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A facile solvent-free route for the one-pot multicomponent synthesis of benzylpyrazolyl coumarins catalyzed by $FeCl_3.SiO_2$ nanoparticles

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The synthesis of benzylpyrazolyl coumarin derivatives is achieved by the four-component reaction of arylhydrazine/hydrazine hydrate, ethyl acetoacetate, aromatic aldehydes and 4-hydroxycoumarin. $FeCl_3/SiO_2$ nanoparticles are used as an efficient and green catalyst for the present research work. This method is fast and affords high yields. It is also clean, safe, cost-effective and importantly, the $FeCl_3/SiO_2$ nanocatalyst is easily recovered and reused for at least five cycles, which confirms its good stability.

Keywords: $FeCl_3/SiO_2$ nanoparticles, multicomponent, solvent-free, pyrazolone.

INTRODUCTION

Compounds containing the pyrazolone ring system have received considerable attention due to the attractive pharmacological properties associated with this heterocyclic moiety. Since many of these heterocycles like phenazone, propyphenazone, ampyrone (Fig. 1a) exhibit biological activities such as anti-inflammatory, postmenopausal, anti-osteoporosis, angiotensin antagonist, and anticoagulant activities [1-3], these derivatives have become an integral part of pharmacologically important heterocyclic compounds. 3-Substituted 4-hydroxycoumarins, particularly 3-benzylsubstituted 4-hydroxycoumarin derivatives are of much importance because they are present in many natural products.

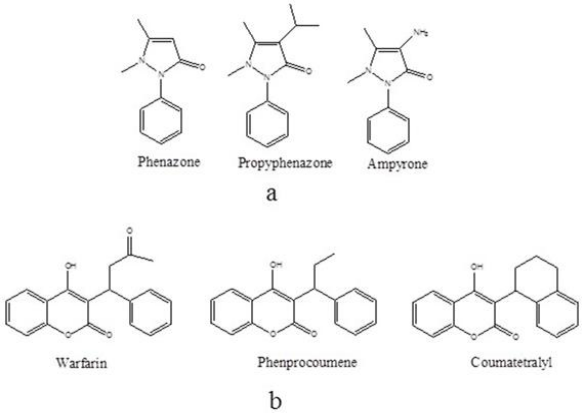


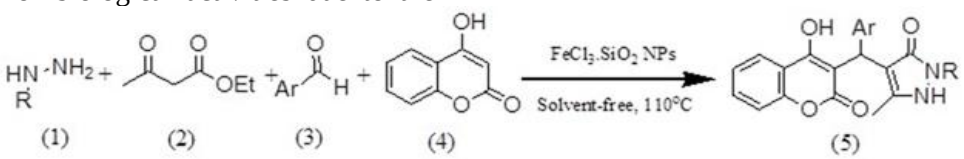
Fig. 1. (a) Bio-active pyrazolone moieties; (b) Some biologically active 3-substituted coumarins.

It is also established that these compounds show a wide range of biological activities due to their abundance in medicinal scaffolds, namely warfarin, phenprocoumon, coumatetralyl (Fig. 1b) offering antibacterial, anti-HIV [4], antiviral [5], anticoagulant [6], antioxidant [7] and anticancer activities [8].

Multicomponent reactions (MCRs) are a promising and vital field of chemistry because the synthesis of complicated molecules can be achieved in a very fast, efficient, and time saving manner without the isolation of any intermediate. Multicomponent reactions are some of the most important protocols in organic synthesis and medicinal chemistry [9,10].

Heterogeneous supported catalysts have gained an important role in organic synthesis due to high activity and selectivity, available active sites, easy catalyst separation, long catalytic life, thermal stability, easy handling and reusability [11,12]. Therefore, the use of supported and recoverable catalysts in organic transformations has economical and environmental benefits [13-18]. Among various silica-based heterogeneous catalysts, $FeCl_3$–SiO_2 has the advantages of low cost, ease of preparation and recyclability [19-21].

In this work, which is a continuation of our studies of catalytic multicomponent reactions using inorganic solids as heterogeneous catalysts [22-24], we describe the preparation of benzylpyrazolyl coumarin derivatives in the presence of $FeCl_3$–SiO_2 nanoparticles (NPs) under solvent-free conditions (Scheme 1).



