# Fluorine Reactivity in 2-(Trifluoromethyl)imidazoles

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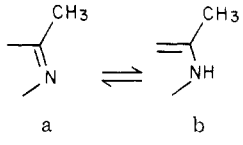
2-(Trifluoromethyl)imidazole undergoes facile alkaline hydrolysis to imidazole-2-carboxylic acid (in 0.1 N KOH at 30 °C, $t_{1/2}$ = 5.8 h), the 4-methyl derivative being 12-fold as reactive as the parent compound. The rate-limiting step is the solvent-assisted internal elimination of fluoride ion from the imidazolate anion to give a transient difluorodiazafulvene. Formation of the carboxylic acid is retarded by addition of fluoride ion, demonstrating the reversibility of the elimination step. Alcoholysis to orthoesters involves the same difluorodiazafulvene intermediate but is 200-fold slower than hydrolysis because of the weaker solvating power of alcohols. In alkaline media, the triethyl orthoester loses a molecule of alcohol to form the moderately stable diethoxydiazafulvene. Protonation of the imidazole ring retards acid hydrolysis of the orthoesters 60-fold relative to trialkyl orthobenzoates. 2-(Trifluoromethyl)imidazoles are converted directly to 2-cyanoimidazoles (90% yield) in aqueous ammonia; as in hydrolysis and alcoholysis, formation of the difluorodiazafulvene is rate limiting. The value of $k_{obsd}$ for cyanoimidazole formation increases with the *water* content of the ammonia solution and follows the rate law $k_{obsd} = k_r[H_2O]^n(f_{Im^-})$, with $n$ = 5.0. The reactivity of the trifluoromethyl group is lost following N-alkylation of the imidazole ring.

Our recent development of a facile synthetic route to 2-(trifluoromethyl)imidazoles (**1**)[2] prompted us to explore the utilization of such compounds as precursors of other 2-substituted imidazoles, some of which are not easily available through alternative routes.[3] In the course of our earlier studies, we noted that 2-(trifluoromethyl)imidazoles are rather unstable in aqueous base, even at ambient temperature, and are converted quantitatively to imidazole-2-carboxylic acids (**6**). A similar instability had already been observed for some 4-(trifluoromethyl)-imidazoles, providing a convenient route to the corresponding imidazole-4-carboxylic acids.[4a] A series of 4,5-diaryl-2-(trifluoromethyl)imidazoles has been prepared;[4b] according to their isolation procedures, these compounds appear to be significantly more stable to hydrolysis than **1**. On the other hand, 4,5-dialkyl-2-(trifluoromethyl)imidazoles were found unstable to hydrogen sulfide[4b] and are probably also sensitive to aqueous base.

A reasonable pathway for the hydrolysis of **1** (Scheme I) begins with an internal elimination of fluoride ion from the imidazolate ion (**2**) to form a transient difluorodiazafulvene species (**3**). Rapid addition of water to **3** produces **4**, which leads to **6** via the acyl fluoride **5**. The intermediacy of **3** is suggested by the demonstration that 1-methyl-2-(trifluoromethyl)imidazole (**7**) is unaltered after 24 h in aqueous 1 N base; furthermore, the rate constant for the hydrolysis of **1a** is a function of the degree of NH ionization (Figure 1). A reciprocal plot of $1/k_{obsd}$ vs. $[H_3O^+]$ (Figure 2) provides a kinetic $pK_2$ at 30 °C (10.11) which is almost identical with the value obtained by titration at 20 °C (10.00).[2] At high pH, the limiting rate constant ($k'_{obsd} = k_{obsd}/f_{Im^-}$) for the formation of **6a** at 30 °C is 2.00 × $10^{-3}$ $min^{-1}$ ($t_{1/2}$ = 5.8 h). 4-Methyl-2-(trifluoromethyl)imidazole (**1b**) is ca. 12-fold as reactive as **1a**, with $k'_{obsd}$ = 2.48 × $10^{-2}$ $min^{-1}$ ($t_{1/2}$ = 0.5 h). The 4-methyl group has also been found to enhance base-catalyzed proton exchange at C-5 of imidazoles,[5] and both phenomena may result from an increased hyperconjugative stabilization of the imine form (a) at the expense of the




