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ORIGINAL PAPER

Imidazole functionalized magnetic Fe_3O_4 nanoparticles as a novel heterogeneous and efficient catalyst for synthesis of dihydropyrimidinones by Biginelli reaction

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Abstract Dihydropyrimidinone derivatives were synthesized in moderate to high yields in one-pot three-component condensation reactions from the corresponding aldehydes, 1,3-dicarbonyl compounds, and urea in the presence of catalytic amounts of imidazole functionalized on magnetic nanoparticles as an efficient, non-toxic, reusable, and easily available catalyst under solvent-free conditions at 80 °C. Compared to the classical Biginelli reaction, this new method consistently has the advantage of excellent yields, short reaction times, and methodological simplicity. Furthermore, the nanomagnetic catalyst could be readily handled and removed from the reaction mixture via application of an external magnet, allowing straightforward recovery and reuse.

Keywords Dihydropyrimidinone · Biginelli reaction · Magnetic nanoparticles · Imidazole

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Introduction

The Biginelli reaction was first reported more than a century ago and recently reviewed [1]; it involves the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) by multicomponent cyclocondensation reaction of ethylacetoacetate, benzaldehyde, and urea in ethanol.

The dihydropyrimidinone derivatives have attracted considerable interest in recent years because of promising biological activities as calcium channel blockers and as antihypertensive, antibacterial, antiviral, antitumor, antioxidant, and antiinflammatory agents [2–6]. In addition, several alkaloids containing the dihydropyrimidine core unit, which also exhibit interesting biological properties, have been isolated from marine source [7–9]. Therefore, DHPM compounds have not only attracted much attention from chemists for synthesis, but also represent an interesting research challenge.

At present, with awareness of environmental issues and the biological importance of these compounds, several general methods are known for the preparation of dihydropyrimidinones using catalysts such as Brønsted acids like *p*-toluenesulfonic acid [10], silica- sulfuric acid [11], $KHSO_4$ [12], trifluoroacetic acid, trifluoromethanesulfonic acid [13], Lewis acids such as $BF_3{\cdot}Et_2O/Cu(OAc)_2$ [14], $Yb(OTf)_3$ [15], $FeCl_3$ [16], triphenylphosphine [17], hexaaquaaluminium(III) tetrafluoroborate [18], microwave heating [19], sonication [20], organocatalysts [21], and ionic liquids [22].

However, many of these methodologies suffer from several drawbacks such as a long reaction times, low product yields, an excess of organic solvent, harsh conditions, occurrence of several side products, and difficulty in recovery and reusability of the catalysts. Due to these problems, the development of novel, efficient, and versatile catalytic systems for the Biginelli reaction is an active ongoing research area; thus, there is scope for further improvement toward milder reaction conditions, variations of substituents in all three components, and better yields.

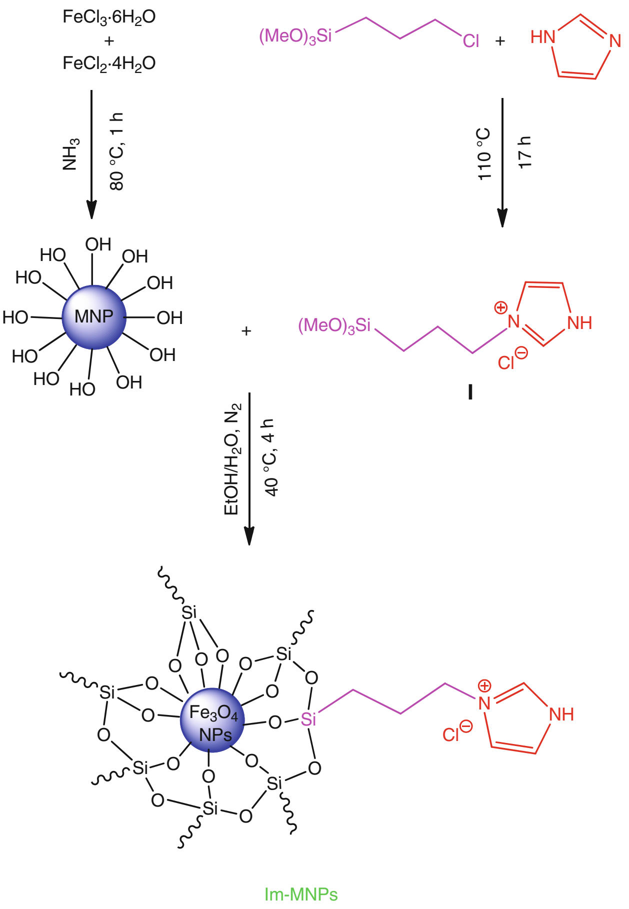
Nowadays, magnetic catalysts have attracted enormous interest because of their specific characteristics. These types of catalysts, because of their high surface area, biocompatibility, and unique magnetic properties, have a broad range of potential uses among the academic and industrial scientific community [23–27]. In addition, they can be easily separated by utilizing the magnetic interaction between the magnetic nanoparticles and an externally applied magnetic field. In view of this, in the present work, imidazole functionalized on iron oxide magnetic nanoparticles was successfully prepared, and its performance as a catalyst for the Biginelli reaction was investigated.

