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Selective electrolytic fluorinations in 70% HF/30% pyridine

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Abstract

The selective fluorination of compounds containing benzylic hydrogen atoms was accomplished by electrolysis in a mixture of 70% HF and 30% pyridine (Olah's reagent) using a square wave alternating current (1.76–2.75 V, 0.02–0.05 Hz) and Pt electrodes. This method can be used in the laboratory to prepare conveniently gram-size quantities of monofluorinated products. An ion radical mechanism has been proposed.

Keywords: Selective fluorination; Benzylic hydrogen

1. Introduction

The electrolytic fluorination of organic compounds in liquid hydrogen fluoride is not usually considered to be a practical method for the preparation of compounds containing only a few fluorine atoms, for it often results in the replacement of most of the hydrogen atoms and the saturation of all multiple bonds with fluorine, and the cleavage of many carbon-to-carbon bonds [1]. In addition, handling the extremely corrosive and poisonous liquid hydrogen fluoride in a laboratory setting is accompanied by many hazards and experimental difficulties. George Olah has shown that an easily handled mixture consisting of 70% hydrogen fluoride and 30% pyridine (Olah's reagent) can often be used to replace hydrogen fluoride [2].

Recently, we have shown that 4-nitrotoluene can be selectively fluorinated in an electrochemical microcell under special conditions (Pt electrodes, applied potential under 2.8 V, pulsed or alternating square wave current of 0.033 Hz) using Olah's reagent as both the solvent and supporting electrolyte [3]. The purpose of this investigation was to determine the scope, limitations and mechanism of this new electrochemical fluorination reaction and the feasibility of preparing gram quantities of fluorine-containing compounds using this method.

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2. Results and discussion

A wide variety of compounds containing benzylic hydrogen atoms have been monofluorinated at the benzylic position in an electrochemical microcell fitted with platinum electrodes using Olah's reagent (70% HF/30% pyridine) as both the solvent and the supporting electrolyte (Scheme 1). These fluorinations were accomplished with a square wave alternating current of 0.05–0.017 Hz and an applied potential of 1.76–2.55 V. Compounds successfully fluorinated include benzenes substituted with alkyl groups and also containing nitro, cyano, chloro, acyl of SO_2F groups, esters of various phenylacetic acids and phenylacetonitrile and several of its substituted derivatives (see Table 1). In many instances, current efficiencies were high, and therefore conversions were also high when the charge passed through the cell was equivalent to or slightly exceeded 2 F mol^{-1}. Difluorinated derivatives were sometimes obtained as byproducts, particularly if a charge in excess of 2 F mol^{-1} was passed through the cell, or if the applied potential was too high.

Although these fluorinations are similar to others that have been carried out in solvents such as acetonitrile using Et_3N/HF or pyridine/HF as a fluoride source [4], cleaner products, higher yields and better current efficiencies were obtained when Olah's reagent was used as the only solvent. For example, when acetonitrile was used as co-solvent, the electrolytic fluorination of 4-fluorophenylacetonitrile gave only a 17%

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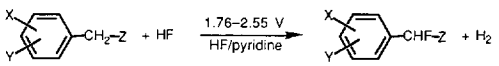
yield of α,4-difluorophenylacetonitrile together with several unidentified byproducts believed to have originated by reactions with the solvent, whereas an 87% yield of the fluorinated product was isolated when acetonitrile was omitted.

2.1. Variables

The applied potential, amount of charge and several other variables were examined which affected the selectivity, current efficiency and time required for the fluorinations.



Scheme 1.

