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One-pot synthesis of 2-aminobenzimidazoles using 2-chloro-1,3-dimethylimidazolinium chloride (DMC)

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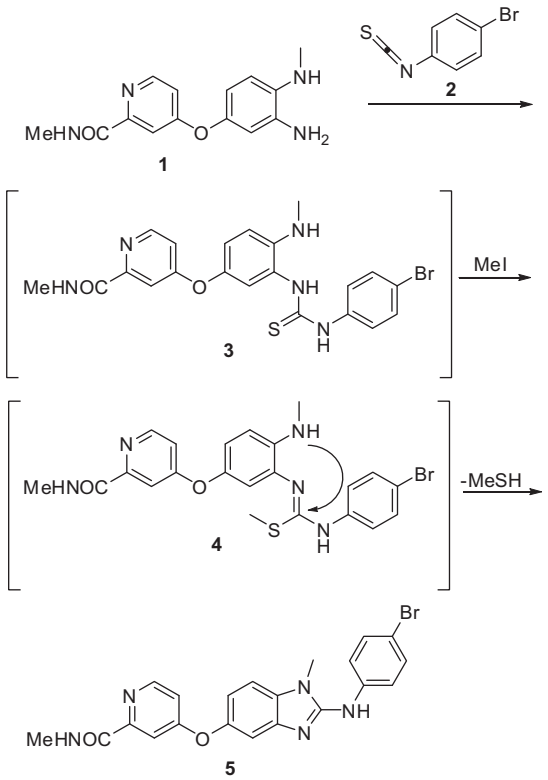
ABSTRACT

2-Chloro-1,3-dimethylimidazolinium chloride (DMC or DMC-Cl) has been found to effectively and rapidly generate 2-aminobenzimidazoles from 1,2-diaminoarenes and isothiocyanates in moderate to good yields at room temperature in a one-pot operation.

2-Aminobenzimidazole is an important chemotype for drug discovery programs in the pharmaceutical industry.[1] For instance, our drug discovery program targeting RAF kinase is based on a 2-aminobenzimidazole core (cf. **5**).[1a] Our initial approach toward this ring system was enabled through a common disconnection as described in Scheme 1. Exposure of the 1,2-diaminoarene **1** to the commercially available isothiocyanate **2** affords the intermediate thiourea **3**. Cyclization of the tethered amino group onto the thiourea to form the 2-aminobenzimidazole can be achieved using a variety of reagents. These include metal-based reagents such as CuI[2] or simple exposure to iodomethane.[3,4] As in the case of benzimidazole **5**, introduction of iodomethane to the intermediate thiourea **3** provides the activated intermediate **4**, which is more amenable to cyclization. Attack of the tethered aniline nitrogen and loss of methanethiol affords the desired product **5**.

Despite the variety of conditions described to prepare 2-aminobenzimidazoles,[4,5] there are drawbacks associated with many of them. For example, the use of metals salts in large amounts often results in tedious workup procedures to ensure complete removal of the metals from the final product. In addition, cyclization using iodomethane can require long reaction times (>24 h) for acceptable yields. Finally, iodomethane in large quantities can present a hazard in accidental exposure to this toxic chemical.

Not satisfied with the current conditions to achieve this key ring closure, we have continued to explore alternative conditions that are more amenable for scale-up of compounds like benzimidazole **5** as well as reducing the toxicity of the reagents employed. To this end, we were drawn to a recent paper by Isobe and Ishikawa describing the dehydrating capabilities of 2-chloro-1,3-dimethylimidazolinium chloride (DMC or DMC-Cl, **6**).[6,7] DMC (**6**) is a stable, colorless solid that is soluble in a variety of organic solvents (CH_3CN, DCE, CH_2Cl_2, etc.) with reduced toxicity. Isobe and Ishika-



Scheme 1.

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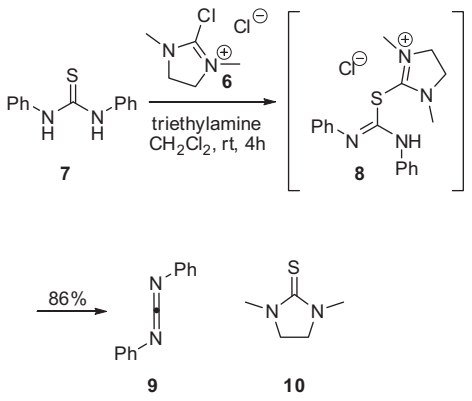


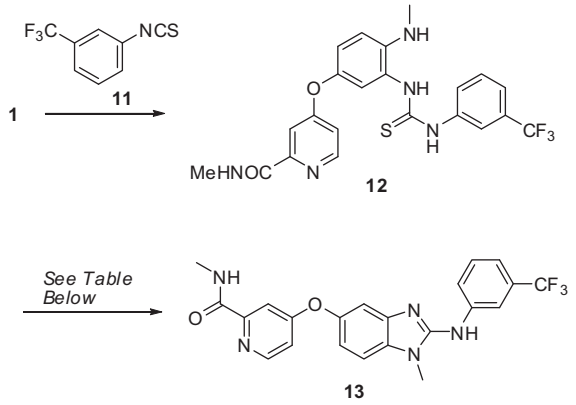
Scheme 2.

