RESEARCH LETTER

Fe₃O₄@SiO₂/Schiff base complex of metal ions as an efficient and recyclable nanocatalyst for the green synthesis of quinoxaline derivatives

M. Esmaeilpour and A.R. Sardarian*

Department of Chemistry, College of Sciences, Shiraz University, Shiraz, Iran

(Received 30 October 2013; final version received 21 July 2014)

Keywords: magnetic nanocatalyst; quinoxaline; solvent-free; phenylene-1,2-diamines; 1,2-diketones

1. Introduction

The synthesis of quinoxaline derivatives has been of considerable interest as they possess various biological activities, such as antibacterial (1), antitumor (3), antitumor (3), antifungal (1), antidepressant (4), and kinase inhibition agents (5). In addition, quinoxalines have been used for the preparation of various dyes (6) and key intermediates in the synthesis of organic semiconductors (7), dehydro annulenes (8), chemically controllable switches (9), and used in the agricultural field as fungicides, herbicides, insecticides (2). They are also used as anti-inflammatory, anti-protozoal, and anti-HIV (10). The importance and utility of quinoxaline derivatives have led to the development of numerous synthetic routes. The condensation of 1,2-diamines with 1,2-diketones in refluxing ethanol or acetic acid has been used as a useful synthetic route toward quinoxalines (11). For this transformation, several catalysts and reagents have been reported, including a oxidative coupling method (12), ceric(IV) ammonium nitrate (13), sulfamic acid (14), a microwave procedure (15), zeolite (16), POCl₃ (17), H₃P₂W₁₈O₆₂·24H₂O (18), CuSO₄·5H₂O (19), LiBr (20), (NH₄)₆Mo₇O₂₄·4H₂O (21), montmorillonite K₁₀(22), ZnL-proline (23), RuCl₃-(PPh₃)₃-TEMPO (24), polyaniline-sulfate salt (25), Yb(OTf)₃ (26), zirconium tetrakis(dodecyl sulfate) (27), o-iodoxybenzoic acid (28), MnO₂ (29), ZrO₂/Ga₂O₃/MCM-41 (30), ammonium chloride (31), SbCl₅/SiO₂ (32), zirconium tetrachloride (33), SnCl₄/SiO₂ (34), gallium triflate (35), and (NH₄)H₂PW₁₂O₄₀ (36). However, these methods have many disadvantages, such as low yields, long reaction times, the use of toxic solvents, and harsh reaction conditions. Thus, the development of a new catalyst for the synthesis of quinoxaline derivatives would be highly desirable.

Recently, magnetic core-shell nanostructures have attracted more attention due to their unique magnetic properties. In contrast to most of solid catalysts that their recovery and reusability are very difficult, recovery and thus reusing of core-shell nanostructure magnetic catalysts can be easily carried out under external magnetic field. Therefore, the magnetic core-shell structure composites for catalysis are very well supported (37–39). As part of our program in the development of expedient methods for the synthesis of heterocyclic and biological important compounds, herein, we report the first use of magnetic nanoparticles Fe₃O₄@SiO₂/Schiff base complex of metal ions for the synthesis of quinoxalines under mild reaction conditions (Scheme 1).

2. Results and discussion

In order to optimize the reaction parameters, the reaction between o-phenylenediamine (1 mmol) and benzil (1 mmol) was performed in the presence of 0.03 g Fe₃O₄@SiO₂/Schiff base/Co(II) nanocatalyst at room temperature in the different solvents, such as acetonitrile, chloroform (CDCl₃), dichloromethane, ethyl acetate, water, ethanol, methanol, and the different mixture of EtOH/H₂O (3/1, v/v). According to the presented results in Table 1, the best yield of
2,3-diphenylquinoxaline was formed in the mixture of EtOH/H2O (3/1; Table 1, entry 10).

The reaction was also studied in the presence of different amount of the catalyst in EtOH/H2O (3/1, v/v), but in the all of investigated cases, the yields did not improve even in higher reaction times (Table 1, entries 11–14 and Figure 1). In order to elucidate the role of the nanocatalyst, a control reaction was conducted using benzil and o-phenylenediamine in the absence of nanocatalyst. Quinoxaline was formed after 12 h with a 40% yield (Table 1, entry 14).

