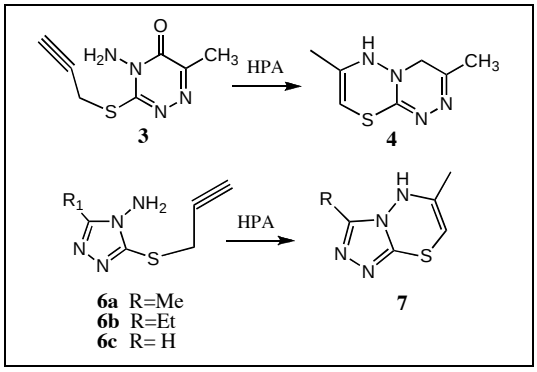
Facile routes to 1,2,4-Triazolo[3,4-*b*][1,3,4]Thiadiazines and 1,2,4-Triazino[3,4-*b*][1,3,4]Thiadiazine by Heteropolyacides

[a]Radineh Motamedi [*], [b]Majid M.Heravi, [c]Fatemeh F. Bamoharram, [b]Anahita Haeri

[a]Department of Chemistry, School of sciences, Payame nourUniversity, Delijan , Iran
[b]Department of Chemistry, School of sciences Azzahra University, Vanak, Tehran, Iran
[c]Department of Chemistry, Islamic Azad University -Mashhad Branch, Mashhad, Iran
E-mail address: r_motamedi@Pnu.ac.ir

Received June 26, 2007



Cyclization of 4-amino-6-methyl-3-propargylmercapto-1,2,4-triazine-5-one **3** and 4-amino-3-propargyl mercapto-1,2,4-triazole derivatives **6** were afforded 1,2,4-triazino[3,4-*b*][1,3,4]thiadiazines **4** and 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines **7** in presence of heteropolyacids, $H_{14}[NaP_5W_{29}MoO_{110}]$ and $H_6P_2W_{18}O_{60}$ in high yields. Among used heteropolyacids, the yields were higher with H_{14}-P_5Mo, caused to their high acid strengths.

J. Heterocyclic Chem., **45**, 1211 (2008).

INTRODUCTION

1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazines and 1,2,4-triazino[3,4-*b*][1,3,4]thiadiazines constitute two classes of compounds interesting from view points of chemical reactivity [1-5] and biological activity. Antibacterial [6-8] and anti-inflammatory [9], antivirial [10,11], antitumor [12,13], and antifungal [14] activity, as well as interesting CNS depressing activity [15] has been reported for certain of the derivatives. Due to their importance, the synthesis of these compounds is interested for the discovery of improved protocols towards milder and high yielding approaches.

We have recently reported the preparation of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine **8** (R=Ph), by refluxing **4** in dimethylsulfoxide for 5 min and in presence of lithium hydride as a base by 60% yield [16]. We have also reported cyclization of compound **5** with a catalytic amount of $PdCl_2(PhCN)_2$ by reflux in acetonitrile for 6 hours (40% yield) [17] .

Green Sustainable Chemistry (GSC) is, in a word, chemistry and chemical technology for environmentally friendly products and processes. Green chemistry has been defined as a set of principles that reduces or eliminates the use or generation of hazardous substances throughout the entire life of chemical materials [18,19].

In this regard, heteropolyacids attracted considerable amounts of interest due to their properties like, being less toxic, safety, quantity of waste and separatability in addition of possessing higher acidity [20-22].

Heteropolyacids are widely used in variety of acid-catalyzed reactions such as esterification [23], etherification [24], hydration of olefin [25], de-esterification [26], dehydration of alcohol [27] and polymerization of tetrahydrofuran [28] in homogenous and heterogeneous systems. In continuation of our attempts to develop selective and preoperatively useful methodology, based on using various heteropolyacids as green catalysts in various organic reactions [29], we wish to report a rapid and convenient method for 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.

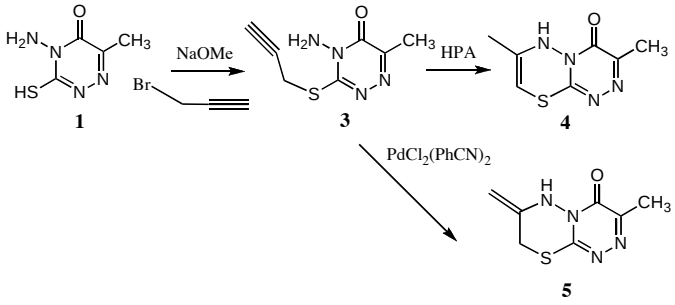
RESULTS AND DISCUSSION

4-Amino-6-methyl-1,2,4-triazine-3(2*H*)-thione-5-one [30] was condensed with propargyl bromide in the presence of sodium methoxide to afford the corresponding 3-propargylmercapto derivatives **3** (Scheme 1) [31a]. Cyclization of **3** could not be undertaken in either aprotic or protic solvents at their refluxing temperature.

