N-Arylations of Nitrogen-Containing Heterocycles with Aryl and Heteroaryl Halides Using a Copper(I) Oxide Nanoparticle/1,10-Phenanthroline Catalytic System

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Received 21 January 2008; revised 12 February 2008

Abstract: A general procedure for solvent-free N-arylations of nitrogen-containing heterocycles, i.e., imidazoles, triazoles, and indoles, with aryl and heteroaryl halides catalyzed by copper(I) oxide (Cu$_2$O) nanoparticles is demonstrated. Four types of Cu$_2$O were evaluated: the bulky compound and its cubic, octahedral, and spherical nanoparticulate forms. The results show that Cu$_2$O nanoparticles, in particular the cubic form, are highly efficient for the N-arylation reaction. In the presence of cubic Cu$_2$O nanoparticles, 1,10-phenanthroline, and tetrabutylammonium fluoride, a variety of nitrogen-containing heterocycles smoothly underwent N-arylation with aryl and heteroaryl halides at 110–145 °C to give the corresponding products in moderate to excellent yields. It is noteworthy that the reaction is conducted under solvent-free conditions. The reaction mechanism is also discussed.

Key words: copper(I) oxide nanoparticles, 1,10-phenanthroline, N-arylations, heterocycles, halides

The transition-metal-catalyzed N-arylation of nitrogen-containing heterocycles (e.g., imidazoles, triazoles, and indoles) with aryl halides is one of the most powerful and versatile methods for the synthesis of N-aryl heterocycles. 1–17 This strategy gives rise to N-aryl heterocyclic moieties that are widely present in various classes of organic compounds, such as natural products, pharmaceuticals, and ligands. 1 Copper-catalyzed processes of nitrogen-containing heterocycles with aryl halides have become the best alternative to the use of noble metal catalysts (often palladium) from an economic and industrial point of view. 1–19 Generally, almost all the copper-catalyzed approaches to the activation of hindered substrates and less-active aryl halides, i.e. aryl bromides and chlorides, rely on the development of either new ligand sets 5–15 or new precatalyst types. 16 Among these ligand sets, such as 1,10-phenanthroline derivatives, 2 dianimes, 6 aminoarethenethiols, 7 amino acid derivatives, 8 quinolin-8-ol, 9 diphenyl pyrrolidine-2-phosphonate, 10 oxime-phosphate oxides, 11 phosphoramidite, 12 2-aminopyrimidine-4,6-diol, 13 (pyrrolidin-2-ylmethyl)imidazoles, 14 and ninhydrin; 15 however, only a few display high activity and extend the scope of the N-arylation reaction to both hindered substrates and less-active aryl halides. For example, Buchwald and co-workers have coupled 2- and 4-substituted imidazoles with aryl bromides using bulky copper(I) oxide (Cu$_2$O)/4,7-dimethoxy-1,10-phenanthroline. 5,c,d In the presence of this catalytic system, a variety of hindered and functionalized imidazoles and aryl halides underwent the N-arylation reaction at 60–150 °C to give the corresponding products in good to excellent yields. However, aryl chlorides were still unsuitable substrates and the reaction required the use of harmful solvents (PrCN or NMP) and a promoter [poly(ethylene glycol)]. In addition, the 4,7-dimethoxy-1,10-phenanthroline ligand is very expensive. In 2006, we reported that copper(I) bromide (CuBr) combined with 2-aminopyrimidine-4,6-diol was an effective catalytic system for solvent-free N-arylations of imidazoles with aryl and heteroaryl halides using tetrabutylammonium fluoride (TBAF) as the base.13 However, the scope of the process was still limited to the coupling of imidazoles with unhindered aryl and heteroaryl halides under harsh conditions. Moreover, heteroaryl chlorides underwent the reaction with only 1H-benzoimidazole to give the products in moderate yields. As a result, the development of a general and efficient N-arylation method that employs both hindered substrates and less-active aryl halides is still a challenge. Recently, Punniyamurthy and co-workers reported that copper(II) oxide (CuO) nanoparticles were an efficient catalyst for the N-arylation reaction; however, the reaction was still limited to using the activated aryl iodides. 19 Around the same time, we found that Cu$_2$O nanoparticles displayed more activity than bulky Cu$_2$O in the Sonogashira reaction. 20 These findings prompted us to examine the feasibility of performing the N-arylation reaction using Cu$_2$O nanoparticles as a catalyst under mild and solvent-free conditions. As expected, the use of Cu$_2$O nanoparticles combined with 1,10-phenanthroline was shown to be highly efficient for the N-arylations of imidazoles with aryl halides, including aryl chlorides and heteroaryl halides, without the aid of any solvent. Furthermore, both triazoles and indoles are also suitable substrates under the standard reaction conditions, as are bulky imidazoles and aryl halides. Herein, we report in detail the modified N-arylation reactions of nitrogen-containing heterocycles, i.e. imidazoles, triazoles, and indoles, with aryl and heteroaryl halides using the cubic Cu$_2$O nanoparticle/1,10-phenanthroline (L2) catalytic system under solvent-free conditions (Scheme 1). 21

