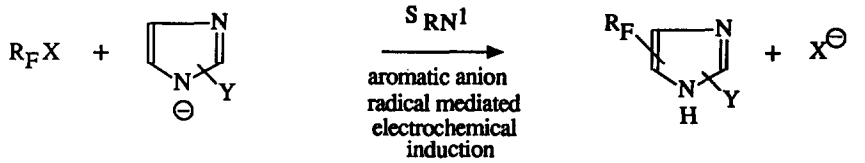
Tetrahedron Letters, Vol.31, No.9, pp 1279-1282, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

PERFLUOROALKYLATION OF IMIDAZOLES BY ELECTROCHEMICALLY INDUCED $S_{RN}1$ SUBSTITUTION.

Maurice Medebielle, Jean Pinson and Jean-Michel Savéant
Laboratoire d'Electrochimie Moléculaire de l'Université Paris 7, Associé au CNRS , 2 Place Jussieu, 75251 Paris Cedex 05, France.

Summary : Indirect electrochemical reduction, by means of aromatic anion radical mediators, of perfluoroalkyl halides in the presence of imidazolate or of substituted imidazolate anions yields the corresponding perfluoroalkylated imidazoles along an $S_{RN}1$ mechanism.



Direct and indirect (*via* electrogenerated one-electron mediators) electrochemistry has been shown to be a transparent and convenient method for triggering $S_{RN}1$ aromatic nucleophilic substitutions[1]. On the other hand, the direct and indirect electrochemical reduction of perfluoroalkyl halides in aprotic solvents leads to the formation of perfluoroalkyl radicals through a concerted one-electron transfer-bond breaking mechanism[2]:

$$R_FX + e^- \longrightarrow R_F^{\bullet} + X^- \qquad (1)$$

unlike the case of aromatic halides where the reaction proceeds through the intermediacy of the anion radical[1]. At the potential where they are thus generated, from the parent iodides or bromides, the reduction of these perfluoro radicals is however slow enough for attempting to make them react with an acceptor, provided this is sufficiently active for overcoming the competition with H-atom abstraction from the solvent[2]. They have been, for example, reacted successfully *in situ* with benzonitrile (homolytic substitution)[2] and with olefinic compounds[3]. It was thus interesting to examine if perfluoroalkyl radicals generated under the same conditions could react with nucleophiles in the context of an $S_{RN}1$ mechanism. This has indeed been deemed to be operative in the reaction of perfluoroalkyl iodides with several anionic nucleophiles: thiolates[4a-c], selenates [4d], sulfinates[4e], 2-nitropropanate[4f], malonates[4g], ethylacetoacetate[4h], imidazolate[4i], anion of 5-nitro tetrahydro-1,3-oxazine[4j] . In most cases the reaction was carried out under photochemical stimulation and shown in several cases to be slowed by radical traps, *viz*, dinitrobenzene and unsaturated compounds. Although *a priori* less reactive, perfluoroalkyl bromides have been shown to react with thiolates[4k,l] and imidazolates[4i] under similar conditions. So far, however, no attempt of direct or indirect electrochemical induction of $S_{RN}1$ reaction involving perfluoroalkyl halides, or more generally sp3 carbon centers, has been reported. We describe, in the following, as preliminary examples of electrochemically induced $S_{RN}1$ processes involving perfluoroalkyl halides, the reaction of CF_3Br

and $C_6F_{13}I$ with imidazolate ions and of $C_6F_{13}I$ with 4-nitroimidazolate and 2-methyl-5-nitroimidazolate ions. There has been an active and continuous interest for the introduction of perfluoroalkyl groups into aromatic and heteroaromatic compounds in the recent litterature[5] and the obtention of nitroimidazoles is of particular interest in view of their biomedical applications[6] and also because the photochemical perfluoroalkylation procedure, which works with imidazole itself, does not with imidazoles substituted by electron withdrawing groups[7].

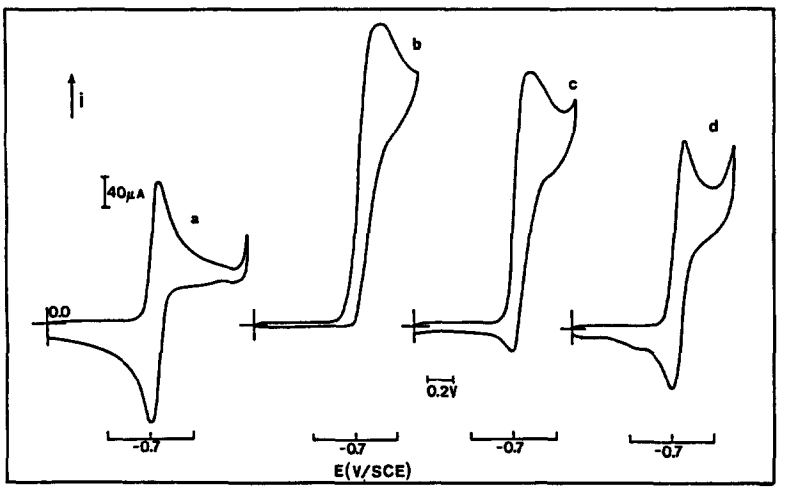
Induction by electrochemically generated aromatic anion radicals (terephthalonitrile, E^0= -1.52V vs SCE with CF_3Br, 4-nitropyridine N-oxide, E^0= -0.77V vs SCE with $C_6F_{13}I$) was employed rather than direct electrochemical induction to avoid blocking of the electrode in the case of $C_6F_{13}I$ and to proceed under less reducing conditions in that of CF_3Br. As shown in the figure below, the cyclic voltammogram of 4-nitropyridine N-oxide (P) alone is reversible and corresponds to the uptake of one electron per molecule:

$$P + 1e \rightleftharpoons P^{\bullet -} \qquad (0)$$

It loses its reversibility and increases in height upon addition of $C_6F_{13}I$ because the reduction of $C_6F_{13}I$ is redox catalyzed[8a] by the $P/P^{\bullet -}$ couple:

$$P^{\bullet -} + R_FX \longrightarrow R_F^{\bullet} + X^- + P \qquad (1')$$

If now the nucleophile, *viz*, 2-methyl-5-nitroimidazolate ion is added to the solution, the peak decreases back and reversibility is eventually restored, demonstrating the occurence of an $S_{RN}1$ process (the overall electron stoichiometry tends toward zero)[8b]:



