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Morpholinium Glycolate Catalyzed: One-pot Green Synthesis of Coumarin linked Pyrazoline Derivatives via in situ-developed Cinnamoyl Coumarins under Solvent-free Conditions

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Abstract: A straightforward one-pot multi-component protocol for the synthesis of pyrazolin-3-yl coumarin derivatives have been developed by using various aryl aldehyde, 3-acetyl coumarin, and hydrazine hydrate/phenyl hydrazine hydrochloride. The reactions accomplished successfully using in situ-developed cinnamoyl coumarins via claisen-schemidt condensation reaction catalyzed by morpholinium glycolate as the homogeneous catalyst under solvent-free conditions at 90 °C. The present synthetic methodology is eco-friendly and economical as it avoids the use of volatile organic solvents as well as the conventional catalysts and has many advantages include the mild reaction conditions, effortless work up, no chromatographic purification, reusability of catalyst, and excellent yields of the products.

Keywords: Coumarin, Pyrazoline, Morpholinium glycolate, Ionic liquids, Multi-component reactions

Introduction

In drug design and discovery, a fusion of two or more biodynamic structural units into a single chemical entity that shows the enhanced therapeutic activities has come to be the fascinating area of research. In this context, many examples of coumarin containing pyrazoline moieties have been pointed out in the literature. Through the Years, coumarin and their derivatives either of natural or synthetic origin endowed the broad application in agriculture, cosmetic, perfume, and pharmaceutical industries[1]. Coumarin-based molecules have frequently been utilized as antioxidants[2], antitumor[3], anti-HIV[4], anticoagulants[5, 6], antimicrobials[7], anti-inflammatories[8], and antidepressants[9]. The coumarin-based drugs like warfarin mainly employed for their blood thinner characteristics (anticoagulant). Additionally, it also helps to prevent the spreading of a new cancerous tumor

[5, 10].

The literature demonstrates that the pyrazoline derivatives have diverse pharmacological activities. Pyrazoline, a small biologically active molecule occupied the prominent position in medicinal chemistry, and because of their importance, ample research has been carried out on this moiety[11]. Pyrazoline based molecules have shown various therapeutic activities such as analgesic, anesthetic, antibacterial, anti-inflammatory, antifungal, anti-depressant and antitumor[12-14]. Therefore, the introduction of pyrazoline moiety into the parent coumarin unit could lead to the potential compound with enhanced pharmacological activities. Based on, few scientific groups reported their synthetic methods[15-17]. Practically these methods were mainly of multi-step synthesis; for example, in a first step, there was the formation of 3-cinnamoyl coumarins followed by the preparation of the title compounds in the later step. These methods were suffered from some drawbacks such as the isolation and purification of each step intermediates, consume a lot of solvents and time, overall yields decreased, and so forth. Whereas, El-Remaily reported[18] one-pot synthesis of coumarins linked to pyrazoline by using bismuth triflate $Bi(OTf)_3$ in dichloromethane. However, as per green chemistry, the use of volatile solvent and lack of reusability of catalyst are the limitations associated with this cited procedure. Therefore, the development of an environmentally benign process to the synthesis of bioactive molecules remains an active field of research.

