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Convenient multi-gram scale synthesis of polybrominated imidazoles building blocks

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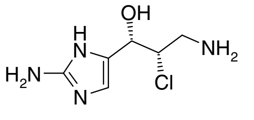
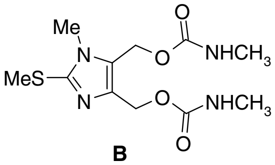
Abstract—The multi-gram scale polybromination of variously substituted imidazoles has been realized using a stoichiometric amount of the Br_2–DMF complex. Good yields have been obtained compared to other methods using large amounts of acetic acid–sodium acetate buffer.

The imidazole ring is a key unit for numerous important biologically active naturally occurring or synthetic substances such as Girolline (**A**)[1] or Carmethizole (**B**).[2]



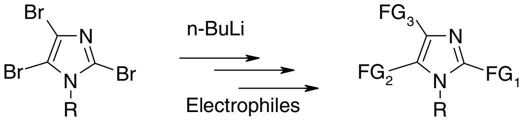
A



B

Imidazoles have also found applications as metal–carbene metathesis catalysts[3] and ionic liquids.[4] The most efficient synthetic routes to polyfunctional compounds involve halogen–metal exchanges on iodo- or bromoimidazoles.[5] The reaction provided a wide range of substitutions on every position of the ring as nicely reported by Lipshutz and co-workers (Scheme 1).[6]

Consequently, the polybromination of the imidazole ring is of high synthetic interest and efforts have to be made to develop this reaction. The pioneering works by Pyman[7] using bromine in refluxing chloroform only led to poor yields. This was attributed to the formation of the hydrobromide and subsequent degradations.[8] Such side-reactions drew other authors to use basic media for the neutralization of hydrogen bromide formed along the reaction. Indeed using an acetic acid/sodium acetate buffer, excellent yields have been obtained.[8,9] However, the amount of buffer is prohibitive for large scale preparations. For example, the polybromination of 0.2 mol of imidazole with 0.6 mol of bromine consumed 250 g of sodium acetate in 2 L of acetic acid.



Scheme 1. Polyfunctionalization of bromoimidazoles.

So, the development of efficient methodologies using low amounts of reagents remains an important subject for research. Singh and co-workers have disclosed the mono bromination of activated nitro-imidazoles using a stoichiometric amount of the DMF–Br_2 complex[10] in basic medium. From our knowledge, no polybromination in the unactivated imidazole series has been described yet. Herein, we report the efficiency of the DMF–Br_2 complex for the large scale preparation of polybrominated imidazoles.

The reaction was investigated with a range of variously substituted imidazoles. The substrates were reacted with

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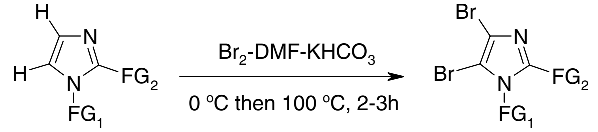
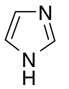
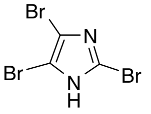
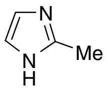
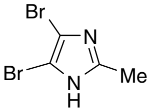
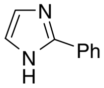
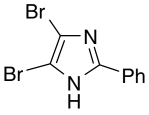
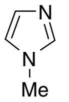
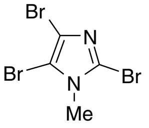
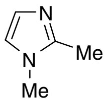
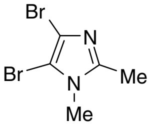
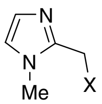
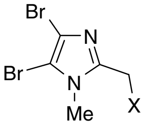
1/1 mixtures of DMF and Br_2 in the presence of $KHCO_3$ (Table 1).[11] As shown, all polyhalogenated products were obtained in acceptable to good yields. The DMF–Br_2 reagent led to the tribromo compounds **2a** and **2d** in acceptable yields similar to those reported in the literature with the acetate buffer.

