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Chemoselective synthesis of quinoxalines and benzimidazoles by silica gel catalysis

Chunmei Li, Furen Zhang *, Zhen Yang, Chenze Qi *

Zhejiang Key Laboratory of Alternative Technologies for Fine Chemicals Process, Shaoxing University, Shaoxing, Zhejiang Province 312000, China

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ABSTRACT

Treatment of nitroolefins and *o*-phenylenediamine with silica gel catalyst produced quinoxalines mainly in THF, but gave benzimidazoles efficiently in water. Such a solvent-dependent chemoselective reaction has prominent features of affording two cyclized products selectively with the same substrate, short reaction time, operational simplicity, as well as available starting materials and nontoxic catalysts. In addition, the scope and limitations were explored and a plausible reaction mechanism is proposed.

Introduction

Quinoxaline is an important class of benzo-heterocyclic pyrazine compound and has been widely used as a key building block in pharmaceutical agents and functional materials. Its derivatives exhibit various biological activities, such as anti-inflammatory,[1] anticancer,[2] antiviral,[3] antibacterial,[4] antibiotic, and kinase inhibition.[5] They have also been applied in dyes,[6] organic semiconductors,[7] electroluminescent materials, and dehydroannulenes.[8] Due to the wide usefulness and growing importance, many powerful methodologies for assembling these heterocycles have been developed. The condensation of aryl-1,2-diamine with two-carbon synthons under a variety of conditions is a conventional approach to construct quinoxalines.[9,10] Other strategies for the synthesis of quinoxaline derivatives were also developed. For example, Chen and co-workers described the synthesis of quinoxalines from *o*-phenylenediamine and nitroolefins in the presence of 10 mol % of $CuBr_2$ in EtOH at 110 °C.[11] Despite the advances of these methodologies, in some cases, most of the reported methods suffer from one or more limitations such as the use of expensive reagents/additives, metal catalysts, special apparatus, or harsh reaction conditions, as well as the tedious work-up procedures. Thus, the development of a mild and eco-friendly synthetic protocol for these highly significant classes of compounds is still desirable.

Silica gel, which is a mild acid, easily available, inexpensive, and nontoxic, can act as a catalyst in the condensation reaction.[12] The usage of such a heterogeneous catalyst instead of traditional homogeneous base and metal catalysts offers several advantages, such as the ease of crude product separation, potential catalyst reuse, and environmentally friendly alternative. In addition, the solvent-dependent chemoselective reactions are of obvious value because it gives one of several products selectively from the same substrate without the need to separate the product(s) from the product mixture. Therefore, the development of solvent-dependent chemoselective reactions is a worthy goal.

Recently, we developed an efficient and mild method for the synthesis of tetrahydro-4*H*-indol-4-one derivatives with cyclohexane-1,3-dione, amines, and nitroolefins.[13] During the continuation of this project, we found that when *o*-phenylenediamine was employed as amine substrate, the reaction afforded quinoxalines or benzimidazoles by varying the reaction media, respectively. We therefore describe here a new solvent-controlled method for the chemoselective synthesis of quinoxalines and benzimidazoles (Scheme 1).

Results and discussion

In the initial experiment, the nitroolefin **1a** which was derived from the reaction of nitroethane with benzaldehyde was subjected to the reaction with *o*-phenylenediamine (**2a**) in the presence of silica gel at 50 °C in different solvents, such as THF, EtOH, *i*-PrOH, DCM, H_2O, DMF, and toluene. The results of the screening of

* Corresponding authors. Tel./fax: +86 575 88345682.
E-mail addresses: frzhang@usx.edu.cn (F. Zhang), qichenze@usx.edu.cn (C. Qi).

