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CONDENSED THIADIAZINES: SYNTHESIS OF [1,2,4]TRIAZINO[3,4-B] [1,3,4]THIADIAZINES

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A [1,2,4]triazino [3,4-b]thiadiazine was prepared by cyclization of 4-amino-3-phenacylmercapto [1,2,4] triazin-5-one **2** in the presence of solid acid *via* an unusual pathway.

Keywords: Thiadiazines; triazine; solid acid; cyclocondensation; phenacyl bromide

INTRODUCTION

A pharmacological test of a variety of antitumor agents from both natural origin and synthetic routes showed that a common chemical structural pattern of the 2-phenylnaphthalene type ring system is necessary for compounds having this type of activity. The 2-phenylnaphthalene type ring systems could be carbocylic or heterocyclic with nitrogen, oxygen or sulfur atoms placed at selected positions[1]. Bicyclic compounds derived from 1,2,4-triazines have shown a broad spectrum of pharmacological activities, which include antimicrobial[2], antitumor[3], antifungal[4] and antiviral[5] activities.

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In view of possible therapeutic effects of new naphthalene analogues, a series of [1,2,4] triazino[3,4-b][1,3,4]thiadiazines have been synthetized.

RESULTS AND DISCUSSION

Cyclocondensation of 4-amino-6-methyl-3-mercapto-1,2,4-triazin-5-one **1** with α-haloketones constitute an ideal approach to the synthesis of the fused [1,2,4] triazino [3,4-b][1,3,4]thiadiazine system.

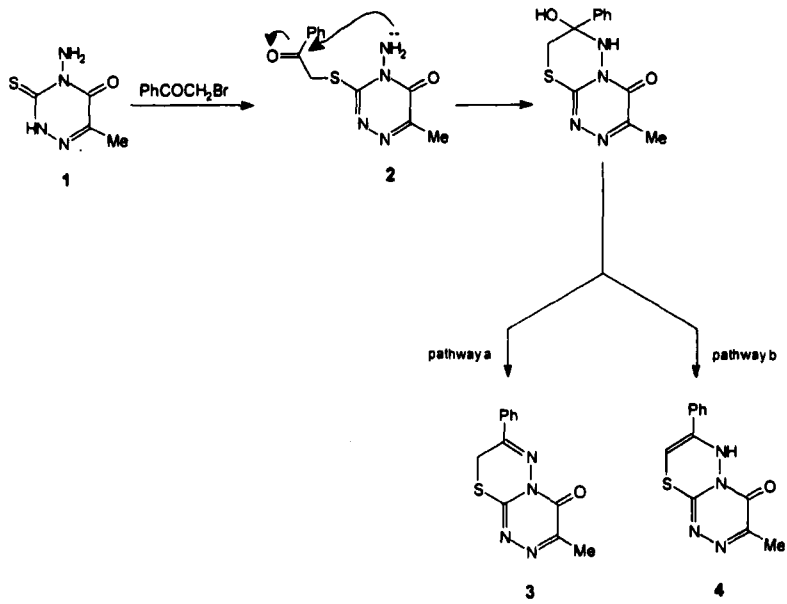
4-Amino-6-methyl-3-mercapto-1,2,4-triazin-5-one[6] **1** was reacted with phenacyl bromide in the presence of triethylamine. The ^{1}HNMR of this compound showed two exchangeable protons at δ 6.03 assigned to the amino group. This data showed that the reaction has proceeded to give the phenacylmercapto derivative **2**. We have recently reported the use of solid acids as a dehydrating agent for heterocyclization[7]. Armed with these experiences compound **2** was refluxed in EtOH in the presence of sulfuric acid supported onto silica gel[8]. The IR spectrum of the product showed no absorption for the carbonyl group indicating that cyclisation has occurred. Depending on the mode of dehydration of the intermediate **3** two tautomers are possible i.e. 8-dihydro-3-methyl-7-phenyl-4-one [1,2,4]triazino [3,4-b][1,3,4] thiadiazine **3** and 3-methyl-7-phenyl-4-oxo-6H-[1,2,4]triazino[3,4-b][1,3,4] thiadiazine **4** (Scheme 1)

According to Tzeng et al.[9] reaction of 5-mercapto-6-amino-1,2,4-triazin-3-one with α-haloketones gave substituted 8H-[1,4] thiazino[2,3-e][1,2,4] triazin-3(2H)-one **5** and not 6H-[1,4]thiazino[2,3-e][1,2,4] triazin-3(2H)-one **6**, (Scheme 2).

