JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

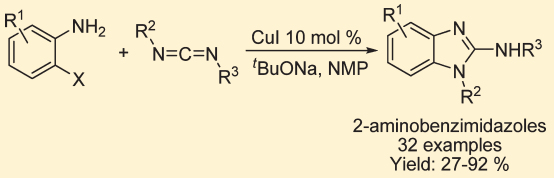
A Protocol to 2-Aminobenzimidazoles via Copper-Catalyzed Cascade Addition and Cyclization of *o*-Haloanilines and Carbodiimides

Fei Wang, Shangjun Cai, Qian Liao, and Chanjuan Xi*

Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China

Supporting Information

ABSTRACT: An efficient strategy for the synthesis of a variety of 2-animobenzimidazole derivatives has been developed. The reaction proceeded from *o*-haloanilines and carbodiimides via copper(I)-catalyzed domino reaction in the presence of *tert*-butoxide to afford the corresponding 2-animobenzimidazole derivatives in good to excellent yields. *o*-Haloanilines could be *o*-iodoaniline, *o*-bromoaniline, and *o*-chloroaniline derivatives. Carbodiimides could be symmetrical and unsymmetrical substrates with aryl or alkyl substituents. The reaction exhibited a good regioselectivity when unsymmetrical carbodiimides were employed.



INTRODUCTION

2-Aminobenzimidazoles as an important subclass of benzimidazoles have attracted much attention due to their varied biological activities toward numerous diseases (Figure1).[1] For example, 2-aminobenzimidazole core structures can be found in commercial drugs such as astemizole,[2] mizolastine,[3] and CID-2858522.[4] More recently, 2-aminobenzimidazole derivatives were once more reported as factor Xa (FXa) inhibitors,[5] poly(ADP-ribose)polymerase (PARP) inhibitors,[6] and as human cytomegalovirus (HCMV) inhibitors.[7] Development of an effective method to construct functionalized benzimidazole scaffold is thus highly relevant to drug discovery. Many methods for syntheses of 2-aminobenzimidazole derivatives have been developed thus far.[8] Conventionally, protocols for their preparation of 2-aminobenzimidazole included the nucleophilic aromatic substitution (S_NAr) reaction of an amino nucleophile with a 2-halobenzimidazole, which often need high temperature or high pressure.[9] This method was greatly improved subsequently owing to the development of palladium- and nickel-catalyzed amination.[10] Another way to prepare 2-aminobenzimidazoles involved reaction of benzene-1,2-diamine with thiocyanate[11,12] or thiourea.[13] Although these protocols provided access to 2-aminobenzimidazoles, they suffered limitations in scope and generality. Furthermore, some protocols proceeded in harsh reaction conditions or low yields.

Recently, one-pot strategies for the synthesis of various useful heterocyclic compounds based on the copper-catalyzed C−X (X = N, O, and S) bond formation have been studied.[14−16] For example, benzimidazoles could be efficiently formed via aryl amination/condensative cyclization processes.[14a−c] More recently, copper-catalyzed methods enabled the coupling of *o*-haloanilines with carbodiimides, which provided a straightforward method to 2-aminobenzimidazoles, although protocol only worked for *N*,*N*′-diphenylcarbodiimide.[17] The development of general, cheap methodology to create 2-aminobenzimidazoles is still desirable. Herein we would like to report a general and practical route to 2-aminobenzimidazoles via copper-catalyzed cascade addition/cyclization of *o*-haloanilines with various carbodiimides.

RESULTS AND DISCUSSION

Initially, we used the *o*-iodoaniline **1a** and *N*,*N*′-dicyclohexylcarbodiimide (DCC) **2a** as the starting materials and CuI as precatalyst, *N*,*N*′-dimethylethane-1,2-diamine (DMEDA) as the ligand, and Cs_2CO_3 as base in toluene at 90 °C. Encouragingly, the product **3a** was obtained in 23% yield monitored by GC (Table 1, entry 1). Then different solvents such as 1,4-dioxane, CH_3CN, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were screened. To our delight, the yield greatly increased to 64% when *N*-methyl-2-pyrrolidone (NMP) was employed as solvent (entries 2−6). Next, the bases were evaluated in the reaction. Clearly, the basicity had a great effect on the reaction. ^{t}BuONa was superior to Cs_2CO_3, K_3PO_4, DBU, and DABCO (entries 7−10). Among the ligands examined in the reaction, *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA), 1,10-phenanthroline, L-proline, and 2,2′-bipyridine (entries 11−14) as ligands showed analogous results. These results suggested that the ligands might not participate in the reaction at all, which is a dramatically different effect of a ligand in usually coupling reactions. Indeed, we were pleased to find that, in the absence of a ligand, the desired product formed in an excellent yield (entry 15). The reaction showed a dependence on the temperature. When the reaction was treated at 70 °C, almost no product formed (entry 16). On the other hand, without use of CuI, the reaction proceeded to less than 12% yield (entry 17).

To confirm the structure of the product, colorless single crystals of **3a** suitable for X-ray diffraction analysis were obtained by recrystallization in dichloromethane/*n*-hexane (1/1) at room temperature. The structure of **3a**[18] clearly shows the formation of

Received: January 5, 2011
Published: March 17, 2011

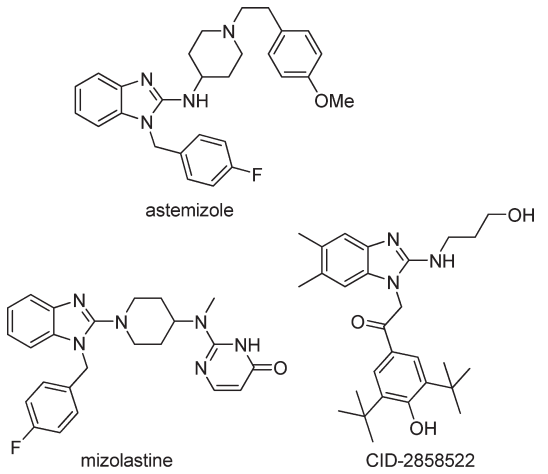
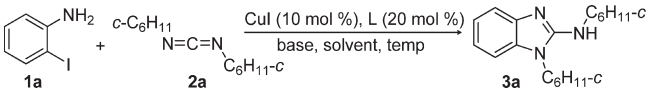


Figure 1. Examples of some biologically active compounds.

