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$H_{14}[NaP_5W_{30}O_{110}]$ Catalyzed One-Pot Three-Component Synthesis of Dihydropyrano[2,3-*c*]pyrazole and pyrano[2,3-*d*]pyrimidine Derivatives

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This is a report of an efficient, clean and facile method for the synthesis of 1,4-dihydropyrano[2,3-*c*] pyrazole and pyrano[2,3-*d*]pyrimidine derivatives *via* three-component one-pot condensation of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one or barbituric acid, aldehydes and malononitrile in the presence of a catalytic amount of preyssler type heteropolyacid as a green and reusable catalyst in water or ethanol under refluxing conditions.

Keywords: 1,4-Dihydropyrano[2,3-*c*]pyrazoles, Pyrano[2,3-*d*]pyrimidines, On water reactions, Preyssler type heteropoly acid, Multi-component reactions

INTRODUCTION

Combinatorial chemistry is being increasingly applied for the discovery of novel biologically active compounds. In this context, multicomponent reactions (MCRs) are a powerful tool in the modern drug discovery process in terms of lead finding and lead optimization [1,2].

The synthesis, reactions and biological activities of 4H-pyrane-containing molecules afford an ever-expanding area of research in heterocyclic chemistry. This structural motif appears in a large number of pharmaceutical agents, drug candidates [3,4], photoactive materials [5] and natural products [6]. These interesting activities have stimulated chemists to develop the chemistry of such a class of compounds [7].

Condensed pyrazoles are also biologically interesting compounds and their chemistry has recently received considerable attention [8,9]. Several pyrano[2,3-*c*]pyrazoles are reported to have useful biological effects, such as analgesic and anti-inflammatory activities [10]. Moreover, the biological activity of fused azoles has led to intensive research on their synthesis [11-13]. Recently, three component one-pot condensation of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one, aldehydes and malononitrile for the construction of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives has been reported under different conditions [14-18]. However, most of the reported methods have their drawbacks. For example, hexadecyltrimethylammonium bromide (HTMAB) is a harmful and irritant catalyst which is dangerous for the environment [16]. In addition, the reusability of the catalysts such as D,L-proline is not reported in a number of cases [17].

In recent years, special attention has been focused on the use of water as a green solvent in various organic transformations. In addition to its abundance and for economical and safety reasons, water has naturally become a substitute and an alternative environmentally benign solvent in organic synthesis [19,20]. The use of aqueous medium as

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solvent further reduces the harmful effects of organic solvents on the environment.

The growing environmental awareness in chemical research and pharmaceutical chemistry, due to their traditionally large volume of waste/product ratios, is perhaps the ripest area for greening [21]. Green chemistry approaches have considerable potential not only for the reduction of by-products, decreasing waste produced and lowering energy costs, but for the development of new methodologies for the previously inaccessible materials, using existing technologies [21]. The importance of green chemistry is highly valued in medicinal chemistry.

There has been considerable interest in the use of heteropolyacids as environmentally benign catalysts due to their unique properties such as high thermal stability, low cost, ease of preparation and recyclability. Numerous chemical reactions can occur in the presence of heteropolyacids [22]. Preyssler type heteropolyacid, $H_{14}[NaP_5W_{30}O_{110}]$, is remarkable owing to its exclusive physicochemical properties. These include strong Bronsted acidity, reversible transformations, solubility in polar and non-polar solvents, high hydrolytic and thermal stability, which are all essential in catalytic processes. Preyssler polyanion, as a large anion, can provide many ‘‘sites’’ on the oval-shaped molecule that are likely to render the catalyst effective [23]. This heteropolyanion with [9] acidic protons, is an efficient ‘‘supper acid’’ solid catalyst which can be used both in the homogeneous and heterogeneous phases [24]. In addition, both pure and supported catalysts can be easily recovered and recycled without degradation and loss of activity.