Scheme 1. Synthesis of benzylpyrazolyl coumarin derivatives.

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EXPERIMENTAL

General

All reagents were purchased from Merck and Aldrich and were used without further purification. The reaction was monitored by TLC using 0.2 mm Merck silica gel 60 F254 pre-coated plates, which were visualized with UV light. Melting points were measured on an Electrothermal 9200 apparatus. The IR spectra were recorded on a FT-IR Magna 550 apparatus using KBr discs. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance DRX-400 MHz instrument using TMS as the internal standard. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Microscopic morphology of products was visualized by SEM (LEO 1455VP).

General procedure for the preparation of nano-silica-supported ferric chloride

In a 100-cm^3 flask, 25 g nano silica gel and 2 g $FeCl_3.6H_2O$ (8 % of the weight of nano-SiO_2) were vigorously stirred under solvent-free conditions at room temperature for 24 h to achieve homogeneous adsorption. A yellow powder was obtained. This powder was heated for 1 h at 100^{o}C to give a brownish powder ("active" $FeCl_3$/nano-SiO_2 reagent).

General procedure for the preparation of benzylpyrazolyl coumarin derivatives

A mixture of 0.05 g $FeCl_3/SiO_2$ NPs, hydrazine 1 (1 mmol), ethyl acetoacetate 2 (1 mmol), aromatic aldehyde 3 (1 mmol) and 4-hydroxycoumarin 4 (1 mmol) was finely ground with a mortar and pestle and then heated in a flask under stirring at 110^{o}C in an oil bath. After completion of the reaction (indicated by TLC), the reaction mixture was dissolved in hot ethanol, and the mixture was stirred for 5 min. The reaction mixture was filtered, and the heterogeneous catalyst was recovered. Then the product was recrystallized from ethanol to get the pure compounds as white or pale yellow crystals. The isolated compounds were characterized by IR, ^{1}H NMR and ^{13}C NMR.

Spectral data of 5a, 5e, 5h and 5k compounds

1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(3-nitrophenyl)methyl)-5-methyl-2-phenylpyrazol-3-one (5a): Pale yellow crystalline solid; mp 241-243 °C, IR (KBr, cm^{-1}): ν_{max} 3074, 1649, 1609, 1560, 1525, 1179, 1103, 749; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (3H, s), 5.79 (1H, s), 7.10-7.21 (3H, m), 7.32-7.44 (4H, m), 7.54-7.59 (3H, m), 7.74-7.76 (2H, d, J=7.8 Hz), 7.92-7.98(2H, m), 12.07 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.8, 34.2, 105.5, 106.5, 115.9, 118.4, 121.2, 121.3, 122.1,123.7, 124.4, 126.9, 129.2, 131.8, 133.7, 135.3, 142.1, 147.1, 148.36, 152.5, 162.6, 164.6, 165.1. Anal. Calcd. for $C_{26}H_{19}N_3O_6$: C 66.48, H 4.07, N 8.93, Found: C 66.50, H 4.08, N 8.92.

1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(4-methoxyphenyl)methyl)-5-methyl-2-phenylpyrazol-3-one (5e): White crystalline solid; mp 207-209 °C, IR (KBr, cm^{-1}): ν_{max} 3072, 1645, 1606, 1563, 1522, 1174, 1103, 746; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (3H, s), 3.61 (3H, s), 5.76 (1H, s), 7.08-7.25 (3H, m), 7.30-7.42 (4H, m), 7.52-7.58 (3H, m), 7.75-7.78 (2H, d, J=7.8 Hz), 7.92-7.98(2H, m), 12.08 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7, 34.5, 105.2, 106.4, 115.7, 118.8, 121.1, 121.3, 122.1,123.4, 124.4, 126.8, 129.2, 131.6, 133.5, 135.5, 142.6, 147.1, 148.42, 152.5, 162.5, 164.4, 165.5. Anal. Calcd. for $C_{27}H_{22}N_2O_4$: C 71.35, H 4.88, N 6.16, Found: C 71.37, H 4.90, N 6.19.

