A Convenient Synthesis of Perfluoroalkylated and Fluorinated-Aryl Nitrogen Bases by Electrochemically Induced $S_{RN}1$ Substitution

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Indirect electrochemical reduction, by means of an aromatic anion mediator, of perfluoroalkyl halides (CF_3Br, *n*-C_4F_9I, *n*-$C_6F_{13}I$, $I(CF_2)_4I$) in the presence of imidazole, 4(5)-nitroimidazole, 2-methyl-5-nitroimidazole, 2-(4′-methoxyphenyl)imidazole, imidazole-2-carboxaldehyde, 4(5)-nitroimidazole-2-carboxaldehyde, 5(6)-nitrobenzimidazole, purines (adenine, hypoxanthine, xanthine, theophylline, lumazine) and pyrimidine anions (uracil, cytosine, barbituric acid) yields the corresponding C-perfluoroalkylated nitrogen bases by an $S_{RN}1$ mechanism. Aromatic nucleophilic substitution of some fluorinated aryl halides 1-iodo-2-(trifluoromethyl)benzene and 1-(4′-iodo-tetrafluorophenyl)-imidazole was also investigated and it was found that 1-iodo-2-(trifluoromethyl)benzene could react successfully under redox-catalyzed conditions with imidazole, 2-(4′-methoxyphenyl)imidazole anion, and uracil anion to give the corresponding 5-(fluorinated-aryl) nitrogen bases. In the case of 1-(4′-iodo-tetrafluorophenyl)imidazole, direct electrochemical radical nucleophilic substitution with 2-methyl-5-nitroimidazole and uracil was possible in DMSO. In this way new, 4-[2′,3′,5′,6′-tetrafluoro-4′-(imidazol-1″-yl)phenyl] nitrogen bases were obtained in good yields.

Introduction

Introduction of fluorine and perfluoroalkyl substituents into aromatic and heteroaromatic compounds appears as an increasingly valuable goal in view of the applications of the resulting species as pharmaceutical, herbicidal, and fungicidal agents.[1] As regards more specifically the introduction of perfluoroalkyl groups, most of the reactions described so far seem to proceed via the prior formation of perfluoroalkyl radicals. These $R_F^{\bullet}$ radicals may be produced from the parent perfluoroalkyl halides by photolysis[2a−f] or thermolysis.[2f−h] They have been allowed to react with unsaturated nitrogen,[2c] aromatic,[2f] and heterocyclic[2d,e,h] (imidazoles, pyrroles, thiophenes, furans) compounds. When investigated, the radical nature of these reactions has been assessed by use of radical traps. Another way of producing the $R_F^{\bullet}$ radical involves the decomposition of peroxides of general formula $(C_nF_{2n+1}CO)_2$.[3] This novel methodology has been successfully used for the perfluoroalkylation of heteroaromatic compounds such as furans, thiophenes, or pyrroles. The substitution of the halogen (chlorine, bromine, iodine) of perfluoroalkyl halides, R_FX, by nucleophiles is not an easy reaction. Because of the strongly electron-withdrawing properties of the perfluoroalkyl group, S_N2 and S_N1 reactions are disfavored as compared with alkyl analogues. As regards nucleophilic substitution by the $S_{RN}1$ mechanism,[4] direct or indirect (by means of electrogenerated outer-sphere electron donors) electrochemistry has been shown to be an efficient means to trigger the reaction in the case of aromatic halide substrates and to allow rigorous demonstration of the nature of the mechanism and of the side reactions.[5] Nucleophilic aromatic substitutions catalyzed by electron injection (electrochemical, photochemical, solvated electrons, redox reagents), *i.e.*, have been shown to occur with a large variety of nucleophiles and leaving groups.[5a−e] For the last ten years there has been a development of the reaction from a synthetic point of view, and some elegant approaches were published for the synthesis of interesting aromatic and heterocyclic compounds,[5f] often prepared by a number of difficult chemical steps. Electrochemically induced nucleophilic substitutions have been thoroughly investigated in the case of aromatic substrates.[5a−e] Several $S_{RN}1$ substitution reactions involving perfluoroalkyl halide that are not triggered electrochemically have been previously described and recently reviewed.[6] More recently,[7] similarly to our own work on the electrochemical induction of the nucleophilic sub-

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stitution of perfluoroalkyl halides[8a−c] with nitrogen bases (imidazoles, purines and pyrimidines) as nucleophiles, the electrochemical substitution of perfluoroalkyl halides and perfluoroalkyl phenyl iodonium salts with thiolates[7a] and selenates[7b] was reported.

Imidazole and benzimidazole derivatives are important in the field of biochemistry and medicine. Many fluoroalkyl benzimidazoles derivatives have shown strong herbicidal as well as fungicidal activities.[9] Most of the benzimidazole derivatives syntheses involved classical condensation of a conveniently substituted *o*-phenylenediamine, 1,2-$(H_2N)_2C_6H_{4-n}R_n$, with an appropriate XC_mF_{2m}-CO_2H (R = halogen, X = H, F; m = 3−9; n =1−4) at elevated temperatures. Some of the compounds were active as insecticides and acaricides.[10] Imidazole and its derivatives undergo facile photochemical trifluoromethylation or perfluoroalkylation with trifluoromethyl iodide or perfluoroalkyl iodide at room temperature. Both carbon-4 (or carbon-5) and carbon-2 trifluoromethylated isomers are obtained, with carbon-4 or carbon-5 being predominant, along with trace amounts of bis-trifluoromethylated materials.[2d,e] ω-(Halogenoperfluoroalkyl)-imidazoles were also prepared by UV-induced reaction of α,ω-dihalogenoperfluoroalkanes ($X(CF_2CF_2)_nX$: X = Br, I; n = 1, 2, 3) and imidazole. The ω-halogenoperfluoroalkyl substitution occurs preferentially at the 4-position of the imidazole ring. In the case of 1, 2-diiodoperfluoroethane, reduction of iodine was accompanied with the fluoroalkylation at the 4-position. A large spectrum of imidazole derivatives has been prepared by reduction, nitration, halogenation, and alkaline solvolysis[11] of the ω-(halogenoperfluoroalkyl)imidazoles. However this elegant methodology could not be extended to biologically important chemotherapeutic 4(5)-nitroimidazoles.

Fluorine-substituted analogues of the naturally occurring nucleic acid components have become established as antiviral, antitumor, and antifungal agents. A number of drugs in which fluorine substitution is a key to biological activity are under intensive investigation. It is well known that a high percentage of fluorinated nucleoside analogues exhibits significant biological activity.[12] The fluorinated substituted pyrimidine nucleosides, 5-fluoro-2′-deoxyuridine and 5-(trifluoromethyl)-2-deoxyuridine, are well established as therapeutic agents. So far, the few reactions describing the introduction of perfluoroalkyl groups into pyrimidine bases,[13] via the formation of complexes such as perfluoroalkylcopper in HMPA,[13a,b] and bis(perfluoroalkyl)mercury,[13c] seem to proceed via prior formation of perfluoroalkyl radicals. The product yields are low to moderate. For example, uracil was allowed to react with bis(trifluoromethyl)mercury in aqueous medium in the presence of azobis (isobutyronitrile) (AIBN). The desired trifluoromethylated material was formed in 56% yield. Similar treatment of uridine with bis(trifluoromethyl)mercury was also effective for introducing the trifluoromethyl group, albeit in lower yield, 11%. However these methods are not satisfactory because of the toxicity of the reagents used in the syntheses, bis(perfluoroalkyl)mercury and HMPA. Kolbe electrolysis of trifluoroacetic acid solution of uracil with a nickel anode and iron cathode also formed 5-(trifluoromethyl)uracil.[13d] Meanwhile we have, in a preliminary form, demonstrated that the electrochemically induced nucleophilic substitution of purine and pyrimidine bases is a useful and practical methodology for the synthesis of fluorinated nitrogen heterocycles.[8c] Synthesis of perfluoroalkylated uracils and uridines at the C-5 position have been achieved recently in a different manner;[14a] perfluoroalkylation at the C-5 position of uracil was achieved in yields of 38−56% by the reaction of its bis(trimethylsilyl) derivative with bis(perfluoroalkanoyl) peroxides and the hydrolytic deprotection of the silylated products. A substituent or nitrogen replacement at C-6 does not interfere with perfluoroalkylation at C-5, but no significant reaction occurs when C-5 is blocked. With the nucleoside analogues, after both the sugar and pyrimidine moieties had been converted to their silyl derivatives, reaction did occur and the desired 5-perfluoroalkyl derivatives were obtained in yields of 26−42%. Unprotected or sugar-acetylated derivatives failed in this reaction. Probably, the success of the first route is due to the combination of increased solubility and increased electron density in the pyrimidine ring. Similarly, some silylated purines reacted with bis(perfluorobutyryl) peroxide to provide ring-C_3F_7 derivatives.[14b] The introduction of the C_3F_7 group occurs predominantly at C-8; 6-methoxypurine also gave the C-2 isomer in isolable yield. Replacement of the 6-amino group of adenine with dimethylamino or methoxy improved the yields of the C_3F_7 derivatives. Pyrimidines modified at the 5-position, by an aryl substituent, have been previously prepared by a number of routes. Most methods for the preparation of these 5-substituted pyrimidines and purines are based on palladium-catalyzed C−C bond formation at the 5-position of uracil or of pyrimidine derivatives.[15] Photochemically induced coupling of the 5-iodopyrimidines or of the nucleoside derivative has been also described.[16] However many of these routes are

