

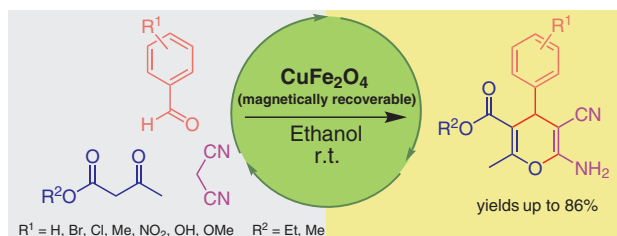
Clean One-Pot Multicomponent Synthesis of Pyrans Using a Green and Magnetically Recyclable Heterogeneous Nanocatalyst

Mina Ghassemi¹Ali Maleki^{1*}

Catalysts and Organic Synthesis Research Laboratory, Department of Chemistry, Iran University of Science and Technology, Tehran 16846-13114, Iran
maleki@iust.ac.ir

Dedicated to Prof. Issa Yavari

Published as part of the Virtual Collection
in Honor of Prof. Issa Yavari



Received: 14.02.2021

Accepted after revision: 25.03.2021

Published online: 25.03.2021

DOI: 10.1055/a-1469-6721; Art ID: so-2021-d0008-l



License terms:

© 2021. The Author(s). This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Abstract Copper ferrite (CuFe_2O_4) magnetic nanoparticles (MNPs) were synthesized via thermal decomposition and applied as a reusable and green catalyst in the synthesis of functionalized 4*H*-pyran derivatives using malononitrile, an aromatic aldehyde, and a β -ketoester in ethanol at room temperature. The nanoparticles were characterized by FT-IR, EDX, SEM, TGA, and DTG analysis. The catalyst was recovered from the reaction mixture by applying an external magnet and decanting the mixture. Recycled catalyst was reused for several times without significant loss in its activity. Running the one-pot three-component reaction at room temperature, using a green solvent under environmentally friendly reaction conditions, ease of catalyst recovery and recyclability, no need for column chromatography and good to excellent yields are advantages of this protocol.

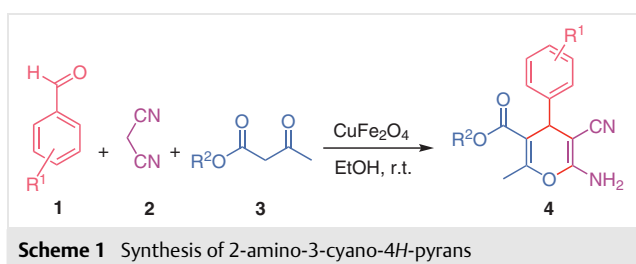
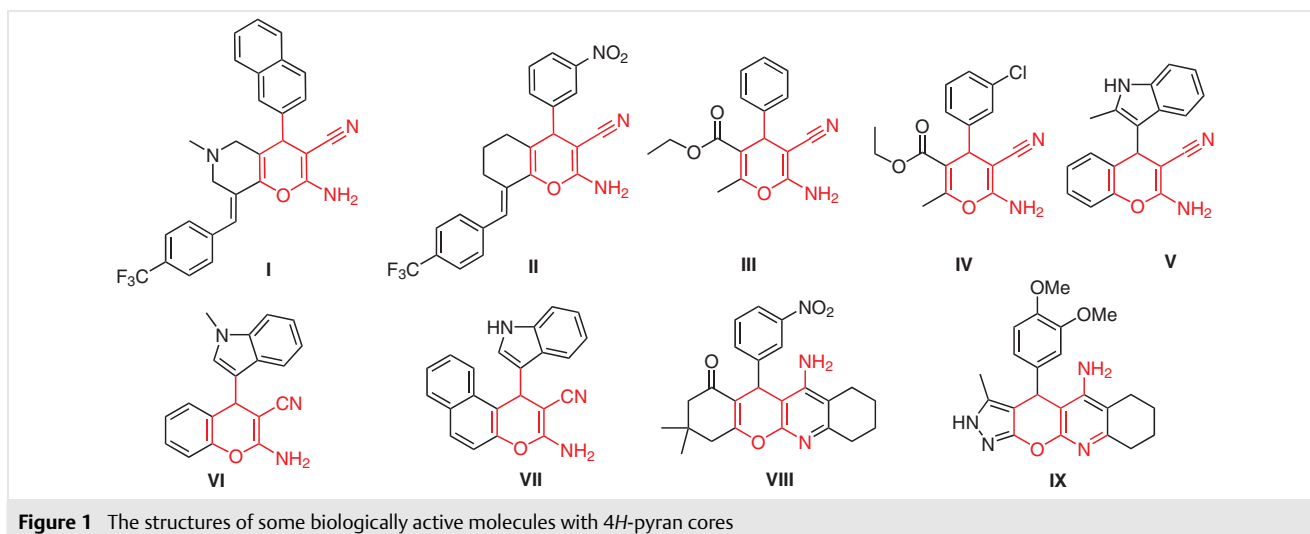
Keywords green chemistry, multicomponent reactions, magnetic nanoparticles, pyran

