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Transformation of Anionically Activated Trifluoromethyl Groups to Heterocycles under Mild Aqueous Conditions

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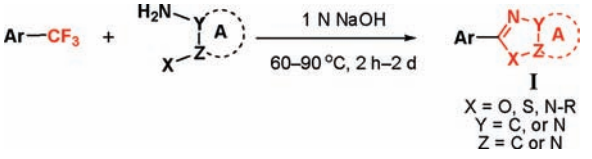
ABSTRACT



The (hetero)aromatic trifluoromethyl group is present in many biologically active molecules and is generally considered to be chemically stable. In this paper, a convenient one-step synthesis of C−C linked aryl−heterocycles or heteroaryl−heterocycles in good to excellent yields via the reaction of anionically activated trifluoromethyl groups with amino nucleophiles containing a second NH, OH, or SH nucleophile in 1 N sodium hydroxide is reported. The method has high functional group tolerability and is potentially useful in parallel synthesis.

The aromatic trifluoromethyl (CF_3) group is extensively present in biologically active molecules because of its unique physical properties and chemical stability.[1] As a result, hundreds of CF_3-containing compounds are commercially available. Recently, it has been reported that the CF_3 group can be readily incorporated via either Qing-modified Chan−Lam coupling from arylboronic acids[2] or Buchwald-modified Hiyama coupling from aryl chlorides.[3] Incorporation of the CF_3 group into a lead molecule may increase lipophilicity, resulting in enhanced binding activity or selectivity, and/or chemical or metabolic stability. However, subsequent analoging from the CF_3 group in an advanced lead molecule is challenging because aromatic CF_3 groups are generally considered inert to organic transformations. Nevertheless, the CF_3 group in phenols, anilines, or NH-containing heterocycles, when appropriately positioned, can be anionically activated, i.e., the CF_3 functionality can be conjugated with ionizable NH or OH groups. The anionically activated CF_3 group has been reported to undergo several transformations,[4−7] such as formation of 2-hydroxybenzoic acid,[4] tertiary amides,[5] and heterocycles such as benzothiazoles and benzoxazoles.[6] These heterocycles were obtained in low to moderate yields from the anions and dianions generated in situ with strong bases such as *n*-BuLi.

In a previous in-house structure−activity relationship (SAR) study, we transformed an anionically activated aromatic CF_3 moiety in a lead molecule to functional groups such as carboxylic acid, esters, nitrile, amides,

(1) (a) Boehm, H.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Mueller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637–643. (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214–231. (c) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432–5446. (d) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975–996. (e) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886. (f) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (g) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369.

(2) (a) Chu, L.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 5060–5063 and refrences cited therein. (b) For a recent review on Chan−Lam coupling, see: Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829−856.

(3) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679–1681 and references cited therein.

(4) (a) Jones, R. G. *J. Am. Chem. Soc.* **1947**, *69*, 2346–2350. (b) Belcher, R.; Stacey, M.; Sykes, A.; Tatlow, J. C. *J. Chem. Soc.* **1954**, 3846–3851.

(5) O'Mahony, G.; Pitts, A. K. *Org. Lett.* **2010**, *12*, 2024–2027.

(6) (a) Wydra, R. L.; Patterson, S. E.; Strekowski, L. *J. Heterocycl. Chem.* **1990**, *23*, 803–805. (b) Kiselyov, A. S.; Hojjat, M.; Van Aken, K.; Strekowski, L. *Heterocycles* **1994**, *37*, 775–782.

(7) (a) Kiselyov, A. S.; Strekowski, L. *Org. Prep. Proced. Int.* **1996**, *3*, 289–318 and references cited therein. (b) Strekowski, L.; Lin, S.; Nguyen, J.; Redmore, N. P.; Mason, J. C.; Kiselyov, A. S. *Heterocycl. Commun.* **1995**, *5*−*6*, 331–334. (c) Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.* **1978**, *5*, 197–204.

