Journal of Fluorine Chemistry, *43* (1989) 131–144

Received: August 19, 1988; accepted: November 7, 1988

NUCLEOPHILIC SUBSTITUTION OF PENTAFLUOROBENZENES WITH IMIDAZOLE

SHOZO FUJII, YASUO MAKI and HIROSHI KIMOTO

Government Industrial Research Institute, Nagoya;
Hirate-cho, Kita-ku, Nagoya 462 (Japan)

SUMMARY

The imidazole substitution of pentafluorobenzenes (C_6F_5R : R = CN, NO_2, $CO_2C_2H_5$, CHO, I, Br, Cl, H) occurred mainly at the para-position to R and corresponding 1-(4'-R-tetrafluorophenyl)imidazoles were obtained in good yields. The reactivity varied markedly with the substituents: nitro- or cyanopentafluorobenzene easily reacted at ambient temperature without any bases; however, methyl- or methoxypentafluorobenzene failed to react even at 100°C in the presence of a strong base.

INTRODUCTION

We have previously reported some convenient preparative methods for the direct introduction of fluorine-containing groups into the imidazole ring, such as photochemical perfluoroalkylation[1] and the thermal condensation with trifluoroacetaldehyde[2]. As an extension of the synthetic aspects of the study, we now describe the nucleophilic substitution of pentafluorobenzenes with imidazole. The desired products, 1-(polyfluorophenyl)imidazoles, may be useful compounds as enzyme inhibitors[3] or as electron-affinity radiation sensitizers[4].

Imidazole is a weak base and is less reactive with alkyl halides than other amines[5]. Therefore, 1-alkylimidazoles are usually prepared from its silver or alkali metal salts. There are only a few reports of the preparation of 1-arylimidazoles by the nucleophilic displacement of a labile aromatic halogen

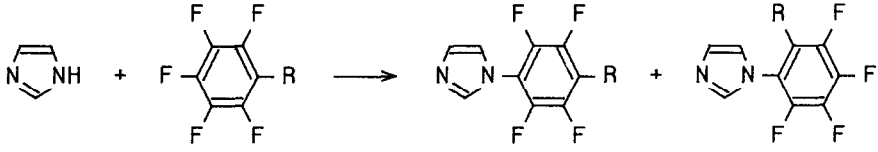
0022-1139/89/$3.50

[6]. This convenient one-step procedure is offset by low yields when the aromatic ring has no electron-withdrawing substituents. Most 1-arylimidazoles have been prepared by a classical four-step Marckwald synthesis[6,7].

Electron poor polyfluorobenzenes have been known to be reactive with nucleophiles, e.g., amines, alcoholates, and thiolates[8]. The property suggested us the possibility of the one-step synthesis of 1-(polyfluorophenyl)imidazoles by the nucleophilic substitution of polyfluorobenzenes with imidazole.

RESULTS AND DISCUSSION

The imidazole substitution of pentafluorobenzenes (I, C_6F_5R) provided mainly 1-(4'-R-tetrafluorophenyl)imidazoles (II), and in some cases, small amounts of 1-(2'-R-tetrafluorophenyl)imidazoles (III). One fluorine at the <u>para</u>- or <u>ortho</u>-position to R was replaced by imidazole.



$I_{a \sim l}$ $II_{a \sim h,j}$ $III_{b,h}$

a) R = CN b) R = NO_2 c) R = CHO d) R = $CO_2C_2H_5$
e) R = CO_2H f) R = I g) R = Br h) R = Cl
i) R = F j) R = H k) R = CH_3 l) R = OCH_3

The products were readily isolated by silica gel chromatography and/or recrystallization. The structure assignment for the products was based on their ^{19}F NMR spectra. Four aromatic fluorines of **II** appear as an AA'XX' pattern[9], while those of **III** show four sets of d-d-d patterns. The reactivity of pentafluorobenzenes varied markedly with the substituents, and the reaction conditions (Table 1) were changed according to the expected reactivity.

