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A practical synthesis of 2-(*N*-substituted)-aminobenzimidazoles utilizing CuCl-promoted intramolecular cyclization of *N*-(2-aminoaryl)thioureas

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Abstract—A practical protocol for synthesis of 2-(*N*-substituted)-aminobenzimidazoles was developed. *N*-(2-Aminoaryl)thioureas undergo a CuCl-promoted intramolecular cyclization to give the corresponding 2-(*N*-substituted amino)benzimidazoles in good to excellent isolated yields.

2-(*N*-substituted)-aminobenzimidazoles are widely used structural motifs in drug discovery and represent the core structure for a variety of biologically significant molecules.[1] A considerable number of synthetic methodologies have been reported for the synthesis of unsubstituted 2-aminobenzimidazoles. However, there are a very limited number of methods for the preparation of 2-(*N*-substituted)-amino derivatives. The most widely used approach is oxidation–cyclization of *N*-(2-aminoaryl)thioureas with highly toxic mercury(II) oxide in absolute ethanol.[2,3] In connection with a drug discovery program, we recently required an efficient entry into a new class of potent inhibitors of the tyrosine kinase p56lck, exemplified by **1** and **2** (Fig. 1).[4] We were particularly interested in the practical synthesis of 2-(*N*-substituted)-aminobenzimidazole moieties from their corresponding *N*-(2-aminoaryl)thioureas since the currently available methods using HgO and dehydration conditions, such as DCC, are impractical for a large scale preparation. Furthermore, cyclocondensation of diamines with 2,6-dichlorophenylcarbonimidoyl dichloride was found to be inefficient to **1** and **2** due to the reduced reactivity of the corresponding diamines.[5] To circumvent these limitations, we have searched for a thiophilic metal reagent that is less toxic and efficient to promote an intramolecular cyclization of *N*-(2-aminoaryl)thioureas.

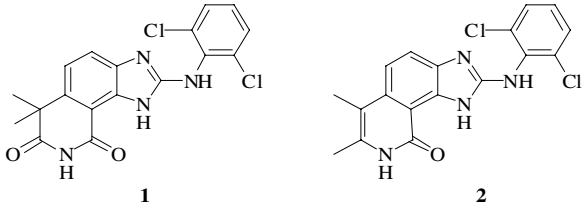

Figure 1.

Herein we disclose that copper(I) salts are highly efficient in promoting an intramolecular cyclization of thioureas to the corresponding 2-(*N*-substituted)-aminobenzimidazoles in good to excellent isolated yields.[6] The initial experiments were performed with thiourea **3** using CuI in the presence of diisopropylethylamine in a 5:1 mixture of toluene and acetonitrile. A portion of Celite was added to the reaction mixture to facilitate filtration after complete conversion. Thus, after heating at 80 °C for 30 min, 2-aminobenzimidazole **4** was isolated in 71% yield without any difficulty.[5a] Encouraged by this result we set out to explore the scope of this cyclization with respect to different copper(I) and copper(II) salts. The results of this investigation are summarized in Table 1. Thiourea **3** was prepared by condensation of 1,2-phenylenediamine with 3,5-dichlorophenyl isothiocyanate and isolated in 90% yield after recrystallization. It

Keywords: Aminobenzimidazole; CuCl; *N*-(2-Aminoaryl)thiourea.
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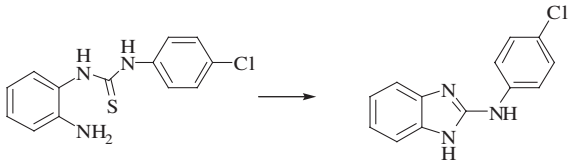
Table 1. Copper(I) and (II) salt-promoted cyclization of **3** to **4**



3 **4**

Entry	Copper reagents	Equivalents	Equivalent of iPr$_2$NEt	Reaction time (h)	Yield[a] (yield)[b](%)
1	CuI	2.0	2.1	0.5	71 (79)
2	CuBr	2.0	2.1	0.5	71 (80)
3	CuBr·SMe$_2$	2.0	2.1	0.5	80 (86)
4[7]	CuCl	2.0	2.1	1.0	87 (93)
5	CuOAc	2.0	2.1	1.0	80 (83)
6	CuBr$_2$	2.0	2.1	1.0	(47)
7	CuCl$_2$	2.0	2.1	1.0	40 (65)

