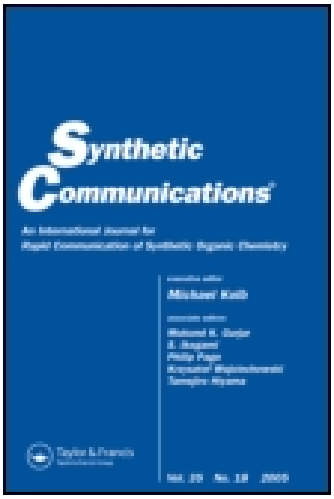

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Silica Sulfuric Acid (SSA)/Polyethylene Glycol (PEG) as a Recyclable System for the Synthesis of Quinoxalines and Pyrazines

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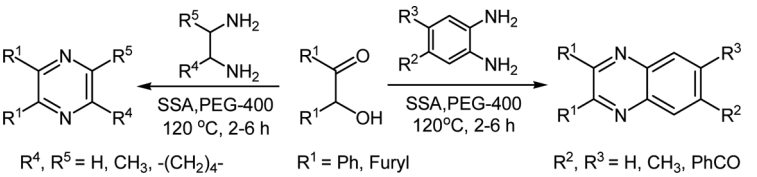
SILICA SULFURIC ACID (SSA)/POLYETHYLENE GLYCOL (PEG) AS A RECYCLABLE SYSTEM FOR THE SYNTHESIS OF QUINOXALINES AND PYRAZINES

Tieqiang Huang,[1] Danna Jiang,[1] Jiuxi Chen,[1] Wenxia Gao,[1] Jinchang Ding,[1,2] and Huayue Wu[1]

[1]*College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, China*

[2]*Wenzhou Vocational and Technical College, Wenzhou, China*

GRAPHICAL ABSTRACT



Abstract *An efficient and facile method has been developed for the condensation of 1,2-diamines with α-hydroxyketones in polyethylene glycol (PEG) to quinoxalines and pyrazines with good yields in the presence of silica sulfuric acid (SSA). The important features of the methodology are simple operations, environmentally friendliness, and no requirement for metal catalysts. Additionally, the catalyst system (SSA/PEG) could be recovered easily and reused.*

Keywords Pyrazines; quinoxalines; recyclable catalyst; silica sulfuric acid

INTRODUCTION

Quinoxaline derivatives have become increasingly noticed in the past few years because they are an important class of heterocycles with a wide range of pharmacological and biological activities.[1] Moreover, the pyrazine ring system is also a useful structural element in medicinal chemistry.[2] In light of this significance, a variety of synthetic strategies have been developed for the preparation of quinoxalines[3] and pyrazines.[4] Oxidative cyclization of α-hydroxy ketones with 1,2-diamines is not a common method but an alternative one. Generally, it can be catalyzed in the presence of various promoting agents, such as $CuCl_2$,[5] FeMPA,[6] TiO_2/2,2,6,6-tetramethylpiperidinyloxy (TEMPO),[7] MnO_2,[8] ceric ammonium nitrate (CAN),[9]

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$Pd(OAc)_2$- or $RuCl_2(PPh_3)_3$-TEMPO,[10] HgI_2,[11] and manganese octahedral molecular sieves,[12] as well as promoted by microwave technology.[13] Although these methods are suitable for certain synthetic conditions, many of these procedures are associated with one or more disadvantages such as long reaction time, use of hazardous organic solvents, and harsh reaction conditions, which leaves scope for further development of new environmentally clean syntheses.

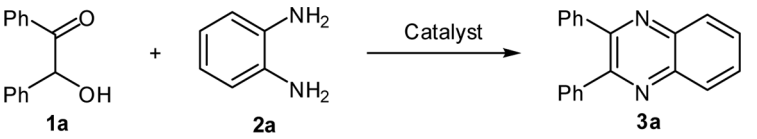
Silica sulfuric acid (SSA), an easily available reagent, has been used for various organic functional group transformations either as reagent or as catalyst,[14] but it has not been carefully studied as a catalyst in the synthesis of quinoxalines and pyrazines until now.

As part of current studies on the development of green and efficient organic methodologies,[15] we herein report a green, simple, and practical method for the synthesis of quinoxaline and pyrazine derivatives from α-hydroxyketones and 1,2-diamines catalyzed by SSA in poly ethylene glycol (PEG).