TABLE 1

Nucleophilic substitution of pentafluorobenzenes (I) with imidazole

I		Solvent	Reaction conditions[1]			Product yields (%)	
			Base	Temp. °C	Time hours	II	III
(Ia)	C_6F_5CN	THF	--	r.t.[2]	3	83.8	--
(Ib)	$C_6F_5NO_2$	THF	--	r.t.	4	51.8	13.9
(Ic)	C_6F_5CHO	THF	--	r.t.	20	83.5	--
(Id)	$C_6F_5CO_2C_2H_5$	THF	--	65	10	81.5	--
(Ie)	$C_6F_5CO_2H$	THF	--	65	10	--	--
(If)	C_6F_5I	DMSO	--	80	43	70.4	--
(Ig)	C_6F_5Br	DMSO	--	80	96	40.3	--
(Ih)	C_6F_5Cl	DMSO	--	100	40	65.9	2.8
(Ih)	C_6F_5Cl	DMSO	KOH[3]	80	4	38.4	4.1
(Ih)	C_6F_5Cl	THF	KOH[3]	60	66	26.8	2.4
(Ih)	C_6F_5Cl	tBuOH	KOH[3]	80	20	54.4	4.3
(Ii)	C_6F_6	DMSO	KOH[3]	80	24	--	--
(Ij)	C_6F_5H	DMSO	KOH[3]	55	3	73.6	--
(Ik)	$C_6F_5CH_3$	DMSO	--	100	24	--	--
(Il)	$C_6F_5OCH_3$	DMSO	--	100	24	--	--

[1] Imidazole 10 mmol; Pentafluorobenzenes (I) 20 mmol; Solvent 30 ml.

[2] Ambient temperature (13~16°C). [3] KOH 15 mmol.

The substitution of pentafluorobenzonitrile (Ia) and pentafluoronitrobenzene (Ib) was achieved in THF at ambient temperature without any bases: Ia gave 1-(4'-cyanotetrafluorophenyl)imidazole (IIa) in 83.8% yield, while Ib gave 1-(4'-nitrotetrafluorophenyl)imidazole (IIb) in 51.8% yield together with 1-(2'-nitrotetrafluorophenyl)imidazole (IIIb) in 13.9% yield. It has been reported [10] that ortho-substitution is incident to the reaction of Ib and amines, and that hydrogen-bonding between amines and the nitro group favors ortho-substitution. In the case of imidazole, IIIb might be formed via the hydrogen-bonded intermediate. Both inductive and resonance electron-withdrawing groups, CN and NO_2, facilitated the nucleophilic substitution. The resonance effect contributes to the orientation of the replaced fluorine.

Pentafluorobenzenes having carbonyl group were also expected to be reactive. Pentafluorobenzaldehyde (Ic) actually reacted in THF at ambient temperature to give 1-(4'-formyltetrafluorophenyl)imidazole (IIc) in 83.5% yield. Recrystallization of IIc was difficult and crystalline ethyl hemiacetal (IIc') was obtained from ethanol-water solution. Ethyl pentafluorobenzoate (Id) afforded 1-(4'-ethoxycarbonyltetrafluorophenyl)imidazole (IId) in 81.5% yield by heating at 65°C in THF. No ortho-fluorine substituted products (IIIc and IIId) were detected by GLC and ^{19}F NMR. Pentafluorobenzoic acid (Ie) gave no fluorine substituted products but only the imidazole salt of Ie. Imidazole does not attack the anionic form of Ie ($C_6F_5COO^-$).

The substitution of less reactive halogenopentafluorobenzenes (If ~ i) was achieved in DMSO which is known to accelerate the reaction of polyfluorobenzenes and amines[11]. Iodopentafluorobenzene (If) and bromopentafluorobenzene (Ig) gave 1-(4'-iodotetrafluorophenyl)imidazole (IIf, 70.4% yield) and 1-(4'-bromotetrafluorophenyl)imidazole (IIg, 40.3% yield), respectively by heating at 80°C. Chloropentafluorobenzene (Ih) provided 1-(4'-chlorotetrafluorophenyl)imidazole (IIh) in 65.9% yield by heating similarly at 100°C. A small amount of 1-(2'-chlorotetrafluorophenyl)imidazole (IIIh) was detected by GLC,

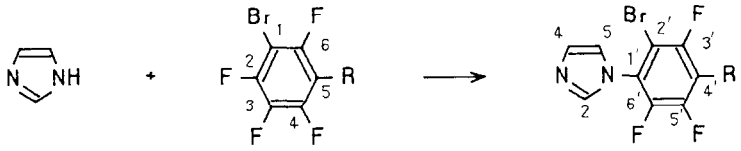
but isolation was unsuccessful because of the low yield, and the structure was assigned by MS and NMR of the crude product. No reaction of hexafluorobenzene (**Ii**) and imidazole occurred in spite of heating with 1.5 eq. of KOH in DMSO or tert-butyl alcohol at 80°C for more than 24 hours.