Table 1. Optimization between *o*-Iodoaniline and *N,N′*-Dicyclohexylcarbodiimide[a]



entry	base	ligand	solvent	temp (°C)	yield (%)[b]
1	Cs_2CO_3	DMEDA	toluene	90	23
2	Cs_2CO_3	DMEDA	dioxane	90	21
3	Cs_2CO_3	DMEDA	CH_3CN	90	10
4	Cs_2CO_3	DMEDA	DMF	90	50
5	Cs_2CO_3	DMEDA	DMSO	90	27
6	Cs_2CO_3	DMEDA	NMP	90	64
7	K_3PO_4	DMEDA	NMP	90	42
8	DBU	DMEDA	NMP	90	15
9	DABCO	DMEDA	NMP	90	23
10	^{t}BuONa	DMEDA	NMP	90	71
11	^{t}BuONa	1,10-phenanthroline	NMP	90	76
12	^{t}BuONa	L-proline	NMP	90	72
13	^{t}BuONa	2,2′-bipyridine	NMP	90	78
14	^{t}BuONa	TMEDA	NMP	90	86
15	^{t}BuONa	no ligand	NMP	90	92
16	^{t}BuONa	no ligand	NMP	70	2
17[c]	^{t}BuONa	no ligand	NMP	90	12

[a] Unless otherwise noted the reactions were performed in a sealed tube with **1a** (0.5 mmol), **2a** (0.5 mmol), base (1.0 mmol), CuI (10 mol %), and ligand (20 mol %) in solvent (1 mL) for 24 h. [b] The yields were evaluated by GC with *n*-dodecane as internal standard. [c] CuI was not added in the reaction.

the *N*,1-disubstituted-1*H*-2-aminobenzimidazoles skeleton, in which the C═N double bond is within the five-membered ring.

On the basis of these results, the optimal condition involved the following parameters: CuI as a precatalyst, ^{t}BuONa as a base, NMP as a solvent, and reaction temperature at 90 °C with ligand free. Under these optimized conditions, a study on the substrate scope was carried out, and the results are summarized in Table 2. First, we used *o*-iodoaniline derivatives **1** to react with **2a**. Both methyl group and fluoro atom on phenyl showed good performance (entries 2 and 3). Then *o*-bromoaniline and its derivatives were applied under the optimized conditions. To our delight, the reaction with *o*-bromoanilines could proceed smoothly (entries 4−5 and 7−16). For example, when 2-bromoaniline **1d** was treated with DCC **2a** under the optimized conditions, the desired product was obtained in 85% yield at 110 °C (entry 4). Although the desired product was also afforded at 90 °C for 24 h with 60% yield, some amount of **1d** still remained. The reaction of monosubstituted 2-bromoanilines with **2a** proceeded always in excellent yields regardless of electron-donating or electron-withdrawing groups linked on the benzene ring (entries 5, 7−9, and 15−16) except for the methoxyl group and the nitrile group (entries 6 and 17, respectively). When the substrates with multisubstitution on the benzene ring were used, the reaction could also proceed well (entries 10−14). Generally, substrate **1** tolerated electron-withdrawing groups were a little favorable in the reaction. When 2-bromopyridin-3-amine was tested under the reaction condition, the target molecule was not detected and the starting material remained (entry 18). Subsequently, 2-chloroanilines were tested under the optimized conditions. In this case, the desired products were obtained in lower yields (entries 19 and 20) even raised the reaction temperature to 120 °C and prolonged the reaction time to 48 h. When 4-nitro-2-chloroaniline was treated with **2a**, product 1-(2-chloro-4-nitrophenyl)-2,3-dicyclohexylguanidine **4** was obtained without ring-closure (entry 21).[19] Next, other carbodiimides (Figure 2) were used in the reaction. The reaction of *N,N′*-diisopropylcarbodiimide (DIC) **2b** could be performed smoothly and the desired products formed in excellent yields (entries 22−26). When *N,N′*-diphenylcarbodiimide **2c** was used as the substrate, the desired products were obtained with moderate yields (entries 27−29). Carbodiimides possessing a combination of aliphatic and aromatic substituents such as *N*-cyclohexyl-*N′*-phenylcarbodiimide **2d**, *N*-butyl-*N′*-phenylcarbodiimide **2e**, *N*-cyclohexyl-*N′*-*p*-tolylcarbodiimide **2f**, and *N*-cyclohexyl-*N′*-*p*-chlorophenyl-carbodiimide **2g** were employed, only *N*-alkyl-1-aryl-2-aminobenzimidazoles **3u**−**z** were afforded in satisfying yields, indicating a high regioselectivity for the reaction (entries 30−35).

With regard to the above presented results, we propose the following approach for this reaction, which is summarized in Scheme 1. In the presence of a proper base and copper(I) catalyst, amine **1** attacks the carbon atom of NCN on carbodiimide **2**.[19] Intermediate **5** could be formed, which undergoes ring-closure to yield product **3** with elimination of copper halide.[20] Preferential cyclization of guanidine occurs from an NH-aryl rather than an NH-alkyl group.

CONCLUSION

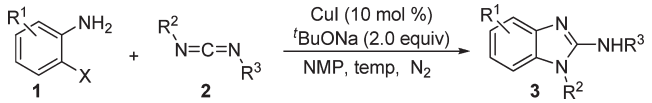
We have developed a concise and efficient one-pot method to synthesize *N*,1-disubstituted-1*H*-2-aminobenzimidazoles using CuI as catalyst under ligand-free conditions. Various *N*,1-disubstituted-1*H*-2-aminobenzimidazoles were conveniently synthesized in good to excellent yields. The present protocol showed a high regioselectivity when unsymmetrical substrates were employed.

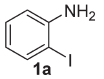
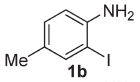
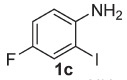
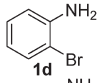
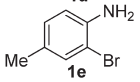
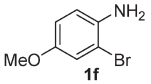
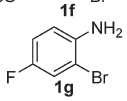
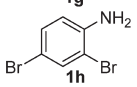
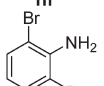
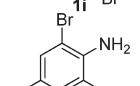
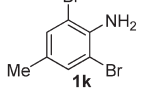
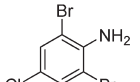
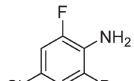
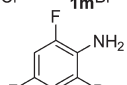
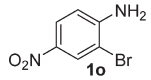
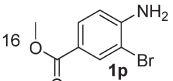
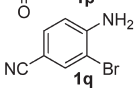
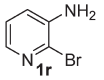
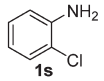
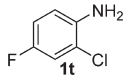
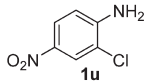
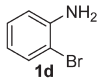
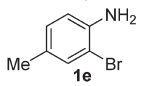
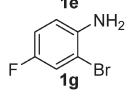
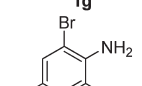
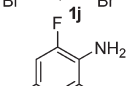
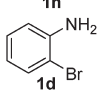
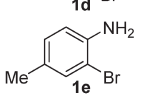
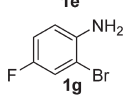
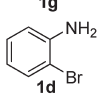
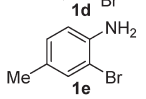
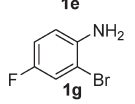
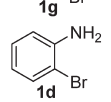
EXPERIMENTAL SECTION

