

Syntheses of (Trifluoromethyl)imidazoles with Additional Electronegative Substituents. An Approach to Receptor-Activated Affinity Labels

Yoshio Hayakawa,[†] Hiroshi Kimoto,[†] Louis A. Cohen,^{‡,1} and Kenneth L. Kirk*,[‡]

National Industrial Research Institute of Nagoya, Hirate-cho, Kita-ku, Nagoya 462, Japan, and
Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases,
National Institutes of Health, Bethesda, Maryland 20892

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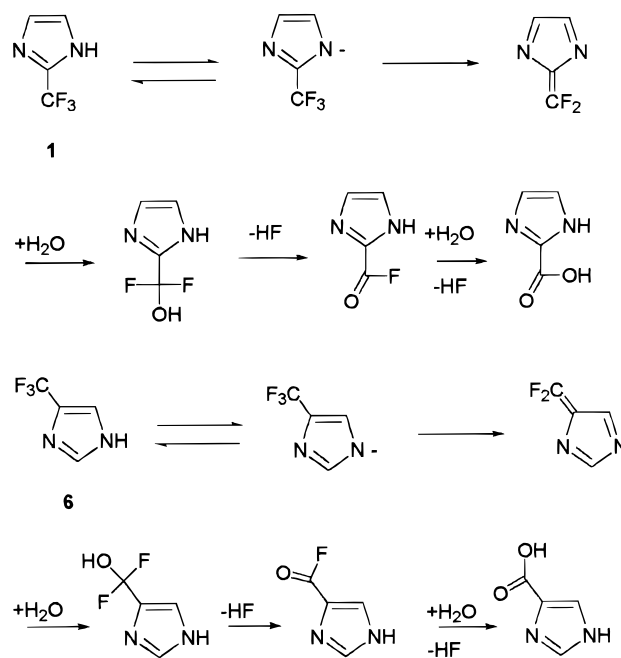
Electrophilic substitution in 2- and 4-(trifluoromethyl)imidazoles provides derivatives containing one or two nitro, chloro, bromo, or iodo groups. Fluoro and chloro derivatives were also prepared by photochemical trifluoromethylation of the respective haloimidazole. The results demonstrate that (trifluoromethyl)imidazoles behave fairly typically under the conditions of electrophilic nitration and halogenation. Of the alternative routes to the desired bifunctional and trifunctional imidazoles, electrophilic substitution on the preformed (trifluoromethyl)imidazole appears to be the method of choice in most cases. A large number of the products show herbicidal or insecticidal activity.

Introduction

Imidazoles bearing a trifluoromethyl group at C-2 or C-4² undergo rapid elimination of hydrogen fluoride under alkaline conditions to form transient difluorodiazafulvenes (Scheme 1).³ These intermediates combine readily with water or other nucleophiles and ultimately form carboxylic acids or their derivatives. (Perfluoroalkyl)imidazoles, in general, show parallel behavior by undergoing hydrolysis to (perfluoroalkyl)ketones; the latter species are slowly converted to imidazolecarboxylic acids via the fluoroform reaction.^{3c} This behavior suggests that the controlled generation of fulvene intermediates at specific sites in biological systems should provide a novel class of irreversible affinity ligands. Since the process is initiated simply by loss of the NH proton from the imidazole ring, affinity labeling with (trifluoromethyl)imidazoles may be applicable to receptors and antibodies, as well as to enzymes.

Titration data and kinetic studies provide pK_2 values of 10.0 for 2-(trifluoromethyl)imidazole (**1**) and 11.4 for 4-(trifluoromethyl)imidazole (**6**).^{3a} At mildly alkaline pH (8–9), the rate of fulvene formation thus is severely limited by the small fraction of imidazolate anion present. Fulvene formation is the rate-limiting step in all cases examined, and kinetic measurements are based on the rate of appearance of the carboxylate chromophore in UV spectra. Thus, at pH 8 (30 °C), $t_{1/2} = 730$ h for **1** and 2000 h for **6**; at pH 9, $t_{1/2}$ is reduced to 80 h for **1** and 200 h for **6**. In order for a more significant concentration of imidazolate ion to be generated within range of physiological pH (7.4), an additional electronegative substituent on a ring carbon would be required to reduce pK_2 . Our preliminary studies had shown, however, that a

Scheme 1



strongly electronegative substituent, while increasing NH acidity as expected, simultaneously retards elimination of fluoride ion (as measured by formation of carboxylate ion). To identify the substituents most suitable to achieve a balance between these opposing effects, we required a detailed study of electronic effects on both pK_2 and k_{rate} . We report here the preparation of a series of (trifluoromethyl)imidazoles to be used in this study.

The variety of (trifluoromethyl)imidazoles needed for such study is accessible either (a) by photochemical trifluoromethylation of an appropriately substituted imidazole^{4,5} or (b) by electrophilic substitution in the preformed (trifluoromethyl)imidazole. These methods are not

[†] National Industrial Research Institute of Nagoya.

[‡] National Institutes of Health.

(1) Deceased, September 12, 1996.

(2) For the sake of simplicity, the imidazole ring is numbered arbitrarily according to one NH tautomer. No tautomer preference is implied by such numbering.

(3) (a) Kimoto, H.; Cohen, L. A. *J. Org. Chem.* **1979**, *44*, 2902. (b) Kimoto, H.; Cohen, L. A. *J. Org. Chem.* **1980**, *45*, 3831. (c) Fujii, S.; Maki, Y.; Kimoto, H.; Cohen, L. A. *J. Fluorine Chem.* **1987**, *35*, 437.

(4) (a) Kimoto, H.; Fujii, S.; Cohen, L. A. *J. Org. Chem.* **1982**, *47*, 2867. (b) Kimoto, H.; Fujii, S.; Cohen, L. A. *J. Org. Chem.* **1984**, *49*, 1060.

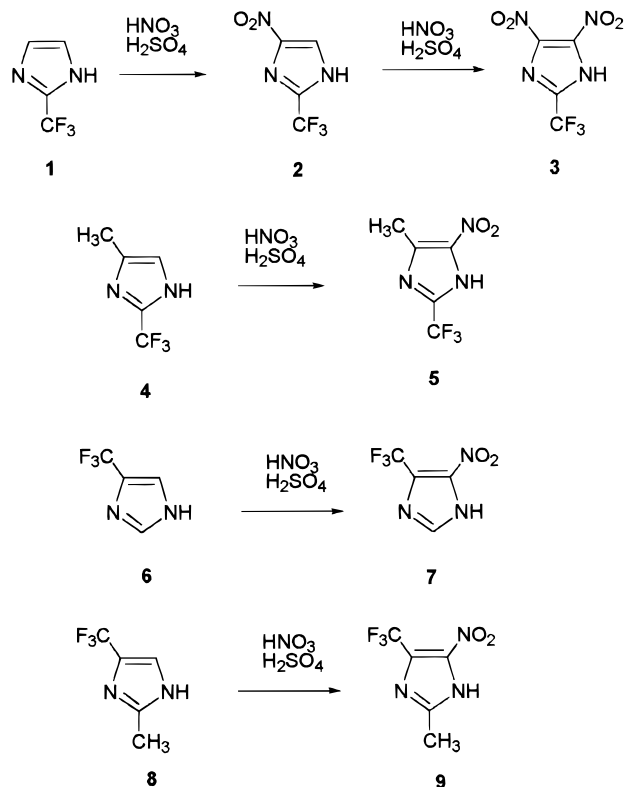
necessarily interchangeable. For example, we had already found that photochemical trifluoromethylation of nitroimidazoles gives unimpressive yields, and we were also concerned that certain substituents (especially the higher halogens) would not survive lengthy irradiation. On the other hand, the strongly electronegative trifluoromethyl group was expected to deactivate the imidazole ring toward electrophilic substitution. In this report, we describe the use of both methods in the syntheses of a variety of (trifluoromethyl)imidazoles with additional electronegative substituents.