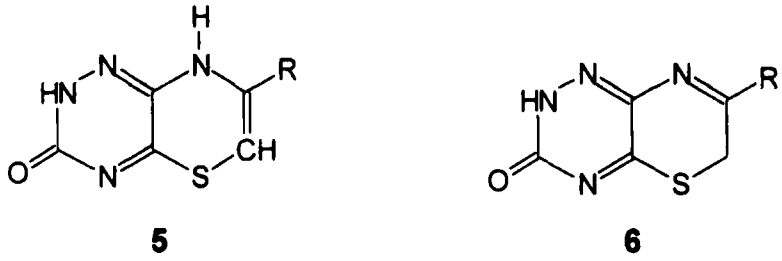
One pot cyclocondensation of **1** with phenacyl bromide in the presence of base has also given a compound which was identified as **4**[10]. Faced with a similar situation we expected that the dehydration product was **4** (pathway b, Scheme **1**). However with careful examination of ^{1}HNMR spectrum it became clear that the data can only be assigned for structure **3**. The proton NMR spectra showed an allyl signal at δ 4.4 and no signal for a vinyl proton.

EXPERIMENTAL SECTION

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



SCHEME 1



SCHEME 2

spectra were recorded on a Bruker (100 MHz) instrument. Mass spectra were obtained from Varian CH-7 at 70 eV. Sulfuric acid supported onto silica gel was prepared according to the reported procedure[8].

4-amino-3-phenacylmercapto [1,2,4] triazin-5-one 2

4-Amino-6-methyl-1,2,4-triazine-3-thion-5-one **1** (316 mg, 2 mmol) was dissolved in acetonitrile (10 mL) containing triethylamine (0.2 mg). To this solution phenacyl bromide (400 mg, 2 mmol) in acetonitrile (2 mL) was added. The reaction mixture was stirred at room temperature for 2 hrs. During this time a solid gradually began to percipitate. This solid was filtered off, washed with acetonitrile and crystallized from acetonitrile to afford the title compound. Yield: 0.4 g (72.5%), mp. 185°C, ^{1}HNMR δ (d_6-DMSO), 2.25(s, 3H, CH_3), 4.74(s, 2H, CH_2), 6.03(s, 2H, NH_2, exchangeable with D_2O), 7.8(m, 3H, Protons of phenyl group), 8.1(m, 2H, protons of phenyl group). IR, (KBr disc): 3150, 3100, 1700, 1620, 1480, 1210, 980 cm^{-1}, Ms, m/z, M^+ 276(2.2), 273(17.7), 239(17.7), 136(12.2), 104(100), 91(32), 79(78.8), 75(54.2).

8-dihydro-3-methyl-7-phenyl-4-one [1,2,4]triazino [3,4-b][1,3,4] thiadiazine 3

Compound **2** (138 mg, 0.5 mmol) was dissolved in hot absolute ethanol (5 mL). Solid acid (sulfuric acid supported on silica gel (15 mL) was added. This mixture was refluxed for 15 hrs. The hot solution is then filtered and allowed to stand at room temperature. The resulting solid was filtered and crystallized from ethanol to afford the title compound. Yield: 84 mg (65%), mp. 211°C, ^{1}HNMR δ (d_6-DMSO), 2.3(s, 3H, CH_3), 4.34(s, 2H, CH_2), 7.58–7.98(m, 5H, Ph). IR, (KBr disc): 1690, 1600, 1480, 1380, 1290, 790, 770, 700 cm^{-1}, Ms, m/z, M^+ 258(3.2), 256(44), 255(88), 226(51.6), 130(22), 120(51.6), 105(100), 101(79), 51(73), 29(47.2).

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