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# Copper-Catalyzed Intramolecular Cyclization to N-Substituted 1,3-Dihydrobenzimidazol-2-ones

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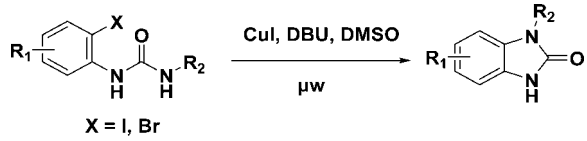
## ABSTRACT




**An efficient and convenient method was developed for preparing N-substituted 1,3-dihydrobenzimidazol-2-ones from N′-substituted N-(2-halophenyl)ureas via a CuI/DBU-catalyzed cyclization in DMSO under microwave heating. High yields were obtained and a variety of functional groups were tolerated under these conditions, including N′-aryl, alkyl, heterocyclic, various N-(substituted 2-halophenyl) and N-(2-iodopyridyl)ureas.**

1,3-Dihydrobenzimidazol-2-ones are an important class of compounds owing to their potency as selective vasopressin 1α receptor antagonists,[1] HIV-1 RT non-nucleoside inhibitors,[2] CGRP receptor antagonists,[3] p38 MAP kinase inhibitors,[4] respiratory syncytial virus fusion inhibitors,[5] and progesterone receptor antagonists.[6] Therefore, much attention has been paid to the development of efficient methods for preparing 1,3-dihydrobenzimidazol-2-ones. Two common approaches were applied for the construction of the dihydrobenzimid-azol-2-one rings. The first approach involves the selective alkylation or arylation of either nitrogen atom of 1,3-dihydrobenzimidazol-2-ones, which often requires a protection strategy.[7] The second one involves nucleophilic displacement of 2-fluoronitrobenzenes with amines and subsequent reduction and cyclization with carbonyldiimidazole,[4,7] which is the limitation of the diversity of the products because of the commercial unavailability of the key reagent of 2-fluoronitrobenzenes.

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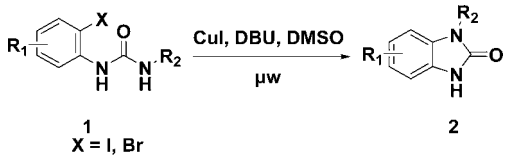
Several studies have reported transition-metal-catalyzed formation of C−N via nitrogen nucleophilic displacement of aryl halogen.[8] Carolina Benedí and co-workers[9] carried out palladium-catalyzed synthesis of 1,3-dihydrobenzimidazol-2-ones and obtained low yields (32%). D. Ma et al.[10] reported the process of cascade coupling/cyclization to N-substituted 1,3-dihydrobenzimidol-2-ones; however, these reactions were only limited to N-alkylated 1,3-dihydrobenzimidol-2-ones and could not be applied to N-aryl or heterocyclic products. As part of our continuing effort to assemble heterocycles by a copper-catalyzed coupling reaction,[11] we aimed to develop a new protocol for synthesizing N-substituted 1,3-dihydrobenzimidol-2-ones via a copper-catalyzed intramolecular cyclization process from N′-substituted-N-(2-halophenyl)ureas in a short time (Scheme 1). In comparison with the existing methods, the present approach offers the following advantages: (i) it proceeds faster and affords good to excellent yields within minutes under microwave heating, (ii) it is very cost-effective and uses the inexpensive catalyst CuI or/and the ligand (L-proline), and (iii) it is applicable to a broader range of substrates, including N′-aryl, alkyl, heterocyclic, and various N-(substituted 2-halophenyl)ureas.

**Scheme 1.** Copper-Catalyzed Synthesis of N-substituted 1,3-Dihydrobenzimidazol-2-ones

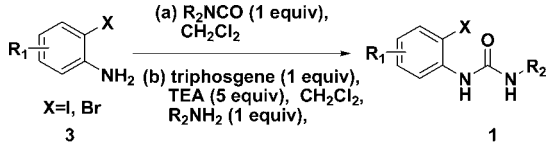



1
X = I, Br

2

The requisite cyclization precursors N′-substituted-N-(2-halophenyl)ureas (**1**) are readily synthesized from commercially available *o*-haloanilines through reactions with triphosgene and different kinds of amines or isocyanates, including aryl, alkyl, and heterocyclic amines[12] or substituted isocyanates[13] (Scheme 2). The desired ureas were obtained in high yields and purity without further purification.

