Synthesis of Imidazo[4,5-*c*]pyridines with a Trifluoromethyl Group at C-4 and/or C-6

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Thermal condensation of histamine with trifluoroacetaldehyde gives 4-(trifluoromethyl)spinacamine and subsequent dehydrogenation with selenium dioxide leads to 4-(trifluoromethyl)-1*H*-imidazo[4,5-*c*]pyridine (42%). Fluorination with sulfur tetrafluoride of L-spinacine, obtained from the condensation of L-histidine with formaldehyde, affords 6-(trifluoromethyl)spinacamine, which can be converted to 6-(trifluoromethyl)-1*H*-imidazo[4,5-*c*]pyridine with selenium dioxide (49%). Application of the sequential reactions to 4-(trifluoromethyl)-L-spinacine gives 4,6-bis(trifluoromethyl)-1*H*-imidazo[4,5-*c*]pyridine. Dehydrogenation of the tetrahydropyridine ring also occurred during the fluorination with sulfur tetrafluoride.

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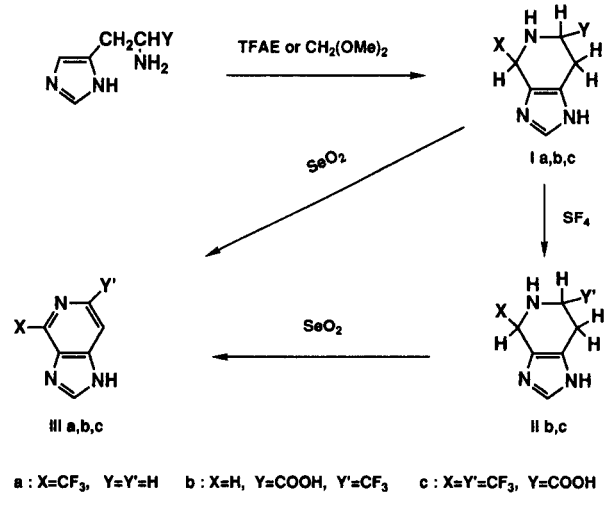
Imidazo[4,5-*c*]pyridines are deaza analogues of purine and are of great interest as antiviral [1a], antiinflammatory [1b], CNS [1c], anticancer [1d] and cardiovascular [1e] agents, and as adenosine deaminase inhibitors [1f]. As part of our continuing studies on the preparation and biological evaluation of fluoroheterocyclic compounds [2], we were stimulated to extend our attention to trifluoromethyl derivatives in this series. A number of imidazo[4,5-*c*]pyridines have been synthesized by condensation of 3,4-diaminopyridines with carboxylic acids, and 2-(trifluoromethyl)-imidazo[4,5-*c*]pyridine has been obtained by such condensation with trifluoroacetic acid [3]. However, regioisomers with the trifluoromethyl group in the pyridine ring have not been described, due to the difficulty in preparation of the corresponding 3,4-diaminopyridines. We now describe a facile synthetic route for the preparation of the latter imidazopyridines by introduction of the pyridine ring into the readily available imidazoles, histamine and L-histidine. We had previously described the 4,5,6,7-tetrahydro- [4] and 6,7-dihydro- [2e] derivatives of 4-(trifluoromethyl)-1*H*-imidazo[4,5-*c*]pyridine. The former series was chosen as the starting point for the present work because of its greater accessibility.

Results and Discussion.

As a precursor of 4-(trifluoromethyl)-1*H*-imibdazo[4,5-*c*]-pyridine **IIIa**, 4-(trifluoromethyl)spinacamine (4,5,6,7-tetrahydro-4-(trifluoromethyl)-1*H*-imidazo[4,5-*c*]pyridine) **Ia** can be prepared by thermal condensation of histamine with trifluoroacetaldehyde ethyl hemiacetal (TFAE) [4]. Dehydrogenation of **Ia** with selenium dioxide gave **IIIa** in 42% yield. A small amount of *N*-oxide (m/z 203) was detected by gc-ms. The structure is supported by nmr and mass spectra. The pyridine ring protons of **IIIa** appear as two doublets at 7.92 and 8.49 ppm coupling each other (5.5 Hz). The imidazole ring proton appears as a singlet at 8.55 ppm. A singlet is found at 12.7 ppm in the ^{19}F nmr. Compound **IIIa** showed a large molecular ion peak (m/z 187).

For introduction of the trifluoromethyl group at C-6, we considered fluorination of the carboxyl group with sulfur tetrafluoride according to the method used with other nitrogen-containing heterocyclic carboxylic acids [5]. Condensation of L-histidine with methylal or with aqueous formaldehyde gives L-spinacine, 6-carboxy-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine **Ib** [6]. Fluorination of **Ib** with sulfur tetrafluoride gave 6-(trifluoromethyl)spinacamine, 4,5,6,7-tetrahydro-6-(trifluoromethyl)-1*H*-imidazo-[4,5-*c*]pyridine, **IIb** in 17% yield together with 6-(trifluoromethyl)-1*H*-imidazo[4,5-*c*]pyridine **IIIb** in 2.7% yield. The reaction was performed with 20 molar-equivalents of sul-



fur tetrafluoride at 70° for 48 hours. The products, **IIb** and **IIIb**, were readily separated by extraction from acidic and neutral aqueous media.

