#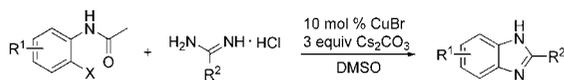 Copper-Catalyzed Synthesis of Benzimidazoles via Cascade Reactions of *o*-Haloacetanilide Derivatives with Amidine Hydrochlorides

Daoshan Yang,[†,‡] Hua Fu,*[,†] Liming Hu,*[,‡] Yuyang Jiang,[†,¶] and Yufen Zhao[†]

Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, People's Republic of China, College of Life Sciences and Bioengineering, Beijing University of Technology, Beijing 100124, People's Republic of China, and Key Laboratory of Chemical Biology (Guangdong Province), Graduate School of Shenzhen, Tsinghua University, Shenzhen 518057, People's Republic of China

fuhua@mail.tsinghua.edu.cn; huliming@bjut.edu.cn

Received July 8, 2008

We have developed an efficient method for the synthesis of benzimidazoles via cascade reactions of *o*-haloacetoanilide derivatives with amidine hydrochlorides. The protocol uses 10 mol % CuBr as the catalyst, Cs_2CO_3 as the base, and DMSO as the solvent, and no ligand is required. The procedure proceeds via the sequential coupling of *o*-haloacetoanilide derivatives with amidines, hydrolysis of the intermediates (amides), and intramolecular cyclization with the loss of NH_3 to give 2-substituted 1*H*-benzimidazoles.

Benzimidazoles have attracted much attention for their wide applications as enzyme inhibitors,[1] drugs,[2] dyes,[3] and polymers.[4] Among the previous methods,[5] the condensation of 1,2-diaminoarene derivatives with carbonyl compounds is perhaps the most common.[6] Substituted *o*-nitroanilines can also be used in the place of the 1,2-diaminoarene derivatives under reducing conditions.[7] However, the preparation of benzimidazoles with these methods depends on the availability of the requisite 1,2-diaminoarene or *o*-nitroaniline derivatives, and some of them are sometimes difficult to prepare.[8] Recently, considerable progress has been made in the area of copper-catalyzed Ullmann *N*-arylations,[9] with some research groups[10−12] and ourselves[13] having developed highly efficient copper catalyst systems to *N*-arylate amines, and therefore construct *N*-heterocycles.[14] Copper[15] and palladium-catalyzed[16] couplings of *o*-haloacetoanilides with amines to form *N*-aryl benzimidazoles have been reported. Herein, we report a novel and efficient copper-catalyzed cascade reaction of *o*-haloacetoanilide derivatives with amidine hydrochlorides to synthesize 2-substituted benzimidazoles.

---

(5) Grimmett M. R. In *Imidazole and Benzimidazole Synthesis, Best Synthetic methods*; Meth-Cohn, O., Ed.; Academic: London, UK, 1997.

(6) (a) Meng, L.; Fettinger, J. C.; Kurth, M. J. *Org. Lett.* **2007**, *9*, 5055. (b) Liao, Y.-L.; Lin, C.-Y.; Wong, K.-T.; Hou, T.-H.; Hung, W.-Y. *Org. Lett.* **2007**, *9*, 4511.

(7) Yang, D.; Fokas, D.; Li, J.; Yu, L.; Baldino, C. M. *Synthesis* **2005**, 47, and references cited therein.

(8) Ebenezer, W. J.; Hutchings, M. G.; Jones, K.; Lambert, D. A.; Watt, I. *Tetrahedron Lett.* **2007**, *48*, 1641.

(9) For recent reviews on copper-catalyzed Ullmann *N*-arylation, see: (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, *15*, 2428. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.

(10) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. (c) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578. (d) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (e) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793. (f) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

(11) (a) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459. (b) Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583. (c) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (d) Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799. (e) Ma, D.; Cai, Q. *Synlett* **2004**, *1*, 128. (f) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (g) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, 888. (h) Ma, D.; Liu, F. *Chem. Commun.* **2004**, 1934. (i) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164.

(12) (a) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (b) van Allen, D.; Venkataraman, D. *J. Org. Chem.* **2003**, *68*, 4590. (c) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, 695. (d) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607. (e) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312. (f) Kelkar, A. A.; Patil, N. M.; Chaudhari, R. V. *Tetrahedron Lett.* **2002**, *43*, 7143. (g) Gajare, A. S.; Toyota, K.; Yoshifuji, M.; Yoshifuji, F. *Chem. Commun.* **2004**, 1994. (h) Yang, M.; Liu, F. *J. Org. Chem.* **2007**, *72*, 8969. (i) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (j) Chen, Y.-J.; Chen, H.-H. *Org. Lett.* **2006**, *8*, 5609.