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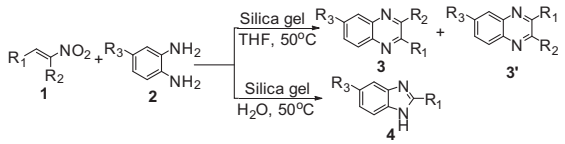


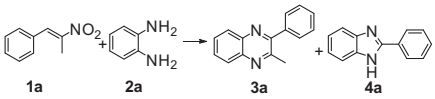
Scheme 1. Solvent-dependent chemoselective synthesis of quinoxalines and benzimidazoles.

solvents are presented in Table 1 (entries 1–7). When ethanol and *i*-PrOH were employed as reaction media, the reaction gave a mixture of **3a** and **4a**. While four aprotic solvents (THF, DCM, DMF, and toluene) were used as the solvent, only quinoxaline **3a** was obtained with 89%, 81%, 18%, and 52% yields, respectively (entries 1–4), whereas the reaction in water gave benzimidazole in 83% yield. Thus, the reaction could be directed cleanly to form two different products, quinoxaline **3a** and benzimidazole **4a**, by changing the reaction medium. Clearly, the nature of solvent greatly influenced the reaction.

For further screening of the reaction conditions for the chemoselective reaction, several other bases or acid catalysts were evaluated for their catalytic efficiency in the reaction (Table 1, entries 8–13). In all case 10% of the catalyst was used and the reaction was carried out at 50 °C in THF. However, none of the tested catalysts proved better than silica gel. To identify the optimum reaction temperature, the reaction was carried out with silica gel at room temperature, 40, and 80 °C in THF, respectively. The results indicated that the yield of **3a** improved and the reaction time was shortened as the temperature increased from rt to 50 °C (Table 1, entries 1, 14, and 15). When further increasing the temperature to 80 °C, no significant improvement in yield was observed (Table 1, entry 16).

Under the above optimized reaction conditions, we then examined the scope of the reaction for the construction of various quinoxaline derivatives by alternating the substituted nitroolefin **1** and *o*-phenylenediamine **2a** (Table 2). As shown in Table 2, a wide range of substituted groups of nitroolefins gave the desired products in good to excellent yields, which include methyl, methoxy,

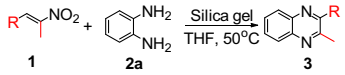
Table 1
Optimization of reaction conditions for the synthesis of **3a** and **4a**[a]



Entry	Solvent	Cat.[b]	*T* (°C)	Yield[c] (%)	
				3a	**4a**
1	THF	Silica gel	50	89	0
2	CH_2Cl_2	Silica gel	50	81	0
3	DMF	Silica gel	50	18	0
4	Toluene	Silica gel	50	52	0
5	EtOH	Silica gel	50	75	20
6	^{i}PrOH	Silica gel	50	65	25
7	H_2O	Silica gel	50	Trace	83
8	THF	Et_3N	50	45	0
9	THF	DMAP	50	40	0
10	THF	HCl	50	31	0
11	THF	TFA	50	77	0
12	THF	HOAc	50	63	0
13	THF	$Y(OTf)_3$	50	37	0
14	THF	Silica gel	rt	42	0
15	THF	Silica gel	40	58	0
16	THF	Silica gel	80	90	0

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.50 mmol), and solvent (3.0 mL), 5 h.
[b] Catalysts (10 mol %) or silica gel (200 mg).
[c] Isolated yields.

Table 2
Synthesis of quinoxalines **3** with *o*-phenylenediamine **2a**[a]



Entry	**3**	R	Time (h)	Yield[b] (%)
1	**3a**	C_6H_5 (**1a**)	5	89[11]
2	**3b**	4-F–C_6H_4 (**1b**)	5	87[10j]
3	**3c**	4-Cl–C_6H_4 (**1c**)	5	92[11]
4	**3d**	4-Br–C_6H_4 (**1d**)	5	86[11]
5	**3e**	4-Me–C_6H_4 (**1e**)	5	88[11]
6	**3f**	4-OMe–C_6H_4 (**1f**)	5	87[11]
7	**3g**	4-NO_2–C_6H_4 (**1g**)	5	71[11]
8	**3h**	2-NO_2–C_6H_4 (**1h**)	6	65[11]
9	**3i**	3-NO_2–C_6H_4 (**1i**)	6	69[10t]
10	**3j**	2,4-Cl–C_6H_3 (**1j**)	5	78[11]
11	**3k**	2-Furyl (**1k**)	6	75[11]
12	**3l**	2-Thienyl (**1l**)	5	86[10t]