[a] Isolated yield by crystallization from toluene or ethyl acetate.
[b] Weight % assay by HPLC.

is important to note that CuCl-promoted cyclization of **3** provided the best result to produce **4** (entry 4). Interestingly, copper(II) salts such as $CuCl_2$ and $CuBr_2$ (entries 6 and 7) were much less effective in promoting this cyclization with a moderate yield of **4**. While a firm explanation for this behavior cannot be given, one can conclude that copper(II) salts may be less thiophilic than copper(I) salts.[6] It is obvious that more air-sensitive copper(I) salts such as CuI, CuBr, and CuOAc (entries 1, 2, and 5) are less effective than more air-stable CuCl (entry 4). This observation may be attributable to the fact that more air-sensitive CuI, CuBr, and CuOAc are readily oxidized to copper(II) salts under the stated reaction condition making them less effective. Subsequently, it

Table 2. Cyclization of *N*-(2-aminoaryl)thioureas to 2-(*N*-substituted)-aminobenzimidazoles with CuCl

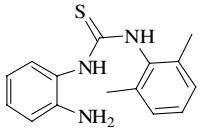
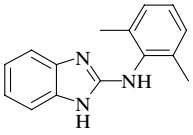
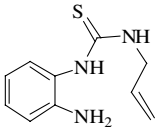
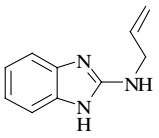
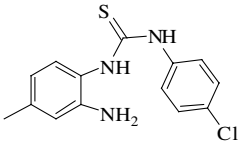
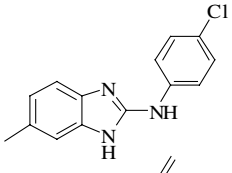
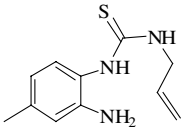
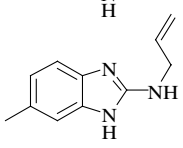
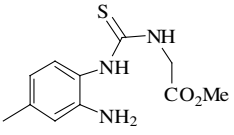
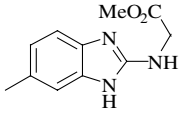
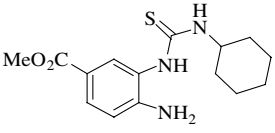
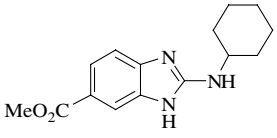
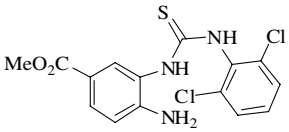
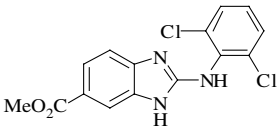
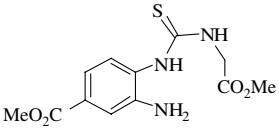
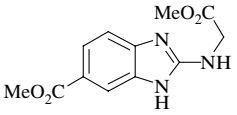
Entry	Thiourea[a]	Product[a]	Time (h)	Yield (%)[b]
1			0.5	78
2			1.5	86
3[8,c]			1.0	78
4[c]			1.5	79
5[c]			2.0	82
6			1.5	74

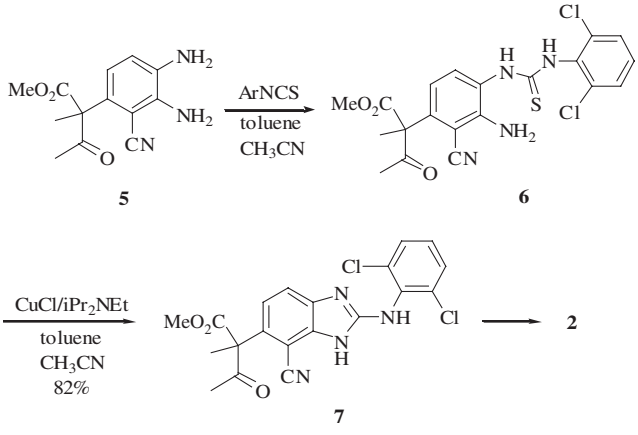
Table 2 (*continued*)

