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DEUTERIUM STUDIES IN THE CYCLIZATION AND ISOMERIZATION OF 3-PROPARGYLMERCAPTO-1,2,4-TRIAZINES TO THIAZOLO[3,2-b]-[1,2,4] TRIAZINES

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Transformation of 3-propargylmercapto-1,2,4-triazin-5(2H)-one (**2**; R=H or Me) to the corresponding 2-dihydro-3-methylenethiazolo[3,2-b][1,2,4]triazin-7-one (**3**; R=H or Me) is performed in a dilute solution of triethylamine in MeOH. Compound (3; R=Me) was isomerized to 3,6-dimethyl-thiazolo[3,2-b][1,2,4]-triazin-5-one (**4**; R=Me) in 5% aqueous sodium hydroxide. Treatment of (**3**; R=Me) with 5% sodium deuteroxide gave 6-methyl-3-monodeuterated methyl-2-D-thiazolo[3,2-b][1,2,4]-triazin-7-one (**5**, R=Me).

Keywords: Deuterium studies; cyclization; Propargylmercapto-triazines; Thiazolo-triazines

INTRODUCTION

Synthesis of a variety of bicyclic compounds derived from 1,2,4-triazin has been reported from our laboratory.[1-6] In continuation of our interest in this field, we now wish to report the base catalyzed cyclization and isomerization of 3-propargyl-mercapto-1,2,4-triazin-5-one (**2**; R=H or Me) to (**3**; R=H or Me) and (**4**; R=Me) respectively. To prove the suggested mechanism, deuterium studies have been implemented. Due to the wide

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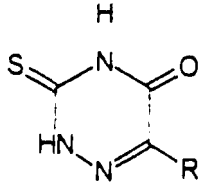
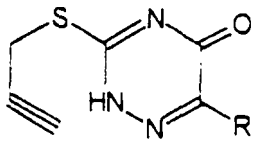
ranging physiological activities of bicyclic compounds derived from 1,2,4-triazine, this attempt was thought to be worthwhile.

1,2,4-Triazin-3(2H)-thion-5(4H)-one (**1**; R=H or Me)[7] was condensed with propargylbromide in presence of sodium methoxide to afford the corresponding 3-propargylmercapto-1,2,4-triazin-5(2H)-one (**2**; R=H or Me). When (**2**; R=Me) was refluxed in aqueous sodium hydroxide for 4 hrs, a solid was isolated, that was crystallized from ethanol to give a single white crystalline compound. The compound was identified as 3,6-dimethyl-7H-thiazolo [3,2-b][1,2,4]- triazin-7-one (**4**; R=Me).

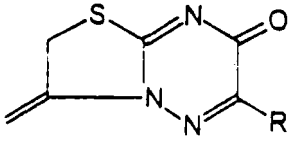
This compound has already been synthesized through the reaction of (**1**; R=Me) with bromoacetone in the presence of sodium carbonate and subsequent dehydration of the hydroxy compound (**6**).



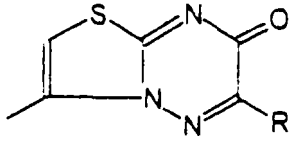
(**1**)



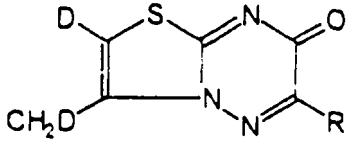
(**2**)



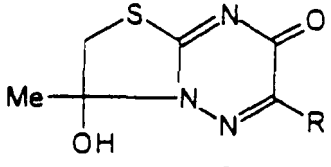
(**3**)



(**4**)

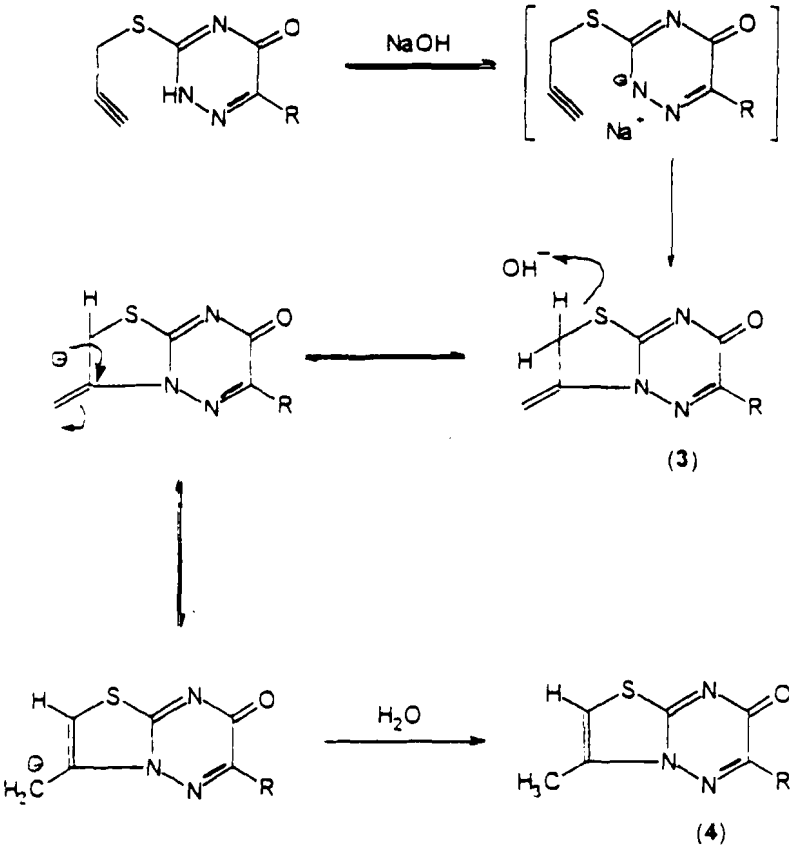


(**5**)



