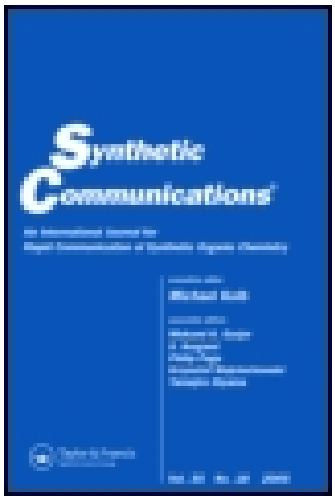

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CuBr-Catalyzed Oxidation/Coupling: An Efficient and Applicable Strategy for the Synthesis of 2-Aryl Benzimidazoles from 1-Fluoro-2-nitrobenzene and Benzylamines

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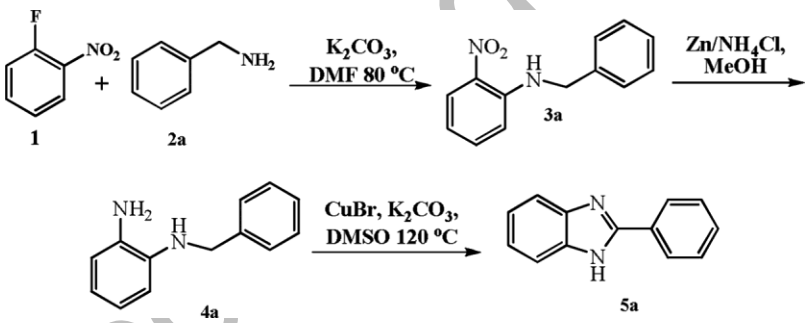
Abstract

A novel and efficient route has been developed for the synthesis of benzimidazole derivatives via ligand-free CuBr-catalyzed oxidation and cyclization of 1,2-diamines derived from 1-fluoro-2-nitrobenzene and different arylamines as starting materials.



KEYWORDS: CuBr; oxidation/coupling; benzimidazoles; 1-fluoro-2-nitrobenzene.

INTRODUCTION

Benzimidazole and its derivatives are a very interesting class of compounds due to their interesting biological activities and potential pharmaceutical applications in a large

number of pharmacological targets.[1,2] These nitrogen containing heterocycles were found to possess important biological activities such as antibacterial,[3-9] anticancer,[10,11] antidiabetic,[12] anthelmintic,[13] analgesic, anti-inflammatory,[14,15] and antioxidant[16] with substitution at various positions. Regarding to their pivotal pharmacological properties, great attention has been devoted to the synthesis of benzimidazole derivatives. The condensation of 1,2-phenylenediamine with carboxylic acids or their derivatives under strong acidic conditions and sometimes high temperature is the most common method to synthesis of benzimidazole derivatives.[17] The other synthetic route is the cyclo-dehydrogenation of aniline Schiff's bases, which generated from the condensation of 1,2-phenylenediamines and aldehydes,[18] follows by oxidation with different oxidants such as Oxone,[19] I_2:KI:K_2CO_3:H_2O,[20] $NaHSO_3$,[21] MnO_2,[22] applying hexafluorophosphoric acid under microwave condition,[23] and catalytic use of AlKIT-5.[24] Recently, copper-catalyzed N-arylation has been reported as an efficient strategy for the cross coupling and synthesis of N-heterocyclic compounds.[25-28]

Under these circumstances, this study was disclosed during the course of seeking for a more efficient catalytic system on the preparation of different catalyst supporting agents to synthesis of 2-Aryl Benzimidazoles. As part of our continuing efforts for the expeditious synthesis of biologically relevant heterocyclic compounds,[29,30] herein we describe an efficient and practical synthesis of benzimidazoles via copper-catalyzed oxidation and cyclization reaction of o-phenylenediamines derived from 1-fluoro-2-nitrobenzene and benzyl amines as starting materials.

RESULTS AND DISCUSSION

By virtue of the aforementioned advantages of benzimidazoles, the synthetic route to target compounds namely 2-aryl-1*H*-benzo[*d*]imidazole derivatives **5a-h** from 1-fluoro-2-nitrobenzene was studied (Scheme 1). Initially, the selective aromatic nuclephilic substitution reaction of 1-fluoro-2-nitrobenzene by a primary amine was carried out to obtain the corresponding o-nitroaniline. As known, the displacement of the substituent at 1-position is faster when the aromatic ring contains electron-withdrawing substituents at ortho or/and para positions.[31] To determine the best operative reaction condition, the later reaction was tried with benzylamine **2a** in various solvents and bases. The N-phenylmethyl-o-nitroaniline **3a** was obtained in excellent yields (> 90%) using K_2CO_3 at 80 °C and in DMF as solvent.[32] In the next step, the obtained o-nitroaniline was afforded to 2-N-phenylmethylaniline **4a** via treatment with Zinc and ammonium chloride (Zn-NH_4Cl) in methanol at room temperature within 8-15 min.[33] The work-up of the products and purification were simple and excellent yields were obtained (~95%).

