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An Efficient Domino Synthesis of Quinoxalin-2(1*H*)-ones *via* an S_NAr/Coupling/Demesylation Reaction Catalyzed by Copper(I) as Key Step

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Abstract: An efficient copper-catalyzed method for the synthesis of quinoxalin-2(1*H*)-ones derivatives *via* domino S_NAr/coupling/demesylation reaction of *N*-(2-halophenyl)methylsulfonamides with 2-halo amides has been developed. Various quinoxalinones with diversity at three positions on their scaffold have been obained, and the method is valuable for the construction of this kind of molecules with biological and pharmaceutical activities.

Keywords: copper; cyclization; demesylation; domino reaction; quinoxalin-2(1*H*)-ones

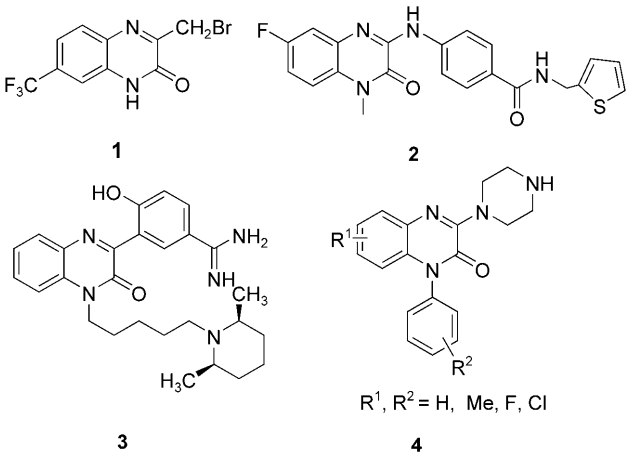


Figure 1. Several quinoxalin-2(1*H*)-one derivatives reported as biologically active and pharmaceutical compounds.

As an important pharmacophore in numerous biologically active compounds, the quinoxalin-2(1*H*)-one scaffold has attracted much attention during the past few years.[1] Quinoxalinone derivatives exhibit various biological and medicinal functions. For example (Figure 1), a quinoxalinone containing the electron-withdrawing group CF_3 (**1**) showed anticancer activity *in vitro* against a subpanel of cell lines, such as leukemia, non-small cell lung, melanoma cell lines and so on.[2a] *N*-Alkylqunioxalinone (**2**) was reported to show potential glycogen phosphorylase-inhibitory activity and **3** is a specific inhibitor of Fxa, which was expected to be therapeutically useful in the treatment of thromboembolic disease.[2b,c] *N*-Arylqunioxalinones or their hydrochloride (**4**) are norepinephrine reuptake inhibitors for the treatment of central nervous system disorders.[2d] Moreover, other biological activities have been reported, including acting as antimicrobial agents, kinases inhibitors, benzodiazepine receptor agonist, etc.[2e–g]

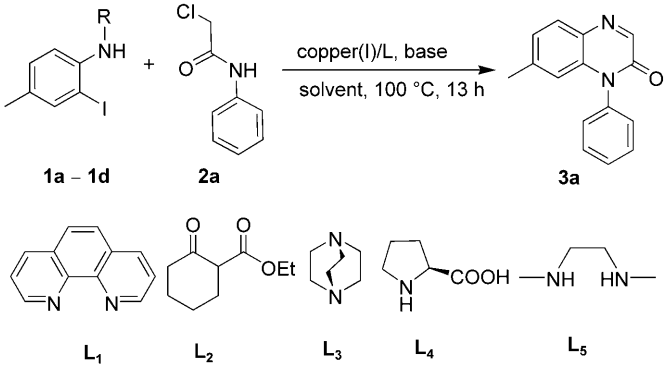
The typical methods for assembling quinoxalin-2(1*H*)-ones are based on the condensation of a substituted *o*-phenylenediamine with an α-ketone acid, α-aldehyde acid, α-ketone acid ester or α-aldehyde acid ester.[3a–c] Although these methods are relatively simple and straightforward for the synthesis of quinoxalinones, multiple by-products were obtained when unsymmetrical diamines were used, which resulted in extremely low yields of the desired compounds.[2e] Li et al. and Wu et al. reported regioselective methodologies for the synthesis of substituted quinoxalinones.[3d,e] 2-Chloro-*N*-(2-nitrophenyl)acetamide or methyl 2-(2-nitrophenylamino)acetate were used as intermediates, followed by reduction, intramolecular cyclization and oxidation steps, but these routes were often troublesome. *N*-Substituted quinoxalinones could also be synthesized by reacting quinoxalin-2(1*H*)-one with halohydrocarbons, but the mixtures of

N- and *O*-substituted products were obtained.[3f–h] Therefore, it is still highly desirable to develop more convenient and efficient approaches for these heterocycles.