Results and discussion

Synthesis of imidazole functionalized magnetic Fe_3O_4 nanoparticles (Im-MNPs) and its structural and morphological analysis

MNP-supported systems have the potential to improve the efficiency, selectivity, and yield of catalytic processes. The higher surface-to-volume ratio means that much more of the catalyst is actively participating in the reaction. When the size of the support is decreased to the nanometer scale, the surface area is substantially increased, and easy access of reactants to the active sites can also be achieved [30]. A study comparing the catalytic activity of immobilized catalysts depending on support size indicated that nanoscale supports gave the highest regioselectivities and product yields [31]. In the present study, naked magnetic Fe_3O_4 nanoparticles were prepared through the chemical coprecipitation method from Fe^{2+} and Fe^{3+} ion solutions in basic media. In the next step, the reaction of Cl groups of (3-chloropropyl)-trimethoxysilane with imidazole led to product **1** (Si-Im). Ultimately, MNPs were coated with Si-Im to achieve imidazole functionalized magnetic nanoparticles (Scheme 1).

Scheme 1



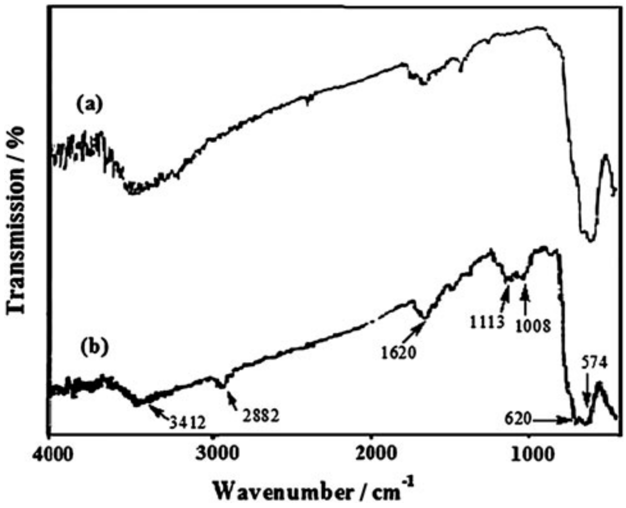


Fig. 1 FT-IR spectra of **a** MNPs and **b** Im-MNPs

The grafting of imidazole on the surface of magnetic nanoparticles was verified by FT-IR studies. Figure 1 shows the FT-IR spectra of MNPs and Im-MNPs in the 500–4,000 cm^{-1} wavenumber range. The IR spectrum of the Im-MNPs shows characteristic adsorption bands at 3,412 and 620 cm^{-1} assigned to the stretching vibration of N–H groups [32] and characteristic peaks of the imidazole fragment [33], respectively. The existence of linker to the surface of MNPs is proved by the bands at 1,113 and 1,008 cm^{-1} assigned to the Si–O stretching vibrations [29]. The presence of the anchored propyl group is confirmed by C–H stretching vibrations that appear at 2,800 and 2,900 cm^{-1}. In addition, the infrared band at 574 cm^{-1} was associated with the stretching and torsional vibration

