HETEROCYCLES, Vol. 86, No. 1, 2012, pp. 555 - 563. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 23rd June, 2012 Accepted, 27th July, 2012, Published online, 8th August, 2012
DOI: 10.3987/COM-12-S(N)53

N-CHLOROSUCCINIMIDE/SODIUM HYDROXIDE-MEDIATED SYNTHESIS OF BENZIMIDAZOLES FROM AMIDINES UNDER MILD CONDITIONS

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Abstract – A convenient room-temperature one-pot procedure for the preparation of benzimidazoles derivatives from *N*-arylamidines has been developed. The reaction of *N*-aryl-*N*'-chloro amidines, generated by the treatment of *N*-aryl-amidines with *N*-chlorosuccinimide, in presence of sodium hydroxide provides benzimidazoles in good to excellent yields. Nitrogen anion generated *in situ* from succinimide (by-product of the chlorination step using NCS) and hydroxide anion was found to be highly effective as Brønsted base to promote the cyclization into benzimidazole of *N*-aryl-*N*'-chloroamidine.

INTRODUCTION

Compounds bearing benzimidazole moiety are frequently found in biologically active and therapeutically useful molecules. Their significant importance to medicinal chemistry is obvious.[1] For these reasons, a simpler approach to the synthesis of these heterocyclics was thought to be of great value. The classical methods for the preparation of benzimidazoles consist in condensing *o*-phenylenediamines with either carboxylic acid derivatives[2] under drastic conditions (strong acid/high temperature) or aldehydes[3] under oxidative conditions. There have been other procedures for the construction of benzimidazole heterocycles starting from aniline derivatives making use of *o*-substitituents for cyclization.[4] Although these transformations are widely used in the preparation of benzimidazoles, further developments of selective methods based on direct C-H functionalization transformation to this structure are of considerable interest. These methods represent one of the most effective and atom economical approach for C-N bond-forming reactions. The oxidative cyclization of *N*-arylamidines[5] to benzimidazoles have

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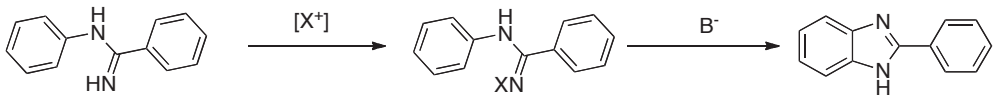
Dedicated to Prof. Ei-ichi Negishi on the occasion of his 77th birthday.

been reported earlier using oxidizing agents such as NaOCl/NaOH,[5a,b] $Pb(OAc)_4$,[5c] hypervalent iodine reagents.[5d,e] Although these methods can be applied to a wide range of substrates, the use of stoichiometric amounts of toxic,[5c] expensive[5d,e] reagents along with possible formation of nuclear chlorinated side products[5a] are major disadvantages. Recently, copper-[6a,b] and palladium-[6c] catalyzed C-N aerobic oxidative cross-coupling methodologies have been applied successfully in the synthesis of benzimidazole derivatives 2-substituted by an aryl,[6a,c] *t*-butyl[6a] or amino[6b] groups. While the use of gaseous oxygen as oxidizing agent is an interesting feature, these catalyzed methods suffer from elevated temperatures, long reaction times, use of solvents which are difficult to remove (DMSO, *N*-methyl-2-pyrrolidone). Moreover, compared to older methods[5] using stoichiometric amounts of oxidizing reagents, 2-alkylbenzimidazoles (except *t*-butyl) could not be obtained by the metal-catalyzed methods,[6] and *ortho*-substituted benzamidine structure was required to ensure high conversion.[6a]

Our interest in the synthesis of benzimidazole moiety led us to reexamine the transformation of *N*-aryl-amidines into benzimidazoles with the aim to limit these drawbacks.

Herein, we disclosed the results of our study on the synthesis of benzimidazoles via a 2-step sequence (i) *N*-halogenation of *N*-arylamidines, (ii) base-promoted cyclization, which offers a simple synthetic method for benzimidazoles derivatives under mild conditions (Scheme 1).



