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LETTERS

An Efficient Copper-Catalyzed Coupling of Aryl Halides with Imidazoles

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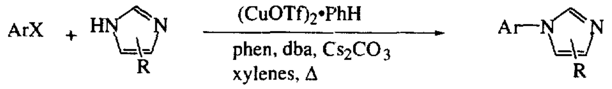
Abstract. Copper-catalyzed N-arylation of imidazoles can be accomplished using $(CuOTf)_2$•benzene as a copper source and Cs_2CO_3 as a base in xylenes at 110–125 °C. Addition of 1,10-phenanthroline (phen) and *trans,trans*-dibenzylideneacetone (dba) was crucial to the success of the process. The products, *N*-arylimidazoles, were isolated in high yields.

N-Arylimidazoles are important compounds, particularly in pharmaceutical research. A number of them have been reported to have significant biological activity as, e.g., thromboxane synthase inhibitors,[1a-c] cyclic AMP phosphodiesterase inhibitors,[1b,d-g] AMPA receptor antagonists,[1h] and antiglaucoma agents.[1i] As such, there is significant interest in developing efficient methods for their preparation.

The most straightforward routes to *N*-arylimidazoles involve the direct formation of the aryl–nitrogen bond. Two methods for constructing the C–N bond have been most commonly used: (1) nucleophilic aromatic substitution,[1a,d,e,h] and (2) Ullmann-type coupling of imidazoles with aryl halides.[1b,c,e,i,j] The former method requires that the aryl halide substrate possess strongly electron withdrawing substituents, which limits its scope. The reaction is performed in a polar solvent such as DMF or DMSO usually at high temperatures (>150 °C). The Ullmann protocol has a broader substrate scope with respect to the aryl halide. However, this copper-mediated or -catalyzed reaction also requires the use of high temperatures and polar solvents such as nitrobenzene, DMF, or *N*-methylpyrrolidone.[2]

We have recently reported a general method for Ullmann diaryl ether synthesis using $(CuOTf)_2$•benzene as the catalyst.[3] In view of this, we examined copper-catalyzed N-arylation of imidazoles and found that the coupling proceeds fairly smoothly in the presence of 1,10-phenanthroline (phen) and *trans,trans*-dibenzylideneacetone (dba) as additives, with $(CuOTf)_2$•benzene as a copper source and Cs_2CO_3 as a base, in xylenes at relatively low temperatures (110–125° C) (Eq. 1).[4] The results are shown in Table 1.



(1)

The reaction proceeds cleanly with little, if any, formation of arene or biaryl by-products. For combinations of aryl halides and imidazoles both lacking ortho-substituents, the *N*-arylimidazole is formed in

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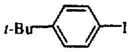
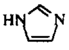
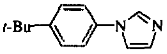
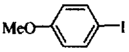
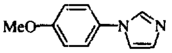
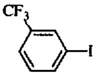
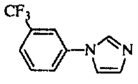
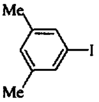
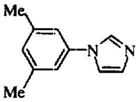
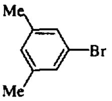
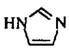
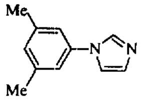
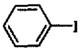
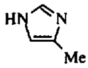
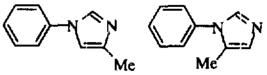
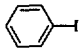
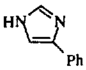
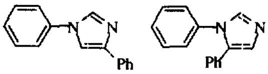
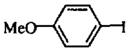
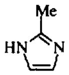
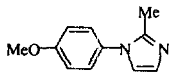
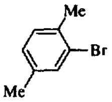
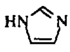
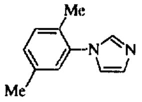
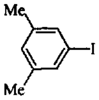
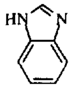
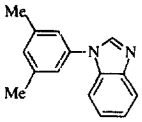
Table 1. N-Arylation of Imidazoles[a]