[a] Reaction conditions: **1** (0.50 mmol), **2a** (0.50 mmol), silica gel (200 mg), and THF (3.0 mL).
[b] Isolated yields.

fluoro, chloro, bromo, and nitro groups. It is worth noting that strong electron-withdrawing substituted groups of nitroolefins such as nitro had a noticeable impact on yield (entries 7–9). Additionally, it should be noted that good results were also obtained by using other aromatic systems, such as 2-thienyl-1-nitroethene and 2-furyl-1-nitroethene (entries 11 and 12). However, when (*E*)-(2-nitroprop-1-en-1-yl)benzene was replaced with (*Z*)-bromonitrostyrene, (*E*)-(2-nitrovinyl)benzene, and (*E*)-(2-nitrobut-1-en-1-yl)benzene, respectively, none of target product was obtained at similar conditions, probably because of the action of the strong inductive effect of the bromine atom and the σ–π hyperconjugation between C—H bond and double bond, which influence the stability of the substrates.

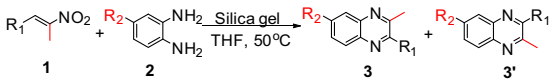
To further expand the scope of diamine substrates, we employed different nitroolefins as model substrates and examined different diamines, including 4-methylbenzene-1,2-diamine, 4-chlorobenzene-1,2-diamine, and (*R*/*S*)-cyclohexane-1,2-diamine. When 4-methylbenzene-1,2-diamine and 4-chlorobenzene-1,2-diamine were used under the optimized conditions, the reactions proceeded smoothly to provide moderate to good yields and different ratios of isomers **3** and **3′** were observed, confirmed by ^{1}H NMR (Table 3). However, (*R*/*S*)-cyclohexane-1,2-diamine failed to give the desired products.

Subsequently, we found that the desired product **3** can be obtained, but with poor yield by the one-pot, three-component reaction, while modifying the conditions slightly. In an attempt to enhance further, the reaction of *o*-phenylenediamine, benzaldehyde, and nitroethane was tested under a variety of different conditions. Unfortunately, only 35% yield of **3a** was obtained in the presence of silica gel at 100 °C in 24 h. The method could also be successfully extended to substituted-benzaldehydes **5** for synthesizing corresponding quinoxaline derivatives with low to moderate yields (Table 4, entries 2–13).

In addition, the scope of the reaction of using silica gel catalyst in water to give benzimidazoles was validated with similar conditions. To our delight, a wide range of substituted groups of nitroolefins can give benzimidazole products in good to excellent yields (Table 5).

Although the effect of solvent to direct the subsequent processes to quinoxaline and benzimidazole systems, respectively, remains to be fully clarified, the nature of solvent must play a role in determining the product distribution. To probe the mechanism of the reaction, several control experiments were performed. The reactions were carried out with **1a** (0.5 mmol) and **2a** (0.5 mmol),

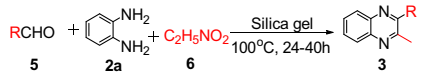
Table 3
Synthesis of quinoxalines **3**/**3′** with 4-substituted *o*-phenylenediamine **2**[a]