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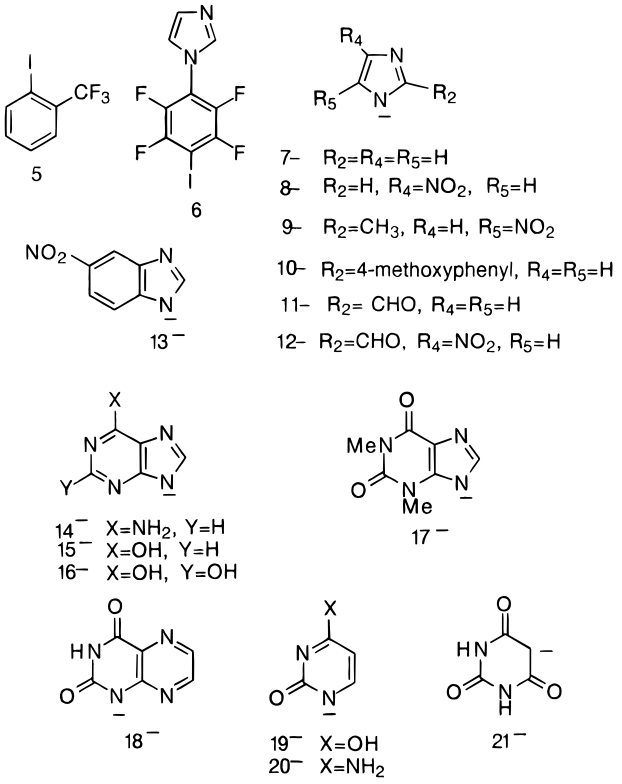
Chart 1



specific to the particular type of group which has to be transferred to the 5-position of the pyrimidine ring, and most of these procedures require the preparation of specific reagents. New and mild methods for the synthesis of substituted pyrimidines and purines, by a perfluoroalkyl, aryl, or heteroaryl substituent would therefore be worth designing.

We describe, in the following, a full characterization of some of the products we have already mentioned in preliminary reports[8] and new synthetic examples of electrochemically induced $S_{RN}1$ processes involving several perfluoroalkyl halides and fluorinated aryl halides as substrates and nucleophiles deriving from imidazoles, purines, and pyrimidines. As we have shown before, methodologies for introducing perfluoroalkyl and fluorinated aryl substituents into biologically important heterocycles are not straightforward, and most of the methods required different steps with sometimes low yields. Our major objective was to contribute to the search of a practical synthesis of fluorinated nitrogen heterocycles for potential biological applications.

Substrates **1-6**, CF_3Br (**1**), *n*-C_4F_9I (**2**), *n*-$C_6F_{13}I$ (**3**), $I(CF_2)_4I$ (**4**), 1-iodo-2-(trifluoromethyl)benzene (**5**), 1-(4′-iodo-tetrafluorophenyl)imidazole (**6**), and nucleophiles **7-21** deriving from imidazole (**7**), 4(5)-nitro imidazole (**8**), 2-methyl-5-nitroimidazole (**9**), 2-(4′-methoxyphenyl)imidazole (**10**), imidazole-2-carboxaldehyde (**11**), 4(5)-nitroimidazole-2-carboxaldehyde (**12**), 5(6)-nitro benzimidazole (**13**), adenine (**14**), hypoxanthine (**15**), xanthine (**16**), theophylline (**17**), lumazine (**18**), uracil (**19**), cytosine (**20**), and barbituric acid (**21**), were used. Compounds are shown in Charts 1 and 2. The corresponding protonated species are numbered **7H**, **8H**, etc.

Results

Perfluoroalkyl Halide as Substrates. In all cases, reduction of **1-4** in the presence of the nitrogen nucleophiles was performed under redox catalysis[17] using as mediators, terephthalonitrile for the reduction of **1**, nitrobenzene for the reduction of **2** and **4**, and 4-nitropyridine *N*-oxide for the reduction of **3**. This approach is made necessary at the preparative scale by the fact that the electrode is rapidly passivated upon direct electrolysis of *n*-$C_6F_{13}I$[8b] and also to operate under less reducing conditions. As a typical experiment the reduction of **3** in the presence of $\mathbf{12}^-$ using 4-nitropyridine *N*-oxide as the mediator is presented. As shown in Figure 1, the cyclic voltammogram of 4-nitropyridine *N*-oxide (**P**, $E° = -0.79$ V/SCE) alone is reversible and corresponds to the uptake of one electron per molecule (Figure 1a).

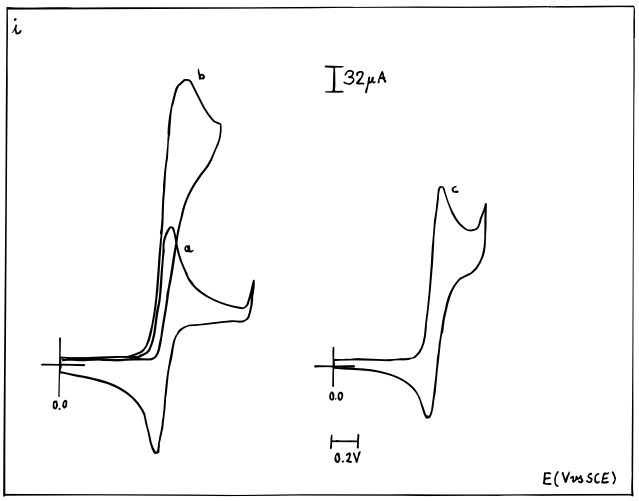


Figure 1. Redox catalysis of *n*-$C_6F_{13}I$ (**3**) by the anion radical of 4-nitropyridine *N*-oxide in CH_3CN + 0.1 M *n*-Bu_4BF_4 in the absence (a, b) and in the presence of 4(5)-nitro imidazole-2-carboxaldehyde anion ($\mathbf{12}^-$) (c). (a) catalyst alone, $c = 3.12$ mM; (b) a + *n*-$C_6F_{13}I$ (6.22 mM); (c) b + $\mathbf{12}^-$ (221 mM); scan rate 0.2 V/s.

$$\mathbf{P} + e^- \rightleftarrows \mathbf{P}^{\bullet -} \quad (1)$$

It loses its reversibility and increases in height upon addition of *n*-$C_6F_{13}I$ because the reduction of *n*-$C_6F_{13}I$ is then redox catalyzed[17] by the $\mathbf{P}/\mathbf{P}^{\bullet -}$ couple (Figure 1b). If the nucleophile $\mathbf{12}^-$ is now added to the solution, the peak decreases and reversibility is restored (Figure 1c), demonstrating the occurrence of an $S_{RN}1$ process (the overall electron stoichiometry tends toward zero):

$$\mathbf{P}^{\bullet -} + R_FX \rightarrow R_F^{\bullet} + X^- + \mathbf{P} \quad (2)$$

$$R_F^{\bullet} + Nu^- \rightarrow R_FNu^{\bullet -} \quad (3)$$

$$R_FNu^{\bullet -} + \mathbf{P} \rightleftarrows R_FNu + \mathbf{P}^{\bullet -} \quad (4)$$

In all cyclic voltammetric experiments, we have checked that the decrease of the wave was not due to a reaction between the catalyst (or its reduced form) and the nucleophile. As a typical experiment, we carried out a preparative-scale electrolysis of **3** in the presence of $\mathbf{12}^-$ at the reduction potential of the 4-nitropyridine *N*-oxide in CH_3CN. Using a two-compartment cell with a Nafion

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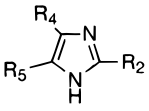
Chart 2



7aH R_2=H, R_4 = n-C_6F_{13}, R_5=H

7bH R_2= n-C_6F_{13}, R_4=R_5=H

7cH R_2=H, R_4=CF_3, R_5=H

7dH R_2=trifluoromethyl, R_4=H, R_5=H

7eH R_2=2-trifluoromethylphenyl, R_4= R_5=H

7fH R_2=H, R_4=2-trifluoromethylphenyl, R_5 = H

8aH R_2= H, R_4=NO_2, R_5= n-C_6F_{13}

8bH R_2= n-C_6F_{13}, R_4=NO_2, R_5=H

9aH R_2= CH_3, R_4= n-C_6F_{13}, R_5=NO_2

9bH R_2=CH_3, R_4=2,3,5,6-tetrafluoro-4-imidazol-1-yl-phenyl R_5=NO_2

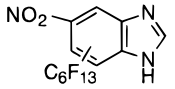
10aH R_2=4-methoxyphenyl, R_4= n-C_6F_{13}, R_5=H

10bH R_2=4-methoxyphenyl, R_4=CF_3, R_5=H

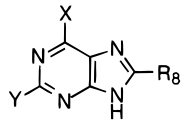
10cH R_2=4-methoxyphenyl, R_4=2-trifluoromethylphenyl R_5=H

