One-Pot Copper-Catalyzed Three-Component Synthesis of Quinoxalines by Condensation and C−N Bond Formation

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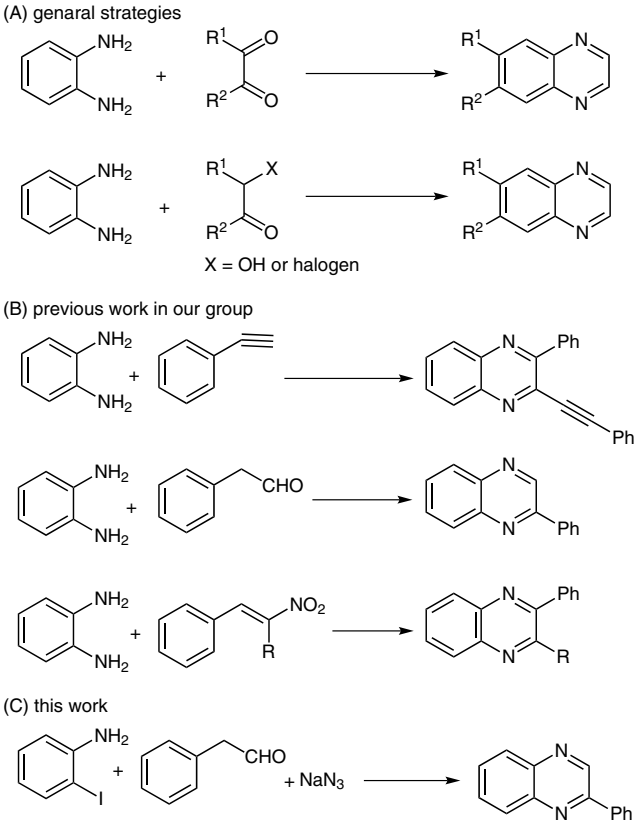
Abstract: A novel way of synthesizing quinoxalines has been developed that involves condensation and C−N bond formation in a copper-catalyzed, one-pot, three-component reaction. The reaction was optimized when 2-iodoanilines (1.0 equiv), arylacetaldehydes (2.0 equiv), sodium azide (1.2 equiv), CuI (10 mol%), DMEDA (10 mol%), and K_2CO_3 (1.0 equiv) were reacted in DMSO at 80 °C for 20 hours. This approach was used to directly synthesize a variety of quinoxalines in moderate to good yields.

Key words: quinoxalines, arylacetaldehydes, sodium azide, three-component reaction

Nitrogen-containing heteroaromatic compounds are important structures that are found in many natural and synthetic compounds. Among them, quinoxalines are crucial core structures that are used to create pharmaceuticals and agrochemicals.[1] In addition, they are useful as electroluminescent materials,[2] organic semiconductors,[3] dehydroannulenes,[4] and dyes.[5] During the last decades, a number of synthetic strategies have been developed for the preparation of substituted quinoxalines. Traditionally, condensation of 1,2-diamines with 1,2-dicarbonyl compounds,[6] and oxidative cyclization of α-hydroxy ketones or α-halide ketones with 1,2-diamines have been widely used (Scheme 1, A).[7]

Recently, we have reported a copper-catalyzed synthetic approach to quinoxalines with *o*-phenylenediamine and terminal alkyne in the presence of bases.[8] Subsequent to this discovery, the synthesis of quinoxalines with *o*-phenylenediamine and phenylacetaldehyde under metal-free conditions was reported.[9] As part of our ongoing studies on quinoxaline derivatives, we also reported a copper-catalyzed synthesis of quinoxalines from *o*-phenylenediamine and nitroolefin without additional base (Scheme 1, B).[10] Although these systems showed broad scope and high efficiency under mild conditions, they all resulted in the formation of regioisomers of the products when 1,2-diamines were employed as starting materials. Nevertheless, encouraged by these transformations, we envisaged that by using sodium azide as a nitrogen source, quinoxalines could be synthesized through copper-catalyzed, one-pot, there-component reaction from 2-iodoanilines, phenylacetaldehydes and NaN_3 in the presence of base. This approach avoids the production of regioisomers in the products when using 2-iodoanilines as starting materials and provides a novel, convenient, economical, and practical synthetic route to quinoxalines.



