



Full paper/Mémoire

EtOAc-dispersed magnetic nanoparticles (DMNPs) of γ -Fe₂O₃ in the single-pot domino preparation of 5-oxo-2-thioxo-3-thiophenecarboxylate derivatives

Sadegh Rostamnia

Organic and Nano Group (ONG), Department of Chemistry, Faculty of Science, University of Maragheh, PO Box 55181-83111, Maragheh, Iran

ARTICLE INFO

Article history:

Received 31 December 2012

Accepted after revision 1st March 2013

Available online 15 April 2013

Keywords:

Multicomponent reaction

Rhodanine

Nano- γ -Fe₂O₃

Dispersed magnetic nanoparticles (DMNPs)

ABSTRACT

EtOAc-dispersed magnetic nanoparticles (DMNPs) of γ -Fe₂O₃ represent a straightforward and green catalyst for the rapid three-component synthesis of 5-oxo-2-thioxo-3-thiophenecarboxylate derivatives as rhodanine skeletons via a single-pot domino process. The rhodanines were prepared over magnetic nanoparticles of γ -Fe₂O₃ without any salt or additives. Dispersed nano- γ -Fe₂O₃ have many advantages, such as stability in air, reusability, reactions with high efficiency, simple separation with magnetic external field from mixture reactions, chemical stability, and also low toxicity.

© 2013 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.

1. Introduction

Rhodanine heterocyclic skeletons are known to possess multiple biological activities, including the inhibition of numerous targets, such as PMT1 mannosyl transferase [1], PRL-3 and JSP-1 phosphatases [2]. Classical methods for the preparation of alkylidene rhodanine need several steps and generally involve the preparation of the rhodanine moiety followed by a Knoevenagel condensation with aldehydes [3]. Recent methods are limited by the requirement of highly reactive functional groups in the substrates and by the fact that they do not proceed in smooth and mild conditions. Several methods have been reported for the synthesis of rhodanines [3]. However, they all rely on multistep reactions with either hard conditions or low yields, and the reaction times are long. Thus, the development of new synthetic methods remains an attractive goal.

Organic processes catalyzed by non-toxic magnetic nanoparticles (MNPs), such as Fe₃O₄ and Fe₂O₃, are often

considered as following the principles of green chemistry, i.e. they consume a minimum of energy and reagents or auxiliaries, and minimize wastes [4]. Magnetic separation of MNPs is simple, economical and promising for industrial applications. From both economic and environmental viewpoints, organic reactions in aqueous medium using recoverable catalysts have gained attention in recent years [5].

For the above reasons, we were, thus, intrigued by the possibility of applying nano- and green chemistry to the design of an active, recyclable, and magnetically recoverable dispersed nano- γ -Fe₂O₃ catalyst in EtOAc-medium for the synthesis of alkyl rhodanines under mild reaction conditions.

2. Results and discussion

Recently, we have developed synthetic methods for the synthesis of biologically interesting heterocycles via multicomponent reactions [6]. The challenge in this field was to develop efficient and rapid green methods. Moreover, the synthesis of these heterocycles has usually been carried out in polar solvents, such as DMF and DMSO,

E-mail addresses: rostamnia@gmail.com, rostamnia@maragheh.ac.ir.

