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Acid-mediated formation of trifluoromethyl sulfonates from sulfonic acids and a hypervalent iodine trifluoromethylating agent†‡

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A variety of sulfonic acids have been trifluoromethylated using 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one under mild conditions in good to excellent yields. Initial mechanistic investigations of this reaction show a clean second-order kinetics and only very weak substrate electronic effects.

Since 1957, when the first fluorine-containing drug was developed, the number of fluorinated drugs on the market has risen steadily. Today, nearly 20% of new pharmaceutical compounds contain one or more fluorine atoms and for agrochemicals this percentage is even higher.[1] This wide range of applications is due to the drastic influence on metabolic stability, lipophilicity, bioavailability, binding affinity and selectivity conferred by fluorine and perfluoroalkyl substituents.[2]

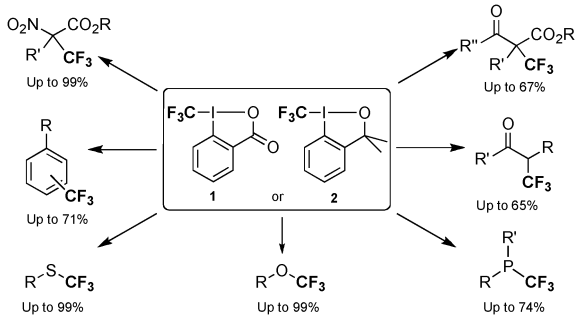
Recently, the syntheses of recyclable electrophilic trifluoromethylating agents **1** and **2** based on hypervalent iodine have been developed.[3–7] Both reagents are easily accessible from inexpensive starting materials in high overall yields. As outlined in Scheme 1, various substrates, including thiols, primary and secondary phosphines, active-methylene compounds and aromatic compounds, can be trifluoromethylated under mild conditions in, partly, excellent yields.[4–6] Recently, the scope of the reagents has been extended to primary and secondary alcohols, yielding the corresponding trifluoromethyl ethers.[6]

During a study directed towards the trifluoromethylation of alkynes we made an interesting and unexpected observation. When $Zn(OTf)_2$ was used as an additive, trifluoromethylation of the alkyne was unsuccessful, but the triflate anion was nearly quantitatively converted to trifluoromethyl triflate (TFMT) instead. Similar experiments using sodium, potassium or copper(II) salts as triflate sources did not yield TFMT. However, addition of zinc bromide to such reaction mixtures did afford TFMT, along with considerable amounts of trifluoromethyl bromide, thus suggesting that zinc salts are necessary for the successful trifluoromethylation of the triflate anion. TFMT itself is a well known material which may be prepared by several methods and has found a variety of synthetic applications.[8,9] However, other trifluoromethanesulfonates have been prepared only recently by direct trifluoromethylation of sulfonic acids and sulfonates using a method which suffers from several shortcomings, thus making it impractical for larger-scale applications.[10] In addition, there is one very recent report of the synthesis of difluoromethyl sulfonates.[11] Even so, the chemical properties and potential utility of di- and trifluoromethyl sulfonic acid esters have yet to be investigated.

Following the above-mentioned observation that zinc salts are necessary for successful trifluoromethylation, further investigations were carried out which showed that **1** could not only be activated by zinc salts (Lewis acids) but also by Brønsted acids. When sulfonic acids were mixed with the hypervalent iodine reagent **1** formation of trifluoromethyl sulfonates took place under ambient conditions overnight in good to excellent yields (see Scheme 2 and Table 1).

The presence of a strong Brønsted acid was crucial for the reaction to take place, since trifluoromethylation of sodium, potassium or ammonium toluenesulfonate failed. Addition of a strong acid such as $HBF_4{\cdot}OEt_2$ to mixtures of **1** and sulfonate salts did in fact trigger the formation of the trifluoromethyl esters, although in lower yields. Also, sulfonic acids having an internal base such as **3j** and **3k** failed to afford the desired product.

