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Assembly of Substituted 1*H*-Benzimidazoles and 1,3-Dihydrobenzimidazol-2-ones via CuI/L-Proline Catalyzed Coupling of Aqueous Ammonia with 2-Iodoacetanilides and 2-Iodophenylcarbamates

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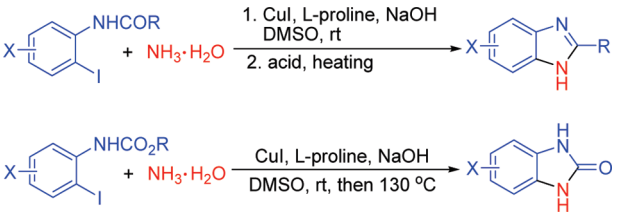

CuI/L-proline catalyzed coupling of aqueous ammonia with 2-iodoacetanilides and 2-iodophenylcarbamates affords the aryl amination products at room temperature, which undergo in situ additive cyclization under acidic conditions or heating to give substituted 1*H*-benzimidazoles and 1,3-dihydrobenzimidazol-2-ones, respectively. A wide range of functional groups including ketone, nitro, iodo, bromo, and ester are tolerated under these reaction conditions, providing these heterocycles with great diversity.

Substituted 1*H*-benzimidazoles and 1,3-dihydrobenzimidazol-2-ones are pharmaceutically important heterocycles that display a wide range of biological activities, such as antitumor,[1] antibacterial,[2] δ-opioid receptor antagonism,[3] and enzyme inhibition.[4] For these reasons their synthesis has received considerable attention.[5] The typical methods for assembling these heterocycles are highly dependent on using benzene-1,2-diamines as the key intermediates.[6] Recently, we have revealed that 1,2-disubstituted benzimidazoles[7] and N-substituted 1,3-dihydrobenzimidazol-2-ones[8] could be synthesized via a CuI/amino acid catalyzed coupling reaction of primary amines with 2-haloacetanilides and 2-halophenylcarbamates. Subsequent to this discovery, aqueous ammonia was reported as a suitable coupling partner for copper-catalyzed N-arylation.[9,10] We envisaged that using this new coupling partner we could elaborate substituted 1*H*-benzimidazoles and 1,3-dihydrobenzimidazol-2-ones from 2-iodoacetanilides and 2-iodophenylcarbamates. The investigations thus undertaken are disclosed here.

As indicated in Table 1, we initiated our studies by screening suitable conditions for coupling aqueous ammonia with 2-iodophenylbenzamide. It was found that under the catalysis of 10 mol % of CuI and 20 mol % of *trans*-4-hydroxy-L-proline, this reaction took place in DMSO at room temperature to afford aniline **2a** in 78% yield (entry 1). A similar result was observed when ligand was changed to L-proline (entry 2). The best yield was obtained by decreasing the amount of NaOH (entry 3). Solvent plays a crucial role for this coupling reaction, as is evident from DMF giving a satisfactory yield, while a moderate yield was observed in the case of NMP, and no coupling occurred when toluene, dioxane, and methylene chloride were employed. Among the bases we examined, NaOH gave the best result, although Cs_2CO_3 and K_2CO_3 also worked for this coupling reaction (compare entries 3, 9, and 10 in Table 1). Noteworthy is that

