Council, and the donors of the Petroleum Research Fund, administered by the American Chemical Society. Continuing support is generously provided by a grant from the National Science Foundation. The FT-80A NMR used in these studies was purchased with the aid of a Special Grant from the Camille and Henry Dreyfus Foundation.

Registry No. 1 (isomer 1), 52167-27-8; 1 (isomer 2), 89849-44-5; **2**, 5194-85-4; **3a** (isomer 1), 89849-45-6; **3a** (isomer 2), 89849-46-7; **3a** (isomer 3), 89849-47-8; **3a** (isomer 4), 89849-48-9; **3b** (isomer 1), 89849-49-0; **3b** (isomer 2), 89849-50-3; **3b** (isomer 3), 89849-51-4; **3b** (isomer 4), 89849-52-5; (*E*)-**4a**, 82194-08-9; (*Z*)-**4a**, 82194-09-0; **5a** (isomer 1), 89849-53-6; **5a** (isomer 2), 89849-54-7; **5b** (isomer 1), 89849-55-8; **5b** (isomer 2), 89849-56-9; (*E*)-**6** (R = H), 82194-10-3; (*E*)-**6** (R = Me), 89849-57-0; **7a**, 59222-87-6; **7b**, 89849-58-1; **7c**, 89849-59-2; **8a**, 82194-07-8; **8b**, 89849-60-5; **8c**, 89849-61-6; **9a**, 82194-12-5; **9b**, 85687-68-9; **9c**, 89849-62-7; $(CH_3)_2C{=}CH(CH_2)_2C(O)CH_3$, 110-93-0; MeI, 74-88-4; $MeO(CH_2)_2I$, 4296-15-5; $MeO(CH_2)_2Br$, 6482-24-2; $BrCH_2C(O)OEt$, 105-36-2; acetone oxime, 127-06-0; 1,3-dichloro-2-butene, 926-57-8; 1,3-dichloropropene, 542-75-6; *trans*-cinnamyl chloride, 21087-29-6; (*Z*)-2-butanone oxime, 10341-59-0.

Photochemistry of Diazonium Salts. 5. Syntheses of 2,4-Difluoroimidazole-5-carboxylic Acid and Related Compounds[1f]

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Catalytic hydrogenolysis, effective for the synthesis of 2-aminoimidazoles from 2-(arylazo)imidazoles, cannot be used to prepare 2-amino-4-fluoroimidazoles because the fluorine atom is lost simultaneously; formamidinesulfinic acid, however, achieves the required conversion in good yield. Ethyl 2,4-difluoroimidazole-5-carboxylate is obtained by photolysis of ethyl 2-diazonio-4-fluoroimidazole-5-carboxylate in fluoroboric acid. The ester is saponified to the acid in 1 N base (without loss of fluorine) but is stable in 0.05 N base; the ester also resists ammonolysis to the carboxamide or hydride reduction to the carbinol. Ammonolysis of ethyl 2-amino-4-fluoroimidazole-5-carboxylate is successful, however, and the resulting carboxamide is converted, via diazotization and photolysis, into 2,4-difluoroimidazole-5-carboxamide. *N*-Alkyl derivatives of the difluoro ester undergo facile hydride reduction of the ester function, but only with prior reductive loss of fluorine at C-2. The difluoro acid is stable to diborane reduction over 1 month. These examples of resistance to normal carboxyl modification are ascribed to the facile generation of the imidazolate ion in basic media and a resulting large increase in electron density at the carbonyl carbon by resonance overlap.

