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Copper(I)-Catalyzed One-Pot Synthesis of 2*H*-1,4-Benzoxazin-3-(4*H*)-ones from *o*-Halophenols and 2-Chloroacetamides

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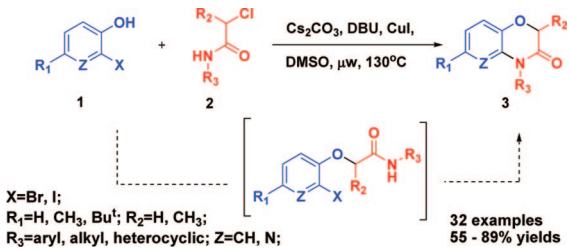

We developed an efficient and convenient method for preparing N-substituted 2*H*-1,4-benzoxazin-3-(4*H*)-ones from 2-halophenols via a nucleophilic substitution with 2-chloroacetamides followed by a CuI-catalyzed coupling cyclization. A broad spectrum of substrates can be effectively employed to afford the desired products in good yields. Since this method involves simple reaction conditions, a short reaction time, and a broad substrate scope, it is particularly attractive for the efficient preparation of biologically and medicinally interesting molecules.

The 2*H*-1,4-benzoxazin-3-(4*H*)-ones scaffold has been studied extensively as an important heterocyclic system for building natural[1] and synthetic compounds.[2] Its derivatives are now known to possess useful biological and medicinal activities (Figure 1). For example, compound **4**, a novel antibacterial agent, is an inhibitor of bacterial histidine protein kinase.[3] Compound **5** is a potential drug for treating heart disease, myocardial necrosis, and arrhythmia.[4] Compound **6** is a potential agent for treating anxiety and depression.[5] The 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acid derivative **7** was found to be a potent immunostimulant.[6] It is known that 2*H*-1,4-benzoxazin-3-(4*H*)-ones bearing a carboxylate and a benzamidine side chain are fibrinogen receptor antagonists,[7] and compound **8** exhibits a dual antithrombotic action, exhibiting both thrombin inhibitory and fibrinogen receptor antagonistic activities.[8] Similar biologically active derivatives have been briefly described in a broader-context review.[9]

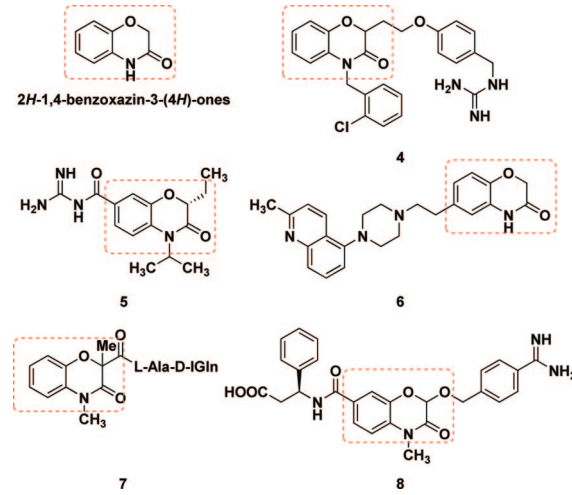

FIGURE 1. Structures of 2*H*-1,4-benzoxazin-3-(4*H*)-one and some biologically important derivatives.

Most of the available literature indicates that 2-aminophenols or substituted 2-nitrophenols are common building blocks for the synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones.[10] Recently, Zuo and co-workers[11] used 2-chlorophenols to synthesize diverse 2*H*-1,4-benzoxazin-3-(4*H*)-ones via Smiles rearrangement.[12] Although this method is encouraging, its disadvantage

