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$ZrOCl_2 \cdot 8H_2O$ in water: An efficient catalyst for rapid one-pot synthesis of pyridopyrazines, pyrazines and 2,3-disubstituted quinoxalines

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ABSTRACT

Zirconium(IV) oxide chloride was found to be a rapid and efficient catalyst for the synthesis of pyrazines and 2,3-disubstituted quinoxalines in water. A variety of pyridopyrazine and 2,3-disubstituted quinoxaline derivatives are readily prepared in high yields under green conditions by cyclocondensation of the desired 1,2-diamine and 1,2-diketone using a catalytic amount of zirconium(IV) oxide chloride in water. Less active diamines, such as 2,3- and 3,4-diaminopyridines took part in this protocol to provide the desired products in good to excellent yields.

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1. Introduction

Quinoxaline and pyrazine derivatives represent an imperative class of nitrogen-containing heterocycles as they have received considerable interest from pharmaceutical to academic and industrial perspectives. For example, drug formulations with the core of quinoxaline, such as Lamprene, are currently available and they are privileged structures in combinatorial drug discovery. Besides their interesting therapeutic properties, such as antiviral, antibacterial, anti-inflammatory, and antiprotozoal and as kinase inhibitors [1,2], they have also been evaluated as anticancer, anthelmintic, antifungal, and insecticidal agents [3]. The quinoxaline nucleus is a part of several antibiotics, such as echinomycin, levomycin, and actinomycin that are known to inhibit the growth of Gram-positive bacteria and are active against various transplantable tumours [4,5]. Furthermore, they have found applications as dyes, electroluminescent materials, organic semiconductors, cavitands, chemically controllable switches, and DNA cleaving agents [6–8]. In this regards, various strategies have been introduced for the synthesis of these scaffolds, which include condensation of arene-1,2-diamines with 1,2-ketones (I_2, DMSO; I_2, MeCN; montmorillonite K-10; PEG-400; solid phase); CAN; MeOH–AcOH (9:1); Ac_2O, reflux; carbon-doped MoO_3–TiO_2 (CMT); *p*-toluene sulfonic acid (PTSA) as Brønsted acid catalyst in aqueous sodium *p*-toluene sulfonate (NaPTS) solution (Brønsted acid hydrotrope-combined catalyst (BAHC); lead (II) bromide; lithium chloride), oxidative cyclization of α-hydroxy ketones with 1,2-diamines (MnO_2; 1 mol% MnO_2, microwaves; $Pd(OAc)_2$; MnO_2–$NaBH_4$; PEG-400), cyclization–oxidation of phenacyl bromides with 1,2-diamines ($HClO_4$–silica gel), and oxidative coupling of epoxides with ene-1,2-diamines [bismuth powder, $Cu(OTf)_2$] [9–23]. However, many of these methods suffer from several drawbacks such as the use of strong oxidizing agents and expensive metal catalysts, and also the yields are far from satisfactory. Therefore, the development of a simple, convenient, and general approach would certainly be

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useful in generating combinatorial libraries for drug discovery.

Over the past decade, zirconium compounds have been found to play an ever-increasing role in organic synthesis, which has been recognized by a number of excellent review articles and books covering various aspects of zirconium compounds as the catalysts or reagents in synthetic organic chemistry [24,25].

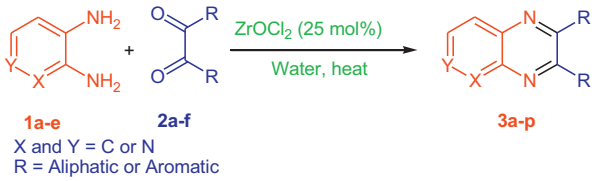
Herein, we set out to explore a new green synthetic method for the synthesis of 2,3-disubstituted quinoxalines, pyrazines and pyridopyrazines via zirconium(IV) oxide chloride-catalyzed condensation of related 1,2-diamines and 1,2-dicarbonyl compounds in water.

A survey of the literature shows that there are not many reports on the synthesis of pyridopyrazine derivatives [15]. The most convenient method for the synthesis of these compounds is the reaction of 2,3- and 3,4-diaminopyridines with different diketones. The problem is that these diaminopyridines are almost unreactive toward diketones in normal conditions. Herein, our contribution is intended to extend the scope of available methods for the synthesis of pyridopyrazines, pyrazines and 2,3-disubstituted quinoxalines, and to describe the application of a new transition metal-based catalyst in their synthesis.

