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Nano-magnetite as an eco-friendly and magnetically separable catalyst for a one-pot synthesis of pyrano [2, 3-c]pyrazoles and bis(4-hydroxycoumarin-3-yl)methane derivatives

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KEYWORDS

Nano-magnetite; Biscoumarin; Pyranopyrazole; Magnetically recoverable catalyst; Green chemistry. **Abstract.** A facile and environmentally benign procedure for the synthesis of pyranopyrazoles and biscoumarin derivatives, using non-toxic and magnetically separable catalyst in water as green solvent, is reported.

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1. Introduction

Nanoscience is an outstanding field of research in which nanostructures are designed and synthesized for different applications in modern sciences such as chemical transformations [1]. The design and synthese of nanocatalysts being used in such transformations have attracted much attention as the central field of nanotechnology and nanoscience. In nanometer scale, along with decreasing the size of the particles, the surface-to-volume ratio increases significantly. This unique property provides more active sites per unit area and is responsible for higher activity of nanocatalysts and efficiency in organic reactions in comparison with other types [2]. Utilizing magnetic nanoparticles offers several advantages including semi-quantitative recovery of the catalyst from the reaction mixture easily, using an efficient magnetic bar [3]. In addition to the aforementioned merits for nanocatalysts, Fe_3O_4 nanoparticles are considered as eco-friendly, economically available and comparatively non-toxic catalyst [4]. These important properties open gates to numerous applications, such as drug delivery [5], as a magnetic resonance imaging contrast agent [6] and as a catalyst in different chemical industries [7].

Due to widely occurrence of heterocyclic moieties in bioactive substances and natural products [8], developing of novel methodologies toward synthesis of these valuable compounds has been always of interest among the organic synthetic chemists.

Pyranopyrazoles and biscoumarins are important fused heterocyclic compounds. Pyranopyrazoles, as key synthetic intermediates, exhibit great biological properties, such as analgesic [9], antimicrobial [10], anti-inflammatory [11] and molluscicidal [12] activities. Furthermore, 4-(6-amino-2,4-dihydro-3,5dimethylpyrano [2, 3-c]pyrazolol-4-yl)benzene-1,2-diol has been reported to act as potential inhibitor of human chk1 kinase [13]. The aforementioned appreciable characteristics have evoked extensive studies toward the synthesis of pyranopyrazol deriva-The first pyrano [2, 3-c]pyrazole derivatives. tives were synthesized from a two-component reaction between 3-methyl-1-phenylpyrazoline-5-one and

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tetracyanoethylene [14]. Afterwards, many methods have been introduced for the synthesis of 6-amino,5cyano,4-aryl,dihydropyrano [2, 3-c]pyrazoles. Triethylamine [15], piperazine [16], MgO [17] and heteropolyacid [18] have been reported being as suitable catalysts for a two-component or three-component reaction for their syntheses. Moreover in this ongoing interest, a 4-component catalyzed syntheses have also been accomplished utilizing piperidine [19], imidazole [20], L-proline [21] and trichloroacetic acid [22] as catalysts.

Some of biscoumarins are naturally occurring compounds which can serve as anticoagulant, anti-HIV and anticancer agents [23]. They have also been synthesized via the reaction of 4-hydroxycoumarine and different aldehydes, using several catalysts including piperidine [24], molecular iodine [25], glacial acetic acid [26], ruthenium (III) chloride hydrate [27] and sulfated titania [28].

Despite the efficiency of the reported catalyzed pathways for the synthesis of 1,4-dihydropyrano [2, 3-c]pyrazoles and biscoumarins, some of them suffer from drawbacks, such as use of toxic solvents, tedious workup, toxicity, non-recoverability or corrosive inherent of the employed catalyst.

Thus, as a step forward on the development of novel protocols in organic synthesis considering the green chemistry concept and in continuation of our interest in the synthesis of heterocyclic compounds using nanocatalysts [29-34], particularly nano magnetite [35,36], herein we wish to report a relatively green synthesis of pyrano [2, 3-c]pyrazoles and biscoumarins in water employing nano-Fe₃O₄ as catalyst.

2. Results and discussion

In this article, we wish to disclose a clean and convenient method for the synthesis of pyranopyrazoles and biscoumarins in water. Our initial efforts were directed to synthesize pyranopyrazole derivatives (Scheme 1).