Pentafluorobenzene (**Ij**) was warmed with imidazole and 1.5 eq. of KOH in DMSO at 55°C for 3 hours to give 1-(4'-hydrotetrafluorophenyl)imidazole (**IIj**) in 73.6% yield.

Methylpentafluorobenzene (**Ik**) and methoxypentafluorobenzene (**Il**) gave almost unchanged starting materials under even more vigorous reaction conditions (100°C) than those of **Ii**.

In the imidazole substitution, the reactivity of **I** depends upon the substituent: thus, electron-withdrawing groups facilitate the replacement of a para-fluorine[12]. The reactions were monitered by GLC, and the observed order of the reactivity is as follows: CN, NO_2 > CHO > $CO_2C_2H_5$ > I > Br > Cl > H > F, CH_3, OCH_3. Although, no quantitative examination has been achieved, the relative reactivity of **I** seems to parallel the relative stability of the Wheland-type intermediates. The regioselectivity is superior to those of amines and alcoholates: the para-fluorine was replaced specifically except in the case of **Ib** and **Ih**.

In order to investigate the selectivity, the imidazole substitution of two tetrafluorobenzenes (**IV**) was examined.



IV$_{m,n}$ **V**$_{m,n}$

m) R = Br n) R = H

By heating at 80°C for 20 hours in DMSO, 1,3-dibromotetrafluorobenzene (**IVm**) gave 1-(2',4'-dibromotrifluorophenyl)-imidazole (**Vm**) in 69.9% yield. No other products were observed by GLC and ^{19}F NMR. The structure of **Vm** is easily elucidated

by ^{19}F NMR. By heating similarly for 90 hours, 1-bromo-2,3,4,6-tetrafluorobenzene (**IV**n) provided specifically 1-(2'-bromo-3',5',6'-trifluorophenyl)imidazole (**V**n) in 67.5% yield. The structure is assigned on the bases of ^{1}H, ^{19}F and ^{13}C NMR. In ^{19}F and ^{1}H NMR spectra, the coupling constants of F-5' were J_{F-F} 21 and 4 Hz and J_{H-F} 10Hz, and those of H-4' were J_{H-F} 10, 9 and 7 Hz. In the ^{13}C NMR spectrum, the C-4' signal appeared at 107.50 ppm as a strong peak because of bonding to hydrogen. The large d-d splitting (J_{C-F} 29 and 23 Hz) of the peak showed the presence of two fluorines on both neighbouring carbons[13]. Only one fluorine (F-2), in the position <u>para</u> to hydrogen, was replaced by imidazole. The nucleophilic substitution of **IV**n with sodium methoxide or dimethylamine is known[14]: methoxide replaces mainly <u>para</u>-F (F-2) together with <u>ortho</u>-F (F-4) to hydrogen, while dimethylamine replaces <u>para</u>-F (F-4) to bromine predominantly. The results have been explained by steric hindrance. Therefore, the high selectivity of imidazole seems to be due to its less reactivity and less steric hindrance which arises from the tautomeric nature of the imidazole nucleus.

Mass fragments of the products show characteristic pattern of N-substituted imidazoles: in most cases, the largest peak is parent peak (M^+), and M-HCN, M-$(HCN)_2$ and M-HCN-CH_2CN are characteristic fragments.

EXPERIMENTAL

<u>Materials</u>

Ethyl pentafluorobenzoate (**I**d) was prepared by a one-step procedure from pentafluorobenzonitrile (**I**a), based on Org. Synth.[15]: **I**a (9.65g, 50 mmol), 95% ethanol (20 ml) and conc.

sulfuric acid (10 ml) were agitated at reflux temperature for 40 hours to give Id 8.6g, 59% yield, bp 87.7 ~ 88.0°C/20 Torr. (lit. bp 63°C/5 Torr[16]).

Pentafluorobenzoic acid (Ie) and methoxypentafluorobenzene (Il) were prepared from Ia and hexafluorobenzene (Ii), respectively: Ie mp 101 ~ 102°C (lit. mp 103 ~ 104°C [17]), Il bp 58.7 ~ 58.9°C/41 Torr (lit. bp 138 ~ 139°C [18]). Other polyfluorobenzenes were obtained from various commercial sources.

