Journal of Fluorine Chemistry 129 (2008) 1133–1138

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Novel ring-cleaving reaction of 4-nitro-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane with nucleophiles

William R. Dolbier Jr.*, Yian Zhai, Wei Xu, Will Wheelus, Florian Dulong, Efram Goldberg, Ion Ghiviriga, Merle A. Battiste

Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, United States

ARTICLE INFO

Article history:
Received 9 July 2008
Received in revised form 12 August 2008
Accepted 13 August 2008
Available online 23 August 2008

Keywords:
[2.2]Paracyclophane
AF4
Nucleophilic substitution
Fluorine reactivity effects

ABSTRACT

When 4-nitro-AF4 is treated with nucleophiles such as alkoxides and cyanide, a novel ring opening, cyclophane destroying reaction is observed whereby, via an S_NAr mechanism, the nucleophile attacks the bridgehead aryl carbon vicinal to the nitro group with subsequent aryl-CF_2 bond cleavage.

1. Introduction

Over the last decade, our broad studies of octafluoro[2.2]paracyclophane (AF4) and its derivatives have demonstrated that the highly electron-deficient aromatic rings of AF4 exhibit a rich diversity of chemical behavior, including clean, high yield electrophilic substitution and disubstitution [1,2] unique aryne reactivity [3] and excellent $S_{RN}1$-reactivity with soft nucleophiles such as phenyl thiolate and malonate anion (Scheme 1) [4]. In the present communication, we wish to report the unexpected discovery of an unusual ring-opening reaction of nitro-AF4 when it is treated with hard nucleophiles, such as alkoxides and cyanide ion.

2. Results and discussion

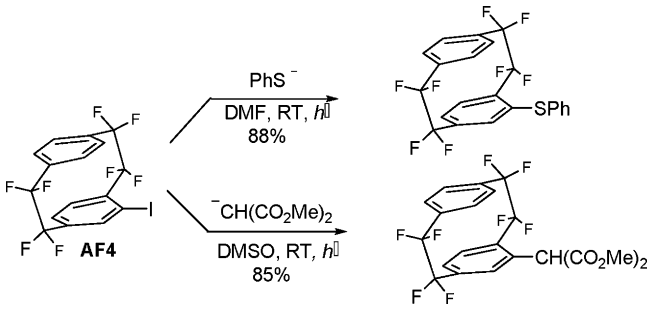
Thus, upon treatment of 4-nitro-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane with KO-*t*-Bu in *t*-BuOD, an experiment designed to induce deuterium exchange at the 5-position, it was found that instead of exchange the reaction resulted in total destruction of the [2.2]paracyclophane structure. As is the case for 4-nitro-AF4 (Fig. 1), all monosubstituted derivatives of AF4 exhibit four characteristic AB systems in their ^{19}F NMR spectra. It was apparent upon examination of the ^{19}F NMR spectrum of the product isolated from this reaction (Fig. 2) that the [2.2]paracyclophane system was no longer present.

When the reaction with *t*-BuO^- was worked up and isolated by column chromatography, phenol **1a** was isolated in 83% yield (Scheme 2). The product was characterized by ^1H, ^{13}C, and ^{19}F NMR, and by elemental analysis (Fig. 3). Examination of the crude product mixture indicated that more than one compound bearing a CF_2H group was present, but once the mixture was subjected to isolation and column chromatography, only the phenol remained. When other alkoxides, such as methoxide or trifluoroethoxide were used instead of *t*-butoxide, in each case only the phenol product could be isolated. Table 1 provides the results that were obtained from the reactions of 4-nitro-AF4 with various nucleophiles.

