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An efficient and convenient protocol for the synthesis of quinoxalines and dihydropyrazines via cyclization–oxidation processes using $HClO_4{\cdot}SiO_2$ as a heterogeneous recyclable catalyst☆

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Abstract—A convenient and straightforward method has been developed for the synthesis of quinoxalines and dihydropyrazines (DHPs) using α-bromo ketones and 1,2-diamines in the presence of silica supported perchloric acid ($HClO_4{\cdot}SiO_2$) at room temperature. The quinoxalines and DHPs were presumably formed via cyclization–oxidation. The catalyst works under heterogeneous conditions and can be recycled.

Quinoxalines and pyrazines are important heterocycles in medicinal chemistry.[1] Quinoxalines display a broad spectrum of biological activity[2] which has made them privileged structures in combinatorial drug discovery libraries.[3] They have also found applications as dyes,[4a] efficient electroluminescent materials,[4b] organic semiconductors,[4c] dehydroannulenes,[4d] cavitands[4e] and chemically controllable switches.[4f] The biological and physical roles of dihydropyrazines (DHPs) such as DNA cleavage,[5a] growth inhibition of *Escherichia coli*[5b] and cyclooxygenase inhibitory activity[5c] are well documented. A number of methods have been developed for the synthesis of substituted quinoxalines and DHPs involving condensation of 1,2-diamines with α-diketones,[6] 1,4-addition of 1,2-diamines to diazenylbutenes,[7] oxidation-trapping of α-hydroxy ketones with 1,2-diamines,[8] cyclization–oxidation of phenacyl bromides and *o*-phenylenediamines through solid-phase synthesis[3b,9] and oxidative coupling of epoxides with ene-1,2-diamines.[10] Nevertheless, most of these methods suffer from unsatisfactory yields, difficult experimental procedures, expensive and detrimental metal precursors and harsh reaction conditions. Therefore, the development of improved methods for the synthesis of quinoxaline and DHP derivatives has acquired relevance to current research.

In recent years, heterogeneous catalysts have gained more importance due to enviro-economic factors. They have successfully been utilized in several organic transformations to minimize undesirable waste causing environmental pollution. As a part of our endeavors towards the development of efficient and environmentally benign synthetic methodologies using economic and eco-friendly heterogeneous catalysts,[11] we have investigated the synthesis of quinoxalines and DHPs from α-bromoketones and 1,2-diamines in the presence of silica-supported perchloric acid ($HClO_4{\cdot}SiO_2$) at room temperature[12] (Scheme 1).

Our initial efforts were directed towards the catalytic evaluation of $HClO_4{\cdot}SiO_2$ for the synthesis of quinoxalines and DHPs. Initially, a blank reaction was carried out using phenacyl bromide **1a** and *o*-phenylene diamine **2a** in CH_3CN at room temperature, which resulted in no quinoxaline derivative after 5 h. The same reaction using a catalytic amount of $HClO_4{\cdot}SiO_2$ in CH_3CN afforded the desired quinoxaline in 94% yield within 15 min at

Keywords: α-Bromoketone; 1,2-Diamine; $HClO_4{\cdot}SiO_2$; Cyclization–oxidation processes; Quinoxaline; Dihydropyrazine; Heterogeneous recyclable catalyst.

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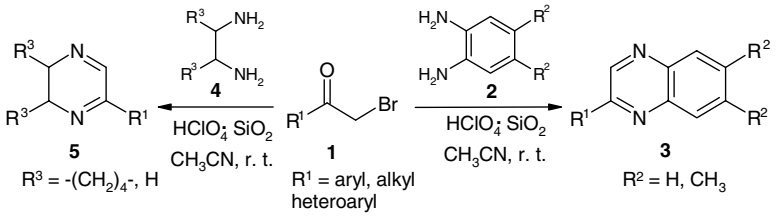
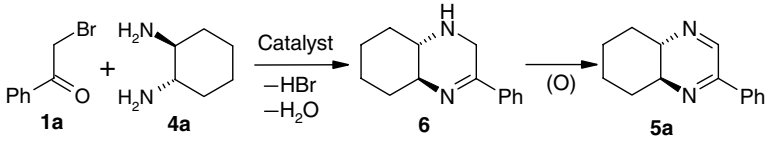


Scheme 1. Synthesis of quinoxalines **3** and dihydropyrazines **5**.



