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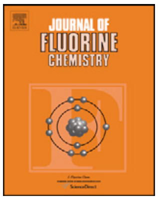

Synthesis and molecular structure of a perfluorinated pyridyl carbanion

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ABSTRACT

Reaction of pentafluoropyridine with sodium nitromethanide allowed the isolation and characterisation of the first perfluorinated pyridyl carbanion system, sodium nitrobis(perfluoropyridin-4-yl)methanide, by X-ray crystallography.

1. Introduction

A ‘mirror-image’ relationship between the chemistry of perfluorinated systems, which are dominated by nucleophilic processes, and hydrocarbon systems, which largely react via electrophilic processes, has developed [1]. For example, a range of perfluoroalkyl carbanion systems, such as $(CF_3)_3C^-Cs^+$, have been observed [2,3] by ^{19}F NMR techniques that mirror the classic studies by Olah concerning the observation of long lived carbocations such as $(CH_3)_3C^+$ species [4]. In addition, electrophilic aromatic substitution reactions of hydrocarbon systems [4] are mirrored by nucleophilic aromatic substitution processes of highly fluorinated aromatic and heteroaromatic derivatives [5]. Consequently, the developments of hydrocarbon chemistry, well established over many years, may be complemented by ‘mirror-image’ reactions, reagents, reaction mechanisms and molecular structures of highly fluorinated derivatives [1].

Nucleophilic aromatic substitution reactions (S_NAr) involving displacement of fluorine from highly fluorinated heteroaromatic systems by nitrogen, oxygen and sulfur centred nucleophiles are well documented [5] and the chemistry of perfluoroheteroaromatic systems continues to develop. As part of a wide ranging research programme in this field, we have recently reported chemistry of perfluoroheteroaromatic systems that allows the synthesis of a wide range of ring fused polycyclic scaffolds for drug discovery [6–9], macrocycles [10], glycosyl donors [11] and polyfunctional heteroaromatic derivatives [8]. As part of ongoing projects at Durham concerning the development of perfluoroheteroaromatic and fluoro-peptide chemistry, we targeted the synthesis of a range of novel perfluoroheteroaromatic amines following a synthetic strategy outlined in Scheme 1, involving reaction of pentafluoropyridine with carbon based nucleophiles derived from nitroalkanes and subsequent reduction.

In the vast majority of reported cases, reactions of nucleophiles with pentafluoropyridine are regiospecific and give products arising from substitution of fluorine attached to the most activated site *para* to ring nitrogen following well established mechanistic principles [5]. Whilst many reactions of nucleophiles with pentafluoropyridine have been reported [5,12,13], processes involving carbon centred nucleophiles are less common and largely limited to reactions involving various alkyl, vinyl and phenyl lithium derivatives and perfluoroalkyl anions [5].

In this paper, we describe reactions of pentafluoropyridine with carbon nucleophiles derived from nitromethane in Henry-type processes and the isolation of an unexpected stable perfluorinated pyridyl carbanion system.

2. Results and discussion

Reaction of pentafluoropyridine **1** with one equivalent of carbanion species, prepared by deprotonation of nitromethane by sodium hydride, gave a complex mixture of products which did not include the desired product **2** (Scheme 2) and a low yield of product **3** (8%). Subsequently, reaction of two equivalents of pentafluoropyridine **1** with one equivalent of carbanion species gave higher yields of the unexpected major product of the reaction, anion **3**, based on ^{19}F NMR analysis of the crude reaction mixture. Anion **3**

