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Research Note

A fast and highly efficient protocol for synthesis of dihydropyrano[2,3]pyrazole compounds using acidic ionic liquid 3-methyl-1-sulfonic acid imidazolium chloride ([Msim]Cl) as catalyst and green solvent

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Ionic liquid;
Heterocycle.

Abstract. A new, efficient, and environmentally benign protocol for the one-pot, four-component synthesis of dihydropyrano[2,3-c]pyrazoles by condensation of ethylacetoacetate, hydrazine hydrate, aromatic aldehyde, and malononitrile catalyzed by 3-methyl-1-sulfonic acid imidazolium chloride ([Msim]Cl) as an ecofriendly catalyst with high catalytic activity and reusability at 30°C under solvent-free conditions is reported. The reactions proceed to be completed within 5-15 min in 87-97% yield.

1. Introduction

Multi-Component Reactions (MCRs) play an important role in organic and medicinal chemistry because of the ability to synthesize target compounds with greater efficiency and atom economy by generating structural complexity in a single step from three or more reactants [1-5]. Moreover, MCRs offer the advantages of simplicity and synthetic efficiency to the conventional chemical reactions [6]. Therefore, the design of Multi-Component Reactions (MCRs) for the synthesis of diverse groups of compounds, especially ones that have biological activity, attracted great attention in green organic synthesis [7-9].

One of the most important aspects of green chemistry is the use of Ionic Liquids (ILs) as solvents in organic reactions which have some advantages such as control of product distribution [10], enhanced rate [11] and/or reactivity [12], ease of product recovery [13], catalyst immobilization [14], and recycling [15].

Organic reactions can be carried out in a homogeneous phase and the ionic liquid compounds can be recycled in green procedures [16,17]. The ionic liquid compound has been effectively utilized for the synthesis of novel bioactive materials [18].

Pyrano[2,3-c]pyrazole is an emerging class of heterocycles, which is widely explored as an important core of the emerging drugs with numerous medicinal activities, including anticancer [19], anti-in-ammatory [20], antimicrobial [21], analgesic properties [22], and Chk1 kinase inhibitory activities [23].

It is ideally synthesized by multi-component reaction of ethylacetoacetate, hydrazine hydrate, aldehyde, and malononitrile in the presence of base catalysts [24-29]. Recently, some environment-compatible catalysts, such as l-proline [30], alumina [31], and per-6-amino-β-cyclodextrin [32], were also used to achieve this transformation, but most of the reactions were carried out at elevated temperature.

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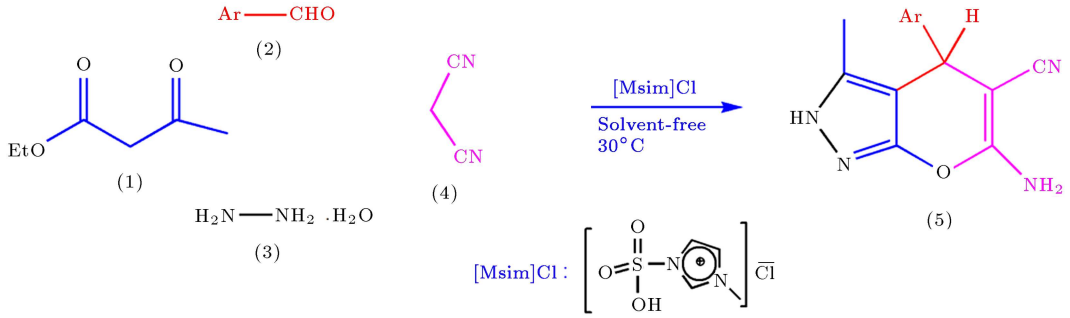


Scheme 1. Solvent-free four-component synthesis of 5,10-dihydro-3-methyl-5,10-dioxo-1-phenyl-1H-pyrazolo[1,2-b] phthalazine-2-carbox ylates using sulfonic acid imidazolium salt.

Because of the importance of these compounds, there has been considerable interest to explore green, rapid, and higher yielding protocols.