Scheme 2. Cyclization–oxidation processes in the formation of dihydropyrazines.

Table 1. Catalyst screen[a]

Entry	Catalyst	Time (h)	Isolated yield (%)	
			6	**5a**
1	$ClSO_3H{\cdot}SiO_2$ (wet)	3	41	22
2	PTSA·SiO_2	3	46	12
3	Amberlyst-15	3	52	—
4	Sulfonic-acid-functionalized silica	3	71	—
5	$NaHSO_4{\cdot}SiO_2$	3	62	—
6	Silica chloride	3	37	—
7	$HClO_4{\cdot}SiO_2$	0.25	3	92

[a] All the reactions were performed using diamine **4a** (1.25 mmol), phenacyl bromide **1a** (1.0 mmol) and 50 mg of catalyst in CH_3CN (5 mL) at rt.

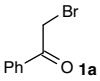
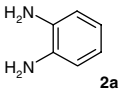
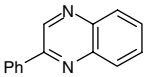
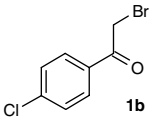
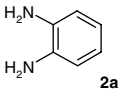
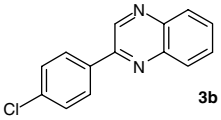
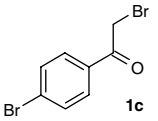
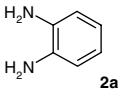
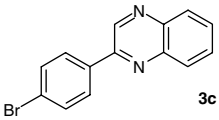
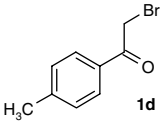
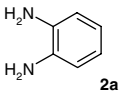
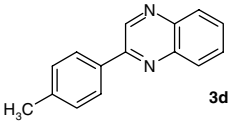
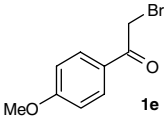
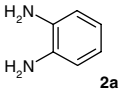
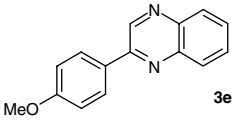
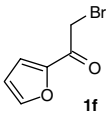
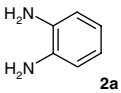
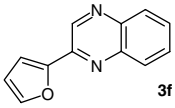
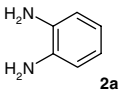
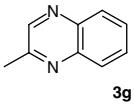
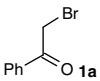
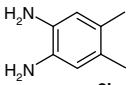
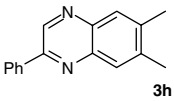
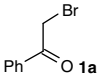
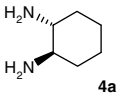
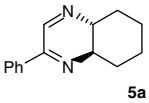
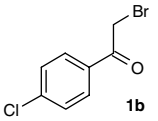
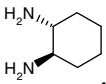
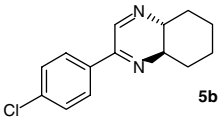
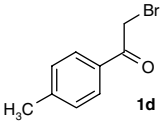
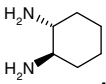
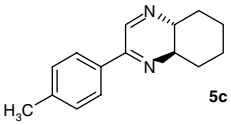
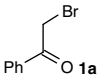
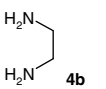
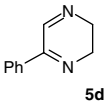
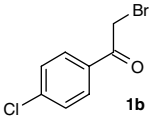
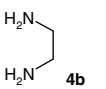
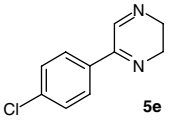
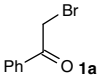
room temperature. The role of $HClO_4{\cdot}SiO_2$ in the cyclization–oxidation processes (Scheme 2) was confirmed by the treatment of (±)-*trans*-1,2-diaminocyclohexane (**4a**) with phenacyl bromide **1a** employing various heterogeneous catalysts (Table 1). Tetrahydropyrazine **6** was produced as the major product with incomplete oxidation in the presence of other catalysts (entries 1–6), while DHP **5a** was obtained in 92% within 15 min using $HClO_4{\cdot}SiO_2$ (entry 7). In the formation of **5a** from **6** in the presence of $HClO_4{\cdot}SiO_2$, aerial oxygen is presumably the oxidant under the reaction conditions. In the absence of air, the conversion of **6** into **5a** using a catalytic amount of the catalyst was found to be very low. Pure **6** also separately underwent oxidation to **5a** in the presence of $HClO_4{\cdot}SiO_2$ under similar experimental conditions.