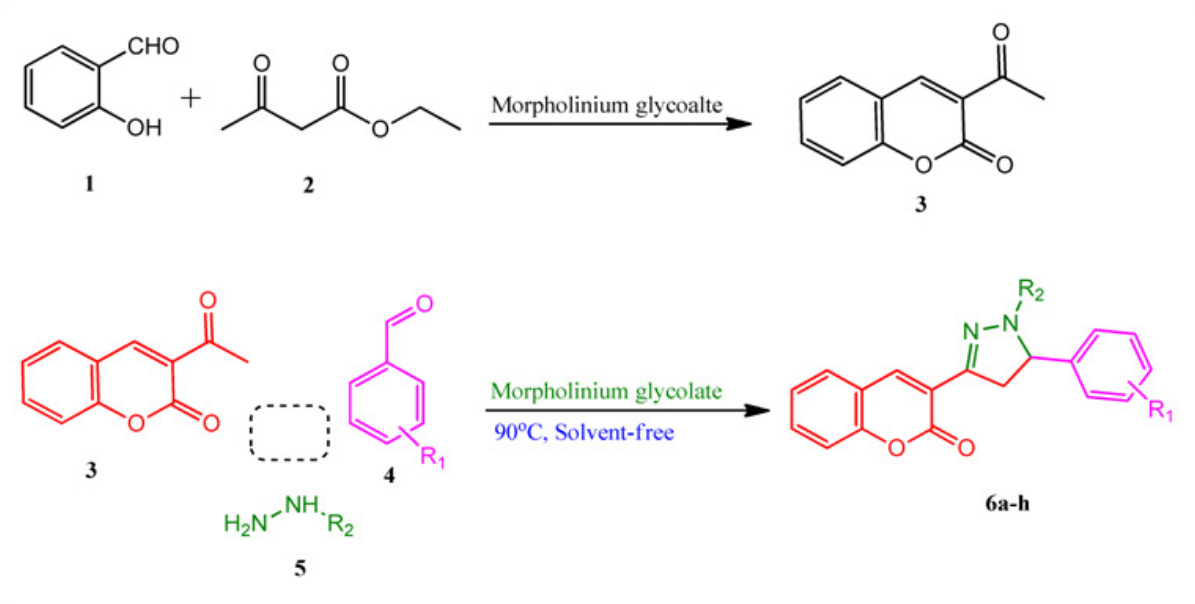
Multicomponent reactions (MCRs) have proven to be as an essential modern synthetic tool for affording the diverse range of products with excellent yields in a single step and are eco-compatible than the multi-step reactions. Additionally, the use of green solvents or solvent-free conditions[19-21] and ionic liquids as a recyclable catalyst in MCRs can deliver more efficient, rapid, cleaner and safer synthetic process[22].

Nowadays, Ionic liquids(ILs) have been immensely attracted to the synthetic organic chemist, because not just for their important role to control the organic reactions as the catalyst[23-27] but also their ability to be reused for multiple times[28, 29]. In catalysis science, Ionic liquids being as the catalyst have obtained an intense attention due to their low toxicity, reusability, high efficiency in comparison with some other catalytic systems. Since many years ionic liquids have been used as green solvents because of their distinctive properties such as the controlled miscibility, thermal stability, nonvolatility, nonflammability, acidity/coordination properties[30, 31]. These properties can be tailored by simply changing the structure of ILs with the variety of anions/cations according to the requirements of synthetic processes. As of late, Ionic liquids based on ammonium, pyridinium, phosphonium, sulfonium, imidazolium, and so forth as organic cations have frequently been addressed in the literature[32]. Irrespective of their valuable properties, few of ionic liquids are not cost-effective and reveal toxic effect towards the living organisms[33, 34]. Hence, the designing of inexpensive and eco-compatible ionic liquids is highly considerable. Literature shows that the morpholinium based ILs possess less toxicity as compared to the commonly used imidazolium, pyridinium, and tetraalkylammonium based ionic liquids[35, 36].

Keeping in mind the environmental concerns and to our continued interest towards the development of novel synthetic methodologies for the biologically significant molecules. In the present work, we employed morpholinium glycolate as a reusable ionic liquid catalyst for the eco-friendly synthesis of pyrazolin-3-yl coumarin derivatives (**6a-h**) under solvent-free conditions in a one-pot method (Scheme **1**).

Experimental

Materials



Scheme 1. Synthesis of pyrazolin-3-yl coumarin derivatives (**6a-h**)

The chemicals were commercially available and used as such. All reactions monitoring and purity of synthesized compounds were carried out by thin-layer chromatography on silica-gel $60F_{254}$ aluminum plates. The FT-IR spectrum of the samples was determined on Thermo Nicolet Avatar 370 FT-IR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) on Bruker Advance II 400 spectrometer were recorded by using DMSO-d_6/$CDCl_3$ as solvents. TG-DTG analysis of the catalyst was performed on Perkin Elmer STA 6000, and the melting points were read in an open capillary tube and are uncorrected.