Analytical methods and instrumentations

Melting points were uncorrected. ^{1}H NMR (90 MHz) spectra were recorded on a Hitachi R22 spectrometer with TMS as internal reference. ^{19}F NMR (56.45 MHz) spectra were recorded on a Hitachi R20b spectrometer; positive δ values are downfield from external reference, hexafluorobenzene. ^{13}C NMR (22.6MHz) were obtained using a Hitachi R-90H FT spectrometer, with TMS as internal reference. ^{1}H and ^{19}F NMR spectra were measured in 5% acetone-d_6 solution, and ^{13}C NMR spectra were in 10% acetone-d_6 solution. Mass spectral and GC-MS data were obtained from a Hitachi M-80 instrument (electron-impact ionization at 70 eV). NMR and Mass spectral data are given in the following forms as chemical shift δ (splitting, coupling constants J, number, assignment) and m/e assignment (relative intensity). GLC was recorded on a Shimadzu instrument (Model GC-6A); separation were performed at 70 ~ 270°C with helium carrier gas, using a glass column (3mm x 200cm) packed with 15% OV-17 Chromosorb WAW DMCS (60 ~ 80mesh). Elemental analysis was performed by a Perkin-Elmer instrument (Model 240). The homogeneity and identity of each product were verified by NMR, MS, GLC and TLC. All the products synthesized by these nucleophilic reactions are new compounds and are listed in Table 2 together with their melting points, crystal forms and elemental analyses.

Reaction of pentafluorobenzonitrile (Ia) in THF

To a solution of imidazole (1.36g, 20 mmol) in THF (10 ml), was added a solution of Ia (1.93g, 10 mmol) in THF (20

TABLE 2

Products obtained from the nucleophilic substitution

Compounds	mp (°C)	Crystal form (solvent)[1]	Formula	Calcd.(%)			Found.(%)		
				C	H	N	C	H	N
IIa	52 ~ 53	needles (B)	$C_{10}H_3F_4N_3$	49.81	1.25	17.42	49.54	1.05	17.14
IIb	--	oil	$C_9H_3F_4N_3O_2$	41.40	1.16	16.09	41.17	1.21	15.64
IIIb	94 ~ 96	needles (B)	$C_9H_3F_4N_3O_2$	41.40	1.16	16.09	41.43	1.13	16.02
IIc	--		$C_{10}H_4F_4N_2O$	49.20	1.65	11.47			
IIc'	78 ~ 80	granules (C-E)	$C_{12}H_{10}F_4N_2O_2$	49.66	3.47	9.65	49.32	3.36	9.65
IId	184 ~ 185	plates (C-E)	$C_{12}H_8F_4N_2O_2$	50.01	2.80	9.72	49.73	2.83	9.54
IIf	185 ~ 86	plates (A)	$C_9F_4N_2I$	31.61	0.88	8.19	31.83	0.91	8.33
IIg	130 ~ 31	prisms (A-D)	$C_9H_3F_4N_2Br$	36.64	1.02	9.49	36.63	0.92	9.54
IIh	86 ~ 89	plates (B-D)	$C_9H_3F_4N_2Cl$	43.14	1.21	11.18	43.06	1.17	11.15
IIj	93 ~ 94	needles (B-D)	$C_9H_4F_4N_2$	50.01	1.87	12.96	49.97	1.85	12.93
Vm	107 ~ 08	plates (C-E)	$C_9H_3F_3N_2Br_2$	30.37	0.85	7.87	30.54	0.79	7.84
Vn	86 ~ 89	prisms (B)	$C_9H_4F_3N_2Br$	39.02	1.46	10.11	39.08	1.45	10.21

[1] Solvents for recrystalization A:ethyl acetate, B:diethyl ether, C:ethanol, D:hexane, E:water.

ml). The solution was agitated at ambient temperature (15°C) for 3 hours. The reaction was occasionally monitored by GLC in order to decide termination of the reaction. The reaction mixture was poured into water and extracted three times with ethyl acetate (30 ml x 3). The extracts were combined and washed with aq. NaCl solution and then dried over anhydrous sodium sulfate. The solution was evaporated to dryness and the residual material (2.9g) was applied to a column of silica gel (90 ml), and the column was eluted with diethyl ether. The combined eluents were evaporated to give 1-(4'-cyanotetrafluorophenyl)imidazole (IIa), 2.02g (83.8% yield), recrystallized from diethyl ether, yellowish needles, mp 52~53°C: MS 241 M^+ (95), 214 M-HCN (61), 187 M-$(HCN)_2$ (37), 174 M-HCN-CH_2CN (29), 162 (21), 124 M-HCN-CH_2CN-CF_2 (100): ^1H NMR 7.24 (s, 1, H-4), 7.54 (t, J = 1 Hz, 1, H-5), 8.02 (t, J = 1 Hz, 1, H-2): ^{19}F NMR 18.85 (AA'XX'-d-d, J = 23, 12, 5, 2, 1 and 1 Hz, 2, F-2' and F-6'), 31.67 (AA'XX', J = 23, 12, 5 and 2 Hz, 2, F-3' and F-5').

