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One-Pot Synthesis of Quinoxalines Starting from Aldehydes Under Metal-Free Conditions

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An efficient and convenient synthesis of quinoxalines from easily available aldehydes was performed as a one-pot procedure in good to excellent yields under metal-free conditions, *via* sequential benzoin condensation, aerobic formation of benzils and condensation of the latter with 1,2-diaminobenzenes.

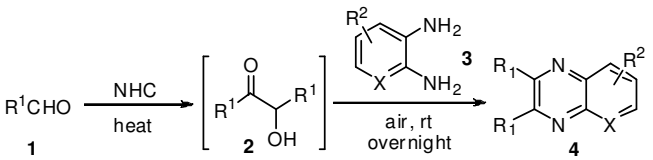
Key Words: Quinoxalines, Aldehydes, One-pot synthesis, N-Heterocyclic carbene.

INTRODUCTION

Functionalized quinoxalines represent an important class of nitrogen-containing heterocyclic compounds due to their broad spectrum of biological activities[1]. Furthermore, they have been used as building blocks for the synthesis of organic semiconductors[2], electroluminescent materials[3] and DNA cleaving agents[4].

Considering their chemical and biological significance, numerous synthetic strategies have been developed for the preparation of quinoxaline derivatives. The most common and straightforward route to quinoxalines is the condensation of 1,2-dicarbonyl compounds with 1,2-diaminobenzenes under various conditions, including the employment of microwave irradiation[5], different solvents and catalysts such as heteropolyacids[6], polyethylene glycol (PEG)[7], montmorillonite K-10[8], molecular iodine[9], ceric ammonium nitrate (CAN)[10], $Bi(OTf)_3$[11], $Ga(OTf)_3$[12] and so on. Some other synthetic methods using non-1,2-dicarbonyl compounds or non-1,2-diaminebenzenes as starting materials have also been documented[13]. However, most of existing methods suffer from one or more drawbacks such as tedious work-up procedures, use of toxic metal catalysts and not easily accessible materials like 1,2-diketones, α-substituted ketones or functionalized alkynes[13]. Hence, the pursuit of more mild and efficient methods, especially using readily available materials and green catalysts, is still demanded.

In modern organic chemistry, the synthetic strategies involving one-pot synthesis and organocatalysis are much desired because of environmental regulations. In recent years, N-heterocyclic carbenes (NHCs) have been widely applied as organocatalysis in a large number of chemical transformations such as Benzoin condensation and Stetter reaction[14]. As part of our ongoing program to explore efficient and environmentally benign methodologies for heterocyclic synthesis using N-heterocyclic carbenes as organocatalysts[15], we find that 2,3-disubstituted quinoxalines **4** could be synthesized from easily accessible aldehydes **1**, proceeding *via* sequential N-heterocyclic carbenes-catalyzed synthesis of benzoins **2**, aerobic oxidation of benzoins into benzils and condensation of the latter with aryl 1,2-diamines **3** in a one-pot procedure (**Scheme-I**). The results are reported herein.



Scheme-I: One-pot synthesis of quinoxalines **4** starting from aldehydes **1**

EXPERIMENTAL

All solvents and materials were obtained from commercial sources.

General procedure: To a 25 mL three-necked flask was charged with catalyst **E** (35 mg, 0.16 mmol), aldehyde **1** (1.6 mmol) and THF (3 mL) under nitrogen atmosphere. Then DBU (45 μL, 0.32 mmol) was added and the mixture was stirred at 65 ºC for 3 h. After the completion of benzoin condensation monitored by analytical thin-layer chromatography (TLC), the reaction was cooled to room temperature, followed by addition of a solution of aryl 1,2-diamines **3** (0.4 mmol) in EtOAc

(8 mL). The mixture was next stirred overnight under air at room temperature. The solvent was evaporated in vacuum and the residue was purified by silica gel chromatography to afford quinoxalines **4**. 2,3-Diphenylquinoxaline (**4a**), white solid, m.p. 125-126 ºC (lit.[6] 128-129 ºC). ^{1}H NMR (300M, $CDCl_3$): 8.19 (dd, J = 3.4 Hz, J = 6.4 Hz, 2H), 7.77 (dd, J = 3.4 Hz, J = 6.4 Hz, 2H), 7.51-7.54 (m, 4H), 7.30-7.44 (m, 6H).

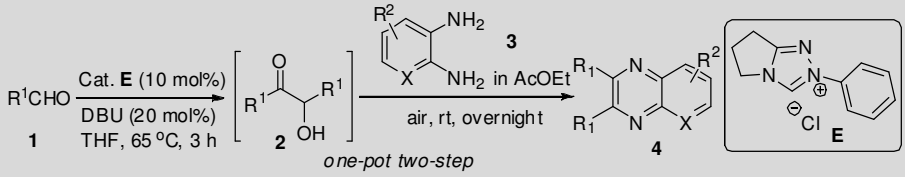
Detection method: The products are all known compounds and identified by ^{1}H NMR and melting point. ^{1}H NMR spectra were recorded with a spectrometer at 300 MHz (^{1}H NMR) in $CDCl_3$: chemical shifts (δ) are given in ppm, coupling constants (J) in Hz, the solvent signals were used as references (residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm). Melting points were obtained on a Yanaco-241 apparatus and are uncorrected.