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(1) (a) Zhen, Y. S.; Ming, X. Y.; Yu, B.; Otani, T.; Saito, H.; Yamada, Y. *J. Antibiot.* **1989**, *42*, 1294. (b) Sugimoto, Y.; Otani, T.; Oie, S.; Wierzba, K.; Yamada, Y. *J. Antibiot.* **1990**, *43*, 417.
(2) For a representative review, see: Ilas, J.; Anderluh, P. S.; Dolenc, M. S.; Kikelj, D. *Tetrahedron* **2005**, *61*, 7325–7348.
(3) (a) Frechette, R.; Beach, M. WO9728167-A. (b) Frechette, R.; Weidner-Wells, M. A.; Weidnerwells, M. A. WO9717333-A.
(4) Hori, M.; Watanabe, I.; Ohtaka, H.; Harada, K.; Maruo, J.; Morita, T.; Yamamoto, T.; Tsutsui, H. EP719766-A.
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(6) Kikelj, D.; Suhadolc, E.; Rutar, A.; Pecar, S.; Puncuh, A.; Urleb, U.; Leskovsek, V.; Marc, G.; Sollner, M.; Krbavcic, A.; Sersa, G.; Novakovic, S.; Povsic, L.; Stalc, A. EP695308-A; WO9424152-A.
(7) Stefanic, P.; Simoncic, Z.; Breznik, M.; Plavec, J.; Anderluh, M.; Addicks, E.; Giannis, A.; Kikelj, D. *Org. Biomol. Chem.* **2004**, *2*, 1511.
(8) Stefanic Anderluh, P.; Anderluh, M.; Ilas, J.; Mravljak, J.; Sollner Dolenc, M.; Stegnar, M.; Kikelj, D. *J. Med. Chem.* **2005**, *48*, 3110.
(9) Achari, B.; Mandal, S. B.; Dutta, P. K.; Chowdhury, C. *Synlett* **2004**, 2449.
(10) For selected examples, see: (a) Feng, G.; Wu, J.; Dai, W.-M. *Tetrahedron* **2006**, *62*, 4635. (b) Hashimoto, Y.; Ishizaki, T.; Shudo, K. *Tetrahedron* **1991**, *47*, 1837. (c) Wu, J.; Nie, L.; Luo, J.; Dai, W.-M. *Synlett* **2007**, *17*, 2728. (d) Xing, X.; Wu, J.; Feng, G.; Dai, W.-M. *Tetrahedron* **2006**, *62*, 6774. (e) Dai, W.-M.; Wang, X.; Ma, C. *Tetrahedron* **2005**, *61*, 6879. (f) Feng, G.; Wu, J.; Dai, W.-M. *Tetrahedron Lett.* **2007**, *48*, 401. (g) Yuan, Y.; Liu, G.; Li, L.; Wang, Z.; Wang, L. *J. Comb. Chem.* **2007**, *9*, 158. (h) Rybczynski, P. J.; Zeck, R. E.; Combs, D. W.; Turchi, I.; Burris, T. P.; Xu, J. Z.; Yang, M.; Demarest, K. T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 235. (i) Matsumoto, Y.; Uchida, A.; Nakahara, H.; Yanagisawa, I.; Shibanuma, T.; Nohira, H. *Chem. Pharm. Bull.* **2000**, *48*, 428.
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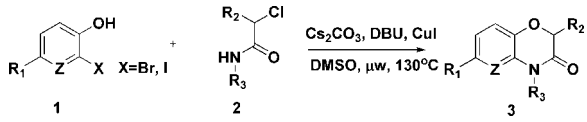
SCHEME 1. Copper-Catalyzed Synthesis of *N*-Substituted-2*H*-1,4-benzoxazin-3-(4*H*)-ones



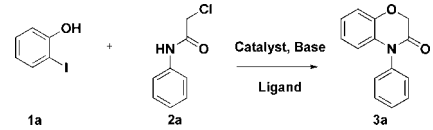
is that only a limited number of substrates can be employed. For example, it is problematic for the synthesis of *N*-aryl-2*H*-1,4-benzoxazin-3-(4*H*)-ones. Up to now, no protocols for the construction of *N*-substituted-2*H*-1,4-benzoxazin-3-(4*H*)-ones based on coupling reactions have been reported. Apparently, the development of an alternative and improved procedure with wide applications still remains a formidable task.