Entry	3/3′	R_1	R_2	Yield[b] (%) (3/3′)[c]
1	**3ab/3′ab**	C_6H_5 (**1a**)	Me(**2b**)	80 (3/2)[11]
2	**3bb/3′bb**	4-F–C_6H_4 (**1b**)	Me(**2b**)	79 (3/2)
3	**3cb/3′cb**	4-Cl–C_6H_4 (**1c**)	Me(**2b**)	81 (3/2)
4	**3eb/3′eb**	4-Me–C_6H_4 (**1e**)	Me(**2b**)	76 (1/1)
5	**3fb/3′fb**	4-OMe–C_6H_4 (**1f**)	Me(**2b**)	81 (7/3)
6	**3ac/3′ac**	C_6H_5 (**1a**)	Cl(**2c**)	78 (3/2)[11]
7	**3bc/3′bc**	4-F–C_6H_4 (**1b**)	Cl(**2c**)	72 (4/1)[14]
8	**3cc/3′cc**	4-Cl–C_6H_4 (**1c**)	Cl(**2c**)	80 (3/2)
9	**3dc/3′dc**	4-Br–C_6H_4 (**1d**)	Cl(**2c**)	69 (3/2)

[a] Reaction conditions: **1** (0.50 mmol), **2** (0.50 mmol), silica gel (200 mg), and THF (3.0 mL), 5 h.
[b] Total isolated yields of compounds **3** and **3′**.
[c] Determined by ^{1}H NMR of the crude mixture.

Table 4
Three-component synthesis of quinoxalines **3**[a]



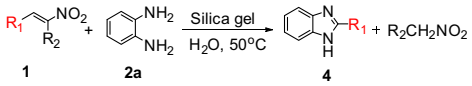
Entry	3	R	Time (h)	Yield [b] (%)
1	**3a**	C_6H_5 (**5a**)	24	35[11]
2	**3b**	4-F–C_6H_4 (**5b**)	24	43[10j]
3	**3c**	4-Cl–C_6H_4 (**5c**)	24	44[11]
4	**3d**	4-Br–C_6H_4 (**5d**)	24	23[11]
5	**3e**	4-Me–C_6H_4 (**5e**)	24	35[11]
6	**3f**	4-OMe–C_6H_4 (**5f**)	24	26[11]
7	**3g**	4-NO_2–C_6H_4 (**5g**)	24	34[11]
8	**3h**	2-NO_2–C_6H_4 (**5h**)	36	30[11]
9	**3i**	3-NO_2–C_6H_4 (**5i**)	36	26[10t]
10	**3j**	2,4-Cl–C_6H_3 (**5j**)	36	18[11]
11	**3k**	2-Furyl (**5k**)	24	23[11]
12	**3l**	2-Thienyl (**5l**)	24	39[10t]

[a] Reaction conditions: **5** (0.50 mmol), **2a** (0.50 mmol), $C_2H_5NO_2$ (3.0 mL), silica gel (200 mg), and THF (3.0 mL).
[b] Isolated yields.

in the presence of silica gel in THF and water, respectively, at 50 °C with TLC monitoring for the formation of intermediates. We found that THF and water afforded the same intermediate **B**, which was separated and identified by various spectral data. Based on the above observations and the analogous mechanisms discussed in the literature,[15] a plausible mechanism for this reaction was proposed as shown in Scheme 2. Firstly, the intermediate **A**, which further isomerized to **B**, was obtained from the Michael addition of nitroolefins **1** to *o*-phenylenediamine **2a**. Then, it is our supposition that the intermediate **A** was more stable in aprotic solvent THF and provided a route *i* to give desired product **3**. With silica gel serving as mild acid, the intermediate **C** was produced via intramolecular cyclization. Subsequently, the intermediate **C** underwent elimination of H_2O and HNO followed by aromatization under aerial oxidation to the desired product **3**. In protic solvent water, the intermediate **A** was unstable and underwent elimination of $R_2CH_2NO_2$ followed by imine **E** formation and the resulting imine further reacted with another $-NH_2$ group of 1,2-phenylenediamine resulting in the formation of the intermediate **F**, which further aromatized under aerial oxidation to give benzimidazole **4**.