Synthesis

Synthesis of Morpholinium glycolate

Morpholinium glycolate was synthesized from our previously reported method[37] by adding glycolic acid (65%, 5 mmol) to the morpholine (5 mmol) at room temperature in a 25mL round bottom flask. Afterward, the reaction mixture was stirred at 80°C for two hours and dried under reduced pressure until the weight of the catalyst remained constant.

Brownish liquid (88% yield); TG-DTG analysis (40 to 730 °C): decomposition point above 206 °C; FT-IR (ν_{max}, cm^{-1}): 3600-2460, 1591, 1452, 1405, 1239, 1103; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.03 (t, J = 4.9 Hz, 4H), 3.67 (s, 2H), 3.75 (t, J = 4.8 Hz, 4H), 4.09 (s, 1H), 6.57 (s, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ (ppm) 42.89, 61.54, 63.86, 177.35.

General procedure for the Preparation of 3-acetyl coumarin

A mixture of salicylaldehyde (**1**) (10 mmol), ethyl acetoacetate (**2**) (10 mmol) and morpholinium glycolate (245 mg, 15 mol%) was stirred at 80 °C for 20 minutes. Upon completion of the reaction (monitored by TLC methanol:*n*-hexane 2:8), the reaction content was cooled and washed with 2X20 mL water, filtered, and recrystallized from ethanol. Finally, the catalyst was recovered from water under reduced pressure.

Yellow solid (89% yield); M.P: 118-120 °C[38]; ^{1}H NMR (400 MHz, $CDCl_3$): δ =2.49 (s, $COCH_3$, 3H), 7.31-7.75 (m, ArH, 4H), 8.46 (s, C4-H chromene, 1H).

Synthesis of pyrazolin-3-yl coumarin derivatives (6a-h)

To a 25 mL round bottom flask, 3-acetyl coumarin (**3**) (2 mmol), aryl aldehydes (**4a-h**) (2 mmol), and (81 mg, 25 mol%) morpholinium glycolate as the catalyst was added, and the reaction mixture was heated at 90 °C for ten to fifteen minutes with proper stirring. Then hydrazine hydrate/ phenyl hydrazine hydrochloride (**5**) (2 mmol) was added and stirred at the same temperature for the appropriate time as mentioned in Table **1**. After completion of the reaction (monitored by TLC methanol:ethyl acetate:*n*-hexane 1:2:7), water (5 mL) added and stirring was kept continuous before reaction cooled to the room temperature. The solid products were separated by filtration and recrystallized from ethanol to afford pure products (**6a-g**) with excellent yields. The product **6h** was washed with 5 mL of 20% $NaHCO_3$ solution followed by 2x5 mL water. Then **6h** was recrystallized from a mixture of ethyl acetate and ethanol (1:9). The filtrate was concentrated under high vacuum to recover morpholinium glycolate.

Characterization data of some representative compounds

*3-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2H-chromen-2-one (**6a**):*

Yellowish brown solid, mp: 164-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.10 (dd, J_{AM} = 19.4 and J_{AX} = 7.2 Hz, C4-H_A pyrazoline, 1H), 3.76 (dd, J_{MA} = 19.4 and J_{MX} = 7.2 Hz, C4-H_M pyrazoline, 1H), 4.92 – 5.14 (m, C5-H_X pyrazoline, 1H), 7.22 – 7.77 (m, aromatic proton, 11H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.98, 57.94, 111.16, 116.25, 116.75, 123.97, 125.10, 125.54, 127.23, 127.71, 128.18, 128.39, 130.36, 131.13, 141.40, 151.68, 152.15, 161.39.

