One-pot synthesis of β-amino esters by recyclable magnetic organocatalyst-catalysed Mannich-type reaction

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L-cysteine supported on an iron oxide magnetic nanoparticle was prepared by a facile and simple method. The catalyst was effectively applied to the one-pot synthesis of β-amino esters in moderate to good yield. Moreover, the magnetic organocatalyst could be readily recovered and reused up to five times without significant loss of its catalytic activity.

Keywords: magnetic nanoparticle, organocatalyst, one-pot synthesis, β-amino esters

β-Amino esters are important structural units in various biologically-active compounds[1] and are useful building blocks in some drugs such as β-lactams and β-peptides.[2,3] Hence, there is interest in developing convenient method for preparing these compounds. The classic multicomponent Mannich reaction has been widely used for the synthesis of β-amino carbonyl compounds, including the β-Amino esters.[4,5] It has been reported that some Lewis acids can effectively promote such transformation.[6–10] However, these methods suffer from some disadvantages such as high catalyst loading, long reaction time, reagents which are sensitive to the atmosphere as well as the lack of recyclability of the catalysts.

Magnetic nanomaterials are envisaged to have a major impact on many areas, including biotechnology, environmental remediation, and especially catalysis.[11,12] Since 2007, magnetic nanoparticle immobilisation techniques have gradually been developed to immobilise organocatalysts as shown by the Connon[13–15] and Varma groups.[16–18] A magnetic nanoparticle immobilised organocatalyst is a quasi-homogeneous system that combines the advantages of high dispersion, high reactivity, and easy magnetic separation. It has been developed as a powerful tool for recycling organocatalyst.[19] However, previous reports suffer from the drawback due to complex synthetic procedures.

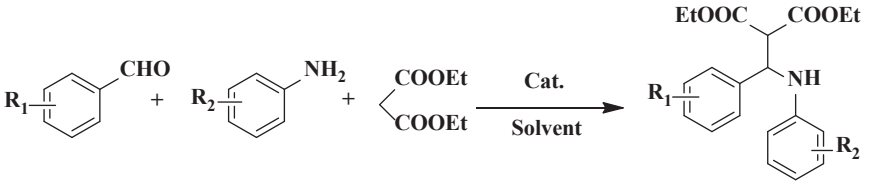
In continuation of our work on catalyst immobilisation and recovery[20,21], we now report the preparation of nano-Fe_3O_4 immobilised *L*-cysteine and its catalytic activity in the one-pot synthesis of β-amino esters. The recovery and reusability of such a catalyst were also investigated (Scheme 1).

Results and discussion

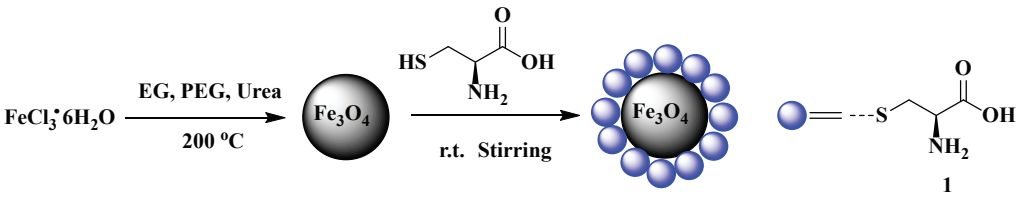
The nano-Fe_3O_4 immobilised *L*-cysteine was prepared from Fe_3O_4 and *L*-cysteine by simple mechanical stirring (Scheme 2).[12] The interaction of nano-ferrites and *L*-cysteine was due to weak hydrogen bonds and van der Waals forces. The immobilised catalyst was then characterised by XRD, TEM and FT-IR.

The crystalline structure of the catalyst **1** was determined by power XRD (Fig. 1). The diffraction patterns and relative intensities of all the peaks matched well with those of magnetite standard spectra (JCPDS card no. 00-002-1035). No other oxide or hydroxide phase was observed and the broad XRD peaks clearly indicated the nanocrystalline nature of the catalyst. In addition, TEM analysis (Fig. 2) showed that most of particles were microspheres with an average size range of ~150 nm. Furthermore, the size distribution of catalyst **1** was broad. The minute tendency to form clusters was observed due to the weak forces between the Fe_3O_4-*L*-cysteine molecules.

Then, the catalyst was examined by FT-IR. The characteristic absorptions due to V_{asym} (asymmetric vibration) COO^- of carboxylic groups appeared at about 1620 cm^{-1}. Moreover, the S–H stretching peak at 2100 cm^{-1} disappeared. All these changes indicated the successful attachment of *L*-cysteine on the surface of nanoparticles.



Scheme 1 The synthesis of β-amino diethyl malonate.



