Photochemical Trifluoromethylation of Some Biologically Significant Imidazoles

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Received September 6, 1983

The trifluoromethyl radical, generated by UV irradiation of trifluoromethyl iodide in methanol solution, reacts with *N*-acylhistamines and *N*-acylhistidine esters to effect ring substitution at C-2 (13–27% yield) and at C-4 (23–34% yield). Small amounts of the 2,4-bis products are also obtained. 2-(4-Methoxyphenyl)imidazole is substituted selectively on imidazole in 55% yield and 2-(4-pyridyl)imidazole in 28% yield. Phototrifluoromethylation of methyl *trans*-urocanate provides low yields of the 4-CF_3 cis and 4-CF_3 trans ester, as well as products resulting from substitution and addition at the olefinic double bond.

We have recently described[1] the facile photochemical trifluoromethylation of a variety of simple imidazoles with trifluoromethyl iodide. The electrophilic trifluoromethyl radical was found to have varying degrees of preference for attack at C-4 (or C-5) over that at C-2 and exhibits very high selectivity for attack on imidazole relative to other heteroaromatic or benzenoid rings. Thus, at equimolar concentration, imidazole is ca. 20-fold times as reactive as pyridine in trapping the radical species. We have tested the utility of this method further by exploring the trifluoromethylation of several more complex imidazoles of biological and medicinal significance.

The results of photochemical trifluoromethylation of N-acylated histamines and L-histidine methyl esters (Scheme I) are given in Table I. Since the C-2 isomers had already been prepared by unequivocal, chemical syntheses[2] and the C-2 and C-4 isomers show clearly different δ values in their ^{19}F NMR spectra,[1] structural assignments could be made without difficulty. As with simpler imidazoles, the 4-trifluoromethyl products are somewhat favored over the 2-isomers and small amounts of 2,4-bis derivatives are also formed. Direct examination of the reaction mixtures by ^{19}F NMR showed no significant signals other than those given in Table I. Separation of photoproducts was readily achieved by silica gel chromatography. Protective groups were removed by acid hydrolysis[2,3] to provide the isomeric trifluoromethyl derivatives of histamine and L-histidine (as their hydrochloride salts). We have explored protection of the α-amino group with both acetyl and trifluoroacetyl functions; although it does not offer any material increase in yield, we prefer the latter group because of its greater lipophilicity, easier column separation, and more convenient acylation–deacylation procedures. For the large-scale preparation of the 2-trifluoromethyl derivatives (**5e**, **5f**), the ring-closure synthesis[2] is preferable because of higher yields and less costly reagents. The literature method for 4-(trifluoromethyl)imidazoles involves ring closures with bromotrifluoroacetone[4] and is most suitable for simple imidazoles; elaboration of compounds such as **6e** and **6f** would require a lengthy series of steps, some of questionable success.

Table I. Yields[a] and ^{19}F NMR Data[b] for Ring-Trifluoromethylated Histamines and Histidines

substrate	yield, % (^{19}F δ value)		
	2	3	4
1a	13.0 (13.9)	23.3 (17.2)	5.9 (12.9, 16.6)[c]
1b	22.5 (14.2)	30.5 (18.1)	trace (13.6, 17.2)
1c	21.1 (13.8)	34.0 (17.2)	trace (13.0, 16.9)
1d	27.3 (14.0)	32.0 (17.7)	trace (13.4, 17.2)

[a] Experimental conditions are somewhat variable; see Experimental Section for details. [b] NMR spectra for series a and c were measured in CD_3OD; for series b and d, in acetone-d_6. [c] The increased yield of the bis product may be related to the absence of triethylamine from the irradiation mixture.

We had already shown that trifluoromethylation of phenylimidazoles results in insignificant attack on the benzene ring;[1] a more reactive aromatic ring, however, might be more competitive. Accordingly, 2-(4-methoxyphenyl)imidazole (**7**) was subjected to phototrifluoromethylation and **8** was isolated in 55% yield (Scheme II). Although ^{19}F NMR of the crude reaction mixture gave only one signal, later fractions in the chromatographic purification of **8** gave ca. 5% of a mixture of two byproducts, in which trifluoromethylation had apparently occurred ortho and meta to the methoxy group. Compound **8**, an intermediate in drug synthesis, had been previously prepared from trifluoroacetone with an overall yield of 15%.[4]

