



Morpholinium Glycolate: A Reusable Ionic Liquid Catalyst for the Eco-friendly Synthesis of Dihydropyrano[2,3-c]pyrazol-5-carbonitriles

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Authors' contributions

This work was carried out in collaboration between all authors. Author SMA designed the study, wrote the protocol and wrote the first draft of the manuscript. Author SMA also performed the experiments and analyzed the spectral data of the obtained compounds. Authors SA and MF reviewed the experimental design and all drafts of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Morpholinium glycolate was found to be highly potent and reusable ionic liquid as a catalyst for the synthesis of dihydropyrano[2,3-c]pyrazol-5-carbonitriles via a one-pot multicomponent condensation reaction of aryl aldehydes with ethyl acetoacetate, hydrazine hydrate, and malononitrile in an aqueous medium at room temperature. The key advantage of this present protocol is an economical, excellent yield, shorter reaction time, easy work-up, no chromatographic purification and the catalyst can be effortlessly recovered and reused in several runs.

Keywords: Dihydropyrano[2,3-c]pyrazol-5-carbonitriles; morpholinium glycolate; ILs; MCRs.

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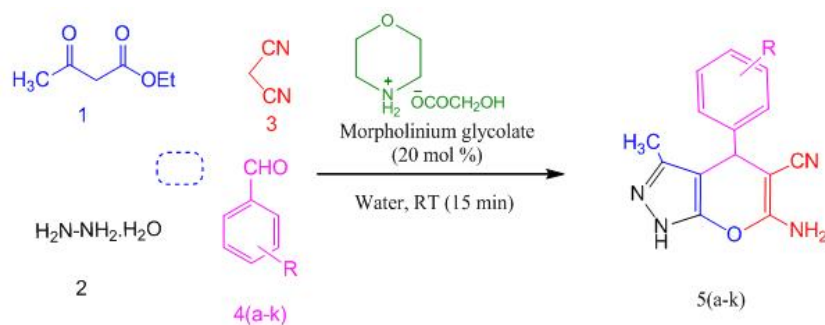
1. INTRODUCTION

In a context to build the libraries of biologically relevant scaffolds, multicomponent reactions (MCRs) has been emerged as an exceptionally valuable synthetic tool in a green and sustainable chemistry as well as in drug discovery programs [1-4]. Furthermore, using of eco-compatible solvents such as water or ethanol gaining considerable interest among the scientific community owing to their benefits over the conventional organic solvents are the principal source of waste that wind up in groundwater or the atmosphere [5,6]. When such MCRs execute in an aqueous medium with reusable ionic liquids (ILs) as catalysts at ambient temperature, then the reaction can be achieved without penetrating any dangerous and toxic things to the environment [7].

Many natural and synthetic heterocyclic compounds contain pyrans and its derivatives as a basic structural unit that showed a variety of therapeutic activities [8,9]. Among them, dihydropyrano[2,3-c]pyrazole explored an ample spectrum of biological activities such as anticancer [10], anti-inflammatory [11], antimicrobial [12], human Chk1 kinase inhibitory activity [13], insecticidal and molluscicidal activities [14,15]. Most of the previously reported synthetic designs for the constructions of dihydropyrano[2,3-c]pyrazole involves, a one pot four component coupling reaction of aromatic aldehydes, ethyl acetoacetate, hydrazine hydrate and malononitrile; Via various catalysts such as glycine [16], per-6-amino-b-cyclodextrin [17], β -cyclodextrin-SO₃H [18], L-proline [19], gamma alumina [20], heteropolyacids [21], [(CH₂)₄SO₃HMIM][HSO₄] [22], amberlyst A21 [23], lipase [24], nano-ZnO [25], meglumine [26], Molecular sieves [27], and [MNP-PIIm-SO₃H]Cl as a heterogeneous catalyst [28] and various

base catalysts [29-31]. The reported methods have their own merits with certain drawbacks such as use of toxic and expensive catalysts, higher temperature, time-consuming reactions, low yield of products, tedious workup procedure and lack of recyclability. Thus, development of environmentally benign catalysts and simple, greener approaches are highly desirable.