The discovery and development of the photochemical Schiemann reaction,[1] in this laboratory, led to the synthesis and biological investigation of a variety of ring-fluorinated imidazoles; for example: 4-fluoroimidazole-5-carboxamide riboside, a broad-spectrum antiviral agent;[2] 2-fluorourocanic acid, a potent inhibitor of urocanase;[3] and 4-fluoroimidazole-TRH, an analogue of thyrotropin-releasing hormone (TRH) that is inactive in pituitary functions but shows strong cardiovascular and central nervous system activities.[4] The 2-fluoro analogue of L-histidine shows bacteriostatic,[1e,5] antiviral,[6] antiparasitic,[7] and antileukemic[8] properties; furthermore, it can partially substitute for histidine in protein biosynthesis in both bacterial[5] and mammalian[9] systems. In contrast, 4-fluoro-L-histidine shows none of these properties.[1e,5-9]

Fluorine at C-2 of the imidazole ring is readily displaced by nucleophiles if a ring nitrogen is first protonated.[1c,7,10] We had hoped to utilize this property as a basis for affinity labeling of histamine and histidine recognition sites in proteins; to date, however, we have found no clear case of irreversible binding. Although 4-fluoroimidazoles show no reactivity toward nucleophiles, one of the fluorine atoms in 4-5-difluoroimidazole is subject to facile displacement;[11] we anticipated, therefore, that a second fluorine atom would also enhance the reactivity of a 2-fluoroimidazole.

In addition, we hoped that biological studies with difluorohistidine might help explain the striking differences in biological activity between 2- and 4-fluorohistidine. Differentiation based on steric effects seems improbable, in view of the very small size of the substituent.[1e] Basicity of the imidazole ring should not be a factor since both compounds are very weak bases (pK 1-2) and show little difference in basicity.[12] On the other hand, 2-fluoroimidazoles are somewhat more acidic than the 4-fluoro isomers[12] and we could not ignore the possibility that the 2-fluoroimidazolate ion is the active species in biological

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(3) Klee, C. B.; Kirk, K. L.; Cohen, L. A.; McPhie, P. *J. Biol. Chem.* **1975**, *250*, 5033-5040. Klee, C. B.; LaJohn, L. E.; Kirk, K. L.; Cohen, L. A. *Biochem. Biophys. Res. Commun.* **1977**, *75*, 674-681.

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(6) De Clercq, E.; Billiau, A.; Edy, V. G.; Kirk, K. L.; Cohen, L. A. *Biochem. Biophys. Res. Commun.* **1978**, *82*, 840-846.

(7) Work in progress.

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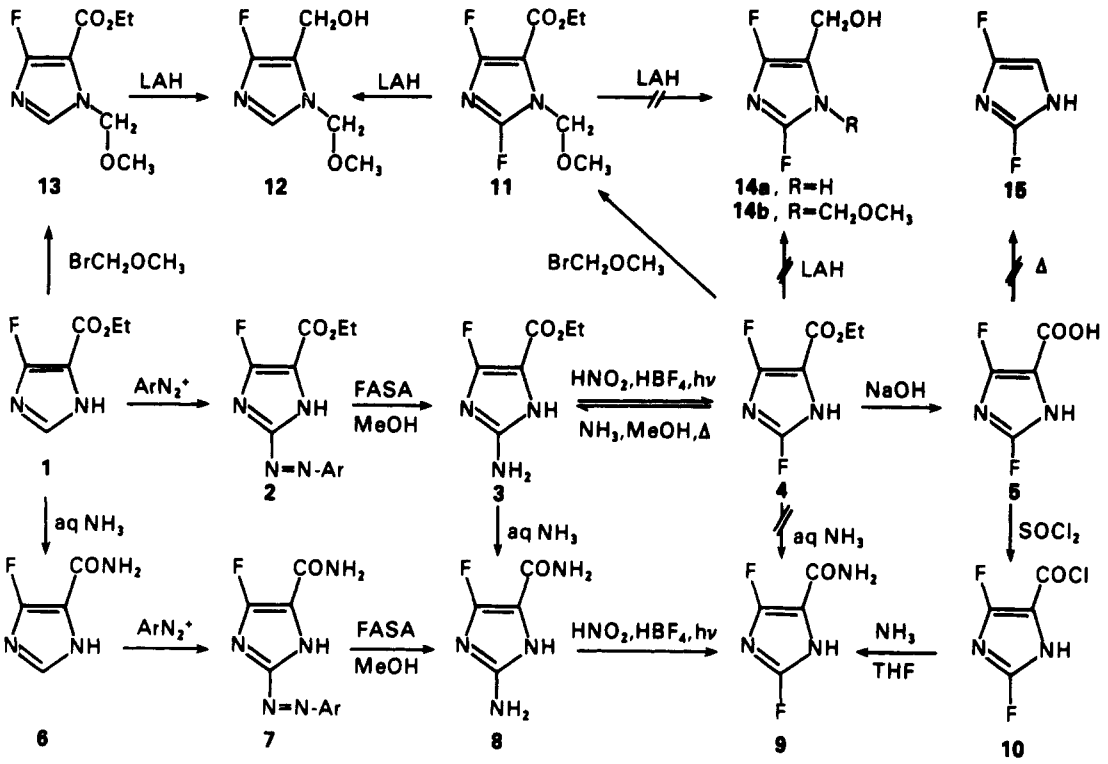
(9) Torrence, P. F.; Friedman, R. M.; Kirk, K. L.; Cohen, L. A.; Creveling, C. R. *Biochem. Pharmacol.* **1979**, *28*, 1565-1567. Klein, D. C.; Kirk, K. L.; Weller, J. L.; Oka, T.; Parfitt, A.; Owen, I. S. *Mol. Pharmacol.* **1976**, *12*, 720-730. Klein, D. C.; Weller, J. L.; Kirk, K. L.; Hartley, R. W. *Ibid.* **1977**, *13*, 1105-1110. Creveling, C. R.; Kirk, K. L.; Cohen, L. A., manuscript in preparation.