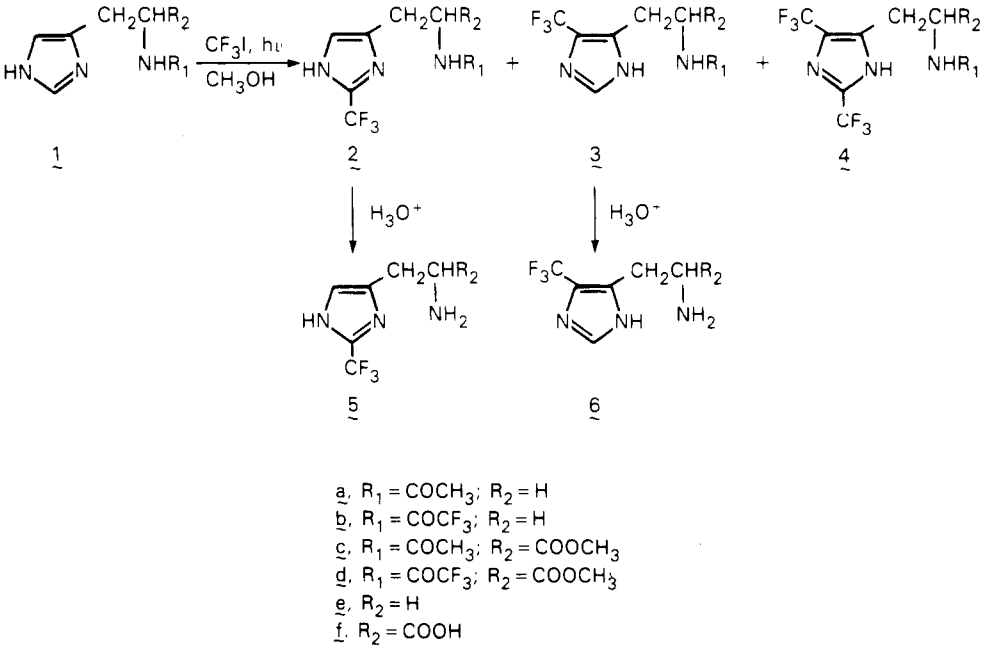
As noted above, pyridine is only weakly competitive with imidazole for the trifluoromethyl radical. The same selectivity is observed with 2-(4-pyridyl)imidazole (**9**), which provided **10** in 28% yield. Several byproducts were detected by ^{19}F NMR and by GC–MS; these materials, in a total yield of 3%, were readily separated from **10** on silica gel; the major byproduct is an isomer of **10** and probably involves substitution ortho to the pyridine nitrogen. Compound **10**, also of medicinal interest, had been prepared from trifluoroacetone in an overall yield of 26%.[4]

In view of the interesting and potentially important biological properties of 2-fluorourocanic acid,[5] we were prompted to attempt the syntheses of the trifluoromethyl analogues. Since urocanic acid is very poorly soluble in all common solvents, we chose to work with the methyl

(1) Kimoto, H.; Fujii, S.; Cohen, L. A. *J. Org. Chem.* **1982**, *47*, 2867–2872.
(2) Kimoto, H.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1978**, *43*, 3403–3405.
(3) (Trifluoromethyl)imidazoles are labile under alkaline conditions: Kimoto, H.; Cohen, L. A. *J. Org. Chem.* **1979**, *44*, 2902–2906.
(4) Baldwin, J. J.; Kisinger, P. A.; Novello, F. C.; Sprague, J. H. *J. Med. Chem.* **1975**, *18*, 895–900.
(5) Klee, C. B.; La John, L. E.; Kirk, K. L.; Cohen, L. A. *Biochem. Biophys. Res. Commun.* **1977**, *75*, 674–681.

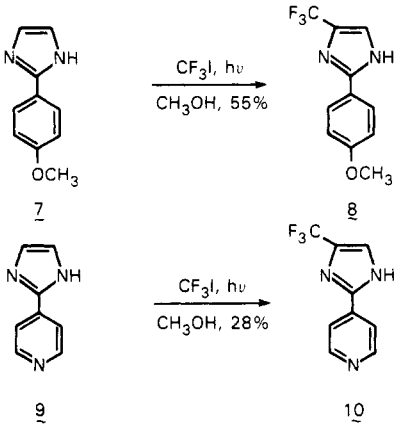
0022-3263/84/1949-1060$01.50/0

Scheme I



a, $R_1 = COCH_3$; $R_2 = H$
b, $R_1 = COCF_3$; $R_2 = H$
c, $R_1 = COCH_3$; $R_2 = COOCH_3$
d, $R_1 = COCF_3$; $R_2 = COOCH_3$
e, $R_2 = H$
f, $R_2 = COOH$

Scheme II



ester (**11a**). Low yields and complex mixtures were anticipated, not only because of the electron-withdrawing effect of the acrylic ester moiety but also because of the high reactivity of olefins toward the trifluoromethyl radical. Indeed, both these expectations were realized. The isolated and identified products are shown in Scheme III (yield in parentheses). Structural assignments for **12** and **13** follow directly from MS, ^1H NMR, and ^{19}F NMR data. The ^{19}F δ values are consistent with those found for other 4-(trifluoromethyl)imidazoles[1] and are readily differentiated from values for the C-2 series. Both the δ and J values for the olefinic protons correspond well with those observed for the simple *cis*- and *trans*-urocanic esters (**11a**, **11b**).[6] Our assignments for **14** and **15**, although not quite as conclusive, are supported by the NMR data for less equivocal structures; values of $J_{H,F}$ for geometrical isomers of trifluoromethyl olefins[7] are too similar to provide a basis for assignment. Instead, we have compared the ^1H δ values for the olefinic protons with published data for α-cyanocinnamic esters.[8] Structure **16** is proposed for an unresolved mixture of diasteroisomers on the basis of GC–MS and ^{19}F NMR data. The assumption that methanol has coupled at carbon follows from the radical nature of the reaction. No products were found with trifluoromethyl substitution of 2-H or of β-H; these results are reminiscent of those obtained with benzimidazole[1] and may be based on the most effective resonance stabilization of the intermediate radicals. While the isomeric pair **12** and **13** were obtained in almost equal amount, it is interesting that the geometrical isomers of **14** and **15** were not observed. These *E* products may be preferred for steric and/or electronic reasons or the double bond of the cis ester (**11b**) may be the more reactive toward the trifluoromethyl radical. Kinetic data (see Experimental Section and ref 1) show that light-catalyzed trans–cis isomerization of **11a** occurs more rapidly than does trifluoromethylation; thus, a unique sequence of steps cannot yet be assigned and further experiments are in progress.