RESULTS AND DISCUSSION

Our initial efforts were directed toward the catalytic evaluation of SSA for the synthesis of quinoxalines and pyrazines. A blank reaction was carried out using benzoin (**1a**) and 1,2-diaminobenzene (**2a**) in EtOH, which resulted in no quinoxaline derivative after 2 h (Table 1 entry 1). The same reaction using SSA in EtOH afforded the desired quinoxaline in 62% yield (Table 1, entry 2). Encouraged by this promising

Table 1. Effects of solvents on the reaction of benzoin with 1,2-diaminobenzene[a]



Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]
1	None	EtOH	80	NR[c]
2	SSA	EtOH	80	62
3	SSA	H_2O	100	71
4	SSA	PEG-400	120	90
5	SSA	CH_3CN	80	77
6	SSA	1,4-Dioxane	100	66
7	SSA	DMSO	120	69
8	SSA	PEG-400	120	80[d]
9	SSA	PEG-400	120	82[e]
10	SSA	PEG-400	120	90[f]

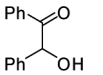
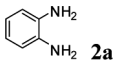
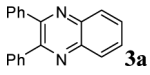
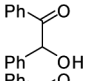
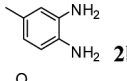
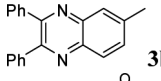
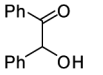
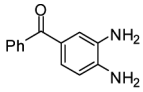
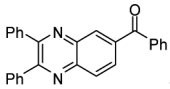
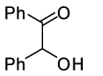
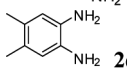
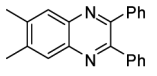
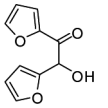
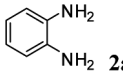
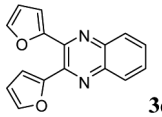
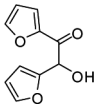
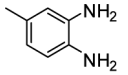
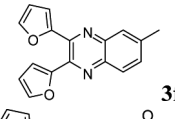
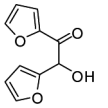
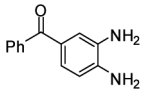
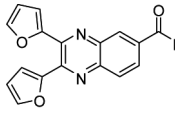
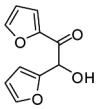
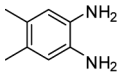
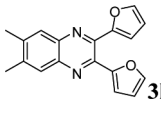
[a]All the reactions were performed using benzoin **1a** (0.5 mmol), 1,2-diaminobenzene **2a** (1.0 mmol), and 300 mg of SSA for 2 h.
[b]Isolated yield.
[c]NR, no reaction.
[d]100 mg of catalyst.
[e]200 mg of catalyst.
[f]400 mg of catalyst.

result, we next planned to determine the influence of solvent on the catalytic property of the model reaction. Clearly, PEG-400 stands out as the solvent of choice, with its fast conversion and good yield (Table 1, entry 8), so we chose to perform this reaction in PEG-400. In addition, we also studied the influence of the amount of catalyst on the reaction yields. Decreasing the amount of catalyst (Table 1, entries 8 and 9) in the system reduced the yield slightly. The amount of catalyst (300 mg) was sufficient, and excessive amount of catalyst did not increase the yield remarkably (Table 1, entry 10).

With the optimized conditions in hand, the reactions of various α -hydroxyketones with different 1,2-diamines were examined to explore the scope and generality of this present protocol for the synthesis of various quinoxalines (**3**) and pyrazines (**5**), and the results are summarized in Tables 2 and 3.

As shown in Table 2, we investigated the influence of electronic factors of 1,2-diamine on the reaction results. It was observed that the reaction of 1,2-diamine bearing an electron-donating group (-Me) on the benzene ring, such as

Table 2. Synthesis of quinoxalines using SSA in PEG[a]

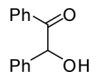
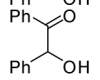
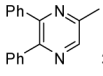
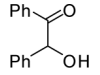
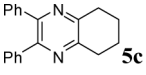
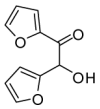
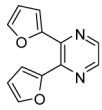
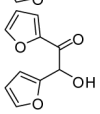
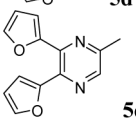
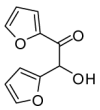
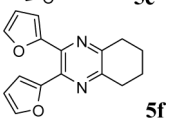
Entry	α-Hydroxyketone	1,2-Diamine	Product	Yields (%)[b]
1		 **2a**	 **3a**	90
2		 **2b**	 **3b**	81
3		 **2c**	 **3c**	51[c]
4		 **2d**	 **3d**	85
5		 **2a**	 **3e**	81
6		 **2b**	 **3f**	75
7		 **2c**	 **3g**	52[c]
8		 **2d**	 **3h**	83

[a]All the reactions were performed using α-hydroxyketone **1** (0.5 mmol), aromatic 1,2-diamine **2** (1.0 mmol), and 300 mg of SSA in PEG-400 (5 mL) at 120 °C for 2 h.