As a part of our continuing effort to assemble heterocycles by copper-catalyzed cross-coupling reactions,[13,14] we aimed to develop a novel protocol for synthesizing *N*-substituted-2*H*-1,4-benzoxazin-3-(4*H*)-ones via copper(I)-catalyzed intramolecular cyclization of 2-iodophenols **1** and 2-chlor-acetamides **2**, which can be readily prepared in high yields from commercially available amines with 2-chloroacetyl chloride. The studies undertaken are presented in Scheme 1. In comparison with existing methods, the present approach offers the following advantages: (i) it is the first highly efficient and practical protocol based on coupling reactions for the construction of *N*-substituted-2*H*-1,4-benzoxazin-3-(4*H*)-ones; (ii) it uses inexpensive CuI/DBU (1,8-diazabicyclo[5.4.0 undec-7-ene) without requiring any other additives; (iii) it proceeds rapidly and affords good to excellent yields within minutes under microwave heating; and (iv) it encompasses a much broader substrate scope, both *N*-aryl- and *N*-alkyl-2*H*-1,4-benzoxazin-3-(4*H*)-ones, as well as *N*-heterocyclic substituted ones, can be employed in this protocol.

2-Iodophenol **1a** and 2-chloro-*N*-phenylacetamide **2a** were used as the model substrates to optimize the reaction conditions in terms of bases, solvents, reaction time, and catalyst-loading. The results are summarized in Table 1.

We initially employed the conditions used in our previously published studies[13,15] on the copper-catalyzed C−N bond formation from halides and amines. Almost no coupling occurred in the absence of the base, while the addition of 1.6 equiv of NaOH resulted in the formation of the desired coupling product in 39% yield after 20 min of irradiation at 130 °C in the presence of DBU (Table 2, entries 1 and 2). The nature of the base was found to have a pronounced impact on the process, and Cs_2CO_3 was proven to be more effective than NaOH, K_2CO_3, K_3PO_4, and DABCO.[16] A moderate amount of the expected product **3a** was obtained when using CuI (0.2 equiv) as the catalyst, DMSO (dimethyl sulfoxide) as the solvent, Cs_2CO_3 as the base, and DBU as the ligand (Table 1, entry 3).

TABLE 1. Optimization for the Synthesis of 4-Phenyl-2*H*-1,4-benzooxazin-3-(4*H*)-one[a]



entry	catalyst	ligand	ratio (**1a**/**2a**)	base	time (min)	yield (%)
1	CuI	DBU	1:1		10	8
2	CuI	DBU	1:1	NaOH	20	39
3	CuI	DBU	1:1	Cs_2CO_3	10	59
4		DBU	1:1	Cs_2CO_3	10	0
5	CuI		1:1	Cs_2CO_3	10	trace
6[b]	CuI	DBU	1:1	Cs_2CO_3	20	35
7	CuI	DBU	1:1	Cs_2CO_3	30	61
8	CuI	DBU	1:1.5	Cs_2CO_3	10	85/81[c]
9	CuI	DBU	1:2	Cs_2CO_3	10	84
10	CuCl	DBU	1:1.5	Cs_2CO_3	10	65
11	Cu_2O	DBU	1:1.5	Cs_2CO_3	10	70
12	$Cu(OAc)_2$[d]	DBU	1:1.5	Cs_2CO_3	10	15
13	$CuSO_4$[e]	DBU	1:1.5	Cs_2CO_3	10	12
14[f]	CuI	DMEDA	1:1.5	Cs_2CO_3	10	75
15[g]	CuI	L-proline	1:1.5	Cs_2CO_3	10	25
16[h]	CuI	DBU	1:1.5	Cs_2CO_3	210	75

[a] Reaction conditions: catalyst (0.2 equiv), base (1.6 equiv), DBU (1.5 equiv), DMSO (2 mL), MW, 130 °C. [b] MW, 120 °C. [c] A subsequential procedure was conducted. [d] $Cu(OAc)_2$ (0.5 equiv). [e] $CuSO_4$ (0.5 equiv). [f] DMEDA (*N*,*N*′-dimethylethylenediamine) (0.4 equiv), Cs_2CO_3 (2.0 equiv). [g] L-Proline (0.4 equiv), Cs_2CO_3 (2.0 equiv). [h] The general method without microwave heating was adopted, 130 °C, CuI (0.5 equiv).

