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Hypervalent Iodine in Synthesis 85: An Efficient Method for the Synthesis of *N*-Arylbenzimidazoles by the Copper-Catalyzed N-Arylation of Benzimidazole with Diaryliodonium Salts

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ABSTRACT: *N-arylbenzimidazoles were prepared in moderate yields by copper-catalyzed N-arylation of benzimidazole with diaryliodonium salts.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:617–619, 2002; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10043

INTRODUCTION

N-arylbenzimidazoles are important compounds particularly in pharmaceutical research because of their biological activities, such as spasmolytic activity [1]. The method for the preparation of *N*-arylbenzimidazoles mainly deals with the Ullmann coupling reaction, which requires harsh reaction conditions. Usually this coupling reaction is carried out in nitrobenzene [2] or pyridine [3] and very often gives low yields. Recently, other methods have also been developed, such as N-arylation of benzimidazole with aryllead triacetates [4], organobismuth reagents [5], arylboronic acids [6], or by nucleophilic aromatic substitution [7]. These methods also have some disadvantages, such as the use of toxic or inaccessible reagents, and limitation of substrates. Therefore, the development of an efficient and convenient method for the synthesis of *N*-arylbenzimidazoles is still in demand.

Recently, our research into synthetic applications of transition metal-catalyzed arylation reactions with diaryliodonium salts [8] showed that they are efficient arylation reagents. This prompted us to investigate copper-catalyzed N-arylation of benzimidazole to provide an efficient synthesis of *N*-arylbenzimidazoles. Here, we report a convenient method for the synthesis of *N*-arylbenzimidazoles by copper-catalyzed N-arylation of benzimidazole with diaryliodonium salts (Scheme 1).

RESULTS AND DISCUSSION

We found that N-arylation of benzimidazole with diaryliodonium salts could proceed smoothly in the presence of a copper catalyst at 80°C in DMF and gave *N*-arylbenzimidazoles in moderate yields. Among the tested copper catalysts, including CuI, $Cu(OAc)_2$, and $Cu(acac)_2$, CuI is the most effective although each of them can catalyze this reaction. Several diaryliodonium salts with various substituents, such as methyl, chloro, methoxy, bromo, and nitro groups were tested. It was found that the reaction is general for these substrates. The results are

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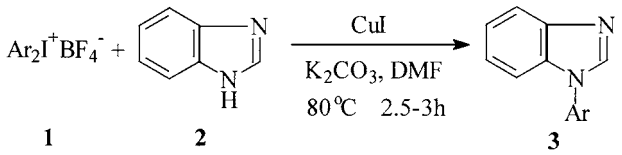

SCHEME 1

summarized in Table 1. All products gave satisfactory m.p., IR, and ^{1}H NMR spectra.

In summary, we provide a convenient synthesis for *N*-arylbenzimidazoles by copper-catalyzed N-arylation of benzimidazole with diaryliodonium salts. It has some advantages over the existing methods such as mild reaction conditions, simplicity of procedure, using nonpoisonous, accessible reagents, and reasonable yields.

EXPERIMENTAL

Melting points were uncorrected. ^{1}H NMR data were recorded on an Avance 400 spectrometer using $CDCl_3$ as the solvent with TMS as an internal standard. IR spectra were determined on a Vector 22 infrared spectrometer with KBr pellets. MS spectra were recorded on an HP5859B mass spectrometer. Elemental analyses were performed on an EA1110 instrument.

General Procedure for Preparation of N-Arylbenzimidazoles

A mixture of diaryliodonium salt **1** (1 mmol), benzimidazole **2** (1 mmol), K_2CO_3 (2 mmol), CuI (10 mol%), and DMF (5 ml) was stirred under a nitrogen atmosphere at 80°C or 2.5–3 h. After cooling, the reaction mixture was diluted with $CHCl_3$ (30 ml), and then aqueous H_2S (40 ml) was added, and the biphasic system was vigorously stirred for 1 h and filtered to remove the insoluble inorganic species. The $CHCl_3$ layer was washed with brine (2 × 40 ml), dried over anhydrous sodium sulfate and evaporated under a vacuum. The residue was chromatographed on a silica gel plate using cyclohexane/ethyl acetate (2:1) as a developer to give pure product.