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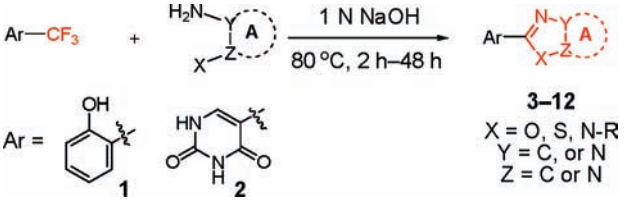
and nitrogen-containing heterocyclic compounds.[8] A common theme runs throughout these reactions and the aforementioned literature examples: the activated CF_3 group eliminates HF with the assistance of a base, to generate a key quinodifluoromethide intermediate that is susceptible to nucleophilic addition. Repetitive base-induced HF elimination and addition of nucleophiles leads to the replacement of all three fluorine atoms in the CF_3 group by the nucleophiles. This implies that in drug design, one either can *utilize* an anionically activated CF_3 to design suicide substrates[9] or *avoid* an activated CF_3 in a drug molecule to prevent the potential formation of the active difluoromethide intermediate in vivo.

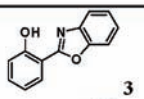
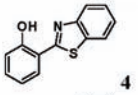
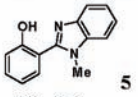
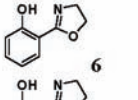
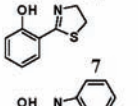
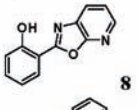
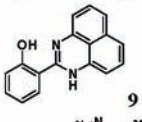
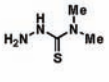
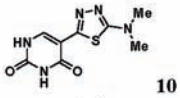
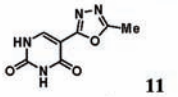
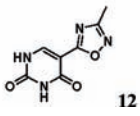
C−C linked aryl−heterocycle or heteroaryl−heterocycle structure motifs with a general structure of **I** are used extensively as building blocks to construct numerous pharmaceutical agents with a diverse range of biological properties. The most popular approaches to construct **I** involve either condensation of an aromatic/heteroaromatic carboxylic acid or its derivatives to form the second heterocyclic ring, or Suzuki−Miyaura coupling of aromatic/heteroaromatic boronic acid or derivatives with the halide of the second heterocyclic ring. These methods have limitations, however: some of the condensation reactions are performed under harsh conditions with strong acids at high temperature; some of the heterocyclic carboxylic acids are water-soluble and are not easy to handle; while some of the heteroaromatic boronic acids or derivatives and the halides of the heterocyclic rings are either expensive or not readily available. Therefore, there continues to be a need for alternate mild methods, as illustrated by the many recent publications.[10]

Herein, we report an efficient one-step transformation of anionically activated aromatic/heteroaromatic trifluoromethyl groups into a variety of nitrogen-containing heterocycles in good to excellent yields under mild aqueous conditions in the absence of organic solvents to form C−C linked aryl−heterocycles and heteroaryl−heterocycles, a subset of compounds with general structure **I**.

Treating the anionically activated aromatic CF_3 group as a masked carboxylic acid group, we synthesized different types of heterocycles **3**−**12** in good to excellent yields from two commercially available substrates 2-CF_3-phenol **1** or 5-CF_3-uracil **2** (1.0 equiv) and a list of representative NH_2-containing nucleophiles (1.0−1.4 equiv) in 1 N NaOH (3−4 equiv) at 40 to 90 °C (Table 1). To the best of our knowledge, this is the first report of the formation of

Table 1. Formation of Heterocycles from 2-CF_3-Phenol **1** and 5-CF_3-Uracil **2**



entry	Ar–CF_3	NH_2–Y–Z–X	product	time (h)	yield (%)[a]
1	1		 **3**	2	94
2	1		 **4**	2	88
3	1		 **5**	5	71
4	1		 **6**	6[b]	55
5	1		 **7**	6[b]	74
6	1		 **8**	2	68
7	1		 **9**	12[c]	82
8	2		 **10**	48	69
9	2		 **11**	48	88
10	2		 **12**	48	80

[a] Isolated yield of analytically pure products. [b] Reaction performed at 40 °C. [c] Reaction performed at 90 °C.