a b

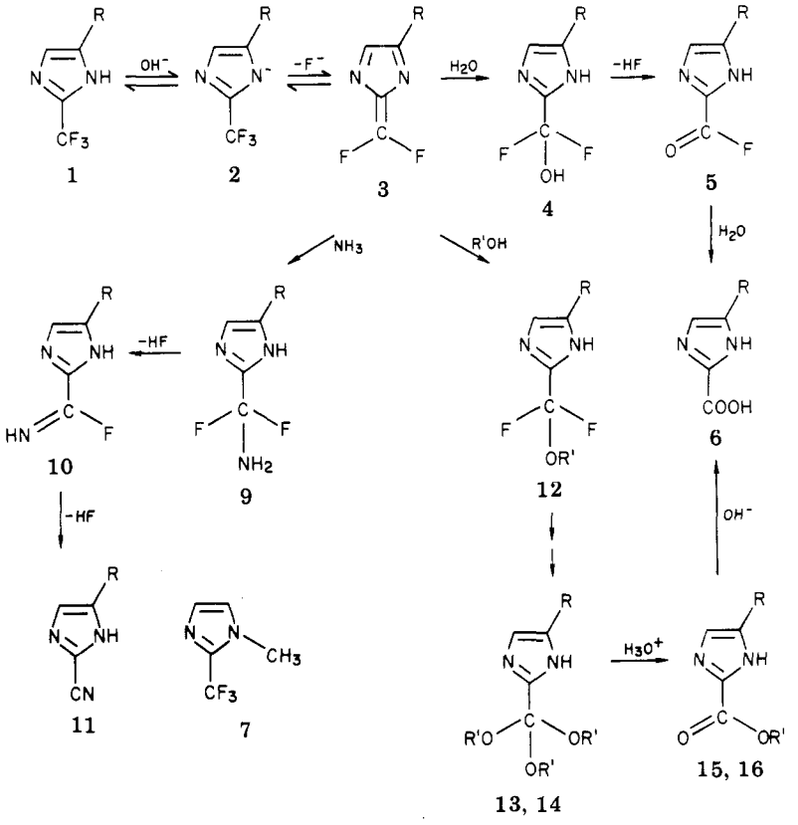
predominant enamine tautomer (b).

In the sequence of Scheme I, we consider the formation of **3** to be the rate-limiting step (see below); accordingly, the transient species should not be, and was not, detected by UV or NMR spectroscopy. In the pH range (8–9) in which the degree of ionization of **1** is very small, buffer-assisted proton abstraction is observed, and the conversion of **1** to **3** may approach a concerted elimination mechanism (E2). Thus, $k_{obsd}$ for **1a** is increased 20–70% in the presence of 0.1 M phosphate or borate buffer (pH 8–9). In the presence of strong bases in nonnucleophilic solvents (acetonitrile, dimethoxyethane, and dimethylformamide), **1** is unreactive; apparently, effective solvation is a critical factor in promoting the departure of fluoride ion (see below). The normally poor leaving ability of fluoride ion in both displacement[6] and elimination[7] reactions, even in protic solvents, and the stability of **7** argue against early ionization of the carbon–fluorine bond and an E1 mechanism; the reaction may then be considered to follow a vinylogous E1cB mechanism.

Fluoride ion is also a poor nucleophile, toward both tetrahedral[6a] and trigonal[8] carbon; yet the hydrolysis of **1a** (0.01 N KOH, 30 °C) is retarded 5.5-fold in the presence of 1 M KF. A plot of $[k'_{obsd}$ (with $F^-$)$]/k'_{obsd}$ vs. $[F^-]$ is linear, with a slope (the mass law constant[9]) = 4.5. Coincidentally, the hydrolysis of 6-(trichloromethyl)purine, which follows a pathway analogous to that of **1a**, is retarded by chloride ion to about the same extent.[9] This demonstration of reversibility between **2a** and **3a** adds support to the intermediacy of **3** and to the assignment

(1) Visiting Fellow, National Institutes of Health, 1977–present.
(2) H. Kimoto, K. L. Kirk, and L. A. Cohen, *J. Org. Chem.*, **43**, 3403 (1978).
(3) Another approach to 2-substituted imidazoles has recently been developed in this laboratory: K. L. Kirk, *J. Org. Chem.*, **43**, 4381 (1978).
(4) (a) J. J. Baldwin, P. A. Kisinger, F. C. Novello, and J. M. Sprague, *J. Med. Chem.*, **18**, 895 (1975); (b) J. G. Lombardino and E. H. Wiseman, *ibid.*, **17**, 1182 (1974); J. G. Lombardino, *J. Heterocycl. Chem.*, **10**, 697 (1973).
(5) Y. Takeuchi, K. L. Kirk, and L. A. Cohen, *J. Org. Chem.*, **43**, 3570 (1978).
(6) (a) E. R. Thornton, "Solvolysis Mechanisms", Ronald Press, New York, 1964, p 163; (b) D. S. Noyce and J. A. Virgilio, *J. Org. Chem.*, **37**, 2643 (1972).
(7) (a) C. H. DePuy and C. A. Bishop, *J. Am. Chem. Soc.*, **82**, 2535 (1960); (b) W. H. Saunders, Jr., S. R. Fahrenholtz, E. A. Caress, J. P. Lowe, and M. Schreiber, *ibid.*, **87**, 3401 (1965); (c) H. C. Brown and R. L. Klimisch, *ibid.*, **88**, 1425 (1966).
(8) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).
(9) S. Cohen and N. Dinar, *J. Am. Chem. Soc.*, **87**, 3195 (1965).

