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Synthesis of quinoxalines promoted by eco-friendly nano-kaoline/BF_3/Fe_3O_4 nano-catalyst under grinding condition

B.F. Mirjalili* and **M. Dehghani Tafti**

Department of Chemistry, College of Science, Yazd University, Yazd, P.O. Box. 89195-741, Iran.

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KEYWORDS
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Magnetic catalyst;
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Abstract. Nano-kaoline/BF_3/Fe_3O_4 as an eco-friendly nanocatalyst was used for quinoxaline preparation *via* condensation of 1,2-phenylene diamines and 1,2-diketones. This simple protocol proceeds under grinding condition and has many advantages such as easy workup and high product yields.

1. Introduction

Quinoxalines (benzopyrazines) as an important class of heterocyclic compounds have interesting properties such as low melting point and water misciblility [1]. These compounds have been applied in electron luminescent materials [2], fluorescent dyes [3], chemically controllable switches [4], organic semiconductors [5], building blocks for the synthesis of anion receptor [6], dehydroannulenes [7], and DNA cleaving agents [8]. Quinoxalines play an important role in the design of a number of antibiotics such as echinomycin [9], actinomycin [10], and levomycin [10]. These compounds inhibit the growth of gram-positive bacteria and are active against various transplantable tumors [9,10]. In addition, quinoxalines have biological activities such as antiviral [11], anticancer [12], antibacterial [13], antifungal [14], antidepressant [15], anti-HIV [16], and anti-inflammatory [17]. The best reported method for the synthesis of quinoxaline is the reaction of 1,2-diamine with a 1,2-dicarbonyl compound in the presence of an acid catalyst, e.g., $ZrCl_4$ [18], NZ-PSA [19], sodium dodecyl sulfate [20], NH_2SO_3H [21], $H_3PW_{12}O_{40}$/MCM-41 [22], PEG-400 [23], polyaniline-sulfate salt [24], nano-TiO_2 [25], and silic-gel [26].

Kaoline is a clay mineral mainly consisting of hydrated aluminum silicate. Its structure can be described as one tetrahedral sheet (SiO_4) linked through oxygen atoms to one octahedral sheet of alumina octahedral (AlO_6) [27] and is usually represented by the formula $Al_2Si_2O_5(OH)_4$ or $Al_2O_3.2SiO_2.2H_2O$ [28,29]. It is a very cheap and abundant raw material and has a variety of industrial applications, e.g., in paper coating, plastic and rubber industry, ceramic, tile, and sanitary ware [30]. In continuing our previous works [31,32], in this work, nano-kaoline/BF_3/Fe_3O_4 as an efficient supported Lewis acid catalyst was synthesized and applied for synthesis of quinoxaline derivatives.

2. Experimental

2.1. Materials and methods

All required compounds were purchased from Merck, Aldrich, and Fluka chemical companies and used

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*. *Corresponding author. Tel.: +98 353 1232672; Fax: +98 38210644; E-mail address: fmirjalili@yazd.ac.ir (B.F. Mirjalili)*

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without any additional purification. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus. FT-IR spectra were run on a Bruker, Equinox 55 spectrometer. A Bruker (DRX-400 Avance) NMR was used to record the ^{1}H-NMR and ^{13}C-NMR spectra. X-Ray Diffraction (XRD) spectrum was obtained by a Philips Xpert MPD diffractometer equipped with a Cu Ka anode (λ = 1.5418 Å) in the 2θ range from 5 to 80°. Energy-Dispersive X-ray Spectroscopy (EDS) of kaoline/BF_3/Fe_3O_4 was done by phenom pro X. Field Emission Scanning Electron Microscopy (FESEM) and Transmission Electron Microscopy (TEM) images of catalyst were obtained on a Mira 3-XMU and Philips CM120 with a LaB6 cathode and accelerating voltage of 120 kV, respectively. XRF analysis was done with BRUKER, S4 EXPLORER instrument. VSM measurements were performed by using a vibrating sample magnetometer (Meghnatis Daghigh Kavir Co., Kashan Kavir, Iran). Brunauer–Emmett–Teller (BET) surface area analysis of catalyst was done with Micromeritics, Tristar II 3020 analyzer.

