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Reactivity of a Hypervalent Iodine Trifluoromethylating Reagent toward THF: Ring Opening and Formation of Trifluoromethyl Ethers

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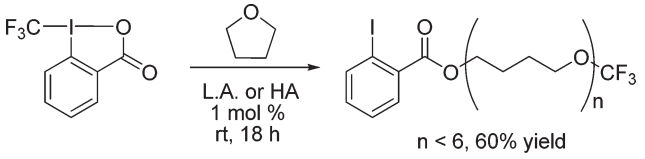

1-Trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one (**1**) is able to transfer the electrophilic CF_3 group to the oxygen atom of THF in the presence of a Lewis or Brønsted acid. This results in a new ring-opening reaction of THF yielding trifluoromethyl ethers. Details of this reaction and the insight gained into the mechanism of action of reagent **1** are reported.

Due to the special properties fluorine atoms impart to organic molecules,[1] organofluorine compounds have come into wide application in fields such as crop treatment, medicinal chemistry, and materials science.[2] Notably, the introduction of trifluoromethyl moieties has recently attracted considerable attention.[3] The main strategies are based on nucleophilic trifluoromethylation.[4] The development of complementary electrophilic approaches has, however, proven to be a nontrivial task.[5,6] Successful methods in this challenging area have utilized sulfonium salt-based reagents active toward sulfur, phosphorus, and carbon nucleophiles.[7] Several years ago, our group developed a new class of easily synthesized reagents for electrophilic trifluoromethylation based on hypervalent iodine derivatives.[8] These compounds have shown high activities toward a variety of nucleophiles.[9] Remarkably, the CF_3-bearing 1,2-benziodoxole **1** (Figure 1) can be applied to directly trifluoromethylate alcohols under mild conditions.[10] Previously, such transformations were only possible using Umemoto's *O*-(trifluoromethyl)dibenzofuranium salts.[11]

Trifluoromethyl ethers are an interesting class of potentially important pharmacophores. However, aside from the aforementioned examples, hazardous reagents and harsh conditions, incompatible with sensitive functional groups, are required for their synthesis.[12] Since the field of electrophilic trifluoromethylation is still in its infancy, exploration and understanding of the reactivity of appropriate reagents toward oxygen nucleophiles is of extreme importance as it may guide the design of future reagents and reaction conditions.[13] Herein we report the unprecedented transfer of a CF_3 moiety to the oxygen atom of tetrahydrofuran and information concerning the reactivity of reagent **1**.

During an effort to improve our current system for trifluoromethylation of alcohols,[10] we observed that reaction of reagent **1** with 4-nitrobenzyl alcohol in THF in the presence of a catalytic amount of $Y(NTf_2)_3$ gave rise to several products other than, but not including, the desired 4-nitrobenzyl trifluoromethyl ether.

Although the ^{19}F NMR spectrum of the reaction mixture showed a resonance at $\delta = -60.1$ ppm ($J_{F-C} = 254$ Hz), typical of an OCF_3 group and corresponding to a 41% yield (based on integration against an internal standard), the ^1H NMR spectrum of the isolated material clearly indicated the

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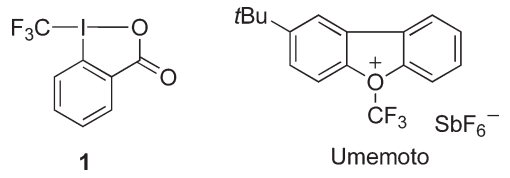
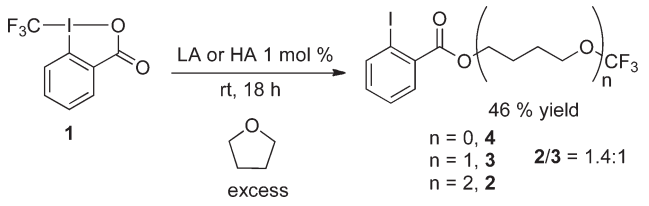


FIGURE 1. Reagents for direct trifluoromethylation of alcohols.

