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Original article

An environmentally friendly synthesis of 1,4-dihydropyrano [2,3-*c*]pyrazole derivatives catalyzed by tungstate sulfuric acid

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Aromatic aldehyde
Malononitrile
Tungstate sulfuric acid

ABSTRACT

An efficient three-component synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazoles *via* a reaction between 3-methyl-1-phenyl-2-pyrazolin-5-one, aromatic aldehydes and malononitrile using tungstate sulfuric acid as a catalyst was described. Mild conditions, good to excellent yields, easily available catalyst and easy work-up are the key features of this method.

1. Introduction

There has been considerable interest in syntheses, reactions and biological activities of 4*H*-pyrane-containing molecules. Furthermore, 4*H*-pyrane derivatives also constitute a structural unit of some pharmaceutical agents, drug candidates, photoactive materials and natural products [1,2]. These high profile applications and variety of biological activities have promoted extensive studies for the synthesis of 1,4-dihydropyrano[2,3–*c*]pyrazole derivatives [3].

Condensed pyrazoles are also biologically interesting compounds and their chemistry has recently received considerable attention [4]. Several pyrano[2,3-*c*]pyrazoles are reported to have useful biological effects, such as analgesic and anti-inflammatory activities [5]. Moreover, the biological activity of fused azoles has led to intensive research on their synthesis [6,7]. Recently, the 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 using different conditions [8,9].

Solid acids have been used as eco-friendly and reusable catalysts in various organic transformations. The solid acid catalysts were well received by the synthetic community because of their reusability, lack of toxicity, and easy work-up [10]. Recently, we found that anhydrous sodium tungstate (**1**) reacts with chlorosulfonic acid (**2**) to give tungstate sulfuric acid (**3**) (Scheme 1).

2. Experimental

Catalyst preparation: Firstly, 25 mL of dry *n*-hexane was taken in a 100 mL round bottom flask, equipped with ice bath and overhead stirrer, and 5.876 g (2 mmol) of anhydrous sodium tungstate was added to the flask, then 0.266 mL (4 mmol) of chlorosulfonic acid was added dropwise to the flask in 30 min. This solution was stirred for 1.5 h, the reaction mixture was slowly poured into 25 mL of chilled distilled water with agitation. The yellowish solid was filtered, washed with distilled water five times till the filtrate showed negative for chloride ion test, and dried at 120 °C for 5 h. The catalyst was obtained in 98% yield and decomposed at 285 °C [11].

General procedure for the preparation of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazoles: A mixture of 3-methyl-1-phenyl-2-pyrazolin-5-one (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol), and TSA (10 mol%) in ethanol (10 mL) was refluxed for an appropriate period of time. After the completion of the reaction (monitored by TLC analysis), the catalyst was separated by filtration. The solvent was removed

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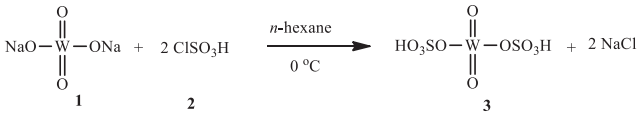
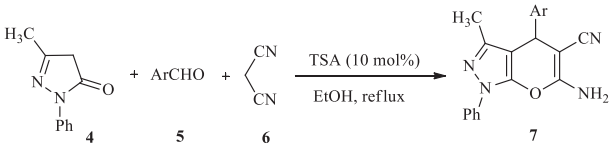


Scheme 1. Preparation of tungstate sulfuric acid (TSA).



Scheme 2. TSA-catalyzed synthesis of 1,4-dihydropyrano[2,3-c]pyrazoles 7.

under vacuum and the products **7** were purified by recrystallization from EtOH/H_2O.

3. Results and discussion

Fig. 1(A) shows the XRD patterns of tungstate sulfuric acid (TSA). It was reported that high degree mixing of W–S in chlorosulfonic acid often led to the absence of XRD pattern for anhydrous sodium tungstate. The broad peak around 25.7° (2θ) (θ is the Bragg's angle) from the smaller inset could be attributed to insertion of W into the framework of chlorosulfonic acid.

The FT-IR spectra of anhydrous sodium tungstate and TSA are shown in Fig. 1(B). The spectrum of tungstate sulfuric acid shows the characteristic bonds of anhydrous sodium tungstate and chlorosulfonic acid. The adsorption bands in 3406, 1820, 1725, 1702, 1620, 1290, 1060, 1005 and 860 cm^{-1} in the catalyst spectrum reveal both bonds in anhydrous sodium tungstate and the –OSO_3H group. Hence titration of catalyst with NaOH (0.1 mol/L) was conducted. Catalyst (1 mmol) was dissolved in 100 mL of water and titrated with NaOH (0.1 mol/L) using phenolphthalein as an indicator. It was found that for 1 mmol of catalyst, 4 mmol of NaOH was utilized. This result shows that each complex contains two acidic groups. The XRF data of tungstate sulfuric acid indicates the presence of WO_4 and SO_3 in this catalyst (Table 1).