2.2. General procedure for synthesis of quinoxalines

A mixture of benzil (1mmol), 1,2-phenylendiamines (1 mmol), and nano-kaoline/BF_3/Fe_3O_4 (0.03 g) was grinded at room temperature. The progress of the reacion was monitored by TLC. After completion of the reaction, the mixture was dissolved in hot ethanol and the catalyst was separated by an external magnet. After cooling the residue mixture, the crystalline products appeared.

2.3. Preparation of nano-kaoline/BF_3

In a well-ventilated system, BF_3 (10 mL) was added dropwise to the mixture of nano-kaoline (10 g) in dichloromethane. The mixture was stirred for one hour at room temperature. The resulting suspension was filtered, washed with dichloromethane, and dried at room temperature.

2.4. Preparation of nano-kaoline/BF_3/Fe_3O_4

A mixture of nano-kaoline/BF_3 (1.58 g), nano-Fe_3O_4 (1.58 g), and dichloromethane (5 ml) was placed at ultrasonic condition for 40 minutes. The resulting magnetic particles were collected by external magnet, washed with dichloromethane, and dried at room temperature.

2.5. Selected spectral data

2, 3-Diphenylquinoxaline (**3a**): FTIR (ATR) $\bar{\nu}$/cm^{-1} 3057, 1479, 1442, 762, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 6H), 7.50 (m, 4H), 7.79 (dd, *J*= 6.3, 3.4, 2H), 8.01 (dd, *J*= 6.3, 3.6, 2H).

2, 3-Bis (4-flouro-phenyl) quinoxaline (**3b**): FT-IR (ATR) $\bar{\nu}$/cm^{-1} 3073, 1598, 1555, 1222, 837; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (m, 4H), 7.31 (m, 4H), 7.60 (dd, *J*= 6.4, 3.2, 2H), 7.96 (dd, *J* = 6.4, 3.2, 2H).

2, 3-Bis (4-flouro-phenyl) 6-methylquinoxaline (**3c**): FTIR (ATR) $\bar{\nu}$ /cm^{-1} 3056, 2927, 1620, 1599, 1509, 1346, 1218, 833; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.5 (s, 3H), 6.86 (m, 4H), 7.30 (m, 4H), 7.42 (dd, *J* = 8.6, 1.6, 1H), 7.74 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 1H).

2, 3-Bis (4-flouro-phenyl) 6-nitroquinoxaline (**3d**): FTIR (ATR) $\bar{\nu}$ / cm^{-1} 3083, 1664, 1595, 1509, 1398, 1227, 840; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (m, 4H), 7.38 (m, 4H), 8.09 (d, *J* = 9.2, 1H), 8.34 (d, *J* = 2.4, 1H), 8.87 (d, *J* = 2.4, 1H).

2, 3-Dimethyl-quinoxaline (**3e**): FTIR (ATR) $\bar{\nu}$ / cm^{-1} 2924, 1603, 1569, 1489, 1352, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (s, 6H), 7.77 (dd, *J*= 8.8, 2.5 Hz, 2H), 7.79 (dd, *J*= 8.8, 2.3, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 23.54, 30.09, 128.69, 129.21, 141.45, 153.85.

2, 3, 6-Trimethyl-quinoxaline (**3f**): FTIR (ATR) $\bar{\nu}$ / cm^{-1}2922, 1620, 1547, 1496, 1443, 1371, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.52 (s, 6H), 7.30 (dd, *J*= 8.3, 1.8 Hz, 1H), 7.54 (s, 1H), 7.65 (d, *J* = 8.4, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.96, 23.29, 23.39, 127.50, 128.04, 131.21, 139.27, 139.67, 141.32, 152.72, 153.59.