SYNTHESIS 2008, No. 11, pp 1707–1716
Advanced online publication: 11.04.2008
DOI: 10.1055/s-2008-1067014; Art ID: F01708SS
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**Scheme 1**

In one of our previous reports, the N-arylation reaction of 1H-imidazole (1a) with 1-chloro-4-nitrobenzene (2a), CuBr, 2-aminopyrimidine-4,6-diol (L1), and TBAF was unsuccessful at 140–145 °C after 24 hours (Table 1, entry 1). Identical results were observed in the reaction using bulky Cu₂O instead of CuBr (entry 2). To our delight, the target product 3 was obtained in 83% yield from the same reaction employing cubic Cu₂O nanoparticles as the catalyst (entry 3). The other two types of Cu₂O nanoparticles, i.e. octahedral and spherical, were also tested and they both provided good results (entries 4 and 5, respectively). Encouraged by these results, we subsequently examined the effect of the ligand on the reaction (entries 6–10). A series of ligands were investigated, i.e. 1,10-phenanthroline derivatives L2–L4, 2,2’-bipyridine (L5), and N-[2-(phenylimino)ethylidene]benzenamine (L6), and both 1,10-phenanthroline (L2) and 4,7-dimethoxy-1,10-phenanthroline (L4) displayed high efficiency in the N-arylation reaction catalyzed by cubic Cu₂O nanoparticles. Because 1,10-phenanthroline (L2) is far cheaper than the 4,7-dimethoxy derivative L4, we chose L2 combined with cubic Cu₂O nanoparticles as the catalytic system to use when screening base and temperature effects on the reaction. It was found that among the four bases tested, i.e. TBAF, cesium carbonate, potassium fluoride, and triethylamine, TBAF was the most effective (entries 6 and 11–13). While cubic Cu₂O nanoparticles combined with L2 provided the target product 3 in 100% yield (entry 6), the yield of 3 was reduced to 84% when the bulky Cu₂O catalyst was used instead (entry 15); identical results were observed for the latter even after prolonging the reaction time to 48 hours (entry 16). Product 3 was still obtained in good yield using cubic Cu₂O nanoparticles when the synthesis was conducted at a lower temperature of 110–115 °C for 48 hours (entry 14).