(10) The neutral imidazole is also reactive toward nucleophiles, but significantly less so.

(11) Reepmeyer, J. C.; Kirk, K. L.; Cohen, L. A., manuscript in preparation.

(12) Cf. Yeh, H. C.; Kirk, K. L.; Cohen, L. A.; Cohen, J. S. *J. Chem. Soc., Perkin Trans. 2* **1975**, 928-934.

Scheme I



systems. The 2,4-difluoroimidazoles, of course, would be even more acidic. Finally, we had to consider conformational differences in the amino acid side chain (perhaps involving hydrogen bonds to fluorine) as a basis for biological selection.[13] Thus, we were provided with an ample number of motives to pursue synthetic routes to 2,4-difluoroimidazoles. Practical syntheses of difluorohistamine and difluorohistidine have not yet been achieved; however, we have now obtained some simpler members of the series, but even these compounds proved elusive and challenging in their chemistry.

Results and Discussion

In view of the chemical reactivity of 2-fluoroimidazoles,[1c,14] we anticipated that electronegative groups at C-4 might render the 2-fluoro substitutent even more reactive. Accordingly, our major efforts were directed at the introduction of appropriate C-2 functionality in preformed 4-fluoroimidazoles.[15] Ethyl 4-fluoroimidazole-5-carboxylate (**1**)[1b] readily undergoes aryldiazonium coupling at C-2 (**2**) (Scheme I). Catalytic hydrogenolysis of the azo linkage provided the expected 2-aminoimidazole[15] but invariably resulted in simultaneous loss of fluorine.[16] Classical chemical reducing agents, such as stannous chloride or sodium dithionite, gave negligible yields of **3** or intractable tars; however, formamidinesulfinic acid (FASA)[17] proved effective in the reductive conversion of **2** to **3** in 65% yield. The photochemical transformation of **3** to **4**, via the diazonium fluoroborate, proceeded smoothly, with an isolated yield (53%) better than we had ever achieved for monofluoroimidazoles. Thus, the compound that was to serve as the key intermediate for a variety of metabolite analogues was finally obtained, and in unexpectedly high yield.