Electronegatively substituted imidazoles, in general, have attracted considerable attention because of their special activities in biological systems. For example, both 2- and 4-nitroimidazoles show antimicrobial^{6a} and radiation sensitizer^{6b} properties, while 2-fluoro- and 2-iodohistidine have potent antimalarial activity.⁷ Imidazoles substituted by halogen, cyano, and nitro groups are known to have herbicidal activity.⁸ Some halogenated (trifluoromethyl)imidazoles also have activity as herbicides^{9,10} and as pesticides. Thus, apart from our interest in enhancing the reactivity of the trifluoromethyl group in compounds intended to serve as models for more complex bioimidazoles, we expect these polysubstituted imidazoles to be worthy of examination as antimetabolites in their own right.

Results and Discussion

Nitro Derivatives. Nitration of 2-(trifluoromethyl)imidazole (**1**) (Scheme 2) with a mixture of fuming nitric and concentrated sulfuric acids occurs rapidly at reflux (10 min) and provides a mixture of the mononitro (**2**, 46%) and dinitro (**3**, 39%) derivatives. The very strong acidity of **3** ($pK_a = -1.9$) leads to unusual properties, e.g., an ether-soluble sodium salt (see Experimental Section). Efforts to limit the degree of nitration were unsuccessful. Thus, the use of concentrated nitric acid ($d = 1.38$) at 80 °C gave no nitration while, at 100 °C, **2** and **3** were again

Scheme 2



formed in approximately equal amounts. Since **2** is converted completely to **3** under the first set of conditions, dinitration appears to occur sequentially. Nitration of 4-methyl-2-(trifluoromethyl)imidazole (**4**) provides 4-methyl-5-nitro-2-(trifluoromethyl)imidazole (**5**) in only 21% yield, possibly because of further oxidative degradation of the activated methyl group in **5**.¹¹ Nitration at C-5 is more strongly retarded by a proximate electronegative trifluoromethyl group at C-4 than by a more distant group at C-2 and requires much longer reaction time even with the use of fuming nitric acid. Thus, 4-(trifluoromethyl)imidazole (**6**, Scheme 3) gave less than 20% nitration in 10 min, and 86% of the 5-nitro derivative (**7**) only after 24 h at reflux, but 2-methyl-4-(trifluoromethyl)imidazole (**8**) gave 76% of 2-methyl-5-nitro-4-(trifluoromethyl)imidazole (**9**) after 4 h at reflux. Apparently, the 2-methyl group in **8** partially counteracts the deactivating effect of the trifluoromethyl substituent but is itself not sufficiently activated by the 5-nitro group in **9** to undergo oxidative destruction.¹¹ As expected, **7** does not undergo further nitration at C-2, nor does **6** produce the isomeric 2-nitro derivative.¹²

Since the nitro group ($\sigma_p = 0.79$) should destabilize an adjacent carbocation somewhat more strongly than will the trifluoromethyl group ($\sigma_p = 0.61$), it is surprising that further nitration of **2** occurs so much more readily than does nitration of **6**. While we considered the possibility that **3** is formed by simultaneous radical addition of the elements of N_2O_4 to C-4 and C-5, the facile conversion of **2** to **3** appears to rule out the need for an alternative mechanism. Electrophilic nitration of imidazole has been shown to involve the predominant imidazolium ion in

(5) Some trifluoromethyl and (perfluoroalkyl)imidazoles are also accessible via electrolytic generation of the corresponding radical: Medebielle, M.; Pinson, J.; Saveant, J. M. *Tetrahedron Lett.* **1990**, 31, 1279; *J. Am. Chem. Soc.* **1991**, 113, 6872. Whether this method lends itself to large-scale synthesis has not been established. Introduction of the trifluoromethyl group via transition-metal-mediated intermediates usually requires temperatures too severe for most bioimidazoles and histidine peptides, cf.: Labroo, V. M.; Labroo, R. B.; Cohen, L. A. *Tetrahedron Lett.* **1990**, 31, 5705. For a review of metal-mediated syntheses, cf. ref 4a. We and others have also described methods involving ring closure of acyclic precursors: Kimoto, H.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1978**, 43, 3403. Baldwin, J. J.; Kisinger, P. A.; Novello, F. C.; Sprague, J. M. *J. Med. Chem.* **1975**, 18, 895. Lombardini, J. G.; Wiseman, E. H. *J. Med. Chem.* **1974**, 17, 1182. Such methods are generally restricted to the preparation of (trifluoromethyl)imidazoles with alkyl or aryl substituents. Only the photochemical and electrolytic methods have been explored for the synthesis of electronegatively substituted (trifluoromethyl)imidazoles.

(6) (a) Nair, M. D.; Nagarajan, K. In *Progress in Drug Research*; Jucker, E., Ed.; Birkhauser Verlag: Basel, 1983; Vol. 27, pp 163–252. (b) For example: Jenkins, T. C.; Naylor, M. A.; O'Neill, P.; Threadgill, M. D.; Cole, S.; Stratford, I. J.; Adams, G. E.; Fielden, E. M.; Suto, M. J.; Stier, M. A. *J. Med. Chem.* **1990**, 33, 2603. Adams, G. E.; Stratford, I. J. *Biochem. Pharmacol.* **1986**, 35, 71.

(7) (a) Howard, R. J.; Andrutis, A. T.; Leech, J. H.; Ellis, W. Y.; Cohen, L. A.; Kirk, K. L. *Biochem. Pharmacol.* **1986**, 35, 1589. (b) Pantan, L. J.; Rossan, R. N.; Escajadillo, A.; Matsumoto, Y.; Lee, A. T.; Labroo, V. M.; Kirk, K. L.; Cohen, L. A.; Aikawa, M.; Howard, R. J. *Antimicrob. Agents Chemother.* **1988**, 32, 1655.

(8) Draber, W.; Falbe, J. F.; Buchell, F. W. A.; Korte, G. K. U.S. Pat. 3 501 286, 1970; *Chem. Abstr.* **1970**, 72, 120339.

