Heterocycle Synthesis

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Benzylic C(sp^3)–H Perfluoroalkylation of Six-Membered Heteroaromatic Compounds

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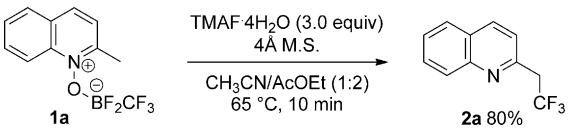
Abstract: *Successful benzylic C(sp^3)–H trifluoromethylation, pentafluoroethylation, and heptafluoropropylation of six-membered heteroaromatic compounds were achieved as the first examples of a practical benzylic C(sp^3)–H perfluoroalkylation. In these reactions, $BF_2C_nF_{2n+1}$ ($n=1$–3) functioned as both a Lewis acid to activate the benzylic position and a C_nF_{2n+1} ($n=1$–3) source. The perfluoroalkylation proceeded at both terminal and internal positions of the alkyl chains. Perfluoroalkylated products were obtained in moderate to excellent yields, even on gram scale, and in a sequential procedure without isolation of the intermediates. By using this method, trifluoromethylation of a bioactive compound, as well as introduction of a CF_3 group into a bioactive molecular skeleton, proceeded regioselectively.*

Fluorinated functional groups, including a trifluoromethyl group, play important roles in many drugs, agrochemicals, and organic functional materials,[1] and generally improve the bioactivity, metabolic stability, lipophilicity, and physical properties of organic functional molecules. Thus, the development of highly efficient and practical methods to introduce fluorinated functional groups is highly desirable. Together with C(sp^2)–CF_3 bond-forming reactions,[2–4] there are many examples of reactions to construct a C(sp^3)–CF_3 bond, such as the addition of anionic CF_3 species to carbonyl groups,[5] trifluoromethylation at the α-position of carbonyl compounds,[6] addition of a CF_3 radical to alkenes,[7] and cross-coupling reactions.[8] However, the examples of C(sp^3)–CF_3 bond-formation reactions by C(sp^3)–H trifluoromethylation are still rare.[9,10]

Herein we successfully developed a new C(sp^3)–CF_3, C(sp^3)–C_2F_5, and C(sp^3)–C_3F_7 bond-forming reactions through benzylic C(sp^3)–H trifluoromethylation, pentafluoroethylation, and heptafluoropropylation, respectively, of six-membered heteroaromatic compounds. This reaction can efficiently provide pyridine and quinoline derivatives with either a trifluoroethyl,[11,12] pentafluoropropyl, or heptafluorobutyl group. The characteristic features of this reaction are as follows: 1) using N-heteroaromatic *N*-oxide/$BF_2C_nF_{2n+1}$ ($n=1$–3) complexes as substrates; the boranes $BF_2C_nF_{2n+1}$ work as both Lewis acids and perfluoroalkylation reagents; 2) this is a rare example of a C(sp^3)–C_nF_{2n+1} bond-formation reaction by C(sp^3)–H perfluoroalkylation; and 3) the C(sp^3)–C_nF_{2n+1} bond formation can be achieved without using a transition-metal catalyst. In C(sp^3)–H perfluoroalkylation, reductive elimination to form the C–CF_3 bond is generally difficult, therefore, the use of an oxidant is necessary to generate a higher oxidation state of the catalytic center to achieve reductive elimination.[4a]

We previously reported that BF_2CF_3 complexes of heteroaromatic *N*-oxides are stable, yet very strongly activated electrophilic aromatic compounds, thus allowing C2-selective aromatic C(sp^2)–H trifluoromethylation with a very weak CF_3 nucleophile.[4f] Applying these reaction conditions [Me_3SiCF_3 (3.0 equiv) and CsF (3.0 equiv) in ethyl acetate at 25 °C for 3 h] to the 2-methylquinoline *N*-oxide/BF_2CF_3 complex **1a** gave 2-(2,2,2-trifluoroethyl)quinoline (**2a**) in 9% yield. To improve the yield of **2a**, we screened several bases other than CsF. Tetramethylammonium fluoride tetrahydrate (TMAF·4H_2O) proved to be a better base, and **2a** was obtained in 38% yield. Interestingly, the trifluoromethylation reaction also proceeded without the use of Me_3SiCF_3, thus giving **2a** in 30% yield. This finding indicated that the BF_2CF_3 group acted as both a Lewis acid and a trifluoromethylation reagent, and is in sharp contrast to our previous C(sp^2)–H trifluoromethylation in which the BF_2CF_3 group did not function as a CF_3 source and Me_3SiCF_3 was essential as an external trifluoromethylation reagent.[4f] Optimization of the reaction conditions dramatically improved the yield of **2a**. Treatment of **1a** with TMAF·4H_2O in acetonitrile/ethyl acetate (1:2) at 65 °C for 10 minutes gave **2a** in 80% yield [94% yield (NMR); Eq. (1); M.S. = molecular sieves].[13] The



(1)

reaction even proceeded at 25 °C and **2a** was obtained in 80% yield (NMR) after 11 hours. In some cases, an acetonitrile adduct [3-(quinolin-2-yl)propanenitrile] was formed in acetonitrile. Therefore, a mixed solvent (acetonitrile and ethyl acetate) was used to suppress the formation of the adduct. The trifluoromethylation of the quinoline ring did not occur at all.