With the standard conditions in hand, we decided to explore the scope of the reaction using both different imidazoles and aryl halides (Table 2). The results showed that a variety of aryl and heteroaryl halides undergo the reaction smoothly with hindered and unhindered imidazoles to give the corresponding products in predominantly moderate to excellent yields. 1H-Imidazole (1a) treated with aryl bromides 2b–f, including the bulky bromide 2d, efficiently reacted in the presence of cubic Cu₂O nanoparticles, L2, and TBAF at 140–145 °C to afford the corresponding products 4–8 in 100, 98, 52, 89, and 86% yield, respectively (entries 1–5). Notably, compound 5 was also isolated in moderate yield as the desired product from the reaction of 1H-imidazole (1a) with chlorobenzene (2g) (entry 6). We were also pleased to observe that the reaction of substrate 1a with heteroaryl halides 2h–j proceeded well to give the corresponding products in moderate to good yields under the standard conditions (entries 7–9). In the presence of cubic Cu₂O nanoparticles,
L2, and TBAF, another imidazole substrate, 1b, smoothly underwent the N-arylation reaction with aryl and heteroaryl halides to give products 11–16 in moderate to excellent yields (entries 10–15, respectively). Again, it is noteworthy that chlorobenzene (2g) also worked well with substrate 1b to provide the target product 13 in 82% yield (entry 12). However, an attempt to couple 4-chlorotoluene (2m) with 1H-benzoimidazole (1b) failed (entry 16). Next, we examined the use of hindered imidazoles 1c–e as substrates in the N-arylation reaction under the standard conditions (entries 17–22). Although the reaction between substrate 1c and chloride 2a was unsuccessful (entry 17), that of substrate 1c with heteroaryl chloride 2j or aryl bromide 2n occurred smoothly giving the corresponding products in moderate yields (entries 18 and 19, respectively). Gratifyingly, the reaction of substrate 1d, another hindered imidazole, and heteroaryl chloride 2j in the presence of cubic Cu2O nanoparticles, L2, and TBAF was achieved giving product 19 in excellent yield (entry 20). The phenyl-substituted derivative 1e was also successfully N-arylated with bromide 2n in 58% yield, but the reaction with chloride 2j failed (entries 21 and 22, respectively).

Table 2  N-Arylation of Imidazoles with Aryl or Heteroaryl Halides Catalyzed by Cubic Copper(I) Oxide Nanoparticles in the Presence of 1,10-Phenanthrolinea

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Product number</th>
<th>Yieldb (%)</th>
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<tr>
<td>2</td>
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<tr>
<td>4</td>
<td>1a</td>
<td>2e</td>
<td>7</td>
<td>89</td>
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<td>5</td>
<td>1a</td>
<td>2f</td>
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<td>86</td>
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<tr>
<td>9</td>
<td>1a</td>
<td>2j</td>
<td>10</td>
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Table 2  N-Arylation of Imidazoles with Aryl or Heteroaryl Halides Catalyzed by Cubic Copper(I) Oxide Nanoparticles in the Presence of 1,10-Phenanthroline* (continued)

![Chemical Reaction Diagram]

<table>
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<td>Cl</td>
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<td>Me-Br</td>
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<td>O2N-Br</td>
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<td>Cl</td>
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*a Reaction conditions: 1 (0.5 mmol), 2 (0.6 mmol), 10 mol% cubic Cu$_2$O nanoparticles, 20 mol% L$_2$, and TBAF (3 equiv) under an Ar atmosphere at 140–145 °C for 24 h.

*b Isolated yield.

*c For 36 h.

*d In this reaction, >95% of the imidazole substrate was recovered.
The reactions of a variety of aryl iodides with imidazoles were conducted to further examine the efficiency of the cubic Cu₂O nanoparticle/L₂ catalytic system (Scheme 2). We are happy to disclose that, using the same molar quantities for the heterocyclic and halo substrates as described above, 1H-imidazole (1a) efficiently underwent N-arylation with aryl iodides in the presence of 5 mol% of cubic Cu₂O nanoparticles, 10 mol% of L₂, and 3 equivalents of TBAF at 110–115 °C after a reaction time of 24–48 hours to afford the target products in good to excellent yields. Treatment of 1a with the bulky 1-iodo-2-methylbenzene, for example, provided the corresponding desired product 6 in 81% yield. Gratifyingly, 1H-benzoimidazole (1b) also reacted well with 4-iodoanisole to give product 12 in good yield under the same conditions.