In continuation of our research on green catalytic systems, such as ionic liquids, $LaCl_3/ClCH_2COOH$, and their applications in organic synthesis [33-34], we decided to investigate 3-methyl-1-sulfonic acid imidazolium chloride ([Msim]Cl) as a green catalyst for the practically and environmentally benign, one-pot, and four-component synthesis of dihydropyrano[2,3] pyrazoles at 30°C under solvent-free conditions (Scheme 1).

2. Materials and methods

Chemicals were either prepared in our laboratory or purchased from Merck or Fluka companies, and were used without any further purification. All reactions were monitored by TLC, petroleum-ethyl acetate (3:1). Melting points were determined with a hot-plate microscope apparatus. IR spectra were recorded in KBr using a BRUKER FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Bruker 300-MHz and 400-MHz spectrometers using DMSO and TMS as solvent and internal standard, respectively.

2.1. Experimental section

2.1.1. General procedure for synthesis of ionic liquid [Msim]Cl

A round-bottomed flask (100 mL) was charged with 1-methylimidazole (0.410 g, 5 mmol) in dry CH_2Cl_2 (50 mL), and then chlorosulfonic acid (0.605 g, 5.2 mmol) was added dropwise over a period of 5 min at room temperature. After the addition was completed, the reaction mixture was stirred for 20 min, stood for 5 min, and the CH_2Cl_2 was decanted. The residue was washed with dry CH_2Cl_2 (3×50 mL) and was dried under vacuum to give [Msim]Cl as a viscous colorless oil in 92% yield, 0.912 g [35].

2.1.2. Spectral data of [Msim]Cl

Viscous colorless oil [36]: ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.84 (s, 3H, CH_3), 7.57 (s, 1H), 7.64(s, 1H), 9.01 (s, 1H), 14.29 (s, 1H): ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 36.90, 121.01, 124.64, 137.04.

Table 1. Synthesis of dihydropyrano[2,3-c]pyrazoles.

Entry	Ar	Time (min)	Yield[a] (%)	M.p. (°c)	
				Found	Reported
2a	C_6H_4	8	95	243-244	244-245 [37]
2b	3-$O_2NC_6H_4$	6	96	214-216	216-217 [32]
2c	4-ClC_6H_4	7	97	234-235	233-234 [37]
2d	2,4-$(Cl)_2C_6H_3$	6	89	229-230	230-232 [37]
2e	4-MeC_6H_4	12	90	172-173	170-172 [37]
2f	4-OHC_6H_4	14	89	222-224	224-226 [37]
2g	4-$O_2NC_6H_4$	5	87	250-252	251-252 [37]
2h	4-$OMeC_6H_4$	15	92	211-213	211-212 [37]

[a] Yields refer to pure isolated yields.

2.2. General procedure for the preparation of pyanopyrazoles using acidic ionic liquid 3-methyl-1-sulfonic acid imidazolium chloride [Msim]Cl

To a mixture of hydrazine hydrate (80% assay) (1 mmol) and ethyl acetoacetate (1 mmol), [Msim]Cl (0.5 mmol, 50 mol%) was added and stirred vigorously for 5 min to make a homogenous solution. Then, benzaldehyde (1 mmol) and malononitrile (1 mmol) were added to the solution. The mixture was heated at 30°C under stirring for the appropriate time (Table 1). The reactions were followed by Thin Layer Chromatography (TLC) using petroleum/ ethyl acetate (3:1) as an eluent. After completion of the reaction, water (20 mL) was added and stirred magnetically for 5 min. Insoluble crude products were filtered, dried, and recrystallized in ethanol.

Other substituted aromatic aldehydes also reacted well under the same conditions, giving the corresponding product with excellent yields (Table 1). All the obtained products were characterized by spectroscopic methods, such as IR, ^1H NMR, and ^{13}C NMR, identified by comparison of the spectral data and melting point with those obtained in authentic samples.

The spectra of some selected compounds are as follows.

2.2.1. Spectra data of 6-amino-2,4-dihydro-3-methyl-4-phenylpyrano[2, 3-c]pyrazole-5carbonitrile (3a)

Yield 95%; Yellowish solid, m.p.: 167-196, IR (KBr) υ (cm^{-1}): 3372 (NH, NH_2), 2190.74 (CN), ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm): 1.17 (s, 3H, CH_3), 4.62 (1H, s), 6.93 (s, br, 2H), 7.17-7.37 (m, 5H, arom), 12.14 (1H, s, NH), ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm): 11.36, 37.19, 55.37, 99.05, 122.44, 130.05, 130.95, 132.66, 137.42, 145.04, 156.26, 162.50.