11aH R_2=CHO, R_4=CF_3, R_5=H

12aH R_2=CHO, R_4=NO_2, R_5= n-C_6F_{13}



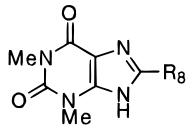
13aH + 13bH + 13cH



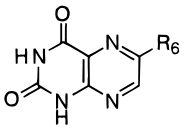
14aH X=NH_2, Y=H, R_8 = n-C_4F_9

15aH X=OH, Y=H, R_8 = n-C_4F_9

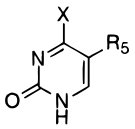
16aH X=OH, Y=OH, R_8 = n-C_4F_9



17aH R_8 = n-C_4F_9



18aH R_6 = n-C_4F_9



19aH X=OH, R_5 = n-C_4F_9

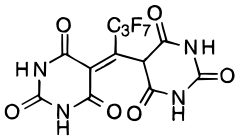
19bH X=OH, R_5 = -$(CF_2)_4$I

19cH X=OH, R_5 = 2-trifluoromethylphenyl

19dH X=OH, R_5 = 2,3,5,6-tetrafluoro-4-imidazol-1-yl-phenyl

20aH X=NH_2, R_5 = n-C_4F_9

20bH X=NH_2, R_5 = -$(CF_2)_4$I



21aH

Table 1. Preparative-Scale Electrolyses of the Perfluoroalkylated Imidazole Derivatives

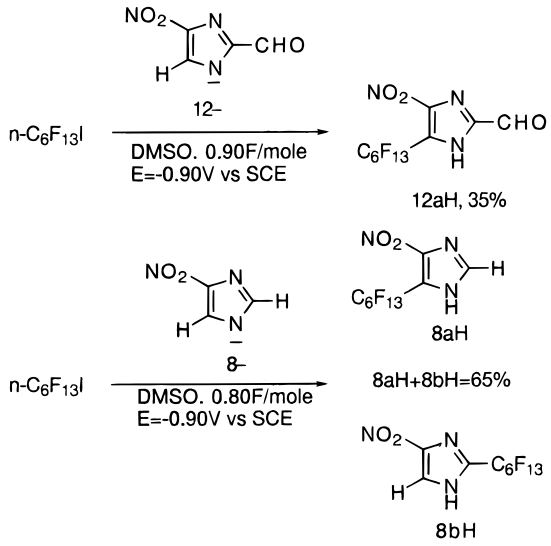
substrate	nucleophile[a]	substituted product	yield (%)	F/mol[b]
n-C_6F_{13}I[c] (**3**)	imidazole anion (**7**$^-$)	4(5)-(tridecafluorohexyl)imidazole (**7aH**) 2-(tridecafluorohexyl)imidazole (**7bH**)[d]	70[e] (55[f])	0.80
n-C_6F_{13}I[c] (**3**)	4(5)-nitroimidazole anion (**8**$^-$)	4-nitro-5-(tridecafluorohexyl)imidazole (**8aH**) 4-nitro-2-(tridecafluorohexyl)imidazole (**8bH**)[g]	94[e] (65[f])	0.80
n-C_6F_{13}I[c] (**3**)	2-methyl-5-nitroimidazole anion (**9**$^-$)	2-methyl-5-nitro-4-(tridecafluorohexyl) imidazole (**9aH**)	51[f]	0.80
n-C_6F_{13}I[c] (**3**)	5(6)-nitrobenzimidazole anion (**13**$^-$)	**13aH** + **13bH** + **13cH**[h]	54[e] (30[f])	1.20
n-C_6F_{13}I[c] (**3**)	4(5)-nitroimidazole-2-carboxaldehyde anion (**12**$^-$)	4-nitro-5-(tridecafluorohexyl)imidazole-2-carboxaldehyde (**12aH**)	35[i]	0.90
n-C_6F_{13}I[c] (**3**)	2-(4′-methoxyphenyl)imidazole anion (**10**$^-$)	2-(4′-methoxyphenyl)-4-(tridecafluorohexyl)imidazole (**10aH**)	56[i]	0.90
CF_3Br[j] (**1**)	imidazole anion (**7**$^-$)	4(5)-(trifluoromethyl)imidazole (**7cH**) 2-(trifluoromethyl)imidazole (**7dH**)	*k*	–
CF_3Br[j] (**1**)	2-(4′-methoxyphenyl)imidazole anion (**10**$^-$)	2-(4′-methoxyphenyl)-4-(trifluoromethyl) imidazole (**10bH**)	*l*	–
CF_3Br[j] (**1**)	imidazole-2-carboxaldehyde anion (**11**$^-$)	4(5)-(trifluoromethyl)imidazole-2-carboxaldehyde (**11aH**)	*m*	–

[a] Tetramethylammonium salt, C = 0.21 M. [b] Faradays per mole of starting R_FI. [c] $C = 2.5 \times 10^{-2}$ M in DMSO + 0.1 M NEt_4BF_4; 4-nitropyridine *N*-oxide (0.62×10^{-2} M) is used as mediator, electrolysis potential $E = -0.90$ V vs SCE. [d] **7aH**/**7bH** = 0.47/0.29 by ^{19}F NMR. [e] ^{19}F NMR overall yield. [f] Isolated yields of the two isomers. [g] **8aH**/**8bH** = 0.47/0.29 by ^{19}F NMR. [h] Three isomers are obtained (see Experimental Section). [i] Isolated yield. [j] CF_3Br (5.26×10^{-2}M) was continuously bubbled in the solution in DMF + 0.1 M NEt_4BF_4; terephthalonitrile (4.3×10^{-2} M) is used as mediator; electrolysis potential $E = -1.75$ V/SCE. [k] The overall production of the two isomers is 4.35×10^{-3} mol/h; **7cH**/**7dH** = 2/1. [l] The production of **10bH** is 6.22×10^{-3} mol/h. [m] The production of **11aH** is 5.34×10^{-3} mol/h.

membrane as separator (or a glass frit), the 4-nitro-5-(tridecafluorohexyl)imidazole-2-carboxaldehyde (**12aH**) was obtained in 35% isolated yield. The yield is lower compared with the reaction with 4(5)-nitroimidazole anion (**8**$^-$) because the product was found to be somewhat unstable during column chromatography. Using 4(5)-nitroimidazole anion (**8**$^-$), two isomers, the 4-nitro-5-(tridecafluorohexyl)imidazole (**8aH**) and 4-nitro-2-(tridecafluorohexyl)imidazole (**8bH**),[18] were obtained after column chromatography with a 65% overall yield (Table 1). Both isomers could be separated by preparative thin-layer chromatography.

Similar votammetric patterns were observed for the redox-catalyzed reduction of **3** with imidazole anion **7**$^-$, and preparative-scale electrolysis at the reduction potential of 4-nitropyridine *N*-oxide gave the two isomers 4(5)-(tridecafluorohexyl)imidazole (**7aH**) and 2-(tridecafluorohexyl)imidazole (**7bH**) in an overall yield of 70%. A number of 4-(trifluoromethyl)imidazoles had already been prepared from (trifluoromethyl)glyoxal by classical condensation methods.[19] All of these condensations

(18) Kimoto, H.; Fujii, S.; Muramatsu, H.; Maki, Y.; Naonori, H.; Kamoshita, K.; Hamada, T.; Yoshida, A. *Chem. Abstr.* **1987**, *106*, 156476c.



required numerous sequences so we have examined the possibility of introducing directly a perfluoroalkyl group into interesting preformed imidazoles. The methodology is the same as described for the redox-catalyzed perfluoroalkylation of **1** and **3** with, respectively, terephthalonitrile and 4-nitropyridine *N*-oxide as catalysts. 2-(4′-Methoxyphenyl)-4-(trifluoromethyl)imidazole is an important intermediate in drug synthesis;[19] 2-(4-methoxyphenyl)imidazole anion (**10**$^-$) was subjected to electrochemical perfluoroalkylation with **3** as substrate; as already observed by L. A. Cohen et al.[2e] in the photochemical trifluoromethylation of 2-(4′-methoxyphenyl)-imidazole, we found that the only product isolated in 56% yield after column chromatography was the corresponding 2-(4′-methoxyphenyl)-4-(tridecafluorohexyl)imidazole (**10aH**). Imidazole-2-carboxaldehyde anion (**11**$^-$) reacts with electrochemically generated trifluoromethyl radical to give the corresponding 4(5)-(trifluoromethyl)imidazole-2-carboxaldehyde (**11aH**), an important intermediate in the synthesis of 2,2′-bi-1*H*-imidazole-4,4′-dicarbonitrile[20] via 4(5)-(trifluoromethyl)-2,2′-bi-1*H*-imidazole. Similarly a range of substituted imidazole anions **9**−**13** were successfully perfluoroalkylated with *n*-$C_6F_{13}I$ or CF_3Br (Table 1). From the results summarized in Table 1, we can observe that the preponderance of attack at C-5 (or C-4) is consistent with the electrophilic nature of the perfluoroalkyl radicals. L. A. Cohen et al.[21] have shown by ^{1}H NMR that these positions have higher electron density than C-2, which is not surprising since C-2 is adjacent to two nitrogen atoms. Trifluoromethylation of the nitroimidazole was impossible because the reduction of the corresponding anions (**8**$^-$, **9**$^-$, **12**$^-$, and **13**$^-$) occurred at potentials very close to that of the catalyst. We note that with imidazole anions,[22a] only C-perfluoroalkylated products are obtained unlike the case of *p*-nitrobenzyl and α-nitroalkyl radicals where N-substitution is observed.[22b,c] It furthermore appears that the (perfluoroalkylated)imidazole compounds synthesized in this work are stable under our conditions and do not form diazafulvenes as observed with pentafluoroethyl imidazole in 1 N NaOH[23] or 2-(trifluoromethyl)imidazoles.[24] Next, purine anions derived from adenine **14**, hypoxanthine **15**, xanthine **16**, theophylline **17**, and lumazine **18**, and pyrimidine anions derived from uracil **19**, cytosine **20**, and barbituric acid **21**, were used as nitrogen base nucleophiles for the synthesis of potential biologically interesting compounds. As model substrates, *n*-C_4F_9I (**2**) and $I(CF_2)_4I$ (**4**) were chosen in these new examples of electrochemically induced $S_{RN}1$ processes involving perfluoroalkyl halide. Using perfluorobutyl iodide as the substrate, single electron transfer induction by electrochemically generated nitrobenzene anion radical ($E° = -1.10$ V/SCE) was employed rather than direct electrochemical induction so as to operate under less reducing conditions. As presented before with imidazole anions, the cyclic voltammetry behavior is typical of an $S_{RN}1$ process, and an example with uracil anion (**19**$^-$) is presented in Figure 2. Upon addition of a large excess of nucleophile ($C = 59.4$ mM, Figure 2c), an irreversible reduction wave could be observed at −1.45 V vs SCE which was assigned to the anion of the substituted product **19a**$^-$ on the basis of the following observations: **19aH** (an authentic sample prepared by a constant potential electrolysis) exhibits an irreversible peak located at −0.90 V vs SCE (at 0.2 V/s). This wave disappears in the presence of an excess of **19**$^-$, and a new irreversible peak appears at −1.42 V vs SCE altogether with the reduction wave of uracil (**19H**) ($E_p = -2.37$ V

