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Formation of synthetically relevant CF_3-substituted phenonium ions in superacid media†

Anthony J. Fernandes, [a] Bastien Michelet, [b] Armen Panossian, [a] Agnès Martin-Mingot, [b] Frédéric R. Leroux *[a] and Sébastien Thibaudeau *[b]

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Predestined to be transient theoretical species, phenonium ions can now be considered as cationic intermediates of choice in organic synthesis. Here, we demonstrate that under non-nucleophilic and superacidic conditions, CF_3-substituted phenonium ions can be generated to furnish original CF_3-substituted dihydrostilbenes of interest.

Since the pioneering studies of Cram[1] (Fig. 1a), considerable interest has been focused on phenonium ions. The first observations of the anthrylethyl bridged cation and *p*-anisonium ion respectively by Eberson, Winstein[2] and Olah[3] (Fig. 1b) triggered numerous studies to understand the stability/reactivity of these original cations.[4] These studies greatly participated in shifting the phenonium ion from a fundamental phenomenon to a synthetically useful cationic intermediate.[5] The participation of an aryl neighbouring group to form a phenonium ion after leaving group activation can surprisingly favour processes that should not occur without such a stabilization. This is especially evident when electron-withdrawing groups adorn the phenonium cation (Fig. 1c).[6] In this context, fluorinated phenonium ions have also recently been elegantly exploited (Fig. 1d).[7] Among destabilized carbocations, CF_3-substituted carbocations[8] are rarely considered as affordable intermediates for synthetic perspectives, despite an evident potential for modern applications to the design of fluorinated products.[9] To the best of our knowledge, only one example of a CF_3-substituted phenonium ion has been postulated.[7e] Herein, we describe the first evidence of this species and its selective exploitation to design trifluoromethylated dihydrostilbene derivatives (Fig. 1e).

In due course of our recent ongoing efforts to generate and exploit destabilized cations and polycations[10,11] in superacid HF/SbF_5,[12] we thus envisioned to generate trifluoromethylated phenonium ions from CF_3-substituted alcohols. To favour a substantial stabilization of the resonance-demanding phenonium ion by the lone pair of an amino group, 3-(4-(dimethylamino)phenyl)-1,1,1-trifluoropropan-2-ol **1** was chosen as a model substrate (Scheme 1a). Treatment of **1** with HF/SbF_5 furnished a clean ionic species whose NMR signals did not match with the ones of a phenonium ion. Nevertheless, the clean spectra allowed to identify dication **A** as the sole species generated in solution. In the ^1H NMR spectrum, the methyl groups of the amine function appear as a doublet at 1.84 ppm confirming the formation of the ammonium ion. The protonation of the OH group is also confirmed by the presence of a doublet at 9.72 ppm [13] and by the presence of a quadruplet in the ^{13}C NMR spectrum at 119.2 ppm. This dicationic species was surprisingly stable up to 20 °C. Considering the difficulty to

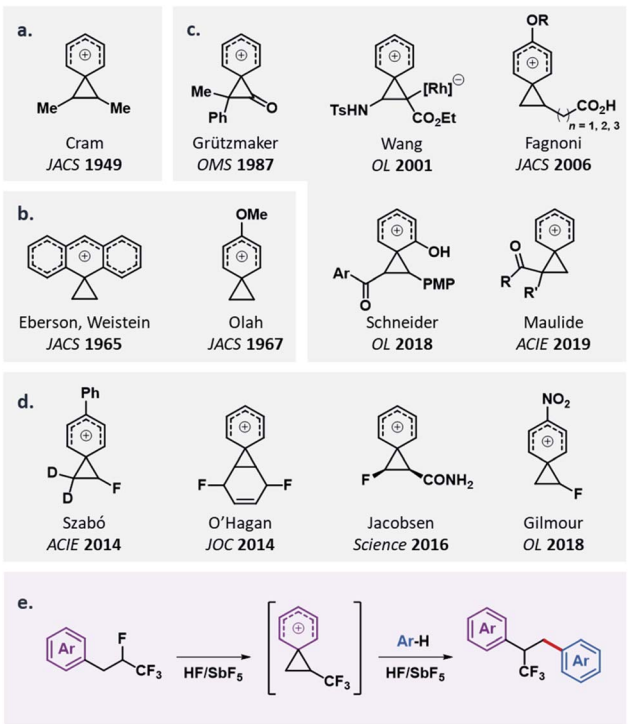

Fig. 1 (a) First postulated phenonium ion; (b) first observed phenonium ions; (c) postulated destabilized phenonium ions; (d) postulated fluorinated phenonium ions; (e) this work.

