Transition-Metal-Free Synthesis of Quinoxalines from *o*-Phenylenediamines and Arylacetaldehydes under Basic Conditions

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Abstract: A novel method for the synthesis of quinoxalines via transition-metal-free cyclization of *o*-phenylenediamine and arylacetaldehyde in a one-pot procedure has been developed. In this process, an inorganic base (K_2CO_3) is the only reagent required, and it proceeds smoothly in the absence of adding transition metal catalysts. The reaction appears to be very general and suitable for the construction of a variety of quinoxalines.

Key words: quinoxalines, *o*-phenylenediamine, arylacetaldehyde, oxidation, condensation, transition-metal-free

Quinoxalines are one of the most important nitrogen-containing heterocycles since they are useful as biologically active compounds,[1] antibiotics,[2] electroluminescent materials,[3] and dyes.[4] Furthermore, they can serve as precursors for a variety of pharmacological active compounds.[5] Consequently, various synthetic strategies[6] were developed for the preparation of substituted quinoxalines, and the most common methods relied on the direct condensation *o*-phenylenediamines with α-dicarbonyls.[7] In addition, several new methods that utilized metal-catalytic systems for synthesizing quinoxalines have been developed: PdI_2,[8] $Yb(OTf)_3$,[9] $Bi(OTf)_3$,[10] $Ce(NH_4)_2(NO_3)_6$,[11] $RuCl_2(PPh_3)_3$,[12] and $Ga(OTf)_3$.[13] In spite of the wide applicability of these methodologies in modern organic synthesis, a limitation of the general approach is the requirement of metals, either as catalysts or in stoichiometric amounts, which in many cases can make these preparative procedures environmentally unfriendly and expensive.

Recently, some examples have been discovered in the development of metal-free transformations to form quinoxalines. In general, there are two routes. The first route is the direct reaction of 1,2-diaminobenzenes with ketones in the presence of potassium hydroxide in PEG-400 for 60 hours.[14] The second route is the condensation of 1,2-diaminobenzene with ketones via their α-hydroxylimino ketone derivatives under microwave irradiation at 125 °C or 140 °C.[15] Although they are efficient processes, there are very few general methods that convert commercially available or readily accessible materials in one step into quinoxalines, and they suffer from one or more limitations, for example, the use of expensive reagents, long reaction times, elevated temperature, and poor scope of substrates. As a part of our ongoing studies on N-heterocyclization, we also reported a copper-catalyzed approach to quinoxalines with *o*-phenylenediamine and terminal alkyne in the presence of bases.[16] Encouraged by these transformations, we conceived that the reaction between *o*-phenylenediamine and phenylacetaldehyde may be possible. In addition, many methods that utilized metal-free and basic conditions have been reported for synthesizing other organic compounds.[17,18]

Herein, we report a novel approach for the synthesis of quinoxalines in good to excellent yields by the direct oxidative condensation of *o*-phenylenediamine with arylacetaldehyde. The process involves a one-pot procedure and proceeds smoothly in air without adding any transition-metal catalyst. An inorganic base (K_2CO_3) is the only reagent required. The method is highly efficient and provides a novel, convenient, economical, and environmentally friendly practical route to quinoxalines.

At the beginning of our study, *o*-phenylenediamine (**1a**) and phenylacetaldehyde (**2a**) were chosen as the test substrates for this cyclization using CuI in toluene at 90 °C in air to achieve the transformation. Gratifyingly, the desired 2-phenylquinoxaline (**3aa**) was obtained in 67% yield after eight hours (Table 1, entry 1). Compared with $CuBr_2$ and other catalysts, the reaction in the absence of catalyst showed the highest activity and resulted in 83% yield (see, Table 1, entries 2 and 3, and Supporting Information). When the reaction was carried out in the absence of catalysts and bases, a lower yield was obtained (Table 1, entry 4). Therefore, the presence of K_2CO_3 was essential for the effective formation of **3aa**. Similar methodologies by adding K_2CO_3 in the absence of transition-metal catalysts for the synthesis of 3-carboxylated indoles have been reported.[18] However, there was a lower yield, both increasing and decreasing temperatures, or prolonging and shortening reaction times, or a nitrogen atmosphere (Table 1, entries 5–7). When oxygen was employed as the oxidant, only 81% of **3aa** was isolated (Table 1, entry 8). Thus, air was chosen as one of the best conditions for its low cost and convenience. What's more, different bases including organic and inorganic bases were also evaluated, but no better results were obtained (see, Table 1, entries 3, 9, 10, and Supporting Information). Further inspection of the reaction conditions revealed that the reaction proceeded more efficiently in toluene, while other solvents such as

