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Copper-Catalyzed Synthesis of 2-Unsubstituted, *N*-Substituted Benzimidazoles

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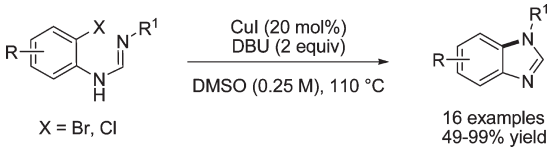
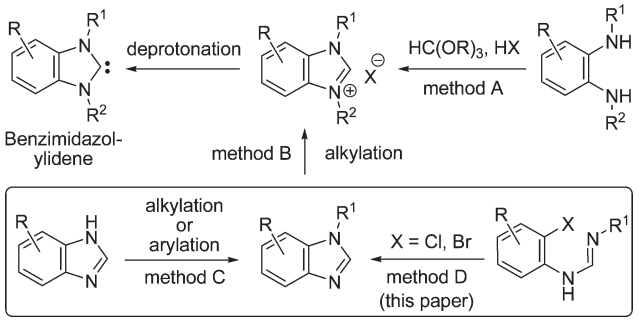


An efficient copper-catalyzed intramolecular arylation of formamidines forming 2-unsubstituted benzimidazoles in excellent yields is reported. Sixteen examples bearing sterically demanding substituents on nitrogen like Mes, 2,6-diisopropylphenyl, or 2-*tert*-butylphenyl and tolerating various functional groups demonstrate the utility of this method.

N-Heterocyclic carbenes (NHCs) have found widespread applications as organocatalysts[1,2] and as ligands in transition metal catalysis.[3,4] The success of NHCs is based on many attractive properties like extraordinary electron-richness, stability of metal−NHC complexes, and on their often large steric demand.[3] Consequently, the development of modular, highly efficient methods[5] for the synthesis of NHC-precursors is of great interest. Benzimidazolylidenes, most often prepared by deprotonation of 2-unsubstituted benzimidazolium salts, are an important class of NHCs and have been successfully utilized in organocatalytic processes[6,7] as well as in transition metal catalysis.[8] The required 2-unsubstituted benzimidazolium salts can be prepared either by cyclization of substituted 1,2-diaminoarenes with orthoformate as the C1-building block (method A, Scheme 1)[9] or, much more common,[10] by quaternization of the nitrogen atom of *N*-substituted benzimidazoles with alkyl electrophiles (method B).[11,12]

SCHEME 1. Representative Methods for the Synthesis of Benzimidazolium Salts



(1) For excellent reviews, see: (a) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (c) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534.

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(10) A Beilstein Crossfire search on the 30th of August 2009 revealed only 11 entries for the formation of benzimidazolium salts from substituted 1,2-diamino arenes, whereas the alkylation (including activated alkyl groups like benzyl or α-carbonyl) of benzimidazoles was found 322 times.

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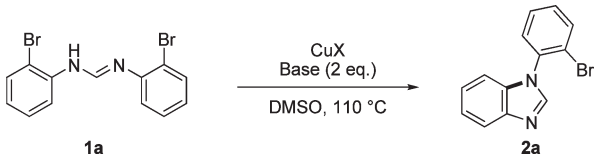
Several different methods for the synthesis of *N*-substituted benzimidazoles exist. Besides the *N*-alkylation or *N*-arylation[13] of benzimidazoles (method C), Pd- and Cu-catalyzed intramolecular cyclization reactions to 2-substituted benzimidazoles as reported by Brain et al. (2-methyl and 2-phenylbenzimidazoles)[14] and Batey and Evindar (2-aminobenzimidazoles)[15] as well as others[16,17] represent an important alternative; however, the latter methods were not described for 2-unsubstituted substrates.