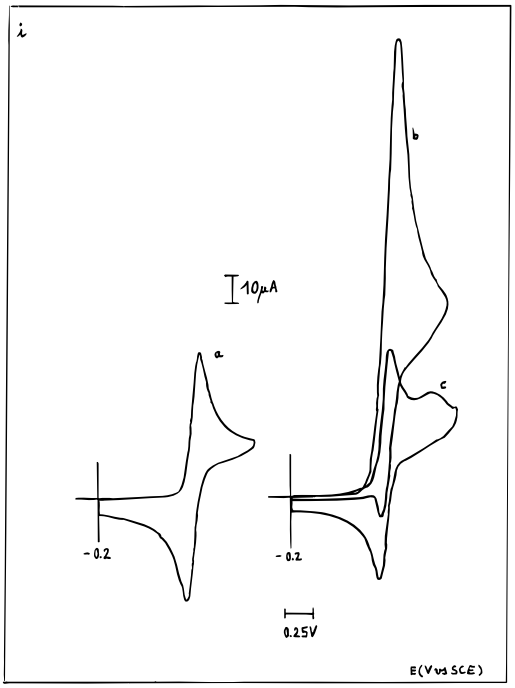
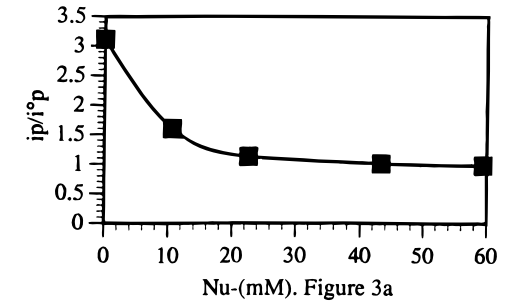
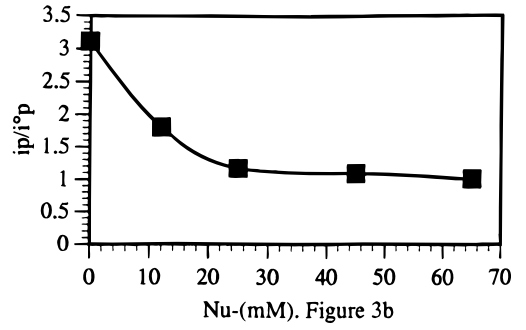


Figure 2. Cyclic voltammetry of nitrobenzene (3.0 mM) in DMSO + 0.1 M NEt_4BF_4 at 25 °C (a) alone; (b) after addition of 6.0 mM *n*-C_4F_9I; (c) after further addition of 59.4 mM uracil anion (**19**$^-$). Scan rate: 0.2V/s.

(19) Baldwin, J. J.; Kisinger, P. A.; Novello, F. C.; Sprague, J. M. *J. Med. Chem.* **1975**, *18*, 895.
(20) Matthews, D. P.; Whitten, J. P.; McCarthy, J. R. *J. Org. Chem.* **1986**, *51*, 3228.
(21) Takeuchi, Y.; Yeh, H. J. C.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1978**, *43*, 3565.
(22) (a) That imidazoles anions could act as nucleophiles in $S_{RN}1$ reactions was first shown by Bowman et al.[22b] using *p*-nitrobenzyl chloride and *gem*-nitro alcanes as substrates. Later Beugelmans et al.[22c] have also shown some interesting syntheses involving imidazoles as nucleophiles in $S_{RN}1$ reactions. (b) Adebayo, A. T. O. M.; Bowman, W. R.; Salt, W. G. *J. Chem. Soc. Perkin. Trans. 1* **1989**, 1415 and references cited therein. (c) Benhida, R.; Gharbaoui, T.; Lechevallier, A.; Beugelmans, R. *Bull. Soc. Chim. Fr.* **1994**, *131*, 200 and references cited therein.
(23) Fujii, S.; Maki, Y.; Kimoto, H.; Cohen, L. A. *J. Fluorine Chem.* **1987**, *35*, 437.
(24) Kimoto, H.; Cohen, L. A. *J. Org. Chem.* **1979**, *44*, 2902.





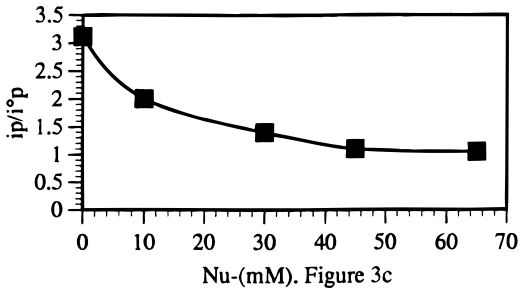


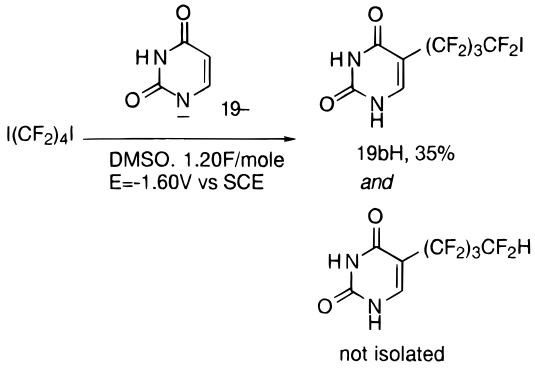
Figure 3. Analysis of the cyclic voltammetric peak current of the redox-catalyzed electrochemical induction of the substitution of *n*-C_4F_9I (6 mM) by **19**$^-$ (a), **14**$^-$ (b), and **15**$^-$ (c). Mediator: nitrobenzene (2 mM); scan rate = 0.2 V/s; DMSO + 0.1 M Et_4NBF_4 at 25 °C.

vs SCE, by comparison with an authentic sample) showing that the following reaction takes place:

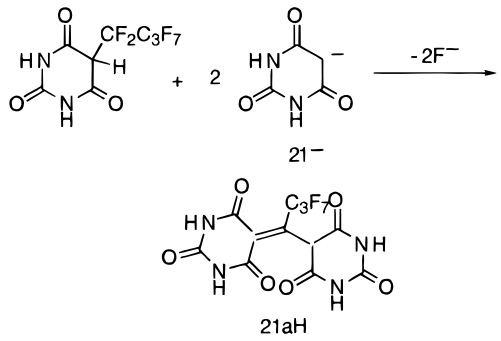
$$19aH + 19^- \rightleftarrows 19a^- + 19H$$

Uracil anion (**19**$^-$) was found to be very reactive as it can be observed by the decrease of the catalytic peak, $i_p/i°_p$ ($i°_p$ = height of the mediator cathodic peak in the absence of substrate, i_p = height of the catalytic wave) upon the addition of increasing amounts of nucleophile (Figure 3a). Similar behavior was observed with the purine anions **14**$^-$ and **15**$^-$ (Figures 3, parts b and c).

Preparative-scale electrolyses in DMSO (as reported in the Table 2) at the reduction potential of the nitrobenzene yield the substituted products. The C-perfluoroalkylated derivatives are precipitated from the reaction mixture by acid hydrolysis of the electrolysis solution followed by careful washings with water (in order to remove any trace of DMSO) and with an organic solvent (Et_2O or EtOAc) to remove the nitrobenzene. By this procedure the products are obtained in high purity form as checked by TLC and NMR. Some of the electrolyses were performed on a glassy carbon crucible electrode as cathode material, but it was found that the yields could be improved using carbon cloth as cathode and anode. We note that in the reaction of $I(CF_2)_4I$ (**4**) with uracil anion (**19**$^-$), no production of the disubstituted product was observed. However the isolated yield was low, due to difficulties to purify the product and to some reduction of the terminal $-CF_2I$ bond (observed by ^{19}F NMR analysis of the raw solution).