In continuation of our interest in using solid catalysts in the synthesis of heterocycles [11–13], in this work, we describe a simple and green strategy based on the condensation of 3-methyl-1-phenyl-2-pyrazolin-5-one (**4**), aromatic aldehydes (**5**) and malononitrile (**6**) using TSA as a powerful, recyclable and safe catalyst for the preparation of novel and known 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazoles (**7**) (Scheme 2).

To determine the suitable reaction conditions, a solvent-free reaction of 3-methyl-1-phenyl-2-pyrazolin-5-one, benzaldehyde and malononitrile was performed at room temperature. A low conversion was observed. Then, the reaction was heated for 4 h, but again full conversion was not achieved. So, we studied the effect of solvent, temperature and various catalytic amount of the TSA catalyst on the model reaction (Table 2).

As can be seen, the best results were obtained by performing the reaction in the presence of 10 mol% of TSA in refluxing ethanol. Then the generality of the procedure was evaluated using various aromatic aldehydes under optimized reaction conditions. It was found that both, electron rich and electron poor aryl aldehydes reacted well in this process to afford the corresponding products in good to excellent yields (Table 3).

Table 2
Optimization of the reaction conditions.

Entry	Solvent	Catalyst loading	Temperature (°C)	Time (min)	Yield (%)
1	None	–	80–90	240	20
2	EtOH	–	70–80	240	25
3	EtOH	1 mol%	70–80	120	60
4	EtOH	5 mol%	70–80	100	60
5	EtOH	10 mol%	70–80	10	95
6	CH_3CN	10 mol%	70–80	70	50
7	CH_2Cl_2	10 mol%	40	120	40
8	H_2O	10 mol%	90–100	120	70
9	None	10 mol%	70–80	50	60
10	None	10 mol%	100	40	65
11	None	5 mol%	70–80	60	60
12	None	1 mol%	70–80	100	65

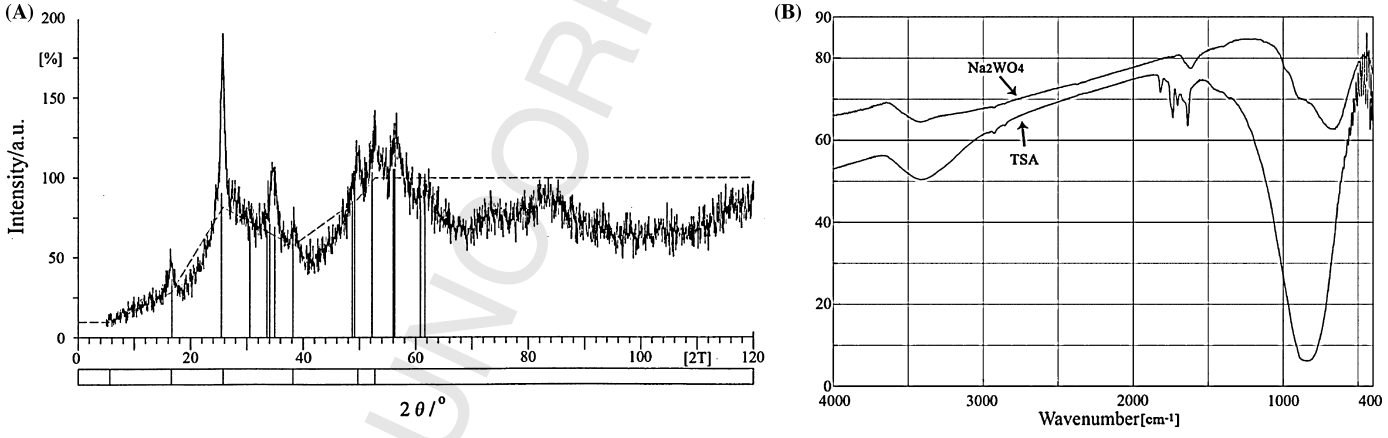


Fig. 1. (A): The powder X-Ray diffraction pattern of the tungstate sulfuric acid. (B): FT-IR spectra of TSA and sodium tungstate.

Table 1
XRF data of TSA.

