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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

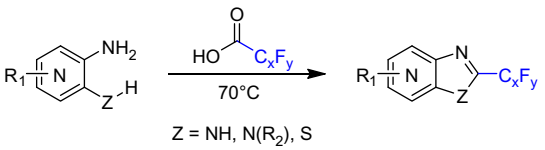

Figure 1. Efficient approach to fluoroalkyl-heterocycles.

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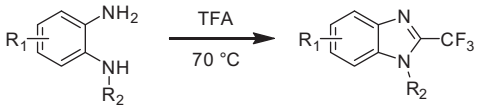
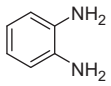
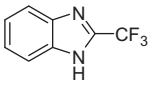
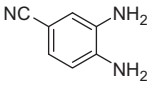
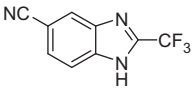
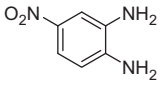
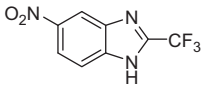
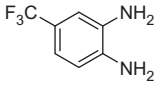
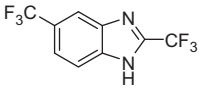
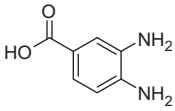
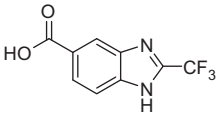
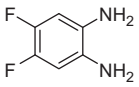
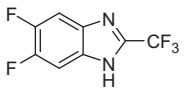
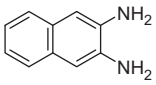
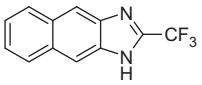
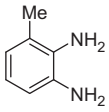
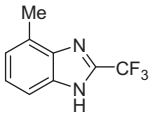
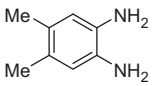
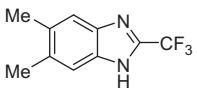
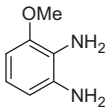
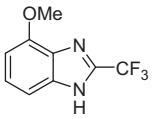
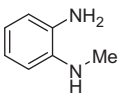
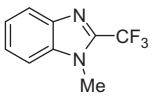
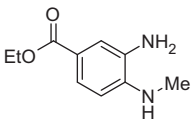
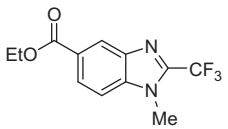
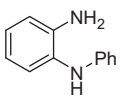
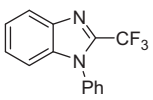
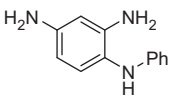
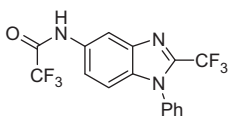
Table 1
Variation of the substituted *o*-phenylenediamines