2.1.1. Applied potential

Selective fluorinations were found to occur at applied potentials below 2.8 V, the approximate oxidation potential of fluoride ion when referenced to the standard hydrogen electrode [5]. Above this potential, non-selective polyfluorination occurred. However, regardless of the potential used no fluorination products of pyridine were observed. The

Table 1
Electrochemical fluorination of compounds containing benzylic hydrogen atoms [a]

Substrate	Potential (V)	F mol^{-1}	Time (h)	Product(s)	Conversion (%)	Current efficiency	Unreacted substrate [b]
4-Nitrotoluene	2.40	2.00	1.00	α-Fluoro-4-nitrotoluene	65	0.65	21
				2-Fluoro-5-nitrotoluene	14	0.14	
4-Nitrotoluene [c]	2.40	2.00	0.83	α-Fluoro-4-nitrotoluene	20	0.20	77
				2-Fluoro-5-nitrotoluene	3	0.03	
4-Nitrotoluene [c]	2.40	2.00	1.13	α-Fluoro-4-nitrotoluene	23	0.23	68
				2-Fluoro-5-nitrotoluene	9	0.09	
α-Fluoro-4-nitrotoluene	2.40	2.00	1.75	α,α-Difluoro-4-nitrotoluene	32	0.32	61
2-Fluoro-5-nitrotoluene	2.67	1.50	0.68	2,α-Difluoro-5-nitrotoluene	36	0.54	64
2-Nitrotoluene	2.40	2.00	0.81	α-Fluoro-2-nitrotoluene	27	0.27	58
				2-Fluoro-6-nitrotoluene	15	0.15	
3-Nitrotoluene	2.40	2.00	2.13	α-Fluoro-3-nitrotoluene	28	0.38	62
				2-Fluoro-4-nitrotoluene	Trace		
				2-Fluoro-5-nitrotoluene	Trace		
4-Nitrotoluene-d_7	2.40	2.00	1.33	α-Fluoro-4-nitrotoluene-d_7	9	0.09	59
				2-Fluoro-5-nitrotoluene-d_7	32	0.32	
1-Ethyl-4-nitrobenzene	2.25	2.00	2.96	α-Fluoroethyl-4-nitrobenzene	100	1.00	0
1-Isopropyl-4-nitrobenzene	2.20	4.00	1.78	1-(1,2-Difluoro-1-methylethyl)-4-nitrobenzene	100	1.00	0
4-Methylbenzonitrile	2.40	2.00		4-(Fluoromethyl)benzonitrile	41	0.41	33
3-Methylbenzonitrile	2.40	2.00		3-(fluoromethyl)benzonitrile	58	0.58	28
2-Methylbenzonitrile	2.40	2.00		2-(Fluoromethyl)benzonitrile	47	0.47	3
4-Methylbenzenesulfonyl fluoride	2.40	2.00		4-(Fluoroethyl)benzenesulfonyl fluoride	67	0.67	21
Phenylacetonitrile	2.35	2.00		α-Fluorophenylacetonitrile	65	0.65	35
4-Bromophenylacetonitrile	2.02	1.94	1.57	4-Bromo-α-fluorophenylacetonitrile	89	0.89	11
3-Bromophenylacetonitrile	2.04	2.06	1.87	3-Bromo-α-fluorophenylacetonitrile	36	0.35	62
4-Chlorophenylacetonitrile	2.11	2.00	2.08	4-Chloro-α-fluorophenylacetonitrile	92	0.92	3
4-Fluorophenylacetonitrile	2.23	2.25	1.97	4,α-Difluorophenylacetonitrile	94	0.84	<1
2,4-Difluorophenylacetonitrile	2.33	2.06	2.07	α,2,24-Trifluorophenylacetonitrile	Low	0.89	<1
Ethyl phenylacetate	2.00	2.00	1.30	Ethyl α-fluorophenylacetate	Low	Low	<1
Ethyl 4-chlorophenylacetate	1.76	2.25	0.62	Ethyl 4-chloro-α-fluorophenylacetate	95	0.84	<1
Ethyl 4-fluorophenylacetate	2.04	2.50	1.07	Ethyl α,4-difluorophenylacetate	70	0.56	<1
				Ethyl α,α,4-trifluorophenylacetate	27	0.43	
Ethyl 4-fluorophenylacetate	1.76	2.06	5.30	Ethyl α,4-difluorophenylacetate	87	0.85	<1
4′-Methylacetophenone	2.75	2.00	1.82	4′-(Fluoromethyl)acetophenone	51	0.51	>1
				4′-(Difluoromethyl)acetophenone	24	0.48	
4′-Methylacetophenone	2.45	1.00	0.76	4′-(Fluoromethyl)acetophenone	35	0.70	65
4′-(Methyl-d_3)acetophenone-2′,3′,5′,6′-d_4	2.45	1.00	0.52	4′-(Fluoromethyl-d_2)acetophenone-2′,3′,5′,6′-d_4	21.5	0.43	78.5
4-Methylbenzophenone	2.45	2.00	3.08	4′-(Fluoromethyl)benzophenone	32	0.32	67
3′-Methylacetophenone	1.93	1.00	4.70	3′-(Fluoromethyl)acetophenone	42	0.84	58
4,4′-Dimethylbenzophenone	2.00	1.00	4.30	4-(Fluoromethyl)-4′-methyl-benzophenone	12	0.24	85
				4,4′-Di(fluoromethyl)benzophenone	3	0.06	
4′-Ethylacetophenone	2.30	2.00	1.92	4′-(1-Fluoroethyl)acetophenone	38	0.38	62
4′-Methylpropiophenone	2.00	2.00	2.01	4′-(Fluoromethyl)propiophenone	32	0.32	68

