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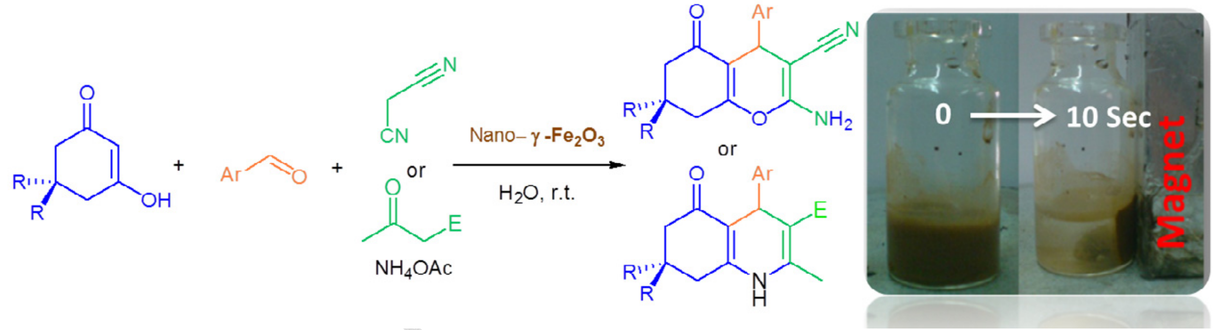

Water dispersed magnetic nanoparticles (H_2O-DMNPs) of γ-Fe_2O_3 for multicomponent coupling reactions: a green, single-pot technique for the synthesis of tetrahydro-4*H*-chromenes and hexahydroquinoline carboxylates

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Abstract- Water dispersed magnetic nanoparticles (DMNPs) of γ-Fe_2O_3 represent a simple and green catalyst for the rapid three-component synthesis of tetrahydro-4*H*-chromene and hexahydroquinoline carboxylate skeletons via single-pot domino Knoevenagel-Michael-cyclization reactions.

Key words: Nano-γ-Fe_2O_3; Dispersed magnetic nanoparticles (DMNPs); Tetrahydro-4*H*-Chromene; Hexahydroquinoline Carboxylates; Multicomponent Reaction; Green Chemistry.

Benzopyran and its tetrahydro-4*H*-chromene derivatives are important products which have been investigated as biologically and pharmacologically active compounds (Figure 1).[1-4] Tetrahydro-4*H*-chromenes can be utilized as cognitive enhancers, for the treatment of neurodegenerative diseases, including Huntington’s disease, Alzheimer’s disease, amyotrophic lateral sclerosis and Parkinson’s disease, and as therapeutics for myoclonus and schizophrenia.[4]

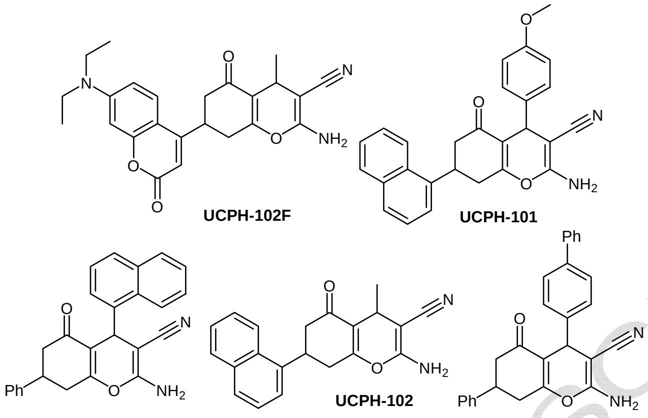


Figure 1. Examples of biologically active tetrahydro-4*H*-chromenes.