The hydroxymethyl derivative **2f** was obtained in poor yield due to degradations and, in our hands, the acetic acid/sodium acetate buffer gave a better outcome in this case. The chloromethyl group in **1g** was found more compatible with the reaction medium leading to **2g** in fair yield. The best results were obtained with 2-substituted imidazoles **1b** and especially **1c**. This probably resulted in an acidifying effect of the phenyl group enhancing the proton abstraction. The introduction of substituents on nitrogen led to lower yields probably due to the enhancement of the basicity of this site leading to the formation of the hydrobromide. The brominations were performed with only stoichiometric amounts of the Br_2–DMF complex based on the number of protons to be substituted. 1.5 Equiv instead of the normally required 2 equiv of reagent was used for the dibrominations. Higher amounts were found to be deleterious leading to complex mixtures from which the target compound was hardly separated.

Table 1. Polyhalogenation of imidazoles[a]



1a-f **2a-f**

Imidazole		Product		Yield%[b]
	**1a**		**2a**	64 (68)[c]
	**1b**		**2b**	65 (62)
	**1c**		**2c**	75 (76)
	**1d**		**2d**	47 (51)[d]
	**1e**		**2e**	50 (49)
	**1f, X=OH** **1g, X=Cl**[e]		**2f, X=OH** **2g, X=Cl**[f]	27 (48) 43 (40)

[a] Reactions carried out on 0.1 mol of **1a**–**g** using 3 equiv of Br_2–DMF with **1a**, **1d** and 1.5 equiv with **1b**, **1c** and **1e**–**g**.

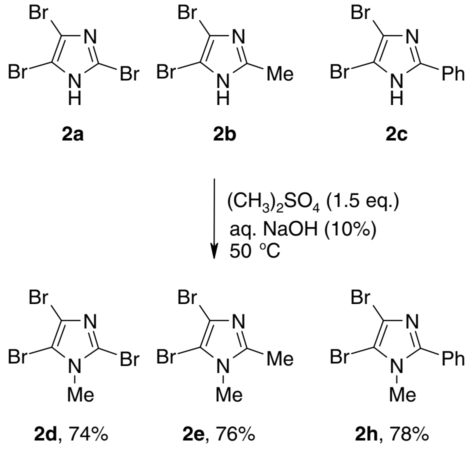
[b] Isolated yields. In parentheses, yields obtained in the acetic acid/sodium acetate buffer.

[c] See Ref. 9.

[d] See Ref. 12.

[e] The hydrochloride was used.

[f] Obtained as the hydrobromide.



Scheme 2. N-Methylation of bromoimidazoles.

Then we examined an alternative way to synthesize the N-substituted polybromo derivatives with the aim to improve the yields. So, we investigated the incorporation of the methyl group on nitrogen after initial polybromination of 1H-imidazoles. The N-methylation of imidazoles have been reported with several reagents such as dimethylsulfate in alcoholic solution of sodium hydroxide[13] or treatment with sodium hydride and iodomethane.[6] In our hands, reaction of **2a**–**c** with dimethylsulfate in aqueous NaOH gave the best results (Scheme 2).[14]

The *N*-methyl derivatives were obtained in good yields although overall yields based on starting imidazoles **1a**–**c** were found to be similar to those obtained from the direct process. However, the two-step procedure remains valuable for the introduction of functional diversity on nitrogen.

In summary, an efficient multi-gram scale straightforward access to polybrominated imidazoles has been performed using stoichiometric amounts of the DMF–Br_2 complex. This reagent gave yields similar to those obtained using large excesses of acetic acid–sodium acetate buffers. The reactivity of the polybromoimidazoles scaffolds is now under investigation.

Acknowledgements

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11. Preparation of 2,4,5-tribromoimidazole **2a** is given as a typical procedure for tribromination. Finely powdered $KHCO_3$ (30 g, 0.3 mol) was added to a solution of 1H-imidazole (6.8 g, 0.1 mol) in DMF (25 mL). The suspension was cooled to 0 °C and bromine (16 mL, 0.3 mol) was added drop-wise during 1 h. The reaction medium was heated to 100 °C and stirred for 2–3 h until completion of the reaction (TLC). A yellow mixture was obtained. After cooling, cold water (150 mL) was added and the precipitate was washed with water, dissolved in NaOH (5%) and treated by HCl (10%). After filtration and aqueous washing until neutralization, the solid was dried yielding 19.5 g (64%) of **2a**[13] as a white powder. All products obtained by this method were characterized by ^{1}H, ^{13}C NMR and melting points, which were found comparable to those reported in the literature.
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