General Information. All the reactions were carried out in predried a screwcapped test tube with a Teflon-lined septum under N_2 atmosphere. Unless otherwise indicated, all materials were obtained from commercial sources and used as received. DMF, toluene, 1,4-dioxane, NMP, and DMSO were fresh distilled. Column chromatography was performed on silica gel (particle size 10−40 μm). ^{1}H NMR and ^{13}C NMR spectra were recorded on

dx.doi.org/10.1021/jo200014v |*J. Org. Chem.* 2011, 76, 3174–3180

Table 2. CuI-Catalyzed One-Pot Reactions of 2-Haloanilines 1 with Carbodiimides 2[a]



entry	substrate 1	substrate 2	temp (°C)	time (h)	product	yield (%)[b]
1	 1a	2a	90	24	3a	88
2	 1b	2a	90	24	3b	87
3	 1c	2a	90	16	3c	92
4	 1d	2a	110	24	3a	85
5	 1e	2a	110	24	3b	79
6[c]	 1f	2a	110	24	–	trace
7	 1g	2a	110	16	3c	86
8	 1h	2a	110	24	3d	82
9	 1i	2a	110	24	3e	85
10	 1j	2a	110	16	3f	89
11	 1k	2a	110	24	3g	84
12	 1l	2a	110	16	3h	87
13	 1m	2a	110	16	3i	84
14	 1n	2a	110	16	3j	91
15	 1o	2a	110	24	3k	62
16	 1p	2a	110	24	3l	82
17[c]	 1q	2a	110	24	–	trace
18	 1r	2a	110	24	–	NR
19	 1s	2a	120	48	3a	27
20	 1t	2a	120	48	3c	42
21	 1u	2a	120	24	4[d]	32
22	 1d	2b	110	24	3m	86
23	 1e	2b	110	24	3n	83
24	 1g	2b	110	24	3o	90
25	 1j	2b	110	24	3p	87
26	 1n	2b	110	16	3q	89
27	 1d	2c	110	24	3r	65
28	 1e	2c	110	24	3s	60
29	 1g	2c	110	24	3t	72
30	 1d	2d	110	24	3u	64
31	 1e	2d	110	24	3v	57
32	 1g	2d	110	24	3w	76
33	 1d	2e	110	24	3x	79
34	1d	2f	110	24	3y	62
35	1d	2g	110	24	3z	55

[a] Unless otherwise noted the reactions were performed in a sealed tube with **1** (0.5 mmol), **2** (0.5 mmol), ^{t}BuONa (1.0 mmol), CuI (10 mol %) in NMP (1 mL) for 24 h. [b] Isolated yield. [c] The reaction was monitored by GC-MS but the product was not isolated. [d] 1-(2-Chloro-4-nitrophenyl)-2,3-dicyclohexylguanidine **4** was obtained under the reaction conditions.

dx.doi.org/10.1021/jo200014v |*J. Org. Chem.* 2011, 76, 3174–3180

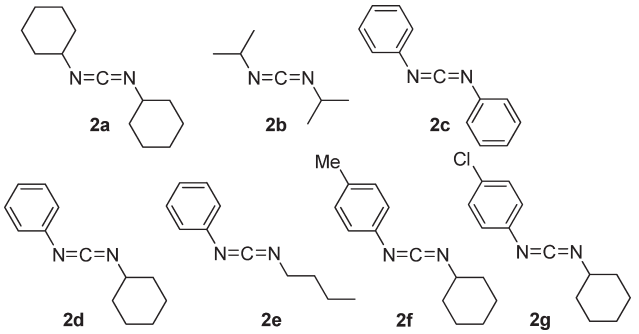
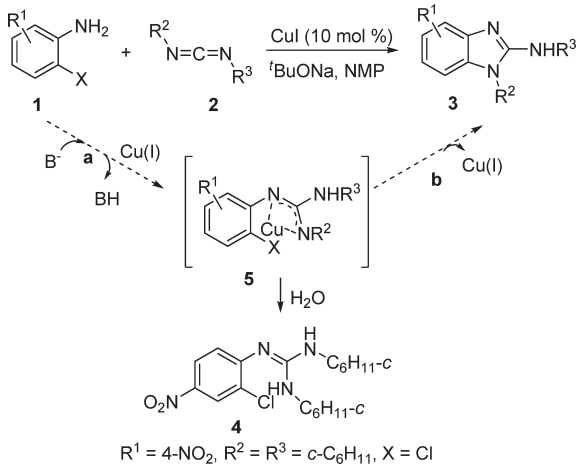


Figure 2. Varieties of carbodiimides.

Scheme 1. Proposed Reaction Pathway



a 300 MHz NMR spectrometer at ambient temperature with $CDCl_3$ as the solvent and TMS as internal standard. Chemical shifts (δ) were given in ppm, referenced to the residual proton resonance of TMS, to the carbon resonance of $CDCl_3$ (77.16). Coupling constants (J) were given in hertz (Hz). The terms m, d, s refer to multiplet, doublet, and singlet. The melting points were measured on a digital melting point apparatus and were uncorrected. GC-MS spectra were recorded on GC-MS system and the reaction progress was monitored by GC. GC yields, using *n*-dodecane as internal standard, were obtained in proportion to the integral area of the *n*-dodecane signal.

General Procedure for the Synthesis of *N*,1-Disubstituted-1*H*-2-aminobenzimidazoles 3. A sealed tube was charged with the mixture of *o*-haloaniline **1** (0.5 mmol), ^{t}BuONa (1.0 mmol, 0.096 g), CuI (10 mol %, 10 mg), and carbodiimide[21] **2** (0.5 mmol) then stirred in NMP (1 mL) at room temperature under nitrogen atmosphere. Half an hour later, the tube was sealed and the mixture was allowed to stir at 90−110 °C for 16−48 h. After completion of the reaction, the mixture was cooled to room temperature, then H_2O (5 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL) and dried by anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel (petroleum ether/ethyl acetate = 3/1 or dichloromethane/methanol = 100:1 or petroleum ether/ethyl acetate/triethyamine = 16/4/1) provided the corresponding product **3**.

***N*,1-Dicyclohexyl-1*H*-2-aminobenzimidazole (3a):** light brown solid, 127 mg (88% yield), mp 237−239 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20−1.31 (m, 4 H), 1.35−1.50 (m, 4 H), 1.64−1.82 (m, 4 H), 1.89−1.98 (m, 4 H), 2.05−2.19 (m, 4 H), 3.79−3.87 (m, 1 H), 3.97 (br, 2 H, N*H*, NC*H*), 6.97 (t, J_{H-H} = 14.1 Hz, J_{H-H} = 7.6 Hz, 1 H), 7.06 (t, J_{H-H} = 14.1 Hz, J_{H-H} = 1.9 Hz, 1 H), 7.24 (d, J_{H-H} = 8.6 Hz, 1H), 7.48 (d, J_{H-H} = 7.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 25.5, 25.9, 26.3, 31.0, 34.1, 52.0, 54.9, 109.5, 116.5, 118.9, 120.7, 133.4, 142.9, 153.1; GC-MS (EI, *m*/*z*) 297 (M^+), 214, 133; HRMS calcd for $C_{19}H_{27}N_3$ 298.2278 $(M + H)^+$, found 298.2281.

***N*,1-Dicyclohexyl-6-methyl-1*H*-2-aminobenzimidazole (3b):** light brown solid, 136 mg (87% yield), mp 209−211 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24−1.31 (m, 4 H), 1.36−1.49 (m, 4 H), 1.63−1.81 (m, 4 H), 1.87−1.98 (m, 4 H), 2.09−2.17 (m, 4 H), 2.42 (s, 3 H), 3.77−3.81 (m, 1 H), 3.92 (br, 2 H, N*H*, NC*H*), 6.88 (d, J_{H-H} = 7.2 Hz, 1 H), 7.04 (s, 1 H), 7.35 (d, J_{H-H} = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 25.1, 25.5, 25.9, 26.3, 31.0, 34.1, 52.0, 54.8, 110.0, 116.1, 121.7, 128.5, 133.5, 140.6, 153.0; GC-MS (EI, *m*/*z*) 311 (M^+), 228, 147; HRMS calcd for $C_{20}H_{29}N_3$ 312.2434 $(M + H)^+$, found 312.2431.

