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Unexpected reactivity of 2-fluoro-4-(trifluoromethyl)-phenylacetonitrile: isolation and characterization of a trimeric impurity

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ABSTRACT

An uncommon reactivity of 2-fluoro-4-(trifluoromethyl)-phenylacetonitrile, with the loss of three fluorine atoms, is herein reported, the resulting trimeric compound was isolated and characterized by NMR and MS/MS studies. An unprecedented mechanism has been proposed.

We recently reported the synthesis of arylacetonitrile derivatives in view of their importance as key building blocks for more complex heterocyclic compounds.[1] In particular, we focused our attention on the process development for the making of 2-fluoro-4-(trifluoromethyl)-phenylacetonitrile, to rapidly access multigram quantities of this compound. During the process definition studies, we ended up exposing the 2-fluoro-4-(trifluoromethyl)-phenylacetonitrile to strong basic conditions (NaHMDS in THF or KO*t*Bu in THF), observing the presence of a high molecular weight impurity, which undermined the final recovery. Despite not knowing the nature of this impurity, we hypothesized a certain structure similarity with the 2-fluoro-4-(trifluoromethyl)-phenylacetonitrile in lieu of the inverse proportionality with the isolated yield of the final compound: higher concentration of this impurity corresponded to a lower process yield and, in parallel, an increased difficulty in the final product purification. The very first empirical observation was that at a temperature higher than 10 °C this impurity represented the main product in the reaction mixture, in a way that was pivotal to understanding its nature and the mechanism of its formation. The aim was not limited to the simple optimization of the reaction conditions but intended to remove the tight control of the process parameters. The unknown compound was isolated by column chromatography.

^{1}H NMR spectra were initially collected using different solvents. All of them resulted in very broad lines with little information helping the structure elucidation. However, we found out that the addition of acids allowed us to get sharp lines and promoted further investigations by means of 2D NMR as well as ^{19}F NMR experiments. In particular, the spectra in acetone-d_6 with the addition of TFA resulted in the observation of two resonances in the region 6.5–5.7 ppm. They could be associated to C–H protons, showing a ^{1}H–^{13}C correlations in a gHSQC experiment, easily exchangeable with deuterium as demonstrated by their absence in the spectrum collected in CD_3COOD (Fig. 1).

The ^{1}H NMR integrals evaluation suggested also that we were in the presence of a mixture of two compounds, possibly isomers, in a molar ratio ca. 55/45. This was confirmed by the integration of the resonances in ^{19}F NMR spectra. Here, the presence of three Aryl-F groups and only two CF_3 groups was detected for each component of the mixture. The sample was also analyzed by negative ES and the resulting spectrum contained *m*/*z* 548 as the base peak. A series of 1D and 2D NMR experiments, in conjunction with MS/MS data (Fig. 2), confirmed the initial hypothesis of a product (**7**) derived from a degradation of 2-fluoro-4-(trifluoromethyl)-phenylacetonitrile. The confirmation of *E* and *Z* isomerism for the two components in the mixture was achieved by analysis of the NOE contacts observed in a 2D ROESY experiment. ^{1}H–^{13}C gHSQC, ^{1}H–^{13}C gHMBC, and ^{1}H–^{15}N gHNMQC allowed further structure confirmation and almost complete ^{13}C and ^{15}N NMR assignments.

From a chemical point of view, we proposed the mechanism reported in Scheme 1. Deprotonation of **1** was followed by F^- loss, to end up with **2**. This intermediate could subsequently be attacked by **1** twice affording **4**. Loss of F^- again followed by deprotonation of **5** gave the final compound **6**, in which the negative charge was highly delocalized, this being the possible cause of the broad sig-

