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$POCl_3$-mediated synthesis of hydrolysis-prone 2-trifluoroethylbenzimidazoles

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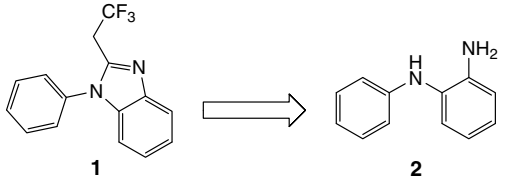
ABSTRACT

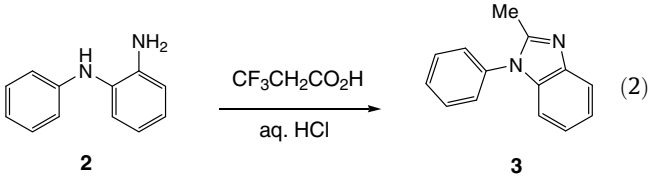
Loss of a trifluoromethyl group has been observed as an unproductive side reaction in the formation of 2-trifluoroethylbenzimidazoles. A hydrolytic mechanism for this transformation is proposed that is consistent with evidence for the identity of reaction intermediates. Cyclodehydration with $POCl_3$ suppresses hydrolysis of the trifluoromethyl group and provides 2-trifluoroethylbenzimidazoles in good yields.

Fluorine containing molecules are found in increasing numbers in small molecule drug discovery efforts.[1] Because of its small size and high electronegativity, fluorine often imparts unique properties to a molecule. Investigators at Johnson & Johnson recently reported that trifluoroethyl substitution at the 2-position of benzimidazole androgen receptor antagonists enhanced activity.[2] Our own efforts to incorporate fluorinated functionality in the course of a recent drug discovery project led us to investigate the synthesis of 2-trifluoroethylbenzimidazoles from precursor diamines **2** (Eq. 1).



1 **2** (1)

Precedent for the preparation of 2-trifluoroethylbenzimidazoles is limited to a few examples found in the patent literature. In these cases, the desired benzimidazoles were prepared either by condensation of 1,2-diaminobenzene with 3,3,3-trifluoropropionic acid in aqueous HCl or by cyclodehydration of *N*-2-aminophenyl-3,3,3-trifluoropropanamides under acidic conditions.[3] However, attempts to apply these conditions[3a] to directly transform diamine **2** did not produce any desired benzimidazole **1** (Eq. 2). Instead, 2-methylbenzimidazole **3**[4] was observed in small amounts.



2 **3** (2)

Diamine **2** could be acylated to provide trifluoromethylacetyl derivative **4** (Eq. 3). Subjecting **4** to acidic conditions[3b,c] again afforded **3**, this time with complete conversion (Table 1, entries 1 and 2). No evidence for formation of **1** was observed. However, upon expanding our survey to additional cyclodehydration conditions, we were pleased to find that $POCl_3$[5] effected complete conversion to **1** with no detectable contamination by **3**.

Because **3** is produced from **1** even when acetic acid is not present in the reaction mixture (entry 2), formation of **3** appears to proceed via loss of the trifluoromethyl group of **4**. We hypothesized that desired product **1** might be formed under acid-mediated conditions before decomposing to **3.** To test this hypothesis, **1** was heated in acetic acid or ethanolic HCl, and we observed a clean conversion to **3** under both conditions (Scheme 1).

While LC/MS monitoring of this reaction did not reveal any intermediate species, we postulated that carboxylic acid **5** might be formed under acidic conditions and subsequently undergo rapid decarboxylation to give **3**. Hydrolysis of **1** is consistent with earlier reports of methanolysis of trifluoromethyl groups under acidic[6] or basic[7] conditions. To capture the carboxylic acid intermediate, **1** was treated with 1(N) aqueous NaOH solution. This indeed effected a clean conversion of **1** to **5** (confirmed by LC/MS and HRMS). Attempted isolation of **5** from the basic medium resulted in a mixture of **5** and **3** (2:1); this observation is consistent with rapid decarboxylation of **5** under non-basic conditions.