azabenzoxazole (entry 6), 1*H*-pyrimidine (entry 7), 1,3,4-thiadiazole (entry 8), 1,3,4-oxadiazole (entry 9), and 1,2,4-oxadiazole (entry 10) from an anionically activated CF_3 group. Thus, reaction of **1** with 3-aminopyridin-2-ol and 1,8-diaminonapthalene gave azabenzoxazole **8** and 1*H*-pyrimidine **9** in 68% and 82% yield, respectively. Similarly, treatment of **2** with thiohydrazide, hydrazide, and hydroxyamidine in 1 N NaOH (4 equiv) at 80 °C for two days afforded the corresponding 1,3,4-thiadiazole **10**, 1,3,4-oxadiazole **11**, and 1,2,4-oxadiazole **12** in 68%, 88%, and 80% yield, respectively. In contrast, compound **12**, a

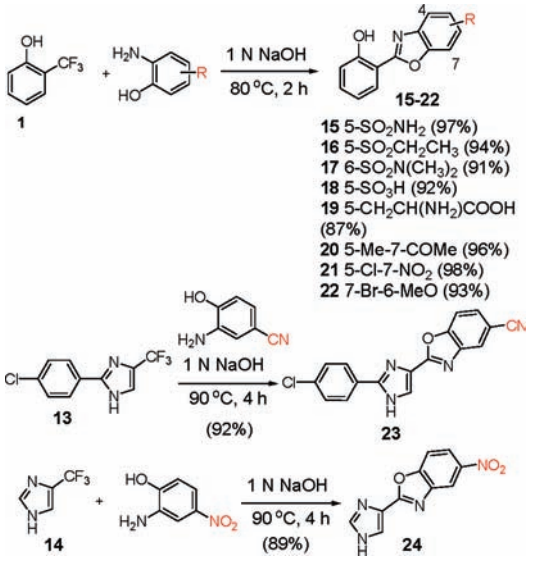
(8) Detailed chemistry and SAR results will be disclosed in due course.

(9) Betley, J. R.; Cesaro-Tadic, S.; Mekhalfia, A.; Rickard, J. H.; Denham, H.; Partridge, L. J.; Pluckthun, A.; Blackburn, G. M. *Angew. Chem., Int. Ed.* **2002**, *5*, 775–777.

(10) Examples of recent developments in the synthesis of C−C linked aryl−heterocycles and heteroaryl−heterocycles: (a) Sardarian, A. R.; Shahsavari-Fard, Z. *Synlett* **2008**, 1391–1393. (b) Moghaddam, F. M.; Bardajee, G. R.; Ismaili, H.; Taimoory, S. M. D. *Synth. Commun.* **2006**, *36*, 2543–2548. (c) Ma, D.; Xue, P.; Jiang, Y.; Xie, S.; Zhang, X.; Dong, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4222–4225. (d) Mukhopadhyay, C.; Datta, A. *Heterocycles* **2007**, *71*, 1837–1842. (e) Bahrami, K.; Khodaei, M. M.; Naali, F. *J. Org. Chem.* **2008**, *73*, 6835–6837. (f) Bahrami, K.; Khodaei, M. M.; Naali, F. *Synlett* **2009**, 569–572.

substructure in a series of potential modulators of dopamine D3 receptors, was made as crude in 4 steps from 2,4-dimethoxypyrimidine-5-carbaldehyde in 10% yield.[11]

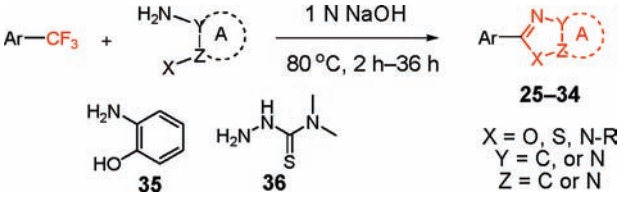
Scheme 1. Functional Group Tolerability in the Transformation of 2-CF_3-Phenol **1** and 4-CF_3-Imidazoles **13** and **14** to Benzoxazole **15**−**24**