The reactivity of the trifluoromethyl sulfonic acid esters **5a** and **5f** has been investigated. In contrast to their non-fluorinated counterparts, trifluoromethyl sulfonates do not act as alkylating agents. Kobayashi has shown that TFMT acts as a sulfonylating agent with nucleophilic attack of the substrate at the sulfur atom.[12] Kolomeitsev also reported the use of TFMT for the synthesis of trifluoromethanolates and their application as a source of the trifluoromethoxy anion in nucleophilic substitution reactions.[8] It has been suggested that the reaction of nucleophiles with TFMT is directed to sulfur since it is relatively electron-poor due to the high electronegativity of the neighbouring CF_3 group (Scheme 3).[9]



Scheme 1 Applications of hypervalent iodine trifluoromethylation reagents **1** and **2**.

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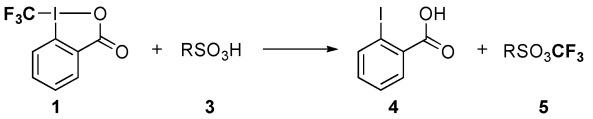
‡ Electronic supplementary information (ESI) available: Experimental procedures, characterization data, ^1H, ^{13}C and ^{19}F NMR spectra of new compounds and detailed kinetic data. See DOI: 10.1039/b913962a



Scheme 2 Trifluoromethylation of sulfonic acids using reagent **1**.

Table 1 Trifluoromethylation of sulfonic acids by **1**

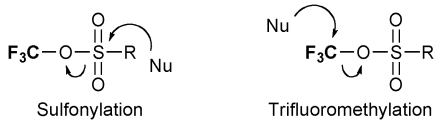
Entry	Substrate	**1**	Yield[a] (%)
a	2-Naphthalenesulfonic acid	1.1 equiv.	87 (67)
b	(±)-10-Camphorsulfonic acid	1.1 equiv.	99 (75)
c	4-Nitrobenzenesulfonic acid	1.1 equiv.	76[b]
d	4-Chlorobenzenesulfonic acid	1.1 equiv.	70[b] (60)
e	Benzenesulfonic acid	1.1 equiv.	96[b] (42)
f	4-Methylbenzenesulfonic acid	1.1 equiv.	90[b] (51)
g	4-Ethylbenzenesulfonic acid	1.1 equiv.	67 (32)
h	4-Hydroxybenzenesulfonic acid	1.1 equiv.	83[b] (45)
i	4-Methoxybenzenesulfonic acid	1.1 equiv.	75[b]
j	4-Aminobenzenesulfonic acid	1.1 equiv.	0
k	2-Amino-3-sulfopropanoic acid	1.1 equiv.	0

[a] Yields based on ^{19}F-NMR with CF_3Ph as internal standard. Isolated yields in parentheses. All reactions run in $CHCl_3$ unless specified otherwise. [b] Reaction run in 5 : 1 $CDCl_3$: ^{t}BuOH.

We speculated that for trifluoromethyl sulfonates bearing less electron-withdrawing substituents the attack by an appropriate nucleophile might be directed to the oxygen, thus resulting in a formal trifluoromethylation.

Therefore, esters **5a** and **5f** were treated with phenyl lithium. After several hours reaction time at room temperature and aqueous workup both esters were recovered intact. In pentanol as both nucleophile and solvent the esters showed a similarly inert behaviour at room temperature. At elevated temperatures the reagents decomposed slowly. However, no fluorinated products could be observed by ^{19}F NMR spectroscopy, apart from SiF_6^- (arising from F^- and borosilicate glass). This implies a cleavage of the S–OCF_3 bond releasing trifluoromethanolate which decomposes to fluoride and fluorophosgene. Lastly, given the substantial stability of the O–CF_3 bond one may view this trifluoromethylation reaction as a mild and selective protection of sulfonic acids, provided an appropriate deprotection reaction is found.