wa have described many uses of DMC (**6**), but it was the formation of carbodiimides from thioureas that made this reagent particularly interesting to our synthetic needs (Scheme 2). Isobe and Ishikawa reported that the exposure of a thiourea-like **7** to DMC (**6**) and triethylamine in CH_2Cl_2 results in the formation of the activated intermediate **8**.[6a] This then transforms to the carbodiimide **9** in good yield, producing the water-soluble 1,3-dimethylthioimidazilone (**10**) as the main byproduct. In light of this finding and the similarities between intermediates **4** and **8**, we decided to explore the application of DMC (**6**) in the formation of 2-aminobenzimidazoles from 1,2-diaminoarenes and isothiocyanates.[8]

To test the application of DMC (**6**), we tried to prepare the benzimidazole **13** from the 1,2-diaminoarene **1** (vide supra) and the commercially available 3-(trifluoromethyl)phenyl isothiocyanate (**11**) under a variety of known conditions (Table 1). Using EDC (entry 1), CuI (entry 2) or $FeCl_3$/pyridine to facilitate cyclization resulted in no or little conversion at room temperature. These conditions only provided reasonable yields after the reaction mixtures were heated at 80 °C for several hours. $FeCl_3$/MeOH (entry 4) provided the best yield but it required an extended reaction time (15 h) at room temperature. However, exposure of thiourea **12** to DMC (**6**) and DIPEA in refluxing MeCN readily afforded the desired benzimidazole **13** in 87% yield (entry 5). In addition, it was noticed that under these conditions, the reaction was completed in less than 15 min. Based on this encouraging result, it was then found that the reaction could be carried out in dichloromethane at room temperature (entry 6): the formation of the benzimidazole was achieved in less than 5 min and in 86% yield. Furthermore, we found that the isolation of the desired product was readily achieved through basic aqueous workup to remove much of the residual 1,3-dimethylthioimidazilone. The resulting crude product was purified either by silica gel flash chromatography using a 0–100% EtOAc–heptane gradient or through trituration from MeOH. Finally, we recognized that a one-pot procedure may be possible by performing the thiourea formation in CH_2Cl_2 rather than the MeOH/THF mixture previously employed. To this end, we repeated the synthesis of **13** using a one-pot procedure. Much to our delight, the one-pot synthesis (entry 7) gave similar yield to the previous two-step sequence (entries 5 and 6). Two things are worth noting: (1) in the first step of the one-pot procedure, dithiourea is a likely side-product (especially on a large scale), which can be minimized by slow addition of the isothiocyanate; (2) since DMC-induced cyclization is quite exothermic, an ice-water bath and portion-wise addition of DMC are recommended for large-scale reactions.

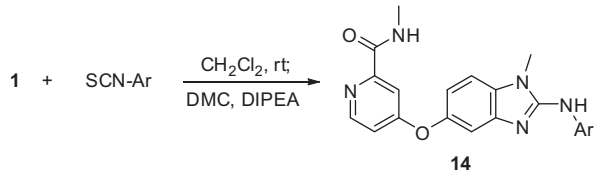
To demonstrate the versatility of these reaction conditions, a series of commercially available isothiocyanates were screened under the one-pot DMC conditions.[8,9] Exposure of compound **1** to the isothiocyanates listed in Table 2 resulted in the rapid formation of the desired benzimidazoles with moderate to good isolated yields. The electronic nature of the arene ring seems important: electron-withdrawing substituents such as fluorine (entries a–e) or cyano (entry g) led to higher yields, whereas more electron-rich aromat-

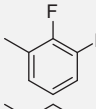
Table 1
Comparison of reported benzimidazole formation conditions to DMC (**6**)



Entry	Conditions	Results (%)
1	EDC, CH_3CN, 80 °C	24
2	CuI, DIPEA MeCN, PhMe, 80 °C	50
3	$FeCl_3$, MeOH, 80 °C	45
4	$FeCl_3$, MeOH, rt	61
5	DMC (**6**) DIPEA, MeCN, reflux	87
6	DMC (**6**) DIPEA, CH_2Cl_2, rt	86
7	One-pot in CH_2Cl_2	84

Table 2
Scope of DMC (**6**) conditions in one-pot operation with commercially available isothiocyanates



Entry	Ar	Yield (%)
a		57
b		76
c		71
d		69
e		70
f		37
g		61
h		49

ics such as the benzodioxole (entry f), phenyl (entry h) resulted in lower yields.

In conclusion, we have found DMC (**6**) to be an effective, less toxic reagent for the preparation of 2-aminobenzimidazoles from 1,2-diaminoarenes and isothiocyanates using a room temperature, one-pot procedure. These conditions will allow other chemists to rapidly access this heterocyclic ring system.

Acknowledgments

We would like to thank Savithri Ramurthy, Paul A. Renhowe, and Baoqing Gong for their many helpful discussions regarding this heterocyclic system.