Scheme 1 Synthesis of quinoxaline derivatives

As a model reaction, 2-iodoaniline (**1a**), phenylacetaldehyde (**2a**), and sodium azide (**3**) were reacted under a variety of reaction conditions (Table 1). The desired 2-phenylquinoxaline (**4aa**) was not obtained in the absence of metal catalyst when **1a** (1.0 equiv), **2a** (2.0 equiv), **3** (1.2 equiv), 10 mol% DMEDA, and K_2CO_3 (1.0 equiv) were reacted in DMSO at 80 °C for 20 hours (Table 1, entry 1); therefore, we employed and tested several copper catalysts. Gratifyingly, the desired product **4aa** was obtained in 61% yield with 10 mol% CuCl (Table 1, entry 2). Furthermore, when the copper salts were changed to CuBr, CuI, CuO, $Cu(OAc)_2$, $CuCl_2$ and $CuBr_2$, it was found that CuI showed the highest activity for this reaction,

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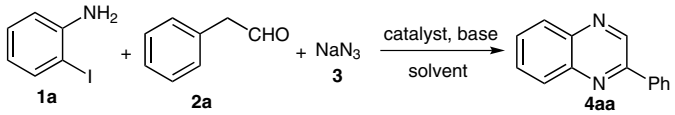
resulting in 75% yield (Table 1, entries 3–8). Performing the reaction for a shorter time (12 h) resulted in a lower yield, and no improvement was achieved when the reaction time was prolonged to 24 hours (Table 1, entry 9).

When the temperature of the reaction was reduced to room temperature, none of the desired product was formed, and a lower yield was obtained when the temperature was increased to 100 °C (Table 1, entry 10). Other ligands such as TMEDA, 1,10-phenanthroline and 2,2′-bipyridine were evaluated, but no better result was obtained (Table 1, entries 11–13). Several bases (Na_2CO_3, $KHCO_3$, DMAP, Cs_2CO_3, KOH, Li_2CO_3) were also tested, however, these bases were less efficient than K_2CO_3 (Table 1, entries 14–19). We then attempted several different solvents, including DMF, toluene and 1,4-dioxane, however no products were formed.

Having established the optimal reaction conditions, the scope of the reaction was then examined; the results are illustrated in Table 2. Various 2-iodoanilines were examined. Generally, the reaction of a series of 2-iodoanilines **1** with phenylacetaldehyde (**2a**) and sodium azide (**3**) proceeded smoothly and led to the desired product **4** in moderate to good yields. Upon examining the electronic effects of these reactions, we found that 2-iodoanilines with electron-donating groups, such as methoxy and methyl groups (Table 2, entries 1–3) showed better activities and gave higher yields than those with electron-withdrawing groups such as chloro and bromo (Table 2, entries 4–7). To our delight, strongly electron-withdrawing substituents (CF_3, NO_2) were also compatible with the reaction conditions. However, when 3-iodopyridin-2-

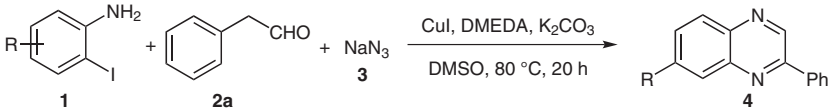
Table 1 Optimization of Reaction Conditions[a]



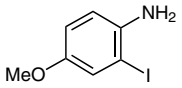
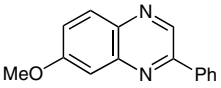
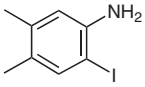
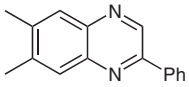
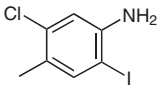
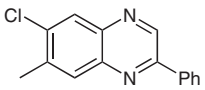
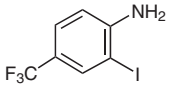
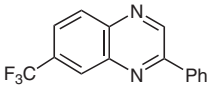
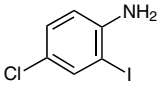
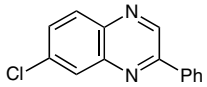
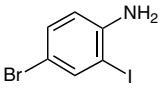
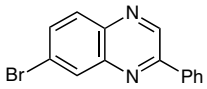
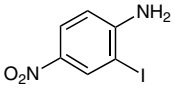
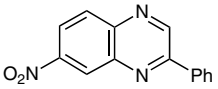
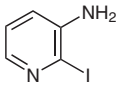
Entry	Catalyst	Ligand	Base	Yield (%)[b]
1	–	DMEDA	K_2CO_3	0
2	CuCl	DMEDA	K_2CO_3	61
3	CuBr	DMEDA	K_2CO_3	54
4	**CuI**	**DMEDA**	**K_2CO_3**	**75**
5	CuO	DMEDA	K_2CO_3	0
6	$Cu(OAc)_2$	DMEDA	K_2CO_3	23
7	$CuCl_2$	DMEDA	K_2CO_3	34
8	$CuBr_2$	DMEDA	K_2CO_3	28
9	CuI	DMEDA	K_2CO_3	56,[c] 74[d]
10	CuI	DMEDA	K_2CO_3	0,[e] 71[f]
11	CuI	TMEDA	K_2CO_3	48
12	CuI	1,10-phenanthroline	K_2CO_3	0
13	CuI	2,2′-bipyridine	K_2CO_3	0
14	CuI	DMEDA	Na_2CO_3	64
15	CuI	DMEDA	$KHCO_3$	68
16	CuI	DMEDA	DMAP	0
17	CuI	DMEDA	Cs_2CO_3	60
18	CuI	DMEDA	KOH	0
19	CuI	DMEDA	Li_2CO_3	trace