2.2.2. Spectra data of 6-amino-3-methyl-4-(3-nitrophenyl)-2,4dihydropyra no[2,3-c] pyrazole-5carbonitrile, (3b)

Yield 96%; Yellowish solid, m.p.:214-216, IR (KBr) υ (cm^{-1}): 3385 (NH, NH_2), 3278, 2189 (CN), 1622, 1648, 1456, ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm): 1.74 (s, 3H, CH_3), 4.55 (1H, s), 6.86 (s, 2H), 7.14-7.86 (m, 5H, arom), 12.08 (1H, s, NH),^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm): 11.35, 37.82, 58.78, 99.26, 128.35, 129.06, 130.05, 130.53, 137.26, 146.02, 162.46.

2.2.3. Spectra data of 6-amino-3-methyl-4-(4-chloro)-2,4dihydropyrano[2,3-c] pyrazole-5carbonitrile, (3c)

Yield 97%; White solid, m.p.: 174-175; IR (KBr) υ (cm^{-1}): 3380 (NH, NH_2), 3281, 2193 (CN), 1622, 1454, ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 1.76 (s, 3H, CH_3), 4.84 (1H, s), 7.02 (s, 2H), 7.62-8.09 (m, 5H, arom), 12.07 (1H, s, NH), ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm): 11.35, 37.28, 57.78, 98.26, 123.46, 123.57, 131.79, 135.98, 137.58, 148.39, 156.32, 162.76.

3. Results and discussion

Solvent-optimization for this reaction was investigated by choosing the model of four-component reaction between benzaldehyde (2a; 1 mmol), hydrazine hydrate (1 mmol), malononitrile (1 mmol), and ethyl acetoacetate (1 mmol) in different solvents; the results are summarized in Table 2 (entries 1-5).

It is found that the reaction in [Msim]Cl furnished 3a in an excellent yield of 95% (Table 2, entry 1) in short reaction time compared to other organic solvents.

Table 2. Optimization of reaction conditions.

No	Solvent	Condition	Time	Yield[a] (%)
1	THF	Reflux	6 h	50
2	CH_2Cl_2	Reflux	5 h	Trace
3	CCl_4	Reflux	3 h	20%
4	EtOH/H_2O	80	50 min	60%
5	[Msim]Cl	30°C	8 min	95%

[a]: Experimental conditions: benzaldehyde (1 mmol), hydrazine hydrate (1 mmol), malononitrile (1 mmol), ethyl acetoacetate (1 mmol).

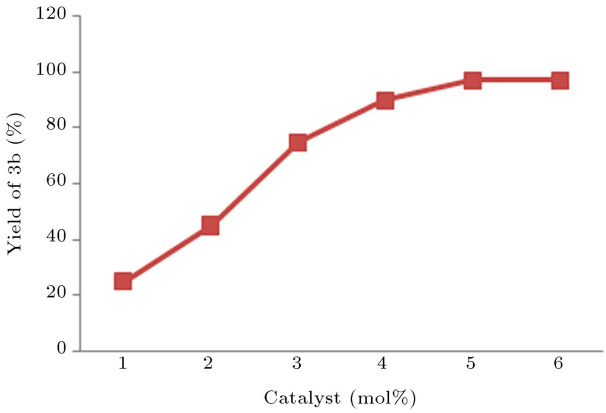


Figure 1. Optimization amount of catalyst on the reaction of phthalic anhydride, ethyl acetoacetate, hydrazine hydrate, and benzaldehyde under thermal solvent-free conditions.

Hence, all the subsequent reactions were affected by heating an equimolar mixture of the reactants in [Msim]Cl in an oil-bath at 30°C for 5-15 min. After completion of the reaction (TLC), the product was isolated and purified by recrystallization in ethanol (Table 1), whilst the ionic liquid could be recovered and reused.