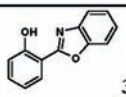
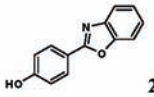
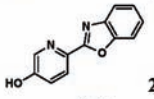
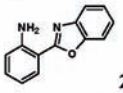
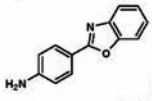
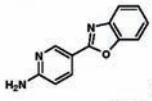
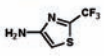
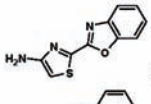
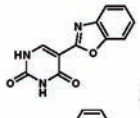
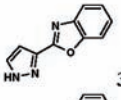
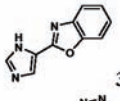
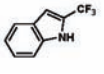
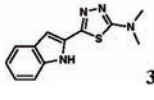


We next evaluated the functional group tolerability in the formation of substituted benzoxazoles from either 2-CF_3-phenol **1** or imidazole analogues **13** and **14** with substituted 2-aminophenols as nucleophiles. As shown in Scheme 1, novel 2-(2′-hydroxy)phenylbenzoxazoles **15**−**24** were obtained in high yields in the presence of a variety of functional groups, such as amino, nitro, halogen, carboxylic acid, cyano, ether, ketone, sulfone, sulfonamide, and sulfonic acid. The transformation is evidently more advantageous than the dianion chemistry[6] with use of strong bases, and complementary to the condensation reactions with acids such as *p*-TSA.[12] In addition, the functional groups in **15**−**24** can be transformed into other groups, further diversifying the structures of C−C linked aryl−heterocycles and heteroaryl−heterocycles.

Several commercially available anionically activated aromatic/heteroaromatics CF_3 substrates were successfully transformed to heterocycles **3** and **25**−**34** by using either 2-aminophenol **35** or *N*,*N*-dimethylhydrazinecarbothioamide **36** as the nucleophile (Table 2). 2- and 4-CF_3-phenol as well as 5-OH-2-CF_3-pyridine afforded benzoxazole **3**, **25**, and **26** in excellent yields. 4-CF_3-aniline afforded **28** in 84% yield; 2-CF_3-aniline, on the other hand, reacted much more slowly to give **27** in only 42% yield, with ca. 50% remaining of 2-CF_3-aniline. The anionically activated CF_3 group in amino heterocycles (entries 6 and 7) can also afford the corresponding benzoxazoles **29** and **30**

Table 2. Regioisomeric and Other Anionically Activated CF_3 Groups in the Formation of Heterocycles **3** and **25**−**34**



entry	Ar–CF_3	NH_2–Y–Z–X	product	time (h)	yield (%)[a]
1		35	 **3**	2	94
2		35	 **25**	2	98
3		35	 **26**	6	95
4		35	 **27**	24	42
5		35	 **28**	2	84
6		35	 **29**	16	84
7		35	 **30**	24	45
8		35	 **31**	2	98
9		35	 **32**	24	86
10		35	 **33**	4[b]	76
11		36	 **34**	36	58

[a] Isolated yield of analytically pure products. [b] Reaction performed at 90 °C.

in good yields. Previously, 5-(6-methoxybenzo[*d*]oxazol-2-yl)pyridin-2-amine, an analogue of **29**, was prepared by using Suzuki−Miyaura coupling of 2-Br-6-MeO-benzoxazole and the 5-pinacol boronic ester of 2-aminopyridine in 32% yield.[13] Anionically activated CF_3 groups in NH-containing heterocycles, such as 5-CF_3-uracil (entry 8),

(11) Bertani, B.; Cardullo, F.; Dambruoso, P.; Marzorati, P.; Micheli, F.; Pasquarello, A.; Seri, C.; Tedesco, G. WO2009/043883 A1.

(12) Samota, M. K.; Seth, G. *Heteroat. Chem.* **2010**, *21*, 44–50.

(13) Malmstrom, J.; Pyring. D.; Slivo, C.; Sohn, D.; Swahn, B.-M.; Wensbo, D. WO2007/149030 A1.