The typical procedure to synthesize chromene derivatives is usually a two-step reaction carried out between a Michael acceptor and β-dicarbonyl compounds in the presence of a catalyst. Several three-component reactions have been reported for the synthesis of tetrahydro-4*H*-chromenes by condensation of an aldehyde, dimedone and malononitrile in the presence of an ionic liquid,[5] sodium selenate,[6] hexadecyldimethylbenzyl ammonium bromide (HDMBAB),[7] magnesium oxide,[8] Amberlite IRA-40,[9] ZnO-Zeolite,[10] $H_6P_2W_{12}O_{62}.H_2O$,[11] molecular iodine[12] and organocatalysts.[13] However, many of these methods have drawbacks such as low yields of products, long reaction times, toxic solvents, harsh reactions conditions, tedious work-ups leading to the generation of large amounts of toxic waste, the requirement for an inert atmosphere and the use of stoichiometric or relatively expensive reagents.[5-13] As a result, the development of clean, safe, effective, economical, high-yielding and mild or environmentally benign protocols is still desirable.

Non-toxic magnetic nanoparticles (MNPs) such as Fe_3O_4- and Fe_2O_3-catalyzed organic processes are often considered to follow the principles of green chemistry, i.e. these catalyzed processes consume a minimum of energy and reagents or auxiliaries and minimize waste.[14] In nanochemistry, based on particles size, the nature of the nanoparticles and solvent, it has been possible to prepare dispersed heterogeneous catalysts as materials that might have properties intermediate between those of bulk and single particles due to large surface areas and high densities of active sites.[15] Investigations of dispersed heterogeneous nanoparticles as catalysts is rare. On the other hand, the strategy of using dispersed magnetic nanoparticles (DMNPs) as magnetically separable nanocatalysts is typically more effective than filtration or centrifugation as it prevents loss of the catalyst.[16] Magnetic separation of magnetic nanoparticles is simple, economical and promising for industrial applications. From both economic and environmental viewpoints, organic reactions in water using recoverable catalysts have gained attention in recent years.[16]

For the above reasons, we were intrigued by the possibility of applying nano and green chemistry to the design of an active, recyclable, and magnetically recoverable water medium dispersed nano-γ-Fe_2O_3 catalyst for the synthesis of tetrahydro-4*H*-chromene and hexahydroquinoline carboxylates under mild reaction conditions.

Previously, we developed synthetic methods for the synthesis of biologically interesting heterocycles via multicomponent reactions.[17] The challenge in this field, was the development of efficient and rapid green methods. Moreover, the synthesis of these heterocycles has usually been carried out in polar solvents such as DMF and DMSO, leading to complex isolation and recovery procedures. Also, based on our recent success on the preparation of magnetic nanoparticles as catalysts,[17] in this paper, we present the results of an extended investigation on the activity of the water dispersed γ-Fe_2O_3 as a green, magnetically separable nanocatalyst in a domino Knoevenagel-Michael-cyclization process leading to the formation of tetrahydro-4*H*-chromenes without any salts or additives. The method involves the condensation of an aldehyde, dimedone and malonitrile using a dispersed technique with small (~30 nm range, Figure 2) unfunctionalized γ-Fe_2O_3 as the active catalyst (see the supporting information). The condensation of benzaldehyde, dimedone and malononitrile was selected as a model system (Table 1).

The γ-Fe_2O_3 magnetic nanoparticles were synthesized by basic precipitation of an iron source.[18] To confirm the size distribution, TEM analysis was carried out (see the supporting information).).