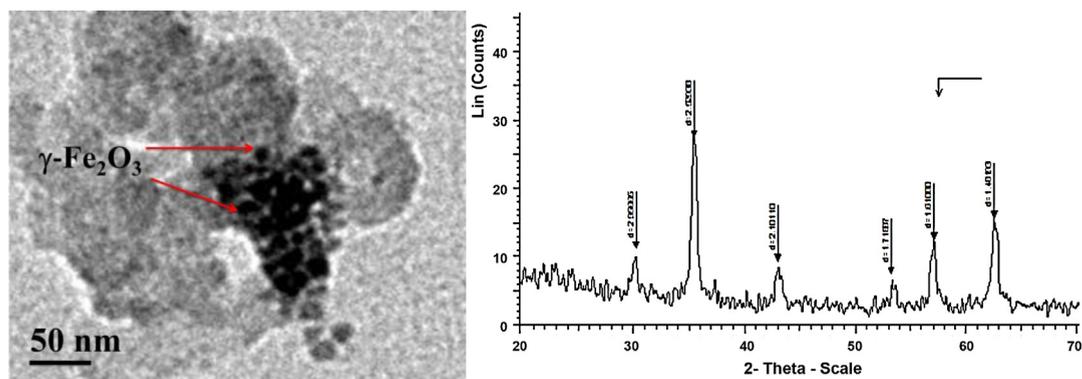


Fig. 1. Transmission electron microscopy (TEM) image of the γ -Fe₂O₃ nanoparticles.

leading to complex isolation and recovery procedures. Also, based on our recent success in the preparation of MNPs as catalysts [6], combined with our achievements in this area, we present, in this paper, the results of an extended investigation on the activity of dispersed γ -Fe₂O₃ in EtOAc-medium as a green magnetic separable nanocatalyst in a domino three-component process leading to the formation of alkyl rhodanines without any salts or additives. We have developed a synthetic method for the preparation of 5-oxo-2-thioxo-3-thiophenecarboxylate via the condensation of an aliphatic amine, carbon disulfide and the electron-deficient acetylene using a dispersed technique of small size (~30 nm range, Fig. 1) of γ -Fe₂O₃ as the active catalyst. Herein, the condensation of benzyl amine, carbon disulfide and dimethyl acetylenedicarboxylate (DMAD) was selected to be the model (Table 1). Also, the MNP to form γ -Fe₂O₃ was synthesized by basic precipitation from the iron source [8].

Initial studies of the influence of the reaction conditions were carried out with the model reaction. By screening a wide range of iron sources, mol% of catalyst and different solvents and temperatures, we found that the product **3a** could be obtained in yields ranging from 17 to 95% (entry 1–12, Table 1). When we have changed the amount of the catalysts from 5 mol% to 15 mol%, finding out that 10 mol% was enough for the best yield.

With these results in hand and to demonstrate the diversity of the dispersed MNPs (DMNPs) of γ -Fe₂O₃ 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.

The catalytic activity of γ -Fe₂O₃ in the domino three-component process for synthesizing rhodanine **3a** and **4** was also studied under optimized conditions. When we set the reaction with a mixture of an aromatic amine (aniline) and an aliphatic amine (benzyl amine) in the presence of

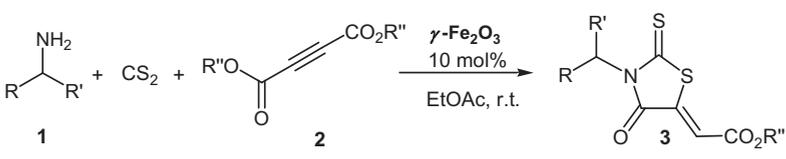
Table 1
Optimization of reaction conditions for the synthesis of rhodanine **3a**^a.

Entry	Fe-source	Solvent	Cat. (mol%)	T (°C)	Time (min)	Yield (%)
1	FeCl ₃ ·6H ₂ O	THF	5	40	5	24
2	FeSO ₄	CCl ₄	5	r.t.	5	17
3	γ -Fe ₂ O ₃ /SiO ₂ -MNPs ^b	CCl ₄	5	50	5	26
4	Bulk-Fe ₃ O ₄	CCl ₄	5	r.t.	5	20
5	Nano-Fe ₃ O ₄	CCl ₄	5	r.t.	5	31
6	γ -Fe ₂ O ₃ -MNPs	CCl ₄	4	r.t.	5	37
7	γ -Fe ₂ O ₃ -MNPs	H ₂ O	5	r.t.	5	43
8	γ -Fe ₂ O ₃	EtOAc	5	r.t.	5	61
9	γ -Fe ₂ O ₃	EtOAc	5	r.t.	10	75
10	γ -Fe ₂ O ₃	EtOAc	10	r.t.	5	73
11	γ-Fe₂O₃	EtOAc	10	r.t.	10	95
12	γ -Fe ₂ O ₃	EtOAc	15	r.t.	10	94