**Scheme 2.** Synthesis of N′-Substituted-N-(2-halophenyl)ureas from *o*-Haloaniline

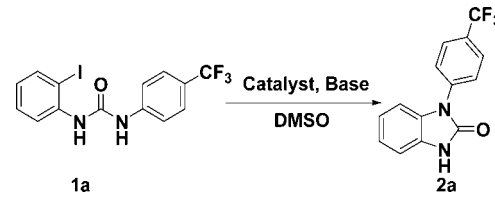



3

1

*N*′-(4-Trifluoromethylphenyl)-*N*-(2-iodophenyl)urea (**1a**) was first used as the model substrate to optimize the reaction conditions, including different bases, various solvents, reaction temperatures, reaction times, and different amounts of catalyst (Table 1).

**Table 1.** Optimization for Synthesis of N-Substituted 1,3-Dihydrobenzimidazol-2-ones[a]




1a

2a

| entry | catalyst | base | temp (°C) | time (min) | yield (%) |
|---|---|---|---|---|---|
| 1 | - | - | 100 | 5 | 0 |
| 2[b] | $Pd(OAc)_2$ | $Cs_2CO_3$ | 100 | 5 | 0 |
| 3 | CuI | NaOH | 100 | 5 | 5 |
| 4 | CuI | TEA | 100 | 5 | 0 |
| 5 | CuI | DBU | 100 | 5 | 64 |
| 6 | CuI | DBU | 120 | 5 | 73 |
| 7 | CuI | DBU | 120 | 10 | 82 |
| 8 | CuI | DBU | 120 | 20 | 93 |
| 9 | CuI[c] | DBU | 120 | 20 | 46 |
| 10 | $Cu(OAc)_2$[d] | DBU | 120 | 20 | 73 |
| 11[e] | CuI | DBU | 120 | 90 | 87 |

[a] Reaction conditions: **1a** (0.5 mmol), catalyst (0.1 mmol), base (1 mmol), DMSO (2 mL). [b] The solvent was dry DMF. [c] CuI (0.05 mmol). [d] $Cu(OAc)_2$ (0.25 mmol). [e] The general method without microwave heating was adopted, CuI (0.1 mmol).

The reaction could not be conducted and no target compound was generated in the base-free condition without a catalyst, which indicated that the presence of a catalyst and base was very crucial to the intramolecular cyclization (entry 1, Table 1). There is no improvement in yield when $Pd(OAc)_2$ is adopted as a catalyst (entry 2, Table 1). Subsequently, we employed the conditions used in our previously published study[11] for copper-catalyzed formation of C−N from a halide and an amine. Moderate conversion of **1a** to **2a** was observed using CuI (0.2 equiv) as the catalyst, dimethyl sulfoxide (DMSO) as the solvent, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base. The nature of bases was found to have a pronounced impact on the process. DBU was proven to be better than the inorganic base NaOH, while triethlyamine (TEA) was ineffective (entries 3 to 5, Table 1). The yields improved significantly when the temperature was up to 120 °C and the reaction


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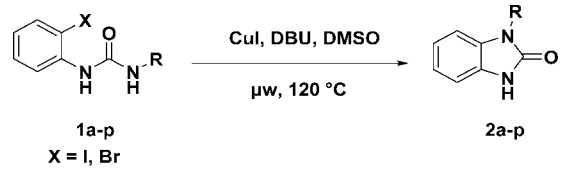
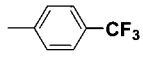
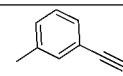
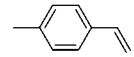
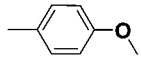
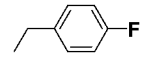
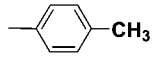
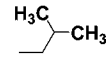
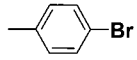
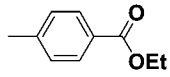
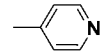
**Table 2.** Synthesis of N-Substituted 1,3-Dihydrobenzimidazol-2-ones




