

Brønsted acidic ionic liquid as a recyclable catalyst for the one pot four-component synthesis of substituted pyrano[2,3-c]pyrazoles

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ABSTRACT

An efficient, mild and environmentally friendly method was reported for the synthesis of pyranopyrazoles from aryl aldehydes, ethyl acetoacetate, malononitrile and hydrazine hydrate in the presence of catalytic amounts of methyl imidazolium hydrogen sulfate ([Hmim][HSO₄]) as an efficient catalyst. These syntheses were performed via a one-pot four-component condensation in water/ethanol (50%) at 50 °C. This method easily provides the corresponding products in good yield and relatively short reaction times. Also the reusability of the catalyst was investigated, the catalyst could be employed four times, although its activity gradually decreased.

Keywords: Four-component reaction, Pyranopyrazole, Aldehydes, Hydrazine hydrate, Methyl imidazolium hydrogen sulfate.

1. Introduction

Green chemistry emphasizes the development of environmentally benign chemical processes and technologies [1]. Multi-component reactions (MCRs) are those reactions in which three or more reactants react together to give the product in a single step under suitable reaction conditions [2]. As MCRs are one-pot reactions, they are easier to carry out than the multistep syntheses. Recently, multicomponent reactions (MCRs) have played an increasingly important role in organic and medicinal chemistry [3-5]. Moreover, this approach is known as an important, economical and environmentally benign process in synthetic chemistry due to decreasing a number of reaction steps, lower costs, shorter reaction times, high atom-economy, energy saving, and the avoidance of time consuming, waste consumption and expensive purification processes [6]. Hence, the development of multi-component reaction protocols for the synthesis of heterocyclic compounds has attracted significant interest from pharmaceutical groups.

Multicomponent reactions (MCRs) are very important for the construction of many heterocyclic compounds.

The synthesis of nitrogen heterocycles is of great interest because they constitute an important class of natural and synthetic products, which many of them exhibit useful biological activity and application in pharmaceutical preparations [7-10].

Pyranopyrazoles are an important class of heterocyclic compounds. Dihydropyrano [2,3-c] pyrazoles play an essential role as biologically active compounds and represent an interesting template for medicinal chemistry [11]. Many of these compounds are known for their antimicrobial, [12] insecticidal [13] and anti-inflammatory activities [14]. Furthermore dihydropyrano [2,3-c] pyrazoles show molluscicidal activity [15,16] and are identified as a screening kit for Chk1 kinase inhibitor [17]. They also find applications as pharmaceutical ingredients and biodegradable agrochemicals [18-20]. Pyranopyrazole was first synthesized by the reaction between 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene [21]. Sharanin et al. have reported a three-component reaction between pyrazolone, an aldehyde and malononitrile in ethanol using triethylamine as a catalyst [22]. Also the synthesis of pyrazolopyran via a three-component condensation between *N*-methylpiperidone, pyrazoline-5-one and malononitrile in absolute ethanol has been reported

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[23]. Peng and co-workers have developed a two-component reaction involving pyran derivatives and hydrazine hydrate to obtain pyranopyrazoles in water [24]. Recently some four component reaction of aldehydes, ethyl acetoacetate, malononitrile and hydrazine hydrate for the synthesis of 1,4-dihydropyrano [2,3-c] pyrazoles by using various catalysis are reported [25-31]. However, the majority of these methods are associated with disadvantages such as: use of expensive and environmentally hazardous reagents, low yields of products, drastic reaction conditions and tedious work-up procedures.

In continuation of our works on the synthesis of biologically active heterocyclic organic compounds [32-35]; herein, we report an efficient and convenient procedure for the synthesis of 1,4-dihydropyrano[2,3-c]pyrazoles by a four component reaction of aromatic aldehydes, ethyl acetoacetate, malononitrile and hydrazine hydrate in the presence of catalytic amount of methylimidazolium hydrogen sulfate as a green and reusable Brønsted acidic ionic liquid in water/ethanol (50%) at 50°C (Scheme 1).

2. Experimental

2.1. General

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to the isolated products after purification. The products were characterized by comparison with authentic samples and by spectroscopic data (IR, ¹H NMR, ¹³C NMR spectra and melting point). All melting points were taken on a Gallenkamp melting apparatus and were uncorrected. IR spectra were recorded on a JASCO FT/IR-680 PLUS spectrometer. ¹H NMR spectra were recorded on a Bruker 400 MHz. [Hmim]HSO₄ was prepared according to a previously reported method[36].