(13) (a) Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2005**, *70*, 8107. (b) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Eur. J.* **2006**, *12*, 3636. (c) Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672. (d) Jiang, Q.; Jiang, D.; Jiang, Y.; Fu, H.; Zhao, Y. *Synlett* **2007**, *72*, 1836. (e) Guo, X.; Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Adv. Synth. Catal.* **2006**, *348*, 2197.

(14) For recent studies on the synthesis of *N*-heterocycles via Ullmann-type couplings, see:(a) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529. (b) Martin, R.; Rodríguez, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (c) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (d) Bonnaterre, F.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2006**, *8*, 4351. (e) Yuan, X.; Xu, X.; Zhou, X.; Yuan, J.; Mai, L.; Li, Y. *J. Org. Chem.* **2007**, *72*, 1510. (f) Yang, T.; Lin, C.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2005**, *7*, 4781.

(15) (a) Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2598. (b) Zheng, N.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 4749.

(16) Zheng, N.; Anderson, K. W.; Huang, X.; Nguyen, H. N.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7509.

* To whom correspondence should be addressed. Fax: 86-10-62781695.
† Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Tsinghua University.
‡ College of Life Sciences and Bioengineering, Beijing University of Technology.
¶ Key Laboratory of Chemical Biology (Guangdong Province), Tsinghua University.

(1) (a) Baudy, R. B.; Fletcher, H., III.; Yardley, J. P.; Zaleska, M. M.; Bramlett, D. R.; Tasse, R. P.; Kowal, D. M.; Katz, A. H.; Moyer, J. A.; Abou-Gharbia, M. *J. Med. Chem.* **2001**, *44*, 1516. (b) Zarrinmayeh, H.; Nunes, A. M.; Ornstein, P. L.; Zimmerman, D. M.; Arnold, M. B.; Schober, D. A.; Gackenheimer, S. L.; Bruns, R. F.; Hipskind, P. A.; Britton, T. C.; Cantrell, B. E.; Gehlert, D. R. *J. Med. Chem.* **1998**, *41*, 2709. (c) White, A. W.; Almassy, R.; Calvert, A. H.; Curtin, N. J.; Griffin, R. J.; Hostomsky, Z.; Maegley, K.; Newell, D. R.; Srinivasan, S.; Golding, B. T. *J. Med. Chem.* **2000**, *43*, 4084. (d) Hauel, N. H.; Nar, H.; Priepke, H.; Ries, U.; Stassen, J.; Wienen, W. *J. Med. Chem.* **2002**, *45*, 1757.

(2) Vellk, J.; Baliharova, V.; Fink-Gremmels, J.; Bull, S.; Lamka, J.; Skalova, L. *Res. Vet. Sci.* **2004**, *76*, 95, and reference cited therein.

(3) Schwartz, G.; Fehse, K.; Pfeiffer, M.; Walzer, K.; Leo, K. *Appl. Phys. Lett.* **2006**, *89*, 083509.

(4) Asensio, J. A.; Gomez-Romero, P. *Fuel Cells* **2005**, *5*, 336.

SCHEME 1. Copper-Catalyzed Couplings of Butyramidine Hydrochloride with *o*-Bromoacetoanilide (1b) or *o*-Bromoaniline
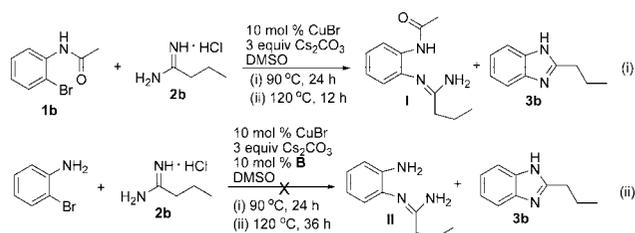
TABLE 1. Copper-Catalyzed Synthesis of 2-Propyl-1*H*-benzimidazole (3b) via Cascade Reaction of *o*-Bromoacetanilide with Butyramidine Hydrochloride: Optimization of the Catalysis Conditions[a]