Our experience, to date, suggests that electron-withdrawing groups deactivate the imidazole ring, resulting in longer reaction times and reduced yields (e.g., **10**, **12**, **13**). At the same time, these substrates have strong UV absorption at the principal wavelength of the light source (254 nm) and are probably competing with CF_3I for the available photons. We are currently exploring alternative sources for the trifluoromethyl radical.

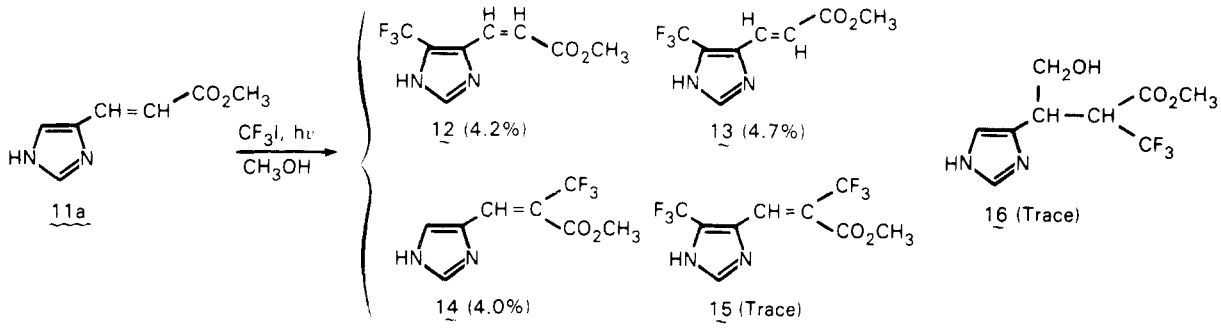
The representative cases described herein demonstrate the feasibility of direct photochemical introduction of the trifluoromethyl group into polyfunctional imidazoles. Our interest in the biological properties of even more complex cases (analogues of peptide hormones, purine precursors, antihistamines) provides the basis for additional studies now in progress.

Experimental Section

Analytic methods, light sources, and instrumentation have been described prevously.[1] GC–MS data were recorded on a Shimadzu instrument (Model 7000); the column (3 mm × 300 cm) was packed with 1.5% OV-17 Chromosorb WAW DMCS (80-100 mesh); separations were perfomed at 150-200 °C with helium as carrier gas. ^1H NMR spectra were recorded with Me_4Si or DSS (for D_2O) as internal reference; ^{19}F NMR spectra are reported with positive δ values downfield from the external reference, trifluoroacetic acid. Elemental analyses were performed by the Microanalytical and Instrumental Section of the Laboratory of

(6) The isomeric urocanic acids show the same values of $J_{H,H}$: Baden, H. P.; Pathak, M. A.; Butler, D. *Nature (London)* **1966**, *210*, 732–733.
(7) Gregory, R.; Haszeldine, R. N.; Tipping, A. E. *J. Chem. Soc. C* **1971**, 1216–1223.
(8) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. "Spectrometric Identification of Organic Compounds", 4th ed.; Wiley: New York, 1981; pp 227–228.

Scheme III



Chemistry, NIADDK, under the direction of Dr. D. F. Johnson. The homogeneity and identity of each product were verified by NMR, MS, GC, and TLC; satisfactory analytical data were reported for compounds indicated.

Phototrifluoromethylation of α-*N*-Acetylhistamine (1a). A solution of 3.83 g (0.025 mol) of **1a** and trifluoromethyl iodide (4.9 g, 0.025 mol) in 20 mL of methanol was irradiated (15-W lamp) for 7 days at ambient temperature. GC–MS and ^{19}F NMR of the crude reaction mixture revealed three fluorine-containing products, which were eluted from 200 mL of silica gel (ethyl acetate–methanol, 9:1) in the following order.

A. α-*N*-Acetyl-2,4-bis(trifluoromethyl)histamine (4a, 0.45 g, 5.9%): mp 209–210 °C (ethanol–ethyl acetate); IR (KBr) 3320 (NH), 1634 (C=O) cm^{-1}; ^1H NMR (5% in CD_3OD) δ 1.86 (s, 3, $COCH_3$), 2.95 (t, 2, J = 7 Hz, β-CH_2), 3.42 (t, 2, J = 7 Hz, α-CH_2); ^{19}F NMR (5% in CD_3OD) δ 12.9 (s, 3, 2-CF_3), 16.6 (br s, 3, 4-CF_3). Anal. ($C_9H_9F_6N_3O$) C, H, N. F.

B. α-*N*-Acetyl-2-(trifluoromethyl)histamine (2a, 0.72 g 13.0%): mp 143–144 °C (ethanol–ethyl acetate); IR (KBr) 3265 (NH), 1646 (C=O) cm^{-1}; ^1H NMR (2% in CD_3OD) δ 1.90 (s, 3, $COCH_3$), 2.80 (t, 2, J = 7 Hz, β-CH_2), 3.44 (t, 2, J = 7 Hz, α-CH_2), 7.02 (s, 1, H-4); ^{19}F NMR (2% CD_3OD) δ 13.9 (s, CF_3). Anal. ($C_8H_{10}F_3N_3O$) C, H, N. F.

