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ORIGINAL PAPER

An efficient catalyst- and solvent-free method for the synthesis of medicinally important dihydropyrano[2,3-*c*]pyrazole derivatives using ball milling technique

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Abstract Dihydropyrano[2,3-*c*]pyrazole annulated heterocyclic compounds with diverse substituents on the 4*H*-pyran ring were efficiently prepared via a one-pot and four-component reaction of ethyl acetoacetate, hydrazine hydrate, aromatic aldehyde, and malononitrile. The procedure proceeds without utilization of any catalyst or solvent using ball milling technique at ambient temperature to afford desired medicinally important dihydropyrano[2,3-*c*] pyrazole derivatives. This protocol offers several advantages such as avoiding the use of any toxic and hazardous catalyst or solvent, mild reaction conditions, high to quantitative yields of products, low cost, and straightforward work-up.

Keywords Catalyst-free conditions · Solvent-free conditions · Ball milling technique · Green chemistry · Multicomponent reactions (MCRs) · Dihydropyrano[2,3-*c*] pyrazole scaffold

Introduction

Multicomponent reactions (MCRs), defined as one-pot reactions in which at least three different substrates join through the covalent bonds, have steadily received considerable attention in synthetic organic chemistry [1–10]. MCRs have emerged as an important tool for the rapid generation of molecular complexity and diversity with predefined functionality especially in chemical biology and drug discovery [11–14]. Indeed, one-pot MCRs often shorten reaction times, giving higher overall chemical yields and atom efficiency than multi-step synthesis, and therefore can reduce waste and the use of energy and manpower [1–14]. If such MCR reactions can be performed in the absence of any catalyst and solvent, they can provide the perfect platform for green synthesis without percolating anything to destroy the environment [15–20]. In this context, reactions carried out using ball milling technique are attractive from both environmental and economic points of view, since reactions between solid reactants or melt reaction mixtures are run in the absence of any organic solvents. Indeed, ball milling refers to the use of friction, collision, or other mechanical actions to provide required energy of organic reactions in situ. Furthermore, near quantitative yields are often obtained using this technique, and subsequent utilization of organic solvents for crystallization or chromatography purification steps is substantially reduced or no longer required. Therefore, synthetic protocols under ball milling can be considered as genuine solvent-free methods.

Ball milling technique, as an environmentally benign method, has received increasing attention for organic synthesis in recent years. Subsequently, some specific review papers and book chapters have been published in the literature on the topic. Some typical examples include carbon–carbon and carbon-heteroatom bond formation, oxidation by solid oxidants, asymmetric organocatalytic reactions, dehydrogenative coupling, and peptide or polymeric materials synthesis [15–22]. Hence, organic reactions run under neat conditions by means of ball milling activation demonstrate significant advantages including better energy balance, short reaction time, providing quantitative yields, straightforward work-up, higher safety, and the potential

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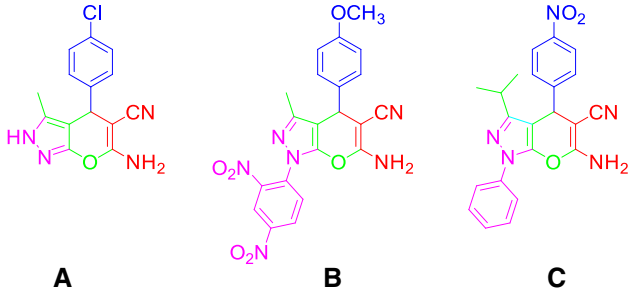
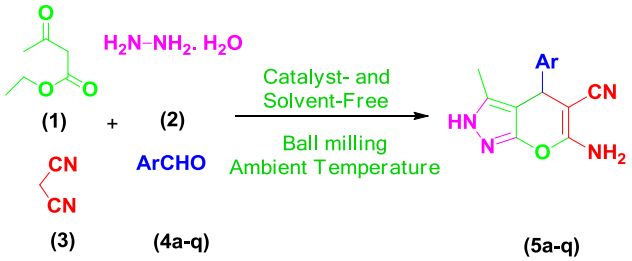


Fig. 1 Chemical structures of some dihydropyrano[2,3-*c*]pyrazole derivatives with anticancer, antifungal, and antibacterial activities



Scheme 1 One-pot four-component synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives using ball milling technique at ambient temperature

for scale-up over other solvent-free conditions [13–22]. On the other hand, a lot of attention has recently been paid to the development of new methods for the synthesis of heterocyclic compounds, due to their potential importance in the pharmaceutical and agricultural fields [7, 13, 14, 23, 24]. Dihydropyrano[2,3-*c*]pyrazole derivatives are of high interest because they generally show diverse biological properties such as fungicidal, bactericidal, and vasodilator activities as well as anticancer agents among others [25–30]. For instance, dihydropyrano[2,3-*c*]pyrazole derivatives, such as **A**, **B**, and **C** are valuable compounds as anticancer [26], antifungal [26], and antibacterial agents [27], respectively (Fig. 1).