Reactions of [2.2]paracyclophanes that lead to ring-opening destruction of the paracyclophane system are not common. Early in their studies of the parent hydrocarbon [2.2]paracyclophane (PCP), Cram and coworkers reported that, due to the system's inherent strain of about 31–33 kcal/mol, the system undergoes reversible thermal homolytic cleavage of one of the benzylic C_1–C_2 bonds to form bis-benzylic diradical **2**, which could be intercepted in a number of ways, including by hydrogen atom transfer, as shown in Scheme 3 [5]. All other examples of ring-opening of [2.2]paracyclophanes have involved SET oxidation of PCP, processes that proceed via radical cation intermediates. Such radical cations have been generated either electrochemically [6], under Birch reduction conditions [7], or via treatment of PCP with cerium(IV) ammonium nitrate (CAN) [8] or the strong one-electron

* Corresponding author.
E-mail address: wrd@chem.ufl.edu (W.R. Dolbier Jr.).

0022-1139/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2008.08.003



Scheme 1. $S_{RN}1$ reactivity.

oxidant, nitrosonium tetrafluoroborate ($NOBF_4$) [9]. As exemplified by the reaction of PCP with CAN in Scheme 4, all of these oxidation reactions involve cleavage of the C_1–C_2 benzylic bond of radical cation **3** to form the bis-benzylic distonic radical cation **4**, which can be trapped either before of after a second oxidative step to form products such as **5**.

Until the current work, there have been no reports of reactions that led to cleavage of an aryl-bridge bond, nor have there, to our knowledge, been any examples of either nucleophile-induced or reductive ring-cleaving reactions of [2.2]paracyclophanes. Although it is possible that the process that we have observed could possibly derive from a reductive SET process, via a radical anion intermediate, we believe that the overall results, as discussed below, are more consistent with the S_NAr mechanism depicted in Scheme 5.

The high reactivity of the substrate, nitro-AF4, towards nucleophiles can be attributed to the great electron deficiency of its nitro-bearing benzene ring. This electron deficiency is reflected by its reduction potential. The respective half-wave potentials for AF4, iodo-AF4 and nitro-AF4, as indicated by cyclic voltammetry experiments, are −2.02, −1.69 and −0.86 (V *versus* saturated calomel reference electrode, SCE). The former two reductions were irreversible, whereas the relative stability of the radical anion of nitro-AF4 allows its reduction to be a reversible process. The addition of the nucleophile at the bridgehead position would be activated by the nitro group, by the two electron deficient bridge fluorinated groups, and by relief of ring strain resulting from this attack. Additional relief of ring strain would also facilitate the second step of the mechanism, the novel opening of the paracyclophane ring system, as would formation of $^{-}CF_2CF_2Ar$, which should not be a bad leaving group and which would be quickly protonated in the presence of cosolvent alcohol.

Of course, neither the expected *t*-butyl nor the methyl ether product is actually isolated from the reaction. Instead, the phenol **1a** is isolated in both cases. We rationalize this fact on the basis

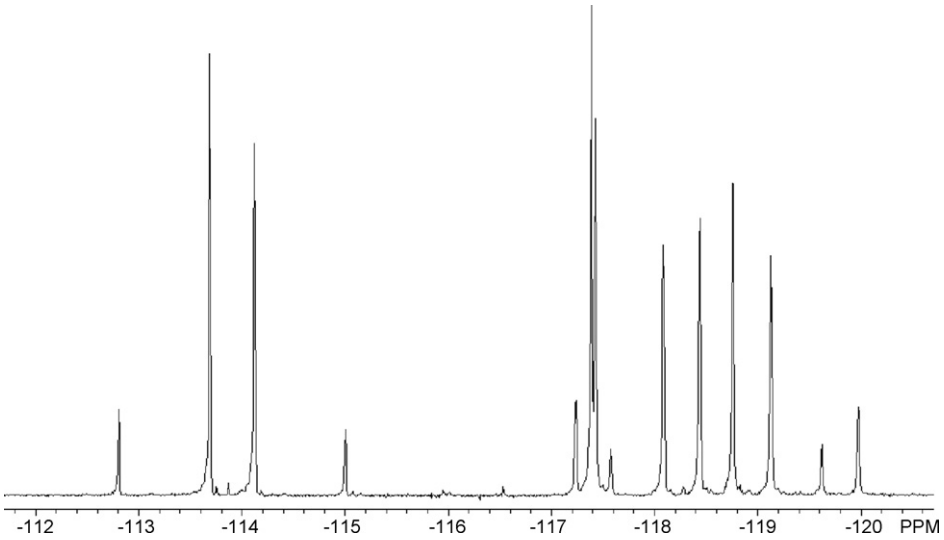


Fig. 1. ^{19}F NMR spectrum of 4-nitro-AF4.

