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Research Note

SYNTHETIC STUDIES IN THE 6H-[1,2,4] TRIAZINO [3,4-*b*] [1,3,4] THIADIAZINES

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Abstract

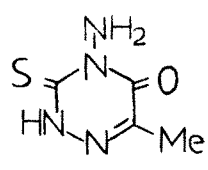
4-Amino-6-methyl-1,2,4-triazine-3(2H)-thione-5-one (**1**) was condensed with propargyl bromide in the presence of sodium methoxide to afford 3-propargylmercapto-4-amino-6-methyl-1,2,4-triazin-5-one (**2**). Transformation of the latter to 8-dihydro-3-methyl-7-methylene-4-oxo-6H-[1,2,4] triazino [3,4-*b*] [1,3,4] thiadiazine (**3**) was performed under the condition of palladium (II) salt. Ring closure of (**1**) with phenacyl bromide provides the 3-methyl-7-phenyl-4-oxo-6H-[1,2,4]triazino[3,4-*b*] [1,3,4] thiadiazine.

An examination of numerous antitumor agents from both natural and synthetic sources suggests that a common chemical structural pattern of 2-phenyl naphthalene type ring system is necessary for designing a compound of this type. The 2-phenylnaphthalene type ring system could either be carbocyclic or heterocyclic with nitrogen, oxygen and/or sulfur atoms placed at selected positions [1]. *as*-Triazine-3,5-dione(6-azauracil) has proved to possess a broad spectrum of therapeutical effects which include antiviral [2,3], antitumor [4,5] and antifungal activities [6]. Synthesis of [1,2,4]triazino [1,2,4] triazines [7] which provides few examples of condensed *as*-triazines belonging to the antitumor 2-phenylnaphthalene type, has already been reported. Now we wish to report the synthesis of the heterocyclic system, 6H-[1,2,4]triazino[3,4-*b*][1,3,4] thiadiazine which provides another example of condensed *as*-triazine belonging to the 2-phenylnaphthalene type ring system.

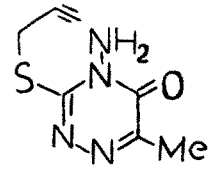
4-Amino-6-methyl-1,2,4-triazin-3(2H)-thione-5-one [8] was condensed with propargyl bromide in the presence of sodium methoxide to afford the corresponding 3-propargylmercapto derivative (**2**). Transformation of **2** to **3** could not be undertaken in either aprotic or protic solvents at their refluxing temperature.

Keywords: Antitumor agents; 2-Phenylnaphthalene; [1,3,4] thiadiazine; [1,2,4] triazino

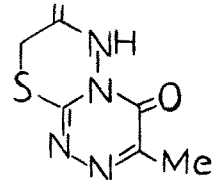
We have recently described the use of Pd-salt for implementation of sequential carbometalation anion capture [9-11] and catalyzed intramolecular cyclization and functionalization of acetylenes [12]. Armed with these experiences, compound (**2**) was refluxed with a catalytic amount of $PdCl_2(PhCN)_2$ [13] in acetonitrile for 6 hrs. After evaporation of solvent, the crude was directly subjected to column chromatography to obtain a crystalline compound as a major product. Most probably Pd-catalyzed cyclization of (**2**) to (**3**) proceeds via a direct attack of $-NH_2$ to acetylenic bond activated by coordination of palladium (II).



(1)



(2)



(3)

4-Amino-6-methyl-1,2,4-triazine-3(2H)-thione-5-one (**1**) was reacted with phenacyl bromide in the presence of sodium carbonate to give a single crystalline product. Mass spectrum showed that condensation and cyclization had occurred. Depending on the mode of dehydration of (**4**), two tautomers are possible i.e. 3-methyl-7-phenyl-4-oxo-6H-[1,2,4] triazino[3,4-*b*] [1,3,4] thiadiazine (**5**) and 8-dihydro-3-methyl-7-phenyl-4-oxo[1,2,4]triazino[3,4-*b*][1,3,4] thiadiazine (**6**). (Scheme 1).

It has been reported that reaction of 2,5,6-triazino-4-mercaptopyrimidine with α-halogenoketones afforded substituted 7H-pyrimido [4,5-*b*][1,4] thiazines [14]. Synthesis of 2-amino-4(3H)-one-6-phenylpyrimido[4,5,b][1,4]thiazine from 2,5-diamino-6--mercaptopyrimidone and phenacyl bromide has also been claimed [15, 16]. Formation of these compounds are reminiscent of the formation of (**6**). Faced with a similar situation we could have come to the same conclusion, that is that the dehydration product was (**6**) (pathway b, scheme 1). However, after careful examination of ^{1}H NMR spectrum it became apparent that only **5** (pathway a) is in accord with the data. The proton NMR spectra of the dehydration product showed a vinyl signal at δ 4.65 ppm and there was no evidence for allylic protons.