1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(4-bromophenyl)methyl)-5-methyl-2-phenylpyrazol-3-one (5h): Cream crystalline solid; mp 244-246 °C, IR (KBr, cm^{-1}): ν_{max} 3068, 1641, 1606, 1562, 1520, 1177, 1103, 747; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (3H, s), 5.76 (1H, s), 7.09-7.25 (3H, m), 7.31-7.43 (4H, m), 7.50-7.58 (3H, m), 7.73-7.78 (2H, d, J=7.8 Hz), 7.91-7.97(2H, m), 12.06 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5, 34.6, 105.1, 106.6, 115.6, 118.8, 121.2, 121.6, 122.1,123.6, 124.4, 126.9, 129.2, 131.5, 133.5, 135.5, 142.8, 147.1, 148.42, 152.5, 162.8, 164.3, 165.7. Anal. Calcd. for $C_{26}H_{19}N_2O_4Br$: C 62.15, H 3.78, N 5.57, Found: C 62.18, H 3.80, N 5.54.

4-((4-Hydroxy-2-oxo-2H-chromen-3-yl)(4-methylphenyl) methyl)-5-methyl-3H-pyrazol-3-one (5k): Cream crystalline solid; mp 226-228 °C, IR (KBr, cm^{-1}): ν_{max} 3083, 1613, 1527, 1347, 1186, 1038, 758; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (3H, s), 2.37 (3H, s), 5.75 (1H, s), 7.09-7.23 (3H, m), 7.30-7.44 (4H, m), 7.49-7.59 (3H, m), 7.73-7.79 (2H, d, J=7.8 Hz), 7.90-7.99 (2H, m), 12.06 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6, 20.9, 33.8, 105.3, 106.7, 115.8, 119.7, 123.3, 124.4, 125.8, 127.1, 128.0, 131.2, 140.7, 144.7, 152.6, 163.3, 165.8. Anal. Calcd. for $C_{21}H_{17}N_2O_4$: C 69.80, H 4.70, N 7.75, Found: C 69.82, H 4.72, N 7.73.

RESULTS AND DISCUSSION

In our initial studies, we attempted to optimize the reaction conditions for the multicomponent

reaction between 3-nitrobenzaldehyde, phenylhydrazine hydrate, ethyl acetoacetate and 4-hydroxycoumarin as model substrates. Since solvent-free syntheses [25] have gathered much interest, so we decided to compare this reaction under solvent-free conditions and in different solvents (Table 1). It was observed that the reaction afforded high yields under solvent-free conditions, but poor yields in solvents.

Table 1. The model reaction using different solvents.

Entry	Solvent	Time (min)	Yield[a] (%)
1	EtOH (reflux)	50	89
2	H_2O (reflux)	120	10
3	CH_2Cl_2	60	50
4	Solvent-free	10	95

[a] Isolated yield.

Then we focused on the systematic evaluation of different catalysts for the model reaction under solvent-free conditions. A wide variety of catalysts including $FeCl_3$, SiO_2, nano SiO_2, $FeCl_3/SiO_2$ and $FeCl_3/SiO_2$ NPs were employed to test their efficacy for the specific synthesis of benzylpyrazolyl coumarins (Table 2).

Table 2. The model reaction carried out in the presence of various catalysts.[a]

Entry	Catalyst (g)	Time (min)	Yield of 5a (%)[b]
1	Without catalyst	210	Trace
2	$FeCl_3$ (0.05)	160	35
3	SiO_2 (0.05)	160	27
4	nano SiO_2 (0.05)	120	60
5	$FeCl_3/SiO_2$ (0.05)	100	70
6	$FeCl_3/SiO_2$ NPs (0.01)	20	79
7	$FeCl_3/SiO_2$ NPs (0.03)	10	85
8	$FeCl_3/SiO_2$ NPs (0.05)	10	95
9	$FeCl_3/SiO_2$ NPs (0.1)	10	95

[a] phenylhydrazine hydrate (1 mmol), ethyl acetoacetate (1 mmol), 3-nitrobenzaldehyde (1 mmol) and 4-hydroxycoumarin (1 mmol).

[b] Isolated yield.