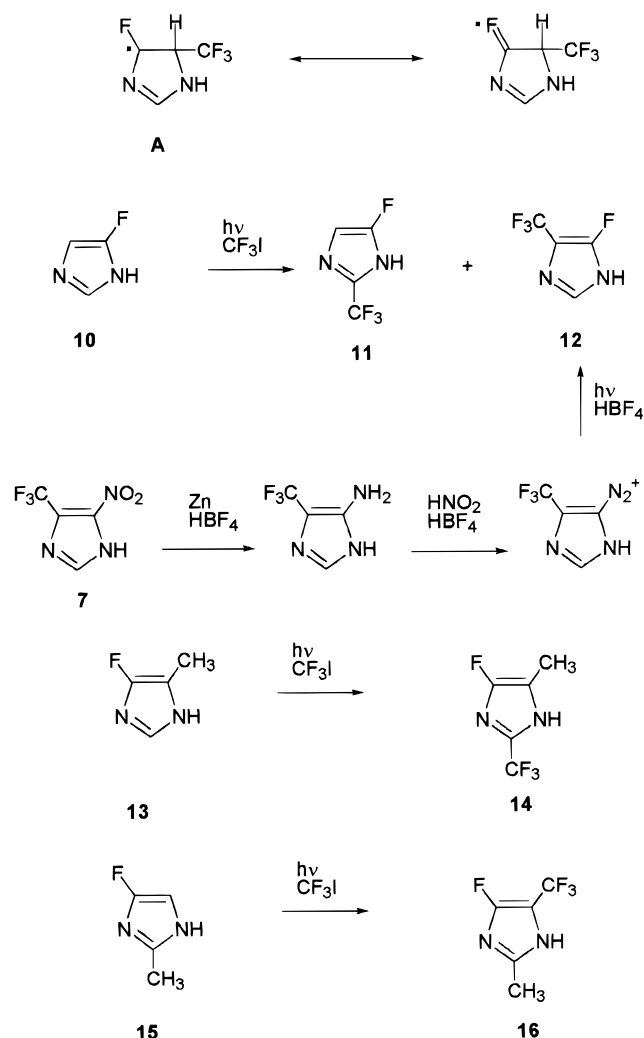
(9) Seng, F.; Sasse, K.; Beck, G.; Eue, L.; Schmidt, R. R. Ger. Pat. 2 646 142, 1978; *Chem. Abstr.* **1978**, 89, 24310.

(10) Swithenbank, C.; Fujimoto, T. T. U.S. Pat. 4 314 844, 1982; *Chem. Abstr.* **1982**, 96, 181287.

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

(12) (a) Takeuchi, Y.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1979**, 44, 4240. (b) Hofmann, K. *Imidazole and Its Derivatives*; Interscience: New York, 1953; p 128.

Scheme 3



strongly acidic media,¹³ although the neutral imidazole is expected to be much more reactive. While the trifluoromethyl group reduces ring basicity sufficiently to provide a more significant fraction of free base in strongly acidic media, it simultaneously destabilizes the carbocation intermediate. We estimate the (trifluoromethyl)imidazoles to be somewhat comparable to the corresponding imidazoles in overall ease of nitration, and thus, these opposing factors apparently offset one another. We have previously noted the remarkable facilitation of nitration when a substituent (e.g., fluorine) can simultaneously reduce ring basicity and stabilize a carbocation intermediate by resonance.^{12a}

Photochemical trifluoromethylation of 4-nitroimidazole was not achieved in our initial attempts because of its very low solubility, while 2-methyl-4-nitroimidazole gave 36% of **9**.¹⁴ Thus, nitration of the preformed (trifluoromethyl)imidazole may be the preferred route in most cases.⁵ All of the nitro(trifluoromethyl)imidazoles that were prepared exhibit strong herbicidal activity, and several also show toxicity to the housefly.¹⁵

(13) Austin, M. W.; Blackborow, J. R.; Ridd, J. H.; Smith, B. V. *J. Chem. Soc.* **1965**, 1051.

(14) The yield of 8% given in ref 4a is the result of an error in calculation.

(15) Kimoto, H.; Fujii, S.; Muramatsu, H.; Hirata, N.; Oshio, H.; Kamoshita, K. *Jpn. Pat.* 61 109 702, 1986; *Chem. Abstr.* **1986**, 105, 185869.

Fluoro Derivatives. Early and extensive efforts to achieve direct or classical fluorination of the imidazole ring proved fruitless and led to our development of the photochemical Balz–Schiemann reaction.¹⁶ The complexity of the reaction and the consistently low yields, however, first discouraged us from attempting the conversion of nitro to fluorine in the presence of the trifluoromethyl group. The alternative route, photochemical trifluoromethylation, seemed equally unpromising since strongly electronegative substituents (NO_2 , CF_3 , etc.) had been found to deactivate the imidazole ring toward attack by the electrophilic trifluoromethyl radical. Despite its high electronegativity, however, the fluoro substituent was thought capable of stabilizing an intermediate radical adduct (**A**) (Scheme 3) by lone pair overlap, in parallel to its ability to stabilize a carbocation ($\sigma_p = -0.07$). Indeed, photochemical trifluoromethylation of 4-fluoroimidazole (**10**, Scheme 3) gave a mixture of isomers **11** and **12** in the ratio 27:73. These isomers were readily separated on a silica gel column to give **11** (14%) and **12** (23%).

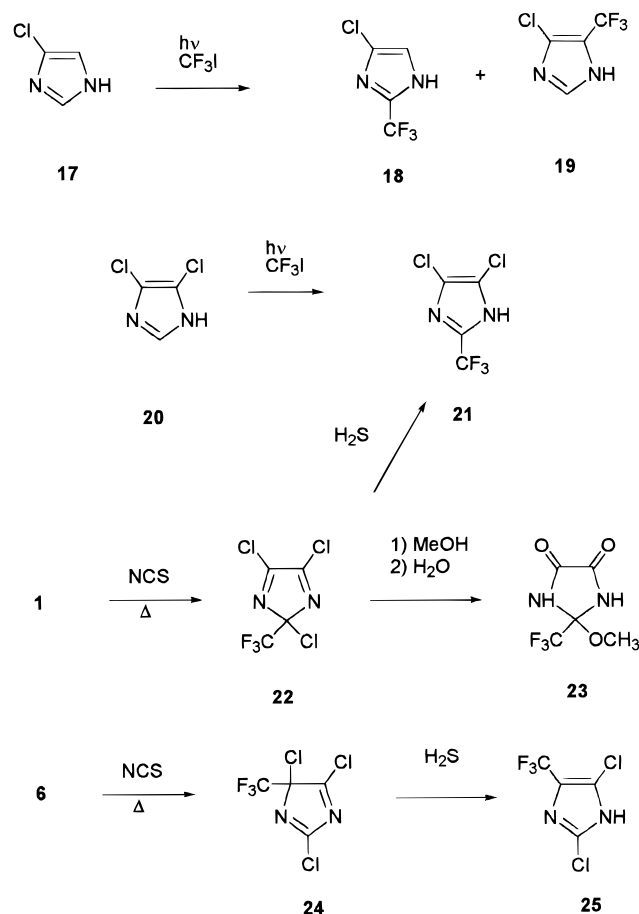
For comparison, the photochemical Balz–Schiemann reaction was applied to **7** (Scheme 3), and **12** was obtained in 8% yield. While the latter route was useful in confirming the structure assigned to **12**, it appears to be less favorable than the first route starting with **10**. Upon consideration, however, of the limitation in yield in the synthesis of **6** (47%)^{4a} (the precursor of **7**) or of **10** (20–30%),¹⁶ the routes from these alternative starting materials overall are actually quite competitive. Ironically, both routes make use of consecutive photochemical syntheses and differ only in the order of events. Photochemical trifluoromethylation of 4-fluoro-5-methylimidazole (**13**) gave the trifluoromethyl derivative (**14**) in 53% yield and that of 4-fluoro-2-methylimidazole (**15**) gave 4-fluoro-2-methyl-5-(trifluoromethyl)imidazole (**16**) in 26% yield. None of these fluoro(trifluoromethyl)imidazoles showed herbicidal or pesticidal activity. In view of the high degree of reactivity of 2-fluoroimidazole,^{16c} trifluoromethylation in this series was postponed for a separate study.

