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Research Article

SYNTHESIS OF 6-ALKYL-3-PHENACYLMERCAPTO-1,2,4-TRIAZIN-5(2*H*)-ONE BY HETEROPOLYACIDES

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ABSTRACT

Cyclization of 6-alkyl-3-phenacylmercapto-1,2,4-triazin-5(2*H*)-one **2** in the presence of Keggin heteropolyacids such as $H_3PMo_{12}O_{40}$, $H_4SiW_{12}O_{40}$, $H_3PW_{12}O_{40}$ and lacunary Keggin structure ($K_7PMo_2W_9O_{40}$) afforded **3** in high yields and short reaction times**.**

Keywords: *1,2,4-Triazines, Heterocyclization, Heteropolyacids, Phenacyl Bromide*

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-inflammatory, sedative (Prinsloo *et al.*, 1995), antibacterial (Omar and Aboulmafe, 1986), antiviral (Falke and Rada, 1970), or antitumor (Creasey *et al.*, 1963). Due to their importance, the synthesis of these compounds is interested for the discovery of improved protocols towards milder and high yielding approaches. In comparison with the liquid mineral acids, solid acids could be easily separated from the reaction mixture by simple filtration with high recovery.

This advantage directly leads to a decrease in of equipment cauterization and environment pollution. Among various solid acids, heteropolyacids (HPAs) have unique physical–chemical properties. Their acidity is significantly higher than those of traditional mineral acids. Furthermore, HPAs are capable of protonating and activating the substrate; and in some cases, HPAs are more effective than usual inorganic acid and the traditional acid catalysts. Therefore, they are widely used as homogeneous and heterogeneous acid catalysts for the synthetic reactions (Heravi and Sadjadi, 2009; Hu *et al.*, 1993).

They have very strong Brønsted acidity approaching the superacid region and this acid–base property can be varied over a wide range by changing the chemical composition. Because of interesting importance of nitrogen-sulfur containing heterocycles and in continuation of our interest in application of heteropolyacids in organic synthesis (Bamoharram *et al.*, 2006; Heravi *et al.*, 2007), in this article we wish to report our results for the heterocyclization of 6-alkyl-3-phenacylmercapto-1,2,4-triazin-5(2*H*)-one (**2**) using different keggin type heteropolyacid catalysts in various conditions.

MATERIALS AND METHODS

Melting points were determined with an Electrothermal 9100. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer. The IR spectra were recorded on a Shimadzu spectrometer 883 (KBr pellets, Nujol mulls, 4000–400 cm−1). ^1H and ^{13}C NMR spectra were recorded on a Bruker- Avance DRX 400 spectrometer using TMS as an external standard.

The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Polyoxometalats were prepared according to litterateurs procedures (Pope, 1983; Massart *et al.*, 1977). 3,4-dihydro-6-methyl-3-thioxo-1,2,4-triazin-5(2*H*)-one (**1a**) and 3,4-dihydro-6-ethyle-3-thioxo-1,2,4-triazin-5(2*H*)-one (**1b**) were prepared in accordance with literature procedure (Massart *et al.*, 1977).

General Procedure

Synthesis of 2a and 2b

Sodium 0.046 g (2mmol) was dissolved in ethanol (30 mL). A mixture of 3,4-dihydro-6-alkyl-3-thioxo-1,2,4-triazin-5(2H)-one (**1**) (2 mmol) and Phenacyl bromide 0.298 (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 3 h. The solid residue was filtered, washed with cold ethanol to afford pale yellow crystals **2a** and **2b**.

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

Pale yellow crystals, m.p. 190-191 ◦C, IR (KBr) (ν_{max} cm^{-1}): 3145 (NH), 1631(C=O), 1577 (CN). ^1H NMR (400 MHz, DMSO): δ 2.04 (3H, s, CH_3), 3.85 (2H, CH_2-S), 8.13 (1H, br, NH), 7.37-7.47 (5H, m, Ph) ppm. Anal. calcd. for $C_{12}H_{11}N_3O_2S$: C, 55.17; H, 4.21; N, 16.09. Found: C, 55.29; H, 4.40; N, 16.00%.