entry	catalyst	ligand	base	solvent	yield[b]
1	CuBr	A	Cs_2CO_3	DMSO	33
2	CuI	A	Cs_2CO_3	DMSO	28
3	Cu_2O	A	Cs_2CO_3	DMSO	31
4	$CuCl_2$	A	Cs_2CO_3	DMSO	10
5	CuBr	A	Cs_2CO_3	DMF	34
6	**CuBr**	**B**	**Cs_2CO_3**	**DMF**	**65**
7	CuBr	C	Cs_2CO	DMF	51
8	CuBr	D	Cs_2CO_3	DMF	36
9	CuBr	B	Cs_2CO_3	DMSO	25
10	**CuBr**		**Cs_2CO_3**	**DMSO**	**63**
11	CuBr		K_2CO_3	DMSO	42
12	CuBr		K_3PO_4	DMSO	59
13	CuBr		Cs_2CO_3	DMF	37

[a] Reaction conditions: under nitrogen atmosphere, reaction temperature (90 °C for 24 h, and then 120 °C for 48 h). *o*-Bromoacetanilide (1 mmol), butyramidine hydrochloride (1.2 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), base (3 mmol), solvent (2 mL). [b] Isolated yield.

Initially, *o*-bromoacetoanilide and butyramidine hydrochloride were chosen as the model substrates to optimize reaction conditions including optimization of the catalysts, ligands, bases, and solvents under nitrogen atmosphere. Reaction temperature was maintained at 90 °C (*N*-arylation temperature of amidine) for 24 h and then at 120 °C (hydrolysis temperature of amide, see reaction mechanism in Scheme 2) for 48 h as shown in Table 1, and 2-propyl-1*H*-benzimidazole (**3b**) was obtained in various yields. The copper salts CuBr, CuI, Cu_2O, and $CuCl_2$ (10 mol % amount relative to *o*-bromoacetoanilide) were tested in DMSO (entries 1−4), using 20 mol % 3,4,7,8-tetramethyl-1,10-phenanthroline as the ligand and 3 equiv of Cs_2CO_3 as the base. CuBr was found to be the most effective catalyst (entry 1). We attempted to use different ligands (entries 5−8) in DMF, and *N*,*N*′-dimethylethylenediamine showed the highest activity (entry 6). We changed solvent from DMF to DMSO, and the results showed that DMF was much better than DMSO (compare entries 6 and 9). Surprisingly, 2-propyl-1*H*-benzimidazole (**3b**) was obtained in 63% yield with Cs_2CO_3 as the base and DMSO as the solvent in the absence of ligand (entry 10), which implied the existence of an ortho-substitutent effect (see the reaction mechanism). The effect of bases was also investigated (entries 10−12), and Cs_2CO_3 proved to be most effective (entry 10). When DMSO was replaced with DMF as the solvent, the

TABLE 2. Copper-Catalyzed Synthesis of 2-Substituted Benzimidazoles via Cascade Reactions of *o*-Haloacetanilide Derivatives with Amidine Hydrochlorides[a]

entry	1	2	product	yield[b]
1	1a	2a	3a	80
2	1a	2b	3b	65
3	1b	2a	3a	82
4	1b	2b	3b	63
5	1c	2a	3c	75
6	1c	2b	3d	62
7	1d	2a	3e	89
8	1d	2b	3f	65
9	1e	2a	3g	74
10	1e	2b	3h	80
11	1b	2c	3i	65
12	1c	2c	3j	70
13	1d	2c	3k	62

[a] Reaction conditions: *o*-haloacetanilide derivative (1 mmol), amidine hydrochloride (1.2 mmol), CuBr (0.1 mmol), Cs_2CO_3 (3 mmol), DMSO (2 mL) under N_2. Reaction temperature and time (60 °C/10 h and then 120 °C/48 h for **1a**; 90 °C/24 h and then 120 °C/48 h for **1b** and **1c**; 70 °C/24 h and then 120 °C/48 h for **1d** and **1e**). [b] Isolated yield.

coupling reaction gave a lower yield (entry 13). After the optimization process for catalysts, ligands, bases, and solvents, the various benzimidazole derivatives were synthesized under our standard conditions: 10 mol % CuBr as the catalyst, 3 equiv of Cs_2CO_3 as the base (relative to *o*-haloacetoanilides), and DMSO as the solvent.