*3-(5-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2H-chromen-2-one (**6h**):*

Reddish brown solid, mp: 199-201 °C; FT-IR (KBr) (ν_{max}, cm^{-1}): 3036.51(aromatic CH), 2860.35 (aliphatic CH), 1728.18 (C=O), 1599.42 (C=N), 1564.67 (C=C), 747.35 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.35 (dd, J_{AM} = 18.3 and J_{AX} = 7.2 Hz, C4-H_A pyrazoline, 1H), 4.09 (dd, J_{MA} = 18.3 and J_{MX} = 12.7 Hz, C4-H_M pyrazoline, 1H), 5.29 (dd, J_{XM} = 12.7 and J_{XA} = 7.2 Hz, C5-H_X pyrazoline, 1H), 6.84 (t, J = 7.3 Hz, C4-H ArH, 1H), 7.06 (d, J = 7.7 Hz, C2-H and C6-H ArH, 2H), 7.18 – 7.24 (m, C3-H and C5-H ArH and C6-H chromene, 3H), 7.27 – 7.33 (m, Ar-Cl, 4H), 7.34 – 7.43 (m, C8-H chromene, 1H), 7.48 – 7.54 (m, C7-H chromene, 1H), 7.58 (d, J = 7.8 Hz, C5-H chromene 1H), 8.41 (s, C4-H chromene 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.12, 64.20, 113.63, 116.42, 119.42, 120.04, 120.59, 124.76, 125.46, 127.20, 128.23, 128.30, 129.66, 129.23, 129.98, 131.50, 131.62, 133.36, 137.83, 140.53, 143.02, 143.78, 153.54, 159.69.

Table 1. Optimization of the reaction conditions for synthesis of (**6a**) catalyzed by morpholinium glycolate[a]

Entry	Solvent	Temperature (°C)	Catalyst (mol%)	Time (min)[b]	Yield (%)[c]
1	H_2O	reflux	25	300	Trace
2	EtOH	reflux	25	180	80
3	MeOH	reflux	25	180	78
4	EtOH:H_2O	reflux	25	230	61
5	ACN	reflux	25	300	40
6	THF	reflux	25	270	43
7	DCM	reflux	25	250	40
8	$CHCl_3$	reflux	25	280	35
9	**solvent-free**	**90**	**25**	**95**	**85**
10	solvent-free	room-temperature	25	300	30
11	solvent-free	50	25	300	45
12	solvent-free	60	25	180	60
13	solvent-free	70	25	110	68
14	solvent-free	80	25	100	82
15	solvent-free	100	25	95	85
16	solvent-free	90	no catalyst	24h	-
17	solvent-free	90	5	180	55
18	solvent-free	90	10	150	60
19	solvent-free	90	15	120	72
20	solvent-free	90	20	95	80
21	solvent-free	90	30	95	85

[a]Reaction conditions: 3-acetyl coumarin (2 mmol), benzaldehyde (2 mmol) and hydrazine hydrate (2 mmol).
[b]Reaction progress monitored by TLC.
[c]Isolated yields.

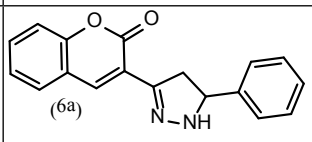
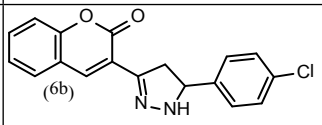
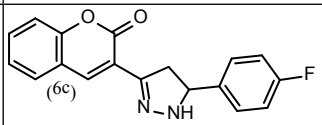
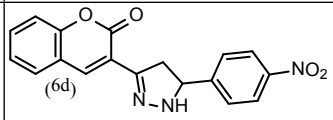
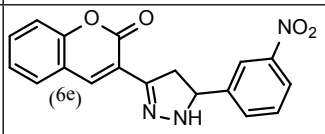
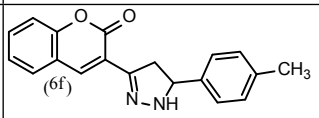
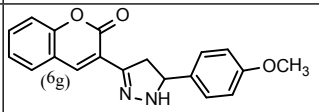
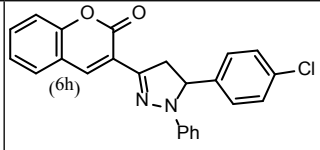
Results and discussion