C. α-*N*-Acetyl-4-(trifluoromethyl)histamine (3a, 1.29 g, 23.3%): mp 198–199 °C (ethanol–ethyl acetate); IR (KBr) 3280 (NH), 1646 (C=O) cm^{-1}; ^1H NMR (5% in CD_3OD) δ 1.85 (s, 3, $COCH_3$), 2.90 (t, 2, J = 7 Hz, β-CH_2) 3.36 (t, 2, J = 7 Hz, α-CH_2), 7.64 (br s, 1, H-2); ^{19}F NMR (5% in CD_3OD) δ 17.2 (br s, CF_3). Anal. ($C_8H_{10}F_3N_3O$) C, H, N. F.

A portion of the starting material served to neutralize the hydrogen iodide liberated and the resulting salt is inert to electrophilic attack.[1] Thus, yields may be increased by use of an excess of **1a** or by addition of triethylamine (see below).

Phototrifluoromethylation of 1b. To 100 mL of trifluoroacetic anhydride was added, with stirring at ambient temperature, 18.4 g (0.1 mol) of histamine dihydrochloride in 4-g portions at 10-min intervals. The reaction mixture was stirred an additional 2 h and the solvent was removed by distillation. The residual material was dissolved in 100 mL of methanol and the solution was refluxed for 1 h. Evaporation of solvent gave a slightly yellow syrup, which was used for trifluoromethylation without further treatment.[9]

A solution of the syrup in 40 mL of methanol was cooled in dry ice and 15.2 g (0.15 mol) of triethylamine was added, followed by 9.8 g (0.05 mol) of trifluoromethyl iodide. The solution was irradiated (60-W lamp) for 3 days; the crude reaction mixture showed two principal ^{19}F NMR signals in the expected region–14.5 (35%) and 18.3 ppm (65%). The solvent was evaporated and the residual material was fractionated on 150 mL of silica gel (ethyl acetate as eluant), the compounds appearing in the following order.

A. α-*N*-(Trifluoroacetyl)-2,4-bis(trifluoromethyl)histamine (4b, trace): mp 173–174 °C (benzene); ^1H NMR (5% in acetone-d_6) δ 3.15 (t, 2, J = 7 Hz, β-CH_2), 3.69 (td, 2, J = 7, 7 Hz, α-CH_2), 8.76 (br t, 1, J = 7 Hz, α-NH); ^{19}F NMR (5% in acetone-d_6) δ 1.3 (s, 3, $COCF_3$) 13.6 (s, 3, 2-CF_3), 14.2 (s, 3, 4-CF_3).

B. α-*N*-(Trifluoroacetyl)-2-(trifluoromethyl)histamine (2b, 3.10 g, 22.5%): mp 147.5–148.5 °C (benzene); ^1H NMR (10% in acetone-d_6) δ 2.99 (t, 2, J = 7 Hz, β-CH_2), 3.69 (td, 2, J = 7, 7 Hz, α-CH_2), 7.15 (s, 1, H-4), 8.84 (br t, 1, J = 7 Hz, α-NH); ^{19}F NMR (10% in acetone-d_6) δ 1.3 (s, 3, $COCF_3$), 14.2 (s, 3, 2-CF_3). Anal. ($C_8H_7F_6N_3O$), C, H, N, F.

C. α-*N*-(Trifluoroacetyl)-4-(trifluoromethyl)histamine (3b, 4.19 g, 30.5%): mp 179.0–179.5 °C (ethyl acetate); ^1H NMR (5% in acetone-d_6) δ 3.11 (t, 2, J = 7 Hz, β-CH_2), 3.65 (td, 2, J = 7, 7 hz, α-CH_2), 7.80 (s, 1, H-2), 8.90 (br t, 1, J = 7 Hz, α-NH); ^{19}F NMR (5% in acetone-d_6) δ 1.4 (s, 3, $COCF_3$), 18.1 (s, 3, 4-CF_3). Anal. ($C_8H_7F_6N_3O$) C, H, N, F.

Phototrifluoromethylation of 1c. To a solution of 1.22 g (0.02 mol) of **1c**[10] in 10 mL of methanol were added 1.01 g (0.01 mol) of triethylamine and 1.96 g (0.01 mol) of trifluoromethyl iodide. The solution was irradiated (60-W lamp) for 3 days, the solvent was removed, and the residual material was fractionated on 180 mL of silica gel (eluant, 5% methanol in ethyl acetate).

A. Initial fractions gave a small amount of colored tar, which, according to GC–MS and ^{19}NMR, contained the bis product **4c**; purification was not attempted.

B. α-*N*-Acetyl-2-(trifluoromethyl)-L-histidine Methyl Ester (2c, 0.59 g, (21.1%): mp 136–137 °C (neat); ^1H NMR (10% in CD_3OD) δ 1.94 (s, 3, $COCH_3$), 3.10 and 3.13 (2 d, 2, J = 6, 8 Hz, β-CH_2), 3.69 (s, 3, OCH_3), 4.75 (dd, 1, J = 6, 8 Hz, α-CH), 7.08 (s, 1, H-4); ^{19}F NMR (10% in CD_3OD) δ 13.8 (s, 2-CF_3); IR (KBr) 1663 and 1745 (C=O's) cm^{-1}. Anal. ($C_{10}H_{12}F_3N_3O_3$) C, H, N, F.