In order to study the catalytic activity of metal ions, we examined the condensation of benzil with 1,2-phenylenediamines to evaluate the efficiency of Fe3O4@SiO2/Schiff base complex of metal ions as catalyst (Table 2).

The catalytic activity of various Lewis acids was found to be of the order Co(II)>Cu(II)>Ni(II)>Mn (II)>Cd(II)>Hg(II) and indicate that the nanocatalyst

Table 1. Optimization of reaction conditions in the synthesis of 2,3-diphenyl quinoxaline catalyzed by Fe3O4@SiO2/Schiff base complex of Co (II).

| Entry | Solvent     | The amount of catalyst (g) | Time (min) | Yield (%) |
|-------|-------------|---------------------------|------------|-----------|
| 1     | EtOH        | 0.03                      | 25         | 91        |
| 2     | MeOH        | 0.03                      | 35         | 85        |
| 3     | H2O         | 0.03                      | 40         | 75        |
| 4     | CH2CN       | 0.03                      | 30         | 84        |
| 5     | CH3CO2Et    | 0.03                      | 60         | 74        |
| 6     | CHCl3       | 0.03                      | 70         | 70        |
| 7     | CH2Cl2      | 0.03                      | 70         | 67        |
| 8     | EtOH/H2O [25/75(v/v)] | 0.03 | 30     | 83        |
| 9     | EtOH/H2O [50/50(v/v)] | 0.03 | 20     | 87        |
| 10    | EtOH/H2O [75/25(v/v)] | 0.03 | 10     | 97        |
| 11    | EtOH/H2O [75/25(v/v)] | 0.01 | 80     | 61        |
| 12    | EtOH/H2O [75/25(v/v)] | 0.02 | 25     | 84        |
| 13    | EtOH/H2O [75/25(v/v)] | 0.04 | 15     | 93        |
| 14    | EtOH/H2O [75/25(v/v)] | – | 12 h    | 40        |

Figure 1. The effect of amount of the catalyst on preparation of 2,3-diphenylquinoxaline.
performance is better for Fe₃O₄@SiO₂/Schiff base complex of Co(II).

To recognize the generality and the scope of our method, various aromatic and aliphatic 1,2-diamines were reacted with benzil in the presence of Fe₃O₄@SiO₂/Schiff base/Co(II) (0.03 g) at room temperature (Table 3). All the reactions with substituted 1,2-phenylenediamines proceeded very cleanly and no undesirable side reactions were observed. Results in Table 3 show that electron-donating groups at the phenyl ring of 1,2-diamine favored the formation of product (Table 3, entries 7–11). However, aliphatic 1,2-diamines afforded the corresponding quinoxaline derivatives in slightly lower yields and longer reaction times (Table 3, entries 20 and 21). In contrast, electron-withdrawing groups such as nitro, benzyol, and chloro gave slightly lower yields (Table 3, entries 12–18). Substrate bearing a strong electron-withdrawing NO₂ group gave lower yield even after longer reaction times (Table 3, entries 13–15). On the other hand, electron-donating substituents associated with aromatic 1,2-diketone decreased the product yields and the effect is contrary with electron-withdrawing groups (Table 3, entries 2, 8, 15, and 17). Therefore, our results demonstrate that Fe₃O₄@SiO₂/Schiff base complex of Co(II) is a very effective nanocatalyst for the one-pot condensations of o-phenylenediamine derivatives and α-diketones to form quinoxalines in excellent yields.

Comparison of the efficiency of Fe₃O₄@SiO₂/Schiff base/Co(II) in the formation of 6-nitro-2,3-diphenylquinoxaline from the reaction of 4-nitrobenzene-1,2-diamine and benzil with those of several reported acid catalyst in the literature, indicates that this reaction is completed, in the most cases, in shorter time with higher yield in green media with simple work-up (Table 4).