In the reaction of lumazine anion **18**$^-$ with *n*-C_4F_9I (**2**), the reduction of the anion is very close to the reduction potential of the catalyst and so it was impossible to overcome the simultaneous reduction of **18**$^-$; this is the reason why the yield is not so high. Because of the very poor solubility of cytosine anion **20**$^-$, yields of the 5-(perfluoroalkyl)cytosine derivatives (**20aH** and **20bH**) were not as satisfactory as expected. An unexpected dimeric product **21aH**, in which two fluorine atoms have been lost, was obtained with a reasonable yield (^{19}F NMR) upon preparative-scale electrolysis, instead of the simple substitution product. The loss of a fluoride ion from carbanions containing perfluoroalkyl groups is precedented.[25] However, despite many efforts we have not be able to isolate this perfluoralkylidene barbituric acid derivative, and its assignment was based on its ^{19}F NMR spectrum. Because of the very close potential of **21aH** ($E_p = -1.75$ V vs SCE as observed by cyclic voltammetry after an exhaustive electrolysis), simultaneous reduction of **21aH** should take place during the electrolysis and could explain the 45% yield.



Fluorinated Aryl Halide as Substrates. Two typical substrates 1-iodo-2-(trifluoromethyl)benzene (**5**) and 1-(4′-iodo-tetrafluorophenyl)imidazole (**6**) were chosen as fluorinated aryl halides to react with imidazoles **7**$^-$, **9**$^-$, and **10**$^-$ and pyrimidine anions (uracil **19**$^-$ and cytosine **20**$^-$) as nucleophiles following the $S_{RN}1$ mechanism. Synthesis of heterocycles substituted by an aryl group or a fluorinated aryl moiety is not straightforward and requires many steps, or sometimes the chemistry is particular to the type of substituent which has to be introduced. Therefore electrochemically induced aro-

(25) Bunnett, J. F.; Galli, C. *J. Chem. Soc., Perkin. Trans. 1* **1985**, 2575.

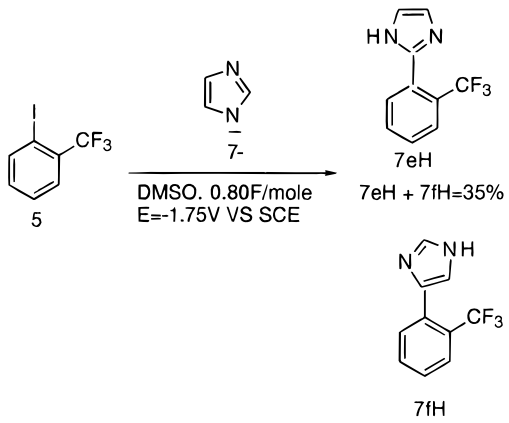
Table 2. Preparative-Scale Electrolyses of the Perfluoroalkylated Purine and Pyrimidine Derivatives

substrate	nucleophile[a]	*C*, M	substituted product	yield[b] (%)	F/mol[c]
n-C_4F_9I[d] (**2**)	uracil anion (**19**$^-$)	0.20	5-(nonafluorobutyl)uracil (**19aH**)	65	0.32
n-C_4F_9I[d] (**2**)	adenine anion (**14**$^-$)	0.21	8-(nonafluorobutyl)adenine (**14aH**)	60	0.80
n-C_4F_9I[d] (**2**)	hypoxanthine anion (**15**$^-$)	0.21	8-(nonafluorobutyl)hypoxanthine (**15aH**)	65	0.80
n-C_4F_9I[d] (**2**)	xanthine anion (**16**$^-$)	0.20	8-(nonafluorobutyl)xanthine (**16aH**)	75	0.70
$I(CF_2)_4I$[d] (**4**)	uracil anion (**19**$^-$)	0.22	5-(iodononafluorobutane)uracil (**19bH**)	35	1.20
n-C_4F_9I[d] (**2**)	theophyline anion (**17**$^-$)	0.20	8-(nonafluorobutyl)-1,3-dimethylxanthine (**17aH**)	35	1.20
n-C_4F_9I[d] (**2**)	lumazine anion (**18**$^-$)	0.20	8-(nonafluorobutyl)pteridine-2,4(1*H*,3*H*)-dione (**18aH**)	40	1.20
n-C_4F_9I[d] (**2**)	barbituric acid anion (**21**$^-$)	0.20	**21aH**	45[e]	0.80
n-C_4F_9I[d] (**2**)	cytosine anion (**20**$^-$)	0.21	5-(nonafluorobutyl)cytosine (**20aH**)	35	0.80
$I(CF_2)_4I$[d] (**4**)	cytosine anion (**20**$^-$)	0.22	5-(iodononafluorobutane)cytosine (**20bH**)	25	1.30

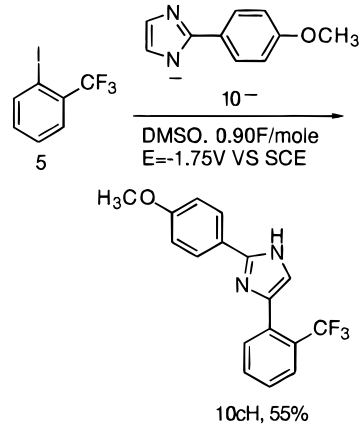
[a] Tetramethylammonium salt. [b] Isolated yield. [c] Faradays per mole of starting R_FI. [d] $C = 4.33 \times 10^{-2}$ M in DMSO + 0.1 M NEt_4BF_4; $PhNO_2$ (1.45×10^{-2} M) is used as mediator, electrolysis potential $E = -1.6$ V vs SCE. [e] ^{19}F NMR yield.

matic nucleophilic substitution is an alternative and mild methodology for the synthesis of fluorinated-aryl substituted nitrogen bases.

1-Iodo-2-(trifluoromethyl)benzene (**5**) exhibits, as do most aryl halides, two successive waves; one is irreversible ($E_p = -1.84$ V/SCE at 0.2 V s^{-1}) and corresponds to the transfer of two electrons and the second one is an irreversible four-electron wave ($E_p = -2.65$ V/SCE at 0.2 V s^{-1}), corresponding, respectively, to the ECE reduction of the aryl halide ArX into ArH ($PhCF_3$) and to the reduction of $PhCF_3$ into defluorinated products. Upon addition of imidazole anion **7**$^-$, no decrease of the two waves was observed even with a very large excess of nucleophile. This is presumably due to the fact that the rate constant of the dissociation of the radical anion $ArX^{\bullet -}$ into the corresponding (trifluoromethyl)phenyl radical is so fast that direct reduction of the aryl radical (at the electrode) is favored. Redox catalysis with phthalonitrile ($E° = -1.60$ V/SCE) was then preferred so as to operate under less reducing conditions and also in order to generate the aryl radical in solution. Upon addition of the nucleophile **7**$^-$, the catalytic wave decreases and reversibility of the catalyst is partially restored. Such phenomena are typical of a radical nucleophilic substitution of the aryl halide, as already presented in the case of the redox-catalyzed reduction of some perfluoroalkyl halides. Preparative electrolysis at a potential behind the peak potential of the catalyst ($E = -1.75$ V/SCE) in DMSO + 0.1 M NEt_4BF_4 gave, after the consumption of 0.8 F/mol of starting material, two products which were identified as the 2-[2′-(trifluoromethyl)phenyl]imidazole (**7eH**), and the 4(5)-[2′-(trifluoromethyl)phenyl]imidazole (**7fH**) on the basis of their ^1H and ^{19}F NMR spectra. At the contrary of the perfluoroalkylated imidazoles, we observed that the ratio of the two isomers, **7eH**/**7fH**, was close to 1.0.



The two isomers were isolated after column chromatography in an overall yield of 35%. The rather low yield obtained in this reaction may be related to the instability of the trifluoromethyl group in basic dimethyl sulfoxide as already observed for the reactions with enolates as nucleophiles.[25] Changing from imidazole anion **7**$^-$ to 2-(4-methoxyphenyl)imidazole (**10**$^-$) gave better results, and one single isomer, the 2-(4′-methoxyphenyl)-4(5)-[2″-(trifluoromethyl)phenyl]imidazole (**10cH**) was obtained in 55% isolated yield.



The better reactivity of this nucleophile is probably due to the increasing electron density on the imidazole ring. Reactivity of the substrate with uracil anion (**19**$^-$) was similar and the product, 5-[2′-(trifluoromethyl)-phenyl]-1*H*-pyrimidine-2,4-dione (**19cH**), was isolated in 35% yield. Attempts to react the 1-iodo-2-(trifluoromethyl)benzene (**5**) with cytosine anion (**20**$^-$) gave only very low yields of substituted product, and probably this is related to the poor solubility of the anion in the electrolytic medium.

