Table II. Melting Points of Methyl-Substituted *cis*-1-Thioniabicyclo[4.3.0]nonane Picrates

salt[b]	mp,[a] °C	salt[b]	mp,[a] °C
4	238–239	15	229–230
5	170–172	16	142–143
7	135–136	17	194–195
10	137–138	18	182–183
14	241–242	19	198–199

[a] Uncorrected. [b] Satisfactory analytical data (C and H) were found for all the compounds in this table.

in a ~9:3:1 ratio. The minor product appears to be the *endo*-9-CH_3 derivative **6**. The major and intermediate products could be identified from their ^{13}C NMR spectra as the *endo*- and *exo*-2-CH_3 derivatives **12** and **13**, respectively. On the other hand, under the basic conditions leading to H–D exchange of the α-protons, the **12**/**13** ratio was found to decrease (undoubtedly via the ylide), **13** being the thermodynamically more stable epimer. No attempt was made to separate the isomers.

Registry No. (*E*)-**2a**, 68013-79-6; (*E*)-**2b**, 74263-06-2; (*E*)-**2c**, 77743-88-5; (*E*)-**2d**, 71411-37-5; (*E*)-**2e**, 77743-86-3; (*E*)-**2f**, 77743-84-1; (*E*)-**2g**, 77743-85-2; (*E*)-**2h′**, 81643-12-1; (*E*)-**2h″**, 81702-61-6; (*Z*)-**3f**, 77743-81-8; (*Z*)-**3g**, 77743-82-9; (*Z*)-**3h**, 81702-62-7; **4** triflate, 81643-14-3; **4** picrate, 81643-15-4; **5** triflate, 81643-17-6; **5** picrate, 81702-63-8; **6** triflate, 81702-65-0; **7** triflate, 81643-19-8; **7** picrate, 81702-66-1; **8** triflate, 81702-68-3; **9** triflate, 81643-21-2; **10** triflate, 81643-23-4; **10** picrate, 81702-69-4; **11** triflate, 81702-71-8; **12** triflate, 81643-25-6; **13** triflate, 81702-73-0; **14** triflate, 81643-27-8; **14** picrate, 81702-74-1; **15** triflate, 81702-76-3; **15** picrate, 81737-59-9; **16** triflate, 81643-29-0; **16** picrate, 81643-30-3; **17** triflate, 81643-32-5; **17** picrate, 81702-77-4; **18** triflate, 81702-79-6; **18** picrate, 81702-77-4; **19** triflate, 81702-81-0; **19** picrate, 81737-60-2; **23** BF_4, 81643-34-7; **23** PF_6, 81643-35-8; **24** BF_4, 81643-37-0; **24** PF_6, 81643-38-1; 2-methyl-2-(1-methylvinyl)thiane, 77743-97-6.

Photochemical Perfluoroalkylation of Imidazoles

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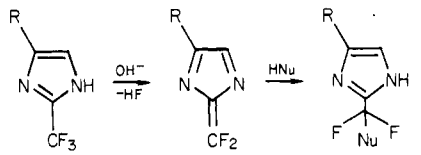
Imidazole and its derivatives undergo facile trifluoromethylation or perfluoroalkylation, in methanol solution at ambient temperature, following radical dissociation of R_FI by γ or UV irradiation. In the case of imidazole, attack occurs preferentially at C-4 with either γ or UV radiation, but the latter method gives consistently higher yields of both C-4 and C-2 isomers. Isolated yields of 4-R_F-imidazoles (R = C_1–C_{10}) ranged from 34% to 61% and those of 2-R_F-imidazoles from 10% to 33%. Trifluoromethylation of substituted imidazoles provided 4-CF_3 isomers in 26–95% yield and 2-CF_3 isomers in 8–46% yield. Small amounts of bis(trifluoromethyl) products are also obtained. The reaction is facilitated by electron-releasing substituents and is retarded by electronegative groups. 1-Alkylimidazoles are trifluoromethylated mainly at C-5 and benzimidazole mainly at C-4. Structural assignments are based on analyses of ^1H and ^{19}F NMR spectra. In the case of 2-R_F-imidazoles (R = C_3–C_{10}), evidence is presented for tautomer stabilization by an intramolecular N–H···F bond.

In continuation of our studies on the chemistry and biochemistry of ring-substituted histamines and histidines,[1] we recently described facile syntheses of the 2-trifluoromethyl derivatives[2] of these biologically essential imidazoles. A general property of ring-trifluoromethylated imidazoles (**1**, and its 4(or 5)-isomer), is the tendency to eliminate hydrogen fluoride under rather mild alkaline conditions to form transient difluorodiazafulvenes (**2**);[3] the



1 **2** **3**

latter species have been found to react rapidly with a variety of nucleophiles (**3**), ultimately providing additional analogues of histamine and histidine.[4] Recognizing the possibility that appropriate difluorodiazafulvenes might serve as covalent affinity labels in biological systems, we have investigated the effects of other ring substituents and of position isomerism on the rate of hydrogen fluoride elimination[5] and found 4-(trifluoromethyl)imidazole to be ca. 10-fold more reactive than the 2-isomer. Since this difference in reactivity might prove important in biological applications, we turned to the problem of general synthetic routes to the 4-trifluoromethyl series. A number of 4-(trifluoromethyl)imidazoles had already been prepared from (trifluoromethyl)glyoxal by classical condensation methods.[6] Syntheses of 4-(trifluoromethyl)histamine and -histidine by analogous procedures would have required laborious sequences and we examined the possibility of direct introduction of the trifluoromethyl group into preformed imidazoles.