This procedure is representative of the imidazole substitution of nitropentafluorobenzene (Ib), pentafluorobenzaldehyde (Ic) and ethyl pentafluorobenzoate (Id). As shown in Table 1, reaction time and temperature were different with the reactivity of the pentafluorobenzenes. In the case of Ib, a mixture of two regio isomers, IIb and IIIb, was obtained, and they were separated by silica gel column eluted with diethyl ether. MS and NMR data are shown as follows:

1-(4'-nitrotetrafluorophenyl)imidazole (IIb): MS 261 M^+ (29), 215 M-NO_2(16), 204 M-NO-CH_2CN(11), 188 M-NO_2-HCN(33), 161 M-NO_2-$(HCN)_2$(31), 148 M-NO_2-HCN-CH_2CN(33), 46 NO_2 (100): ^1H NMR 7.24 (s, 1, H-4), 7.54 (t, J = 1 Hz, 1, H-5), 8.02 (t, J = 1 Hz, 1, H-2) : ^{19}F NMR 18.30 (AA'XX', J= 22, 8, 5 and 1 H, 2, F-3' and F-5'), 18.97 (AA'XX'-d-d, J = 22, 8, 5, 1, 1 and 1 Hz, 2, F-2' and F-6').

1-(2'-nitrotetrafluorophenyl)imidazole (IIIb): MS 262 M+1(2), 261 M^+(5), 233 M-CO(11), 206 M-CO-HCN(88), 205 (71), 204 M-NO-HCN(17), 188 M-NO_2-HCN(41), 161 M-NO_2-$(HCN)_2$(70), 150 (100): ^1H NMR 7.19 (s, 1, H-4), 7.37 (s, 1, H-5), 7.82 (s, 1, H-2):

^{19}F NMR 13.32 (d-d-d, J = 21, 20 and 4 Hz, 1, F-4'), 15.66 (d-d-d, J = 21, 20 and 6 Hz, 1, F-5'), 18.00 (d-d-d, J = 21, 8 and 6 Hz, 1, F-3'), 21.11 (d-d-d, J = 21, 8 and 4 Hz, 1, F-6').

1-(4'-formyltetrafluorophenyl)imidazole (IIc): MS 244 M^+(100), 217 M-HCN(13), 216 M-CO(19), 190 M-$(HCN)_2$(11), 189 M-HCN-CO(10), 188 (15), 162 (15), 149 M-HCN-CO-CH_2CN(18): ^1H NMR 7.24 (s, 1, H-4), 7.54 (t, J = 1 Hz, 1, H-5), 8.02 (t, J = 1 Hz, 1, H-2), 10.33 (t, J = 2 Hz, 1, CHO): ^{19}F NMR 16.26 (AA'XX'-d-d, J = 21, 12, 3, 3, 1 and 1 Hz, 2, F-2' and F-6'), 19.62 (AA'XX'-d-d, J = 21, 12, 3, 3, 2 and 2 Hz, 2, F-3' and F-5').

1-(4'-formyltetrafluorophenyl)imidazole ethyl hemiacetal (IIc'): MS 290 M^+(1), 244 M-C_2H_6O(100), 45 C_2H_5O(6) and the same fragments as IIc: ^1H NMR 1.22 (t, J = 7 Hz, 3, CH_3), 3.92 (q, J = 7 Hz, 2, CH_2), 6.13 (s, 1, CH), 7.21 (s, 1, H-4), 7.49 (t, J = 1 Hz, 1, H-5), 7.94 (t, J = 1 Hz, 1, H-2): ^{19}F NMR 15.09 (AA'XX'-d-d, J = 22, 11, 4, 1, 1 and 1 Hz, 2, F-2' and F-6'), 21.40 (AA'XX', J = 22, 11, 4 and 1 Hz, 2, F-3' and F-5').

1-(4'-ethoxycarbonyltetrafluorophenyl)imidazole (IId): MS 288 M^+(100), 260 M-C_2H_4(23), 243 M-OC_2H_5(72), 233 M-C_2H_4-HCN(13), 216 M-OC_2H_5-HCN(22), 215 M-OC_2H_5-CO(23), 188 M-OC_2H_5-CO-HCN(28), 161 (20): ^1H NMR 1.40 (t, J = 7 Hz, 3, CH_3), 4.48 (q, J = 7 Hz, 2, CH_2), 7.22 (s, 1, H-4), 7.50 (s, 1, H-5), 7.96 (s, 1,H-2): ^{19}F NMR 17.08 (AA'XX', J = 23, 12, 5 and 2 Hz, 2, F-2' and F-6'), 25.05 (AA'XX', J = 23, 12, 5 and 2 Hz, 2, F-3' and F-5').