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7. 2-Chloro-1,3-dimethylimidazolinium chloride is commercially available from several vendors. We purchased our supply of 2-chloro-1,3-dimethylimidazolinium from Sigma–Aldrich, St. Louis, MO.
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9. *General procedure*: To a flame-dried 50 mL round-bottomed flask, compound **1** (1 mmol) was dissolved in DCM (10 mL). In a separate flask, the isothiocyanate (1.2 mmol) was dissolved in DCM (5 mL) and slowly added to the flask containing compound **1** over 10 min via a syringe at room temperature. The reaction mixture was stirred and reaction progress was monitored by TLC or LCMS. Once this step was determined to be complete, DIPEA (2 mmol) was added in a single portion via a syringe followed by DMC (**6**, 1.5 mmol). The reaction was then stirred for 5 min and then checked by TLC or LCMS. Once the reaction was determined to be complete (~5–10 min), the reaction mixture was poured into a 1:2 aqueous solution of concentrated ammonium hydroxide/water (20 mL). The layers were separated and the aqueous layer was extracted CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and dried. The resulting crude product was purified by silica gel chromatography using a Teledyne ISCO CombiFlash Rf instrument (0–100% EtOAc:heptane) to provide **14**. The purity of all the final compounds was greater than 98% by LC–MS and HPLC analysis. ^{1}H NMR data of **14a**–**h** are listed here: compound **14a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.38 (d, J = 5.6 Hz, 1H), 8.08 (d, J = 4.6 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.52 (dd, J = 8.8 Hz, J = 4.6 Hz, 2H), 7.20 (d, J = 1.8 Hz, 1H), 7.08–6.93 (m, 4H), 6.75 (dd, J = 8.3 Hz, J = 2.0 Hz, 1H), 3.45 (s, 3H), 3.02 (d, J = 5.1 Hz, 3H); compound **14b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.40 (d, J = 5.6 Hz, 1H), 8.08 (d, J = 4.8 Hz, 1H), 7.61 (d, J = 2.5 Hz, 1H), 7.49 (d, J = 10.9 Hz, 1H), 7.29–7.20 (m, 3H), 7.11 (d, J = 8.59 Hz, 1H), 7.06 (dd, J = 5.6 Hz, 2.5 Hz, 1H), 6.83 (dd, J = 8.2 Hz, 1.9 Hz, 1H), 6.76–6.67 (m, 1H), 3.58 (s, 3H), 3.02 (d, J = 5.3 Hz, 3H); compound **14c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.38 (d, J = 5.6 Hz, 1H), 8.15 (br s, 1H), 8.01 (d, J = 5.3 Hz, 1H), 7.59 (s, 1H), 7.34 (d, J = 9.6 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.21–7.03 (m, 3H), 7.00 (dd, J = 5.7 Hz, 2.4 Hz, 2H), 3.75 (s, 3H), 3.00 (d, J = 5.3 Hz, 3H); compound **14d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.40 (d, J = 5.6 Hz, 1H), 8.08 (d, J = 4.9 Hz, 1H), 7.67–7.57 (m, 1H), 7.53 (d, J = 2.3 Hz, 1H), 7.22 (d, J = 2.0 Hz, 1H), 7.20–7.11 (m, 2H), 7.10–6.99 (m, 2H), 6.85 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 3.59 (s, 3H), 3.00 (d, J = 5.1 Hz, 3H); compound **14e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.37 (d, J = 5.3 Hz, 1H), 8.01 (br s, 2H), 7.63–7.51 (m, 1H), 7.43–7.24 (m, 3H), 7.12–7.03 (m, 1H), 7.00 (d, J = 4.8 Hz, 1H), 6.93–6.80 (m, 1H), 3.79 (br s, 3H), 3.00 (d, J = 5.1 Hz, 3H); compound **14f**: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.91 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.48 (d, J = 6.0 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.24 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.19 (d, J = 2.2 Hz, 1H), 7.14 (dd, J = 5.7 Hz, 2.7 Hz, 1H), 6.91–6.85 (m, 2H), 5.98 (s, 2H), 3.72 (s, 3H), 2.77 (d, J = 4.9 Hz, 3H); compound **14g**: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.63 (s, 1H), 8.77 (d, J = 5.1 Hz, 1H), 8.49 (d, J = 5.6 Hz, 1H), 7.78 (d, J = 9.1 Hz, 2H), 7.50 (d, J = 8.6 Hz, 1H), 7.33 (dd, J = 7.8 Hz, 2.5 Hz, 2H), 7.15 (dd, J = 5.7 Hz, 2.7 Hz, 1H), 6.97 (dd, J = 8.6 Hz, J = 2.3 Hz, 1H), 3.80 (s, 3H), 2.77 (d, J = 5.1 Hz, 3H); compound **14h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.43 (br s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 8.04 (br s, 1H), 7.61 (d, J = 9.1 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.34 (m, 2H), 7.20–7.10 (m, 3H), 7.08 (dd, J = 5.6 Hz, 2.5 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 3.87 (s, 3H), 2.97 (d, J = 5.1 Hz, 3H).