Numerous reports describe the copper-catalyzed condensation of aryl[7a] and heteroaryl[7] halides with per-

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Table I. Yields and Properties of Isomeric Perfluoroalkylimidazoles Obtained by UV Irradiation of Imidazole with R_FI[a]

	2-isomer				4(or 5)-isomer			
R_F	GC,[b] %	yield,[c] %	mp,[d] °C	δ (H-4, H-5)[e]	yield,[c] %	mp,[d] °C	δ (H-2)[e]	δ (H-4 or -5)[e]
CF_3[f]	42	32	146-147 (E)[g]	7.26	47	150-151 (E)[h]	7.81	7.63 (q, 1.3)[i]
C_2F_5	33	25	120-121 (C)	7.31	46	163-164 (EB)	7.85	7.69 (m)
C_3F_7	29	10	133-134 (EB)	7.24, 7.46[j]	44	146-147 (EB)	7.83	7.69 (br s)
$CF(CF_3)_2$	6	k			38	160-161 (E)	7.86	7.64 (br s)
C_6F_{13}	28	33	123-124 (L)	7.24, 7.48[j]	62	156-157 (M)	7.88	7.72 (br s)
C_7F_{15}	34	14	140-141 (L)	7.23, 7.44[j]	34	164-165 (L)	7.82[l]	7.58 (br s)[l]
C_8F_{17}	29	19	148-149 (YB)	7.23, 7.46[j]	34	177-178 (M)	7.82[l]	7.58 (br s)[l]
$C_{10}F_{21}$[m]	29	28	169-170 (L)	7.24, 7.48[j]	41	193-194 (L)	n	
C_6F_5	21	8[o]	204-205 (AX)	7.29	36[o]	169-171 (AX)	7.94	7.59 (d, 2.1)

[a] Reaction mixtures, consisting of 0.03 mol of R_FI and 0.15 mol of imidazole in 40 mL of methanol, were irradiated for 7 days with a 15-W lamp. [b] Based on relative GC peak areas for the two isomers. [c] Products obtained by crystallization following silica gel chromatography; all column separations were effected with ether as eluant. [d] Solvents for crystallization: A, acetone; B, benzene; C, chloroform; E, ether; L, ethanol; M, methanol; X, cyclohexane; Y, ethyl acetate. [e] ^1H NMR spectra (ppm) were measured in acetone-d_6 unless otherwise noted; all signal are singlets unless otherwise noted. [f] Less than 0.5% of a bis(trifluoromethyl) product was detected by GC-MS. [g] Lit. mp 145-146 °C (ref 2a); 145-147 °C (ref 2b). [h] Lit. mp 148-149 °C (ref 6). [i] H-F coupling in hertz. [j] Apparently, a single tautomer stabilized by an internal H bond to fluorine (see NMR section); assignment of signals to H-4 or H-5 has not been attempted. In CD_3OD solution, these signals merge to a singlet at δ 7.28-7.30. [k] Insufficient material was obtained to permit isolation of a pure product. [l] In CD_3OD; compound is only weakly soluble in acetone-d_6. [m] To achieve solubility of $C_{10}F_{21}I$, 30 mL of Freon 113 (1,1,2-trichloro-1,2,2-trifluoroethane) was added to the methanol. [n] Solubility in common NMR solution solvents was too low to provide significant signals. [o] Eluant in chromatography: ether-ethyl acetate (1:1).

fluoroalkyl iodides at fairly high temperature and, occasionally, without metal catalysis.[8] Such condensations have also been achieved with nonhalogenated benzenes,[9] pyridines,[10] and *N*-alkylpyrroles.[11] We rejected consideration of thermal condensations for several reasons: halogenated imidazoles are themselves difficult to prepare; imidazoles readily form copper chelates; the more complex imidazoles might not survive exposure to high temperature. Trifluoromethylation of aromatics has been achieved under far milder conditions by photochemical generation of the trifluoromethyl radical,[8b,12] and this approach has also been effective for pyridine, pyrrole, and *N*-methylpyrrole.[12,13] Apparently, there had been no attempt to trifluoromethylate imidazoles, either by thermal or photochemical methods, nor had any other heterocycles been considered (except those already mentioned), although adenosine had been found unreactive under photochemical conditions.[12] In this report, we describe our results with UV- and γ-ray-induced perfluoroalkylation of simple imidazoles; results with polyfunctional imidazoles and with other heterocycles will be reported separately.

Results

Imidazole and its derivatives were found to undergo UV- or γ-ray-induced perfluoroalkylation with surprising facility (Tables I–III). With UV irradiation, combined yields of isomeric products were often >80%, with the 4(or 5)-isomer always predominant. Although total yields were consistently lower with γ irradiation, attack at C-4(or 5) was still favored over that at C-2. Methanol was selected as the general reaction solvent because of its ability to dissolve a wide range of imidazoles as well as the perfluoroalkyl iodides, its UV transparency, and its ease of removal; on the other hand, radical perfluoroalkylation in protic solvents had not been described previously[14] and solvent intervention or participation was a matter of concern (which ultimately proved unwarranted). Unfiltered UV light (254 nm) was obtained from a 15-W low-pressure lamp (kitchen sterilizer) made of Vycor glass; this source was used for all UV runs except those specifically noted below. γ radiation was obtained from a ^{60}Co source. Reaction rates and product composition were monitored by ^{19}F NMR and by GC–MS.