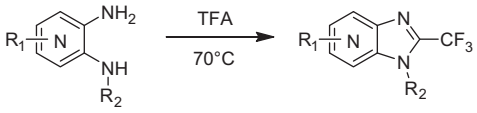


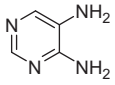
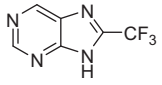
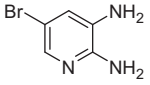
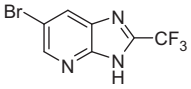
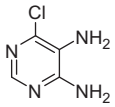
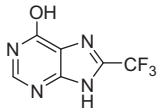
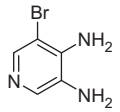
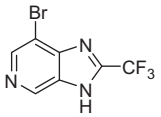
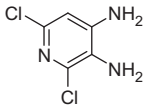
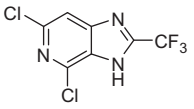
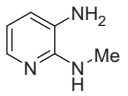
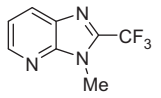
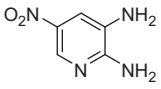
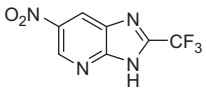
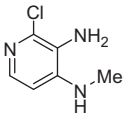
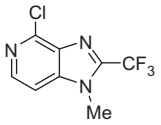
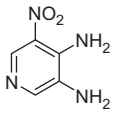
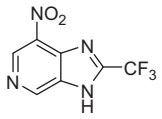
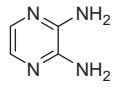
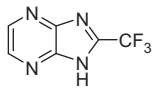
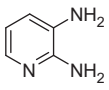
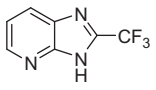
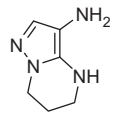
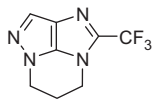
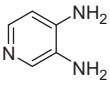
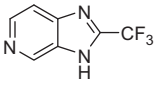
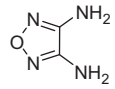
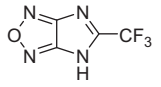
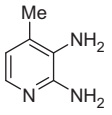
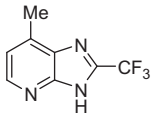
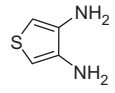
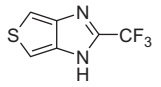
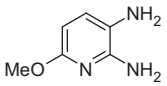
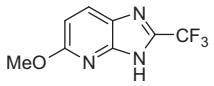
Entry	Diamine	Product	Yield[a] (%)
1			99
2			92
3			99
4			99
5			99
6			99
7			99
8			99
9			98
10			94
11			99
12			99
13			95
14			66

[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

Table 2
Scope of reactions with *o*-diamino-azaheterocycles



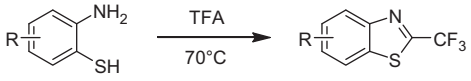
Entry	Diamine	Product	Yield[a] (%)	Entry	Diamine	Product	Yield[a] (%)
1			99	**10**			66[b]
2			61	**11**			79[b]
3			80	**12**			88[b]
4			48	**13**			92[b]
5			75	**14**			54[c]
6			70[b]	**15**			0[c,d]
7			99[b]	**16**			0[c,e]
8			72[b]	**17**			0[c,e]
9			25[b]				

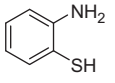
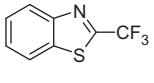
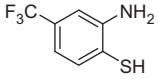
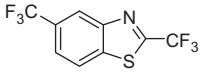
[a] Reaction conditions: 0.5 M diamine in trifluoroacetic acid, 70 °C, 16 h.
[b] The reaction was concentrated to dryness and subsequently treated with Et_3N at 70 °C for 1 h to form the product.
[c] The reaction was conducted in a sealed tube at 120 °C.
[d] Only monoacylation was observed.
[e] Only diacylation was observed.

group, trifluoroacetylation of that amine was observed (Table 1, entry 14).

The same convenient procedure could be utilized to synthesize a variety of azaheterocycles (Table 2). In the case of pyrimidine starting materials, simply heating the reaction to 70 °C was sufficient to directly afford the corresponding fluoroalkyl-purines. For example, 5,6-diamino-pyrimidine (Table 2, entry 1) produced the corresponding 8-(trifluoromethyl)purine in 99% yield. Interestingly, in the case of the 4-chloro-5,6-diaminopyrimidine, water generated in the condensation step of the reaction was sufficient to displace the chloride and yield 8-(trifluoromethyl)-6-hydroxypurine (Table 2, entry 2), whereas 2,6-dichloro-3,4-diaminopyridine reacted to produce the corresponding dichloro-azabenzimidazole in 80% yield (Table 2, entry 3).

Table 3
Reactions with 2-aminothiophenols



Entry	Aminothiophenol	Product	Yield[a] (%)
1			99
2			58

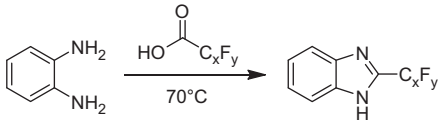
[a] Reaction conditions: 0.5 M diamine in trifluoroacetic acid, 70 °C, 16 h.