In another study, the condensation of hydrazine hydrate, 3-nitrobenzaldehyde, malononitrile, and ethyl acetoacetate was examined in the presence of different quantities of catalyst (Figure 1). As Figure 1 indicates, reasonable results were obtained when the reaction was performed using 0.5 mmol (50 mol %) of the catalyst. No improvement in the reaction results was observed by increasing the amount of catalyst.

To optimize temperature in the mentioned reaction, we have carried out a model study with benzaldehyde, hydrazine hydrate, malononitrile, and ethyl acetoacetate using [Msim]Cl at various temperatures (Table 3). Table 3 clearly demonstrates that 30°C is an effective temperature in terms of reaction time and yields.

After optimizing the conditions, the generality of this method was examined by the reaction of hydrazine hydrate, malononitrile, and ethyl acetoacetate with different kinds of aromatic aldehydes (2a-2h) using [Msim]Cl as catalyst.

Next, we also investigated the reusability and

Table 3. Optimization of temperature using [Msim]Cl (50 mol%) as a catalyst.

Entry	Temperature (°C)	Time (min)	Yield[a] (%)
1	25	18	80
2	30	8	95
3	40	8	95
4	60	8	95

[a]: Isolated yields.

the recyclability of the [Msim]Cl, and found that the catalyst could be easily recovered after completion of the reaction and could be reused in subsequent reactions. The representative reaction, leading to 3c as a model reaction, was again studied. After completion of the reaction, water (20 mL) was added and stirred magnetically for 5 min; filtered [Msim]Cl was soluble in H_2O; however, the reaction mixture was not soluble in H_2O. In the aqueous media, a quantity of [Msim]Cl was hydrolyzed to 1-methylimidazole (as monitored on TLC) and H_2SO_4. To complete hydrolysis of [Msim]Cl and, consequently, formation of 1-methylimidazole, a solution of NaOH (10%) was added to filtrate, and stirred for 5 min.

The solution was extracted with EtOAC, washed with H_2O, and dried. Evaporation of the solvent gave 1-methylimidazole. The recovered 1-methylimidazole was reacted with chlorosulfonic acid to give [Msim]Cl. The catalytic activity of the reproduced [Msim]Cl was the same as that of the first one.