Substituted imidazole-4-carboxamides are of interest as potential antiviral agents.[6] Previously, we had converted **1** to the carboxamide **6** by treatment with concentrated aqueous ammonia.[1b] Under the same conditions, **4** remained unchanged after 8 weeks at ambient temperature. When a solution of **4** in methanolic ammonia was heated at 90 °C (sealed tube, 7 days), fluorine at C-2 was displaced slowly to regenerate **3**. Ammonolysis of **3**, on the other hand, proceeded normally to give **8**. The latter compound was also obtained by reduction of **7** with formamidinesulfinic acid and **7** was prepared by arylazo coupling to **6**. Neither of these pathways for the conversion of **1** to **8** offered an impressive overall yield, and the purification of **8** proved particularly difficult. Our ultimate goal was achieved, however, by the photochemical conversion of **8** to **9** in 28% yield. In contrast to the resistance of **4** to ester ammonolysis, the compound was easily saponified to the acid **5** in 1 N sodium hydroxide (but not in 0.05 N base). In the presence of thionyl chloride, **5** was easily converted into the acid chloride **10** which, without isolation,[18] was exposed to ammonia in tetrahydrofuran and **9** was obtained in nearly quantitative yield. Thus, a third route had been developed, which bypassed **8** entirely and provided **9** in 24% overall yield from **1**.

We offer the following tentative explanation for these seemingly contradictory results. In aqueous ammonia or 0.05 N base, **4** exists almost entirely as its imidazole anion (pK_2 ca. 5);[12] the negative charge on nitrogen increases electron density both at C-2 and at the ester carbonyl via resonance overlap, retarding nucleophilic attack at either

(13) Evidence for the existence of related intramolecular N-H···F-C bonds has been reported: Kimoto, H.; Fujii, S.; Cohen, L. A. *J. Org. Chem.* **1982**, *47*, 2867–2872.

(14) Takeuchi, Y.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1979**, *44*, 4243–4246.

(15) Nagai, W.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1973**, *38*, 1971–1974.

(16) A more detailed study of this phenomenon has been completed: Takeuchi, Y.; Kirk, K. L.; Cohen, L. A., manuscript in preparation.

(17) This reagent has been used for the reduction of ketones and nitro groups: Nakagawa, K.; Minami, K. *Tetrahedron Lett.* **1972**, 343–346. Huang, S.; Chen, T. *J. Chin. Chem. Soc.* **1975**, 91–94; *Chem. Abstr.* **1975**, *83*, 42945*f*.

(18) The spontaneous formation of a tricyclic diacyldiimidazole from **10** has not been excluded.

position. In the less polar solvent, methanol, pK_2 for **4** has been raised sufficiently to permit the existence of a small concentration of neutral **4**, which now undergoes slow nucleophilic displacement by ammonia at C-2. Finally, in 1 N base, both positions are again protected by resonance stabilization in the anion, but the base concentration is now adequate to overcome the reduced electrophilicity of the carbonyl group. Evidently, there is an additional selection factor in that ammonia prefers addition to C-2 while hydroxide ion prefers addition to the carbonyl. The 2-amino group in **3** reduces the acidity of the ring NH sufficiently to permit normal ester ammonolysis to **8**, similarly to the conversion of **1** to **6**.

Our first synthesis of 4-fluorohistidine began with the hydride reduction of **1** to the corresponding primary alcohol.[1b] In parallel with our failure to effect ammonolysis of **4**, however, every attempt to achieve hydride reduction of **4** to **14a** also failed; the reaction mixtures were complex, usually containing **1** and a variety of uncharacterized products. Ester reduction was readily achieved, however, following protective alkylation of N-1 (**11**),[19] but only with prior reductive loss of fluorine at C-2 (**12**). Synthesis of **12**, by alkylation of **1** to **13** and hydride reduction of the latter compound, served to identify the site of hydride displacement of fluorine. After contact of **11** with lithium borohydride in ether for 1.5 h at 0 °C, the reaction mixture contained mainly **13**, thus revealing that displacement of fluorine occurs much faster than ester reduction. Reduction of **11** with sodium borohydride stopped at the stage of **13**. Efforts to reduce **5** to **14a** with diborane also failed; only starting material could be detected after 1 month at ambient temperature. The stabilities of both **4** and **5** to hydride reduction can also be explained on the basis of retardation by the imidazolate anion, as invoked above for ammonolysis.