We have recently described the use of Pd-salt for implementation of sequential carbometallation anion capture [31b-31d] and catalyzed intermolecular

cyclization and functionalization of acetylenes [17]. Armed with these experiences, compound **3** had been refluxed with a catalytic amount of $PdCl_2(PhCN)_2$ [32] by reflux in acetonitrile for 6 hours to give compound **5** in 40% yield.

Scheme 1



Herein, we used heteroployacids (HPA) for inter molecular cyclization of 4-amino-6-methyl-3-propargyl-mercapto-1,2,4-triazine-5-one **3** and 4-amino-3-propargyl-mercapto-1,2,4-triazole derivatives **6**.

4-Amino-6-methyl-3-propargylmercapto-1,2,4-triazin-5-one **3** was refluxed in acetic acid with a catalytic amounts of HPA for 2 hours. Heteropolyacides are separated by filtration and the products were purified by recrystalizing from ethanol. The yields are shown in Table 1.

Such a cyclization and isomerization has been reported on similar heterocycles compounds (6-methyl-3-propargylmercapto-1,2,4-triazine-5-one, 2-propargyl mercapto-1,2,4-benzotriazine, 2-propargylmercapto-pyrimidinone) by using conc H_2SO_4 by our group [33-34].

This function of HPA, in attention to acidity of these catalysts was expected [35]. In comparison with the presently synthetic methods [17] which show drawbacks from the standpoint of yields, price and limited availability of catalyst [$PdCl_2(PhCN)_2$], the efficiency of the present method is apparent from the inexpensive, safe and stable, easy to handle HPA and its high rate as well as its high yield with a back of side products.

Whereas HPA were effective catalysts for cyclization of compound **3**, we were persuaded to study using this catalysts to synthesize similar systems like 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazines.

4-Amino-3-propargylmecapto-1,2,4-triazol derivatives **6** were prepared by the same procedure for compound **3** (Scheme 2). Then, it was refluxed in acetic acid using HPA's as catalyst. The reaction was monitored by TLC and the work up was the same as mentioned in the experimental section. The products were identified by ^{1}H NMR, Mass and IR and were compared to those reported before [16]. In ^{1}H NMR spectrum of these compounds the methyl protons belong 1,3,4-thiadiazine moiety and vinyl proton were appeared in 2.6 δ and 4.5 δ which confirmed

Table 1

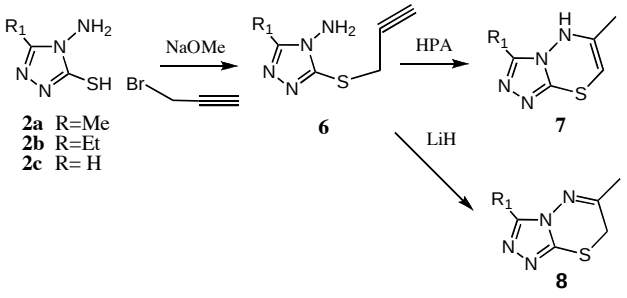
Catalytic synthesis of 6-Substitued-pyrazolo[3,4-*d*]pyrimidn-4(5*H*)-ones **4**.

Compd.	R	Reaction Time (min)	Reaction Time (min)	Yield (%) Using $H_6P_2W_{18}O_{60}$	Yield (%) Using $H_{14}[NaP_5W_{29}MoO_{110}]$	mp(ºC)
4	Me	120	120	72%	83%	198
7a	Me	120	120	83%	86%	215-7
7b	Et	120	120	70%	76%	242-4
7c	H	120	120	65%	75%	205-7

The reaction was monitored by TLC and subsequent workup afforded a single TLC compound. From the spectral data, ^{1}H NMR, Mass and IR as well as comparison with authentic samples, it was identified as the structure **4**. It's ^{1}H NMR showed signals at 2.2 δ and 2.65 δ for the two methyl groups and 4.65 δ for one vinyl proton. By elucidation of the structure, it can be assumed that HPA catalyzed cyclization of **3** to **4** proceeds *via* direct attack of the amino group to the acetylenic bond activated by proton coordination of HPA, followed by isomerization to convert the methylene moiety to a methyl group. The isomerization of **5** to **4** can occur by the catalytic action of HPA in high yield. The results show the best catalyst is the Pryssler catalyst, $H_{14}[NaP_5W_{29}MoO_{110}]$ (Table 1). This kind of acid catalyzed isomerization by H_2SO_4 has been reported previously [33].

the structure **7**. The mechanism must be the same as that which is expected for the synthesis of **4**.

Scheme 2



Attempted cyclization of **6** (R=Me) using LiH in DMSO led to **8** in 60% yield [16]. Although the

Table 2

H^1-NMR, Mass and IR Spectral data for **4**.