The formation of 2-unsubstituted, *N*-substituted benzimidazoles with sterically demanding nitrogen substituents presents a severe present limitation, especially in the context of NHC preparation. The synthesis of the *N*-mesityl benzimidazole requires a multistep synthesis containing two sequential palladium-catalyzed amination steps.[7,18] Moreover, the installation of even more sterically hindered nitrogen substituents—interesting for catalytic applications of the corresponding benzimidazolylidenes—has not been previously reported.

In the course of our studies on the development of the copper-catalyzed heterocycle syntheses[19] and the establishment of general and modular methods rapidly providing NHC-precursors using formamidines,[5b,c] we have discovered an extraordinarily efficient method to install various aryl substituents on the nitrogen atom of benzimidazoles. Herein we report a copper-catalyzed intramolecular amination of formamidines, efficiently leading to 2-unsubstituted benzimidazoles (method D).

The cyclization of *N*,*N*′-bis(2-bromophenyl)formamidine (**1a**)[20] was selected for an optimization study (Table 1). Gratifyingly, the reaction was smoothly catalyzed employing 20 mol % of CuI and 2 equiv of DBU, yielding the desired benzimidazole quantitatively (entry 1). Reducing the catalyst loading to 10 mol % still provided the product in quantitative yield without significant loss of the reaction rate and even 1 mol % of catalyst could keep this excellent yield, albeit the reaction progress got slightly tardy (entries 2 and 3). The use of other copper(I) salts, CuBr and CuCl, gave comparable results (entries 4 and 5). However, a weaker amine base, diisopropylethylamine, was not capable of promoting the reaction efficiently and decomposition of the formamidine was observed (entry 6). On the other hand, a stronger base, KO*t*-Bu, caused partial protodebromination either of the starting material or of the product to give a normal benzimidazol (entry 7). A weaker inorganic base, K_2CO_3, gave the desired benzimidazole in 97% yield, albeit after slightly longer reaction time (entry 8). Obviously, this reaction does not require any external ligand for copper, although the formamidine might act as a ligand generating the active catalyst in situ.

TABLE 1. Optimization of the Reaction Conditions[a]



1a **2a**

entry	CuX (mol %)	base	time [h]	yield [%][b]
1	CuI (20)	DBU	1.3	99
2	CuI (10)	DBU	2.3	99
3	CuI (1)	DBU	6	98
4	CuBr (20)	DBU	1.25	97
5	CuCl (20)	DBU	1.6	98
6	CuI (20)	NEt(*i*-Pr)$_2$	293	29[c]
7	CuI (20)	KO*t*-Bu	3.3	57[d]
8	CuI (20)	K_2CO_3	4.5	97

[a]General procedure: formamidine **1a** (0.5 mmol), CuX, and base (2 equiv) were suspended in DMSO (2 mL). Base was added to the mixture and the reaction was stirred in a preheated oil bath at 110 °C. [b]Isolated yield. [c]Decomposition to 2-bromoaniline was observed. [d]Calculated based on the ^{1}H NMR spectrum after chromatography due to the inseparable debrominated benzimidazole.

Under the best conditions discovered,[21] the substrate scope of this method was evaluated (Table 2). No protodebrominated products were obtained in any case. First, symmetrical formamidines (**1a**−**e**,**o**,**p**) were employed.

A strongly electron-withdrawing CF_3 group was perfectly tolerated under these reaction conditions (**2b**). The substrates bearing a methyl group ortho to the coupling site reduced the reaction rate significantly, while the yields of the desired products were still excellent in both cases (**2c**,**d**). In addition, 2,6-disubstitution of the nucleophilic coupling partner did not disturb the desired amination at all (**2e**). Unsymmetrical formamidines (**1f**−**n**) were examined as well. *N*-Mesityl benzimidazole, which was utilized by Scheidt[7] as a precursor of a NHC catalyst, was obtained in 85% yield (**2f**). The variation on the annulated aromatic part was successfully accomplished and the *N*-mesityl benzimidazoles with alkyl- as well as bromo-substituents were synthesized in quantitative yields (**2g**,**h**). Other 2,6-disubstituted aromatic rings such as a 2,6-diisopropylphenyl or a 9-anthracenyl group were installed on the nitrogen atom in high yields as well (**2i**,**j**). Surprisingly and gratifyingly, the 2-*tert*-butylphenyl group could also be incorporated into the benzimidazole scaffold in 85% yield, albeit the reaction was slower (**2k**). Moreover, the pentabromo benzimidazole **2*l*** was formed in 93% yield without loss of any bromine atom. The formamidine