However, no target compound was generated in the absence of the catalyst or ligand, indicating that both are crucial for the intermolecular nucleophilic substitution and intramolecular cyclization (Table 1, entries 4 and 5). When the temperature was reduced to 120 °C, the starting materials were not consumed completely within 20 min (Table 1, entry 6). The yields failed to improve any further when the reaction time was prolonged to 30 min (Table 1, entries 3 and 7). Thin-layer chromatography (TLC) analysis showed that **1a** was not fully converted, thus inspiring us to further investigate the molar ratios of the building blocks. As anticipated, the best yield of the target compound was obtained when 1.5 equiv of 2-chloro-*N*-phenylacetamide **2a** was added (Table 1, entries 3, 8, and 9).

Both CuCl and Cu_2O were found to be effective catalysts for this coupling reaction (Table 1, entries 10 and 11); however, the bivalent copper salts, $Cu(OAc)_2$ and $CuSO_4$, were not as effective as CuI even though the intramolecular cyclization could proceed to some extent (Table 1, entries 12 and 13). The use of other ligands such as DMEDA or L-proline gave somewhat lower yields (Table 1, entries 14 and 15). Subsequently, we investigated the solvent effect, which revealed that DMSO was superior to dioxane, toluene, and DMF.[17] Finally, we found that when the reaction was performed without microwave heating, it afforded a 75% yield after refluxing at 130 °C for 3.5 h (Table 1, entry 16). We also tried a two-step procedure during our original research (Scheme 2). A mixture of **1a** (1.0 mmol), **2a** (1.0 mmol), and DBU (1.2 mmol) in DMSO (2.0 mL) was treated at 100 °C with microwave heating for 5 min without any catalyst and additive. The mixture was purified by flash column chromatography (petroleum ether/ethyl acetate = 10/

(13) For some of our group studies on the synthesis of *N*-heterocycles, see: (a) Li, Z.; Sun, H.; Jiang, H.; Liu, H. *Org. Lett.* **2008**, *10*, 3263. (b) Li, Z.; Huang, H.; Sun, H.; Jiang, H.; Liu, H. *J. Comb. Chem.* **2008**, *10*, 484.

(14) For recent studies on the synthesis of *N*-heterocycles through Ullmann-type couplings from other groups, see: (a) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133. (b) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529. (c) Yang, T.; Lin, C.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2005**, *7*, 4781. (d) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (e) Rivero, M. R.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973. (f) Martin, R.; Rodriguez Rivero, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (g) Zou, B.; Yuan, Q.; Ma, D. *Org. Lett.* **2007**, *9*, 4291.

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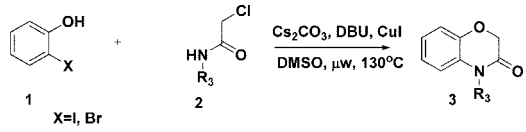
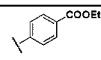
(16) Yields of the desired product for the screening reactions with other bases: K_2CO_3 (20%), K_3PO_4 (0%), DABCO (trace).

(17) Yields of the desired product for the screening reactions with other solvents: toluene (trace), DMF (30%), dioxane (15%).

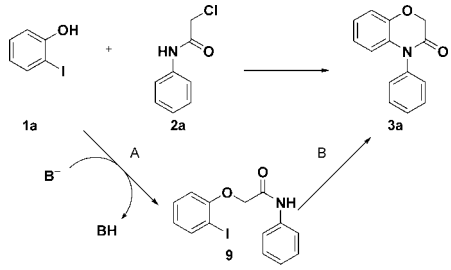
TABLE 2. Synthesis of *N*-Substituted-2*H*-1,4-benzoxazin-3-(4*H*)-ones



entry	R_3	product	Yield (%)	entry	R_3	product	Yield (%)
1		**3a**	85[a]	8		**3h**	75[a]
2		**3b**	89[a] / 48[b]	9		**3i**	72[a]
3		**3c**	84[a]	10		**3j**	75[a]
4		**3d**	85[a]	11		**3k**	67[a]
5		**3e**	86[a]	12		**3l**	82[a]
6		**3f**	82[a] / 51[b]	13		**3m**	70[a]
7		**3g**	82[a] / 45[b]	14		**3n**	65[a]

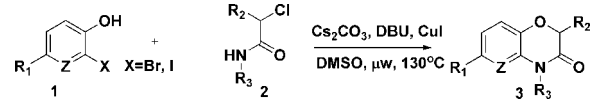
[a] Reaction conditions: X = I, CuI (0.2 equiv), Cs_2CO_3 (1.6 equiv), DBU (1.5 equiv), DMSO (2 mL), MW, 130 °C, 10 min. [b] X = Br, MW, 130 °C, 20 min.