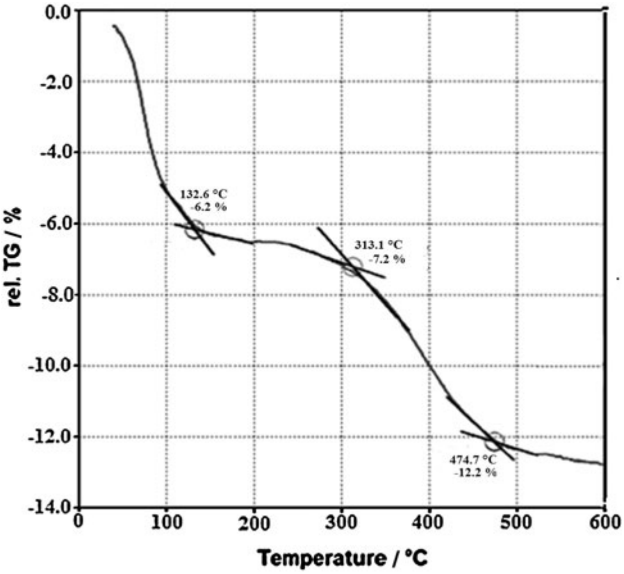


Fig. 2 TGA curve of Im-MNPs

modes of the magnetite Fe–O bonds in tetrahedral sites [34]. Thus, all the above results indicate that imidazole has been grafted successfully on MNPs.

Figure 2 shows the TGA analysis of Im-MNPs. The TGA thermogram exhibits the first weight loss of 6 % below 130 °C, which might be due to the loss of physically adsorbed water adhering to the sample surface and surface hydroxyl groups. The second weight loss step of about 1 % in the region of 230-315 °C may be related to the thermal crystal phase transformation from Fe_3O_4 to γ-Fe_2O_3 [29, 35]. The latest weight loss between 380 and 475 °C (~5 %) was due to the breakdown and decomposition of imidazole moieties [29]. Thus, the TGA curves also convey the obvious information that the imidazole molecules are successfully grafted onto the magnetic nanoparticles.

The structural and morphological characterization of the Im-MNPs nanostructure was performed by measuring SEM using a Philips XL30 scanning electron microscope (Fig. 3). FESEM observations show that nanoparticles in all the samples have a spherical shape, indicating the Im-MNPs has a large surface area. The fabricated nanocatalyst has homogeneous distributions of nanoparticles, and the magnetite particle size distribution has an average of 37 nm.

Application of Im-MNPs as nanomagnetic catalyst for synthesis of dihydropyrimidinones by Biginelli reaction

In continuation of our investigation on the use of magnetic nanocatalysts for chemical transformations [24, 25], herein, we report the one-pot condensation of different dicarbonyl compounds with various aldehydes and urea in the presence of catalytic amounts of Im-MNPs as an efficient and recyclable catalyst (Scheme 2). In order to optimize the reaction conditions, the reaction of benzaldehyde, ethylacetoacetate, and urea was conducted under different conditions in both the absence and presence of Im-MNPs. Results are given in Table 1.

Building upon this result, further studies were conducted, and it was found that with 0.15 g of Im-MNPs was optimum for this reaction and gave product in 91 % yield in just 30 min (Table 1, entry 4). The reaction temperature was also optimized; below 80 °C, the reaction proceeded slowly giving relatively low yield, and no improvement was observed above 80 °C. Moreover, to see the