The role of the imidazolate ion becomes immediately evident following alkylation of N-1: the ester function of **11** is readily hydrolyzed in 0.05 N base; LAH displaces the fluorine atom at C-2 and reduces the ester function, both with ease. Finally, one of the fluorine atoms (presumably at C-2) of **11** is readily replaced by cyanide ion at ambient temperature; under the same conditions, **4** is completely stable.[20]

Although **5** lost carbon dioxide in the mass spectrometer, our efforts to achieve preparative decarboxylation to the parent 2,4-difluoroimidazole (**15**) were unsuccessful, thermolysis leading only to hydrolytic loss of fluorine. Thermolysis of **4** at 200 °C produced mixtures of dimers and cyclotrimers.[14]

Our anticipation of high fluorine reactivity in 2,4-difluoroimidazoles was not confirmed. We were well aware that displacement of the fluorine atom at C-2 occurs far more readily in the imidazolium ion than in the neutral imidazole.[1c,10] A second fluorine atom should facilitate addition of a nucleophile to C-2 by virtue of its electron-withdrawing effect, but that same effect will reduce the concentration of imidazolium ion even further in any but very strongly acidic media. We had no basis to predict which of these opposing factors would be the more significant, but our results now suggest that the effect on pK is the more critical.[21]

(19) The site of alkylation of **4** was assigned by reference to **12** and **13**; in these compounds, assignment of the alkyl group to N-1 is based on the magnitude of $J_{H,F}$: Takeuchi, Y.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1978**, *43*, 3570–3578. See also ref 2.

(20) Unpublished results. The product identified by MS is the imido ester resulting from addition of solvent ethanol to the 2-cyanoimidazole.

(21) Even 4-nitro-2-fluoroimidazoles have been found surprisingly stable, work in progress.

Experimental Section[22]

Irradiation Procedure. The light source was an Hanovia 450-W, medium-pressure mercury vapor lamp, placed in a quartz immersion well. The reaction solution was contained in a 150-mL quartz semicircular flask which was mounted as closely as possibly to the immersion well. No light filter was used unless specifically mentioned. The entire apparatus was immersed in a large Dewar flask charged with dry ice–2-propanol, and the bath temperature was maintained at −60 to −40 °C during irradiation.

Ethyl 4-Fluoroimidazole-5-carboxylate (1).[1b,23] To a solution of 4.65 g (30 mmol) of ethyl 4-aminoimidazole-5-carboxylate[1b] in 100 mL of 50% fluoroboric acid was added, at −10 °C, a solution of 2.28 g (33 mmol) of sodium nitrite in 3 mL of water. After 10 min, the solution was irradiated (without filter) at −60 to −40 °C until the diazonium chromophore (313 nm) had disappeared completely (4 h).[25] The solution was neutralized to pH 5 with 10 N sodium hydroxide while the temperature was maintained at −20 to −10 °C. The resulting solution was extracted with ethyl acetate (3 × 100 mL); the combined extracts were dried (Na_2SO_4) and evaporated. The residual material was extracted with 200 mL of chloroform and the extract was evaporated to dryness. The crystalline solid was washed with petroleum ether and dried to give 1.86 g (39.2%) of **1**, mp 144–145 °C (lit.[1b] mp 147.5–148 °C).

Ethyl 2-[(*p*-Bromophenyl)azo]-4-fluoroimidazole-5-carboxylate (2).[26] A solution of 1.14 g (16.5 mmol) of sodium nitrite in 15 mL of water was added gradually to a stirred, ice-cold solution of 2.84 g (16.5 mmol) of *p*-bromoaniline in 60 mL of 2 N hydrochloric acid. The solution of diazonium salt was added gradually to a stirred, ice-cold solution of 2.37 g (15 mmol) of **1** in 250 mL of 10% sodium carbonate. The mixture was neutralized to pH 6–7 with concentrated hydrochloric acid and was refrigerated for 1 h. The yellow-orange precipitate was collected, dried, and recrystallized from ethyl acetate–methanol (19:1). The product, mp 216–217 °C, was obtained in 90% yield. Anal. ($C_{12}H_{10}BrFN_4O_2$) C, H, N.