Using the optimized conditions, we investigated the scope of substrates. As shown in Table 2, all the examined substrates provided the corresponding benzimidazoles in good yields. For the substituted *o*-haloacetanilides, *o*-iodoacetanilide showed higher reactivity than *o*-bromoacetanilide derivatives, the *N*-

arylation of amidines was performed at 60 °C with *o*-iodoac-etanilide as the partner (entries 1 and 2), but it was necessary to raise the temperature to 90 °C for *o*-bromoacetanilide (entries 3−13). *o*-Haloacetanilides containing electron-withdrawing groups showed higher reactivity than ones containing electron-donating groups. For 2-bromo-4-bromoacetanilide, the *N*-arylation of amidines selectively occurred ortho to the NH-COCH₃ group, therefore revealing an ortho-substituent-effect during the Ullmann coupling reaction (see the reaction mechanism). Although aliphatic amidines showed high reactivity, unfortunately, aryl ones were poor substrates.

We also attempted a one-pot two-step coupling of *o*-haloacetanilides, amidine hydrochlorides, and aryl iodides as shown in Table 3. Reaction conditions for formation of 2-substituted 1*H*-benzimidazoles are similar to those in Table 2. Once the formation of 2-substituted 1*H*-benzimidazoles was completed (TLC determination), 2 or 3 equiv of aryl iodide and 20 mol % 3,4,7,8-tetramethyl-1,10-phenanthroline were added to the resulting solution. *N*-Arylation of the 2-substituted 1*H*-benzimidazoles then smoothly occurred to give 1,2-disubstituted benzimidazoles in good yield. The one-pot two-step coupling of 2-bromo-4-methylacetanilide, acetamidine hydrochloride, and 1-iodobenzene or 1-chloro-4-iodobenzene provided isomeric 1,2-disubstituted benzimidazoles (entries 7 and 8). Interestingly, 2-bromo-4-bromoacetanilide only gave an isomer (entry 9).

We also investigated the reaction mechanism to form 2-substituted benzimidazoles via cascade reactions of *o*-halo-acetanilides with amidine hydrochlorides in the presence of Cs₂CO₃. The reaction mixture was examined by ESI-MS after coupling of *o*-bromoacetoanilide with butyramidine hydrochloride for a time, and intermediate **I** and 2-propyl-1*H*-benzimi-dazole (**3b**) were found (see Figure 1 in the Supporting Information) (Scheme 1, reaction i). However, treatment of *o*-bromoaniline with butyramidine hydrochloride did not produce intermediate **II** and product **3b** (Scheme 1, reaction ii). The results above imply that the NHCOCH₃ substituent in *o*-bromoacetoanilide mediates the *N*-arylation. Since suitable ortho-substituents can promote Ullmann-type couplings,[17] a plausible mechanism to form 2-substituted benzimidazoles is proposed in Scheme 2. Reaction of amidine hydrochloride (**2**) with base (Cs₂CO₃) produces free amidine (**2′**) and water. Coordination of *o*-haloacetanilide with CuBr first forms **III**, oxidation addition of **III** provides coordinate **IV**, and complex-ation of **IV** with amidine gives **V**. Reductive elimination of **V** in the presence of Cs₂CO₃ affords *N*-arylation product (**I**) of amidaine releasing copper catalyst. Hydrolysis of **I** in the presence of base (Cs₂CO₃) provides **II**,[18] which undergoes ring closure and elimination of NH₃ to provide the target product **3**.

In summary, we have developed an efficient method for copper-catalyzed synthesis of 2-substituted benzimidazoles, and the protocol uses inexpensive CuBr as the catalyst and readily available *o*-haloacetanilide derivatives and amidine hydrochlo-rides as the substrates, and no ligand is required. The method has practical applications for the synthesis of enzyme inhibitors and pharmaceutical and medicinal compounds, as well as polymers and materials containing the benzimidazole motif.

(17) (a) Nicolaou, K. C.; Boddy, C. N. C.; Natarajar, S.; Yue, T.-Y.; Li, H.; Bräse, S.; Ramanjulu, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 3421. (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (c) Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986. (d) Cai, Q.; Zou, B.; Ma, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1276.
(18) Majetich, G.; Hicks, R. *Res. Chem. Intermed.* **1994**, *20*, 61.

