Facile One-Pot Synthesis of [1,2,4]Triazolo [3,4-*b*][1,3,4]thiadiazines and 3,7-Dimethyl-4*H*-[1,2,4]triazino [3,4-*b*][1,3,4]thiadiazin-6-one Using Heteropolyacid Catalysts

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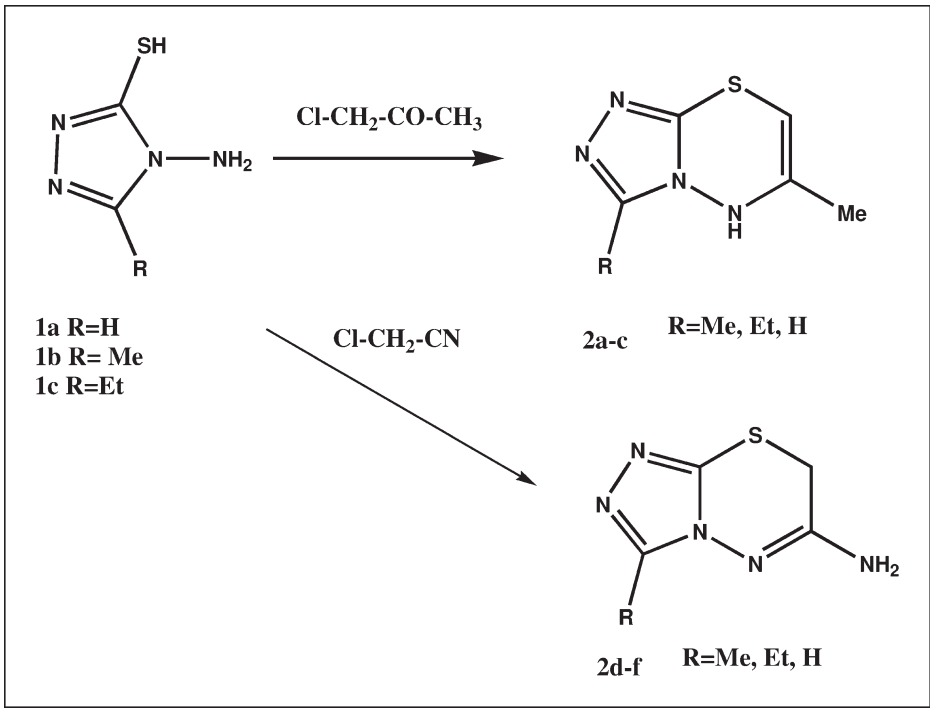

[1,2,4]Triazolo[3,4-b][1,3,4]thiadiazines **2a–f** and 3,7-dimethyl-4*H*-[1,2,4]triazino[3,4-b][1,3,4]thiadiazin-6-one **4** were synthesized by one-pot cyclocondensation reaction with α-chloroacetonitrile and α-haloketones in the presence of catalytic amounts of heteropolyacids in very high yields and rates.

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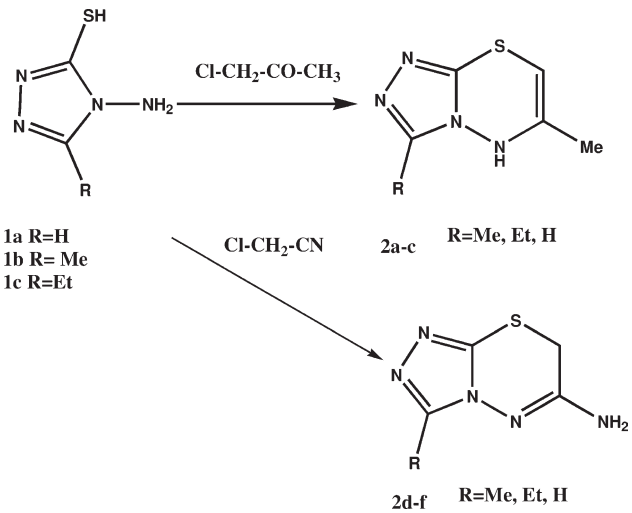
INTRODUCTION

[1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazines and [1,2,4] triazino[3,4-*b*][1,3,4]thiadiazines display a broad spectrum of pharmacological properties and chemical reactivities [1−5]. Certain derivatives have been reported to possess antibacterial [6−8], anti-inflammatory [9], antiviral [10,11], antitumor [12,13], and antifungal [14] activities, as well as interesting CNS depressing activity [15].