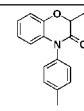
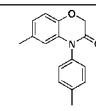
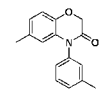
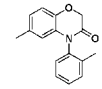
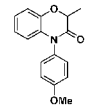
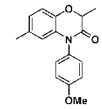
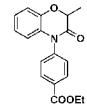
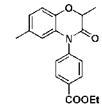
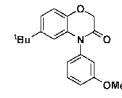
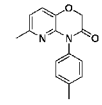
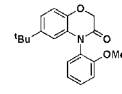
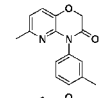
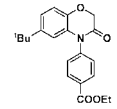
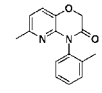
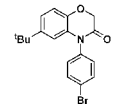
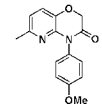
SCHEME 2. Two-Step Synthesis of 2*H*-1,4-Benzoxazin-3-(4*H*)-one via Intermolecular Nucleophilic Substitution (Path A)/Intramolecular C−N Coupling (Path B)



1) to yield the intermediate compound **9**. Then compound **9** (0.5 mmol), CuI (0.1 mmol), Cs_2CO_3 (0.9 mmol), and DBU (0.15 mmol) in DMSO (2.0 mL) were treated at 130 °C with microwave heating for 10 min. The desired product **3a** was isolated in 81% total yield (Table 1, entry 8). We used 1.2 equiv of DBU as the base for the first intermolecular nucleophilic substitution, and the other DBU for purely ligand purpose. Comparing the two methods, the former is superior for its concise single-step manipulation and better yield. Apparently, microwave irradiation in one pot had a significant effect on the increase in the yield and the decrease in the reaction time. Therefore, microwave heating was adopted in the following investigation. Briefly, the optimum results were obtained when 2-chloroacetamide (1.5 equiv) and 2-iodophenol (1.0 equiv) were treated with CuI (0.2 equiv), Cs_2CO_3 (1.6 equiv), and DBU (1.5 equiv) in DMSO at 130 °C with microwave heating for 10 min.

TABLE 3. Synthesis of Various Substituted 2*H*-1,4-Benzoxazin-3-(4*H*)-ones



entry	product		yield(%)	entry	product		yield(%)
1		**3o**	82[a]	10		**3x**	60[b]
2		**3p**	75[a]	11		**3y**	56[b]
3		**3q**	70[a]	12		**3z**	55[b]
4		**3r**	73[a]	13		**3aa**	61[b]
5		**3s**	82[a]	14		**3ab**	59[b]
6		**3t**	84[a]	15		**3ac**	71[a]
7		**3u**	75[a]	16		**3ad**	65[a]
8		**3v**	74[a]	17		**3ae**	56[a]
9		**3w**	82[a]	18		**3af**	75[a]

[a] Reaction conditions: X = I, **1** (0.5 mmol), **2** (0.75 mmol), CuI (0.1 mmol), DBU (0.75 mmol), Cs_2CO_3 (0.9 mmol), MW, 130 °C, 10 min. [b] X = Br, MW, 130 °C, 20 min.

After determining the optimized conditions, we proceeded to examine the generality of the process. As summarized in Table 2, the reaction was compatible with various 2-chloroacetamides to afford different *N*-substituted-2*H*-1,4-benzoxazin-3-(4*H*)-ones. Aryl, alkyl, and heterocyclic substituents are well tolerated. The ortho-, meta-, and para-substituents on the acetamide component had no significant steric effects (Table 2, entries 2−7). Moreover, the electron-donating and electron-withdrawing substituents had no perceptible effect on the yields (Table 2, entries 5, 8, and 9). Furthermore, several functional groups were employed in this copper-catalyzed process. It was observed that the *N*-(4-bromophenyl) and *N*-(4-ethoxycarbonyl)phenyl, which are sensitive to bases or acids, were all tolerated in the cyclization process (Table 2, entries 8 and 10). Reaction involving the *N*-heterocyclic group such as pyridine-3-yl proceeded smoothly to afford the desired product in a good yield (Table 2, entry 11). In addition to *N*-aryl substituents, several *N*-alkyl ones were also obtained in moderate to high yields (Table 2, entries 12−14).