Under the optimized reaction conditions, we investigated the substrate scope of six-membered heteroaromatic com-

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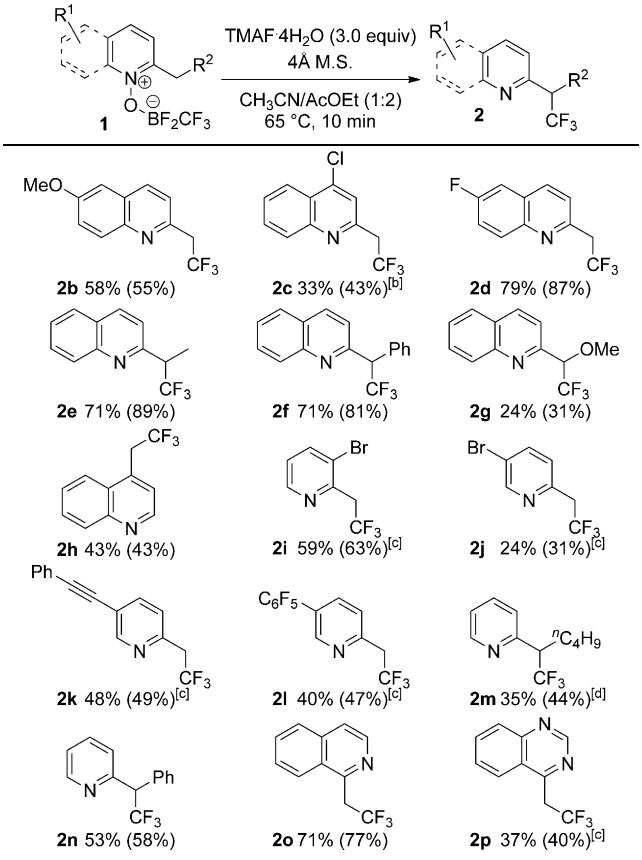
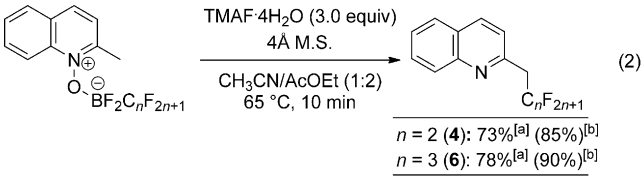
Table 1: Benzylic trifluoromethylation of six-membered heteroaromatic compounds.[a]



[a] Yield of isolated product is given. Value within parenthesis represents the yield as determined by ^{19}F NMR analysis of the crude reaction mixture using 1,4-difluorobenzene as an internal standard. [b] CH_3CN, 25 °C, 24 h. [c] 1 h. [d] CH_3CN, 1 h.

pounds (Table 1). The trifluoromethylation reaction proceeded in moderate to excellent yields using quinoline substrates. Quinoline *N*-oxide/BF_2CF_3 complexes (**1b–d**) bearing either an electron-donating or electron-withdrawing group gave the corresponding trifluoromethylated products (**2b–d**) without loss of the functional groups. The trifluoromethylation reaction also occurred at the internal benzylic positions and produced the trifluoromethylated quinolines **2e–g**. Interestingly, the trifluoromethylation reaction also proceeded at the 4-methyl group of the quinoline *N*-oxide/BF_2CF_3 complex **1h**, and produced the corresponding trifluoromethylated product **2h** without generating any C2-trifluoromethylated product. In contrast, the yields of the trifluoromethylated products **2j–m** were lower when using the pyridine substrates **1j–m**. The yields of **2i** and **2n** were higher when using the complexes **1i** and **1n**, respectively, as substrates. The trifluoromethylated products **2o** and **2p** were also obtained using other heteroaromatic substrates, such as isoquinoline and quinazoline derivatives. The trifluoromethylation reaction also took place at the tertiary C(sp^3)–H bond of 2-isopropylquinoline, but the yield of the product was low (17%). This reaction is a rare example of the construction of tertiary carbon–CF_3 bond.[14] The trifluoromethylation reaction did not proceed using *N*-oxide-BF_2CF_3 complexes of 2-(chloromethyl)quinoline, 6-methylnicotinonitrile, 2-methyl-4-nitropyridine, 2-bromo-6-methylpyridine, (5-acetoxy-6-methylpyridine-3,4-diyl)bis(methylene) diacetate, 4,6-dimethylpyrimidine, and 2,3-dimethylquinoxaline as substrates.