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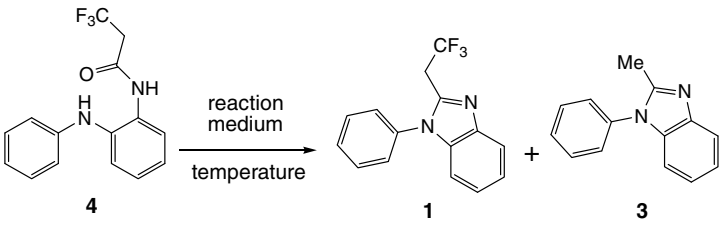
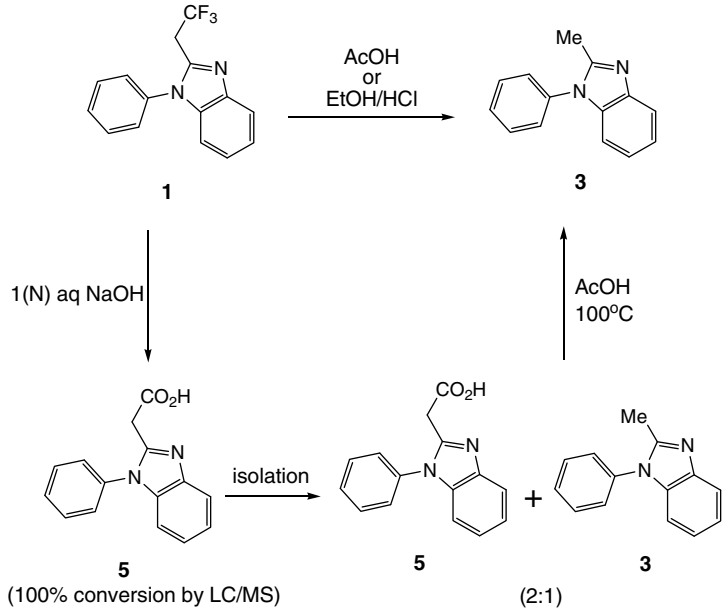
Table 1
Cyclization of amide **4**



4 1 3 (3)

Entry	Reaction medium	Temperature (°C)	Ratio of 1:3[a]
1	AcOH	100	(0:100)[b]
2	EtOH/HCl (satd)	80	(0:100)
3	$POCl_3$	100	(100:0)[c]

[a] Observed by LC/MS.
[b] Isolated yield: 99%.
[c] Isolated yield: 97%.



Scheme 1.

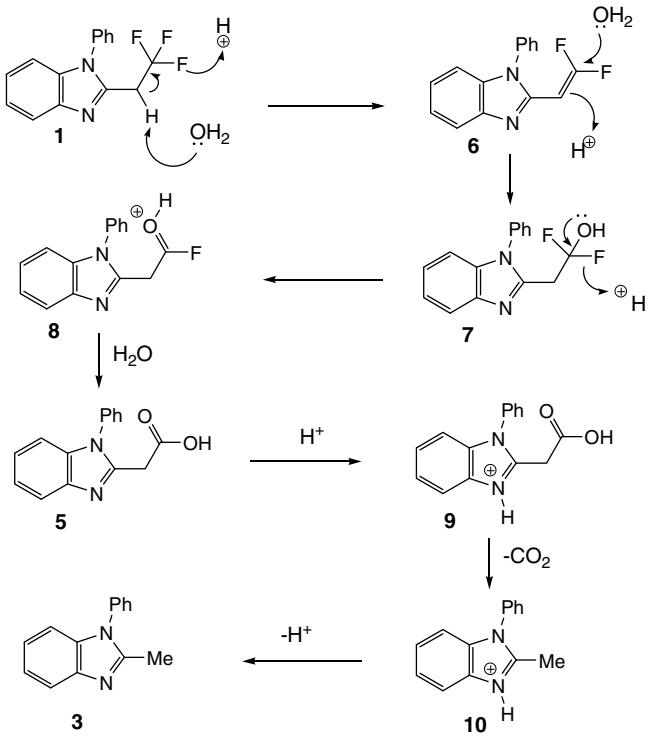
Heating the isolated mixture in acetic acid at 100 °C resulted in complete conversion to **3**.

The proposed mechanism shown in Scheme 2 for loss of the trifluoromethyl group is consistent with these observations. 2-Trifluoroethylbenzimidazole **1** can eliminate HF to give difluoroalkene **6**.[8] Addition of water to **6** provides **7**, which can collapse to acylfluoride **8**. Hydrolysis[9] and decarboxylation would afford **3**.[10] This proposal is also consistent with the successful application of $POCl_3$ to the synthesis of **1**. This reaction medium provides essentially anhydrous conditions and thus precludes the hydrolysis steps necessary to remove the trifluoromethyl group.

The scope of this method was explored using a range of diamines. In practice, treatment of diamines with 3,3,3-trifluoropropionyl chloride under Schotten-Baumann conditions followed by cyclization in $POCl_3$ provides 2-trifluoroethylbenzimidazoles in excellent yields. Table 2 summarizes the results. Steric bulk on the amino group does not affect the efficiency (entries 1, 2, and 3) of this method. The overall yield obtained from the unsubstituted diamine (entry 4) was compromised slightly by the formation of a 1,2-bis(trifluoropropanamide) in the first step. Different functional groups such as ester (entry 3), methoxy (entry 5), and nitrile (entry 6) were also tolerated. This methodology can also be used to make trifluoroethyl-aza-benzimidazoles (entry 8) in good yield.

