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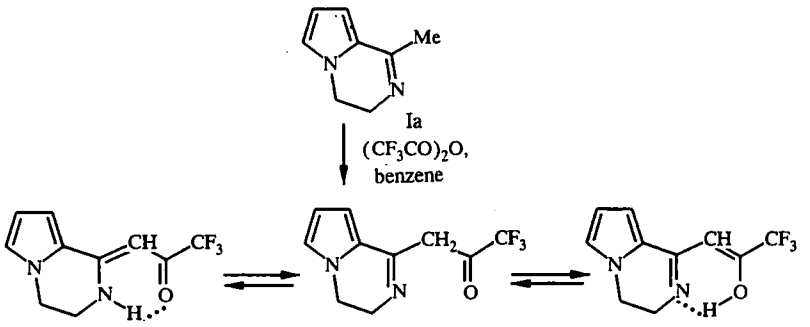
TRIFLUOROACETYLATION OF 1-ALKYL SUBSTITUTED 3,4-DIHYDROPYRROLO[1,2-a]PYRAZINES

V. I. Terenin, E. V. Kabanova, M. A. Kovalkina, and A. V. Borisov

It is known that pyrroles are quite readily acetylated to give products substituted at the α- or β-positions of the pyrrole ring [1]. Hence the reaction with trifluoroacetic anhydride occurs rapidly at 0°C [2].

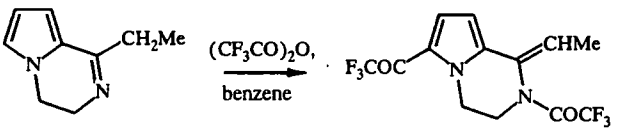
In the molecule of 1-methyl-3,4-dihydropyrrolo[1,2-a]pyrazine (Ia) there are two reactive centers at which attack of an electrophile is most likely, i.e., the N_2 atom in the pyrazine ring and the C_6 carbon atom (α-position in the pyrrole ring). However, treatment of Ia with trifluoroacetic anhydride in benzene led to a 50% yield of 1,1,1-trifluoro-3-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-1-ylidene)acetone (IIa) (from ^1H and ^{13}C NMR and mass spectral data), i.e., formation of the substitution product at the methyl group in position I of the dihydropyrrolopyrazine Ia. It is known that nitrogen containing 1,3-diketones can exist in three tautomeric forms [3], in this case as the isomers IIa-c.



IIa IIb IIc

In the NMR spectra, similarly to known compounds [4], there are observed signals for only one of the tautomeric forms (moreover, signals for the methylene group protons in position 1 of the iminoketone form IIb are absent) and in fact, that of the enaminoketone form IIa.

When exchanging the methyl group in the starting 3,4-dihydropyrrolo[1,2-a]pyrazine for ethyl (compound Ib) under the same conditions there is formed in 48% yield the 2,6-di(trifluoroacetyl)-1-ethylidene-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (III) (from PMR and mass spectral data).



Ib III

Compound III is a mixture of Z- and E-isomers about the double bond in position 1, moreover, each of these isomers can in turn exist as Z and E configurational isomers arising through the absence of free rotation around the C–N bond in the amide group [5]. The PMR spectrum of III shows signals for only two of the four possible isomers.

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1,1,1-Trifluoro-3-(1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-1-ylidene)acetone (II), mp 142-143°C. PMR spectrum ($CDCl_3$, 400 MHz): 3.76 (2H, m, 3-H); 4.17 (2H, m, 4-H); 5.77 (1H, s, 1-CH); 6.30 (1H, dd, J_{76} = 2.4, J_{78} = 3.86 Hz, 7-H); 6.85 (1H, dd, J_{86} = 1.35, J_{87} = 3.86 Hz, 8-H); 6.9 (1H, dd, J_{67} = 2.4, J_{68} = 1.35 Hz, 6-H); 11.05 ppm (1H, br.s, NH). ^{13}C NMR spectrum ($CDCl_3$, 100 MHz): 39.74, 43.55 (3,4-C), 83.11 (CH=C), 110.85, 113.80 (7,8-C), 118.01 (J_{CF} = 288 Hz, CF_3), 122.53 (8a-C), 126.15 (6-C), 155.92 (1-C), 175.09 ppm (J_{CF} = 32 Hz, C=O). Mass spectrum: 230 (M^+).

2,6-Di(trifluoroacetyl)-1-ethylidene-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (III), mp 127°C. PMR spectrum ($CDCl_3$, 400 MHz): major isomer: 2.08 (3H, d, J = 7.33 Hz, $=CH-CH_3$), 4.19-4.28 (2H, m, 3-H), 4.50-4.63 (2H, m, 4-H), 6.11 (1H, m, $=CH-CH_3$), 6.56 (1H, m, 7-H), 7.29 (1H, m, 8-H). Minor isomer: 1.74 (3H, d, J = 7.49 Hz, $=CH-CH_3$), 3.3-5.2 (4H, m, 3,4-H), 6.41 (1H, m, $=CH-CH_3$), 6.52 (1H, m, 7-H), 7.22 (1H, m, 8-H). Mass spectrum: 340 (M^+).

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