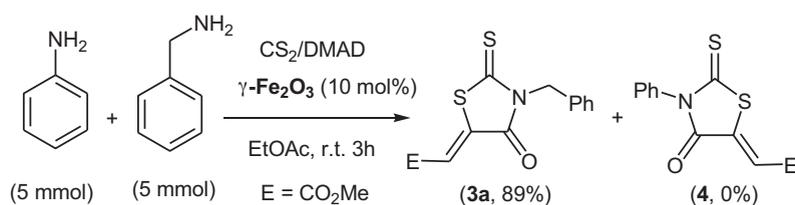
r.t.: room temperature. Bold: final selected row as optimized condition.

^a Reaction scale: 3 mmol.

^b Synthesized based on our previous report [6].

Table 2The synthesis of the 5-oxo-2-thioxo-3-thiophenecarboxylate skeleton by $\gamma\text{-Fe}_2\text{O}_3$.^a


3	R	R''	R'	Yield% 3	Mp (°C)	
					Reported	Found
3a	C ₆ H ₅	CH ₃	H	95	128–130 [6e]	131–133
3b	C ₆ H ₅	CH ₃	CH ₃	95	89–91 [6e]	87–90
3c	<i>o</i> -Cl-C ₆ H ₄	CH ₃	H	93	112–114 [6e]	113–115
3d	<i>o</i> -Cl-C ₆ H ₄	CH ₃ CH ₂	H	90	104–106 [6e]	105–109
3e	<i>p</i> -Cl-C ₆ H ₄	CH ₃	H	90	–	114–117
3f	ⁱ Pr	CH ₃	H	90	88–90	85–90
3g	CH ₃	CH ₃	CH ₃	95	–	60–66
3h	Vinyl	CH ₃	H	85	140–142 [6e]	139–144

^a Reaction scale: 3 mmol.**Scheme 1.** Chemoselective synthesis of alkyl rhodanines.

carbon disulfide and dimethyl acetylenedicarboxylate (DMAD), the yield of **3a** was 89% after 15 min, without any detected product **4** (Scheme 1).

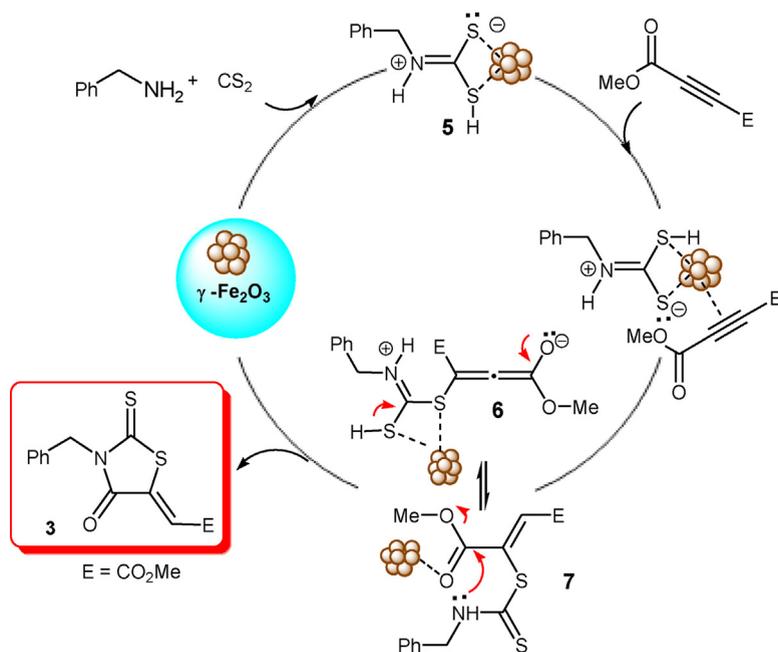
The possibility of recycling the dispersed magnetic catalyst was also studied. When the reaction was completed, the catalyst was easily separated from the product by attaching an external magnet onto the reaction vessel. As illustrated in Table 3, the catalyst could be still reused after the sixth run.