[a]*Université de Strasbourg, Université de Haute-Alsace, CNRS, UMR 7042-LIMA, ECPM, 25 Rue Becquerel, 67087 Strasbourg, France*

[b]*IC2MP, UMR CNRS 7285, Equipe "Synthèse Organique", Université de Poitiers, 4 rue Michel Brunet 86073 Poitiers, Cedex 9, France*

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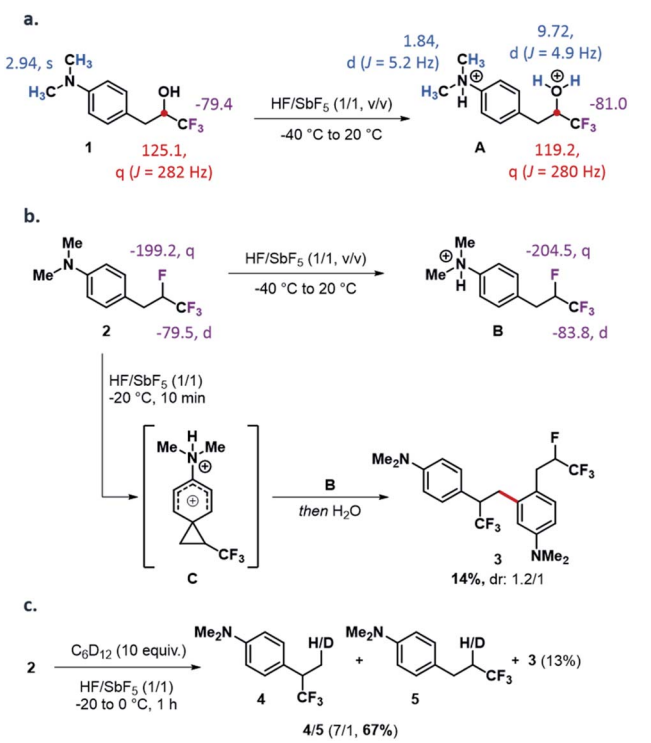
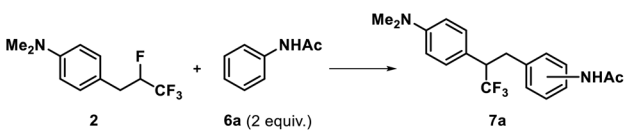
activate the C–OH bond geminal to the trifluoromethyl group, we turned our attention to the fluorinated analogue **2**. This was especially motivated by previous results from Prakash and Olah: attempting to generate the *p*-anisonium ion from β-*p*-anisylethanol in superacid, only a dication coming from the protonation of alcohol and ether functions was observed.[3,14] Interestingly, the targeted phenonium ion could be generated from the corresponding *p*-anisyl-2-chloroethane suggesting that the carbon–halogen bond could be activated in these conditions. Capitalizing on our experience on fluoroalkylamino reagents (FAR) and their exploitation in synthesis,[15] substrate **2** could be generated in two steps from perfluoropropene and ready to be tested under similar superacid conditions (see ESI†). Compound **2** reacted in superacid at −40 °C leading to a mixture of ionic species (Scheme 1b). The ^{1}H NMR spectrum resulting from this solution was difficult to interpret. However, in the ^{19}F NMR spectrum, the signals at −83.8 ppm and −204.5 ppm confirmed the presence of ion **B** in solution. As for the alcohol derivative **1**, the conditions were modified to tentatively favour the C–F bond activation by performing the reaction at higher temperature, but the reaction solution exhibited a complex mixture of different fluorinated species that were difficult to analyse. At −20 °C, after 10 min reaction, the reaction medium was hydrolysed and purified. The dihydrostilbene derivative **3** could be isolated from the reaction mixture in 14% yield. Although generated in a modest yield, the formation of this pseudodimeric compound could result from the reaction between the deactivated aromatic ring of the protonated ion **B** and the CF_3-substituted phenonium superelectrophilic ion **C**.[10] To confirm the involvement of ion **C** in the process, a deuterium labelling experiment was conducted in the presence of cyclohexane-d_{12} (Scheme 1c). With this nucleophilic source, any deuteration transfer reaction in superacid must occur through an ionic mechanism.[11a,16] Under these conditions, in addition to compound **3**, the deuterated compounds **4** and **5** could be isolated after one hour reaction of substrate **2**.[17] The formation of the reduced/deuterated products which must respectively originate from the insertion of a cation into a C–H/C–D bond of the alkane confirms the involvement of a CF_3-substituted phenonium ion **C**. The regioselectivity of the reaction, identical for the formation of **3** and **4** is also in accordance with an ionic mechanism. Interestingly, the formation of compound **5** as a minor product confirms the highly destabilized character of the elusive α-CF_3 carbocation.