Compd.	m/z	IR V^{max} cm^{-1}(KBr)	H^1-NMR δ(ppm)	Molecular Formula	N	H	C
4	196 (M^+)	3490, 1687, 1460, 1235	(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).	$C_7H_8N_4O_5$	28.52	4.10	42.82
7a	168 (M^+)	3300, 1620, 1490, 1300, 1280	($CDCl_3$), 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).	$C_6H_8N_4S$	33.26	4.53	42.50
7b	182 (M^+)	3100, 3050, 3000, 1475, 1450, 1320, 1280, 710	($CDCl_3$), 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).	$C_7H_{10}N_4S$	30.65	5.48	46.13
7c	154 (M^+)	3200, 3050, 1480, 1400, 1180, 650	($CDCl_3$), 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).	$C_5H_6N_4S$	36.12	3.54	38.67

conversion rate showed was less compared to the reaction with LiH, additional advantages due to ease of handling HPA still makes this method more favorable.

The catalysts based on heteropolyacids have many advantages over acid and base liquid catalyst. They are not corrosive and they are environmentally benign, present fewer disposals problem and easy for separation and have thermal stability.

The comparison of the results shows HPA not only catalyzed this kind of reaction, but also showed more advantages compared with using Pd (II) or in acidic and basic media. In study of reaction progress with TLC, we found that the conversion rate and yield were affected by catalyst structure. Among the used heteropolyacids, the yields were higher with H_{14}-P_5Mo, due to their high acid strengths. This result is in agreement with earlier works [29a, 29f, 29j].

In acid-catalyzed reactions several types of acid sites are present [20][33-34]. They are including: proton sites in bulk heteropolyacids, Lewis acid sites in their salt form (metal counteractions), proton sites in acidic form and proton sites generated by partial hydrolysis of polyanions. Generally reactions catalyzed by heteropolyacids may be represented by the conventional mechanisms of Brønsted acid catalysis. The mechanism may include the protonation of substrate by conversion of the ionic intermediate to yield the reaction product [33-34].

EXPERIMENTAL

General procedure for the synthesis 1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazines and 1,2,4-triazino[3,4-*b*][1,3,4]Thiadiazine. A solution of **3** or **6** (0.9 mmol) and appropriate heteropolyacid (0.04 mmol) in acetic acid (10 mL) was refluxed for 2 hours. The catalyst was removed by filtering and washed with warmed acetic acid (the catalyst is not soluble in acetic acid).The catalyst was washed with diethyl ether after filtration. It could be reused and subjected to a second run of reaction. The yields of product were almost identical to yields obtained by using fresh catalyst. The filtrate was cooled and the solid was collected by filtration, washed with water, dried and recrystallized from ethanol to give pure product **4** or **7** (Table 1). All compounds were characterized by Mass; IR and ^{1}H NMR spectra (Table 2).

REFERENCES AND NOTES

[1] Invidiata, F. P.; Furno, G.; Lampronti, L.; Semoni, D. J.; *J. Heterocyclic Chem.* **1997**, *34*, 1255.

[2] Heindel, N. D.; Reid, J. R.; *Org. Prep. Proced. Int.* **1981**, *13*, 123.

[3] Chadha, V. K.; *J. Indian Chem. Soc.* **1978**, *55*, 817.

[4] Chadha, V. K.; Sharma, G. R.; *J. Indian Chem. Soc.* **1980**, *57*, 1112.

[5] Molina, P.; Alajarin, M.; *J. Chem. Soc. Perkin Trans. I* **1987**, 1853.

[6] Mahan, J.; Alajarin, G. S. R.; *J. Chem. Soc., Perkin Trans. I* **1987,** 1853.

[7] Omar, A. M. M. E.; Aboulmafe, O. M.; *J. Heterocyclic Chem.* **1986**, *23*, 1339.

[8] Ghannoum, M. A.; Eweiss, N. F.; Bahajaj, A. A.; Quereshi, M. A.; *Microbios* **1983**, *37*, 151.

[9] Rasad, A. R.; Ramalengamat, T.; Ras A. B.; Drawn, P. W.; Sattur, P. B.; *Indian J. Chem.* **1986**, *26B*, 556.

[10] Falke, D.; Rada, B.; *Acta Virol*, **1970,** *14*, 115.

[11] Sidwell, R. W.; Dixon, G. J.; Schabel, F. M.; *Jr. Appl. Microbiol.* **1968**, *16*, 370.

[12] Creasey, W. A.; Fink, M. E.; Handschurnacker, R. E.; Calabresi, P.; *Cancer Res.* **1963**, *23*, 444.

[13] Walters,T. R.; Aur, R. J.; Hernandez, A. K.; Veetli, T.; Penkel, D.; *Cancer*, **1963**, *29*, 1057.