Nowadays, Ionic liquids (ILs) described as a green or sustainable chemicals and extensively used as solvent and catalyst in organic transformations, due their unique physical and chemical properties including a very low vapour pressure, non-flammability, thermally stable and recyclability [32-34]. These properties can be tailor-made by only their particular combinations, with a universe of anions/cations. The vast majority of studies on cationic head available to date have focused on tetraalkylammonium, pyridinium, phosphonium, piperidinium and imidazolium-based ILs [35]. Besides, from their properties, few of these ILs have shown to some extent toxicity to the environment and less biodegradability [36]. Recently, a wide range of investigations on biodegradation of ILs have been reviewed [37-39], and as per of these studies, the biological degradation of ILs broadly depend on (i) cationic head, (ii) side chain of head cations, (iii) types of anions. Out of several anions, mainly acetate and ethyl or octyl sulphate, and so forth are readily biodegradable [40]. As of late, interest for morpholinium-based ILs has expanded as a result of their practical importance. These ILs have been utilized as a part of different applications, for example, as a relatively large ionic conductivity, corrosion inhibitors, reaction media and catalyst [41-43]. Aside from offered such properties, morpholinium based ILs have less toxicity than the regularly used pyridinium, imidazolium, or tetraalkylammonium-based ILs [44].



Scheme 1. The synthesis of dihydropyrano[2,3-c]pyrazole (5a-k) using morpholinium glycolate as a reusable catalyst

In continuation of our efforts to generate biologically relevant molecules simply by eco-friendly synthetic techniques, here, we investigate the morpholinium glycolate as a homogeneous catalyst for obtaining pyranopyrazole derivatives through, cyclocondensation of ethyl acetoacetate, hydrazine hydrate, aromatic aldehydes and malononitrile in water at room temperature. Morpholinium glycolate as a catalyst for the synthesis of dihydropyrano[2, 3-c]pyrazoles has not so far been reported in the literature.

2. EXPERIMENTAL DETAILS

2.1 General

All the chemicals were purchased of laboratory grade and used without further purification. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were taken on a Bruker Advance II 400 using DMSO- d_6 as solvent and TMS as an internal standard, and the chemical shift in δ ppm. Mass spectra were recorded on the Thermo Scientific TSQ 8000 GC-MS. Melting points were determined in an open capillary tube and are uncorrected. Reactions were monitored by TLC using silica-gel, 60F₂₅₄ aluminium plates.

2.2 Synthesis of Morpholinium Glycolate

To the morpholine (0.87 mL, 10 mmol), a stoichiometric amount of glycolic acid (65%, 10 mmol) was added dropwise at room temperature in a 50 mL of round bottom flask. Then the reaction mixture was stirred at 80°C for two hours and dried under reduced pressure to afford a clear brownish morpholinium glycolate IL in 88% yields (1.43 g, 8.7 mmol).

2.3 Synthesis of Dihydropyrano[2,3-c]pyrazoles (5a-k)

In a 50 mL round bottom flask, ethyl acetoacetate (**1**) (3 mmol) and hydrazine hydrate (**2**) (80%, 3 mmol) were taken, and it immediately precipitated. To this mixture, a malononitrile (**3**) (3 mmol), aromatic aldehydes (**4a-k**) (3 mmol), morpholinium glycolate as catalyst (20 mol%) and water 10 mL were added and stirred at room temperature for a time as indicated in Table 1. After completion of the reaction by TLC (ethyl acetate: n-hexane 2:8), the precipitated products were separated by simple filtration and recrystallized in an aqueous ethanol (90%) to produce the pure products (**5a-k**) in 85-97% yield.

2.3.1 6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5a**)

White solid; IR (KBr, cm^{-1}): 3398, 3321 (N–H stretching), 2193 (CN stretching), 1654 (C=C stretching); ^1H NMR (400 MHz, DMSO- d_6): δ = 1.79 (s, 3H, –CH₃), 4.64 (s, 1H, –CH–), 6.88 (s, 2H, –NH₂), 7.17–7.51 (m, 5H, Ar–H) and 12.95 (s, 1H, –NH); ^{13}C NMR (100 MHz, DMSO- d_6): δ = 9.74, 36.27, 57.29, 94.69, 98.62, 120.80, 127.44, 127.57, 127.64, 128.42, 135.64, 144.40, 159.11 and 160.88; MS (m/z) = 252.1 [M]⁺.

2.4 Recycling and Reuse of the Catalyst

So as to recover the catalyst after the filtration of the products, the filtrate was concentrated under reduce pressure, and the remaining contents were washed with (2 X 3 mL) cyclohexane to remove non-ionic residue. The recovered catalyst was dried and used again for future cycles. The obtained results are outlined in Fig. 1.

