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Efficient copper-catalyzed synthesis of 2-arylbenzimidazole derivatives by reaction of 1-fluoro-2-nitrobenzene with benzamidine hydrochlorides

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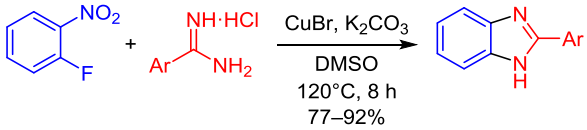


A novel and efficient approach to the preparation of 2-arylbenzimidazoles is described. Heating a mixture of 1-fluoro-2-nitrobenzene and benzamidine hydrochlorides in the presence of CuBr and K_2CO_3 in DMSO afforded 2-arylbenzimidazoles in good to excellent yields. The reaction was initiated by nucleophilic aromatic substitution and further proceeded by intramolecular nucleophilic copper-catalyzed cyclization reaction of benzamidine.

Keywords: 2-arylbenzimidazoles, benzamidine hydrochloride, 1-fluoro-2-nitrobenzene, copper-catalyzed reactions.

Benzimidazole is an important substructure found in a wide range of bioactive compounds and pharmaceuticals. This valuable heterocyclic nucleus also serves as a key intermediate in the synthesis of certain biologically active molecules (Fig. 1).[1] Benzimidazoles exhibit significant activities such as antimicrobial,[2] antitumor,[3a] analgesic and anti-inflammatory,[3b] can be used for treatment of interstitial cystitis,[4] as inhibitors of smooth muscle cell proliferation,[5] as well as in other areas of medicinal chemistry.[6] Also, the imidazole core is a common moiety in a large number of natural products and pharmacologically active compounds.[7]

This broad range of applications has motivated the development of new and efficient methods for the synthesis of 2-arylbenzimidazoles. Therefore, numerous synthetic routes have been reported in the literature for the preparation of benzimidazoles. The most common one involves the cyclization of benzene-1,2-diamine with carboxylic acids[8] or their derivatives under acidic conditions. Benzimidazoles can be also prepared by the coupling of aldehydes with benzene-1,2-diamine under oxidative conditions[9] or with 2-nitroanilines under reductive conditions.[10] The reduction of 2-nitroaniline derivatives has

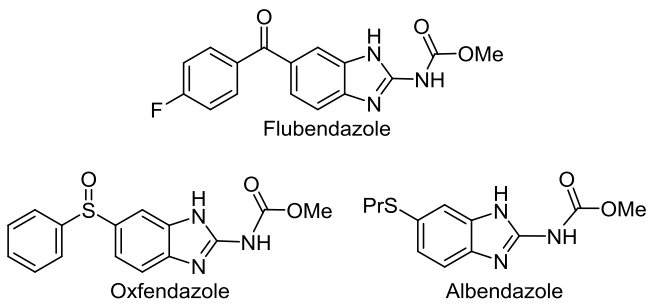


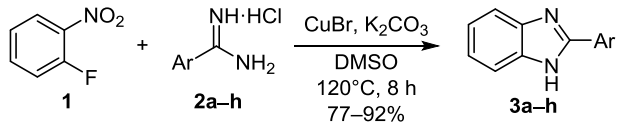
Figure 1. Biologically active benzimidazole derivatives.

been performed in the presence of iron powder, NH_4Cl, and formic acid, and also sodium dithionite and aldehydes.[11]

It has been shown that 1-fluoro-2-nitrobenzenes can undergo nucleophilic aromatic substitution (S_NAr) with aromatic primary amines to produce 2-nitrophenylamines under thermal conditions in powdered anhydrous KF[12,13] and also under microwave irradiation in the presence of KF/K_2CO_3.[14] Furthermore, Kim and Yu have reported palladium-assisted amination of 1-fluoro-2-nitrobenzene.[15] Accordingly, due to the several shortcomings of previous methods for the preparation of 2-nitroanilines, including the low to moderate yields, forcing reaction conditions, and prolonged reaction duration, we decided to present a new procedure for the preparation of substituted benzimidazoles starting from benzamidine hydrochloride *via* CuBr-catalyzed nucleophilic reaction involving NO_2 as the leaving group.

As part of our ongoing program toward developing new and efficient methods for the preparation of biologically active heterocyclic compounds from readily available molecules,[16] here we report a simple and efficient synthesis of benzimidazoles. While previous syntheses of benzimidazoles from 1-fluoro-2-nitrobenzene[17,18] were based on nitro group reduction, our method benefits from one-pot approach, and the nitro group acts as the leaving group. In the first step, we examined the heating of a mixture of 1-fluoro-2-nitrobenzene (**1**) and benzamidine hydrochlorides **2a**–**h** in the presence of CuBr and K_2CO_3 in DMSO. The initial results were satisfactory (Scheme 1). It should be noted that the reaction in the absence of CuBr catalyst did not lead to the product. Accordingly, in the next step we decided to broaden the scope of this reaction by optimizing the reaction conditions. To confirm the structure, the products were completely characterized by ^1H and ^{13}C NMR spectra.