[14] Malolcsy, G. *Acta. Phytopathol.* **1966**, *1*, 245.

[15] Deshmukh, A. A.; Mody, M. K.; Ramalengant, T.; Sattur, P. B.; *Indian J. Chem.* **1985**, *25B*, 793.

[16] Heravi, M. M.; Rahimizadeh, M.; Seyf, M.; Davoodnia, A.; Ghassemzadeh, M.; *Phosphorus, Sulfur and Silicon,* **2000**, *167*, 211.

[17] Heravi, M. M.; Bakavoli, M.; *J. Chem. Res.* **1995**, *11*, 480.

[18] Rani, R. V.; Srinivas, M. R.; Kulkamrani, S. J.; Raghavan K. V.; *Green Chem.* **2001**, *3*, 305.

[19] Clark, J. H.; *Green Chem.* **1999**, *1*, 1.

[20] Okuhara, T.; Mizuno, N.; Misono, M.; *Adv. Catal.*, **1996**, *41*, 113.

[21] Kozhevnikov, V.; *Catal. Rev. Sci. Eng.* **1995**, *37*, 311.

[22] Mizuno, N.; Misono, M.; *Chem. Rev.* **1999**, *98*, 199.

[23] Hu, C.; Hashimoto, M.; Okuhara, T.; Misono, M. *J. Catal.* **1993**, *143*, 437.

[24] Okuhara, T.; Kasai, A.; Misono, M. *Catalyst.* **1980**, *22*, 226.

[25] Yamada, T. *Peterotech.* (Tokyo), **1990**, *13*, 627.

[26] Okuhara, T.; Mishimura, T.; Ohashi, K.; Misono, M. *Chem. Lett*. **1995**, 155.

[27] Okuhara, T.; Mishimura, T.; Ohashi, K.; Misono, M. *Chem. Lett.* **1990**, 1201.

[28] Aoshima, A.; Tonomura, E.; Yamamatsu, S. *Adv. Technol.* **1990**, *2* ,127.

[29a] Heravi, M. M.; Derikvand, F.; Bamoharram, F .F.; *J. Mol. Catal. A Chem.* **2005**, *242,* 173; b) Heravi, M. M.; Bakhtiari, Kh.; Bamoharram, F. F.; *Catal.Commun*. **2006**, *7*, 373; c) Heravi, M. M.; Motamedi, R.; Siefi, N.; Bamoharram, F. F.; *J. Mol. Catal. A Chem.* **2006,** *249*, 1; d) Bamoharram, F. F.; Heravi, M. M.; Roshani, M.; Gharib, A.; Jahangir, M.; *Appl. Catal. A: Gen.* **2006**, *302*, 42; e) Bamoharram, F. F.; Heravi, M. M.; Roshani, M.; Tavakoli, N.; *J. Mol. Catal., A: Chem.* **2006**, 252, 219; f) Heravi, M. M.; Derikvand, F.; Bamoharram, F .F.; *J. Mol. Catal. A Chem.* **2006**, *253,* 16. g) Heravi, M. M.; Bakhtiari, Kh.; Bamoharram, F. F.; *Catal.Commun* **2006**, *7,* 499. h) Heravi, M. M.; Motamedi, R.; Siefi, N.; Bamoharram, F. F.; *Catal. Commun*., **2007**, *7,*1467.

[30] Dornow, A.; Menzel, H.; Maix, P.; *Chem. Ber*. **1964**, *97*, 2173.

[31a] Heravi, M. M.; Khosrofar,P.; *J. Sci. I. R. Iran,* **1996**, *7(*2), 86-88; b) Nuss, J. M.; Levine, B. H. R.; Rennels, A.; Heravi, M. M.; *Tetrahedron Lett*. **1991**, 5243; c) Heravi, M. M.; Bakavoli, M.; *J. Chem. Soc. Pak.I,* **1993**, *15(4),* 257; d) Heravi, M. M.; Nuss, J. M.; *J. Sci. I. R. Iran*. **1993**, *4(3),* 194.

[32] Kharasch, M. S.; Seyler, R. C.; Mayo, F. R.; *J. Am. Chem. Soc*. **1938**, *60*, 882.

[33a] Heravi, M. M.; Zadmard, R.; Bolourtchian S. M.; Aghapoor, K. I.; *J. Sci. Tech*. **1999***, 23(2),* 151-154. ; b) Heravi, M. M.; Aghapoor, K.; Nooshabadi, M. A.; Mojtahedi, M. M.; *Monatshefte für chemie,* **1997**, *128*, 1143-1147.

[34] Zadmard, R.; Heravi, M. M.; Bolurchian, S. M.; *Indian J. Heter. Chem*. **1998**, 7, 239-240.

[35] Kozhevnikov, I. V. *Russ. Chem. Rev*. **1987**, *56,* 811.