Chloro Derivatives. The photochemical trifluoromethylation of 4-chloroimidazole (**17**) forms the isomers, **18** and **19**, in a ratio of 25:75 according to ^{19}F NMR (Scheme 4), almost identical with that observed for 4-fluoroimidazole. The isolated yields of **18** and **19** were 14% and 39%, respectively. Photochemical trifluoromethylation of 4,5-dichloroimidazole (**20**) gave **21** in 32% yield. Compound **21** had been obtained previously by fluoride exchange of the trichloromethyl analogue.⁹

An alternative and preferable route to **21** involved the perchlorination of **1** with *N*-chlorosuccinimide at reflux to give the intermediate trichloro[2*H*]imidazole (**22**) (Scheme 4). This was reduced to **21** with hydrogen sulfide, with an overall yield from **1** of 76%. That **22** has the structure shown was demonstrated by a sequential methanolysis and hydrolysis to give **23**. The symmetry of **23** was confirmed by its IR and ^{13}C NMR spectra, and the ^{19}F NMR spectrum shows a CF_3 signal on the sp^3 carbon. The structure assigned to **23** was confirmed by

(16) Kirk, K. L.; Cohen, L. A. *J. Am. Chem. Soc.* **1971**, 93, 3060. (b) Kirk, K. L.; Cohen, L. A. *J. Am. Chem. Soc.* **1973**, 95, 4619. (c) Kirk, K. L.; Nagai, W.; Cohen, L. A. *J. Am. Chem. Soc.* **1973**, 95, 8389. (d) Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1973**, 38, 3647.

Scheme 4

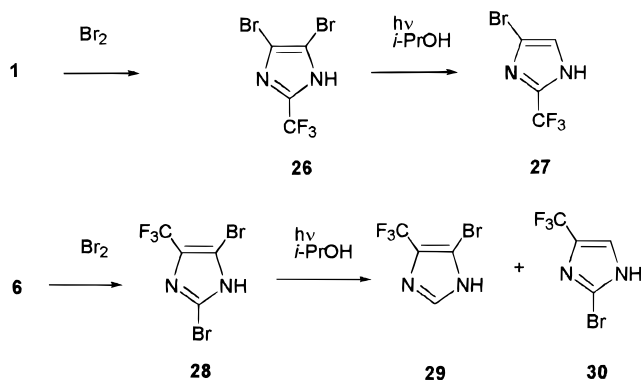


X-ray crystallography.¹⁷ Small amounts of additional methanolysis product were obtained, the structures of which could not be assigned unambiguously.

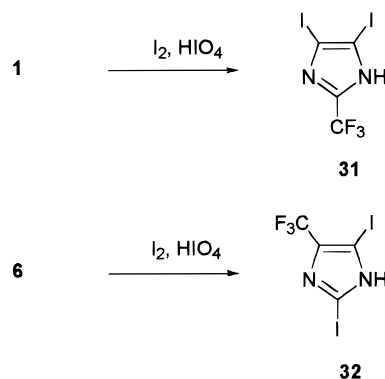
4-(Trifluoromethyl)imidazole (**6**) is less reactive than **1** toward *N*-chlorosuccinimide and produces an inseparable mixture of perchloro[4H]imidazoles (five new trifluoromethyl signals are observed by ¹⁹F NMR), of which **24** may be a representative component (Scheme 4). Reduction of the mixture of chlorinated isoimidazoles, containing **24**, gave **25** in 38% yield from **6**. The literature method for perchlorination of imidazole^{18a} and of some 2-substituted imidazoles^{18b} by the action of excess chlorine on the imidazole hydrochloride, failed with **1** or **6**. Both **21** and **25** show strong herbicidal activity, whereas **18** and **19** are only weakly active.

Bromo and Iodo Derivatives. In contrast to the results with chlorination, bromination of **1** with excess bromine and triethylamine occurred readily and smoothly to give **26** in 82% yield, whereas the monobromo derivative, **27**, was not detected (Scheme 5). The latter compound, however, was readily obtained in 87% yield by photoreduction of **26** in 2-propanol. In view of the reactivity of the trifluoromethyl group in imidazoles, removal of one bromine atom from **26** by sodium sulfite at reflux¹⁹ was not considered. Isomer **6** was significantly less reactive than was **1** toward dibromination, and **28** was obtained in 41% yield. Despite the recovery of nearly

Scheme 5



Scheme 6



half of the starting material, almost no monobrominated product could be detected by GC-MS or by ¹⁹F NMR. Photoreduction of **28** in 2-propanol led to the monobrominated products, **29** and **30**, in almost equal amounts.

Iodination of **1** did not occur under a variety of mild conditions but was achieved with a mixture of iodine and periodic acid to give **31** in 54% yield (Scheme 6). Iodination of **6** using similar conditions gave the diiodo derivative, **32**, in 82% yield. In either case, no more than a trace of monoiodinated product could be detected. We had previously observed that removal of one halogen atom from the highly photosensitive diiodoimidazoles by photoreduction was difficult to control, and preparation of the monoiodo derivatives was not pursued further. All the monobromo, dibromo, and diiodo derivatives of the (trifluoromethyl)imidazoles show strong herbicidal activity.¹⁵

These results demonstrate that (trifluoromethyl)imidazoles behave fairly typically under the conditions of electrophilic nitration and halogenation. Of the alternative routes to the desired bifunctional and trifunctional imidazoles, we believe electrophilic substitution on the preformed (trifluoromethyl)imidazole to be the method of choice in most cases. The halogenation of trifluoromethylated bioimidazoles and histidine peptides is an extension of this work that we are pursuing.

Experimental Section

Materials. The precursor (trifluoromethyl)imidazoles (**1**, **4**, **6**, **8**) were prepared by photochemical trifluoromethylation of the corresponding imidazoles.^{4a} 4-Fluoroimidazoles (**10**, **13**, **15**) were prepared from the corresponding nitroimidazoles by the photochemical Balz-Schiemann reaction.^{12a,16d}

Analytical Methods and Instrumentation. Melting points are uncorrected. ¹H NMR spectra were recorded at 90 MHz

(17) Morikawa, H.; Kato, K.; Kimoto, H.; Cohen, L. A. *Anal. Sci.* **1995**, *11*, 465.

(18) (a) Buchel, K. H.; Erdmann, H. *Chem. Ber.* **1976**, *109*, 1625.

(b) Buchel, K. H.; Erdmann, H. *Chem. Ber.* **1976**, *109*, 1638.

(19) Balaban, I. E.; Pyman, F. L. *J. Chem. Soc.* **1922**, 121, 947.

with TMS as internal reference. ^{19}F NMR spectra were recorded at 84.7 MHz; positive δ values are downfield from the external reference, trifluoroacetic acid. ^{13}C NMR spectra were recorded at 125 MHz. All NMR spectra were measured in acetone- d_6 unless otherwise noted. Mass spectra were measured by electron-impact ionization at 70 eV. GC-MS separations were performed at 100–180 °C with helium carrier gas and using a glass column (3 mm $\times$ 300 cm) packed with 1.5% OV-17 Chromosorb WAW DMCS (80–100 mesh). Elemental analyses were performed by the Takarazuka Research Center of Sumitomo Chemical Co., Ltd. and by Atlantic Microlab, Inc., Norcross, GA. The homogeneity and identity of each product were verified by NMR, IR, MS, GLC, and TLC.