[a] Frequency of alternating current was 0.033 Hz, and platinum electrodes were used unless otherwise noted.
[b] Conversions and amount of unreacted substrate are based on GC analysis.
[c] Palladium electrodes were used.
[d] Gold electrodes were used.

greatest selectivity for monofluorination occurred when the lowest possible voltage was used that would permit conductance of the cell. This voltage varied from compound to compound, and was highest for compounds containing the strongest electron-withdrawing groups (the compounds most difficult to oxidize). However, one disadvantage of using the lowest possible voltage was that the fluorination took a very long time, and it was usually necessary to strike a compromise between the selectivity and time of reaction, and to use a voltage of 0.1–0.2 V higher than the minimum. After monofluorination had occurred, a slightly higher potential was usually necessary to produce difluorination cleanly. In the cases examined, trifluorination was found to be non-selective. For example, attempted trifluorination of 4-nitrotoluene resulted in the production of several trifluoro products as well as tetrafluoro and pentafluoro products, all of undetermined structure (however, no α,α,α-trifluorotoluene was produced).

2.1.2. Amount of charge

In examples in which the current efficiencies were high, good conversions to monofluorinated products were obtained by passing through the cell 2 F of charge (an equivalent amount) per mole of substrate. However, current efficiencies were rarely 100%, so higher conversions could often be obtained by using a slight excess of current (e.g. 2.25–2.50 F mol^{-1}). When larger amounts of current were used, difluorinated products became evident. 4-Nitroethylbenzene was cleanly difluorinated when 4.0 F mol^{-1} was passed through the cell (see Table 1).

2.1.3. Direct vs. alternating current

Direct current produced fluorination, but the resistance of the cell rapidly increased as the electrolysis proceeded, presumably due to some change on the surface of the electrodes. After a few minutes, the current flowing through the cell dropped to such an extent that the fluorination proceeded at a fraction of its original rate. Pulsing the current (e.g. turning the current off and on at regular intervals, such as 20 s on and 10 s off) increased the rate of fluorination, but the current still decayed with time. A low frequency square wave alternating current produced better results, for it almost completely prevented the decay of current and significantly decreased the time needed for fluorination. Normally, alternating current is not used for electrochemical reactions [1], but we believe it is successful in these fluorinations because we are using an undivided cell, and it makes no difference which electrode serves as the anode and which serves as the cathode. By changing the polarities of the cell at regular intervals (e.g. converting the anode to the cathode and vice versa), the surfaces of the electrodes are restored to their original condition. One explanation could be that bubbles of hydrogen gas formed on the cathode push off an insulating film that was formed during the time the present cathode served as the anode. If the frequency of the alternating current was too high, no fluorination occurred. For example, very little fluorination was observed when an alternating current of 10 Hz (polarity switching every 0.05 s) was passed through a cell containing 4-bromophenylacetonitrile; however, maximum fluorination and current efficiency were realized when the current used was 0.033 Hz (polarity switching every 15 s).