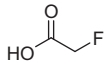
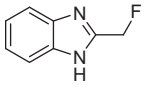
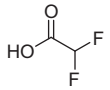
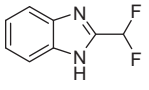
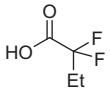
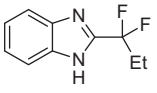
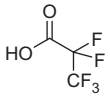
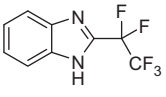
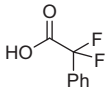
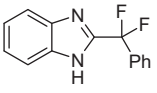
Diaminopyridines bearing an electron-withdrawing group also participated in the cyclization reaction. For example, 2,3-diamino-5-nitropyridine and 3,4-diamino-5-nitropyridine reacted to form the respective products in 48% and 75% yields (Table 2, entries 4 and 5). If the pyridine substrate did not contain an electron-withdrawing group, then the cyclization did not occur and only the trifluoroacetylated intermediates were identified in the reaction mixture via mass-spectrometry analysis. It was presumed that the trifluoroacetate salts of these pyridine substrates reduced their nucleophilicity and did not allow for their condensation to the trifluoromethyl-azabenzimidazole products.[20] Therefore, a two-part procedure was required in which the trifluoroacetic acid was removed via rotary evaporation, followed by treatment with triethylamine to free-base the intermediate. Heating to 70 °C for 1 h provided the desired azabenzimidazoles (Table 2, entries 6-13).[21] 2,3-Diaminopyrazine was also a suitable substrate, but required heating to 120 °C with trifluoroacetic acid in a sealed tube to provide a 54% yield of the 2-(trifluoromethyl)imidazolo[4,5-*b*-]pyrazine product (Table 2, entry 14).

2-Aminothiophenols were also suitable substrates for this reaction leading to the corresponding benzothiazoles, as shown in Table 3. Using this approach, 2-(trifluoromethyl)benzothiazole was obtained in quantitative yield (Table 3, entry 1). Even the electron-deficient 4-(trifluoromethyl)-2-aminobenzenethiol underwent cyclization to form the desired benzothiazole in 58% yield (Table 3, entry 2). 2-Aminophenols also were explored as partners for this condensation reaction, but they only provided the trifluoroacetylated aminophenol intermediates and did not cyclize to the benzoxazole products upon extended heating or subsequent treatment with triethylamine.

In an effort to further evaluate the applicability of this efficient transformation, we also reacted a variety of fluorinated carboxylic acids with *o*-phenylenediamine to afford the respective mono- or polyfluoroalkylbenzimidazoles. For example, 2-fluoroacetic acid (Table 4, entry 1), 2,2-difluoroacetic acid (Table 4, entry 2), 2,2-difluoropropionic acid (Table 4, entry 3), and pentafluoropropionic acid (Table 4, entry 4) were all successful in producing the desired 2-fluoroalkylbenzimidazoles in excellent yields. Additionally, 2,2-difluoro-2-phenylacetic acid was also suitable for the reaction, leading to the product in 71% yield (Table 4, entry 5).

Table 4
Variation of the fluorinated carboxylic acid



Entry	Acid	Product	Yield[a] (%)
1			94
2			99
3			99
4			99
5			71

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

Acknowledgments

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Supplementary data

Supplementary data (synthetic procedures and analytical data for all products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.069.