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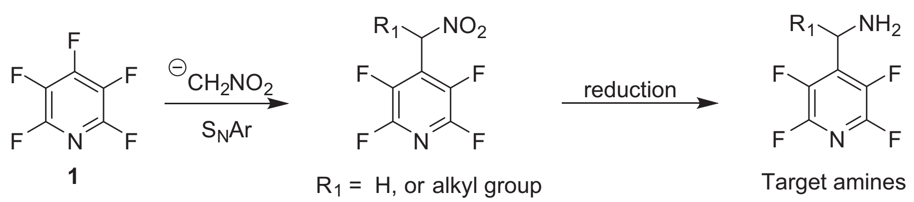
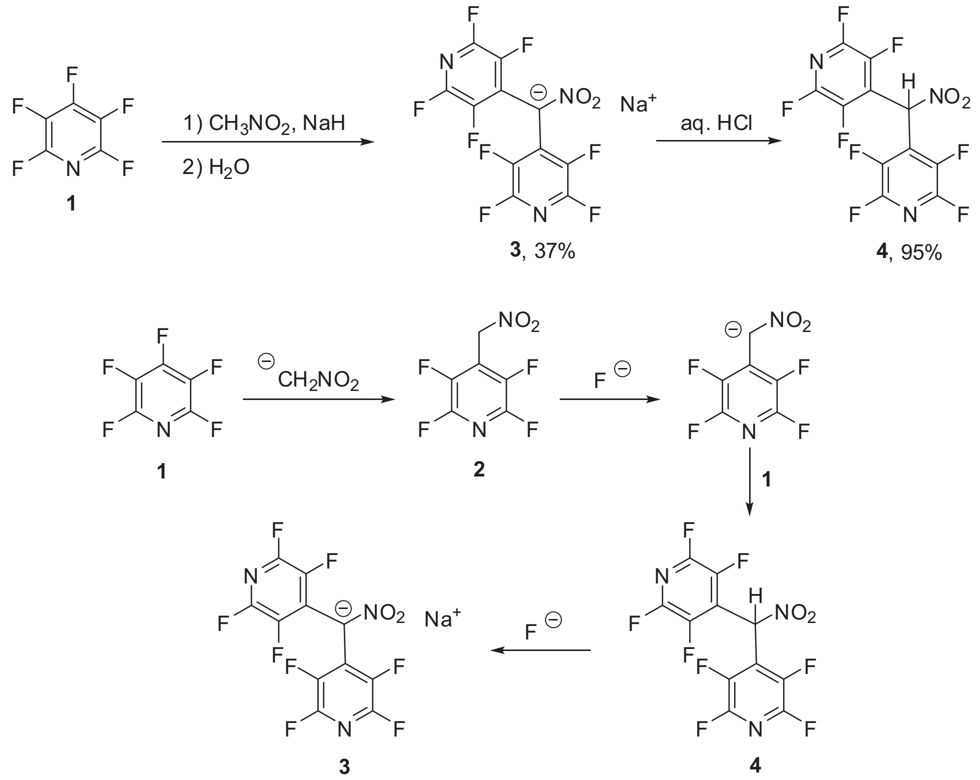


Scheme 1. Synthetic strategy for the synthesis of novel perfluoroheteroaromatic amines.



Scheme 2. Synthesis and mechanism for the formation of carbanion **3** and conjugate acid **4**.

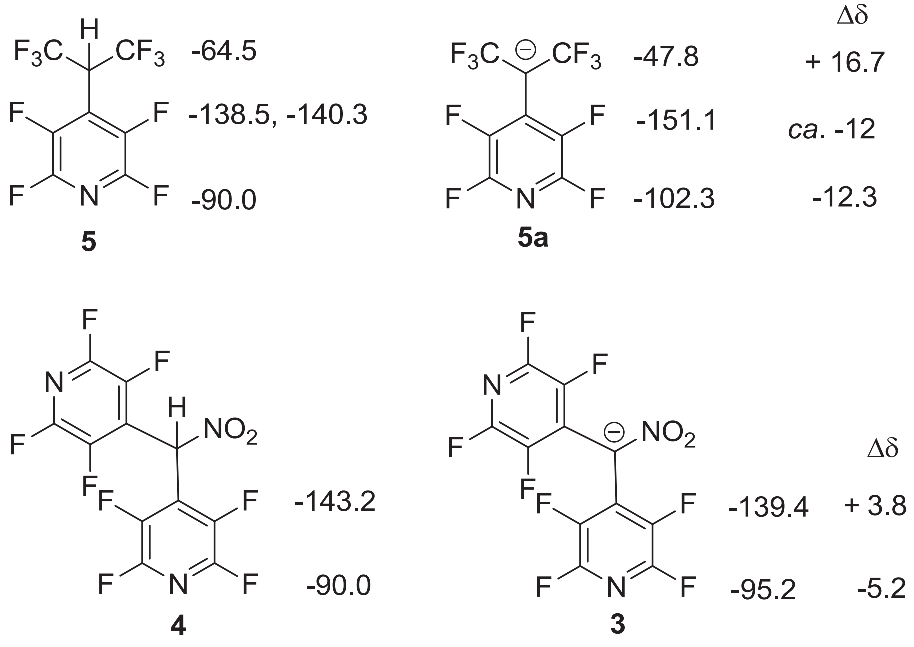


Fig. 1. ^{19}F NMR studies of perfluoropyridyl derivatives.

could be isolated and characterised by ^{19}F and ^{13}C NMR and ES-MS analysis.