1a-p
X = I, Br

2a-p

| entry | R | product | yield (%) | entry | R | product | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 |  | **2a** | 93[a]<br>81[b]/32[c] | 9 |  | **2i** | 85[a]<br>73[b] |
| 2 |  | **2b** | 89[a] | 10 |  | **2j** | 86[a]<br>77[b] |
| 3 |  | **2c** | 95[a] | 11 |  | **2k** | 85[a,d] |
| 4 |  | **2d** | 93[a] | 12 |  | **2l** | 60[a,d] |
| 5 |  | **2e** | 90[a]<br>79[b] | 13 |  | **2m** | 71[a,d]<br>65[b,d] |
| 6 |  | **2f** | 92[a] | 14 |  | **2n** | 59[a,d] |
| 7 |  | **2g** | 81[a] | 15 |  | **2o** | 72[a] |
| 8 |  | **2h** | 89[a] | 16 |  | **2p** | 83[a] |

[a] Reaction conditions: X = I, **1** (0.5 mmol), CuI (0.1 mmol), DBU (1 mmol), MW, 120 °C, 20 min. [b] X = Br, L-Proline (0.25 mmol) was added. [c] X = Br, without L-proline. [d] Run at 140 °C.

time was prolonged to 20 min (entries 5 to 8, Table 1). The conversion of **1a** was poor (entry 9, Table 1) when the concentration of the catalyst was lower (0.1 equiv). The bivalent copper salt $Cu(OAc)_2$ was not as effective as CuI, although the intramolecular cyclization could proceed (entry 10, Table 1). Finally, we performed a reaction under general conditions without microwave heating to compare the difference between the two different conditions, and an 89% yield was obtained under general conditions after refluxing at 120 °C for 90 min. The increase in the yield resulting from decrease in the reaction time under microwave irradiation was significant (entry 11, Table 1); therefore, microwave heating was adopted in the next investigation. To our knowledge, this is the first report of catalytic intramolecular cyclization of N′-substituted-N-(2-halophenyl)ureas using copper salts.

After determining the optimized conditions, we examined the generality of the process. First, we found that the method was applicable to a broad range of substrates for various N′-substituted-N-(2-iodophenyl)ureas, including N′-aromatic-, N′-aliphatic-, and N′-heterocyclic-substituted ureas (Table 2). The electron-donating or electron-withdrawing substituents on the N′-phenyl group of **1** had no perceptible effect on the yields (entries 1 and 3, Table 2), and the ortho and para substituents had no significant steric effects (entries 1 to 4, Table 2). Several functional groups were employed in the copper-catalyzed process. The N′-(4-bromophenyl), N′-(4-ethoxycarbonyl)phenyl, and N′-(3-nitrile)phenyl groups, which are sensitive to alkali or acid, were all tolerated (entries 6 to 8, Table 2), and good conversions were observed for N′-(3-ethynyl)phenyl, N′-(4-ethenyl)phenyl, and N′-vinyl substituents (entries 9, 10, and 12, Table 2) in the cyclization process. Except for N′-aryl substituents, several N′-aliphatic ones were also obtained in moderate to high yields when temperatures were increased to 140 °C (entries 11 to 14, Table 2). N′-heterocyclic groups such as thiazol-2-yl and pyridine-4-yl proceeded well in good yields to afford the desired products (entries 15 and 16, Table 2).