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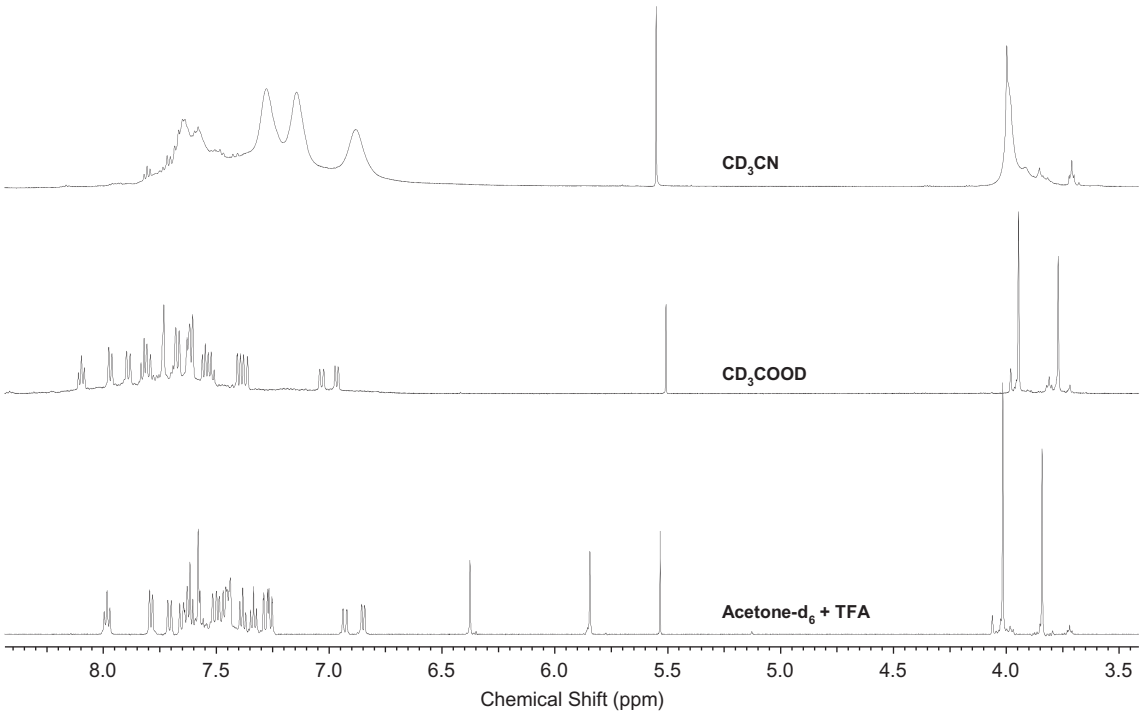
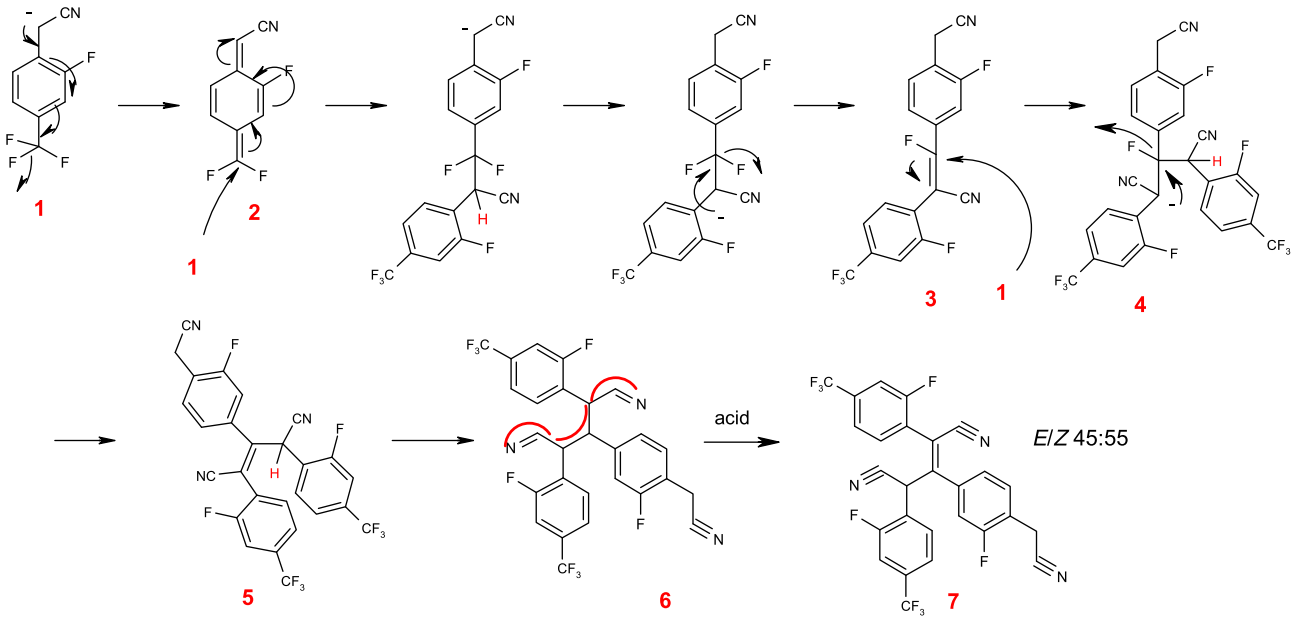


Figure 1. ^{1}H NMR spectra of the isolated unknown impurity collected in different solvents. The resonance at ca. 5.5 ppm (singlet) in all spectra is due to residual DCM.