Scheme 1

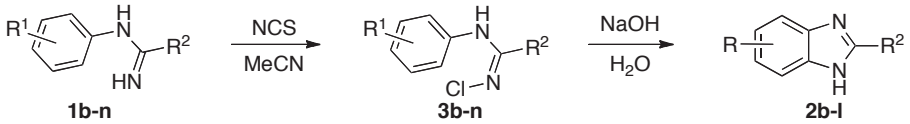
RESULTS AND DISCUSSION

We started our investigation by studying the conversion of phenylbenzimidazole into its *N*-halogenated derivative using *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS), Br_2, I_2, and chloramine-T. We found that both NCS and chloramine-T gave the *N*-chloro product in high conversion (> 95%) under mild conditions (0 °C to rt) in short reaction time (less than 5 min) in different solvents (CH_2Cl_2, MeCN, Et_2O).[7] *N*-Chloroamidine product was relatively stable and could be purified by column chromatography without noticeable degradation. We next explored the one-pot cyclization reaction by adding a base into the reaction mixture obtained from the reaction with NCS in MeCN.[8] A variety of weak organic bases, such as Et_3N, pyridine, DABCO, DIPEA and aqueous inorganic bases, such as $NaHCO_3$, Na_2CO_3 were tested but without success. Interestingly, addition of an aqueous solution of NaOH induced a rapid and clean cyclization of *N*-chloroamidine into 2-phenylbenzimidazole even at low temperature (0 °C). After removal of volatiles *in vacuo*, the desire benzimidazole product was

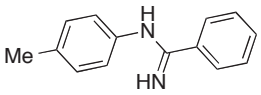
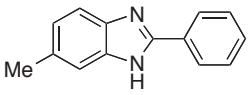
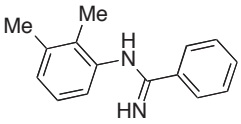
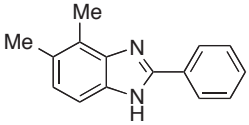
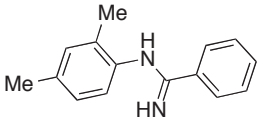
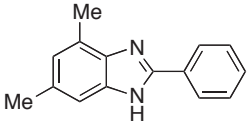
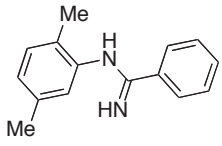
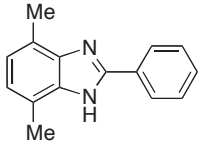
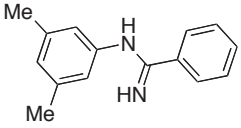
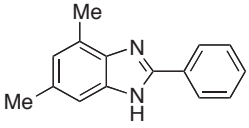
obtained in high purity (87% yield) by simple trituration of the crude mixture with water in order to remove by-product succinimide (as sodium salt) and other impurities.

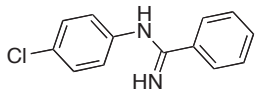
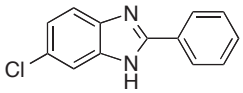
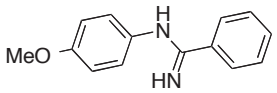
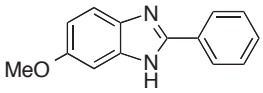
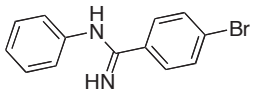
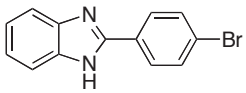
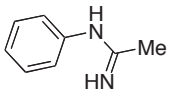
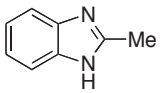
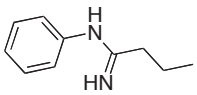
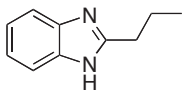
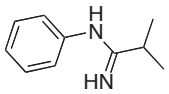
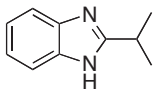
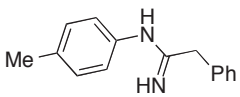
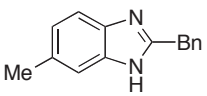
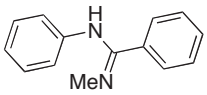
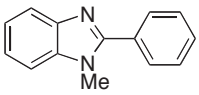
The optimized conditions were next applied to a variety of substituted *N*-arylamidines (Table 1). To our delight, several functional groups including halogens and electron-donating are tolerated well on the *N*-arylring of the amidines. In contrast to the metal-catalyzed C-H functionalization,[6] our method can be extended to the synthesis of 2-alkylated benzimidazoles with methyl, *n*-propyl, *i*-propyl or benzyl substituent (entries 9-12). When *N*-methyl-*N*-phenylamidine **1n** was used as substrate (entry 13), the *N*'-chlorinated intermediate could be obtained, but failed to cyclize under our conditions. Finally, in all cases studied, no trace of nuclear chlorination was observed.