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), **3** (0.30 mmol), catalyst (0.025 mmol), ligand (0.025 mmol), base (1.0 equiv), solvent (1.0 mL), 80 °C, 20 h.
[b] Isolated yield.
[c] Reacted for 12 h.
[d] Reacted for 24 h.
[e] Reacted at r.t.
[f] Reacted at 100 °C.

Table 2 Reactions of Substituted 2-Iodoanilines with Phenylacetaldehyde and Sodium Azide[a]



1 2a 4

Entry	2-Iodoaniline **1**		Product **4**		Yield (%)[b]
1	**1b**		**4ba**		81
2	**1c**		**4ca**		84
3	**1d**		**4da**		74
4	**1e**		**4ea**		52
5	**1f**		**4fa**		54
6	**1g**		**4ga**		64
7	**1h**		**4ha**		37
8	**1i**		**4ia**		0

[a] All reactions were carried out in sealed tubes by using **1** (0.25 mmol), **2a** (0.5 mmol), **3** (0.3 mmol), K_2CO_3 (1 equiv), DMSO, 80 °C, 20 h.
[b] Isolated yield.

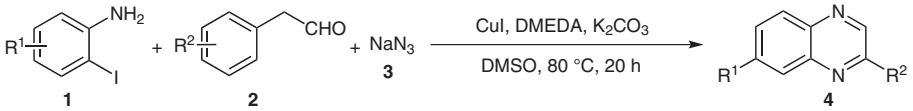
amine was tested, no reaction was observed (Table 2, entry 8).

The substrate scope of the reaction with phenylacetaldehydes **2** was further investigated under the optimized conditions (Table 3). These results indicated that electron-donating phenylacetaldehydes could be successfully employed (Table 3, entries 2 and 3), and gave higher yields than electron-withdrawing substrates (Table 3, entries 4 and 5). Furthermore, substrates with a methoxy moiety on the phenylacetaldehyde and 2-iodoanilines with several substituents also proceeded smoothly with sodium azide and gave good yields (Table 3, entries 6–10). To our disappointment, when an alkylaldehyde and a heteroaryl acetaldehyde were tested, none of the desired product was formed (Table 3, entries 11 and 12).

To understand the reaction mechanism, reaction of 2-iodoaniline (**1a**) with NaN_3 (**3**) was performed under our standard conditions as shown in Scheme 2 (A), but no products were obtained. This indicates that no *o*-phenylenediamine **5** is created in this transformation. On the basis of this result, a possible mechanism of quinoxaline formation was proposed (Scheme 2, B). The reaction of 2-iodoaniline (**1a)** and arylacetaldehyde (**2a**) first affords **I**, which equilibrates to enamine **II**. Coordination of **II** with CuI forms **III**, and exchange of I^- in **III** with N_3^- of NaN_3 gives **IV**. Reductive elimination of **IV** leads to **V** and thus to **VI** by cyclization with leaving N_2. Finally, **VI** could be easily oxidized to the target compound **4aa** in the presence of base. We will focus on the reaction mechanism in further studies.