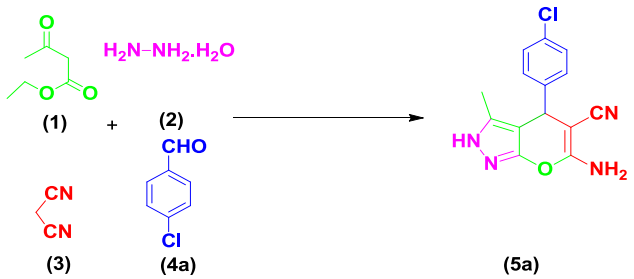
Due to the important aforementioned properties of pyranopyrazole derivatives, considerable attention has been focused on the development of environmentally friendly methodologies for the synthesis of dihydropyrano[2,3-*c*] pyrazole scaffold by cyclization of aromatic aldehydes, malononitrile, ethyl acetoacetate, and hydrazine hydrate [28]. A literature survey shows that several modified methods have been reported using different homogeneous or heterogeneous catalysts such as tetrabutylammonium hydrogen sulfate in acetonitrile or xylene [29], L-proline [30], *N*-methylmorpholine [31], lipase [32], γ-alumina [33], triethylamine [34], piperidine [35], triethylbenzylammonium chloride [36], and cetyltrimethylammonium bromide (CTAB) [37]. However, many of the introduced methods for synthesis of these compounds suffer from disadvantages including relying on the use of volatile organic solvents under reflux conditions and expensive or odorous catalysts, tedious work-up procedure, troublesome waste discarding, long reaction times, and low yields. Therefore, obviation of these limitations is necessary to develop a simple and green synthesis of dihydropyrano[2,3-*c*]pyrazole. Thus, we decided to investigate a catalyst- and solvent-free route for synthesis of dihydropyrano[2,3-*c*]pyrazole scaffold with diverse substituents using ball milling technique. The reaction proceeded smoothly to afford different derivatives of dihydropyrano[2,3-*c*]pyrazole (**5a-q**) through one-pot condensation of ethyl acetoacetate (**1**), hydrazine hydrate (**2**), malononitrile (**3**), and aromatic aldehydes (**4a-q**) by catalyst- and solvent-free methodology under ball milling conditions at ambient temperature (Scheme 1).

Results and discussion

To find the optimized conditions, a systematic study with considering different variables affecting the reaction yield was carried out for the reaction of ethyl acetoacetate (**1**), hydrazine hydrate (**2**), malononitrile (**3**), and 4-chlorobenzaldehyde (**4a**) (molar ratio:1:1:1:1) as the model reaction. The results are summarized in Table 1. Only a trace amount of the desired 6-amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5a**) was obtained under catalyst-free and reflux conditions in water after 5 h (entry 1). Then, the effect of catalyst loading on the completion of the reaction was studied in the next step (entries 2–5). The use of potassium phthalimide-*N*-oxyl (POPINO) and tetraethylammonium 2-(carbamoyl)benzoate (TEACB), as catalyst, in water under reflux conditions improved the yield of the desired product **5a** significantly (entries, 2–5). Interestingly, the yield of the desired product **5a** was improved more when it was run in ball mill under catalyst-free conditions at ambient temperature (entries, 6–8) compared to refluxing water (entries, 1–4). This behavior can be attributed to the less solubility of the substrates and reaction intermediates in water (Scheme 2). As shown in Table 1, the best results in terms of the obtained yield of the desired product **5a**, required temperature and time of reaction were obtained in ball mill under catalyst-free conditions.