Scheme I



a, R = H; R' = $CH_3$, $C_2H_5$
b, R = $CH_3$; R' = $CH_3$, $C_2H_5$

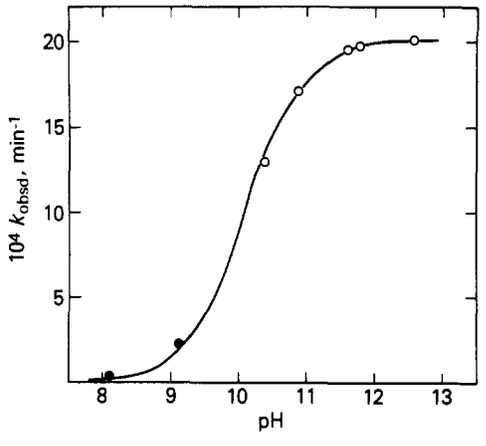



**Figure 1.** pH dependence for the hydrolysis of **1a** to **6a** at 30 °C: (○) without buffer; (●) with phosphate (pH 8.1) and borate (pH 9.1) buffers. Solid line represents the calculated curve based on $pK_2$ = 10.11 and $k'_{obsd}$ = 2.00 min$^{-1}$.

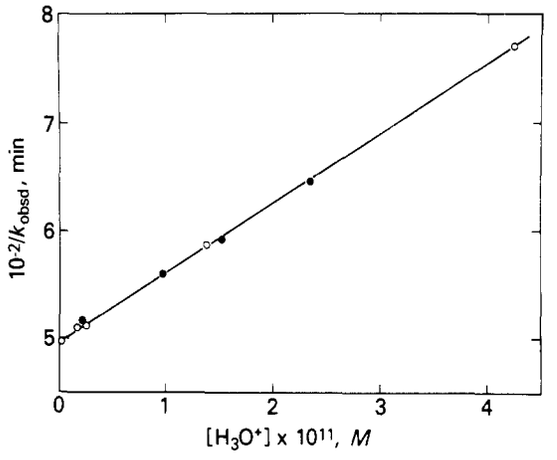



**Figure 2.** Reciprocal plot of $1/k_{obsd}$ vs. $[H_3O^+]$ for the conversion of **1a** to **6a** and to **11a** at 30 °C, according to the equation, $1/k_{obsd} = 1/k'_{obsd} + ([H_3O^+])k'_{obsd}K_2)$: (○) hydrolysis of **1a**; (●) ammonolysis of **1a**.

of its formation as the rate-limiting step.

Trifluoromethyl groups are quite resistant to nucleophilic attack, unless an E1cB mechanism can occur. The alkaline lability of **2** parallels that of *o*- and *p*-(trifluoromethyl)phenolate ions[10] and of the carbanions of *o*- and *p*-(trifluoromethyl)toluene,[11] these species undergoing a rapid loss of fluoride ion not exhibited by the meta isomers. Similar labilities have been demonstrated for 5-(trifluoromethyl)uracil,[12] 6-(trichloromethyl)purine,[9,13] 4- and 6-(trifluoromethyl)indoles,[14] and 2-(trichloromethyl)benzimidazole.[15] For all these cases, internal elimination of halide ion from an anionic species is the

(10) (a) R. G. Jones, *J. Am. Chem. Soc.*, **69**, 2346 (1947); (b) T. T. Sakai and D. V. Santi, *J. Med. Chem.*, **16**, 1079 (1973); (c) N. W. Gilman and L. H. Sternbach, *Chem. Commun.*, 465 (1971); (d) M. R. Pettit and J. C. Tatlow, *J. Chem. Soc.*, 3852 (1954); (e) R. Belcher, M. Stacey, A. Sykes, and J. C. Tatlow, *ibid.*, 3846 (1954); (f) W. B. Whalley, *ibid.*, 3016 (1949); (g) R. Filler and H. Novar, *J. Org. Chem.*, **26**, 2707 (1961); *Chem. Ind. (London)*, 1273 (1960).

(11) A. Streitweiser, Jr., and H. F. Koch, *J. Am. Chem. Soc.*, **86**, 404 (1964).

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(13) (a) S. Cohen, E. Thorn, and A. Bendich, *J. Org. Chem.*, **27**, 3545 (1962); (b) *Biochemistry*, **2**, 176 (1963).

(14) J. Bornstein, S. A. Leone, W. F. Sullivan, and O. F. Bennett, *J. Am. Chem. Soc.*, **79**, 1745 (1957).

(15) (a) G. Holan and E. L. Samuel, *J. Chem. Soc.*, 25 (1967); (b) B. C. Ennis, G. Holan, and E. L. Samuel, *ibid.*, 30 (1967).

