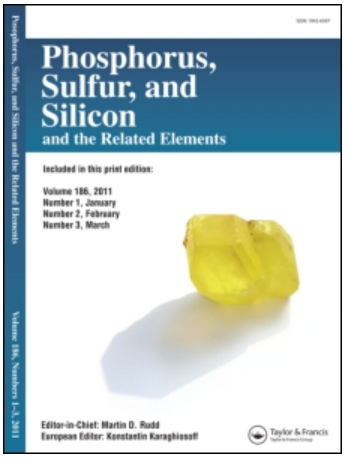

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REGIOSELECTIVE SYNTHESIS OF 2-SUBSTITUTED [1,2,4]TRIAZOLO[5,1-*b*][1,3]THIAZIN-7-ONES BY HETEROPOLYACIDS

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2-Substituted [1,2,4]triazolo[5,1-b][1,3]thiazin-7-ones 3 were synthesized via regioselective cyclization of 4H-[1,2,4]triazol-3-ylsulfanyl-acrylic acids 2 in the presence of catalytic amounts of heteropolyacids at room temperature in very good yields and rates.

Keywords Heteropolyacids; regioselective cyclization; [1,2,4]triazolo[5,1-*b*][1,3]thiazin

INTRODUCTION

[1,3]Thiazine-ones are important heterocyclic systems that are used in biologically active compounds.[1,2] A series of 2-substituted [1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones **3** was synthesized by Peter et al. by cyclization of 1,2,4-triazol-3-thiols **1** with diethylethoxymethylene malonate in good yields.[3] This heterocyclic system has also been afforded by condensation of mercapto-1,2,4-triazole-4-amines **5** with methyl propionates and hydrolysis of the resulting S-acrylic esters to the corresponding S-acrylic acids **2** and subsequent cyclization to **3** or **4**.[4] Cyclization of 2 to **3** or **4** using thionyl chloride has also been reported as an independent synthesis.[4] The regioselective cyclization of **2** to **3** in the presence of conc. H_2SO_4 in good to high yield was reported by Heravi et al.[5]

The identification and use of better and milder conditions for the synthesis of these heterocyclic systems using new catalysts have been the focus of recent attention. In this context, the use of heteropolyacids (HPAs), which are low in toxicity, highly stable toward humidity, recyclable, and air-stable, have attracted increasing attention.[6] The use of HPAs as green catalysts not only gave good yields in shorter reaction times at room temperature, but also provided a procedure that did not use corrosive reagents or solvents. HPAs have been used as industrial catalysts for several liquid-phase reactions[7–10] such as alcohol

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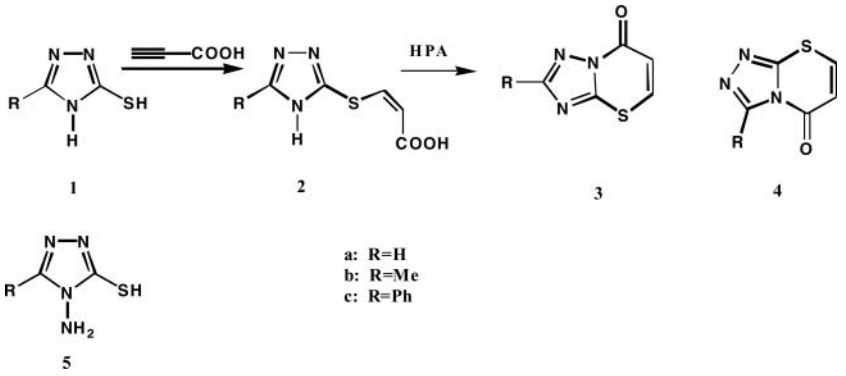
dehydration,[11] alkylation,[12] and esterification.[13] Therefore, in continuing our work using HPA[14–17] to synthesize heterocyclic systems, we investigated the use of this catalyst for the synthesis of some triazolothiazines. Here we report a rapid and ecologically safe method for the synthesis of triazolothiazines **3**.

RESULTS AND DISCUSSION

First, triazoles **1a–c** were prepared by a known reported method.[18] Condensation of equimolar quantities of triazoles **1a–c** and propiolic acid in a Michael-type addition afforded adducts identified as the S-substituted acrylic acids **2** in good yields (70–80%) (Scheme 1). Physical and spectroscopic data of these compounds confirmed the formation of adducts **2**.[5]



