Short communication

Synthesis of 8-aryl-1*H*-pyrazolo[4,3-e][1,2,4]triazolo[4,3-a] pyrimidine-4(5H)-imine by using the Preyssler's anion $[NaP_5W_{30}O_{110}]^{14-}$ as a green and eco-friendly catalyst

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Abstract

Reaction of 6-hydrazino-1,5-diphenyl-1*H*-pyrazolo[3,4-d]pyrimidine-4-imine with aromatic aldehyde in presence of Preyssler catalyst yielded 8-aryl-1*H*-pyrazolo[4,3-e][1,2,4]triazolo[4,3-a] pyrimidine-4(5H)-imine. The performance of different form of Preyssler's anions including $H_{14}[NaP_5W_{30}O_{110}]$, H_{14}-P_5, mixed-addenda $H_{14}[NaP_5W_{29} MoO_{110}]$, H_{14}-P_5Mo, silica supported $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$ and H_{14}-P_5/SiO_2 have been investigated. The reaction results were compared with that of a conventional acid catalyst (H_2SO_4).
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1. Introduction

In recent years, pyrazolo triazolo pyrimidine has been the subject of intense interest due to the interesting pharmacological activities that were discovered in several of their derivatives [1–3]. Various types of this compound have been used as the new pharmacological tool for the characterization of human A_3 adenosine receptor [4]. Therefore, investigation to find out the new synthesis methods drew considerable amount of interest.

Recently, researchers prepared pyrazolo[4,3-e][1,2,4]-triazolo[4,3-a] pyrimidine-4(5H) imine derivatives from the reaction of 6-hydrazino,1,5-diphyenyl-1,5 dihydro-4-H pyrazolo [3,4-d] pyrimidine 4-imine with ortho-esters in presence of mineral acids such as H_2SO_4 [5]. On the other hand green chemistry or sustainable chemistry is spreading into the chemical industry with development of innovative processes by setting of the new principals that reduce or eliminate the use and generation of hazardous substances [6,7].

It is expected that the new type of solid acid catalyst to be developed replacing the conventional catalysts due to high capital costs caused by the equipment corrosion as well as due to the problems associated with environmental pollution. Heteropoly acids have attracted growing attention in the variety of acid catalyzed reactions such as etherification [8], hydration and dehydration [9,10], condensation [11,12] both in homogenous and heterogeneous system. Moreover interest to the chemistry of large polytungstates has recently increased and some examples of species containing more than 18 tungsten atom have been reported by researcher [13,14]. But there are only few published reports about the application of large polytungstate (or magic clusters) including $[NaAs_4W_{40}O_{140}]^{25-}$ [15], $[NaSb_9W_{21}O_{86}]^-$ [16], and $[NaP_5W_{30}O_{110}]^{14-}$ [17]. The latter of these $[NaP_5W_{30}O_{110}]^{14-}$ so called Pressler's anion (Fig. 1) consists of a cyclic arrangement of five $-PW_6O_{22}-$ units assembled with D_{5h} symmetry. A structural study has revealed that the central cavity formed by these units is occupied by a Na ion [20].

Preyssler's anions were introduced as a promising candidate for green catalyst. This catalyst is considered green with respect to the commercial process criteria namely corrosiveness, safety and quantity of waste production. Indeed this catalyst is remark-
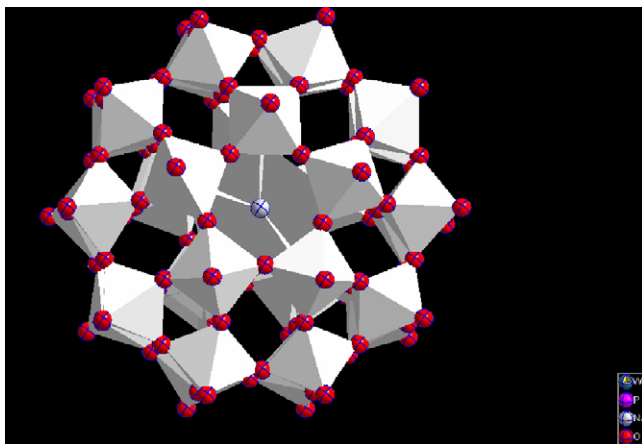
Fig. 1. Preyssler's anion structure.

able owing to its physicochemical properties such as strong Bronsted acidity, reversible transformation, solubility in polar and non-polar solvents, high surface area and high hydrolytic stability (pH 0–12) that are essential in commercial catalytic processes. This heteropoly anion with 14 acidic protons is an efficient "supper acid" catalyst which can be used both in the homogenous and heterogeneous phases [18,19].