4-Nitro-2-(trifluoromethyl)imidazole (2) and 4,5-Dinitro-2-(trifluoromethyl)imidazole (3). A solution of 2-(trifluoromethyl)imidazole (**1**, 1.09 g, 8 mmol) in a mixture of fuming nitric acid (5 mL, d 1.50) and concentrated sulfuric acid (5 mL) was heated at gentle reflux for 10 min. The cooled solution was poured into ice-water, neutralized (pH 5–6) with 20% sodium hydroxide and extracted with ethyl acetate (3 $\times$ 200 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The residual material was fractionated on 100 mL of silica gel with ether as eluent. Initial fractions gave 0.67 g (46%) of **2** as colorless needles from ether-benzene: mp 210–211.5 °C; IR (KBr) 1540 cm^{-1} (NO_2); ^1H NMR δ 8.38 (s, H-5); ^{19}F NMR δ 13.3 (s, 2- CF_3); MS m/e 181 (M^+), 162 ($\text{M}^+ - \text{F}$), 108, 96, 69. Anal. Calcd for $\text{C}_4\text{H}_2\text{F}_3\text{N}_3\text{O}_2$: C, 26.53; H, 1.11; N, 23.23. Found: C, 26.76; H, 1.21; N, 22.99.

Continued elution of the column gave 0.89 g (39%)²⁰ of the sodium salt of **3** (positive flame test) as pale yellow needles or plates from ethyl acetate-benzene: mp 283–286 °C dec; IR (KBr) 1550 cm^{-1} (NO_2); ^{19}F NMR δ 13.2 (s, 2- CF_3); ^{13}C NMR δ 121.0 (q, J = 3.5 Hz, CF_3), 138.2 (q, J = 0.5 Hz, C-2), 140.5 (s, C-4 and C-5); EI MS of this material gave no signal under a variety of conditions; CI MS (NH_3) 249 ($\text{M}^+ + \text{Na} + 1$). Evidently, the sodium salt of **3** not only is soluble in ethyl acetate and ether but also is volatilized as the salt in MS. Anal. Calcd for $\text{C}_4\text{F}_3\text{N}_4\text{O}_4\text{Na} \cdot 2\text{H}_2\text{O}$: C, 16.91; H, 1.42; N, 19.72. Found: C, 16.80; H, 1.44; N, 19.49. Water of hydration was not lost by drying in vacuo at 100 °C. No residual ash was found during combustion analysis, possibly because the compound explodes on burning. Crystal structure analysis of this interesting sodium salt was unsuccessful because of its instability under X-ray irradiation.

The free acid (**3**) was obtained by solution of the salt in concentrated hydrochloric acid, evaporation of the solution to dryness, and repeated extraction of the residual material with ethyl acetate. The extract was dried (Na_2SO_4) and evaporated to give colorless plates: mp 92–93 °C; ^{19}F NMR δ 13.2 (s, 2- CF_3); ^{13}C NMR δ 118.4 (q, J = 3.6 Hz, CF_3), 133.3 (q, J = 0.6 Hz, C-2), 136.6 (s, C-4 and C-5); MS m/e 226 (M^+), 207 ($\text{M}^+ - \text{F}$); HRMS calcd for $\text{C}_4\text{HF}_3\text{N}_4\text{O}_4$ 225.9950 (M^+), 206.9965 ($\text{M}^+ - \text{F}$), found 225.9986 (M^+), 206.9966 ($\text{M}^+ - \text{F}$). In 12 N HCl or 50% H_2SO_4 , λ_{max} 288 nm ($\log \epsilon$ 3.80); in H_2O or 1 N NaOH, λ_{max} 330 nm ($\log \epsilon$ 3.76). Spectroscopic determination of pK_a (based on varying dilutions of HCl) provided an approximate value of -1.9 .

5-Methyl-4-nitro-2-(trifluoromethyl)imidazole (5). Nitration of 4-methyl-2-(trifluoromethyl)imidazole (**4**, 0.45 g, 3 mmol) under the same conditions as for **1** gave 0.12 g (21%) of **5** as colorless needles from ether-benzene: mp 193–196 °C; IR (KBr) 1545 cm^{-1} (NO_2); MS m/e 195 (M^+), 176 ($\text{M}^+ - \text{F}$); ^1H NMR δ 2.70 (s, 5- CH_3); ^{19}F NMR δ 13.2 (s, 2- CF_3). Anal. Calcd for $\text{C}_5\text{H}_4\text{F}_3\text{N}_3\text{O}_2$: C, 30.78; H, 2.07; N, 21.54. Found: C, 30.53; H, 2.07; N, 21.39.

5-Nitro-4-(trifluoromethyl)imidazole (7). A solution of 4-(trifluoromethyl)imidazole (**6**, 0.68 g, 5 mmol) in a mixture of 10 mL of fuming nitric acid and 10 mL of concentrated sulfuric acid was heated at reflux for 24 h. The cooled solution was poured into ice-water and was neutralized (pH 5–6) with 20% sodium hydroxide. A white solid separated and was

collected by filtration. The filtrate was extracted with ethyl acetate (3 $\times$ 50 mL), and the combined extracts were dried and evaporated. The residual material and the white solid were combined and crystallized from ethyl acetate-ether to give 0.78 g (86%) of **7** as colorless plates: mp 190–192 °C; IR (KBr) 1555 cm^{-1} (NO_2); MS m/e 181 (M^+), 165, 108, 96, 69; ^1H NMR δ 8.04 (s, 2-H); ^{19}F NMR δ 17.1 (s, 4- CF_3). Anal. Calcd for $\text{C}_4\text{H}_2\text{F}_3\text{N}_3\text{O}_2$: C, 26.53; H, 1.11; N, 23.21. Found: C, 26.58; H, 1.06; N, 23.27.

2-Methyl-5-nitro-4-(trifluoromethyl)imidazole (9). A solution of 2-methyl-4-(trifluoromethyl)imidazole (**8**, 0.90 g, 6 mmol) in a mixture of 10 mL of fuming nitric acid and 10 mL of concentrated sulfuric acid was heated at reflux for 4 h. Workup as above gave 0.89 g (76%) of **9** as colorless needles from ethanol: mp 182–183.5 °C (lit.^{4a} mp 181–183 °C); MS m/e 195 (M^+), 176 ($\text{M}^+ - \text{F}$), 165 ($\text{M}^+ - \text{NO}$).

4-Fluoro-2-(trifluoromethyl)imidazole (11) and 4-Fluoro-5-(trifluoromethyl)imidazole (12). Trifluoromethyl iodide was bubbled into a solution of 4-fluoroimidazole (**10**, 0.86 g, 10 mmol) in 10 mL of methanol containing triethylamine (0.51 g, 5 mmol)²¹ until the gain in weight (0.98 g) corresponded to 5 mmol of the iodide. The solution was placed in a quartz tube (1 $\times$ 20 cm, 16 mL) and was irradiated by a 60 W low-pressure mercury lamp with a Vycor filter²² for 3 days at ambient temperature. The reaction mixture was analyzed directly by ^{19}F NMR; integration of peak areas for the trifluoromethyl group gave a ratio of 27% for the 2- CF_3 isomer (**11**) and 73% for the 4-isomer (**12**). The reaction mixture was evaporated to dryness under reduced pressure, the residual material was applied to a column of 120 mL of silica gel, and the column was eluted with ether. The initial fractions gave 0.11 g (14%) of **11** as a colorless powder after sublimation: mp 132–134 °C; MS m/e 154 (M^+), 134 ($\text{M}^+ - \text{HF}$), 107, 86; ^1H NMR δ 7.00 (d, J = 8 Hz, 5-H); ^{19}F NMR δ 13.6 (d, 3, J = 1 Hz, 2- CF_3) and -59.7 (d-q, 1, J = 8 and 1 Hz, 4-F); HRMS calcd for $\text{C}_4\text{H}_2\text{F}_4\text{N}_2$ 154.0154, found: 154.0150. Anal. Calcd for $\text{C}_4\text{H}_2\text{F}_4\text{N}_2$: C, 31.18; H, 1.31; N, 18.18. Found: C, 31.24; H, 1.28; N, 18.27. Continued elution of the column gave 0.18 g (23%) of **12** as colorless plates from benzene: mp 108–110 °C; MS m/e 154 (M^+), 135 ($\text{M}^+ - \text{F}$), 134 ($\text{M}^+ - \text{HF}$), 107, 96, 86, 69; ^1H NMR δ 7.62 (br s, 2-H); ^{19}F NMR δ 19.2 (d-d, 3, J = 10 and 0.3 Hz, 5- CF_3) and -54.1 (q, 1, J = 10 Hz, 4-F); HRMS calcd for $\text{C}_4\text{H}_2\text{F}_4\text{N}_2$ 154.0154, found 154.0157. Anal. Calcd for $\text{C}_4\text{H}_2\text{F}_4\text{N}_2$: C, 31.18; H, 1.31; N, 18.18. Found: C, 31.13; H, 1.25; N, 18.31. Further elution of the column allowed recovery of unreacted **10**, which compound is not easily accessible.