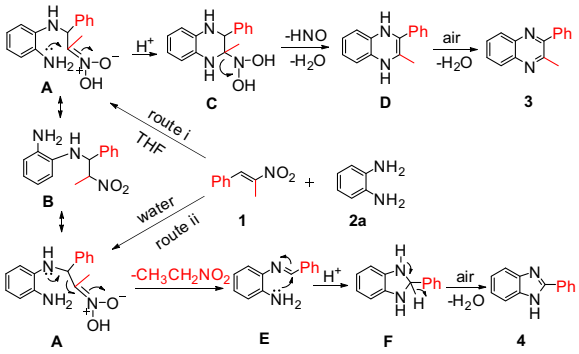
In conclusion, we have demonstrated an efficient and practical approach for the chemo- and regioselective synthesis of quinoxalines **3** and benzimidazoles **4** from the same substrates when

Table 5
Synthesis of benzimidazoles **4** in water[a]



Entry	4	R_1	R_2	Time (h)	Yield[b] (%)
1	**4a**	C_6H_5	Me	5	83[15b]
2	**4b**	4-Cl–C_6H_4	Me	5	82[15b]
3	**4c**	4-Br–C_6H_4	Me	5	77[15a]
4	**4d**	4-Me–C_6H_4	Me	5	77[15b]
5	**4f**	4-OMe–C_6H_4	Me	5	79[15b]
6	**4g**	C_6H_5	H	4	85[15b]
7	**4h**	4-Cl–C_6H_4	H	4	87[15b]
8	**4i**	4-Br–C_6H_4	H	4	80[15a]
9	**4j**	4-Me–C_6H_4	H	4	83[15b]
10	**4k**	4-OMe–C_6H_4	H	4	85[15b]

[a] Reaction conditions: **1** (0.50 mmol), **2a** (0.50 mmol), silica gel (200 mg), and water (3.0 mL).
[b] Isolated yields.



Scheme 2. The plausible mechanism for the formation of **3** and **4**.

different solvents were used. The reaction gave the desired products **3** and **4** with good to excellent yields and chemo- and regioselectivity that avoided tedious workup and purification steps. More importantly, the use of silica gel as catalyst in water or THF at 50 °C makes it quite simple, more convenient, and environmentally benign.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.022.

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14. *General procedure for the synthesis of quinoxalines* ***3bc*** *and* ***3′bc****:* In a 10-mL reaction vial, (*E*)-1-fluoro-4-(2-nitroprop-1-en-1-yl)benzene **1b** (90.5 mg, 0.50 mmol), 4-chlorobenzene-1,2-diamine **2c** (71.0 mg, 0.50 mmol), silica gel (200 mg), and solvents (3.0 mL) were mixed and then capped. The mixture was stirred for 5 h at 50 °C. Upon completion as shown by TLC monitoring, the reaction mixture was cooled to room temperature and exacted with ethyl acetate (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, and concentrated in vacuum. The resulting residue was purified by column chromatography on silica gel with the eluent (ethyl acetate/petroleum ether = 1:20–1:4) to give the pure product. *6-Chloro-2-(4-fluorophenyl)-3-methylquinoxaline (****3bc****) and 6-chloro-3-(4-fluorophenyl)-2-methylquinoxaline (****3′bc****):* yellow solid; mp 110–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, 1H, *J* = 2.0 Hz, ArH), 7.98–8.01 (m, 1H, ArH), 7.65–7.71 (m, 3H, ArH), 7.22–7.27 (m, 2H, ArH), 2.86 (s, 0.6H, CH_3), 2.78 (s, 2.4H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 154.6, 152.6, 141.2, 139.7, 135.0, 134.6, 131.0, 130.9, 130.8, 129.6, 128.0, 115.9, 115.6, 24.4; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{10}ClFN_2$: 273.0589; found: 273.0592.
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