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Synthesis of Quinoxaline Derivatives via Copper(I)-Catalyzed Cross-Coupling Reaction of 1,2-Dihalobenzenes with N,N′-Disubstituted Ethane-1,2-diamines under Ligand- and Solvent-Free Conditions

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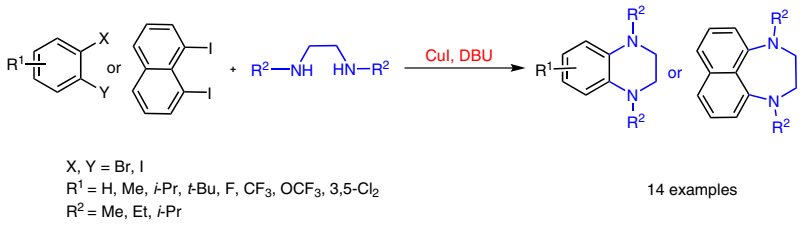


Received: 13.11.2016
Accepted after revision: 14.01.2017
Published online: 03.02.2017
DOI: 10.1055/s-0036-1588145; Art ID: st-2016-w0762-l

Abstract An efficient ligand- and solvent-free method for the synthesis of quinoxaline derivatives via copper(I)-catalyzed cross-coupling process has been developed. 1,2-Halobenzenes or 1,8-diiodonaphthalene coupled with N,N′-disubstituted ethane-1,2-diamines to give the corresponding products in moderate yields under the reaction conditions.

Key words ligand-free, solvent-free, quinoxaline derivatives, copper(I)-catalyzed, cross-coupling reaction, 1,4-disubstituted-1,2,3,4-tetrahydroquinoxalines

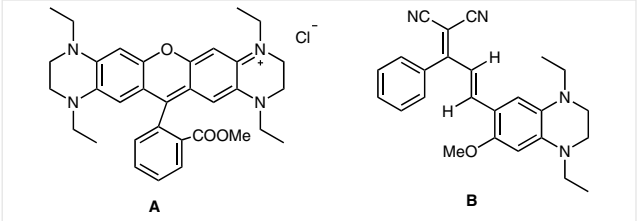


Figure 1 Some useful quinoxaline derivatives

Quinoxaline derivatives are an important class of molecules and heterocyclic scaffolds in pharmaceuticals,[1] dyes,[2] and antibiotics[3] such as olaquindox, carbadox, echinomycin, levomycin, and actinoleutin. The new rhodamine dye Rh Q-Me (**A**) is an effective electron donor, shows large Stokes shift in commonly used solvents (Figure 1).[2b] Another DCM-Q dye (**B**) has been performed as an efficient fluorescence 'off/on' switch for proton determination.[2c] In recent report, 1,4-diethyl-1,2,3,4-tetrahydroquinoxaline could also work as an effective electron donor in styryl,[4] coumarin,[5] and squaraine dyes,[2a] which shifts the absorption and emission to longer wavelength and greatly increases the thermal stability and stokes shift.

Based on the broad spectrum of applications of the quinoxaline derivatives, developing new methodologies is still meaningful. In the previous studies, the method for synthesizing quinoxaline derivatives, especially for the 1,4-disubstituted-1,2,3,4-tetrahydroquinoxaline derivatives, is rarely.[6] The classic method for the synthesis of 1,4-diethyl-1,2,3,4-tetrahydroquinoxalines contains three steps, the condensation of *ortho*-diamines with 1,2-diketones, reduction, and alkylation.[2,7] However, this method is multistep and cannot provide economic way to synthesize 1,4-disubstituted-1,2,3,4-tetrahydroquinoxaline derivatives.