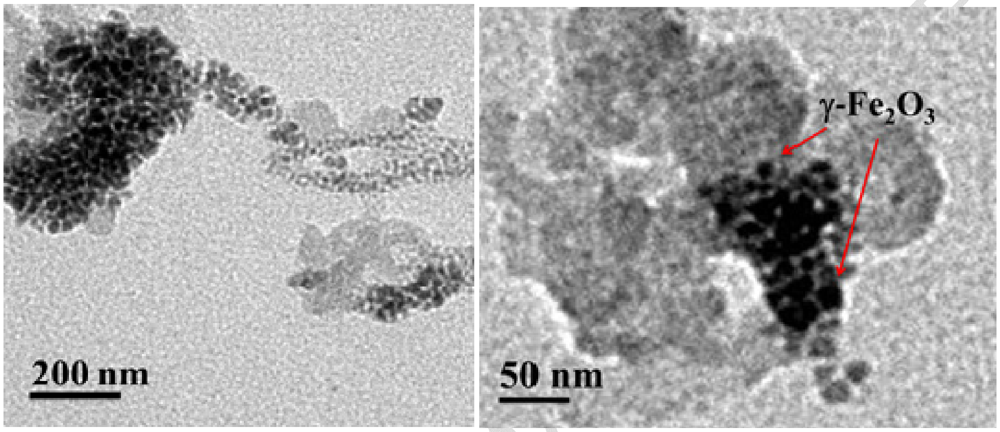
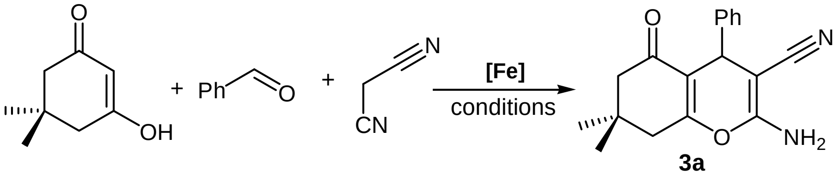


Figure 2. Transmission electron microscopy (TEM) image of γ-Fe_2O_3 nanoparticles.

By screening a wide range of iron sources, we found that product **3a** could be obtained in yields ranging from 17 to 80% using 5 mol% of the catalyst (entries 1-7, Table 1). Dispersion of the γ-Fe_2O_3 magnetic nanoparticles (5 min ultrasonic irradiation) and then use of the obtained DMNPs as the catalyst increased the yield of **3a** from 73% to 80% (entries 7 and 8, Table 1). The reactions with different amounts of γ-Fe_2O_3 were also studied (entries 8-12, Table 1), with 10 mol% proving optimum in terms of the yield.

Table 1. Optimization of the reaction conditions for the synthesis of tetrahydro-4*H*-chromenes. [a]

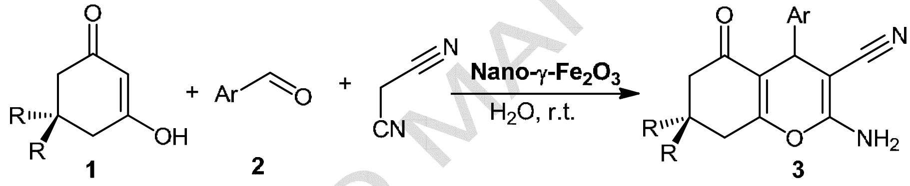


Entry	Fe source	Solvent	Cat. (mol%)	T (°C)	Time (h)	Yield (%)
1	$FeCl_3.6H_2O$	H_2O	5	50	1	24
2	$FeSO_4$	CH_2Cl_2	5	r.t.	0.5	17
3	$Fe(NO)_3$	H_2O	5	50	1.5	21
4	bulk-Fe_3O_4	H_2O	5	r.t.	1	30
5	nano-Fe_3O_4	H_2O	5	r.t.	1	51
6	γ-Fe_2O_3/SiO_2 MNPs [b]	H_2O	4	r.t.	0.5	37
7	γ-Fe_2O_3 MNPs	H_2O	5	r.t.	5	73
8	γ-Fe_2O_3 DMNPs [c]	H_2O	5	r.t.	5	80
9	**γ-Fe_2O_3 DMNPs [c]**	**H_2O**	**10**	**r.t.**	**4**	**93**
10	γ-Fe_2O_3 DMNPs [c]	H_2O	15	r.t.	4	92
11	γ-Fe_2O_3 DMNPs [c]	H_2O	20	r.t.	4	93
12	γ-Fe_2O_3 DMNPs [c]	H_2O	25	r.t.	4	94
13	γ-Fe_2O_3 DMNPs [c]	EtOH	10	r.t.	4	87
14	γ-Fe_2O_3 MNPs	MeOH	10	r.t.	4	85
15	γ-Fe_2O_3 MNPs	CH_3CN	10	r.t.	4	82
16	γ-Fe_2O_3 MNPs	CH_3Cl	10	r.t.	4	84
17	γ-Fe_2O_3 DMNPs [c]	H_2O:EtOH	10	r.t.	4	89
18	γ-Fe_2O_3 MNPs	toluene	10	r.t.	6	82

[a] Reaction conditions: benzaldehyde (1 mmol), malononitrile (1.1 mmol), dimedone (1 mmol), Fe source, solvent (3 mL). [b] Synthesized based on our previous report.[17j] [c] Dispersion of the particles was accomplished by ultrasonic irradiation.