2, 3-Dimethyl-6-nitro-quinoxaline (**3g**): FTIR (ATR) $\bar{\nu}$ / cm^{-1} 2924, 1615, 1526, 1402, 1343, 1330, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (s, 3H), 2.60 (s, 3H), 7.92 (d, *J*= 9.2, 1H), 8.25 (d, *J*= 8.8, 1H), 8.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.72, 23.93, 122.75, 125.29, 130.34, 140.34, 144.13, 147.58, 156.69, 157.62.

2-Methyl-3-propyl-quinoxaline (**3h**): FTIR (ATR) $\bar{\nu}$ / cm^{-1} 3038, 2957, 2870, 1669, 1564, 1487, 1371, 766; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.63 (m, 2H), 2.57 (s, 3H), 2.78 (t, *J* = 8.0 Hz, 2H), 7.47 (m, 2H), 7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.54, 21.80, 23.18, 38.19, 128.66, 128.91, 129.06, 129.11, 141.26, 141.55, 153.50, 157.03.

2, 6-Dimethyl-3-propyl-quinoxaline (**3i**): FTIR (ATR) $\bar{\nu}$ / cm^{-1} 2961, 2872, 1621, 1564, 1495, 1458, 1375, 1327, 825; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.2, 3H), 1.67 (m, 2H), 2.36 (s, 3H), 2.57 (s, 3H), 2.76 (t, *J* = 8.0, 3H), 7.30 (m, 1H), 7.56 (m, 1H), 7.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.57, 21.916, 22.11, 23.12, 38.21, 127.94, 128.21, 131.39, 139.41, 139.72, 141.63, 152.55, 156.98.

2-Methyl-3-propyl-6-nitro-quinoxaline (**3j**): FTIR (ATR) $\bar{\nu}$ cm^{-1} / 3094, 2963, 1618, 1530, 1345, 1330, 823, 741; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.46, 21.14, 23.52, 38.08, 122.61, 125.46, 130.25, 140.35, 144.17, 147.48, 156.44, 160.68.

3. Results and discussion

Nano-kaoline/BF_3/Fe_3O_4 was synthesized via two-step

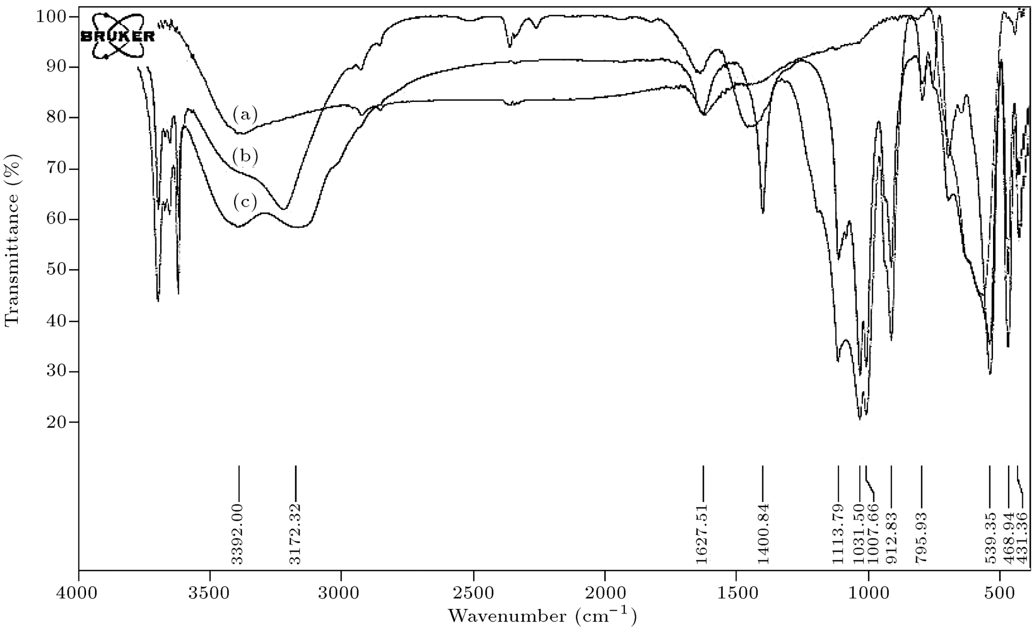
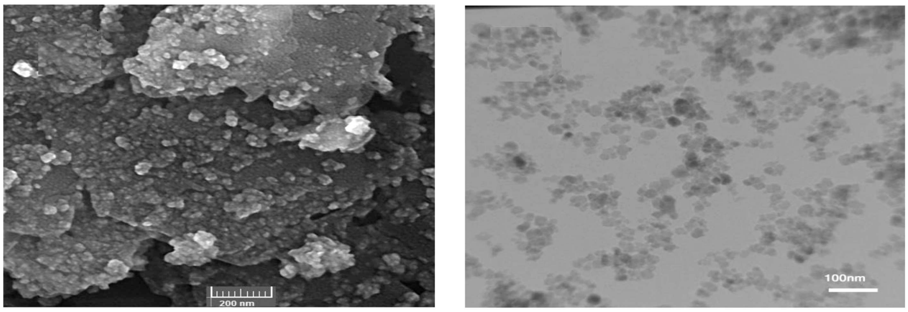


