N-Arylation of Benzimidazole with Arylboronate, Boroxine and Boronic Acids. Acceleration with an Optimal Amount of Water

Katsutoshi Nishiura,[a,*] Yoshio Urawa,[b] Shigeru Soda[b]

[a] Kashima Plant, Eisai Co., Ltd. 22-Sunayama, Hasaki-machi, Ibaraki 314-0255, Japan
   Fax: (+81)-479-46-4953, e-mail: k-nishiura@hhc.eisai.co.jp
[b] Process Research Laboratories, Eisai Co., Ltd., 22-Sunayama, Hasaki-machi, Ibaraki 314-0255, Japan

Abstract: The coupling of benzimidazole **1** with arylboronate, boroxine, and boronic acids is accelerated efficiently by the addition of an optimal amount of water. This coupling reaction proceeds in nearly quantitative yield at 30 °C under an atmosphere of air within 24 hours. Under these conditions, the reaction tolerates both electron-donating and electron-withdrawing substituents at the *ortho*-, *meta*, or *para*-positions of the phenylboronic acid.

Keywords: *N*-arylation; boronic acid; copper; cross-coupling; water

N-Arylimidazoles are important compounds for synthesizing biologically active compounds such as c-AMP phosphodiesterase receptor inhibitors.[1] The copper-promoted *N*-arylation of a number of NH-containing substrates with arylboronic acids has been recently developed because this methodology, as compared to the well-known Ullmann-type[2] and palladium-catalyzed methodology, has several advantages. These advantages include the use of mild conditions, weak base reagents, and the reactions can be performed in the presence of air. Hitherto, Collman[3] and Lam[4] independently reported that the copper-promoted cross-coupling reaction of arylboronic acids with imidazoles could be performed at ambient temperature. However, their procedures used a halogenated hydrocarbon as solvent, and required stoichiometric quantities of a simple copper salt. Alternatively, these methods required a catalytic amount of a copper complex and a stoichiometric amount of a chemical oxidant (e.g., pyridine *N*-oxide, TEMPO, or an atmosphere of O₂). Additionally, the reported yields are not optimal (about 70% [3a]). In order to perform the reaction on a large (or industrial) scale, catalytic reactions under mild conditions in non-halogenated hydrocarbons are preferred because they are safe and environmentally benign. Particularly, low loading of Cu metal is important in the production of pharmaceutical ingredients. More recently, Yu and Xie[5] reported on a simple copper salt-catalyzed the arylation of imidazole

with arylboronic acids in protic solvents (e.g., MeOH, EtOH, THF). However, the procedure requires the use of reflux conditions. In the pilot scale, it is dangerous to introduce oxygen of air into a reactor to regenerate the Cu catalyst under reflux conditions because of possible explosion and fire hazards. In addition, the solvent system (water:protic solvents=1:1) is inconvenient for large-scale work-up. We have therefore explored a practical *N*-arylation of benzimidazole with arylboronic acids using a catalytic amount of a simple copper salt in a non-halogenated hydrocarbon solvent under mild reaction conditions. In this study, we surprisingly found that this coupling reaction was accelerated by adding an optimal amount of water. This contribution describes a practical coupling procedure of benzimidazole with arylboronate, boroxine and boronic acids. The coupling yield is excellent, and the reaction tolerates both electron-donating and electron-withdrawing substituents in *ortho*-, *meta*-, or *para*-positions of the phenylboronic acid. Furthermore, this procedure can be performed at lower cost, safely and is environmentally benign on a large, or industrial, scale (Scheme 1).
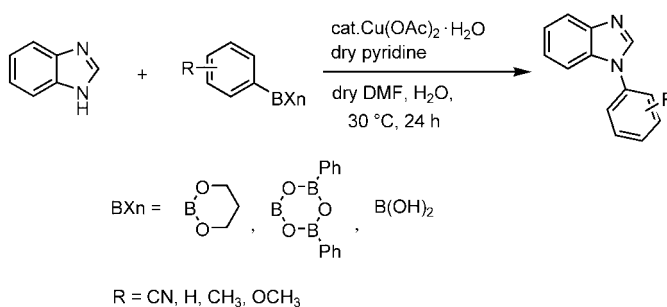
Scheme 1.