We next investigated the application of the developed protocol to N′-substituted-N-(2-bromophenyl)ureas. Unfortunately, the desired product, **2a**, was obtained in a low yield (32%) under the optimized conditions (entry 1, Table 2). Several groups have reported L-proline-catalyzed formation of C−N/C−C.[14,15] When L-proline was adopted in the cyclization process, there was a great improvement in the yields, including those of N′-aryl substituents (entries 1, 5, 9, and 10, Table 2) and N′-alkyl substituents (entries 13,

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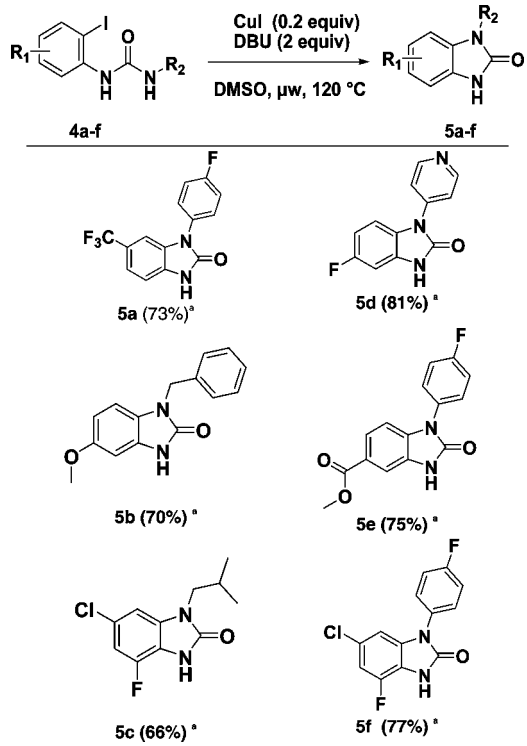
Table 2). The rate of intramolecular cyclization of N′-substituted-N-(2-halophenyl)ureas follows the order I > Br, which was consistent with the order reported previously.[10,16]

To explore the variation possible in the aryl substitutents of N′-substituted-N-(2-halophenyl)ureas, various substitutions of 2-iodophenylureas (**4a**−**f**) were carried out (Scheme 3).

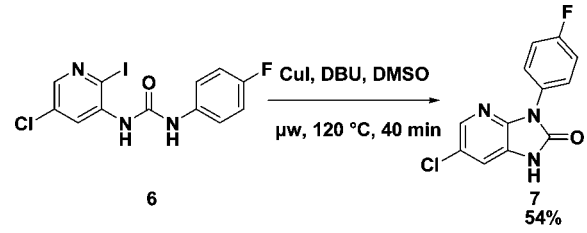
**Scheme 3.** Synthesis of Various N-Substituted 1,3-Dihydrobenzimidazol-2-ones




[a]Yield.

We found that both an electron-donating methoxy substituent and an electron-withdrawing fluorin or ester could be readily incorporated, and good yields of the desired products **5a**−**f** were obtained. Azabenzimidazol-2-ones were identified as potent respiratory syncytial virus inhibitors.[5] Their analogues, namely, imidazopyridin-2(3*H*)-ones, were synthesized in this study (Scheme 4). The yield of product **7** was moderate (54%) when **6** intramolecularly coupled under the catalysis of CuI, with the reaction time prolonged to 40 min.

**Scheme 4.** Synthesis of 6-Chloro-3-(4-fluorophenyl)-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-one




In conclusion, we have demonstrated an efficient method to generate N-substituted 1,3-dihydrobenzimidazol-2-ones using N′-substituted-N-(2-halophenyl)ureas, which can be easily prepared from commercial *o*-haloanilines on reaction with triphosgene and different kinds of amines or isocyanates. Heterocycle formation involves copper-catalyzed formation of C−N by intramolecular cyclization.

A variety of functional groups can be employed, rendering this method particularly attractive for the efficient preparation of biologically and medicinally interesting molecules.

**Acknowledgment.** We gratefully acknowledge the financial support from the State Key Program of Basic Research of China (Grant 2006BAI01B02), the National Natural Science Foundation of China (Grants 20721003, and 20472094), the Basic Research Project for Talent Research Group from the Shanghai Science and Technology Commission, and the 863 Hi-Tech Program of China (Grant 2006AA020602).

**Supporting Information Available:** Reaction procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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