Ethyl 2-Amino-4-fluoroimidazole-5-carboxylate (3). To a solution of 4 g (12 mmol) of **2** in 200 mL of methanol–water (19:1) was added, at 45 °C and under nitrogen, 15 mL of triethylamine. Formamidinesulfinic acid (5.5 g, 51 mmol) was then added in one portion and the mixture was stirred for 20 h at 45–50 °C, or until TLC (silica gel, ethyl acetate) indicated that the hydrazo intermediate had disappeared.[27] The reaction mixture was concentrated under reduced pressure to ca. 50 mL and was diluted with 50 mL of water. A yellow precipitate was collected, and the filtrate was extracted with ethyl acetate (4 × 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated to dryness. The residual material and the yellow precipitate were combined and crystallized from a small volume of ethyl acetate to give 2.87 g (65.5%) of **3**, mp 219–220 °C dec. Anal. ($C_6H_8FN_3O_2$) C, H, F, N.

Ethyl 2,4-Difluoroimidazole-5-carboxylate (4). To a solution of 2.5 g (14.5 mmol) of **3** in 100 mL of chilled 50% fluoroboric acid (−20 to −10 °C) was added a solution of 1.2 g (17.4 mmol) of sodium nitrite in 3 mL of water. The solution was

(22) Microanalyses and mass spectral measurements were performed by the Microanalytical Services Section of this laboratory, under the direction of Dr. D. F. Johnson. Wherever possible, the identity and homogeneity of each compound were confirmed by UV, NMR, and mass spectra, and by TLC and HPLC.

(23) Other investigators[24] have reported difficulties in reproducing our synthesis of **1**.[1b] Although we have now repeated that synthesis many times without incident, we present here a modification that provides the same yield but a cleaner crude product. In order to minimize color and tar formation, it is essential that irradiation be continued until the diazonium chromophore has disappeared. Apparently, color is produced by coupling of **1** with unreacted diazonium imidazole during neutralization.

(24) Brown, T.; Shaw, G.; Durant, G. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2310–2315.

(25) At 0–10 °C, irradiation time was reduced to 3 h with a small reduction in yield. The use of a filter extends the required irradiation time to 12–24 h without change in yield.

(26) This procedure is a variant of one used previously to prepare the same compound (ref 16).

(27) (Arylhydrazo)imidazoles rapidly revert to yellow-orange (arylazo)imidazoles during TLC.

irradiated for 3 h at −60 to −40 °C, at which time the diazonium chromophore (324 nm) had disappeared.[28] The mixture was neutralized to pH 5–6 (at −20 to −10 °C) with cold, 10 N sodium hydroxide and was extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The residual material was extracted with chloroform (2 × 100 mL), and the combined chloroform extracts were evaporated to an oil. The oil was applied to a short silica gel column and the product was eluted with ethyl acetate–chloroform (1:3). Evaporation of solvent gave 1.35 g (53%) of crystalline **4**, mp 107–109 °C. Anal. ($C_6H_6F_2N_2O_2$) C, H, F, N.

2,4-Difluoroimidazole-5-carboxylic Acid (5). The difluoro ester **4** (352 mg, 2 mmol) was dissolved in 4 mL of 1 N sodium hydroxide. After storage for 3 days at ambient temperature, the solution was acidified (pH 1.3) with 2 N hydrochloric acid. The solution was evaporated to dryness in vacuo at 25 °C, and the residue was extracted with ethyl acetate (2 × 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated; the crystalline residue was recrystallized from a small volume of ethyl acetate to give 235 mg (80%) of **5**, mp 178–180 °C dec. Anal. ($C_4H_2F_2N_2O_2$) C, H, F, N.