***N*,1-Dicyclohexyl-6-fluoro-1*H*-2-aminobenzimidazole (3c):** light brown solid, 145 mg (92% yield), mp 229−231 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21−1.34 (m, 4 H), 1.40−1.53 (m, 4 H), 1.64−1.77 (m, 4 H), 1.87−1.99 (m, 4 H), 2.03−2.18 (m, 4 H), 3.74−3.78 (m, 1 H), 3.92 (br, 1 H, NC*H*), 4.00 (br, 1 H, N*H*), 6.79 (t, J_{F-H} = 17.8 Hz, J_{H-H} = 9.3 Hz, 1 H), 6.96 (d, J_{F-H} = 8.9 Hz, 1H), 7.33−7.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 25.4, 25.9, 26.2, 30.9, 34.0, 52.1, 55.1, 97.2 (d, J_{F-C} = 28.0 Hz), 107.7 (d, J_{F-C} = 23.7 Hz), 116.3 (d, J_{F-C} = 10.0 Hz), 133.3 (d, J_{F-C} = 12.2 Hz), 139.0, 153.6, 157.5 (d, J_{F-C} = 232.3 Hz); GC-MS (EI, *m*/*z*) 315 (M^+), 232, 151; HRMS calcd for $C_{19}H_{26}FN_3$ 316.2184 $(M + H)^+$, found 316.2176.

***N*,1-Dicyclohexyl-6-bromo-1*H*-2-aminobenzimidazole (3d):** light brown solid, 154 mg (82% yield), mp 232−233 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19−1.31 (m, 4 H), 1.35−1.53 (m, 4 H), 1.64−1.81 (m, 4 H), 1.87−1.98 (m, 4 H), 2.02−2.18 (m, 4 H), 3.74−3.82 (m, 1 H), 3.91−3.94 (m, 1 H), 4.06 (s, 1 H, N*H*), 7.15 (d, J_{H-H} = 8.6 Hz, 1 H), 7.27−7.34 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.3, 25.8, 26.2, 31.0, 34.0, 52.1, 55.0, 111.4, 112.4, 117.5, 123.7, 134.6, 142.0, 153.5; GC-MS (EI, *m*/*z*) 375 (M^+), 294, 211; HRMS calcd for $C_{19}H_{26}BrN_3$ 376.1383 $(M + H)^+$, found 376.1370.

***N*,1-Dicyclohexyl-4-bromo-1*H*-2-aminobenzimidazole (3e):** light brown solid, 160 mg (85% yield), mp 89−90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24−1.29 (m, 4 H), 1.41−1.53 (m, 4 H), 1.62−1.81 (m, 4 H), 1.87−2.00 (m, 4 H), 2.05−2.18 (m, 4 H), 3.80−3.84 (m, 1 H), 3.95−4.04 (m, 2H, N*H*, NC*H*), 6.82 (t, J_{H-H} = 15.8 Hz, J_{H-H} = 7.9 Hz, 1 H), 7.17 (d, J_{H-H} = 7.9 Hz, 1 H), 7.23 (d, J_{H-H} = 7.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.4, 25.9, 26.2, 31.0, 33.9, 52.0, 55.2, 108.6, 109.8, 119.7, 123.8, 134.0, 141.6, 153.4; GC-MS (EI, *m*/*z*) 375 (M^+), 294, 211; HRMS calcd for $C_{19}H_{26}BrN_3$ 376.1383 $(M + H)^+$, found 376.1370.

***N*,1-Dicyclohexyl-4,6-dibromo-1*H*-2-aminobenzimidazole (3f):** light brown solid, 203 mg (89% yield), mp 182−183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83−0.87 (m, 1 H), 1.18−1.30 (m, 4 H), 1.40−1.53 (m, 4 H), 1.64−1.77 (m, 4 H), 1.86−2.03 (m, 5 H), 2.13−2.17 (m, 2 H), 3.73−3.74 (m, 1 H), 4.02 (br, 2 H, N*H*, NC*H*), 7.27 (s, 1 H), 7.36 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 25.3, 25.8, 26.1, 30.9, 33.8, 52.0, 55.4, 109.9, 111.0, 111.5, 126.1, 134.7, 141.0, 153.7; GC-MS (EI, *m*/*z*) 455 (M^+), 372, 291; HRMS calcd for $C_{19}H_{25}Br_2N_3$ 454.0488 $(M + H)^+$, found 454.0482.

***N*,1-Dicyclohexyl-4-bromo-6-methyl-1*H*-2-aminobenzimidazole (3g):** light brown solid, 164 mg (84% yield), mp 175−177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18−1.30 (m, 4 H), 1.35−1.53 (m, 4 H), 1.63−1.77 (m, 4 H), 1.86−1.99 (m, 4 H), 2.04−2.17 (m, 4 H), 2.39 (s, 3 H), 3.78 (m, 1 H), 3.87−3.90 (br, 1 H, N*H*), 4.00 (m, 1 H), 6.96 (s, 1 H), 7.07 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 25.0, 25.4, 25.9, 26.2, 31.0, 33.9, 52.0, 55.2, 109.1, 109.3, 124.6, 129.7, 134.1, 139.5, 153.2; GC-MS (EI, *m*/*z*) 389 (M^+), 308, 225; HRMS calcd for $C_{20}H_{28}BrN_3$ 390.1539 $(M + H)^+$, found 390.1531.

***N*,1-Dicyclohexyl-4-bromo-6-chloro-1*H*-2-aminobenzimidazole (3h):** light brown solid, 178 mg (87% yield), mp 188−190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21−1.30 (m, 4 H), 1.34−1.53 (m, 4 H), 1.64−1.82 (m, 4 H), 1.86−1.99 (m, 4 H), 2.03−2.17 (m, 4 H), 3.71−3.79 (m, 1 H), 4.01 (br, 2 H, N*H*, NC*H*), 7.14 (s, 1 H), 7.23 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 25.3, 25.8, 26.1, 30.9, 33.8, 52.0, 55.4, 108.8,

dx.doi.org/10.1021/jo200014v |*J. Org. Chem.* 2011, 76, 3174–3180

109.4, 123.5, 124.2, 134.1, 140.6, 153.9; GC-MS (EI, *m/z*) 411 (M^+), 328, 247; HRMS calcd for $C_{19}H_{25}BrClN_3$ 410.0993 $(M + H)^+$, found 410.0991.