2.2. General procedure for the synthesis of pyranopyrazoles

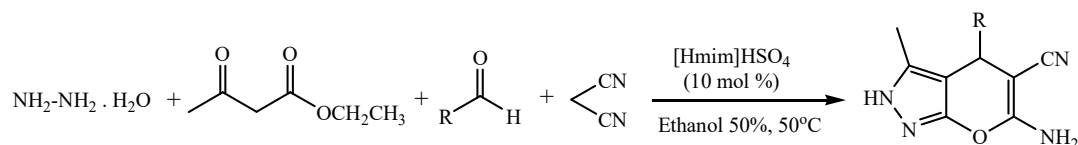
A 25 mL flask was charged with hydrazine hydrate (1.2 mmol) and ethyl acetoacetate (1 mmol). After that 5 mL of ethanol/water 50%, aldehyde (1 mmol), malononitrile (1 mmol) and [Hmim][HSO₄] (0.09 g, 10 mol %) were added. The mixture was vigorously stirred at 50°C. The reaction was followed by TLC (EtOAc/cyclohexane, 1:4). After the completion of the reaction, it was allowed to cool to room temperature.

The residue was filtered and recrystallized from ethanol to afford the pure product.

3. Results and Discussion

To achieve the best reaction conditions for the synthesis of dihydropyrano [2,3-c] pyrazoles, the reaction of hydrazine hydrate (1.2 mmol), ethyl acetoacetate (1 mmol), 4-chlorobenzaldehyde (1 mmol) and malononitrile (1 mmol) was selected as a model reaction. This reaction was studied in various solvents and different temperatures in the presence of different amount of catalyst. It was observed that the best result was obtained when the reaction was carried out at 50°C by using 10 mol% of methylimidazolium hydrogen sulfate ([Hmim]HSO₄) in ethanol 50% (Table 1, entry 4). It should be mentioned that in the absence of the catalyst using the same reaction conditions, the reaction gave low yield of product even after longer reaction time (Table 1, entry 7). According to these results, [Hmim]HSO₄ is necessary for this purpose. A greater amount of the catalyst did not improve the result to a significant extent.

Subsequently, after optimization of the reaction conditions, we studied the generality of this method. A number of 6-amino-4-aryl-3-methyl-2,4-dihydropyrano [2,3-c] pyrazole-5-carbonitriles were prepared in the presence of methylimidazolium hydrogen sulfate (10 mol %) by using different aromatic aldehydes. After simple work-up and purification, the desired products were isolated in excellent yields without any side product formation (Table 2). Irrespective of the presence of electron withdrawing or donating substituents in the ortho, meta or para positions on the ring of various aromatic aldehydes, the reactions proceeded smoothly to furnish the desired products in good yields. But because of the electronic effect on these reactions, electron-withdrawing groups on the aromatic aldehydes increased the yields of the products than those of electron-donating groups in shorter reaction times. The reaction times for 2-nitrobenzaldehyde, 2-methoxybenzaldehyde, 2-chlorobenzaldehyde and 2,4-dichloro benzaldehyde were longer than the others which may be due to the steric effect of ortho-substituents (Table 2, entries 3, 6, 8, 11). It was notable that the reaction conditions were mild enough to perform these reactions with acid sensitive aldehydes such as furfuraldehyde, thiophencarbaldehyde (Table 2, entries 16, 17).



Scheme 1. Synthesis of 6-amino-4-aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles.

Table 1. The model reaction under different conditions.^a

Entry	Solvent	Temperature	[Hmim]HSO ₄ (mol %)	Time (min)	Yield (%)
1	Methanol	50°C	10	30	85
2	Ethanol	50°C	10	30	90
3	Water	50°C	10	30	82
4	Ethanol 50%	50°C	10	25	92
5	Ethanol 50%	50°C	5	25	75
6	Ethanol 50%	50°C	15	25	90
7	Ethanol 50%	50°C	0	100	10
8	Ethanol 50%	r.t.	10	30	45
9	Ethanol 50%	40°C	10	30	60