The important feature of the Preyssler's polyanion from the environmental point of view is that the polyanion in both bulk and supported forms can be easily recovered and recycled without degradation and loss of activity. Concerning these factors, we are reporting for the first time the synthesis of 8-aryl-1H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-a] pyrimidine-4(5H)-imine derivatives by using Preyssler's anion $H_{14}[NaP_5W_{30}O_{110}]$. It seems this catalyst is an excellent and effective acidic catalyst that can be replaced for conventional acids such as H_2SO_4, HCl, HNO_3 and HF by introducing a more environmental friendly alternative process to the fine chemicals and pharmaceutical industries.

2. Experimental

2.1. Chemicals and apparatus

4-Nitrobazaldehyde, 3-nitrobazaldehyde, 4-cholorbazaldehyde, 4-boromobazaldehyde, 3-methylebazaldehyde, acetic acid were obtained from Merck Company (Darmstadt, Germany). The sulfuric acid was commercially available. Preyssler acid H_{14}-P$_5$, $H_{14}[NaP_5W_{30}O_{110}]$, mixed-addenda H_{14}-P$_5$Mo, $H_{14}[NaP_5W_{29} MoO_{110}]$, were prepared by passage of a 11.4 g of their respective potassium salts in 20 ml of water through an ion-exchange column (50 cm × 8 cm) of DOWEX 50W-X8 in the H$^+$ form and evaporation of the elute to dryness in vacuum [17,20].

The molybdenum substituted Preyssler heteropoly anion $H_{14}[NaP_5W_{29} MoO_{110}]$ was prepared by dissolving 5.6 g (0.338 mol) $Na_2WO_4\cdot2H_2O$ and 4 g (0.016 mol) $Na_2MoO_4\cdot2H_2O$ in 70 ml of demineralized water. After stirring at 60 °C for 30 min the mixture was cooled down to the room temperature. Then 30 ml concentrated phosphoric acid was

added. The resulting yellow solution was refluxed for 18 h. The color turned to dark green at the end of reaction. The solution was brought to room temperature, diluted with 30 ml water and then 20 g KCl was added with vigorous stirring. The mixture was stirred and then evaporated to dryness and a greenish solid was obtained. This raw product was dissolved in 60 ml warm water and was cooled down to room temperature. The yellow crystals which were formed collected and recrystallized from boiling water. The substituted Molybdenum heteropoly anion was converted into its corresponding acid form as described earlier for the unsubstituted analog. Elemental analysis of product showed W = 71.73%, Mo = 1.32%, P = 2.09%, Na = 0.31%, H = 0.19% that corresponds with $H_{14}[NaP_5W_{29} MoO_{110}]$ molecular composition.

In addition to Pressler heteropoly anion, $K_6[P_2W_{17}MoO_{62}]$ was recrystallized from the remaining mother liquor overnight as a by-product. The chemical analysis of this by-product gave W = 69.31%, Mo = 2.15%, P = 1.32%, K = 5.16% which is matching up well with W = 69.30, Mo = 2.13, P = 1.37, K = 5.20 of the calculated formula percentages for $K_6[P_2W_{17}MoO_{62}]$. $K_6[P_2W_{17}MoO_{62}]$ was converted to corresponding acid by passing through DOWEX-50W-X8 ion exchange column.

Supported catalyst was prepared using a method essentially similar to the one described by Alizadeh et al. [20]. In a typical preparation an aqueous solution of Pressyler's anion in acid form (0.32 mmol of acid in 20 ml of water) was added to a suspension of 2 g. AEROSIL® 300 commercial (Degussa) silica powder in 25 g of water. AEROSIL® 300 is a hydrophilic fumed silica with a specific surface area of 300 m^2/g and average primary particle size of 7 nm. After stirring of the mixture for 5 h, water was evaporated and the solid was dried at 120 °C and calcined at 250 °C in a furnace prior to use according to the reported procedure [19].