***N*,1-Dicyclohexyl-6-chloro-4-fluoro-1*H*-2-aminobenzimidazole (3i):** light brown solid, 154 mg (88% yield), mp 206−207 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17−1.30 (m, 4 H), 1.34−1.50 (m, 4 H), 1.62−1.81 (m, 4 H), 1.87−1.97 (m, 4 H), 2.00−2.16 (m, 4 H), 3.76−3.84 (m, 1 H), 4.00 (m, 1 H), 4.13 (s, 1 H, N*H*), 6.82 (d, J_{H-H} = 10.0 Hz, 1 H), 7.02 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.3, 25.8, 26.1, 30.8, 33.9, 52.0, 55.2, 106.1, 108.1 (d, J_{F-C} = 21.5 Hz), 123.5 (d, J_{F-C} = 10.0 Hz), 129.9 (d, J_{F-C} = 15.8 Hz), 136.5 (d, J_{F-C} = 11.5 Hz), 151.4 (d, J_{F-C} = 248.1 Hz), 153.5; GC-MS (EI, *m/z*) 349 (M^+), 266, 185; HRMS calcd for $C_{19}H_{26}ClFN_3$ 350.1794 $(M + H)^+$, found 350.1798.

***N*,1-Dicyclohexyl-4,6-difluoro-1*H*-2-aminobenzimidazole (3j):** light brown solid, 151 mg (91% yield), mp 196−197 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18−1.29 (m, 4 H), 1.33−1.51 (m, 4 H), 1.63−1.81 (m, 4 H), 1.88−1.97 (m, 4 H), 2.01−2.17 (m, 4 H), 3.76−3.84 (m, 1 H), 3.99 (m, 1 H), 4.05 (s, 1 H, N*H*), 6.60 (t, J_{F-H} = 20.9 Hz, J_{F-H} = 10.6 Hz, 1 H), 6.80 (d, J_{F-H} = 8.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.3, 25.8, 26.1, 30.8, 33.9, 51.9, 55.2, 93.5 (d, J_{F-C} = 28.7 Hz), 96.0 (dd, J_{F-C} = 28.0 Hz, J_{F-C} = 22.2 Hz), 127.2 (d, J_{F-C} = 15.8 Hz), 135.4 (t, J_{F-C} = 25.8 Hz, J_{F-C} = 14.3 Hz), 151.1 (dd, J_{F-C} = 247.4 Hz, J_{F-C} = 15.1 Hz), 153.4, 156.5 (dd, J_{F-C} = 233.0 Hz, J_{F-C} = 10.8 Hz); GC-MS (EI, *m/z*) 333 (M^+), 250, 169; HRMS calcd for $C_{19}H_{25}F_2N_3$ 334.2089 $(M + H)^+$, found 334.2086.

***N*,1-Dicyclohexyl-6-nitro-1*H*-2-aminobenzimidazole (3k):** light yellow solid, 106 mg (62% yield), mp 249−250 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22−1.37 (m, 4 H), 1.43−1.55 (m, 4 H), 1.67−1.87 (m, 4 H), 1.94−2.05 (m, 4 H), 2.07−2.19 (m, 4 H), 3.85 (m, 1 H, NC*H*), 4.02 (m, 1 H, NC*H*), 4.31 (br, 1 H, N*H*), 7.39 (d, J_{H-H} = 8.9 Hz, 1 H), 8.07 (d, J_{H-H} = 8.9 Hz, 1 H), 8.13 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.3, 25.7, 26.2, 31.1, 33.9, 52.3, 55.5, 105.6, 115.2, 118.4, 132.9, 140.3, 149.2, 156.4; GC-MS (EI, *m/z*) 342 (M^+), 259, 178; HRMS calcd for $C_{19}H_{26}N_4O_2$ 343.2129 $(M + H)^+$, found 343.2125.

***N*,1-Dicyclohexyl-6-(methoxycarbonyl)-1*H*-2-aminobenzimidazole (3l):** white solid, 146 mg (82% yield), mp 218−219 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19−1.30 (m, 4 H), 1.36−1.50 (m, 4 H), 1.64−1.76 (m, 4 H), 1.89−1.97 (m, 4 H), 2.04−2.19 (m, 4 H), 3.86−4.01 (m, 5 H, CH_3, NC*H*), 4.37 (br, 1 H, N*H*), 7.43 (d, J_{H-H} = 8.2 Hz, 1 H), 7.82 (d, J_{H-H} = 8.3 Hz, 1 H), 7.93 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.2, 25.7, 26.1, 31.0, 33.9, 51.9, 52.1, 54.9, 110.9, 115.4, 120.4, 123.3, 133.2, 147.4, 155.1, 168.2; GC-MS (EI, *m/z*) 355 (M^+), 272, 191; HRMS calcd for $C_{21}H_{29}N_3O_2$ 356.2333 $(M + H)^+$, found 356.2338.

***N*,1-Diisopropyl-1*H*-2-aminobenzimidazole (3m):** light brown solid, 94 mg (86% yield), mp 171−173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, J_{H-H} = 6.5 Hz, 6 H), 1.56 (d, J_{H-H} = 6.9 Hz, 6 H), 4.00 (br, 1 H, N*H*), 4.27 (m, 1 H), 4.36 (m, 1 H), 6.99 (t, J_{H-H} = 15.1 Hz, J_{H-H} = 7.6 Hz, 1 H), 7.08 (t, J_{H-H} = 15.1 Hz, J_{H-H} = 7.2 Hz, 1 H), 7.23 (d, J_{H-H} = 7.5 Hz, 1 H), 7.49 (d, J_{H-H} = 7.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 23.6, 45.3, 46.2, 109.3, 116.5, 119.1, 120.8, 133.0, 142.9, 153.0; GC-MS (EI, *m/z*) 217 (M^+), 174, 133; HRMS calcd for $C_{13}H_{19}N_3$ 218.1652 $(M + H)^+$, found 218.1657.

***N*,1-Diisopropyl-6-methyl-1*H*-2-aminobenzimidazole (3n):** light brown solid, 95 mg (83% yield), mp 209−210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J_{H-H} = 6.2 Hz, 6 H), 1.56 (d, J_{H-H} = 7.2 Hz, 6 H), 2.42 (s, 3 H), 3.88 (s, 1 H, N*H*), 4.22 (m, 1 H), 4.34 (m, 1 H), 6.89 (d, J_{H-H} = 8.2 Hz, 1 H), 7.03 (s, 1 H), 7.36 (d, J_{H-H} = 7.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 21.9, 23.6, 45.3, 46.1, 109.8, 116.1, 121.8, 128.6, 133.2, 140.7, 152.8; GC-MS (EI, *m/z*) 231 (M^+), 189, 174, 147; HRMS calcd for $C_{14}H_{21}N_3$ 232.1808 $(M + H)^+$, found 232.1802.