C. α-*N*-Acetyl-4-(trifluoromethyl)-L-histidine Methyl Ester (3c, 0.95 g, 34.0%): mp 178–179.5 °C (ethanol–ethyl acetate); ^1H NMR (2% in CD_3OD) δ 1.92 (s, 3, $COCH_3$), 3.69 (s, 3, OCH_3), 4.32 (br d, 2, J = 8 Hz, β-CH_2), 4.70 (t, 1, J = 8 Hz, α-CH), 7.71 (br s, 1, H-2); ^{19}F NMR (2% in CD_3OD) δ 17.2 (br s, 4-CF_3); IR (KBr) 1653 and 1739 (C=O's) cm^{-1}. Anal. ($C_{10}H_{12}F_3N_3O_3$) C, H, N, F.

Phototrifluoromethylation of 1d. α-*N*-(Trifluoroacetyl)-L-histidine methyl ester trifluoroacetate (**1d**·CF_3COOH) was prepared from 24.2 g (0.1 mol) of L-histidine methyl ester dihydrochloride;[11] the crude product, a viscous liquid, was used directly for irradiation following the procedure used for **1b**. The reaction mixture was evaporated to dryness and the residual material was chromatographed on 150 mL of silica gel with ether and ethyl acetate as successive eluants.

A. Initial fractions gave a small amounts of the bis(trifluoromethyl) derivative **4d**, which could not be crystallized: ^1H NMR (5% in acetone-d_6) δ 3.74 (s, 3, OCH_3), 3.48 (d, 2, J = 7 Hz, β-CH_2, 4.96 (dt, 1, J = 7, 7 Hz, α-CH), 8.93 (br d, 1, J = 7 Hz, α-NH); ^{19}F NMR (5% in acetone-d_6) δ 1.3 (s, 3, $COCF_3$), 13.4 (s, 3, 2-CF_3), 17.2 (s, 3, 4-CF_3).

B. α-*N*-(Trifluoroacetyl)-2-(trifluoromethyl)-L-histidine Methyl Ester (2d, 4.55 g, 27.3%): mp 133.5–134 °C (benzene–ether); ^1H NMR (5% in acetone-d_6) δ 3.24 (d, 2, J = 6 Hz, β-CH_2), 3.71 (s, 3, OCH_3), 4.85 (dt, 1, J = 6, 7 Hz, α-CH), 7.25 (br s, 1, H-4), 8.86 (br d, 1, J = 7 Hz, α-NH); ^{19}F NMR (5% in acetone-d_6) δ 1.2 (br s, 3, $COCF_3$), 14.0 (s, 3, 2-CF_3). Anal. ($C_{10}H_9F_6N_3O_3$) C, H, N, F.

(9) This material is free of chloride ion, shows ^{19}F NMR signals at 1.1 and 1.2 ppm of equal intensity, and crystallizes readily from ethanol, mp 105–106 °C. The same product has been obtained by trifluoroacetylation of histamine (free base): Kirk, K. L.; Nagai, W.; Cohen, L. A. *J. Am. Chem. Soc.* **1973**, *95*, 8389–8392.

(10) The free base has been obtained in crystalline form: Nagai, W.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1973**, *38*, 1971–1974. Matthews, H. R.; Rapoport, H. *J. Am. Chem. Soc.* **1973**, *95*, 2297–2301.

(11) Makisumi, S.; Saroff, H. A. *J. Gas Chromatogr.* **1965**, 21–27.

C. α-*N*-(Trifluoroacetyl)-4-(trifluoromethyl)-L-histidine Methyl Ester (3d, 5.33 g, 32.0%): mp 214.5–215.5 °C (ethyl acetate); ^{1}H NMR (3% in acetone-d_6) δ 3.36 (d, 2, J = 6 Hz, β-CH_2), 3.70 (s, 3, OCH_3), 4.84 (dt, 1, J = 6, 8 Hz, α-CH), 7.70 (s, 1, H-2), 8.86 (br d, 1, J = 8 Hz, α-NH); ^{19}F NMR (3% in acetone-d_6) δ 1.3 (br s, 3, $COCF_3$), 17.7 (br s, 3, 4-CF_3). Anal. ($C_{10}H_9F_6N_3O_3$) C, H, N. F.

4-(Trifluoromethyl)histamine Dihydrochloride (6e·2HCl). A solution of 550 mg (2.0 mmol) of **3b** in 20 mL of 3 N hydrochloric acid was maintained at 60 °C for 3 h. The solution was evaporated to dryness and the residual solid was crystallized from ethanol: mp 231–233 °C; ^{1}H NMR (2% in D_2O) δ 3.32 (s, 4, α- and β-CH_2), 8.72 (s, 1, H-2); ^{19}F NMR (2% in D_2O) δ 19.4 (s, CF_3); Anal. ($C_6H_{10}Cl_2F_3N_3$) C, H, N, Cl, F.