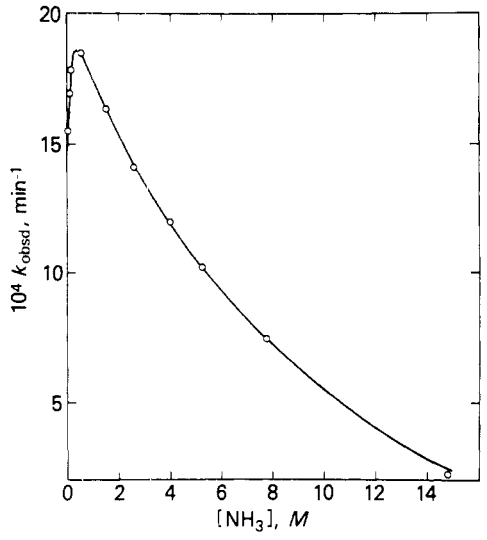
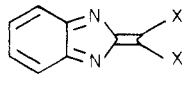



**Figure 3.** Dependence of $k_{obsd}$ for the ammonolysis of **1a** on [$NH_3$] at 30 °C.

most likely pathway. 2-(Trifluoromethyl)benzimidazoles react with nitrogen nucleophiles at high temperature[16] but appear to be completely stable in aqueous base.[16,17] Presumably, the difference in leaving ability of the halogens is enough to drive dearomatization, so that **8b** is



8a, X = F
b, X = Cl

formed readily but **8a** is not. Similarly, the stability to base of 4,5-diaryl-2-(trifluoromethyl)imidazoles[4b] may be due to the resistance of the system to a loss of diphenylethylene resonance.

The one-step conversion of 2-(trichloromethyl)benzimidazole to 2-cyanobenzimidazole has been shown to occur in aqueous or liquid ammonia.[15a] On the other hand, 6-(trichloromethyl)purine forms only the 6-carboxamide in aqueous ammonia.[13a] In an effort to convert **1a** directly to 2-cyanoimidazole (**11a**), the compound was first exposed to a stream of ammonia in refluxing dioxane or ethanol, without event. A slow conversion of **1a** to **11a** was found to occur in concentrated aqueous ammonia and, surprisingly, $k_{obsd}$ for this conversion increased with a *decrease* in the concentration of ammonia (Figure 3). This trend continued until the pH of the solution became too low to effect total ionization of **1a**, at which point $k_{obsd}$ began to decrease again. The maximum rate of conversion was realized with 3–5% ammonia, with isolated yields of **11a** greater than 90%. In no case was amide formation observed, and only at ammonia concentrations below 0.02 M did hydrolysis of **1a** become significantly competitive. At low ammonia concentrations, the rate constants for conversion of **1a** to **6a** and to **11a** coincide (Figure 2); it seems likely, therefore, that the two products arise from a common intermediate and that formation of that intermediate (**3a**) must be rate limiting. The ammonolysis intermediates, **9** and **10**, are formulated in accordance with the pathway suggested for the formation of 2-cyanobenzimidazole,[15a] although the failure of **10** to hydrolyze to the carboxamide is surprising. In parallel with its

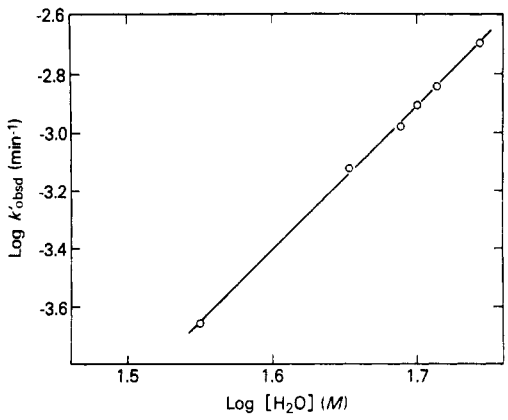



**Figure 4.** Plot of log $k'_{obsd}$ for ammonolysis of **1a** (30 °C) vs. log [$H_2O$].

stability to hydroxide ion, **7** showed no significant reactivity toward aqueous ammonia.

