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Synthesis of 1-Substituted Benzimidazoles from *o*-Bromophenyl Isocyanide and Amines

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Dedicated to Professor Ytzhak Apeloig on the occasion of his 65th birthday

Keywords: Isocyanides / Copper / Homogeneous catalysis / Benzimidazoles / Cyclization

o-Bromophenyl isocyanide (**1**-Br) reacts with various primary amines under Cu^I catalysis to afford 1-substituted benzimidazoles **4** in moderate to good yields (38–70 %, 13 examples). Analogously, 2-bromo-3-isocyanothiophene (**6**) furnishes 3-substituted 3*H*-thieno[2,3-*d*]imidazoles **7** (44–49 %, 3 examples).

Introduction

Compounds containing a benzimidazole core cover a wide range of biological activities and therefore represent "privileged" structures having a significant importance in medicinal chemistry.[1] In fact, certain compounds of this sort with high activity against Hepatitis B and C viruses have been identified,[2] others have been found to be potent lymphocyte-specific kinase (Lck) inhibitors,[3] nonpeptide thrombin inhibitors,[4] and antiallergic agents.[5]

The classical construction of the five-membered heterocycle in benzimidazoles involves the reaction of an *o*-phenylenediamine with a carboxylic acid or one of its equivalents under harsh dehydrating conditions.[6] Alternatively, several transition-metal-catalyzed syntheses of benzimidazoles and related systems have been reported recently.[7] The following precursors have been typically used so far: 2-haloacetanilides, *N*-substituted amidines, *N*-substituted *N*′-(2-halophenyl)amidines and -guanidines, *N*-substituted *N*′-(2-halophenyl)ureas and -thioureas to give the corresponding 2-substituted benzimidazoles. We envisaged, that a different convenient access to 2-*unsubstituted* benzimidazoles, which remained elusive so far, could start from primary amines and *ortho*-haloaryl isocyanides, which have already shown their versatility as building blocks for various other heterocycles.[8] Isocyanides are known to react with amines in the presence of copper[9] as well as other metal salts[10] to form amidines in excellent yields. Amidines formed from *ortho*-haloaryl isocyanides in such a way ought to be able to undergo an intramolecular copper-catalyzed *N*-arylation[11] to furnish benzimidazoles. As both steps require the same type of catalyst, one ought to be able to perform them sequentially in a one-pot operation. This process would provide synthetically useful 2-unsubstituted benzimidazoles, which can be further elaborated by attaching various substituents at the 2-position, e.g. by means of lithiation/electrophilic substitution[12] or transition-metal-catalyzed C–H activation[13] as well as cross-coupling reactions[14] of the easily accessible corresponding 2-halobenzimidazoles.[15]

Results and Discussion

The reaction of *o*-bromophenyl isocyanide (**1**-Br) and benzylamine (**2a**) was chosen as a model system for the optimization of reaction conditions (Table 1). Cesium carbonate was found to be the best base, giving higher yields of 1-benzylbenzimidazole (**4a**) than potassium carbonate (Entry 3), potassium phosphate (Entry 1), lithium or potassium *tert*-butoxides (Entries 4 and 5, respectively) and triethylamine (Entry 6).

With the latter, the formamidine **3a** (52 %) was isolated as the main product along with the benzimidazole **4a** in low yield (11 %). Formation of **3a** was also observed in other cases, in which **4a** was obtained in low yields. This indicates that the initially proposed sequence of an α-addition of the amine to the isocyanide and subsequent intramolecular amination is operational, and apparently the second step is more affected by the conditions used. Dimethylformamide turned out to be the solvent of choice, as the reaction in other solvents (DME, dioxane, toluene, DMSO) afforded **4a** in lower yields (Entries 7–10). Various ligands **L1**–**L9**

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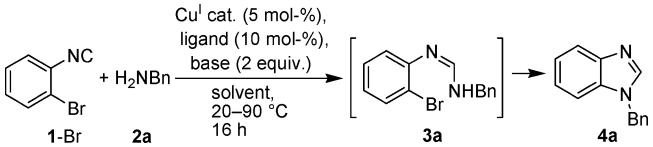
Table 1. Optimization of the reaction conditions for the synthesis of 1-benzylbenzimidazole (**4a**).



Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[a]
1	CuI	**L1**	K_3PO_4	DMF	56
2	CuI	**L1**	Cs_2CO_3	DMF	68
3	CuI	**L1**	K_2CO_3	DMF	27
4	CuI	**L1**	LiO*t*Bu	DMF	58
5	CuI	**L1**	KO*t*Bu	DMF	36
6	CuI	**L1**	Et_3N	DMF	11[b]
7	CuI	**L1**	Cs_2CO_3	DME	54
8	CuI	**L1**	Cs_2CO_3	dioxane	37
9	CuI	**L1**	Cs_2CO_3	toluene	14
10	CuI	**L1**	Cs_2CO_3	DMSO	42
11	CuI	**L2**	Cs_2CO_3	DMF	56
12	CuI	**L3**	Cs_2CO_3	DMF	49
13	CuI	none	Cs_2CO_3	DMF	38
14	CuI	**L4**	Cs_2CO_3	DMF	65
15	CuI	**L5**	Cs_2CO_3	DMF	58
16	CuI	**L6**	Cs_2CO_3	DMF	59
17	CuI	**L7**	Cs_2CO_3	DMF	40
18	CuI	**L8**	Cs_2CO_3	DMF	57
19	CuI	**L9**	Cs_2CO_3	DMF	32
20	CuBr	**L1**	Cs_2CO_3	DMF	70
21	Cu_2O	**L1**	Cs_2CO_3	DMF	26

[a] Yield of isolated product **4a**. [b] In addition, the intermediate **3a** was also isolated in 58% yield.

(Figure 1), usually employed in copper-catalyzed arylations of amines, have been tested. 1,10-Phenanthroline (**L1**) and 2-phenylphenol (**L4**) furnished the best results (68 and 65% yield of **4a**, Entries 2 and 14, respectively), although the ligand effect was not as significant as one would have imagined.

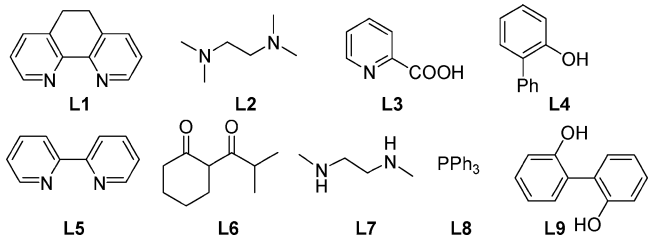
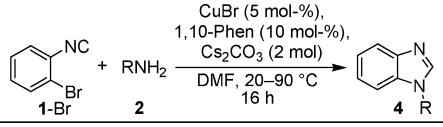


Figure 1. Ligands tested for the synthesis of **4a** (see Table 1).

Replacement of CuI by CuBr slightly improved the yield of **4a** (68 vs. 70%, Entries 2 and 20), whereas Cu_2O was far less effective (Entry 21). Different ways of adding reagents to the reaction mixture as well as temperature conditions have been tested. Thus, when a solution of benzylamine **2a** and **1**-Br was slowly added at 90 °C to the mixture of the other reagents, no benzimidazole **4a** was formed at all. By carrying out the operation first at room temp. within 2 h, then gradually (within 30 min) warming the mixture to 90 °C, and then keeping it at the same temperature for 14 h, gave the best yields of **4a**. Other *o*-halophenyl isocyanides were also tested towards the same transformation. *o*-Chlorophenyl isocyanide (**1**-Cl) did not provide the corresponding benzimidazole neither under the best conditions found for **1**-Br nor at increased temperatures up to 140 °C. *o*-Iodophenyl isocyanide (**1**-I) with benzylamine **2a**, on the contrary, furnished benzimidazole **4a** even at 50 °C, but in 22% yield only. The conditions optimized for **1**-Br (90 °C)

Table 2. Synthesis of *N*-substituted benzimidazoles **4**; 1,10-Phen = 1,10-phenanthroline.



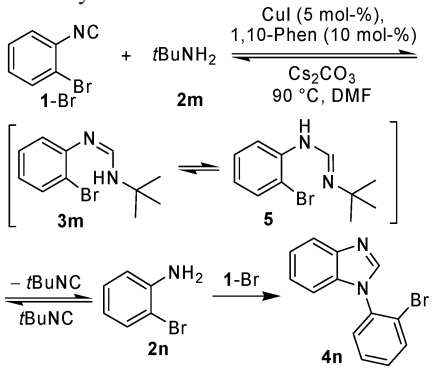
Entry	RNH_2	Product	Yield (%)[a]
1	**2a**	**4a** (Bn)	70
2	**2b**	**4b** (*n*Pr)	65
3	**2c**	**4c** ($(CH_2)_3OBn$)	66
4	**2d**	**4d**	59
5	**2e**	**4e**	42
6	**2f**	**4f** (2-$MeOC_6H_4$)	67
7	**2g**	**4g** (3,5-$(MeO)_2C_6H_3$)	65
8	**2h**	**4h** (2-furyl)	46
9	**2i**	**4i** (4-$F_3CC_6H_4$)	55
10	**2j**	**4j** (*c*Pr)	40
11	**2k**	**4k** (*c*Hex)	46
12	**2l**	**4l** (*p*Tol)	41
13	**2m**	**4n** (*o*-Br-C_6H_4)	38[b]

[a] Yield of isolated product. [b] Only the depicted product **4n** was isolated and identified.

applied to **1**-I, gave **4a** in 40% yield. Accordingly, it was not considered meaningful to test other temperatures for **1**-I, and work was focused on the use of **1**-Br for the synthesis of benzimidazoles **4**. By employing the optimized conditions for **4a**, various *N*-substituted benzimidazoles **4b**–**l** have been synthesized from *o*-bromophenyl isocyanide (**1**-Br) and primary amines **2b**–**l** (Table 2).