Recycling of catalyst and reducing the amount of catalyst are important aspects of green chemistry. According to this topic, reusability of nanocatalyst was tested in the reaction of benzil with o-phenylenediamine in EtOH/H₂O (3/1, v/v). After five times recycling, the nanocatalyst showed no significant change on reactivity and yields slightly decreased with increasing number of cycles of the reaction (97%, 96%, 96%, 95%, and 94%; Figure 2).

### 3. Experimental

#### 3.1. General

Solvents, reagents, and chemicals were obtained from Merck (Germany) and Fluka (Switzerland) chemical companies in high purity. The NMR spectra were recorded on a Bruker Avance DPX-250 MHz spectrometer in CDCl₃ using tetramethylsilane as an internal reference. Melting points were determined by Buchi Melting Point B-545 electrical melting point apparatus and quantitative elemental analysis (CHN) were obtained by reported on a Flash EA instrument. The quinoxaline derivatives were characterized by their melting points and comparison with literature values.
Table 3. Synthesis of quinoxaline derivatives catalyzed by Fe₃O₄@SiO₂/Schiff base complex of Co(II) at room temperature

| Entry | 1,2-Diamine | α-Dicarbonyl | Product | Time (min) | Yield (%) | M.p°C (Lit.) | Ref. |
|-------|-------------|--------------|---------|------------|-----------|--------------|------|
| 1     | NH₂NH₂      |              |         | 10         | 97        | 125–127 (128–129) | (28) |
| 2     | NH₂NH₂      |              |         | 17         | 95        | 149–151 (151–152) | (28) |
| 3     | NH₂NH₂      |              |         | 20         | 93        | Oil          | –    |
| 4     | NH₂NH₂      |              |         | 15         | 96        | 103–105 (105–106) | (41) |
| 5     | NH₂NH₂      |              |         | 17         | 95        | 54–56 (55)   | (14) |
| 6     | NH₂NH₂      |              |         | 10         | 97        | 134–136 (135–137) | (28) |
| 7     | H₃C NH₂     |              |         | 10         | 96        | 133–135 (135–137) | (41) |
| 8     | H₃C NH₂     |              |         | 17         | 95        | 124–126 (125–127) | (19) |
| 9     | H₃C NH₂     |              |         | 11         | 96        | 88–90 (91)   | (42) |
| 10    | H₃C NH₂     |              |         | 20         | 95        | Oil          | –    |
| 11    | H₃C NH₂     |              |         | 10         | 96        | 164–166 (163–165) | (28) |
| 12    | PhCO NH₂    |              |         | 30         | 93        | 140–142 (139–140) | (43) |
Table 3 (Continued)

| Entry | 1,2-Diamine | α-Dicarbonyl | Product | Time (min) | Yield (%) | M.p°C (Lit.) | Ref. |
|-------|-------------|--------------|---------|------------|-----------|--------------|------|
| 13    | NH₂NH₂     | O₂N          |          | 40         | 94        | 191–193 (193–194) | (19) |
| 14    | NH₂NH₂     | O₂N          |          | 70         | 91        | 135–137 (134–135) | (44) |
| 15    | NH₂NH₂     | H₃CO         |          | 100        | 89        | 191–193 (192–194) | (19) |
| 16    | NH₂NH₂     | Cl           |          | 25         | 90        | 117–119 (115–116) | (45) |
| 17    | NH₂NH₂     | Cl           |          | 80         | 88        | 148–150 (151–152) | (34) |
| 18    | NH₂NH₂     | Cl           |          | 25         | 92        | 88–90 (89–91) | (31) |
| 19    | NH₂NH₂     | Cl           |          | 120        | 88        | 165–167 (167) | (13) |
| 20    | NH₂NH₂     | Cl           |          | 120        | 90        | 158–160 (158) | (13) |

*1,2-diamine (1 mmol), benzil (1 mmol), and 0.03 g catalyst were stirred in EtOH/H₂O [3/1 (v/v)] at room temperature; †Isolated yields.