Next, we attempted the N-arylation reaction of triazoles, again using the same molar quantities of the nitrogen-containing heterocycle and halide as described above. To our delight, treatment of triazoles 1f and 1g with aryl halides 2 in the presence of cubic Cu₂O nanoparticles, L₂, and TBAF gave the corresponding products in moderate to good yields (Scheme 3). In the presence of 10 mol% of cubic Cu₂O nanoparticles, 20 mol% of L₂, and 3 equivalents of TBAF, 1H-1,2,4-triazole (1f) was N-arylated with iodobenzene, bromobenzene, 4-bromotoluene, and 4-iodoanisole at 110–115 °C to afford the desired products in 90, 55, 61, and 75% yield, respectively. Triazole 1g also underwent N-arylation with iodobenzene (2o) at 110–115 °C to give product 27 in good yield under the same conditions. Surprisingly, the reaction of fused triazole 1h with iodobenzene (2o) afforded the target product 28 in low yield (19%) together with two N-buty1-substituted products in 63% total yield; the latter products, 2-buty1-2H-benzo[1,2-b]triazole (29) and 1-buty1-1H-benzo[1,2-b]triazole (30), were generated from the reaction of substrate 1h with TBAF. This result prompted us to re-examine the N-arylation of the other nitrogen-containing heterocycles using GC-MS analysis. We found that the butyl side products were observed only in the reaction of 1H-benzo[1,2-b]triazole (1h). The reason for this observation may be that 1H-benzo[1,2-b]triazole as a ligand can improve the generation of butyl radical species from TBAF under copper(I) and heating conditions. Studies of the detailed reactions of 1H-benzo[1,2-b]triazoles with tetraalkylammonium halides and the accurate determination of their mechanism are in progress.

The coupling of 1H-indole (1i), another important nitrogen-containing heterocycle, with aryl and heteroaryl halides 2 using the cubic Cu₂O nanoparticle/L₂ catalytic system and TBAF as the base under solvent-free conditions was also examined (Table 3). It was found that 1H-indole (1i) reacted smoothly with bromides 2c and 2e at 140–145 °C to afford the target products 31 and 32 in 91 and 74% yield, respectively (entries 1 and 2). To our delight, satisfactory yields were also obtained from the reactions of 1H-indole (1i) with nitrogen- and sulfur-containing heteroaryl halides 2h–j and 2p under the same conditions (entries 4–6 and 8). For example, in the presence of cubic Cu₂O nanoparticles, L₂, and TBAF, pyrim...
idin-2-yl chloride (2j) successfully N-arylated 1H-indole (1i) to give product 35 in 68% yield (entry 6). Unfortunately, chlorobenzene (2g) was not a suitable substrate for the reaction with 1H-indole (1i) (entry 3). It is noteworthy that the reaction of substrate 1i with iodobenzene (2o) occurred smoothly at 110–115 °C to give the desired product 31 in quantitative yield (entry 7). The reaction of a hindered indole, the methyl-substituted derivative 1j, with 4-bromoanisole (2e) also occurred smoothly to afford the target product 36 in 45% yield after 48 hours under the standard conditions (entry 9).

To elucidate the above results, we have formulated a mechanism for the reaction (Scheme 4) which is based on that previously proposed.2–17,19,22 Intermediate A can be generated readily from Cu2O and the 1,10-phenanthroline ligand, and this is followed by the complexation of intermediate A with the nitrogen-containing heterocycle to form intermediate B.19,22 This stage is also supported by the results of the reaction of triazole 1h (Scheme 3). Intermediate B then undergoes oxidative addition with the aryl or heteroaryl halide and the aid of the base to afford intermediate C. Intermediate C undergoes reductive elimination to yield the desired product and regenerate the active copper(I) species.