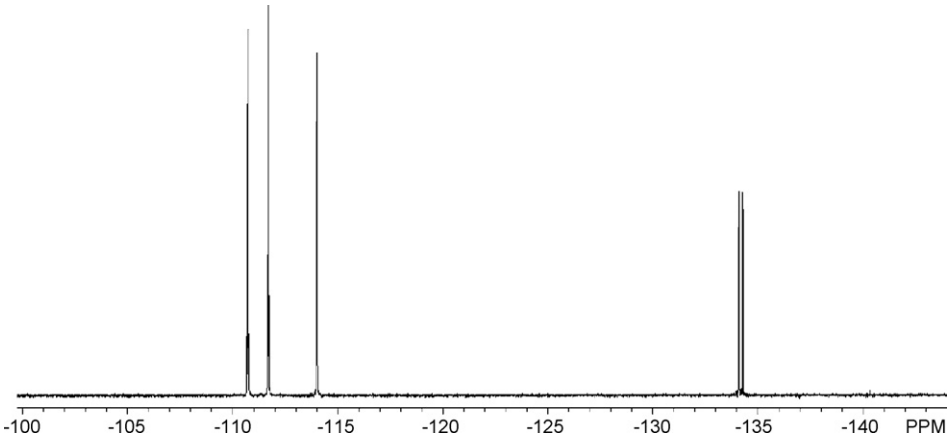
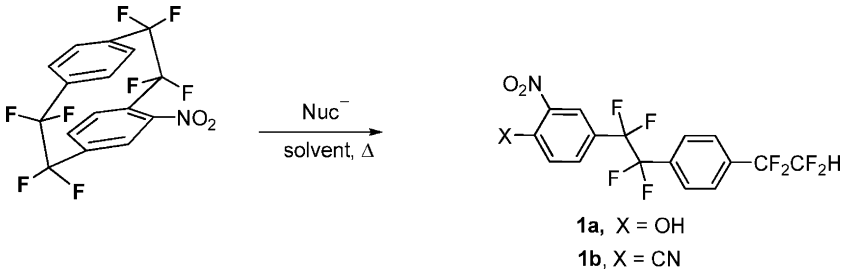


Fig. 2. ^{19}F NMR spectrum of product **1b**.



Scheme 2. Ring opening reaction of 4-nitro-AF4.