In order to demonstrate the versatility of the $HClO_4{\cdot}SiO_2$ promoted synthesis of quinoxalines and DHPs, a series of α-bromoketones were treated with various 1,2-diamines (Table 2). The reactions proceeded at room temperature within a short time to afford the products. The reaction of *o*-phenylenediamines with various bromoketones (entries 1–8) resulted in high yields of substituted quinoxalines. In the case of 4-methyl- and 4-methoxyphenacyl bromides (entries 4 and 5), steric factors played a key role in affecting the rate of the reaction which required longer times, while the reaction with bromoacetone (entry 7) was somewhat faster. The sterically hindered diamine **2b** (entry 8) afforded the corresponding product in moderate yield. When (±)-*trans*-1,2-diaminocyclohexane **4a** was reacted with α-bromoketones (entries 9–11), 5,6-dihydropyrazines **5a–5c** were obtained in excellent yields. However, with ethylene diamine (**4b**) similar reactions furnished DHPs **5d** and **5e** in moderate yields only. The method has also been applied for the preparation of dihydroquinoxaline **8** using phenacyl bromide **1a** and diamine **7**. The structures of the products were determined from spectral (^{1}H NMR and MS) and elemental analysis data.

The catalyst $HClO_4{\cdot}SiO_2$ works under heterogeneous conditions and can easily be prepared from readily available $HClO_4$ and silica gel.[13] It can conveniently be handled and removed from the reaction mixture. The catalyst was recycled three times without the loss of activity.

In summary, we have demonstrated that α-bromoketones can be directly converted into quinoxalines and DHPs by treatment with 1,2-diamines via cyclization–oxidation in the presence of $HClO_4{\cdot}SiO_2$ as catalyst. The mild reaction conditions, simple experimental procedure and reusability of the catalyst are notable advantages of the present method. To our knowledge, this is the first report on the synthesis of quinoxalines and DHPs from 1,2-diamines and α-bromoketones using a heterogeneous catalyst at room temperature.

Table 2. Synthesis of quinoxalines and dihydropyrazines using $HClO_4{\cdot}SiO_2$[a]

Entry	α-Bromoketone	1,2-Diamine	Time (min)	Product	Isolated yield (%)	Ref.
1	 **1a**	 **2a**	15	 **3a**	94	8a
2	 **1b**	 **2a**	20	 **3b**	92	—
3	 **1c**	 **2a**	20	 **3c**	90	8b
4	 **1d**	 **2a**	35	 **3d**	89	8b
5	 **1e**	 **2a**	35	 **3e**	87	8b
6	 **1f**	 **2a**	25	 **3f**	87	8a
7	 **1g**	 **2a**	15	 **3g**	95	8a
8	 **1a**	 **2b**	60	 **3h**	80	8a
9	 **1a**	 **4a**	15	 **5a**	92	8a
10	 **1b**	 **4a**	20	 **5b**	93	—
11	 **1d**	 **4a**	35	 **5c**	92	—
12	 **1a**	 **4b**	30	 **5d**	72	8a
13	 **1b**	 **4b**	35	 **5e**	70	—
14	 **1a**	**7**	60	**8**	73	8b

[a] The structures of the products were determined from spectral (^{1}H NMR and MS) and elemental analysis data.