Recently, we have reported on catalytic behavior of Preyssler’s anion [19]. Making use of the experience gained from this study and based on our previous investigations into the use of heteropolyacids as catalysts to help organic reactions to occur [25-28], we examined the possibility of using $H_{14}[NaP_5W_{30}O_{110}]$ as a catalyst for three-component one-pot synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives (compound II) *via* condensation of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one, malononitrile and a variety of aldehydes in water or ethanol under heating conditions (Scheme 1).

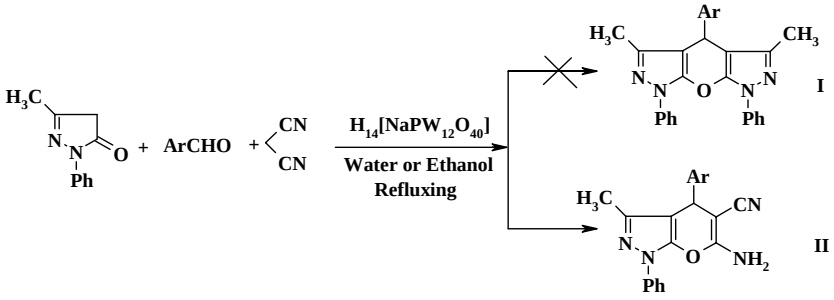
EXPERIMENTAL

All the chemicals were purchased from Merck Company. All products were known compounds and identified by comparing their spectra and all the physical data available in the literature [16,29-32,36]. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}H NMR spectra were recorded on a Bruker ARX 300 (300 MHz) instrument, using TMS as an internal standard (DMSO-d_6 solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. The reactions were monitored by TLC.

Preyssler type heteropolyacid was prepared by the passage of a solution of the potassium salt in water through a column (50 cm × 1 cm) of Dowex 50 W × 8 in the H^+ form and evaporation of the elute to dryness under vacuum.

Synthesis of 1,4-Dihydropyrano[2,3-c]pyrazole Derivatives: General Procedure

A mixture of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one or barbituric acid (1 mmol), aldehyde (1 mmol), malononitrile (1 mmol) and a catalytic amount of $H_{14}[NaP_5W_{30}O_{110}]$ (1 mol%) was refluxed in water or ethanol (5 cc) for indicated time as required to complete the reaction (Table 3). Upon completion



Scheme 1

of the reaction, monitored by TLC, the mixture was cooled to room temperature. The precipitated products were separated by filtration and recrystallized in ethanol.

Recycling of the Catalyst in Aqueos Media

After the filtration of the products, the catalyst was recycled by evaporation of the aqueous solution and washing with diethyl ether in each case. The recovered catalyst was dried and reused for the next reaction with only a modest loss in activity. The catalyst was recovered and reused for five times in the model reaction in aqueous media. The obtained results are summarized in Table 3.

Selected Spectroscopic Data

6-Amino-5-cyano-3-methyl-1,4-diphenyl-1,4-dihydro-pyrano[2,3-*c*]pyrazole. (Table 2, entry 1): ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.93 (s, 3H, CH_3), 4.68 (s, 1H, 4-H), 4.75 (s, 2H, NH_2), 7.16-7.32 (m, 10H, ArH) ppm. IR (KBr): ν_{max} = 3472, 3320, 2195, 1660, 1590, 1264, 1125, 1027, 753 cm^{-1}.

6-Amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano [2,3-*c*]pyrazole. (Table 2, entry 4): ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.78 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.88 (s, 1H, 4-H), 6.82 (d, 2H, *J* = 8.0 Hz, ArH), 6.96 (s, 2H, NH_2), 7.04 (d, 2H, *J* = 8.0 Hz, ArH), 7.20-7.24 (m, 1H, ArH), 7.40 (d, 2H, *J* = 8.0 Hz, ArH), 7.58 (d, 2H, *J* = 8.0 Hz, ArH) ppm. IR (KBr): ν_{max} = 3395, 3322, 2192, 1660, 1595, 1394, 1250, 1128, 813 cm^{-1}.