(1) Kamal, A.; Kumar, P. P.; Sreekanth, K.; Seshadri, B. N.; Ramulu, P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2594.
(2) Hu, L.; Kully, M. L.; Boykin, D. W.; Abood, N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3374.
(3) (a) Balboni, G.; Guerrini, R.; Salvadori, S.; Bianchi, C.; Rizzi, D.; Bryant, S. D.; Lazarus, L. H. *J. Med. Chem.* **2002**, *45*, 713. (b) Balboni, G.; Fiorini, S.; Baldisserotto, A.; Trapella, C.; Sasaki, Y.; Ambo, A.; Marczak, E. D.; Lazarus, L. H.; Salvadori, S. *J. Med. Chem.* **2008**, *51*, 5109.
(4) (a) Wittman, M. D.; Balasubramanian, B.; Stoffan, K.; Velaparthi, U.; Liu, P.; Krishnanathan, S.; Carboni, J.; Li, A.; Greer, A.; Attar, R.; Gottardis, M.; Chang, C.; Jacobson, B.; Sun, Y.; Hansel, S.; Zoeckler, M.; Vyas, D. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 947. (b) Schiffmann, R.; Neugebauer, A.; Klein, C. D. *J. Med. Chem.* **2006**, *49*, 511. (c) Verma, R. P. *Bioorg. Med. Chem.* **2005**, *13*, 1059. (d) Rangarajan, M.; Kim, J. S.; Sim, S. P.; Liu, A.; Liu, L. F.; La Voie, E. J. *Bioorg. Med. Chem.* **2000**, *8*, 2591.
(5) For recent examples, see: (a) Shen, M.; Driver, T. G. *Org. Lett.* **2008**, *10*, 3367. (b) Blacker, A. J.; Farah, M. M.; Hall, M. I.; Marsden, S. P.; Saidi, Q.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2039.
(6) For recent investigations, see: (a) Lim, H.-J.; Myung, D.; Lee, I. Y. C.; Jung, M. *J. Comb. Chem.* **2008**, *10*, 501. (b) Charton, J.; Girault-Mizzi, S.; Sergheraert, C. *Chem. Pharm. Bull.* **2005**, *53*, 492. (c) Du, L.-H.; Wang, Y.-G. *Synthesis* **2007**, *5*, 675. (d) Chen, H.-Y.; Kulkarni, M. V.; Chen, C.-H.; Sun, C.-M. *Tetrahedron* **2008**, *64*, 6387. (e) Zhang, P.; Terefenko, E. A.; McComas, C. C.; Mahaney, P. E.; Vu, A.; Trybulski, E.; Koury, E.; Johnston, G.; Bray, J.; Deecher, D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6067.
(7) Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2598.
(8) Zou, B.; Yuan, Q.; Ma, D. *Org. Lett.* **2007**, *9*, 4291.
(9) (a) Kim, J.; Chang, S. *Chem. Commun.* **2008**, 3052. (b) Xia, N.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 337. (c) Jiang, L.; Lu, X.; Zhang, H.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2009**, *74*, 4542. (d) Xu, H.; Wolf, C. *Chem. Commun.* **2009**, 3035.
(10) For other studies on copper-catalyzed N-arylation, see: (a) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459. (b) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (c) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (d) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. (e) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (f) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607. (g) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (h) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.—Eur. J.* **2006**, *12*, 3636. (i) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (j) Kantam, M. L.; Yadav, J.; Laha, S.; Sreedhar, B.; Jha, S. *Adv. Synth. Catal.* **2007**, *349*, 1938. (k) Ma, H.; Jiang, X. *J. Org. Chem.* **2007**, *72*, 8943. (l) Chen, W.; Zhang, Y.; Zhu, L.; Lan, J.; Xie, R.; You, J. *J. Am. Chem. Soc.* **2007**, *129*, 13879. (m) Maheswaran, H.; Krishna, G. G.; Prasanth, K. L.; Srinivas, V.; Chaitanya, G. K.; Bhanuprakash, K. *Tetrahedron* **2008**, *64*, 2471. (n) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (o) Liang, L.; Li, Z.; Zhou, X. *Org. Lett.* **2009**, *11*, 3294. (p) Haldon, E.; Alvarez, E.; Nicasio, M. C.; Perez, P. J. *Organometallics* **2009**, *28*, 3815. (q) Wang, D.; Ding, K. *Chem. Commun.* **2009**, 1891. (r) Xu, H.; Wolf, C. *Chem. Commun.* **2009**, 1715.