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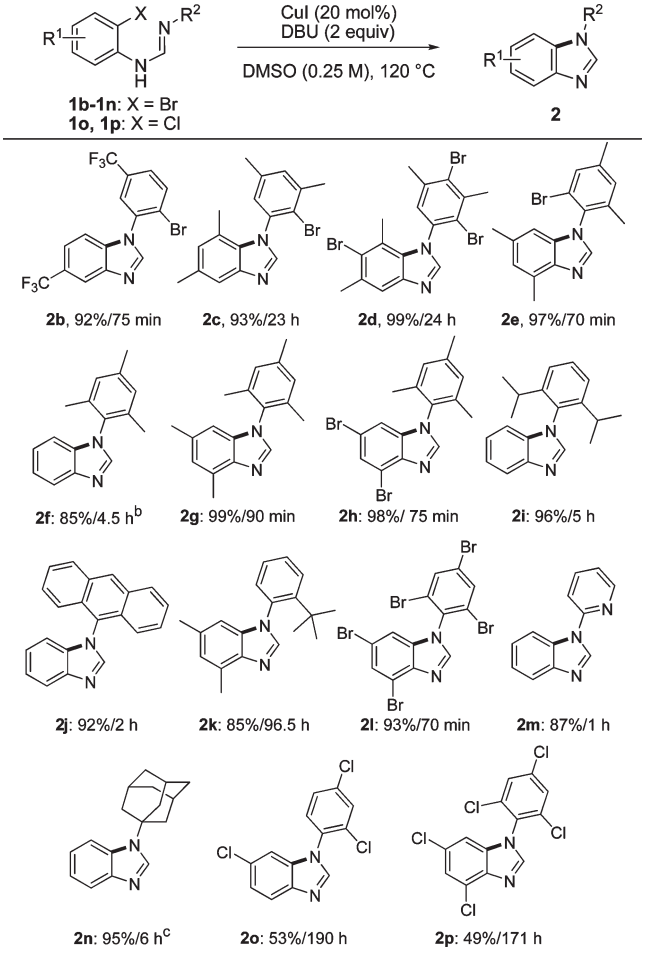
(20) Amidine **1a** was formed in 75% yield from commercially available substrates. See the Supporting Information for further details.

(21) For convenience, 20 mol % of CuI was used under standard conditions. See the Supporting Information for further details.

TABLE 2. Substrate Scope[a]



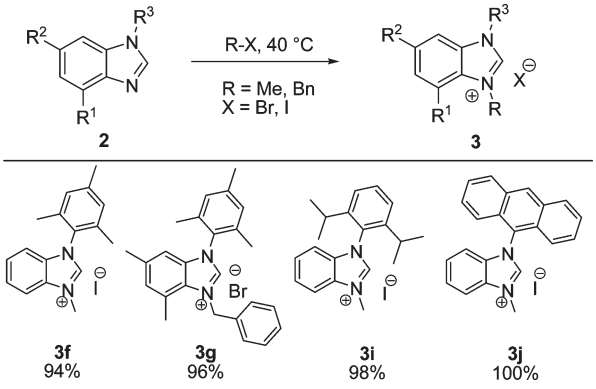
[a]General procedure: formamidine (1 equiv) and CuI (20 mol %) were suspended in DMSO (0.25 M). DBU (2 equiv) was added and the mixture was stirred in a preheated oil bath at 110 °C. Isolated yields are given. [b]On a 20 mmol scale, the same yield was obtained. [c]140 °C.