Table 4. Literature results for the synthesis of 6-nitro-2,3-diphenylquinoxaline at room temperature.

| Entry | Catalyst | Solvent | Time (min) | Yield (%) | Ref. |
|-------|----------|---------|------------|-----------|------|
| 1     | ZrO₂ (17%)/Ga₂O₃ (4%)/MCM-41 | CH₃CN | 120 | 91 | (30) |
| 2     | Ammonium chloride (200 mol%) | CH₃OH | 240 | 66 | (31) |
| 3     | SbCl₅/SiO₂ (2.5 mol%) | CH₃OH | 60 | 92 | (32) |
| 4     | Sulfamic acid (80 mol%) | CH₃OH | 300 | 95 | (14) |
| 5     | Montmorillonite K-10 (10% w/w) | H₂O | 300 | 70 | (22) |
| 6     | Polyaniline sulfate (5% w/w) | C₂H₅OH | 42 | 90 | (25) |
| 7     | Zirconium tetrachloride (5 mol%) | CH₃OH | 240 | 98 | (33) |
| 8     | SnCl₂/SiO₂ (5 mol%) | CH₃OH | 60 | 94 | (34) |
| 9     | Gallium triflate (1 mol%) | C₂H₅OH | 240 | 90 | (35) |
| 10    | (NH₄)H₂PW₁₂O₄₀ | ClCH₂CH₂Cl | 30 | 90 | (36) |
| 11    | Fe₃O₄@SiO₂/Schiff base/Co(II) (0.03 g) | EtOH/H₂O (3/1) | 40 | 94 | This work |
3.2. General procedure for Schiff base complex of metal ions functionalized magnetite and silica nanoparticles

According to a modified Stober method (40), to the solution of 3-aminopropyl (trimethoxy) silane (1 mmol, 0.176 g) in 25 mL ethanol was added dropwise the stoichiometric amount of salicylaldehyde (1 mmol, 0.122 g) in ethanol (25 mL). The yellow obtained solution, due to imine formation, was stirred at room temperature for 6 h. The resulting Schiff base ligand, as the bright yellow precipitate, was separated by filtration and washed with ethanol (5 mL), and then dried in vacuum. The crude product was recrystallized from ethanol to obtain the pure product in 98% yield (0.271 g). Then, to the solution of the Schiff base ligand (2 mmol) in ethanol (25 mL) was added metal acetates (1 mmol) and the mixture was refluxed and the progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the complex formation, the crude product as a colored solid was filtered and washed with ethanol (2 mL × 5 mL). Then the pure product was obtained by recrystallization from ethanol. Then, Fe₃O₄@SiO₂ (2 g) was added to the solution of Schiff complex of metal ions...
(1 mmol) in ethanol (10 mL) and the resultant mixture was under reflux for 12 h. The solvent was removed and the resulting solid was dried at 80°C overnight. The product was washed with ethanol and water to remove unreacted species and dried at 80°C for 6 h (Scheme 2).

3.3. General procedure for the preparation of quinoxalines

To a mixture of 1,2-diamine (1 mmol), 1,2-diketone (1 mmol), and 0.03 g of Fe₂O₄@SiO₂/Schiff base/Co (II) in a 50 mL round-bottomed flask, EtOH/H₂O [12 mL, 3/1 (v/v)] was added, and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate was added to the mixture and the insoluble catalyst was separated by magnetic field. The filtrate was dried on anhydrous sodium sulfate and concentrated with a rotary evaporator under reduced pressure to give the pure product.

3.4. Spectral data of new compounds

Yellow oil; ¹H-NMR (250 MHz, CDCl₃): δ = 1.45 (t, 6H, CH₃), 3.07 (q, 4H, CH₂), 7.49 (d, 1H, CH), 7.78 (s, 1H, CH), 7.96 (d, 1H, CH). ¹³C-NMR (63 MHz, CDCl₃); δ = 12.3, 21.3, 27.9, 27.9, 127.0, 127.6, 130.5, 138.5, 155.9, 156.7. Anal. Found (%): C, 77.32; H, 7.85; N, 13.78. Calc. for C₁₁H₁₄N₂ (%): C, 78.01; H, 7.99; N, 13.99 (Table 3, entry 10).