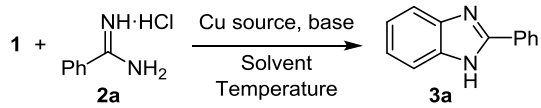
Scheme 1



a Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 4-$MeOC_6H_4$, **d** Ar = 4-HOC_6H_4, **e** Ar = 4-BrC_6H_4, **f** Ar = 4-ClC_6H_4, **g** Ar = 2-ClC_6H_4, **h** Ar = 4-$O_2NC_6H_4$

In order to optimize the reaction conditions, the synthesis of 2-phenyl-1*H*-benzimidazole (**3a**) was investigated as a model reaction. At first, we observed that heating a mixture of benzamidine hydrochloride and 2-nitrobenzaldehyde in the presence of CuI and K_2CO_3 in DMF as solvent at 80°C for 8 h led to the desired product **3a** in 74% yield (Table 1, entry 1). Afterwards, to evaluate the effect of reaction medium, several solvents such as DMSO, THF, toluene, and PEG 400 were investigated (entries 2–5). The best results were obtained in DMSO (82%, entry 2). Then, to choose the best base, the model reaction was examined with Cs_2CO_3, K_3PO_4, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (entries 6–8). As shown in Table 1, the best option was K_2CO_3, while other bases were less effective.

Table 1. Optimization of conditions for the synthesis of product **3a***



Entry	Cu source	Base	Solvent	Temperature, °C	Yield**, %
1	CuI	K_2CO_3	DMF	80	74
2	CuI	K_2CO_3	DMSO	80	82
3	CuI	K_2CO_3	THF	80	42
4	CuI	K_2CO_3	PhMe	80	No reaction
5	CuI	K_2CO_3	PEG 400***	80	24
6	CuI	Cs_2CO_3	DMSO	80	74
7	CuI	K_3PO_4	DMSO	80	47
8	CuI	DBU	DMSO	80	48
9	CuBr	K_2CO_3	DMSO	80	85
10	CuO	K_2CO_3	DMSO	80	18
11	Cu_2O	K_2CO_3	DMSO	80	38
12	$Cu(OAc)_2$	K_2CO_3	DMSO	80	22
13	**CuBr**	**K_2CO_3**	**DMSO**	**120**	**87**
14	CuBr	K_2CO_3	DMSO	60	73
15	CuBr	K_2CO_3	DMSO	25	18

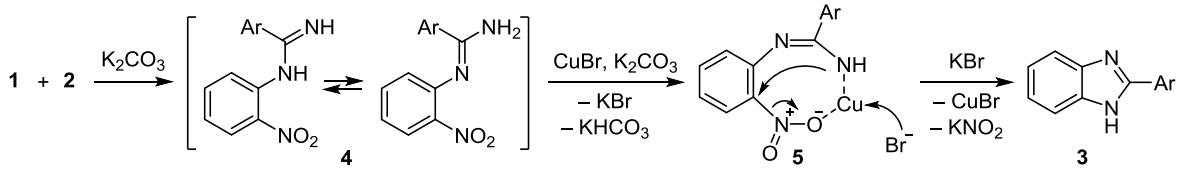
* Reaction conditions: 1-fluoro-2-nitrobenzene (**1**) (1.0 mmol), benzamidine hydrochloride (**2a**) (1.0 mmol), Cu source (0.2 mmol), base (2.0 mmol), solvent (3 ml), 8 h.
** Isolated yield.
*** PEG – polyethylene glycol.

Next, to find the best copper source, we observed that the use of CuBr significantly increased the yield of product **3a** (85%, entry 9), while CuO, Cu_2O, and $Cu(OAc)_2$ did not enhance the yield of the desired product **3a** (entries 10–12). Finally, to examine the effect of temperature, the model reaction was performed at different temperatures in the presence of CuBr and K_2CO_3 in DMSO (entries 13–15). The best yield of the product was obtained at 120°C (87%, entry 13).

Using the optimized conditions for the synthesis of 2-arylbenzimidazoles, we broadened the scope of this methodology by obtaining other derivatives. Aromatic benzamidine hydrochlorides containing electron-donating (Me, OMe, and OH) or electron-withdrawing (Br, Cl, and NO_2) groups provided the corresponding products **3a**–**h** in 77–92% yield (Scheme 1).

A suggested mechanism for the formation of 2-arylbenzimidazoles **3** is depicted in Scheme 2. At first, 1-fluoro-2-nitrobenzene (**1**) underwent nucleophilic aromatic substitution (S_NAr) by benzamidine hydrochloride **2** to produce *N*-arylbenzamidine **4**, which upon coordination with copper(I) species generated intermediate **5**. Intermediate **5** underwent intramolecular cyclization with the elimination of nitrite,[19] producing 2-arylbenzimidazoles **3** (Scheme 2).

Scheme 2



In the conclusion, we present an efficient method for the preparation of 2-arylbenzimidazole derivatives. This approach involves an S_NAr reaction of 1-fluoro-2-nitrobenzene with benzamidine hydrochloride derivatives in DMSO at 120°C in the presence of CuBr as the catalyst. The main advantages of this reaction include use of simple and readily available starting materials, easy workup procedure, and good to excellent product yields.