In the past few years, the formation of aryl C–X bonds (X = N, O, S, etc.) *via* copper-catalyzed Ullmann-type coupling between aryl halides and heteroatom-centered nucleophiles has made great progress.[4] More recently, the Ullmann coupling has been applied to construct various heterocyclic compounds by one-pot strategies. Most of these heterocyclic compounds were N-heterocycles, including pyrrole, indole, benzimidazole, benzothiazole, 1,3-dihydrobenzimidazol-2-one, isoquinoline, isoquinolin-1(2*H*)-one, quninazoline, quinazolinone, 3,4-dihydro-2*H*-1,4-benzoxazine, 1,4-benzodiazepin-3-one rings etc.[5] However, to the best of our knowledge, there is no report about the formation of quinoxalin-2(1*H*)-ones *via* a one-pot copper-catalyzed coupling process. Our research group is interested in the cascade synthesis of heterocycles and has developed Cu-catalyzed tandem addition/coupling, ring-open/coupling, S_NAr/coupling cyclization reactions.[6] Herein, we report a domino S_NAr/coupling/demesylation reaction, an efficient copper-catalyzed one-pot reaction of *N*-(2-halophenyl)methylsulfonamides with 2-halo amides to synthesize quinoxalin-2(1*H*)-ones with diversity at three positions on the scaffold.

As shown in Table 1 *N*-(2-iodo-4-methylphenyl)methylsulfonamide (**1a**) and 2-chloro-*N*-phenylacetamide (**2a**) were chosen as the model substrates to optimize the reaction conditions including bases, solvents, catalysts, and ligands. We began our study under the similar reaction conditions (10 mol% CuI, 20 mol% 1, 10-phenanthroline, Cs_2CO_3 in dioxane) as for our previously reported Cu-catalyzed cascade synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones,[6d] but only a trace amount of product was observed. The yield of product was greatly improved when the bases K_2CO_3 and K_3PO_4 were selected (87% and 68% yield, respectively, entries 2 and 3). The effect of solvent was investigated (entries 4–7). Toluene, DMF, DMSO, NMP provided lower yields than dioxane did. Toluene showed the lowest yield (only 26%). Among the Cu catalysts examined (CuI, CuBr, Cu_2O), CuI acted as the optimal catalyst (entries 2, 8 and 9). Several ligands, including 1,10-phenanthroline, ethyl 2-oxocyclohexanecarboxylate, DABCO, L-proline and DMEDA (**L_1**–**L_5**), were screened. 1,10-Phenanthroline was the best one (entries 2, 10–13). The product could also be obtained without ligand in 19% yield (entry 14). Variation of the *N*-protecting group proved to be crucial. Switching from *N*-(2-iodophenyl)methylsulfonamide (**1a**) to *N*-tosyl- or *N*-trifluoroacyl- or *N*-acyl-*o*-iodoanilines (**1b–d**) resulted in the formation of the desired product **3a** in decreased yields (entries 15–18). Almost no product was observed from **1c**, although a 30% yield could be obtained when the base K_2CO_3 was replaced by Cs_2CO_3.