**Table 1.** Effect of the moisture of the copper salt and the atmosphere on the coupling reaction.[a]
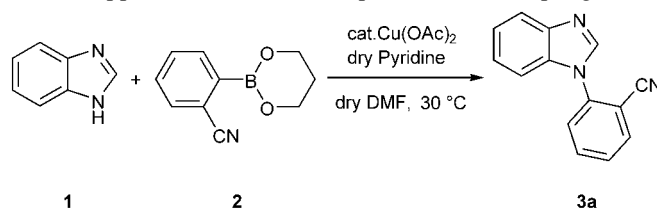
Entry	Copper Salt	Amount [mol %]	Molecular Sieves (MS)[b] (mg)	Yield of 3a[c] [%]
1	Cu(OAc)$_2$	50	50	67
2	Cu(OAc)$_2$	50	100	67
3	Cu(OAc)$_2$	50	none	88
4[d]	Cu(OAc)$_2$·H$_2$O	50	none	88
5	Cu(OAc)$_2$	10	50	94
6	Cu(OAc)$_2$	10	none	96
7[d]	Cu(OAc)$_2$·H$_2$O	10	none	95

[a] Reaction conditions: **1** (1 equiv.), **2** (2 equivs.), dry pyridine (2 equivs.), dry DMF (8 volumes), 30 °C, 48 h. The reaction tube is equipped with a duct of blue silica gel as protection from atmospheric moisture.

[b] The amount of powdered molecular sieves 4 Å is based on **1** (mg of MS/1 mmol of **1**).

[c] Isolated yield.

[d] Not equipped with a duct of blue silica gel.
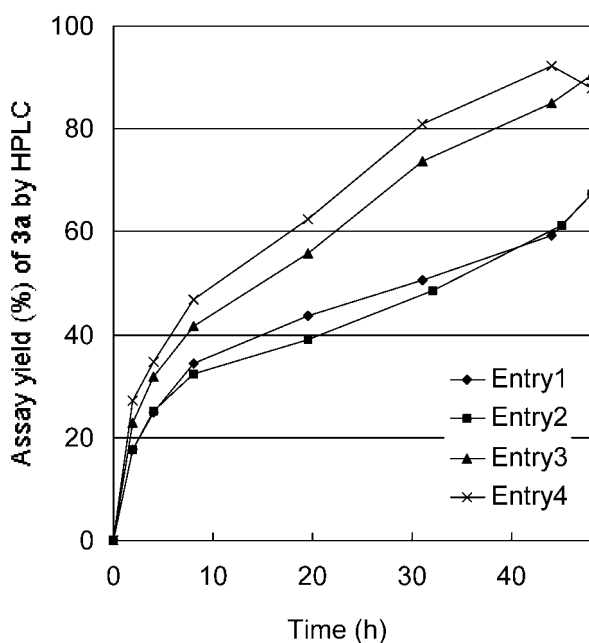
Figure 1. The coupling using 0.5 equivs. of copper salt.
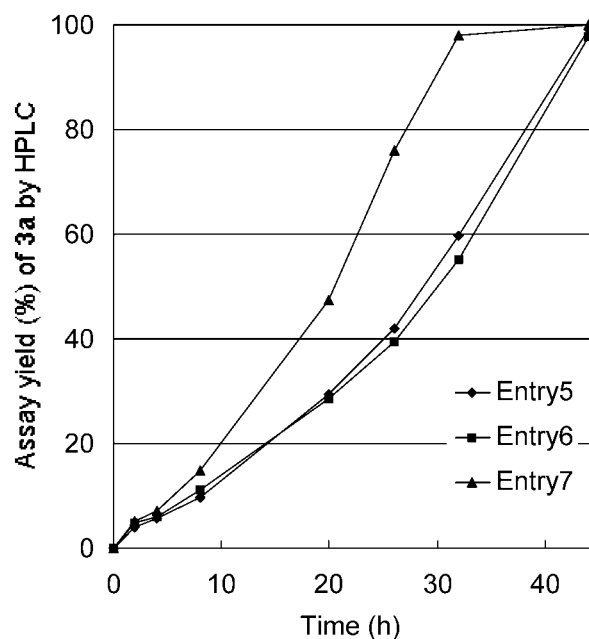
Figure 2. The coupling using 0.1 equiv. of copper salt.