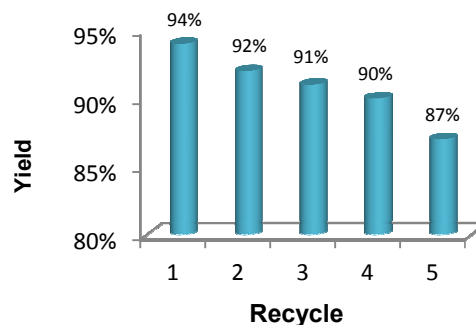


Fig. 1. Recycling and reuse of catalyst

3. RESULTS AND DISCUSSION

In order to optimize the various reaction variables, the one pot four component reactions with hydrazine hydrate, ethyl acetoacetate, benzaldehyde and malononitrile were taken as a model reaction. In our initial experiments, we were primarily focused on water-mediated reactions, as water is a better solvent from an environmental viewpoint, the model reaction was carried out in water at a room temperature and stirred for prolong time, but a trace amount of yield were obtained. When such reaction performs at reflux point, then around 30% yield detected (Table 1, entries1-2). The outcomes were not inspiring, and the result hints that catalyst can perform a crucial role in this reaction. As our research group mainly focused on Ionic liquids, Initially we applied morpholinium

glycolate (5 mol%) as a homogenous catalyst to the model reaction at room temperature and also at reflux in an aqueous medium. Surprisingly, the result of both reaction condition was almost similar with good yield (Table 1, entries 3-4). Considering the above results, the model reaction was set at an ambient temperature and different concentration of catalysts were loaded via; 10, 15, 20, 25, 30 mol% (Table 1, entries 5-9). The best result was obtained with 20 mol% of morpholinium glycolate in 15 minutes (Table 1, entry 7). Further rising the quantity of catalyst, there was no considerable improvement in the yield and reaction time (Table 1, entries 8-9). Above result indicates, 20 mol% of catalyst was enough for catalyzing the reaction completely.

Then, we examined the recyclability of morpholinium glycolate for the model reaction, and it was detected that even after four consecutive runs, morpholinium glycolate was found to appropriately catalyzed the reaction. The details of recycling and reuse of catalyst is given in the experimental section. After that, we investigate the effectiveness of the catalyst within different solvents on model reaction at room temperature in 15 min to obtained (5a) product (Table 1, entries 10-15). The result disclosed that protic solvents such as ethanol, methanol led to better yields (Table 1, entries 10-11) in contrast to the aprotic solvents for example acetonitrile, THF, DCM, chloroform (Table 1, entries 12-15). The model reaction was also carried out by omitting solvents resulted in low yield; It may be

due to the improper stirring of reaction mixture but such reaction when conducted at an elevated temperature then slightly improvement in the yield were noticed (Table 1, entry 16-17). However, the finest results were obtained within the aqueous medium (Table 1, entry 7). Along with optimized reaction parameters in hand, next we were screened various electronically variant aromatic aldehydes to expand the scope of morpholinium glycolate catalyzed reaction which yielded several derivatives of dihydropyrano[2, 3-c]pyrazoles (Table 2). In a case of aromatic aldehydes with the electron withdrawing groups on the phenyl ring offered the maximum yield of the products (Table 2, entries 1-7) then the yield of electron donating aryl aldehydes (Table 2, entries 8-10). Heteroaryl aldehydes as well went through the reaction easily to manage the product in reasonable yield (Table 2, entry 11).

Mechanistically, the 3-methyl-1H-pyrazol-5(4H)-one (I) occurred from the condensation of ethyl acetoacetate (1) and hydrazine hydrate (2) with the liberation of ethyl alcohol then it reacted with morpholinium glycolate to affords enolate (II). Whereas in the presences of catalyst, the activated carbonyl group of aldehydes (4a-k) and malononitrile (3) undergoes Knoevenagel condensation to form arylidenemalononitrile (III). Then, Michael addition of intermediate (II) to (III) taken place, followed by intramolecular cyclization and tautomerization to yield desired (5a-k) products (Scheme 2).

Table 1. Optimization of amount of the catalyst morpholinium glycolate and screening of solvents for the synthesis of pyranopyrazoles (5a)^a

Entry	Catalyst (mol%)	Solvents	Temp (°C)	Time (min)	Yield (%) ^b
1	-	H ₂ O	RT	300	-
2	-	H ₂ O	Reflux	300	30
3	5	H ₂ O	RT	15	48
4	5	H ₂ O	Reflux	15	50
5	10	H ₂ O	RT	15	62
6	15	H ₂ O	RT	15	70
7	20	H ₂ O	RT	15	94
8	25	H ₂ O	RT	15	94
9	30	H ₂ O	RT	15	94
10	20	EtOH	RT	15	92
11	20	MeOH	RT	15	89
12	20	ACN	RT	15	75
13	20	THF	RT	15	68
14	20	DCM	RT	15	56
15	20	CHCl ₃	RT	15	52
16	20	Solvent free	RT	15	43
17	20	Solvent free	100	15	60

