ISSN 1070-3632, Russian Journal of General Chemistry, 2007, Vol. 77, No. 2, pp. 319–320. © Pleiades Publishing, Ltd., 2007.
Original Russian Text © A.E. Krivoshein, D.V. Krivorotov, M.V. Vorob'ev, M.L. Petrov, V.A. Polukeev, 2007, published in Zhurnal Obshchei Khimii, 2007, Vol. 77, No. 2, pp. 347–348.

LETTERS TO THE EDITOR

Reaction of Perfluorocarboxylic Anhydrides with 2-(4-Chlorophenyl)-1-(3,4-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline

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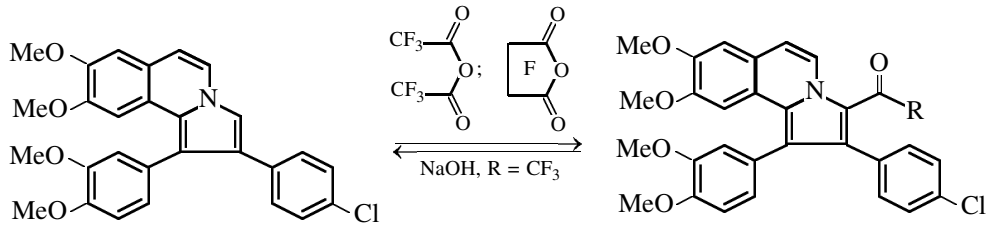
Received July 6, 2006

DOI: 10.1134/S1070363207020247

In the recent years, pyrrolo[2,1-*a*]isoquinolines of the papaverine series attract attention as potential biologically active substances [1–3]. Syntheses of these compounds are based on reaction of papaverine with α-halo carbonyl compounds [1–4]; depending on the structure of the latter, different substituents can be introduced into positions 2 and 3 of the pyrrolo-[2,1-*a*]isoquinoline molecule [1, 3, 4]. Despite apparent simplicity of that synthetic approach, we propose an alternative route to the preparation of hitherto unknown 3-perfluoroacylpyrrolo[2,1-*a*]isoquinolines of the papaverine series via acylation of 2-(4-chlorophenyl)-1-(3,4-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (**I**, pyrrolo[2,1-*a*]papaverine) [4] with perfluorinated carboxylic anhydrides. As the latter we used trifluoroacetic and perfluorosuccinic anhydrides. We have found that the reaction of **I** with perfluorocarboxylic anhydrides in *N,N*-dimethylformamide at room temperature is complete in several hours to give 1-[2-(4-chlorophenyl)-1-(3,4-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin3-yl]-2,2,2-trifluoroethan-1-one (**IIa**) and 4-[2-(4-chlorophenyl)-1-(3,4-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-3-yl]-2,2,3,3-tetrafluoro-4-oxobutanoic acid (**IIb**), respectively, in excellent yield. Alkaline cleavage of trifluoroacetyl derivative **IIa** (like haloform reaction) recovered initial pyrrolo-[2,1-*a*]papaverine **I**, presumably as a result of decarboxylation of intermediate pyrrolo[2,1-*a*]isoquinolin-3-carboxylic acid.



I **IIa, IIb**

R = CF_3 (**a**), CF_2CF_2COOH (**b**).

Thus we have demonstrated the possibility for functionalization of pyrrolo[2,1-*a*]isoquinolines of the papaverine series at the 3 position with perfluorocarboxylic anhydrides. It should be emphasized that the synthesis of compounds **IIa** and **IIb** according to the known schemes [1–4] would require difficultly ac-

cessible and unstable (under the reaction conditions) 2-bromo-1-(4-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione and 5-bromo-6-(4-chlorophenyl)-2,2,3,3-tetrafluoro-4,6-dioxohexanoic acid, respectively.

Reactions of 2-(4-chlorophenyl)-1-(3,4-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (I) with trifluoroacetic and tetrafluorosuccinic anhydrides. The corresponding perfluorinated anhydride, 0.012 mol, was added under stirring (using a magnetic stirrer) to a solution of 0.01 mol of 2-(4-chlorophenyl)-1-(3,4-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (**I**) [4] in 20 ml of anhydrous DMF. The mixture was stirred for 2 h under argon and poured into 400 ml of water, and the precipitate was filtered off.