In the last step of our designed synthesis, we investigated 2-N-phenylmethylaniline **4a** as the model substrate in the presence of CuBr, K_2CO_3, and DMSO, as catalyst, base, and solvent, respectively. The reaction was accomplished under air (1 atm) in order to synthesize 2-phenyl-1*H*-benzo[*d*]imidazole **5a** via the sequential copper-catalyzed aerobic oxidation, and an intramolecular nucleophilic addition process without the addition of any ligand and additive.[34]

After the optimization, we realized that CuBr (0.1 equiv) as catalyst with 3 equiv of K_2CO_3 (relative to amount of substrate) in DMSO as the solvent at 120 °C provided the highest yield (Table 1). Other bases such as Cs_2CO_3 and NaOAc were screened which K_2CO_3 showed the best activity.

To reveal the generality and utility of the protocol, various arylamines **2a-h** were subjected to the reaction with **1** according to the reaction conditions of Scheme 1 which the results are summarized in Table 2. Using this designed synthetic protocol, an array of arylamines **2a-h** having different substitutions reacted with **1** and the corresponding benzimidazoles **5a-h** were prepared in high yields 70-88%.

A possible mechanism for the preparation of benzimidazole derivatives is proposed in Scheme 2 owing to the obtained results. The reaction of 1-fluoro-2-nitrobenzene with benzyl amine leads o-nitroaniline **3a** which formed by the displacement of fluorine in quantitative yields in the presence of K_2CO_3 as base. Then the coupled nitroarene is reduced to **4a** using Zn–NH_4Cl (aq) as reducing agent. Then **4a** is converted to intermediate **6a** containing a C=N bond using copper-catalyzed aerobic oxidation reaction, and the intramolecular nucleophilic addition of the amino nitrogen to the C=N bond in **6a** leads to corresponding 2,3-dihydro-2-phenyl-1*H*-benzo[*d*]imidazole benzimidazoles **7a**. Afterward, the intermediate **7a** is converted to 2-phenyl-1*H*-benzo[*d*]imidazole **5a** using copper-catalyzed aerobic oxidation reaction. The interestingly, no ligand or additive is required in this reaction system.

The presented protocol for the synthesis of benzimidazole derivatives shows good potential as a method of choice for large-scale preparation of these scaffolds. To confirm this capability, the preparation of **5a** was scaled-up to provide multi-gram quantities of this compound (67% total yield).

CONCLUSION

In summary, we have introduced a simple and efficient method for the synthesis of 2-aryl substituted benzimidazole derivatives from 1-fluoro-2-nitrobenzene and aryl amines as starting materials in acceptable yields. This synthetic route utilizes cheap and readily available catalysts and starting materials, and also is an economical and environmentally friendly manner due to the usage of air as the oxidant. This protocol can be a useful example of constructing N-heterocycles via the coupling of 1-fluoro-2-nitrobenzene with different aryl amines, sequential aerobic oxidation, and intramolecular nucleophilic addition process under air. The mild reaction conditions, cost-effective, simple workup procedure and acceptable yields as well as the scope for using air as a green oxidant made our methodology a valuable contribution to the preparation of benzimidazole derivatives.

EXPERIMENTAL

Commercially available chemicals and solvents were purchased from Merck and Fluka chemical company and used without further purification. Melting points are measured with a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were run on a Bruker FT-250 using DMSO-d_6 and TMS as solvent and internal standard,

respectively. IR spectra were recorded on a Shimadzu 470 spectrophotometer (KBr disks).

General Procedure For Synthesis Of 2-Aminoaniline Derivatives 4a-H

To a stirred solution of 2-nitroaniline (1mmol) in MeOH and saturated NH_4Cl solution (4 ml, 1:1) was added zinc dust (10 mmol) portion-wise over 15 min at 0 C. completion of the reaction (TLC), the reaction mixture was filtered through Celite, and the MeOH waremoved under vacuo, then the aqueous residue was extracted with Et_2O. Next, the organic solvent was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography over silica gel.