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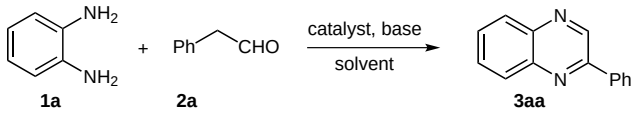
1,4-dioxane, acetonitrile, ethanol, and water were found to be unfavorable (Table 1, entries 11–14).

Table 1 Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	CuI[i]	K_2CO_3	toluene	67
2	$CuBr_2$[i]	K_2CO_3	toluene	12
3	none	K_2CO_3	toluene	83
4	none	none	toluene	28
5	none	K_2CO_3	toluene	58[c], 60[d]
6	none	K_2CO_3	toluene	56[e], 65[f]
7	none	K_2CO_3	toluene	24[g]
8	none	K_2CO_3	toluene	81[h]
9	none	DMAP	toluene	68
10	none	$K_3PO_4 \cdot 3H_2O$	toluene	38
11	none	K_2CO_3	1,4-dioxane	37
12	none	K_2CO_3	MeCN	15
13	none	K_2CO_3	EtOH	19
14	none	K_2CO_3	H_2O	n.r.

[a] All of the reactions were carried out in tubes using 0.25 mmol of **1a**, 0.5 mmol of **2a**, and 2 equiv of base in the solvent at 90 °C for 8 h in air.
[b] Isolated yields.
[c] The reaction was carried out at 110 °C.
[d] The reaction was carried out at r.t.
[e] For 4 h.
[f] For 24 h.
[g] Protected by N_2.
[h] O_2 (1.0133 bar).
[i] Catalyst (0.025 mmol).

With the optimized reaction conditions (Table 1, entry 3), various *o*-diamines (**1**) were examined (Table 2). Generally, the reaction of a series of *o*-phenylenediamines with phenylacetaldehyde proceeded smoothly and afforded the corresponding products in moderate to good yields. For the electronic effects of these reactions, we found that the electron-rich *o*-phenylenediamines showed better reactivity and gave higher yields than electron-deficient ones. To our delight, the strong electron-withdrawing substituent was also compatible with the reaction conditions (Table 2, entry 3). It was noteworthy that regioselectivities were observed in this reaction. The methoxy, chloro, and bromo substituents at the *para* position all underwent the desired reaction and gave the two products **3** and **4**, respectively (Table 2, entries 1, 4, and 5), whereas a substrate having a 4-methyl substituent yielded a mixture of regioisomers. Then the structure of **3ea** was confirmed by X-ray crystallography (Figure 1). Besides, the alkyl-substituted *o*-diamines, such as pyridine-3,4-diamine and ethane-1,2-diamine, were also tested in this reaction, but they did not afford the desired products (Table 2, entries 7 and 8).

To further explore the generality and scope of this approach, a variety of aldehydes **2** were investigated under the optimized conditions (Table 3). It was found that the electron-donating phenylacetaldehydes worked well to afford the corresponding products in good yields (Table 2, entries 2 and 3). Intriguingly, the yield was increased to 81% when we prolonged the reaction time to ten hours. The electron-withdrawing substituents, such as F and Cl, afforded the desired product in a lower yield (Table 3, entry 4) or gave not the desired product (Table 3, entry 5). These differences indicated that the electronic effects had a significant effect on this transformation. In addition, the methoxy moiety on phenylacetaldehyde with several substituents on *o*-phenylenediamines proceeded smoothly and gave the corresponding quinoxalines with great efficiency (Table 3, entries 6–9). However, an alkyl aldehyde could not be converted into the desired product (Table 3, entry 10).