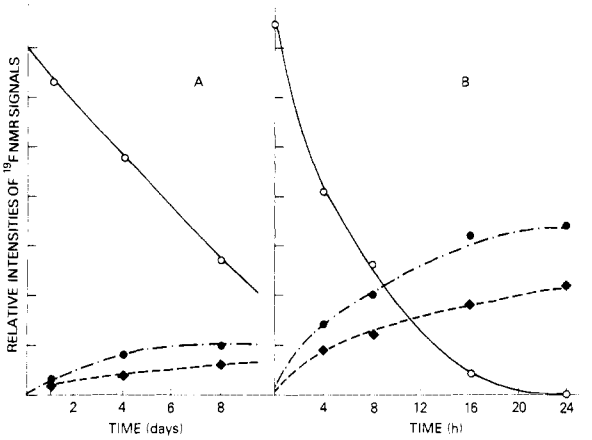

Figure 1. Small-scale trifluoromethylation of imidazole with γ irradiation (A) and with UV irradiation (B). Reaction mixtures contained 3.5 mmol of imidazole and 0.8 mmol of CF_3I in 0.5 mL of methanol. Relative intensities of ^{19}F NMR signals: (○) CF_3I, (●) 4-(trifluoromethyl)imidazole, (♦) 2-(trifluoromethyl)imidazole.

In a small-scale exploratory run with γ irradiation, 40% of the reagent remained after 8 days (Figure 1A); with UV light, however, the CF_3I was fully consumed by excess imidazole in 24 h (Figure 1B). In the UV process, the rate of disappearance of CF_3I is approximately first order, while in the γ irradiation process, the reaction appears to follow zero-order kinetics. Thus, the reactions may have some-

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Table II. Yields and Properties of (Trifluoromethyl)imidazoles Obtained by UV Irradiation of Substituted Imidazoles with CF_3I[a]

product	yield,[b] %	mp,[c] °C	^{1}H NMR, δ[d,e] H-2	H-4(or -5)	other CH's
2-Me-4,5-$(CF_3)_2$	2 (E)	171-172 (C)			2.39
2-Me-4-CF_3	95	179-180 (B)[f]		7.44 (q, 1.4)[g]	2.33
5-Me-2,4-$(CF_3)_2$	3 (E-Y)	174-176 (E)			2.46 (br s)
4-Me-2-CF_3	22	107-108 (B)[h]		6.97	2.25
5-Me-4-CF_3	63	178-179 (BL)	7.69		2.37 (q, 1.6)
2,5-Me_2-4-CF_3	78 (E)	190-191 (B)			2.27[i]
					2.28 (q, 1.8)[j]
4,5-Me_2-2-CF_3	46 (EB)	211-212 (B)			2.12
2-Ph-4-CF_3	26 (EB)	212-213 (L)[k]		7.68 (q, 1.3)	7.2-8.2 (m)
4-Ph-2-CF_3	8 (EB)	151-152 (E)		7.37	7.2-8.2 (m)
5-Ph-4-CF_3	56	238 dec (L)	7.79		7.2-8.2 (m)
5-Me-2-Ph-4-CF_3	62 (EB)	191-192 (C)			2.40 (q, 1.6)
					7.2-8.2 (m)
5-NO_2-2-Me-4-CF_3	8 (MY)	181-183 (L)			2.40
2,4-$(CF_3)_2$-5-CH_2OH	7 (EY)[l]				4.87 (br s)
2-CF_3-4-CH_2OH	26	157-158 (Y)		7.15[m]	4.59[m]
4-CF_3-5-CH_2OH	49	198-199 (Y)	7.70[m]		4.71 (q, 1.3)[m]
1-Me-2-CF_3	10 (E)	liquid		7.03, 7.31[n]	3.88 (q, 1.1)
1-Me-4-CF_3	2	liquid	7.58	7.64 (br s)	3.88
1-Me-5-CF_3	13	ca. 45 (E)	7.75	7.40 (q, 0.6)	3.83 (q, 0.8)
1-Et-2-CF_3	11 (E)	liquid		7.03, 7.39[n]	o
1-Et-4-CF_3	4	liquid	7.71	7.65 (q, 0.7)	o
1-Et-5-CF_3	15	liquid	7.88	7.41 (q, 1.1)	o
2-CF_3-Benz	3 (E-Y)	207-209 (E)[p]			q
4-CF_3-Benz	35	191-192 (E)[r]	8.31		s
5-CF_3-Benz	t				
4,7-$(CF_3)_2$-Benz	2	228 dec (E)	8.50	7.74 (H-5, H-6)	

[a] Reaction mixtures, consisting of 0.03 mol of CF_3I and 0.06 mol of the imidazole in 40 mL of methanol, were irradiated by UV (15 W) for 7 days. [b] Eluants for silica gel chromatography: E, ether; E-Y, ether followed by ethyl acetate; EY, ether-ethyl acetate (1:1); EB, ether-benzene (1:1); MY, 5% methanol in ethyl acetate. For each reaction mixture, compounds were eluted in the order given in the Table. [c] See footnote *d* of Table I. [d] See footnote *e* of Table I. [e] Tautomer assignments are arbitrary; however, see NMR Section. [f] Lit. mp 161-165 °C (ref 6). [g] H-F coupling in hertz. [h] Lit. mp 103-105 °C (ref 2). [i] Substituent at C-2. [j] Substituent at C-4 or C-5. [k] Lit. mp 210-211 °C (ref 6). [l] Based on relative peak areas in GC and identification by MS; quantity obtained was too small to achieve purification. [m] Measured in CD_3OD. [n] Assignment to H-4 or H-5 has not been made. [o] Proton signals for C_2H_5 group: CH_3, 1.43-1.46 (t, 7.5); CH_2, 4.17-4.22 (q, 7.5). [p] Lit. mp 209-210 °C: Belcher, R.; Sykes, A.; Tatlow, J. C. *J. Chem. Soc.* **1954**, 4159. [q] Aromatic proton signals: 7.72 (t, H-4, H-7), 7.38 (t, H-5, H-6), $J_{4,5}$ = 6 Hz, $J_{4,6}$ = 3 Hz. [r] Lit. mp 192.5 °C: Sykes, A.; Tatlow, J. C. *J. Chem. Soc.* **1952**, 4078. [s] Aromatic proton signals: 7.55 (d, $J_{5,6}$ = 7 Hz, H-5), 7.37 (dd, $J_{5,6}$ = 7 Hz, $J_{6,7}$ = 8 Hz, H-6), 7.88 (d, $J_{6,7}$ = 8 Hz, H-7). [t] The product was contaminated with the 4-CF_3 isomer and separation could not be effected.