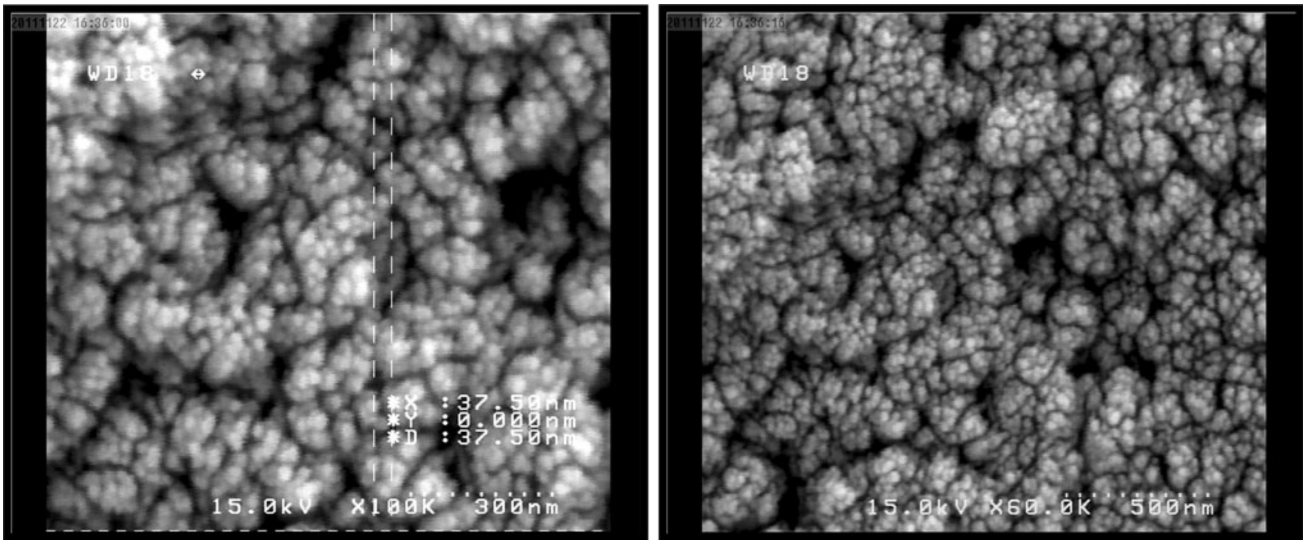


Fig. 3 SEM images of Im-MNPs

Scheme 2

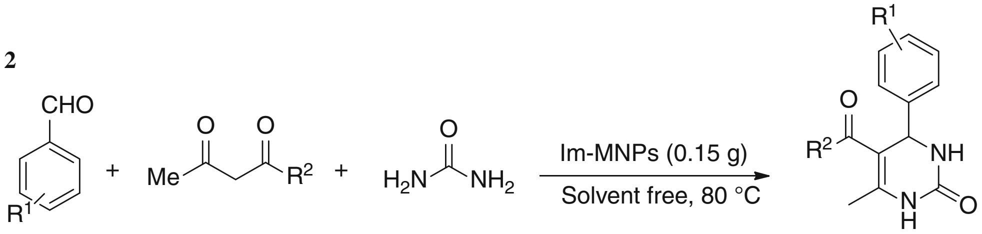


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Table 1 Optimization of reaction conditions for the synthesis of DHPMs

Entry	Im-MNPs/g	Temp./°C	Time	Yield/%
1	–	80	6 h	Trace
2	0.05	80	85 min	65
3	0.1	80	60 min	88
4	0.15	80	30 min	91
5	0.2	80	30 min	88
6	0.15	25	2 h	Trace
7	0.15	60	65 min	70
8	0.15	90	30 min	89

Table 2 One-pot synthesis of substituted 3,4-DHPMs catalyzed by Im-MNP under solvent-free conditions

Entry	R^1	R^2	X	Yield/%	M.p./°C	Lit. m.p./°C
1	C_6H_5	Me	O	93	231–234	233–236 [15]
2	4–NO_2–C_6H_4	Me	O	84	229–230	230 (dec) [15]
3	4–Cl–C_6H_4	Me	O	85	224–225	226–227 [41]
4	4–CH_3O–C_6H_4	Me	O	95	180–182	178–180 [15]
5	4–CH_3–C_6H_4	Me	O	89	228–230	230–231 [42]
6	C_6H_5	OEt	O	93	200–202	203–205 [6]
7	4–CH_3O–C_6H_4	OEt	O	91	203–205	202–204 [6]
8	4–NO_2–C_6H_4	OEt	O	85	226–228	210–211 [42]
9	4–OH–C_6H_4	OEt	O	88	232–234	236–237 [42]
10	4–Cl–C_6H_4	OEt	O	82	214–216	213–215 [14]
11	C_6H_5	OMe	O	92	211–213	210–213 [43]
12	2–Cl–C_6H_4	OMe	O	78	179–182	181–183 [43]
13	4–Cl–C_6H_4	OMe	O	83	201–204	203–205 [43]
14	4–CH_3O–C_6H_4	OEt	S	90	149–150	151–153 [44]

effectiveness of the imidazolium ion on this catalysis reaction, we also examined bare MNPs in separate experiments under optimized conditions. The obtained result showed that in the absence of imidazole support, the reaction proceeded sluggishly, and after a prolonged reaction time, a considerable amount of starting material remained. Therefore, the imidazole groups were strong promoters of the reaction.