Figure 1. FT-IR spectra of (a) Fe_3O_4, (b) nano-kaoline/BF_3, and (c) nano-kaoline/BF_3/Fe_3O_4.



(a) (b)

Figure 2. (a) FESEM and (b) TEM image of nano-kaoline/BF_3/Fe_3O_4.

reaction. Firstly, nano-kaoline was reacted with BF_3. OEt_2 in dichloromethan to result in nano-kaoline/BF_3 as a fine white powder. Secondly, nano-kaoline/BF_3 was reacted with nano-Fe_3O_4 in dichloromethane under ultrasonic condition at room temperature to form nano-kaoline/BF_3/Fe_3O_4 as a brown magnetic powder.

For characterization of nano-kaoline/BF_3/Fe_3O_4, comparison of Fe_3O_4 and nano-kaoline/BF_3 with nano-kaoline/BF_3/Fe_3O_4 was performed by FT-IR (ATR) spectra (Figure 1). Fe/O, Al-O, Si-O, and OH stretching bands appeared in 539, 1031, 1007, and 3392 cm^{-1} in FT-IR spectrum of nano-kaoline/BF_3/Fe_3O_4, respectively.

The particle size of nano-kaoline/BF_3/Fe_3O_4 was investigated by Field Emission Scanning Electron Microscopy (FESEM) and Transmission Electron Microscopy (TEM), in which the dimensions of catalyst were obtained below 25 nm (Figure 2).

The percentage of each element in nanocatalyst was approved by EDS analysis data (Figure 3). The percentage of O, Fe, Si, and Al in nano-kaoline/BF_3/Fe_3O_4 was 44.79, 27.34, 12.13, and 11.97, respectively.

To determine the magnetic property of nanocatalyst, magnetic measurements were carried out using a Vibrating Sample Magnetometer (VSM). As shown in Figure 4, no hysteresis loop and no remanence were detected and the coercivity value was zero for all samples, suggesting typical superparamagnetic property at room temperature. According to VSM spectrum of the catalyst (Figure 4(b)), it was superparamagnetic and removable from reaction medium by an external magnet.