Nucleophilic substitution of halogenated pentafluorobenzenes such as iodo and bromo pentafluorobenzene under electrochemical induction was impossible because these two substrates react spontaneously with nucleophiles such as phenolates[26] and imidazolates[27] to give the corresponding 1-(4′-halogeno-tetrafluorophenyl) substituted compounds. Recently, irradiation of pentafluoroiodobenzene[28a] as well as pentafluorophenyl alkanesulfonates[28b] has been proposed for the synthesis of pentafluorophenylated products. A photoinduced electron-transfer mechanism was suggested. The synthesis of the 1-(4′-halogeno-tetrafluorophenyl)imidazole compounds as substrates is quite easy so we have decided to use 1-(4′-

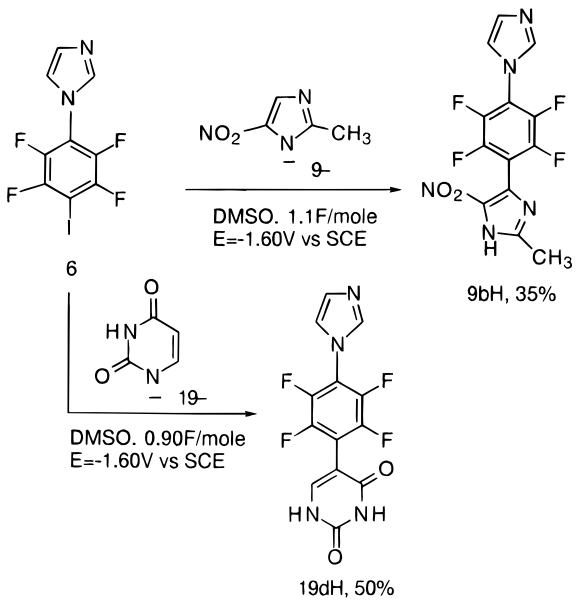
(26) (a) Médebielle, M. Unpublished results. (b) Chen, Q.-Y.; Li, Z.-T. *J. Chem. Soc. Perkin. Trans. 1* **1993**, 1705.
(27) (a) Médebielle, M. Unpublished results. (b) Fujii, S.; Maki, Y.; Kimoto, H. *J. Fluorine Chem.* **1989**, *43*, 131.
(28) (a) Chen, Q.-Y.; Li, Z.-T. *J. Chem. Soc. Perkin. Trans. 1* **1993**, 1705. (b) Chen, Q.-Y.; Li, Z.-T. *J. Org. Chem.* **1993**, *58*, 2599.

Table 3. Preparative-Scale Electrolyses of the Fluorinated Aryl Nitrogen Bases[a]

substrate	*C*, M	nucleophile[b]	substituted product	yield[c] (%)	F/mol[d]
1-iodo-2-(trifluoromethyl) benzene[e] (**5**)	3.94×10^{-2}	imidazole anion ($\mathbf{7}^-$)	2-[2′-(trifluoromethyl)phenyl] imidazole (**7eH**) 4(5)-[2′-(trifluoromethyl)phenyl] imidazole (**7fH**[f])	35	0.8
1-iodo-2-(trifluoromethyl) benzene[e] (**5**)	3.94×10^{-2}	2-(4′-methoxyphenyl) imidazole anion ($\mathbf{10}^-$)	2-(4′-methoxyphenyl)-4(5)-[2″-(trifluoromethyl)phenyl] imidazole (**10cH**)	55	0.9
1-iodo-2-(trifluoromethyl) benzene[e] (**5**)	3.94×10^{-2}	uracil anion ($\mathbf{19}^-$)	5-[2′-(trifluoromethyl)phenyl]-1*H*-pyrimidine-2,4-dione (**19cH**)	38	0.8
1-(4′-iodo-tetrafluorophenyl) imidazole[g] (*6*)	3.87×10^{-2}	2-methyl-5-nitroimidazole anion ($\mathbf{9}^-$)	4-[2′,3′,5′,6′-tetrafluoro-4′-(imidazol-1″-yl)phenyl]-1*H*-2-methyl-5-nitroimidazole (**9bH**)	35	1.1
1-(4′-iodo-tetrafluorophenyl) imidazole[g] (**6**)	3.87×10^{-2}	uracil anion ($\mathbf{19}^-$)	4-[2′,3′,5′,6′-tetrafluoro-4′-(imidazol-1″-yl)phenyl]-1*H*-pyrimidine-2,4-dione (**19dH**)	50	0.9

[a] In DMSO + 0.1 M NEt_4BF_4. [b] Tetramethylammonium salt, $C = 0.25$ M. [c] Isolated yield. [d] Faradays per mole of starting ArX. [e] Phthalonitrile (1.5×10^{-2} M) was used as mediator; electrolysis potential, $E = -1.75$ Vvs SCE. [f] **7eH**/**7fH** = 1.0. [g] Electrolysis potential, $E = -1.60$ V vs SCE.

iodo-tetrafluorophenyl)imidazole (**6**)[27b] as a model substrate in electrochemical radical nucleophilic substitution in order to obtain 1-(4′-substituted-tetrafluorophenyl)-imidazoles which may have some utility as enzymes inhibitors or as photoaffinity labeling reagents. Preparative electrolysis in DMSO + 0.1 M Et_4NBF_4 at a potential close to the peak potential of the substrate ($E_p = -1.65$ V/SCE in DMF at 0.2 V s^{-1}) in the presence of 2-methyl-5-nitroimidazole anion ($\mathbf{9}^-$) gave the corresponding 4-[2′,3′,5′,6′-tetrafluoro-4′-(imidazol-1″-yl)phenyl]-1*H*-2-methyl-5-nitroimidazole (**9bH**) in 35% isolated yield; the yield is not satisfactory because simultaneous reduction of the anion ($E_p = -1.80$ V/SCE) occurs during the electrolysis. Using uracil anion $\mathbf{19}^-$, a 50% isolated yield of the substituted product, 5-[(2′,3′,5′,6′-tetrafluoro-4′-(imidazol-1″-yl)phenyl]-1*H*-pyrimidine-2,4-dione (**19dH**) was obtained.



The preparative electrolyses for the syntheses of the fluorinated aryl nitrogen bases are summarized in Table 3. We note, that the substitution always takes place at the carbon C-5 of the uracil or at the C-2, C-4(5) of the imidazole anions leading to C-arylated products; similar behavior was observed with the substitution of aryl halide with pyrrole anions,[29a] indole anions,[29b] and phenolates.[29c]

Conclusion

These results illustrate the possibility to induce electrochemically $S_{RN}1$ reactions involving perfluoroalkyl and fluorinated aryl halides, leading to valuable heterocyclic compounds. In the case of the perfluoroalkyl halides, the reaction mechanism is a modified version of the classical $S_{RN}1$ mechanism in which the reaction is triggered by dissociative electron transfer, thus not involving the intermediacy of the anion radical of the substrate. For both perfluoroalkyl and fluorinated aryl halides, nitrogen anions react at ring carbons rather than at the negatively charged heteroatom. Despite moderate yields, this mild and quick method offers the advantage of preparing, in one step, compounds for potential biological applications. For example, they can serve as useful synthons for the synthesis of nucleosides. Indeed pyrimidine nucleosides substituted at the 5-position of the pyrimidine ring could represent an interesting class of potentially biologically active compounds, and some of the 5-aryl derivatives have been shown to possess potential antiviral activity against the human immunodefenciency virus (HIV)[12g] and again the herpex simplex virus (HSV). Some of the long chain-perfluoroalkylated purine derivatives synthesized in this work are currently under biological screening as plant growth regulators (cytokinins),[30] and the trifluoromethyl analogues are currently synthesized using our electrochemical approach . Also a more complete list of perfluoroalkylated purine analogues will be synthesized in the near future for determination of structure activity relationships. Compounds **14aH**, **15aH**, **16aH**, and **19aH** were tested against HIV-1 (LAI strain) in CEM-Cl 13 cells: none of these compounds exhibit any activity. We are now extending the reaction to other fluorinated aryl halides and to different types of purine, pyrimidine, and imidazole anions as nucleophiles. An exciting feature would be to synthesize C-8 fluorinated

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(30) Work in progress in collaboration with Drs. S. Fujii and H. Kimoto of the National Industrial Research Institute of Nagoya, Japan.

aryl purine derivatives because of their potential as adenosine receptors agonists.[31]

Experimental Section

The electrochemical equipment as well as the preparation of the tetramethylammonium salts of the nucleophiles were described in reference 8a. All the starting materials are from commercial origin. Solvents were used without purification. E. Merck silica gel (Kieselgel 60H, 15 μm) was employed for the chromatography. Analytical TLC was performed with 0.2 mm coated commercial plates (E. Merck, Kieselgel 60 F254 and aluminum oxide 150 F254 neutral). 2-(4′-methoxyphenyl)-imidazole (**10H**) was prepared as described in reference 2e, imidazole-2-carboxaldehyde (**11H**) and 4(5)-nitroimidazole-2-carboxaldehyde (**12H**) were prepared following the procedures described in references 32 and 33.

The FT ^{19}F NMR spectra were recorded on a 235-MHz Bruker spectrometer and the ^1H NMR spectra on a 200-MHz Bruker spectrometer. The chemical shifts are given in ppm by reference to CCl_3F (^{19}F NMR) and TMS (^1H NMR). Melting points are uncorrected.

A Representative Procedure for the Synthesis of the Perfluoroalkylated Imidazole is Described for the Electrolysis of *n*-$C_6F_{13}I$ in the Presence of the 4(5)-nitroimidazole-2-carboxaldehyde (12^-). Into 100 mL of CH_3CN containing 4.06 g (19 mmol) of the tetramethylammonium salt of the 4(5)-nitroimidazole-2-carboxaldehyde and 0.087 g (0.62 mmol) of 4-nitropyridine *N*-oxide were added 2.17 g (10 mmol) of NEt_4BF_4 and then 1.11 g (2.5 mmol) of *n*-$C_6F_{13}I$. The potential was set at the first reduction wave of the 4-nitropyridine *N*-oxide (−0.90 V/SCE). When 90% of the substrate had reacted (as checked by gas chromatography), the solution was cooled and neutralized with 100 mL of 2 N HCl. Upon cooling in the refrigerator 4(5)-nitroimidazole-2-carboxaldehyde precipitated. After fitration the aqueous solution was extracted three times with Et_2O, the organic solutions were combined, washed three times with water, and dried over $MgSO_4$. The solvent was evaporated to yield 782 mg of a yellow oil which was obtained as crude product and purified by silica gel chromatography ($CHCl_3$/MeOH, 90/10) to give 367.2 mg (0.8 mmol, 35%) of **4(5)-nitro-5(4)-(tridecafluorohexyl)imidazole-2-carboxaldehyde** (**12aH**): white crystals, mp = 202 °C (EtOAc); TLC ($CHCl_3$/MeOH, 90/10): $R_f = 0.55$; ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −81.0 (CF_3), −115.3 ($CF_2\alpha$), −119.5 ($CF_2\beta$), −120.3 ($CF_2\gamma$), −121.6 ($CF_2\delta$), −123.5 ($CF_2\epsilon$); ^1H NMR (DMSO-d_6): δ_H 9.68 (CHO, 1H, singlet); mass (CI/NH_3): m/e = 460 (M + H^+), 478 (M + NH_4^+). Anal. Calcd C 26.14, H 0.43, N 9.15. Found. C 26.44, H 0.62, N 9.42.