Scheme 1. Proposed mechanism for impurity **7** formation.

nals in the NMR spectra under neutral conditions. The surprising reactivity with loss of the three fluorine atoms in the $-CF_3$ group could be due to the favored formation of **2**, stabilized by the electron withdrawing effect of fluorine atom and cyano group, as well as by the conjugative effect.[2] No examples of such displacement in trifluoromethylbenzene derivatives are reported.

To the best of our knowledge such a degradation pathway is one of the few examples of intermolecular C–F bond activation.[3] The pronounced inertness of perfluorocarbons is undoubtedly caused by the high C–F bond dissociation energies and by the weakness of any interaction with fluorocarbons[4] in a way that both thermodynamic and kinetic factors generally disfavor C–F bond activation.

By discovering the nature of this impurity, we were able to design a synthesis of it, simply treating 2-fluoro-4-(trifluoromethyl)-phenylacetonitrile in THF with either NaHMDS or KO*t*Bu at temperature higher than 10 °C, confirming the experimental results obtained during our process development.[5] On the other hand, we could not get away from establishing rigorous processing conditions. In fact, in order to decrease its formation in the process we had to conduct the reaction at a temperature below −5 °C.

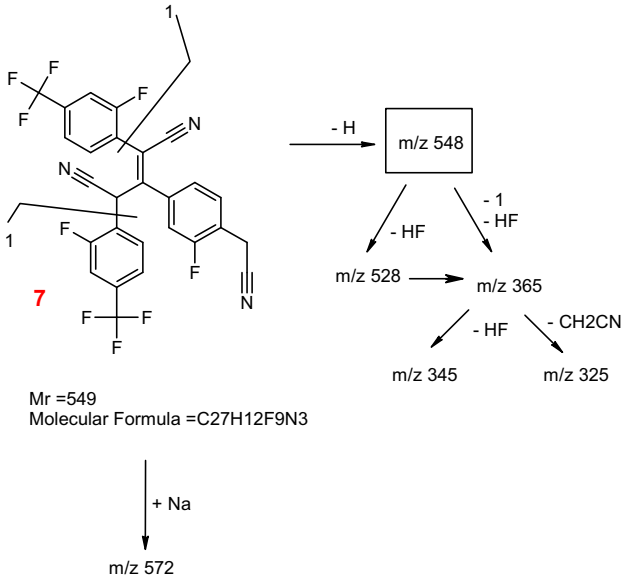


Figure 2. Structure of the impurity (**7**) and its main fragmentations detected in MS/MS.

In conclusion, we herein reported an unexpected reactivity of 2-fluoro-4-(trifluoromethyl)-phenylacetonitrile under basic conditions giving rise to a trimeric compound via a surprising loss of three fluorine atoms. A plausible mechanism was suggested to explain such an unprecedented reactivity. In addition, the impurity was isolated, characterized and then independently synthesized allowing the development of a final process which minimized its formation in the reaction media.

Supplementary data

Supplementary data (MS spectra, ^{19}F NMR spectrum and table of $^{1}H/^{19}F/^{13}C/^{15}N$ NMR assignments) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.007.

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5. *Typical procedure for the synthesis of* **6**: 2-Fluoro-(4-trifluoromethyl)-phenylacetonitrile (1 g) was dissolved in THF (1 mL) under N_2. NaHMDS 2 M in THF (3.2 mL, 1.2 equiv) was slowly added (reaction exothermic). The mixture was stirred at room temperature overnight. The mixture was diluted with MTBE, washed with NaCl 10%, dried over Na_2SO_4 and evaporated to give a dark red-oil. The oil was washed with DCM (3 × 5 vol); the insoluble part was dried to give a brown solid (0.68 mg, 75% yield).