Various reaction conditions including different temperatures, solvents and different amounts of catalyst employed were examined to obtain the optimized reaction conditions. The reaction of hydrazine hydrate (1 mmol), ethyl acetoacetate (1 mmol), malononitrile (1.07 mmol) and benzaldehyde (1 mmol) were tested in water under reflux conditions, in the absence and in the presence of different amounts of Nano-Fe₃O₄ as a typical reaction. As shown in Table 1, in the absence

Table 1. Results of using various amounts of Fe₃O₄ nanoparticles, solvents and temperatures on the synthesis of 6-amino-5-cyano-3-methyl-4-phenyl-1,4 dihydro pyrano [2, 3-c]pyrazole.

Entry	Catalyst amount (mol%)	Solvent	$\begin{array}{c} \mathbf{Temperature} \\ (^{\circ}\mathbf{C}) \end{array}$	Time (min)	${f Yield}\ (\%)^{a}$
1	0	$\rm H_2O$	98	180	50
2	10	${\rm H}_2{\rm O}$	98	100	74
3	13	${\rm H}_2{\rm O}$	98	50	90
4	15	$\rm H_2O$	98	55	90
5	13	EtOH	78	55	78
6	13	${\rm CH}_{3}{\rm CN}$	82	75	61
7	13	$\mathrm{CH}_2\mathrm{Cl}_2$	40	65	58
8	13	$\rm H_2O$	25	85	62
9	13	${\rm H}_2{\rm O}$	50	100	70

^a: Yields refer to isolated products.

of any catalyst the reaction was incomplete even after 180 min, and only slight progress of the reaction was observed. (The progress of the reaction was monitored by TLC.) However when we used different amounts of our nanocatalyst, the progress of the reaction was improved significantly. We found that 13 mol% catalyst was the optimum amount due to the shortest reaction time required, being the fully completed and highest yield obtained (Table 1, entry 3). In order to study the solvent effect, the above model reaction was performed in different solvents under reflux conditions. As can be concluded from Table 1, the highest yield was obtained when the reaction was run in water as a solvent of choice as far as green chemistry concerns (entry 3). The optimized temperature for the above typical reaction was experimentally found to be the reflux temperature (entry 3) and was found to be relatively applicable for general procedure for this reaction. The corresponding results are summarized in Table 1.

Having established the optimum conditions, this multicomponent reaction was carried out using various aromatic aldehydes bearing electron-withdrawing and electron-donating groups. As shown in Table 2, the highest yield and the shortest reaction time were obtained for the product bearing 4-hydroxy phenyl moiety (Table 2, entry 8).

From the proposed mechanism in Scheme 2, it can be concluded that Fe_3O_4 nanoparticles, as Lewis



Scheme 1. Pyranopyrazole synthesis.

Entry	R	\mathbf{Time}	Yield	Found	Reported	Ref.	
		(min)	$(\%)^{\mathrm{a}}$	M.P.	M.P.		
1	C_6H5	50	90	243 - 245	244 - 245	[16]	
2	$4\text{-}\mathrm{NO}_2\ \mathrm{C}_6\mathrm{H}_4$	40	69	250 - 251	251 - 252	[16]	
3	$3-\mathrm{NO}_2 \mathrm{C}_6\mathrm{H}_4$	80	81	193 - 194	190 - 192	[37]	
4	4-OMe C_6H_4	65	80	171	170 - 172	[37]	
5	$3\text{-}\mathrm{OMe}\ \mathrm{C}_{6}\mathrm{H}_{4}$	120	81	175 - 177	174 - 176	[37]	
6	$4\text{-}\mathrm{Me}~\mathrm{C}_{6}\mathrm{H}_{4}$	55	83	205 - 206	206-208	[38]	
7	4-Cl C_6H_4	85	85	233 - 235	235	[16]	
8	$4\text{-OH }C_6H_4$	30	91	226-228	225 - 226	[16]	

Table 2. Synthesis of various pyranopyrazoles in the presence of Fe_3O_4 nanoparticles as catalyst.

^a: Yields refer to isolated products.



Scheme 2. Suggested mechanism for Fe₃O₄ catalyzed pyranopyrazole formation.

acid catalyst, are coordinated to the oxygen atom of the carbonyl group in different steps of the reaction and make them activated, being easier attacked by nucleophiles.

We have also investigated the synthesis of another important heterocycles, biscoumarins (Scheme 3).

Initially, condensation of 4-hydroxycoumarin and benzaldehyde in 2:1 mol ratio was examined as a model reaction in water, under reflux conditions, using nanomagnetite catalyst, and the expected corresponding

$$2 \qquad \qquad OH \qquad \qquad OH \qquad \qquad OH \qquad \qquad OH OH \qquad \qquad OH \qquad \qquad OH \qquad OH \qquad OH \qquad \qquad OH \qquad OH \qquad \qquad OH \qquad \qquad OH \qquad$$

Scheme 3. Biscoumarin synthesis.

biscoumarin was obtained. After this initial success, several experiments were carried out to achieve the optimized reaction conditions.