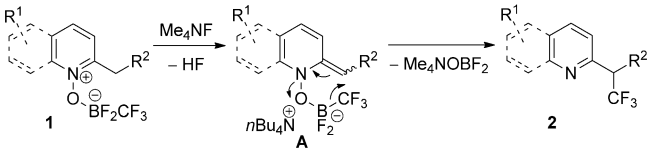
Other fluorinated alkyl groups were also investigated [Eq. (2)]. Pentafluoroethylated and heptafluoropropylated products, **4** and **6**, respectively, were obtained in good yields when the corresponding 2-methylquinoline *N*-oxide/$BF_2C_2F_5$ **3** and 2-methylquinoline *N*-oxide/$BF_2C_3F_7$ complex **5** were used as substrates. The desired reaction did not proceed in the case of 2-methylquinoline *N*-oxide/$BF_2C_6F_5$ complex.



(2)

[a] Yield of isolated product. [b] Yield as determined by ^{19}F NMR analysis.

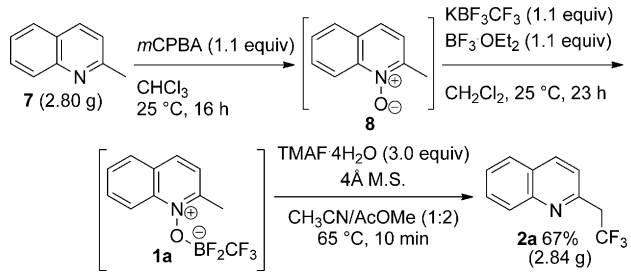
The trifluoromethylation reaction of **1a** was not inhibited by the radical scavenger galvinoxyl (see the Supporting Information), thus indicating that it does not proceed by a radical pathway. A plausible reaction mechanism is described in Scheme 1. 1) Formation of the enamine-type



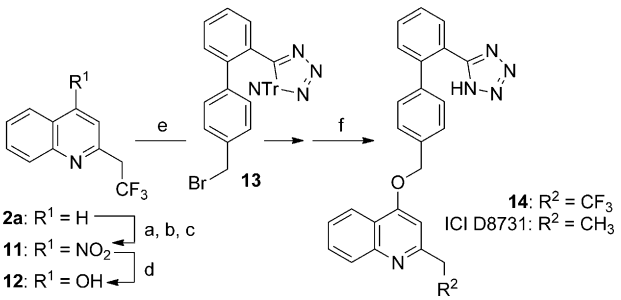
Scheme 1. Proposed mechanism for benzylic C(sp^3)–H trifluoromethylation.

intermediate **A** by deprotonation of the *N*-oxide/BF_2CF_3 complex **1** with TMAF;[15] and 2) nucleophilic attack of the CF_3 group on the enamine moiety to give **2** along with the elimination of Me_4NOBF_2. For **1**, the acidity of the benzylic proton is significantly enhanced by the strong Lewis acid, BF_2CF_3, and electron-withdrawing substituents, thus leading to facile deprotonation by TMAF. In addition, **A** must be stabilized by π-conjugated systems because the trend with respect to the yields of the trifluoromethylated products is as follows: quinoline derivatives > pyridine derivatives; 5-(phenylethynyl)-2-(2,2,2-trifluoroethyl)pyridine (**2k**, 49% yield) > 2-(2,2,2-trifluoroethyl)pyridine (24% yield); and 2-(2,2,2-trifluoro-1-phenylethyl)pyridine (**2n**, 58% yield) > 2-(2,2,2-trifluoroethyl)pyridine (24% yield). Formation of an acetonitrile adduct in acetonitrile also supported the formation of **A**.

The reaction proceeded in excellent yield, even on gram scale. Treatment of 4.83 grams of **1a** with TMAF·4H_2O in acetonitrile/ethyl acetate gave 3.12 grams of **2a** in 85% yield,



Scheme 2. Synthesis of trifluoromethylated product **2a** from 2-methylquinoline (**7**) by sequential reactions. *m*CPBA = *m*-chloroperbenzoic acid.