2. Result and discussion

In continuation of our efforts in applying metal oxides in organic synthesis [26,27], we tried $ZrOCl_2{\cdot}8H_2O$-catalyzed condensation reaction of 1,2-diamines and 1,2-diketones for the preparation of the corresponding pyridopyrazines, pyrazines, and 2,3-disubstituted quinoxalines (Scheme 1).

In this regard, we initially attempted the condensation of 2,3-diaminopyridine (**1a**) and benzil (**2a**, PhCOCOPh) as a model reaction under various reaction conditions. The optimization of the reaction conditions

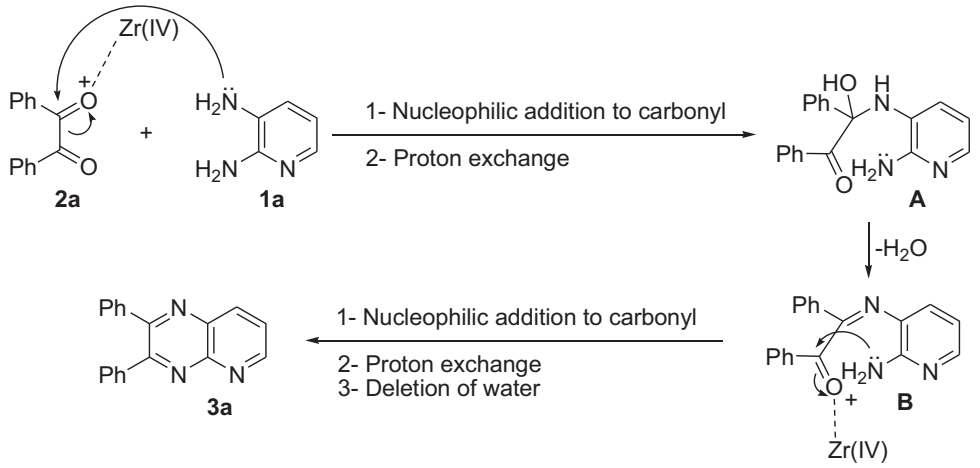


Scheme 1. General route for the synthesis of desired heterocycles.

showed that excellent conversion of the starting material into the product was achieved in 2 h by using $ZrOCl_2{\cdot}8H_2O$ as a catalyst under refluxing water. In a typical procedure, the reaction of 2,3-diaminopyridine **1a** (1.0 mmol, 1.0 equiv) and benzil **2a** (1 mmol, 1 equiv) in the presence of $ZrOCl_2{\cdot}8H_2O$ (25 mol%) under refluxing water for 2 h afforded compound **3a** in 92% yield (Table 1, entry 1). The proposed mechanism for the synthesis of **3a** in the presence of $ZrOCl_2$ is shown in Scheme 2.

In order to show the generality and scope of this new protocol, a variety of 1,2-diamines and 1,2-diketones were examined. The results are summarized in Table 1 (entries 1–16). Most of the reactions proceeded very cleanly and no undesirable side products were observed. The results showed that besides electron-rich diamines, such as ethylene dimine and 1,2-phenylene diamine, the electron-deficient ones, such as 2,3-diaminopyridine and 3,4-diaminopyridine can provide the desired products in good to excellent yields (Table 1, entries 1–15). Furthermore, our protocol proved to be a good route for the synthesis of multifunctional and highly conjugated pyrazines (Table 1, entries 4, 8, 9, 11 and 12).

Finally, we investigated the recycling of reaction media in a subsequent reaction, for example, in the reaction of *o*-phenylenediamine (**1e**) with benzil (**2a**), and $ZrOCl_2$ was reused five times without any appreciable loss of activity.



Scheme 2. Proposed mechanism for the formation of **3a** from starting materials in the presence of $ZrOCl_2$.

Table 1
Synthesis of desired heterocyclic derivatives catalyzed by $ZrOCl_2 \cdot 8H_2O$ in water.