SCHEME 1. Formation of Trifluoromethyl Ethers from 1 and THF

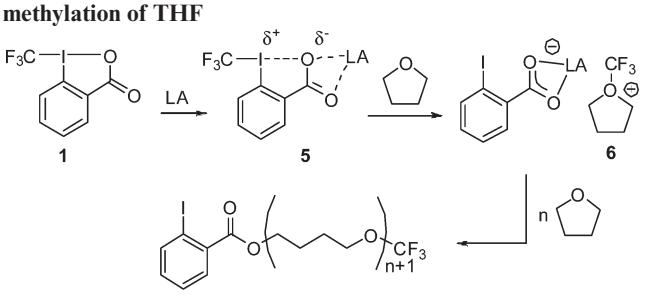


absence of 4-nitrobenzyl trifluoromethyl ether. Structural assignment was then carried out using 2D NMR techniques ($^{19}F-^{13}C$ HMQC, $^{1}H-^{13}C$ HMBC; see the Supporting Information), thus revealing that the major products of this reaction are the two trifluoromethyl ethers **2** (27% yield) and **3** (19% yield, ^{19}F NMR $\delta = -60.2$ ppm) derived from a THF ring-opening process (see Scheme 1). In addition to these two compounds, the trifluoromethyl ester **4** was also isolated in 24% yield (^{19}F NMR $\delta = -57.1$ ppm for **4**). Furthermore, a FAB-mass analysis of the crude reaction mixture showed qualitatively that higher oligomers of **2** were also formed (mainly analogues incorporating 3, 4, and 5 molecules of THF), which may explain the large discrepancy between NMR and isolated yields of **2**.

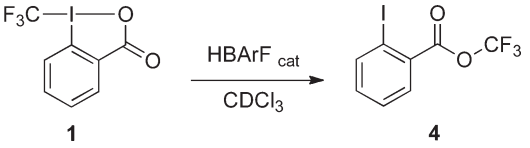
Further investigations showed that the presence of alcohol in the reaction mixture was unnecessary. However, traces of water were essential to avoid decomposition of reagent **1**.[14] Moreover, screening different NTf_2 lanthanide salts as Lewis acids (M = Y, La, Sm, Eu, Gd) showed that the product distribution was independent of the catalyst used. Finally, $HNTf_2$ was also found to promote the reaction, suggesting that the reaction is acid catalyzed.

From the nature of the products, it was clear that two different reactions were occurring: the ring opening of THF and the formation of an $O-CF_3$ bond. Determination of the sequence of these reactions is paramount to understanding the reactivity of **1** toward oxygen nucleophiles. It is well-known that ring-opening polymerization of THF can be promoted by strong Lewis or Brønsted acids.[15] However, solutions of $Y(NTf_2)_3$ in THF appeared to be stable and no polymerization was observed, suggesting that the lanthanide is not primarily responsible for the ring opening of THF. This observation seems to exclude a mechanism in which an initial ring opening is followed by transfer of CF_3 to the resulting alkoxide. It is well-known that the first step in polymerization of THF is formation of a tetrahydrofuranium (oxonium) cation through protonation (or coordination) by the acid. This oxonium species then undergoes

SCHEME 2. Proposed Mechanism for Ring-Opening Trifluoromethylation of THF



SCHEME 3. Rearrangement of 1 Assisted by a Strong Brønsted Acid



attack by a second molecule of THF at the α-carbon, initiating the polymerization.[15] Therefore, the mechanism depicted in Scheme 2 seems to most plausibly explain the formation of **2** and **3** and their higher oligomers.

Carbonyl coordination of reagent **1** to $Y(NTf_2)_3$ (or protonation by $HNTf_2$) would lead to the reactive intermediate **5** in which the CF_3-I bond is activated. Transfer of the CF_3 group to THF would form **6**, an "Umemoto-like"[11] CF_3-bearing oxonium salt. Compound **6** could then undergo ring opening by another molecule of THF to form **2** or 2-iodobenzoate to form **3**. Higher oligomers could be formed by further additions of THF before termination of the oligomerization process by 2-iodobenzoate.