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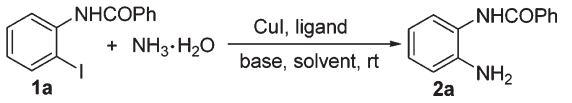
TABLE 1. Coupling of Aqueous Ammonia and 2-Iodophenylbenzamide under Different Conditions[a]



entry	ligand[b]	base	solvent	yield (%)
1	A	NaOH	DMSO	78
2	B	NaOH	DMSO	82
3[c]	B	NaOH	DMSO	91[c]
4	A	NaOH	DMF	75
5	A	NaOH	NMP	48
6	A	NaOH	toluene	
7	A	NaOH	dioxane	
8	A	NaOH	CH_2Cl_2	
9	B	Cs_2CO_3	DMSO	89[d]
10	B	K_2CO_3	DMSO	32[d]
11	B	K_2CO_3	DMSO	83[e]
12	B	NaOH	DMSO	63[f]

[a]Reaction conditions: **1a** (0.25 mmol), aqueous ammonia (0.375 mmol), CuI (0.025 mmol), ligand (0.05 mmol), base (0.75 mmol), slovent (1 mL), rt. [b]A: *trans*-4-hydroxy-L-proline. B: L-proline. [c]0.375 mmol of NaOH was used. [d]0.375 mmol of Cs_2CO_3 or K_2CO_3 was used. [e]0.75 mmol of K_2CO_3 was used. [f]NH_4Cl was used to replace aqueous ammonia.

in the case of K_2CO_3, 3 equiv of base was required to obtain a satisfactory result (compare entries 10 and 11 in Table 1), indicating that the base and its amount have great influence to this reaction. Additionally, when NH_4Cl was used as an amine source a relatively low yield was observed.

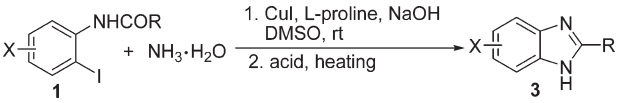
After obtaining the optimized coupling reaction conditions, we attempted to develop a one-pot procedure to prepare 1*H*-benzimidazoles. Accordingly, after completion of the coupling reaction of aqueous ammonia and 2-iodophenylbenzamide, the reaction mixture was directly treated with HOAc at 80 °C. We were pleased to find that the desired 2-phenylbenzimidazole **3a** was isolated in 83% yield (Table 2, entry 1). In view of this encouraging result, a number of 2-iodoacetanilides were examined for this one-pot process to explore it scope and limitation. It was found that three 2-iodoacetanilides bearing electron-withdrawing groups are suitable substrates for this process, delivering the corresponding benzimidazoles in good yields (Table 2, entries 2−4).

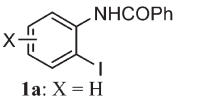
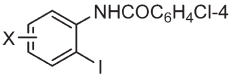
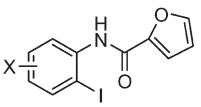
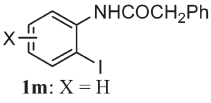
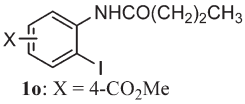
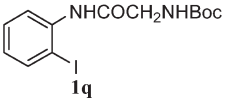
In the cases of methoxy substituted 2-iodoacetanilides as the substrates, the coupling step worked well to give the primary aryl amines. However, their conversion to benzimidazoles did not take place by treatment with HOAc. After some experiments, we discovered that this additive cyclization could be achieved by using 15% H_2SO_4 as the promoter (Table 2, entries 5 and 6). This phenomena is inconsistent with our observation in the synthesis of 1,2-disubstituted benzimidazoles,[7] although the reason is not clear.