Scheme 2 Preparation of nano-Fe_3O_4 immobilised *L*-cysteine organocatalyst **1**.

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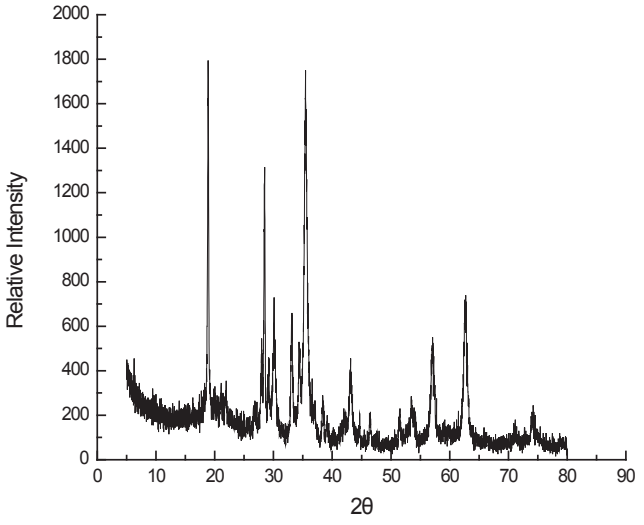


Fig. 1 The XRD of catalyst **1**.

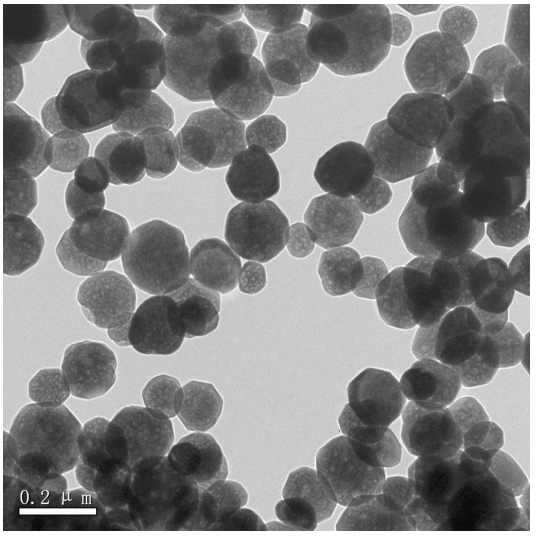


Fig. 2 The TEM of catalyst **1**.

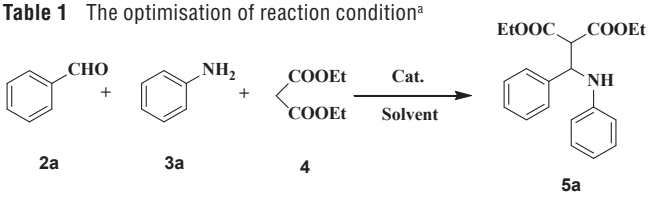
The catalyst and solvent effects on the synthesis of β-amino malonic esters

With the catalyst in hand, we began to explore its catalytic activity for the one-pot synthesis of *β*-amino esters. Initially, the reaction conditions were optimised using the model reaction of benzaldehyde **2a**, aniline **3a**, and diethyl malonate in different conditions. As shown in Table 1, the model reaction did not work without any catalyst, with only aryl aldimines were observed as by-products. In the presence of Fe_3O_4, the yield that was obtained was very low (18% yield, entry 2). However, an 83% yield was obtained using *L*-cysteine as catalyst. By comparison, our nano-organocatalyst **1** also showed good catalytic activity for the model reaction, affording the product in 81% yield (entry 4). In addition, different solvents were evaluated and dichloromethane was the best choice (87% yield, entry 5). When the catalyst loading varied from 3 wt% to 10 wt%, the yield increased from 83% to 88% (entries 5, 8 and 9) and 5 wt% amount of catalyst was sufficient.

Synthesis of different β-amino diethyl malonate

Using the optimised reaction condition, we investigated the reactions of various aldehydes and amines using nano-Fe_3O_4-*L*-cysteine as catalyst. The results are summarised in Table 2. Generally, most of reactions proceeded smoothly. Benzaldehyde

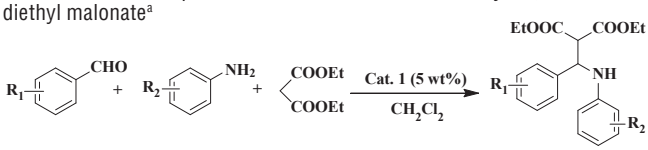
Table 1 The optimisation of reaction condition[a]



Entry	Catalyst	Solvent	Yield/%[b]
1	No catalyst	MeOH	NR
2	Fe_3O_4	MeOH	18
3	*L*-Cysteine	MeOH	83
4	**1**	MeOH	81
5	**1**	DCM	87
6	**1**	CH_3CN	72
7	**1**	$CHCl_3$	78
8[c]	**1**	DCM	83
9[d]	**1**	DCM	88

[a]Reaction condition: **2a** (0.5 mmol), **3a** (0.5 mmol), **4** (0.55 mmol), catalyst loading (5 wt% with respect to the amount of **2a)**, reaction temperature 30 °C, solvent 3 mL, reaction time 12 h.
[b]Isolated yield.
Catalyst loading: [c]3 wt%; [d]10 wt%.