We required large quantities of (*o*-cyanophenyl)benzimidazole derivatives for the preparation of an active pharmaceutical ingredient (API). Typically, the coupling reaction of imidazoles with arylboronic acids is performed under anhydrous conditions. It is thought that the coupling yield is diminished by copper(II)-catalyzed oxidation of arylboronic acids to phenols in the presence of released water from arylboronic acids through triarylboroxine formation.[6] Therefore, our initial attempt was conducted on benzimidazole **1** and 2-
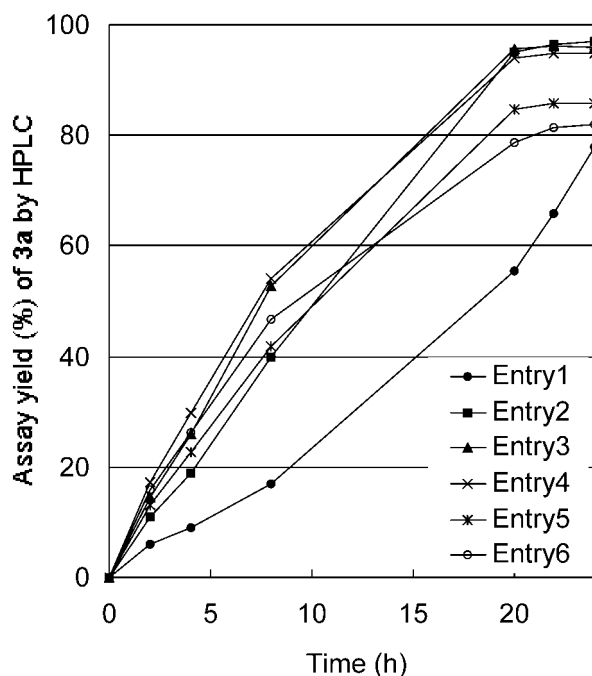
(1,3,2-dioxaborinan-2-yl)benzonitrile **2** instead of (*o*-cyanophenyl)boronic acid. The reaction using **2** with 4 Å molecular sieves proceeded slowly, and the conversion was low even after 48 hours. By contrast, the yield of the reaction in the absence of 4 Å molecular sieves was excellent. Although it is believed that anhydrous conditions are preferred in this type of reaction, there is no report describing the use of boroxine and boronate as a starting material that does not release water. From this point of view, the effect of moisture in this reaction

Table 2. Effect of the amount of water on the coupling reaction.[a]

