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Mechanistical insight into 'electrophilic' trifluoromethylation with *S*-(trifluoromethyl)dibenzothiophenium salts

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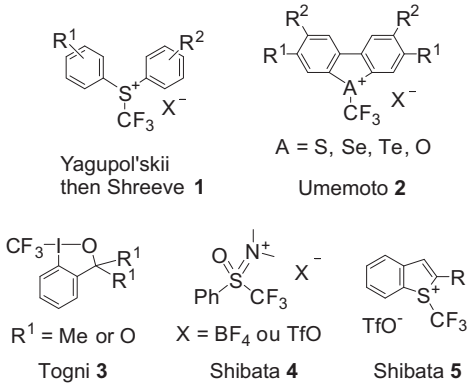
ABSTRACT

Trifluoromethyl sulfonium salts are widely used for the introduction of a trifluoromethyl group through reaction with a wide range of nucleophiles. Nevertheless, the reaction mechanism is far from obvious and has been the subject of various literature discussions. In this Letter, we show, through trapping experiments with a radical probe that, at least in the case of nucleophiles such as enol silyl ethers, the reaction proceeds by SET.

The synthesis of trifluoromethylated compounds is an important area which has significant applications in the pharmaceutical and agrochemical industries as well as in the materials science and catalysis.[1] The impressive properties induced by the presence of this group have greatly stimulated the development of new methods for its introduction into organic molecules.[2] After a latent period in this field, the invention of electrophilic trifluoromethylating reagents has been particularly abundant in the past five years. The first electrophilic reagents, biaryl trifluoromethyl sulfonium salts **1**, were described in 1984 by Yagupolskii and co-workers and improved preparations were published by the group of Shreeve and more recently by Yagupolskii (Scheme 1).[3] During this period, Umemoto has described numerous dibenzothiophenium salts **2** which have shown a greatly enhanced reactivity compared to molecules **1**.[4] More recently, Togni and co-workers succeeded in the preparation of hypervalent iodine(III)–CF_3 reagents **3**.[5] Shibata and co-workers disclosed both a fluorinated analog **4** of a Johnson-type methyl-transfer reagent based on a sulfoximine skeleton and an easy preparation of *S*-(trifluoromethyl)thiophenium salts **5** as extended versions of Yagupolskii–Umemoto reagents.[6] Our contribution to this field concerns the vast improvement of the benchmark synthesis of sulphur-based reagents including sulfonium salts of type **1** and **2** and also sulfoximine derivatives **4**.[7]

Thanks to these recent advances, reports on the use of such trifluoromethylating reagents have increased considerably in the literature. Nevertheless, the mechanistic pathway of trifluoromethylation is still unclear. In this Letter, we focus our interest on trifluoromethylsulfonium salts and more precisely on their reactivity. There are numerous nucleophiles which are able to react with compounds **1** or **2**, for example, enols, enolates of β-ketoesters, silyl enol ethers, enamines, thiolates, and electron-rich aromatics. This non-exhaustive list holds a wide range of candidates, and a careful examination of its members clearly reveals that they all belong to the soft nucleophiles family. Alcoholates are indeed not transformed into trifluoromethoxy ether in the presence of **1** or **2**, the only reaction being the degradation of the fluorinated reagent. If the reaction of **1** or **2** with a nucleophile results in the introduction



Scheme 1. Electrophilic trifluoromethylating reagents.

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of a CF_3 group, there is no clear evidence to demonstrate that a '(CF_3^+)' species is involved during the transition step.

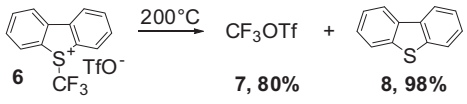
Initially, Umemoto described compounds **2** as a pure electrophilic source of the trifluoromethyl group.[4] This assertion was essentially based on the thermolysis of **6** which afforded trifluoromethyl triflate **7** in a high yield (Scheme 2). Nevertheless, in the same article, the author agreed with the idea that the reaction pathway can change with the nature of the nucleophile and may occur via a bimolecular ionic substitution mechanism competing with a free radical chain mechanism.