In attempts to mitigate the greenhouse effect and environmental pollution, chemical and pharmaceutical companies look to environmentally friendly protocols to reduce environmental pollution using so-called green and sustainable chemistry.¹ Multicomponent reactions (MCRs), in which one-pot reactions involving more than two reactants to produce a single product, represent one of the important strategies in green chemistry.² These reactions produce multifunctionalized products using fewer steps compared to classical synthesis approaches.³ Strecker reported first MCR in 1850 for the synthesis of α -amino cyanides,⁴ and nowadays MCRs have been applied to the synthesis of a wide range of complex molecules.^{5–8} In this context, cata-

lysts play a major role; in particular nanocatalysts provide a large surface-to-volume ratio, which increases their activity further.^{9–11} However, because of their nanoscale size, separating them from the reaction mixture by conventional methods is not efficient, but use of magnetic nanoparticles (MNPs) can overcome this issue.^{12,13} These particles can be synthesized in various forms such as metal nanoparticles, iron oxides, and ferrites.¹⁴ Copper ferrite (CuFe_2O_4) is one member of the ferrite family that has been widely applied as a catalyst in organic transformations.^{15–17}

2-Amino-3-cyano-4*H*-pyrans are important heterocyclic scaffolds considering their varied biological activities and pharmaceutical properties such as antitumor (Figure 1, **I**, **II**),¹⁸ antibacterial (Figure 1, **III**, **IV**), antiviral, antiallergic, spasmolytic, anticoagulant, antianaphylactic,^{5,19,20} and antioxidant (Figure 1, **V–VII**) activities.²¹ They have also been applied to treatment of neurodegenerative disorders including Alzheimer's disease (Figure 1, **VIII**, **IX**),^{22,23} amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease.²⁴ Additionally, they can be found in cosmetic products.²⁵ Some examples of biologically active 4*H*-pyrans are shown in Scheme 1. 4*H*-Pyrans are also components of some plant-derived natural products.²⁶ In addition, 4*H*-pyrans can be efficiently applied as precursors to produce different classes of heterocycles.²⁷ Many examples of 4*H*-pyran synthesis using different catalyst systems have been reported in the literature, including potassium phthalimide-*N*-oxyl,²⁸ baker's yeast,⁵ MgO ,¹⁹ Mg/La ,²⁰ SiO_2 ,²⁴ $\text{SnCl}_2/\text{nano SiO}_2$,²⁹ ionic liquids such as $[\text{2-aemim}][\text{PF}_6]$,³⁰ and catalyst-free conditions have also been disclosed.³¹

In continuation of our interest in the design, discovery, and application of new catalysts in organic syntheses via MCRs to develop green procedures,⁷ we present herein an environmentally friendly synthesis of 4*H*-pyrans **4** via a green one-pot three-component reaction of an aldehyde **1**, malononitrile **2**, and methyl/ethyl acetoacetate **3** using



CuFe_2O_4 magnetic nanoparticles as an efficient and green catalyst under mild reaction conditions in good to excellent yields (Scheme 1). To the best of our knowledge, this is the first time that copper ferrite magnetic nanoparticles have been applied as catalyst for the synthesis of this class of heterocycles.

The CuFe_2O_4 nanoparticles were prepared by thermal decomposition of copper(II) nitrate and iron(III) nitrate by a published method^{16,32} and characterized by FT-IR spectroscopy (Figure S11), EDX analysis (Figure S12), SEM analysis (Figure S13), and TGA/DTG analysis (Figure S15). To optimize conditions, the three-component reaction of 3-nitrobenzaldehyde (0.5 mmol), malononitrile (0.5 mmol), ethyl acetoacetate (0.5 mmol), and CuFe_2O_4 was run in various solvents at room temperature, as the model reaction for pyran derivative synthesis. Initially, the amount of CuFe_2O_4 catalyst was optimized. Best results were obtained with 20 mol% of the catalyst. No further increase in yield was observed with additional amounts of catalyst. Next, the role of the solvent was reconsidered with the best yield being obtained in ethanol³³ (Table 1). Following the optimization efforts, a range of reactions was run under optimized conditions, and the desired products were obtained in good to excellent yields (Table 2). Known compounds were identified by comparison of their physical data (melting points)

with those of authentic samples. In addition, ^1H NMR and IR analyses were carried out. These data are provided in the Supporting Information.

