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The *N*-Aryl Aminocarbonyl *ortho*-Substituent Effect in Cu-Catalyzed Aryl Amination and Its Application in the Synthesis of 5-Substituted 11-Oxo-dibenzodiazepines

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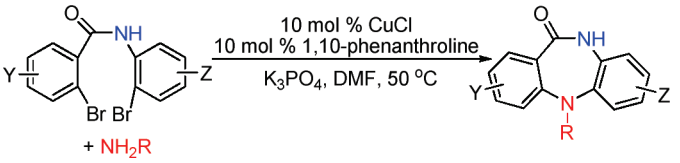
ABSTRACT



Double amination of *ortho*-substituted aryl bromides proceeded under mild conditions to afford 5-substituted 11-oxo-dibenzodiazepines, which revealed that there is a strong *ortho*-substituent effect caused by *N*-aryl aminocarbonyl groups during copper-catalyzed aryl amination.

A considerable number of bioactive compounds contain an 11-oxo-dibenzodiazepine moiety, including the clinical antidepressant dibenzepin (**1**, Figure 1), nonpeptidyl endothelin receptor antagonist **2**,[1] histone deacetylase inhibitor **3**,[2] muscarinic acetylcholine receptor modulator **4**,[3] potent and selective Chk-1 inhibitor **5**,[4] and potential agent for the treatment of angiogenesis-related indications **6**.[5] The classical approach for assembling these compounds is dependent on the selective alkylation[1−3] of 1,6-unsubstituted 11-oxo-dibenzodiazepines of general structure **8**. These tricyclic heterocycles typically require several steps for their preparation, beginning with the copper-catalyzed coupling reactions of anthranilic acids with 2-halonitrobenzenes (or 2-halobenzoic acids with *o*-phenylendiamines).[1−6] The classical approach suffers both from length of sequence from commercially available starting materials and generally

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moderate yields of the diaryl amine alkylation steps due to poor amine reactivity.[1−3,5]

During our investigations on the development of new copper-catalyzed coupling reactions for heterocycle synthesis,[7−9] we became interested in the potential double coupling reactions of dibromides **9** with primary amines. Such transformations would provide an alternative and direct pathway for preparing 5-substituted 11-oxo-dibenzodiazepines **7**. In subsequent studies, we discovered that *N*-aryl aminocarbonyl groups greatly promoted the copper-catalyzed coupling of aryl halides with amines. This effect allows formation of 5-substituted 11-oxo-dibenzodiazepines via double amination under very mild conditions. A complete account of our results is provided herein.