The X-Ray Diffraction (XRD) patterns of nano-kaoline/BF_3/Fe_3O_4 are shown in Figure 5. The values of 2θ and FWHM (Full Width at Half Maximum) are shown in Table 1. According to XRD pattern, the six signals in 2θ equal to 12.52, 20.45, 21.48, 25.05, 26.85,

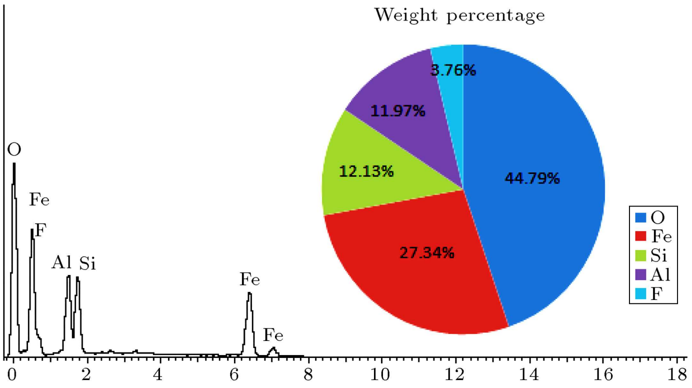


Figure 3. EDX spectra of nano-kaoline/BF_3/Fe_3O_4.

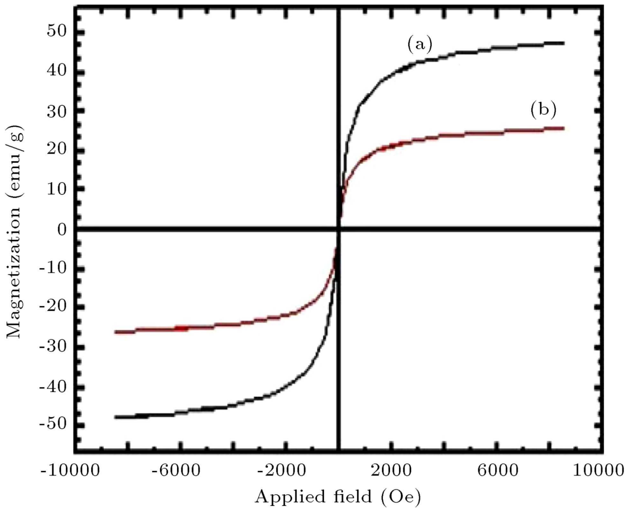


Figure 4. VSM spectra of (a) Fe_3O_4 and (b) nano-kaoline/BF_3/Fe_3O_4.

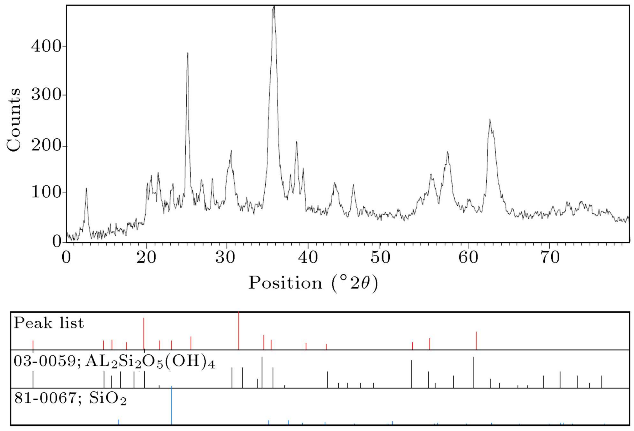


Figure 5. XRD pattern of nano-kaoline/BF_3/Fe_3O_4.

and 45.67 show the existence of kaoline. Also, signals in 2θ at 30, 35, 43, and 63 are related to Fe_3O_4.

The thermal stability of nano-kaoline/BF_3/Fe_3O_4 was investigated by Thermo-Gravimetric Analysis (TGA) in the temperature range of 50-400°C (Figure 6). According to TGA thermograph, at 100°C, the catalyst lost 1% of its weight due to evaporation of water. This catalyst is almost stable up to 100°C and is suitable for promotion of some organic reactions bellow 100°C.