In this research, first, morpholinium glycolate was prepared from morpholine and glycolic acid. The starting material 3-acetyl coumarin was also synthesized using an ionic liquid as the catalyst and is outlined in scheme **1**. Then, we have investigated the different reaction variables such as solvents, temperature, and amount of catalyst for the synthesis of representative compound (**6a**). For this purpose, benzaldehyde (**4a**), 3-acetyl coumarin and hydrazine hydrate were selected as the model substrates. In continuation to our research on ionic liquids, and with this aim, we used morpholinium glycolate (25 mol%) as the homogeneous catalyst to explore the reaction. Initially, the model reaction was executed in different solvents at reflux point. In water, a trace amount of product was obtained as a sticky material with prolonged reaction time (Table **1**, entry 1). The use of protic solvents like ethanol, methanol resulted in better yields of the products (Table**1**, entries 2-3). The model reaction was also executed in aqueous ethanol (Table **1**, entry 4), but there was significantly dropped in the product yield. In acetonitrile, tetrahydrofuran, dichloromethane, and chloroform, the products were obtained in small quantity with lengthened reaction time (Table **1**, entries 5-8). Moreover, the model reaction was also carried out by omitting solvents at 90 ^{o}C, and the reaction offered an excellent yield of the product in shorter reaction time. Thus, it can be concluded from the obtained results that the solvent-free condition is highly suitable for this transformation (Table **1**, entry 9).

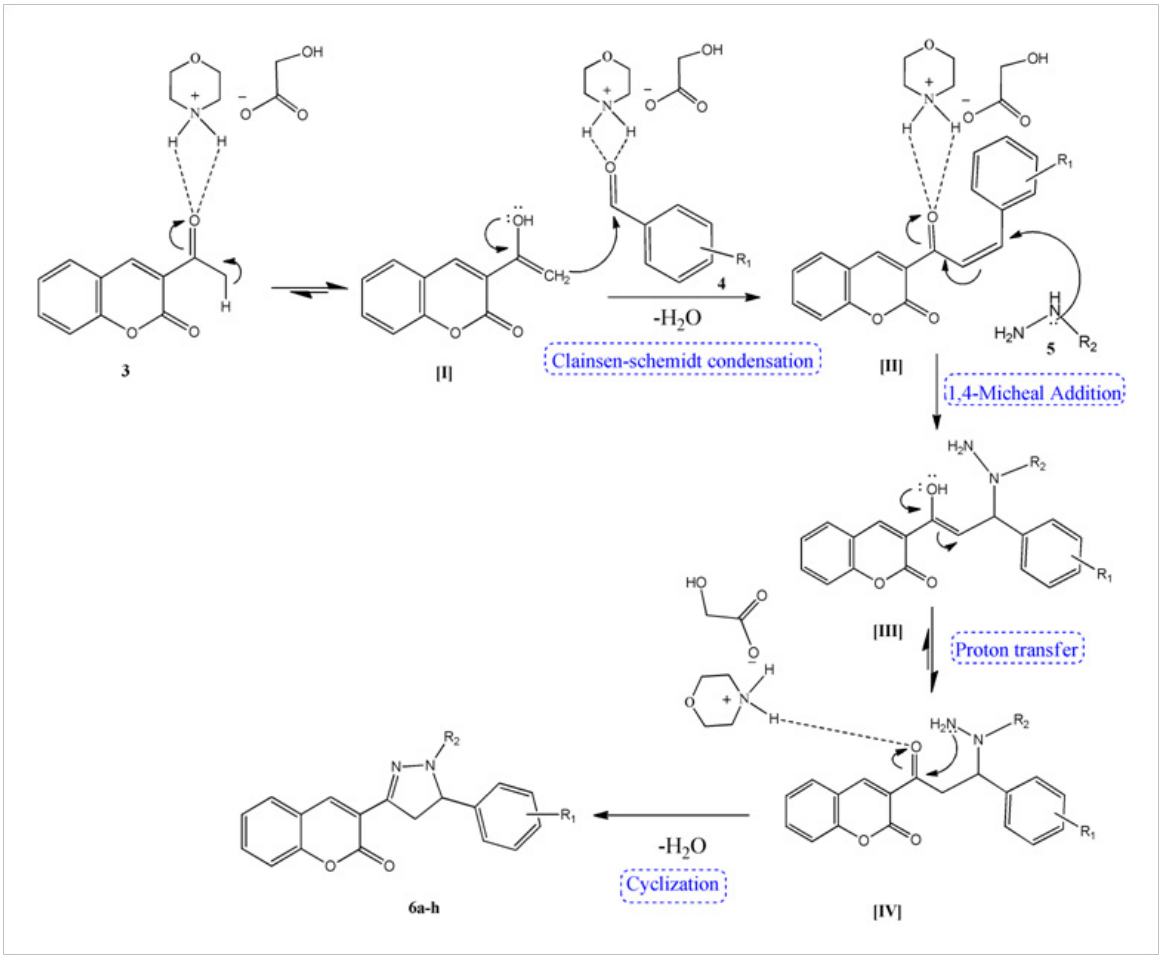
Next, to determine optimum temperature, the model reaction was first performed at room temperature, followed by 50 ^{o}C, 60 ^{o}C, 70 ^{o}C, 80 ^{o}C and 100 ^{o}C respectively. The (Table **1**, entries 10-15) indicates that there was an improvement in the product yields, with raising the temperature of the reaction up to 90 ^{o}C and above 90 ^{o}C, no additional improvement was observed. As a result, the model reaction temperature was established at 90 ^{o}C (Table **1**, entry 9). After that, to figure out the concentration of catalyst, at first, the model reaction was examined without the catalyst, but the reaction did not lead to form the product (Table **1**, entry 16). Then the reaction was further investigated at 5, 10, 15, 20, and 30 mol% of morpholinium glycolate at 90 ^{o}C under solvent-free conditions (Table **1**, entries 17-21). From the Table **1**, it can be concluded that the 25 mol% of catalyst is sufficient to complete the reaction and hence, all further reactions were performed by using 25 mol% of morpholinium glycolate under solvent-free conditions at 90 ^{o}C.