We used water as the solvent because it is inexpensive, non-toxic, and environmentally benign, also, the highest dispersion of MNPs was achieved in water. A water dispersion of the MNPs, produced using ultrasound and maintained in non-magnetic conditions, did not produce a bulk precipitate of γ-Fe_2O_3, even after 2 hours. When we dispersed the MNPs in toluene, under the same conditions, a bulk precipitate (γ-Fe_2O_3) was obtained after 20-25 min. With these results in hand and to demonstrate the diversity of the dispersed magnetic nanoparticles (DMNPs) of γ-Fe_2O_3 as a nanocatalyst, and to expand the scope of the process, the optimized conditions were applied to a series of substrates **1**, and **2** as shown in Table 2.

Table 2. The synthesis of tetrahydro-4*H*-chromenes using DMNPs. [a]



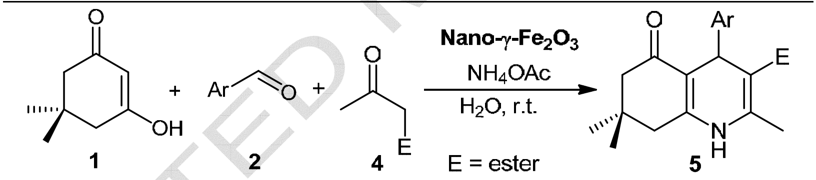
Entry	R	Ar	Time (h)	3	Yield (%) of **3** [c]	Mp (°C)	
						Reported	Found
1	CH_3	C_6H_5	5	**3a**	95	233-234 [20a]	227-230
2	CH_3	furfural	6	**3b**	93	205-206 [20b]	206-208
3	CH_3	2-NO_2-C_6H_4	5	**3c**	90	182-184 [20c]	182-183
4	H	4-MeO-C_6H_4	5	**3d**	90	198-200 [20d]	203-205
5	CH_3	2-MeO-C_6H_4	6	**3e**	90	195-197 [20b]	196-198
6	CH_3	3-NO_2-C_6H_4	4.5	**3f**	95	208-211 [20b]	209-211
7	CH_3	4-HO,3-OMe-C_6H_3	6	**3g**	85	-	-
8	CH_3	4-Cl-C_6H_4	5	**3h**	90	218-220 [20c]	216-219
9	H	4-Cl-C_6H_4	5	**3i**	90	225-227 [20d]	222-225

10	CH_3	4-Me-C_6H_4	6	**3j**	90	214-216 [20b]	213-215
11	CH_3	4-NC-C_6H_4	4.5	**3k**	85	225-228 [20b]	231-233
12	CH_3	4-NO_2-C_6H_4	4.5	**3l**	95	177-178 [20e]	176-178
13	H	4-NO_2-C_6H_4	4.5	**3m**	95	235-237 [20d]	233-236
14	CH_3	4-Me_2N-C_6H_4	6	**3n**	85	212-213 [20e]	211-214

[a] Reaction conditions: aldehyde (1 mmol), malononitrile (1.1 mmol), -*CH* nucleophile (1 mmol), H_2O-DMNPs (γ-Fe_2O_3, 10 mol% , 3 mL H_2O).

We next explored the scope of this method (H_2O-DMNPs) in the four-component synthesis of polyhydroquinolines **5**, via the condensation of dimedone, an aldehyde, β-dicarbonyl compounds **4** and ammonium acetate. The results are summarized in Table 3.