^aThe yields refer to the isolated pure products.**Table 2.** Synthesis of pyranopyrazoles by using catalytic amount of methylimidazolium hydrogen sulfate.^a

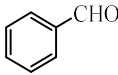
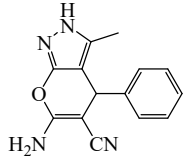
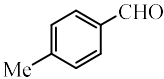
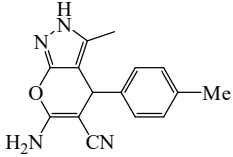
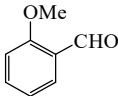
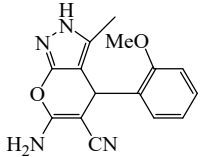
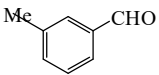
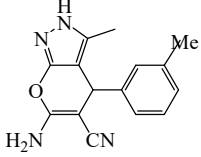
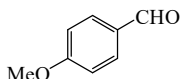
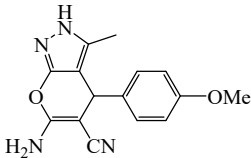
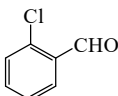
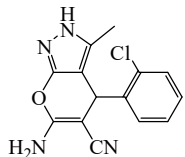
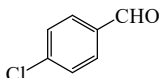
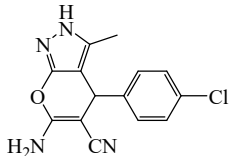
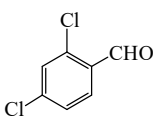
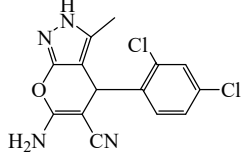
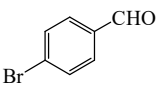
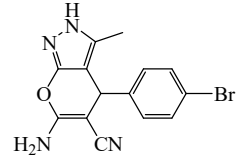
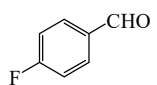
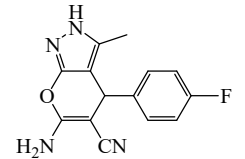
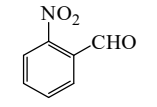
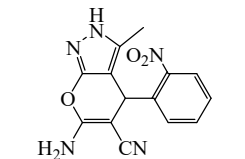
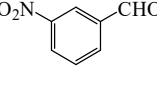
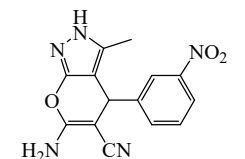
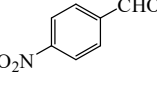
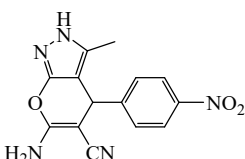
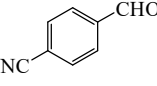
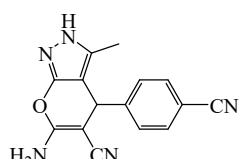
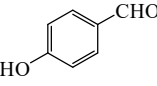
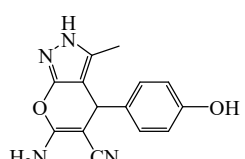
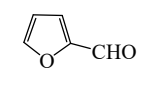
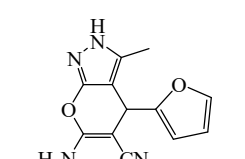
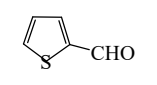
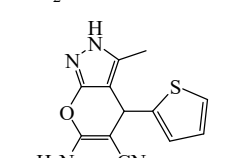
Entry	Aldehyde	Product	Time (min)	Yield (%)	m.p. (°C)		Ref.
					Found	Reported	
1			40	80	240-242	244-246	[38]
2			30	85	207-209	206-208	[38]
3			90	75	253-255	250-252	[39]
4			40	88	172-174	171-173	[40]
5			40	87	210-212	210-212	[38]
6			90	78	144-147	145-147	[38]
7			25	92	233-235	234-236	[38]

Table 2. (Continued).

8			90	75	210-212	208-209	[41]
9			40	84	180-181	178-180	[38]
10			40	85	170-171	171-172	[40]
11			70	79	220-222	220-222	[38]
12			20	92	194-196	193-195	[38]
13			15	91	250-253	251-253	[38]
14			20	90	212-214	-	-
15			25	86	223-225	224-226	[38]
16			30	85	174-176	171-173	[40]
17			30	83	220-221	221-223	[42]

^aThe yields refer to isolated pure products which were characterized from their spectroscopic data and by comparison with authentic samples.