Table III. Trifluoromethylation of *N*-Alkylimidazoles

N-alkyl	source	ratios,[a] % 2-CF_3	4-CF_3	5-CF_3	yield,[b] %
CH_3	UV	42.8	7.5	49.6	24.8
CH_3	γ ray	37.5	17.4	45.1	14.6
C_2H_5	UV	40.5	14.9	44.6	31.0
C_2H_5	γ ray	37.5	21.9	40.6	23.4

[a] Based on integration of peak areas in ^{19}F NMR spectra. [b] Based on combined weights of partially resolved mixtures of isomers eluted from silica gel columns.

what different mechanisms[15] but have in common the fact that the 4(or 5)-isomer is formed preferentially over the 2-isomer (Figure 1). The rate of consumption of CF_3I and the rate of formation of the isomer mixture increase with increasing concentration of imidazole and increasing excess over CF_3I (Figure 2). Similar rate curves were obtained for reaction with C_2F_5I and C_3F_7I.

In preparative-scale UV runs, ca. 7 days was required for total consumption of the reagent in the presence of 5 equiv of imidazole. Neither ^{19}F NMR nor GC–MS revealed the formation of any significant side products, except for small amounts of iodoimidazole and CF_3H. As the concentration of imidazole was increased, fluoroform formation decreased markedly; we assume, therefore, that CF_3H is generated by hydrogen atom abstraction from the solvent rather than from the substrate. The hydrogen iodide formed in the reaction is neutralized by the excess imid-

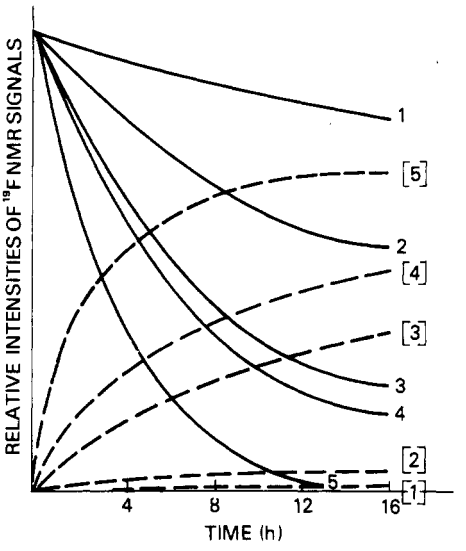


Figure 2. Effect of CF_3I/imidazole ratio on rate of trifluoromethylation by UV irradiation. Each reaction mixture, in 2 mL of methanol, contained 1 mmol of CF_3I and varying millimoles of imidazoles: (1) 0.25, (2) 0.50, (3) 1.00, (4) 2.00, (5) 4.00. Solid lines, rate of decrease in ^{19}F signal for CF_3I; dashed lines, rate of increase in total ^{19}F signals for trifluoromethylated imidazoles.

(15) Presumably, the energy of the trifluoromethyl radical may vary with the source of excitation.

azole and the salt is inert to radical attack. When triethylamine or pyridine was used as the acid acceptor, the rate of consumption of CF_3I increased, but more CF_3H was also formed. In the experiments with pyridine only trace amounts of trifluoromethylpyridines were detected, and it would appear that imidazole is the more reactive of the two heterocyclic systems.

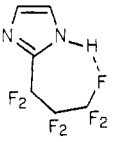
In preparative-scale runs, trace amounts of a bis(trifluoromethyl)imidazole were detected by GC–MS, but the quantities were too small for isolation or characterization. Reirradiation of either the 2- or 4-(trifluoromethyl)-imidazole with excess CF_3I failed to produce any bis product, nor was there any evidence for light-induced interconversion of the isomers. On the other hand, a small amount of the bis product was obtained upon reirradiation of 4-methyl-2-(trifluoromethyl)imidazole but not in the case of 5-methyl-4-(trifluoromethyl)imidazole.

In the UV-induced perfluoroalkylation of imidazole, total product yields ranged from 50% to 95%; there appeared to be no relationship between yield and length of carbon chain. The ratios of isomers formed, as determined by integration of GC peak areas, are essentially the same for UV and γ irradiation; generally, the 4(5)-isomer is favored by a factor of 2-3 (Table I). We prefer the use of UV because of its greater technical simplicity and higher overall yields. Furthermore, γ irradiation results in the generation of hydrogen and in a gradual increase in pressure in the sealed reaction tube. A few experiments were performed with a 60-W low-pressure mercury lamp (with Vycor filter)[16] as the UV source. Reactions were generally complete in 3 days at the higher intensity, without significant alterations in yields or ratios of isomers. Preparative separation of isomers was achieved readily on silica gel columns, and the products were crystallized to analytical purity without undue difficulty. In GC and column chromatography, the order of elution was invariably bis, 2, 4, starting material.