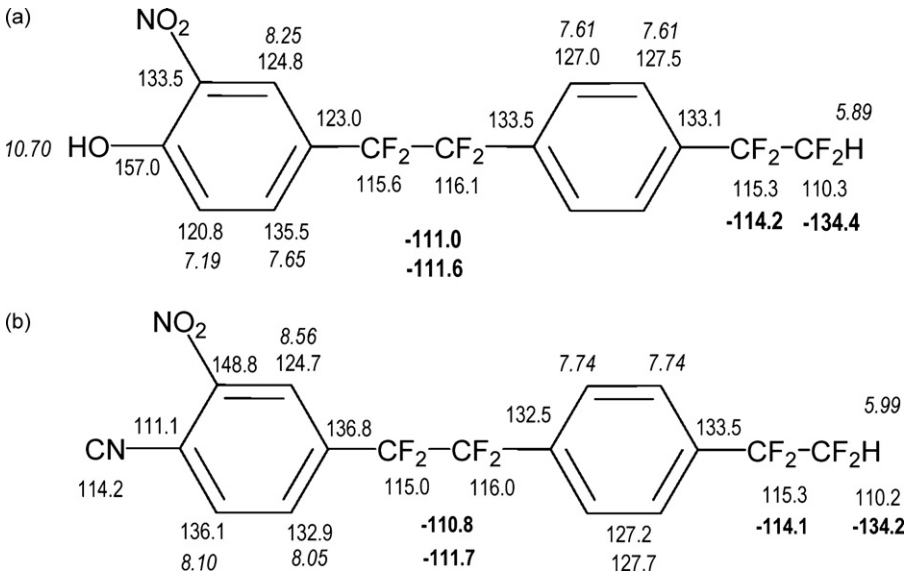
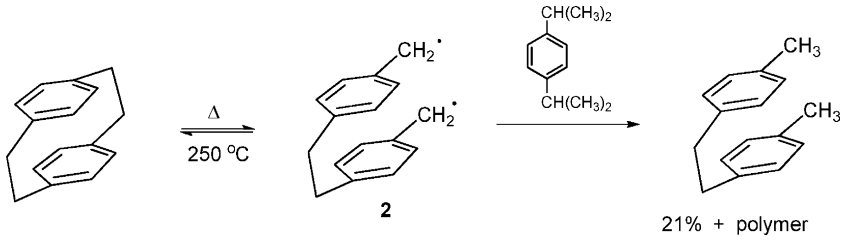


Fig. 3. Assignment of peaks in ^{1}H, ^{13}C, and ^{19}F NMR spectra.



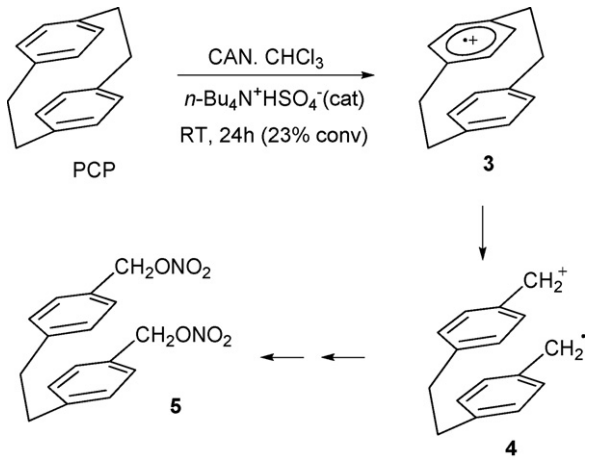
Scheme 3.

that the presence of the nitro group and two perfluoroalkyl (bridge) groups on the ether product benzene ring should make the phenolate anion produced by either an S_N2 or an E_2 reaction quite a good leaving group. Therefore, under the highly basic, highly nucleophilic conditions of the reaction, conversion of the methyl or *t*-butyl ethers to the observed phenol product should be quite facile (Scheme 6).

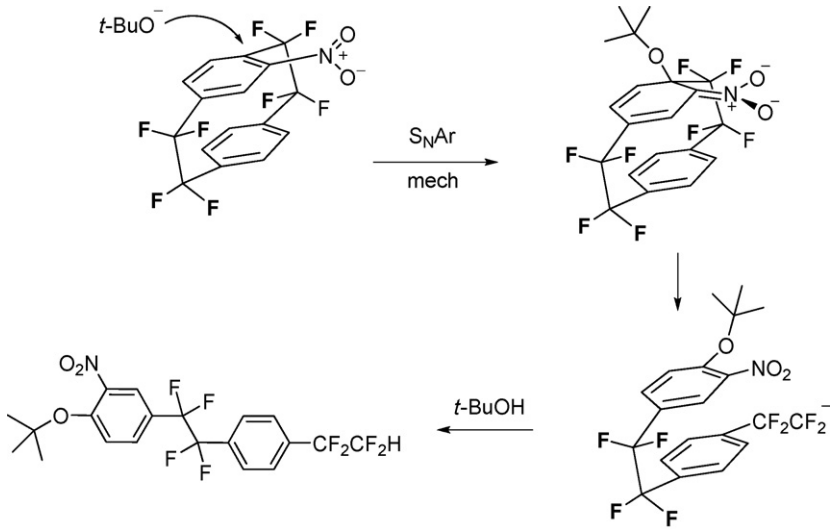
Indirect evidence for this hypothesis was derived from the results that were obtained when either cyanide or trifluoroeth-