6-Amino-4-(4-methylphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole. (Table 2, entry 8): ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.78 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.62 (s, 1H, 4-H), 6.96 (s, 2H, NH_2), 7.02 (d, 2H, *J* = 8.4 Hz, ArH), 7.08 (d, 2H, *J* = 8.4 Hz, ArH), 7.30-7.34 (m, 1H, ArH), 7.46 (d, 2H, *J* = 8.0 Hz, ArH), 7.78 (d, 2H, *J* = 8.0 Hz, ArH) ppm. IR (KBr): ν_{max} = 3414, 3314, 2178, 1658, 1594, 1398, 1258, 1128, 1026, 754 cm^{-1}.

RESULTS AND DISCUSSION

In order to get the best reaction conditions the efficiency of a variety of solvents in the synthesis of 6-amino-5-cyano-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole in the presence of a catalytic amount of $H_{14}[NaP_5W_{30}O_{110}]$ (1 mol%) as a model reaction was studied.

Firstly, we carried out the model reaction under solvent-free conditions at room temperature. The reaction was not completed. The temperature of the reaction mixture started to rise for 4 h but the reaction was not completed. Then, we examined the effect of the solvent on the reaction. As shown in Table 1, the best results were obtained in refluxing water and ethanol. This could be due to two reasons: *a*) the first stage of the reaction includes Knoevenagel condensation, which is faster in water [28]; *b*) the PK_a of HPA depends on the solvent [33].

We also studied the relation between the rate of the model reaction and temperature. It was found that there was a correlation between reaction rate and the temperature and the best results were obtained in refluxing water and ethanol (Table 1).

In order to establish the scope of this novel methodology, we tested a variety of aldehydes and methylene active

Table1. Optimization of the Reaction Conditions in the Model Reaction

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	Solvent free	100	4	44
2	$CHCl_3$	62	4	46
2	H_2O	25	2	80
3	H_2O	100	1	89
4	CH_2Cl_2	40	4	40
5	EtOH	25	2	75
6	EtOH	78	1	84

[a]Yields are related to isolated pure products.

compounds under the optimized reaction conditions. The reaction was found to be tolerating a range of Ar groups with different electronic demands including aromatic rings involving electron-donating and electron-withdrawing groups (Scheme 1). Unfortunately, ethylcyanoacetate, diethyl-malonate, ethylbenzoylacetate, ethylacetoacetate and acetophenone were not active under these conditions (Table 2, entries 9-12). We also examined the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one with chalcone, but the desired product was not obtained even after prolonged reaction times (Table 2, entry 13). When 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one was replaced by barbituric acid the related products (III) were obtained in good yields (Table 2, entries 14-18).

It is noteworthy that the catalyst is recyclable and could be reused without any significant loss of activity. $H_{14}[NaP_5W_{30}O_{110}]$ is soluble in water and could be recovered by filtration of the product, evaporation of the residue solution and washing with diethyl ether. The recycled catalyst could be subjected to a second or even a third reaction. In the case of the model reaction in water, after five runs, the catalytic activity of the catalyst was almost the same as that of the freshly used catalyst. (Table 3)

Bykova has reported an unprecedented route for this kind of condensation reaction [34]. He obtained compound (I) as the major product in the presence of piperidine as a basic catalyst (Scheme 1). For another derivative, as reported by Madkour, compound (I) was obtained under the same reaction conditions in 15% but the major product was compound (II) [35]. We did not obtain the same byproduct (I) under our optimized conditions.