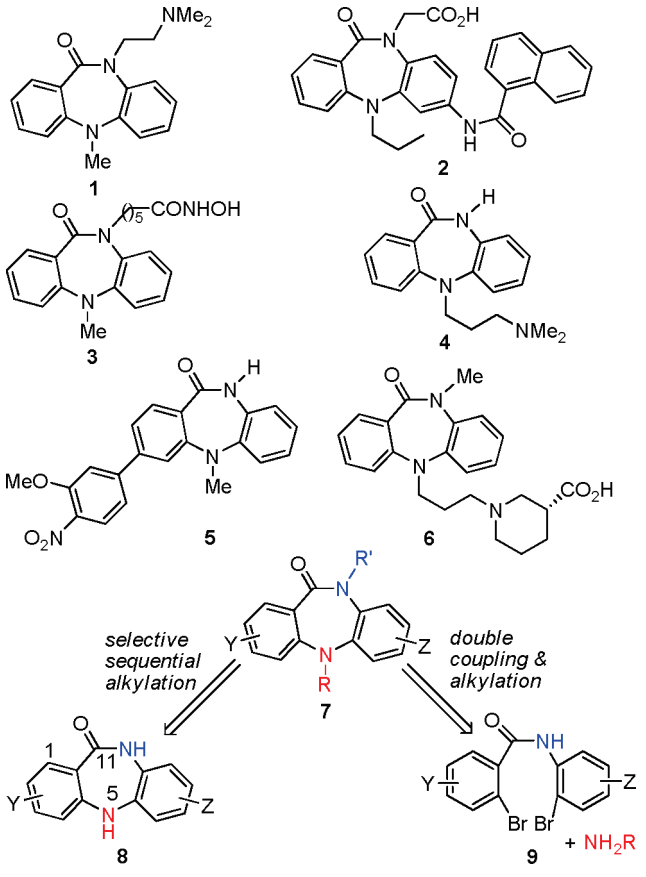
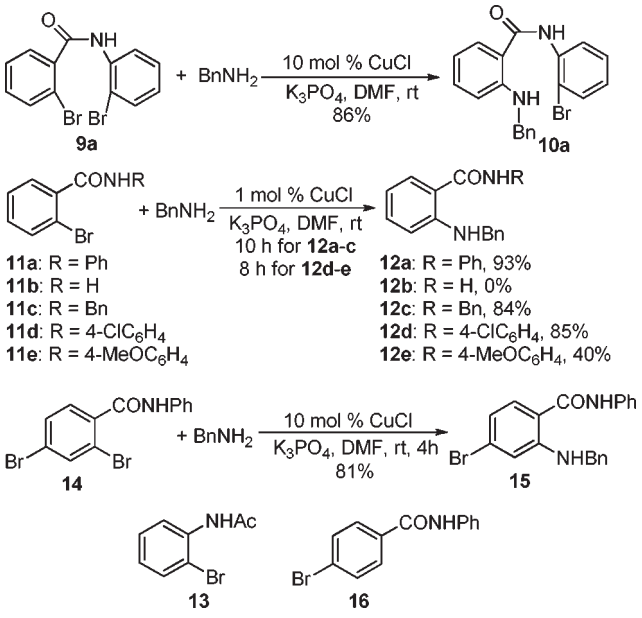


Figure 1. Structures of bioactive 11-oxodibenzodiazepines and methods for their preparation.

When model dibromide **9a** (Scheme 1) was subjected to experimental coupling conditions with benzylamine and CuCl at room temperature in DMF, we were surprised to isolate the open anthranilamide **10a** in 86% yield. This result suggested that *N*-aryl aminocarbonyl groups might

Scheme 1. CuCl-Catalyzed Coupling Reactions of Benzylamine with Different *ortho*-Substituted Aryl Bromides



have stronger *ortho*-substituent effects than amido groups. To verify this hypothesis, we conducted a series of control experiments. When 2-bromo-*N*-phenylbenzamide **11a** was treated with 1 mol % CuCl and benzylamine for 10 h at room temperature, anthranilamide **12a** was isolated in 93% yield with complete consumption of starting material. In contrast, *no conversion* was observed when 2-bromobenzamide **11b** and 2-bromoacetanilide **13** were subject to the same reaction conditions. These results clearly demonstrate that *N*-phenyl aminocarbonyl groups are more powerful directors for amination than acetamido[10] and simple aminocarbonyl groups.[11] Interestingly, under the same conditions, 2-bromo-*N*-benzylbenzamide **11c** underwent approximately 95% conversion to give **12c** with 84% yield, indicating that *N*-substituents might have dramatic influence on the *ortho*-substituent effect of aminocarbonyl groups in general. This hypothesis was further supported by comparing the reactivity of *N*-(4-chlorophenyl)-substituted bromide **11d** and *N*-(4-methoxyphenyl)-substituted bromide **11e**, which gave 84 and 40% coupling yields after 8 h at room temperature, respectively. Additionally, coupling reaction of dibromide **14** with benzylamine afforded amination product **15** exclusively, whereas no conversion was observed in case of bromide **16** as a coupling partner. The reactivity difference between these two substrates clearly indicated that the mild coupling conditions resulted from the *ortho*-substituent effect but not the simple inductive effect of the *N*-phenyl aminocarbonyl groups.