Table 1
Results for reaction of nucleophiles with nitro-AF4

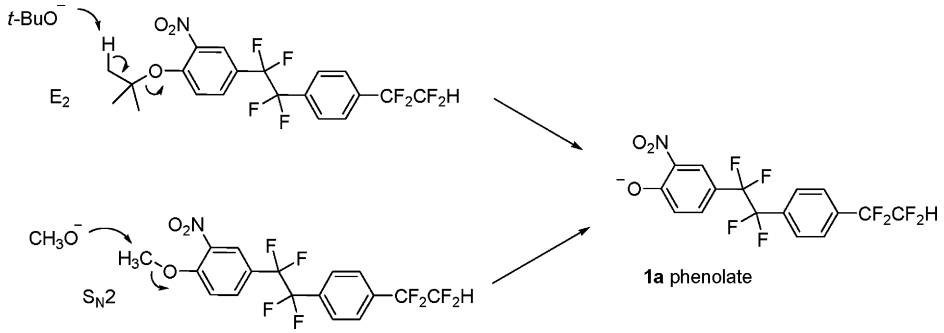
Nucleophile (equiv.)	Solvent	Temperature (°C)	Time (h)	Product (%)
t-BuO⁻ (6.0)	*t*-BuOH/*n*-Bu_2O (1:1)	110	18	**1a** (78%)
CH_3O^- (6.5)	CH_3OH/*n*-Bu_2O 1:1	110	19	**1a** (73%)
$CF_3CH_2O^-$ (18)	THF/CH_3CH_2OH 1:1	80	8	**1a** (67%)
CN^- (2.9)	CH_3CN	80	0.5	**1b** (52%)



Scheme 4.



Scheme 5. Suggested mechanism.



Scheme 6. Formation of phenol product **1a**.

oxide were used as nucleophile in the reaction. As Scheme 1 indicates, when cyanide was used as nucleophile, the product that was obtained (in 52% yield after chromatography) retained the cyano group. Cyanide is not considered to be a good SET nucleophile, which speaks in favor of the S_NAr mechanism, and the reaction is carried out in the absence of any other reactive base or nucleophile, so it remains intact.

When trifluoroethoxide was used as the nucleophile in reaction with nitro AF4, although the phenol **1a** was still the only product observed (67%) after chromatographic purification, an NMR analysis (^{19}F) of the crude reaction product indicated that the major observable product after 24 h at 80 °C was not the phenol, but what appeared to be the trifluorethyl ether, as evidenced by a significant signal for its CF_3 group at −74.8 ppm, a signal clearly distinct from the analogous signal for the remaining trifluoroethanol, which was at −79.9 ppm. A chemical shift of −75 ppm is consistent with expectations for a trifluoroethyl aryl ether [10]. It was somewhat surprising to us that the relatively non-basic nucleophile, $CF_3CH_2O^-$, would be as effective as it was in the S_NAr process. However, trifluoroethoxide has previously been shown to be an effective nucleophile in S_NAr processes [11], and it was used at a considerably larger concentration than were the other alkoxides. Also, in all likelihood the rate determining step in this S_NAr process is NOT the nucleophilic addition step, but the second, ring-cleavage step. Thus the relative nucleophilicity of the attacking nucleophile should not be very relevant with regard to the relative efficacy of the overall reaction. The trifluoroethyl ether product, in contrast to the *t*-butyl ether cannot undergo an E_2 elimination to the phenol, and it will be much less reactive than the methyl ether with respect to S_N2 chemistry.