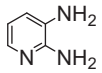
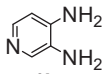
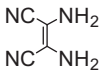
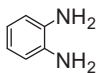
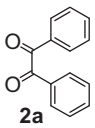
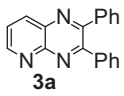
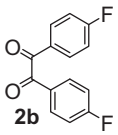
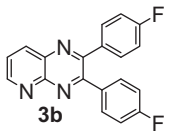
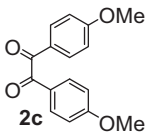
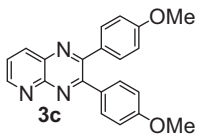
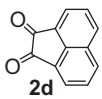
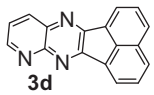
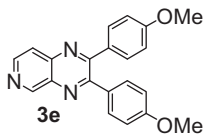
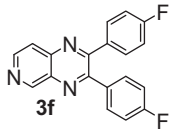
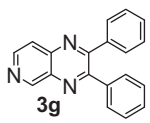
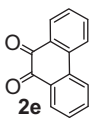
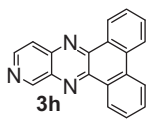
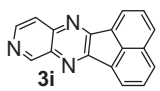
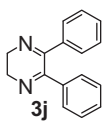
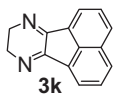
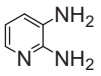
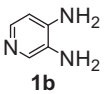
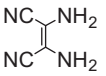
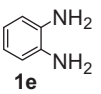
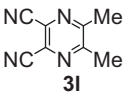
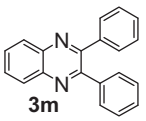
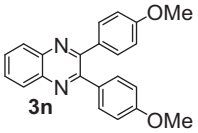
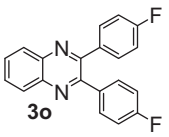
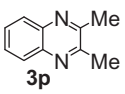
	 1a	 1b	 1c	 1d	 1e
Entry	Diamine 1	Dicarbonyl 2	Product 3[a]	Time (h)	Yield (%)[b]
1	**1a**	 **2a**	 **3a**	2	92
2	**1a**	 **2b**	 **3b**	2	93
3	**1a**	 **2c**	 **3c**	3	88
4	**1a**	 **2d**	 **3d**	2.5	85
5	**1b**	**2c**	 **3e**	3	86
6	**1b**	**2b**	 **3f**	2.5	88
7	**1b**	**2a**	 **3g**	2.5	91
8	**1b**	 **2e**	 **3h**	2.5	87
9	**1b**	**2d**	 **3i**	2.5	86
10	**1c**	**2a**	 **3j**	1	95
11	**1c**	**2d**	 **3k**	1	91

Table 1 (*Continued*)

	 1a	 1b	 1c	 1d	 1e	
Entry	Diamine 1	Dicarbonyl 2	Product 3[a]	Time (h)	Yield (%)[b]	
12	**1d**	 **2f**	 **3l**	1	90	
13	**1e**	**2a**	 **3m**	1	97	
14	**1e**	**2c**	 **3n**	2	92	
15	**1e**	**2b**	 **3o**	1	95	
16	**1e**	**2f**	 **3p**	0.5	98	

[a] All reactions were run under the following conditions: 1,2-diamine **1** (1 mmol, 1 equiv), diketone **2** (1.0 mmol, 1 equiv) and catalyst (25 mol%) in refluxing water (2 mL) were heated for appropriate times.
[b] Isolated yield.

3. Conclusions

In summary, we successfully developed a simple, efficient and eco-friendly method for the synthesis of pyridopyrazines, pyrazines and quinoxalines from 1,2-diamines and various 1,2-diketones using the cheap and readily available $ZrOCl_2{\cdot}8H_2O$ catalyst. Not only the electron-rich diamines (ethylene dimine and 1,2-phenylene diamine), but also the electron-deficient ones (2,3-diaminopyridine and 3,4-diaminopyridine), provided the desired products in good to excellent yields in water as a green solvent.

4. Experimental method

4.1. General

Commercial grade of 1,2-phenylenediamine, diaminopyridines, 1,2-dicarbonyl compounds and zirconium(IV) oxide chloride were purchased from Sigma–Aldrich, Merck and Acros organics companies. The solvents were of analytical grade and used as received. Silica gel (Merck, grade 9385, 230–400 mesh, 60 A°) for column chromatography was used as received. All other reagents were purchased from Merck and used as received unless otherwise noted. The course of the synthesis and purity of the products were followed by TLC on silica gel plates (Merck, silica gel 60 F_{254}, ready to use), using dichloromethane:methanol (9:1) or *n*-hexane:ethyl acetate (1:3) as eluents. The eluent for column chromatography was the same as for TLC.