2.1.4. Composition of electrodes

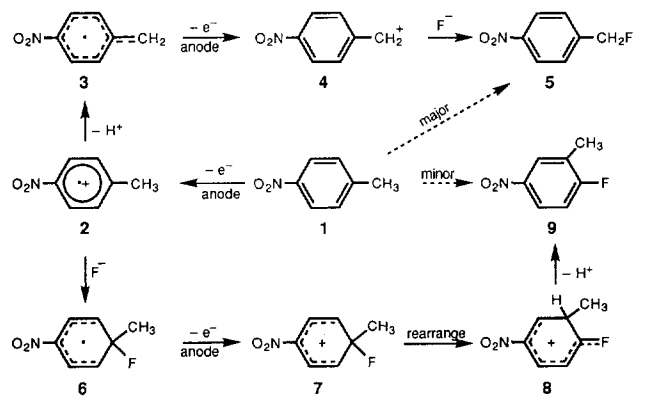
Platinum electrodes were found to be far superior to the other electrodes examined. Although both palladium and gold electrodes also gave selective fluorinations at equivalent potentials, their current efficiencies for the fluorination of 4-nitrotoluene were less than half those of platinum. Electrodes composed of nickel (the anode normally used for the polyfluorination of organic compounds in liquid HF [1]), copper or iron did not conduct current at potentials below 2.8 V, and thus were not suitable to give selective fluorinations. Other metals examined, including silver and lead, dissolved when a potential was applied across the cell, although no reaction occurred if these metals were immersed in Olah's reagent and no potential was applied.

2.1.5. Temperature

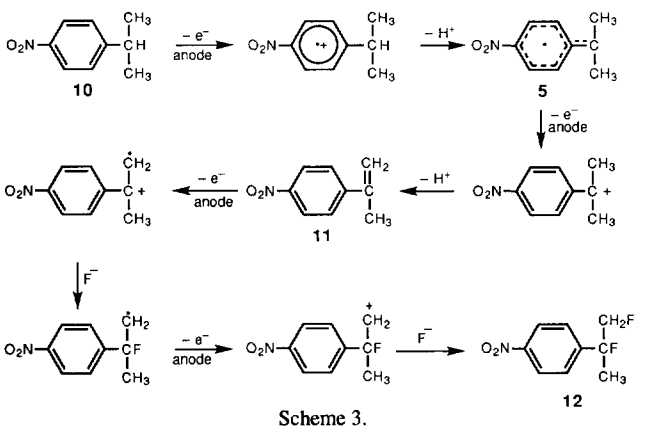
There appeared to be no appreciable difference in product composition or current efficiency when the electrolysis was carried out at different temperatures ranging from 0 to 40 °C, but no fluorination occurred at −78 °C. Temperatures higher than 40 °C were not examined because Olah's reagent starts to decompose at temperatures above 50 °C [2]. All of the electrolytic fluorinations shown in Table 1 were conducted at room temperature (approximately 25 °C), the most convenient temperature to use.

2.2. Substrates

The alkyl-substituted benzenes that were successfully fluorinated were those that contained benzylic hydrogen atoms and also an electronegative group substituted on the benzene ring, such as nitro, cyano or acyl. Compounds containing no electron-withdrawing groups and those containing electron-releasing groups did not give clean reaction products, but instead gave what appeared to be polymeric products. When the electronegative group was in the para or meta position to the alkyl group, current efficiencies were usually high, but when the electronegative group was in the ortho position, much lower current efficiencies were observed, and in one instance (*o*-methylacetophenone), no fluorinated product was obtained. No electronegative substituent on the aromatic ring was needed to obtain α-fluoro derivatives of phenylacetonitriles and esters of phenylacetic acids, but conversions were higher when such substituents were present. In addition to the expected benzylic fluorinations, toluenes substituted with NO_2, CN and SO_2F groups also gave smaller amounts of compounds that resulted from aromatic fluorinations. For example, 4-nitrotoluene gave two monofluorinated products, **5** and **9**, in the ratio 82:18 (see Scheme 2).