3. Conclusions

In conclusion, nitro-AF4 has been found to be highly receptive to attack by nucleophiles, such reactions resulting in an unprecedented overall ring-cleaving process that destroys the [2.2]paracyclophane entity. These reactions appear to proceed via an addition–elimination process (S_NAr) with initial attack at the aromatic bridgehead carbon vicinal to the nitro substituent, with the intermediate delocalized carbanion undergoing rate-determining fragmentation of the aryl bridge bond with resultant extrusion of the tetrafluoroethyl anion, which is then protonated. Although results are presented for use of only a limited number of nucleophiles, it seems likely that the process will have some generality.

4. Experimental

4.1. General

H1–C13 correlation spectra were recorded on a Varian Inova spectrometer equipped with a 5 mm indirect detection probe, operating at 500 MHz for ^1H and at 125 MHz for ^{13}C. Chemical shifts are reported in ppm relative to TMS.

^{19}F and H1-F19 HOESY spectra were recorded on a Varian Mercury spectrometer operating at 300 MHz for ^{1}H and 282 MHz for ^{19}F. ^{19}F chemical shifts are reported in ppm relative to $CFCl_3$.

4.2. 4-Nitro-AF4 with t-butoxide: 2-nitro-4-(1,1,2,2-tetrafluoro-2-(4-(1,1,2,2-tetrafluoroethyl)phenyl)ethyl)phenol (**1a**)

A 50 mL three-necked round bottom flask was charged with 4-nitro-AF4 (1.20 g, 3.02 mmol), potassium *t*-butoxide (2.01 g, 17.91 mmol, 5.93 equiv.), 10 mL anhydrous *t*-butanol, and 10 mL *n*-butyl ether. The mixture was heated to 110 °C and was maintained at this temperature overnight. Upon cooling, the mixture was acidified to a pH of 5 by dropwise addition of concentrated HCl. Multiple extractions were performed using diethyl ether/water and washing with brine. The organic layers were combined, dried over anhydrous $MgSO_4$ and then filtered. The solvent was evaporated under vacuum and the residue purified by silica gel column chromatography eluting initially with neat hexanes. The product was then eluted incrementally with increasingly polar mixtures of hexanes/dichloromethane ending in a ratio of 5:1, respectively. The desired product eluted as a yellow band. Upon evaporation, the crystals appeared as bright yellow rosettes. Like fractions were combined, and the phenol product (**1a**) was obtained in a yield of 0.98 g (78%): ^{1}H NMR, δ 5.95 (tt, J = 54 and 2.1 Hz, 1H), 7.25 (d, J = 9 Hz, 1H), 7.71 (d, J = 9 Hz, 1H), 7.67 (s, 4H), 8.31 (s, 1H), 10.76 (s, OH); ^{13}C NMR, δ 110.3 (tt, J = 251 and 44 Hz), 115.3 (tt, J = 250 and 45 Hz), 115.6 (tt, J = 250 and 45 Hz), 116.1 (tt, J = 250 and 45 Hz), 120.8 (s), 123.0 (t, J = 25 Hz), 124.8 (t, J = 6.6 Hz), 127.0 (t, J = 6 Hz), 127.5 (t, J = 6 Hz), 133.1 (t, J = 26 Hz), 133.5 (s), 133.5 (t, J = 26 Hz), 135.6 (T, J = 6 Hz), 157.0 (s); ^{19}F NMR, δ −111.0 (t, J = 9 Hz), −111.6 (t, J = 9 Hz), −114.2 (s), −134.4 (d, J = 54 Hz); Anal. Calcd. for $C_{16}H_9F_8NO_3$: C, 46.3; H, 2.2; N, 3.4. Found: C, 46.5; H, 2.3; N, 3.2.