4-(Trifluoromethyl)-L-histidine Dihydrochloride (6f·2HCl). Acid hydrolysis of **3d** was performed as for **3b**; the product was obtained as an amorphous powder, which could not be crystallized: mp 230–240 °C dec; ^{1}H NMR (5% in D_2O) δ 3.70 (d, 2, J = 8 Hz, β-CH_2), 4.55 (t, 1, J = 8 Hz, α-CH), 9.08 (s, 1, H-2); ^{19}F NMR (5% in D_2O) δ 19.8 (s, CF_3); $[\alpha]^{24}_D$ +28.6° (0.85, H_2O). Anal. ($C_7H_{10}Cl_2F_3N_3O_2$) C, H, N, Cl, F.

2-(Trifluoromethyl)histamine (5e) and 2-(Trifluoromethyl)-L-histidine (5f). These compounds were obtained, as their hydrochlorides, by acid hydrolysis of **2b** and **2d**, respectively, according to the procedure described above. The products were identical in every respect (including optical rotation of **5f**) with those obtained by the ring-closure route.[2]

2-(4-Methoxyphenyl)-4-(trifluoromethyl)imidazole (8). A solution of 4.36 g (0.025 mol) of **7**,[12] 1.26 g (0.0125 mol) of triethylamine, and 2.45 g (0.0125 mol) of trifluoromethyl iodide in 20 mL of methanol was irradiated (60 W lamp) for 3 days. Direct ^{19}F NMR analysis showed only one peak (ca. 15 ppm). The solvent was evaporated and the residual material was purified on 250 mL of silica gel with ethyl acetate as eluant. The product was crystallized from benzene to give 1.65 g (55%) of **8**: mp 210–212 °C (lit.[4] mp 204–206 °C); ^{1}H NMR (2% in acetone-d_6) δ 3.80 (s, 3, OCH_3), 7.61 (q, 1, J = 1.3 Hz, H-5), 6.97 and 7.90 (AA'BB', 4, J = 8 Hz, aryl H's); ^{19} F NMR (2% in acetone-d_6) δ 15.3 (d, J = 1.3 Hz, CF_3).

Continued elution of the column provided 150 mg of material isomeric with **8** (according to MS); ^{19}F NMR showed signals at 15.4 and at 18.7 ppm in the ratio 1:3. These products, undoubtedly resulting from trifluoromethylation of the anisole ring, were not investigated further.

2-(4-Pyridyl)imidazole (9).[13] Isonicotinaldehyde (25 g, 0.233 mol) was added slowly to a mixture of 80 mL of 28% aqueous ammonia and 50 mL of ethanol. The reaction mixture was heated to reflux and 70 mL (0.466 mol) of 40% glyoxal (aqueous) was added dropwise with stirring. Reflux was continued for 6 h, ethanol was removed in vacuo, and the dark, aqueous solution was filtered to remove a black solid. The filtrate was extracted ten times with 60 mL of ethyl acetate and three times with 100 mL of methanol in ethyl acetate (1:9);[14] the two sets of extracts were dried separately ($MgSO_4$) and evaporated to give 15.5 and 15.7 g, respectively, of tarry residue. These materials were fractionated by preparative HPLC (silica gel, 5% methanol in ethyl acetate) to give a total of 14.9 g of crude **9**. A second purification by preparative HPLC gave 6.7 g (20%) of pale yellow crystals. Recrystallization from ethyl acetate afforded colorless plates, mp 211–213 °C.[13]

2-(4-Pyridyl)-4-(trifluoromethyl)imidazole (10). A solution of 2.90 g (0.02 mol) of **9**, 1.01 g (0.01 mol) of triethylamine, and 1.96 g (0.01 mol) of trifluoromethyl iodide in 20 mL of methanol was irradiated (60 W lamp) for 3 days. ^{19}F NMR analysis showed peaks at 14.8, 67.3 (CF_3I), −1.1 and −2.5 (CF_3H) ppm. The solvent was evaporated and the residual material was purified on 180 mL of silica gel with ethyl acetate as eluant. The product (0.59 g, 28%) was recrystallized from benzene–ethyl acetate: mp 211–212 °C (lit.[4] mp 211–212 °C); ^{1}H NMR (5% in acetone-d_6) δ 7.83 (q, 1, J = 1.3 Hz, H-5), 7.91 and 8.69 (AA'BB', 4, J = 4.5, 1.7 Hz, pyridine H's); ^{19}F NMR (5% in acetone-d_6) δ 15.0 (d, J = 1.3 Hz, CF_3).

(*E*)-Methyl Urocanate (11a). Dry hydrogen chloride was passed into a suspension of 25 g (0.18 mol) of *trans*-urocanic acid in 500 mL of methanol. After the solid material had dissolved completely (10 min), the solution was heated at reflux for 3 h and was stored overnight at ambient temperature. A crystalline mass was removed by filtration; concentration of the mother liquor provided additional material, and the combined solids were recrystallized from methanol to give 28.4 g (83%) of **11a·HCl**: mp 233–234 °C dec (lit.[15] mp 233–235 °C).