[b]Isolated yield.

[c]The reaction was carried out for 6 h.

Table 3. Synthesis of pyrazines using SSA in PEG[a]

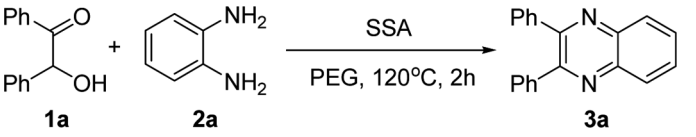
Entry	α-Hydroxyketone	1,2-Diamine	Product	Yields (%)[b]
1		 **4a**	 **5a**	75
2		 **4b**	 **5b**	72
3		 **4c**	 **5c**	82
4		 **4a**	 **5d**	76
5		 **4b**	 **5e**	75
6		 **4c**	 **5f**	81

[a]All the reactions were performed using α-hydroxyketone **1** (0.5 mmol), aliphatic 1,2-diamine (1.0 mmol), and 300 mg of SSA in PEG-400 (5 mL) at 120 °C for 6 h.
[b]Isolated yield.

4-methylbenzene-1,2-diamine (**2b**) and 4,5-dimethylbenzene-1,2-diamine (**2d**) with α-hydroxyketones, was examined, and the corresponding products **3b, 3d, 3f**, and **3h** were obtained in good yields (Table 2, entries 2, 4, 9, and 11). However, the presence of an electron-withdrawing group on the benzene ring decreased the reactivity of the substrate. For instance, 1,2-diamines containing electron-withdrawing group (PhC=O) such as benzoyl on the benzene ring, such as 4-benzoylbenzene-1,2-diamine (**2c**), afforded the corresponding products **3c** and **3g** in moderate yields (Table 2, entries 3 and 7), which showed an obvious electronic effect.

On the other hand, we examined the synthesis of pyrazines from the reaction of aliphatic 1,2-diamines with α -hydroxyketones. As shown in Table 3, compared with the aromatic 1,2-diamines, the reaction of most aliphatic 1,2-diamines, with α-hydroxyketones required a longer reaction time. It is worth mentioning that α-hydroxyketones can react with aliphatic 1,2-diamines, resulting in the formation of pyrazines (**5**) in good yields, which can react in poor yields or result in the formation of dihydropyrazines as reported in the literature.[8]

The catalyst SSA works under heterogeneous conditions and can easily be prepared from readily available $ClSO_3H$ and silica gel, which can conveniently be handled and removed from the reaction mixture.[14e] Thus, we investigated the recycling of SSA in the subsequent condensation reaction, for example, the reaction of benzoin (**1a**) and 1,2-diaminobenzene (**2a**). As shown in Scheme 1, SSA could be reused five times (with the yields of the corresponding product being 90%, 87%, 85%, 82%, and 80%, respectively).



1a 2a 3a

Run 1, 90%; run 2, 87%; run 3, 85%; run 4, 82% and run 5, 80%

Scheme 1. Reusing SSA.

In conclusion, we have developed an efficient and facile synthesis of quinoxalines and pyrazines catalyzed by SSA in PEG-400. Compared to previous reported methodologies, the present protocol features simple operations, no requirement for metal catalysts, reusability of the catalyst, and an environmentally benign process. Further investigations on the reaction mechanism, scope, limitations, and biological activity evaluation of these new classes of compounds are under way.

EXPERIMENTAL

Melting points were recorded on digital melting-point apparatus WRS-1B and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Equinox55 spectrometer. Mass spectra were measured with Thermo Finnigan LCQ-Advantage. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury Plus-300 instrument using $CDCl_3$ as the solvent with tetramethylsilane (TMS); as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS; the coupling constants J are given in hertz (Hz). Elemental analysis was determined on a Carlo-Erba 1108 instrument. All reactions were conducted using standard Schlenk techniques. Column chromatography was performed using EM silica gel 60 (300–400 mesh).

