Unusual transformations of 1-vinyl-4,5,6,7-tetrahydro-5-methyl-4,6-ethanopyrrolo[3,2-*c*]pyridine to cyclohepteno[b]pyrroles under acetylation conditions

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Abstract

Heating 1-vinyl-4,5,6,7-tetrahydro-5-methyl-4,6-ethanopyrrolo[3,2-*c*]pyridine (1) in the presence of acetic or trifluoroacetic anhydride resulted in bicyclic saturated fragment cleavage, affording cyclohepteno[b]pyrroles 2a,b in low yields. In the case of trifluoroacetic anhydride, the major product of the reaction, -trifluoroacetylsubstituted tetrahydropyrrolo[3,2-*c*]pyridine 3 was isolated in 34% yield.

Keywords: Cyclohepteno[b]pyrroles, trifluoroacetic anhydride, acetylation

Introduction

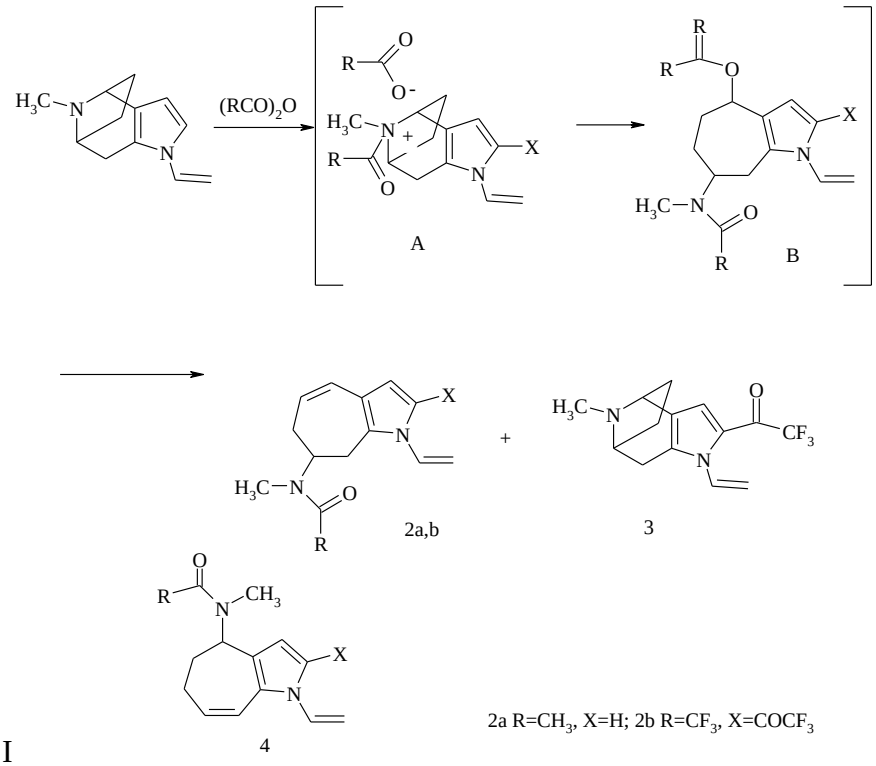
Recently we have reported piperidine ring cleavage in tetrahydropyrrolo[3,2-*c*]pyridines under the action of acetic anhydride at 70 °C resulting with the formation of 2-(α-methyl-β-acetamidoethyl)-3-vinylpyrroles in moderate yields, while the target 2-acetyl substituted pyrroles have not been isolated.[1]

We have studied the reactions of acetylation and trifluoroacetylation of *N*-vinylsubstituted tetrahydropyrrolo[3,2-*c*]pyridine 1 with bicyclic saturated fragment, synthesized by applying the Trofimov reaction to the oxime of tropinone.[2,3]

The reaction of 1 with acetic anhydride at 70 °C leads to the bicyclic fragment cleavage at C_4–N bond affording cyclohepteno[b]pyrrole 2a in 12% yield. The reaction was accompanied by significant tarring and there was no observable trace of α-acetyl substituted tetrahydropyrrolo[3,2-*c*]pyridine which would have resulted from pyrrole fragment acetylation.