2.2. Synthesis of 4-amino-pyrazolo [3,4-d]pyrimidines 2(a–e)]

A solution 1 mmol of **1(a–b)** (Scheme 1), 1 mmol of an aromatic aldehyde **2** and an appropriate heteropoly acid
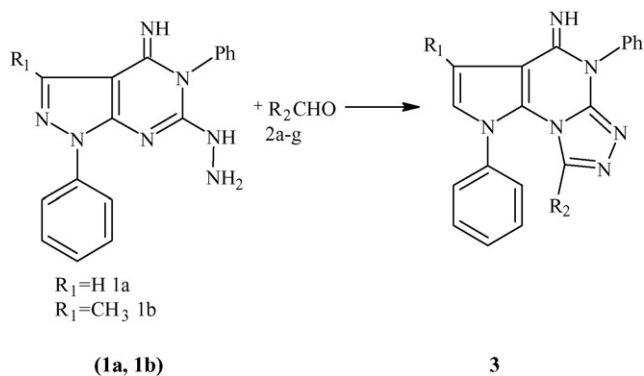
Scheme 1. Reaction of 6-hydrazino-1,5-diphennyl-1H-pyrazolo[3,4-d]pyrimidine-4-imine (**1a**, **1b**) with aromatic aldehyde **2(a–g)** in presence of solid acid to give 8-aryl-1H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-a] pyrimidine-4(5H)-imine **3**.

Table 1
Catalytic synthesis of 8-aryl-1*H*-pyrazolo[4,3e][1,2,4]triazolo[4,3-a]pyrimidine-4(5H)-imine **3** with 6–7 h reflux

Entry	R_1	R_2	Yield of product (%)			
			H_{14}-P$_5$	H_{14}-P$_5$Mo	H_{14}P$_5$/SiO$_2$	H_2SO_4
3a	H	Ph	86	79	68	51
3b	H	4-MeC$_6$H$_4$	83	71	63	49
3c	H	3-MeC$_6$H$_4$	85	78	61	46
3d	H	4-NO$_2$C$_6$H$_4$	78	68	58	39
3e	H	3-NO$_2$C$_6$H$_4$	75	65	58	38
3f	H	4-ClC$_6$H$_4$	71	64	52	41
3g	H	4-BrC$_6$H$_4$	68	61	55	40
3h	CH$_3$	Ph	88	81	68	56
3i	CH$_3$	4-MeC$_6$H$_4$	82	76	56	48
3j	CH$_3$	3-MeC$_6$H$_4$	83	75	58	49
3k	CH$_3$	4-NO$_2$C$_6$H$_4$	73	62	54	38
3l	CH$_3$	3-NO$_2$C$_6$H$_4$	75	63	51	35
3m	CH$_3$	4-ClC$_6$H$_4$	73	68	56	42
3n	CH$_3$	4-BrC$_6$H$_4$	71	65	51	46

(0.05 mmol) in acetic acid was refluxed for 6–7 h. The progress of the reaction was monitored by thin layer chromatography (TLC). The solid catalyst was separated from reaction products by filtration and washed with warm acetic acid (the catalyst is not soluble in acetic acid). The filtrate was cooled down and the crystallized product was filtered, washed with cold dimineralized water, dried and recrystallized by ethanol to give pure product **3** in Scheme 1 (Tables 2 and 3). After removing the reaction product by filtration and washing the solid catalyst with diethyl ether, it can be reused and subjected to a second run of the reaction. The result of the first experiment and subsequent experiment were almost consistent in yields. All compounds were characterized by IR, ^{1}H NMR spectroscopy and elemental analyses.

The melting points were obtained by using an Electrothermal IA 9100 Digital Melting Point apparatus. The IR spectra were recorded on a Bruker IR spectrometer and ^{1}H NMR spectra were collected by a 100 MHz NMR spectrometer using TMS as internal standard. Elemental analyses were performed by Ferdowsi University, Mashhad, Iran.