Reaction of iodopentafluorobenzene (If) in DMSO

To a solution of imidazole (1.39g, 20 mmol) in DMSO (20 ml), was added a THF (10 ml) solution of iodopentafluorobenzene (If) (2.95g, 10 mmol) at ambient temperature. The mixture was agitated at 80°C for 43 hours. The reaction mixture was poured into cold water (120 ml) and a white solid was deposited. The solid was collected by filtration to give almost pure 1-(4'-iodotetrafluorophenyl)imidazole (IIf), 2.41g (70.4% yield). Recrystallization from diethyl ether gave colorless needles: mp 186~187°C: MS 342 M^+(100), 315 M-HCN(14), 288 M-$(HCN)_2$ (15), 215 M-I(10), 188 M-I-HCN(21), 161 M-I-$(HCN)_2$(18), 148 M-I-HCN-

CH_2CN(25), 127 I(8): ^{1}H NMR 7.19 (s, 1, H-4), 7.43 (t, J = 1 Hz, 1, H-5), 7.88 (t, J = 1 Hz, 1, H-2): ^{19}F NMR 17.71 (AA'XX'-d-d, J = 24, 10, 3, 3, 1 and 1 Hz, 2, F-2' and F-6'), 44.53 (AA'XX', J = 24, 10, 3 and 3 Hz, 2, F-3' and F-5').

This procedure is representative of the imidazole substitution of bromopentafluorobenzene (**Ig**), chloropentafluorobenzene (**Ih**), 1,3-dibromotetrafluorobenzene (**IV**m) and 1-bromo-2,3,4,6-tetrafluorobenzene (**IV**n). In the case of **Ih**, a mixture of **II**h and **III**h was obtained and they were separated by a silica gel column (100ml, eluted with diethyl ether). MS and NMR data are shown as follows:

1-(4'-bromotetrafluorophenyl)imidazole (**II**g): MS 296 M^+(97), 294 M^+(100), 269 M-HCN(27), 267 M-HCN(28), 256 M-CH_2CN(4), 254 M-CH_2CN(49), 242 M-$(HCN)_2$(22), 240 M-$(HCN)_2$(22), 229 M-HCN-CH_2CN(11), 227 M-HCN-CH_2CN(11), 215 M-Br(11), 188 M-Br-HCN(29), 161 M-Br-$(HCN)_2$(37), 148 M-Br-HCN-CH_2CN(51): ^{1}H NMR 7.23 (s, 1, H-4), 7.50 (t, J = 1 Hz, 1, H-5) ,7.95 (t, J = 1 Hz, 1, H-2): ^{19}F NMR 17.43 (AA'XX'-d-d, J = 23, 9, 4, 4, 1 and 1 Hz, 2, F-2' and F-6'), 31.53 (AA'XX', J = 23, 9, 4 and 4 Hz, 2, F-3' and F-5').

1-(4'-chlorotetrafluorophenyl)imidazole (**II**h): MS 252 M^+(32), 250 M^+(100), 225 M-HCN(14), 223 M-HCN(42), 215 M-Cl(6), 198 M-$(HCN)_2$(13), 196 M-$(HCN)_2$(42), 188 M-Cl-HCN(23), 185 M-HCN-CH_2CN(8), 183 M-HCN-CH_2CN(26), 161 M-Cl-HCN-CH_2CN(31), 148 M-Cl-HCN-CH_2CN(11), 133 (34): ^{1}H NMR 7.20 (s, 1, H-4), 7.46 (t, J = 1 Hz, 1, H-5), 7.91 (t, J = 1 Hz, 1, H-2): ^{19}F NMR 17.11 (AA'XX'-d-d, J = 22, 8, 4, 4, 1 and 1 Hz, 2, F-2' and 6'), 23.84 (AA'XX', J = 22, 8, 4 and 4 Hz, 2, F-3' and F-5').