Subsequently, we investigated the application of the developed protocol to 2-bromophenol. Unfortunately, the desired product **3b** was obtained in a low yield under the optimized conditions. When the reaction time was prolonged to 20 min, there was a moderate improvement in the yield (Table 2, entries 2, 6, and 7). As compared to iodides, bromides exhibited lower reactivity. These results indicated that the reactivity order of aryl halides was iodides > bromides, which was consistent with the order reported previously.[15]

Finally, we focused on employing different 2-chloroacetamides and 2-halophenols. Fortunately, as shown in Table 3, the method was applicable to a broad range of substrates including both 2-chloroacetamides and 2-halophenols. First, this new process was applied to 2-methyl-2-chloroacetamides. The ortho-, meta-, and para-substituents on the acetamide component had no significant steric effects, and the electronic effects on the reactions were also limited (Table 3, entries 1−5). Second, 4-*tert*-butyl-2-iodophenol, 4-methyl-2-bromophenol, and 6-methyl-2-iodopyridin-3-ol were investigated, and the corresponding *N*-substituted-2*H*-1,4-benzoxazin-3-(4*H*)-ones were obtained in moderate to excellent yields (Table 3, entries 6−18). Therefore, our method is an alternative approach for the synthesis of these heterocyclic molecules. The product **3x** was recrystallized from methanol and was characterized crystallographically.

In conclusion, we have developed a novel protocol for the elaboration of 2*H*-1,4-benzoxazin-3-(4*H*)-ones via a cascade reaction with a nucleophilic substitution followed by a CuI/DBU-catalyzed coupling cyclization. This method enables the use of a wide range of 2-halophenols and 2-chloroacetamides to assemble various products in moderate to good yields. In this regard, this approach would be particularly attractive for the efficient preparation of biologically and medicinally interesting molecules.

Experiment Section

General Procedure for Synthesis of 2-Chloroacetamides 2. To a solution of amine (0.5 mmol) and triethylamine (TEA) (0.5 mmol) in CH_2Cl_2 (5 mL) at −5 °C was added 2-chloroacetyl chloride (0.6 mmol) dropwise. After 10 min, the reaction mixture was allowed to warm to room temperature. When the starting materials were consumed monitored with TLC, the solution was diluted with CH_2Cl_2 (20 mL), washed with water and brine, and dried over anhydrous Na_2SO_4. On evaporation of the solvent, the desired *N*-substituted-2-chloroacetamides **2** were obtained in high yields and purity without further purification.

General Procedure for Synthesis of 2*H*-1,4-Benzooxazin-3-(4*H*)-ones 3. To a solution of 2-halophenol (0.5 mmol) and **2** (0.75 mmol) in DMSO (2 mL) were added CuI (0.1 mmol), Cs_2CO_3 (0.9 mmol), and DBU (0.75 mmol). The vial was sealed and the mixture was then irradiated for 10 min at 130 °C. The cold mixture was diluted with CH_2Cl_2 (20 mL), washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuum. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 10/1) to yield the expected product. Selected example, compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 4.78 (s, 2H), 6.43 (dd, J = 1.5, 6 Hz, 1H), 6.83−6.88 (m, 1H), 6.96−7.07 (m, 2H), 7.28−7.31 (m, 2H), 7.44−7.57 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 68.2, 116.9, 167.0, 122.6, 124.1, 128.8, 128.9, 130.0, 135.8, 145.0, 164.3; EI-MS m/z (M^+) 225; EI-HRMS calcd for $C_{14}H_{11}NO_2$ (M^+) 225.0790, found 225.0790. (For details, please see the Supporting Information.)

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Supporting Information Available: Detailed experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all products, and crystallographic information files (CIF) of **3x**. This material is available free of charge via the Internet at http://pubs.acs.org.

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