3. Result and discussion

We have previously reported the cyclocondensation reaction of 5-amino-1-phenyl-1*H*-pyrazolo-4-carboxamide with aromatic aldehyde in presence of heteropolyacid to corresponding 6-aryl-1-H-pyrazolo[3,4-d]pyrimidine-4[5H]-one [21]. Pursuing our interest in the catalytic synthesis of heterocyclic compounds by using solid acids [22], we are reporting in present paper the catalytic synthesis of 8-aryl-1*H*-pyrazolo[4,3-e] [1,2,4]triazolo[4,3-a]pyrimidine-4(5H)-imine by using the well-Dowson's and Preyssler's heteropoly acid in different forms, pure $H_6[PW_{18}O_{62}]$, mixed-addenda $H_6[PW_{17}MoO_{62}]$, pure H_{14}-P$_5$,$H_{14}[NaP_5W_{30}O_{110}]$, mixed-addenda H_{14}-P$_5$Mo, $H_{14}[NaP_5W_{29}\ MoO_{110}]$ and silica supported $H_{14}[NaP_5 W_{30}O_{110}]/SiO_2$ and H_{14}-P$_5$/SiO$_2$. Moreover the performance of Wells-Dowson and Preyssler's anion has been compared with that of a known classical catalyst namely sulfuric acid.

In this work, a mixture of an aldehyde and 1-substitute 6-hyrazinio, 1,5-diphyenyl 1,-di-hydro-4-h pyrazolo[3,4-d]

Table 2
Melting point and elemental analysis data of reaction products

Entry	mp (°C)	Molecular formula	Analysis (calculated/experimental)				
			C%	H%	N%	Cl%	Br%
3a	230–231	C$_{24}$H$_{17}$N$_7$	71.45, 72.08	4.20, 4.21	24.35, 23.71		
3b	241–242	C$_{25}$H$_{19}$N$_7$	72.36, 72.19	4.61, 4.58	23.03, 23.23		
3c	241–243	C$_{25}$H$_{19}$N$_7$	72.36, 71.99	4.61, 4.73	23.03, 23.38		
3d	248–249	C$_{24}$H$_{16}$N$_8$O$_2$	64.29, 64.21	3.59, 3.59	24.99, 25.07		
3e	247–248	C$_{24}$H$_{16}$N$_8$O$_2$	64.29, 64.11	3.59, 3.71	24.99, 25.05		
3f	252–253	C$_{24}$H$_{16}$N$_7$Cl	65.83, 66.01	3.67, 3.45	22.41, 22.4	8.09, 8.14	
3g	258–259	C$_{24}$H$_{16}$N$_7$Br	59.77, 60.01	3.34, 3.38	20.33, 20.1		16.56, 16.54
3h	231–232	C$_{25}$H$_{19}$N$_7$	71.93, 72.11	4.58, 4.46	23.48, 23.43		
3i	236–237	C$_{26}$H$_{21}$N$_7$	72.4, 72.99	4.88, 4.82	22.72, 22.19		
3j	235–236	C$_{26}$H$_{21}$N$_7$	72.4, 72.3	4.88, 4.79	22.72, 22.68		
3k	249–250	C$_{25}$H$_{18}$N$_8$O$_2$	64.93, 65.08	3.91, 3.88	24.23, 24.13		
3l	248–249	C$_{25}$H$_{18}$N$_8$O$_2$	64.93, 64.88	3.91, 3.93	24.23, 23.71		
3m	251–252	C$_{25}$H$_{18}$N$_7$Cl	66.44, 65.92	4.03, 4.01	21.69, 22.19	7.84, 7.88	
3n	267–268	C$_{25}$H$_{18}$N$_7$Br	60.49, 61.03	3.66, 3.62	19.76, 19.21		16.09, 16.14