(**6**)

By elucidation of the structure, it can be assumed that the base abstracts a hydrogen from the nitrogen 2 of (**2**). The nitrogen then attacks the acetylenic group to give the cyclized intermediate (**3**; R=Me). Isomerization and aromatization of the intermediate produces compound (**4**; R=Me) (Scheme 1).



SCHEME 1

For isolation of (**3**; R=H and Me) time and concentration of the base were decreased but it could not be isolated. Compound (**3**; R=H and Me) was obtained when triethylamine in ethanol was used as a base and stopped at an appropriate conversion. Exclusive cyclization on the N-2

atom is remeniscent of the alkylation of 3-methylmercapto-1,2,4-triazin-5(2H)-ones with alkyl halides under basic condition.[8] The assignment of Structure (**3**; R=H and Me) was based on their physical and spectral data. The exo methylene protons in (**3**) seperated by 0.5 ppm and appeared as two doublets. When (**3**; R=Me) was refluxed in 5% aqueous sodium hydroxide compound (**4**; R=Me) was quantitatively obtained.

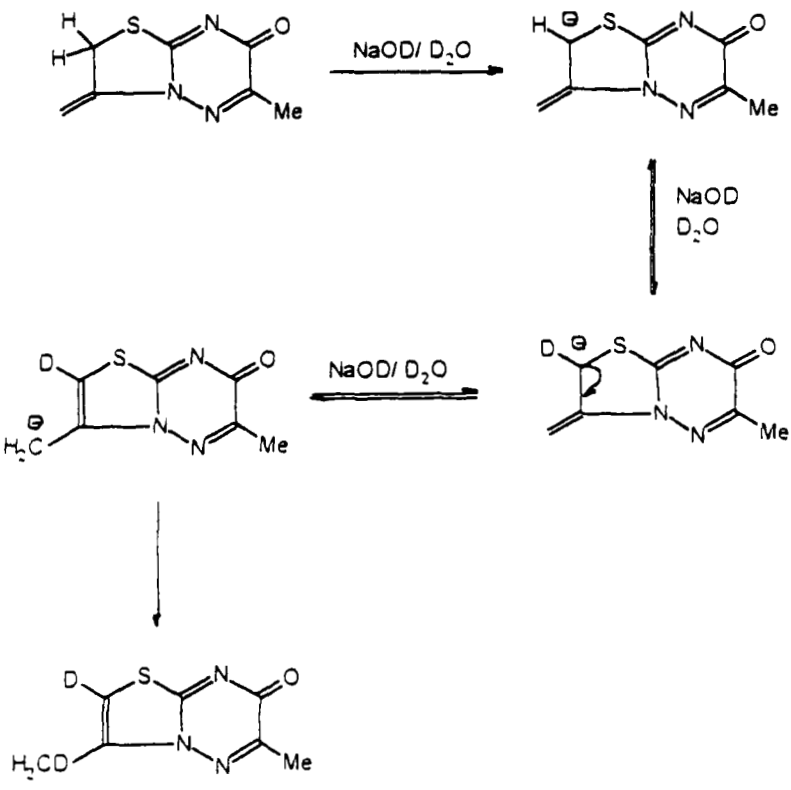
To establish the mechanisms deuterium studies were contemplated. Compound (**3**; R=Me) was refluxed in 5% sodium deuteroxide in D_2O. The isolated product showed m/e at 183 corresponding to exchange of two ^1H with ^2H. In the ^1H nmr of this compound the two exo methylene signals and a signal at δ 4.1 for CH_2 in the five membered heterocycle disappeared and there was no sign for any aromatic proton. Based on these spectroscopic data we could assign structure (**5**; R=Me) for the obtained compound. The suggested mechanism is as follows (Scheme 2).

EXPERIMENTAL

The melting points are uncorrected and were obtained by a Kofler Heizbank Richert type 7841, melting point apparatus. Ir spectra were obtained on a Pye Unicam SP 1100 and 4300 Shimatzu spectrometer. The ^1H nmr spectra were recorded on a Varian 50 A Spectrometer using TMS as internal reference and mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV.