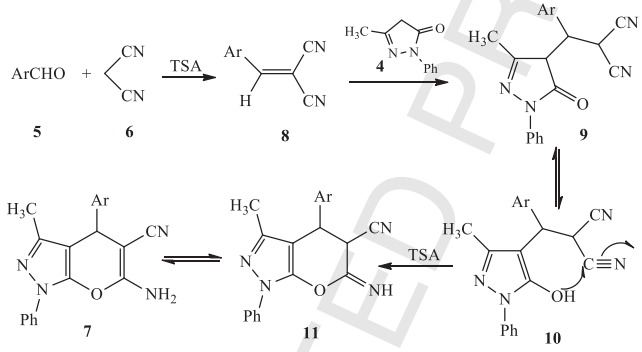
Compound	WO_4	SO_3	Na_2O	Cl	CuO	Fe_2O_3	CaO	LOI[a]	Total
Concentration (% w/w)	19.49	0.317	0.190	0.056	0.023	0.015	0.014	79.82	99.93

[a] Loss on ignition.

Table 3
Synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazoles by TSA.

Entry	Ar	Time (min)	Yield (%)[a]	Mp (°C)	Ref.
7a	C_6H_5	10	95	171–173	[8]
7b	2-Cl-C_6H_4	20	92	145–146	[8]
7c	3-Br-C_6H_4	30	88	159–160	[9]
7d	3-NO_2-C_6H_4	20	80	190–192	[8]
7e	4-MeO-C_6H_4	32	88	174–175	[8]
7f	4-Me-C_6H_4	30	86	176–177	[8]
7g	4-Br-C_6H_4	35	85	182–184	[4]
7h	4-NO_2-C_6H_4	20	95	195–197	[8]
7i	4-*Iso*-propyl-C_6H_4	35	92	167–169[b]	
7j	4-Bisphenyl-C_6H_4	20	88	175–176[b]	
7k	4-Benzyloxy-C_6H_4	25	90	158–159[b]	
7l	1-Naphthyl	15	90	159–160[b]	
7m	2,4-Cl_2-C_6H_3	30	85	185–186	[6]
7n	3-OEt-4-HO-C_6H_3	20	88	170–171[b]	

[a] Isolated yields.
[b] Novel compounds.



Scheme 3. The proposed mechanism for the TSA-catalyzed formation of 1,4-dihydropyrano[2,3-c]pyrazoles 7.

Table 4
Comparison of the results for the synthesis of **7a** by the other catalysts.

Entry	Catalyst	Catalyst loading	Condition	Time (min)	Yield (%)	Ref.
1	Mg/Al HT	0.1 g	EtOH, rt	60	87	[14]
2	γ-Alumina	30 mol%	H_2O, reflux	50	80	[15]
3	$H_{14}[NaP_5W_{30}O_{110}]$	1 mol%	H_2O or EtOH, reflux	55–60	93	[6]
4	Triethylbenzylammoniumchloride	0.15 g	H_2O, 90 °C	360	99	[16]
5	*p*-Toluene sulfonic acid	0.05 g	H_2O, reflux	55	86	[17]
6	Tungstate sulfuric acid	10 mol%	EtOH, reflux	10	95	

We propose the possible following mechanism for the reaction. One molecule of malononitrile is firstly condensed with the aromatic aldehyde activated by the strong solid acid TSA to afford α-cyanocinnamonitrile derivative **8**. Then nucleophilic attack of the active methylene of **4**–**8** gives the intermediate **9** followed by tautomerization to produce **10**. Cyclization of **10** by the nucleophilic attack of the OH group in the cyano moiety gives **11** and subsequently products **7** (Scheme 3).

As an eco-friendly procedure, the recovery and reusability of the catalyst are quite preferable. The recovered TSA from the model reaction was regenerated by washing with ethylacetate and dried at 100 °C for 1 h. The recycled catalyst can be used at least four consecutive times in the model reaction, albeit in gradually decreased yields.

From these results, we identified the best conditions for the synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazoles with the TSA catalyst. Comparison of this method with others in the synthesis of 6-Amino-5-cyano-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (**7a**) as a model reaction is shown in Table 4. These results show that this catalyst compared favorably in the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives with the other reported catalysts and methods.

4. Conclusion

In summary, the reaction between 3-methyl-1-phenyl-2-pyrazolin-5-one, aromatic aldehydes and malononitrile using tungstate sulfuric acid as a catalyst provides a simple and efficient one-pot entry for the synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives. The use of a green and recyclable catalyst, high yield of products, and a simple workup procedure make the present method a valuable contribution in accord with green chemistry principles.

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