In order to generalize the optimum conditions, different derivatives of 6-amino-3-methyl-4-aryl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5a-q**) were prepared from the one-pot reaction mixture of ethyl acetoacetate (**1**), hydrazine hydrate (**2**), malononitrile (**3**), and aromatic aldehydes (**4a-q**) under ball milling conditions in the absence of any catalyst at ambient temperature. The results are summarized in Table 2. As it is shown in Table 2, aromatic aldehydes with electron-withdrawing groups (entries 1–7) accelerate the reaction compared to the electron-donating groups (entries 9–15). In

Table 1 Optimization of the reaction conditions for preparation 6-amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5a**)



Entry	Catalyst loading (mol%)	Conditions	Temp.(°C)	Time (min)	Yield[a] (%)
1	–	H_2O	Reflux	5	Trace
2	POPINO[b] (10)	H_2O	Reflux	2	25
3	POPINO[b] (20)	H_2O	Reflux	2	45
4	TEACB[c] (5)	H_2O	Reflux	2	50
5	TEACB[c] (5)	EtOH	50	90	80
6	–	Ball milling	Ambient	40	83
7	–	Ball milling	Ambient	45	99[d]
8	–	Ball milling	Ambient	60	99[d]

Reaction conditions: Ethyl acetoacetate (**1**, 1 mmol), hydrazine hydrate (**2**, 1 mmol), malononitrile (**3**, 1 mmol), and 4-chlorobenzaldehyde (**4a**, 1 mmol) under various conditions

[a] The yields refer to the desired product **5a**

[b] Potassium phthalimide-*N*-oxyl

[c] Tetraethylammonium 2-(carbamoyl)benzoate

[d] The yields refers to isolated yield

addition to the aromatic aldehydes, the reaction was also proceeded smoothly using heterocyclic aldehydes in high to excellent yields (entries 16 and 17).

The mechanism suggested in Scheme 2 seems to be reasonable for the one-pot four-component reaction of ethyl acetoacetate (**1**), hydrazine hydrate (**2**), malononitrile (**3**), and aromatic aldehydes **4a-q** using ball milling technique. The first step includes cyanocinnamonitriles (**7**) formation from the reaction between aldehydes **4a-q** and malononitrile (**3**). Then, Michael addition by the enol form of 5-methyl-2,4-dihydro-pyrazol-3-one intermediate (**8E**) on the intermediate **7**, cyclization and final tautomerization of intermediate **9** affords the desired products **5a-q**.

Comparison of the present method with those reported in the literature in respect to the catalyst loading, time, required reaction conditions, yield, simplicity, and performance reveals that the method presented here is a simple and efficient method for the preparation of dihydropyrano[2,3-*c*]pyrazole derivatives (Table 3).

Conclusion

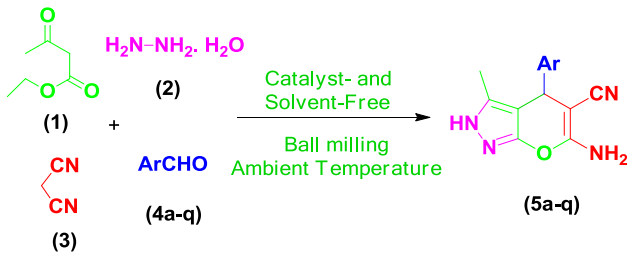
In conclusion, we have developed a highly efficient and green one-pot methodology for the synthesis of a wide range of dihydropyrano[2,3-*c*]pyrazole derivatives, which are often encountered in biologically and pharmacologically actives compounds. The procedure proceeds under catalyst- and solvent-free conditions at ambient temperature using ball milling technique. The most important advantages of this method include the use of catalyst- and solvent-free conditions, excellent yields, and clean and simple work-up procedure that make this method an instrumental alternative to the previous methodologies for the scale-up of this one-pot four-component reaction.

Experimental section

General

All commercially available chemicals were obtained from Merck and Aldrich, and used without further purifications, except for benzaldehyde, which was used as a fresh distilled sample. The ball mil was a Retsch MM 400 swing mill with its 3D driving of the balls. A 10-mL stainless steel double-walled beaker was applied. Two stainless steel balls with 12-mm diameter were used, and the milling frequency was at 28 Hz and the ambient

Table 2 Catalyst- and solvent-free four-component synthesis of 6-amino-3-methyl-4-aryl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives (**5a-q**) under ball milling conditions at ambient temperature