The results presented in Table 2 show that in presence of $FeCl_3/SiO_2$ NPs, the desired product was obtained in 95% yield within 10 min. Therefore, this catalyst appears to be superior to any of the other catalysts tested. This also checked that the quantity of the catalyst can play a vital role in realizing the optimal product yield. An increase in the amount of $FeCl_3/SiO_2$ NPs from 0.01 to 0.05 g increased the yield of the desired product to a great extent.

During the optimization of the reaction conditions, the effect of temperature was monitored (Fig. 2). At 110 °C the maximum yield of the product was obtained. The yield of the reaction was very poor at a temperature below 110 °C and at a higher temperature there might be some sort of polymerization of the Knoevenagel condensation product which lowers the yield of the desired product.

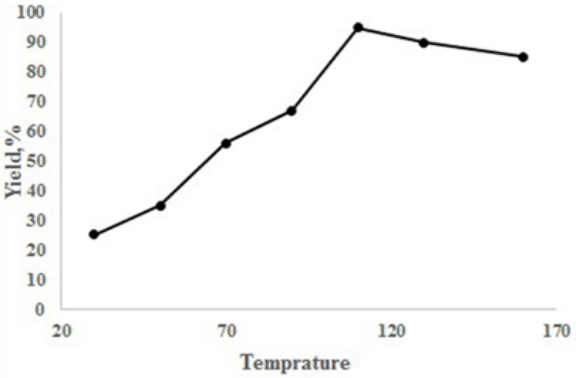


Fig. 2. Effect of temperature on the synthesis of benzylpyrazolyl coumarins.

On the basis of the above results during the optimization of solvent, catalyst and temperature, we then devised to employ a wide range of aldehydes with 4-hydroxycoumarin, arylhydrazine/ hydrazine hydrate and ethyl acetoacetate. As can be seen from Table 3 (following Scheme 1), the reaction proceeded smoothly with unsubstituted benzaldehyde, electron-withdrawing, and electron-releasing para-substituted benzaldehydes.

Table 3. Synthesis of benzylpyrazolyl coumarins.

Entry	Hydrazine (R)	Aldehyde (Ar)	Product	Time (min)	Yield[a] (%)	M.p. [ref]
1	C_6H_5	3-$NO_2C_6H_4$	5a	10	95	241-243[26]
2	C_6H_5	4-ClC_6H_4	5b	12	94	225-227[26]
3	C_6H_5	4-$NO_2C_6H_4$	5c	15	93	247-249[26]
4	C_6H_5	C_6H_5	5d	18	91	233-235[26]
5	C_6H_5	4-$OMeC_6H_4$	5e	20	89	207-209[26]
6	C_6H_5	4-MeC_6H_4	5f	20	92	223-225[26]
7	C_6H_5	4-FC_6H_4	5g	16	93	241-243[26]
8	C_6H_5	4-BrC_6H_4	5h	17	91	244-246
9	H	3-$NO_2C_6H_4$	5i	9	91	205-207[26]
10	H	4-$OMeC_6H_4$	5j	10	90	201-203[26]
11	H	4-MeC_6H_4	5k	10	90	226-228
12	H	C_6H_5	5l	12	92	232-234[26]

[a] Isolated yield.

In order to investigate the morphology and particle size of $FeCl_3/SiO_2$ NPs, a SEM image of $FeCl_3/SiO_2$ NPs was recorded (Fig. 3). As can be seen, the sample shows a nanocrystalline structure. The reusability of the catalyst in the model reaction was studied. The separated catalyst was collected and washed several times with acetone to remove all organic substances. It was then dried at 100°C and was recycled five consecutive times with almost unaltered catalytic activity (Table 4).