To find the optimum amount of the catalyst, the model reaction was performed in the absence and in the presence of different amounts of nanocatalyst. From Table 3, it is inferred that in the absence of the catalyst, the reaction proceeded sluggishly and the expected product resulted only in very low yield (entry 1). However, by using the catalyst, the yield

Table 3. Study of various catalyst amounts, solvent type and temperature effects on the

Entry	Catalyst amount (mol%)	Solvent	$\begin{array}{c} \mathbf{Temperature} \\ (^{\circ}\mathbf{C}) \end{array}$	Time (min)	Yield (%) ^a
1	0	$\rm H_2O$	98	360	48
2	10	${\rm H}_2{\rm O}$	98	120	70
3	13	$\mathrm{H}_{2}\mathrm{O}$	98	100	77
4	15	$\rm H_2O$	98	90	83
5	20	${\rm H}_2{\rm O}$	98	90	83
6	15	EtOH	78	90	70
7	15	${\rm CH}_{3}{\rm CN}$	82	65	37
8	15	$\mathrm{CH}_{2}\mathrm{Cl}_{2}$	40	75	Trace
9	15	${\rm H}_2{\rm O}$	25	85	54
10	15	$\rm H_2O$	50	100	63

bis(4-hydroxycoumarin-3-yl)(phenyl)methane synthesis.

^a: Yields of isolated products.

was improved and the use of 15 mol% of the catalyst was found to be the optimum amount, leading to full conversion and obtaining the product in excellent yield (entry 4).

In order to find the best solvent, the model reaction was performed in different solvents. We found that water as a protic solvent gives the best yield. Due to known advantages of water as solvent in chemical transformations, it was selected to be used in the general procedure (Table 3, entry 4).

To find a suitable temperature, the reaction was performed at 25°, 50°C and under reflux conditions. As shown in Table 3, by raising the temperature, yields increased and reflux conditions gave the highest yield (entry 4).

Thus, condensation between 4-hydroxycoumarin and various aromatic and aliphatic aldehydes were performed to afford the corresponding biscoumarines, under the concluded optimized conditions. The results are listed in Table 4. The plausible mechanism is illustrated in Scheme 4.

The magnetically separated nano-Fe₃O₄ catalyst in the above reaction was washed with ethanol thoroughly and then dried for 1 hour at 100° C in an oven. The recovered catalyst was reused in a three

Entry	R	Time (min)	${f Yield}\ (\%)^{a}$	Found M.P.	Reported M.P.	Ref.
1	C_6H5	90	83	230-232	228-230	[25]
2	$4\text{-}\mathrm{NO}_2\ \mathrm{C}_6\mathrm{H}_4$	60	99	243-244	242 - 245	[39]
3	$3-\mathrm{NO}_2 \mathrm{C}_6\mathrm{H}_4$	50	75	214	212 - 215	[39]
4	$4\text{-}OMe \ C_6H_4$	80	75	237	238 - 240	[39]
5	$2\text{-}OMe C_6H_4$	60	80	234	236	[24]
6	$3\text{-}\mathrm{OMe}\ \mathrm{C}_{6}\mathrm{H}_{4}$	120	75	236	238	[24]
7	4-Cl C_6H_4	75	88	254 - 255	252 - 254	[25]
8	4-OH C_6H_4	60	71	223 - 224	222 - 225	[40]
9	$-CH_3$	65	90	176 - 178	175	[24]
10	-CH=CH C_6H_5	65	94	219-221	220-224	[41]

Table 4. Synthesis of biscoumarin derivatives using Fe₃O₄ nanoparticles as catalyst.

^a: Yields of isolated products.



Scheme 4. Proposed mechanism for biscoumarin synthesis.

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	Run 1		Run 2		Run 3	
\mathbf{Entry}	Yield	\mathbf{Time}	Yield	\mathbf{Time}	Yield	\mathbf{Time}
	(%)	(min)	(%)	(min)	(%)	(\min)
Pyranopyrazole model reaction	90	50	90	55	88	60
Biscoumarin model reaction	83	90	82	95	80	95

Table 5. Reusability results for nano catalyst.

consecutive fresh model reaction which showed no significant loss of activity [42] (Table 5).

3. Conclusion

In summary, we revealed an efficient, clean, facile and relatively green protocol for the synthesis of pyrano [2, 3-c]pyrazoles and biscoumarins in water. Use of green nanocatalyst, water as solvent and excellent yields are other advantages of this presented method.