Table 1. Optimization of the reaction conditions for the synthesis of 7-methyl-1-phenylquinoxalin-2(1*H*)-one.[a]



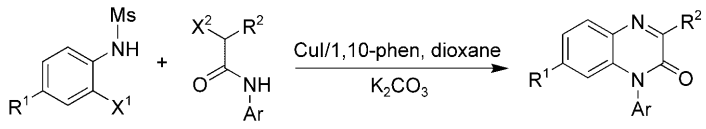
Entry	R	Cat.	L	Base	Solvent	Yield [%][b]
1	Ms	CuI	L_1	Cs_2CO_3	dioxane	trace
2	**Ms**	**CuI**	**L_1**	**K_2CO_3**	**dioxane**	**87**
3	Ms	CuI	L_1	K_3PO_4	dioxane	68
4	Ms	CuI	L_1	K_2CO_3	toluene	26
5	Ms	CuI	L_1	K_2CO_3	DMF	72
6	Ms	CuI	L_1	K_2CO_3	DMSO	62
7	Ms	CuI	L_1	K_2CO_3	NMP	48
8	Ms	CuBr	L_1	K_2CO_3	dioxane	42
9	Ms	Cu_2O	L_1	K_2CO_3	dioxane	53
10	Ms	CuI	L_2	K_2CO_3	dioxane	15
11	Ms	CuI	L_3	K_2CO_3	dioxane	34
12	Ms	CuI	L_4	K_2CO_3	dioxane	30
13	Ms	CuI	L_5	K_2CO_3	dioxane	21
14	Ms	CuI	–	K_2CO_3	dioxane	19
15	Ts (**1b**)	CuI	L_1	K_2CO_3	dioxane	46
16	Tfac (**1c**)	CuI	L_1	K_2CO_3	dioxane	trace
17	Tfac	CuI	L_1	Cs_2CO_3	dioxane	30
18	Ac (**1d**)	CuI	L_1	Cs_2CO_3	dioxane	trace

[a] *Reaction conditions:* *N*-(2-iodophenyl)amides **1a** (0.75 mmol), 2-chloro-*N*-phenylacetamide **2a** (0.5 mmol), copper source (0.05 mmol), ligand (0.1 mmol) and base (2.0 mmol) in solvent (2.0 mL) under N_2 at 100 °C for 13 h.

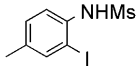
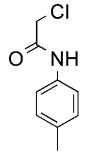
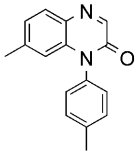
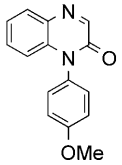
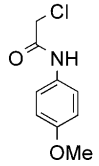
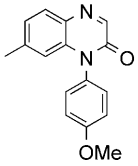
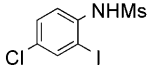
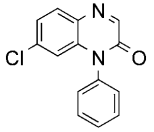
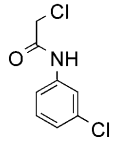
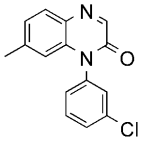
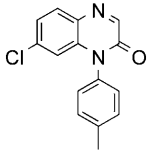
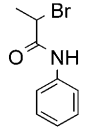
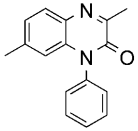
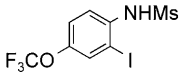
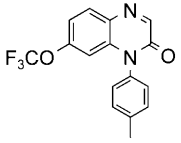
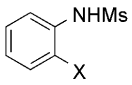
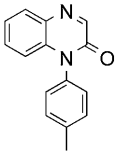
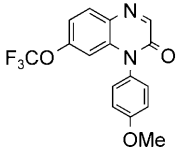
[b] Isolated yield. Tfac = trifluoroacyl .

The scope of copper-catalyzed one-pot synthesis of quinoxalin-2(1*H*)-ones from substituted *N*-(2-halophenyl)methylsulfonamides and 2-halo amides was investigated. As shown in Table 2, most of the substrates examined provided good yields. The majority of the *N*-arylquinoxalin-2(1*H*)-ones could be prepared under the optimized conditions (10 mol% CuI, 4 equiv. of K_2CO_3, dioxane as the solvent at 100 °C under a nitrogen atmosphere). The substrates 2-halo-*N*-phenylacetamides with an electron-donating group on the phenyl ring showed a higher reactivity than the others with no substituted group and electron-withdrawing groups (entries 1–3, 8 and 9). The substrates *N*-(2-iodophenyl)methylsulfonamide or those

Table 2. CuI-catalyzed one-pot synthesis of quinoxalin-2(1*H*)-ones from *N*-(2-halophenyl)methylsulfonamides and 2-halo-*N*-arylacetamides.[a]