Acknowledgement

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12. General procedure for the preparation of quinoxalines or dihydropyrazines: To a suspension of a α-bromoketone (1 mmol) and $HClO_4{\cdot}SiO_2$ (50 mg) in CH_3CN (5 mL), 1,2-diamine (1.25 mmol) was added slowly and the mixture was stirred at room temperature. The reaction was monitored by TLC. After completion, the reaction mixture was filtered. The catalyst was washed with $CHCl_3$ (2×5 mL), EtOH (2×5 mL) and Et_2O (2×5 mL) and subsequently dried at 80 °C for reuse. The filtrate was concentrated and the residue was subjected to column chromatography (silica gel, hexane–EtOAc) to obtain pure quinoxaline or dihydropyrazine.
The recovered catalyst was reused three times with only a little variation in the yields of the products. For example, in the synthesis of quinoxaline **3a** (reaction time: 15 min in each case) the catalyst was used in four consecutive runs to furnish **3a** in yields of 94%, 94%, 91% and 90%.
Conversion of **6** into **5a**: A suspension of **6** (1 mmol) and $HClO_4{\cdot}SiO_2$ (30 mg) in CH_3CN (5 mL) was stirred at room temperature. The conversion was followed by TLC. After completion (10 min), the reaction mixture was filtered. The filtrate was concentrated and the viscous mass was purified by column chromatography (silica gel, hexane–EtOAc, 4:1) to furnish **5a** (yield 95%).
Spectral (^{1}H NMR and MS) and elemental analysis data for new products are given below.
Compound **3b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.27 (1H, s), 8.18 (2H, d, $J=8.0$ Hz), 8.13–8.03 (2H, m), 7.82–7.67 (2H, m), 7.51 (2H, d, $J=8.0$ Hz); EIMS: *m*/*z* 240, 242 ($M^{+\cdot}$); Anal. Calcd for $C_{14}H_9ClN_2$: C, 69.85; H, 3.74; N, 11.64. Found: C, 69.91; H, 3.68; N, 11.72.
Compound **5b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.25 (1H, d, $J=2.4$ Hz), 7.81 (2H, d, $J=8.0$ Hz), 7.40 (2H, d, $J=8.0$ Hz), 2.89–2.58 (2H, m), 2.51–2.32 (2H, m), 2.02–1.76 (2H, m), 1.71–1.29 (4H, m); EIMS: *m*/*z* 246, 248 ($M^{+\cdot}$); Anal. Calcd for $C_{14}H_{15}ClN_2$: C, 68.15; H, 6.08; N, 11.36. Found: C, 68.10; H, 6.01; N, 11.45.
Compound **5c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.31 (1H, br s), 7.74 (2H, d, $J=8.0$ Hz), 7.19 (2H, d, $J=8.0$ Hz), 2.90–2.57 (2H, m), 2.52–2.17 (5H, m), 2.08–1.72 (2H, m), 1.64–1.09 (4H, m); EIMS: *m*/*z* 226 ($M^{+\cdot}$); Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.65; H, 7.96; N, 12.39. Found: C, 79.73; H, 7.88; N,12.28.
Compound **5e**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.32 (1H, br s), 7.78 (2H, d, $J=8.0$ Hz), 7.40 (2H, d, $J=8.0$ Hz), 3.72–3.63 (2H, m), 3.61–2.99 (2H, m); EIMS: *m*/*z* 192, 194 ($M^{+\cdot}$); Anal. Calcd for $C_{10}H_9ClN_2$: C, 62.34; H, 4.67; N, 14.54. Found: C, 62.27; H, 4.72; N, 14.47.
Compound **6**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.91 (2H, dd, $J=8.0$, 2.0 Hz), 7.45–7.29 (3H, m), 6.69 (1H, br s), 3.28–3.11 (2H, m), 2.54–2.33 (1H, m), 2.10–1.79 (3H, m), 1.59–1.17 (6H, m); EIMS: *m*/*z* 214 ($M^{+\cdot}$); Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.50; H, 8.41; N, 13.08. Found: C, 78.60; H, 8.36; N, 12.96.
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