The reaction was carefully investigated later in a kinetic study from the same group.[8] The critical difference in reactivity between the *S*-(methyldibenzothiophenium) salt **9** and the *S*-(trifluoromethyldibenzothiophenium) salt **6** with aniline (N-alkylation versus C-alkylation) was indicative of a mechanism different from a classical S_N2 (Scheme 3), despite the *S*-methyl and the *S*-trifluoromethyl groups adopting similar orientations in the crystal structure. S_N2 substitution directly at the trifluoromethyl carbon is clearly inhibited by the steric hindrance brought about by the fluorines. It is therefore expected that the trifluoromethyl salt displays a different pattern of reactivity to the hydrocarbon compound. Thermodynamic and electronic considerations led Umemoto to propose a nucleophilic attack side-on to the carbon-trifluoromethylsulfur bond, accompanied by one- or two-electron exchange.[9] The ratio of *ortho*/*para* compounds (8:2) obtained during the trifluoromethylation of aniline cannot be used to discriminate between a (CF_3^+) or a ($CF_3\cdot$) species, the latter being electrophilic contrary to the methyl radical.[11]

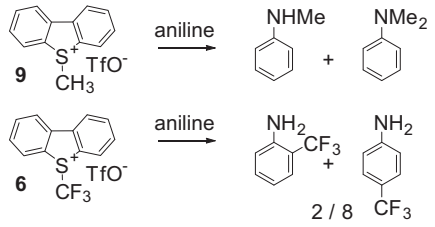
Some ten years later, Umemoto and co-workers published the preparation of *O*-(trifluoromethyl)dibenzothiophenium salts **2** (A=O) and studied their reactivity.[12] Unlike their sulfur analogs, these salts are able to react with an alcoholate to afford the corresponding trifluoromethyl ether. Those reagents were thus believed to be a pure (CF_3^+) source. The comparison with sulfonium salts led Umemoto to then consider that the 'S-CF_3 salt may undertake a different reaction mechanism varying from ($CF_3\cdot$) to (CF_3^+) depending on the reactivity of nucleophiles'.

This hypothesis was partially supported by our work devoted to the preparation of perfluoroalkyl estradiol (Scheme 4).[13] Clear yield enhancement was observed upon UV–irradiation during the trifluoromethylation reaction of silyl enol **10**, strongly suggesting a single electron-transfer pathway.

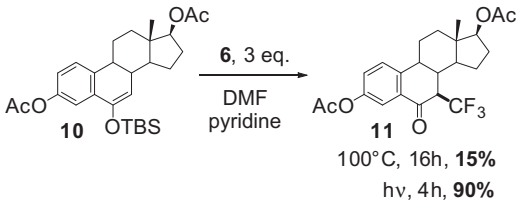
These results are reminiscent of early pioneering work of our laboratory, demonstrating that a SET process was involved in the reaction between soft nucleophiles and perfluoroalkyl bromides or iodides.[14] The 'inverse' polarization ($C^{\delta-}$–$X^{\delta+}$) of the carbon–bromide (or iodide) bond of R_FX prevents indeed a classical nucleophilic pathway from being the case. In the presence of such reactive species, the attack occurs at the most electropositive center inducing a halogenophilic mechanism.



Scheme 2. Thermolysis of Umemoto's reagent.



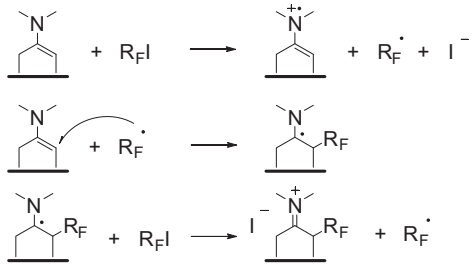
Scheme 3. Reaction of sulfonium salts with aniline.



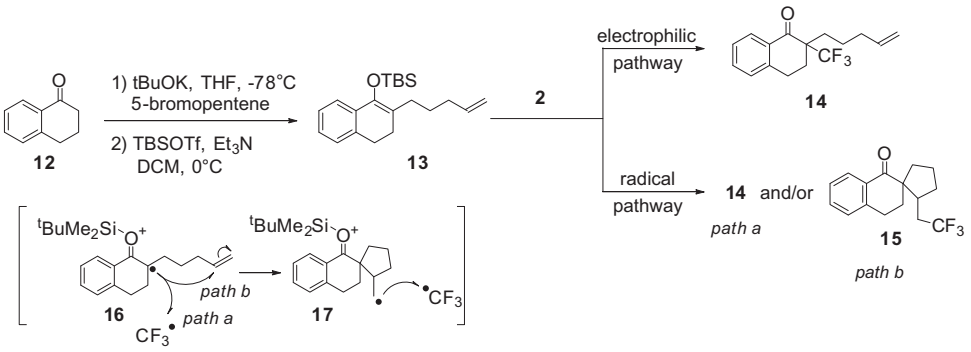
Scheme 4. Trifluoromethyl estradiol synthesis.