According to the pathway shown in Scheme I, the concentration of ammonia in the medium should not influence the rate of formation of **11**, since the first reaction with ammonia to form **9** follows the rate-limiting step. On the other hand, the rate of formation of **3** seems to depend very strongly on solvation of the departing fluoride ion.[7c] In concentrated ammonia solutions, a large fraction of the water molecules are undoubtedly locked into a hydrogen-bonded network with the solute;[18] thus, the availability of *free* water for solvation of fluoride ion should increase with decreasing ammonia content. Indeed, a linear correlation can be demonstrated (eq 1 and 2 and Figure 4) between log $k'_{obsd}$ for the formation of **11a** (or **3a**) and the

$$k'_{obsd} = k_r[H_2O]^n \quad (1)$$

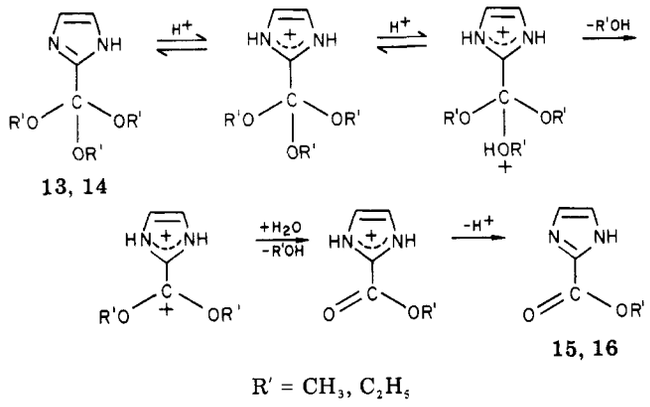
$$\log k'_{obsd} = \log k_r + n \log [H_2O] \quad (2)$$

log of the molar concentration of water in the medium. The slope of Figure 4 ($n$ in eq 2) has a value of 5.0, which may represent the number of water molecules needed for effective solvation of the fluoride ion; $k_r$ ($3.9 \times 10^{-12}$ $M^{-n}$ $min^{-1}$) is the extrapolated rate constant for the formation of **3a** at an infinitely low concentration of water. The effectiveness of increasingly aqueous media might also be interpreted as the result of increased polarity alone; however, the transition state for the formation of **3** involves dispersion of a ground state negative charge, and increased polarity of the medium should have little effect (even a retardation) in such a case. As already noted, **2a** is unreactive in dipolar, aprotic solvents.

The importance of fluoride ion solvation is also evident from studies of the alcoholysis of **1a**. In methanolic KOH at 30 °C, the rate of conversion of **1a** to the orthoester (**13a**) is almost 200-fold less than that for hydrolysis to **6a**. As for both the hydrolysis and ammonolysis reactions, formation of **3a** is considered to be the rate-limiting step. Addition of alcohol (or alkoxide ion) to form **12a** is followed by two further elimination–addition sequences to produce **13a**. The reduction in $k_{obsd}$ may result, therefore, from the fact that methanol is significantly inferior to water in its ability to solvate fluoride ion. The temperature dependence for methanolysis of **1a** provides values of $E_a$ = 24.9 kcal/mol, $\Delta H^{\ddagger}$ = 24.3 kcal/mol, $\Delta F^{\ddagger}$ = 26.5 kcal/mol, and $\Delta S^{\ddagger}$ = −7.4 eu (all calculated at 30 °C). For an E1cB mechanism, $\Delta S^{\ddagger}$ should be slightly positive;[19] when this

(16) R. Belcher, A. Sykes, and J. C. Tatlow, *J. Chem. Soc.*, 4159 (1954); E. S. Lane, *ibid.*, 534 (1955).
(17) W. T. Smith, Jr., and E. C. Steinle, Jr., *J. Am. Chem. Soc.*, **75**, 1292 (1953).
(18) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", Interscience, New York, 1966, p 333.
(19) J. Hine, R. Wiesboeck, and O. B. Ramsay, *J. Am. Chem. Soc.*, **83**, 1222 (1961).

Scheme II

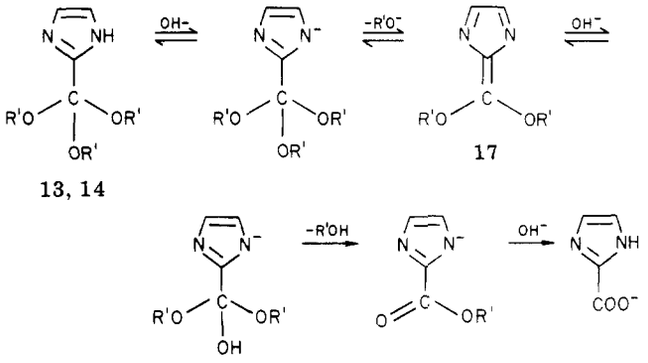


13, 14

15, 16

R′ = $CH_3$, $C_2H_5$

Scheme III



13, 14

17

R′ = $CH_3$, $C_2H_5$

factor is balanced against the degree of participation of solvent molecules in removal of fluoride ion, however, the value obtained for $\Delta S^{\ddagger}$ seems quite reasonable. Values of $k_{obsd}$ and the temperature dependence for ethanolysis of **1a** almost coincide with those for methanolysis; this result is surprising in that one would expect ethanol to be somewhat less effective in ion solvation.