Entry	Aryl Halide	Imidazole	Product	Conditions[b]	Rxn Time (h)	Yield (%)[c]
1				A	24	97
2				A	24	96
3				A	24	94
4				A	30	96
5				A B	48 36	80 99
6				C	36	94[d]
7				A	36	93[e]
8				B	48	62[f]
9				B	48	79[g]
10				B	48	91

[a] Reactions were carried out with 2.0 mmol aryl halide, 3.0 mmol imidazole, 2.2 mmol Cs_2CO_3, 0.1 mmol $(CuOTf)_2$•PhH (0.2 mmol Cu), 2.0 mmol phen, 0.1 mmol dba, and xylenes. The volume of xylenes was either 0.8 mL or 0.4 mL. [b] Reaction temperatures and concentrations of aryl halide: A = 110 °C, 2.5 M; B = 125 °C, 5.0 M; C = 110 °C, 5.0 M. [c] Products were isolated by flash chromatography on silica gel. All yields reported are isolated yields (average of two or more runs) of compounds estimated to be >97% pure by ^1H NMR and GC analysis. All compounds were characterized by NMR (^1H, ^{13}C) and EI-MS. [d] The combined yield of the two regioisomers (ratio 4-substituted/5-substituted = 4.5/1) is shown. [e] The combined yield of the two regioisomers (ratio 4-substituted/5-substituted = 99/1) is shown. [f] The reaction proceeded to 65% conversion in 48 h. [g] The reaction proceeded to 80% conversion in 48 h.

nearly quantitative yield. As is usually the case with Ullmann-type coupling processes, the protocol works for both electron-rich and electron-poor aryl halides. Aryl iodides undergo coupling with imidazole at 110 °C and the reactions go to completion in 24–30 h, while the use of aryl bromides require a higher reaction temperature, a higher concentration of the substrates, and longer reaction times.

Substitution on either the imidazole or at the ortho position of the aryl halide slows the rate of the reaction. Thus, coupling of 2-bromo-*p*-xylene with imidazole at 125 °C at [ArBr] = 5 M gave the desired product in 79% yield after 48 h (entry 9), although the reaction did not go to completion. Reaction of 5-bromo-*m*-xylene gave a 99% yield of the corresponding *N*-arylimidazole in 36 h under the same reaction conditions (entry 5, condition B).

For 4-methylimidazole or 4-phenylimidazole, a mixture of 4- and 5-subsituted 1-arylimidazoles was obtained. In the former case a 4:1 mixture of the products was formed, whereas a 99:1 mixture of isomers was seen in the latter case. The major product was the 4-substituted isomer for both cases,[6] indicating that, as expected, the coupling occurred preferentially at the less hindered nitrogen atom.

The inclusion of a stoichiometric quantity of 1,10-phenanthroline is one key to the success of the process.[7] For example, the reaction of 5-bromo-*m*-xylene with imidazole in the presence of 1,10-phenanthroline at 125 °C provides the desired product in 99% yield after 36 h. In contrast, <10% *N*-arylimidazole was formed in the absence of 1,10-phenanthroline under similar conditions. As ligands are known to inhibit copper-assisted coupling reactions,[5,8] it is interesting that this reaction is promoted by adding a 10-fold excess of a chelating ligand (relative to the amount of copper). The reason for this rate enhancement is at present unclear. Possible explanations include these: (1) 1,10-phenanthroline prevents the aggregation of or improves the solubility of intermediate copper complexes; (2) decomposition of the catalyst is inhibited by 1,10-phenanthroline; (3) 1,10-phenanthroline prevents the multiple ligation of imidazoles to a single copper center, a process which might lead to the formation of inactive copper complexes. It was also found that the inclusion of 5 mol % of dba in the reaction mixture is also beneficial, significantly increasing the reproducibility of this reaction. The effect of dba was most obvious when the reaction was performed in an atmosphere of moist air. For example, the reaction of 5-bromo-*m*-xylene and imidazole under argon gave an 80% yield of product (entry 5, condition A). When the same reaction was carried out under ambient conditions, a good yield of product was obtained (67%) when 5 mol % of dba was included in the reaction mixture. However, in the absence of this additive, <5% of the desired product was formed.[9] Although copper species of different oxidation states (0, I, II) have been used as precatalysts for Ullmann type reactions, a copper(I) complex is most commonly invoked as the actual catalytic species.[5] Copper(I) complexes can be oxidized to copper(II) complexes or can undergo disproportionation to give copper(0) and copper(II) complexes. Thus, it is conceivable that dba is either preventing undesirable disproportionation or in some way stabilizing the catalytically active copper(I) species.