We have previously suggested that **1** may be activated either by Lewis[10] or Brønsted acid.[16] This has also found further confirmation in the behavior of the present system, since reagent **1** is stable in THF in the absence of acid. Solutions of **1** in $CHCl_3$ or benzene are also stable by themselves, but **1** is converted to **4** when $Y(NTf_2)_3$ or HX (X = NTf_2, BArF (3,5-$(CF_3)_2C_6H_3)_4B\cdot(OEt_2)_2$)) was added, providing further evidence of acid-mediated activation of **1**. In addition, the formation of trifluoromethyl ethers from alcohols and **1** is also accompanied by the formation of **4** when the alcohol is not present in excess.[10] Therefore, an understanding of the formation of **4** from **1** under acidic conditions might also be useful.

To this end, rate studies were utilized to provide information concerning the mechanism of conversion of **1** to **4**. ^{19}F NMR spectroscopy was used to monitor the reaction of **1** to **4** in wet $CDCl_3$ in the presence of various quantities of the strong Brønsted acid HBArF (Scheme 3).[17]

Additionally, a series of experiments were also run in which the concentration of acid was constant and the concentration of **1** was varied. The time vs concentration reaction profiles collected (see Figure 2 for a representative example) do not show the simple linear or exponential behavior expected under the pseudo first-order conditions

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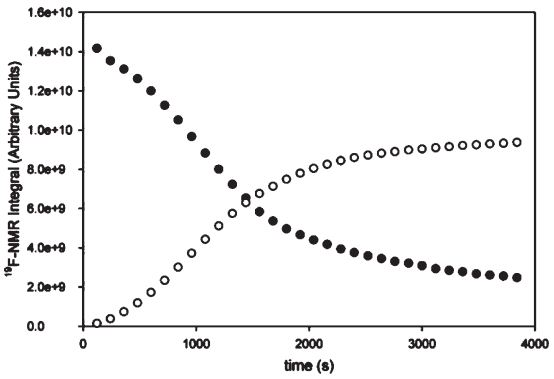

FIGURE 2. Plot of ^{19}F NMR integrals versus time (reaction profile) showing decay of **1** (filled circles) and formation of **4** (unfilled circles) for the reaction of 0.1 M **1** with 0.020 M $[(3,5\text{-}(CF_3)_2C_6H_3)_4B]^-[H(OEt_2)_2]^+$ in $CDCl_3$ at 300 K.

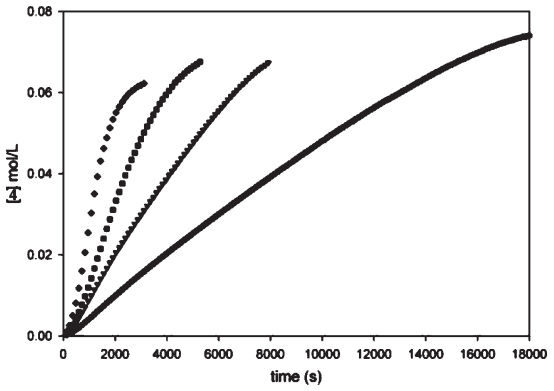

FIGURE 3. Plot of [**4**] against time for the reaction of 0.1 M **1** with 0.005 M (circles), 0.01 M (triangles), 0.015 M (squares), and 0.02 M (diamonds) HBArF in wet $CDCl_3$ at 300 K.

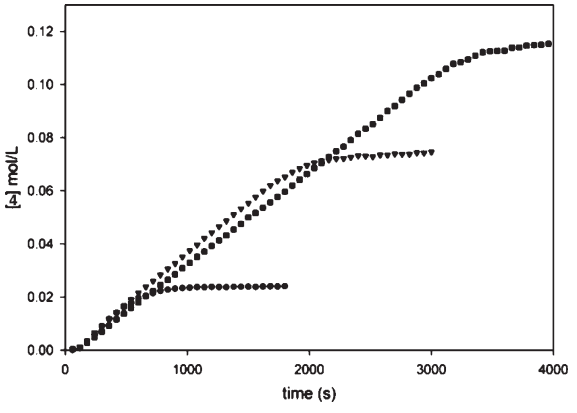

FIGURE 4. Plot of [**4**] against time for the reaction of 0.003 M HBArF with 0.03 M (circles), 0.09 M (triangles), and 0.15 M (squares) **1** in wet $CDCl_3$ at 320 K.

used. Indeed, the profile shapes are a strong indicator of a more complex mechanism.