2-[(*p*-Bromophenyl)azo]-4-fluoroimidazole-5-carboxamide (7). By use of a procedure analogous to that for azo coupling with 1, 2.45 g (19 mmol) of 4-fluoroimidazole-5-carboxamide (**6**)[1b] was coupled with the *p*-bromophenyldiazonium salt prepared from 3.59 g (21 mmol) of *p*-bromoaniline and 1.31 g (19 mmol) of sodium nitrite. The yellow precipitate was collected, dried, and washed with ethyl acetate (4.79 g, 81%). For an analytical sample, the product was recrystallized from ethyl acetate, mp 265–267 °C dec. Anal. ($C_{10}H_7BrFN_5O$) C, H, N.

2-Amino-4-fluoroimidazole-5-carboxamide (8). To a solution of 4.68 g (15 mmol) of **7** in 300 mL of methanol–water (19:1) was added, at 45 °C and under nitrogen, 18 mL of triethylamine. Formamidinesulfinic acid (6.48 g, 0.06 mol) was added to the solution and the mixture was stirred for 18 h at 45–50 °C, at which time TLC (silica gel, ethyl acetate) indicated the absence of the hydrazo intermediate.[27] The mixture was evaporated in vacuo, the resulting syrup was applied to a neutral alumina column (200 mL), and the column was eluted with ethyl acetate–methanol (1:1). The fractions which gave a UV-detectable spot at R_f 0.31 on silica gel plates (ethyl acetate–methanol, 19:1) were combined and concentrated at ambient temperature until crystallization began. The product, mp 270–272 °C, was obtained in 35% yield. Anal. ($C_4H_5FN_4O$) C, H, F, N.

Ammonolysis of 3 to 8. A suspension of 1.4 g (8 mmol) of **3** in 100 mL of concentrated aqueous ammonia was chilled in ice and ammonia gas was introduced until the suspension had dissolved. The mixture was stored for 4 weeks at ambient temperature and was concentrated to ca. 50 mL in vacuo. A pale yellow solid, identified as **3**, separated during concentration and was removed by filtration (420 mg). The filtrate was evaporated to dryness, the residual material was extracted with 100 mL of ethyl acetate, and the extract was evaporated to dryness. The residue was applied to an alumina column, and the product was eluted with chloroform–methanol (1:1). Combined fractions were evaporated and the residual material was washed with a small volume of acetone to give 250 mg (21%) of **8**.

2,4-Difluoroimidazole-5-carboxamide (9). To a solution of 560 mg (3.9 mmol) of **8** in 10 mL of 50% fluoroboric acid was added (at −20 to −10 °C) a solution of 268 mg (3.9 mmol) of sodium nitrite in 0.5 mL of water. The solution was irradiated without filter for 5 h at −60 to −40 °C, at which time the diazonium chromophore (326 nm) had disappeared. The mixture was neutralized to pH 5 with cold 10 N sodium hydroxide (at −20 to −10 °C). The solution was extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The residual material was applied to a silica gel column, and the column was developed with ethyl acetate. The first fractions that gave a TLC spot detectable under UV were collected and evaporated to give 160 mg (28%) of **9**. For an analytical sample, the solid was recrystallized from ethyl acetate, mp 203–204 °C. Anal. ($C_4H_3F_2N_3O$) C, H, F, N.

Conversion of 5 to 9 via 10.[18] A suspension of 200 mg (1.4 mmol) of **5** in 5 mL of thionyl chloride was stirred at ambient temperature for 3 days at which point solution was complete. The solvent was removed in vacuo, the residual material was dissolved in 5 mL of tetrahydrofuran, and the solution was saturated with ammonia at 0 °C. After storage for 1 h at ambient temperature, the solution was evaporated and the residual solid was purified on silica gel. The column was eluted with ethyl acetate–methanol (9:1) to give 190 mg (95%) of **9**, identical with the product obtained from **8**.