The key point of the process is the stabilization and activation of the active copper(I) species.22 Compared with Buchwald’s results,5 however, the present protocol showed higher efficiency using only TBAF as the base. Thus, we deduce that TBAF may play several roles in the reaction based on the above mechanism and reported results:2–17,23 (1) activation of the active copper(I) species, (2) stabilization of the low-coordinated copper(I) species,23 (3) as a phase-transfer catalyst for the substrate/catalyst/ligand/product phases,23 (4) as base, and (5) as a medium to improve the reaction due to the melting point of TBAF trihydrate being about 65 °C.

In summary, we have developed an efficient modified protocol for the N-arylations of nitrogen-containing heterocycles, i.e. imidazoles, triazoles, and indoles, with aryl and heteroaryl halides using a cubic Cu2O nanoparticle/1,10-phenanthroline catalytic system. By comparison with previous reports on copper-catalyzed N-arylation reactions promoted by 1,10-phenanthroline derivatives,5 several features of the modified reaction are established: (1) Cubic Cu2O nanoparticles combined with 1,10-phenanthroline display high efficiency and general applicability for the N-arylation reaction. The scope of the reaction can be extended to hindered substrates (imidazoles and aryl halides) as well as less-active aryl and heteroaryl halides. In addition, triazoles and indoles are also suitable substrates under the same conditions. (2) The reaction can be conducted under solvent-free conditions. (3) The reaction of aryl iodides, and even an aryl chloride, could be carried out successfully under mild conditions. (4) The yields are affected by both the particle size and shape of Cu2O. While the reaction involving cubic Cu2O nanoparticles combined with 1,10-phenanthroline provided the product in 100% yield, use of the bulky Cu2O catalyst reduced the yield to 84%. The particle shape’s contribution

Table 3  N-Arylation of Indoles with Aryl or Heteroaryl Halides Catalyzed by Cubic Copper(I) Oxide Nanoparticles in the Presence of 1,10-Phenanthrolinea

<table>
<thead>
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<th>Yield (%)</th>
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</tr>
<tr>
<td>2</td>
<td>2e</td>
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<td>9d</td>
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*Reaction conditions: 1 (0.5 mmol), 2 (0.6 mmol), 10 mol% cubic Cu2O nanoparticles, 20 mol% L2, and TBAF (3 equiv) under an Ar atmosphere at 140–145 °C for 24 h.

b Isolated yield.

* At 110–115 °C for 36 h.

* Using 2-methyl-1H-indole (1j) as the substrate and a reaction time of 48 h.

In summary, we have developed an efficient modified protocol for the N-arylations of nitrogen-containing heterocycles, i.e. imidazoles, triazoles, and indoles, with aryl and heteroaryl halides using a cubic Cu2O nanoparticle/1,10-phenanthroline catalytic system. By comparison with previous reports on copper-catalyzed N-arylation reactions promoted by 1,10-phenanthroline derivatives,5 several features of the modified reaction are established: (1) Cubic Cu2O nanoparticles combined with 1,10-phenanthroline display high efficiency and general applicability for the N-arylation reaction. The scope of the reaction can be extended to hindered substrates (imidazoles and aryl halides) as well as less-active aryl and heteroaryl halides. In addition, triazoles and indoles are also suitable substrates under the same conditions. (2) The reaction can be conducted under solvent-free conditions. (3) The reaction of aryl iodides, and even an aryl chloride, could be carried out successfully under mild conditions. (4) The yields are affected by both the particle size and shape of Cu2O. While the reaction involving cubic Cu2O nanoparticles combined with 1,10-phenanthroline provided the product in 100% yield, use of the bulky Cu2O catalyst reduced the yield to 84%. The particle shape’s contribution

Scheme 4  A possible mechanism
to the yield is also clear. For the copper-catalyzed reaction in the presence of 2-aminopyrimidine-4,6-diol, the yields were reduced in the following order: cubic CuO nanoparticles > octahedral Cu2O nanoparticles > spherical Cu2O nanoparticles > bulky CuO. Efforts to explore the mechanism of the reaction in detail and to extend the applications of CuO nanoparticles to other coupling transformations are underway in our laboratory.

