JOC Note

Highly Functional Group Tolerance in Copper-Catalyzed *N*-Arylation of Nitrogen-Containing Heterocycles under Mild Conditions

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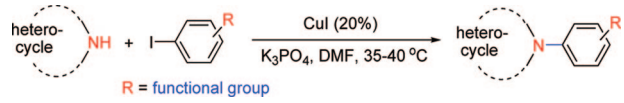
Received December 4, 2008



A copper-catalyzed process has been developed for the *N*-arylation reaction under very mild conditions in the absence of additional ligand. This protocol could not only tolerate an array of thermally sensitive functional groups, but also achieve high chemoselectivity.

Transition-metal-catalyzed Ullmann-type coupling is one of the most important methods for the formation of C(aryl)−N, C(aryl)−C, C(aryl)−O, and C(aryl)−S bonds.[1] However, the classic Ullmann reactions are generally conducted under harsh reaction conditions such as elevated temperatures as high as 200 °C, use of stoichiometric amounts of copper reagents, and moderate yields.[1,2] In the past few years, much attention has been paid to improvement of these types of transformations, and a number of ligands have thereby been developed to expedite the reaction rates and substantially lower the reaction temperatures (mostly to the range of 110−130 °C).[3,4] In spite of significant progress, most of these methodologies remain restricted to a certain degree owing to unavailability, high expense, air or moisture sensitivity, and/or specificity of ligands.[1−4] Consequently, taking into consideration an industrial and practical standpoint, some new strategies are starting to attract interest. First, considerable attention has been focused on the development of cheap, experimentally simple, ligand-free catalytic systems.[5] Second, the use of aryl iodides to obtain the mild reaction conditions or to replace the expensive transition metal catalyst, usually palladium or rhodium, with a cheaper one would also be highly desirable.[5e,f,6,7] Herein we wish to disclose a surprising discovery that the copper-catalyzed *N*-arylation of nitrogen-containing heterocycles with aryl iodides is easily performed in the absence of additional ligand under very mild conditions.

Considering *N*-arylimidazoles have been recurrent templates in medicinal chemistry, a preliminary survey of reaction conditions was conducted with iodobenzene (**1a**) and imidazole (**2a**) as model arylating agents. Among the solvents tested, DMF was clearly the best choice (entries 1−4, Table 1). After screening a variety of bases (i. e., K_2CO_3, K_3PO_4, and Cs_2CO_3), we found that K_3PO_4 gave the best result of 93% yield in DMF (entries 4−6, Table 1). Among these copper sources, CuI is the most effective (entries 4, 7, and 8, Table 1). Subsequently, we studied the effect of the amount of CuI on the reaction efficiency, and found that the negative effect was observed while the amount of CuI was reduced (entries 4 and 9−11, Table 1). In addition, we further investigated the cross-coupling reaction by adding some nitrogen-containing ligands. However, we surprisingly found that the effect of ligand is almost ignored as compared to the reactions without additional ligand. For example, using 20 mol % of L-proline as ligand afforded the desired product in 92% yield (entry 13, Table 1).

With optimized conditions now in hand, we explored the scope of this process with respect to aryl iodide structure. To our delight, the *N*-arylation of imidazole was smoothly performed with the extensive pool of aryl iodides to afford the corresponding products in good to excellent yields although the amount of catalyst used is slightly high and the reaction time is relatively longer if compared to other protocols reported in the

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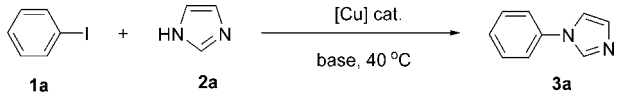
10.1021/jo802669b CCC: $40.75
Published on Web 02/05/2009

TABLE 1. Some Representative Results from the Screening of Reaction Conditions for the *N*-Arylation of Imidazole with Iodobenzene[a]