Further investigations revealed that changing the substituents at the 2-position was possible by using different amides (Table 2, entries 7−17). These substituents include aryl, heteroaromatic, benzyl, simple alkyl, and functionalized alkyl groups. Another notable character was that a wide range of functional groups were found to be tolerated under the reaction conditions. These groups include ketone, nitro, iodo, bromo, and ester, which are ready for further transformations to give more complicated benzimidazoles. When compound **1i**, a substrate with an additional iodo group at the 4-position, was used, a double aryl amination product was determined in the coupling step, and the desired product **3i** was isolated in 61% yield (entry 9). However, only monoaryl amination product was formed when a bromo substituted 2-iodoacetanilide was used (Table 2, entry 16). These results demonstrated that the regioselectivity between two iodo groups (at the ortho-position of the amido group and the other positions) is not so good, while the reactivity difference between bromo and iodo groups is still significant in the coupling step. It is notable that under the same conditions 2-bromoacetanilide gave low yields of products. More experimental studies are required to overcome this drawback.

It was known that substituted 1*H*-benzimidazoles could tautomerize (**3** to **4**, Scheme 1) and thereby give a mixture of

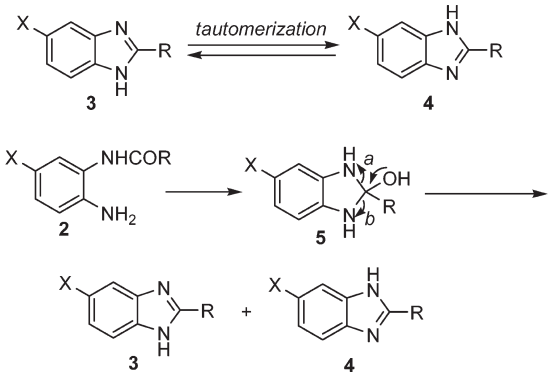
TABLE 2. Synthesis of Benzimidazoles via Coupling of Aqueous Ammonia and 2-Iodoacetanilides[a]



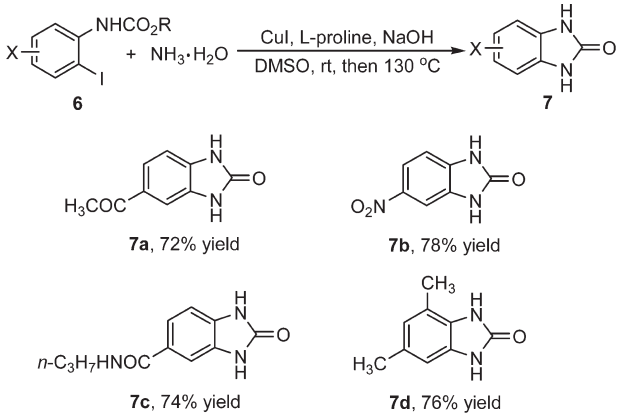
Entry	Aryl iodide	Product	Yield (%)
1	 **1a**: X = H	**3a**	83
2	**1b**: X =4-F	**3b**	74
3	**1c**: X = 4-Cl	**3c**	68
4	**1d**: X = 4-$COCH_3$	**3d**	79
5	**1e**: X = 4-OMe	**3e**	75[b]
6	**1f**: X = 5-OMe	**3f**	77[b]
7	 **1g**: X = 4-Cl	**3g**	82
8	**1h**: X = 4-NO_2	**3h**	66
9	**1i**: X = 4-I, 6-Cl	**3i**	61
10	 **1j**: X = H	**3j**	77
11	**1k**: X = 4-Me	**3k**	65
12	**1l**: X = 4-F	**3l**	81
13	 **1m**: X = H	**3m**	79
14	**1n**: X = 4-Cl	**3n**	72
15	 **1o**: X = 4-CO_2Me	**3o**	86
16	**1p**: X = 4-Br	**3p**	81
17	 **1q**	**3q**	82

[a]Reaction conditions: **1a** (0.25 mmol), aqueous ammonia (0.375 mmol), CuI (0.025 mmol), L-proline (0.05 mmol), NaOH (0.375 mmol), DMSO (1 mL), rt, 3−7 h; then HOAc (3 mL), 50−80 °C, 3−12 h. [b]15% H_2SO_4 (3 mL) was used for the condensative cyclization step.