NMR spectroscopy was performed on a Varian INOVA-400 or INOVA-500 spectrometer operating at 400 (1H NMR) and 100 MHz (13C NMR) or 500 (1H NMR) and 125 MHz (13C NMR), respectively, using TMS as an internal standard and CDCl3 as the solvent. Mass spectrometric analysis was performed using GC-MS on a Shimadzu GCMS-QP2010 instrument.

Solvent-Free, Copper-Catalyzed N-Arylation of a Nitrogen-Containing Heterocycle: General Procedure

A mixture of nitrogen-containing heterocycle 1 (0.5 mmol), aryl or heteroaryl halide 2 (0.6 mmol), cubic CuO nanoparticles (5–10 mol%), 1,10-phenanthroline (1.2: 10–20 mol%), and TBAF (1.5 mmol) was stirred at 110–145 °C for 24–48 h until complete consumption of the starting material was observed (monitored by TLC). After completion of the reaction, EtOAc (10 mL) was poured into the mixture, which was then washed with sat. aq NaCl (3 × 5 mL) and extracted with EtO (2 × 10 mL). The organic layers were then dried (anhyd Na2SO4) and evaporated under vacuum. The residue was purified by flash column chromatography (EtOAc or hexane–EtOAc) to afford the desired product.

1-(4-Nitrophenyl)-1H-imidazole (3)5d

1H NMR (400 MHz, CDCl3): δ = 8.40 (d, J = 8.8 Hz, 2 H), 8.01 (s, 1 H), 7.61 (d, J = 8.8 Hz, 2 H), 7.41 (s, 1 H), 7.29 (s, 1 H).

13C NMR (125 MHz, CDCl3): δ = 150.4, 120.8, 117.8, 26.6.

LRMS (EI, 70 eV): m/z (%) = 189 (M+, 100).

1-(2-Toly1)-1H-imidazole (6)5d

1H NMR (400 MHz, CDCl3): δ = 7.60 (s, 1 H), 7.34–7.27 (m, 3 H), 7.23 (d, J = 8.0 Hz, 2 H), 7.07 (s, 1 H), 2.17 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 137.3, 136.4, 133.6, 131.1, 129.1, 128.6, 126.6, 126.2, 120.2, 17.5.

LRMS (EI, 70 eV): m/z (%) = 158 (M+, 100).

1-(4-Methoxyphenyl)-1H-imidazole (7)5d

1H NMR (400 MHz, CDCl3): δ = 7.78 (s, 1 H), 7.30 (d, J = 8.8 Hz, 2 H), 7.20 (d, J = 9.2 Hz, 2 H), 6.99 (d, J = 8.8 Hz, 2 H), 3.85 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 158.7, 135.6, 130.4, 129.8, 123.0, 118.6, 114.7, 55.4.

LRMS (EI, 70 eV): m/z (%) = 174 (M+, 100).

1-(3,5-Dimethylphenyl)-1H-imidazole (8)5d

1H NMR (400 MHz, CDCl3): δ = 8.51 (d, J = 4.5 Hz, 1 H), 8.40 (s, 1 H), 7.87–7.84 (m, 1 H), 7.69 (s, 1 H), 7.39 (d, J = 3.5 Hz, 1 H), 7.29–7.26 (m, 2 H).

13C NMR (100 MHz, CDCl3): δ = 149.1, 139.0, 135.0, 130.6, 122.0, 121.6, 116.1, 112.3.

LRMS (EI, 70 eV): m/z (%) = 145 (M+, 100).

1-(1H-Iimidazol-1-yl)pyridine (9)5d,13

1H NMR (500 MHz, CDCl3): δ = 8.72 (d, J = 4.8 Hz, 2 H), 8.64 (s, 1 H), 7.92 (s, 1 H), 7.23 (t, J = 4.8 Hz, 1 H), 7.19 (s, 1 H).

13C NMR (125 MHz, CDCl3): δ = 158.7, 156.3, 136.2, 130.7, 118.8, 116.5.

LRMS (EI, 20 eV): m/z (%) = 146 (M+, 100).