3-CF_3-pyrazole (entry 9), 2-CF_3-indole (entry 10), and 4-CF_3-imidazole (entry 11), were also transformed to the corresponding heterocycles **31**−**34** in good yields. Reaction yields for known compounds were generally better than or similar to those reported with use of other synthetic methods.[10,14] Products collected after simple workup were usually more than 95% pure judged by ^1H, ^{13}C NMR, and orthogonal HPLC. Impure products were purified by either flash chromatography or recrystallization. In most cases, the corresponding carboxylic acid side product[4] was not observed.

Hydroxy, amino group, or NH-containing heterocycles in products **3**−**12** and **15**−**34** can serve as an anchor point to further diversify the molecular structure. For example, in the literature, 1-benzyl-3-benzoxazole pyrazole **37** was assembled by a two-step *N*-benzylation/Suzuki coupling sequence from 3-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazole in 20% yield.[15] Complementarily, addition of 1.0 equiv of 3-CF_3-benzyl bromide to the mixture of entry 9 in Table 2 (crude **32**) at 80 °C for 1 h gave **37** in 25% yield. The other regioisomer was obtained in 13% yield.

The limitation of the methodology is obvious: only substrates containing an activated CF_3 group that can eliminate HF with the assistance of OH^- to form a quinone methide intermediate **39** may react (see Scheme 2 for the proposed mechanism of NaOH-induced benzoxazole formation of **3**). Thus, 3-CF_3-phenol and 6-CF_3-uracil remained unchanged under the reaction conditions. When the heterocycle ring formed was not aromatic, such as in entry 4 of Table 1, a substantial amount of uncyclized 2-hydroxy-*N*-(2-hydroxyethyl)-benzamide **38** was produced, though **38** can be converted to cyclic **6** with thionyl chloride.[10f] When using *N*-methyl-hydrazine-carbothioamide instead of **36** as the nucleophile, ca. 1:1 mixture of **41** and **42** was observed by LC-MS, indicating both NHMe and S can act as the nucleophile in the final ring formation step, different from the normal condensation reaction wherein thiadiazole **41** would be exclusively formed.

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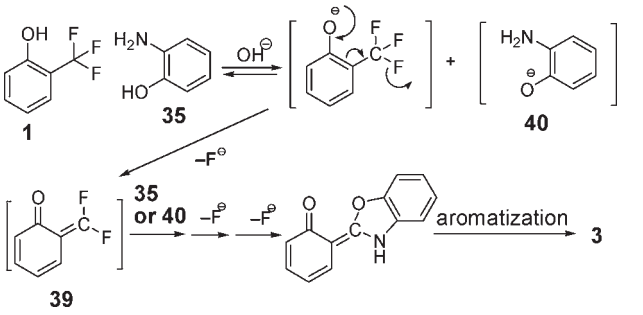
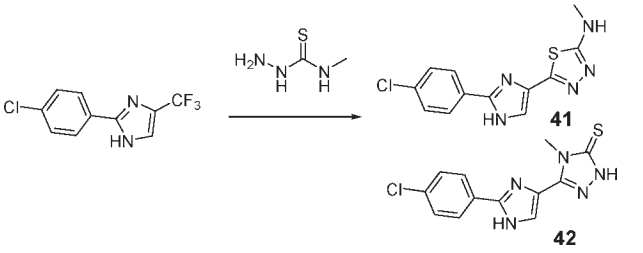
Scheme 2. Proposed Mechanism for the Formation of Heterocycles Such As Benzoxazole **3** from **1** and **35**





In summary, we developed a one-step, mild, and efficient transformation of anionically activated (hetero)aromatic CF_3 groups to various nitrogen-containing heterocycles to form a diverse set of C−C linked aryl−heterocycles or heteroaryl−heterocycles. The advantages of this method include the following: mild aqueous conditions and an organic solvent-free reaction, high functional group tolerability, high-yielding reactions with simple workup and purification procedures, opportunity for further diversification on either ring or functional groups, and the potential for scale-up and parallel synthetic applications.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.