RESULTS AND DISCUSSION

Preliminary studies were initiated in a stepwise manner by first selection of the optimal conditions for N-heterocyclic carbene-catalyzed benzoin condensation. After screening several N-heterocyclic carbenes and bases, we found that the condensation of benzaldehyde **1a** afforded benzoin **2a** in 85 % yield catalyzed by carbene precursor **E** (10 mol %) using DBU (20 mol %) as a base in THF at 65 ºC for 3 h (Entry 1, Table-1). Then, we turned our attention to explore the protocol for one-pot synthesis of quinoxalines starting from aldehydes. Benzoins were known to be oxidized into benzils under various conditions, which can be followed by tandem trapping with 1,2-diamines to give quinoxalines[13d]. Due to the advantages of aerobic oxidation that made the oxidation procedures more economical and environmentally benign, we selected air/base combination[16] for the oxidation of benzoins. It was surprising that after completion of benzoin condensation monitored by TLC, followed by addition of a solution of 1,2-diaminobenzene **3a** in EtOAc, the mixture was allowed to react overnight at room temperature under air to afford quinoxaline **4a** in 91 % yield (Entry 1, Table 1). In this process, benzoin **2a** formed *in situ* from benzaldehyde **1a** was oxidized into benzil under air with a catalytic amount of DBU, which subsequently condensed with **3a** to produce quinoxaline **4a**.

With the optimized conditions in hand, we moved on to test various aldehydes **1** and aryl 1,2-diamines **3** to investigate the scope of the process (Table-1). We found that substituents on the aryl ring of substrates **1** and **3** significantly affected the yields. No benzoin intermediate was detected for benzaldehydes **1b** bearing strongly electron-donating groups (-OMe), resulting in failure to give quinoxalines (Entry 2). However, benzaldehydes **1c-h** substituted with methyl or halogen groups at 4- or 3-position of phenyl ring, reacted smoothly with 1,2-diaminobenzene **3a** to produce quinoxalines **4b-g** in excellent yields (Entries 3-8). Quinoxaline **4h** could be also obtained in moderate yield, although the benzoin condensation of 4-cyanobenzaldehyde **1i** was complex (Entry 9). Moreover,

TABLE-1
ONE-POT SYNTHESIS OF QUINOXALINES **4** FROM ALDEHYDES **1**



Entry	R^1	1	R^2	X	3	4	Yield (%)[b]
1	Ph	**1a**	H	CH	**3a**	**4a**	91
2	(4-OMe)Ph	**1b**	H	CH	**3a**	–	–
3	(4-Me)Ph	**1c**	H	CH	**3a**	**4b**	93
4	(4-F)Ph	**1d**	H	CH	**3a**	**4c**	87
5	(4-Cl)Ph	**1e**	H	CH	**3a**	**4d**	95
6	(4-Br)Ph	**1f**	H	CH	**3a**	**4e**	91
7	(4-I)Ph	**1g**	H	CH	**3a**	**4f**	95
8	(3-Cl)Ph	**1h**	H	CH	**3a**	**4g**	94
9	(4-CN)Ph	**1i**	H	CH	**3a**	**4h**	46
10	(2-F)Ph	**1j**	H	CH	**3a**	**4i**	72
11	(2-Cl)Ph	**1k**	H	CH	**3a**	–	–
12		**1l**	H	CH	**3a**	**4j**	98
13		**1m**	H	CH	**3a**	**4k**	99
14		**1n**	H	CH	**3a**	**4l**	85
15	*n*-Pr	**1o**	H	CH	**3a**	–	–
16	Ph	**1a**	4-Me	CH	**3b**	**4m**	88
17	Ph	**1a**	4-Cl	CH	**3c**	**4n**	78
18	Ph	**1a**	4-NO_2	CH	**3d**	**4o**	65
19	Ph	**1a**	H	**N**	**3e**	**4p**	56

[a]Reaction conditions: aldehydes **1** (1.6 mmol), cat. **E** (0.16 mmol), DBU (0.32 mmol), THF (3 mL), 65 ºC, N_2, 3 h; then 1,2-diamines **3** (0.4 mmol) in 8 mL EtOAc, room temperature, air, overnight. [b]Isolated yields based on 1,2-diamines.

o-substituted benzaldehydes which were not good substrates for benzoin condensation because of the steric effect at 2-position were examined for this one-pot process. Remarkably, the reaction of *o*-fluorobenzaldehyde **1j** with 1,2-diaminobenzene **3a** gave product **4i** in 72 % yield (Entry 10), whereas the reaction of more sterically hindered *o*-chlorobenzaldehyde **1k** with **3a** failed to gave desired product (Entry 11). It was of delight to find that heteroaromatic aldehydes **1l-n** equally showed good tolerance with this one-pot procedure (Entries 12-14). Compared to aromatic aldehydes, aliphatic aldehyde **1o** proved to be ineffective (Entry 15). Several aryl 1,2-diamines were next tested to react with **1a**. 4-Methyl-1,2-diaminobenzene **3b** gave a comparable yield to **3a**, while **3c** and **3d** bearing electron-withdrawing group, as well as pyridine-2,3-diamine **3e**, led to decreased yields (Entries 16-19).

Conclusion

We have demonstrated a mild and convenient one-pot method to deliver quinoxalines from various aryl aldehydes and 1,2-diamines. This reaction proceeded *via* sequential benzoin condensation, aerobic formation of benzils and condensation of the latter with aryl 1,2-diamines. The advantages that using easily available materials, mild and metal-free conditions and operational simplicity made this protocol an alternative pathway to efficiently construct quinoxaline framework.

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