The SET pathway mentioned above was first demonstrated with enamines as nucleophiles.[15] These compounds spontaneously reacted with R_FI to produce a perfluoroalkyl iminium and the corresponding alkylated ketone after subsequent hydrolysis (Scheme 5). Experimental and theoretical evidence exists for the following chain radical mechanism. As an initiation step, a perfluoroalkylated radical anion and then a perfluoroalkylated radical are formed from the starting iodide, the enamine being the reducing partner. The propagation steps involve the attack of the double bond giving rise to a radical species able to reduce the perfluoroalkyl iodide, thus generating an iminium and a new radical. This mechanism is also true for the reaction between a thiolate and a perfluoroalkyl iodide and is the one currently accepted, more generally, for the reaction of such an electrophile with a soft nucleophile.

In light of the previous results, it is tempting therefore to postulate a single electron transfer mechanism for the formation of α-trifluoromethyl ketones from enol derivatives, analogous to that observed for the reaction of similar nucleophiles with trifluoromethyl halides (Scheme 4). In order to further demonstrate our hypothesis, we planned to run the trifluoromethylation reaction with a nucleophile bearing a radical scavenger. The design of the candidate should satisfy two criteria: having sufficient reactivity with sulfonium salts and possessing the ability to be oxidized into a stable radical that is able to realize an intramolecular cyclization. A tetralone skeleton seemed to suit these requirements, the reactivity of this family of molecules with trifluoromethyl sulfonium reagents has been extensively studied and its structure is closely related to that of the AB ring systems of molecule **10** (Scheme 4). Nevertheless, the tedious preparation of the enamine from the 1-tetralone system encouraged us to work with silyl enol ether. Compound **13** was thus easily obtained from tetralone **12** and will allow us to distinguish between the electrophilic and radical pathways (Scheme 6). If the reaction follows a pure ionic route, only the compound **14** should be detected. In the other case, the species **16**, resulting from an oxidizing process, can give rise to **14** (path a) or evolve to a 5-exotrig cyclization to afford product **15** (path b). The isolation of this molecule, even in small quantities, would then be proof of our hypothesis.

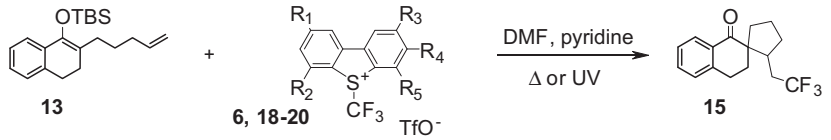


Scheme 5. SET reaction of enamines with perfluoroalkyl iodides.



Scheme 6. Trifluoromethylation pathways.

Table 1
Trifluoromethylation of enol ether **13**



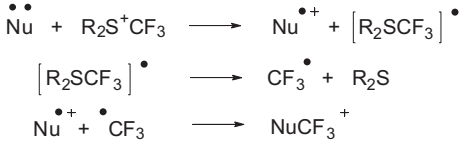
Entry	Sulfonium	R_1	R_2	R_3	R_4	R_5	Conditions	
							Heating[a] Yield[c] (%)	Irradiation[b] Yield[c] (%)
1	**6**	H	H	H	H	H	15	9
2	**18**[d]	CH_3	CH_3	H	H	H	12	13
3	**19**[d]	CH_3	CH_3	CH_3	H	CH_3	17	25
4	**20**[d]	CH_3	CH_3	H	NO_2	H	12	20

[a] 100 °C, 16 h.
[b] With a 245 nm high pressure Hg lamp, 3.5 h.
[c] Isolated yield.
[d] Prepared according to our method.[7b]

Subsequent treatment of compound **13** under the conditions devised for trifluoromethylation of silyl enol ethers, using the Umemoto reagent and ultraviolet irradiation, led to the isolation of only one fluorinated product, which was identified as the tricycle **15** (Table 1).[16] Careful examination of the ^{19}F NMR spectrum of the crude mixture revealed no traces of compound **14**. The somewhat low yields are explained in that only one equivalent of the trifluoromethylating agents was used. Recovered substrate accounts for the mass balance. Interestingly, exposure of the silyl enol ether **13** to thermal conditions also led to formation of the tricycle **15**. The same results were observed with sulfoniums **18**–**20** with an albeit increased yield under irradiation conditions.