The melting points were recorded using a Buchi B540 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at room temperature on a Bruker AC 300, 400 or 500 MHz spectrometers using $CDCl_3$ or DMSO-d_6 as the NMR solvents. ^1H NMR spectra are referenced to tetramethylsilane (0.00 ppm) and ^{13}C NMR spectra are referenced from the solvent central peak (for example, 77.23 ppm for $CDCl_3$). Chemical shifts are given in ppm. IR spectra were taken as KBr pellets using a Jasco 4200 FT-IR spectrophotometer. IR is reported as characteristic bands (cm^{-1}) at their maximum intensity.

4.2. General procedure for the synthesis of compounds 3a–3p

For the synthesis of entitled heterocycles, a round bottom flask equipped with a stir bar was charged with 1,2-phenylenediamine (1.0 mmol), 1,2-diketones (1.0 mmol), water (2 mL) and zirconium(IV) oxide chloride (25 mol%). The resulting mixture was heated in an oil bath at 100 °C for the appropriate time, and the course of the

reaction was monitored using TLC on silica gel. Finally, the reaction mixture was cooled and the crude mixture was purified by column chromatography or crystallization to give the desired product. The authenticity of the products was established by comparing their melting points with data of the literature and by analyzing the spectroscopic data of ^{1}H and ^{13}C NMR and IR [9–16,26,27].

4.3. Spectral data for compounds 3a–3p

4.3.1. 2,3-Diphenylpyrido[2,3-b]pyrazine (3a)

Yield 92%; yellow solid, mp: 141–143 °C. IR (KBr) υ (cm^{-1}): 3056, 1544, 1430, 1384, 1332, 1068, 1019, 780, 697. ^{1}H NMR (500 MHz, DMSO, d_6) δ (ppm): 7.31–7.49 (m, 10H), 7.86 (dd, J = 8.2, 4.1 Hz, 1H), 8.56 (dd, J = 8.2, 1.2 Hz, 1H) 9.14 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 156.5, 155.3, 154.9, 150.0, 139.1, 138.7, 136.5, 130.6, 130.6, 130.0, 129.9, 128.9, 126.8.

4.3.2. 2,3-Bis(4-fluorophenyl)pyrido[2,3-b]pyrazine (3b)

Yield 93%; yellow solid, mp: 140–142 °C. IR (KBr) υ (cm^{-1}): 2925, 1728, 1597, 1548, 1508, 1446, 1386, 1331, 1226, 832. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.02–7.09 (m, 4H), 7.53–7.63 (m, 4H), 7.72 (q, J = 8.3 Hz, 1H), 8.49 (dd, J = 8.3, 1.7 Hz, 1H), 9.17 (dd, J = 4.1, 1.7 Hz, 1H) ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.2, 165.1, 161.9, 161.8, 154.9, 154.3, 153.3, 149.7, 138.0, 136.1, 134.4, 134.3, 134.0, 133.9, 132.3, 132.2, 131.8, 131.7, 125.4, 115.8, 115.6, 115.5, 115.3. Anal. Calcd for $C_{19}H_{11}F_2N_3$ (319.3): C, 71.47; H, 3.47; N, 13.16. Found: C, 71.64; H, 3.59; N, 13.38.

4.3.3. 2,3-Bis(4-methoxyphenyl)pyrido[2,3-b]pyrazine (3c)

Yield 88%; yellow solid, mp: 137–139 °C. IR (KBr) υ (cm^{-1}): 2933, 2839, 1605, 1513, 1447, 1384, 1251, 1175, 1023, 833. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.84 (d, 6H), 6.85–6.91 (m, 4H), 7.53–7.68 (m, 5H), 8.45 (dd, J = 8.4, 1.8 Hz, 1H), 9.11 (dd, J = 4.2, 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.7, 155.7, 154.2, 153.5, 149.8, 137.8, 135.8, 131.8, 131.2, 131.1, 130.7, 124.7, 113.9, 113.6, 55.3, 55.3.