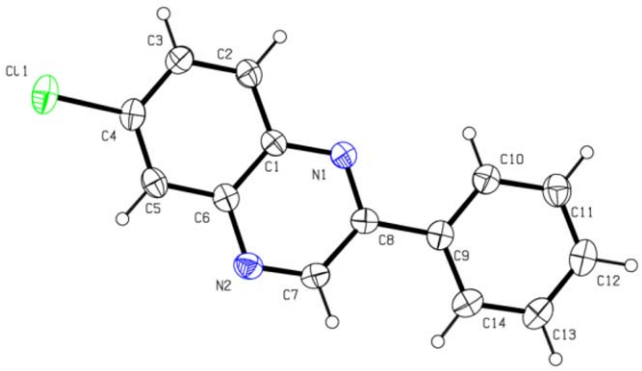
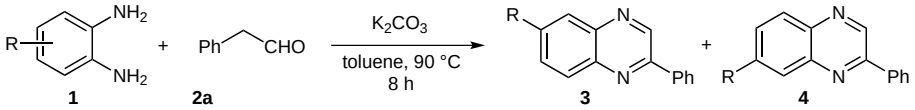
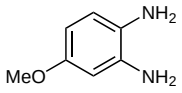
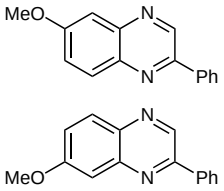
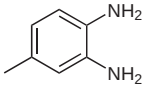
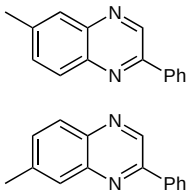
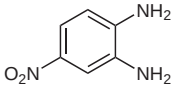
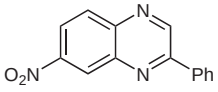
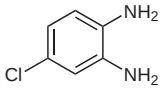
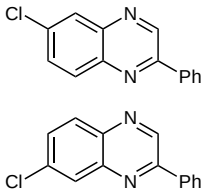
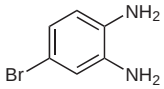
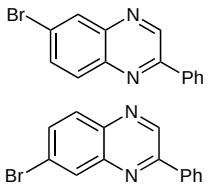
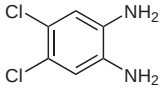
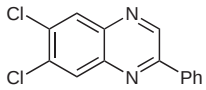
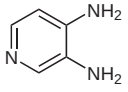


Figure 1 X-ray crystal structure of **3ea**[21]

To probe the reaction mechanism, we carried out a few experiments. 2-Oxo-2-phenylacetaldehyde (**5**) was not detected in the reaction of **2a** under the standard reaction conditions (Scheme 1). This result indicates that **5** is not the intermediate of this transformation, and path a is not reasonable. On the basis of the results obtained above, a plausible mechanism of this reaction is illustrated in Scheme 1. *o*-Phenylenediamine (**1a**) and phenylacetaldehyde (**2a**) react to form imine **7** (Scheme 1, path b).[19] Imine **7** equilibrates to enamine **8**. Then, enamine **8** seems to be followed by intramolecular hydroamination to form **9**.[14] Finally, **9** could be easily oxidized to the target compound **3aa** by air.[20] We will focus on the reaction mechanism in further studies.

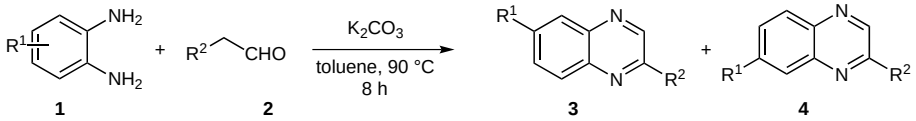
Table 2 Reactions of Substituted *o*-Diamines with Phenylacetaldehyde[a]



Entry	1	Product	Yield (%)[b]
1	 **1b**	 **3ba**/**4ba** = 1:1.7	87
2	 **1c**	 **3ca**/**4ca** = 1:1.6	82
3	 **1d**	 **4da**	21
4	 **1e**	 **3ea**/**4ea** = 1:1.35	57
5	 **1f**	 **3fa**/**4fa** = 1:1.22	70
6	 **1g**	 **3ga**	65
7	 **1h**	**3ha**	0
8	$NH_2CH_2CH_2NH_2$ **1i**	**3ia**	0

[a] All of reactions were carried out in sealed tubes using 0.25 mmol of **1**, 0.5 mmol of **2a**, 2 equiv of base (K_2CO_3) in toluene at 90 °C for 8 h in air.
[b] Isolated yields.