In order to prepare the target compound, **IIIb**, directly, the fluorination of **Ib** was attempted under more severe conditions: 30 mole-equivalents of sulfur tetrafluoride at 130° for 72 hours. A tarry product was obtained and only a trace of **IIIb** was detected by ms. On the other hand, dehydrogenation of **IIb** with selenium dioxide gave **IIIb** in 49% yield. The nmr and mass spectra are consistent with the structures.

The thermal condensation of L-histidine with TFAE gives 4-(trifluoromethyl)-L-spinacine **Ic** [4]. The fluorination of **Ic** under the milder conditions provided 4,5,6,7-tetrahydro-4,6-bis(trifluoromethyl)-1*H*-imidazo[4,5-*c*]pyridine **IIc** in 53% yield, together with a small amount of 4,6-bis(trifluoromethyl)imidazo[4,5-*c*]pyridine **IIIc** (5.3% yield). Under the more severe conditions, only **IIIc** was obtained in 23% yield. To our surprise and gratification, dehydrogenation occurred during the fluorination with sulfur tetrafluoride to form the desired product. Presumably, the NH of **IIc** was converted to NF by sulfur tetrafluoride, followed by elimination of HF; isomerization and repetition of this process led to **IIIc**. However, no intermediates were detected by nmr or ms. The presence of two trifluoromethyl groups may render the tetrahydropyridine ring of **IIc** more stable than that of **IIb**, resulting in less side products during the dehydrogenation step. Dehydrogenation of **IIc** with selenium dioxide gave **IIIc** in low yield (12%).

The condensation of L-histidine with TFAE produces a 2:1 mixture of diastereoisomers; from ^{1}H nmr spectra, the major isomer was determined to have a *cis* relationship of the trifluoromethyl and carboxyl groups [4]. In the case of **IIc**, the ^{19}F nmr shows presence of two diastereoisomers again in the ratio of 2:1. The major isomer crystallized preferentially from an ethyl acetate solution of the mixture. However, the ^{1}H nmr spectra of the isomers appear as complex multiplets and configurations of the isomers could not be assigned; nor did ^{19}F nmr provide any clues. If we assume that the reaction with sulfur tetrafluoride does not alter configuration at the carboxyl group (the isomer ratio did not change), the major isomer of **IIc** may then be considered the *cis* isomer.

All the (trifluoromethyl)imidazo[4,5-*c*]pyridines were found stable to 1*N* aqueous sodium hydroxide solution for 24 hours at ambient temperature. These stabilities parallel those found for 6-(trifluoromethyl)indole [7], 2-(trifluoromethyl)indole [8] and 2-(trifluoromethyl)benzimidazole [9], but stand in contrast to the very high labilities of both 2- and 4-(trifluoromethyl)imidazoles [9].

EXPERIMENTAL

Materials.

4-(Trifluoromethyl)spinacamine **Ia** and 4-(trifluoromethyl)-L-spinacine **Ic** were prepared by the method reported in our previous work [4]. The thermal condensations of histamine and L-histidine with trifluoroacetaldehyde ethyl hemiacetal gave **Ia** and **Ic** in nearly quantitative yields. Similar condensation of L-histidine with methylal gave L-spinacine **Ib** [6]. Other reagents were obtained from commercial sources and used without further purification.

Analytical Methods and Instrumentation.

Melting points determined on a Büchi SMP-20 melting point apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on a Hitachi R-90 FT spectrometer (90 MHz) with TMS as an internal reference. The ^{19}F nmr were recorded on the same spectrometer (84.7 MHz); positive δ value are downfield from trifluoroacetic acid an external reference. All nmr spectra were measured in acetone-d_6. Mass spectral data were obtained on a Hitachi M-80 instrument (electron-impact ionization at 70 eV).

Fluorination of L-Spinacine **Ib** with Sulfur Tetrafluoride.