SCHEME 1. Possible Courses for Formation of Two Regioisomers for 1*H*-Benzimidazoles



SCHEME 2. Assembly of 1,3-Dihydrobenzimidazol-2-ones 7



two regioisomers in some cases.[5a,11] Indeed, a common intermediate **5** might form in our additive cyclization step, which might undergo dehydration from two possible directions (a and b) to afford regioisomers **3** and **4** (Scheme 1). On the basis of this consideration, we checked the analytical data of our products carefully. It was found that all products (even for **3i**) showed only one set of peaks in their ^{1}H NMR spectrum. However, this observation could not rule out the possibility of the existence of two regioisomers because the identical ^{1}H NMR data were observed for two regioisomers **3e** and **3f**.

After success in the elaboration of substituted 1*H*-benzimidazoles, we moved our attention to synthesize 1,3-dihydrobenzimidazol-2-ones via coupling of 2-iodophenylcarbamates **6** with aqueous ammonia. As depicted in Scheme 2, it was found that the coupling step proceeded smoothly at room temperature, and the resulting amines were in situ converted into 1,3-dihydrobenzimidazol-2-ones by heating at 130 °C. Four 1,3-dihydrobenzimidazol-2-ones **7a**−**d**, which contain ketone, nitro, amido, and methyl groups, were assembled to illustrate the generality of this method.

In conclusion, a new method for assembling substituted 1*H*-benzimidazoles has been developed, which relied on a one-pot coupling of 2-haloacetanilides with aqueous ammonia and subsequent additive cyclization. A wide range of 1*H*-benzimidazoles, which have different functional groups such as ketone, ester, methoxy, bromo and iodo at the aromatic ring, and aryl, simple, and functionalized alkyl groups at the 2-position, could be elaborated from suitable substrates. Additionally, by coupling of 2-halophenylcarbamates with aqueous ammonia at room temperature, and subsequent intramolecular condensation at 130 °C, several 1,3-dihydrobenzimidazol-2-ones were constructed. These two processes provide simple and reliable approaches for assembly of the pharmaceutically important heterocycles, and therefore may find applications in organic synthesis.

Experimental Section

General Procedure for the Synthesis of Substituted 1*H*-Benzimidazole. A Schlenk tube was charged with 2-iodoacetanilides (0.25 mmol), CuI (5 mg, 0.025 mmol), L-proline (6 mg, 0.05 mmol), and NaOH (15 mg, 0.375 mmol). The tube was evacuated and backfilled with argon (3 times). Aqueous ammonia (0.375 mmol) and 1 mL of DMSO was added into the tube. After the reaction mixture was stirred at room temperature for 3−7 h, 3 mL of AcOH (in the cases of **1e** and **1f** as the substrates, 3 mL of 15% H_2SO_4 was used) was added and the reaction mixture was stirred at 50−80 °C for 3−12 h. The cooled reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with 3:1 to 1:1 petroleum ether/ethyl acetate) to provide the desired product.

2-(4-Chlorophenyl)-6-nitro-1*H*-benzimidazole (3h): ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.70 (br s, 1H), 8.48 (s, 1H), 8.23 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.0, 143.2 (2C), 136.1, 130.4, 129.6 (2C), 129.0 (2C), 128.8, 128.3, 118.5, 115.2; ESI-MS m/z 274.1 $(M + H)^+$; ESI-HRMS calcd for $C_{13}H_9ClN_3O_2$ $(M + H)^+$ requires m/z 274.0378, found 274.0389.