Alternate Synthesis of 12. A sample of **7** (1.81 g, 10 mmol) was reduced with zinc dust to the amine, the amine was diazotized with nitrous acid, and the diazonium salt was subjected to photochemical fluorination via the Balz-Schiemann reaction, as described below for the synthesis of **15**. Following adjustment of the reaction mixture to pH 5–6, the product was recovered by extraction with 3 $\times$ 200 mL of ether. Ether was used as the eluent for silica gel chromatography. The product was purified by sublimation (10 mmHg, 100–150 °C) and then recrystallized from benzene to give 0.12 g (7.8%) of **12** as colorless plates, mp 108–110 °C.

4-Fluoro-5-methyl-2-(trifluoromethyl)imidazole (14). Photochemical trifluoromethylation of 4-fluoro-5-methylimidazole (**13**, 0.50 g, 5 mmol) was performed as described for **10** and gave 0.224 g (53%) of **14** as colorless plates from ether: mp 149–150 °C; MS m/e 168 (M^+), 167 ($\text{M}^+ - \text{H}$), 149 ($\text{M}^+ - \text{F}$), 147; ^1H NMR δ 2.21 (dq, J = 1.0 Hz, 5- CH_3); ^{19}F NMR δ 14.0 (m, 3, CF_3) and -65.7 (q, 1, J = 1.0 Hz, 4-F); HRMS calcd for $\text{C}_5\text{H}_4\text{F}_4\text{N}_2$ 168.0311, found 168.0315. Anal. Calcd for $\text{C}_5\text{H}_4\text{F}_4\text{N}_2$: C, 35.73; H, 2.40; N, 16.67. Found: C, 35.62; H, 2.33; N, 16.64.

(21) The addition of excess triethylamine had been found to reduce yields in photochemical perfluoroalkylation. Apparently, the perfluoroalkyl radical is diverted from the desired reaction by abstracting a hydrogen atom from the amine to form the corresponding H-perfluoroalkane.

(22) A Vycor filter was used to cut off light below 200 nm; short-wavelength radiation was found to promote side reactions and polymerization.

(20) Reflux of the original reaction mixture for 30 min increases the yield of **3** (as its sodium salt) to 65%.

4-Fluoro-2-methylimidazole (15). The following procedure is patterned after the syntheses of other fluoroimidazoles^{12a,16d} with some modifications. A solution of 2-methyl-4-nitroimidazole (5.08 g, 40 mmol) in tetrafluoroboric acid (42%, 200 mL) was cooled to -10°C , and zinc dust (5.08 g, 130 mmol) was added in portions of ca. 0.1 g with rapid stirring. Each addition was made only after the prior portion had dissolved and the temperature had fallen to at least -5°C . The addition required ca. 1 h. Small aliquots were removed, diluted with water, and examined by UV. Total loss of the chromophore at 310 nm was taken to indicate complete reduction. A solution of sodium nitrite (2.04 g, 44 mmol) in 10 mL of water was then added dropwise. The resulting solution of the diazonium compound was diluted to 380 mL with cold 42% tetrafluoroboric acid and was irradiated under argon in a Pyrex immersion-well photoreactor using a 400 W high-pressure mercury lamp (Riko 400-HA).²³ After 90 min, the diazonium chromophore at 280 nm had disappeared. The solution was cooled to -10°C with dry ice, neutralized slowly with 25% aqueous sodium hydroxide to pH 5–6, and extracted with 5×200 mL of ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated. The residual material was purified on 100 mL of silica gel with ethyl acetate as eluent to give 1.06 g (27%) of **15** as a colorless powder: mp $142\text{--}144^{\circ}\text{C}$ (lit.^{12a} mp $142\text{--}143^{\circ}\text{C}$); MS m/e 100 (M^+), 99, 86, 72, 58.

4-Fluoro-2-methyl-5-(trifluoromethyl)imidazole (16). Photochemical trifluoromethylation of 4-fluoro-2-methylimidazole (**15**, 1.00 g, 10 mmol) was performed as described above for **10** and gave 0.22 g (26%) of **16** as colorless plates from ethyl acetate–benzene: mp $179\text{--}181^{\circ}\text{C}$; MS m/e 168 (M^+), 149 ($\text{M}^+ - \text{F}$), 148 ($\text{M}^+ - \text{HF}$), 147, 121, 86, 72; ^1H NMR δ 2.33 (q, $J = 0.8$ Hz, 2- CH_3); ^{19}F NMR δ 19.4 (dq, 3, $J = 11$ and 0.8 Hz, 5- CF_3) and -63.6 (q, 1, $J = 11$ Hz, 4-F). Anal. Calcd for $\text{C}_5\text{H}_4\text{F}_4\text{N}_2$: C, 35.73; H, 2.40; N, 16.67. Found: C, 35.82; H, 2.41; N, 16.73.

Chlorination of Imidazole. To a solution of imidazole (34 g, 0.5 mol) in 300 mL of chloroform was added slowly a solution of chlorine (7.1 g, 0.1 mol) in 100 mL of chloroform. An exothermic reaction occurred, and a white precipitate was generated. The reaction mixture was stirred for 1 h, stored overnight at ambient temperature, and then poured into aqueous sodium bisulfite. The organic layer was separated, and the water layer was extracted with ethyl acetate (3×150 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residual material was fractionated on 180 mL of silica gel with ether as eluent. Initial fractions gave 1.33 g (19%) of 4,5-dichloroimidazole (**20**) as colorless plates from benzene, mp $181\text{--}182^{\circ}\text{C}$ (lit.²⁴ mp $179\text{--}180^{\circ}\text{C}$, lit.²⁵ mp $180\text{--}181^{\circ}\text{C}$).²⁶ Further elution gave 2.58 g (25%) of 4-chloroimidazole (**17**) as colorless plates from ethyl acetate–ether, mp $119\text{--}119.5^{\circ}\text{C}$ (lit.²⁴ mp $117\text{--}118^{\circ}\text{C}$, lit.²⁵ mp $115\text{--}117^{\circ}\text{C}$).