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

Pale yellow crystals, m.p. 138-139 ◦C, IR (KBr) (ν_{max} cm^{-1}): 3065 (NH), 1616 (C=O), 1567(CN). ^1H NMR (400 MHz, DMSO): δ 1.15 (3H, t, $^3J_{HH}$ =7 Hz, CH_3), 2.63 (2H, q, $^3J_{HH}$ =7 Hz, CH_2), 3.95 (2H, s, CH_2-S), 7.370 (1H, br, NH), 7.41-7.62 (5H, m, Ph) ppm. Anal. calcd. for $C_{13}H_{13}N_3O_2S$: C, 56.72; H, 4.73; N, 15.27. Found: C, 56.66; H, 4.68; N, 15.16%.

Synthesis of 3a and 3b

In a round-bottomed flask, equipped with a thermometer and reflux condenser, compound 2 0.54g (1 mmol), was heated with stirring with appropriate heteropolyacid 0.04g (0.25 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/ethylacetat (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 excellent yields.

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

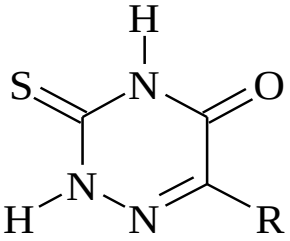
Colorless solid, m.p.181-183 ◦C, IR (KBr) (ν_{max} cm^{-1}): 1697(C=O), 15434(CN). ^1H NMR (400 MHz, DMSO): δ 2.14 (3H, s, CH_3), 5.73 (1H, s, S-CH), 7.50-7.60 (5H, m, Ph)ppm. Anal. calcd. for $C_{12}H_9N_3OS$: C, 59.25; H, 3.70; N, 17.28. Found: C, 59.23; H, 3.63; N, 17.11%.

6-ethyl- 3- Phenyl -7H- thiazolo [2,3-b][1,2,4]- triazin-7-one **(3b)**

Pale yellow solid, m.p. 146-148 ◦C, IR (KBr), υ(cm^{-1}): IR (KBr) (ν_{max} cm^{-1}): 1615(C=O), 1535(CN). ^1H NMR (400 MHz, DMSO): δ 1.20 (3H, t, $^3J_{HH}$ =7 Hz, CH_3), 2.60 (2H, q, $^3J_{HH}$ =7 Hz, CH_2), 4.80 (1H, s, S-CH); 7.47 (5H, m, Ph); Anal. calcd. for $C_{13}H_{11}N_3OS$: C, 60.70; H, 4.28; N, 16.34. Found: C, 60.52; H, 4.32; N, 16.28%.

RESULTS AND DISCUSSION

Compound 6-alkyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one **1** is well known heterocyclic thiones derived from thiosemicarbazide (Pope, 1983) and it exists in two thione and thiole tautomeric form.



1a: R=Me

1b: R=Et

Condensation reaction of **1** with propargyl bromide in the presence of sodium ethoxide led to corresponding 6-alkyl-3-propargyl-mercapto-1,2,4-triazin-5(2*H*)-one and recently we have described the use of sulfuric acid and heteropolyacids for cyclization of 6-alkyl-3-propargylmercapto-1,2,4-triazin-5(2*H*)-one (Massart *et al.*, 1977). Herein, we wish to report the condensation reaction of **1** with phenacyl bromide in the presence of sodium ethoxide and intermolecular cyclization of 6-alkyl-3-phenacylmercapto-1,2,4-triazin-5(2*H*)-one (**2**) using different keggin type heteropolyacid (HPAs) as catalyst (Figure 1).

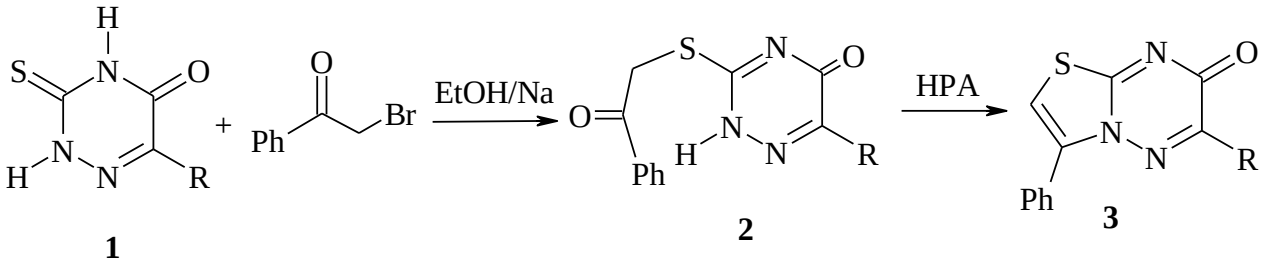


Figure 1: Intermolecular cyclization of 6-alkyl-3-phenacylmercapto-1,2,4-triazin-5(2*H*)-one (2) using different keggin type heteropolyacid (HPAs) as catalyst.