Considering that the trifluoromethylated 1,2-diarylethane motif could be considered as an interesting pharmacophore for further applications,[18] we explored the ability to regioselectively trap the phenonium ion **C** with representative arenes. As a first instance, and encouraged by the formation of product **3** from intermolecular addition of the aniline, acetanilide **6a** was chosen as a model nucleophilic partner and **2** as a source of phenonium ion to screen the reaction conditions (Table 1). Gratifyingly, a first attempt in HF/SbF_5 allowed to generate the targeted fluorinated product **7a**, albeit in a modest 15% yield (Table 1, entry 1). Extending the reaction time and increasing the temperature throughout the reaction course was found ideal to favour a clean reaction (Table 1, entries 2–4) and product **7a** could eventually be obtained in 97% yield. The necessity to use HF/SbF_5 superacid conditions to activate the C–F bond[19] was



Scheme 1 (a) Exclusive formation of dication **A** after reaction of 3-(4-(dimethylamino)phenyl)-1,1,1-trifluoropropan-2-ol **1** in HF/SbF_5 at low temperature and characteristic NMR signals (δ in ppm); (b) reactivity of *N*,*N*-dimethyl-4-(2,3,3,3-tetrafluoropropyl)aniline **2** in HF/SbF_5 and characteristic NMR signals (δ in ppm); (c) deuterium labelling experiment supporting the involvement of dication **C**.

Table 1 Optimization of the reaction conditions between phenonium ion precursor **2** and acetanilide **6a**



Entry	Acid[a] (v/v)	Conditions	Yield[b] [%]
1	HF/SbF_5 (1/1)	−20 °C, 0.5 h	15
2	HF/SbF_5 (1/1)	−20 °C, 4 h	65
3	HF/SbF_5 (1/1)	−20 to 0 °C, 0.5 h	71
4	HF/SbF_5 (1/1)	−20 to 0 °C, 1 h	97
5	TfOH	20 °C, 1 h	0[c]
6	TfOH/SbF_5 (1/1)	−20 to 0 °C, 1 h	0[d]
7	HFIP/CH_2Cl_2 (1/1)	20 °C, 16 h	0[c]
8	SbF_5	0 to 20 °C, 1 h	0[c]
9	$BF_3 \cdot OEt_2$ (10 equiv.)[e]	20 °C, 1 h	0[c]
10	$B(C_6F_5)_3$ (5 mol%)[f]	20 °C, 16 h	0[c]

[a] Used as solvent, unless stated otherwise. [b] **7a** was isolated in each case as a 1/1 mixture of *para*/*meta* isomers. [c] Recovery of the starting material. [d] Complex mixture. [e] In CH_2Cl_2. [f] In $MeNO_2$.