References and notes

1. Navarrete-Vázquez, G.; Cedillo, R.; Hernández-Campos, A.; Yépez, L.; Hernández-Luis, F.; Valdez, J.; Morales, R.; Cortés, R.; Hernández, M.; Castillo, R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 187.
2. Kazimierczuk, Z.; Andrzejewska, M.; Kaustova, J.; Klimesova, V. *Eur. J. Med. Chem.* **2005**, *40*, 203.
3. Hernández-Luis, F.; Hernández-Campos, A.; Castillo, R.; Navarrete-Vázquez, G.; Soria-Arteche, O.; Hernández-Hernández, M.; Yépez-Mulia, L. *Eur. J. Med. Chem.* **2010**, *45*, 3135.
4. Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.
5. Phillips, M. A. *J. Chem. Soc., C* **1928**, 2393.
6. Smith, W. T.; Steinle, E. C. *J. Am. Chem. Soc.* **1953**, *75*, 1292.
7. Holan, G.; Samuel, E. L.; Ennis, B. C.; Hinde, R. W. *J. Chem. Soc., C* **1967**, 20.
8. Fonesca, T.; Gigante, B.; Marques, M.; Gilchrist, T. L.; De Clercq, E. *Bioorg. Med. Chem.* **2004**, *12*, 103.
9. Barlow, M. G.; Bell, D.; O'Reilly, N. J.; Tipping, A. E. *J. Fluorine Chem.* **1983**, *23*, 293.
10. Ge, F.; Wang, Z.; Wan, W.; Lu, W.; Hao, J. *Tetrahedron Lett.* **2007**, *48*, 3251.
11. Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298.
12. Middleton, R. W.; Monney, H.; Parrick, J. *Synthesis* **1984**, 740.
13. Buckle, D. R.; Foster, K. A.; Taylor, J. F.; Tedder, J. M.; Thody, V. E.; Webster, R. A. B.; Bermudez, J.; Markwell, R. E.; Smith, S. A. *J. Med. Chem.* **1987**, *30*, 2216.
14. Jones, B. G.; Branch, S. K.; Thompson, A. S.; Threadgill, M. D. *J. Chem. Soc. Perkin Trans. 1* **1996**, 2685.
15. Mewshaw, R. E.; Zhao, R.; Shi, X.; Marquis, K.; Brennan, J. A.; Mazandarani, H.; Coupet, J.; Andree, T. H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 271.
16. Rückle, T.; Biamonte, M.; Grippi-Vallotton, T.; Arkinstall, S.; Cambet, Y.; Camps, M.; Chabert, C.; Church, D. J.; Halazy, S.; Jiang, X.; Martinou, I.; Nichols, A.; Sauer, W.; Gotteland, J.-P. *J. Med. Chem.* **2004**, *47*, 6921.
17. Pete, B.; Szokol, B.; Tőke, L. *J. Heterocycl. Chem.* **2008**, *45*, 343.
18. Pelletier, J. C.; Chengalvala, M.; Cottom, J.; Feingold, I.; Garrick, L.; Green, D.; Hauze, D.; Huselton, C.; Jetter, J.; Kao, W.; Kopf, G. S.; Lundquist, J. T.; Mann, C.; Mehlmann, J.; Rogers, J.; Shanno, L.; Wrobel, J. *Bioorg. Med. Chem.* **2008**, *16*, 6617.
19. The authors recognize that the following entries included in this Letter have been previously synthesized using the featured methodology: Table 1, entries 1, 4, 7, and 10; Table 3, entry 1. These examples were subjected to the featured methodology within our labs, and the corresponding yields we achieved are reported in this Letter.
20. Calculations for the theoretical pK_a's of the conjugate acids were conducted using the Molecular Discovery Ltd. *MoKa* v1.1.0 software package (2009). Calculated conjugate acid pK_a's for Table 2, entry 3 starting material = 2.58; entry 4 starting material = 3.57; entry 5 starting material = 3.04; entry 6 starting material = 6.87; entry 7 starting material = 9.31; entry 8 starting material = 7.47; entry 9 starting material = 5.04; entry 10 starting material = 5.10; entry 11 starting material = 7.54; entry 12 starting material = 5.11; and entry 13 starting material = 5.91. The methods for these calculations are described further in: Milletti, F.; Storchi, L.; Sforna, G.; Cruciani, G. *J. Chem. Inf. Model* **2007**, *47*, 2172.
21. Based on the observed differential reactivity of the substituted diamino-pyridines (Table 2, entries 3–13) and analyses of their respective calculated conjugate acid pK_a's (Ref. 19), we propose a guideline that diamino-pyridines with conjugate acid pK_a's <4 will probably accommodate the one-step TFA cyclization protocol. Whereas pyridine substrates with calculated conjugate acid pK_a's >4 will probably require subsequent treatment with triethylamine to facilitate formation of the azabenzimidazole products.