The formation of **3** can be explained as shown in Scheme 2. Initial attack of the carbanion derived from nitromethane at the most activated 4-position of pentafluoropyridine, *para* to ring nitrogen, leads to the formation of **2**. This intermediate is relatively acidic and abstraction of the pyridyllic proton by the displaced highly basic fluoride ion or remaining nitromethane anion in solution leads to a pyridyllic carbanion which reacts with a further equivalent of pentafluoropyridine to give the protonated system **4**. Further deprotonation in the basic reaction medium yields the major product carbanion **3**. In a subsequent experiment, protonation of carbanion **3** in dilute hydrochloric acid solution allowed the isolation of conjugate acid **4**.

Both **3** and **4** were isolated and characterised by ^{19}F NMR (Fig. 1) and X-ray crystallography (Figs. 2 and 3) and this data provides the opportunity to probe the effect of the nitro and tetrafluoropyridyl groups on the extent of negative charge delocalisation in the carbanion **3** in comparison with the conjugate acid **4**. Benzyl and pyridyl carbanions are of particular interest in organofluorine chemistry due to their relationship to Meisenheimer complexes in S$_N$Ar processes which mirror corresponding Wheland intermediates in hydrocarbon chemistry and, indeed, several relatively stable perfluorinated benzyllic carbanions such as **5a** (Fig. 1) have been observed in solution by ^{19}F NMR spectroscopy [14]. For pyridyl system **5a**, the ^{19}F NMR shifts of all ring fluorine atoms are shifted upfield by 12 ppm with respect to the conjugate acid **5** indicating that the ring fluorine atoms in carbanion **5a** are connected to carbon atoms that bear partial negative charge.

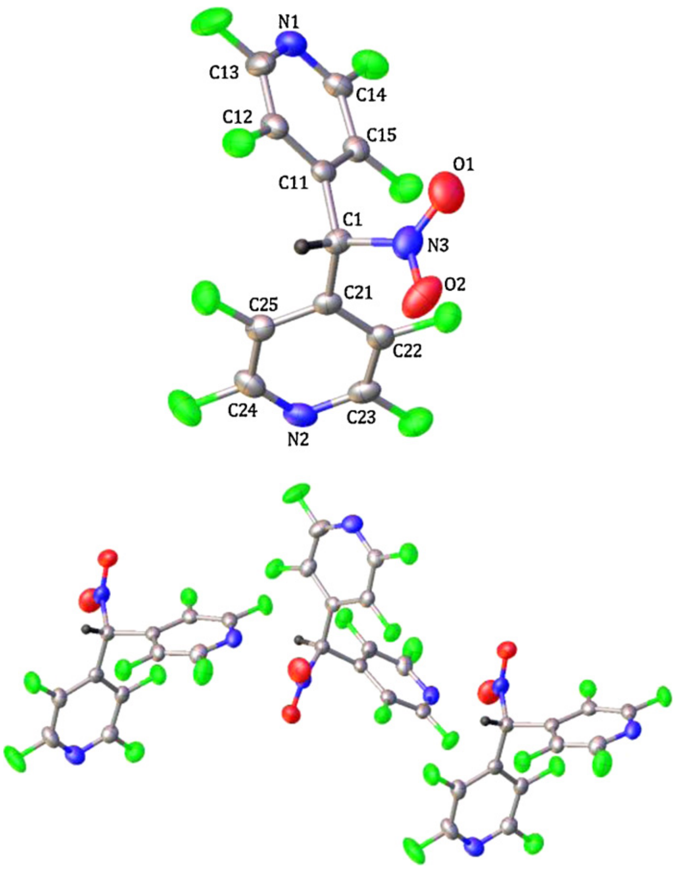


Fig. 2. Molecular structure showing 50% probability anisotropic displacement ellipsoids (above) and crystal packing arrangement (below) of conjugate acid **4**.