A series of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines has been synthesized by one-pot cyclocondensation of triazoles **1a−c** with α-chloroacetonitrile and α-haloketones [16]. We have recently reported the synthesis of these compounds in high yields by two-step reactions involving addition of propargyl bromide to 4-amino-5-substituted-1,2,4-triazole-3-thiones **1a−c** and 4-amino-6-methyl-1,2,4-triazine-3(2*H*)-thion-5-one **3** in the presence of sodium methoxide, followed by cyclization in the presence of heteropolyacids (HPAs), such as $H_{14}[NaP_5W_{29}MoO_{110}]$ or $H_6P_2W_{18}O_{60}$ [17].

Because of the environmental restrictions on using harmful mineral acids, solid acid catalysts are becoming popular in the chemical industry [18−23]. Among solid acid catalysts, HPAs have attracted considerable interest by virtue of their favorable properties, such as low toxicity, safety, low quantity of waste, and ease of

Scheme 1



separation, in addition to possessing higher acidity [23−25]. HPAs are widely used in a variety of acid-catalyzed reactions, such as esterification [26], etherification [27], hydration of olefins [28], de-esterification [29], dehydration of alcohols [30], and the polymerization of tetrahydrofuran [31] in homogeneous and heterogeneous systems.

In continuation of our recent studies [32] on reactions catalyzed by HPAs leading to heterocyclic compounds of biological significance, we wish to report a one-pot, rapid, and green method for the synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines and [1,2,4]triazino[3,4-*b*][1,3,4]thiadiazines with the aid of HPAs.

RESULTS AND DISCUSSION

Heravi *et al*. found that the one-pot cyclocondensation of triazoles **1a**−**c** with α-chloroacetonitrile and α-haloketones could be carried out by refluxing in ethanol for 5 h over sulfuric acid adsorbed on silica gel to give the desired 6-phenyl-, methyl-, and amino-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines in 60−82% yields [16]. The structure assigned to these compounds was as shown for **2a**−**f** (Scheme 1), with a double bond linking the 5- and 6-positions, based on analytical and spectral data.

In the work described herein, we have used triazoles **1a**−**c** and α-chloroacetonitrile or α-chloroacetone as reagents, which were reacted in refluxing acetic acid in the presence of a catalytic amount of HPA for reaction times of 20 min to 3 h. When the reaction was carried out in the absence of HPA, reaction products are not produced. As expected, 5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazines **2a**−**c** were prepared by using α-chloroacetone and HPA. The HPA was separated by filtration and the products were purified by crystallization from ethanol; the yields are shown in Table 1.

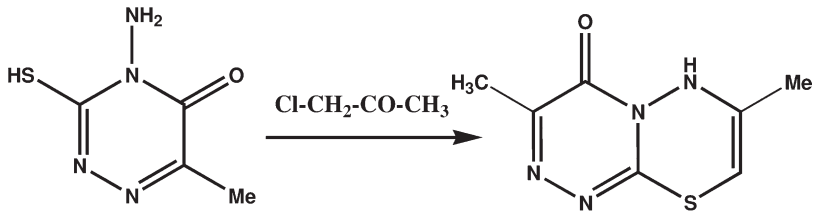
The reactions were monitored by TLC and subsequent work-up afforded a single compound by TLC in each case. The products were subjected to ^{1}H NMR and mass spectrometric analyses, and were also compared with authentic samples [16]. The presence of the 5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine moiety in **2a**−**c** was confirmed by ^{1}H NMR signals at $\delta = 4.51-4.55$ and $\delta = 5.60-5.64$, attributable to one vinyl proton and an NH group, respectively. The mechanism must involve two steps, namely nucleophilic substitution of sulfur by chlorine and cyclization through direct attack of the amino group on the carbonyl group. From elucidation of the structure, it can be assumed that HPA catalyzes the second step by activating the carbonyl group to direct attack of the amino group, which is followed by isomerization to convert the methylene moiety to a methyl group. Such a cyclization and isomerization has been reported for the two-step synthetic route to

Table 1

Catalytic synthesis of triazolothiadiazine **2a–f** and triazinothiadiazin **4** by heteropolyacids.