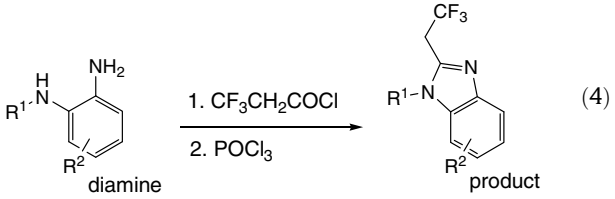
In summary, we have identified an unusual hydrolytic transformation of 2-trifluoroethylbenzimidazoles.[11] While this transformation prevents formation of fluorinated heterocycles under conventional acidic cyclization conditions, use of $POCl_3$ to establish an anhydrous reaction medium provides access to **1**. The conditions established here provide straightforward and reliable access to this class of fluorinated heterocycles.

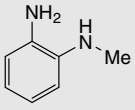
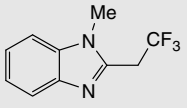
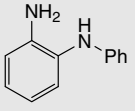
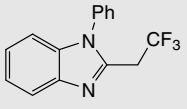
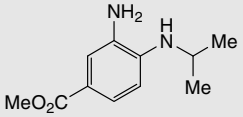
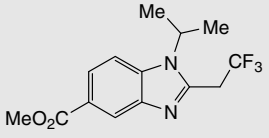
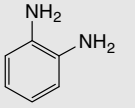
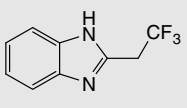
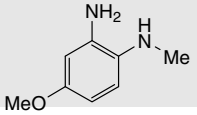
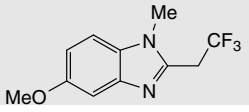
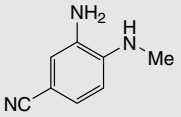
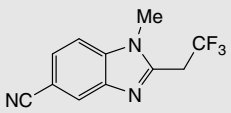
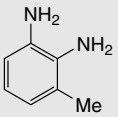
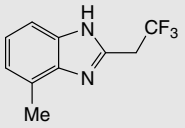
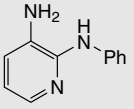
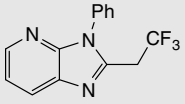
Typical reaction procedure: To a vigorously stirred biphasic mixture of a solution of *N*-phenyl-*o*-phenylenediamine (500 mg, 2.714 mmol) in dichloromethane (40 mL) and saturated aqueous $NaHCO_3$ solution (25 mL) at 0 °C was added a solution of 3,3,3-trifluoropropionyl chloride (0.711 g, 2.985 mmol) in dichloromethane (10 mL) dropwise. After stirring the reaction mixture for 1 h, the aqueous solution was extracted with dichloromethane (3×). The combined organic solutions were dried over Na_2SO_4 and concentrated to give *N*-(2-anilinophenyl)-3,3,3-trifluoropropanamide



Scheme 2.

Table 2
Formation of 2-trifluoroethylbenzimidazoles



Entry	Diamine	Product	Yield[a] (%)
1			94
2			97
3			76
4			70
5			67
6			66
7			80
8			72

[a] Isolated yield from diamine. All compounds were >95% pure by ^{1}H NMR and were positively identified by HRMS analysis.

(800 mg, 100%). The crude *N*-(2-anilinophenyl)-3,3,3-trifluoropropanamide (225 mg, 0.765 mmol) was dissolved in $POCl_3$ (15 mL) and heated at 100 °C for 3.5 h. The reaction mixture was then cooled to room temperature and concentrated. The resulting viscous residue was dissolved in dichloromethane (30 mL) and cooled to 0 °C, and a saturated aqueous $NaHCO_3$ solution was added slowly until the aqueous layer became basic. The aqueous solution was separated and extracted with dichloromethane (3×). The combined organic solutions were dried over Na_2SO_4 and concentrated. Purification by reversed phase HPLC (30 × 100 mm Phenomenex Gemini (5–85% MeCN/water containing 0.05% NH_4OH over 20 min at 50 mL/min) afforded 1-phenyl-2-(2,2,2-trifluoroethyl)-1-*H*-benzimidazole as a white solid (205 mg, 97%). HRMS calcd for $C_{15}H_{12}F_3N_2$ ($M+H^+$): 277.0947; found 277.0948. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, 1H, J = 8.08 Hz), 7.64–7.56 (m, 3H), 7.38–7.31 (m, 3H), 7.28 (dd, 1H, J = 7.75, 1.04 Hz), 7.12 (dd, 1H, J = 8.10, 1.05 Hz), 3.67 (q, 2H, J = 9.87 Hz).