Electrolysis of *n*-$C_6F_{13}I$ in the presence of the anion of 4(5)-nitroimidazole anion (8^-) gave after evaporation of the ethereal extracts 1.54 g of an orange oil which crystallizes upon cooling. The solid was purified by silica gel chromatography (CH_2Cl_2/MeOH, 9:1 as eluent) to give 720 mg (65%) of a mixture of the two isomers which can be separated by preparative TLC (CH_2Cl_2/MeOH, 20:1). These two isomers were identified by comparison (^{19}F and ^1H NMR and TLC) with authentic samples offered by Dr. Hiroshi Kimoto.[18] **4-Nitro-5-(tridecafluorohexyl)imidazole** (**8aH**): white powder, mp = 175−177 °C. Anal. Calcd C 25.05, H 0.46, N 9.75. Found. C 25.09, H 0.56, N 9.82 and the **4(5)-nitro-2-(tridecafluorohexyl)imidazole** (**8bH**): white crystals, mp > 260 °C. Anal. Calcd C 25.05, H 0.46, N 9.75. Found. C 25.12, H 0.62, N 9.55.

2-Methyl-5-nitro-(tridecafluorohexyl)imidazole (**9aH**) has been described in reference 8a.

Electrolysis of *n*-$C_6F_{13}I$ in the presence of imidazole anion (7^-) gave after evaporation of the ethereal extracts 1.6 g of crude material (oil) which was purified by silica gel chromatography (CH_2Cl_2) to give 550 mg (50%) of a white solid which can be separated by preparative TLC (Et_2O). These two isomers were identified by comparison (^{19}F and ^1H NMR) with the spectroscopic data of L. A. Cohen et al.[2e] **4(5)-(Tridecafluorohexyl)imidazole** (**7aH**): white powder, mp = 160 °C (MeOH). Anal. Calcd C 27.97, H 0.77, N 7.25. Found. C 28.11, H 0.89, N 7.35. **2-(tridecafluorohexyl)imidazole** (**7bH**): white powder, mp = 128 °C (EtOH). Anal. Calcd C 27.97, H 0.77, N 7.25. Found. C 28.02, H 0.93, N 7.56.

Electrolysis of *n*-$C_6F_{13}I$ in the presence of the anion of 2-(4′-methoxyphenyl)imidazole (10^-) gave after evaporation of the ethereal extracts 1112 mg of a yellow oil was obtained as crude product which was purified by silica gel chromatography (EtOAc) to give 689 mg (56%) of **2-(4′-methoxyphenyl)-4(5)-(tridecafluorohexyl)imidazole** (**10aH**): white plates, mp = 208 °C (benzene); TLC (EtOAc): $R_f = 0.50$; ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −81.0 (CF_3), −110.3 ($CF_2\alpha$), −115.5 ($CF_2\beta$), −122.3 ($CF_2\gamma$), −124.6 ($CF_2\delta$), −126.6 ($CF_2\epsilon$); ^1H NMR (DMSO-d_6): δ_H 3.80 (OCH_3, 3H, singlet), 7.61 (H-5, 1H, broad singlet), 6.97 and 7.90 (AA′BB′, 4H, J = 8Hz, aryl H's); mass (CI/NH_3): m/e = 493 (M + H^+), 510 (M + NH_4^+). Anal. Calcd C 39.02, H 1.83, N 5.69. Found. C 39.38, H 1.85, N 5.99.

Electrolysis of CF_3Br with the Anion of 2-(4′-Methoxyphenyl)imidazole (10^-). In this case the electrolysis was stopped after 112C. The solution was neutralized with 150 mL of an aqueous solution of 2 N HCl. The aqueous solution was extracted three times with EtOAc, and the organic solutions were combined, washed three times with water, and dried over $MgSO_4$. The solvent was evaporated to give 825.2 mg of a yellow solid which was purified by silica gel chromatography (EtOAc) to give 515.2 mg of a white solid which was recrystallized from benzene (mp = 216 °C, lit.[2e] mp = 210−212 °C). The ^1H NMR and ^{19}F NMR are consistent with the literature data of **2-(4′-methoxyphenyl)-4-(trifluoromethyl)imidazole** (**10bH**).[2e] Anal. Calcd C 54.54, H 3.72, N 11.57. Found. C 54.79, H 4.10, N 11.79.

Electrolysis of CF_3Br with the Anion of Imidazole-2-carboxaldehyde (11^-). In this case the electrolysis was stopped after 252C. The solution was neutralized with 150 mL of an aqueous solution of 2 N HCl. The aqueous solution was extracted three times with EtOAc, and the organic solutions were combined, washed three times with water, and dried over $MgSO_4$. The solvent was evaporated to give 625.2 mg of a yellow solid which was purified by silica gel chromatography (EtOAc) to give 425.2 mg of a white solid which was recrystallized from EtOH/H_2O (mp = 172 °C, lit.[20] mp = 168−169 °C). The ^1H NMR and ^{19}F NMR are consistent with the literature data of **2-(carboxaldehyde)-4(5)-(trifluoromethyl)imidazole (11aH)**.[20] Anal. Calcd C 36.58, H 1.83, N 17.07. Found. C 36.81, H 2.15, N 17.23.

A Representative Procedure for the Synthesis of the Perfluoroalkylated Purine and Pyrimidine is Described for the Electrolysis of *n*-C_4F_9I in the Presence of the Uracil Anion (19^-). Into 100 mL of DMSO containing 4.6 g (25 mmol) of the tetramethylammonium salt of uracil were added 2.17 g (10 mmol) of NEt_4BF_4 and then 1.0 g (3.87 mmol) of *n*-C_4F_9I. The potential was set at the first reduction wave of the nitrobenzene. When 90% of the substrate had reacted (as checked by gas chromatography), the solution was cooled and neutralized with 100 mL of 2 N HCl; the resulting precipitate was filtered, carefully washed with water (4 × 50 mL), and triturated with hot Et_2O to yield 0.56 g (1.92 mmol, 55%) of the chromatographically pure compound (TLC). The ^1H NMR and ^{19}F NMR are consistent with the literature data of **5-(nonafluorobutyl)uracil** (**19aH**).[13b] Anal. Calcd C 29.09, H 0.91, N 8.48. Found. C 28.69, H 0.84, N 8.56.

8-(Nonafluorobutyl)adenine (14aH): cream powder, mp > 260 °C; TLC (EtOAc−MeOH, 75:25): $R_f = 0.60$; ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −80.0 (CF_3), −109.1 ($CF_2\alpha$), −122.0 ($CF_2\beta$), −125.0($CF_2\gamma$); ^1H NMR (DMSO-d_6): δ_H 8.34 (H-2, 1H, singlet), 14.1 (NH_2, broad singlet); mass (CI/NH_3): m/e = 354 (M + H^+), 371 (M + NH_4^+). Anal. Calcd C 30.50, H 0.85, N 15.81. Found. C 30.90, H 0.84, N 16.11.

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8-(Nonafluorobutyl)hypoxanthine (15aH), 8-(Nonafluorobutyl)xanthine (16aH), and 5-(Iodo-nonafluorobutane)uracil (19bH) were described in reference 8c.

6-(Nonafluorobutyl)pteridine-2,4(1*H*,3*H*)-dione (18aH): beige powder, mp > 260 °C; TLC (CH_2Cl_2−EtOH, 85:15): R_f = 0.50; ^{19}F NMR (acetone-d_6/$CFCl_3$): δ_F −81.1 (CF_3), −112.6 ($CF_2\alpha$), −121.3 ($CF_2\beta$), −124.7 ($CF_2\gamma$); ^1H NMR (Acetone-d_6): δ_H 9.18 (H-7, 1H, singlet), 10.92 (H-1, 1H, broad singlet), 11.37 (H-3, 1H, broad singlet); mass (CI/NH_3): m/e = 383 (M + H^+), 400 (M + NH_4^+). Anal. Calcd C 31.41, H 0.78, N 14.60. Found. C 31.65, H 0.95, N 14.85.

8-(Nonafluorobutyl)-1,3-dimethylxanthine (17aH): orange powder, mp > 260 °C; TLC (CH_2Cl_2−EtOH, 75:25): R_f = 0.50; ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −81.2 (CF_3), −110.0 ($CF_2\alpha$), −120.2 ($CF_2\beta$), −122.4 ($CF_2\gamma$); ^1H NMR (DMSO-d_6): δ_H 3.17 (CH_3, 3H, singlet), 3.45 (CH_3, 3H, singlet); mass (CI/NH_3): m/e = 399 (M + H^+), 416 (M + NH_4^+). Anal. Calcd C 21.91, H 0.68, N 16.39. Found. C 22.31, H 0.72, N 16.78.