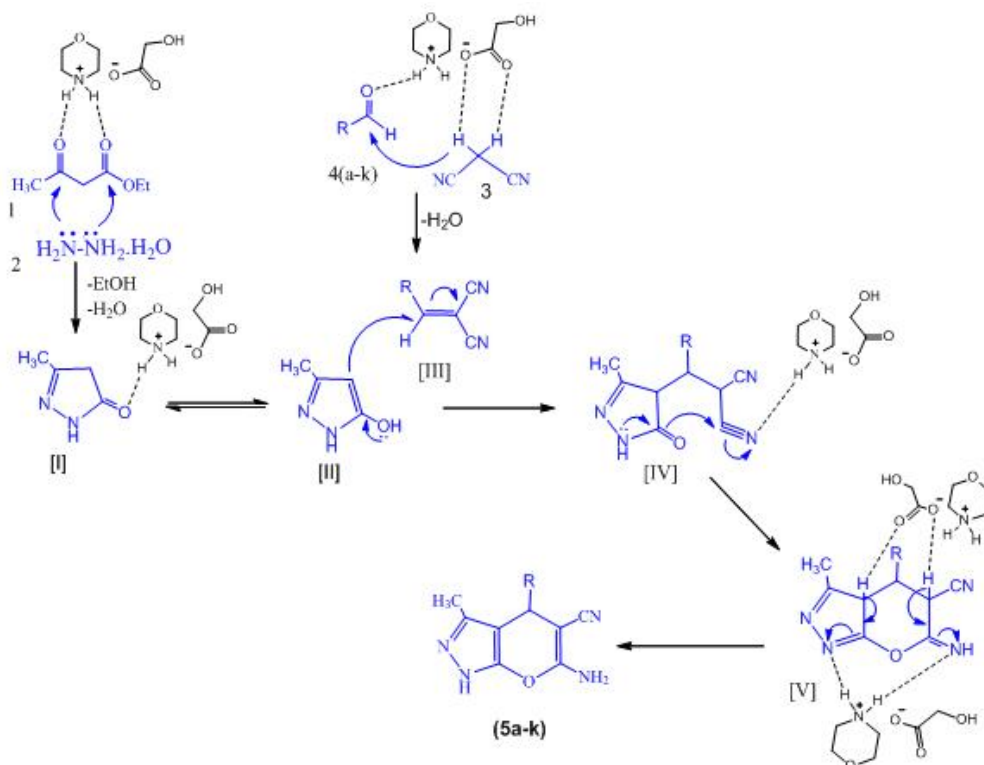
^aReaction conditions: ethyl acetoacetate (3 mmol), hydrazine hydrate (3 mmol), benzaldehyde (3 mmol), and malononitrile (3 mmol) catalyzed by morpholinium glycolate in 10mL water; ^bIsolated yields

Table 2. The Synthesis of dihydropyrano[2,3-c]pyrazoles (5a-k)^a

Entry	Product	R	Time (min)	Yield (%) ^b	M.P (°C)	
					Found	Reported
1	5a	-Ph	15	94	245-248	245-247 [45]
2	5b	4-Cl-Ph	10	97	231-234	234-235 [45]
3	5c	4-F-Ph	10	96	172-174	170-171 [17]
4	5d	4-NO ₂ -Ph	12	97	253-255	250-252 [46]
5	5e	3-Cl-Ph	15	95	169-173	176-177 [23]
6	5f	3-Br-Ph	15	94	221-223	223-225 [45]
7	5g	2-Cl-Ph	20	90	243-245	245-246 [46]
8	5h	4-CH ₃ -Ph	20	90	204-207	206-208 [20]
9	5i	4-HO-Ph	20	87	223-225	225-227 [45]
10	5j	4-OCH ₃ -Ph	22	89	210-212	210-212 [47]
11	5k	2-furyl	25	85	170-173	175-177 [17]

^aReaction conditions: ethyl acetoacetate (3 mmol), hydrazine hydrate (3 mmol), aldehydes (3 mmol), and malononitrile (3 mmol) catalyzed by morpholinium glycolate in 10mL water at room temperature.

^bIsolated yields



Scheme 2. The plausible mechanism for the synthesis dihydropyrano[2,3-c]pyrazole derivatives (5a-k)

4. CONCLUSION

To conclude, we have reported the synthesis of a broad array of dihydropyrano[2,3-c]pyrazole derivatives (5a-k) using ionic liquid morpholinium glycolate as a reusable homogeneous catalyst in

the aqueous medium. The important highlights of the presented approach were high yields, simple work-up, no column purification, no hazardous solvents, and catalyst could be easily recovered and used again with no significant drop in catalytic activity.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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