Acknowledgments

We thank Charles Ross and Joan Murphy for HRMS data.

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2. (a) Ng, R. A.; Guan, J.; Alford, V. C., Jr.; Lanter, J. C.; Allan, G. F.; Sbriscia, T.; Linton, O.; Lundeen, S. G.; Sui, Z. *Bioorg. Med. Chem. Lett.* **2007**, 784; (b) Ng, R. A.; Guan, J.; Alford, V. C., Jr.; Lanter, J. C.; Allan, G. F.; Sbriscia, T.; Lundeen, S. G.; Sui, Z. *Bioorg. Med. Chem. Lett.* **2007**, 955; (c) Ng, R. A.; Lanter, J. C.; Alford, V. C., Jr.; Allan, G. F.; Sbriscia, T.; Lundeen, S. G.; Sui, Z. *Bioorg. Med. Chem. Lett.* **2007**, 1784.
3. (a) Ng, R.; Sui, Z.; Guan, J.; Lanter, J. C.; Alford, V. C., Jr. Novel Benzimidazole Derivatives Useful As Selective Androgen Receptor Modulators (SARMS). WO 2006/039243 A1, 2006; (b) Liu, Z.; Milburn, C.; Page, D.; Walpole, C.; Yang, H. Benzimidazole Derivatives, Compositions Containing Them, Preparation Thereof And Uses Thereof. WO 2005/030762 A1, 2006; (c) Anderskewitz, R.; Martyres, D.; Dollinger, H.; Pouzet, P.; Birke, F.; Bouyssou, T. Haloalkyl- and Piperidine-Substituted Benzimidazole-Derivatives. WO 2005/019203 A1, 2005.
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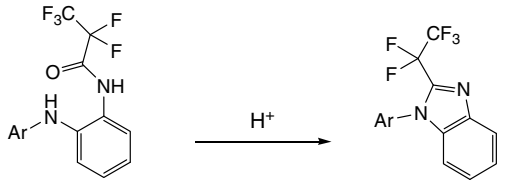
5. While $POCl_3$ has not been previously employed in the synthesis of 2-trifluoroethylbenzimidazoles, this reagent has been successfully used to prepare non-fluorinated benzimidazoles by cyclodehydration. For example: (a) Kurasawa, Y.; Shimabukuro, S.; Okamoto, Y.; Takeda, A. *Heterocycles* **1985**, *23*, 65; (b) Walser, A.; Flynn, T.; Mason, C. J. *J. Heterocycl. Chem.* **1991**, *28*, 1121; (c) Stefancich, G.; Artico, M.; Corelli, F.; Massa, S. *Synthesis* **1983**, 757.
6. South, M. S. *J. Heterocycl. Chem.* **1991**, *28*, 1013.
7. (a) Ramig, K.; Englander, M.; Kallashi, F.; Livchits, L.; Zhou, J. *Tetrahedron Lett.* **2002**, *43*, 7731; (b) Mechoulam, R.; Cohen, S.; Kaluszyner, A. *J. Org. Chem.* **1956**, *21*, 801; (c) Haider, N.; Wanko, R. *Heterocycles* **1994**, *38*, 1805; (d) Kobayashi, Y.; Kumadaki, I.; Hirose, Y.; Hanzawa, Y. *J. Org. Chem.* **1974**, *39*, 1836; (e) King, J. F.; Gill, M. S. *J. Org. Chem.* **1996**, *61*, 7250; (f) Uneyama, K.; Morimoto, O. *Tetrahedron Lett.* **1989**, *30*, 109.

8. Consistent with this is our observation that compound **11**, which cannot eliminate HF, converts cleanly to **12** under acidic conditions. No evidence for loss of the trifluoromethyl group was observed.



11 **12**

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9. Hydrolysis of perfluorinated alkenes has been observed under acidic and basic conditions. For example: (a) England, D. C. *J. Org. Chem.* **1981**, *46*, 147; (b) Ishikawa, N.; Takaoka, A.; Ibrahim, K. *J. Fluorine Chem.* **1984**, *25*, 203.
10. Protonation of the benzimidazole nitrogen is likely under acidic conditions and may favor the decarboxylation event. Consistent with this, indole-2-acetic acids are stable and can be prepared by hydrolysis of the corresponding esters. For example: (a) Weber, D.; Berger, C.; Eickelmann, P.; Antel, J.; Kessler, H. *J. Med. Chem.* **2003**, *46*, 1918; (b) Karrick, G. L.; Peet, N. P. *J. Heterocycl. Chem.* **1986**, *23*, 1055.
11. All 2-trifluoroethylbenzimidazoles listed in Table 2 are transformed to the corresponding 2-methylbenzimidazoles when heated in AcOH at 100 °C (observed by LC/MS).