Table 1 Optimization of Reaction Conditions in the Synthesis of 5-Ethoxycarbonyl-2-amino-4-(3-nitrophenyl)-3-cyano-6-methyl-4H-pyran (**4e**)^a

Entry	Catalyst (mol%)	Solvent	Time (h) ^b	Yield (%) ^c
1 ^d	–	EtOH	6	53
2	–	EtOH	3	trace
3 ^e	–	EtOH	3	70
4 ^f	–	EtOH	2	75
5	1	EtOH	3	10
6	5	EtOH	3	59
7	10	EtOH	3	59
8	20	EtOH	3	86
9	20	EtOH	2	86
10 ^f	20	EtOH	0.75	85
11	20	–	10	23
12	20	H ₂ O	20	12
13	20	MeCN	4	25

^a Room temperature unless otherwise temperature is mentioned.

^b Reactions were followed by TLC.

^c Isolated yields.

^d Optimization studies of this entry are omitted, and just highest yield in the shortest time is noted.

^e This reaction was run at 40 °C.

^f This reaction was run at 60 °C.

To investigate the catalyst reusability, the catalyst was recovered and washed with distilled water and ethanol, and the model reaction was run again in the presence of recycled

Table 2 Synthesis of 2-Amino-4-aryl-3-cyano-6-methyl-4*H*-pyran Derivatives **4a–t**^a

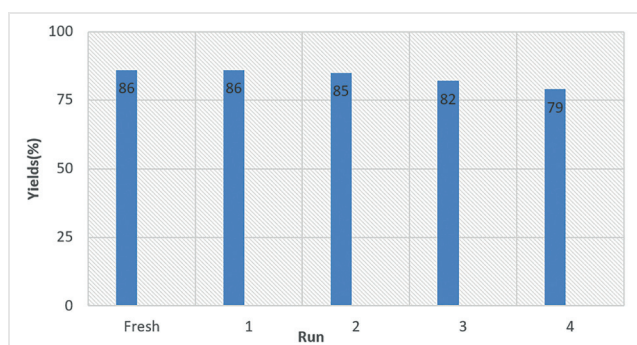
Entry	R ¹	R ²	Product	Time (h)	Yield (%) ^b	mp (°C)	
						Found	Reported
1	H	Et	4a	3	77	189–193	189–191 ²⁹
2	2-NO ₂	Et	4b	3	73	178–179	176–178 ²⁴
3	2-Cl	Et	4c	3.5	79	190–192	191–193 ³⁴
4	3-OH	Et	4d	3	83	168–171	162–164 ²⁹
5	3-NO ₂	Et	4e	2	86	187–188	181–183 ²⁹
6	4-OH	Et	4f	3	75	196–198	192–193 ³⁵
7	4-NO ₂	Et	4g	2	78	179–181	180–182 ²⁹
8	4-Cl	Et	4h	2	73	174–176	174–176 ²⁴
9	4-Br	Et	4i	3.5	70	176–177	176–178 ³⁵
10	4-Me	Et	4j	3	79	139–140	158 ³⁶
11	4-OMe	Et	4k	2	72	133–136	138–140 ³⁵
12	2-NO ₂	Me	4l	4	70	187–189	181 ³⁷
13	2-Cl	Me	4m	3	75	151–153	148–150 ³⁸
14	3-OH	Me	4n	3.5	70	136–139 ^c	–
15	3-NO ₂	Me	4o	3	84	210–212	212–213 ³⁸
16	4-OH	Me	4p	4	65	163–165	160–162 ³⁸
17	4-NO ₂	Me	4q	3	70	155–157	165 ³⁷
18	4-Cl	Me	4r	3	79	171–173	172–173 ³⁹
19	4-Me	Me	4s	3	71	165–167	164–165 ³⁸
20	4-OMe	Me	4t	3	76	141–143	138–140 ³⁸

^a Reaction conditions: aldehyde (1 mmol), malononitrile (1 mmol), ethyl/methylacetoacetate (1 mmol), catalyst (20 mol%), ethanol (5 mL), room temperature.

^b Isolated yield.