4-Chloro-2-(trifluoromethyl)imidazole (18) and 4-Chloro-5-(trifluoromethyl)imidazole (19). Into a solution of **17** (2.05 g, 20 mmol) and triethylamine (1.01 g, 10 mmol) in methanol (20 mL) was bubbled trifluoromethyl iodide until 1.96 g (10 mmol) had been absorbed. The solution, in a quartz tube, was irradiated for 3 days by a low-pressure, 60 W mercury lamp. The reaction mixture was analyzed directly by ^{19}F NMR; integration of peak areas gave the ratio of compounds **18** and **19** as 1:3, respectively. The reaction mixture was evaporated to dryness, and the residual material was fractionated on 180 mL of silica gel with ether–ethyl acetate (1:1) as eluent. The first fractions gave 0.24 g (14%) of **18** as colorless plates from benzene: mp $142\text{--}144^{\circ}\text{C}$; MS m/e 172

and 170 (M^+), 152 and 150 ($\text{M}^+ - \text{HF}$), 125, 123; ^1H NMR δ 7.37 (s, 5-H); ^{19}F NMR δ 13.6 (s, 2- CF_3). Anal. Calcd for $\text{C}_4\text{H}_2\text{ClF}_3\text{N}_2$: C, 28.17; H, 1.18; N, 16.43. Found: C, 28.29; H, 1.17; N, 16.39. Continued elution gave **19** (0.66 g, 39%) as colorless needles from ether: mp $158\text{--}159^{\circ}\text{C}$; MS m/e 172 and 170 (M^+), 153 and 151 ($\text{M}^+ - \text{F}$), 152 and 150 ($\text{M}^+ - \text{HF}$), 145, 143, 115; ^1H NMR δ 7.82 (s, 2-H); ^{19}F NMR δ 17.3 (s, 5- CF_3). Anal. Calcd for $\text{C}_5\text{H}_4\text{F}_4\text{N}_2$: C, 28.17; H, 1.18; N, 16.43. Found: C, 28.25; H, 1.20; N, 16.49.

4,5-Dichloro-2-(trifluoromethyl)imidazole (21). Similar photochemical trifluoromethylation of 4,5-dichloroimidazole (**20**, 1.10 g, 8 mmol) gave 0.26 g (32%) of **21** as colorless plates from benzene: mp $188\text{--}189^{\circ}\text{C}$ (lit.⁹ mp $186\text{--}188^{\circ}\text{C}$); MS m/e 208, 206, and 204 (M^+), 186, 184, 176, 123; ^{19}F NMR δ 13.2 (s, 2- CF_3).

4,5-Dichloro-2-(trifluoromethyl)imidazole (21) by Chlorination. To a suspension of **1** (0.544 g, 4 mmol) in 200 mL of tetrachloromethane was added *N*-chlorosuccinimide (5.34 g, 40 mmol), and the mixture was heated at reflux with stirring for 10 h. The solution was cooled to ambient temperature and was aerated with argon for 1 h. A white solid (consisting of succinimide and *N*-chlorosuccinimide) was removed by filtration. The filtrate was evaporated to dryness, and the residual material was dissolved in acetonitrile (200 mL). Passage of hydrogen sulfide through the solution for 2 h resulted in the separation of a pale yellow solid (sulfur), which was removed by filtration. The filtrate was evaporated, and the residual material was purified on 100 mL of silica gel, with dichloromethane–hexane (1:1) as eluent. Pale yellow crystals were obtained, which were recrystallized from benzene to give 0.62 g (76%) of **21** as colorless plates, mp $188\text{--}189^{\circ}\text{C}$.

2,5-Dichloro-4-(trifluoromethyl)imidazole (25). Chlorination of **6** (1.36 g, 10 mmol) with 13.4 g (100 mmol) of *N*-chlorosuccinimide and subsequent reduction with H_2S , following the procedure described for **21**, gave 0.78 g (38%) of **25** as pale yellow needles from chloroform–cyclohexane: mp $135\text{--}139^{\circ}\text{C}$; MS m/e 208, 206 and 204 (M^+), 189, 187, and 185 ($\text{M}^+ - \text{F}$), 188, 186, and 184 ($\text{M}^+ - \text{HF}$), 151 and 149 ($\text{M}^+ - \text{HF} - \text{Cl}$); ^{19}F NMR δ 16.7 (s, 4- CF_3). Anal. Calcd for $\text{C}_4\text{HCl}_2\text{F}_4\text{N}_2$: C, 23.44; H, 0.49; N, 13.67. Found: C, 23.55; H, 0.45; N, 13.74.

Isolation and Methanolysis/Hydrolysis of 2,4,5-Trichloro-2-(trifluoromethyl)[2H]imidazole (22). To a suspension of **1** (1.36 g, 10 mmol) in 150 mL of ethanol-free chloroform²⁷ was added *N*-chlorosuccinimide (4.01 g, 30 mmol), and the mixture was heated at reflux for 4 h. The reaction mixture was evaporated to dryness, and the residual material was purified on 180 mL of silica gel with ether as eluent. There was obtained 1.98 g (containing solvent) of **22** as a colorless oil with a penetrating chlorine-like odor: IR (neat) 1568 and 1595 cm^{-1} ($\text{C}=\text{N}$); MS m/e 244, 242, 240, and 238 (M^+), 207, 205, and 203 ($\text{M}^+ - \text{Cl}$), 186, 184, 179, 177, 123, 85, 83, 69; ^{19}F NMR δ 1.3 (s, 2- CF_3). Continued elution of the column gave 0.40 g (20%) of **21**, which was followed by recovery of 0.26 g (19%) of **1**.

The crude **22** was added to 20 mL of methanol; the solution was stirred, and an exothermic reaction occurred. After the solution had reacted for 10 min, an effort was made to isolate a characterizable reaction product, without success. The solution was then evaporated and the residual material was dissolved in 10 mL of water. The solution was neutralized with sodium hydroxide and evaporated to dryness. The residual material was fractionated on 120 mL of silica gel with ether as eluent to give 1.24 g (63% based on **1**) of 2-methyl-2-(trifluoromethyl)tetrahydroimidazole-4,5-dione (**23**) as colorless plates from chloroform: mp $193\text{--}195^{\circ}\text{C}$; IR (KBr) 1775 cm^{-1} ($\text{C}=\text{O}$); MS m/e 198 (M^+), 167 ($\text{M}^+ - \text{OCH}_3$), 155, 139, 129 ($\text{M}^+ - \text{CF}_3$), 127, 107, 98, 96, 69; ^1H NMR δ 3.36 (s, 2- OCH_3); ^{19}F NMR δ -7.1 (s, 2- CF_3); ^{13}C NMR (CD_3OD) δ 125.0 (q, $J = 3.6$ Hz, CF_3), 163.7 (s, OCH_3), 94.0 (s, $\text{C}=\text{O}$). Anal. Calcd for $\text{C}_5\text{H}_5\text{F}_3\text{N}_2\text{O}_3$: C, 30.32; H, 2.54; N, 14.14. Found: C, 30.36; H, 2.56; N, 14.06.

(27) Commercial chloroform was washed three times with water, dried over MgSO_4 , distilled, and stored over molecular sieves (4A).

(23) The earlier synthesis made use of a medium-pressure mercury lamp and a quartz photoreactor. If a high-pressure mercury lamp is used, a more readily available Pyrex reaction vessel is acceptable because sufficient energy is transmitted in the absorption range of the diazonium salt beyond 300 nm.

(24) Lutz, A. W.; DeLorenzo, S. J. *Heterocycl. Chem.* **1967**, 4, 399.

(25) Imbach, J. L.; Jacquier, R.; Romane, A. J. *Heterocycl. Chem.* **1967**, 4, 451.

(26) Although chlorination of imidazole with *N*-chlorosuccinimide in chloroform was also achieved, separation of the product from succinimide proved extremely tedious, even on a small scale.