A suspension of 18.9 g (0.10 mol) of **11a·HCl** in 100 mL of methanol was cooled with dry ice and a solution of potassium hydroxide (5.6 g, 0.10 mol) in 50 mL of methanol was added slowly. The resulting solution was evaporated to dryness in vacuo and the residual solid was extracted with five 50-mL portions of ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated to give 10.3 g (68%) of crystalline **11a**, which was used for irradiation experiments without further purification: prisms (ethyl acetate), mp 94–96 °C; IR (KBr) 1716 (C=O), 1645 (C=C) cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.78 (s, 3, OCH_3), 6.45 (d, 1, J = 16 Hz, α-CH=), 7.62 (d, 1, J = 16 Hz, β-CH=), 7.55 (s, 1, H-4), 7.83 (s, 1, H-2).

Photoisomerization of Methyl Urocanate Isomers. A solution of **11a** (0.2 g) in CD_3OD (0.5 mL) was irradiated (60-W lamp) in a quartz NMR tube and the rate of isomerization was followed directly by ^{1}H NMR. After 24 h, a trans–cis ratio of 52:48 was obtained by integration and k_{app} = 0.029 h^{-1} (uncorrected for reversibility).[16] After irradiation for 24 h, a sample of methyl *cis*-urocanate showed a trans–cis ratio of 44:56 and k_{app} = 0.022 h^{-1}. The isomers are separable on silica gel, the cis form eluting first with methanol–ethyl acetate (1:19). Methyl *cis*-urocanate (**11b**) was obtained as an oil: IR (neat) 1698 (C=O), 1622 (C=C) cm^{-1}; NMR (CD_3OD) δ 3.77 (s, 3, OCH_3), 5.73 (d, 1, J = 13 Hz, α-CH=), 6.95 (d, 1, J = 13 Hz, β-CH=), 7.66 (s, 1, H-4), 7.92 (s, 1, H-2).

Phototrifluoromethylation of 11a. To a solution of **11a** (7.60 g, 0.05 mol) in 30 mL of methanol was added triethylamine (2.53 g, 0.025 mol) and trifluoromethyl iodide (4.90 g, 0.025 mol). The solution, contained in two 20-mL quartz ampules, was irradiated for 7 days with a 60-W lamp. Both ^{19}F NMR and GC–MS indicated three principal products and a number of minor ones. The solvent was removed and the residual material was fractionated on 180 mL of silica gel, with ethyl acetate as eluant. The trifluoromethylated products were eluted rapidly; the first fractions provided a small amount of an oil whose MS and NMR spectra are consistent with structure **15**: ^{1}H NMR (2% in acetone-d_6) δ 3.94 (s, 3, OCH_3), 7.64 (br s, 1, β-CH=), 8.08 (s, 1 H-2); ^{19}F NMR (2% in acetone-d_6) δ 14.5 (br s, 3, α-CF_3), 17.2 (s, 3, 4-CF_3). Further elution with ethyl acetate provided a mixture, which was fractionated on a second silica gel column (120 mL), using ether–ethyl acetate (1:1) and ethyl acetate as successive eluants.

A. (*Z*)-Methyl 4-(Trifluoromethyl)urocanate (12, 0.23 g, 4.2%): prisms (chloroform), mp 102–103 °C; IR (KBr) 1708 (C=O), 1636 (C=C) cm^{-1}; ^{1}H NMR (5% in acetone-d_6) δ 3.83 (s, 3, OCH_3), 6.02 (d, 1, J = 13 Hz, α-CH=), 7.12 (d, 1, J = 13 Hz, β-CH=), 7.99 (s, 1, H-2); ^{19}F NMR (5% in acetone-d_6) δ 18.3 (s, 4-CF_3).

B. (*E*)-Methyl 4-(Trifluoromethyl)urocanate (13, 0.26 g, 4.7%): prisms (ethyl acetate), mp 199–200 °C; IR (KBr) 1744 (C=O), 1665 (C=C) cm^{-1}; ^{1}H NMR (10% in acetone-d_6) δ 3.77 (s, 3, OCH_3), 6.56 (d, 1, J = 16 Hz, α-CH=), 7.68 (d, 1, J = 16 Hz, β-CH=) 7.95 (s, 1, H-2); ^{19}F NMR (10% in acetone-d_6) δ 17.7 (br s, 4-CF_3).

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(14) Continuous extraction with ethyl acetate for 24 h afforded similar results.

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(16) A similar photostationary state ratio is observed for the isomerism of urocanic acid: Baden, H. P.; Pathak, M. A. *J. Invest. Dermatol.* **1967**, *48*, 11–17. Morrison, H.; Avnir, D.; Bernasconi, C.; Fagan, G. *Photochem. Photobiol.* **1980**, *32*, 711–714.

C. (*E*)-Methyl α-(Trifluoromethyl)urocanate (14, 0.22 g, 4.0%): oil; IR (neat) 1730 (C=O), 1635 (C=C) cm^{-1}; ^1H NMR (10% in acetone-d_6) δ 3.87 (s, 3, OCH_3), 7.57 (qd, 1, J = 1.4, 0.4 Hz, β-CH=), 7.92 and 7.94 (2 s, 2, H-2, H-4); ^{19}F NMR (10% in acetone-d_6) δ 15.3 (s, α-CF_3).

Further elution of the original column with methanol–ethyl acetate (1:19) afforded a small amount of material whose GC–MS and ^{19}F NMR spectra suggested a mixture of diastereoisomers of structure **16**. This material was followed by elution of 1.79 g of **11b** and 2.09 g of **11a**. In a second run with equimolar quantities of **11a** and trifluoromethyl iodide, the yields of **12–14** were reduced somewhat, while those of **15** and **16** were somewhat higher.