Although the extraction of numerical rate information from the profiles obtained would be a difficult task, simple inspection shows that the reaction is strongly accelerated by increasing acid concentration (see Figure 3) and is largely unaffected by the concentration of **1** (see Figure 4). Although the rate experiments do not exclude any particular possible reaction pathway or set of pathways leading to the formation of **4**, they do conclusively demonstrate that reagent **1** is activated (rate of reaction increases) under acidic conditions.

Lastly, attempts were made to determine if the reactivity of **1** toward THF can be extended to other ethers. Preliminary experiments with HBArF as acid showed that **4** is produced predominantly when dioxane or diethyl ether are used as solvent. More interestingly, in both cases ^{19}F NMR spectroscopy showed the presence of a peak in the OCF_3 region, accounting for 10% ($\delta = -60.5$ ppm) and 6% yield respectively ($\delta = -60.7$ ppm). Although deeper studies are needed to fully characterize the products of these reactions, the data obtained strongly suggest that reactivity of **1** toward ethers is general.

In conclusion, both Lewis and Brønsted acids activate reagent **1** toward transfer of the CF_3 group. Once activated, **1** is a highly potent source of the electrophilic trifluoromethyl group which can react with THF or other ethers at oxygen or undergo rearrangement/decomposition to the trifluoromethyl ester **4**. These results demonstrate the higher than previously supposed reactivity and potentially broader applicability of reagent **1**. Further efforts to expand the scope of trifluoromethylation with **1** and to gain insight into the mechanistic aspects thereof continue in our laboratories.

Experimental Section

Formation of 2−4. A 5 mL vial was charged with **1** (50 mg, 0.158 mmol) and $Y(NTf_2)_3$ (1.5 mg, 1.58 μmol). THF (1 mL) was added, and the mixture was stirred for 18 h at room temperature. The solvent was removed under reduced pressure, and the different products were separated and isolated through column chromatography on silica gel (eluent: hexane/ethyl acetate 92:8). When the reaction was performed in deuterated THF, **2**-d_{16} and **3**-d_8 were obtained.

2: colorless oil; $R_f = 0.26$, 27% yield; ^{1}H NMR (C_6D_6, 400 MHz) 7.67 (d, $^3J = 8$ Hz, 1H, CH), 7.63 (d, $^3J = 8$ Hz, 1H, CH), 6.81 (t, $^3J = 8$ Hz, 1H, CH), 6.48 (t, $^3J = 8$ Hz, 1H, CH), 4.19 (t, $^3J = 6$ Hz, 2H, OCH_2), 3.55 (t, $^3J = 6$ Hz, 2H, OCH_2), 3.10 (t, $^3J = 6$ Hz, 2H, OCH_2), 3.03 (t, $^3J = 6$ Hz, 2H, OCH_2), 1.63 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.39 (m, 2H, CH_2), 1.33 (m, 2H, CH_2); ^{1}H NMR (C_6D_6, 200 MHz) 7.65 (t, $^3J = 8$ Hz, 2H, CH), 6.81 (t, $^3J = 8$ Hz, 1H, CH), 6.48 (t, $^3J = 8$ Hz, 1H, CH), 4.19 (t, $^3J = 6$ Hz, 2H, OCH_2), 3.55 (t, $^3J = 6$ Hz, 2H, OCH_2), 3.10 (t, $^3J = 6$ Hz, 2H, OCH_2), 3.03 (t, $^3J = 6$ Hz, 2H, OCH_2), 1.4−1.8 (m, 8H, CH_2); ^{13}C NMR (C_6D_6, 100.6 MHz) 166.6 (CO_2), 141.6 (CH arom), 136.7 (CCO_2), 132.5 (CH arom), 131.1 (CH arom), 127.9 (CH arom), 122.6 (quartet, $^1J_{C-F} = 254$ Hz, CF_3), 94.5 (CI), 70.5 (OCH_2), 70.1 (OCH_2), 67.8 (quartet, $^3J_{C-F} = 3$ Hz, CH_2OCF_3), 65.6 (OCH_2) 26.8 (CH_2), 26.1 (CH_2), 26.1 (CH_2), 26.1 (CH_2); ^{19}F NMR (C_6D_6, 188.3 MHz) −60.1 (s, CF_3); exact mass (ESI^+) calcd for $C_{16}H_{20}F_3INaO_4$ ([M] + Na^+) 483.0251, found 483.0272.