The XRF analyses of nano-kaoline/BF_3/Fe_3O_4, pure H_3BO_3, and NaF were done. The amount of Count Per Second (KCPS) in kilograms and the amounts of Boron (B) and Fluorine (F) in percent are recorded in Table 2. The KCPS of 2.5 for H_3BO_3 is related to 17.7% of B; thus, KCPS of 0.3 for catalyst is related to 2.12% of B. Similar correlation is established for fluorine in NaF and nano-kaoline/BF_3/Fe_3O_4. By using amounts of B and F in catalyst in percent and their atomic masses, the ratio of B:F was obtained equal to 3:1.

The specific surface area of catalyst was measured by Brunauer-Emmett-Teller (BET) theory. Single point surface area at $p/p_0 = 0.990$ was 5.5355 m^2/g, mean pore diameter 11.934 nm, and total pore volume

Table 1. Nano-kaoline/BF_3/Fe_3O_4 reflexes in XRD diffractogram.

Pos. [°2Th.]	12.5268	20.4502	21.4826	23.1633	25.0542	26.8537	28.1639	30.3915
FWHM [°2Th.]	0.3149	0.7872	0.4723	0.3149	0.3149	0.4723	0.2362	0.7872
Pos. [°2Th.]	35.7518	38.6110	39.4276	43.4262	45.6732	55.4050	57.3505	62.5893
FWHM [°2Th.]	0.3149	0.3149	0.2362	0.7872	0.4723	0.6298	0.9446	0.4800

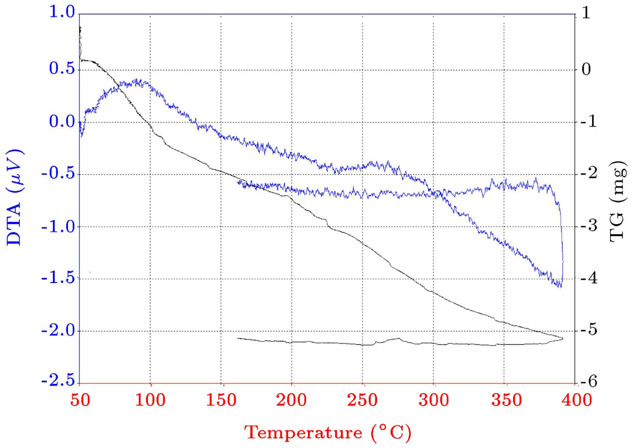


Figure 6. TGA pattern of nano-kaoline/BF_3/Fe_3O_4.

Table 2. XRF analysis data for nano-kaoline/BF_3/Fe_3O_4

Sample	**H_3BO_3**	**NaF**	**Nano-kaoline /BF_3/ Fe_3O_4**	
KCPS	2.5 H_3BO_3	40.7 NaF	0.3 (B)	1.3 (F)
Amount of element (%)	17.7 (B)	45 (F)	2.12 (B)	1.43 (F)

0.1651 cm^3g^{-1}. The N_2 adsorption isotherm of catalyst is depicted in Figure 7.

According to the above-mentioned data, we have proposed a structure for nano-kaoline/BF_3/Fe_3O_4 (Figure 8).

In order to determine the optimum reaction conditions and to achieve the highest yields, the reaction of benzil with 1,2-phenylenediamine was examined as a model reaction under various conditions and compared with other reported catalysts (Table 3).

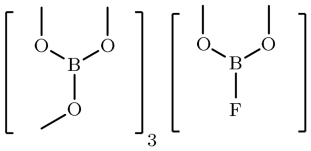


Figure 8. The Proposed structure for nano-kaoline/BF_3/Fe_3O_4.

The best reaction condition was solvent-free grinding condition at room temperature using 0.03 g of nano-kaoline/BF_3/Fe_3O_4 for 1 mmol of substrates.