Compd.	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**4**
R	H	Me	Et	H	Me	Et	
R′	Me	Me	Me	NH_2	NH_2	NH_2	
mp(°C)	204	215	242–244	271–273	255	223–225	197–198
Lit.	205 [17]	215–217 [17]	242–244 [17]	270–271 [16]	255–256 [16]		198 [17]
Yield (%) and time using $H_{14}[NaP_5W_{29}MoO_{110}]$	98%, 20 min	91%, 3 h	83%, 1 h	95%, 20 min	90%, 3 h	92%, 1 h	98%, 10 min
Yield (%) and time using $K_3PW_9Mo_3O_{40}$	85%, 30 min	70%, 3 h	67%, 1 h	80%, 30 min	70%, 3 h	80%, 1 h	98%, 10 min
Yield (%) and time using $K_7PW_9Mo_2O_{39}$	67%, 30 min	40%, 3 h	50%, 1 h	67%, 30 min	42%, 3 h	45%, 1 h	98%, 4 h
Yield (%) and time using $H_6P_2Mo_{18}O_{62}$	65%, 30 min	65%, 3.5 h	62%, 1 h	60%, 30 min	45%, 3 h	60%, 1 h	98%, 4 h
Yield (%) and time using $H_6P_2W_{18}O_{62}$	72%, 30 min	72%, 3.5 h	68%, 3 h	70%, 30 min	53%, 3 h	65%, 3 h	98%, 2 h

Scheme 2



3 **4**

these compounds [17]. 6-Amino-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **2d**−**f** were prepared by using α-chloroacetonitrile and HPA as the catalyst. The ^{1}H NMR spectra of the products featured signals at δ = 3.1−3.7 for the methylene group and δ = 7.0−7.1 for the NH_2 group. The structure of these compounds may have been preferred in the presence of the amino group due to hydrogen-bonding interactions. The results showed the best catalyst for this reaction to be the Pryssler catalyst, $H_{14}[NaP_5W_{29}MoO_{110}]$ (Table 1).

This function of the HPA catalysts as a result of their acidity was expected [32]. Having established HPAs as effective catalysts for the synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **2a**−**f**, we were persuaded to study the use of these catalysts for the synthesis of similar systems, such as 3,7-dimethyl-4*H*-[1,2,4]triazino[3,4-*b*][1,3,4]thiadiazin-6-one **4**. 4-Amino-3-mercapto-6-methyl-4*H*-[1,2,4]triazin-5-one **3** and α-chloroacetone were refluxed in acetic acid using HPA as the catalyst (Scheme 2). The reaction was monitored by TLC and work-up was carried out as described in the Experimental Section. The yield is shown in Table 1. The product was identified by its ^{1}H NMR, mass, and IR spectra, which were compared to those reported previously [26c]. In the ^{1}H NMR spectrum of compound **4**, the signals of the methyl protons of the 1,3,4-thiadiazine moiety and the vinyl proton appeared at δ = 2.65 and δ = 4.66, respectively, which confirmed the proposed structure. The mechanism must be the same as that outlined earlier for the syntheses of **2a**−**f**. An attempt to synthesize 7-amino-3-methyl-4*H*-[1,2,4]triazino[3,4-*b*][1,3,4]thiadiazin-6-one by using α-chloroacetonitrile as a reagent was unsuccessful.