Pale yellow oil, ¹H-NMR (250 MHz, CDCl₃): δ = 1.37 (t, 6H, CH₃), 2.55 (s, 3H, CH₃), 3.06 (m, 4H, CH₂), 7.49 (d, 1H, CH), 7.78 (s, 1H, CH), 7.96 (d, 1H, CH). ¹³C-NMR (63 MHz, CDCl₃); δ = 12.2, 12.3, 21.3, 27.9, 27.9, 127.0, 127.6, 130.5, 138.5, 155.9, 156.7. Anal. Found (%): C, 77.32; H, 7.85; N, 13.78. Calc. for C₁₁H₁₄N₂ (%): C, 78.01; H, 7.99; N, 13.99 (Table 3, entry 3).

Acknowledgment

Authors gratefully acknowledge the financial support of this work by the research council of University of Shiraz.

References

(1) Badran, M.M.; Moneer, A.A.; Refaat, H.M.; El-Malah, A.A. J. Chin. Chem. Soc. 2007, 54, 469–478.
(2) Sakata, G.; Makino, K.; Karasawa, Y. Heterocycles. 1988, 27, 2481–2515.
(3) Hadzeldine, S.T.; Polin, L.; Kushner, J.; White, K.; Bourgeois, N.M.; Crantz, B.; Palomino, E.; Corbett, T.H.; Horwitz, J.P. J. Med. Chem. 2002, 45, 3130–3137.
(4) Sarges, R.; Howard, H.; Browne, R.R.C.; Label, L.A.; Seymour, P.A. J. Med. Chem. 1990, 33, 2240–2254.
(5) Kim, Y.B.; Kim, Y.H.; Park, J.Y.; Kim, S.K. Bioorg. Med. Chem. Lett. 2004, 14, 541–544.
(6) Brock, E.D.; Lewis, D.M.; Youssaf, T.I.; Harper, H.H. The Procter and Gamble Company, USA. World Patent WO9951688, 1999.
(7) Dailey, S.; Feast, J.W.; Peace, R.J.; Sage, I.C.; Till, S.; Wood, E.L. J. Mater. Chem. 2001, 11, 2238–2243.
(8) Sascha, O.; Rudiger, F. Synlett. 2004, 6, 1509–1512.
(9) Crossley, M.J.; Johnston, L.A. Chem. Commun. 2002, 9, 1122–1123.
(10) Hui, X.; Desrivot, J.; Bories, C.; Loiseau, P.M.; Franck, X.; Hocquemiller, R.; Fidadere, B. Bioorg. Med. Chem. Lett. 2006, 16, 815–820.
(11) Brown, D.J. Quinoxalines Supplement II, the Chemistry of Heterocyclic Compounds; Wiley: Hoboken, NJ, 2004; pp 1–92.
(12) Antoniotti, S.; Donach, E. Tetrahedron. Lett. 2002, 43, 3971–3973.
(13) More, S.V.; Sastry, M.N.V.; Yao, C.F. J. Organomet. Chem. 2006, 6, 89–95.
(14) Darabi, H.R.; Mohandessi, S.; Aghapoor, K.; Mohsenzadeh, F. Catal. Commun. 2007, 8, 389–392.
(15) Zhao, Z.; Wisnoski, D.D.; Wolkenberg, S.E.; Leister, W.H.; Wang, Y.; Lindsley, C.W. Tetrahedron. Lett. 2004, 45, 4873–4876.
(16) Venugopal, D.; Subrahmanyam, M. Catal. Commun. 2001, 2, 219–224.
(17) Venkatesh, C.; Singh, B.; Mahata, P.K.; Junjappa, H. Org. Lett. 2005, 7, 2169–2172.
(18) Heravi, M.M.; Bakhtiari, K.; Bamoharram, F.F.; Tehrani, M.H. Monatsh. Chem. 2007, 138, 465–467.
(19) Heravi, M.M.; Tehre, S.; Bakhtiari, K.; Osokooie, H.A. Catal. Commun. 2007, 8, 211–214.
(20) Hasaninejad, A.; Zare, A.; Mohammadizadeh, M.R.; Shekouhy, M. Green. Chem. Lett. Rev. 2010, 3, 143–148.
(21) Hasaninejad, A.; Zare, A.; Mohammadizadeh, M.R.; Karami, Z. J. Iran. Chem. Soc. 2009, 6, 153–158.
(22) Huang, T.; Wang, R.; Shi, L.; Lu, X. Catal. Commun. 2008, 9, 1143–1147.
(23) Heravi, M.M.; Tehrani, M.H.; Bakhtiari, K.; Osokooie, H.A. Catal. Commun. 2007, 8, 1341–1344.
(24) Robinson, R.S.; Taylor, R.J.K. Synlett. 2005, 6, 1003–1005.
(25) Srinivas, C.; Kumar, C.N.S.S.P.; Rao, V.J.; Palaniappan, S. J. Mol. Catal. A: Chem. 2007, 265, 227–230.
(26) Wang, L.; Liu, J.; Tian, H.; Qian, C. Synth. Commun. 2004, 34, 1349–1357.
(27) Hasaninejad, A.; Zare, A.; Zolfigol, M.A.; Shekouhy, M. Synth. Commun. 2009, 39, 569–579.
(28) Heravi, M.M.; Bakhtiari, K.; Tehrani, M.H.; Javadi, N.M.; Osokooie, H.A. ARKIVOC. 2006, xvi, 16–22.
(29) Raw, S.A.; Wilfred, C.D.; Taylor, R.J.K. Org. Biomol. Chem. 2004, 2, 788–796.
(30) Ajaikumar, S.; Pandurangan, A. Appl. Catal. A: Gen. 2009, 357, 184–192.
(31) Darabi, H.R.; Tahoori, F.; Aghapoor, K.; Taala, F.; Mohsenzadeh, F. J. Braz. Chem. Soc. 2008, 1646–1652.
(32) Darabi, H.R.; Aghapoor, K.; Mohsenzadeh, F.; Taala, F.; Asadollahnejad, N.; Badiei, A. *Catal. Lett.* **2009**, *133*, 84–89.