Treating tetrahydropyrrolopyridine 1 with trifluoroacetic anhydride under the same reaction conditions, as distinct from the reaction of 4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-*c*]pyridine derivatives,[1] also led to the bicyclic saturated moiety opening giving cyclohepteno[b]pyrrole 2b in 16% yield. The major product of this reaction, α-

trifluoroacetylsubstituted tetrahydropyrrolo[3,2-*c*]pyridine 3 was isolated in 34% yield. Cyclohepteno[b]pyrroles 2a,b exist as mixtures of two isomers due to the amide fragment hindrance. The alternative cyclohepteno[b]pyrroles 4 , that could have been formed as the result of the C_6–N bond cleavage, were not detected.



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The reaction seems to proceed through the intermediacy of quaternary salt A, which then predictably is cleaved by the acyloxy anion. This transformation can proceed either like Brown[4] or Hofmann[5] reaction, however the current experimental material does not permit to make a definite conclusion about the mechanism. Further work aimed at exploring the scope and limitations of this process is under way.

Experimental Section

General Procedures. Melting points are uncorrected. IR spectra of samples were obtained as KBr pellets. ^{1}H NMR chemical shifts are given as values with reference to Me_4Si as internal standard. All column chromatography was carried out on Fluka aluminum oxide (activated, II grade, 150 mesh) at medium pressure (200 mbar). All solvents were distilled before use.

1-Vinyl-7-(*N*-methyl-*N*-acetylamino)cyclohept-4-ene[*b*]pyrrole (2a). To a stirred solution of tetrahydropyrrolo[3,2-*c*]pyridine 1 (0.45 g, 2.4 mmol) in 40 mL of anhydrous toluene, freshly

distilled acetic anhydride (2.3 mL, 24 mmol) was added dropwise. The solution was stirred for 2 h at 70 ºC, the excess of acetic anhydride and toluene were distilled off under reduced pressure. The residue was treated with saturated aqueous potassium carbonate (50 mL) and extracted with dichloromethane (4x50 mL).

The organic extract was dried over magnesium sulfate. Evaporation of the solvent under reduced pressure left an oily residue, which was purified by column chromatography (heptane: ethyl acetate, 5:1), affording compound 2a in 12% yield as a mixture of isomers (52:48), pale-yellow solid: mp 129−130 ºC (ethyl acetate-heptane); ^{1}H NMR (200 MHz, $CDCl_3$) *major isomer* δ 2.1 (s, 3H), 2.94 (s, 3H), 2.2−3.2 (m, 4H), 4.68 (dd, 1H, *J* = 8.5 and 0.9 Hz), 4.94 (m, 1H), 5.08 (dd, 1H, *J* = 15.6 and 0.9 Hz), 5.55 (m, 1H), 6.05 (d, 1H, *J* = 3.1 Hz), 6.20 (dd, 1H, *J* = 11.3 and 3.1 Hz), 6.79 (dd, 1H, *J* = 8.5 Hz, 15.6 Hz), 6.88 (d, 1H, *J* = 3.1 Hz); *minor isomer* δ 2.12 (s, 3H), 2.89 (s, 3H), 2.2−3.2 (m, 4H), 4.76 (dd, 1H, *J* = 8.5 and 0.9 Hz), 4.24 (m, 1H), 5.13 (dd, 1H, *J* = 15.6 and 0.9 Hz), 5.55 (m, 1H), 6.08 (d, 1H, *J* = 3.1 Hz), 6.24 (dd, 1H, *J* = 11.3 and 3.1 Hz), 6.79 (dd, 1H, *J* = 8.5 Hz, 15.6 Hz), 6.92 (d, 1H, *J* = 3.1 Hz); IR (KBr) 1650 cm^{-1}; HRMS calcd for $C_{14}H_{18}N_2O$ *m/z* 230.1419, found *m/z* 230.1422; MS (m/z, rel. intensity) 230 (M^+, 13), 203(24), 180(11), 168(7), 157(100), 156(52), 144 (10), 130 (10). Anal. Calcld for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 73.32; H, 7.98; N, 12.41.