Using the optimized reaction conditions, we then synthesized a series of pyrazolin-3-yl coumarin derivatives from hydrazine hydrate, 3-acetyl coumarin, and aromatic aldehydes possessing electron-withdrawing and electron-donating substituents. The obtained results are summarized in Table **2**. It was observed that the aromatic aldehydes having electron-withdrawing groups such as 4-Cl-, 4-F-, 4-nitro-, 3-nitro-, reacted faster and afforded the corresponding products in 92%, 91%, 90%, 80% yields respectively (Table **2**, entries 2-5). Whereas, aldehydes bearing electron-donating groups like 4-methyl, 4-methoxy, were also smoothly converted into the desired products (Table **2**, entries 6-7). Further to examine the scope of the present protocol with regards to the hydrazine derivatives, we treated phenyl hydrazine hydrochloride and 3-acetyl coumarin with 4-chlorobenzaldehyde. In this case, the reaction smoothly proceeded but consumed little more time as compared to the hydrazine hydrate and afforded the product **6h** in 90% yield (Table **2**, entry 8). According to the literature[39, 40], the proposed mechanism for the synthesis of pyrazolin-3-yl coumarin derivatives (**6a-h**) under the optimized reaction conditions using an ionic liquid as the catalyst is shown in Scheme **2**. Initially, 3-acetyl coumarin and aromatic aldehydes underwent claisen-schemidt condensation type`s reaction

Table 2. Synthesis of Pyrazolin-3-yl Coumarin Derivatives (**6a-h**)[a]

Entry	R_1	R_2	Product	Time (min)[b]	Yield (%)[C]	Melting point (°C)	
						Found	Reported
1	C_6H_5	H	 (6a)	95	85	164-166	-
2	4-ClC_6H_4	H	 (6b)	75	92	172-174	175-177[17]
3	4-FC_6H_4	H	 (6c)	75	91	181-183	183-185[17]
4	4-$NO_2C_6H_4$	H	 (6d)	70	90	196-198	199-201[18]
5	3-$NO_2C_6H_4$	H	 (6e)	80	80	185-187	189-190[18]
6	4-$CH_3C_6H_4$	H	 (6f)	100	78	164-166	160-162[18]
7	4-$CH_3OC_6H_4$	H	 (6g)	110	75	180-182	183-185[18]
8	4-ClC_6H_4	Ph	 (6h)	110	91	199-201	-

[a]Reaction conditions: 3-acetyl coumarin (2 mmol), aromatic aldehydes (2 mmol) and Hydrazine hydrate/Phenyl hydrazine hydrochloride (2mmol) catalyzed by 25 mol% morpholinium glycolate under solvent-free conditions at 90°C.
[b]Reaction progress monitored by TLC.
[c]Isolated yield.