In a Hastelloy C autoclave (100 ml), **Ib** (4.11 g, 24.6 mmoles) and hydrogen fluoride (20 ml) were placed, and sulfur tetrafluoride (53.1 g, 0.49 mole) was charged with cooling with liquid nitrogen. The autoclave was heated at 70° for 48 hours. Gaseous products and hydrogen fluoride were released at *ca.* 40°, and the contents of the autoclave were poured into ice-water (100 ml). The acidic solution was extracted twice with ethyl acetate (100 ml each). The organic layers were dried over sodium sulfate and evaporated to give a small amount of crude 6-(trifluoromethyl)-1*H*-imidazo[4,5-*c*]pyridine **IIIb**. The water layer was neutralized with a 10% potassium hydroxide solution and was extracted twice with ethyl acetate (100 ml each). The organic layers were dried and evaporated to give crude 6-(trifluoromethyl)spinacamine **IIb**. Both crude products were purified by silica gel chromatography (eluted with 3% methanol in ethyl acetate) and recrystallized separately. There were obtained **IIb** (0.80 g, 17% yield), colorless needles from ethyl acetate, mp 170-171°; ^{1}H nmr: δ 2.74 (m, 2H, H-7), 3.6 (m, 1H, H-4), 3.85 (br s, 2H, H-6), 7.48 (s, 1H, H-2); ^{19}F nmr: δ 1.04 (d, J = 7.5 Hz, 6-CF_3); ms: (m/z) 191 (M^+, 42), 122 (M^+-CF_3, 100), 120 (M^+-CF_3-H, 20) and **IIIb** (0.13 g, 2.8% yield), colorless needles from ethyl acetate, mp 251-252°; ^{1}H nmr δ 8.08 (s, 1H, H-7), 8.52 (s, 1H, H-2), 9.06 (s, 1H, H-4); ^{19}F nmr δ 11.3 (s, 6-CF_3); ms: (m/z) 187 (M^+, 100), 118 (M^+-CF_3, 37).

Anal. Calcd. for $C_7H_4N_3F_3$: C, 44.9; H, 2.2; N, 22.5. Found: C, 44.9; H, 2.2; N, 22.6.

This procedure is representeative of the fluorinations with sulfur tetrafluoride. A 2:1 isomer mixture of 4-(trifluoromethyl)-L-spinacine **Ic** gave a mixture of two diastereoisomers (ratio 2:1) of 4,6-bis(trifluoromethyl)spinacamine **IIc** (53% total yield), the major isomer as colorless needles from ethyl acetate, mp 194-195°; ^{1}H nmr: δ 2.5-3.2 (m, 2H, H-7), 3.7-4.1 (m, 1H, H-6), 4.4-4.8 (m, 1H, H-4), 7.63 (s, 1H, H-2); ^{19}F nmr: δ 1.04 (d, J = 7.4 Hz, 6-CF_3), 3.68 (d, J = 7.4 Hz, 4-CF_3); ms: (m/z) 259 (M^+, 15), 190 (M^+-CF_3, 100); the minor isomer obtained as a mixture with the major isomer; ^{1}H nmr: δ 2.5-3.2 (m, 2H, H-7), 3.7-4.1 (m, 1H, H-6), 4.6-5.0 (m, 1H, H-4), 7.71 (s, 1H, H-2); ^{19}F nmr: δ 1.27 (d, J = 7.5 Hz, 6-CF_3), 3.94 (d, J = 7.5 Hz, 4-CF_3) together with a small amount of 4,6-bis(trifluoromethyl)-1*H*-imidazo[4,5-*c*]pyridine **IIIc** (5.3% yield), colorless needles, mp 176-177°; ^{1}H nmr: δ 8.41 (s, 1H, H-7), 8.75 (s, 1H,

H-2); ^{19}F nmr: δ 11.2 (s, 6-CF_3), 12.2 (s, 4-CF_3); ms: (m/z) 255 (M^+, 100), 236 (M^+-F, 26), 235 (M^+-HF, 23), 186 (M^+-CF_3, 39), 185 (M^+-CF_3-H, 42).

Anal. Calcd. for $C_8H_3N_3F_6$: C, 37.7; H, 1.2; N, 16.5. Found: C, 37.6; H, 1.3; N, 16.6.

The fluorination of **Ib** under severe conditions (with 30 molar-equivalents of sulfur tetrafluoride at 130° for 72 hours) gave tarry matter; a trace of **IIIb** was detected by gc-ms. However, **Ic** afforded **IIIc** in 23% yield.

Dehydrogenation of 4-(Trifluoromethyl)spinacamine **Ia** with Selenium Dioxide.

A solution of **Ia** (1.98 g, 11.7 mmoles) and selenium dioxide (1.31 g, 11.7 mmoles) in acetic acid (85 ml) was heated at reflux with stirring for 3 hours. After cooling, a black solid (selenium metal) was filtered off and the filtrate was evaporated to dryness. The residual material was applied to a silica gel column (120 ml) and was eluted with ethanol-ethyl acetate (1:9). Recrystallization from ethyl acetate gave **IIIa** (0.92 g, 42% yield) as colorless columns, mp 237-238°; ^1H nmr: δ 7.92 (d, J = 5.5 Hz, 1H, H-7), 8.49 (d, J = 5.5 Hz, 1H, H-6), 8.55 (s, 1H, H-2); ^{19}F nmr: δ 12.7 (s, 4-CF_3); ms: (m/z) 187 (M^+, 100), 168 (M^+-F, 11), 167 (M^+-HF, 23), 140 (21), 118 (M^+-CF_3, 17).

Anal. Calcd. for $C_7H_4N_3F_3$ (187.12): C, 44.9; H, 2.2; N, 22.5. Found: C, 44.9; H, 2.2; N, 22.6.

This procedure is representative of the dehydrogenations with selenium dioxide; **IIb** gave **IIIb** in 49% yield and **IIc** gave **IIIc** in 12% yield.

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