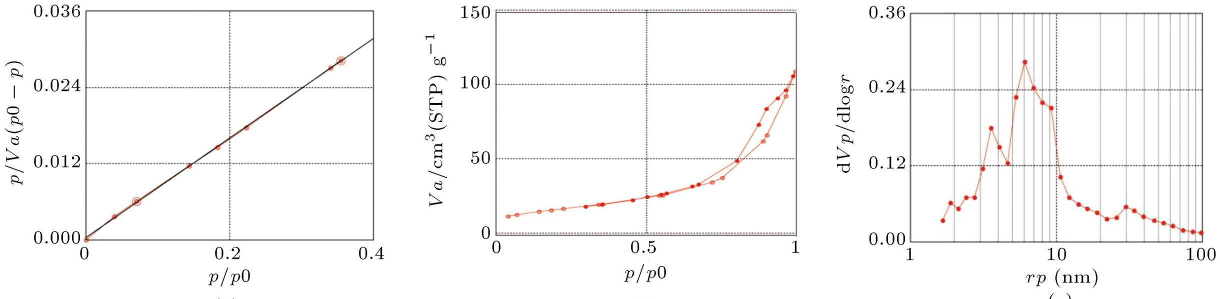
According to the obtained data in Table 3, some catalysts such as CAN or $H_3PW_{12}O_{40}$/MCM-41 are very fast, but they are toxic or expensive and need solvent for promotion of reaction (Table 3, entries 8 and 9). Silica-Gel needs high temperature for quinoxaline formation, but nano-kaoline/BF_3/Fe_3O_4 can catalyze the reaction at room temperature in short time. Among all catalysts mentioned in Table 3, only nano-kaoline/BF_3/Fe_3O_4 is magnetic catalyst with commercial kaoline source.

Finally, according to the obtained best condition, several quinoxaline derivatives were synthesized, of which the resulting data are shown in Table 4.

All compounds were identified by physical and spectroscopic data (m.p., FT-IR and ^1H NMR). In FT-IR spectrum of quinoxalines, C=N stretching frequency band appeared around 1669 cm^{-1}. In the ^1H NMR spectra, signals around $\delta = 7.76 - 7.82$ ppm were assigned to the protons of the aromatic rings.

The examination of nano-kaoline/BF_3/Fe_3O_4 reusability was also performed. After each run, hot ethanol was added to reaction medium and the catalyst was isolated by external magnet, washed with acetone, dried, and reused (Table 3, entries 2 and 3). This catalyst was reusable, although a gradual decline in activity was observed.

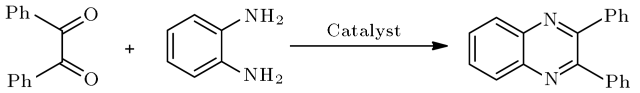
The applicability of the presented method for large-scale preparations was examined. We condensed 10 mmol of 1,2-phenylenediamine and 10 mmol of benzil in the presence of 0.3 g of nano-kaoline/BF_3/Fe_3O_4 under grinding conditions at room temperature, which gave 2,3-diphenylquinoxaline in 95% yield.



(a) (b) (c)

Figure 7. (a) BET (Brunauer-Emmett-Teller), (b) adsorption/desorption isotherm, and (c) BJH (Barrett-Joyner-Halenda) plots of nano-kaoline/BF_3/Fe_3O_4.

Table 3. The synthesis of 2,3-diphenylquinoxaline under various conditions[a]