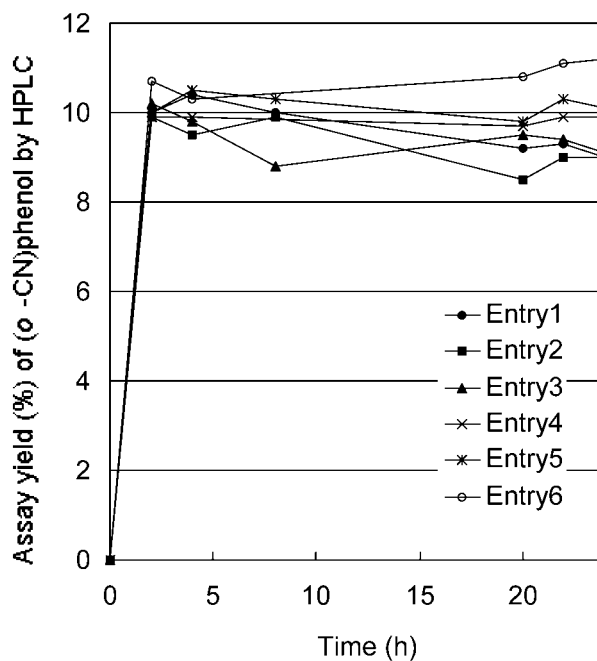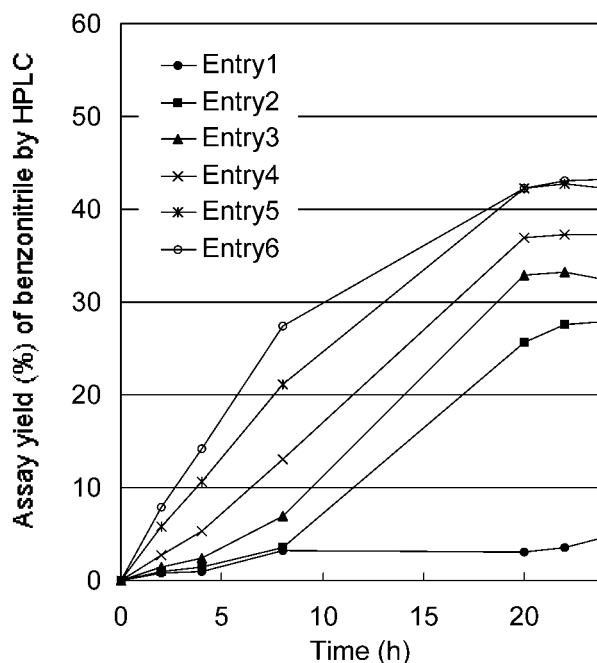| Entry	Amount of Water (equivalents)	Yield of 3a [%][b]
1	0.1	81
2	0.5	93
3	1.0	93
4	2.0	90
5	4.0	84
6	6.0	75

[a] Reaction conditions: **1** (1 equiv.), **2** (2 equivs.), Cu(OAc)$_2\cdot$H$_2$O (10 mol %), dry pyridine (2 equivs.), dry DMF (8 volumes), 30 °C, 24 h. The reaction tube is equipped with a duct of blue silica gel as protection from atmospheric moisture.
[b] Isolated yield.

Figure 3. Effect of the amount of water on the coupling reaction.

Figure 4. Transition of formed (*o*-cyano)phenol.

Figure 5. Transition of formed benzonitrile.

was checked over time by HPLC monitoring. As shown in Table 1 and Figures 1 and 2, more moist conditions were surprisingly preferable for this coupling reaction than anhydrous conditions (Table 1, entry 4 in Figure 1, and entry 7 in Figure 2). Furthermore, the effect of acceleration was particularly observed when a lower amount of a copper salt was used. Accordingly, it was thought that the hydrate of Cu(OAc)$_2$ and atmospheric moisture would play a significant role as a source of water to activate the catalytic system in this reaction.

Subsequently, the potency of acceleration effect was confirmed by the addition of varying amounts of water to the reaction mixture (Table 2 and Figure 3). We found

that the addition of water dramatically accelerated the reaction. Specifically, 0.5 – 2 equivs. of water worked to give *N*-(2-cyano-1-phenyl)benzimidazole **3a** in excellent yields within 24 hours (Figure 3, entries 2, 3 and 4). On the other hand, 0.1 equiv. of water was inadequate to accelerate the reaction, and the addition of more water decreased the yield of **3a** (Table 2 and Figure 3, entries 5 and 6). It is well known that the diminish-

Table 3. Effect of water on the coupling reaction of benzimidazole with boroxine **4**[a] or boronic acid **5a**.[b]
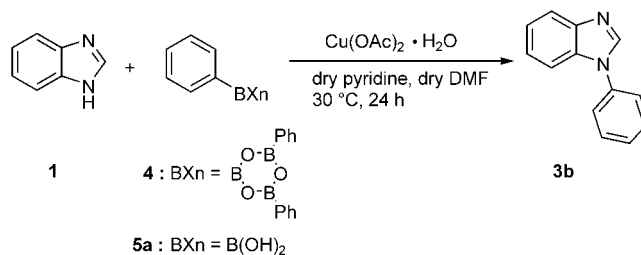