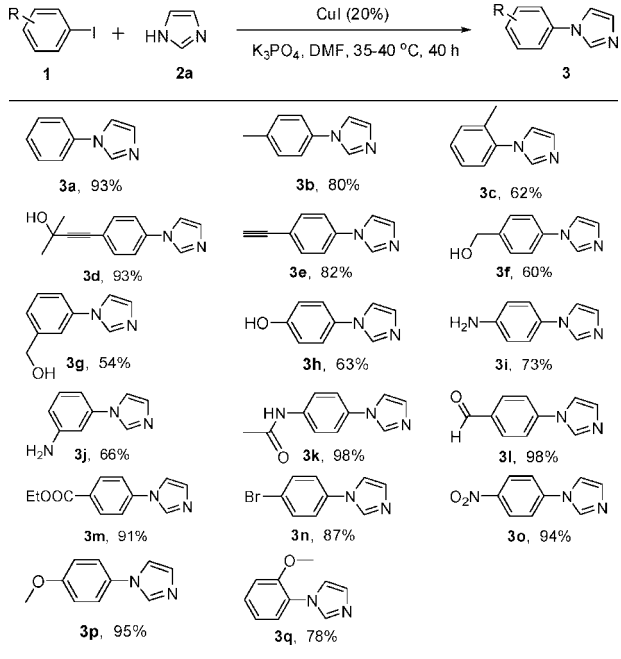


1a 2a 3a

entry	[Cu] cat. (mol %)	solvent	base	yield,[b] %
1	CuI (20)	toluene	K_3PO_4	0
2	CuI (20)	CH_3OH	K_3PO_4	0
3	CuI (20)	DMSO	K_3PO_4	84
4	CuI (20)	DMF	K_3PO_4	93
5	CuI (20)	DMF	Cs_2CO_3	85
6	CuI (20)	DMF	K_2CO_3	80
7	CuBr (20)	DMF	K_3PO_4	82
8	Cu_2O (20)	DMF	K_3PO_4	0
9	CuI (15)	DMF	K_3PO_4	88
10	CuI (10)	DMF	K_3PO_4	77
11	CuI (5)	DMF	K_3PO_4	40
12[c]	CuI (20)	DMF	K_3PO_4	34
13[d]	CuI (20)	DMF	K_3PO_4	92
14[d]	CuI (10)	DMF	K_3PO_4	83
15[e]	CuI (20)	DMF	K_3PO_4	84

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.4 mmol), base (2.0 mmol) in the presence of [Cu] cat. in 1.0 mL of solvent at 35−40 °C under N_2 atmosphere for 40 h. [b] Yields (average of two runs) based on **1a**. [c] Reaction under air. [d] L-Proline (20 mol %) as ligand. [e] L-Proline (20 mol %) as ligand, 24 h.

TABLE 2. Catalytic *N*-Arylation of Imidazole with Aryl Iodides by CuI[a,b]



[a] Reaction conditions: **1** (1.0 mmol), **2a** (1.4 mmol), K_3PO_4 (2.0 mmol) in the presence of CuI (0.2 mmol) in 1.0 mL of DMF at 35−40 °C under N_2 atmosphere. [b] Yields (average of two runs) based on **1**.

literature, and the results are summarized in Table 2. To the best of our knowledge, this is the first example describing the copper-catalyzed *N*-arylation of *N*-heterocycles with aryl halides at the range of room temperature (35−40 °C) in the absence of additional ligand although the Ullmann-type couplings have been developed more than one hundred years.[8] The performance of *N*-arylation at these comparatively lower temperatures represents a major practical advance and it may be of significant interest for the industrial community.

A great number of natural products, biologically active compounds, pharmaceuticals, chemicals, and advanced materials involve the *N*-arylazole motifs with a variety of functional groups. Therefore, it is highly desirable to develop the *N*-arylation of nitrogen-containing heterocycles, in which substrates contain functional groups. However, two factors make this process difficult: first, the generally required harsh conditions of the well-established Ullmann-type *N*-arylation have seriously restricted the range of functional groups tolerated, and second, it may be subject to issues to make a difference among the aforementioned competitive C(aryl)−N, C(aryl)−O, and C(aryl)−C Ullmann-type coupling reactions.[1,2,6b,9] More recently, Buchwald, our laboratory, and others demonstrated highly efficient copper/ligand systems that could tolerate functional groups to a certain degree at 110−130 °C.[10] In this study, we surprisingly found that our new protocol was suitable for a broad range of functional groups (e.g., alkynyl, hydroxy, amino, amido, aldehyde, ester, haloid, nitro, and methoxy substituents).