Table 1. One-pot synthesis of benzimidazoles from *N*-arylamidines



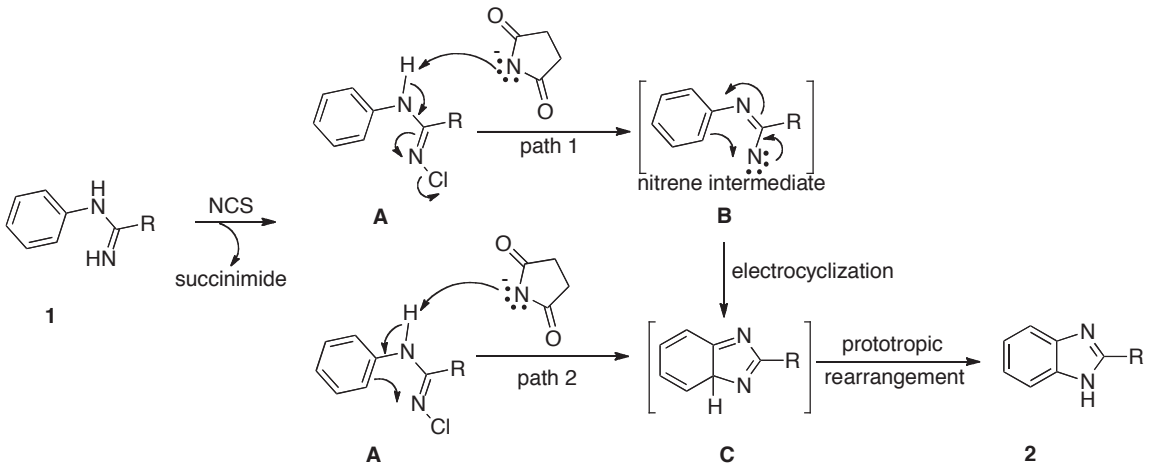
1b-n **3b-n** **2b-l**

entry	substrate	product	yield (%)
1	 **1b**	 **2b**	90
2	 **1c**	 **2c**	92
3	 **1d**	 **2d**	87
4	 **1e**	 **2e**	86
5	 **1f**	 **2d**	95

6	 **1g**	 **2f**	79
7	 **1h**	 **2g**	75
8	 **1i**	 **2h**	92
9	 **1j**	 **2i**	84
10	 **1k**	 **2j**	85
11	 **1l**	 **2k**	87
12	 **1m**	 **2l**	72
13	 **1n**	 **2m**	0

We tentatively propose the mechanism (Scheme 2) of the transformation based on literature precedent of related process using NaOCl.[5a] Amidine **1** reacts with NCS to give *N*-chloroamidine **A**. The dehydrochlorination of **A** promoted by a base would follow either path 1 to produce the nitrene intermediate **B**, which undergoes cyclization to **C** and prototropic rearrangement to provide benzimidazole **2** or path 2 to generate directly the cyclized product **C**. This dehydrochlorination seems not impossible when *N*-methyl-*N*-phenyl benzamidine **1n** was used. The reaction rate enhancement of the transformation from **A** to **2** under our conditions (5 min, 0 °C to rt) compared to the literature reported result (30 min, refluxing aqueous solution)[5a] could be explained by the involvement of succinimide in the

reaction. In the presence of hydroxide anion, succinimide (pK_a = 9.66)[9] is deprotonated into succinimide anion. Due to its lower propensity to be solvated by water compared to OH^-, succinimide anion could participate in the dehydrochlorination of **A** more efficiently.[10]



Scheme 2

In conclusion, we have developed a convenient room-temperature one-pot procedure for the preparation of benzimidazoles derivatives **2** from *N*-aryl amidines **1** via *N*-aryl-*N*'-chloroamidine intermediate **A**. Nitrogen anion generated *in situ* from succinimide (by-product of the chlorination step using NCS) and NaOH was found to be highly effective as Brønsted base to promote the cyclization into benzimidazole **2** of *N*-aryl-*N*'-chloro amidine **A**.

EXPERIMENTAL

The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC-300 or AC-500 spectrometer operating at 300 MHz or 500 MHz respectively. Flash chromatography was performed using SDS silicagel 60 (35-70 μm). Thin layer chromatography (TLC) was carried out on plates with a layer thickness of 0.25 mm (SDS Silicagel 60 F254). Visualization was achieved under a UVP mineralight UVGL-58 lamp or with vanilline stain. All reagents were obtained from commercial suppliers unless otherwise stated.