1-(2'-chlorotetrafluorophenyl)imidazole (**III**h): MS 252 M^+(32), 250 M^+(100), 225 M-HCN(9), 223 M-HCN(27), 215 M-Cl(15), 210 M-CH_2CN(7), 199 (12), 198 M-$(HCN)_2$ (11), 196 M-$(HCN)_2$(30), 188 M-Cl-HCN(41), 185 M-HCN-CH_2CN(8), 183 M-HCN-CH_2CN(23), 162 (10), 161 M-Cl-HCN-CH_2CN(34), 148 M-Cl-HCN-CH_2CN(11), 133 (33): ^{1}H NMR 7.1 (s, 1, H-4), 7.4 (d, J = 1 Hz, 1, H-5), 7.8 (d, J = 1 Hz, 1, H-2): ^{19}F NMR 8.18 (d-d-d, J = 21, 21 and 2 Hz, 1, F-5'), 11.02 (d-d-d, J = 21, 21 and 3 Hz, 1, F-4'), 19.84 (d-d-d-d, J = 21, 8, 3, 1 and 1 Hz, 1, F-6'), 26.50 (d-d-d, J = 21, 8 and 2 Hz, 1, F-3').

1-(2',4'-dibromotrifluorophenyl)imidazole (**Vm**): MS 358 M^+(49), 356 M^+(100), 354 M^+(51), 331 M-HCN(4), 329 M-HCN(7), 327 M-HCN(4), 304 M-$(HCN)_2$(2), 302 M-$(HCN)_2$(5), 300 M-$(HCN)_2$(2), 277 M-Br(5), 275 M-Br(5), 250 M-Br-HCN(15), 248 M-Br-HCN(15), 223 M-Br-$(HCN)_2$(8), 221 M-Br-$(HCN)_2$ (8), 210 M-Br-HCN-CH_2CN(7), 208 M-Br-HCN-CH_2CN(6), 167 M-Br (7): ^1H NMR 7.22 (s, 1, H-4), 7.40 (s, 1, H-5), 7.81 (s, 1,H-2): ^{19}F NMR 21.43 (d-d-m, J = 22 and 10 Hz, 1,F-6'), 36.68 (d, J = 22 Hz, 1, F-5'), 65.53 (d, J = 10 Hz, 1, F-3').

1-(2'-bromo-3',5',6'-trifluorophenyl)imidazole (**Vn**): Ms 278 M^+(98), 276 M^+(100), 251 M-HCN(5), 249 M-HCN(6), 238 M-CH CN(2), 224 M-$(HCN)_2$(2), 222 M-$(HCN)_2$(3), 211 M-HCN-CH_2CN(10), 209 M-HCN-CH_2CN(10), 197 M-Br(16), 170 M-Br-HCN (60), 143 M-Br-$(HCN)_2$(32), 130 M-Br-HCN-CH_2CN(35): ^1H NMR 7.19 (d-d, J = 1 and 1 Hz, 1, H-4), 7.36 (d-d-d, J = 1, 1 and 1 Hz, 1, H-5), 7.72 (d-d-d, J = 10, 9 and 7 Hz, 1, H-4'), 7.82 (d-d, J = 1 and 1 Hz, 1, H-2): ^{19}F NMR 18.81 (d-d-d-d, J = 21, 11, 7 and 1 Hz, 1, F-6'), 32.14 (d-d-d, J = 21, 10 and 4 Hz, 1, F-5'), 59.61 (d-d-d, J = 11, 9 and 4 Hz, 1, F-3'): **^{13}C NMR** 105.63 (d-d-d, J = 25, 5 and 1 Hz, C-2'), 107.50 (d-d, J = 29 and 23 Hz, strong, C-4'), 121.24 (d, J < 1 Hz, strong, C-5), 128.68 (d-d, J = 14 and 3 Hz, weak, C-1'), 130.25 (s, strong, C-4), 138.47 (d, J = 1, strong, C-2), 144.72 (d-d-d, J = 251, 15 and 5 Hz, C-6'), 150.51 (d-t, J = 251 and 14 Hz, C-5'), 155.68 (d-d-d, J = 245, 12 and 4 Hz, C-3').