Table 2. Synthesis of 1,4-Dihydropyrano[2,3-c]pyrazole Derivatives under Optimized Conditions in Refluxing Water or Ethanol

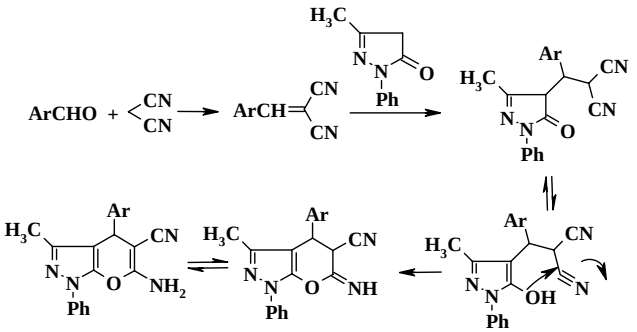
Entry	Ar-	Methylene active compound	Product	Yield (%)[a]		Time (min)		m.p. (^oC)
				H_2O	EtOH	H_2O	EtOH	Obtained, Reported
1	Ph-	Malononitrile	IIa	94	93	60	55	167-171, 169-171 [21]
2	3-NO_2-Ph-	Malononitrile	IIb	95	92	45	55	190-192, 191-192 [21]
3	4-NO_2-Ph-	Malononitrile	IIc	95	90	45	50	195-197, 196-198 [21]
4	4-MeO-Ph-	Malononitrile	IId	92	91	50	60	174-177, 174-176 [21]
5	2-Cl-Ph-	Malononitrile	IIe	90	87	60	60	145-147, 145-146 [34]
6	4-Cl-Ph-	Malononitrile	IIf	95	90	50	55	174-177, 175-177 [21]
7	4-HO-Ph-	Malononitrile	IIg	90	90	50	60	210-213, 211-212 [21]
8	4-Me-Ph-	Malononitrile	IIh	85	84	60	65	178, 177-179 [21]
9	Ph-	Ethylcyanoacetate	-	N.R	N.R	24 h	24 h	-
10	Ph-	Ethylacetoacetate	-	N.R	N.R	24 h	24 h	-
11	Ph-	Diethylmalonate	-	N.R	N.R	24 h	24 h	-
12	Ph-	Ethylbenzoylacetate	-	N.R	N.R	24 h	24 h	-
13	Ph-[b]	Acetophenone[b]	-	N.R	N.R	24 h	24 h	-
14	Ph-[c]	Malononitrile	IIIa	-	85	-	60	223-226, 224-5 [36]
15	3-NO_2-Ph-	Malononitrile	IIIb	-	90	-	30	265, 262-263 [36]
16	4-NO_2-Ph-	Malononitrile	IIIc	-	90	-	50	270-272, 238-239 [36]
17	4-Cl-Ph-	Malononitrile	IIId	-	90	-	30	245-247, 242-244 [36]
18	4-MeO-Ph-	Malononitrile	IIIe	-	88	-	45	230-233, 280-281 [36]

[a]Yields are related to isolated pure products. [b]In this reaction, firstly benzaldehyde, acetophenone, catalyst and solvent were treated together under refluxing conditions, to produce the chalcone and then pyrazolone derivative was added to the mixture. [c]In 14-18 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one was replaced by barbituric acid.

Table 3. Reusability of the Catalyst in the Model Reaction in Refluxing Water

Entry	Number of recycle	Time (min)	Yield (%)[a]
1	Fresh	60	94
2	1	60	89
3	2	60	85
4	3	60	83
5	4	60	78

[a]Yields are related to isolated pure products.



Scheme 2

The suggested mechanism is schematized in Scheme 2 which fully accords with the obtained results. A similar mechanism has also been proposed by Tong-Shou Jin *et al*. [29].

CONCLUSIONS

In summary, the synthesis of 1,4-dihydropyrano[2,3-*c*] pyrazole derivatives in the presence of an inexpensive, reusable, easy to handle, non-corrosive, highly hydrolytic, thermally stable and environmentally benign solid acid catalyst was investigated. Using this catalyst offers advantages including the simplicity of operation due to the heterogeneous nature of reaction, easy work-up, high yields of products, high selectivity and the recyclability of the catalyst. Barbituric acid showed the same activity in this reaction. Our findings will not only lead to a practical synthetic method but will also expand the versatility of clean organic reactions in water.

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