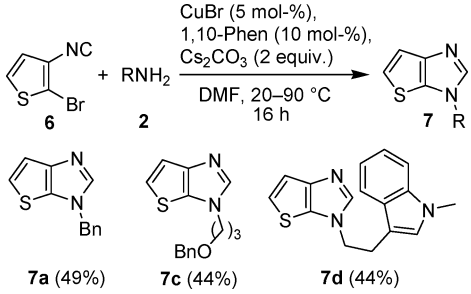
n-Alkylamines and benzylamines in general gave slightly better yields of benzimidazoles **4** than *sec*-alkylamines like cyclopropylamine and cyclohexylamine (Entries 10 and 11, respectively), whereas 2-methoxybenzylamine with an *ortho* substituent still afforded the corresponding benzimidazole **4f** in 65% yield (Entry 6). Amines with decreased nucleophilicity, such as 4-(trifluoromethyl)benzylamine and 4-methylaniline (Entries 9 and 12), furnished the corresponding benzimidazoles in slightly lower yields (55, 40%, respectively). The twofold reaction of ethylenediamine with **1**-Br afforded the 1,2-bis(benzimidazolyl)ethane **4e** in 42% yield (Entry 5). The reaction of *o*-bromophenyl isocyanide (**1**-Br) with *tert*-butylamine (**2m**) surprisingly did not provide *N*-(*tert*-butyl)benzimidazole (**4m**) at all. The major product, isolated in 38% yield, was identified as 1-(2-bromophenyl)-benzimidazole (**4n**).

The formation of **4n** (Scheme 1) can be rationalized by assuming a reversible addition of *tert*-butylamine onto the isocyano group of **1**-Br. Similar reversible additions of *N*-unsubstituted indoles onto aryl isocyanides have previously been observed in a ruthenium-catalyzed formation of indoles.[16] The corresponding formamidine **3m**, due to its bulky *tert*-butyl group, does not undergo cyclization to the *N*-(*tert*-butyl)benzimidazole (**4m**), but equilibrates under the basic reaction conditions with its tautomer, the formamidine **5**, which would reversibly release *tert*-butyl isocyanide and form *o*-bromoaniline (**2n**). The latter would react with *o*-bromophenyl isocyanide (**1**-Br), still existing in the reaction mixture, just as 4-methylaniline does (see Table 2, Entry 12), irreversibly forming benzimidazole **4n**. In a control experiment, the reaction of **1**-Br with *o*-bromoaniline (**2n**) under the same conditions also provided the benzimidazole **4n** in 42% yield.[17]



Scheme 1. Proposed mechanism for the formation of the benzimidazole **4n**; 1,10-Phen = 1,10-phenanthroline.

To broaden the scope of the new method, 2-bromo-3-isocyanothiophene (**6**) was employed in the copper-catalyzed reaction with amines. Indeed, the three examples **7a**, **7c** and **7d** of the less common 3-substituted 3*H*-thieno[2,3-*d*]imidazoles **7** (Scheme 2) were isolated, albeit in slightly lower yields (49, 44 and 44%, respectively) than the corresponding benzimidazoles.



Scheme 2. Synthesis of 3-substituted 3*H*-thieno[2,3-*d*]imidazoles **7**; 1,10-Phen = 1,10-phenanthroline.

Conclusions

A novel copper-catalyzed synthesis of benzimidazoles from *o*-bromoaryl isocyanides and primary amines has been developed. This new sequential reaction consisting of a copper-catalyzed addition of an amine onto an isocyano group followed by a copper-catalyzed intramolecular arylation of a thus formed amidine provides a convenient access to 1-substituted benzimidazoles **4** and related 3-substituted 3*H*-thieno[2,3-*d*]imidazoles **7** in moderate to good yields.