(33) Aghapoor, K.; Darabi, H.R.; Mohsenzadeh, F.; Bala- var, Y.; Daneshyar, H. *Transit. Metal. Chem.* **2010**, *35*, 49–53.

(34) Darabi, H.R.; Aghapoor, K.; Mohsenzadeh, F.; Jalali, M.R.; Talebian, Sh.; Ebadi-Nia, L.; Khatemifar, E.; Aghae, A. *Bull. Korean. Chem. Soc.* **2011**, *32*, 213–218.

(35) Cai, J.J.; Zou, J.P.; Pan, X.Q.; Zhang, W. *Tetrahedron. Lett.* **2008**, *49*, 7386–7390.

(36) KunKuma, V.; Prabhavathi Devi, B.L.A.; Giri, B.Y.; Prasad, R.B.; Sai Prasad, P.S. *Eur. J. Chem.* **2011**, *2*, 495–498.

(37) Deng, Y.H.; Qi, D.W.; Deng, C.H.; Zhang, X.M.; Zhao, D.Y. *J. Am. Chem. Soc.* **2008**, *130*, 28–29.

(38) Xu, X.Q.; Deng, C.H.; Gao, M.X.; Yu, W.J.; Yang, P. Y.; Zhang, X.M. *Adv. Mater.* **2006**, *18*, 3289–3293.

(39) Shao, D.D.; Xu, K.K.; Song, X.J.; Hu, J.H.; Yang, W. L.; Wang, C.C. *J. Colloid. Interface. Sci.* **2009**, *336*, 526–532.

(40) Esmaeilpour, M.; Sardarian, A.R.; Javidi, J. *Appl. Catal. A. Gen.* **2012**, *445–446*, 359–367.

(41) Aly, M.M.; Al-Shatti, N.I. *Transition. Met. Chem.* **1998**, *23*, 361–369.

(42) Mason, T.J. *Chem. Soc. Trans.* **1893**, *63*, 1284–1293.

(43) Dobrodei, A.N.; El’tsov, A.V. *J. Gen. Chem.* **1999**, *69*, 1658–1668.

(44) Ghsoh, B.; Mukherjee, S.; Jha, S. *Synthesis* **1985**, *3*, 313–321.

(45) Niknam, K.H.; Saberi, D.; Mohaghehnejad, M. *Molecules* **2009**, *14*, 1915–1926.