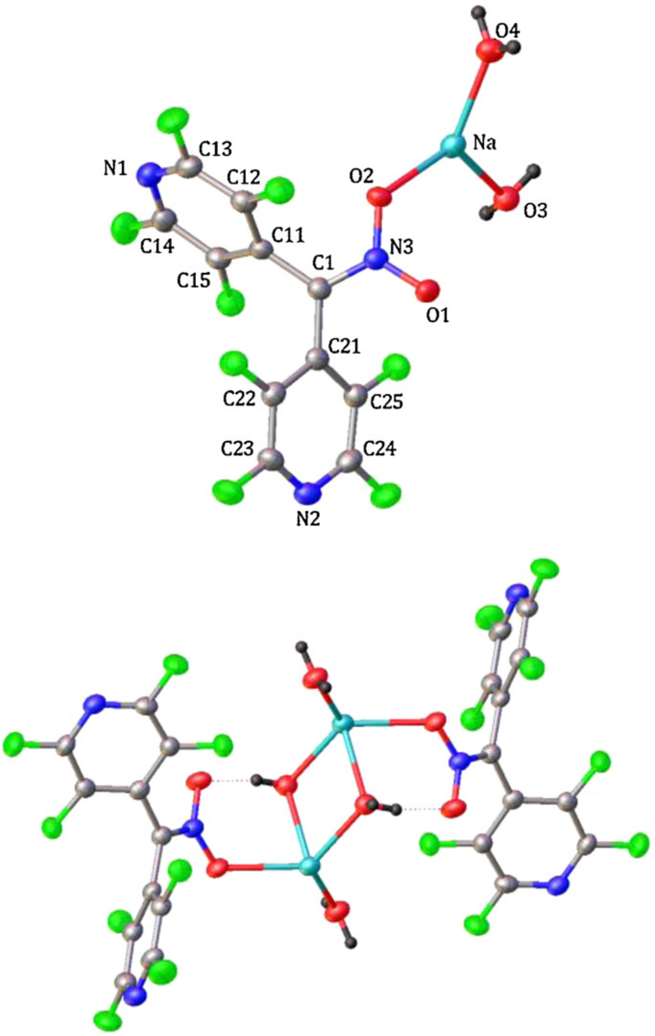
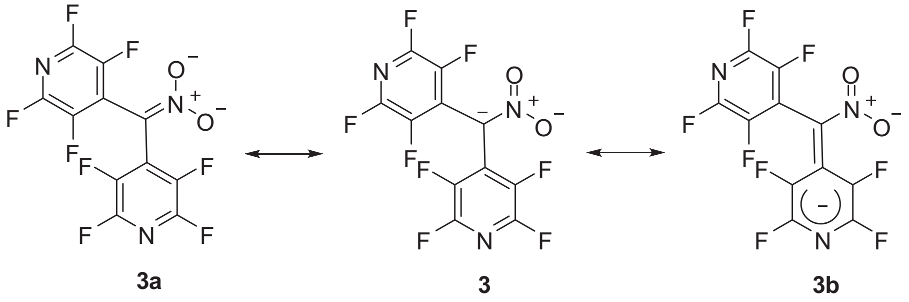


Fig. 3. Molecular structure showing 50% probability anisotropic displacement ellipsoids (above) and crystal packing arrangement (below) of carbanion **3**.

For the anion **3**, the ^{19}F NMR chemical shifts in acetonitrile solution are observed at −95.2 (F-2) and −139.4 (F-3) ppm and the corresponding resonances observed for the conjugate acid **4**, also in acetonitrile solution, occur at −90.0 and −143.2 ppm respectively, reflecting a change in chemical shift ($\Delta\delta$) from conjugate acid **4** to anion **3** of −5.8 and +3.8 ppm, respectively. These chemical shifts are difficult to explain in comparison with the data obtained for carbanion **5a** observed previously but indicate that charge may be located more favourably on the nitro group.

Crystals of carbanion **3** and conjugate acid **4** were obtained by slow evaporation of acetonitrile and ethanol at room temperature, respectively, allowing an X-ray crystallographic study of these two systems to be performed. Conjugate acid **4** (Fig. 2) has a tetrahedral arrangement around C1, and the C1–N3 and C1–C21 bonds are clearly singular, with bond lengths of 1.487(4) Å and 1.514(4) Å, respectively. Hydrogen bonds formed between the hydrogen atom and N2 stabilise the crystal packing at a distance of 2.467 Å. Bond lengths in the perfluoropyridyl groups indicate the electrons are delocalised evenly over the heterocyclic rings.