Scheme 2.



Scheme 3.

An unexpected result was also obtained in the fluorination of 4-isopropylnitrobenzene: a difluoro derivative, **12**, was formed to the virtual exclusion of the monofluoro derivative (see Scheme 3 for a proposed mechanism).

2.3. Preparative procedures

A larger electrochemical cell was constructed on the model of our microcells, and gram quantities of four representative substrates (4-nitroethylbenzene, 4-fluorophenylacetonitrile, ethyl 4-chlorophenyl acetate and α-fluoro-4-nitrotoluene) were fluorinated to determine if electrolysis in Olah's reagent would be a practical method for the laboratory preparation of these compounds. In all cases, good yields (70%–90%) of the isolated benzylic fluorinated product were obtained. In addition, 4-isopropylnitrobenzene (**10**) was difluorinated to give a 67% isolated yield of 1-(1,2-difluoroethyl-1-methyl)-4-nitrobenzene (**12**).

2.4. Mechanism studies

An ECEC (electrochemical, chemical, electrochemical, chemical) mechanism is widely accepted for electrochemical fluorinations in solvents other than HF when conducted with platinum electrodes at potentials below 2.8 V [1,4,6]. We recently proposed a similar mechanism for the benzylic electrolytic fluorination of 4-nitrotoluene in Olah's reagent, although this reagent is 70% HF [3] (see Scheme 2). Since all of the fluorinations observed in this study occur at a voltage too low to generate fluorine radical or elemental fluorine from fluoride ion, we believe this same general type of mechanism applies in all cases. In the proposed mechanism for the fluorination of 4-nitrotoluene, the major product (benzylic fluorination) is formed by oxidation (E) at the anode to give the ion radical **2**; the ion radical loses a benzylic proton (C) to form the radical **3**; the radical is oxidized (E) at the anode to form the benzylic carbocation **4**; finally, the carbocation combines with a fluoride ion (C) to give the product **5**. The formation of the minor product (aromatic fluorination) is slightly more involved, since it requires a rearrangement. We propose that this occurs by an ECECC mechanism, in which the first E step is identical to the benzylic fluorination, but the first C step is the combination of the ion radical **2** with a fluoride ion at the ipso position to give the radical **6**. The radical is then oxidized (E) to give the carbocation **7**, which rearranges (C) to the more stable carbocation **8** before combining with a fluoride ion (C) to give the product **9**. We now have additional evidence to support this proposed mechanism. Both the benzylic and aromatic fluorination mechanisms share a common intermediate – the ion radical **2**. If the benzylic hydrogens are replaced with deuterium atoms in this intermediate, the ratio of aromatic fluorination to benzylic fluorination should increase, because the rate of loss of a proton from the ion radical should decrease but the rate of combination with a fluoride ion should remain about the same. The fluorination of the deuterium-labeled compound 4-nitroluene-d_7 indeed resulted in a much higher ratio of aromatic to benzylic fluorination (3.56 compared with 0.22 for the unlabeled compound; approximately 16 times greater) and thus supports the proposed mechanism.

We also propose that the fluorinations in which very stable ion radical intermediates are formed result in poor current efficiencies, since if the ion radical has a sufficiently long lifetime, it could migrate to the cathode and be reduced back to the starting material, thus lowering the current efficiency. The current efficiencies in the fluorination of deuterium-labeled compounds are consistent with this supposition. Thus the fluorination of 4-nitrotoluene to monofluorinated products gave a combined current efficiency of 0.79, whereas the current efficiency of the deuterium-labeled compound was only 0.41; the fluorination of 4-methylacetophenone gave a current efficiency of 0.70, and that of its deuterium-labeled analog was only 0.43. The ion radicals containing the deuterium atoms should be more stable and have longer lifetimes because it requires more energy to break a C–D than a C–H bond. The other variable that can affect the current efficiencies is the frequency of the alternating current. If the polarity switch of the electrode is too rapid, the ion radical that was absorbed on the anode or in close proximity to it will be reduced back to the starting material when the anode becomes the cathode. This theory is also consistent with our observations (see Section 2.1.3).