Generally, aryl halides tethering terminal alkyne make such an *N*-arylation process difficult because the copper catalytic system may likewise facilitate Sonogashira reaction at relatively high temperature.[11] To our knowledge, no example of the coupling of azole with terminal alkynyl-substituted aryl halide has been disclosed so far. In this study, the protocol effectively suppressed the self-coupling of 1-ethynyl-4-iodobenzene, and thus accelerated the *N*-arylation of imidazole with aryl halide (Table 2, **3e**). Another problematic situation is the competition from the formation ofthe C(aryl)−N or C(aryl)−O bond as there is a free OH or NH group on aryl halide. It is known that *N*-[(hydroxymethyl)phenyl]azoles are potential in medicinal applications.[12] However, the *N*-arylation of azoles with hydroxymethyl-substituted iodobenzenes may meet a problem owing to the undesired formation of benzyl phenyl ether at high reaction temperature.[13] Herein we were pleased to find that our catalytic system could be applicable to the *N*-arylation of imidazole with iodophenyl methanols (**3f** and **3g**). It is important to note that this protocol could promote the *N*-arylation of imidazole with 4-iodophenol (**3h**), 4-iodoaniline (**3i**), and 3-iodoaniline (**3j**) to provide the corresponding *N*-arylimidazoles in good yields, avoiding the formation of diaryl ethers and

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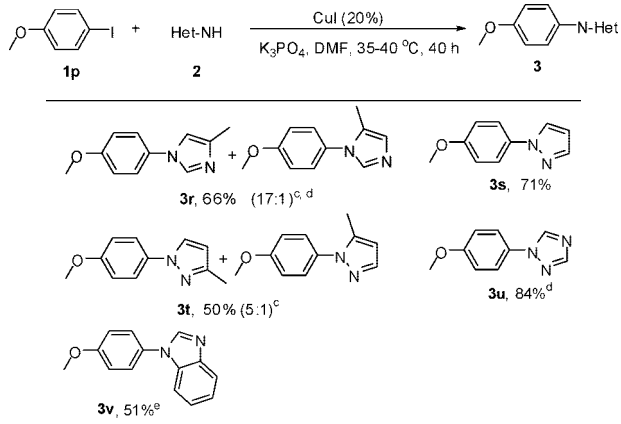
TABLE 3. Catalytic *N*-Arylation of Azoles with 4-Iodoanisole by CuI[a,b]



[a] Reaction conditions: **1p** (1.0 mmol), **2** (1.4 mmol), K_3PO_4 (2.0 mmol) in the presence of CuI (0.2 mmol) in 1.0 mL of DMF at 35−40 °C under N_2 atmosphere. [b] Yields (average of two runs) based on **1p**. [c] The regioselectivity was determined by GC-mass analysis and is described in parentheses. [d] 50 °C. [e] 60 °C.

diarylamines. As *N*-(4-iodophenyl)acetamide was used as substrate, the *N*-arylation was conducted to provide the *N*-arylimidazole in 98% yield, and no trace of aryl amidation was detected (**3k**). Our reaction conditions could also tolerate other functional groups such as aldehyde,[14] ester, and nitro (**3*l*−o**). It is worth noting that the deactivated 4-iodoanisole could afford a good yield of 95% (**3p**). The reaction of the hindered 2-iodoanisole also gave the corresponding *N*-arylimidazole product (**3q**) in 78% yield.

