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FACILE SYNTHESES OF 4-(TRIFLUOROMETHYL)-L-SPINACINE AND 4-(TRIFLUOROMETHYL)SPINACEAMINE

SHOZO FUJII, YASUO MAKI, HIROSHI KIMOTO*

Government Industrial Research Institute, Nagoya;
Hirate-cho, Kita-ku, Nagoya 462 (Japan)

LOUIS A. COHEN

Laboratory of Chemistry; National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases; National Institutes of Health; Bethesda, Maryland 20892 (U.S.A.)

SUMMARY

Reaction of L-histidine with trifluoroacetaldehyde ethyl hemiacetal (TFAE) in boiling water provides 4-(trifluoromethyl)-L-spinacine, 4-(trifluoromethyl)-L-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid, in near quantitative yield. The product contains two diastereoisomers in the ratio 68 : 32. The isomers were separated (silica gel) as their protected derivatives, 5-N-(trifluoroacetyl)-4-(trifluoromethyl)-L-spinacine methyl esters, and were regenerated by acid hydrolysis. The analogous reaction with histamine provides 4-(trifluoromethyl)spinaceamine in 91% yield.

INTRODUCTION

We have recently described the thermal condensation of imidazole[1] and its simple derivatives[2] with trifluoroacetaldehyde ethyl hemiacetal (TFAE). As a demonstration of the scope and utility of the condensation, we now describe the facile reactions observed with L-histidine and histamine.

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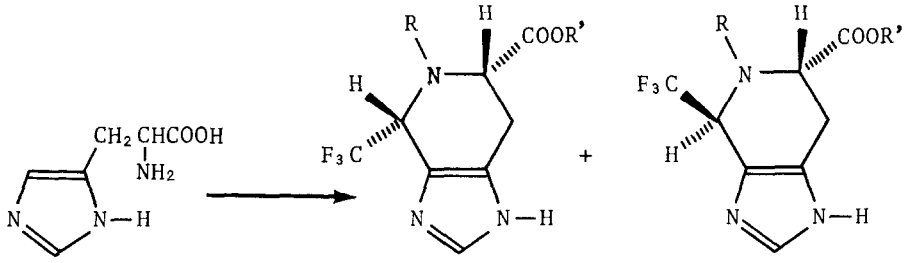
RESULTS AND DISCUSSION

Condensation of TFAE with L-histidine (in boiling water) leads to 4-(trifluoromethyl)-L-spinacine (I), 4-(trifluoromethyl)-L-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid, in nearly quantitative yield. 4-Monosubstituted spinacines contain two chiral centers and, thus, diastereoisomers are to be expected in the synthesis. Direct ^{19}F NMR analysis of crude I shows the presence of two products in the ratio 68 : 32. Separation of these products by fractionation



A B

I, R = H, R' = H

II, R = $COCF_3$, R' = CH_3

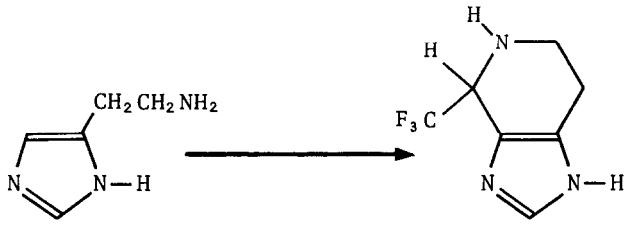
could not be effected. The total material was then converted into a mixture of N-trifluoroacetyl methyl esters (II) and separation was achieved by silica gel chromatography. The pure esters, which proved to be diastereoisomers, were deprotected by acid hydrolysis to give IA and IB. No interconversion between IA and IB occurred in acidic conditions.