The proposed mechanism for the difluorination of **10**, shown in Scheme 3, is more speculative because it requires the formation of α-methyl-4-nitrostyrene (**11**) as an intermediate, and the addition of fluorine to the newly generated double bond. An attempt to add fluorine to the double bond of 4-nitrostyrene (without the α-methyl group) under the same conditions failed and yielded only polymeric products. The addition of fluorine to the double bond of **11** may have been successful, because **11** was never at a sufficiently high concentration to polymerize, but instead was formed as an adsorbate on the electrode and was immediately oxidized to the ion radical before it could polymerize.

3. Experimental details

3.1. General

The ^{1}H NMR spectra were obtained with a Varian EM-360 NMR spectrometer; chemical shifts are reported in parts per million relative to TMS. Electron impact mass spectra were obtained with a Hewlett-Packard GC/MSD (HP 5890 Series gas chromatograph equipped with an HP 5971A mass selective detector). Except as noted, Olah's reagent (pyridinium polyhydrogen fluoride) and other chemicals were purchased from Aldrich Chemical Company. The electrolytic microcell, the power supply and the monitoring and control circuitry were similar to those described previously [3]. The larger capacity cell was fashioned from a 125 ml polyethylene bottle fitted with two concentric Pt gauss electrodes; the inner electrode had a diameter of 2 cm and a height of 5 cm; the outer electrode had a diameter of 3.5 cm and a height of 5 cm. The term "applied potential" used in this paper refers to the potential difference between the anode and the cathode. Since reference electrodes were not used, the true anodic potentials were not determined, but are thought to be close to the applied potential because hydrogen is formed at the platinum anode.

3.2. General procedure for small-scale electrolytic fluorinations (see Table 1)

The microcell was charged with a mixture of 70% HF and 30% pyridine (2.00 g) and the substrate to be fluorinated (1.00–1.25 mmol), the cell contents were stirred, and a charge of 1.00–4.00 F mol^{-1} was passed through the cell at a potential of 1.76–2.75 V with the polarities of the electrodes being reversed at 10–30 s intervals (e.g. 0.02–0.05 Hz). The liquid contents of the cell were poured into water (10 ml) and the resulting aqueous mixture was extracted with ether. The ether extract was washed with water, dried by passing through a short column of alumina and analyzed by GC/MSD/IRD. Except as noted, products were identified by comparison of their spectral properties and GC retention times with those of authentic samples purchased from Aldrich Chemical Company, prepared by literature methods [3,7,8] or prepared as indicated later.

3.3. General procedure for larger scale electrolytic fluorinations

A 125 ml cell was charged with a mixture of 70% HF and 30% pyridine (40 ml) and the substrate to be fluorinated (20 mmol), the cell contents were stirred magnetically, and a charge of 2.25 F mol^{-1} was passed through the cell at a potential of 2.10–2.50 V with the polarities of the electrodes being reversed at 15 s intervals (e.g. 0.033 Hz). The liquid contents of the cell were poured into water (200 ml) and the resulting aqueous mixture was extracted with ether. The ether extract was washed with water and then with 5% aqueous $NaHCO_3$, dried ($MgSO_4$) and distilled under reduced pressure.