Entry	Boron Compound	Amount of Copper Salt (mol %)	Amount of Water (equivs.)	Yield of **3b** [%][d]
1	boroxine **4**[c]	50	0	48
2	boroxine **4**	50	1	93
3	boronic acid **5a**	50	1	95
4	boroxine **4**	50	6	91
5	boronic acid **5a**[c]	30	0	36
6	boronic acid **5a**[c]	30	0	56
7	boronic acid **5a**	30	1	94

[a] Reaction conditions: **1** (1 equiv.), **4** (0.67 equivs.), dry pyridine (2 equivs.), dry DMF (8 volumes), 30 °C, 24 h. Entry 1: Cu(OAc)$_2$, entries 2–4: Cu(OAc)$_2 \cdot$H$_2$O, entry 3: the use of **5a** (2 equivs.) instead of **4**.
[b] Reaction conditions: **1** (1 equiv.), **5a** (2 equivs.), dry pyridine (2 equivs.), dry DMF (8 volumes), 30 °C, 24 h. Entries 5 and 6: Cu(OAc)$_2$, entry 5: MS 4 Å (50 mg/mmol of **1**) is added to the reaction mixture.
[c] The reaction tube is equipped with a duct of blue silica gel as protection from atmospheric moisture.
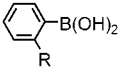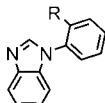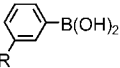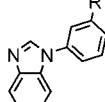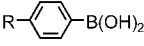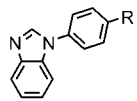[d] Isolated yield.
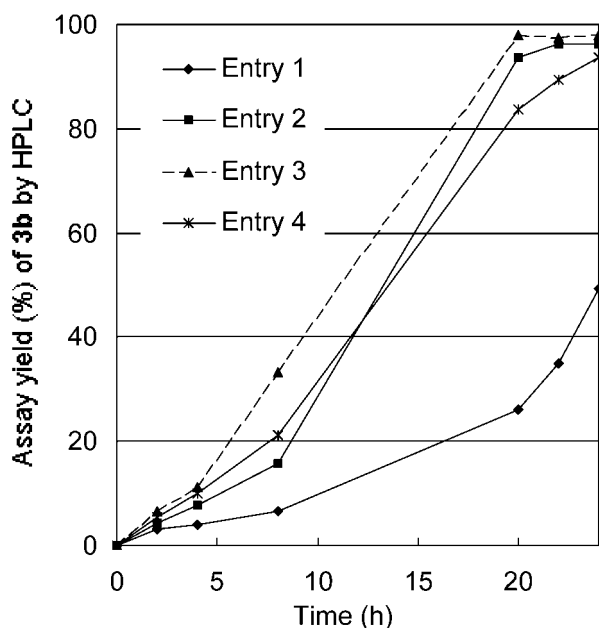
Figure 6. Effect of water on the coupling reaction using boroxine **4**, and comparison to the reaction using boronic acid **5a**.
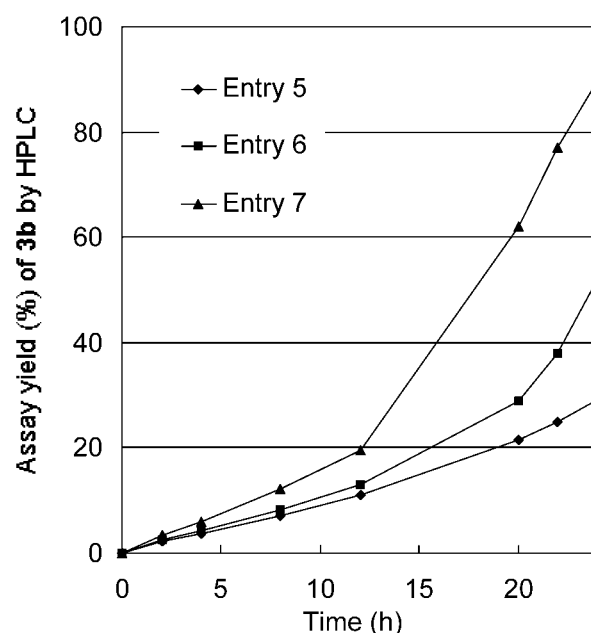
Figure 7. Effect of water on the coupling reaction using boronic acid **5a**.