with a 2-pyridyl substituent did not cause any catalyst poisoning and afforded the desired benzimidazole **2m** in high yield. To prove the utility of this method an *N*-adamantyl-*N*′-2-bromophenylformamidine was also examined in this reaction. The formation of the *N*-adamantyl benzimidazole **2n** was realized by elevation of the reaction temperature to 140 °C. Moreover, this method is applicable also to chlorinated formamidines, but distinctly longer reaction times were required and partial decomposition of the starting materials was observed.[21]

Due to the synthetic versatility of the 2-unsubstituted benzimidazoles, the simple manipulation of their structures leads to valuable compounds for catalytic applications. In the context of our general interest in the synthesis of new NHC architectures, we have carried out the *N*-alkylation of benzimidazoles **2** leading to the formation of the corresponding benzimidazolium salt **3** in quantitative yield (Scheme 2). The protocol presented herein represents an efficient and straightforward method for the synthesis of benzimidazolium salts in three steps from the corresponding aromatic amines.

In conclusion, a highly efficient copper-catalyzed synthesis of *N*-substituted benzimidazoles is reported. This unprecedented method provides rapid access especially to benzimidazoles with sterically demanding aromatic groups on the nitrogen

SCHEME 2. Synthesis of Benzimidazolium Salts



atom and compares favorably with known procedures. The application of these benzimidazole derivatives in catalysis is ongoing in our laboratories.[22]

Experimental Section

Procedure for the Synthesis of 1-(2-Bromophenyl)-1*H*-benzoimidazole (2a). Formamidine **1a** (177 mg, 0.50 mmol, 1 equiv) was solved in 2 mL of DMSO. CuI (19.0 mg, 0.1 mmol, 20 mol %) and DBU (149.3 μL, 152 mg, 1.0 mmol, 2 equiv) were added and the reaction was stirred for 1 h and 20 min at 110 °C. H_2O (20 mL) and EtOAc (20 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layers were treated with brine and dried over Na_2SO_4. The purification by column chromatography (i.d. 2 cm, SiO_2: 14 cm, *n*-pentane/EtOAc 3:1) yielded the benzimidazole **2a** as a colorless oil (135 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H, NCHN), 7.89 (dd, J = 7.2, 1.1 Hz, 1H, Ar−H), 7.81 (dd, J = 8.0, 1.3 Hz, 1H, Ar−H), 7.54−7.48 (m, 1H, Ar−H), 7.45 (dd, J = 7.9, 1.8 Hz, 1H, Ar−H), 7.43−7.38 (m, 1H, Ar−H), 7.37−7.28 (m, 2H, 2 × Ar−H), 7.21−7.17 (m, 1H, Ar−H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 142.9, 135.1, 134.3, 134.2, 130.6, 129.1, 128.6, 123.7, 122.7, 121.4, 120.4, 110.5. IR (ATR): ν/cm^{-1} 3061, 1731, 1614, 1587, 1493, 1454, 1306, 1288, 1260, 1230, 1203, 1158, 1142, 1056, 1030, 1007, 977, 889, 865, 786, 743, 716, 654, 634, 581, 553, 535. R_f (*n*-pentane/EtOAc 1:1): 0.29. MS (GC-MS): m/z (%) 272 (100), 193 (86), 155 (5), 77 (5), 76 (18). EM (ESI): m/z [M + H$^+$] calcd for $C_{13}H_{10}BrN_2$ 273.0022, found 273.0028. Elemental Anal. Calcd for $C_{13}H_9BrN_2$ (273.13): C 57.17, H 3.32, N 10.26. Found: C 57.27, H 3.26, N 10.04.

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Supporting Information Available: General experimental methods and full characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(22) Very recently, a related paper on the 'Synthesis of 1-Substituted Benzimidazoles from *o*-Bromophenyl Isocyanide and Amines' appeared: Lygin, A. V.; de Meijere, A. *Eur. J. Org. Chem.* **2009**, 5138−5141.