1-Vinyl-2-trifluoroacetyl-7-(*N*-methyl-*N*-trifluoroacetylamino)cyclohept-4-ene[b]pyrrole (2b) and 1-vinyl-2-trifluroacetyl-4,5,6,7-tetrahydro-5-methyl-4,6-ethanopyrrolo[3,2-*c*]pyridine (3). Using the same procedure, tetrahydro-pyrrolo[3,2-*c*]pyridine 1 (0.46 g, 2.5 mmol) was treated with trifluoroacetic anhydride (4.9 g, 25 mmol) at 70 ºC. Usual work-up gave oily residue, which was purified by column chromatography (heptane: ethyl acetate, 5:1), first providing compound 2b as a mixture of two isomers (60:40) in 16% yield, green solid: mp 142−144 ºC (heptane-ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$) *major isomer* δ 3.1 (s, 3H), 2.54−3.30 (m, 4H), 4.70 (tt,1H, *J* = 10.7 and 2.8 Hz) , 5.16 (d, 1H, *J* = 15.9 Hz), 5.50 (d, 1H, *J* = 8.5 Hz), 5.69 (ddd, 1H, *J* = 11.9, 7.0 and 3.0 Hz), 6.27(dd, 1H, *J* = 11.9 and 3.1 Hz), 7.08 (q, 1H, *J* = 2.1 Hz), 7.15 (dd, 1H, *J* = 8.5 Hz, 15.9 Hz); *minor isomer* δ 3.1 (s, 3H), 2.54−3.30 (m, 4H), 4.40 (m, 1H) , 5.14 (d, 1H, *J* = 15.9 Hz), 5.52 (d, 1H, *J* = 8.5 Hz), 5.69 (ddd, 1H, *J* = 11.9, 7.0 and 3.0 Hz), 6.29 (dd, 1H, *J* = 11.9 and 3.1 Hz), 7.06 (q, 1H, *J* = 2.1 Hz), 7.14 (dd, 1H, *J* = 8.5 Hz, 15.9 Hz); IR (KBr) 1680 cm^{-1}; HRMS calcd for $C_{16}H_{14}F_6N_2O_2$ *m/z* 380.0959, found *m/z* 380.0951; MS (*m/z*, rel. intensity) 380 (M^+, 8), 253(100), 252(25), 184(55), 156(50), 128(11), 127(10), 69(20); Anal. Calcld for $C_{16}H_{14}F_6N_2O_2$: C, 50.53; H, 3.71; N, 7.37. Found: C, 50.32; H, 4.02; N, 6.96.

Continued elution of the chromatography column provided 3 as a yellow oil in 34% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (m,1H), 1.81 (m, 1H), 2.1−2.3 (m, 2H), 2.35 (s, 3H), 2.40 (d, 1H, *J* = 17.7 Hz), 3.15 (dd, 1H, *J* = 17.7 and 4.6 Hz), 3.57 (m, 1H), 3.91 (d, 1H, *J* = 5.5 Hz), 5.18 (dd, *J* = 15.9 and 0.9 Hz), 5.20 (dd, 1H, *J* = 8.9 and 0.9 Hz), 7.02 (q, 1H, *J* = 2.1 Hz), 7.41 (dd, *J* = 15.9 and 8.9 Hz); IR (KBr) 1690 cm^{-1}; MS (*m/z*, rel. intensity) 284 (M^+, 44), 269(6), 255(100), 243(5), 229(5), 157(6); Anal. Calcld for $C_{14}H_{15}F_3N_2O$: C, 59.15; H, 5.32; N, 9.85. Found: C, 59.12; H, 4.98; N, 9.46.

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