3.3.1. α,4-Difluorophenylacetonitrile

This compound was prepared by the fluorination of 4-fluoroacetonitrile at a potential of 2.21 V with a charge of 2.25 F mol^{-1} being passed through the cell over a period of 3.79 h, and was obtained as a colorless liquid: 2.51 g (82% yield); b.p. 95–96 °C (3 mmHg); MS (EI, 70 eV) *m/e* 153 (M^+, 90), 152 ($M^+ - H$, 100), 134 ($M^+ - F$, 20), 127 ($M^+ - CN$, 41), 126 ($M^+ - HCN$, 76); ^{1}H NMR ($CDCl_3$) δ 6.10 (d, 1H, J_{HF} = 48 Hz, CHF), 7.10–7.70 (m, 4H, aromatic). Anal. Calc. for $C_8H_5F_2N$: C, 62.75%; H, 3.29%; N, 9.15%; Found: C, 62.60%; H, 3.41%; N, 8.97%.

3.3.2. α,α-Difluoro-4-nitrotoluene

This compound was prepared by the fluorination of α-fluoro-4-nitrotoluene at a potential of 2.30 V with a charge of 4.50 F mol^{-1} being passed through the cell over a period of 9.57 h, and was obtained as a light yellow liquid: 2.42 g (70% yield); b.p. 111–112 °C (0.5 mmHg); MS (EI, 70 eV) *m/e* 173 (M^+, 79), 127 ($M^+ - NO_2$, 100), 101 ($M^+ - NO_2$ and C_2H_2, 33); ^{1}H NMR ($CDCl_3$) δ 6.91 (t, 1H, J_{HF} = 56 Hz, CF_2H), 7.82 (d, J = 8.5 Hz, 2H). The IR spectrum was identical to that of a previously prepared authentic sample [3].

3.3.3. 1-(1-Fluoroethyl)-4-nitrobenzene

This compound was prepared by the fluorination of 1-ethyl-4-nitrobenzene at a potential of 2.25 V with a charge of 2.25 F mol$^-$ being passed through the cell over a period of 4.07 h, and was obtained as a light yellow liquid: 2.60 g (77% yield); b.p. 80–82 °C (2.5 mmHg); MS (EI, 70 eV) *m/e* 169 (M^+, 79), 154 ($M^+ - CH_3$, 48), 151 ($M^+ - F$, 26), 124 ($M^+ - NO_2$ and CH_3, 24), 123 ($M^+ - C_2H_4F$, 56), 107 ($M^+ - NO_2$ and CH_3, 33), 77 ($C_6H_5^+$, 100); ^{1}H NMR ($CDCl_3$) δ 1.80 (dd, 3H, J_{HF} = 24 Hz, J = 8 Hz, CH_3), 6.00 (dq, 1H, J_{HF} = 24 Hz, J = 8 Hz, CHF), 7.90 (m, 2H, aromatic), 8.60 (m, 2H, aromatic). Anal.: Calc. for $C_8H_8FNO_2$: C, 56.80%; H, 4.77%; N, 8.28%; Found: C, 56.60%; H, 5.01%; N, 7.98%.

3.3.4. Ethyl 4-chloro-α-fluorophenylacetate

This compound was prepared by the fluorination of ethyl 4-chlorophenylacetate at a potential of 2.25 V with a charge of 2.25 F mol^{-1} being passed through the cell over a period of 3.87 h and was obtained as a colorless liquid: 3.63 g (84% yield); b.p. 112–114 °C (2.1 mmHg); MS (EI, 70 eV) *m/e* 216 (M^+, 13), 218 ($M^+[^{37}Cl]$, 4), 143 ($M^+ - CO_2C_2H_5$, 100), 145 ($M^+[^{37}Cl] - CO_2C_2H_5$, 41); IR (l) 1275 cm^{-1} (C=O ester); ^1H NMR ($CDCl_3$) δ 1.35 (t, 3H, $J=7$ Hz, CH_3), 4.42 (q, 2H, $J=7$ Hz, CH_2), 6.00 (d, 1H, $J_{HF}=48$ Hz, CHF), 7.42–7.86 (m, 2H, aromatic). Anal.: Calc. for $C_{10}H_{10}ClFO_2$: C, 55.44%; H, 4.65%; Cl, 16.36%; Found: C, 55.60%; H, 4.85%; Cl, 16.48%.