Reaction of pentafluorobenzene (**Ij**) in the presence of base in DMSO

To a solution of imidazole (1.36g, 20 mmol) and KOH (0.62g, 15 mmol) in DMSO (10 ml), was added a DMSO (10 ml) solution of **Ij** (1.68g, 10 mmol) at ambient temperature. The mixture was agitated at 55°C for 3 hours. The reaction mixture was poured into cold aqueous NaCl solution (150 ml), and was extracted with ethyl acetate (30 ml x 3). The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give white powder. The residual material (2.24g) was applied to a column of silica gel (130 ml), and the column

was eluted with diethyl ether. There was obtained total 1.59g (73.6% yield) of 1-(2,3,5,6-tetrafluorophenyl)imidazole (IIj): recrystallized from diethyl ether, colorless prisms, mp 93 ~ 94°C, MS 216 M^+(100), 189 M-HCN(28), 176 M-CH_2CN(7), 162 M-$(HCN)_2$(36), 149 M-HCN-CH_2CN(33), 99 M-HCN-CH_2CN-CF_2(31): ^1H NMR 7.20 (s, 1, H-4), 7.47 (t, J = 1 Hz, 1, H-5), 7.70 (t-t, J = 10 and 7 Hz, 1, H-4'), 7.92 (t, J = 1 Hz, 1, H-2): ^{19}F NMR 15.76 (AA'XX'-d-d-d, J = 22, 12, 4, 0, 7, 1 and 1 Hz, 2, F-2' and F-6'), 26.39 (AA'XX'-d, J = 22, 12, 4, 0 and 10 Hz, 2, F-3' and F-5').

Reaction with Ih in the presence of base in tert-butanol

To a solution of imidazole (1.36g, 20 mmol) and KOH (0.62g, 15 mmol) in tert-butanol (20 ml), was added a tert-butanol (10 ml) solution of Ih (2.03g, 10 mmol) at 50°C. The mixture was agitated at 80°C for 20 hours. The reaction mixture was poured into cold water (120 ml) and extracted with diethyl ether (30 ml x 3). The combined ether solution was dried over Na_2SO_4 and evaporated under reduced pressure to give white powder (1.47g). The product was a mixture of IIh and IIIh (93 : 7 by GLC).

REFERENCES

1 H. Kimoto, S. Fujii and L.A. Cohen, J. Org. Chem., 47 (1982) 2867; 49 (1984) 1060: S. Fujii, Y. Maki, H. Kimoto and L.A. Cohen, J. Fluorine Chem., 35 (1987) 437.

2 S. Fujii, Y. Maki, H. Kimoto and L.A. Cohen, J. Fluorine Chem., 30 (1986) 415; 32 (1986) 329; 35 (1987) 581.

3 C.F. Wilkinson, K. Hetnarski and L.J. Hicks, Pesticide Biochemistry and Physiology, 4 (1974) 299.

4 G.E. Adams, I.R. Flockhart, C.E. Smithen, I.J. Stratford, P. Wardman and M.E. Watts, Radiat. Res., 67 (1976) 9.

5 S. Oae, Y. Kadoma and Y. Yano, Bull. Chem. Soc. Jap., 42 (1969) 1110.

6 A.L. Johnson, J.C. Kauer, D.C. Sharma and R.I. Dorfman, J. Med. Chem., 12 (1969) 1024.

7 a) A. Wohl and W. Marckwald, Ber.,22 (1889) 568, 1353;
b) W. Marckwald, ibid.,25 (1892) 2354;

8 L.S. Kobrina, Fluorine Chemistry Reviews, Vol.7, Marcel Dekker, New York, 1974, p.1.

9 J.W. Emsley, J. Feeney and L.H. Sutcliffe,'High Resolution Nuclear Magnetic Resonance Spectroscopy', Pergamon Press, New York, 1965, p.392.

10 a) G.M. Brooke, J. Burdon and J.C. Tatlow, J. Chem. Soc., (1961) 802;
b) J.G. Allen, J. Burdon and J.C. Tatlow., ibid., (1965) 1045.

11 S.M. Shein and P.P. Rodionov, Kinetika i Kataliz, 15 (1974) 1131.

12 J. Burdon, Tetrahedron, 21 (1965) 3373.

13 a) F.J. Weigert and J.D. Roberts, J. Am. Chem. Soc., 93 (1971) 2361.
b) J. Elguero, C. Margin and J.D. Roberts, J. Org. Chem., 39 (1974) 357.

14 J. Burdon, D.R. King and J.C. Tatlow, Tetrahedron, 22 (1966) 2541.

15 R. Adams and A.F. Thal, Organic Synthesis, Coll. Vol.I, John Wiley & Sons, New York, 1941, p.270.

16 A.T. Prudchenko, V.A. Barkhash and N.N. Vorohtsov, Jr., Izv. Akad. Nauk SSSR, Ser. Khim., 1965 1798.

17 A.K. Barbour, M.W. Buxton, P.L. Coe, R. Stephens and J.C. Tatlow, ibid., (1961) 808.

18 E.J. Forbes, R.D. Richardson, M. Stacey and J.C. Tatlow, J. Chem. Soc., (1959) 2019.