The reaction of **1** with sulfonic acids generates a minimum of side products, it goes to completion on a reasonable timescale under ambient conditions and it is easily monitored by ^{19}F-NMR spectroscopy. Therefore, it seemed an almost ideal model system to begin investigations into the mechanism of trifluoromethylation by **1** using rate studies. Initially, two series of pseudo-first order rate experiments were carried out in a 5 : 1 mixture of chloroform and *tert*-butanol. In the first group of experiments, the concentration of the limiting reagent **1** was fixed and the concentration of **3f** was varied and in the



Scheme 3 Substitution at the sulfur leading to sulfonylation *vs.* the (as yet unknown) attack at carbon leading to a formal trifluoromethylation.

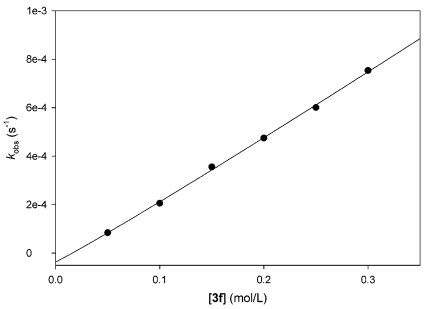


Fig. 1 Plot of k_{obs} *versus* [**3f**] for the trifluoromethylation of **3f** with **1** (0.005 M) in a 5 : 1 mixture of $CDCl_3$ and ^{t}BuOH at 298 K. The curve depicts the result of an unweighted least-squares fit to $k_{obs} = y_0 + a[\mathbf{3f}]^b$ where $y_0 = (-4 \pm 3) \times 10^{-5}$, $a = (2.8 \pm 0.2) \times 10^{-3}$ and $b = 1.04 \pm 0.08$.

second set of experiments the concentration of **3f** was fixed to be the limiting reagent and the concentration of **1** was varied. The results of these experiments are plotted in Fig. 1 and 2, respectively, and clearly show a first-order dependence of the reaction rate on the concentration of both reaction partners.

In addition, the possibility of a competitive trifluoromethylation of 2-iodobenzoic acid formed as a by-product of reagent **1** was also investigated. Using the solvent system described above, the reaction rate appears to be independent of 2-iodobenzoic acid concentration (see supporting information for a plot of k_{obs} *versus* [2-iodobenzoic acid] and further details‡).

Investigation of the effect of the solvents used (the addition of *tert*-butanol is necessary to completely solvate toluenesulfonic acid monohydrate) and the water present in the reaction mixture on the rate of reaction proved to be a complex task. Although toluenesulfonic acid is easily dehydrated in vacuum at elevated temperature yielding a strongly acidic and hygroscopic material soluble in chloroform, the addition of water or *tert*-butanol to solutions of anhydrous sulfonic acid leads to immediate precipitation of the less soluble monohydrate, rendering rate studies under these conditions impractical. In order to circumvent solubility problems, the test substrate was changed to **3b** which is readily available as anhydrous material. Pseudo-first order rates were measured for the reaction of 0.005 M **1** with 0.15 M **3b** in chloroform and variable amounts of *tert*-butanol. The results of these studies are shown as a plot in Fig. 3. The reaction rate is

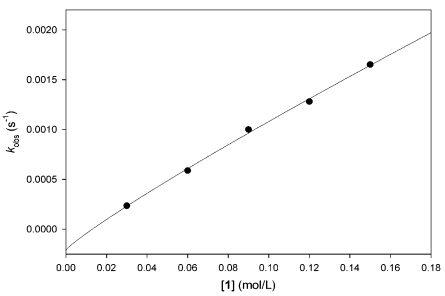


Fig. 2 Plot of k_{obs} *versus* [**1**] for the trifluoromethylation of **3f** (0.003 M) with **1** in a 5 : 1 mixture of $CDCl_3$ and ^{t}BuOH at 313 K. The curve depicts the result of an unweighted least-squares fit to $k_{obs} = y_0 + a[\mathbf{1}]^b$ where $y_0 = (-2 \pm 2) \times 10^{-4}$, $a = (1.0 \pm 0.2) \times 10^{-2}$ and $b = 0.9 \pm 0.2$.