General Procedure for the Preparation of SSA

A 500-mL suction flask was used. It was equipped with a constant-pressure dropping funnel containing chlorosulfonic acid (23.3 g, 0.2 mol) and gas inlet tube for conducting HCl gas over an adsorbing solution (i.e., water). It was charged with 60.0 g of silica gel. Chlorosulfonic acid was added dropwise over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately. After the addition was complete, the mixture was shaken for 30 min. A white solid (silica sulfuric acid) of 76.0 g was obtained.

General Procedure for the Preparation of Quinoxalines and Pyrazines

1,2-Diamines (1 mmol) were added slowly to a mixture of a α-hydroxyketone (0.5 mmol) and SSA (300 mg) in PEG-400 (5 mL), and the mixture was stirred at 120 °C for 2 or 6 h. The reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, water (10 mL) was added, and the mixture was extracted with ethyl acetate (3×10 mL). The organic layer was washed with

brine (3×10 mL), dried over anhydrous Na_2SO_4, and concentrated. The product was separated and purified by column chromatography on silica gel (300–400 mesh) using an ethyl acetate/petrol mixture as the eluent to afford a pure product. After extraction with ethyl acetate, the catalyst in the aqueous phase was concentrated in an oven at 130 °C for 6 h, and the solution of the recovered SSA and PEG could be reused in the next reaction batch. When necessary, the products were purified by recrystallizion with ethanol.

Characterization Data of All the Products

2,3-Diphenylquinoxaline (3a). Solid, mp 128–129 °C (lit.[16] 130–131 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$–7.36 (6H, m), 7.53–7.55 (4H, m), 7.74–7.78 (2H, m), 8.18–8.21 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 128.3$, 128.8, 129.2, 129.8, 123.0, 139.0, 141.2, 153.4. MS (ESI) m/z (%): 283 ($[M+1]^+$, 100).

6-Methyl-2,3-diphenylquinoxaline (3b). Solid, mp 117–118 °C (lit.[16] 115–117 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.62$ (s, 3H), 7.32–7.35 (m, 6H), 7.50–7.53 (m, 5H), 7.96 (s, 1H), 8.07 (d, $J = 8.55$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 21.9$, 127.6, 127.6, 127.9, 127.9, 128.0, 128.2, 128.6, 128.7, 129.9, 132.3, 139.2, 139.7, 140.5, 141.3, 152.6, 153.3. MS (ESI) m/z (%): 297 ($[M+1]^+$, 100).

6-Benzoyl-2,3-diphenylquinoxaline (3c). Solid, mp 138–139 °C (lit.[17] 140–142 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$–7.40 (m, 6H), 7.51–7.57 (m, 6H), 7.63 (d, $J = 7.26$ Hz, 1H), 7.91 (d, $J = 7.41$ Hz, 2H), 8.28 (s, 2H), 8.54 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 111.8$, 128.3, 128.5, 129.1, 129.3, 129.7, 129.8, 129.8, 129.9, 130.1, 132.4, 132.8, 137.2, 138.3, 138.6, 138.6, 140.2, 143.0, 154.6, 155.1, 195.8. MS (ESI) m/z (%): 387 ($[M+1]^+$, 100).

6,7-Dimethyl-2,3-diphenylquinoxaline (3d). Solid, mp 174–176 °C (lit.[16] 177–179 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.54$ (6H, s), 7.34–7.37 (6H, m), 7.52–7.56 (4H, m), 7.96 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 20.4$, 127.9, 128.2, 128.5, 129.9, 139.4, 140.2, 140.5, 152.5. MS (ESI) m/z (%): 311 ($[M+1]^+$, 100).

2,3-Di(2-furyl)quinoxaline (3e). Solid, mp 134–136 °C (lit.[18] 131 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.55$ (s, 2H) 6.66 (d, $J = 3.34$ Hz, 2H), 7.72 (dd, $J = 6.33$, 3.41 Hz, 2H), 7.61 (s, 2H), 8.12 (dd, $J = 6.33$, 3.41 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 111.9$, 113.0, 129.1, 130.4, 140.6, 142.6, 144.2, 150.8. MS (ESI) m/z (%): 263 ($[M+1]^+$, 100).