1-(4-Nitrophenyl)-1H-benzoimidazole (11)16a

1H NMR (400 MHz, CDCl3): δ = 8.50 (d, J = 8.8 Hz, 2 H), 7.83 (s, 1 H), 7.63 (d, J = 8.8 Hz, 2 H), 7.35–7.26 (m, 4 H).

13C NMR (125 MHz, CDCl3): δ = 146.7, 144.5, 141.8, 141.5, 132.9, 125.8, 124.6, 123.7 (2 C), 121.2, 110.2.

LRMS (EI, 70 eV): m/z (%) = 239 (M+, 100).

1-(4-Methoxyphenyl)-1H-benzoimidazole (12)5d

1H NMR (400 MHz, CDCl3): δ = 8.05 (s, 1 H), 7.87 (d, J = 8.8 Hz, 1 H), 7.46 (d, J = 9.2 Hz, 1 H), 7.40 (d, J = 8.8 Hz, 2 H), 7.32 (t, J = 3.6 Hz, 2 H), 7.06 (d, J = 8.8 Hz, 2 H), 3.88 (s, 3 H).

13C NMR (125 MHz, CDCl3): δ = 159.2, 143.7, 142.5, 132.1, 129.0, 125.6, 123.5, 122.5, 120.4, 115.0, 110.3, 55.6.

LRMS (EI, 70 eV): m/z (%) = 224 (M+, 100).

1-Phenyl-1H-benzoimidazole (13)5d

1H NMR (400 MHz, CDCl3): δ = 8.25 (s, 1 H), 7.91 (s, 1 H), 7.58 (t, J = 7.6 Hz, 3 H), 7.53–7.45 (m, 3 H), 7.35–7.33 (m, 2 H).

13C NMR (100 MHz, CDCl3): δ = 144.0, 142.3, 136.3, 133.7, 130.0, 128.0, 124.0, 123.6, 122.7, 120.5, 110.4.

LRMS (EI, 70 eV): m/z (%) = 194 (M+, 100).

1-Phenyl-1H-benzoimidazolide (14)5d,13

1H NMR (400 MHz, CDCl3): δ = 9.10 (s, 1 H), 8.78 (d, J = 4.8 Hz, 2 H), 8.61 (d, J = 8.8 Hz, 1 H), 7.85 (d, J = 8.4 Hz, 1 H), 7.45–7.36 (m, 2 H), 7.21 (t, J = 4.8 Hz, 1 H).

13C NMR (125 MHz, CDCl3): δ = 158.5, 156.4, 145.1, 141.8, 131.9, 124.6, 123.8, 120.4, 118.0, 115.6.

LRMS (EI, 70 eV): m/z (%) = 196 (M+, 100).

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1-(4-Tolyl)-1H-benzoimidazole (15)\textsuperscript{5d}

[H NMR (400 MHz, CDCl\textsubscript{3}):
\begin{align*}
\delta &\approx 8.54 \text{ (s, 1 H)}, 7.88 \text{ (d, J = 8.4 Hz, 1 H)}, 7.51 \text{ (d, J = 8.8 Hz, 1 H)}, 7.40 \text{–} 7.30 \text{ (m, 6 H), 2.45 (s, 3 H).} \\
\end{align*}

1\textsuperscript{3}C NMR (100 MHz, CDCl\textsubscript{3}):
\begin{align*}
\delta &\approx 143.9, 142.4, 138.2, 133.9, 133.8, 130.6, 124.0, 123.6, 122.7, 120.5, 110.5, 21.1. \\
\end{align*}

LRMS (EI, 70 eV): \textit{m/z} (%) = 208 (M\textsuperscript{+}, 100).