Returning to the monocoupling product **10a**, we sought to find suitable conditions to complete our initially desired

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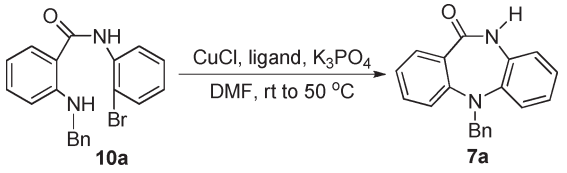
cyclization. When 20 mol % of CuCl was used, the desired cyclization product **7a** could be isolated with 22% yield (Table 1, entry 1). We then focused our attention on using ligands to promote the cyclization.[9] Introducing L-proline to the reaction mixture was found to be ineffective for this coupling reaction (Table 1, entry 2). However, improved yields were observed when *trans*-4-hydroxy-L-proline and *N*,*N*-dimethylglycine were utilized (Table 1, entries 3 and 4). Our best result was obtained when 1,10-phenanthroline was employed (Table 1, entry 5). Further investigation revealed that in this case, the catalytic loading necessary for timely reaction completion could be reduced to 10 mol % if the reaction temperature was raised to 50 °C (Table 1, entry 6).

Table 1. Condition Screening for Cyclization of Aryl Bromide **10a**[a]

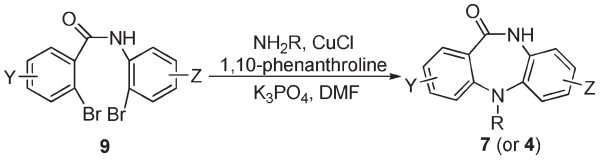


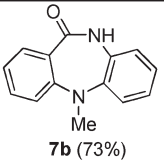
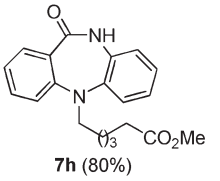
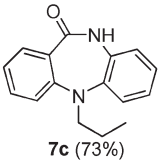
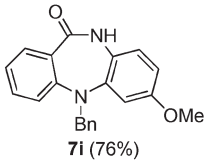
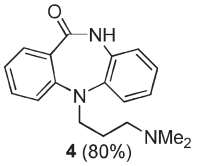
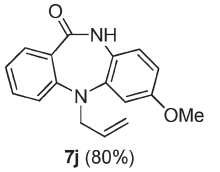
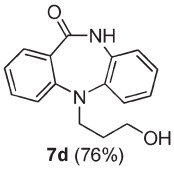
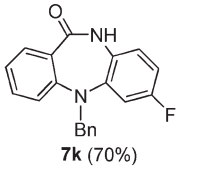
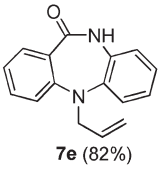
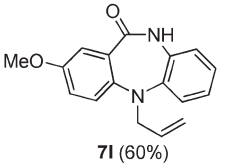
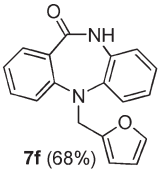
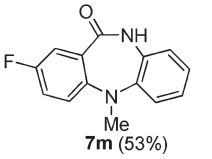
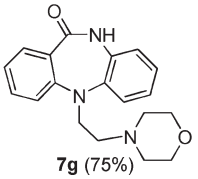
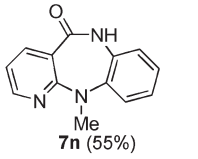
entry	ligand	yield[b] (%)
1		22
2	L-proline	trace
3	*trans*-4-hydroxy-L-proline	41
4	*N*,*N*-dimethylglycine	85
5	1,10-phenanthroline	93
6	1,10-phenanthroline	90[c]

[a] Reaction conditions: **10a** (0.5 mmol), CuCl (0.1 mmol), ligand (0.2 mmol, 0.1 mmol for entry 5), K_3PO_4 (1.5 mmol), DMF (1 mL), rt (or 50 °C for entry 6), 24 h. [b] Isolated yield. [c] 0.05 mmol of CuCl and 0.05 mmol of ligand were used.