Assignment of configuration to the isomers (A = cis, B = trans) is based on their ^1H NMR spectra and on the assumption of absence of racemization during the manipulations. The high value of $J_{H_6 - H_7}$ (8-10 Hz) in both compounds corresponds to axial-axial coupling; thus, the carboxyl group at C-6 is probably equatorial in both isomers[3]. Since axial hydrogen is generally found at higher field than equatorial[4], isomer A (H-4, δ 4.99) is considered the cis isomer and B (H-4, δ 5.29)

is considered trans. Judging from NMR, N-trifluoroacetyl methyl esters (II) seem to have different conformations from I. In condensations of L-histidine with benzaldehyde[5] and with pyridoxal[3], the trans isomers predominate to varying degree; with L-histidine methyl ester, however, the cis isomer is formed in excess[3]. Thus, it would appear that the diastereoisomers are not markedly different in energy and that the ratio may be sensitive to small structual differences. Furthermore, we cannot exclude some stabilization of IA by hydrogen bonding between imidazole-NH and the equatorial trifluoromethyl group.

The analogous condensation of histidine with formaldehyde, to give the parent spinacine, was first reported in 1913[6]. Subsequently, spinacine was isolated from shark liver[7] and from crabs[8]. The 5-N-hydroxymethyl derivative of spinacine (a by-product of the condensation[6b]) is claimed to have activity against several types of cancer in mice[9]. Condensation of histidine with other aldehydes and ketones leads to 4-substituted spinacines; derivatives of these compounds show long-acting antihypertensive activity[10] and antagonism to benzodiazepine receptors[5]. The latter work suggests that activity may be enhanced by reduction in the basicity of the piperidine and/or imidazole nitrogen. Since none of the 4-substituted spinacines described or evaluated, to date, contain electronegative substituents, the present work also serves as a starting point for a series of such compounds.

The parallel reaction of histamine with TFAE leads to 4-(trifluoromethyl)spinaceamine(III), 4-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-imidazo-[4,5-c]pyridine, in 91% yield.



III

Histamine dihydrochloride does not react with TFAE. Spinaceamine and its 5-N-methyl derivative have been found in the skin of frogs native to tropical America[11] and to Oceania[12]. The parent compound is readily obtained from histamine and formaldehyde[6a,13] and it, as well as its 5-methyl derivative, show strong (but narrow spectrum) antibacterial properties[14]. As in the case of histidine, condensation of histamine with other aldehydes and ketones occurs readily[15]; derivatives of certain of these spinaceamine homologues show significant anti-ulcer activity[16]. Again, no homologues have been described containing strong electron-withdrawing groups at C-4 and III represents the first entry in this direction.

The 4-methyl and 4-phenyl derivatives of spinaceamine have been resolved[15c], and the enantiomers are reported to undergo facile racemization under acid conditions, and even in water. Racemization is presumed to occur by reopening of the six-membered ring to generate the C-4 carbonium ion (which effected the intramolecular electrophilic cyclization originally). It is quite surprising, therefore, that the acid hydrolyses of IIA and IIB occur without any evidence of cis-trans interconversion at C-4. The total stability of 4-substituted spinacines to racemization has been noted in earlier work[3b,5]. The role of the C-6 carboxyl group in effecting such an apparent increase in stability to ring opening is both remarkable and puzzling.

EXPERIMENTAL

Materials, analytical methods, and instrumentation have been described previously[1,2].

4-(Trifluoromethyl)-L-spinacine (I)

To a suspension of L-histidine (3.10 g, 20 mmol) in 5mL of water was added TFAE (3.17 g, 22 mmol) and the mixture was heated at reflux under argon (oil bath, 150-160 °C). The reaction mixture became homogeneous after 10 min and reflux was continued for 6 h. Direct analysis by ^{19}F NMR showed two doublets, at 3.8 ppm and 5.0 ppm, in the ratio 68 : 32; no other

^{19}F signals were detected except for TFAE or $F_3CCH(OH)_2$. Solvents and excess reagent were removed under reduced pressure; the residual material was dried by repeated evaporation with benzene and the crude product (4.7 g) was obtained as a colorless amorphous solid. At this point, the mass spectrum provided no evidence for products other than I, presumably a mixture of diastereoisomers. Fractional precipitation of the amino acids from water with ethanol afforded neither separation nor enrichment of either isomer.