In conclusion, the copper-catalyzed N-arylation of imidazoles, using $(CuOTf)_2$•benzene as a copper source and Cs_2CO_3 as a base, has been demonstrated to be an efficient process. The products, *N*-arylimidazoles, were isolated in high yields using either aryl bromides or aryl iodides.

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(2) Avendaño et al. have reported that treating imidazole with (*p*-tolyl)Pb(OAc)$_3$ in the presence of a copper salt gives *N-p*-tolylimidazole in good yield: López-Alvarado, P.; Avendaño, C.; Menéndez, J. C. *J. Org. Chem.* **1995**, *60*, 5678–5682.

(3) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540.

(4) Representative Procedure: An oven-dried re-sealable Schlenk tube was charged with (CuOTf)$_2$•benzene (0.1 mmol), phen (2.0 mmol), dba (0.1 mmol) and Cs_2CO_3 (2.2 mmol), evacuated, and backfilled with argon. The flask was opened and charged with imidazole (3.0 mmol), 5-iodo-*m*-xylene (2.0 mmol), and xylenes (0.8 mL), while it was purged with argon. After the flask was sealed, the dark brown mixture was heated with stirring at 110 °C for 30 h. The mixture was then cooled to room temperature, and partitioned between CH_2Cl_2 (35 mL) and saturated aqueous NH_4Cl (5 mL). The organic layer was separated, washed with brine, and dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (1:4 hexanes–ethyl acetate eluant) to afford the desired product as a pale yellow oil in 96% yield.

All the reagents, including xylenes, were purchased from commercial sources and used without purification. Cs_2CO_3 (1.1 equiv) was employed as a base in this reaction and found to be superior to K_2CO_3 or K_3PO_4. Although 1.5 equiv of the imidazole was typically employed, an excess amount of the aryl halide could alternatively be used: 3.0 mmol of iodobenzene was coupled with 2.0 mmol of 4-phenylimidazole to give the desired products in 96% yield based on the imidazole. When the amount of iodobenzene was reduced to 2.0 mmol, an 86% yield was realized under the same conditions.

(5) Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456 and references therein.

(6) The synthesis and characterization of these 4-substituted imidazoles has been reported: (a) 4-methyl-1-phenylimidazole: see reference 1j. (b) 1,4-diphenylimidazole: Dodson, R. *J. Am Chem. Soc.* **1950**, *72*, 1478; Ali, A.; Saksena, R. K. *J. Indian Chem. Soc.* **1981**, *58*, 624–625.

(7) Use of pyridine-type ligands in copper-assisted nucleophilic substitution reactions has been reported. For example, see: Ito, T.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 419–423; Kondratov, S. A.; Shein, S. M. *Zh. Org. Khim.* **1979**, *15*, 2387–2390.

(8) Bacon, R. G. R.; Hill, H. A. O. *J. Chem. Soc.* **1964**, 1097.

(9) It is noteworthy that dba is completely consumed in the course of the reactions, although no products derived from dba could be detected by GC analysis of the reaction mixture. This resulted in products which were yellow- or orange-colored after chromatographic purification, although they were found to be pure by NMR, GC, and conbustion analysis. Decolorization of these was possible either by recrystallization or by distillation.