Although we have not established the exact mechanism for our method in an experimental manner, the following rationalization may be advanced to explain the product formation [6e,7]. Presumably, the $\gamma\text{-Fe}_3\text{O}_4$ stabilized zwitterion **5** from amine and carbon disulfide was attached by active acetylene to furnish a cumulene **6** or dithiocarbamate **7** intermediate. The final product **3a** is produced by $\gamma\text{-Fe}_3\text{O}_4$ accelerated methanol elimination and cyclization of **6** or **7** (Scheme 2).

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

Run	1	2	3	4	5	6 ^a
Yield% 3a	95	93	91	87	88	73

^a Time of the reaction was 2 h.



Scheme 2. Plausible mechanism for the magnetic nanoparticles-catalyzed synthesis of rhodanine.

3. Conclusion

In summary, an extensive and systematic study allowed us to identify MNPs of $\gamma\text{-Fe}_2\text{O}_3$ as a heterogeneous, green and reusable catalyst for the synthesis of rhodanines via a domino process. This rapid, green method, in which the catalyst can be recycled, should be an interesting alternative to other synthesis methods. The method has several advantages, including high yields of products, recyclability of the catalyst, non-toxicity, easy experimental work-up procedure, and the fact that the catalyst is environmentally friendly.

4. Experimental

All the reagents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. IR spectra were recorded on a Shimadzu IR-460 spectrometer. The melting points were measured on an Electrothermal 9100 apparatus. The progress of reactions was monitored by thin layer chromatography (TLC).

4.1. Synthesis magnetic nanoparticles of $\gamma\text{-Fe}_2\text{O}_3$ (MNPs)

Maghemite $\gamma\text{-Fe}_2\text{O}_3$ nanoparticles were synthesized based on an interesting method reported by Kolvari, Khazaei and Zolfigol [8], with minor modifications. After adding a Fe-source and a reductive reagent, and after the color of the solution turned back from red to light yellow, the solution was added to an ammonia solution under stirring; to achieve uniform particle size and stability of MNPs, oleic acid was added.

4.2. General procedure for the preparation of compound 3a–h: preparation of 3a

Benzyl amine (3 mmol) and carbon disulfide (3.3 mmol) were added to a dispersion of MNPs (10 mol%) in ethyl acetate (3 mL), and the mixture was stirred at room temperature for 30 s; then 3 mmol of DMAD were added to the mixture during 30 s. The reaction progress was monitored by TLC. Finally, the catalyst was extracted under a magnetic external field, and reaction products were diluted in water, then the organic phase was extracted and the pure product was recrystallized. All isolated products gave satisfactory spectral and physical data. All the products were previously reported [6e] and were characterized by comparison with IR and physical data. Spectral data for the selected product: *Ethyl 2-[3-((4-chlorophenyl)methyl)-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene]ethanoate (3e)* Orange powder. IR (KBr) (ν_{max} , cm^{-1}): 1728 (CO), 1649 (CC), 1310 and 1177 (CS). ^1H NMR (500 MHz, CDCl_3): δ_{H} = 3.87 (3 H, s, OCH_3), 5.24 (2 H, s, CH_2Ph), 6.84 (1 H, s, C=CH), 7.28 (2 H, d, $^3J_{\text{HH}}$ = 8.4 Hz, 2 CH of Ar), 7.37 (2 H, d, $^3J_{\text{HH}}$ = 8.4 Hz, 2 CH of Ar) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ_{C} = 46.62 (OCH_3), 52.89 (CH_2Ph), 117.16 (C=CH), 128.86 (2 CH of Ar), 130.49 (2 CH of Ar), 132.79 (C_{ipso} of Cl), 134.36 (C_{ipso} of NC), 141.82 (C=CH), 165.45 (CON), 166.46 (CO_2CH_3), 195.43 (C=S) [6e,7].