3-Propargylmercapto-1,2,4-triazin-5(2H)-one (2; R=H)

Sodium (1 g) was dissolved in MeOH (100 mL). To this solution, the compound (**1**; R=H) (4.5 g, 0.035 mol) was added. To this mixture propargylbromide (4.65 mL, of 80% solution in toluene) was added dropwise at room temperature. The reaction mixture was stirred for 4 hrs at ambient temperature. The solid was filtered, washed with water and crystallized from methanol to afford the title compound. Yield: 2.2 g (38%), mp.: 171 °C (from methanol). ^1H nmr δ (d6-DMSO), 3.1 (s, 1H, CH), 3.9 (s, 2H, CH2), 7.5 (s, 1H, H of triazine ring). M+. m/e: 167 (rel. intensity), 167 (2), 164 (18), 137 (13), 110 (38), 106 (100), 82 (20), 78 (23), 68 (41), 67 (90). IR (KBr disc, cm^{-1}) 3230, 2150, 1620, 1425, 1365.



SCHEME 2

6-Methyl-3-propargylmercapto-1,2,4-triazin-5(2H)-one (2; R=Me)

Sodium (1 g) was dissolved in MeOH (100 mL). To this solution, the compound (**1**; R=Me) (5 g, 0.035 mol) was added. To this mixture propargylbromide (4.65 mL, of 80% solution in toluene) was added dropwise at room temperature. The reaction mixture was stirred for 4 hrs at ambient temperature. The solid was filtered, washed with water and crystallized from methanol to afford the title compound. Yield: 5.5 g (87%), mp.: 180–1°C (from ethanol). ^{1}H nmr δ (d6-DMSO), 2 (s, 3H, Me), 3.1 (s, 1H, CH), 3.9 (s, 2H, CH_2). M+. m/e: 181 (rel. intensity), 181 (M+, 100), 151 (4), 141 (3), 140 (25), 75 (8), 71 (8), 71 (6). IR (KBr disc, cm^{-1}) 3456, 2262, 1625, 1512, 1465, 1361, 1271.

3,6-Dimethyl-7H-thiazolo[3,2-b][1,2,4]-triazin-7-one (4; R=Me)

Compound (**2**; R=Me) (1 g, 0.0055 mol) was added to a 5% sodium hydroxide solution (20 mL) and the reaction mixture was refluxed for 4 hrs. The solution was cooled to room temperature and the solid was filtered, washed with water and crystallized from MeOH. Yield: 0.7 g (70%), mp.: 226°C. ^{1}H nmr δ ($CDCl_3$); 2.2 (s, 1H, 2Me), 6.5 (s, 1H, CH). M+ m/e 181 (rel. intensity) 181 (2), 174(36), 178 (73), 150 (9), 137 (100), 106 (9), 68 (40), 67 (40), 43 (9).

2-Dihydro-3-methylene-thiazolo-[3,2-b][1,2,4]-triazin-7-one (3; R=H)

Compound (**2**; R=H) (1.67 g, 0.001 mol) was dissolved in a mixture of NaOH (0.2 g) in MeOH (100 mL). The reaction mixture was refluxed for 4 hrs. The solvent was evaporated and the crude was directly subjected to column chromatography on silicagel using $CHCl_3$:MeOH, 90:10 as eluent. Yield: 0.6 g (32%), mp. 154–5 °C. ^{1}H nmr δ ($CDCl_3$): 4.2 (s, 2H, CH_2), 4.9 (d, 1H, exo methylene), 5.5 (d, 1H, exo methylene), 7.5 (s, 1H, H of triazine ring). M+; m/e (rel. intensity): 167 (8), 165 (100), 142 (90), *127* (24), 72 (92), 71 (56), 67 (40). IR (KBr disc, cm^{-1}): 1650, 1470, 1370

2-Dihydro-3-methylene-6-methyl-thiazolo-[3,2-b][1,2,4]-triazin-7-one (3; R=Me)

Compound (**2**; R=Me) (5 g, 0.027 mol) was dissolved in a mixture of triethylamine (50 mL) and ethanol (250 mL). The reaction mixture was refluxed for 2 hrs. The solvent was evaporated and the crude was directly subjected to column chromatography on silicagel, a mixture of $CHCl_3$:MeOH 90:10 was used as an eluent.

Yield: 2.9 g (58%). Mp. 193°C, ^{1}H nmr δ ($CDCl_3$) 2.2 (s, 3H, Me), 4.1 (s, 2H, CH_2), 4.8 (d, 1H, exo methylene), 5.5 (d, 1H, exo methylene). M+ m/e (rel. Intensity) 181 (5), 179 (5), 178 (50), 137 (64), 68 (100), 67 (36). IR (KBr disc, cm^{-1}): 2260, 1620, 1460, 1340.

6-Methyl-3-monodeuterated methyl-2D-thiazolo[3,2-b][1,2,4]-triazin-5-one (5; R=Me)

Compound (**3**; R=Me) (0.25 g, 0.0013 mol) was dissolved in 5% sodium deuteroxide in D_2O (10 mL). The reaction mixture was refluxed for 2 hrs

and chilled in an ice bath. The precipitated solid was filtered and washed with water to afford the title compound. Yield: 0.15 g (60%). Mp: 224 °C. ^{1}H nmr δ ($CDCl_3$) 2.2 (s, 3H, Me), 2.3 (s, 2H, CH_2D). M+ m/e 183.

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