***N*,1-Diisopropyl-6-fluoro-1*H*-2-aminobenzimidazole (3o):** light brown solid, 105 mg (90% yield), mp 221−222 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, J_{H-H} = 6.5 Hz, 6 H), 1.55 (d, J_{H-H} = 6.9 Hz, 6 H), 3.96 (s, 1 H, N*H*), 4.21 (m, 1 H), 4.31 (m, 1 H), 6.81 (t, J_{F-H} = 18.5 Hz, J_{H-H} = 10.0 Hz, 1 H), 6.94 (d, J_{H-H} = 9.3 Hz, 1 H), 7.36 (dd, J_{F-H} = 8.6 Hz, J_{H-H} = 5.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 23.5, 45.5, 46.4, 97.0 (d, J_{F-C} = 28.7 Hz), 107.8 (d, J_{F-C} = 23.7 Hz), 116.4 (d, J_{F-C} = 10.0 Hz), 132.9 (d, J_{F-C} = 12.9 Hz), 139.0, 153.6, 157.5 (d, J_{F-C} = 231.6 Hz); GC-MS (EI, *m/z*) 235 (M^+), 192, 151; HRMS calcd for $C_{13}H_{18}FN_3$ 236.1558 $(M + H)^+$, found 236.1562.

***N*,1-Diisopropyl-4,6-dibromo-1*H*-2-aminobenzimidazole (3p):** light brown solid, 162 mg (87% yield), mp 155−156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, J_{H-H} = 6.5 Hz, 6 H), 1.54 (d, J_{H-H} = 6.9 Hz, 6 H), 3.97 (s, 1 H, N*H*), 4.27 (m, 1 H), 4.33 (m, 1 H), 7.26 (d, J_{H-H} = 1.7 Hz, 1 H), 7.38 (d, J_{H-H} = 1.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 23.5, 45.5, 46.8, 110.0, 111.2, 111.3, 126.1, 134.3, 141.1, 153.7; GC-MS (EI, *m/z*) 375 (M^+), 333, 291; HRMS calcd for $C_{13}H_{17}Br_2N_3$ 373.9862 $(M + H)^+$, found 373.9867.

***N*,1-Diisopropyl-4,6-difluoro-1*H*-2-aminobenzimidazole (3q):** light brown solid, 112 mg (89% yield), mp 195−196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J_{H-H} = 6.2 Hz, 6 H), 1.55 (d, J_{H-H} = 6.3 Hz, 6 H), 4.05 (s, 1 H, N*H*), 4.28−4.36 (m, 2 H), 6.61 (t, J_{F-H} = 20.6 Hz, J_{F-H} = 10.6 Hz, 1 H), 6.78 (d, J_{H-H} = 8.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 23.4, 45.4, 46.7, 93.2 (dd, J_{F-C} = 28.0 Hz, J_{F-C} = 3.6 Hz), 96.1 (dd, J_{F-C} = 28.0 Hz, J_{F-C} = 22.2 Hz), 127.2 (d, J_{F-C} = 15.8 Hz), 135.1 (dd, J_{F-C} = 15.1 Hz, J_{F-C} = 12.2 Hz), 151.1 (dd, J_{F-C} = 246.7 Hz, J_{F-C} = 14.3 Hz), 153.3, 156.6 (dd, J_{F-C} = 244.5 Hz, J_{F-C} = 10.8 Hz); GC-MS (EI, *m/z*) 253 (M^+), 210, 169; HRMS calcd for $C_{13}H_{17}F_2N_3$ 254.1463 $(M + H)^+$, found 254.1460.

***N*,1-Diphenyl-1*H*-2-aminobenzimidazole (3r):**[17]**.** light brown solid, 92 mg (65% yield), mp 176−177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (s, 1 H, N*H*), 6.99−7.09 (m, 3 H), 7.17−7.21 (m, 1 H), 7.30−7.31 (m, 2 H), 7.46−7.48 (m, 2 H), 7.52−7.62 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.4, 117.6, 118.3, 121.0, 122.3, 122.5, 127.5, 129.3, 129.4, 130.8, 134.5, 134.6, 139.3, 142.3, 149.0; GC-MS (EI, *m/z*) 285 (M^+), 269, 208.

***N*,1-Diphenyl-6-methyl-1*H*-2-aminobenzimidazole (3s):**[17]**.** light brown solid, 90 mg (60% yield), mp 196−198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3 H, CH_3), 6.22 (s, 1 H, N*H*), 6.81 (s, 1 H), 6.98−7.03 (m, 2 H), 7.25−7.35 (m, 3 H), 7.48−7.51 (m, 2 H), 7.61−7.65 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 108.7, 117.2, 118.1, 118.3, 122.4, 123.4, 127.6, 129.3, 129.5, 130.8, 134.7, 134.7, 139.4, 140.24, 148.7; GC-MS (EI, *m/z*) 299 (M^+), 283, 220.

***N*,1-Diphenyl-6-fluoro-1*H*-2-aminobenzimidazole (3t):** light brown solid, 109 mg (72% yield), mp 185−186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1 H, N*H*), 6.69−6.72 (m, 1 H), 6.91 (m, 1 H), 6.99−7.04 (m, 1 H), 7.25−7.35 (m, 2 H), 7.46−7.51 (m, 2 H), 7.54−7.65 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.0 (d, J_{F-C} = 28.0 Hz), 109.5 (d, J_{F-C} = 24.4 Hz), 117.8 (d, J_{F-C} = 9.3 Hz), 118.2, 122.6, 127.3, 129.3, 129.7, 131.0, 134.1, 134.7 (d, J_{F-C} = 12.9 Hz), 138.5, 139.1, 149.5, 158.8 (d, J_{F-C} = 235.2 Hz); GC-MS (EI, *m/z*) 303 (M^+), 287, 226; HRMS calcd for $C_{19}H_{14}FN_3$ 304.1245 $(M + H)^+$, found 304.1252.

***N*-Cyclohexyl-1-phenyl-1*H*-2-aminobenzimidazole (3u):** light brown solid, 93 mg (64% yield), mp 52−53 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03−1.21 (m, 3 H), 1.39−1.47 (m, 2 H), 1.60−1.72 (m, 3 H), 2.11−2.14 (m, 2 H), 3.94−3.98 (m, 1 H, NC*H*), 4.05 (s, N*H*), 6.91−6.99 (m, 2 H), 7.12 (t, J_{H-H} = 6.9 Hz, 1 H), 7.42 (d, J_{H-H} = 7.2 Hz, 2 H), 7.47−7.62 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.7, 33.8, 51.6, 107.8, 116.3, 119.7, 121.8, 127.0, 128.8, 130.6, 135.0, 135.2, 142.9, 153.0; GC-MS (EI, *m/z*) 291 (M^+), 209; HRMS calcd for $C_{19}H_{21}N_3$ 292.1808 $(M + H)^+$, found 292.1811.