After optimizing the conditions, the scope and generality of this protocol were examined by subjecting a broad range of building block combinations such as aromatic aldehydes carrying either electron-donating or -withdrawing substituents, different *β*-ketoesters, and urea using Im-MNPs as a catalyst under solvent-free conditions. All the building block combinations reacted very well, giving moderate to excellent yields with high purity of the desired products under optimized reaction conditions (Table 2). In addition, the condensation protocol was fairly general, and several functionalities, including nitro, chloro, methoxy, and hydroxy, survived during the course of the reaction.

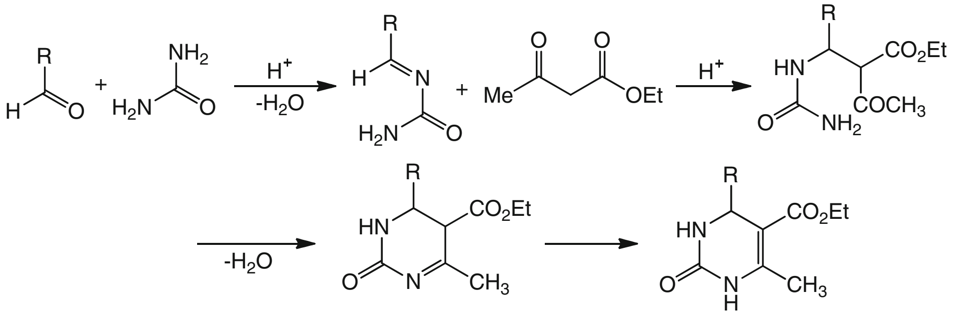
In a proposed mechanism that is supported by the literature [36–38], Im-MNPs promoted this heterocyclization reaction by virtue of their inherent Brønsted acidity conferred by the most acidic N–H hydrogen. This makes the Im-MNPs capable of bonding with the carbonyl oxygen, increasing the reactivities of the parent carbonyl compounds. Then nucleophilic attack of the nitrogen of urea on the activated carbonyl group resulted in the formation of acylimine, followed by the addition of *β*-ketoester to the imine bond, and consequently the ring was closed by the nucleophilic attack by the amine on the carbonyl group (Scheme 3) [36, 39, 40].

In view of environmentally friendly methodologies, recovery and reuse of the Im-MNPs is highly preferable. Im-MNPs did not suffer from extensive mechanical degradation and were quantitatively recovered simply by adding ethanol to the stirred reaction mixture followed by application of an external magnet and washing with water and acetone. It could be reused for subsequent reactions. Recycled Im-MNPs showed no significant loss of efficiency with regard to yield after four successive runs; hence, this procedure can be regarded as a novel, facile, convenient, and environmentally benign method for the synthesis of 3,4-dihydropyrimidine-2(1*H*)-one derivatives.

Conclusion

In this work, imidazole functionalized magnetic Fe_3O_4 nanoparticles were successfully prepared, and their performance as a nanomagnetic catalyst for the Biginelli

Scheme 3



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reaction was investigated. The most interesting features of the present work include the durability as well as efficient catalytic activity for one-pot synthesis of dihydropyrimidinone derivatives via three-component coupling reactions of aldehydes, β-ketoesters, and urea under solvent-free conditions at 80 °C. The attractive features of this method are high yield, short reaction time, clean reaction profiles, simple workup procedure, ease of separation, and recyclability of the magnetic catalyst, as well as the ability to tolerate a wide variety of substitutions in the reagents.

Experimental

Iron(II) chloride tetrahydrate (99 %), iron(III) chloride hexahydrate (98 %), imidazole, aldehydes, and other chemical materials were purchased from Fluka and Merck and used without further purification. Products were characterized by comparison of their physical data, IR and ^1H NMR, and ^{13}C NMR spectra with known samples. NMR spectra were recorded in $CDCl_3$ on a Bruker Avance DPX 400 MHz spectrometer using TMS as internal standard. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates. The FT-IR spectra were measured on a BOMEM MB-Series 1998 FT-IR spectrophotometer using the potassium bromide pressed disc method. The particle morphology was examined by measuring SEM using a Philips XL30 scanning electron microscope operating at 20 kV. The TGA curve of the imidazole functionalized on Fe_3O_4 magnetic nanoparticles was recorded on a BAHR SPA 503 at heating rates of 10 °C min^{-1}. The thermal behavior was studied by heating 1–3 mg of samples in aluminum-crimped pans under nitrogen gas flow over a temperature range of 25–600 °C.