Very few molecular structures of perfluorinated carbanion systems [15], such as trifluoromethoxide and perfluorocyclobutyl salt derivatives [16,17], have been determined by X-ray crystallography and, indeed, perfluorinated carbanion **3** represents the



Scheme 3. Resonance structures of carbanion **3**.

first reported molecular structure of a perfluorinated pyridyllic carbanion derivative. The molecular structure of carbanion **3** (Fig. 3) indicates that C1 is trigonal and the C1–N3 bond displays double bond character, as shown by the bond length of 1.338(3) Å. The carbanion C1–C21 bond length of 1.459(3) Å is 0.05 Å shorter than the corresponding bond in the conjugate acid **4** indicating partial double bond character. The carbon–carbon bond lengths in the perfluoropyridyl rings indicate the electrons are delocalised, as exemplified by the equivalency in C24–N2 and C23–N2, C24–C25 and C22–C23, and finally C21–22 and C21–25. The sodium ion co-ordinates to four oxygen atoms in a distorted tetrahedral conformation, rather than the expected octahedral co-ordination, leading to the crystal packing arrangement shown in Fig. 3.

These observations indicate that, in the solid state, the negative charge of carbanion **3** is present mainly on the nitro group as in the resonance form **3a** (Scheme 3), reflecting the stronger electron withdrawing ability of the nitro group in comparison to the tetrafluoropyridine units, although coordination of the nitro group with the sodium cation will be a factor. Although it is very difficult to compare structures in the solid state and in solution, the crystallographic data indicating that most negative charge is present on the nitro group is in reasonable agreement with the ^{19}F NMR data of **3** described above.

3. Conclusions

Reaction of sodium nitromethanide with pentafluoropyridine gives a stable pyridyllic carbanion system **3** which was isolated and characterised by NMR and X-ray crystallography. The spectroscopic and crystallographic data suggest that a significant fraction of negative charge of the carbanion is delocalised over the nitro group rather than onto the tetrafluoropyridine ring.

4. Experimental

4.1. General

Unless otherwise stated, commercially available reagents and solvents were used without purification. Flash column chromatography was carried out using Fluorochem Silicagel LC60A (40–63 μm). Proton, carbon and fluorine nuclear magnetic resonance spectra were recorded on a Bruker Avance 400 (^{1}H NMR, 400 MHz, ^{13}C NMR, 100 MHz, ^{19}F NMR, 376 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR, CD_3CN at 1.94 ppm; ^{13}C NMR, CD_3CN at 118.3 ppm; ^{19}F NMR, $CFCl_3$ at 0.00 ppm). ^{13}C and ^{19}F spectroscopic data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and assignment. ESI-MS analysis was performed using a Micromass LCT ToF operating in negative ion mode.

4.2. Sodium nitrobis(perfluoropyridin-4-yl)methanide 3

A mixture of nitromethane (0.61 g, 10 mmol) and DMF (10 mL) was cooled to 0 °C with stirring. Sodium hydride (60% dispersion in oil, 0.44 g, 12 mmol) was added in two equal portions over a period of 5 min and the resulting reaction mixture was left to stir at 0 °C for a further 20 min. Pentafluoropyridine **1** (3.38 g, 20 mmol) in DMF (10 mL) was added to the reaction mixture over a period of 10 min. The reaction was left to warm to rt over 40 min before it was quenched by addition to cold water (150 mL). The resulting solution was separated using ethyl acetate and the organic layer washed with water and brine before being dried (Na_2SO_4) and concentrated under reduced pressure to give an orange oil. Column chromatography over silica gel using ethyl acetate: hexane (1:1) as elutant gave *sodium nitrobis(perfluoropyridin-4-yl)methanide* **3** (1.40 g, 37%) as a white powder; δ_F (CD_3CN) −95.16 (2F, ddd, $^3J_{FF}$ 38, $^4J_{FF}$ 15, $^5J_{FF}$ 15, F-2), −139.35 (2F, ddd, $^3J_{FF}$ 38, $^4J_{FF}$ 15, $^5J_{FF}$ 15, F-3); δ_C (CD_3CN) 93.9 (s, C^-), 129.34 (tm, $^2J_{CF}$ 14, C-4), 140.2 (ddm, $^1J_{CF}$ 250, $^2J_{CF}$ 33, C-3), 144.2 (dddd, $^1J_{CF}$ 239, $^2J_{CF}$ 14, $^3J_{CF}$ 14, $^4J_{CF}$ 3, C-2); m/z (ESI^-) 358.1 ($[M]^-$, 100%).

Table 1
Crystallographic data for **3** and **4**.

