained from Varian CH-7 at 70 eV.

4-Amino-6-methyl-3-methylthio-1,2,4-triazine-5-thione 2

Compound **1** (3.44 g, 20 mmol) was dissolved in pyridine (100 mL) and phosphorus pentasulfide (2.68 g) was added to this solution. The reaction mixture was refluxed for 4 hrs. After cooling the red solution was decanted and evaporated under reduced pressure. The residue then was taken up in

water (40 mL) and the solution was adjusted to a pH value of 9 by the addition of 2N sodium hydroxide solution and treated with charcoal. The solution was filtered and the filtrate was acidified to a pH value of 3 with 2N hydrochloric acid. The orange solid, which appeared, filtered, washed with water and recrystallized from water to afford the title compound as yellow needles. Yield: 1.88 g (44%), mp: 149–50°C, ^{1}HNMR, δ ($CDCl_3$) 2.65 (s, 3H, Me), 2.67 (s, 3H, Me), 5.86 (s, 2H, NH_2), IR, $\tilde{\nu}$ (KBr disc): 3550, 3450, 1600, 1480, 1350 cm^{-1}, Ms, m/z, M^+188(2.5), 187(27), 185(87), 170(37), 88(75), 70(100), 69(52), 59(50), 46(80), 41(73).

4-Amino-6-methyl-1,2,4-triazin-5-thion-3-one 3

Compound **2** (1.88 g, 10 mmol) was refluxed in 10% hydrochloric acid for 2 hrs. The solution was cooled to room temperature and the precipitated solid was filtered off, washed with water and crystallized from methanol to afford the title compound as yellow needles.

Yield: 1.18 g (75%), mp: 213–4°C, IR, $\tilde{\nu}$ (KBr disc): 3400, 3200, 1710, 1590, 1400, 1310, 750, 710 cm^{-1}, Ms, m/z, M^+ 158(1), 157(6.1) 155(32), 100(20), 86(100), 74(44), 44(20.7).

4-Amino-6-methyl-5-propargylthio-1,2,4-triazin-3-one 4

Compound **3** (0.47 g, 3 mmol) was dissolved in a solution of methanol (15 mL) and triethylamine (1 mL). To this solution, propargyl bromide (0.5 mL, excess) was added at room temperature. The reaction mixture was refluxed for 6 hrs. The solvent was removed under reduced pressure and the residue was directly subjected to column chromatography using silica gel and $CHCl_3$ as eluent to afford the title compound as colorless crystals. Yield: 0.4 g (68%), mp: 95–6°C, ^{1}HNMR, δ ($CDCl_3$) 2.3 (t, J=1.8 Hz, 1 H, -C≡CH), 2.4 (s, 3H, Me), 4.7 (d, J=1.8 Hz, 2H, CH_2) IR, $\tilde{\nu}$ (KBr disc): 3500, 3400, 1700, 1580, 1400, 1210 cm^{-1}, Ms, m/z, M^+ 196(8), 195(20), 194(100), 165(4), 84(37), 44(77), 45(47).

Treatment of 4 with sulfuric acid

Compound **4** (0.2 g, 2 mmol) was dissolved in conc. sulfuric acid (3 mL) and left at room temperature for 3 hrs and then poured into ice-water. The

solution was neutralized with 20% ammonium hydroxide solution and extracted with $CHCl_3$. The solvent was evaporated to dryness and the crude product was subjected to column chromatography using $CHCl_3$-MeOH, 95:5 to give a pure compound. This product was identified as 4-amino-6-methyl-5-acetonylthio-1,2,4-triazin-3 (4H)-one **5**. Yield: (63%), mp: 145–6°C, ^{1}HNMR, δ ($CDCl_3$) 2.29 (s, 3H, Me), 2.45 (s, 3H, Me), 4.8 (s, 2H, CH_2), IR, $\tilde{\nu}$ (KBr disc): 3550, 3200, 1700, 1580, 1520, 1400, 1210, 1180, 990 cm^{-1}, Ms, m/z, M^+ 214(1.2), 213(3), 211(56), 163(30), 162(48), 69(66), 43(100), 41(38)

3,9-Dimethyl-4H, 6H[1,2,4]-triazino[5,4-b] 1,3,4-thiadiazin-6-one 7

Compound **5** (214 mg, 1 mmol) was dissolved in a solution of sodium carbonate (0.1 g in water 5 mL) and the reaction mixture was refluxed for 1 hr. After cooling the solution was neutralized by the addition of 2N hydrochloric acid and extracted with $CHCl_3$. The solvent was evaporated to dryness and the residue was directly subjected to column chromatography using $CHCl_3$:MeOH 95:5 as eluent to obtain the pure product. Yield: 95 mg (48%), mp: 210–11°C, ^{1}HNMR, δ ($CDCl_3$) 2.3 (s, 3H, Me), 2.35 (s, 3H, Me), 4.8 (s, 1H, CH), 5.2 (s, H, NH, exchangeable with D_2O), IR, $\tilde{\nu}$ (KBr disc): 3450, 1680, 1580, 1410 cm^{-1}, Ms, m/z, M^+196(4), 154(12), 153(27), 95(20.6), 69(100), 43(62).

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