Entry	Aldehyde **4**	Time (min)	Product **5**[a]	Yield[b] (%)	References
1	4-Chlorobenzaldehyde (**4a**)	45	**5a**	99	[38]
2	4-Bromobenzaldehyde (**4b**)	45	**5b**	95	[39]
3	4-Fluorobenzaldehyde (**4c**)	45	**5c**	95	[36]
4	2-Chlorobenzaldehyde (**4d**)	60	**5d**	92	[34]
5	2,4-Dichlorobenzaldehyde (**4e**)	60	**5e**	90	[40]
6	4-Nitrobenzaldehyde (**4f**)	30	**5f**	99	[38]
7	3-Nitrobenzaldehyde (**4g**)	35	**5g**	90	[40]
8	Benzaldehyde (**4h**)	70	**5h**	87	[38]
9	4-Hydroxybenzaldehyde (**4i**)	60	**5i**	88	[38]
10	4-Methoxybenzaldehyde (**4j**)	90	**5j**	85	[38]
11	2-Hydroxybenzaldehyde (**4k**)	90	**5k**	90	[39]
12	4-Dimethylaminobenzaldehyde (**4l**)	90	**5l**	90	[39]
13	4-Hydroxy-3-methoxybenzaldehyde (**4 m**)	105	**5m**	85	[38]
14	2, 4-Dimethoxybenzaldehyde (**4n**)	105	**5n**	87	[40]
15	3-Benzyloxy-4-hydroxybenzaldehyde (**4o**)	120	**5o**	85	This work
16	Furan-2-carbaldehyde (**4p**)	70	**5p**	90	[40]
17	Thiophen-2-carbaldehyde (**4q**)	70	**5q**	90	[41]

Reaction conditions: ethyl acetoacetate (**1**, 1 mmol), hydrazine hydrate (**2**, 1 mmol), malononitrile (**3**, 1 mmol), and aromatic aldehyde (**4a-q**, 1 mmol), under catalyst- and solvent-free conditions, at ambient temperature using ball mill technique

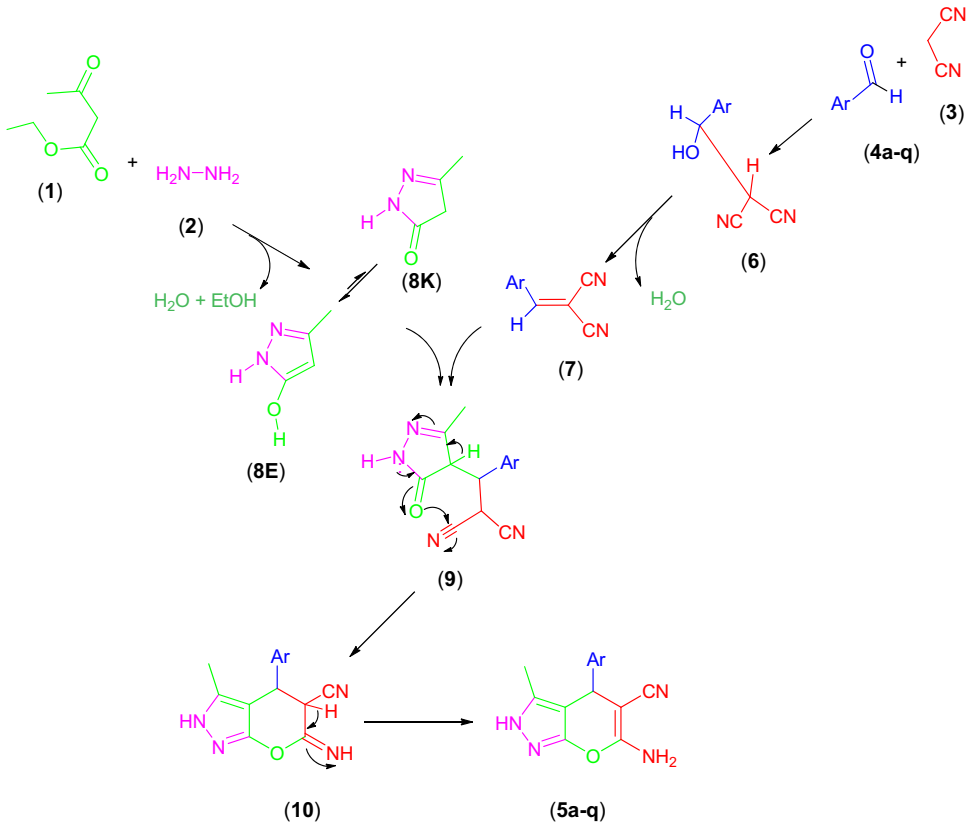
[a] All compounds are known and their structures were established from their spectral data and melting points as compared with the authentic samples or literature values [29–43]