	Carbanion **3**	Conjugate acid **4**
Empirical formula	$C_{11}N_3O_4F_8Na$	$C_{11}HN_3O_2F_8$
Mr	413.11	359.15
T [K]	99.69	99.81
Crystal system	Monoclinic	Monoclinic
Space group	$P2_{1/n}$	$P2_{1/n}$
a [Å]	5.635(2)	8.552(2)
b [Å]	16.467(4)	12.540(2)
c [Å]	16.432(4)	11.831(2)
α, γ [°]	90.00	90.00
β [°]	99.29(2)	107.965(5)
V [Å^3]	1504.8(7)	1206.9(4)
Z	4	4
ρ_{calc} [mg mm^{-3}]	1.687	1.977
μ [mm^{-1}]	1.925	2.022
$F(000)$	748	704
Reflections collected	6216	15,399
Independent reflections	2304	2068
Data/restraints/parameters	2304/4/256	2068/0/217
R_1, wR_2 [$I > 2\sigma(I)$]	0.0366, 0.0974	0.0532, 0.1540
R_1, wR_2 [all data]	0.0445, 0.1023	0.0561, 0.1570
Largest diff. peak, hole [e Å^{-3}]	0.250, −0.024	0.531, −0.447

Selected bond lengths [Å]. *Carbanion* **3**: C1–N3 1.338(3), N3–O1 1.282(2), N3–O2 1.288(2), C1–C21 1.459(3), C21–C22 1.395(3), C21–C25 1.396(3), C22–C23 1.367(4), C23–N2 1.313(3), N2–C24 1.326(3), C24–C25 1.359(4), C1–C11 1.468(3), C11–C12 1.393(4), C11–C15 1.389(3), C12–C13 1.370(4), C13–N1 1.315(3), N1–C14 1.304(3), C14–C15 1.375(4). *Conjugate acid* **4**: C1–N3 1.487(4), N3–O1 1.200(4), N3–O2 1.246(4), C1–C21 1.514(4), C21–C22 1.379(4), C21–C25 1.380(4), C22–C23 1.380(4), C23–N2 1.307(4), N2–C24 1.311(4), C24–C25 1.376(4), C1–C11 1.503(4), C11–C12 1.372(4), C11–C15 1.389(4), C12–C13 1.377(5), C13–N1 1.297(4), N1–C14 1.295(4), C14–C15 1.371(4).

4.3. 4,4′(Nitromethylene)bis(2,3,5,6-tetrafluoropyridine) **4**

A solution of carbanion **3** (50 mg, 0.13 mmol) in ethyl acetate (10 mL) and conc. hydrochloric acid (0.5 mL) was stirred at rt for 30 min. Water (10 mL) was added to the mixture and the ethyl acetate layer was separated, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give *4,4′(nitromethylene)bis(2,3,5,6-tetrafluoropyridine)* **4** (45 mg, 95%) as a white powder; δ_H (CD_3CN) 7.85 (br s); δ_F (CD_3CN) −90.0 (2F, ddd, $^3J_{FF}$ 38, $^4J_{FF}$ 15, $^5J_{FF}$ 15, F-2), −143.22 (2F, ddd, $^3J_{FF}$ 38, $^4J_{FF}$ 15, $^5J_{FF}$ 15, F-3); δ_C (CD_3CN) 129.1 (t, $^2J_{CF}$ 13, C-4), 140.7 (ddm, $^1J_{CF}$ 266, $^2J_{CF}$ 37, C-3), 144.8 (dm, $^1J_{CF}$ 243, C-2), 177.16 (m, C-NO_2); *m/z* (ESI^-) 358.2 ($[M-H]^-$, 100%).

4.4. X-ray crystallography

Crystals of carbanion **3** and conjugate acid **4** were obtained by slow evaporation of acetonitrile and ethanol at room temperature respectively. Crystallographic data for both compounds were collected at approximately 100 K on a Bruker MicroStar diffractometer using a Cu-rotating anode, equipped with Helios mirror optics as a monochromator and a Platinum 135 CCD detector. Measurements were performed using Cu Kα radiation ($\lambda = 1.5417$). All data were integrated and scaled using SAINT (Bruker, 2000). The structures were solved by direct methods (SHELXS-97) and refined by least squares methods against F^2 (SHELXL-97) [18]. All non-hydrogen atoms were refined with anisotropic displacement parameters and all hydrogen atoms were unambiguously identified and refined isotropically on calculated positions using a riding model. Molecular graphics were created using Olex2 software [19]. Crystallographic data for structures of **3** and **4** are summarised in Table 1. Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 845592-845593.

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