Ethyl 1-(Methoxymethyl)-2,4-difluoroimidazole-5-carboxylate (11). To an ice-cold solution of 704 mg (4 mmol) of **4** in 60 mL of dichloromethane was added 1.1 mL of triethylamine, followed by a solution of 0.68 mL (8 mmol) of bromomethyl methyl ether in 5 mL of dichloromethane. After the reaction mixture had been stirred for 2 h at ambient temperature, it was washed with water, dried (Na_2SO_4), and evaporated. The residual syrup was applied to a silica gel column that was developed with chloroform. The first UV-positive fractions were pooled and evaporated to give 706 mg (81%) of **11** as an oil: NMR ($CDCl_3$) δ 1.34 (t, 3, CH_2CH_3), 3.34 (s, 3, OCH_3), 4.30 (q, 2, CH_2CH_3), 5.50 (s, 2, NCH_2O).

Ethyl 1-(Methoxymethyl)-4-fluoroimidazole-5-carboxylate (13). The ester **1** (1.58 g, 0.01 mol) was treated with 1.7 mL (0.02 mol) of bromoethyl methyl ether, as described above for **11**. The product was obtained in a yield of 62%: mp 39–40 °C; NMR ($CDCl_3$) δ 1.40 (t, 3, CH_2CH_3), 3.36 (s, 3, OCH_3), 4.35 (q, 2, CH_2CH_3), 5.60 (s, 2, NCH_2O), 7.50 (d, 1, $J_{H,F}$ = 2 Hz, H-2). Anal. ($C_8H_{11}N_2O_3F$) C, H, N, F.

1-(Methoxymethyl)-4-fluoroimidazole-5-methanol (12). To a suspension of lithium aluminum hydride (0.5 g) in 10 mL of ice-cold, absolute ether was added slowly 1.2 g (0.06 mol) of **13**. The mixture was stirred for 30 min in the cold and an additional 30 min at ambient temperature. The reaction mixture was chilled, and 1 mL of water was added. The ethereal solution was poured into 100 mL of methanol that had been previously saturated with carbon dioxide. After the mixture had been stirred for 1 h, a white precipitate was removed and the filtrate was evaporated to dryness. The residue was extracted with 2 × 50 mL of chloroform and the combined extracts were evaporated. The resulting oily residue was applied to a silica gel column (50 mL) and the column was developed with 500 mL of ether–petroleum ether (1:1) and 500 mL of ethyl acetate. The ethyl acetate fractions were pooled and evaporated to give 0.8 g (59%) of **12** as an oil; NMR ($CDCl_3$) δ 3.26 (s, 3, OCH_3), 4.00 (s, 1, OH), 4.55 (s, 2, CH_2OH), 5.20 (d, 2, $J_{H,F}$ = 1.0 Hz, NCH_2O), 7.10 (d, 1, $J_{H,F}$ = 1.5 Hz, H-2).

Hydride Reduction of 11. Conversion of **11** to **12** with LAH in ether was found to be complete within 30 min at ambient temperature. The same conversion with lithium borohydride (ether) was effected within 2 h; however, exposure of **11** to lithium borohydride for 1.5 h at ice temperature gave mainly **13**. Ester **13** was also formed by reduction of **11** with sodium borohydride in 1-propanol (overnight at ambient temperature); no ester reduction was observed in this case.

Registry No. **1**, 33235-31-3; **2**, 89676-57-3; **3**, 89676-58-4; **4**, 89676-59-5; **5**, 89676-60-8; **6**, 33300-35-5; **7**, 89676-61-9; **8**, 89676-62-0; **9**, 89676-63-1; **10**, 89676-64-2; **11**, 89676-65-3; **12**, 89676-66-4; **13**, 89676-67-5; **14a**, 89676-68-6; **14b**, 89676-69-7; **15**, 89676-70-0; ethyl 4-aminoimidazole-5-carboxylate, 21190-16-9; formamidinesulfinic acid, 1758-73-2.

(28) Use of a Vycor filter increased the required irradiation time to 15 h without alteration in yield. Irradiation at −10 to 0 °C reduced the yield of **4** to 40–45%.