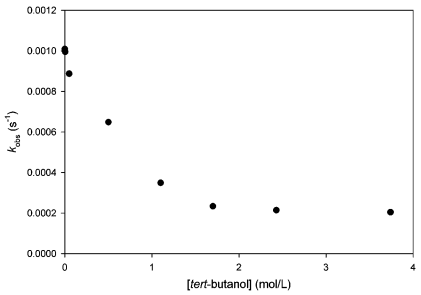


Fig. 3 Plot of k_{obs} *versus* [*tert*-butanol] for the trifluoromethylation of **3b** (0.15 M) with **1** (0.005 M) in $CDCl_3$–*tert*-butanol mixtures at 300 K.

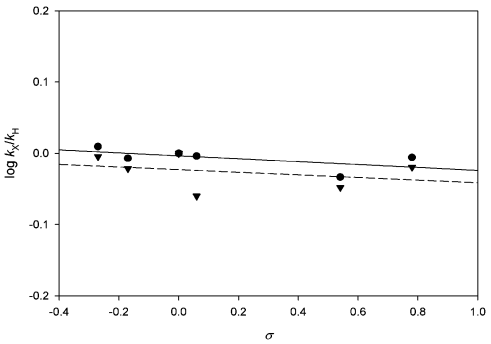


Fig. 4 Plot of log k_X/k_H (where log k_X/k_H has been determined by a competition experiment involving 1 equiv. of substituted sulfonic acid, –OMe, –Me, –F, $–CF_3$ or $–NO_2$, 1 equiv. of benzenesulfonic acid and 1 equiv. of **1** at 298 K, solid line and 323 K, dashed line) *versus* σ_p for various *para*-substituted benzenesulfonic acids. σ_p values taken from reference 13, p. 144. ρ values were determined by linear least-squares regression to log $k_X/k_H = \rho\sigma + b$ to be -0.02 ± 0.01 with $r = 0.60$ at 298 K and -0.02 ± 0.03 with $r = 0.31$ at 323 K.[14]

strongly decreased by the addition of *tert*-butanol. However, the behaviour does not fit any simple, idealised inverse order dependence. Such behaviour suggests that when *tert*-butanol is used as a co-solvent, it participates in the rate determining transition state and that the exact nature (stoichiometry) of this species varies with *tert*-butanol concentration. Similar behaviour for water or any other coordinating solvent might reasonably be expected, but has yet to be exhaustively demonstrated.

In addition to absolute rate studies, competition experiments were utilized to compare the rate of trifluoromethylation of various *para*-substituted benzenesulfonic acids. A plot of the data acquired at 298 and 323 K against the Hammett parameter σ_p shows an apparent linear relationship with only slightly negative slopes (ρ), as shown in Fig. 4. The linear relationship to σ_p suggests that the mechanism of reaction remains constant across the range of substituents tested. This seems to substantiate (though not rigorously prove) the assumption that under the conditions used the reaction mechanisms for **3f** and **3b** with **1** are very similar if not identical. The very small value of ρ indicates that substituent effects on the reaction rate are minimal. This may indicate that single electron transfer (SET) plays a role in the trifluoromethylation of sulfonic acids by **1** and/or that protons from the sulfonic acid are involved in the rate determining transition structure and the sulfonate portion is not.

In conclusion, sulfonic acids are easily trifluoromethylated in good to excellent yields under mild conditions by **1** to form trifluoromethyl sulfonates. Initial investigations suggest that these materials are largely unreactive toward nucleophiles. Rate studies show the involvement of both sulfonic acid and **1** in the rate-determining step, as well as coordinating co-solvent, when present. We are currently continuing our investigations of the mechanism of trifluoromethylation by **1** and **2** as well as of the properties and potential synthetic utility of trifluoromethyl sulfonates.

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