1-[2-(4-Chlorophenyl)-1-(3,4-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-3-yl]-2,2,2-trifluoroethan-1-one (IIa). Yield 95%, mp 245–247°C (from toluene). ^{1}H NMR spectrum, δ, ppm: 3.30 s (3H, OCH_3), 3.65 s (3H, OCH_3), 3.76 s (3H, OCH_3), 3.91 s (3H, OCH_3), 6.76 m (2H, H_{arom}), 6.91 m (2H, H_{arom}), 7.24 m (4H, H_{arom}), 7.36 s (1H, H_{arom}), 7.42 d (1H, H_{arom}, *J* 7 Hz), 9.55 d (1H, H_{arom}, *J* 7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 54.88 (1C, OCH_3), 55.58 (3C, OCH_3), 104.96 (1C), 106.39 (1C), 110.80 (1C), 114.18 (1C), 114.31 (1C), 116.87 (1C), 118.46 (1C), 121.64 (1C), 123.64 (2C), 125.86 (1C), 126.47 (1C), 126.82 (2C), 131.94 (3C), 133.23 (1C), 134.15 (1C), 137.63 (1C), 148.25 (1C), 148.68 (1C), 149.22 (1C), 150.65 (1C), 113.55 119.30 127.79 128.62 (1C, *C*F_3), 169.54 d.d (1C, *C*=O). ^{19}F NMR spectrum, δ_F, ppm: –68.62 s (3F, CF_3). Found, %: C 63.32; H 4.00; N 2.45. $C_{30}H_{23}ClF_3NO_5$. Calculated, %: C 63.22; H 4.07; N 2.46.

4-[2-(4-Chlorophenyl)-1-(3,4-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-3-yl]-2,2,3,3-tetrafluoro-4-oxobutanoic acid (IIb). Yield 73%, mp 140–142°C (from diethyl ether). ^{1}H NMR spectrum, δ, ppm: 3.28 s (3H, OCH_3), 3.65 s (3H, OCH_3), 3.75 s (3H, OCH_3), 3.89 s (3H, OCH_3), 4.39 s (1H, OH), 6.76 d (1H, H_{arom}, *J* 8 Hz), 6.81 s (1H, H_{arom}), 6.85 s (1H, H_{arom}), 6.92 d (1H, H_{arom}, *J* 8 Hz), 7.25 d.d (4H, H_{arom}), 7.35 s (1H, H_{arom}), 7.39 d (1H, H_{arom}, *J* 8 Hz), 9.38 d (1H, H_{arom}, *J* 8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 54.96 (1C, OCH_3), 55.63 (3C, OCH_3), 105.09 (1C), 106.42 (1C), 109.16, 117.82, 122.94 (2C, CF_2CF_2), 110.92 (1C), 113.99 (1C), 114.31 (1C), 118.57 (1C), 121.70 (1C), 123.75 (1C), 123.99 (1C), 126.01 (1C), 126.66 (1C), 126.87 (2C), 131.99 (3C), 133.18 (1C), 134.31 (1C), 137.41 (1C), 148.22 (1C), 148.68 (1C), 149.19 (1C), 150.70 (1C), 158.84 (1C, *C*OOH), 175.39 (1C, *C*=O). ^{19}F NMR spectrum, δ_F, ppm: –120.51 s (2F, CF_2), –110.67 s (2F, CF_2). Found, %: C 59.32; H 4.05; N 2.55. $C_{32}H_{24}ClF_4NO_7$. Calculated, %: C 59.50, H 3.74; N 2.17.

Reaction of 1-[2-(4-chlorophenyl)-1-(3,4-dimethoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-3-yl]-2,2,2-trifluoroethan-1-one (IIa) with a solution of sodium hydroxide. Compound **IIa**, 0.01 mol, was added to a mixture of 100 ml of water, 200 ml of alcohol, and 0.10 mol of sodium hydroxide. The mixture was stirred for 24 h at 70°C, and the colorless precipitate was filtered off and recrystallized from acetonitrile. We thus isolated compound **I** in 95% yield, mp 191–192°C [4].

The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded from 1% solutions in DMSO-d_6 on a Bruker AM-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C and ^{19}F). The elemental compositions were determined on a Perkin–Elmer 240 analyzer. The melting points were measured on an NMK Kofler hot stage. The progress of reactions was monitored by TLC on Silufol UV-254 plates using hexane–acetone–diethyl ether (10 : 2 : 1) as eluent.

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