The (trifluoromethyl)imidazoles and the orthoesters show UV absorption only below 225 nm, and reaction kinetics could not be followed continuously (as for the conversion of **1** to **6** or **11**); accordingly, aliquots of the alcoholysis reaction mixtures were diluted with aqueous hydrochloric acid, and the absorption of the corresponding carboxylic ester was measured. Prior to spectral assay of the esters, particularly **15a**, samples of orthoester in aqueous acid must be warmed or kept at 30 °C for several hours to effect complete hydrolysis. For the conversion of **13a** to **15a** (1 N HCl, 30 °C), $k_{obsd} = 4.67 \times 10^{-2}$ min$^{-1}$ ($t_{1/2}$ = 14.8 min), and for the conversion of **14a** to **16a**, $k_{obsd}$ = 0.214 min$^{-1}$ ($t_{1/2}$ = 3.2 min); under the same conditions, the conversion of triethyl orthobenzoate to ethyl benzoate occurs 60 times as fast ($k_{obsd}$ = 13 min$^{-1}$)[20a] as the hydrolysis of **14a** and 280 times as fast as that of **13a**. We attribute the unusual stabilities of **13a** and **14a** to the fact that ring protonation (Scheme II) electrostatically retards further protonation on oxygen[21a] or formation of the carbonium ion[21b] as the rate-limiting step.[21c] The trimethyl orthoester (**13a**) is 4.6-fold as stable to acid hydrolysis as is the triethyl orthoester (**14a**); similarly, the hydrolysis of trimethyl orthobenzoate is ca. fivefold slower than that of triethyl orthobenzoate.[20] In both series, the difference can be attributed to the greater electron-releasing ability of the ethyl group,[22] resulting in enhanced oxygen basicity in the orthoester and in more effective stabilization of the carbonium ion.

In the reaction of **1a** with methanolic KOH, the orthoester **13a** is obtained in 75–80% yield after 50 h of reflux, together with small amounts of the carboxylic acid (**6a**). Since the content of **6a** increases slowly with time (as determined by UV analysis of reaction aliquots), we believe that it is formed primarily via base-promoted breakdown of the orthoester (Scheme III).[23] Such breakdown occurs to a far greater extent during ethanolysis, a consequence of the higher reflux temperature of ethanol. Thus, after 8 h of reflux in ethanolic KOH, the product consists of 20% **14a** and 80% **6a**. When a solution of pure **13a** in ethanolic KOH is heated at reflux, the compound is gradually transformed into **14a** by successive elimination–addition steps involving intermediate dialkoxydiazafulvenes (**17**). After 5 h of reflux, the reaction mixture contains 52% **6a** and 26% **14a**. The mass spectrum, at this point, also reveals small amounts of the ester **16a**, the mixed diethoxymethoxy orthoester, and the diethoxydiazafulvene (**17**). Following borohydride reduction of the reaction mixture, the mass spectral signal for **17** is replaced by that of imidazole-2-methanol. Thus, **17** is not formed by mass spectral fragmentation of an orthoester but is a reaction intermediate of moderate stability. Orthoester interchange is rarely observed in alkaline media, and elimination to ketene acetals requires forcing conditions;[21c,24] the facility of such reactions, in the present case, is probably the result of the ease of formation of the imidazolate anion and the E1cB pathway. The apparent stability of **17**, relative to **3**, may be due to more effective overlap by the lone pairs of oxygen than of fluorine in resonance stabilization of the fulvene species; on the other hand, the greater electrophilic character of the difluorovinyl group may simply accelerate the addition of nucleophiles to **3**.

## Experimental Section[25]

**Imidazole-2-carboxylic Acid (6a).** A solution of 68 mg (0.5 mmol) of **1a**[2] in 50 mL of 1 N sodium hydroxide was stored at ambient temperature for 100 h. The solution was acidified to pH 3 with 1 N hydrochloric acid at 0 °C and was evaporated to dryness under reduced pressure. The residue was extracted with two 10-mL portions of concentrated hydrochloric acid, and the combined extracts were evaporated to dryness under reduced pressure. The colorless residual solid was dissolved in 2 mL of water, and the solution was adjusted to pH 2.0 with 20% sodium hydroxide. The solution was refrigerated overnight and gave 26.4 mg of colorless plates; an additional 27.3 mg was obtained from the mother liquor for a total yield of 53.7 mg (96%) of **6a**, mp 163–164 °C (lit.[26] mp 163–164 °C).

**4-Methylimidazole-2-carboxylic Acid (6b).** The hydrolysis of **1b**[2] followed the procedure used for **1a**, except that the reaction time was reduced to 50 h. The product was recrystallized from

(20) (a) R. H. DeWolfe and J. L. Jenser, *J. Am. Chem. Soc.*, **85**, 3264 (1963); (b) J. G. Fullington and E. H. Cordes, *J. Org. Chem.*, **29**, 971 (1964).