[b] The yields refers to isolated yield of **5a-q**

temperatures. Analytical thin-layer chromatography (TLC) for monitoring reactions was performed using Merck 0.2 mm silica gel 60 F-254 Al-plates. Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. Microanalysis of the products was carried out by a CHNS/O analyzer (Perkin–Elmer Series II, 2400). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker DRX-400 Avance spectrometers with DMSO as solvent at room temperature. All yields refer to isolated products. All compounds were well characterized using melting points, IR and NMR spectral data as compared with those obtained from authentic samples or reported in the literature [29–43].

Typical procedure for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives (5a-q)

A clean, dry, 10-mL ball mill vessel with two stainless steel balls was charged with ethyl acetoacetate (**1**, 1 mmol) and hydrazine hydrate (**2**, 1 mmol). The vessel was closed and the milling was started at ambient temperatures at a speed of 28 Hz for 30 s. Then, malononitrile (**3**, 1 mmol) and aromatic aldehyde (**4a-q**, 1 mmol) were added to the vessel, and milling was started under ambient temperature for the specific times as indicated in Table 2. The reaction progress was monitored by TLC. After completion of the reaction, the obtained solid was suspended in water (60 °C, 5 mL) for 5 min, filtered through a Buchner funnel, and dried in an oven at 60 °C for 1 h.



Scheme 2 A plausible mechanism for the one-pot four-component reaction of ethyl acetoacetate (**1**), hydrazine hydrate (**2**), malononitrile (**3**), and aromatic aldehydes (**4a-q**) under catalyst- and solvent-free conditions using ball milling technique at ambient temperature

Table 3 Comparison of the present method with other methods for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivative of **5a**

Entry	Catalyst	Conditions	Temp. (°C)	Time (min)	Yield (%)	References
1	TEBA[a]	H_2O	90	360	99	[36]
2	γ-Alumina	H_2O	Reflux	35	90	[33]
3	L-Proline	H_2O	Reflux	180	97	[27]
4	Lipase	EtOH	30	60	88	[30]
5	Imidazole	H_2O	80	20	90	[42]
6	–	H_2O	Reflux	240	80	[43]
7	–	Ball milling	Ambient	45	99	This work

[a] Triethylbenzylammonium chloride

Selected spectral data

*6-Amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (**5a**)*

White crystals, mp 235–236 °C, yield: 99 %, IR (KBr) $\bar{\upsilon}_{max}$ 3439, 3246, 2193, 1639, 1599, 752 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.80 (s, 3H, CH_3), 4.64 (s, 1H, $CH_{benzylic}$), 6.95 (br s, 2H, NH_2), 7.19–7.21 (d, 2H, J = 8.4 Hz, $CH_{aromatic}$), 7.38–7.40 (d, 2H, J = 8.4 Hz, $CH_{aromatic}$), 12.15 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 9.7, 35.5, 56.7, 97.2, 120.1, 131.2, 131.4, 135.6, 143.5, 143.3, 154.7, 160.9 ppm [44].

*6-Amino-4-(4-hydroxy-3-phenoxymethyl-phenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5o**)*

White crystals, mp 189–191 °C, yield: 85 %, Elemental analysis for $C_{21}H_{18}N_4O_3$: C 67.37, H 4.85, N 14.96; found: C 67.31, H 4.79, N 14.99; IR (KBr) $\bar{\upsilon}_{max}$ 3479, 3236,

3117, 2187, 1635, 1610, 1596, 1587, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.78 (s, 3H, CH_3), 3.39 (s, 2H, $CH_{2benzylic}$), 4.45 (s, 1H, $CH_{benzylic}$), 6.82 (br s, 2H, NH_2), 6.83-6.85 (m, 3H, $J = 10.4$ Hz, $CH_{aromatic}$), 7.37–7.40 (m, 5H, $J = 6.8$ Hz $CH_{aromatic}$), 12.06 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 9.7, 35.7, 55.5, 57.3, 97.6, 111.9, 113.2, 120.0, 120.9, 127.9, 128.3, 135.6, 136.8, 137.0, 147.3, 148.0, 154.7, 160.7 ppm.

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