TABLE 3. Copper-Catalyzed Synthesis of 1,2-Disubstituted Benzimidazoles via One-Pot Two-Step Reactions[a]

entry	1	4	product	total yield[b]
1	1b	4a	5a	62
2	1b	4a	5b	65
3	1b	4b	5c	70
4	1b	4b	5d	57
5	1b	4c	5e	49
6	1b	4d	5f	62
7	1c	4a	5g, 5′g	57, 5g/5′g (1.35:1)[c]
8	1c	4b	5h, 5′h	60, 5h/5′h (1.22:1)[c]
9	1d	4a	5i	45

[a] Reaction conditions: For step 1, *o*-haloacetanilide derivative (1 mmol), amidine hydrochloride (1.2 mmol), CuBr (0.1 mmol), Cs₂CO₃ (3 mmol), DMSO (2 mL) under N₂, reaction temperature and time are the same as given in Table 2. For step 2, aryl iodide (3 mmol for **4a**, 2 mmol for others), ligand **A** (0.2 mmol), reaction temperature and time (130 °C/36 h for entry 8; 120 °C/36 h for others). [b] Isolated yield. [c] Ratio of **5** to **5′** was determined by ¹H NMR.

SCHEME 2. Plausible Reaction Mechanism To Form Benzimidazoles via Copper-Catalyzed Cascade Reactions of *o*-Haloacetanilide Derivatives with Amidine Hydrochlorides in the Presence of Cs$_2$CO$_3$
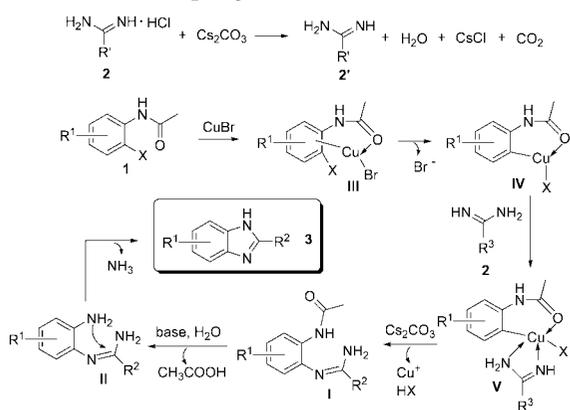
Experimental Section

General Procedure for Copper-Catalyzed Synthesis of 2-Substituted 1*H*-Benzimidazoles (3a−k) and 1,2-Disubstituted Benzimidazoles (5a−i). A flask was charged with CuBr (14 mg, 0.1 mmol), Cs$_2$CO$_3$ (977 mg, 3 mmol) (see Tables 2 and 3) in 2 mL of DMSO, and *o*-haloacetanilide (1 mmol) and amidine hydrochloride (1.2 mmol) (see Tables 2 and 3) were added to the flask at room temperature under nitrogen atmosphere. The mixture was stirred at 60−90 °C (see Tables 2 and 3) under nitrogen atmosphere. After the coupling reaction for a time as shown in Tables 2 and 3, the resulting solution was raised to 120 °C, and the reaction was maintained for 48 h. The reaction system was cooled to room temperature, and then the workup was performed for synthesis of 2-substituted benzimidazoles in Table 2. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to provide the desired product. For synthesis of disubstituted benzimidazoles in Table 3, aryl iodide (2 mmol) and 3,4,7,8-tetramethyl-1,10-phenanthroline (47 mg, 0.2 mmol) were added to the resulting solution, and the reaction was carried out at 120 or 130 °C for 36 h under nitrogen atmosphere. The following workup was similar to the former (2-substituted benzimidazoles). Two examples are shown as follows.

5-Bromo-2-methylbenzimidazole (3e). Eluent: ethyl acetate. Yield 86% (180 mg). White solid, mp 232−233 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ 7.65 (s, 1H), 7.43−7.40 (d, 1H, J = 9.0 Hz), 7.26−7.23 (d, 1H, J = 9.0 Hz), 2.50 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz, ppm) δ 153.4, 141.3, 138.2, 124.4, 117.7, 116.1, 113.8, 15.1. ESI-MS M$^+$ 210.5, 212.4.

1-Phenyl-2-propylbenzoimidazole (5b). Eluent: petroleum ether/ethyl acetate (6:1). Yield 65% (153 mg). Pale yellow viscous liquid. ^{1}H NMR (CDCl$_3$, 300 MHz, ppm) δ 7.80−7.10 (m, 9H), 2.77 (t, 2H, J = 7.6 Hz), 1.83 (dt, 2H, J = 7.6 Hz), 0.94 (t, 3H, J = 7.6 Hz). ^{13}C NMR (CDCl$_3$, 75 MHz, ppm) δ 155.3, 136.6, 136.1, 130.0, 129.6, 129.0, 127.5, 122.6, 122.4, 119.2, 29.7, 21.3, 14.0. ESI-MS [M + H]$^+$ *m/z* 236.5.

Supporting Information Available: General experimental procedures, characterization data, and ^{1}H, ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8014984