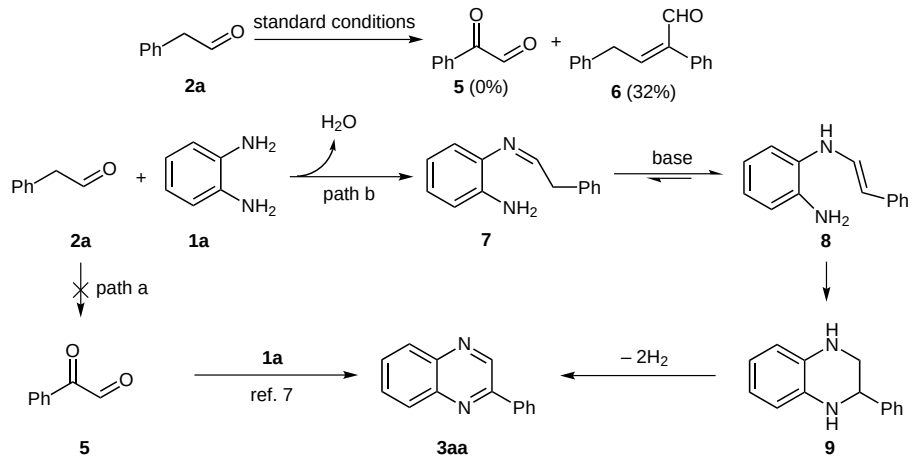
Table 3 Reactions of Substituted Phenylacetaldehyde with Various *o*-Diamines[a]



1 2 3 4

Entry	R^1	R^2	Product	Yield (%)[b]
1	**1a** H	**2a** Ph	**3aa**22	83
2	**1a** H	**2b** 4-$MeOC_6H_4$	**3ab**	58 (81[c])
3	**1a** H	**2c** 4-MeC_6H_4	**3ac**	56
4	**1a** H	**2d** 4-FC_6H_4	**3ad**	30
5	**1a** H	**2e** 4-ClC_6H_4	**3ae**	0
6	**1b** 4-MeO	**2b** 4-$MeOC_6H_4$	**3bb**/**4bb** = 1.32:1	71
7	**1e** 4-Cl	**2b** 4-$MeOC_6H_4$	**3eb**/**4eb** = 1:1.21	72
8	**1f** 4-Br	**2b** 4-$MeOC_6H_4$	**3fb**/**4fb** = 1:1.60	62
9	**1g** 4,5-Cl_2	**2b** 4-$MeOC_6H_4$	**3gb**	67
10	**1a** H	**2f** *n*-Pr	**3af**	0

[a] All of the reactions were carried out in sealed tubes using 0.25 mmol of **1**, 0.5 mmol of **2**, 2 equiv of base (K_2CO_3) in toluene at 90 °C for 8 h in air.
[b] Isolated yields.
[c] The reaction time was prolonged to 10 h.



Scheme 1 Proposed mechanism of the reaction

In conclusion, we have developed a novel and transition-metal-free method for the synthesis of quinoxalines from *o*-phenylenediamines and arylacetaldehydes. K_2CO_3 is the only reagent required for the procedure, and the reaction proceeds smoothly in air in the absence of any transition-metal catalyst. Various substituents are tolerated in this reaction, which proceeds smoothly in moderate to good yields. The procedure, using metal-free conditions as the synthetic system, is a simple, economical, and environmentally friendly protocol for the synthesis of quinoxalines.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(21) The crystal structure of **3ea** ($C_{14}H_9ClN_2$) has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number 887263.

(22) **General Procedure of the Reaction between *o*-Phenylenediamines and Arylacetaldehydes – Synthesis of 2-Phenylquinoxaline (3aa)**

o-Phenylenediamine (**1a**, 27 mg, 0.25 mmol), phenylacetaldehyde (**2a**, 58 μL, 0.5 mmol), K_2CO_3 (69 mg, 0.5 mmol), and toluene (2 mL) were added to a flask with a magnetic stirred bar. The reaction mixture was stirred for 8 h at 90 °C. The solution was then cooled to r.t., diluted with EtOAc and filtered. The filtrate was removed under the reduced pressure to get the crude product. The crude product was purified by column chromatography on silica gel (PE–EtOAc = 20:1) to afford **3aa** (83% yield) as light yellow solid; mp 62–64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.32 (s, 1 H), 8.20–7.80 (m, 4 H), 7.79–7.71 (m, 2 H), 7.59–7.51 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.8, 143.3, 142.2, 141.5, 136.7, 130.2, 130.1, 129.6, 129.5, 129.1, 127.5 ppm. ESI-HRMS: *m/z* calcd for $C_{14}H_{10}N_2$ $[M + H]^+$: 207.0917; found: 207.0913.