ing coupling yield is due to several possible side reactions. It has been reported that arylboronic acids are oxidized by copper(II) in the presence of water to form the corresponding phenol, which is subsequently coupled with arylboronic acids.[7] In addition, water plays a role for the oxygen source of phenol formation.[4d] Moreover, arylboronic acids are known to undergo deboronation in

the presence of water.[6b] It was interesting to note that the formation of the corresponding (*o*-cyano)phenol did not depend on the amount of water, and did not exceed approximately 10% initial yield (Figure 4). On the other hand, benzonitrile, another competitive by-product formed by protodeboronation of **2**, increased along with the amount of water (Figure 5).

Table 4. Coupling of benzimidazole **1** with various phenyl-boronic acids.

Entry	Ar(OH)₂	Product	Yield [%][a]
1	**5b**: R = CN	**3a**	48
2	**5c**: R = CH₃	**3c**	82
3	**5d**: R = CN	**3d**	99
4	**5e**: R = CH₃	**3e**	98
5	**5f**: R = CN	**3f**	96
6	**5g**: R = CH₃	**3g**	96
7	**5h**: R = OMe	**3h**	97

Conditions: **1** (1 equiv.), boronic acid (2 equivs.), water (1 equiv), Cu(OAc)₂·H₂O (30 mol %), dry pyridine (2 equivs.), dry DMF, 30 °C, 24 h.
[a] Isolated yield.

As with **2**, the presence of water demonstrated the effect to accelerate the reaction using non-substituted triphenylboroxine **4** and phenylboronic acid **5a** (Table 3, Figures 6 and 7). In this case, the desired *N*-phenylbenzimidazole **3b** was obtained in excellent yield within 24 hours. We also found that boronic acid **5a** was more reactive than boroxine **4** (Figure 6, entries 2 and 3). On the other hand, as discussed above, the amount of formed phenol did not depend on the amount of water and did not exceed initial conversion. However, the yield was approximately 50% to 2 equivs. of phenylboronic acid at the start (after 2 hours). Benzene, in addition to other by-products, was observed in minor amounts within 24 hours.

Finally, several substituted boronic acids were evaluated under the above-mentioned reaction conditions (Table 4). We found that the reaction conditions tolerated both electron-donating and electron-withdrawing substituents at the *ortho*-, *meta*- or *para*-positions of the phenylboronic acid. However, we found that one boronic acid derivative **5b** (Table 4, Entry 1) was not well tolerated by the reaction conditions. It is thought that this particular boronic acid derivative is less stable due to the presence of an electron-withdrawing substituent at the *ortho*-position.[8] However, the presently reported reaction conditions allowed the coupling of benzimidazole with *p*-tolylboronic acid to give *p*-tolylbenzimidazole **3g** in 96% yield (Table 4, Entry 6). In contrast, the previously reported methods using anhydrous con-ditions with Cu(OAc)₂ (1.5 equivs.) gave *p*-tolylbenzimidazole **3g** in only a 69% yield after 4 days.[4b]

In conclusion, we have developed a novel procedure for the *N*-arylation of imidazole with arylboronates, boroxines and boronic acids. The presence of an optimal amount of water plays a significant role to accelerate the reaction. The effect of acceleration made the reaction more than twice as fast as that under the hitherto known anhydrous conditions with molecular sieves. Owing to this effect, *N*-arylation was achieved with a catalytic amount of a simple copper salt under mild conditions, and the desired compound was obtained in excellent yield. On the other hand, the formation of phenols as by-products did not depend on the amount of water, and the formed phenols did not affect the yield of the desired *N*-arylimidazoles. This finding is especially beneficial for large-scale manufacture because there is no need for commonly used dehydrating agents such as molecular sieves. Such reagents are unfavorable for a large (or industrial) scale production. Further work and the study on the mechanism are in progress.