5-(Nonafluorobutyl)cytosine (20aH): white powder, mp > 260 °C; TLC (alumina plates, $CHCl_3$−MeOH−H_2O, 60:35:0.5): R_f = 0.50; ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −81.2 (CF_3), −116.6 ($CF_2\alpha$), −124.3 ($CF_2\beta$), −128.7 ($CF_2\gamma$); ^1H NMR (DMSO-d_6): δ_H 8.45 (H-6, 1H, singlet); mass (CI/NH_3): m/e = 330 (M + H^+), 347 (M + NH_4^+). Anal. Calcd C 29.17, H 1.21, N 12.76. Found. C 29.22, H 1.45, N 12.89.

5-(Iodo-nonafluorobutane)cytosine (20bH): creme powder, mp > 260 °C; TLC (alumina plates, $CHCl_3$−MeOH−H_2O, 60:35:0.5): R_f = 0.30; ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −68.7 (CF_2I), −109.3 ($CF_2\alpha$), −116.2 ($CF_2\beta$), −120.4 ($CF_2\gamma$); ^1H NMR (DMSO-d_6): δ_H 8.65 (H-6, 1H, singlet); mass (CI/NH_3): m/e = 328 (M − I + H^+ + NH_4^+), 455 (M + NH_4^+). Anal. Calcd C 21.97, H 0.91, N 9.61. Found. C 22.02, H 1.06, N 9.85.

Compound **21aH**: After 0.80 F/mol of starting material, the electrolysis solution was directly analyzed by ^{19}F NMR: ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −79.2 (CF_3), −98.2 ($CF_2\alpha$), −117.5 ($CF_2\beta$) which was assigned to the structure described in the text.

A Typical Procedure for the Electrolysis of 1-Iodo-2-(trifluoromethyl)benzene in the Presence of the Uracil Anion. Into 100 mL of DMSO containing 4.6 g (25 mmol) of the tetramethylammonium salt of uracil and 1.20 mmol of phthalonitrile were added 2.17 g (10 mmol) of NEt_4BF_4 and then 1.0 g (3.94 mmol) of 1-iodo-2-(trifluoromethyl)benzene. The potential was set at the first reduction wave of the catalyst. When 90% of the substrate had reacted (as checked by cyclic voltammetry), the solution was cooled and neutralized with 100 mL of 2 N HCl; the resulting precipitate was filtered, carefully washed with water (4 × 50 mL), and triturated with hot Et_2O to yield 0.35 g (1.37mmol, 38%) of the chromatographically pure compound (TLC) of **5-[2′-(trifluoromethyl)-phenyl]-1*H*-pyrimidine-2,4-dione (19cH):** yellowish powder, mp > 260 °C; TLC ($CHCl_3$-MeOH, 75−25): R_f = 0.50; ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −62.2 (CF_3); ^1H NMR (DMSO-d_6): δ_H 7.4−7.8 (H-aromatic, 4H, multiplet), 8.02 (H-6, 1H, singlet), 11.4 (NH-1, 1H, singlet); mass (CI/NH_3): m/e = 257 (M + H^+), 274 (M + NH_4^+). Anal. Calcd C 51.56, H 2.73, N 10.93. Found. C 51.62, H 2.86, N 11.06.

Electrolysis of 1-Iodo-2-(trifluoromethyl)benzene in the Presence of the Imidazole Anion (7^-). The potential was set at the first reduction wave of the catalyst. When 90% of the substrate had reacted (as checked by cyclic voltammetry), the solution was cooled and neutralized with 100 mL of 2 N HCl. The aqueous solution was extracted three times with Et_2O, and the organic solutions were combined, washed three times with water, and dried over $MgSO_4$. The solvent was evaporated to yield 2.1 g of an orange oil which was purified by silica gel chromatography (CH_2Cl_2/MeOH, 9:1 as eluent) to give 290 mg (35%) of a mixture of the two isomers, **2-[2′-(trifluoromethyl)phenyl]imidazole (7eH)** and the **4(5)-[2′-(trifluoromethyl)phenyl]imidazole (7fH)**. These two isomers could be separated by preparative TLC (EtOAc as eluent) to give as the more polar isomer the **4(5)-[2′-(trifluoromethyl)phenyl]imidazole (7fH)**: white plates, mp = 128 °C (EtOH); TLC (EtOAc): R_f = 0.45; ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −61.5 (CF_3); ^1H NMR (DMSO-d_6): δ_H 7.35 (H-4 or H-5, 1H, singlet), 7.7−8.02 (H-aromatic, 4H, multiplet); mass (CI/NH_3): m/e = 213 (M + H^+), 230 (M + NH_4^+). Anal. Calcd C 56.60, H 3.30, N 13.20. Found. C 57.01, H 3.45, N 13.58. **2-[2′-(trifluoromethyl)phenyl]imidazole (7eH)**: white columns, mp = 160 °C (MeOH); TLC (EtOAc): R_f = 0.60; ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −62.5 (CF_3); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ_H 7.72 (H-4 or H-5, 1H, singulet), 7.86 (H-2, 1H, singlet), 8.1−8.42 (H-aromatic, 4H, multiplet); mass (CI/NH_3): m/e = 213 (M + H^+), 230 (M + NH_4^+). Anal. Calcd C 56.60, H 3.30, N 13.20. Found. C 56.95, H 3.65, N 13.48.

Electrolysis of 1-Iodo-2-(trifluoromethyl)benzene in the Presence of the 2-(4′-methoxyphenyl)imidazole Anion (10^-). After evaporation of the EtOAc extracts, 1.7 g of an orange oil was obtained as crude material which was purified by silica gel chromatography (EtOAc) to give 687 mg (2.16 mmol, 55%) of **2-(4′-methoxyphenyl)-4(5)-[2-(trifluoromethyl)phenyl]imidazole (10cH)**: white plates, mp = 248 °C (benzene); TLC (EtOAc): R_f = 0.50; ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −62.8 (CF_3); ^1H NMR (DMSO-d_6): δ_H 3.80 (OCH_3, 3H, singlet), 7.61 (H-5, 1H, broad singlet), 6.97 and 7.90 (AA′BB′, 4H, J = 8Hz, aryl H's of the methoxyphenyl ring), 7.82−8.1 (H-aromatic, 4H, multiplet); mass (CI/NH_3): m/e = 319 (M + H^+), 336 (M + NH_4^+). Anal. Calcd C 64.15, H 4.08, N 8.80. Found. C 64.25, H 4.58, N 8.93.

Electrolysis of 1-(4′-Iodo-tetrafluorophenyl)imidazole in the Presence of the 2-Methyl-5-nitroimidazole Anion (9^-). When 90% of the substrate had reacted (as checked by cyclic voltammetry), the solution was cooled and neutralized with 100 mL of 2 N HCl; the resulting precipitate was filtered, carefully washed with water (4 × 50 mL), and triturated with hot Et_2O to yield 0.46 g (1.35mmol, 35%) of the chromatographically pure compound (TLC): **4-[2′,3′,5′,6′-tetrafluoro-4′-(imidazol-1″-yl)phenyl]-1*H*-2-methyl-5-nitroimidazole (9bH)**: white plates, mp = 185 °C (benzene); TLC (EtOAc): R_f = 0.50; ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F - 120.2 (2F, AA′XX′d-d, J = 23, 12, 3, 3, and 1 Hz, F-2′ and F-6′), −160.4 (2F, AA′XX′, J = 21, 10, 3, and 3 Hz, F-3′ and F-5′); ^1H NMR (DMSO-d_6): δ_H 2.55 (CH_3, 3H, singlet), 7.22 (H-4, 1H, singlet), 7.45 (H-5, 1H, singlet), 7.96 (H-2, 1H, singlet); mass (CI/NH_3): m/e = 342 (M + H^+), 359 (M + NH_4^+). Anal. Calcd C 45.75, H 2.05, N 20.52. Found. C 45.86, H 2.35, N 20.82.

Electrolysis of 1-(4′-Iodo-tetrafluorophenyl)imidazole in the Presence of the Uracil Anion (19^-). As described before, the resulting precipitate was filtered, carefully washed with water (4 × 50 mL), and triturated with hot Et_2O to yield 0.63 g (1.93 mmol, 50%) of the chromatographically pure compound (TLC): **5-[2′,3′,5′,6′-tetrafluoro-4′-(imidazol-1″-yl)-phenyl]-1*H*-2,4-pyrimidine-2,4-dione (19dH)**: white powder, mp > 260 °C; TLC (EtOAc−MeOH, 75:25): R_f = 0.50; ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −121.4 (2F, AA′XX′-d-d, J = 26, 10, 3, 3, 1, and 1 Hz, F-2′ and F-6′), −161.7 (2F, AA′XX′, J = 25, 10, 3, and 3 Hz, F-3′ and F-5′); ^1H NMR (DMSO-d_6): δ_H 7.26 (H-4, 1H, singlet), 7.65 (H-5, 1H, singlet), 7.96 (H-6 of the uracil, 1H, singlet), 8.01 (H-2, 1H, singlet); mass (CI/NH_3): m/e = 327 (M + H^+), 344 (M + NH_4^+). Anal. Calcd C 47.85, H 1.84, N 17.18. Found. C 48.03, H 2.05, N 17.52.

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