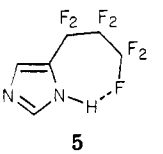
For the trifluoromethylation of substituted imidazoles, UV irradiation with a 15-W source was used routinely. The results (Table II) show that substitution at C-4 is again preferred over C-2. For *C*-methylimidazoles, significant amounts of bis-substitution products were formed, consistent with the electron-releasing effect of the methyl group; conversely, an electron-withdrawing substituent renders the introduction of even the first trifluoromethyl group more difficult. Trifluoromethylation of the phenylimidazoles did not result in significant attack on the benzene ring; in the case of 5-phenylimidazole, substitution occurred overwhelmingly at C-4. This high degree of selectivity may be due to resonance stabilization of the intermediate C-5 radical by the attached benzene ring. The pattern of substitution in benzimidazole may also be determined by resonance factors: the principal product is 4-(trifluoromethyl)benzimidazole, with smaller amounts of the 2- and 5-trifluoromethyl and the 4,7-bis(trifluoromethyl) derivatives. On the basis of ^{19}F NMR peak areas, the ratio of isomers formed was 73.2% (4-), 6.5% (2-), 16.2% (5-), and 4.1% (4,7-bis-).

Limited studies were also performed with *N*-methyl- and *N*-ethylimidazole (Table III), the preparative separation of isomers proving much more difficult in these cases. Total product yields were lower than for NH imidazoles; it is also noteworthy that a greater fraction of the C-4 isomer is produced by γ irradiation than by UV irradiation.

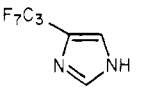
NMR Spectra. The 2- and 4-(perfluoroalkyl)imidazoles are readily differentiated on the basis of their ^1H NMR spectra (Table I).[17] The C-4 and C-5 protons of the 2-isomers all show the singlet expected for the tautomerically equivlent forms in CD_3OD solution. In acetone-d_6 solution, 2-(trifluoromethyl)- and 2-(perfluoroethyl)imidazole also show the expected singlets; we were surprised, however, to find that the H-4 and H-5 signals for 2-(perfluoropropyl)- and the higher 2-(perfluoroalkyl)imidazoles appear as *two* broad singlets separated by ca. 0.2 ppm. This phenomenon is probably due to the stabilization of one tautomer by an intramolecular hydrogen bond to fluorine involving a seven-membered ring (**4**)[18] The effect is observed only when spectra are measured at low concentrations (1–2%); at higher concentrations, intermolecular N–H···N bonding becomes competitive and only a singlet is seen. No separation of signals is seen in CD_3OD solution, since bonding of ND to the solvent would be more favorable, nor is tautomer stabilization observed for 2-(trifluoromethyl)- or 2-(perfluoroethyl)imidazole in any solvent, presumably because of geometrical limitations to ring formation.



4



5



6

If analogous N–H···F bonding exists in the 4(or 5)-perfluoroalkyl series (**5**), it is not easily demonstrable. As the length of the 4(or 5)-perfluoroalkyl chain is increased, no striking variation is found in the ring-proton or ^{19}F NMR signals.[17,18] We see no obvious geometrical restrictions to the formation of **5**, yet prefer to assume that the 1,4-tautomer (**6**), which cannot achieve intramolecular hydrogen bonding, is overwhelmingly preferred.[19]

The isomers obtained by trifluoromethylation of monosubstituted imidazoles were readily identified on the basis of proton–fluorine coupling (Table II).[20] The trifluoromethyl group at C-4 is coupled to a proton, methyl, or hydroxymethyl group at C-5. In the compounds containing H, CH_3, or Ph at C-2, the coupling between C-4 and C-5 substituents is usually seen in expanded scale spectra; however, electronegative substituents at C-2 (including CF_3) reduce the magnitude of the 4,5-coupling significantly and broad singlets are often observed.[5,21] Thus, the ^{19}F NMR signals for 2,4-bis(trifluoromethyl) compounds could not be assigned unequivocally on the basis of splitting patterns; they were identified, however, by the fact that the signal for the CF_3 group at C-4 appears consistently at lower field than that at C-2 (both are downfield from CF_3COOH) and is often a broad singlet. The signal for the CF_3 group at C-2 is also broadened or split by weak coupling to the proton at N-1 (d, J = 0.1–0.3 Hz in acetone-d_6), but such coupling is lost after proton exchange in CD_3OD. We have no evidence of similar coupling of NH to the CF_3 group at C-5 and believe, as already discussed, that the 1,4-tautomer is the prepon-

(16) In the absence of a filter, product yields were significantly reduced and large amounts of tar were formed.

(17) ^{19}F NMR spectra gave δ values and splitting patterns consistent with assigned structures. See paragraph at end of paper about supplementary material.

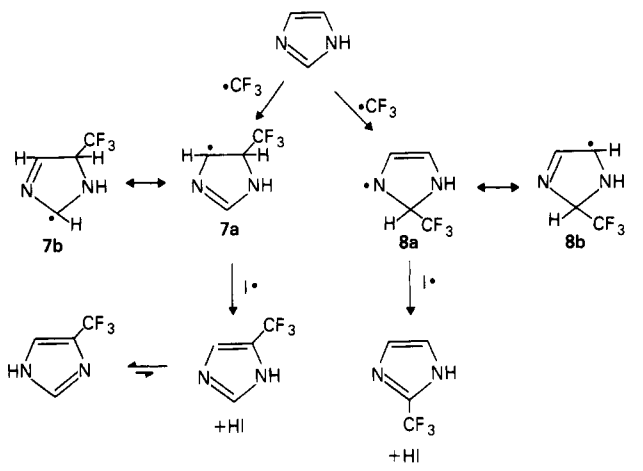
(18) One broad NH band at 3200 cm^{-1} was observed in IR spectra in acetone or tetrahydrofuran solvent, at 1–10% concentration. Neither the chain length nor position of the substitutent had any significant effect on the wavelength or shape of the NH band.

(19) Ganellin, C. R. *J. Pharm. Pharmacol.* **1973**, *25*, 787.

(20) Günther, H. "NMR Spectroscopy"; Wiley: New York, 1980; Chapter 10.

(21) White, R. F. M. In "Physical Methods in Heterocyclic Chemistry"; Katritzky, A. R., Ed.; Academic Press: New York, 1963; Vol. 2, Chapter 9.