(21) (a) A. J. Kresge and R. J. Preto, *J. Am. Chem. Soc.*, **87**, 4593 (1965); (b) A. M. Wenthe and E. H. Cordes, *ibid.*, **87**, 3173 (1965); (c) for a review of the chemistry of orthoesters, see E. H. Cordes in "The Chemistry of Carboxylic Acids and Esters", S. Patai, Ed., Interscience, New York, 1969, Chapter 13.

(22) S. Takahashi, L. A. Cohen, H. K. Miller, and E. G. Peake, *J. Org. Chem.*, **36**, 1205 (1971).

(23) The water content of the methanolic KOH is too low to permit significant hydration of fluoride ion but adequate to effect fairly rapid hydrolysis of **15** and **16**.

(24) S. M. McElvain and G. R. McKay, Jr., *J. Am. Chem. Soc.*, **77**, 5601 (1955); S. M. McElvain and R. E. Starn, Jr., *ibid.*, **77**, 4571 (1955); S. M. McElvain and J. T. Venerable, *ibid.*, **72**, 1661, (1950).

(25) Melting points are uncorrected. Microanalyses and mass spectral measurements were performed by the Microanalytical Services Section of this Laboratory, under the direction of Dr. David F. Johnson. Wherever possible, identity and homogeneity of each compound were confirmed by NMR and mass spectra and by TLC.

(26) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 383 (1949).

Table I. Spectral Properties of 2-Substituted Imidazoles

| compd | $\lambda_{max}(H_2O)$, nm (log $\epsilon$) | | | $\delta$, ppm[a] | |
|---|---|---|---|---|---|
| | $ImH^+$ | Im | $Im^-$ | H-4, H-5 | other |
| 1a | 219 (3.87) | 217 (3.85) | 220[b] | 7.29 | |
| 1b | 228 (3.78) | 225 (3.74) | 228[b] | 6.96 | 2.26 (4-$CH_3$) |
| 6a | 238 (4.06) | 236 (4.06)[c] | 248 (4.08) | d | |
| 6b | 251 (3.90) | 248 (3.90)[c] | 258 (3.93) | | |
| 7 | | 221 (infl) | | 7.02 (H-4)<br>6.92 (H-5) | 3.76 (N-$CH_3$)[e] |
| 11a | | 247 (4.03) | 256 (4.07) | 7.39 | |
| 11b | | 258 (4.16) | 265 (4.19) | 6.99 | 2.19 (4-$CH_3$) |
| 13a | | 214 (3.86) | | 7.15 | 3.23 ($OCH_3$) |
| 15a | 249 (4.04) | 260 (4.08) | 276 (4.12) | 7.30 | 3.79 ($OCH_3$) |

[a] NMR spectra were measured in hexadeuterioacetone solution, except for 7 ($CDCl_3$) and 6a and 6b ($D_2O$). [b] Value of $\epsilon$ was not determined because of instability in strong base. [c] Exists as a zwitterion in water. [d] $ImH^+$-COOH, $\delta$ 7.60; $ImH^+$-$COO^-$, $\delta$ 7.59; Im-$COO^-$, $\delta$ 7.41; $Im^-$-$COO^-$, $\delta$ 7.14. [e] $J_{HF}$ = 0.8 Hz; $J_{HH}$ = 1.0 Hz.

0.01 N hydrochloric acid as fine needles: 63% yield; mp 165–167 °C dec (lit.[27] mp 175 °C); IR (KBr) 1626 $cm^{-1}$ ($COO^-$).

**Imidazole-2-carbonitrile (11a).** A solution of 68 mg of **1a** in 50 mL of 5% aqueous ammonia was stored at ambient temperature for 100 h.[28] The solution was evaporated to dryness under reduced pressure, and the colorless, solid residue was dissolved in 20 mL of 0.1 M phosphate buffer (pH 7). The solution was extracted with two 50-mL portions of ether, and the combined ether extracts were dried ($Na_2SO_4$) and evaporated to give a crystalline residue. Recrystallization from benzene gave 42.8 mg (92%) of **11a** as colorless needles: mp 176–177 °C (lit.[29] mp 176–178 °C); IR (KBr) 2262 $cm^{-1}$ (CN); $pK_2$ = 8.84.

**4-Methylimidazole-2-carbonitrile (11b).** The synthesis of **11b** from **1b** followed the procedure used with **1a**, except that the reaction time was reduced to 50 h. The product was recrystallized from benzene as clusters of prisms: 87% yield; mp 170–171 °C; IR(KBr) 2222 $cm^{-1}$ (CN).

Anal. Calcd for $C_5H_5N_3$ (107.11): C, 56.06; H, 4.71; N, 39.23. Found: C, 55.58; H, 4.86; N, 39.38.

