Heteropoly Acid Catalyzed Selective Cyclization of 6-Alkyl-3-propargylmercapto-1,2,4-triazin-5(2*H*)-one

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Abstract: Cyclization of 6-alkyl-3-propargylmercapto-1,2,4-triazin-5(2*H*)-one, derivatives (**2**) in the presence of Keggin heteropoly acids, $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, $H_4SiW_{12}O_{40}$ and lacunary Keggin structure ($K_7PMo_2W_9O_{40}$) afforded **3** (**3a** = 6-dimethyl-7*H*-thiazolo[2,3-*b*][1,2,4]-triazin-7-one and **3b**=6-ethyl-3-methyl-7*H*-thiazolo[2,3-*b*][1,2,4]-triazin-7-one) in high yields and short reaction times

Keywords: Heterocyclization, Thiazolotriazine, Heteropolyacids, 1,2,4-Triazines

Introduction

Thiones of nitrogen-containing heterocycles have excited the attention of researchers because of their synthetic possibilities and useful properties. Many compounds containing sulfur and nitrogen atoms are anti-inflammatory¹, sedative², antibacterial^{3,4}, antiviral^{5,6} or antitumor^{7,8}. Synthesis of the corresponding heterocyclic compounds could be of interest from the viewpoint of chemical reactivity and biological activity. Heteropoly acids are widely used in variety of acid catalyzed reactions⁹⁻¹⁴. Heteropoly acids as solid acid catalysts are green with respect to corrosiveness, safety, quantity of waste and separability and it is well known that the use of heteropoly acid catalysts for organic synthesis reactions can give a lot of benefits. One of the unique features that make solid heteropoly acids economically and environmentally attractive is their stability and bronsted acidity. Because of interesting importance of nitrogen-sulfur containing heterocycles and in continuation of our interest in application of heteropoly acids in organic synthesis¹⁵⁻¹⁸, in this article we wish to report our results for the selective heterocyclization of 6-alkyl-3-propargyl-mercapto-1,2,4-triazin-5(2*H*)-one (**2**) using different keggins type heteropoly acid catalysts in various conditions. The effects of various parameters such as amount of catalysts, solvent and time were studied.

Experimental

All solvents were purchased from commercial sources. Polyoxometalates were prepared according to literature procedures¹⁹. 3,4-Dihydro-6-methyl-3-thioxo-1,2,4-triazin-5(2*H*)-one (**1a**) and 3,4-dihydro-6-ethyl-3-thioxo-1,2,4-triazin-5(2*H*)-one (**1b**) were prepared in accordance with literature procedure²⁰ (2-oxobutyric acid was used instead of pyruvic acid to prepare **1b**). The IR spectra were recorded on a Shimadzu spectrometer 883 (KBr pellets, Nujol mulls, 4000-400 cm⁻¹). ¹H and ¹³C NMR spectra were recorded on a Bruker-Advance DRX 400 spectrometer using TMS as an external standard. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer.

Synthesis of 6-alkyl-3-propargyl-mercapto-1,2,4-triazin-5(2H)-one (2)

Sodium 0.046 g (2 mmol) was dissolved in ethanol (30 mL). A mixture of 3,4-dihydro-6-alkyl-3-thioxo-1,2,4-triazin-5(2*H*)-one (**1**) (2 mmol) and propargyl bromide (2 mmol) was added to a magnetically stirred solution of sodium (0.046 g, 2 mmol) in ethanol (30 mL). The reaction mixture was stirred for further 2 h. The solid residue was filtered, washed with cold ethanol to afford pale yellow crystals **2a** and **2b**.

Selected physical data

6-Methyl-3-propargyl-mercapto-1,2,4-triazin-5(2H)-one (2a)

M.p. 184-196 °C; IR (KBr), $\nu(\text{cm}^{-1})$: NH 3415, CO 1645, CN (triazine) 1586; ¹H NMR (CDCl₃), δ : 2.08 (s, 3H, CH₃), 3.19 (s, 1H, CH $\equiv$ C), 3.94 (s, 2H, CH₂), 13.90 (br, 1H, NH); ¹³C NMR (DMSO), δ : 17.18 (1, CH₃), 29.17 (1, CH₂), 95.27 (1, CH $\equiv$), 105.65 (1, C $\equiv$), 151.05, 160.82, (2, C triazine ring), 168.27 (1, C=O); Anal. calcd. for C₇H₇N₃OS: C, 46.41; H, 3.87; N, 23.20. Found: C, 46.38; H, 3.80; N, 23.27.

6-Ethyl-3-propargyl-mercapto-1,2,4-triazin-5(2H)-one (2b)

M.p. 158-160 °C; IR (KBr), $\nu(\text{cm}^{-1})$: NH 3434, CO 1665, CN (triazine) 1584; ¹H NMR (CDCl₃), δ : 1.15 (t, 3H, CH₃), 2.63 (q, 2H, CH₂), 3.95 (s, 1H, CH $\equiv$ C), 4.10 (s, 2H, CH₂), 10.390 (br, 1H, NH); ¹³C NMR (DMSO), δ : 10.65 (1, CH₃), 24.5 (1, CH₂), 29.17 (1, CH₂), 95.00 (1, CH $\equiv$), 104.65 (1, C $\equiv$), 151.05, 160.82, (2, C triazine ring), 168.27 (1, C=O); Anal. calcd. for C₈H₉N₃OS: C, 49.23; H, 4.61; N, 21.54. Found: C, 49.18; H, 4.52; N, 21.57.