^c The products were characterized by ¹H NMR and IR spectroscopy.

catalyst. The results shown in Figure 2 indicate that very slight decreases in yields were observed after 3 cycles and after the 5th cycle, catalyst activity was still satisfying.

**Figure 2** Catalyst recyclability for model reaction (**4e**)

In order to demonstrate the advantages of this methodology, some other methods for the synthesis of 4*H*-pyran (**4e**) were compared with the present protocol. Some of the methods need an external source of energy such as heating or ultrasonic radiation. In some cases, the catalysts are ex-

pensive or may not be recyclable. Typical results are gathered in Table 3.

Table 3 Comparison of the Present Work with other Methods for the Synthesis of Pyran **4e**

Entry	Catalyst	Solvent/conditions	Temp (°C)	Time (min)	Yield (%)
1	MgO	water/grinding/two steps	r.t.	25	92 ¹⁹
2	Mg/La	MeOH/reflux	65	60	86 ²⁰
3	SiO ₂	EtOH	r.t.	120	86 ²⁴
5	SnCl ₂ /SiO ₂	EtOH/reflux	reflux	30	93 ²⁹
6	CuFe ₂ O ₄	EtOH	r.t.	120	86 ^a

^a This work.

In summary, we have represented clean, efficient, one-pot methodology for the synthesis of highly functionalized 4*H*-pyrans using CuFe₂O₄ magnetic nanoparticles as a reusable and green nanocatalyst. Reactions are run at room temperature in ethanol providing a green synthesis of

4H-pyran heterocycles. Short reaction times, nontoxic catalyst, ease of catalyst separation by using an external magnet, catalyst recyclability, no need for heating, good to excellent yields, and mild conditions are advantages of the reported protocol. Moreover, the high tolerance of this procedure towards various functional groups, easy and simple work-up procedure, exceptionally high yields of the desired products, and scalability are the added advantages.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

The authors gratefully acknowledge the partial support from the Research Council of the Iran University of Science and Technology.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/a-1469-6721>.

