Angewandte Highlights

Trifluoromethanide Anion

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The (Not So) Ephemeral Trifluoromethanide Anion**

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The strategic value of the trifluoromethyl group in molecular design has generated considerable interest in the development of efficient synthetic methods for its introduction.[1,2] General strategies for the incorporation of this important motif encompass functional group interconversion reactions or more direct processes relying on the transfer of the complete moiety. Stoichiometric and catalytic variants of what might be considered nucleophilic (CF_3^-), electrophilic (CF_3^+), and radical ($CF_3^\cdot$) trifluoromethylation have been described (Figure 1).[3] In recent years, a plethora of (catalytic) electrophilic and radical trifluoromethylation reagents and methods have emerged,[4] many as a consequence of advances in metal and organocatalysis.[5] This is in stark contrast to nucleophilic trifluoromethylation, which is arguably less well developed. Thus far, the field has been dominated by trifluoromethyltrimethylsilane (TMSCF$_3$;[6] more commonly referred to as the Ruppert–Prakash reagent in recognition of its discoverers).

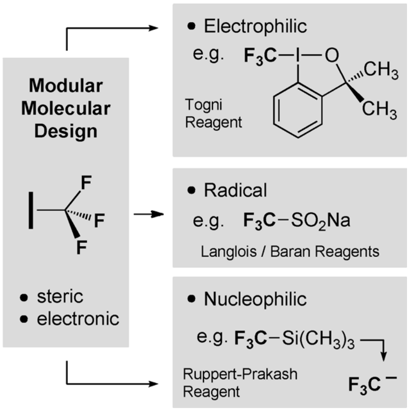

Figure 1. Electrophilic, nucleophilic, and radical trifluoromethylating strategies.

First reported by Ruppert et al. in 1984, in a study entitled "*Die ersten CF$_3$-substituierten organyl(chlor)silane*",[7] the reagent was identified by Prakash et al. as a convenient in situ trifluoromethanide (CF_3^-) equivalent.[8] Compared to the Seyferth reagents (Me_3SnCF_3 and $PhHgCF_3$), TMSCF$_3$ is notably less toxic, and is widely accepted as the nucleophilc trifluoromethylation reagent of choice. It has also featured prominently in the recent development of numerous catalytic trifluoromethylation processes. Indeed, a variety of [L$_n$M-CF$_3$] complexes have already been reported and/or commercialized (e.g. Hartwig's Trifluoromethylator, [(Phen)Cu-CF$_3$]).[9]

Despite the importance of the Ruppert–Prakash reagent in nucleophilic trifluoromethylation reactions, the isolation and characterization of the trifluoromethanide anion remained a major challenge. Until recently, it was believed to be an ephemeral intermediate with little direct evidence to support the existence of the unbound species. Indeed, the well-described decomposition to singlet difluorocarbene ($CF_3^- \rightarrow :CF_2 + F^-$) appears to have galvanized the notion that this species was not isolable. However, the ability of TMSCF$_3$ to behave as both a latent source of difluorocarbene and concurrently as a trifluoromethanide equivalent in a one-pot trifluoromethylation–difluoromethylation sequence suggests that the anion could be intercepted prior to α-defluorination.[10] A major breakthrough in the quest for the elusive anion came from the ground-breaking study by Prakash et al., in which it was found that fluoroform (CHF_3) can be employed as a convenient trifluoromethylating reagent. The transformation has attracted widespread attention, since a major greenhouse gas with little synthetic value can now be exploited for the direct nucleophilic trifluoromethylation of various carbon, silicon, boron, and sulfur electrophiles.[11] Following this report, Shibata and co-workers demonstrated that sterically demanding organo-superbases assist in circumventing the decomposition of the trifluoromethanide anion derived from fluoroform (CHF_3).[12]

In a recent study, Prakash and co-workers describe "the long-lived trifluoromethanide anion", thereby completing a story that began decades ago.[13] The study provides unequivocal evidence that the anion can be generated in relatively large quantities and can be fully characterized by variable-temperature NMR spectroscopy. This latest discovery is one in a long and distinguished list of reactive