Entry	Thiourea[a]	Product[a]	Time (h)	Yield (%)[b]
7			3.0	86
8			0.5	90

[a] All new compounds had satisfactory ^{1}H and ^{13}C NMR, MS and elemental analyses.
[b] Isolated yield by recrystallization from ethyl acetate (not optimized).
[c] Thiourea as a 3:1 to 5:1 mixture of two regioisomers.

was also found that cyclization of **3** with fresh CuI and CuBr was faster and generally higher yielding. Clearly, CuCl is a more amenable reagent for this transformation on a large scale considering that CuCl is easier to handle and more economical. The cyclization proceeds fairly efficiently in many organic solvents; however, toluene was found to be more desirable because copper byproducts precipitated from the reaction mixture, which can be efficiently removed by filtration. Addition of acetonitrile was necessary to facilitate dissolution of both copper reagents and thiourea **3** for cyclization process. Interestingly, triethylamine and *N*-methylmorpholine provided sluggish cyclization, which may be due to the precipitation of their copper complexes.

The scope of this newly-discovered methodology was extended to a variety of *N*-(2-aminoaryl)thioureas using CuCl as the promoter. The results summarized in Table 2 illustrate that CuCl-promoted cyclization of *N*-(2-amino aryl)thioureas provides 2-(*N*-substituted)-aminobenzimidazoles bearing a wide range of substituents in good to excellent isolated yields. Thioureas were prepared by condensation of appropriate 1,2-arylenediamines with either commercially available or in situ prepared isothiocyanates[3] in excellent yields by simple recrystallization. We next applied this methodology to the synthesis of lck inhibitor **2** (Scheme 1). Thus, condensation of 1,2-arylenediamine **5** with 2,6-dichlorophenyl isothiocyanate in a 2:1 mixture of toluene and acetonitrile led to thiourea **6**. Without work-up or isolation, this reaction mixture was directly subjected to CuCl in the presence of *i*Pr_2NEt and Celite. After 1 h at 80 °C, the cyclization was completed. Crystallization of the crude product from ethyl acetate afforded **7** in an 82% overall yield (two steps). Compound **7** was then converted to **2** using a known literature procedure without any difficulty.[4]



Scheme 1.

In conclusion, we have developed a very simple and practical procedure for preparation of a wide variety of 2-(*N*-substituted)-aminobenzimidazoles via CuCl/*i*Pr_2NEt mediated thiourea cyclization. This procedure is amenable to scale-up for many aminobenzimidazoles, and it is general and can be applied to many biological targets.

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6. For complexes between copper(I) and (II) salts with thioureas, see: (a) Taylor, I. F., Jr.; Weininger, M. S.; Amma, E. *Inorg. Chem.* **1974**, *13*, 2835–2842; (b) Weininger, M. S.; Hunt, G. W.; Amma, E. *Chem. Commun.* **1972**, *20*, 1140–1141, and references cited therein.
7. A typical experimental procedure: To a suspension of thiourea **3** (12.1 g, 43.56 mmol) and Celite (4.0 g) in a 4:1 mixture of toluene and acetonitrile (135 mL) was added diisopropylethylamine (16.7 mL, 95.83 mmol), followed by CuCl (9.0 g, 90.92 mmol). The resulting mixture was heated to 80 °C and kept at this temperature for 30 min. The reaction mixture was then cooled to 40 °C and filtered. The

filtrate was washed with a 4:1 mixture of toluene and acetonitrile (40 mL). The combined filtrates were washed with 7% ammonium hydroxide (120 mL) and concentrated to about 100 mL. The solution was cooled to room temperature and kept at room temperature for 5 h. The slurry was filtered to give **4** as a light brown solid (9.2 g, 87%). An analytical sample of **4** was obtained by recrystallization from ethyl acetate: mp 195–197 °C;[5a] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (br s, 1H), 9.62 (s, 1H), 7.85 (ABq, J = 8.8 Hz, 2H), 7.37 (ABq, J = 8.8, 2H), 7.37 (m, 2H), 7.02 (m, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 150.2, 139.9, 128.5, 123.9, 120.2, 118.5; LRMS *m/z* 244 ($M^+ + 1$); HRMS (APCI) calcd for $C_{13}H_{11}ClN_3$ ($M^+ + 1$) 244.0636, found 244.0636.

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