References

- [1] M.G. Orchard, J.C. Neuss, C.M.S. Galley, A. Carr, D.W. Porter, P. Smith, D.I.C. Scopes, D. Haydon, K. Vousden, C.R. Stubberfield, K. Young, M. Page, *Bioorg. Med. Chem. Lett.* 14 (2004) 3975.
- [2] (a) J.H. Ahn, S.J. Kim, W.S. Park, S.Y. Cho, J.D. Ha, S.S. Kim, S.K. Kang, D.G. Jeong, S.K. Jung, S.H. Lee, H.M. Kim, S.K. Park, K.H. Lee, C.W. Lee, S.E. Ryu, J.K. Choi, *Bioorg. Med. Chem. Lett.* 16 (2006) 2996;

- (b) N.S. Cutshall, C. O'Day, M. Prezhdo, *Bioorg. Med. Chem. Lett.* 15 (2005) 3374.
- [3] (a) M. Radi, L. Botta, G. Casaluce, M. Bernardini, M. Botta, *J. Comb. Chem.* 12 (2010) 200;
(b) B.B. Lohray, V. Bhushan, P.B. Rao, G.R. Madhavan, N. Murali, K. Rao, K.A. Reddy, B.M. Rajesh, P.G. Reddy, R. Chakrabarti, R. Rajagopalan, *Bioorg. Med. Chem. Lett.* 7 (1997) 785;
(c) C.L. Lee, M.M. Sim, *Tetrahedron Lett.* 41 (2000) 5729;
(d) W.D. Rudolf, R. Schwarz, *Heterocycles* 24 (1986) 3459;
(e) A.I. Khodair, J. Nielsen, *Heterocycles* 57 (2002) 1017.
- [4] (a) L. Mamani, A. Heydari, M. Sheykhani, *Appl. Catal. A: Gen.* 384 (2010) 122;
(b) S. Shylesh, V. Schunemann, W.R. Thiel, *Angew. Chem., Int. Ed.* 49 (2010) 3428.
- [5] (a) M. Sheykhani, L. Mamani, A. Ebrahimi, A. Heydari, *J. Mol. Catal. A: Chem.* 335 (2011) 253;
(b) L. Mamani, M. Sheykhani, A. Heydari, *Appl. Catal. A: Gen.* 395 (2011) 34.
- [6] (a) S. Rostamnia, A. Alizadeh, L.G. Zhu, *J. Comb. Chem.* 143 (2009) 143;
(b) A. Alizadeh, S. Rostamnia, *Synthesis* (2010) 1543;
(c) S. Rostamnia, *Res. J. Chem. Environ.* 15 (2011) 89;
(d) A. Alizadeh, S. Rostamnia, A. Esmaili, *Synthesis* (2007) 709;
(e) A. Alizadeh, S. Rostamnia, N. Zohreh, R. Hosseinpour, *Tetrahedron Lett.* 50 (2009) 1533;
(f) S. Rostamnia, Z. Karimi, M. Ghavidel, *J. Sulf. Chem.* 33 (2012) 313;
(g) S. Rostamnia, K. Lamei, *Chin. Chem. Lett.* 23 (2012) 930;
(h) S. Rostamnia, A. Zabardasti, *J. Fluorine Chem.* 144 (2012) 69;
(i) S. Rostamnia, K. Lamei, M. Mohammadquli, M. Sheykhani, A. Heydari, *Tetrahedron Lett.* 53 (2012) 5257;
(j) S. Rostamnia, K. Lamei, *Synthesis* (2011) 3080.
- [7] S. Rostamnia, *Investigation of the novel multicomponent reactions based on binucleophilic systems and zwitterions*. Ph.D. Dissertation, Tarbiat Modares University, Tehran, Iran, 2010.
- [8] N. Koukabi, E. Kolvari, A. Khazaei, M.A. Zolfigol, B. Shirmardi, H.R. Khavasi, *Chem. Commun.* 47 (2011) 9230.