4.3.4. Acenaphtho[1,2-b]pyrido[2,3-e]pyrazine (3d)

Yield 85%; yellow solid, mp: 225–227 °C. IR (KBr) υ (cm^{-1}): 3051, 1612, 1561, 1433, 1373, 1212, 1098, 1034, 826, 771. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.69–7.90 (m, 3H), 8.12 (dd, J = 8.2, 2.7 Hz, 2H), 8.40–8.57 (m, 3H), 9.12 (d, J = 4.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 157.1, 154.9, 152.4, 150.6, 138.3, 137.2, 136.4, 131.2, 130.9, 130.2, 130.0, 129.9, 128.9, 128.7, 124.3, 123.3, 122.3. Anal. Calcd for $C_{17}H_9N_3$ (255.2): C, 79.99; H, 3.55; N, 16.46. Found: C, 79.75; H, 3.80; N, 16.52.

4.3.5. 2,3-Bis(4-methoxyphenyl)pyrido[3,4-b]pyrazine (3e)

Yield 86%; yellow solid partial to green, mp: 145–147 °C. IR (KBr) υ (cm^{-1}): 3025, 2923, 1604, 1510, 1460, 1383, 1248, 1173, 1028, 835. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.84 (S, 6H), 6.89 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.93 (d, J = 5.7 Hz, 1H), 8.77 (d, J = 5.7 Hz, 1H), 9.53 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.9, 160.6, 157.4, 154.9, 154.1, 146.9, 143.4, 136.2, 131.4, 131.2, 130.9, 130.8, 121.2, 113.9, 55.3.

4.3.6. 2,3-Bis(4-fluorophenyl)pyrido[3,4-b]pyrazine (3f)

Yield 88%; orange solid, mp: 132–134 °C. IR (KBr) υ (cm^{-1}): 3049, 1597, 1509, 1381, 1325, 1230, 835. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.07 (m, 4H), 7.51–7.55 (m, 4H), 7.96 (d, J = 5.8 Hz, 1H), 8.83 (d, J = 5.8 Hz, 1H), 9.58 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.3, 165.2, 162.0, 161.8, 156.6, 154.4, 154.0, 147.5, 143.5, 136.2, 134.1, 132.0, 131.8, 131.8, 131.7, 121.2, 115.9, 115.6. Anal. Calcd for $C_{19}H_{11}F_2N_3$ (319.3): C, 71.47; H, 3.47; N, 13.16. Found: C, 71.64; H, 3.59; N, 13.33.

4.3.7. 2,3-Diphenylpyrido[3,4-b]pyrazine (3g)

Yield 91%; white solid partial to green, mp: 170–172 °C. IR (KBr) υ (cm^{-1}): 3047, 2963, 1590, 1542, 1383, 1326, 1024, 808, 696. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.34–7.55 (m, 10H), 7.99 (d, J = 5.7 Hz, 1H), 8.83 (d, J = 5.7 Hz, 1H), 9.60 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 157.9, 155.3, 154.4, 147.3, 143.5, 138.2, 136.3, 129.8, 129.8, 129.7, 129.4, 128.4, 121.3.

4.3.8. Dibenzo[f,h]pyrido[3,4-b]quinoxaline (3h)

Yield 87%; yellow solid, mp: 216–218 °C. IR (KBr) υ (cm^{-1}): 3025, 2921, 1600, 1499, 1387, 1343, 1216, 1041, 828, 754, 719. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.69–7.84 (m, 4H), 8.07 (d, J = 5.7 Hz, 1H), 8.48 (d, J = 7.8 Hz, 2H), 8.86 (d, J = 6.0 Hz, 1H), 9.30 (d, J = 7.8 Hz, 2H), 9.73 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 155.1, 146.2, 143.9, 136.9, 135.9, 132.8, 131.5, 131.0, 130.5, 129.5, 129.4, 128.2, 128.1, 127.0, 126.5, 123.9, 123.0, 122.9, 121.3.

