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PRELIMINARY NOTE

A Facile Synthesis of 1-Trifluoromethyl-β-carboline

YASUO MAKI, HIROSHI KIMOTO and SHOZO FUJII

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

SUMMARY

The two-step synthesis of the title compound has been achieved by Mannich-type condensation of tryptamine with trifluoroacetaldehyde, followed by dehydrogenation with selenium dioxide; the overall yield was 79.3%.

Heterocyclic compounds containing the trifluoromethyl group have been of great interest because of their utility as drugs, pesticides, etc. We have previously reported the syntheses of trifluoromethylated imidazoles [1] and imidazo[4,5-c]pyridines [2]. As an extension of the synthetic aspects of the study, we now describe a facile synthesis of 1-trifluoromethyl-β-carboline (1-trifluoromethyl-9H-pyrido[3,4-b]indole, II), which may not only be a useful intermediate for new drugs and pesticides but show interesting biological activities of its own.

The thermal condensation of tryptamine with trifluoroacetaldehyde ethyl hemiacetal (TFAE) was achieved by simple reflux and 1-trifluoromethyl-1,2,3,4-tetrahydro-β-carboline (1-trifluoromethyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole,I) was obtained in nearly quantitative yield. No other products were detected by ^{19}F NMR or TLC analysis. Dehydrogenation of I to produce the fully aromatic β-carboline (II) was accomplished by heating I with selenium dioxide in acetic acid.

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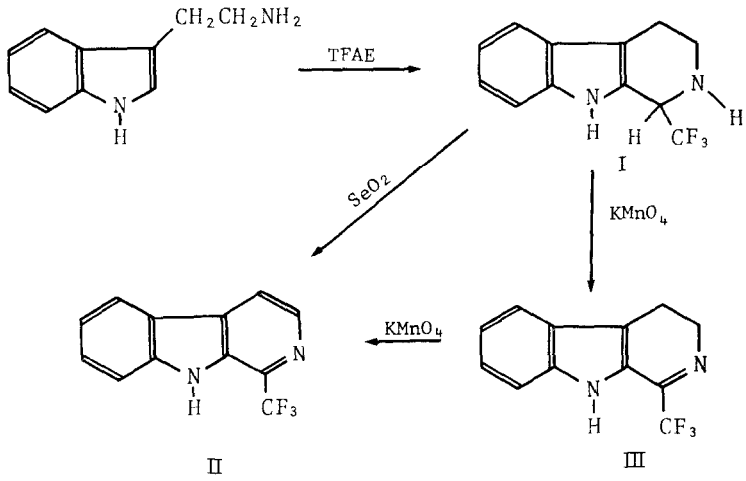

The nonfluorinated parent compound of II, 1-methyl-β-carboline (named harman or aribine) has been found in plants [3] and tobacco smoke [4], and shows a variety of biological activities, e.g., inhibition of enzymes, enhancement of mutagenicity, and antagonism of the benzodiazepine receptor. Since the parent compound of I(1-methyl-1,2,3,4-tetrahydro-β-carboline or eleagnine) also has been isolated from plants [5], it has been suggested that the β-carboline nucleus arises in the plants by a Mannich-type condensation of tryptamine or tryptophane with acetaldehyde [6]. The same condensation has been achieved in vitro [7]. In an analogous reaction, D,L-tryptophane has been condensed with free, gaseous trifluoroacetaldehyde [8]. the latter reagent, however, is inconvenient to prepare and use. We have already shown that TFAE is a simple, in situ source for trifluoroacetaldehyde for the condensation with imidazoles [9]. The result with tryptamine shows it to be an equally useful reagent for condensation with indoles.

The dehydrogenation of the parent compound of I apparently proceeds stepwise: partial dehydrogenation with potassium permanganate in acetone has been reported to give 1-methyl-3,4-dihydro-β-carboline (harmalan)[10]. A similar dehydrogenation of I with potassium permanganate gave a mixture of 1-trifluoromethyl-3,4-dihydro-β-carboline (III), I, and II. Chroma-

tographic separation of II and III was unsuccessful. Further investigation is in progress to synthesize trifluoroanalogues of harmalol and harmaline (the 7-hydroxy and 7-methoxy derivatives, respectively, of III), which also occur naturally.

A suspension of tryptamine (8.01g, 50 mmol) in TFAE (7.92g, 55 mmol) was heated at reflux (100～105°C) under argon for 7 hours. With a rise in temperature, the mixture became homogeneous. Excess TFAE, ethanol, and water were removed by evaporation and the residual material was recrystallized from ethanol to give 10.81g of 1-trifluoromethyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (nc, I) as colorless grains; mp. 147～149°C; MS m/e (relative intensity) 240 (33) M^+, 236 (13), 216 (15), 211 (18), 191 (24), 171 (100), 140 (27); ^1H NMR (2% in $CDCl_3$, TMS as internal reference) δ 4.49 (q, 1, J = 8Hz, 1-H), 1.92 (s, 1, 2-NH), 3.24 (t, 2, J = 6Hz, 3-H), 2.73 (t, 2, J = 6Hz, 4-H), 7.0～7.6 (m, 4, 5～8-H), 7.92 (broad s, 1, 9-NH); ^{19}F NMR (trifluoro-acetic acid as external reference) δ 4.67 (d, J = 8Hz, 1-CF_3); Elemental analysis Found C 59.61%, H 4.67%, N 11.54%, Calcd. as $C_{12}H_{11}F_3N_2$ C 60.00%, H 4.62%, N 11.66%. From the mother liquor, additional I (1.03g, total yield 98.6%) was obtained as slightly yellow grains.

To a solution of I (3.84g, 16 mmol) in acetic acid (200 ml) selenium dioxide (3.55g, 32 mmol) was added and the mixture was heated at reflux with stirring for 2 hours. A black precipitate was filtered off and the filtrate was evaporated to dryness. The residual material was extracted with chloroform (2 x 100 ml), and the combined extracts were concentrated to 10 ml. Pale yellow columns (1.96g) were collected and the mother liquor was purified by passage through a silica gel column (100 ml, eluted with chloroform). There was obtained a total of 3.04g (yield 80.9%) of 1-trifluoromethyl-9H-pyrido[3,4-b]indole (nc, II) as colorless columns, recrystallized from chloroform; mp. 116～117°C; MS 236 (95) M^+, 216 (100), 166 (24), 139 (14); ^1H NMR δ 8.47 (d, 1, J = 5Hz, 3-H), 8.01 (d, 1, J = 5Hz, 4-H), 8.03 (d-d, 1, J = 8Hz and 1Hz 5-H), 7.26 (d-d-d, 1, J = 8Hz, 6Hz, and 1Hz, 8-H), 9.06 (broad s, 1, 9-NH); ^{19}F NMR δ 14.5 (s, 1-CF_3); Elemental analysis Found C 61.18%, H 2.78%, N 11.82%, Calcd. as $C_{12}H_7F_3N_2$ C 61.02%, H 2.99%, N 11.86%.

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