Experimental Section

Typical Procedure for the Cross Coupling Reaction

To a 20-mL vial were added benzimidazole **1** (0.5 g, 4.23 mmol), boronate **2** (1.6 g, 8.46 mmol), Cu(OAc)₂ monohydrate (84.6 mg, 0.42 mmol), dry DMF (4 mL), water (75 μL, 4.23 mmol) and then dry pyridine (0.68 mL, 8.46 mmol). The reaction mixture was vigorously stirred under an atmosphere of air at 30 °C for 24 h, poured into 12.5% aqueous NH₃ (13 mL) and then extracted with toluene (50 mL, 2 times). The combined organic layers were concentrated under reduced pressure at 50 °C, and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate, 10/1 to 1/1) to give *N*-(2-cyano-1-phenyl)benzimidazole **3a**; yield: 0.87 g (93%); mp 107.8 °C (lit.[9] mp 106–107.5 °C); slightly yellowish-white solid (Table 2, entry 3); ¹H NMR (CDCl₃, 400 MHz): δ = 7.36–7.41 (m, 3H), 7.63 (t, *J* = 7.22 Hz, 2H), 7.83 (td, *J* = 7.94 Hz, 1.48 Hz, 1H), 7.90–7.94 (m, 2H), 8.19 (s, 1H); MS (ESI): *m/z* = 220.4 [MH]⁺.

N-**Phenylbenzimidazole (3b):** ¹H NMR (CDCl₃, 400 MHz): δ = 7.33–7.36 (m, 2H), 7.46–7.61 (m, 6H), 7.88–7.90 (m, 1H), 8.13 (s, 1H); MS (ESI): *m/z* = 195.3 [MH]⁺.

N-**(2-Methyl-1-phenyl)benzimidazole (3c):** ¹H NMR (CD₃OD, 400 MHz): δ = 2.05 (s, 3H), 7.11–7.14 (m, 1H), 7.28–7.36 (m, 3H), 7.38–7.44 (m, 1H), 7.48–7.49 (m, 2H), 7.74–7.79 (m, 1H), 8.23 (s, 1H).

N-**(3-Cyano-1-phenyl)benzimidazole (3d):** ¹H NMR (CDCl₃, 400 MHz): δ = 7.37–7.42 (m, 2H), 7.51–7.55 (m, 1H), 7.72–7.82 (m, 3H), 7.86 (t, *J* = 1.46 Hz, 1H), 7.89–7.93 (m, 1H), 8.12 (s, 1H); mp 104.4 °C (lit.[9] mp 98–105 °C).

N-**(3-Methyl-1-phenyl)benzimidazole (3e):** ¹H NMR (CD₃OD, 400 MHz): δ = 2.43 (s, 3H), 7.30–7.38 (m, 5H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.50–7.55 (m, 1H), 7.71–7.76 (m, 1H), 8.33 (s, 1H).

N-(4-Cyano-1-phenyl)benzimidazole (3f): ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.38 – 7.42 (m, 2H), 7.56 – 7.61 (m, 1H), 7.68 – 7.71(m, 2H), 7.89 – 7.93 (m, 3H), 8.16 (s,1H); mp 126.4 °C.

N-(4-Methyl-1-phenyl)benzimidazole (3g): ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 2.46 (s, 3H), 7.32 – 7.41 (m, 6H), 7.50 – 7.53 (m, 1H), 7.86 – 7.89 (m, 1H), 8.09 (s, 1H).

N-(4-Methoxy-1-phenyl)benzimidazole (3h): ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 3.90(s, 3H), 7.06 – 7.10 (m, 2H), 7.29 – 7.36 (m, 2H), 7.40 – 7.48 (m, 3H), 7.85 – 7.89 (m, 1H), 8.06 (s, 1H).

Acknowledgements

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