4. Experimental

4.1. Materials and methods

All the chemicals were purchased from Merck Company and used without further purification. All of the compounds were known and characterized by comparison of their physical data with those of the authentic samples already reported in literatures. Melting points were obtained, using a capillary tube method with a Barnstead Electrothermal 9200 apparatus. For some selected compounds (Table 2, entry 1) and (Table 4, entries 2 and 4) FTIR spectra were recorded on a FTIR Brucker Tensor 27 instrument using KBr discs. ¹H NMR spectra were recorded on a Bruker AQS-AVANCE spectrometer at 500 MHz, using TMS as an internal standard. Mass spectra were obtained using an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV.

4.2. Synthesis of pyranopyrazoles: General procedure

Hydrazine hydrate (1 mmol), ethyl acetoacetate (1 mmol), malononitrile (1.07 mmol), an appropriate aromatic aldehyde (1 mmol), nano-Fe₃O₄ (13 mol%) and 3 ml water were added successively into a 25 ml round-bottomed flask. The reaction mixture was refluxed for indicated time listed in Table 2. Progress of the reaction was monitored by Thin-Layer Chromatography (TLC) (eluent ethyl acetate/petroleum ether 3:7 v/v and 1-2 drops of ethanol). After completion of the reaction, nanocatalyst was removed from the reaction mixture using an external magnet. The precipitated product was filtered and washed with cool ethyl acetate/petroleum ether (2:8, 10 ml). The nearly pure product was crystallized from hot

ethanol in sake of further purification and magnetic separation of any remained nanoparticles. The product was filtered to obtain the corresponding titled compounds.

4.3. Synthesis of biscoumarins: General procedure

15 mol% of nano-Fe₃O₄ was added to a mixture of 4hydroxycoumarin (2 mmol) and aldehyde (1 mmol). The mixture was stirred in 3 mL water under reflux conditions for the specified reaction time (Table 4). Progress of the reaction was monitored by TLC (eluent ethyl acetate/petroleum ether 1:4 v/v and 1-2 drops ethanol). Upon completion of the reaction, the catalyst was separated from the precipitated crude product, utilizing an external magnet. The solid was then filtered; the crude was crystallized from hot ethanol to separate any remained catalyst already removed magnetically. The recrystallized pure product was collected to afford the corresponding titled compounds (Table 4).

6-Amino-5-cyano-3-methyl-4-phenyl-1,4

dihydro pyrano [2, 3-c]pyrazole (Table 2, entry 1) M.p 243-245, IR (KBr) 3373, 3310, 3169, 2192, 1609, 1488, 1400, 1274, 1044, 867 cm⁻¹, ¹H-NMR (500 MHz, DMSO-d₆) $\delta = 12.08$ (s, 1H, NH), 7.51-7.16 (m, 5H, ArH), 6.85 (s, 2H, NH₂), 4.58 (s, 1H, CH), 1.82 (s, 3H, CH₃.), Ms (m/z) 252(M⁺).

Bis(4-hydroxycoumarin-3-yl)(4-nitrophenyl)

methane (Table 4, entry 2) M.p 243-244°C, IR (KBr) 3075, 1664, 1605, 1563, 1521, 1349, 769 cm⁻¹, ¹H-NMR (500 MHz, CDCl₃): $\delta = 11.60$ (s, 1H, OH), 11.40 (s, 1H, OH), 8.22 (d, J = 8.79 Hz, 2H), 8.13 (d, J = 7.74 Hz, 1H), 8.04 (d, J = 7.72 Hz, 1H), 7.71 (t, J = 7.73 Hz, 2H), 7.46 (m, 6H), 6.16 (s, 1H), Ms (m/z) 475 (M⁺).

Bis(4-hydroxycoumarin-3-yl)(4-

methoxyphenyl)methane (Table 4, entry 4) M.p 237°C, IR (KBr) 3069, 1669, 1611, 1564, 1509, 1351, 1308, 1257, 1037, 768 cm⁻¹, ¹H-NMR (500 MHz, CDCl₃) δ = 11.53 (s, 1H, OH), 11.33 (s, 1H, OH), 8.10 (s, 1H), 8.04 (s, 1H), 7.66 (t, J = 7.55 Hz, 2H), 7.43 (d, J = 8.12 Hz, 4H), 7.16 (d, 916

J = 8.37 Hz, 2H), 6.88 (d, J = 8.63 Hz, 2H), 6.09 (s, 1H), 3.83 (s, 3H), Ms (m/z) 442 (M⁺).

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