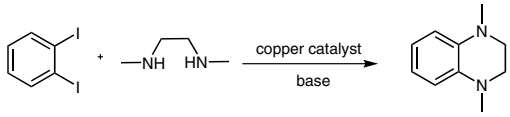
In the past decades, copper-catalyzed C–X (X = C, N, O, S, etc.) bond formation and its application for the synthesis of heterocyclic compound reactions have drawn considerable attention for their low cost, convenience, and efficiency.[8] In continuation of our ongoing efforts to assemble heterocycles, we report an efficient and economic copper(I)-catalyzed cross-coupling reaction of 1,2-dihalobenzenes or 1,8-diiodonaphthalene with N,N′-disubstituted ethane-1,2-diamines to synthesize 1,4-disubstituted-1,2,3,4-tetrahydroquinoxalines under ligand- and solvent-free conditions.

The synthesis of 1,4-disubstituted-1,2,3,4-tetrahydroquinoxaline derivatives with 1,2-diiodobenzene **1a** and *N*,*N*′-dimethylethane-1,2-diamine (DMEDA, **1b**) was investigated in the presence of copper catalyst to identify and optimize the reaction parameters (Table 1). Firstly, the reaction was carried out with CuI (10 mol%), 1,2-diiodobenzene (0.5 mmol), DMEDA (0.5 mmol), and K_2CO_3 (1.0 mmol) in toluene (1.0 mL) at 100 °C under nitrogen for 24 hours, the

desired product could not be detected (Table 1, entry 1). There were also no reaction using DMF, DMSO, 1,4-dioxane, or *n*-PrCN as solvents (Table 1, entries 2–5). Interestingly, we used *N*,*N*′-dimethylethane-1,2-diamine (**1b**, 1.0 mL) as reaction substrate and solvent to repeat the reaction, the product 1,2,3,4-tetrahydroquinoxaline (**1c**) was got in 35% yield (Table 1, entry 6). It was found that the reaction temperature affected the product yield significantly. The product yield was improved to 52% with the increasing of the reaction temperature to 110 °C (Table 1, entry 7). Higher temperature (120 °C) did not improve the reaction yield further (Table 1, entry 8). KOH and DBU were also explored as bases (Table 1, entries 9 and 10), and DBU was found to be the best. But the low yield was got in the absence of base (Table 1, entry 11). From the atom-economy point of view, the influence of the amount of DMEDA on the reaction was also examined (Table 1, entries 12–15). The results showed that two equivalents of DMEDA provided the best yield (Table 1, entry 14). Different copper catalysts were also tested, and CuI was the best choice (Table 1, entries 16–18). With other ligands to repeat the reaction, the yields did not change obviously (Table 1, entries 19–21). An excess amount of DMEDA (2.5 equiv) was also applied in toluene to repeat the reaction, and the product was isolated in 4% yield (Table 1, entry 22). Without CuI, the reaction could not proceed (Table 1, entry 23). Thus, the optimized reaction conditions involved using CuI (10 mol%) as the catalyst, DBU (2.0 equiv) as the base, DMEDA (2.0 equiv) as dually aminating reagent and solvent, and conducting the reaction at 110 °C under nitrogen for 24 hours.

With the optimal conditions established, we tried to expand the scope of substrates. The substituted 1,2-diiodobenzenes **a** bearing both electron-donating groups (4-Me, 4-*i*-Pr and 4-*t*-Bu) and electron-withdrawing groups (4-F, 4-F_3C, 4-F_3CO, and 3,5-Cl) were able to couple with DMEDA (**1b**) in moderate yields (Table 2, entries 2–8). When *N*,*N*′-diethylethane-1,2-diamine (DEEDA, **2b**) was used to run the reaction, the yield obviously decreased to 21% (Table 2, entry 9). No product was detected when *N*,*N*′-diisopropylethane-1,2-diamine (**3b**) was used (Table 2, entry 10). 1,8-Diiodonaphthalene **9a** could also reacted with DMEDA (**1b**) or DEEDA (**2b**) to get the corresponding seven-membered heterocyclic products (Table 2, entries 11 and 12). From the results we concluded that the yields were affected more obviously by the steric hindrance of N,N′-disubstituted ethane-1,2-diamines **b** than the electronic effect of 1,2-dihalobenzenes **a**. The optimal conditions were also suitable for the substrates 1-bromo-2-iodobenzene (**10a**) and 1,2-dibromobenzene (**11a**), but the yields were not high (Table 2, entries 13 and 14). *N*,*N*′-Diphenylethane-1,2-diamine was also used to repeat the reaction, and no product was detected (Table 2, entry 15).