***N*-Cyclohexyl-6-methyl-1-phenyl-1*H*-2-aminobenzimidazole (3v):** light brown solid, 87 mg (57% yield), mp 75−76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09−1.26 (m, 3 H), 1.38−1.50 (m, 2 H), 1.60−1.71 (m, 3 H), 2.10−2.13 (m, 2 H), 2.35 (s, 3 H, CH_3), 3.91−4.01 (m, 2 H, N*H*, NC*H*), 6.72 (s, 1 H), 6.93 (d, J_{H-H} = 7.9 Hz, 1 H), 7.39−7.42 (m, 3 H), 7.51 (d, J_{H-H} = 7.2 Hz, 1 H), 7.57−7.62 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 25.0, 25.8, 33.9, 51.7, 108.3, 115.9, 122.8, 127.2, 128.7, 129.5, 130.6, 135.2, 135.4, 140.7, 152.8; GC-MS (EI, *m/z*) 305 (M^+), 223; HRMS calcd for $C_{20}H_{23}N_3$ 306.1965 $(M + H)^+$, found 306.1971.

dx.doi.org/10.1021/jo200014v |*J. Org. Chem.* 2011, 76, 3174–3180

***N*-Cyclohexyl-6-fluoro-1-phenyl-1*H*-2-aminobenzimidazole (3w):** light brown solid, 87 mg (57% yield), mp 93−94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09−1.26 (m, 3 H), 1.38−1.50 (m, 2 H), 1.60−1.72 (m, 3 H), 2.10−2.13 (m, 2 H), 3.90−3.96 (m, 1 H, NC*H*), 4.04 (s, 1 H, N*H*), 6.63 (dd, J_{F-H} = 8.6 Hz, J_{H-H} = 2.4 Hz, 1 H), 6.80−6.86 (m, 1 H), 7.38−7.41 (m, 3 H), 7.48−7.53 (m, 1 H), 7.57−7.62 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 25.7, 33.7, 51.7, 95.6 (d, J_{F-C} = 28.7 Hz), 108.7 (d, J_{F-C} = 23.7 Hz), 116.3 (d, J_{F-C} = 10.0 Hz), 126.9, 129.1, 130.7, 134.6, 135.3 (d, J_{F-C} = 12.9 Hz), 138.9, 153.4, 158.1 (d, J_{F-C} = 233.8 Hz); GC-MS (EI, *m*/*z*) 309 (M^+), 227; HRMS calcd for $C_{19}H_{20}FN_3$ 310.1714 $(M + H)^+$, found 310.1719.

***N*-Butyl-1-phenyl-1*H*-2-aminobenzimidazole (3x):** light brown oil, 104 mg (79% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J_{H-H} = 7.2 Hz, 3 H), 1.34−1.44 (m, 2 H), 1.56−1.68 (m, 2 H), 3.49−3.56 (m, 2 H), 4.20 (br, 1 H, N*H*), 6.90−7.00 (m, 2 H), 7.12 (m, 1 H), 7.41 (d, J_{H-H} = 7.9 Hz, 2 H), 7.48−7.60 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 20.1, 32.0, 43.1, 107.8, 116.4, 119.8, 122.8, 127.0, 128.8, 130.5, 134.9, 135.3, 142.8, 153.7; GC-MS (EI, *m*/*z*) 265 (M^+), 222, 208; HRMS calcd for $C_{17}H_{19}N_3$ 266.1652 $(M + H)^+$, found 266.1654.

***N*-Cyclohexyl-1-*p*-tolyl-1*H*-2-aminobenzimidazole (3y):** light brown solid, 94 mg (62% yield), mp 48−50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12−1.26 (m, 3 H), 1.43−1.47 (m, 2 H), 1.60−1.72 (m, 3 H), 2.09−2.13 (m, 2 H), 2.46 (s, 3 H, CH_3), 3.96 (m, 1 H, NC*H*), 4.03 (br, 1 H, N*H*), 6.88−6.98 (m, 2 H), 7.08−7.13 (m, 1 H), 7.28 (d, J_{H-H} = 8.2 Hz, 2 H), 7.38 (d, J_{H-H} = 8.3 Hz, 2 H), 7.51 (d, J_{H-H} = 7.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 25.0, 25.8, 33.8, 51.6, 107.8, 116.3, 119.6, 121.7, 126.9, 131.2, 132.2, 135.4, 138.9, 142.9, 153.2; GC-MS (EI, *m*/*z*) 305 (M^+), 223; HRMS calcd for $C_{20}H_{23}N_3$: 306.1965 $(M + H)^+$, found 306.1961.

***N*-Cyclohexyl-1-(4-chlorophenyl)-1*H*-2-aminobenzimidazole (3z):** light brown solid, 90 mg (55% yield), mp 65−66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05−1.21 (m, 3 H), 1.42−1.47 (m, 2 H), 1.61−1.73 (m, 3 H), 2.10−2.14 (m, 2 H), 3.98 (br, 2 H, NC*H*, N*H*), 6.89 (d, J_{H-H} = 7.8 Hz, 1 H), 6.98 (m, 1 H), 7.13 (m, 1 H), 7.37 (d, J_{H-H} = 8.7 Hz, 2 H), 7.51 (d, J_{H-H} = 7.8 Hz, 1 H), 7.57 (d, J_{H-H} = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.7, 33.8, 51.7, 107.7, 116.5, 119.9, 122.1, 128.5, 130.9, 133.5, 134.7, 135.0, 142.9, 152.8; GC-MS (EI, *m*/*z*) 325 (M^+), 243; HRMS calcd for $C_{19}H_{20}ClN_3$ 326.1419 $(M + H)^+$, found 326.1415.

2-(2-Chloro-4-nitrophenyl)-1,3-dicyclohexylguanidine (4): light brown solid, 57 mg (32% yield), mp 163−164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10−1.20 (m, 6 H), 1.29−1.41 (m, 4 H), 1.60−1.74 (m, 6 H), 2.00−2.05 (m, 4 H), 3.43 (m, 1 H, NC*H*), 3.75 (s, 1 H, N*H*), 6.96 (d, J_{H-H} = 8.6 Hz, 1 H), 8.00 (d, J_{H-H} = 8.9 Hz, 1 H), 8.26 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 25.6, 33.8, 50.7, 123.5, 123.6, 126.1, 128.3, 141.1, 150.0, 155.0; GC-MS (EI, *m*/*z*) 378 (M^+), 343, 261; HRMS calcd for $C_{19}H_{27}ClN_4O_2$ 379.1895 $(M + H)^+$, found 379.1893.

■ ASSOCIATED CONTENT

Supporting Information. Copies of spectra and the crystallographic data of product **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: cjxi@tsinghua.edu.cn.

■ ACKNOWLEDGMENT

This work was supported by the National Natural Science Foundation of China (20872076, 20972085, and 21032004) and by Specialized Research Fund for the Doctoral Program of Higher Education (200800030072)

■ REFERENCES

(1) (a) Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. *J. Med. Chem.* **1985**, *28*, 1925. (b) Iemura, R.; Hori, M.; Saito, T.; Ohtaka, H. *Chem. Pharm. Bull.* **1989**, *37*, 2723. (c) Ellingboe, J. W.; Spinelli, W.; Winkley, M. W.; Nguyen, T. T.; Parsons, R. W.; Moubarak, I. F.; Kitzen, J. M.; Engen, D. V.; Bagli, J. F. *J. Med. Chem.* **1992**, *35*, 705. (d) Jung, F.; Boucherot, D.; Delvare, C.; Olivier, A. *J. Antibiot.* **1993**, *46*, 993. (e) Mohamed, H. S.; Fahmy, H. H.; Nofal, Z. M. *Arch. Pharmacal Res.* **2002**, *25*, 28. (f) Hernández-Luis, F.; Hernández-Campos, A.; Yépez-Mulia, L.; Cedillo, R.; Castillo, R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1359.

(2) Cooper, D. G.; Young, R. C.; Durant, G. J.; Gamelline, C. R. *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon Press: Oxford, UK, 1990; Vol. 3, p 323.