TABLE 1 Copper-Catalyzed N-Arylation of Benzimidazole

Entry	*Iodonium Salt*	*Copper Catalyst*	*Product*	*Yield (%)*[a]
1	$Ph_2\ I^+BF_4^-$ (**1a**)	$Cu(OAc)_2$	**3a**	41
2	**1a**	$Cu(acac)_2$	**3a**	62
3	**1a**	CuI	**3a**	80
4	$(p\text{-Tol})_2\ I^+BF_4^-$ (**1b**)	CuI	**3b**	76
5	$(p\text{-}ClC_6H_4)_2 \times I^+BF_4^-$ (**1c**)	CuI	**3c**	68
6	$(p\text{-}CH_3OC_6H_4)_2 \times I^+BF_4^-$ (**1d**)	CuI	**3d**	71
7	$(p\text{-}BrC_6H_4)_2 \times I^+BF_4^-$ (**1e**)	CuI	**3e**	63
8	$(m\text{-}NO_2C_6H_4)_2 \times I^+BF_4^-$ (**1f**)	CuI	**3f**	54

[a] Yield of isolated pure product.

DATA OF PRODUCTS

N-Phenylbenzimidazole (**3a**): m.p. 92–94°C (lit. [2(b)], m.p. 95–96°C). ^{1}H NMR δ_H 7.36 (m, 2H), 7.49–7.61 (m, 6H), 7.91 (m, 1H), 8.25 (s, 1H). IR ν_{max} cm^{-1} 3070, 1600, 1500, 1455, 1293, 1228.

N-(4-Methylphenyl) benzimidazole (**3b**): oil (lit. [4], oil). ^{1}H NMR δ_H 2.47 (s, 3H), 7.39–7.44 (m, 6H), 7.53 (m, 1H), 7.95 (m, 1H), 8.42 (m, 1H). IR ν_{max} cm^{-1} 3060, 1520, 1485, 1455, 1290, 1230.

N-(4-Chlorophenyl) benzimidazole (**3c**): m.p. 89–91°C (lit. [9], m.p. 92°C). ^{1}H NMR δ_H7.36 (m, 2H), 7.49 (m, 3H), 7.56 (m, 2H), 7.90 (m, 1H), 8.16 (s, 1H). IR ν_{max} cm^{-1} 3095, 3033, 1597, 1507, 1455, 1300, 1235, 1092, 897, 731.

N-(4-Methoxyphenyl) benzimidazole (**3d**): m.p. 98–99°C (lit. [9], m.p. 99°C). ^{1}H NMR δ_H 3.89 (s, 3H), 7.07 (m, 2H), 7.34 (m, 2H), 7.41 (m, 2H), 7.46 (m, 1H), 7.88 (m, 1H), 8.09 (m, 1H). IR ν_{max} cm^{-1} 3065, 1515, 1487, 1457, 1290, 1245, 1211, 1030, 848, 750.

N-(4-Bromophenyl) benzimidazole (**3e**): m.p. 112–113°C. ^{1}H NMR δ_H 7.36 (m, 2H), 7.42 (m, 2H), 7.51 (1H), 7.71 (m, 2H), 7.89 (m, 1H), 8,11 (s, 1H). IR ν_{max} cm^{-1} 3053, 1590, 1498, 1457, 1315, 1291, 1231, 1208, 1071, 1012, 870, 841, 745. MS *m/z* 272 (M^+, 100), 274 (M^++2, 99.17). Anal. Calcd. for $C_{13}H_9BrN_2$: C 57.17, H 3.32, N. 10.25. Found: C 57.12, H 3.31, N 10.17%.

N-(3-Nitrophenyl) benzimidazole (**2f**): m.p. 148–150°C (lit. [3], 151–152°C). ^{1}H NMR δ_H 7.41 (m, 2H), 7.55 (m, 1H), 7.82 (m, 1H), 7.91 (m, 2H), 8.22 (s, 1H), 8.35 (m, 1H), 8.45 (m, 1H). IR ν_{max} cm^{-1} 3035, 1610, 1542, 1057, 1456, 1347, 1297, 1238, 1206, 1163, 894, 870, 812, 784, 734, 685.

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