Comparison of the results shows that HPA not only catalyzed this kind of reaction but also showed more advantages compared with using mineral acidic media, such as H_2SO_4. In studying the progress of the reactions by TLC, we found that conversion rate and yield were affected by catalyst structure. Among the various HPAs used, the yields were higher with the Pryssler catalyst, $H_{14}[NaP_5W_{29}MoO_{110}]$ systems as a result of their high acid strengths. This result is in agreement with the findings of earlier work [32].

In acid-catalyzed reactions, several types of acid sites are present [27,33−35]. These include proton sites in bulk HPAs, Lewis acid sites in their salt form (metal counterions), proton sites in acidic form, and proton sites generated by partial hydrolysis of polyanions. Generally, reactions catalyzed by HPAs may be represented by the conventional mechanisms of Brønsted acid catalysis. The mechanism may involve protonation of the substrate by conversion of the ionic intermediate to yield the reaction product [33−35].

EXPERIMENTAL

Chemicals and all solvents used in this study were purchased from Merck AG and Alderich Chemical. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were obtained on a Shimatdzu 470 spectrophotometer (potassium bromide disks).^{1}H NMR spectra

Table 2

^{1}H NMR and mass spectral data for triazolothiadiazine **2a–f** and triazinothiadiazin **4**.

Compd.	*m/z*	^{1}H NMR δ (ppm)
2a	154 (M^+)	($CDCl_3$), 2.65 (3H, s, CH_3), 4.5 (1H, s, CH), 5.6 (s, 1H, NH, exchanged with D_2O), 8.42 (1H, s, CH)
2b	168 (M^+)	($CDCl_3$), 2.6 (3H, s, CH_3), 2.7 (3H, s, CH_3), 4.5 (1H, s, CH), 5.6 (s, 1H, NH, exchanged with D_2O)
2c	182 (M^+)	($CDCl_3$), 1.39 (3H, t, CH_3), 2.93 (2H, q, CH_2), 2.6 (3H, s, CH_3), 4.5 (1H, s, CH), 5.64 (s, 1H, NH, exchanged with D_2O)
4	196 (M^+)	(d_6-DMSO), 2.2 (3H, s, CH_3), 2.65 (3H, s, CH_3) 4.66 (1H, s, CH), 5.8 (s, 1H, NH, exchanged with D_2O)
2d	155 (M^+)	($CDCl_3$), 3.19 (2H, s, CH_2), 7.10 (s, 2H, NH_2, exchanged with D_2O), 9.80 (1H, s, CH)
2e	169 (M^+)	($CDCl_3$), 2.28 (3H, s, CH_3), 3.78 (2H, s, CH_2), 7.02 (s, 2H, NH_2, exchanged with D_2O)
2f	183 (M^+)	($CDCl_3$), 1.21 (3H, t, J =7.0 Hz, CH_3), 2.40 (2H, q, J = 7.0 Hz, CH_2), 3.72 (2H, s, CH_2), 7.04 (s, 2H, NH_2, exchanged with D_2O)

were measured using a Bruker FT-500 spectrometer, and chemical shifts are expressed as δ (ppm) with tetramethylsilane as internal standard. The mass spectra were run on a Finnigan TSQ-70 spectrometer at 70 eV. Merck silica gel 60 F254 plates were used for analytical TLC; column chromatography was performed on Merck silica gel (70-230 mesh).

General procedure for the synthesis of [1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazines and [1,2,4]triazino[3,4-*b*][1,3,4] thiadiazine. The appropriate HPA (0.04 mmol) was suspended in a solution of **1a**−**c** or **3** (0.9 mmol) in acetic acid (10 mL) and the mixture was refluxed for the indicated time (Table 1). The catalyst was removed by filtration and washed with warm acetic acid (the catalyst is not soluble in acetic acid). The catalyst was further washed with diethyl ether after filtration. It could be reused for a second run of the reaction. The yields of product were almost identical to those obtained using fresh catalyst. The filtrate was cooled and the precipitated solid was collected by filtration, washed with water, dried, and recrystallized from ethanol to give pure product **2a**−**f** or **4** (Table 1). All compounds were characterized by their mass and ^{1}H NMR spectra (Table 2).

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