2-d_{16}: ^{1}H NMR (C_6D_6, 200 MHz) 7.65 (t, $^3J = 8$ Hz, 2H, CH), 6.81 (t, $^3J = 8$ Hz, 1H, CH), 6.47 (t, $^3J = 8$ Hz, 1H, CH); ^{19}F NMR (C_6D_6, 188.3 MHz) −60.1 (s, CF_3); exact mass (ESI^+) calcd for $C_{16}H_4D_{16}F_3INaO_4$ ([M] + Na^+) 499.1255, found 499.1264.

3: obtained as colorless oil; $R_f = 0.42$, 19% yield; ^{1}H NMR (C_6D_6, 300 MHz) 7.67 (d, $^3J = 8$ Hz, 1H, CH), 7.58 (d, $^3J = 8$ Hz, 1H, CH), 6.82 (t, $^3J = 8$ Hz, 1H, CH), 6.48 (t, $^3J = 8$ Hz, 1H, CH), 3.95 (t, $^3J = 6$ Hz, 2H, OCH_2), 3.39 (t, $^3J = 6$ Hz, 2H, OCH_2), 1.25 (m, 4H, CH_2); ^{13}C NMR (C_6D_6, 75.5 MHz) 166.0 (CO_2), 141.3 (CH arom), 136.0 (C arom), 132.2 (CH arom),

130.7 (CH arom), 127.6 (CH arom), 122.1 (quartet, $^{1}J_{C-F}$ = 254 Hz, CF_3) 94.0 (CI), 66.8 (quartet, $^{3}J_{C-F}$ = 3 Hz, CH_2OCF_3), 64.4 (OCH_2), 25.2 (CH_2), 24.5 (CH_2); ^{19}F NMR (C_6D_6, 188.3 MHz) −60.2 (s, CF_3); GC−MS retention time = 21.73 min, mass = 388.10 (calcd = 387.98); exact mass (ESI^+) calcd for $C_{12}H_{12}F_3INaO_3$ ([M] + Na^+) 410.9675, found 410.9666.

3-*d*$_8$: ^{1}H NMR (C_6D_6, 200 MHz) 7.67 (d, ^{3}J = 8 Hz, 1H, CH), 7.58 (d, ^{3}J = 8 Hz, 1H, CH), 6.81 (t, ^{3}J = 8 Hz, 1H, CH), 6.47 (t, ^{3}J = 8 Hz, 1H, CH); ^{19}F NMR (C_6D_6, 188.3 MHz) −60.2 (s, CF_3); GC−MS retention time = 21.62, mass = 396.14 (calcd = 396.03).

4: obtained as white solid; R_f = 0.67, 24% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.13 (d, ^{3}J = 8 Hz, 1H, CH), 7.98 (d, ^{3}J = 8 Hz, 1H, CH), 7.51 (t, ^{3}J = 8 Hz, 1H, CH), 7.29 (t, ^{3}J = 8 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 157.9 (C, CO_2), 142.6 (CH), 134.7 (CH), 132.5 (CH), 130.3 (CCO_2), 128.7 (CH), 119.7 (quartet, $^{1}J_{C-F}$ = 267 Hz, CF_3), 95.6 (C, CI); ^{19}F NMR ($CDCl_3$, 188.3 MHz) −57.1 (s, CF_3); exact mass (ESI^+) calcd for $C_8H_4F_3IO_2$ 315.9203, found 315.9201

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Supporting Information Available: General experimental methods, experimental procedures, and full characterization data and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.