The combination of CuCl and 1,10-phenanthroline was then examined for direct conversion of dibromides **9** into 5-substituted 11-oxo-dibenzodiazepines, and the results are summarized in Table 2. To our delight, this catalytic system performed well for this transformation, providing the desired tricyclic heterocycles in 52–82% yield. From methylamine and *n*-propylamine, dibenzodiazepines **7b** and **7c** were isolated with 73% yield (Table 2, entries 1 and 2), which could be used for synthesizing antidepressant dibenzepin **1**, histone deacetylase inhibitor **3**[2] and non-peptidyl endothelin receptor antagonist **2**,[1] respectively. Using N^1,N^1-dimethyl-propane-1,3-diamine as a coupling partner, the muscarinic acetylcholine receptor modulator **4**[3] was directly obtained in 80% yield (Table 2, entry 3). Furthermore, coupling of 3-aminopropan-1-ol with **9a** produced dibenzodiazepine **7d** (Table 2, entry 4), a suitable precursor for the preparation of bioactive compound **6**.[5] Four other functionalized amines were also found to be applicable in this process, affording the corresponding products **7e**–**h**, all in good yields (Table 2, entries 5–8).

Table 2. CuCl-Catalyzed Formation of 11-Oxodibenzodiazepines from Dibromides[a]



entry	product	entry	product
1	 **7b** (73%)	8	 **7h** (80%)
2	 **7c** (73%)	9	 **7i** (76%)
3	 **4** (80%)	10	 **7j** (80%)
4	 **7d** (76%)	11	 **7k** (70%)
5[b]	 **7e** (82%)	12[b]	 **7l** (60%)
6	 **7f** (68%)	13[b]	 **7m** (53%)
7	 **7g** (75%)	14[b]	 **7n** (55%)

[a] Reaction conditions: **9** (0.5 mmol), amine (0.55 mmol), CuCl (0.05 mmol), 1,10-phenanthroline (0.05 mmol), K_3PO_4 (1.5 mmol), DMF (1 mL), rt–50 °C, 24–36 h. [b] 0.1 mol CuCl was used, and the reaction was carried out at rt.

Further explorations indicated that introducing functional groups at both aromatic rings was possible, as evidenced by the successful generation of dibenzodiazepines **7i**–**m** from the corresponding elaborated dibromides

(Table 2, entries 9–13). In the case of **7m**, relatively low yield was observed because of incomplete cyclization (Table 2, entry 13). We reasoned that this problem resulted from the fluorine-induced poor nucleophilicity of aniline intermediate in the second coupling step. A similar problem was also observed in the formation of pyridine embodied tricyclic heterocycle **7n** (Table 2, entry 14). The wide range of examples taken together leads us to conclude that the present method should allow for the preparation of a wide range of 5-substituted 11-oxo-dibenzodiazepines.

In conclusion, we have revealed that *N*-substituted aminocarbonyl groups possess a strong *ortho*-substituent effect, allowing the ligandless CuCl-catalyzed coupling of 2-bromo-*N*-phenylbenzamides and primary amines at room temperature with a low catalyst loading. On the basis of this observation, we have developed a facile method for assembling 5-substituted 11-oxo-dibenzodiazepines via double aryl amination.[12] The mild conditions and convenient availability of the starting materials make this approach very competitive in the synthesis of these biologically important heterocycles. The detailed coupling reaction mechanism behind this *ortho*-substituent effect and its further applications in organic synthesis are actively investigated, and the results will be disclosed in due course.

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Supporting Information Available. Experimental procedures and copies of ^{1}H NMR and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) For an example on Pd-catalyzed double aryl amination, see: Nozaki, K.; Takahashi, K.; Nakano, K.; Hiyama, T.; Tang, H.-Z.; Fujiki, M.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2051.