2-Phenyl-1H-benzoimidazole (16)\textsuperscript{24}

[H NMR (500 MHz, CDCl\textsubscript{3}):
\begin{align*}
\delta &\approx 8.54 \text{ (s, 1 H), 8.51 (d, J = 4.8 Hz, 1 H), 8.01 (d, J = 8.8 Hz, 1 H), 7.84 (d, J = 8.8 Hz, 1 H), 7.76 (t, J = 8.0 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.32 (t, J = 3.6 Hz, 2 H), 7.18 (d, J = 5.2 Hz, 1 H).} \\
\end{align*}

1\textsuperscript{3}C NMR (100 MHz, CDCl\textsubscript{3}):
\begin{align*}
\delta &\approx 149.5, 149.0, 144.3, 141.0, 138.6, 131.8, 123.9, 123.0, 121.5, 120.2, 113.9, 112.5. \\
\end{align*}

LRMS (EI, 70 eV): \textit{m/z} (%) = 195 (M\textsuperscript{+}, 100).

2-Methyl-1-(4-nitrophenyl)-1H-benzoimidazole (17)\textsuperscript{5d,13}

[H NMR (400 MHz, CDCl\textsubscript{3}):
\begin{align*}
\delta &\approx 8.48 \text{ (d, J = 8.8 Hz, 2 H), 7.77 (d, J = 7.2 Hz, 1 H), 7.62 (d, J = 8.8 Hz, 2 H), 7.32 (t, J = 7.2 Hz, 1 H), 7.27 (d, J = 7.6 Hz, 1 H), 7.19 (d, J = 8.0 Hz, 1 H), 2.58 (s, 3 H).} \\
\end{align*}

1\textsuperscript{3}C NMR (100 MHz, CDCl\textsubscript{3}):
\begin{align*}
\delta &\approx 147.2, 142.7, 141.6, 135.6, 127.5, 125.4, 123.3, 123.1, 119.4, 109.7, 109.5, 14.7. \\
\end{align*}

LRMS (EI, 70 eV): \textit{m/z} (%) = 253 (M\textsuperscript{+}, 100).

2-Methyl-1-pyrimidin-2-yl-benzoimidazole (18)\textsuperscript{5d,13}

[H NMR (400 MHz, CDCl\textsubscript{3}):
\begin{align*}
\delta &\approx 8.83 (d, J = 4.8 Hz, 2 H), 8.26 (br s, 1 H), 7.73 (br s, 1 H), 7.36–7.30 (m, 2 H), 7.24 (t, J = 4.8 Hz, 1 H), 2.97 (s, 3 H). \\
\end{align*}

1\textsuperscript{3}C NMR (125 MHz, CDCl\textsubscript{3}):
\begin{align*}
\delta &\approx 158.3, 157.2, 152.7, 142.7, 134.0, 123.4, 119.0, 118.0, 114.4, 18.4. \\
\end{align*}

LRMS (EI, 70 eV): \textit{m/z} (%) = 210 (M\textsuperscript{+}, 100).

2-(2-Methyl-1H-imidazol-1-yl)pyrimidine (19)\textsuperscript{5d,13}

[H NMR (400 MHz, CDCl\textsubscript{3}):
\begin{align*}
\delta &\approx 8.73 (d, J = 5.2 Hz, 2 H), 7.98 (br s, 1 H), 7.20 (t, J = 4.8 Hz, 1 H), 7.09 (br s, 1 H), 2.80 (s, 3 H). \\
\end{align*}

1\textsuperscript{3}C NMR (100 MHz, CDCl\textsubscript{3}):
\begin{align*}
\delta &\approx 158.4, 156.3, 146.7, 127.5, 118.4, 118.2, 18.0. \\
\end{align*}

LRMS (EI, 70 eV): \textit{m/z} (%) = 160 (M\textsuperscript{+}, 100).
Acknowledgment
The authors thank the National Natural Science Foundation of China (No. 20572020), the Fok Ying Tung Education Foundation (No. 101012), and the Program for New Century Excellent Talents in University (No. NCET-06-0711) for financial support.

References


(4) For a paper on N-arylations of imidazoles with aryl halides mediated by stoichiometric copper, see: Lindley, J. Tetrahedron 1984, 40, 1433.