The stable catalyst HPA is easily prepared (Hakimi *et al.*, 2011). and used for intermolecular cyclization of 6-alkyl-3-phenacylmercapto-1,2,4-triazin-5(2*H*)-one (**2**). The yields are shown in Table 1.
The heteropolyacid play important role to protonation and activation of carbonyl group for nucleophilic attack of NH group, followed by elimination of H_2O and formation of **3** (Figure 2).

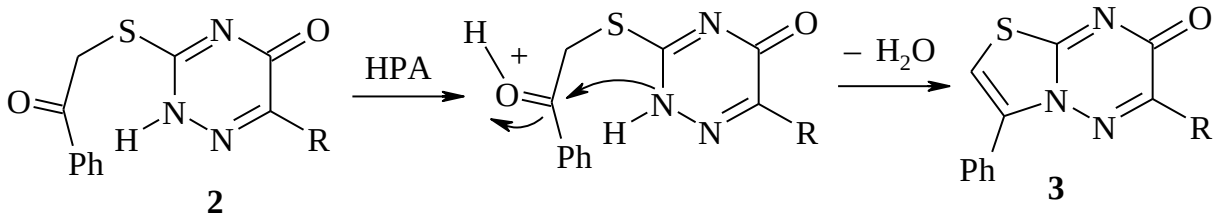


Figure 2: Suggested mechanism for formation of compound 3

^{1}H NMR of **3a** showed a signals at 2.14 ppm for the methyl group, 5.73 ppm for one vinyl proton and 7.45- 8.03 ppm for the phenyl protons, these signals are observed at 1.20 and 2.60 ppm for the methyl and methylen groups, 4.80 ppm for one vinyl proton and 7.47 ppm for the phenyl protons for **3b**.

Table 1: Effect of different reaction time and amount of various heteropolyacids on Heterocycization of 2

Entry	Catalyst (g)	Time (min)	Yield[a](%)	
			Product 3a	Product 3b
1	$H_3[PMo_{12}O_{40}]$(0.01)	300	82	84
2	$H_3[PMo_{12}O_{40}]$(0.02)	240	85	86
3	$H_3[PMo_{12}O_{40}]$(0.04)	180	95	96
4	$H_3[PMo_{12}O_{40}]$(0.08)	120	90	91
5	$H_4[SiW_{12}O_{40}]$(0.01)	300	84	85
6	$H_4[SiW_{12}O_{40}]$(0.02)	240	84	84
7	$H_4[SiW_{12}O_{40}]$(0.04)	180	86	85
8	$H_4[SiW_{12}O_{40}]$(0.08)	120	90	91

9	$H_3[PW_{12}O_{40}](0.01)$	300	86	84
10	$H_3[PW_{12}O_{40}](0.02)$	240	87	85
11	$H_3[PW_{12}O_{40}](0.04)$	180	88	85
12	$H_3[PW_{12}O_{40}](0.08)$	120	92	93
13	$K_7[PMo_2W_9O_{40}]$ (0.01)	300	86	88
14	$K_7[PMo_2W_9O_{40}]$ (0.02)	240	88	87
15	$K_7[PMo_2W_9O_{40}]$ (0.04)	180	91	92
16	$K_7[PMo_2W_9O_{40}]$ (0.06)	120	90	91

[a]*Isolated yield*

The results of the comparison among the Keggin HPAs such as $H_3PMo_{12}O_{40}$, $H_4SiW_{12}O_{40}$, $H_3PW_{12}O_{40}$ they are almost the same regarding the yields and reaction times (Table) but lacunary Keggin structure ($K_7PMo_2W_9O_{40}$) is more efficient catalyst. In study of reaction progress with TLC, we found that the conversion rate and yield were affected by amounts of catalyst and a single compound was observed in the presence of 0.04g of $H_3[PMo_{12}O_{40}]$ after 180 min.

Conclusion

In summary, we report herein cyclization of 6-alkyl-3-phenacylmercapto-1,2,4-triazin-5(2*H*)-one **2** in the presence of Keggin heteropolyacids such as $H_3PMo_{12}O_{40}$, $H_4SiW_{12}O_{40}$, $H_3PW_{12}O_{40}$ and lacunary Keggin structure ($K_7PMo_2W_9O_{40}$) afforded **3** in high yields and short reaction times**.**

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