(3) Coon, T.; Moree, W. J.; Li, B.; Yu, J.; Zamani-Kord, S.; Malany, S.; Santos, M. A.; Hernandez, L. M.; Petroski, R. E.; Sun, A.; Wen, J.; Sullivan, S.; Haelewyn, J.; Hedrick, M.; Hoare, S. J.; Bradbury, M. J.; Crowe, P. D.; Beaton, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4380.

(4) (a) Peddibhotla, S.; Shi, R.; Khan, P.; Smith, L. H.; Mangravita-Novo, A.; Vicchiarelli, M.; Su, Y.; Okolotowicz, K. J.; Cashman, J. R.; Reed, J. C.; Roth, G. P. *J. Med. Chem.* **2010**, *53*, 4793. (b) Tracey, K. J.; Cerami, A. *Annu. Rev. Cell Biol.* **1993**, *9*, 317. (c) Baud, V.; Karin, M. *Nat. Rev. Drug Discovery* **2009**, *8*, 33. (d) Okolotowicz, K. J.; Shi, R.; Zheng, X.; MacDonald, M.; Reed, J. C.; Cashman, J. R. *Bioorg. Med. Chem.* **2010**, *18*, 1918.

(5) Zhao, Z. S.; Arnaiz, D. O.; Griedel, B.; Sakata, S.; Dallas, J. L.; Whitlow, M.; Trinh, L.; Post, J.; Liang, A.; Morrissey, M. M.; Shaw, K. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 963.

(6) 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.

(7) Zhu, Z.; Lippa, B.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2000**, *43*, 2430.

(8) (a) Taniguchi, K.; Shigenaga, S.; Ogahara, T.; Fujitsu, T.; Matsuo, M. *Chem. Pharm. Bull.* **1993**, *41*, 301. (b) Brain, C. T.; Brunton, S. A. *Tetrahedron Lett.* **2002**, *43*, 1893. (c) Senanayake, C. H.; Hong, Y.; Xiang, T.; Wilkinson, H. S.; Bakale, R. P.; Jurgens, A. R.; Pippert, M. F.; Butler, H. T.; Wald, S. A. *Tetrahedron Lett.* **1999**, *40*, 6875. (d) Hong, Y.; Senanayake, C. H.; Xiang, T.; Vandenbossche, C. P.; Tanoury, G. J.; Bakale, R. P.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 3121. (e) He, H.-F.; Wang, Z.-J.; Bao, W. *Adv. Synth. Catal.* **2010**, *352*, 2905. (f) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (g) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133.

(9) (a) Barrett, I. C.; Kerr, M. A. *Tetrahedron Lett.* **1999**, *40*, 2439. (b) Kawasaki, I.; Taguchi, N.; Yoneda, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1996**, *43*, 1375.

(10) (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (b) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240. (c) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133. (d) Paul, F.; Patt, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (e) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708. (f) Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481.

(11) (a) Bendale, P. M.; Sun, C. *J. Comb. Chem.* **2002**, *4*, 359. (b) Smith, J. M.; Gard, J.; Cummings, W.; Kanizsai, A.; Krchňák, V. *J. Comb. Chem.* **1999**, *1*, 368. (c) Huang, K.-T.; Sun, C.-M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1001. (d) Cee, V. J.; Downing, N. S. *Tetrahedron Lett.* **2006**, *47*, 3747.

(12) (a) Snow, R. J.; Butz, T.; Hammach, A.; Kapadia, S.; Morwick, T. M.; Prokopowicz, A. S.; Takahashi, H.; Tan, J. D.; Tschantz, M. A.; Wang, X. *Tetrahedron Lett.* **2002**, *43*, 7553. (b) Wu, C.-Y.; Sun, C.-M. *Tetrahedron Lett.* **2002**, *43*, 1529.

(13) Perkins, J. J.; Zartman, A. E.; Meissner, R. S. *Tetrahedron Lett.* **1999**, *40*, 1103.

(14) For recent one-pot reactions based on copper-catalyzed C−N coupling, see: (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. (c) Zou, B.; Yuan, Q.; Ma, D. *Org. Lett.* **2007**, *9*, 4291. (d) Chen, Y.; Wang,

Y.; Sun, Z.; Ma, D. *Org. Lett.* **2008**, *10*, 625. (e) Martín, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (f) Viña, D.; del Olmo, E.; López-Pérez, J. L.; Feliciano, A. S. *Org. Lett.* **2007**, *9*, 525. (g) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843. (h) Chen, Y.; Xie, X.; Ma, D. *J. Org. Chem.* **2007**, *72*, 9329. (i) Liu, F.; Ma, D. *J. Org. Chem.* **2007**, *72*, 4844. (j) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968. (k) Tanimori, S.; Ura, H.; Kirihata, M. *Eur. J. Org. Chem.* **2007**, 3977. (l) Wang, F.; Zhao, P.; Xi, C. *Tetrahedron Lett.* **2011**, *52*, 231. (m) Martin, R.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 5521. (n) Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719. (o) Lv, X.; Bao, W. *J. Org. Chem.* **2009**, *74*, 5618.

(15) For recent one-pot reactions based on copper-catalyzed C−O coupling, see: (a) Lu, B.; Wang, B.; Zhang, Y.; Ma, D. *J. Org. Chem.* **2007**, *72*, 5337. (b) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978. (c) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452.

(16) For recent based on copper-catalyzed intra C−S coupling, see: (a) Lv, X.; Liu, Y.; Qian, W.; Bao, W. *Adv. Synth. Catal.* **2008**, *350*, 2507. (b) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035. (c) Zhao, Q.; Li, L.; Fang, Y.; Sun, D.; Li, C. *J. Org. Chem.* **2009**, *74*, 459. (d) Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7064. (e) Ding, Q.; He, X.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 587. (f) Shen, G.; Lv, X.; Bao, W. *Eur. J. Org. Chem.* **2009**, 5897. (g) Wei, Y.; Yan, X.; Liao, Q.; Xi, C. *Org. Lett.* **2010**, *12*, 3930. (h) Guo, Y.-J.; Tang, R.-Y.; Zhao, P.; Li, J.-H. *Tetrahedron Lett.* **2010**, *51*, 649.

(17) Shen, G.; Bao, W. *Adv. Synth. Catal.* **2010**, *352*, 981.

(18) See detailed data see the Supporting Information.

(19) (a) Ong, T.-G.; O'Brien, J. S.; Korobkov, I.; Richeson, D. *Organometallics* **2006**, *25*, 4728. (b) Alonso-Moreno, C.; Carrillo-Hermosilla, F.; Garcés, A.; Otero, A.; López-Solera, I.; Rodríguez, A. M.; Antiñolo, A. *Organometallics* **2010**, *29*, 2789. (c) Koller, J.; Bergman, R. G. *Organometallics* **2010**, *29*, 5946.

(20) (a) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133. (b) Szczepankiewicz, B. G.; Rohde, J. J.; Kurukulasuriya, R. *Org. Lett.* **2005**, *7*, 1833.

(21) Ali, A. R.; Ghosh, H.; Patel, B. K. *Tetrahedron Lett.* **2010**, *51*, 1019.