References and Notes

- (1) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, **1998**. (b) Tundo, P.; Anastas, P.; Black, D. S.; Breen, J.; Collins, T.; Memoli, S.; Miyamoto, J.; Polyakoff, M.; Tumas, W. *Pure Appl. Chem.* **2000**, *72*, 1207.
- (2) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
- (3) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083.
- (4) Streckler, A. *Eur. J. Org. Chem.* **1850**, *75*, 27.
- (5) Pratap, U. R.; Jawale, D. V.; Netankar, P. D.; Mane, R. A. *Tetrahedron Lett.* **2011**, *52*, 5817.
- (6) Baral, E. R.; Sharma, K.; Akhtar, M. S.; Lee, Y. R. *Org. Biomol. Chem.* **2016**, *14*, 10285.
- (7) Maleki, A.; Azizi, M.; Emdadi, Z. *Green Chem. Lett. Rev.* **2018**, *114*, 573.
- (8) Eslami, M.; Dekamin, M. G.; Motlagh, L.; Maleki, A. *Green Chem. Lett. Rev.* **2018**, *11*, 36.
- (9) Maleki, A.; Jain, A. K.; Firouzi-Haji, R. *Pure Appl. Chem.* **2018**, *90*, 387.
- (10) Hajipour, A. R.; Tadayoni, N. S.; Khorsandi, Z. *Appl. Organomet. Chem.* **2016**, *30*, 590.
- (11) Safari, J.; Zarnegar, Z. *New J. Chem.* **2014**, *38*, 358.
- (12) Doustkhah, E.; Rostamnia, S. *J. Colloid Interface Sci.* **2016**, *478*, 280.
- (13) Rostamnia, S.; Doustkhah, E. *J. Magn. Magn. Mater.* **2015**, *386*, 111.
- (14) Wang, D.; Astruc, D. *Chem. Rev.* **2014**, *114*, 6949.
- (15) Gholinejad, M.; Karimi, B.; Mansouri, F. *J. Mol. Catal. A: Chem.* **2014**, *386*, 20.
- (16) Dandia, A.; Jain, A. K.; Sharma, S. *RSC Adv.* **2013**, *3*, 2924.
- (17) Maleki, A.; Firouzi-Haji, A.; Farahani, P. *Org. Chem. Res.* **2018**, *4*, 86.
- (18) Wang, D. C.; Xie, Y. M.; Fan, C.; Yao, S.; Song, H. *Chin. Chem. Lett.* **2014**, *25*, 1011.
- (19) Kumar, D.; Reddy, V. B.; Sharad, S.; Dube, U.; Kapur, S. *Eur. J. Med. Chem.* **2009**, *44*, 3805.
- (20) Babu, N. S.; Pasha, N.; Rao, K. T. V.; Prasad, P. S. S.; Lingaiah, N. *Tetrahedron Lett.* **2008**, *49*, 2730.
- (21) Shanthi, G.; Perumal, P. T.; Rao, U.; Sehgal, P. K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2009**, *48*, 1319.
- (22) Marco-Contelles, J.; León, R.; Ríos, C. D. L.; García, A. G.; López, M. G.; Villarroya, M. *Bioorg. Med. Chem.* **2006**, *14*, 8176.
- (23) Khoobi, M.; Ghanoni, F.; Nadri, H.; Moradi, A.; Pirali, Hamedani, M.; Homayouni, Moghadam, F.; Emami, S.; Vosooghi, M.; Zadmard, R.; Foroumadi, A.; Shafiee, A. *Eur. J. Med. Chem.* **2015**, *89*, 296.
- (24) Banerjee, S.; Horn, A.; Khatri, H.; Sereda, G. *Tetrahedron Lett.* **2011**, *52*, 1878.
- (25) Kim, D. H.; Hwang, J. S. S.; Baek, H. S.; Kim, K. J. J.; Lee, B. G.; Chang, I.; Kang, H. H.; Lee, O. S. *Chem. Pharm. Bull.* **2003**, *51*, 113.
- (26) Wickel, S. M.; Citron, C. A.; Dickschat, J. S. *Eur. J. Org. Chem.* **2013**, 2906.
- (27) Das, P.; Dutta, A.; Bhaumik, A.; Mukhopadhyay, C. *Green Chem.* **2014**, *16*, 1426.
- (28) Dekamin, M. G.; Eslami, M.; Maleki, A. *Tetrahedron* **2013**, *69*, 1074.
- (29) Safaei-Ghomi, J.; Teymuri, R.; Shahbazi-Alavi, H.; Ziarati, A. *Chin. Chem. Lett.* **2013**, *24*, 921.
- (30) Peng, Y.; Song, G. *Catal. Commun.* **2007**, *8*, 111.
- (31) Survase, D. N.; Chavan, H. V.; Dongare, S. B.; Helavi, V. B. *Synth. Commun.* **2016**, *46*, 1665.
- (32) **Preparation of Copper Ferrite Nanoparticles**
Fe(NO₃)₃·9H₂O (3.34 g, 8.2 mmol) and Cu(NO₃)₂·3H₂O (1.0 g, 4.1 mmol) were dissolved in distilled water (75 mL), then NaOH (3.0 g, 75 mmol) dissolved in distilled water (15 mL) was added at room temperature over 10 min, during which time a reddish-black precipitate was formed. Then the reaction mixture was warmed to 90 °C with stirring under ultrasonic irradiation for 2 h and then cooled to room temperature. The magnetic particles so formed were separated by an external magnet then washed with distilled water (3 × 30 mL) and kept in an oven at 80 °C overnight. The powder was further grounded in a mortar, heated at 700 °C for 5 h, and then cooled to room temperature.
- (33) A mixture of aryl aldehyde (1 mmol), malononitrile (1 mmol), methyl/ethyl acetoacetate (1 mmol), and CuFe₂O₄ (20 mol%) was stirred in ethanol (5 mL) at room temperature until completion of the reaction as indicated by TLC. After completion of the reaction, the catalyst was removed from the reaction mixture via an external magnet and the product allowed to precipitate. The solid product was filtered and recrystallized from ethanol. All the products are known compounds that were identified by comparison of their physical data (melting points) with those authentic samples.
- (34) Amirnejad, M.; Naimi-Jamal, M. R.; Tourani, H.; Ghafuri, H. *Monatsh. Chem.* **2013**, *144*, 1219.
- (35) Ramesh, R.; Lalitha, A. *Res. Chem. Intermed.* **2015**, *41*, 8009.
- (36) Bhattacharyya, P.; Pradhan, K.; Paul, S.; Das, A. R. *Tetrahedron Lett.* **2012**, *53*, 4687.
- (37) Molla, A.; Hossain, E.; Hussain, S. *RSC Adv.* **2013**, *3*, 21517.
- (38) Kalla, R. M. N.; Kim, M. R.; Kim, I. *Tetrahedron Lett.* **2015**, *56*, 717.
- (39) Yi, F.; Peng, Y.; Song, G. *Tetrahedron Lett.* **2005**, *46*, 3931.