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Efficient syntheses of 2-fluoroalkylbenzimidazoles and -benzothiazoles

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ABSTRACT

We report an efficient one-step route to 2-fluoroalkylbenzimidazoles and -benzothiazoles via the condensation of fluorinated carboxylic acids and aromatic diamines or aminothiophenols. Additionally, we describe the syntheses of fluoroalkyl-azabenzimidazoles, -purines, and -imidazolopyrazines. This method is high-yielding with broad scope and is operationally simple with potential application to parallel synthesis.

2-Fluoroalkylbenzimidazoles are widely applicable in the syntheses of pharmaceuticals and agrochemicals because of their ability to improve physiochemical properties, metabolic stabilities, and binding potencies relative to their non-fluorinated analogs.[1–4] Introduction of fluoroalkyl groups at the 2-position of benzimidazole has been the focus of several publications, and the synthetic approaches can be classified into the following reaction types: Phillips condensation[5] with *o*-phenylenediamine and a carboxylic acid under refluxing aqueous HCl conditions,[1–4,6–8] reaction of a diamine with a fluorinated dichloroazine,[9] reaction of a diamine with a fluorinated imidoyl chloride,[10] and installation of the trifluoromethyl group onto the heterocycle via C-H oxidation chemistry.[11]

There have been scattered reports of a simplified Phillips condensation in which *o*-phenylenediamines were treated with neat trifluoroacetic acid (TFA) to generate the corresponding 2-(trifluoromethyl)benzimidazoles.[12–18] However, these initial reports have been limited to the reaction of TFA with *o*-phenylenediamines with no additional exploration of scope. Herein, we would like to report the expanded scope for this efficient condensation and its use in the syntheses of 2-fluoroalkylbenzimidazoles, -azabenzimidazoles, -purines, -imidazolopyrazines, and -benzothiazoles (Fig. 1).[19]

This improved one-step process, first reported by Middleton and Parrick,[12] is operationally simple using the fluorinated carboxylic acid as the reagent, catalyst, and solvent. We demonstrate that this procedure allows for broad substrate scope and high yield to form a variety of heterocycles.

In a typical procedure, *o*-phenylenediamine was combined with trifluoroacetic acid (TFA) at 0.5 M overall concentration and heated to 70 °C for 2 h to provide the corresponding 2-(trifluoromethyl)benzimidazole. Evaporation of the excess TFA afforded the product in quantitative yield. Optionally, the product could also be purified by silica gel column chromatography to obtain analytically pure material in quantitative yield.

This convenient and efficient procedure allows for the rapid generation of 2-(trifluoromethyl)benzimidazole products, and illustrative examples of the scope of the transformation are shown in Table 1. In addition to *o*-phenylenediamine (Table 1, entry 1), electron-withdrawing substituents on the ring, such as 4-cyano (Table 1, entry 2), 4-nitro (Table 1, entry 3), 4-trifluoromethyl (Table 1, entry 4), 4-carboxylic acid (Table 1, entry 5), 4,5-difluoro (Table 1, entry 6), and a fused arene (Table 1, entry 7) were well tolerated giving the corresponding products in 92% to 99% yields.

Sterically encumbered substrates containing an adjacent 3-methyl (Table 1, entry 8) or 3-methoxy substituent (Table 1, entry 10) also provided the desired products in 99% and 94% yields, respectively. The 4,5-dimethyl substrate also afforded the corresponding product in 98% yield (Table 1, entry 9).

In addition to 1*H*-benzimidazoles, *N*-alkyl and *N*-phenyl benzimidazoles also can be prepared using this one-step procedure from the corresponding diamine starting materials (Table 1, entries 11–14). For example, starting with *N*-methyl-*o*-phenylenediamine

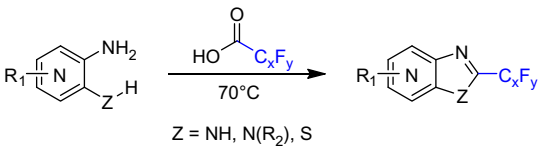

Figure 1. Efficient approach to fluoroalkyl-heterocycles.

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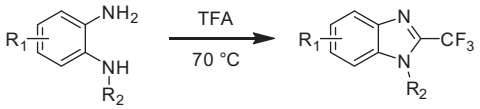
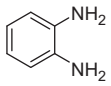
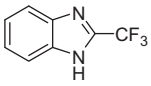
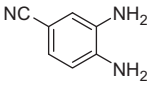
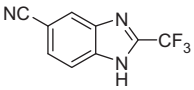
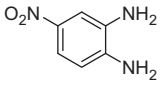
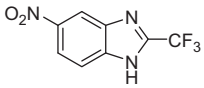
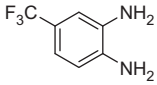
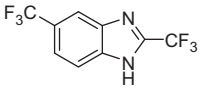
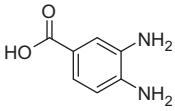
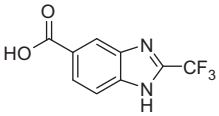
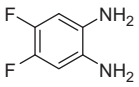
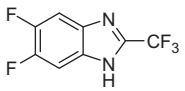
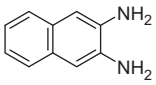
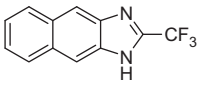
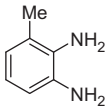
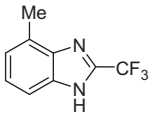
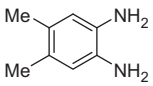
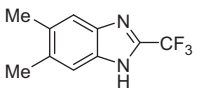
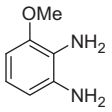
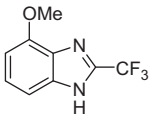
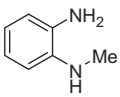
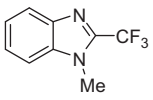
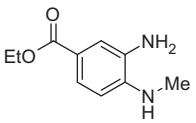
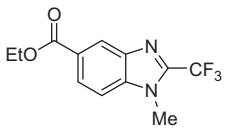
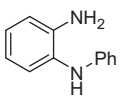
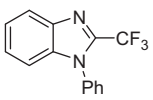
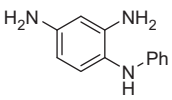
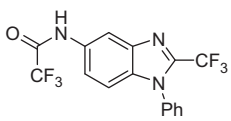
Table 1
Variation of the substituted *o*-phenylenediamines



Entry	Diamine	Product	Yield[a] (%)
1			99
2			92
3			99
4			99
5			99
6			99
7			99
8			99
9			98
10			94
11			99
12			99
13			95
14			66

[a] Reaction conditions: 0.5 M diamine in trifluoroacetic acid, 70 °C, 16 h.

(Table 1, entry 11) or an analogous starting material bearing an electron-withdrawing ethyl ester (Table 1, entry 12), the *N*-methylbenzimidazoles were obtained in 99% yields. Similarly, the reaction was also compatible with *N*-phenyl diamines to give the corresponding *N*-phenylbenzimidazoles (Table 1, entries 13 and 14). In the case of a substrate bearing an additional 4-amino