Experimental Section

General Remarks: NMR (^{1}H, ^{13}C) spectra were recorded at 300 (^{1}H) and 75.5 [^{13}C, APT (Attached Proton Test)] with a Varian Unity-300 instrument for DMSO[D_6] or $CDCl_3$ (with tetramethylsilane) solutions. TLC: Macherey–Nagel, TLC plates Alugram® Sil G/UV254; detection under UV light at 254 nm or development with MOPS reagent (10% solution of molybdophosphoric acid in ethanol). Chromatography: Separations were carried out on Merck Silica 60 (0.063–0.200 mm, 70–230 mesh ASTM). IR: Measured as KBr pellets or as films between KBr plates. MS: EI-MS: Finnigan MAT 95, 70 eV; DCI-MS: Finnigan MAT 95, 200 eV, reactant gas NH_3; ESI-MS: Finnigan LCQ; High-resolution mass spectrometry (HRMS): APEX IV 7T FTICR, Bruker Daltonic. M.p.: Büchi 540 capillary melting point apparatus, values are uncorrected. Starting materials: [3-(benzyloxy)propyl]amine[18] was prepared according to a literature procedure. All other chemicals were used as commercially available.

General Procedure for the Synthesis of *N*-Substituted Benzimidazoles (GP): In a 10-mL Schlenk flask were placed 2-bromophenyl isocyanide (364 mg, 2 mmol), cesium carbonate (652 mg, 4 mmol), CuBr (14.4 mg, 5 mol-%), 1,10-phenanthroline (36 mg, 10 mol-%) and the respective amine (if solid). The flask was sealed with a rubber septum, evacuated and refilled with dry nitrogen three times. Anhydrous degassed DMF (or a solution of a respective liquid amine in DMF) was introduced to the flask from a syringe. The septum was replaced with a glass stopper. The mixture was stirred at room temp. for 2 h, then warmed to 90 °C for ca. 30 min and stirred at this temperature for 14 h. After this time, the mixture was cooled, and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and water (60 and 15 mL, respectively), the

aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic phases were washed with brine, dried with Na_2SO_4 and concentrated to give a crude product, which was purified by flash chromatography on silica gel.

1-Benzyl-1*H*-benzo[*d*]imidazole (4a):[19] Compound **4a** (283 mg, 68%) was obtained from 2-bromophenyl isocyanide (**1**-Br) (364 mg, 2 mmol) and benzylamine (**2a**) (214 mg, 2 mmol) according to the GP, after column chromatography (CH_2Cl_2/MeOH, 20:1; R_f = 0.27) as a colorless solid, m.p. 115–116 °C (ref.[19] 116–117 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (s, 1 H, N=CH), 7.83 (d, J = 7.2 Hz, 1 H, Ar-H), 7.35–7.21 (m, 6 H, Ar-H), 7.16 (m, 2 H, Ar-H), 5.32 (s, 2 H, CH_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 144.2 (C), 135.4 (CH), 128.9 (CH), 128.5 (C), 128.2 (CH), 127.4 (C), 127.0 (CH), 123.0 (CH), 122.0 (CH), 120.4 (CH), 110.0 (CH), 48.7 (CH_2) ppm. MS (70 eV, EI): *m*/*z* (%) = 208.1 (74) [M$^+$], 91.1 (100). IR (KBr): $\tilde{\nu}$ = 3010, 2943, 2154, 1609, 1466, 1184, 1076, 753, 720, 694 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{13}N_2^+$ [M + H$^+$] 209.10732; found 209.10730.

3-Benzyl-3*H*-thieno[2,3-*d*]imidazole (7a): Compound **7a** (210 mg, 49%) was obtained from 2-bromo-3-isocyanothiophene (**6**) (376 mg, 2 mmol) and benzylamine (**2a**) (214 mg, 2 mmol) according to the GP, after column chromatography (CH_2Cl_2/MeOH, 40:1; R_f = 0.30) as a colorless solid, m.p. 102–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (s, 1 H, NCH), 7.36 (m, 3 H, Ph), 7.27 (m, 2 H, Ph), 7.12 (d, J = 5.3 Hz, 1 H, thienyl-H), 6.92 (d, J = 5.3 Hz, 1 H, thienyl-H), 5.19 (s, 2 H, CH_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 148.7 (C), 141.8 (CH), 134.1 (C), 131.6 (C), 129.0 (CH), 128.7 (CH), 128.1 (CH), 120.7 (CH), 116.6 (CH), 51.2 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 1635, 1516, 1456, 1436, 1392, 1354, 1252, 1188, 1092, 1035, 907, 734 cm^{-1}. MS (EI): *m*/*z* (%) = 214.2 (44) [M$^+$], 91.1 (100). HRMS (ESI): calcd. for $C_{12}H_{11}N_2S$ [M + H$^+$] 215.06375; found 215.06369.

Supporting Information (see footnote on the first page of this article): Experimental details for all prepared compounds and copies of ^{1}H and ^{13}C NMR spectra.

Acknowledgments

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