Scheme I



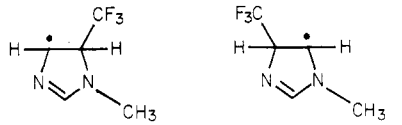
derant species in acetone solution.[19]

Discussion

Extensive studies on the mechanism of photochemical trifluoromethylation of aromatics[8a,8b] have shown that the first step involves the formation of a σ complex with the substrate, i.e., addition to a double bond rather than hydrogen abstraction. An analogous mechanism (Scheme I) seems reasonable for the reaction with imidazoles. The iodine atom, and not a second trifluoromethyl radical, must be considered the ultimate hydrogen atom acceptor, since much more than 50% of reagent can often be accounted for in the products and since CF_3H is not found in significant amount. Furthermore, final reaction mixtures contain almost no I_2 and hydriodide salts of the imidazoles were isolated in several cases. As a variation of Scheme I, however, we cannot exclude the possibility that an intermediate iodo(trifluoromethyl) adduct is formed, which then undergoes rapid elimination of hydrogen iodide. Initial abstraction of a hydrogen atom may also be excluded by bond-energy considerations and by the fact that imidazolyl radicals show a strong tendency to dimerize.[5] Since neither 2- nor 4-(trifluoromethyl)imidazole undergoes further attack by the trifluoromethyl radical, we suggest that the disubstituted products which are obtained arise from combinations of 7 or 8 (Scheme I) with a second trifluoromethyl radical.[8b] The resulting dihydroimidazole can then be dehydrogenated by two iodine atoms. This pathway is consistent with our data showing that addition of the highly electrophilic trifluoromethyl radical is aided by electron-releasing groups and is retarded by electronegative groups (Table II). The preponderance of attack at C-5 (or C-4) is also consistent with the electrophilic nature of perfluoroalkyl radicals. ^1H NMR data suggest these positions to have a higher electron density than C-2,[22] which is not surprising since C-2 is adjacent to two nitrogen atoms. In contrast, attack on imidazoles by the moderately nucleophilic methyl[23] or phenyl[24] radicals occurs predominantly at C-2.

The selectivity of perfluoroalkylation at C-4 over C-2 is greatest for the C_6F_5 radical, approximately the same for the C_2F_5–$C_{10}F_{21}$ radicals, and least for the CF_3 radical; this order is consistent with the expected decrease in electrophilicity along the series. The perfluoroisopropyl group shows an exceptional preference for C-4, which may have a steric basis although we prefer to view this radical as the most electrophilic of all those examined. Similar selectivity has been observed for the perfluoroisopropyl radical in its addition to olefins.[25]

In the trifluoromethylation of *N*-alkylimidazoles, the preference for substitution at C-5 over C-4 is quite clear (Table III). In the intermediate radicals **9** and **10**, **10**



should have the weaker resonance stabilization since a nitrogen radical would have to be a contributing form. The difference in resonance stabilization of the intermediate radical may also be invoked as a basis for the preferential formation of 4-(trifluoromethyl)benzimidazole over the 5-CF_3 isomer.

Preliminary efforts to apply the same trifluoromethylation technique to other nitrogen heterocycles provided only poor yields of substitution products. Whether the seemingly unique reactivity of the imidazole ring is determined by electron-density distribution, overall basicity, resonance stabilization of intermediate radicals, or by π-electron localization[26] is yet uncertain; further studies are in progress.

Experimental Section

Materials. All perfluoroalkyl iodides were obtained from PCR, Inc. and were distilled prior to use (except for the gaseous members of the series). Imidazoles were obtained from various commercial sources, except for 4,5-dimethylimidazole, which was prepared according to a literature method.[27]

Analytical Methods and Instrumentation. Ultraviolet irradiations were performed by use of a Toshiba 15-W low-pressure mercury lamp (kitchen sterilizer) with air cooling. The principal output for this lamp occurs at 254 nm, at which wavelength the perfluoroalkyl iodides have ϵ values of 250–300. For a few runs, a 60-W low-pressure mercury lamp (Eikosya EL-J-60) with Vycor filter was used. The 15-W lamp was made of Vycor glass and required no additional filter. γ radiation (2×10^5 R/h) was obtained from a ^{60}Co source (35 kCi), provided by the irradiation facilities of the Government Industrial Research Institute, Nagoya, under the direction of Mr. H. Imai.

^1H NMR spectra were recorded on a Hitachi spectrometer (Model R22) at 90 MHz, with Me_4Si as internal reference. ^{19}F NMR spectra were recorded on a Hitachi instrument (Model R20b) at 56.45 MHz; positive δ values are downfield from the external reference, trifluoroacetic acid. Mass spectral data were obtained on Hitachi spectrometers (Models RMU-7 and M-80) by electron-impact ionization. GC–MS data were recorded on a Shimadzu instrument (Model 7000). Analytical GC data were obtained on a Shimadzu instrument (Model GC-3AH) and preparative GC was performed on a Varian instrument (Model 920). The aluminum column (5 mm × 300 cm) was packed with 10% OV-17 Chromosorb WAW DMCS (60–80 mesh); separations were performed at 150–175 °C with helium as carrier gas.

Since perfluoroalkyl compounds tend to give incomplete combustion, elemental analysis was performed at high ignition temperature in the presence of vanadium pentaoxide. Satisfactory results (±0.3% for C, H, N) were obtained for the new compounds

(22) Takeuchi, Y.; Yeh, H. J. C.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1978**, *43*, 3565. (b) See also Pachler, K. G. R; Pachter, R. *J. Mol. Struct.* **1981**, *76*, 49.