Table 1 Optimization of the Reaction Conditions[a]



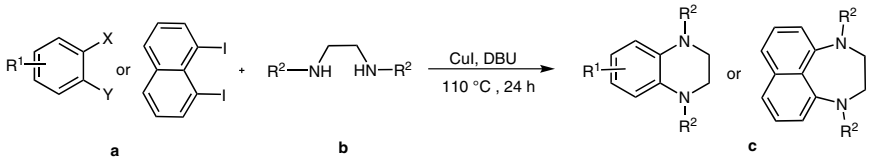
1a **1b** **1c**

Entry	Copper catalyst	Base	Solvent	Temp (°C)	Yield (%)[b]
1	CuI	K_2CO_3	toluene	100	0
2	CuI	K_2CO_3	DMF	100	0
3	CuI	K_2CO_3	DMSO	100	0
4	CuI	K_2CO_3	*n*-PrCN	100	0
5	CuI	K_2CO_3	1,4-dioxane	100	0
6	CuI	K_2CO_3	DMEDA	100	35
7	CuI	K_2CO_3	DMEDA	110	52
8	CuI	K_2CO_3	DMEDA	120	50
9	CuI	KOH	DMEDA	110	56
10	CuI	DBU	DMEDA	110	75
11	CuI	–	DMEDA	110	25[c]
12	CuI	DBU	DMEDA	110	60[d]
13	CuI	DBU	DMEDA	110	70[e]
14	CuI	DBU	DMEDA	110	78[f]
15	CuI	DBU	DMEDA	110	75[g]
16	CuBr	DBU	DMEDA	110	72
17	CuCl	DBU	DMEDA	110	60
18	CuO	DBU	DMEDA	110	11
19	CuI/1,10-phenanthroline	DBU	DMEDA	110	77
20	CuI/*N*,*N*-dimethylglycine	DBU	DMEDA	110	70
21	CuI/Ph_3P	DBU	DMEDA	110	72
22	CuI	DBU	toluene	110	4[g]
23	–	DBU	DMEDA	110	0[f]

[a] Reaction conditions: CuI (0.05 mmol), 1,2-diiodobenzene (0.5 mmol), DMEDA (0.5 mmol), base (1.0 mmol), and solvent (1.0 mL) under N_2 atmosphere for 24 h.
[b] Isolated yield after flash chromatography based on 1,2-diiodobenzene (**1a**).
[c] No base was used.
[d] Conditions: 0.5 mmol (1.0 equiv) DMEDA was used.
[e] Conditions: 0.75 mmol (1.5 equiv) DMEDA was used.
[f] Conditions: 1.0 mmol (2.0 equiv) DMEDA was used.
[g] Conditions: 1.25 mmol (2.5 equiv) DMEDA was used.

In summary, an efficient 'ligand- and solvent-free' method for the synthesis of quinoxaline derivatives via copper(I)-catalyzed cross-coupling process has been developed.[9] A variety of 1,4-disubstituted 1,2,3,4-tetrahydroquinoxalines and 1,4-disubstituted 1,2,3,4-tetrahydronaphtho[1,8-*ef*][1,4]diazepines, which might be potentially applicable in the pharmaceutical, dyes, and biochemical areas, were conveniently synthesized in moderate yields.