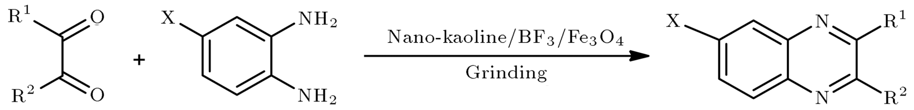


Entry	Catalyst, mol% (g)	Condition	Yield[b] [Ref.]
1	Nano-kaoline/BF_3/Fe_3O_4 (0.03)	Solvent-free, r.t, 20 min	98
2	Nano-kaoline/BF_3/Fe_3O_4 (0.03), 2nd run	Solvent-free, r.t, 20 min	90
3	Nano-kaoline/BF_3/Fe_3O_4, (0.03), 3rd run	Solvent-free, r.t, 20 min	88
4	$ZrCl_4$, 5	MeOH, r.t, 5 min	100 [18]
5	NZ-PSA (0.01)	Water, r.t, 10 min	98 [19]
6	Sodium dodecyl sulfate, 15	Water, r.t, 2 h	95 [20]
7	NH_2SO_3H, 5	CH_2Cl_2, r.t, 6 h	92 [21]
8	$H_3PW_{12}O_{40}$/MCM-41, 10%w	EtOH, r.t, 0.25 min	99 [22]
9	CAN, 15	PEG-400, 120°C, 3 min	96 [23]
10	Polyanilinesulfate salt, 5%w	DCE, r.t, 20 min	95 [24]
11	Nano-TiO_2, 2.5	DCE, 25°C, 15 min	99 [25]
12	Silica-Gel (1)	Grinding, 100°C, 45 min	94 [26]

[a]The ratio of benzil (mmol) to 1,2-phenylendiamine (mmol) is 1:1;

[b]Isolated yield.

Table 4. Preparation of quinoxalines in the presence of nano-kaoline/BF_3/Fe_3O_4 under grinding condition[a]



(1) (2) (3_{a-j})

Prod.	*X*	*R*^{1}	*R*^{2}	Time(min)	Yield (%)[b]	M.p. (°C) [Ref.]
3a	H	Ph	Ph	20	98	126-128 [33]
3b	H	4-F-C_6H_4	4-F-C_6H_4	10	95	135-137 [33]
3c	CH_3	4-F-C_6H_4	4-F-C_6H_4	35	90	165-167 [33]
3d	NO_2	4-F-C_6H_4	4-F-C_6H_4	60	80	174-176 [33]
3e	H	CH_3	CH_3	45	69	Oil [34]
3f	CH_3	CH_3	CH_3	40	74	Oil [34]
3g	NO_2	CH_3	CH_3	75	60	Oil [34]
3h	H	CH_3	$CH_2CH_2CH_3$	45	80	Oil [34]
3i	CH_3	CH_3	$CH_2CH_2CH_3$	30	86	Oil [34]
3j	NO_2	CH_3	$CH_2CH_2CH_3$	30	60	Oil [34]
3k	H	4-OMeC_6H_4	4-OMeC_6H_4	60	79	151-152 [35]
3l	CH_3	4-OMeC_6H_4	4-OMeC_6H_4	60	82	126-128 [35]

[a] The ratio of α-diketone (mmol), 1,2-phenylendiamine (mmol), and nano-kaoline/BF_3/Fe_3O_4 (g) is 1:1:1:0.03;

[b] Isolated yield.

4. Conclusions

In summary, the synthesis of quinoxaline derivatives in the presence of nano-kaoline/BF_3/Fe_3O_4 under grinding condition has many advantages such as being solvent-free; easy work up; and good to excellent yields using non-toxic, inexpensive, and reusable catalyst.

Acknowledgements

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Biographies

Bi Bi Fatemeh Mirjalili was born in Yazd, Iran, in 1961. She obtained a BS degree in Chemistry from Alzahra University, Tehran, Iran, in 1986, MS degree in Organic Chemistry from Tarbiat Moalem University, Tehran, Iran, in 1990, and PhD degree in Organic Chemistry from Sharif University of Technology, Tehran, Iran, in 2000. She has been professor at Yazd University, Yazd, Iran, since 2010.

Marzieh Dehghani Tafti was born in Yazd, Iran, in 1990. She obtained her BS and MS degrees in Chemistry and Organic Chemistry, in 2014 and 2016, respectively, from Yazd University, Yazd, Iran.