5-N-(Trifluoroacetyl)-4-(trifluoromethyl)-L-spinacine methyl ester (IIA and IIB)

The mixture of IA and IB was dissolved in methanol (200 mL), the solution was saturated with hydrogen chloride, was heated at reflux for 1 h and was evaporated to dryness. The residual material was added to trifluoroacetic anhydride (30 mL) and the mixture was refluxed for 3 h. Following removal of solvent, the residue was dissolved in methanol (100 mL) and the solution was refluxed for 0.5 h. Solvent was removed and the residual material was analyzed by GC-MS (at 200 °C, 3 mm x 2 m glass column packed with 1.5% OV-1 Chromosorb WAW DMCS 80~100 mesh): two peaks were found at retention times 3.5 min and 4.2 min. Each mass spectrum showed a molecular ion peak at m/e 345, corresponding to II. The mixture was applied to a column of silica gel (180 mL) and the column was eluted with (a) ether-ethyl acetate, 1 : 1, (b) ethyl acetate, and (c) ethyl acetate-methanol, 9 : 1. The impure fractions were rechromatographed on small silica gel columns (100 mL). The minor isomer (IIB, RT 3.5 min) was eluted mainly with solvent (a), faster than the major isomer (IIA, RT 4.2 min) with solvent (b). Although the stereoisomers were separated without difficulty, each fraction failed to crystallize. There was obtained IIA as a colorless amorphous solid: MS m/e (relative intensity) 345 (28) M^+, 325 (55) $M^+ - HF$, 286 (42) $M^+ - CO_2CH_3$, 276 (38) $M^+ - CF_3$, 266 (23), 248 (73) $M^+ - COCF_3$, 244 (39), 216 (100) $M^+ - CO_2CH_3 - CHF_3$; ^1H NMR (in acetone-d_6, TMS as internal reference) δ 3.14 (AB-d, 1, J = 16 Hz and 6 Hz, 7-H), 3.57 (AB-s, 1, 7-H), 3.69 (s, 3, 6-CO_2CH_3), 5.39 (d, 1, J = 6 Hz, 6-H), 6.02 (q, 1, J = 7 Hz,

4-H); ^{19}F NMR (in acetone-d_6, trifluoroacetic acid as external reference) δ 7.8 (d, 3, J = 7 Hz, 4-CF_3), 9.5 (s, 3, 5-$COCF_3$), and IIB as a colorless amorphous solid: MS m/e (relative intensity) 345 (32) M^+, 325 (51) M^+ - HF, 286 (64) M^+ - CO_2CH_3, 276 (81) M^+ - CF_3, 266 (33), 248 (76) M^+ - $COCF_3$, 244 (57), 216 (100) M^+ - CO_2CH_3 - CHF_3; ^1H NMR (in acetone-d_6, TMS as internal reference) δ 3.29 (AB-d, 1, J = 16 Hz and 5 Hz, 7-H), 3.70 (s, 3, 6-CO_2CH_3), 5.02 (d-d, 1, J = 6 Hz and 5 Hz, 6-H), 5.86 (q, 1, J = 6 Hz, 4-H); ^{19}F NMR (in acetone-d_6, trifluoroacetic acid as external reference) δ 5.2 (d-q, 3, J = 6 Hz and 2.5 Hz, 4-CF_3), 8.2 (q, 3, J = 2.5 Hz, 5-$COCF_3$).

Regeneration of IA and IB

Both isomers, IIA and IIB, were deprotected by heating at 60-70°C for 3h in 3N hydrochloric acid. Evaporation to dryness and recrystallization from ethanol gave IA·HCl as colorless needles, mp 270-272°C dec; Analysis Found C = 35.11%, H = 3.44%, N = 15.81%; $C_8H_8F_3N_3O_2$·HCl (271.63) requires C = 35.37%, H = 3.34%, N = 15.47%; MS m/e (relative intensity) 235 (15) M^+ - HCl, 190 (100) M^+ - CO_2H - HCl, 166 (48) M^+ - CF_3 - HCl, 162 (35) M^+ - CO_2H - CHNH - HCl, 142 (35) M^+ - CO_2H - CHNH - HF - HCl, 120 (66) M^+ - CF_3 - HCO_2H - HCl; ^1H NMR (in D_2O, TSP as internal reference) δ 2.92 (AB-d-d,1, J = 16 Hz, 10 Hz and 2 Hz, 7-axial H), 3.18 (AB-d-d, 1, J = 16 Hz, 5 Hz and 2 Hz, 7-equatorial H), 3.94 (d-d, 1, J = 10 Hz and 5 Hz, 6-axial H), 4.99 (q-t, 1, J = 6 Hz and 2 Hz, 4-axial H), 8.65 (s, 1, 2-H); ^{19}F NMR (in D_2O, trifluoroacetic acid as external reference) δ 4.10 (d, J = 6 Hz, 4-CF_3); $[\alpha]_D^{20}$ - 93.9° (c 0.5, H_2O).