Scheme 2. The proposed mechanism for the synthesis of pyrazolin-3-yl coumarin derivatives (**6a-h**) in the presence of morpholinium glycolate.

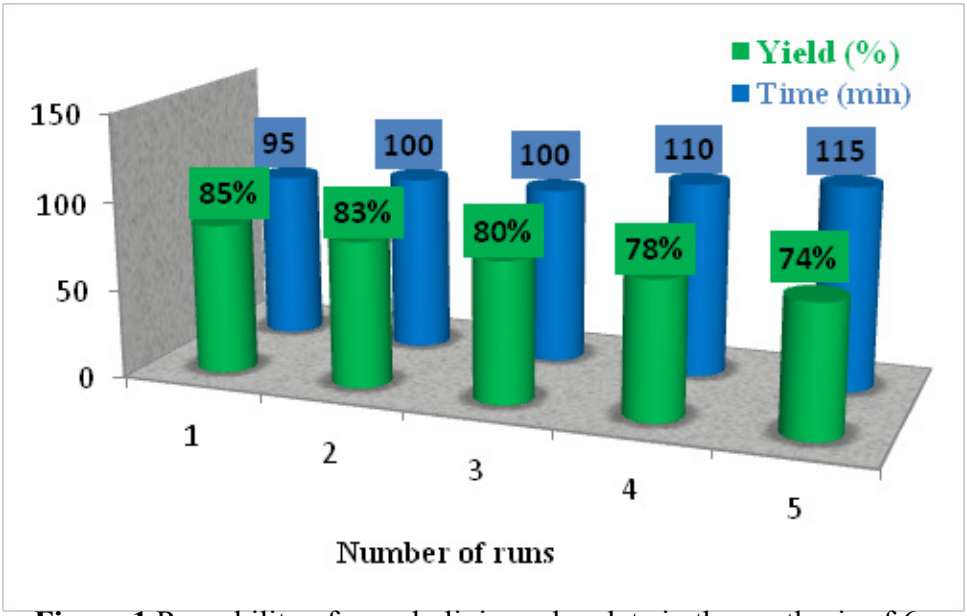


Figure 1. Reusability of morpholinium glycolate in the synthesis of 6a

in the presence of morpholinium glycolate to produced cinnamoyl coumarins (II). Then, the 1,4-Michael addition of hydrazine derivatives on the activated α, β- unsaturated carbonyl intermediate (II) was taking place, followed by proton transfer to form intermediate(IV). After that, (IV) undergoes intramolecular cyclization with the elimination of a water molecule to affords the corresponding products (**6a-h**).

Furthermore, the recovery and reusability of morpholinium glycolate was also examined in the reaction of benzaldehyde, 3-acetyl coumarin and hydrazine hydrate under the optimized reaction conditions. After completion of the reaction, water was added to the hot reaction mixture and stirred for few minute then allowed it to cool to the room temperature. The ionic liquid was dissolved in water, and the solid product was separated by simple filtration. The catalyst was recovered by evaporating the water under reduced pressure, and the recovered catalyst was washed with cyclohexane, dried and reused for the next successive runs (Figure **1**).

Conclusion

In summary, we have reported, for the first time, morpholinium glycolate catalyzed one-pot multicomponent approach for the synthesis of biologically potent pyrazolin-3-yl coumarin derivatives via claisen-schemidt condensation followed by the 1, 4-Michael addition reaction under solvent-free conditions. The promising points of this research are the straightforward and clean reaction procedure, maximum products yields, brief reaction time, an ease of products isolation, the avoidance of environmentally unfriendly reagents and organic solvents, and reusability of the catalyst.

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