Table 3
Characteristic IR and ^{1}H NMR peaks of product **3**

Compound	IR V^{max}, cm^{-1} (KBr)	^{1}H NMR, δ (ppm)
3a	1680 str (C=NH)	(DMSO), 7.4–8.5 (m, 16-arom. and 1*H*-pyrazol rig), 10.6 (1H, br, NH)
3b	1670 str (C=NH)	(DMSO), 7.1–8.7 (m, 15-arom. and 1*H*-pyrazol rig), 2.38 (s, 3H, CH$_3$), 9.9 (1H, br, NH)
3c	1690 str (C=NH)	(DMSO), 7.5–8.9 (m, 15-arom. and 1*H*-pyrazol rig), 2.45 (s, 3H, CH$_3$), 10.2 (1H, br, NH)
3d	1680 str (C=NH) 1550–1600 (N–O str)	(DMSO), 7.3–8.8 (m, 15-arom. and 1*H*-pyrazol rig), 9.8 (1H, br, NH)
3e	1670–1680 (C=NH)	(DMSO), 7.4–8.8 (m, 15-arom. and 1*H*-pyrazol rig), 9.7 (1H, br, NH)
3f	1650–1690 (C=NH)	(DMSO), 7.2–8.7 (m, 15-arom. and 1*H*-pyrazol rig), 10,3 (1H, br, NH)
3g	1650–1680 (C=NH)	(DMSO), 7.3–8.5 (m, 15-arom. and 1*H*-pyrazol rig), 10,3 (1H, br, NH)
3h	1690 (C=NH)	(DMSO), 2.32 (s, 3H, CH$_3$), 7.3–8.8 (m, 14-arom.), 10,1 (1H, br, NH)
3i	1650–1695 (C=NH)	(DMSO), 2.42 (3H, s, CH$_3$), 7.1–8.3 (m, 14-arom.), 10,1 (1H, br, NH), 3.02 (s, 3H, CH$_3$)
3j	1695 (C=NH)	(DMSO), 3.05 (s, 3H, CH$_3$), 2.45 (s, 3H, CH$_3$), 6.6–7.9 (m, 14-arom.), 9.7 (1H, br, NH)
3k	1600–1650 (C=NH) 1510–1580 (N–O str)	(DMSO), 3.1 (s, 3H, CH$_3$), 7.3–8.2 (m, 14-arom.), 10.2 (1H, br, NH)
3l	1620–1680 (C=NH) 1520–1580 (N–O str)	(DMSO), 2.47 (s, 3H, CH$_3$), 7.2–8.1 (m, 14-arom.), 10.4 (1H, br, NH)
3m	1650–1680 (C=NH)	(DMSO), 2.29 (s, 3H, CH$_3$), 7.3–8.3 (m, 14-arom), 10.5 (1H, br, NH)
3n	1650–1695 (C=NH)	(DMSO), 2.25 (s, 3H, CH$_3$), 7.36–8.2 (m, 14-arom.), 10.3 (1H, br, NH)

pyrimidine 4-imine [5] (1) in acetic acid and in presence of catalytic amount of solid acid were refluxed inside a glass reactor equipped with a water cooling condenser for a specific amount of time (6–7 h). The derivatives of 8-aryl-1*H*-pyrazolo[4,3-e][1,2,4]triazolo[4,3-a]pyrimidine-4(5H)-imine were obtained (Scheme 1). All reaction products were well characterized by using IR, proton NMR and elemental chemical analysis and the results were summarized in Tables 1–3. The catalyst is not soluble in acetic acid and enables an easy separation and recovery by filtration for its immediate reuse.

The performance of Preyssler catalyst is comparable with those of known conventional catalyst such as sulfuric acid. Heteropoly acid with Preyssler structure H$_{14}$-P$_5$ shows higher yields than mixed-addenda H$_{14}$-P$_5$Mo and silica supported H$_{14}$-P$_5$/SiO$_2$. Interestingly, by replacing one of the tungsten atoms with molybdenum in the Preyssler type heteropoly acid, the product yield was decreased. So far the reason of this effect is not clear but it is probably caused by the high reducibility of molybdenum atom, considering the fact that a heteropoly acid with molybdenum atom shows higher reduction potential in organic substance [23].

The result of the comparison between H$_{14}$-P$_5$ and H$_{14}$-P$_5$/SiO$_2$ shows that, in all cases, the supported polyacid is less active than non-supported one. One plausible interpretation of this observation is that in the H$_{14}$-P$_5$/SiO$_2$ there could be an acid–base nature of interaction between the polyanion and SiO$_2$ support. Some protons of the polyacid and some basic sites of the support (for example hydroxyl groups) can interact. This could lead to diminished availability of acid sites due to this extra ionic interaction [24]. Comparing the overall yield of reaction products the following trend was observed regarding the catalytic activity:

$$H_{14}\text{-}P_5 > H_{14}\text{-}P_5Mo > H_{14}\text{-}P_5/SiO_2 > H_2SO_4$$
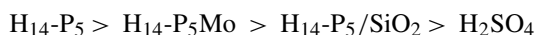
4. Conclusion

Preyssler's anion is a very efficient and environmentally benign heterogeneous catalyst for synthesis of 8-aryl-1*H*-pyrazolo[4,3-e][1,2,4]triazolo[4,3-a]pyrimidine-4(5H)-imine. Among the different form of Preyssler catalyst and sulfuric acid, H$_{14}$-P$_5$ was found to produce the highest yield of product. It is noteworthy to mention that the catalyst in both homogeneous and heterogeneous condition can be recovered and reused without loss of structure and activity.

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