Cyclic voltammetry of 4-nitropyridine N-oxide (3.21mM) in acetonitrile+0.1M NEt_4BF_4 at 22°C. (a): alone. (b):after addition of 6.42 mM $C_6F_{13}I$. (c), (d): after further addition of 40.8 and 220.9 mM 2-methyl-5-nitroimidazolate ion respectively. Scan rate: 0.2V/s.

$$R_F^{\bullet} + Nu^- \longrightarrow R_FNu^{\bullet -} \qquad (2)$$

$$R_FNu^{\bullet -} + P \longrightarrow R_FNu + P^{\bullet -} \qquad (3)$$

Preparative-scale electrolysis at the reduction potential of P allows one to obtain the substituted products as reported in the table below. We note that only C-perfluoroalkylated products are obtained unlike the case of p-nitrobenzyl and a-nitroalkyl radicals where N-substitution is observed[9].The only side-product which has been observed in the case of $C_6F_{13}I$ is $C_6F_{13}H$, in yields lower than 5% (by GC analysis of the raw solution) except for the reaction with 2-methyl-5-nitro imidazole anion , where the yield of the hydrogenolysis product was 25%. It furthermore appears that the perfluoroalkylated compounds are stable in our conditions and do not form diazafulvenes as observed for pentafluoroethyl imidazoles in 1N NaOH[7c]. It is also interesting to note that we never observed further reduction of the nitroperfluoroalkylated imidazoles.

Preparative-Scale Electrolyses.

Substrate	Nucleophile	Substitution product	Yield[a](%)	F/mole[b]
CF_3Br[c] 1	Imidazole Anion C=0.18M	4-Trifluoromethyl imidazole 2 [d] 2-Trifluoromethyl imidazole 3	4.35×10^{-3} [e] mole/hour	/
$C_6F_{13}I$[f] 4	4-Nitroimidazole Anion C=0.2M	4-Nitro-5-perfluoro-hexyl imidazole 5 4-Nitro-2-perfluoro-hexyl imidazole 6 [g]	94(65)	0.72
$C_6F_{13}I$[f] 4	2-methyl-5-nitro imidazole anion C=0.2M	2-methyl-5-nitro-4-perfluorohexyl imidazole 7	63(51)	0.70
$C_6F_{13}I$[f] 4	Imidazolate anion C=0.14M	4-perfluorohexyl imidazole 8 [h] 2-perfluorohexyl imidazole 9	50(50)	0.2

(a): raw yield as determined by ^{19}F NMR, isolated yield: between parentheses.(b): Faradays per mole of starting R_FX (c): CF_3Br is continuously bubbled in the solution (5.26 mM in DMF+0.1M NEt_4BF_4). Terephthalonitrile (4.33 mM) is used as mediator. (d): 2/3= 0.67/0.33 from ^{19}F and ^1H NMR. (e): the reaction being carried out under a continuous stream of CF_3Br with an excess of nucleophile, it is not possible to determine the yield in the same way as for $C_6F_{13}I$ The figure is given in mole/hour for a flow of CF_3Br= 315.6×10^{-3} mole/hour (f).c= 2.5×10^{-2}M in CH_3CN,0.1M NEt_4BF_4 ; 4-Nitropyridine N-oxide (6.2 mM) is used as mediator (g): 5/6= 0.65/0.35 from ^{19}F and ^1H NMR. (h): 8/9= 0.8/0.2 from ^{19}F and ^1H NMR.

The above-described results demonstrate the possibility of inducing electrochemically $S_{RN}1$ reactions involving perfluoroalkyl halides .The examples investigated here lead to interesting products that would be difficult to obtain from other types of reactions. Investigation of the reaction with other nucleophiles is currently under way.

Experimental.

2 , 3 , 8 and 9 were identified by comparison of their spectroscopic characteristics with those reported in the litterature[7a]. 5 and 6 were identified by comparison with authentic samples[10].

2-methyl-5-nitro-4-perfluorohexyl imidazole 7. Yellow crystals (ethyl acetate/pentane) m.p= 156°C, ^{19}F NMR.($CDCl_3$ + CD_3COCD_3, $CFCl_3$) : δ=-79.7 (CF_3) , δ=-105.7 (α-CF_2), δ=-119.6, -120.7, -121.6, -

124.9 (β to ε-CF_2); ^1H NMR.($CDCl_3$ + CD_3COCD_3, TMS) : δ=2.31 (s, CH_3) ; Mass (C.I/NH_3) : m/e=446 ($M+H^+$), 463 ($M+NH_4^+$); Analysis : Calcd. C 26.96, H 0.9, N 9.43. Found. C 27.30, H 1.12, N 9.64.

Acknowledgment. We are indebted to Dr.Hiroshi Kimoto (Government Industrial Research Institute , Nagoya) for the gift of pure samples of 5 and 6 and for helpful discussions. Dr.Y.Besace (ENSCP) is gratefully thanked for his help with ^{19}F NMR.

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(Received in France 27 December 1989)