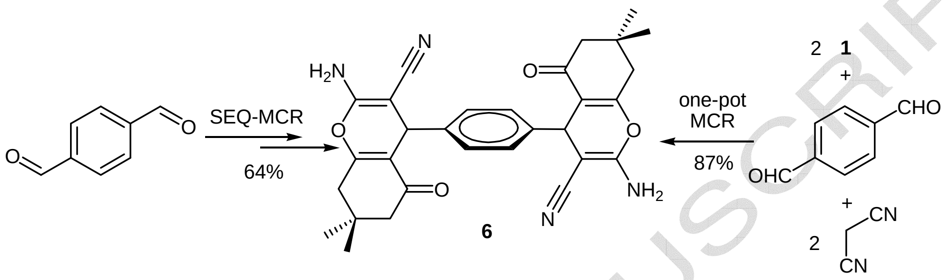
Table 3. One-pot synthesis of polyhydroquinolines **6**.[a]



Entry	Ar	E	Time (h)	Product	Yield (%)[b]
1	C_6H_5	CO_2Me	3	**5a**	92
2	2-Cl-C_6H_4	CO_2Me	2.5	**5b**	91
3	2-Me-C_6H_4	CO_2Me	3	**5c**	90
4	4-Cl-C_6H_4	CO_2Me	2	**5d**	95
5	4-MeO-C_6H_4	CO_2Me	3	**5e**	92
6	2-Me-C_6H_4	CO_2Et	3	**5f**	90
7	2-Cl-C_6H_4	CO_2Et	2.5	**5g**	91
8	4-Cl-C_6H_4	CO_2Et	2	**5h**	96

[a] Reaction conditions: aldehyde (1 mmol), dimedone (1 mmol), β-dicarbonyl compound (1.2 mmol), NH_4OAc (1.5 mmol), H_2O-DMNPs (γ-Fe_2O_3, 10 mol% , 3 mL H_2O).

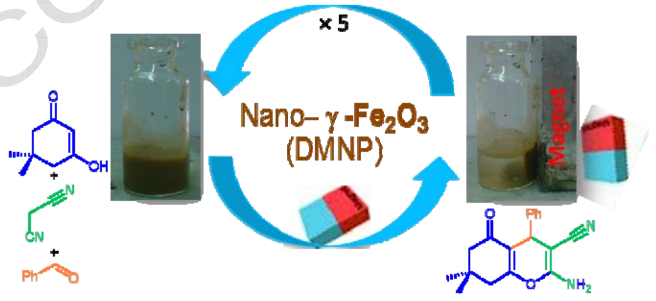
The catalytic activity of γ-Fe_2O_3 using the DMNPs method in domino Knoevenagel-Michael-cyclization reactions to synthesis of bis-tetrahydro-4*H*-chromene **6** was also studied under the optimized conditions.[18] When we examined the reaction under the sequential multicomponent (SEQ-MCR) method the yield was 64% after 5 hours, but, the yield of product **6** was 87% using the one-step multicomponent reaction (Scheme 2).



Scheme 2. The use of dispersed γ-Fe_2O_3 for the synthesis of bis-tetrahydro-4*H*-chromene **6**.

The possibility of recycling the dispersed magnetic catalyst was also studied. When the reaction was complete, the catalyst was easily separated from the product by attaching an external magnet onto the reaction vessel. As illustrated in Table 4, the catalyst could be reused over five consecutive runs.

Table 4. Recyclability study on the synthesis of model compound **3a**.



Run	Yield (%) **3a**
1	95
2	95
3	95
4	95
5	83[a]

[a] Time of the reaction was 10 h.

In summary, an extensive and systematic study identified water dispersed magnetic nanoparticles (DMNPs) of γ-Fe_2O_3 as a heterogeneous, green and reusable catalyst for the synthesis of tetrahydro-4*H*-chromenes and polyhydroquinolines via domino Knoevenagel-Michael-cyclization coupling reactions. A variety of annulated tetrahydro-4*H*-chromenes and polyhydroquinolines are accessible under mild conditions using this method. This rapid, green process, in which the catalyst can be recycled, should be an interesting alternative to other synthetic methods. The method offers several advantages including high yields of products, recyclability of the catalyst, use of an environmentally favorable of solvent and an easy experimental work-up procedure.