These results are an unambiguous proof of the radical character of the proposed mechanism pathway. The nucleophile can behave as a SET reductor to give rise to a radical cation species ($Nu^{\cdot+}$) and a radical ($R_2SCF_3^{\cdot}$), the latter fragments into a neutral sulfur derivative (R_2S) and a trifluoromethyl radical ($CF_3^{\cdot}$) (Scheme 7). The recombination of the two radicals then produces the final compound.

In the particular case of nucleophile **13**, the cyclization of the radical species **16** is more rapid than the production of the radical



Scheme 7. The SET mechanism.

($CF_3^{\cdot}$) thus accounting for the isolation of **15** as the exclusive fluorinated product.[17,18] The principal argument of Umemoto to initially refute a single electron pathway was that the trifluoromethylation of *p*-hydroquinone, a radical scavenger occurred. This was successfully accomplished along with the trifluoromethylation of aniline in the presence of *p*-dinitrobenzene, which is also known for its ability to inhibit a radical pathway. Nevertheless, this assertion can only exclude a radical chain process. We assume that the entire process occurs in the solvent cage and so cannot be inhibited by a radical scavenger.

We are confident that our mechanism assertion is not restricted to silyloxanes and can be extended to soft nucleophiles such as β-ketoesters (or ketones), enamines, and thiolates, which are the most common compounds able to react with trifluoromethyl sulfoniums. Even if a pure ionic mechanism cannot be totally excluded, we assume that the radical pathway is the predominant route for the trifluoromethylation with sulfoniums salts. Our results justify *a posteriori* the term of 'power variable' trifluoromethylating agents coined by Umemoto,[4] and may give a renewed interest in open salts of type **1**.[20]

The applications of this mechanistic study for synthetic purposes are under current development in our laboratory.

Acknowledgments

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16. *General procedure for the trifluoromethylation reaction: Under thermal conditions.* Silyl enol ether **13** (0.43 mmol, 1 equiv) and pyridine (35 μl, 0.43 mmol, 1 equiv) were dissolved in DMF (2.0 mL). Sulfonium salt (0.43 mmol, 1 equiv) was added and the mixture was heated at 100 °C for 16 h. The mixture was then allowed to cool, and was poured into pentane (25 mL). The organic phase was washed with water (3 × 15 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (ether/pentane 98:2) to give the desired compound.
Under irradiation. Silyl enol ether **13** (0.43 mmol, 1 equiv) and pyridine (35 μl, 0.43 mmol, 1 equiv) were dissolved in DMF (2.0 mL) in a quartz vessel. Sulfonium salt (0.43 mmol, 1 equiv) was added and the mixture subjected to irradiation with a 245 nm high pressure Hg lamp for 3.5 h. Subsequent work-up and purification as described above afforded the desired compound.
2-(2,2,2-Trifluoroethyl)spiro[cyclopentane-1,2'-tetralin]-1'-one (**15**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 8.00 (dd, 1H, J = 7.7, 1.5 Hz), 7.48 (td, 1H, J = 7.4, 1.3 Hz), 7.32 (t, 1H, J = 7.3 Hz), 7.27 (d, 1H, J = 7.6 Hz), 3.12–2.90 (m, 2H); 2.54–1.69 (m, 11H). ^{19}F NMR ($CDCl_3$, 188 MHz) δ: −65.4 (dd, J = 12.8, 10.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 200, 143.1, 133.3, 132.0, 129.3 (q, J = 280.3 Hz), 128.5, 127.8, 126.8, 55.7, 44.0, 35.5, 35.0, 22.7. DCi (m/z): 283 (MH^+), 263 ([M-HF]$^+$). Anal. Calcd. for $C_{16}H_{17}F_3O$: C, 68.07; H, 6.07. Found: C, 67.87; H, 6.31.
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