1 2 3

Entry	1	2	Product	Yield [%][b]	Entry	1	2	Product	Yield [%][b]
1	**1a** 	**2b** 	**3b** 	94	7	**1e**	**2c**	**3g** 	86
2	**1a**	**2c** 	**3c** 	91	8	**1g** 	**2a**	**3h** 	76
3	**1a**	**2d** 	**3d** 	60	9	**1g**	**2b**	**3i** 	87
4	**1a**	**2e** 	**3e** 	51[c]	10	**1h** 	**2b**	**3j** 	61[e]
5	**1e** X = I			91					
6	**1f** X = Br 	**2b**	**3f** 	58[d]	11	**1h**	**2c**	**3k** 	55[e]

[a] *Reaction conditions: N*-(2-halophenyl)methylsulfonamides **1** (0.75 mmol), 2-halo amides **2** (0.5 mmol), CuI (0.05 mmol), ligand (0.1 mmol) and K_2CO_3 (2.0 mmol) in dioxane (2.0 mL) under N_2 at 100 °C for 13 h.

[b] Isolated yield.

[c] Cs_2CO_3 (2.0 mmol), at reflux, 36 h.

[d] DMF (2.0 mL), 115 °C, 24 h.

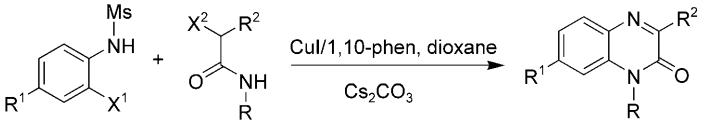
[e] 36 h.

bearing electron-donating groups could react with 2-chloro-*N*-phenylacetamides to afford products in excellent yield (entries 1, 2, 5 and 7), while those bearing electron-withdrawing groups reacted slowly and gave lower yields (entries 8–11), for example, products **3j** and **3k** were obtained in only 61% and 55% yields, respectively, even after the reaction time was prolonged to 36 h. Reaction of *N*-(2-bromophenyl)-methylsulfonamide with 2-halo-*N*-*p*-tolylacetamide also provided the target product **3f** in moderate yield (58%) under the conditions (DMF as the solvent at 115 °C).

N-Alkylquinoxalin-2(1*H*)-ones could also be synthesized, but the base must be Cs_2CO_3 instead of K_2CO_3, and the reaction time was shortened, only 9 h were needed. The yield of *N*-benzylquinoxalin-2(1*H*)-one was higher than that of *N*-butyl- or *N*-propylquinoxalinones (Table 3, entries 1, 2, and 5–8). The electronic effect of the substituent group on substrates was the consistent with the above discussed observations. In addition, when there were both R^2 and R^3 (R^3 = aryl or alkl) substituted groups in the 2-haloacetamide, the reactions could also be completed, but the the base Cs_2CO_3 must be used and a low yield was obtained (Table 2, entry 4 and Table 3, entry 4). It was obvious that the R^2 group showed a little steric hindrance effect. 7-Methylquinoxalin-2(1*H*)-one **3n** could also be obtained in 52% yield, when the ratio of **1a** to 2-chloroacetamide **2h** was changed to 1:1.5.

The following pathway for the construction of quinoxalin-2(1*H*)-ones is proposed, which has three steps (Scheme 1). The reaction might proceed through an intermolecular nucleophilic substitution between *N*-(2-halophenyl)methylsulfonamide **1** and 2-halo amide **2** in the presence of a base (step a, the plausible intermediate **I** would be formed), followed by the formation of 3,4-dihydroquinoxalin-2-(1*H*)-one intermediate *II via* an intramolecular C–N coupling (step b). This is converted into the target product **3** through an elimination reaction (step c). The intermediate **I** has been monitored by TLC and isolated, its structure was determined by spectral data (see Supporting Information). However the intermediate **II** has not been found by TLC and GC-MS. According to our previ-