Synthesis of 3, 6-dimethyl-7H- thiazolo [2,3-b][1,2,4]- triazin-7-one (3a) and 6-ethyl- 3-methyl-7H- thiazolo [2,3-b][1,2,4]- triazin-7-one (3b)

In a round-bottomed flask, equipped with a thermometer and reflux condenser, compound **2** (1 mmol), was heated with stirring with appropriate heteropoly acid (0.04 mmol) and solvent (15 mL) for the indicated time at reflux temperature (boiling point of solvents). The progress of the reaction was monitored by TLC using hexane/ethyl acetate (1/2) as eluent. After completion of the reaction, the catalyst was filtered and the solvent evaporated under reduced pressure. The pure product **3** was obtained in high to excellent yields (Table 1).

Selected physical and spectroscopic data

3, 6-Dimethyl-7H- thiazolo [2,3-b][1,2,4]- triazin-7-one (3a)

Pale yellow solid, m.p. 224-226 °C; IR (KBr), $\nu(\text{cm}^{-1})$: CO 1631, CN (triazine) 1583, 1490, 1367, 1248, 798, 766, 639; ¹H NMR (DMSO), δ : 2.27 (s, 3H, CH₃), 2.34 (s, 3H, CH₃), 7.05 (s, 1H, S-CH); ¹³C NMR (DMSO), δ : 13.18, 18.17 (2, CH₃), 104.00 (1, CH), 153.04, 159.51, (2, C triazine ring), 168.32 (1, C=O); Anal. calcd. for C₇H₇N₃OS: C, 46.41; H, 3.87; N, 23.20. Found: C, 46.35; H, 3.86; N, 23.18.

6-Ethyl- 3-methyl-7H- thiazolo [2,3-b][1,2,4]- triazin-7-one (3b)

Pale yellow solid, m.p. 214-216 °C; IR (KBr), $\nu(\text{cm}^{-1})$: CO 1636, CN (triazine) 1587, 766,639; ^1H NMR (DMSO), δ : 1.14 (t, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.70 (q, 2H, CH_2), 6.95 (s, 1H, S-CH); ^{13}C NMR (DMSO), δ : 10.65 (1, CH_3), 20.5 (1, CH_3), 24.17 (1, CH_2), 100.00 (1, CH), 153.04, 159.51, (2, C triazine ring), 168.32 (1, C=O); Anal. calcd. for $\text{C}_8\text{H}_9\text{N}_3\text{OS}$: C, 49.23; H, 4.61; N, 21.54. Found: C, 49.14; H, 4.32; N, 21.48.

Results and Discussion

Compound **1** is well known heterocyclic thiones derived from thiosemicarbazide and it exists in two thione and thiol tautomeric forms.

1
1a: R=Me
1b: R=Et

Condensation reaction of **1** with propargyl bromide (equation 1) in the presence of sodium ethoxide led to corresponding 6-alkyl-3-propargyl-mercapto-1,2,4-triazin-5(2H)-one (**2**)²¹. Cyclization of **2** could not be undertaken in either aprotic or protic solvents at their refluxing temperature. We recently have described the use of sulfuric acid for cyclization of **2a**. Compound **2a** had been heated in warm sulfuric acid to give compound **3a**. Herein, we wish to report the use of keggin type heteropoly acids (HPA) for intermolecular cyclization of 6-alkyl-3-propargyl-mercapto-1,2,4-triazin-5(2H)-one (**2**). Compound **2** was refluxed in acetic acid with catalytic amounts of HPA to afford a single (TLC) compound. Heteropoly acids are separated by filtration and the products were purified by recrystallization from ethanol. The yields are shown in Table 1.

Table 1. Keggin heteropoly acids catalyzed heterocyclization of **2** (in CH_3COOH)

Amount of % mol/mol	Reaction time, min	Yield, % using $\text{H}_3\text{PW}_{12}\text{O}_{40}$		Yield, % using $\text{H}_3\text{PMo}_{12}\text{O}_{40}$		Yield, % using $\text{H}_4\text{SiW}_{12}\text{O}_{40}$		Yield, % using $\text{K}_7\text{PMo}_2\text{W}_9\text{O}_{40}$	
		3a	3b	3a	3b	3a	3b	3a	3b
0.01	180	88	86	84	85	86	84	81	85
0.02	120	87	87	84	84	87	85	80	80
0.04	45	92	90	86	85	88	87	86	83
0.08	30	94	95	90	91	94	94	92	92

Heterocyclization of **2** can lead to the formation of two isomers (**3** and **4**) according to Scheme 1.

Scheme 1

^1H NMR of **3a** showed signals at 2.27 δ and 2.34 δ for the two methyl groups and 7.05 δ for one vinyl proton, these signals are observed at 1.14, 2.20 and 6.95 δ for **3b**. Comparison of physical and spectroscopic data of obtained product with those of authentic compounds²¹ proved the selective formation of **3**. As shown in scheme 2, heteropoly acid play important role to protonation and activation of acetylenic carbon for nucleophilic attack of NH group, followed by isomerization to convert the methylene moiety to a methyl group.

Scheme 2

The results of the comparison among the Keggin HPAs ($\text{H}_3\text{PW}_{12}\text{O}_{40}$, $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ and $\text{H}_4\text{SiW}_{12}\text{O}_{40}$) and Lacunary Keggin structure ($\text{K}_7\text{PMo}_2\text{W}_9\text{O}_{40}$) showed, they are almost the same regarding the yields and reaction times (Table 1). In study of reaction progress with TLC, we found that the conversion rate and yield were affected by amounts of catalyst and a single (TLC) compound was observed in the presence of 4% (mol/mol) of catalyst after 30 min. Reactions were done in various solvent and we find that the catalytic system composed of acetic acid as solvent shows best catalytic behaviors for heterocyclization reaction.

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