***N*-Arylamidines (1a-n)** were prepared according to literature.[6a]

***N*-Phenylbenzamidine (1a).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87 (d, *J* = 6.1 Hz, 2H), 7.48-7.42 (m, 3H), 7.35 (m, 2H), 7.05 (m, 1H), 6.98 (d, *J* = 7.4 Hz, 2H).

***N*-*p*-Tolylbenzamidine (1b).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, *J* = 7.0 Hz, 2H), 7.49-7.40 (m, 3H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H).

***N*-(2,3-Dimethylphenyl)benzamidine (1c).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (d, *J* = 6.7 Hz, 2H), 7.47-7.42 (m, 3H), 7.06 (dd, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 2.29 (s, 3H), 2.10 (s, 3H).

***N*-(2,4-Dimethylphenyl)benzamidine (1d).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, *J* = 6.5 Hz, 2H), 7.47-7.41 (m, 3H), 7.02 (s, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 2.29 (s, 3H), 2.15 (s, 3H).

***N*-(2,5-Dimethylphenyl)benzamidine (1e).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87 (d, *J* = 6.4 Hz, 2H), 7.49-7.40 (m, 3H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.69 (s, 1H), 2.29 (s, 3H), 2.15 (s, 3H).

***N*-(3,5-Dimethylphenylbenzamidine (1f).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, *J* = 7.0 Hz, 2H), 7.45-7.40 (m, 3H), 6.69 (s, 1H), 6.60 (s, 2H), 2.29 (s, 6H).

***N*-(4-Chlorophenyl)benzamidine (1g).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, *J* = 7.0 Hz, 2H), 7.47-7.39 (m, 3H), 7.29 (d, *J* = 8.5 Hz), 6.90 (d, *J* = 8.5 Hz, 2H).

***N*-(4-Methoxyphenyl)benzamidine (1h).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (d, *J* = 7.0 Hz, 2H), 7.46-7.41 (m, 3H), 6.91-6.89 (m, 4H), 3.79 (s, 3H).

4-Bromo-*N*-phenylbenzamidine (1i). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, *J* = 7.1 Hz, 2H), 7.55 (d, *J* = 7.1 Hz, 2H), 7.34 (m, 2H), 7.06 (m, 1H), 6.95 (d, *J* = 7.9 Hz, 2H).

***N*-Phenylacetamidine (1j).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32-7.29 (m, 2H), 7.05-7.02 (m, 1H), 6.89-6.87 (m, 1H), 4.50 (broad s, 2H), 2.05 (broad s, 3H).

***N*-Phenylbutyramidine (1k).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (m, 2H), 6.98 (m, 1H), 6.69 (s, 1H), 6.84 (m, 2H), 2.25 (t, *J* = 7.3 Hz, 2H), 1.69 (sextuplet, *J* = 7.3 Hz, 2H), 1.00 (t, *J* = 7.3 Hz, 3H).

***N*-Phenylisobutyramidine (1l).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (m, 2H), 6.98 (m, 1H), 6.69 (s, 1H), 6.84 (m, 2H), 2.52 (septuplet, *J* = 6.9 Hz, 1H), 1,23 (d, *J* = 6.9 Hz, 6H).

***N*-(*p*-Tolyl)phenylacetamidine (1m).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34-7.24 (m, 5H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.80 (d, *J* = 7.9 Hz, 2H), 4.19 (broad s, 2H), 3.65 (s, 2H), 2.28 (s, 3H).

***N*-Phenyl-*N*-methylbenzamidine (1n).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.27 (m, 2H), 7.22-7.14 (m, 5H), 7.04-6.98 (m, 3H), 3.53 (s, 3H).

General Procedure for the Synthesis of Benzimidazoles from *N*-arylamidines 1

To a cooled solution of *N*-arylamidine **1** (1 mmol) in MeCN (4 mL) at 0 °C was added solid NCS (133.5 mg, 1mmol). After stirring at the same temperature for 5 min, an aqueous solution of NaOH (200 mg in 0.2 mL H_2O) was added. The reaction mixture was stirred at 0 °C for 5 min, then concentrated in vacuo. The residue was washed with H_2O (3 × 5 mL) and dried to afford the benzimidazole as light brown solid (yields are reported in Table 1).

2-Phenyl-1*H*-benzo[*d*]imidazole (2a).[1m] mp 298–300 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.90 (broad s, 1H), 8.19 (d, *J* = 7.4 Hz, 2H), 7.60-7.48 (m, 5H), 7.22-7.19 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 151.5, 144.1, 135.2, 130.5, 130.1, 129.2, 126.7, 122.7, 122.0, 119.1, 111.5.