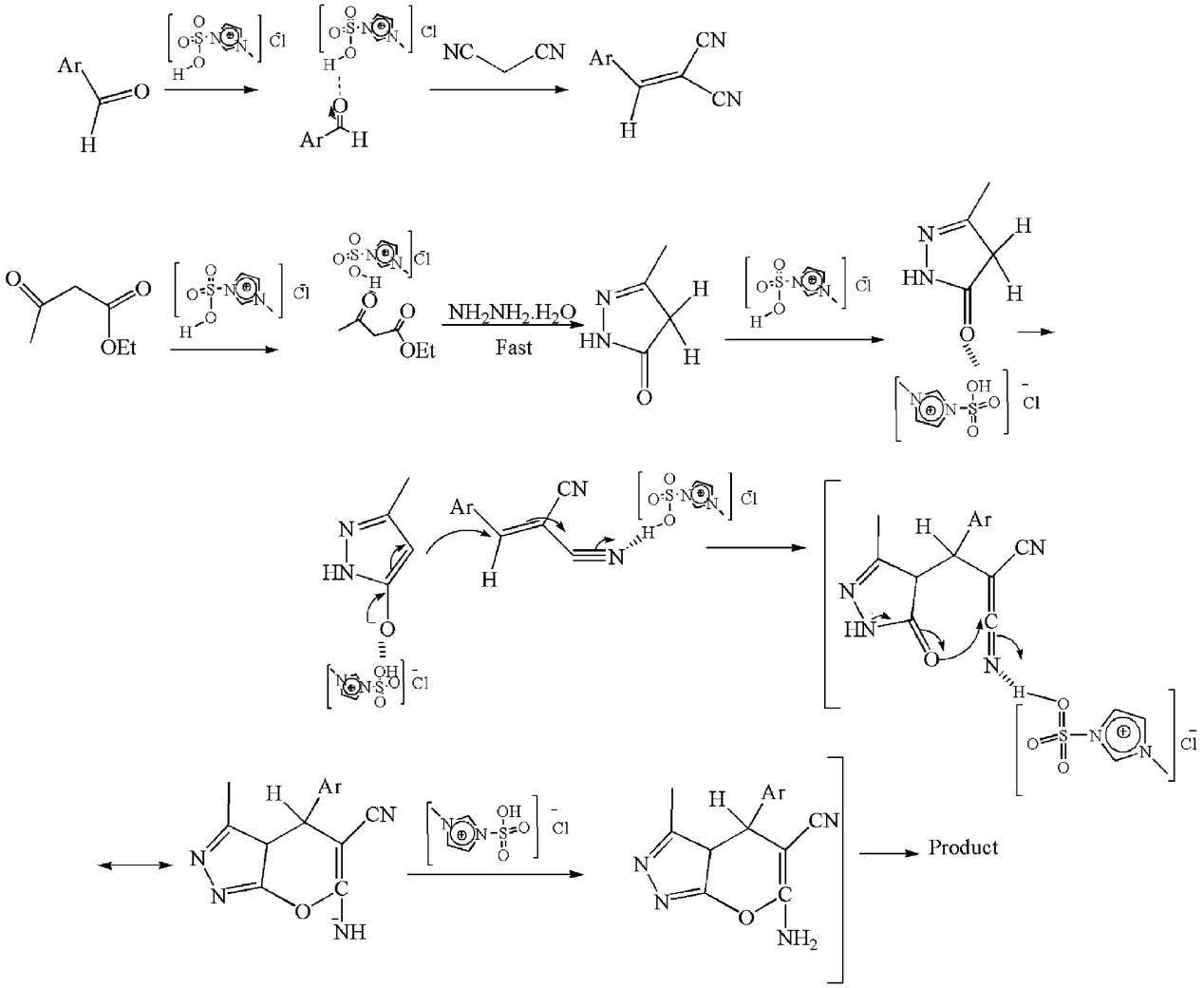
Table 4. Recyclability of the catalyst in the reaction of ethyl acetoacetate, hydrazine hydrate, malononitril, and p-chlorobenzaldehyde in the presence of [Msim]Cl under solvent-free condition at 30°C.

Entry	Yield (%)
1	97
2	94
3	94

The activity of the catalyst did not show any significant decrease after 3 runs (Table 4).

Finally, in order to show the efficiency of the proposed method, [Msim]Cl was compared with other catalysts reported earlier for the synthesis of 2a. As demonstrated in Table 5, the use of this catalyst leads to an improved protocol in terms of compatibility with environment, reaction time, and yield when compared with other catalysts.

The proposed mechanism for synthesis of pyranopyrazoles has been shown in Scheme 2.



Scheme 2. The proposed mechanism for synthesis of ethyl 5,10-dihydro-3-methyl-5,10-dioxo-1-aryl-1H-pyrazolo[1,2-b] phtha- lazine-2-carboxylates.

Table 5. Comparison of our results with those of previously reported methods.

Entry	Catalyst	Reaction condition	Time (min)	Yield (%) [ref]
1	Amberlyst A21 (50 mg)	EtOH, rt	20	90 [38]
2	Et_3N (20 mol%)	EtOH, reflux	15	65 [39]
3	HDBAC (30 mol%)	EtOH, reflux	45	73 [40]
4	L-proline (10 mol%)	[Bmim]BF_4, 50°C	10	90 [30]
5	L-proline (10 mol%)	H_2O, reflux	10	9090 [30]
6	Piperidine (5 mol%)	H_2O, rt	10	83 [25]
7	This catalyst	Solvent-free, 30°C	8	95

4. Conclusion

In summary, we have developed a highly efficient and greener approach for the one-pot, four-component synthesis of pyranopyrazole derivatives using 3-methyl-1-sulfonic acid imidazolium chloride ([Msim]Cl) as an inexpensive and reusable catalyst. The attractive features of this protocol are its efficiency, generality, very good to excellent yield of the products, short reaction time, simplicity, not-elevated temperature, ease of product isolation, cleaner reaction profile, evasion of hazardous catalysts or solvents, and agreement with the green chemistry protocols, which makes it a useful and attractive process for the synthesis of pyranopyrazoles.

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