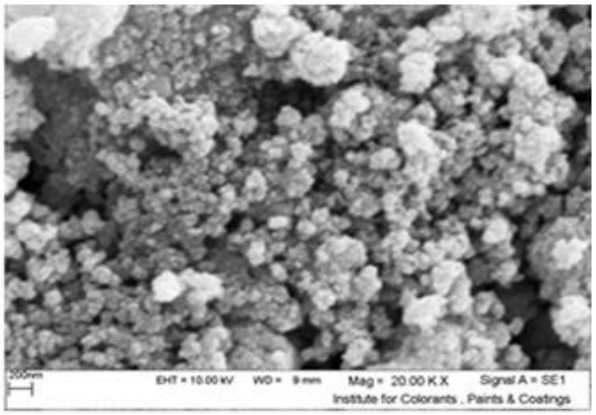


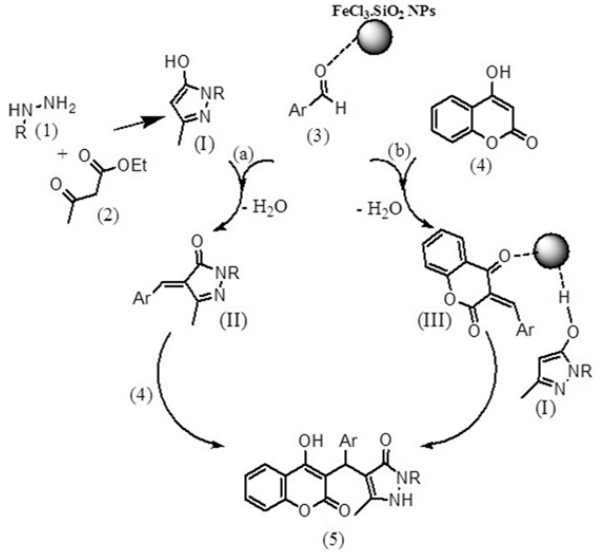
Fig 3. SEM image of $FeCl_3/SiO_2$ NPs.

Table 4. Catalyst reusability for the synthesis of benzylpyrazolyl coumarins.

Entry	Cycle	Yield[a], %
1	Fresh	95
2	1	95
3	2	94
4	3	94
5	4	94
6	5	93

[a] Isolated yield.

In view of these results, we offer a mechanistic scheme for this reaction which involves Knoevenagel condensation, Michael addition, and cyclization catalyzed by $FeCl_3/SiO_2$ NPs as presented in Scheme 2. There are two paths for this reaction: path (a) and path (b). Initially, aryl hydrazine/hydrazine hydrate (1) reacts with ethyl acetoacetate (2) to generate the pyrazolone ring (I). In path (a) Knoevenagel reaction between pyrazolone ring (I) and aromatic aldehyde (3) takes place to form the intermediate (II) and then condensation of this intermediate with 4-hydroxycoumarin (4) affords the desired product (5). In another path, Knoevenagel reaction between 4-hydroxycoumarin (4) and aromatic aldehyde (3) takes place to form the Knoevenagel product (III). Subsequently, during the Michael addition step, nucleophilic attack on (III) by the pyrazolone (I) affords the desired product (5).



Scheme 2. Plausible mechanism for the formation of benzylpyrazolylcoumarins.

CONCLUSIONS

In conclusion, a simple and convenient method was developed for the synthesis of benzylpyrazolyl coumarins by the reaction of arylhydrazine/ hydrazine hydrate, ethyl acetoacetate, aromatic aldehydes and 4-hydroxycoumarin using $FeCl_3/SiO_2$ NPs as a catalyst under solvent free conditions. The attractive features of this protocol are: simple reaction procedure, short reaction time, easy product separation and purification, reusability of $FeCl_3/SiO_2$ NPs and its high adaptability to the synthesis of a broad spectrum of benzylpyrazolyl coumarin derivatives in good to excellent yields.

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ПРОСТ МЕТОД ЗА ЕДНОСТАДИЙНА СИНТЕЗА НА БЕНЗИЛ-ПИРАЗОЛИЛОВИ КУМАРИНИ, КАТАЛИЗИРАНА ОТ НАНОЧАСТИЦИ ОТ $FeCl_3.SiO_2$ БЕЗ РАЗТВОРИТЕЛ

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(Резюме)

Постигната е синтеза на бензил-пиразолил-кумаринови производни чрез четири-компонентна реакция на арил-хидразин/хидразин-хидрат, етилацето-ацетат, ароматни алдехиди и 4–хидроксикумарин. Използвани са наночастици от $FeCl_3/SiO_2$ като катализатор като ефективен и „зелен“ катализатор. Методът е бърз и позволява високи добиви. Освен това той е чист, безопасен, евтин и което е важно, катализаторът лесно се оползотворява и използва петкратно.