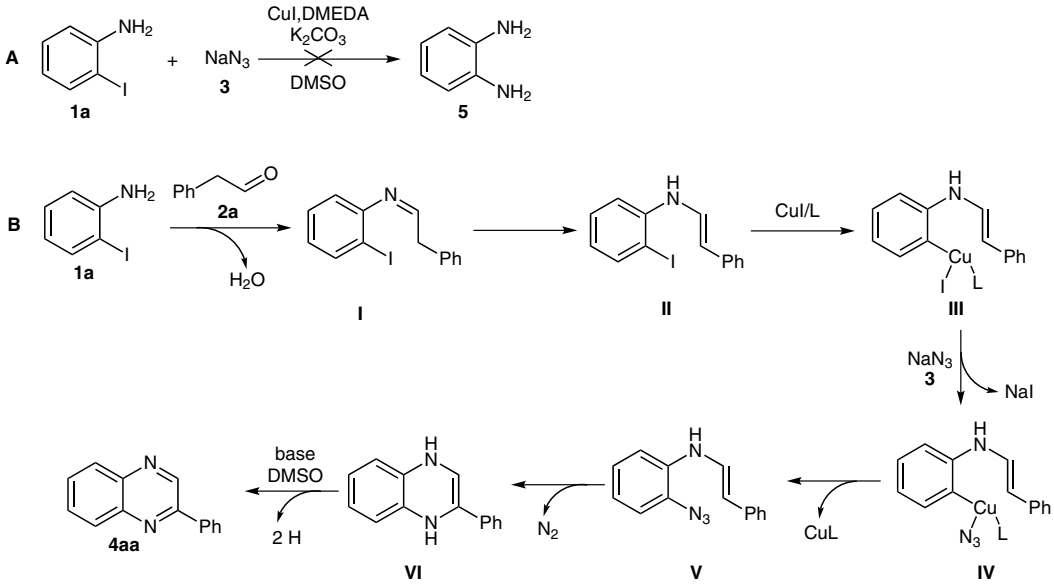
In summary, an efficient method with which to synthesize quinoxalines was developed involving copper-catalyzed, one-pot, three-component reactions of 2-iodoanilines, phenylacetaldehydes and NaN_3 in the presence of K_2CO_3.[11] The approach avoids production of regioisomers in the products through the use of sodium azide as the nitrogen source. The reaction requires commercially available substrates as starting materials and is suitable for the construction of a variety of quinoxalines in moderate to good yields.

Table 3 Reactions of Substituted Phenylacetaldehydes with 2-Iodoanilines and Sodium Azide[a]



Entry	1	R^1	2	R^2	Product 4	Yield (%)[b]
1	**1a**	H	**2a**	Ph	**4aa**	75
2	**1a**	H	**2b**	4-$MeOC_6H_4$	**4ab**	64
3	**1a**	H	**2c**	4-MeC_6H_4	**4ac**	60
4	**1a**	H	**2d**	4-ClC_6H_4	**4ad**	52
5	**1a**	H	**2e**	4-$O_2NC_6H_4$	**4ae**	0
6	**1c**	4,5-Me_2	**2b**	4-$MeOC_6H_4$	**4cb**	68
7	**1d**	4-Cl-5-Me	**2b**	4-$MeOC_6H_4$	**4db**	65
8	**1e**	4-CF_3	**2b**	4-$MeOC_6H_4$	**4eb**	67
9	**1f**	4-Cl	**2b**	4-$MeOC_6H_4$	**4fb**	62
10	**1g**	4-Br	**2b**	4-$MeOC_6H_4$	**4gb**	58
11	**1a**	H	**2f**	*n*-Pr	**4af**	0
12	**1a**	H	**2g**	heteroaryl[c]	**4ag**	0

[a] All reactions were carried out in sealed tubes by using **1** (0.25 mmol), **2a** (0.5 mmol), **3** (0.3 mmol), K_2CO_3 (1 equiv), DMSO, 80 °C, 20 h.
[b] Isolated yield.
[c] 2-(Pyridin-4-yl)acetaldehyde.



Scheme 2 Proposed mechanism of the reaction

Acknowledgment

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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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(11) **Synthesis of 2-Phenylquinoxaline (4aa); Typical Procedure:** 2-Iodoaniline (**1a**; 54.8 mg, 0.25 mmol), sodium azide (**3**; 19.5 mg, 0.3 mmol), CuI (4.8 mg, 0.025 mmol), K_2CO_3 (34.5 mg, 0.25 mmol), phenylacetaldehyde (**2a**; 58 μL, 0.5 mmol), DMEDA (3 μL, 0.025 mmol), and DMSO (1.0 mL) were added to a round-bottom flask equipped with stirrer, and the reaction mixture was heated to 80 °C for 20 h. After cooling to room temperature, the reaction mixture was added to water (2 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (2 × 5 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was subjected to flash column chromatography (petroleum ether–EtOAc, 20:1) to afford the final product **4aa** (75% yield) as a light-yellow solid (mp 63–65 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.33 (s, 1 H), 8.11–8.22 (m, 4 H), 7.74–7.88 (m, 2 H), 7.57–7.72 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.0, 143.5, 142.5, 141.7, 136.9, 130.4, 130.3, 129.8, 129.7, 129.3, 129.3, 127.7. MS (ESI): *m*/*z* = 207 $[M + H]^+$.