Recrystallization of the minor isomer from a minimum amount of water afforded IB·2HCl·H_2O as colorless needles: mp 242-243°C dec; Analysis Found C = 29.25%, H = 3.98%, N = 12.94%; $C_8H_8F_3N_3O_2$·2HCl·H_2O (326.10) requires C = 29.47%, H = 3.71%, N = 12.89%; MS m/e (relative intensity) 235 (60) M^+ - 2HCl, 190 (88) M^+ - CO_2H - 2HCl, 166 (74) M^+ - CF_3 - 2HCl, 162 (39) M^+ - CO_2H - CHNH - 2HCl, 142 (47) M^+- CO_2H - CHNH - HF - 2HCl, 120 (100) M^+ - CF_3 - HCO_2H - 2HCl; ^1H NMR (D_2O, TSP as internal reference) δ 3.12 (AB-d-d, 1, J = 17 Hz, 8 Hz and 1 Hz, 7-axial H), 3.37 (AB-d-d, 1, J = 17 Hz, 5 Hz and 1 Hz, 7-equatorial H),

4.38 (d-d, 1, J = 8 Hz and 5 Hz, 6-axial H), 5.29 (q-t, 1, J = 7 Hz and 1 Hz, 4-equatorial H), 8.84 (s, 1, 2-H); ^{19}F NMR (D_2O, trifluoroacetic acid as external reference) δ 5.85 (d, J = 7 Hz, 4-CF_3); $[\alpha]_D^{20}$ - 44.7° (c 0.5, H_2O).

No interconversion between the isomers (IA and IB) was observed by ^{19}F NMR after refluxing for 5 h in 3N hydrochloric acid.

4-(Trifluoromethyl)spinaceamine (III)

A solution of histamine dihydrochloride (3.68 g, 20 mmol) in 5 mL of water was neutralized with potassium hydroxide, and then TFAE (3.17 g, 22 mmol) was added. The mixture was heated at reflux under argon (oil bath, 150-160°C) for 6 h. After standing overnight at ambient temperature, colorless crystals (KCl) generated was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residual material was applied to a column of silica gel (100 mL) and the column was eluted with (a) ethyl acetate and (b) ethyl acetate-methanol 9 : 1. A crude product eluted mainly with solvent (b) was recrystallized from ethyl acetate to give 1.71 g of III. From the mother liquid, there was obtained additional 1.77 g (total yield 91%) of III as colorless plates, mp 273-274°C dec; Analysis Found C = 44.19%, H = 4.29%, N = 22.09%; $C_7H_8F_3N_3$ (191.16) requires C = 43.98%, H = 4.22%, N = 21.98%; MS m/e (relative intensity) 191 (12) M^+, 162 (16) M^+ - CH_2NH, 143 (18) M^+ - CH_2NH - F, 122 (100) M^+ - CF_3, 95 (20) M^+ - CF_3 - HCN; ^{1}H NMR (in acetone-d_6, TMS as internal reference) δ 2.58 (t, 2, J = 6 Hz, 7-CH_2), 3.11 (t, 2, J = 6 Hz, 6-CH_2), 4.40 (q, 1, J = 8 Hz, 4-CH), 7.53 (s, 1, 2-H); ^{19}F NMR (in acetone-d_6, trifluoroacetic acid as external reference) δ 3.76 (d, J = 8 Hz, 4-CF_3).

All the products synthesized in this work are new compounds.

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