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18. Maghemite γ-Fe_2O_3 nanoparticles were synthesized based on the reported method of Kolvari, Khazaei and Zolfigol *at. al.* with minor modifications by adding oleic acid

(see the supporting information). Dispersed magnetic nanoparticles of γ-Fe_2O_3 (DMNPs): before using γ-Fe_2O_3 as the catalyst, γ-Fe_2O_3 (prepared in oleic acid - see the supporting information) were added to an open vessel and then the resulting mixture was washed with acetonitrile (×3) under sonication conditions. Next, an appropriate amount (Table 1) of dried γ-Fe_2O_3 was sonicated by ultrasound irradiation for 15 min in water to give the H_2O-DMNPs of γ-Fe_2O_3 (Table 1).

Typical procedure for preparation of compounds 3 and 5: Preparation of 3b A mixture of *γ*-Fe_2O_3 and H_2O was subjected to ultrasonic irradiation for 15 min. Malononitrile [or β-dicarbonyl compound] (1.2 mmol), furfural (1.0 mmol) and dimedone (1.0 mmol) was added and the mixture stirred at room temperature for 6 h. The reaction progress was monitored by TLC as well as by the extend precipitation of the products from the reaction mixture. After completion (TLC) of the reaction, the catalyst was separated with an external magnet. Finally the filtrate mixture diluted and recrystallized with EtOAc. All isolated products gave satisfactory spectral and physical data (see the supporting information). **2-amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (3b).** White solid. Mp: 206-208 ^{o}C. IR (KBr ν_{max}/cm^{-1}): 3396, 3327, 3214, 2196 (CN), 1661, 1365 cm^{-1}. ^{1}H NMR (500.13 MHz, DMSO-d_6): δ = 1.2 (3 H, s, 3 H of CH_3), 1.3 (3 H, s, 3 H of CH_3), 2.2 (1 H, d, $^{2}J_{HH}$ = 15.5 Hz, 2 H of CH_2), 2.3 (1 H, d, $^{2}J_{HH}$ = 15.4 Hz, 2 H of CH_2), 2.6 (2 H, m, 2 H of CH_2), 4.5 (1 H, s, 1 H of CH), 6.1 (1 H, s, 1 H of CH), 6.4 (1 H, s, 1 H of CH), 7.2 (2 H, s, 2 H of NH_2), 7.5 (1 H, s, 1 H of CH).

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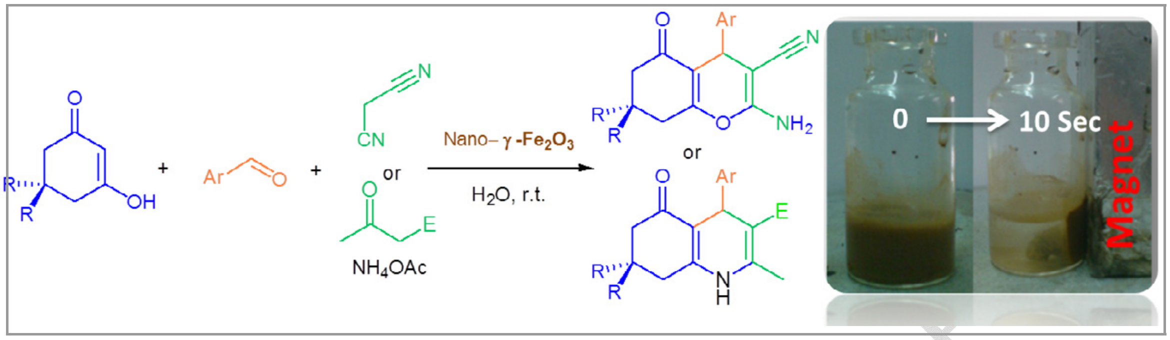
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