2,3-Di(2-furyl)-6-methylquinoxaline (3f). Solid, mp 118–121 °C (lit.[17] 116–118 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.55$ (s, 3H), 6.52–6.53 (m, 2H), 7.88 (s, 1H), 6.60 (d, $J = 3.44$ Hz, 2H), 7.53 (d, $J = 8.59$ Hz, 1H), 7.59 (d, $J = 0.65$ Hz, Hz, 2H), 7.99 (d, $J = 8.57$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 21.9$, 111.8, 111.8, 112.5, 112.8, 113.0, 127.9, 128.6, 132.7, 139.0, 140.7, 141.0, 141.8, 142.5, 143.9, 144.1, 150.9. MS (ESI) m/z (%): 277 ($[M+1]^+$, 100).

6-Benzoyl-2,3-di(2-furyl)quinoxaline (3g). Solid, mp 135–137 °C (lit.[17] 132–134 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.58$–6.61 (m, 2H), 6.74–6.77 (m,

2H), 7.52–7.67 (m, 5H), 7.87–7.90 (m, 2H), 8.25 (d, $J = 0.74$ Hz, 2H), 8.48 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 112.0$, 112.2, 113.6, 114.2, 128.5, 129.5, 130.0, 130.2, 132.2, 132.8, 137.1, 138.5, 139.5, 142.4, 143.4, 143.9, 144.5, 144.8, 150.4, 150.5, 195.6. MS (ESI) m/z (%): 367 ($[M + 1]^+$, 100).

2,3-Di(2-furyl)-6,7-dimethylquinoxaline (3h). Solid, mp 131–133 °C (lit.[19] 134–136 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.43$ (s, 6 H), 6.50 (dd, $J = 3.3$, 1.73 Hz, 2 H), 6.57 (d, $J = 3.21$, 2 H), 7.57 (s, 2 H), 7.83 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.4$, 111.8, 112.3, 128.1, 139.5, 141.1, 141.7, 143.8, 151.0. MS (ESI) m/z (%): 291 ($[M + 1]^+$, 100).

2,3-Diphenylpyrazine (5a). Solid, mp 121–122 °C (lit.[20] 119–120 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.28$–7.34 (m, 6H), 7.45–7.49 (m, 4H), 8.59 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 128.3$, 128.7, 129.6, 138.6, 142.1, 152.8. MS (ESI) m/z (%): 233 ($[M + 1]^+$, 100).

5-Methyl-2,3-diphenylpyrazine (5b). Solid, mp 91–92 °C (lit.[21] 88–89 °C). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.66$ (s, 2H), 7.27–7.31 (m, 6H), 7.42–7.47 (m, 4H), 8.48 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$, 128.2, 128.2, 128.3, 128.5, 129.6, 129.7, 138.7, 138.8, 141.9, 149.7, 151.2, 151.6. MS (ESI) m/z (%): 247 ($[M + 1]^+$, 100).

2,3-Diphenyl-5,6,7,8-tetrahydroquinoxaline (5c).[22] Solid, mp 152–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.99$–2.01 (m, 4H), 3.09 (m, 4H), 7.28–7.31 (m, 6H), 7.42–7.45 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.8$, 31.8, 128.1, 128.2, 129.7, 139.0, 149.5, 150.5. MS (ESI) m/z (%): 287 ($[M + 1]^+$, 100).

2,3-Di(2-furyl)pyrazine (5d). Solid, mp 78–80 °C (lit.[23] 81 °C).^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.52$–6.69 (m, 4H), 7.54–7.55 (m, 2H), 8.50 (d, $J = 1.7$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 111.8$, 112.1, 112.3, 141.7, 143.8, 150.4. MS (ESI) m/z (%): 213 ($[M + 1]^+$, 100).

2,3-Di(2-furyl)-6-methylpyrazine (5e).[24] Solid, mp 62–65 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.59$ (s, 3H), 6.46–6.59 (m, 4H), 7.49–7.52 (m, 2H), 8.35 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.4$, 111.5, 111.7, 111.7, 112.1, 139.2, 140.9, 141.8, 143.4, 143.7, 150.5, 150.6, 151.3. MS (ESI) m/z (%): 227 ($[M + 1]^+$, 100).

2,3-Di(2-furyl)-5,6,7,8-tetrahydroquinoxaline (5f).[25] Solid, mp 150–151 °C.^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.90$–1.95 (m, 4H), 2.97–3.02 (m, 4H), 6.44–6.49 (m, 4H), 7.49–7.50 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.6$, 31.8, 111.3, 111.6, 139.2, 143.3, 150.7, 150.8. MS (ESI) m/z (%): 267 ($[M + 1]^+$, 100).

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