Registry No. **1a**, 673-49-4; **1b**, 50580-77-3; L-**1c**, 36097-48-0; L-**1d**, 1604-44-0; **2a**, 88181-33-3; **2b**, 88181-34-4; L-**2c**, 88181-35-5; L-**2d**, 88181-36-6; **3a**, 88181-37-7; **3b**, 88181-38-8; L-**3c**, 88181-39-9; L-**3d**, 88181-40-2; **4a**, 88181-41-3; **4b**, 88181-42-4; L-**4c**, 88181-43-5; L-**4d**, 88181-44-6; **5e**·HCl, 88181-45-7; L-**5f**·HCl, 88181-46-8; **6e**·2HCl, 88181-47-9; L-**6f**·2HCl, 88181-48-0; **7**, 52091-37-9; **8**, 33469-37-3; **9**, 21202-42-6; **10**, 33468-83-6; (*E*)-**11a**, 70346-51-9; (*E*)-**11a**·HCl, 54260-89-8; (*Z*)-**11b**, 88181-49-1; (*Z*)-**12**, 88181-50-4; (*E*)-**13**, 88181-51-5; (*E*)-**14**, 88181-52-6; (*E*)-**15**, 88181-53-7; **16** (isomer 1), 88181-54-8; **16** (isomer 2), 88181-55-9; trifluoromethyl iodide, 2314-97-8; *trans*-urocanoic acid, 3465-72-3; isonicotinaldehyde, 872-85-5; glyoxal, 107-22-2.

Hydroboration. 66. Addition of Lithium Triethylborohydride to Substituted Styrenes. A Simple, Convenient Procedure for the Markovnikov Hydroboration of Aromatically Conjugated Olefins and the Synthesis of Unusual Mixed Trialkylboranes

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Received August 9, 1983

The addition of lithium trialkylborohydride to substituted styrenes and the synthetic applications of the products are described. Styrene, α- and β-methyl-, *p*-chloro-, and *p*-methoxystyrene readily undergo the addition reaction in refluxing tetrahydrofuran or in diglyme at 100 °C. 1,1-Diphenylethylene reacts readily, even at 0 °C. The double bond in cinnamaldehyde also adds the reagent following initial reduction to the cinnamyl derivative. Substituents that decrease the electron density at the double bond increase the rate of the addition. For the system, p-$XC_6H_4CH{=}CH_2$, the rate is in the order of X = Cl > H > OMe. *trans*-β-Methylstyrene and α-methylstyrene react slower than styrene itself. Lithium tri-*n*-butylborohydride also undergoes these reactions. However, hindered trialkylborohydrides, such as lithium triisobutylborohydride and lithium tri-*sec*-butylborohydride, exhibit a slower reaction, which fails to go to completion, even with styrene. The resulting addition products, lithium tetraalkylborates, are transformed into the corresponding aromatic hydrocarbons by hydrolysis. More significantly, the protonolysis of these borates with strong acids yields mixed trialkylboranes by selective protonation of the ethyl group. Oxidation of these boranes gives only α-ols, indicating that the boron atom is attached exclusively to the α-carbon. The observed regiochemistry and electronic effects suggest that the reaction involves a nucleophilic attack of R_3BH^- on the styrene double bond to form the carbanion $ArCHMe^-$, which is trapped by R_3B to form the tetraalkylborate product. Consequently, the present method provides a Markovnikov hydroboration of substituted styrenes with exceptional regioselectivity.

Addition of complex metal hydrides to aromatically conjugated olefins has been reported with a variety of reagents. Lithium aluminum hydride reacts with dibenzofulvenes,[2] 9-methylenexanthenes,[3,4] methylenebenzanthrene,[4] and 1,1-diphenylethylenes[4-6] but not with styrene.[5] Cinnamaldehyde and cinnamyl alcohols are reduced to dihydrocinnamyl alcohol[2,7,8] or to phenylcyclopropanes[9] with lithium aluminum hydride and to dihydrocinnamyl alcohol with lithium trimethoxyaluminohydride.[10] Similarly, sodium bis(2-methoxyethoxy)aluminum hydride[11] reduces some aromatically conjugated olefins such as 1,1-diphenylethylene. Reductive alkylations of aromatic olefins have also been reported with lithium aluminum hydride[5] and with sodium bis(2-methoxyethoxy)aluminum hydride.[11]

Reduction of carbon–carbon double bonds conjugated with strong anion-stabilizing groups (e.g., COR, CO_2R, CN, SO_2R, NO_2) has been observed with sodium borohydride,[12] with potassium tri-*sec*-butylborohydride,[13] and with the "ate" complex of copper(I) hydride.[14] However, these reactions were shown to involve the 1,4-addition of the hydride molecule.

Sodium triethylborohydride has been reported to react with ethylene at high pressure and temperature to form sodium tetraethylborate (eq 1).[15] However, no study was reported with aromatically conjugated olefins.

$$NaEt_3BH + CH_2{=}CH_2 \xrightarrow[80\ atm,\ 2\ h]{140\text{–}150\ ^\circ C} NaEt_4B \qquad (1)$$

(1) Graduate research assistant on Grant No. DA-ARO-D-31-124-73-G148, supported by the U.S. Army Research Office (Durham), 1971–1976.
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