(23) (a) Begg, C. G.; Grimmitt, M. R.; Yu-man, L. *Aust. J. Chem.* **1973**, *26*, 415. (b) Heilman, W. J.; Rembaum, A.; Szwarc, M. *J. Chem. Soc.* **1957**, 1127.

(24) Lynch, B. M.; Chang, H. S. *Tetrahedron Lett.* **1964**, 2965. Dou, H. J. M.; Lynch, B. M. *Bull. Soc. Chim. Fr.* **1966**, 3815.

(25) Fleming, G. L.; Haszeldine, R. N.; Tipping, A, E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 574. Ashton, D. S.; Mackay, A. F.; Tedder, J. M.; Tipney, D. C.; Walton, J. C. *J. Chem. Soc., Chem. Commun.* **1973**, 496.

(26) Rav-Acha, C.; Cohen, L. A. *J. Org. Chem.* **1981**, *46*, 4717.

(27) Brederick, H.; Theilig, G. *Chem. Ber.* **1953**, *86*, 88.

listed in Tables I and II. Fluorine was determined colorimetrically with AMDAC-F. Acceptable values (within 0.5%) were obtained for the CF_3–C_3F_7 compounds; for the higher perfluoroalkyl compounds, however, fluorine values were consistently 2–12% lower because of the formation of the very stable CF_4. The homogeneity and identity of each reaction product were verified by NMR, MS, GC, and TLC. Melting points are uncorrected.

UV-Induced Perfluoroalkylation of Imidazole. Pentafluoroethyl iodide was bubbled into a solution of imidazole (10.2 g, 0.15 mol) in 40 mL of methanol, contained in a quartz tube (2 × 20 cm) equipped with a Teflon stopper. When the weight of the tube had increased by 7.4 g (0.03 mol of C_2F_5I), the remaining air space was filled with dry argon and the tube was stoppered. The tube was mounted 5 cm from the 15-W lamp and was irradiated for 7 days at ambient temperature. There was no noticeable increase in temperature or pressure in the tube. The reaction mixture was analyzed directly by GC–MS: a ratio of 32.8% A (2-(pentafluoroethyl)imidazole, *m/e* 186) and 67.2% B (4-(pentafluoroethyl)imidazole, *m/e* 186) was obtained by integration of the peak areas. The reaction mixture was evaporated to dryness under reduced pressure, the residual material was suspended in 50 mL of water and was extracted 3 times with 50-mL samples of ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated to dryness. The residual material was applied to a column of 200 mL of silica gel and the column was eluted with ether. There was obtained (after crystallization) 1.39 g (24.9%) of A as colorless needles, mp 120–121 °C from chloroform, 2.57 g (46.0%) of B as colorless plates, mp 163–164 °C from ether–benzene.

This procedure is representative of all the preparative runs for the UV-induced perfluoroalkylation (including trifluoromethylation) of imidazole. In the case of $C_{10}F_{21}I$, 30 mL of Freon 113 (1,1,2-trichloro-1,2,2-trifluoroethane) was added as a cosolvent.

γ-Ray-Induced Perfluoroalkylation of Imidazole. Imidazole (10.2 g, 0.15 mol) and pentafluoroethyl iodide (7.4 g, 0.03 mol) were dissolved in 40 mL of methanol, and the solution was sealed in a Pyrex tube (2 × 22 cm) under argon and was irradiated at a ^{60}Co γ-ray source (2 × 10^5 R/h) for 7 days. The pressure increased as hydrogen was generated. The reaction mixture was analyzed by GC–MS and was then separated by column chromatogaphy as described for the UV reaction. The ratio of the products obtained by GC was 27.7% A and 72.3% B. The yields were 0.97 g (17.8%) of A and 2.18 (39.1%) of B.

For the the higher perfluoroalkyl iodides, irradiation time was reduced to 3 days.

Trifluoromethylation of Substituted Imidazoles. 4-Methylimidazole (8.21 g, 0.1 mol) and trifluoromethyl iodide (9.8 g, 0.05 mol) were dissolved in 40 mL of methanol, and the solution was irradiated under the same conditions described for UV perfluoroalkylation of imidazole. The reaction mixture was analyzed directly by ^{19}F NMR: integration of peak areas gave a ratio of 25.6% A (4-methyl-2-(trifluoromethyl)imidazole), 69.2% B (5-methyl-4-(trifluoromethyl)imidazole), and 5.1% C (5-methyl-2,4-bis(trifluoromethyl)imidazole). The only other ^{19}F NMR signal consisted of a small amount of trifluoromethane. GC–MS showed *m/e* 150 (A), 150 (B), 218 (C), and 82 (4-methylimidazole). The reaction mixture was evaporated to dryness under reduced pressure, the residual material was applied to a column of 200 mL of silica gel, and the column was eluted with ether and ethyl acetate. There was obtained (after crystallization) 1.61 g (21.5%) of A as colorless plates, mp 107–108 °C from benzene (lit.[2a] mp 103–105 °C from water), 4.76 g (63.4%) of B as plates, mp 178-179 °C from benzene–ethanol, and 0.32 g (2.9%) of C as needles, mp 174–176 °C from ether.

This procedure is representative of all preparative experiments for the trifluoromethylation of substituted imidazoles. Ratios of the imidazoles to trifluoromethy iodide were generally 2:1; for compounds of limited solubility in methanol and for the more costly imidazoles, a 1:1 ratio was used and triethylamine (3 equiv) was added as an acid acceptor. Isomer mixtures were separated on silica gel columns with ether or ether–ethyl acetate as the eluting solvent. In all cases, the order of elution of isomers was bis, 2-, 4-, and starting material.