To study the reusability of the present catalyst, after each run, the reaction mixture was filtrated and the solvent (ethanol/water 50%) was collected. To recycle the catalyst, all the collecting solvents washed with CH_2Cl_2 (3×10 ml) to remove organic impurities. Then solvent was evaporated and the catalyst was dried at 65°C under reduced pressure for 2 h. This catalyst reused for the reaction of hydrazine hydrate (1.2 mmol), ethyl acetoacetate (1 mmol), 4-cholorobenzaldehyde (1 mmol) and malononitrile (1 mmol) in water/ethanol (50%) at 50°C . The catalyst could be employed four times, although its activity gradually decreased from 92 to 84%. This demonstrates that methylimidazolium hydrogen sulfate ($[\text{Hmim}]\text{HSO}_4$) can be used as the effective and reusable catalyst for the synthesis of substituted dihydropyrano[2,3-c] pyrazoles.

The proposed mechanism for the formation of dihydropyrano[2,3-c]pyrazole is shown in Scheme 2. First, pyrazolone (I) is formed by reaction between hydrazine hydrate and ethyl acetoacetate. Next, Knoevenagel condensation between aldehyde and malononitrile is carried out and intermediate (II) is formed. After that Michael addition between (I) and (II), is followed by cyclization and tautomerization (Scheme 2) [29, 37].

4. Conclusions

In summary, we introduced methyl imidazolium hydrogen sulfate as an inexpensive, easily available,

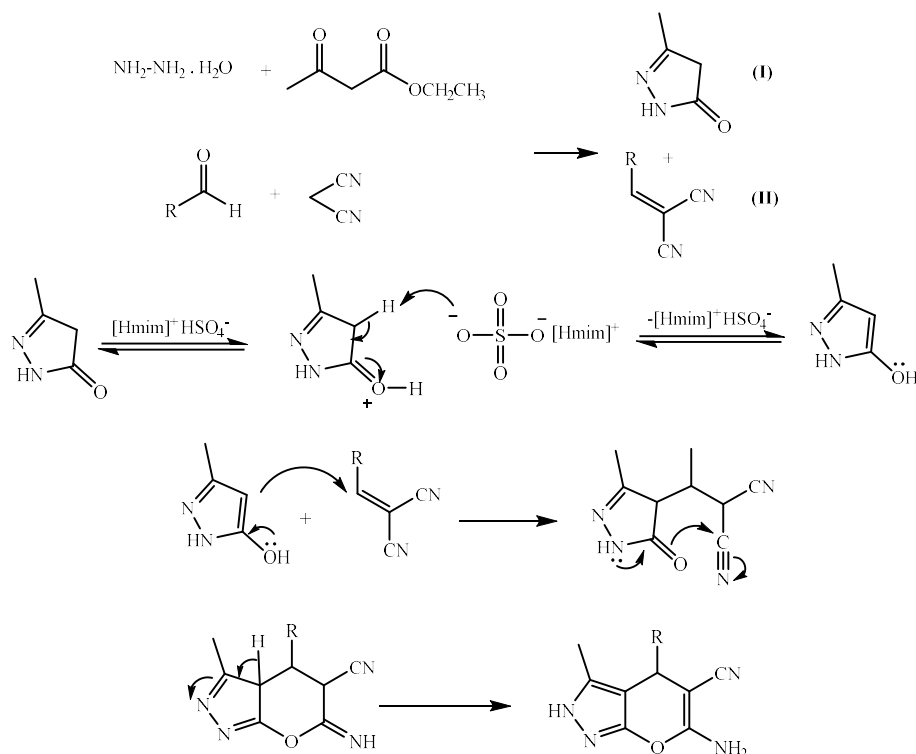
non-corrosive, environmentally benign catalyst and reusable Brønsted acidic ionic liquid for the synthesis of substituted dihydropyrano [2,3-c] pyrazoles derivatives by one-pot four component condensation reactions. Using non-toxic and inexpensive materials, simple and clean work-up, short reaction times and high yields of the products are the advantages of this method.

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Scheme 2. Proposed mechanism for the formation of pyrano[2,3-c]pyrazoles.

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