Table 2 Three-component reactions of aromatic aldehydes, amines and diethyl malonate[a]



Entry	R_1	R_2	Product	Melting point/°C		Yields/%[b]
				Determined	Reported	
1	H	H	**5a**	92–93	92–93[22]	88
2	H	4-Cl	**5b**	81–82	81–82[23]	76
3	H	3-Cl	**5c**	110–112	111–112[24]	78
4	H	4-CH_3O	**5d**	70–72	–	21
5	4-Cl	H	**5e**	118–120	118–119[23]	82
6	4-Br	4-Cl	**5f**	88–89	88–89[22]	82
7	4-CN	H	**5g**	74–75	–	88
8	3-NO_2	3-Cl	**5h**	98–100	99–100[22]	90
9	4-Br	4-Br	**5i**	106–108	107–108[22]	80
10	2-Cl	4-Br	**5j**	105–107	106–107[22]	81

[a]Reaction conditions: aldehyde (0.5 mmol), amine (0.5 mmol), diethyl malonate (0.55 mmol), CH_2Cl_2 (3 mL), catalyst loading (5 wt% with respect to the amount of aldehyde), reaction temperature 30 °C, reaction time 12 h.
[b]Isolated yield.

and some electron-deficient aromatic aldehydes were easily transformed to the corresponding products (entries 1, 7 and 8). Halogenated aromatic aldehydes and aromatic amines also could obtain good yields (entries 6 and 9). But for electron-rich aromatic amines, the yield is too low to be detected by LC-MS (entry 4).

Recovery of nano-organocatalyst

The most important feature is the ease of separation and reusability for a heterogeneous catalyst. The recyclability of our magnetic organocatalyst **1** was investigated. After finishing the reaction, the catalyst was separated by simple filtration with an exterior magnetic field. The catalyst was then washed with water, dried under vacuum and reused for next run. The results clearly indicated that the catalyst could be reused for five consecutive cycles without obvious changes in its activity (Fig. 3).

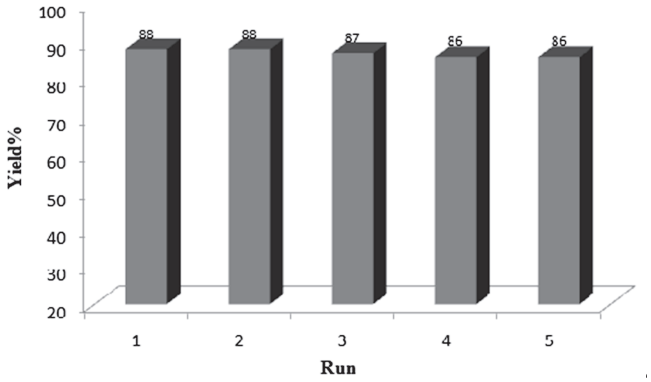


Fig. 3 The recovery of magnetic organocatalyst **1**.

Conclusion

In summary, the nano-ferrite immobilised *L*-cysteine organocatalyst was easily prepared and successfully applied in the one-pot synthesis of *β*-amino malonic esters. The magnetic organocatalyst was stable and could be recovered by simple magnetic decantation. The simple procedure for catalyst preparation, easy recovery and reusability of the catalyst can be expected to contribute to its utilisation for the development of benign chemical process and products.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker AM 300 spectrometer using $CDCl_3$ as a solvent and TMS as an internal standard. FT-IR spectra were recorded on a Perkin-Elmer FT-IR X 1760 instrument. Mass spectra were obtained on TSQ Quantum LC-MS. HR-Mass were recorded on Bruker ultrafine MALDI-TOF-TOF. TEM were recorded on JEM-2000 transmission electron microscope with an acceleration voltage of 200 kV. X-ray diffraction (XRD) patterns of samples were recorded on a Bruker AXS D8 ADVANCE X-ray diffractometer.

Synthesis of nano-Fe_3O_4-L-cysteine; general procedure

$FeCl_3{\cdot}6H_2O$ (5 mmol, 1.35 g) was dissolved in ethylene glycol (40 mL) to form a clear solution, followed by the addition of urea (2.0 g) and polyethylene glycol (1.0 g). The mixture was stirred vigorously for 30 min and then sealed in a Teflon-lined stainless-steel autoclave (50 mL capacity). The autoclave was heated to and maintained at 200 °C for 12 h, and then allowed to cool to room temperature. The black products were washed several times with ethanol and dried at 60 °C for 6 h.