In the trifluoromethylation of 1-methyl- and 1-ethylimidazole, the 2-CF_3 isomer could be separated from a mixture of the 4- and 5-isomers by silica gel chromatography, and the latter mixtures were resolved by preparative GC; on the other hand, the 2- and 5-isomers overlapped in GC elution and, thus, the combination of chromatographic procedures was found necessary.

Registry No. 2-(Trifluoromethyl)-1*H*-imidazole, 66675-22-7; 2-(pentafluoroethyl)-1*H*-imidazole, 81769-46-2; 2-(heptafluoropropyl)-1*H*-imidazole, 81769-47-3; 2-[1-(trifluoromethyl)tetrafluoroethyl]-1*H*-imidazole, 81790-00-3; 2-(tridecafluorohexyl)-1*H*-imidazole, 81769-48-4; 2-(pentadecafluoroheptyl)-1*H*-imidazole, 81769-49-5; 2-(heptadecafluorooctyl)-1*H*-imidazole, 81769-50-8; 2-(heneicosafluorodecyl)-1*H*-imidazole, 81769-51-9; 2-(pentafluorophenyl)-1*H*-imidazole, 81654-41-3; 4-(trifluoromethyl)-1*H*-imidazole, 33468-69-8; 4-(pentafluoroethyl)-1*H*-imidazole, 81769-52-0; 4-(heptafluoropropyl)-1*H*-imidazole, 81769-53-1; 4-[1-(trifluoromethyl)-tetrafluoroethyl]-1*H*-imidazole, 81790-01-4; 4-(tridecafluorohexyl)-1*H*-imidazole, 81769-54-2; 4-(pentadecafluoroheptyl)-1*H*-imidazole, 81769-55-3; 4-(heptadecafluorooctyl)-1*H*-imidazole, 81769-56-4; 4-(heneicosafluorodecyl)-1*H*-imidazole, 81769-57-5; 4-(pentafluorophenyl)-1*H*-imidazole, 81769-58-6; 2-methyl-4,5-bis(trifluoromethyl)-1*H*-imidazole, 81769-59-7; 2-methyl-4-(trifluoromethyl)-1*H*-imidazole, 33468-67-6; 5-methyl-2,4-bis(trifluoromethyl)-1*H*-imidazole, 81769-60-0; 4-methyl-2-(trifluoromethyl)-1*H*-imidazole, 66675-23-8; 5-methyl-4-(trifluoromethyl)-1*H*-imidazole, 81769-61-1; 2,5-dimethyl-4-(trifluoromethyl)-1*H*-imidazole, 81769-62-2; 4,5-dimethyl-2-(trifluoromethyl)-1*H*-imidazole, 81769-63-3; 2-phenyl-4-(trifluoromethyl)-1*H*-imidazole, 33469-36-2; 4-phenyl-2-(trifluoromethyl)-1*H*-imidazole, 81769-64-4; 5-phenyl-4-(trifluoromethyl)-1*H*-imidazole, 81769-65-5; 5-methyl-2-phenyl-4-(trifluoromethyl)-1*H*-imidazole, 81769-66-6; 5-nitro-2-methyl-4-(trifluoromethyl)-1*H*-imidazole, 81769-67-7; 2,4-bis(trifluoromethyl)-1*H*-imidazole-5-methanol, 81769-68-8; 2-(trifluoromethyl)-1*H*-imidazole-4-methanol, 80421-74-5; 4-(trifluoromethyl)-1*H*-imidazole-5-methanol, 59608-85-4; 1-methyl-2-(trifluoromethyl)-1*H*-imidazole, 70631-94-6; 1-methyl-4-(trifluoromethyl)-1*H*-imidazole, 81769-69-9; 1-methyl-5-(trifluoromethyl)-1*H*-imidazole, 81769-70-2; 1-ethyl-2-(trifluoromethyl)-1*H*-imidazole, 81769-71-3; 1-ethyl-4-(trifluoromethyl)-1*H*-imidazole, 81769-72-4; 1-ethyl-5-(trifluoromethyl)-1*H*-imidazole, 81769-73-5; 2-(trifluoromethyl)benzimidazole, 312-73-2; 4-(trifluoromethyl)benzimidazole, 392-11-0; 5-(trifluoromethyl)benzimidazole, 326-55-6; 4,7-bis(trifluoromethyl)benzimidazole, 81769-74-6; 1*H*-imidazole, 288-32-4; trifluoroiodomethane, 2314-97-8; pentafluoroiodoethane, 354-64-3; 1,1,1,2,2,3,3-heptafluoro-3-iodopropane, 754-34-7; 1,1,1,2,3,3,3-heptafluoro-2-iodopropane, 677-69-0; 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-6-iodohexane, 355-43-1; 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7-pentadecafluoro-7-iodoheptane, 335-58-0; 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-heptafluoro-8-iodooctane, 507-63-1; 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-heneicosafluoro-10-iododecane, 423-62-1; pentafluoroiodobenzene, 827-15-6; 1-methyl-1*H*-imidazole, 616-47-7; 1-ethyl-1*H*-imidazole, 7098-07-9; 2-methyl-1*H*-imidazole, 693-98-1; 4-methyl-1*H*-imidazole, 822-36-6; 2,4-dimethyl-1*H*-imidazole, 930-62-1; 4,5-dimethyl-1*H*-imidazole, 2302-39-8; 2-phenyl-1*H*-imidazole, 670-96-2; 4-phenyl-1*H*-imidazole, 670-95-1; 2-phenyl-4-methyl-1*H*-imidazole, 827-43-0; 4-nitro-2-methyl-1*H*-imidazole, 696-23-1; 1*H*-imidazole-4-methanol, 822-55-9; benzimidazole, 51-17-2.

Supplementary Material Available: ^{19}F NMR data for all compounds and elemental analyses (4 pages). Ordering information is given on any current masthead page.