Experimental Section

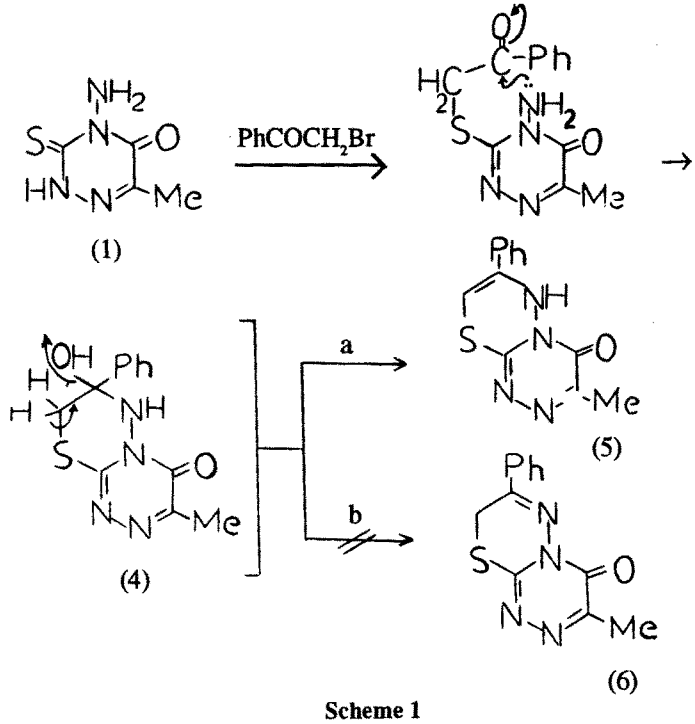
The melting points are uncorrected and were obtained by a Kofler Hazbank Richert type 7841 melting point apparatus. IR spectra were obtained on a 4300 Schimadzu spectrometer. The ^{1}H NMR spectra were recorded on a Varian 50A spectrometer using TMS as internal reference and mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Propargyl bromide and phenacyl bromide were purchased from Aldrich.

4-Amino-3-propargylmercapto-6-methyl-1,2,4-triazin-5-one(2)

Sodium (0.2 g, 0.009 mol) was dissolved in MeOH (20 ml). Compound **1** was dissolved in this solution. To this stirred solution, propargyl bromide (0.9 ml) (excess) was added dropwise. The reaction mixture was stirred for 2 hrs. The solid was filtered off, washed with water and crystallized from MeOH. Yield 0.8 g, m.p. 189°C, ^{1}H NMR, δ (d_6-DMSO) 2.2 (s, 3H, Me), 3 (t, 1H, CH), 3.8 (d, 2H, CH_2), 5.8 (s, 2H, NH_2, exchanged with D_2O). M+, m/e 196, (rel. intensity) 196 (8), 195 (16), 194 (20), 193 (100). IR (KBr disk) $\bar{\nu}$ 3300, 1680, 1600 cm^{-1}.

8-Dihydro-3-methyl-7-methylene-4-oxo-6H-[1,2,4] triazino[3,4-*b*][1,3,4] thiadiazine(3)

Compound **2** (0.4 g; 0.002 mol) was refluxed in acetonitrile (25 ml) containing $PdCl_2(PhCN)_2$ (0.01 g) for 4 hrs. After evaporation of solvent, the crude was directly subjected to column chromatography. Elution with 95:5, $CHCl_3$: MeOH afforded the title compound as a major product. Yield 0.16 g; 40% m.p. 192°C, ^{1}H NMR δ (d_6-DMSO) 2.2 (s, 3H, Me), 3.5 (s, 2H, CH_2), 5.55 (d, 1H), 5.85 (d, 1H), 6.8 (s, 1H, NH, exchanged with D_2O). M+, m/



Scheme 1

e 196, (rel. intensity), 196 (1), 195 (5), 193 (100). IR (KBr disk) $\bar{\nu}$ 3193, 1687, 1610, 1479, 1240 cm^{-1}.

3-Methyl-7-phenyl-4-oxo-6H-[1,2,4]triazino[3,4-*b*][1,3,4]thiadiazine (5)

Compound **1** (0.8 g; 0.005 mol) was dissolved in a solution of sodium carbonate [sodium carbonate (0.5 g) in water (25 ml)]. To this solution, phenacyl bromide (0.99 g; 0.005 mol) in ethanol (20 ml) was added dropwise. The reaction mixture was stirred at room temperature for 2 hrs. The solid was filtered off and crystallized from water to afford the title compound. Yield 0.7 g; 53%, m.p. 215°C, ^{1}H NMR, δ (d_6-DMSO) 2.2 (s, 3H, Me), 4.65 (s, 1H, vinyl CH), 5.8 (s, 1H, NH, exchanged with D_2O), 7.5-7.8 (m, 5H, Ph). M+, m/e for $C_{12}H_{10}N_4OS$, 258 (rel. intensity), 258 (37), 255 (37), 225 (21), 222 (21), 172 (12), 155 (29), 144 (100), 132 (82). IR (KBr disk) $\bar{\nu}$ 3195, 1687, 1541, 1479, 1344, 1078, 966 cm^{-1}.

Acknowledgements

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