Synthesis of β-amino diethyl malonate; general procedure

A mixture of aldehyde (0.5 mmol), amine (0.5 mmol), diethyl malonate (0.55 mmol), and catalyst (wt 5% with respect to amount of aldehyde) in CH_2Cl_2 (3 mL) was sealed in the tube and stirred under 30 °C for 12 h. Then after simple magnetic decantation by external field, the catalyst was separated, washed, dried and immediately reused. After removing the solvent in vacuum, the crude residues were purified by the flash column chromatography on gel silica with ethyl acetate : hexane (1 : 10) as eluent to afford pure products. The identity of all known products were confirmed by comparing their physical and spectra data with reported values. Some characterisation data were selected as follows.

Diethyl 2-(phenyl(phenylamino)methyl)malonate (**5a**):[22] White solid, m.p. 92–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.32 (m, 2 H), 7.31–7.28 (m, 2 H), 7.23–7.18 (m, 1 H), 7.07–7.03 (m, 2 H), 6.62–6.60 (m, 1 H), 6.54–6.52 (m, 2 H), 5.18 (d, J = 9.2 Hz, 1 H), 4.18–4.06 (m, 4 H), 3.83 (d, J = 9.2 Hz, 1 H), 1.20 (t, J = 7.2 Hz, 3 H), 1.12 (t, J = 7.2 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 166.6, 147.7, 141.9, 129.3, 128.7, 127.7, 127.4, 117.9, 114.3, 62.2, 61.9, 56.3, 53.8, 14.1, 13.9 ppm. MS (ESI) *m/z* ([M + 1]$^+$) 342.

Diethyl 2-(phenyl(4-methoxyphenylamino)methyl)malonate (**5d**): Yellow solid, m.p. 70–72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5 H), 6.69–6.67 (d, J = 7.2 Hz, 2H), 6.58–6.55 (d, J = 7.2 Hz, 2 H), 5.10 (d, J = 5.8 Hz, 1 H), 4.14–4.10 (m, 4 H), 3.68 (s, 3H), 3.38 (d, J = 5.8 Hz, 1 H), 1.20 (t, J = 7.2 Hz, 3 H), 1.12 (t, J = 7.2 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 166.9, 146.1, 141.6, 131.6, 129.5, 128.0, 118.8, 118.6, 62.4, 62.0, 57.5, 56.4, 55.2, 14.1, 13.8 ppm. HR-Mass $C_{21}H_{25}NO_5$ for M$^+$, calcd 371.1727, found 371.1728.

Diethyl 2-(4-bromophenyl(4-chlorophenylamino)methyl)malonate (**5f**):[22] White solid, m.p. 88–89 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.34 (m, 2 H), 7.16–7.12 (m, 2 H), 6.97–6.34 (m, 2 H), 6.41–6.38 (m, 2 H), 5.04 (d, J = 5.5 Hz, 1 H), 3.83 (d, J = 5.5 Hz, 1H), 4.16–4.02 (m, 4 H), 1.10–1.04 (m, 6 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 167.1, 145.0, 138.5, 132.0, 129.2, 128.9, 121.9, 114.9, 62.1, 61.9, 57.8, 56.8, 14.1, 14.0 ppm; MS (ESI) *m/z* ([M + 1]$^+$) 454.

Diethyl 2-(4-cyano-phenyl(phenylamino)methyl)malonate (**5g**): White solid, m.p. 74–75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.54 (m, 2 H), 7.50–7.45 (m, 2 H), 7.18–7.04 (m, 2 H), 6.78–6.62 (m, 1 H), 6.58–5.52 (m, 2 H), 5.26 (d, J = 7.2 Hz, 1 H), 4.18–4.08 (m, 4 H), 3.88 (d, J = 7.2 Hz, 1 H), 1.20–1.14 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 167.0, 146.1, 145.6, 132.6, 129.5, 128.0, 118.8, 118.6, 62.3, 62.1, 57.7, 56.9, 14.1, 14.0 ppm. HR-Mass $C_{21}H_{22}N_2O_4$ for M$^+$, calcd 371.1727, found 371.1728.

We thank National Natural Science Foundation of China (21302014), the Natural Science Foundation for Colleges and Universities of Jiangsu Province (13KJB150002), Jiangsu Overseas Research & Training Program for University Prominent Young and Middle-aged Teachers in 2011, and Changzhou Scientific Application Program on Basic Research (CJ20130003) for financial support.

Received 16 December 2013; accepted 13 March 2014
Paper 1302347 doi: 10.3184/174751914X13968767247911
Published online: 6 May 2014

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