4.3.9. Acenaphtho[1,2-b]pyrido[3,4-e]pyrazine (3i)

Yield 86%; orange solid, mp: 245–247 °C. IR (KBr) υ (cm^{-1}): 3031, 2922, 1611, 1569, 1424, 1296, 1103, 961, 830, 771. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.82 (m, 2H), 7.97 (d, J = 5.7 Hz, 1H), 8.11 (m, 2H), 8.37 (m, 2H), 8.79 (d, J = 8.7 Hz, 1H), 9.54 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 157.5, 155.2, 154.0, 147.0, 144.1, 137.1, 136.3, 130.8, 130.6, 130.0, 129.9, 128.8, 128.7, 122.9, 122.4, 122.0.

4.3.10. 5,6-Diphenyl-2,3-dihydropyrazine (3j)

Yield 95%; white solid, mp: 154–156 °C. IR (KBr) υ (cm^{-1}): 3028, 2943, 2831, 1610, 1551, 1439, 1261, 986, 766, 698. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.69 (s, 4H), 7.23 (d, J = 7.8 Hz, 4H), 7.30 (m, 2H), 7.39 (d, J = 8.0 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 45.8, 127.9, 128.1, 129.6, 137.7, 160.3.

4.3.11. 8,9-Dihydroacenaphtho[1,2-b]pyrazine (3k)

Yield 91%; yellow solid, mp: 165–167 °C. IR (KBr) υ (cm^{-1}): 2929, 2838, 1671, 1627, 1483, 1429, 1329, 1111, 961, 824, 771. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.94 (s, 4H) 7.71 (m, 2H), 7.94–8.01 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 158.6, 131.7, 130.6, 128.5, 128.3, 118.7, 118.6, 44.9.

4.3.12. 5,6-Dimethylpyrazine-2,3-dicarbonitrile (3l)

Yield 90%; white solid, mp: 162–164 °C. IR (KBr) υ (cm^{-1}): 3006, 2239, 1770, 1717, 1536, 1389, 1197, 1123, 986, 793, 695. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.70 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 158.4, 130.7, 113.6, 23.3.

4.3.13. 2,3-Diphenylquinoxaline (3m)

Yield 97%; white solid, mp: 121–123 °C. IR (KBr) υ (cm^{-1}): 3048, 2923, 1544, 1441, 1336, 765, 691. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.32–7.38 (m, 6H), 7.52 (d, J = 7.8 Hz, 4H), 7.77 (q, J = 6.4 Hz, 2H), 8.18 (q, J = 9.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 153.5, 141.2, 139.0, 129.9, 129.8, 129.2, 128.8, 128.2.

*4.3.14. 2,3-Bis(4-methoxyphenyl)quinoxaline (**3n**)*

Yield 92%; white solid, mp: 145–147 °C. IR (KBr) υ (cm^{-1}): 2932, 2836, 1605, 1510, 1462, 1344, 1291, 1244, 1173, 1026, 832. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.83 (s, 6H), 6.88 (d, J = 8.7 Hz, 4H), 7.50 (d, J = 8.7 Hz, 4H), 7.72 (m, 2H), 8.13 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.1, 153.0, 141.0, 131.5, 131.2, 129.5, 129.0, 113.7, 55.3.

*4.3.15. 2,3-Bis(4-fluorophenyl)quinoxaline (**3o**)*

Yield 95%; white solid, mp: 133–135 °C. IR (KBr) υ (cm^{-1}): 3063, 1600, 1510, 1476, 1395, 1342, 1227, 1158, 1051, 842, 763. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.03–7.09 (m, 4H), 7.49–7.54 (m, 4H), 7.80 (q, J = 9.6 Hz, 1H), 8.16 (q, J = 9.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.8, 161.5, 152.1, 141.2, 135.0, 134.9, 131.8, 131.7, 130.2, 129.1, 115.6, 115.4. Anal. Calcd for $C_{20}H_{12}F_2N_2$ (318.3): C, 75.46; H, 3.80; N, 8.80. Found: C, 75.58; H, 3.71; N, 8.91.

*4.3.16. 2,3-Dimethylquinoxaline (**3p**)*

Yield 98%; white solid, mp: 102–104 °C. IR (KBr) υ (cm^{-1}): 2998, 1564, 1484, 1433, 1393, 1321, 1206, 1161, 982, 760. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.69 (s, 6H), 7.63 (d, J = 6.3 Hz, 2H), 7.94 (d, J = 6.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 153.3, 141.0, 128.7, 128.2, 23.1.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.crci.2013.02.018

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