Preparation of the magnetic Fe_3O_4 nanoparticles (MNPs)

Naked Fe_3O_4 nanoparticles were prepared via an improved chemical coprecipitation method [28]. According to this method, 3.17 g $FeCl_2 \cdot 4H_2O$ (1.6 mmol) and 7.57 g $FeCl_3 \cdot 6H_2O$ (2.8 mmol) were dissolved in 320 cm^3 of deionized water, such that $Fe^{2+}/Fe^{3+} = 1/1.75$. The mixed solution was stirred under N_2 at 80 °C for 1 h; 40 cm^3 of $NH_3 \cdot H_2O$ was injected into the reaction mixture in one portion, stirred under N_2 for another 1 h, and then cooled to room temperature. The black precipitated particles were washed with doubly distilled water and 0.02 M solution of NaCl through magnetic decantation. Practically, the NaCl solution helped delete the excess amount of ammonia, providing a better and faster decantation of suspended Fe_3O_4 nanoparticles in water when an external magnet was used. Finally, Fe_3O_4 magnetic nanoparticles were dried under vacuum at 70 °C.

Preparation of imidazole functionalized magnetic Fe_3O_4 nanoparticles (Im-MNPs)

In the first step, a mixture of 2.00 g 3-chloromethoxypropylsilane (10.0 mmol) and 0.68 g imidazole (10.0 mmol) was heated at 110 °C for 17 h with continuous stirring under N_2 atmosphere. The product of this step (Si-Im) was dissolved in 100 cm^3 ethanol/water (volume ratio 1:1) solution. The obtained MNP powder (1.5 g) was also dispersed in 200 cm^3 ethanol/water solution by sonication for 30 min and then was added to the ethanolic solution of Si-Im. After mechanical agitation under N_2 atmosphere at 40 °C for 4 h [29], the expected final product, imidazole functionalized MNPs, was separated by magnetic decantation, washed with acetonitrile and dichloromethane, and left to dry in a desiccator.

General procedure for the synthesis of dihydropyrimidinones

A mixture of aldehyde (10 mmol), ethyl acetoacetate (10 mmol), urea (15 mmol), and 0.15 g Im-MNPs was stirred at 80 °C for the appropriate time (Table 2). Progress of the reaction was monitored by TLC using *n*-hexane - ethyl acetate as eluent. Upon completion of the reaction (20–55 min), the reaction mixture was diluted with 20 cm^3

ethanol, the reaction mass was stirred and allowed to cool, and the catalyst was concentrated on the sidewall of the reaction vessel using an external magnet and washed with ethanol. Then the solvent was evaporated under reduced pressure to obtain a solid residue. The crude product was washed with cold water and a mixture of EtOH:H_2O (1:1). Finally, the solid was recrystallized from hot ethanol to afford pure product. All products are known compounds and were characterized by IR and ^1H NMR spectroscopic data and melting points and compared with reported values.