4.3. 4-Nitro-AF4 with methoxide

A 50 mL three-necked round bottom flask was charged with 4-nitro-AF4 (1.15 g, 2.90 mmol), sodium methoxide (1.02 g, 18.88 mmol, 6.51 equiv.), 10 mL anhydrous methanol, and 10 mL *n*-butyl ether. The mixture was heated to 110 °C and was maintained at this temperature overnight. Upon cooling, the mixture was acidified to a pH of 5 by dropwise addition of concentrated HCl. Multiple extractions were performed using diethyl ether/water and washing with brine. The organic layers were combined and were dried over anhydrous $MgSO_4$, then filtered. The solvent was evaporated under vacuum and the residue purified by silica gel column chromatography eluting initially with neat hexanes. The product was then eluted incrementally with increasingly polar mixtures of hexanes/dichloromethane ending in a ratio of 5:1, respectively. The product was eluted as a yellow band. Upon evaporation, the crystals appeared as bright yellow rosettes. The like fractions were combined and the phenol product was obtained with a yield of 0.85 g (71%).

4.4. 4-Nitro-AF4 with 2,2,2-trifluoroethoxide

A 50 mL three-necked round bottom flask was charged with sodium hydride (0.43 g, 17.92 mmol), 10 mL anhydrous THF, and then 2,2,2-trifluoroethanol (1.30 mL, 1.81 g, 18.09 mmol). The mixture was heated to 80 °C and was maintained at this temperature for 2 h. To this was added 4-nitro-AF4 (0.50 g, 1.26 mmol) and 10.00 mL anhydrous ethanol and the reaction run an additional 6 h at 80 °C. Upon cooling, the mixture was acidified to a pH of 5 by dropwise addition of concentrated HCl. Multiple extractions were performed using diethyl ether/water and washing with brine. The organic layers were combined and were dried over anhydrous $MgSO_4$, then filtered. The solvent was evaporated under vacuum and the residue purified by silica gel column chromatography eluting initially with neat hexanes. The product was then eluted incrementally with increasingly polar mixtures of hexanes/dichloromethane ending in a ratio of 5:1, respectively. The product was eluted as a yellow band. Upon evaporation the crystals appeared as bright yellow rosettes. The like fractions were combined and the phenol product was obtained with a yield of 0.35 g (67%).

4.5. 4-Nitro-AF4 with cyanide ion: 2-nitro-4-(1,1,2,2-tetrafluoro-2-(4-(1,1,2,2-tetrafluoroethyl)phenyl)ethyl)benzonitrile (**1b**)

In a three necked round bottom flask, bearing a condenser, sodium cyanide (0.37 g, 7.55 mmol) was stirred in acetonitrile (10 mL) for 30 min. Then 4-nitro-AF4 (1.01 g, 2.54 mmol), dissolved in acetonitrile (5 mL), was added slowly to the mixture drop wise over a period of about 10 min. The reaction medium turned instantly light yellow at addition of the first drop, later inducing a strong orange color. The mixture was then heated to reflux (~80 °C) for 30 min, checking the efficiency of the reaction by TLC samples, until the starting material had totally disappeared (Rf = 0.81 in hexane 2:1 ethyl acetate, compared to Rf = 0.89 for 4-nitro AF4). At this time, the reaction medium, which had turned to dark orange, was permitted to cool to room temperature, and it was then poured into ethyl acetate (30 mL). The solids in the flask, sodium cyanide in excess, were dissolved in water (30 mL), which had been poured into the ethyl acetate mixture. The aqueous layer, brown, was then washed with more ethyl acetate, leading to an emulsion that needed nearly ten minutes to be separated. Similar additional washings continued until no product was seen by TLC. The organic layers were combined, dried by magnesium sulfate, and filtered, with the magnesium sulfate salts being washed by ethyl acetate. After rotary evaporation, a dark brown solid was obtained, and it was chromatographed (silica gel) using hexane 2:1 ethyl acetate to give 0.56 g (52%) of light-brown product **1b**: mp 139 °C; ^{1}H NMR (499 MHz, $CDCl_3$), δ 8.56 (s, 1H), 8.10 (d, ^{3}J = 8.0 Hz, 1H), 8.05 (d, ^{3}J = 8.2 Hz, 1H); 7.74 (s, 4H), 5.99 (tt, $^{2}J_{HF}$ = 54 Hz, $^{3}J_{HF}$ = 1.8 Hz); ^{19}F NMR (470 MHz, $CDCl_3$), δ −110.75 (t, $^{3}J_{FF}$ = 9.7 Hz), −111.71 (t, $^{3}J_{FF}$ = 9.7 Hz), −114.06 (s), −134.24 (d, $^{2}J_{HF}$ = 53.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$), δ 148.8, 136.8 (t, ^{2}J = 42 Hz), 136.1, 133.5 (t, ^{2}J = 42 Hz), 132.9, 132.5 (t, ^{2}J = 45 Hz), 127.7, 127.2, 124.7, 116.0 (tt, ^{1}J = 253, ^{2}J = 51 Hz), 115.3 (tt, ^{1}J = 250, ^{2}J = 40 Hz), 115.0 (tt, ^{1}J = 255, ^{2}J = 51 Hz) 114.2, 111.1, 110.2 (tt, ^{1}J = 250, ^{2}J = 54 Hz); Anal. Calcd. for $C_{17}H_8F_8N_2O_2$: C, 48.1; H, 1.9; N, 6.6. Found: C, 48.6; H, 1.9; N, 6.2; HRMS m/z calcd. for $C_{17}H_8F_8N_2O_2Na$ (M+Na): 447.0350, found 447.0364.