3.3.5. 1-(1,2-Difluoro-1-methylethyl)-4-nitrobenzene

This compound was prepared by the fluorination of 1-isopropyl-4-nitrobenzene at a potential of 2.20 V with a charge of 4.50 F mol^{-1} being passed through the cell over a period of 9.17 h, and was obtained as a light yellow liquid: 2.42 g (66% yield); b.p. 106–107 °C (10 mmHg); MS (EI, 70 eV) *m/e* 201 (M^+, 13), 168 ($M^+ - CH_2F$, 100), 163 ($M^+ - NO - F$, 20); IR (neat) 1605, 1543, 1352, 1056, 852 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (dd, 3H, $J_{HF}=24$, 4 Hz, CH_3), 4.60 (dd, $J_{HF}=50$, 24 Hz, CHF), 7.80 (m, 2H, aromatic), 8.40 (m, 2H, aromatic). Anal. Calc. for $C_9H_9F_2NO_2$: C, 53.73%; H, 4.51%; N, 6.96%; Found: C, 53.53%; H, 4.61%; N, 7.18%.

3.4. 4'-(Methyl-d_3)acetophenone-2',3',5',6'-d_4 (13)

Anhydrous aluminum chloride (7.40 g, 0.0560 mol) was added to a stirred solution of toluene-d_8 (2.50 g, 0.0250 mol) in 10 ml of dry carbon disulfide and the mixture was heated gently to reflux. Acetic anhydride (1.89 ml, 0.022 mol) was added dropwise, the refluxing was continued for 1 h, and the carbon disulfide was removed by distillation. The residue was poured over crushed ice containing concentrated HCl (10 ml), and the resulting aqueous mixture was extracted with ether (2×50 ml). The ether extracts were washed with dilute NaOH and then water, dried ($MgSO_4$) and distilled to give **13** (2.60 g, 92%) as a colorless liquid: b.p. 64 °C; MS (EI, 70 eV) *m/e* 141 (M^+, 30), 126 ($M^+ - CH_3$, 100), 98 ($M^+ - COCH_3$, 62).

3.5. 4-Nitrotoluene-d_7

A 50:50 mixture of concentrated nitric and sulfuric acids (10 ml) was added dropwise to toluene-d_8 (5.0 g, 0.05 mol) which was stirred and cooled in an ice bath. Stirring was continued for 2 h and the reaction mixture was then poured over crushed ice (25 ml). The aqueous mixture was extracted with ether, the ether extracts were washed with water, dried ($MgSO_4$) and then distilled to give 5.2 g (72%) of a light yellow mixture containing approximately equal amounts of 4-nitrotoluene-d_7 and 2-nitrotoluene-d_7: b.p. 65–67 °C (10 mmHg). The 4-nitrotoluene-d_7 was separated from the mixture by cooling a hexane solution and then recrystallizing the precipitated solid from hexane, and was obtained as colorless needles: m.p. 50–53 °C; MS (EI, 70 eV) *m/e* 144 (M^+, 21), 126 ($M^+ - CD_3$, 79), 98 ($M^+ - NO_2$, 100), 70 ($C_5D_5^+$, 87).

3.6. 4-(Fluoromethyl)benzonitrile

This compound was prepared, but not isolated, by the reaction of 4-methylbenzonitrile with *N*-bromosuccinimide in CCl_4 (catalyzed with benzoyl peroxide); the precipitated succinimide was filtered off, the solvent was removed by evaporation and the resulting residue, 4-(bromomethyl)-benzonitrile, was redissolved in actonitrile and treated with tris(dimethylamino)sulfonium difluorotrimethylsilicate [6]; the precipitated sulfonium bromide was filtered off and the resulting solution of 4-(fluoromethyl)benzonitrile was used to authenticate (by GC/MS) the product obtained by the electrochemical fluorination of 4-methylbenzonitrile. 3-(Fluoromethyl)benzonitrile was prepared in a similar manner.

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