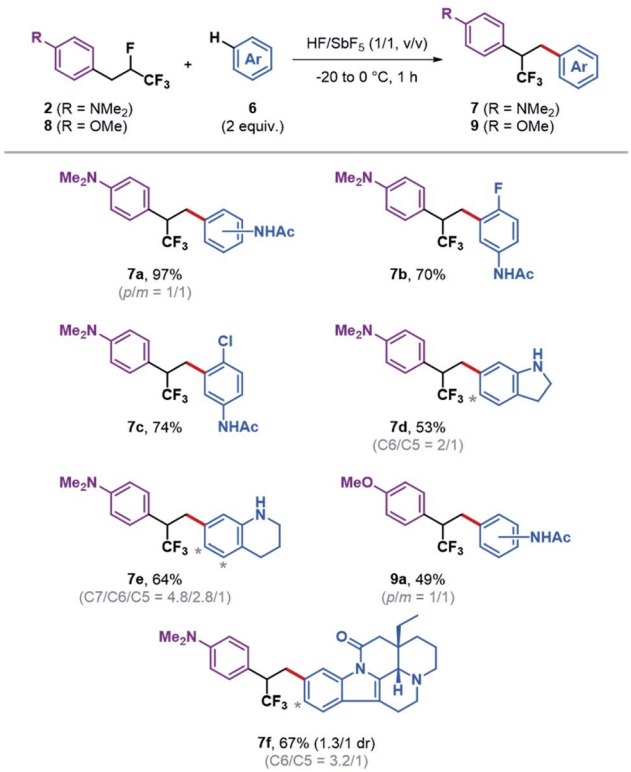


Fig. 2 Formation of CF_3-containing diarylethanes **7** and **9** in superacid.

demonstrated by the recovery of the starting material after exploring the reaction in trifluoromethanesulfonic superacid solutions, and thus whatever conditions used (Table 1, entries 5-6). Trying to activate the C–F bond[20] through a hydrogen bonding strategy in a hexafluoroisopropanol solution[21] was unsuccessful (Table 1, entry 7). Lewis acid activation of the C–F bond[22] was also explored with SbF_5, $BF_3{\cdot}OEt_2$ or $B(C_6F_5)_3$ but remained inefficient (Table 1, entries 8–10). This seems to confirm that highly acidic conditions and the absence of any nucleophilic counter-anions in solution[23] are needed to activate the C–F bond that is geminal to the CF_3 group to form the targeted phenonium ion.

With these optimized conditions in hand, to determine whether the external aromatic nucleophilic trapping of the CF_3-substituted phenonium ion can be extended to more elaborate substrates, compound **2** was submitted to superacid in the presence of different aromatic partners (Fig. 2).

The reaction could be applied to the synthesis of halogen-substituted products **7b** and **7c** in good yields after reaction with 4-fluoro and 4-chloroacetanilide. Not limited to aromatic amides, the reaction was also found to be efficient with indoline and tetrahydroquinoline affording the trifluoromethylated dihydrostilbenes **7d** and **7e**.[24] The regioselectivity of the Friedel–Crafts type reaction is dictated by the orientating effect of the alkyl chain, the amine being protonated under its ammonium form under these conditions. The reaction was found not limited to the trapping of the phenonium ion **C**, as its oxygenated analogue that must be generated from substrate **8** could also be trapped by acetanilide to generate product **9a**. At this stage it is also important to note that the reaction is highly regioselective, as the phenonium ion is selectively opened at the external position, in accordance with an ionic mechanism. No steric or electronic effect from the nucleophilic partner seems to affect this selectivity. To test this method on a more complex target, such as those that might be encountered in pharmaceutical research, vinburnine was tested as nucleophilic partner. Delightfully, the corresponding trifluoromethylated diarylethane analogue **7f** could be generated in 67% yield as a mixture of regio- and diastereomers.

To conclude, the ability to generate CF_3-containing phenonium ions in superacid HF/SbF_5 was demonstrated. These cations can react with poor nucleophilic partners such as deactivated nitrogen-containing arenes, suggesting a superelectrophilic character for this family of cations. Following recent and excellent contributions demonstrating the synthetic utility of phenonium ions, this work opens perspectives to exploit their CF_3-substituted counterpart for synthetic purposes.

Conflicts of interest

There are no conflicts to declare.

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