Scheme 1

Regioselective cyclization of propynylmercapto heterocyclic compounds to condensed thiazoles **3** occurred in the presence of conc. H_2SO_4 after 2 h at 50°C in 68–80% yield.[5] Fusion of triazole and triazine moieties can occur in two different ways, as represented by **3** and **4**. The structures of **3** and **4** can be distinguished by differences in chemical shift of the substituent (R group) on C-5 of the triazolo ring. The carbonyl group in structure **4** is in the *peri* position to these substitutes; in the case of a methyl group at this position, a considerable anisotropic effect would be expected.[4] The ^{1}H NMR spectrum of **3b** showed the ring signal at $\delta = 2.75$ ppm, indicating almost no downfield shift.[5] In accordance to the cyclization product structure **3b**, **3a** and **3c** are assigned to the cyclization products of **2a** and **2c**. In a recent publication, we demonstrated the utility of HPAs (Keggin, $K_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, $K_7PWMo_{11}O_{39}$; Wells–Dawson, $H_6P_2W_{18}O_{62}$, $H_6P_2Mo_{18}O_{62}$; Preyssler, $H_{14}[NaP_5W_{29}MoO_{110}]$) for regioselective cyclization of **2** to **3**. Thus, compounds **2** were treated with catalytic amounts of HPAs in acetic acid as solvent at room temperature. The yields and reaction times are reported in Table I.

Comparison of physical and spectroscopic data for the products confirmed the structure of **3**.[5] As shown in Table I, the rate was four to 12 times faster in the presence of HPAs compared to the use of H_2SO_4.

Generally, the results demonstrate that a Preyssler HPA is the most efficient catalyst for these reactions owing to a higher number of acidic protons. It seems that the presence of molybdenum ions in mixed HPAs enhances the yield and cyclization rate. Accordingly,

Table I Catalytic synthesis of 2-substituted [1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones by heteropolyacids

Compd.	3A	3B	3C
R	H	Me	Ph
Mp (°C)	232–233	195–196	264–265
Lit.	230–232[3]	196–197[3]	264–265[3]
Yield (%) and time using $H_{14}[NaP_5W_{29}MoO_{110}]$	78%; 15 min	88%; 10 min	90%; 10 min
Yield (%) and time using $H_3PMo_{12}O_{40}$	75%; 20 min	82%; 15 min	85%; 15 min
Yield (%) and time using $K_3PW_{12}O_{40}$	74%; 35 min	82%; 25 min	80%; 30 min
Yield (%) and time using $K_7PWMo_{11}O_{39}$	70%; 25 min	82%; 20 min	85%; 20 min
Yield (%) and time using $H_6P_2Mo_{18}O_{62}$	68%; 20 min	85%; 15 min	85%; 15 min
Yield (%) and time using $H_6P_2W_{18}O_{62}$	68%; 35 min	85%; 25 min	85%; 20 min

$K_7PWMo_{11}O_{39}$ and $H_6P_2Mo_{18}O_{62}$ were more reactive than $K_3PW_{12}O_{40}$ and $H_6P_2W_{18}O_{62}$, which is in good agreement with the more oxidative effect reported for Mo compounds compared to W.[12]

The catalyst is not soluble in acetic acid, which allows for easy separation and recovery by filtration for immediate reuse. No significant decrease in catalyst reactivity was observed after three uses.

In this article, we have developed a method using an ecofriendly and reusable heterogeneous inorganic catalyst for regioselective synthesis of 2-substituted [1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones. The reasonable reaction times, good yields, simple workup procedure, and environmentally friendly conditions are the main advantages of this method.

EXPERIMENTAL

Most chemicals were purchased from Merck Chemical Company (Darmstadt, Germany) and Fluka (Buchs, Switzerland). 1,2,4-Triazol-3-thiols **1** were prepared using a previously published method.[14–18]

Preparation of 5-Substituted-3-(4H-[1,2,4]triazol-3-ylsulfanyl)-acrylic Acids (2a–c): General Procedure

A solution of 1,2,4-triazol-3-thiol **1** (0.01 mol) and propiolic acid (0.01 mol) in methanol (30 mL) was refluxed for 5 h. The solvent was evaporated to dryness under reduced pressure, and the crude product was crystallized from H_2O to afford **2a–c** in 78–85% yield. The products are known compounds and were identified by their spectral and physical data.[5]

Preparation of 2-Substituted [1,2,4]Triazolo[5,1-*b*][1,3]thiazin-7-ones (3a–c): General Procedure

A mixture of **2** (0.9 mmol) and the appropriate heteropolyacid (0.04 mmol) in acetic acid (20 mL) was stirred for the indicated time (Table I) at room temperature. Reaction progress was monitored by TLC. After completion of the reaction, the catalyst was removed by filtration and washed with acetic acid (the catalyst is not soluble in acetic acid) and then diethyl ether. It could be reused and subjected to a second run of reaction; the yield of product was almost identical to yield obtained by using fresh catalyst. The solvent was

evaporated to dryness under reduced pressure, and the crude product was crystallized from H_2O to afford **3a–c** (Table I). The products are known compounds and were identified by comparison of spectral and physical data.[5]

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