4.6. Electrochemistry

The cyclic voltammetry (CV) experiments were performed on an EG&G Potentiostat/Galvanostat (Model 273A). All experiments were carried out with 5 mM solution in CH_3CN containing 0.1 M tetra-*n*-butylammonium perchlorate (TBAP) as supporting electrolyte, and were performed with a 0.02 cm^2 Pt button working electrode, a Pt wire counter electrode and a silver wire pseudo reference electrode (calibrated with ferrocene and expressed as V *versus* SCE) in an argon filled dry box. The half wave potential $E_{1/2}$ refers the saturated calomel Ag wire as reference electrode, the system was calibrated with ferrocene/ferrocenium (Fc/Fc^{+}) redox system ($E_{1/2}$(FC) = 0.3927 V *versus* SCE).

Acknowledgment

The authors are grateful to Specialty Coating Systems, Inc. for a generous donation of AF4.

References

[1] A.J. Roche, W.R. Dolbier Jr., J. Org. Chem. 64 (1999) 9137–9143.
[2] A.J. Roche, W.R. Dolbier Jr., J. Org. Chem. 65 (2000) 5282–5290.
[3] W.R. Dolbier Jr., Y.-A. Zhai, W. Wheelus, M.A. Battiste, I. Ghiviriga, M.D. Bartberger, J. Org. Chem. 72 (2007) 550–558.
[4] K. Wu, W.R. Dolbier Jr., M.A. Battiste, Y.-A. Zhai, Mendeleev Commun. (2006) 146–147.
[5] H.J. Reich, D.J. Cram, J. Am. Chem. Soc. 91 (1969) 3517–3526.
[6] T. Sato, K. Torizuka, M. Shimizu, Y. Kurihara, N. Yoda, Bull. Chem. Soc. Jpn. 52 (1979) 2420–2423.
[7] J.L. Marshall, T.K. Folson, Tetrahedron Lett. 12 (1971) 757–760.
[8] W. Adam, M.A. Miranda, F. Mojarrad, H. Sheikh, Chem. Ber. 127 (1994) 875–879.
[9] S. Sankararaman, H. Hopf, I. Dix, P.G. Jones, Eur. J. Org. Chem. (2000) 2711–2716.
[10] T.D. Quach, R.A. Batey, Org. Lett. 5 (2003) 1381–1384.
[11] X.Y. Xu, X.H. Qian, Z. Li, G.H. Song, J. Fluorine Chem. 88 (1998) 9–13.