General Procedure For Synthesis Of Benzimidazole Derivatives 5a-H

A solution of 2-aminoaniline **4a-h** (0.2 mmol), K_2CO_3 (0.6 mmol, 83 mg) and CuBr (0.02 mmol, 2.8 mg) in DMSO (2 mL) was provided. The mixture was allowed to stir under air (1atm) at 120 ℃ for 14 h. After completion of the reaction, the resulting solution was cooled to room temperature and filtered. Afterward, the filtrate was evaporated using a rotary evaporator. Then the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (3:1 to 2:1) as eluent to provide **5a-h**. All the products were identified and characterized by comparison of mp, IR, and ^{1}HNMR and ^{13}CNMR spectroscopy with those reported in literatures.[35]

Selected Data

2-Phenyl-1*H*-Benzimidazole (5a)

Colorless solid; mp 282-284 °C; IR (KBr); υ(cm^{-1}): 1620 (C=N); ^{1}H NMR (DMSO-d_6, 250 MHz): δ = 7.14–7.25 (m, 2 H), 7.44–7.61 (m, 5 H), 8.20 (d, *J* = 7.2 Hz, 2 H), 12.94 (s, 1 H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 122.1, 126.4, 128.4, 128.9, 129.2, 129.8, 130.1, 151.2.

2-(4-Chlorophenyl)-1*H*-Benzimidazole (5b)

Colorless solid; mp 292–293 °C; IR (KBr); υ(cm^{-1}): 1626 (C=N); ^{1}H NMR (DMSO-d_6, 250 MHz): δ = 7.18–7.21 (m, 2 H), 7.60 (m, 4 H), 8.17 (d, *J* = 8.6 Hz, 2 H), 12.99 (s, 1 H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 111.4, 118.9, 121.9, 122.7, 128.1, 129, 134.5 150.1.

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SUPPORTING INFORMATION

Full experimental details, ^{1}H and ^{13}C NMR spectra for this article can be accessed on the publisher's website.

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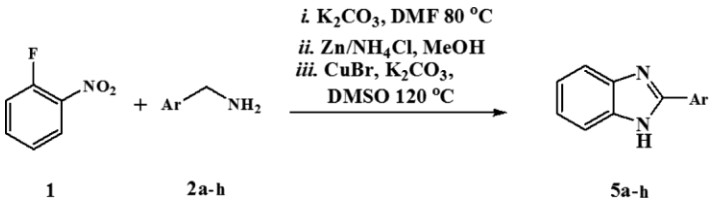
Table 1. The optimal reaction condition for the synthesis of benzimidazoles **5a.**

Entry	Base[a]	CuBr (equiv)	Solvent	Temp.(°C)	Time (h)	Yield (%)
1	K_2CO_3	___	DMSO	120	24	trace
2	K_2CO_3	0.1	DMSO	120	24	81
3	**K_2CO_3**	**0.1**	**DMSO**	**120**	**12**	**88**
4	K_2CO_3	0.2	DMSO	120	12	74
5	K_2CO_3	0.2	CH_3CN	80	12	25
6	K_2CO_3	0.2	DMF	100	12	34
7	Cs_2CO_3	0.1	DMSO	120	12	45
8	Cs_2CO_3	0.2	DMSO	120	12	63
9	NaOAc	0.1	DMSO	120	12	21
10	NaOAc	0.2	DMSO	120	12	18

[a](3 equiv)

Table 2. The synthesis of benzimidazoles **5a-h** from 1-fluoro-2-nitrobenzene and arylamines.

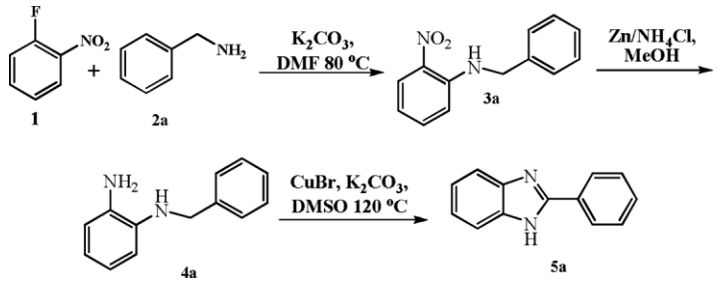


1 **2a-h** **5a-h**

Entry	**Ar-**	**Product**	**Yield (%)**[a]
1	Ph-	**4a**	88
2	4-Cl-Ph-	**4b**	73
3	4-CH_3-Ph-	**4c**	80
4	4-NO_2-Ph-	**4d**	81
5	4-MeO-Ph-	**4e**	71
6	2-Cl-Ph-	**4f**	70
7	4-OH-Ph-	**4g**	75
8	4-CN-Ph-	**4h**	77

[a] Isolated yields

Scheme 1. The synthesis route of 2-phenyl-1*H*-benzo[*d*]imidazole **5a.**



Scheme 2. The plausible mechanism for the synthesis of **5a.**