**1-Methyl-2-(trifluoromethyl)imidazole (7).** To a stirred solution of 68 mg (0.5 mmol) of **1a** in 10 mL of dry tetrahydrofuran was added 40 $\mu$L (0.56 mmol) of thallous ethoxide (Aldrich Chemical Co.) at ambient temperature. A slightly brownish precipitate formed immediately, and stirring was continued for 1 h. Methyl iodide (0.324 mL, 5.2 mmol) was added slowly, and stirring was continued for 3 h after addition. The reddish yellow precipitate was filtered, and the solution was evaporated to dryness. The residue was dissolved in 20 mL of ethyl acetate, and the solution was washed with 20 mL of 0.1 M phosphate buffer (pH 7). The organic layer was dried ($Na_2SO_4$) and evaporated to give 8 mg of a pale yellow liquid. Further purification was effected by preparative TLC (silica gel GF), with ethyl acetate as developing solvent, to give ca. 2 mg of a pale yellow solid. Identity was confirmed by NMR (Table I) and mass spectra.

**2-(Trimethoxymethyl)imidazole (13a).** To a solution of **1a** (68 mg, 0.5 mmol) in 20 mL of absolute methanol was added 1.0 g (18 mmol) of potassium hydroxide, and the mixture was heated at reflux for 50 h.[30] The solution was cooled to 0 °C, 0.1 g of sodium bicarbonate was added as a buffer, and the pH was adjusted to 8.0–8.5 with 15 mL of 1 N hydrochloric acid. The solution was extracted with three 20-mL portions of ethyl acetate, and the combined extracts were dried ($Na_2SO_4$) and evaporated to give 67 mg (78%) of colorless crystals. Recrystallization from benzene gave needles, mp 145–147 °C. The structure was confirmed by NMR (Table I) and mass spectra.

Anal. Calcd for $C_7H_{12}N_2O_3$ (172.18): C, 48.83; H, 7.03; N, 16.27. Found: C, 48.87; H, 7.28; N, 16.32.

**2-(Ethoxycarbonyl)imidazole (16a).** A solution of 25 mg (0.18 mmol) of **1a** and 280 mg (5 mmol) of potassium hydroxide in 5 mL of absolute ethanol was refluxed for 6 h. The solution was cooled, neutralized with 1 N hydrochloric acid, and evaporated to dryness. The colorless residue was extracted with two 20-mL portions of ethyl acetate, and the combined extracts were dried ($Na_2SO_4$) and evaporated to give 0.1 g of oil. The oil crystallized overnight and the product was recrystallized from ether, mp 173–174 °C (lit.[3] mp 178–179 °C).

**2-(Methoxycarbonyl)imidazole (15a).** A solution of 34 mg (0.25 mmol) of **1a** and 1.0 g of potassium hydroxide in 10 mL of methanol was refluxed for 13 h. The solution was cooled and acidified with 1 N hydrochloric acid; after 3 h of storage at ambient temperature, a precipitate of potassium chloride was removed and the filtrate was evaporated to dryness. The colorless residue was extracted with two 20-mL portions of ethyl acetate, and the combined extracts were dried ($Na_2SO_4$) and evaporated. The residue crystallized from benzene–methanol as needles, mp 195.5–196 °C (lit.[31] mp 194–195 °C).

**Kinetic and Analytical Methods.** Rates of formation of **6a**, **6b**, and **11a** were followed by UV spectroscopy at the wavelengths given in Table I for the anions of these compounds. For the alcoholysis reactions, aliquots were removed, and UV spectra were recorded after dilution with water. The absorption intensity at 248 nm provided a measure of the concentration of **6**. Separate aliquots were added to 1 N hydrochloric acid, and UV absorption at 250 nm was followed until no further increase was observed. The final intensity, after adjustment for the contribution of **6** at this wavelength, provided a measure of the concentration of **15** or **16** and, thus, of **13** or **14**, respectively.

**Registry No.** **1a**, 66675-22-7; **1b**, 66675-23-8; **6a**, 16042-25-4; **6b**, 70631-93-5; **7**, 70631-94-6; **11a**, 31722-49-3; **11b**, 70631-95-7; **13**, 70631-96-8; **14**, 70631-97-9; **15**, 17334-09-7; **16**, 33543-78-1.

(27) W. John, *Chem. Ber.*, **68**, 2283 (1935).

(28) The reaction time can be reduced 15–20% by use of 1–2% ammonia solutions; however, the yield may be somewhat diminished by hydrolysis to **1a**.

(29) P. J. Lont, H. C. van der Plas, and A. Koudijs, *Recl. Trav. Chim. Pays-Bas*, **90**, 207 (1971).

(30) With shorter reaction times, the product is contaminated with small amounts of **1a**, and its purification proved difficult.

(31) S. Iwasaki, *Helv. Chim. Acta*, **59**, 2738 (1976).