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intermediates isolated and characterized by the Prakash/Olah research group. The authors present a convincing case that the CF_3^- ion ought to be persistent at low temperatures. This is supported by a consideration of the C−F bond strength and Lewis acidity of the corresponding singlet difluorocarbene. The adiabatic enthalpy for C−F bond dissociation and the free energy of the anion in THF also serve to strengthen the working hypothesis. Importantly, the computational study also reveals that the α-defluorination enthalpy can be significantly reduced in the presence of a potassium cation. Thus, the authors concluded that the species ought to be thermally stable at low temperatures, but that strong cation–anion interactions are likely to be detrimental. Reaction screening identified a reagent system comprising potassium-based activators or bases and 18-crown-6 as being likely to furnish the naked, and thus presumably longer lived, CF_3^- ion. Indeed, initial experiments employing *t*-BuOK/18-crown-6 and a stock solution of CHF_3 in THF in an equimolar ratio provided tangible support for this rationale, with the formation of a new species being clearly identifiable by low-temperature ^{19}F NMR techniques ($\delta_F \approx -19$ ppm). The attempted preparation of this same species failed when starting from $TMSCF_3$ (TMS = trimethylsilyl) and Me_4NF in anhydrous THF, a finding that can be attributed to the formation of the stable pentavalent silicate $[Me_3SiF(CF_3)]^-$ ($\delta_F = -63.9$ ppm). Replacing the relatively small fluoride activator by the bulkier *t*BuO$^-$ anion led predominantly to the formation of $[Me_3Si(CF_3)_2]^-$ ($\delta_F = -65.6$ ppm), but still failed to provide the desired trifluoromethanide anion in significant amounts. Only by careful warming of the sample to −56 °C was productive decomposition of this complex to the desired CF_3^- ion achieved. A significant improvement was noted when using the sterically more demanding $TIPSCF_3$ analogue (TIPS = triisopropylsilyl) of the Ruppert–Prakash reagent in combination with an excess of *t*BuOK (2.2 equiv) and 18-crown-6 (2.2 equiv). Gratifyingly, under these conditions at −78 °C, only the diagnostic signal at $\delta_F = -18.7$ ppm (singlet) was detected after a few minutes. Analysis of the coupling constants ($^1J_{C\text{-}F}$) from the ^{13}C satellite signals in the ^{19}F NMR spectrum revealed an expectedly large value of 429.3 Hz (from $TMSCF_3$) or 434.0 Hz (from $TIPSCF_3$; Figure 2). Directly recording a ^{13}C NMR spectrum starting from $TMSCF_3$ at −56 °C essentially gave the same value, with a quartet arising at $\delta_C = 175.0$ ppm ($^1J_{C\text{-}F} = 432.5$ Hz). In contrast, the conjugated acid fluoroform (CHF_3) was detected at $\delta_C = 122.2$ ppm with an associated $^1J_{C\text{-}F}$ coupling constant of 293.3 Hz. The computationally derived chemical shifts closely matched those determined experimentally ($\delta_F = -23.7$ ppm and $\delta_C = 170.3$ ppm). However, the computationally determined coupling constant value was slightly underestimated at $^1J_{C\text{-}F} = 393.0$ Hz. In several experiments with R_3SiCF_3, the occurrence of CHF_3 was observed, most likely stemming from the deprotonation of the solvent or the crown ether additive. Intriguingly, this process outcompeted the α-defluorination and, thus, slow warming of preformed [K(18-crown-6)][CF_3] in THF from −50 to −35 °C preferentially afforded CHF_3. Finally, the authors conducted a series of experiments to trap the trifluormethide anion of [K(18-crown-6)][CF_3] generated from $TIPSCF_3$ and *t*BuOK at −78 °C. In general, yields were found to be strongly dependent on the electrophile and ranged from 7 to 76 %, as determined by ^{19}F NMR spectroscopy. Interestingly, gaseous CO_2 proved to be one of the best electrophiles examined, furnishing potassium trifluoroacetate in 76 % yield. In addition to organic trapping reagents, CuI also reacted and furnished the highly topical $CuCF_3$ species in 66 % yield.

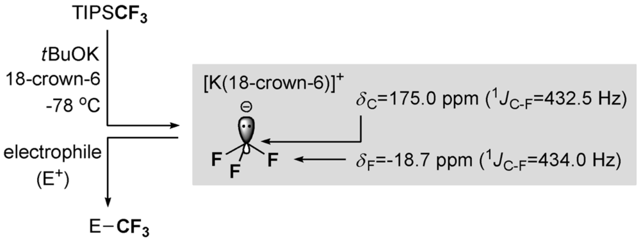

Figure 2. The generation of the long-lived trifluoromethanide anion and its spectroscopic characterization.

This beautiful study by Prakash et al. not only dispels the myth that the CF_3^- ion is a fleeting intermediate in nucleophilic trifluoromethylation chemistry, but it also serves as a valuable platform for future mechanistic studies in this exciting research field.

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