In an endeavor to expand the scope of the methodology, the protocol based on the use of our catalytic system was suitable for other nitrogen-containing heterocycles as demonstrated in Table 3. The arylations of 4-iodoanisole with 4-methyl-1*H*-imidazole, pyrazole, 3-methyl-1*H*-pyrazole, and 1*H*-1,2,4-triazole afforded the corresponding *N*-arylated products in reasonable yields (**3r**−**u**). It is known that the *N*-arylation of substituted imidazoles and pyrazoles with aryl halides may lead to regioselectivity (*N*-1 versus *N*-2 or *N*-3). In this study, the mild reaction conditions provided an excellent *N*-1 regioselectivity (17:1) for the coupling of 4-methyl-1*H*-imidazole, a significant improvement over our previous method (reaction temperature: 120 °C; regioselectivity: 4.3:1) (**3r**).[10d] The coupling of 1*H*-benzimidazole required a slightly increased reaction temperature to improve the yield of product (**3v**).

(14) Before the *N*-arylation of imidazole with aryl halide containing the aldehyde moiety, the formyl group needed to be protected as ketal: Velaparthi, U.; Wittman, M.; Liu, P.; Stoffan, K.; Zimmermann, K.; Sang, X.; Carboni, J.; Li, A.; Attar, R.; Gottardis, M.; Greer, A.; Chang, C.Y. Y.; Jacobsen, B. L.; Sack, J. S.; Sun, Y.; Langley, D. R.; Balasubramanian, B.; Vyas, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2317.

In summary, we have developed an experimentally simple and mild CuI-catalyzed *N*-arylation of nitrogen-containing heterocycles with a variety of aryl iodides in the absence of additional ligand. Our catalytic system can reduce reaction temperature to below 40 °C while the Cu-catalyzed *N*-arylations of *N*-heterocycles with aryl halides generally require elevated temperatures (110−130 °C). It is particularly noteworthy that this protocol cannot only tolerate an array of thermally sensitive functional groups, but also achieve high levels of chemoselectivity, avoiding the occurrence of other competitive coupling reactions such as *O*-arylation, *N*-arylation of amine, aryl amidation, and Sonogashira reaction. The preliminary findings would be of wide-ranging significance in the construction of heterocyclic systems.

Experimental Section

General Procedure. A flame-dried Schlenk test tube with a magnetic stirring bar was charged with CuI (38.4 mg, 0.2 mmol), K_3PO_4 (0.422 g, 2.0 mmol), nitrogen-containing heterocycle (1.4 mmol), aryl halide (1.0 mmol), and DMF (1 mL) under N_2 atmosphere. A rubber septum was replaced with a glass stopper, and the system was then evacuated twice and back filled with N_2. After being stirred at 35−40 °C for 40 h, the reaction mixture was diluted with 2−3 mL of ethyl acetate, filtered through a plug of silica gel, and washed with 10−20 mL of ethyl acetate. The filtrate was concentrated and the resulting residue was purified by column chromatography on silica gel to provide the desired product.

4-(4-(1*H*-Imidazol-1-yl)phenyl)-2-methylbut-3-yn−2-ol (3d). The crude product was purified over a silica gel column with ethyl acetate/petroleum ether (1/1) to give a white solid (93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (s, 6H), 7.22 (s, 1H), 7.27−7.30 (m, 3H), 7.48 (d, J = 8.4 Hz, 2H), 7.88 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 65.2, 80.6, 95.9, 117.9, 121.0, 122.3, 130.5, 133.1, 135.5, 136.7 ppm. HRMS (ES) calcd for $[C_{14}H_{14}N_2O + K]^+$ 265.0743, found 265.0732.

1-(4-Ethynylphenyl)-1*H*-imidazole (3e). The crude product was purified over a silica gel column with ethyl acetate/petroleum ether (1/1) to give a white solid (82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17 (s, 1H), 7.24 (br s, 1H), 7.31 (br s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.89 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.6, 82.3, 117.9, 121.1, 121.4, 130.9, 133.7, 135.5, 137.4 ppm. HRMS (ES) calcd for $[C_{11}H_8N_2 + K]^+$ 207.0325, found 207.0325.

Acknowledgment. This work was supported by grants from the National Natural Science Foundation of China (Nos. 20572074 and 20602027). We thank the Centre of Testing and Analysis, Sichuan University for NMR measurement.

Supporting Information Available: Detailed experimental procedures for the synthesis of *N*-arylazoles and characterizational NMR spectral data (^{1}H and ^{13}C) of *N*-arylazoles. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802669B