4,5-Dibromo-2-(trifluoromethyl)imidazole (26). To a solution of **1** (272 mg, 2 mmol) in 40 mL of chloroform and 10 mL of methanol were added triethylamine (404 mg, 4 mmol) and a solution of bromine (400 mg, 5 mmol) in 10 mL of chloroform. The reaction mixture was left at ambient temperature for 30 min and then was poured into 50 mL of cold, 10% aqueous sodium bisulfite. The organic layer was separated, and the water layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried and evaporated. The residual material was purified on 100 mL of silica gel by elution with dichloromethane. Recrystallization from cyclohexane gave 480 mg (82%) of **26** as colorless prisms: mp 190.5–191.5 °C (lit.¹⁰ mp 174–179 °C); MS *m/e* 296, 294, and 292 (M^+), 276, 274, and 272 ($M^+ - HF$), 195 and 193 ($M^+ - HF - Br$), 120, 118, 69; ¹⁹F NMR δ 13.1 (s, 2- CF_3).

2,5-Dibromo-4-(trifluoromethyl)imidazole (28). Reaction of **6** (680 mg, 5 mmol) with bromine (1.92 g, 12 mmol) was performed as for **1**, but the reaction mixture was left at ambient temperature for 20 h. Workup gave 600 mg (41%) of **28** as colorless prisms from cyclohexane: mp 166–168 °C (lit.¹⁰ mp 162–164 °C); MS *m/e* 296, 294, and 292 (M^+), 276, 274 and, 272 ($M^+ - HF$), 215 and 213 ($M^+ - Br$), 195 and 193 ($M^+ - HF - Br$), 134, 133; ¹⁹F NMR δ 16.5 (s, 4- CF_3). Continued elution of the silica gel column gave 320 mg of recovered **6**.

Bromination of **6** was also performed in acetic acid in the absence of a base: to a solution of **6** (680 mg, 5 mmol) in 20 mL of acetic acid was added a solution of 3.2 g bromine (20 mmol) in 2 mL of chloroform. The solution was heated at reflux for 8 h. The cooled reaction mixture was poured into 100 mL of 10% aqueous sodium bisulfite containing ice, and the mixture was extracted with 3 × 100 mL of ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated. Residual acetic acid was largely removed by several evaporations with hexane at aspirator pressure. The residual material was fractionated on 100 mL of silica gel with dichloromethane as eluent, to give 750 mg (51%) of **28** and 41% of recovered **6**.

4-Bromo-2-(trifluoromethyl)imidazole (27). A solution of **26** (588 mg, 2 mmol) in 2 mL of 2-propanol was divided into two quartz NMR tubes, and the solutions were irradiated for 2 days with a low-pressure mercury lamp (60 W with a Vycor filter). The reaction mixture was analyzed directly by ¹⁹F NMR: integration showed the ratio of **26**:**27** to be 12:88. The solvent was evaporated and the residual material was purified on 100 mL of silica gel with ether as eluent. Recrystallization from benzene gave 374 mg (87%) of **27** as colorless needles: mp 139–140 °C; MS *m/e* 216 and 214 (M^+), 196 and 194 ($M^+ - HF$), 169, 167, 115 ($M^+ - HF - Br$), 108, 69; ¹H NMR δ 7.48 (s, 5-H); ¹⁹F NMR δ 13.9 (s, 2- CF_3). Anal. Calcd for $C_4H_2BrF_3N_2$: C, 22.35; H, 0.94; N, 13.03. Found: C, 22.30; H, 0.97; N, 12.93.

5-Bromo-4-(trifluoromethyl)imidazole (29) and 2-Bromo-4-(trifluoromethyl)imidazole (30). A solution of **28** (1.47 g, 5 mmol) in 5 mL of 2-propanol was irradiated for 3 days in a quartz tube (10 × 200 mm). Direct analysis by ¹⁹F NMR showed the ratio of **28**:**29**:**30** to be 31:36:33. The mixture was fractionated on 120 mL of silica gel, eluting first with ether and then with ether–ethyl acetate (1:1). The first compound eluted was unreacted **28**. Continued elution gave **30**, which was recrystallized as colorless plates from benzene (0.31 g, 29%); mp 185–187 °C; MS *m/e* 216 and 214 (M^+), 197 and 195 ($M^+ - F$), 196 and 194 ($M^+ - HF$), 108; ¹H NMR δ 7.72 (q, $J = 1.3$ Hz, 4-H); ¹⁹F NMR δ 14.8 (q, $J = 1.3$ Hz, 5- CF_3). Anal. Calcd for $C_4H_2BrF_3N_2$: C, 22.35; H, 0.94; N, 13.03. Found: C, 22.48; H, 1.09; N, 13.02.

The third compound eluted was **29**, recrystallized from ether–benzene as colorless plates (0.33 g, 31%); mp 196–198 °C; MS *m/e* 216 and 214 (M^+), 197 and 195 ($M^+ - F$), 196 and 194 ($M^+ - HF$), 135, 115, 108; ¹H NMR δ 7.95 (s, 2-H); ¹⁹F NMR δ 17.2 (s, 5- CF_3). Anal. Calcd for $C_4H_2BrF_3N_2$: C, 22.35; H, 0.94; N, 13.03. Found: C, 22.40; H, 1.02; N, 12.85.

4,5-Diiodo-2-(trifluoromethyl)imidazole (31). To a solution of **1** (0.68 g, 5 mmol) in 15 mL of acetic acid were added iodine (3.81 g, 15 mmol), periodic acid dihydrate (2.28 g, 10 mmol), and chloroform (5 mL). The mixture was heated at reflux with stirring for 3 h. The cooled reaction mixture was poured into 10% aqueous sodium bisulfite containing ice, and the mixture was extracted with 3 × 50 mL of ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated. The residual material was purified on 100 mL of silica gel with 10% ether in dichloromethane as eluent. The eluate was recrystallized from chloroform–ether to give 1.04 g (54%) of **31** as colorless grains: mp 238–240 °C dec; MS *m/e* 388 (M^+), 261 ($M^+ - I$); ¹⁹F NMR δ 13.6 (s, 2- CF_3). HRMS *m/e* calcd for $C_4HF_3I_2N_2$ 387.8183 (M^+), 368.8199 ($M^+ - F$), 260.9137 ($M^+ - I$), found 387.8149 (M^+), 368.8213 ($M^+ - F$), 260.9088 ($M^+ - I$). Anal. Calcd for $C_4HF_3I_2N_2$: C, 12.39; H, 0.26; N, 7.22. Found: C, 12.61; H, 0.22; N, 7.42.

2,5-Diiodo-4-(trifluoromethyl)imidazole (32). Compound **6** (0.68 g, 5 mmol) was iodinated as for **1** with reflux for 8 h to give 1.58 g (82%) of **32** as colorless plates from chloroform: mp 191–194 °C dec; MS *m/e* 388 (M^+), 261 ($M^+ - I$), 134 ($M^+ - I_2$); ¹⁹F NMR δ 16.8 (s, 5- CF_3). HRMS *m/e* calcd for $C_4HF_3I_2N_2$ 387.8183 (M^+), 368.8199 ($M^+ - F$), 260.9137 ($M^+ - I$), found 387.8139 (M^+), 368.8204 ($M^+ - F$), 260.9096 ($M^+ - I$). Anal. Calcd for $C_4HF_3I_2N_2$: C, 12.39; H, 0.26; N, 7.22. Found: C, 12.69; H, 0.16; N, 7.44.

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