6-Fluoro-2-(furan-2-yl)-1*H*-benzimidazole (3*l*): mp 218−220 °C (EtOAc/hexane); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.58 (dd, J = 5.0, 9.0 Hz, 1H), 7.38 (dd, J = 2.0, 9.5 Hz, 1H), 7.22 (d, J = 3.5 Hz, 1H), 7.09 (dt, J = 2.5, 9.5 Hz, 1H), 6.75 (dd, J = 2.0, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.1 (d, J_{CF} = 233.8 Hz), 145.6, 145.2, 139.9, 135.9, 116.0, 112.8, 111.2, 110.8, 110.6, 101.5; ^{19}F NMR (376 MHz, DMSO-d_6) δ −73.38; ESI-MS m/z 203.1 $(M + H)^+$; ESI-HRMS calcd for $C_{11}H_8FN_2O$ $(M + H)^+$ requires m/z 203.0611, found 203.0615.

Methyl 2-*n*-propyl-1*H*-benzimidazole-6-carboxylate (3o): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H), 2.83 (t, J = 7.6 Hz, 2H), 1.83−1.78 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.9, 157.8 (2C), 138.1, 124.1, 123.8, 116.7, 114.6, 52.1, 31.3, 21.5, 13.9; ESI-MS m/z 219.0 $(M + H)^+$; ESI-HRMS calcd for $C_{12}H_{15}N_2O_2$ $(M + H)^+$ requires m/z 219.1128, found 219.1119.

General Procedure for the Synthesis of Substituted 1,3-Dihydrobenzimidazol-2-ones. A Schlenk tube was charged with 2-iodophenylcarbamates **6** (0.25 mmol), CuI (5 mg, 0.025 mmol), L-proline (6 mg, 0.05 mmol), and NaOH (15 mg, 0.375 mmol). After the tube was evacuated and backfilled with argon (3 times), aqueous ammonia (0.375 mmol) and 1 mL of DMSO were added into the tube. The reaction mixture was stirred at room temperature for 3−7 h before it was heated at 130 °C for 3−12 h. The cooled reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with 3:1 to 1:1 petroleum ether/ethyl acetate) to provide the desired product.

(11) (a) Elguero, J.; Katritzky, A. R.; Denisko, O. V. *Adv. Heterocycl. Chem.* **2000**, *76*, 1. (b) Zheng, N.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 4749.

5-Acetyl-1*H*-benzimidazol-2(3*H*)-one (7a): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (br s, 1H), 10.89 (br s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.46 (s, 1H), 7.01 (d, J = 8.4 Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.0, 155.9, 134.5, 130.4, 130.1, 123.0, 108.34, 108.30, 26.8; ESI-MS m/z 177.1 $(M + H)^+$; ESI-HRMS calcd for $C_9H_9N_2O_2$ $(M + H)^+$ requires m/z 177.0988, found 177.1002.

2-Oxo-*N*-*n*-propyl-2,3-dihydro-1*H*-benzo[*d*]imidazole-5-carboxamide (7c): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 10.82 (s, 1H), 8.29−8.32 (m, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.43 (s, 1H), 6.94 (d, J = 8.0 Hz, 1H), 3.21−3.16 (m, 2H), 1.54−1.49 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.8, 156.0, 132.5, 129.8, 127.7, 120.8, 108.3, 108.2, 41.5, 22.9, 11.9; EI-MS m/z 219 (M^+), 177, 161, 133; EI-HRMS calcd for $C_{11}H_{14}N_3O_2$ (M^+) requires m/z 219.1008, found m/z 219.1011.

4,6-Dimethyl-1*H*-benzimidazol-2(3*H*)-one (7d): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.49 (br s, 1H), 10.40 (br s, 1H), 6.52 (s, 1H), 6.50 (s, 1H), 2.19 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.1, 129.9, 129.7, 126.8, 122.7, 118.26, 107.1, 21.4, 16.5; ESI-MS m/z 163.0 $(M + H)^+$; ESI-HRMS calcd for $C_9H_{11}N_2O$ $(M + H)^+$ requires m/z 163.0793, found 163.0800.

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