4-Methyl-2-phenyl-1*H*-benzo[*d*]imidazole (2b).[1m] mp 242–244 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.37 (broad s, 1H), 8.21-8.189 (m, 2H), 7.49-7.35 (m, 4H), 7. 30 (m, 1H), 6.91 (dd, *J* = 8.1, 1.5 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 153.0, 141.1, 139.8, 132.1, 129.8, 128.8, 128.6, 126.3, 122.4, 115.1, 114,6, 21.4.

4,5-Dimethyl-2-phenyl-1*H*-benzo[*d*]imidazole (2c).[1m] ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.25-8.22 (m, 2H), 7.40-7.25 (m, 2H), 7.30-7.25 (m, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 2.46 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.3, 144.4, 141.7, 135.0, 128.1, 127.3, 126.3, 125.2, 122.6, 121.6, 112.1, 19.2, 13.8.

4,6-Dimethyl-2-phenyl-1*H*-benzo[*d*]imidazole (2d).[1m] ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.50 (broad s), 8.26 (d, *J* = 7.1 Hz, 1H), 7.57-7.48 (m, 3H), 6.88 (s, 2H), 2.53 (s, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 150.3, 130.5, 129.5, 128.7, 126.6, 122.5, 16.7.

4,7-Dimethyl-2-phenyl-1*H*-benzo[*d*]imidazole (2e). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 12.48 (broad s, 1H), 8.29- 8.26 (m, 2H), 7.59-7.47 (m, 3H), 6.90 (s, 2H), 2.55 (s, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 150.3, 130.4, 129.5, 128.7, 126.6, 122.6, 16.7.

5-Chloro-2-phenyl-1*H*-benzo[*d*]imidazole (2f).[1m] mp 211–213 °C. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 12.95 (br s, 1H), 8.15 (d, *J* = 7.5 Hz, 2H), 7.61-7.49 (m, 5H), 7.17 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 153.1, 130.6, 130.2, 129.5, 127.1, 122.8.

5-Methoxy-2-phenyl-1*H*-benzo[*d*]imidazole (2g).[1m] mp 148-150 °C. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 12.50 (broad s, 1H), 8.11 (d, *J* = 6.5 Hz, 2H), 7.52-7.40 (m, 4H), 7.02 (br s, 1H), 6.80 (d, *J* = 6.5 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 156.0, 150.7, 130.5, 129.7, 129.0, 126.3, 111.5, 55.7.

2-(4-Bromophenyl)-1*H*-benzo[*d*]imidazole (2h). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.14- 8.09 (m, 2H), 7.79-7.74 (m, 2H), 7.63-7.57 (m, 2H), 7.24-7.18 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 150.3, 131.9, 129.5, 129.2, 128.3, 123.1, 122.2, 115.2 (broad peak).

2-Methyl-1*H*-benzo[*d*]imidazole (2i). ^{1}H NMR (MeOD, 300 MHz) δ 7.47-7.44 (m, 2H), 7.17-7.14 (m, 2H), 2.54 (s, 4H). ^{13}C NMR (MeOD, 75 MHz) δ 153.1, 139.7, 123,2, 115.3 (broad peak), 14.4.

2-Propyl-1*H*-benzo[*d*]imidazole (2j). ^{1}H NMR (MeOD, 300 MHz) δ 7.49-7.46 (m, 2H), 7.18-7.15 (m, 2H), 2.85 (t, *J* = 7.3 Hz, 2H), 1.85 (sextuplet, *J* = 7.3, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (MeOD, 75 MHz) δ 156.9, 139.7, 123,2, 115.5 (broad), 31.8, 22.8, 14.2.

2-Isopropyl-1*H*-benzo[*d*]imidazole (2k). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.11 (broad s, 1H), 7.47-7.44 (m, 2H), 7.11-7.08 (m, 2H), 3.13 (septuplet, *J* = 6.9 Hz, 1H), 1.34 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.0, 121.0, 28.3, 21.3.

2-Benzyl-5-methyl-1*H*-benzo[*d*]imidazole (2l). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.38 (broad s, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.32 (d, *J* = 1.3 Hz, 1H), 7.26-7.19 (m, 5H), 7.09 (dd, *J* = 8.3, 1.3 Hz, 1H), 4.19 (s, 2H), 2.49 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.8, 138.8, 137.2, 137.0, 132.0, 129.0, 128.8, 127.0, 123.7, 114.8, 114.5, 35.7, 21.7.

ACKNOWLEDGEMENTS

We thank Imma Arco and Minh Quan Tran for technical assistance.

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