Experimental

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance 300 NMR spectrometer (300 and 75 MHz, respectively) for solutions in DMSO-d_6, using TMS as internal standard. Melting points were determined in capillaries and were not corrected. Merck silica gel 60 was used for preparative column chromatography.

All reagents, solvents, and materials were purchased from commercial suppliers and used without further purification.

Synthesis of benzimidazole derivatives 3a–h (General method). A mixture of 1-fluoro-2-nitrobenzene (**1**) (0.141 g, 1.0 mmol), the appropriate benzamidine hydrochloride **2a–h** (1.0 mmol), CuBr (0.029 g, 0.2 mmol), and K_2CO_3 (0.276 g, 2.0 mmol) in dry DMSO (3.0 ml) was heated in a round-bottom flask for 8 h at 120°C. After the reaction was complete (TLC), the mixture was cooled, quenched with water (20 ml), and extracted with EtOAc (3 × 20 ml). The extract was washed with 20% aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using petroleum ether – ethyl acetate, 4:1, as eluent to afford the pure products.

2-Phenyl-1*H*-benzimidazole (3a). Yield 0.17 g (87%), colorless solid, mp 282–284°C (mp 288–290°C[20]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.14–7.25 (2H, m, H Ar); 7.44–7.61 (5H, m, H Ar); 8.20 (2H, d, *J* = 7.2, H Ar); 12.94 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 122.1; 126.4; 128.4; 128.9; 129.2; 129.8; 130.1; 151.2.

2-(4-Methylphenyl)-1*H*-benzimidazole (3b). Yield 0.19 g (90%), colorless solid, mp 270–272°C (mp 271°C[21]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, CH_3); 7.15–7.20 (2H, m, H Ar); 7.33 (2H, d, *J* = 8.1, H Ar); 7.46–7.56 (2H, m, H Ar); 8.07 (2H, d, *J* = 8.1, H Ar); 12.84 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 20.9; 121.9; 126.3; 127.4; 128.4; 128.9; 129.4; 139.5; 151.3.

2-(4-Methoxyphenyl)-1*H*-benzimidazole (3c). Yield 0.21 g (92%), colorless solid, mp 216–218°C (mp 223–226°C[21]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.78 (3H, s, CH_3); 7.10 (2H, d, *J* = 8.8, H Ar); 7.16 (2H, dd, *J* = 3.1, H Ar); 7.50–7.56 (2H, m, H Ar); 8.12 (2H, d, *J* = 8.8, H Ar); 12.76 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 55.2; 111.0; 118.4; 121.5; 122.0; 122.6; 128.0; 151.3; 160.5.

2-(4-Hydroxyphenyl)-1*H*-benzimidazole (3d). Yield 0.16 g (77%), pale-yellow solid, mp 254–255°C (mp 256°C[22]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.93 (2H, dd, *J* = 8.5, *J* = 1.2, H Ar); 7.10–7.22 (2H, m, H Ar); 7.52–7.53 (2H, m, H Ar); 8.02 (2H, d, *J* = 8.6, H Ar); 10.07 (1H, s, H Ar); 12.65 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 111.4; 115.7; 121.0; 121.6; 122.5; 128.1; 151.8; 159.1.

2-(4-Bromophenyl)-1*H*-benzimidazole (3e). Yield 0.24 g (88%), colorless solid, mp 292–295°C (mp 299–300°C[23]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.22–7.24 (2H, m, H Ar); 7.50–7.70 (2H, m, H Ar); 7.97 (2H, d, *J* = 8.3, H Ar); 8.31 (2H, d, *J* = 8.3, H Ar); 13.17 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 111.8; 119.3; 122.2; 123.2; 126.9; 132.9; 134.2; 149.3.

2-(4-Chlorophenyl)-1*H*-benzimidazole (3f). Yield 0.19 g (85%), colorless solid, mp 292–293°C (mp 292–294°C[23]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.18–7.21 (2H, m, H Ar); 7.60–7.68 (4H, m, H Ar); 8.17 (2H, d, *J* = 8.6, H Ar); 12.99 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 111.4; 118.9; 121.9; 122.7; 128.1; 129.0; 134.5; 150.1.

2-(2-Chlorophenyl)-1*H*-benzimidazole (3g). Yield 0.19 g (83%), white crystals, mp 253–255°C (mp 233–234°C[23]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.25 (1H, s, H Ar); 7.27 (1H, s, H Ar); 7.57–7.52 (3H, m, H Ar); 7.67 (2H, dd, *J* = 8.4, *J* = 1.2, H Ar); 7.92 (1H, dd, *J* = 7.8, *J* = 1.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 127.9; 130.5; 130.8; 131.7; 132.1; 132.6; 149.6.

2-(4-Nitrophenyl)-1*H*-benzimidazole (3h). Yield 0.20 g (84%), yellow solid, mp 302–304°C (mp 303–304°C[20]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.23–7.27 (2H, m, H Ar); 7.63–7.65 (2H, m, H Ar); 8.36–8.65 (4H, m, H Ar); 13.26 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 119.3; 123.4; 124.1; 127.2; 129.6; 135.9; 147.6; 148.9.

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