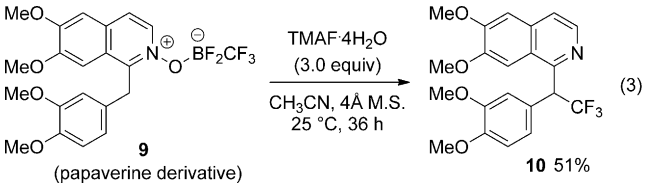
Scheme 3. Synthesis of trifluoromethylated analogue of ICI D8731. Reagents and conditions: a) *m*CPBA (1.1 equiv), $CHCl_3$, 25 °C, 6 h, 95%; b) $NaNO_3$ (5.0 equiv), CF_3CO_2H, 50 °C, 0.5 h, 82%; c) $P(OMe)_3$ (1.5 equiv), white LED irradiation, CH_2Cl_2, 25 °C, 5 h, 89% (**11**); d) 1.0 M H_2SO_4 (6.2 equiv), CF_3CO_2H, 60 °C, 2 h, 92% (**12**); e) **13** (1.5 equiv), Cs_2CO_3 (1.5 equiv), acetone, reflux, 3 h, 80%; f) 1.0 M HCl, MeOH/1,4-dioxane (1:2), 25 °C, 2 h, 89% (**14**). Tr = trityl.

which was comparable to the yield of **2a** on a smaller scale [Eq. (1): 80%, **1a**: 169 mg].

A trifluoromethylated product could be obtained from 2-methylquinoline (**7**) by sequential reactions without isolating the quinoline *N*-oxide **8** and **1a** (Scheme 2). Oxidation of 2.80 grams of **7** with *m*CPBA, and treatment of a mixture of KBF_3CF_3 and $BF_3{\cdot}OEt_2$ with the formed quinoline *N*-oxide **8** led to **1a**, which was treated with TMAF·4H_2O to give the desired trifluoromethylated product **2a** in 67% overall yield (2.84 g).

The method was applied to benzylic trifluoromethylation of a more complex molecule. Papaverine is an antispasmodic drug which contains an isoquinoline moiety with a benzylic substituent at the 1-position.[16] Treatment of the papaverine *N*-oxide/BF_2CF_3 complex **9** with TMAF·4H_2O produced the trifluoromethylated papaverine **10** in 51% yield [Eq. (3)]. This result reveals that the present reaction enables late-stage trifluoromethylation of bioactive molecules with N-heteroaromatic ring(s) and functional groups.

Finally, a unique analogue (**14**) of an angiotensin II receptor antagonist, ICI D8731,[17] was synthesized for the



first time to demonstrate the utility of the present benzylic trifluoromethylation (Scheme 3; see the Supporting Information). Starting from **2a**, introduction of a nitro group at the 4-position, hydrolysis, and O-alkylation with **13** produced **14**, after deprotection, in high overall yield.

In summary, we developed selective C(sp^3)–H trifluoromethylation, pentafluoroethylation, and heptafluoropropylation at the benzylic positions of 2-alkylpyridines, 2-alkylquinolines, and their related compounds. This protocol is the first example of regioselective perfluoroalkylation at the benzylic C(sp^3)–H bond of six-membered heteroaromatic compounds. In this reaction, boranes, $BF_2C_nF_{2n+1}$ ($n = 1$–3), function as both a Lewis acid, to activate the benzylic position of six-membered heteroaromatic compounds, and a C_nF_{2n+1} ($n = 1$–3) source. The reaction proceeds at both the terminal and internal positions of the alkyl chains. The practicality of the reaction was demonstrated by the good to excellent yields of the perfluoroalkylation reaction, even on gram scale, and the ability to perform sequential reactions without isolating the intermediates. Trifluoromethylation of a bioactive compound (papaverine) proceeded regioselectively by using this method. Moreover, a CF_3-containing drug lead, an analogue of ICI D8731, was synthesized. This method will be useful for the efficient and practical introduction of fluorinated alkyl groups into the benzylic position of six-membered heteroaromatic compounds.

Experimental Section

Gram-scale synthesis of 2-(2,2,2-trifluoroethyl)quinoline (**2a**): 4 Å M.S. (3.48 g, 200 mg mmol^{-1}) were added to a three necked 1 L round bottom flask, and then flame-dried under vacuum. After cooling to room temperature, TMAF·4H_2O (8.62 g, 52.2 mmol), difluoro((2-methylquinolin-1-ium-1-yl)oxy)(trifluoromethyl)borate (**1a**; 4.82 g, 17.4 mmol), AcOEt (348 mL), and MeCN (174 mL) were added. The mixture was heated at 65 °C and stirred at the same temperature for 10 min. After cooling to room temperature, an insoluble solid in the reaction mixture was filtered off through a pad of Celite, washed with CH_2Cl_2, and then the solvent was removed under reduced pressure. AcOEt (150 mL), *n*-hexane (150 mL), and H_2O (100 mL) were added to the crude reaction mixture, and the mixture was extracted two times. The combined organic phases were dried over $MgSO_4$, and then the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 10:1) to give 2-(2,2,2-trifluoroethyl)quinoline (**2a**, 3.12 g, 85% yield).

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