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References

1. Biginelli P (1893) Gazz Chim Ital 23:360
2. Rovnyak GC, Kimball SD, Beyer B, Cucinotta G, Dimarco JD, Gougoutas J, Hedberg AO, Malley M, McCarthy JP, Zhang R, Moreland S (1995) J Med Chem 38:119
3. Grover GJ, Dzwonczyk S, McMullen DM, Normadinam CS, Sleph PG, Moreland SJ (1995) J Cardiovasc Pharmacol 26:289
4. Snider BB, Chen J, Patil AD, Freyer A (1996) Tetrahedron Lett 37:6977
5. Singh K, Singh J, Deb PK, Singh H (1999) Tetrahedron 55:12873
6. Fu NY, Yuan YF, Cao Z, Wang SW, Wang JT, Peppe C (2002) Tetrahedron 58:4801
7. Patil AD, Kumar NV, Kokke WC, Bean MF, Freyer AJ, Debrosse C, Mai S, Truneh A, Faulkner DJ, Carte B, Breen AL, Hertzberg RP, Johnson RK, Westly JW, Ports BCM (1995) J Org Chem 60:1182
8. Ohtani K, Kusumi T, Kakisawa H, Kashman Y, Hirsh S (1992) J Am Chem Soc 114:8472
9. Overman LE, Rabinowitz MH, Renhowe PA (1995) J Am Chem Soc 117:2657
10. Jin T, Zhang S, Li T (2002) Synth Commun 32:1847
11. Salehi P, Dabiri M, Zolfigol MA, Bodaghi Fard MA (2003) Tetrahedron Lett 44:2889
12. Tu S, Fang F, Zhu S, Li T, Zhang X, Zhuang Q (2004) Synlett 537
13. Adibi H, Samimi HA, Beygzadeh M (2007) Catal Commun 8:2119
14. Hu EH, Sidler DR, Dolling UH (1998) J Org Chem 63:3454
15. Ma Y, Qian C, Wang L, Yang M (2000) J Org Chem 65:3864
16. Lu J, Bai Y (2002) Synthesis 466
17. Debache A, Amimour M, Belfaitah A, Rhouati S, Carboni B (2008) Tetrahedron Lett 49:6119
18. Litvic M, Vecenaj I, Ladisic ZM, Lovric M, Vinkovic V, Litvic MF (2010) Tetrahedron 66:3463
19. Khrustalev DP (2009) Russ J Gen Chem 79:164
20. Yadav JS, Reddy BVS, Reddy KB, Raj KS, Prasad AR (2001) J Chem Soc Perkin Trans 1:1939
21. Ding D, Zhao C (2010) Eur J Org Chem 20:3802
22. Fang D, Zhang D, Liu Z (2010) Monatsh Chem 141:419
23. Sheykhan M, Mamani L, Ebrahimi A, Heydari A (2011) J Mol Catal A: Chem 335:253
24. Kiasat AR, Nazari S (2012) J Mol Catal A: Chem 365:80
25. Kiasat AR, Nazari S (2013) J Incl Phenom Macrocycl Chem 76:363
26. Pfeifer A, Zimmermann K, Plank C (2012) Pharm Res 29:1161
27. Kassaee MZ, Masrouri H, Movahedi F (2010) Monatsh Chem 141:317
28. Can K, Ozmen M, Ersoz M (2009) Colloids Surf B 71:154
29. Kassaee MZ, Masrouri H, Movahedi F (2011) Appl Catal A 395:28
30. Stevens PD, Fan J, Gardimalla HMR, Yen M, Gao Y (2005) Org Lett 7:2085
31. Yoon TJ, Kim JI, Lee JK (2003) Inorg Chim Acta 345:228
32. Su KM, Pan TY, Zhang YL (2002) The Analytic Method of Spectrum. East China University of Science & Technology Press, Shanghai, p 100
33. Talaty ER, Raja S, Storhaug VJ, Dolle A, Carper WR (2004) J Phys Chem B 108:13177
34. Badruddoza AZM, Hidajat K, Uddin MS (2010) J Colloid Interface Sci 346:337
35. Cornell RM, Schwertmann U (1996) The Iron Oxides. VCH, New York
36. Siddiqui SA, Narkhede UC, Palimkar SS, Daniel T, Lahoti RJ, Srinivasan KV (2005) Tetrahedron 61:3539
37. Kappe CO (1997) J Org Chem 17:7201
38. Chen WY, Qin SD, Jin JR (2007) Catal Commun 8:123
39. Suzuki I, Iwata Y, Takeda K (2008) Tetrahedron Lett 49:3238
40. Shaterian HR, Ranjbar M (2011) J Mol Liq 160:40
41. Shaabani A, Rahmati A (2005) Catal Lett 100:177
42. Besoluk S, Kucukislamoglu M, Nebioglu M, Zengin M, Arslan M (2008) J Iran Chem Soc 5:62
43. Mahdavinia GH, Sepehrian H (2008) Chin Chem Lett 19:1435
44. Cheng J, Qi DY (2007) Chin Chem Lett 18:647