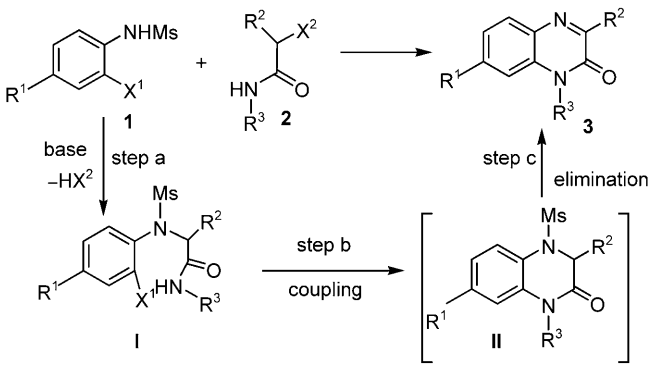
Table 3. CuI-catalyzed one-pot synthesis of quinoxalin-2(1*H*)-ones from *N*-(2-halophenyl)methylsulfonamides and 2-halo-*N*-alkylacetamides.[a]



1 **2** **3**

Entry	1	2	Product	Yield [%][b]	Entry	1	2	Product	Yield [%][b]
1	**1a**	**2f**	**3l**	88	5	**1e**	**2e**	**3p**	80
2	**1a**	**2g**	**3m**	68	6	**1e**	**2j**	**3q**	62
3	**1a**	**2h**	**3n**	52[c]	7	**1g**	**2e**	**3r**	70
4	**1a**	**2i**	**3o**	35[d]	8	**1g**	**2f**	**3s**	60

[a] *Reaction conditions:* *N*-(2-halophenyl)methylsulfonamides **1** (0.75 mmol), 2-halo amides **2** (0.5 mmol), CuI (0.05 mmol), ligand (0.1 mmol) and Cs_2CO_3 (2.0 mmol) in dioxane (2.0 mL) under N_2 at 100 °C for 9 h.
[b] Isolated yield.
[c] **1a** (0.5 mmol), **2h** (0.75 mmol).
[d] At reflux, 36 h.



Scheme 1. Proposed reaction pathway for the one-pot synthesis of quinoxalin-2(1*H*)-ones.

ous work[6d] and the experiment, the confirmed intermediate **I** should be cyclized before being demesylated, but not the opposite, because the imine is unstable in alkaline solution. And perhaps step c was accomplished rapidly after the step b under the basic conditions at high temperature, which has been proved by the reported literature.[7] Therefore, we believe that the proposed pathway is reasonable.

In summary, an efficient method for the assembly of quinoxalin-2(1*H*)-ones has been developed, which relied on copper-catalyzed one-pot reaction of *N*-(2-halophenyl)methylsulfonamides with 2-halo amides *via* a domino S_NAr/coupling/demesylation process. Most of the quinoxalin-2(1*H*)-one derivatives with diversity at three substituents on their scaffold were obtained in good to excellent yields. This method should be valuable for the construction of this kind of molecule with biological and medicinal activities, so it may find application in organic synthesis.

Experimental Section

General Experimental Procedures for the Cu(I)-Catalyzed One-Pot Synthesis of Quinoxalin-2(1*H*)-ones

An oven-dried Schlenk tube was charged with a magnetic stir bar, CuI (10 mg, 0.05 mmol, 10 mol%), 1,10-phenanthroline (20 mg, 0.1 mmol, 20 mol%), and base (2.0 mmol), *N*-(2-halophenyl)methylsulfonamide **1** (0.75 mmol), 2-halo amide **2** (0.5 mmol). The Schlenk tube was capped, and then evacuated and backfilled with N_2 (3 times). Under a counter-flow of N_2, dioxane (2.0 mL) was added by syringe and the mixture was stirred at 100 °C. After the reaction was finished, the mixture was directly passed through Celite and rinsed with an additional 30 mL of CH_2Cl_2. The combined filtrate was concentrated and purified by column chromatography on silica gel (eluting with 5:1 to 2:1 petroleum ether/ethyl acetate) to give the corresponding product **3**.

7-Methyl-1-phenylquinoxalin-2(1*H*)-one (3a): Yellow solid; mp 165–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.65–7.57 (m, 3H), 7.30–7.28 (m, 2H), 7.15 (d, J = 8.0 Hz,1H), 6.48 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 149.6, 141.7, 135.3, 133.8, 131.4, 130.3, 129.8, 129.5, 128.2, 125.3, 115.5, 21.9; anal. calcd. for $C_{15}H_{12}N_2O$: C 76.25, H 5.12, N 11.86; found: C 75.98, H 5.29, N 11.67; EI-MS: m/z = 236 (M^+).

Acknowledgements

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