Table 2 Copper(I)-Catalyzed Cross-Coupling Reactions of 1,2-Dihalobenzenes **a** with N,N′-Disubstituted Ethane-1,2-Diamines[a]



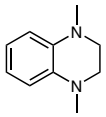
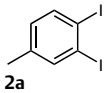
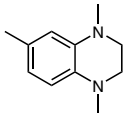
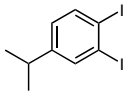
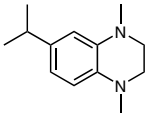
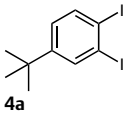
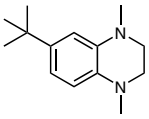
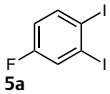
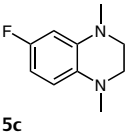
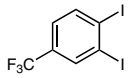
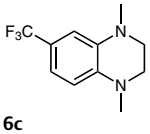
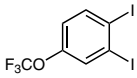
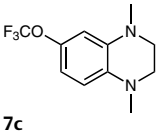
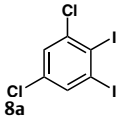
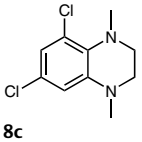
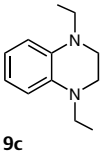
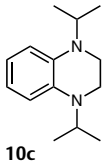
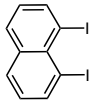
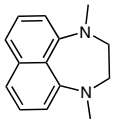
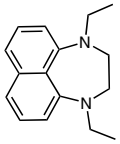
Entry	a	R^2	Product	Yield (%)[b]
1	 **1a**	Me	 **1c**	78
2	 **2a**	Me	 **2c**	70
3	 **3a**	Me	 **3c**	65
4	 **4a**	Me	 **4c**	64
5	 **5a**	Me	 **5c**	73
6	 **6a**	Me	 **6c**	68
7	 **7a**	Me	 **7c**	66
8	 **8a**	Me	 **8c**	73
9	**1a**	Et	 **9c**	21

Table 2 (continued)

Entry	a	R^2	Product	Yield (%)[b]
10	**1a**	*i*-Pr	 **10c**	–[c]
11	 **9a**	Me	 **11c**	65
12	**9a**	Et	 **12c**	20
13	 **10a**	Me	**1c**	34
14	 **11a**	Me	**1c**	12
15	**1a**	Ph	**13c**	–[c]

[a] Reaction conditions: CuI (0.05 mmol), 1,2-halobenzenes or 1,8-diiodonaphthalene **a** (0.5 mmol), N,N′-disubstituted 1,2-diamines **b** (1.0 mmol), and DBU (1.0 mmol) under N_2 atmosphere for 24 h.
[b] Isolated yield after flash chromatography based on 1,2-diiodobenzenes **a**.
[c] No product was detected.

Acknowledgment

This work was financially supported by the National Natural Science Foundation (21402079 and 31401217), the Doctoral Scientific Research Startup Foundation of Liaocheng University (318051419 and 318051403), and the College Students' Innovation and Entrepreneurship Training Program of Liaocheng University (201410447007).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588145.

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(9) **General Procedure for the Synthesis of Quinoxaline Derivatives**

An oven-dried Schlenk tube equipped with a Teflon valve was charged with a magnetic stir bar, CuI (0.05 mmol), 1,2-diiodobenzenes or 1,8-diiodonaphthalene **a** (0.5 mmol), and DBU (1.0 mmol). The tube was placed under vacuum for 20 min and backfilled with N_2. Then N,N′-disubstituted 1,2-diamines **b** (1.0 mmol) was added through a syringe. The reaction mixture was stirred at 110 °C for 24 h. The reaction was monitored by TLC. When 1,2-diiodobenzenes or 1,8-diiodonaphthalene **a** consumed completely, the reaction was stopped and purified directly by column chromatography on silica gel to give the pure products **c** (PE–EtOAc, 10:1 v/v).

Typical Analytical Data of 1,4,6-Trimethyl-1,2,3,4-tetrahydroquinoxaline (2c)

Brown oil, 62 mg, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 6.51–6.46 (m, 2 H), 6.38 (s, 1 H), 3.37–3.34 (m, 2 H), 3.29–3.27 (m, 2 H), 2.88 (s, 3 H), 2.85 (s, 3 H), 2.26 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 136.95, 134.66, 127.82, 118.26, 111.88, 111.18, 50.28, 50.22, 39.68, 39.22, 21.09. ESI-HRMS: *m/z* calcd for $C_{11}H_{17}N_2$ $[M + H]^+$: 177.1392; found: 177.1390.