ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 9, pp. 1694–1696. © Pleiades Publishing, Ltd., 2014.
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CsF-Catalyzed Alkylation of Gamma-Carbolines with Fluorine-Containing 3-Vinylpyridines

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Received May 29, 2014

Abstract—CsF-Catalyzed alkylation of gamma-carbolines with 3-vinyl-5-fluoropyridine and 3-vinyl-6-trifluoromethylpyridine led to the formation of 5-[2-(5-fluoropyrid-2-yl)ethyl]-2,3,4-tetrahydro-1*H*-pyrido[4,3-*b*]-indoles and 5-[2-(6-trifluoromethylpyrid-2-yl)ethyl]-2,3,4-tetrahydro-1*H*-pyrido[4,3-*b*]indoles.

Keywords: gamma-carbolines, vinylpyridine, the Michael reaction, fluoride ion

DOI: 10.1134/S1070363214090084

Gamma-carboline derivatives are widely used in medical and pharmaceutical chemistry due to their antihistamine [1], antidopamine [2] and antiserotonin activity [3]. For example, the Russian antihistamine drug Dimebon also exhibits a pronounced therapeutic effect against a number of neurodegenerative and neurological diseases [4–6]. Studies in the field of purposeful search for new neuroprotectors among gamma-carbolines derivatives are promising for designing effective agents for the treatment of various neuropathies [7–9].

In this work we developed an approach towards synthesis of fluorinated analogs of Dimebon containing 5-fluoro- and (6-trifluoromethypyridin-3-yl)ethyl-substituted indole fragment. This method was based on a catalyzed alkylation of gamma-carbolines with 3-vinyl-5-fluoropyridine and 3-vinyl-6-trifluoromethylpyridine.

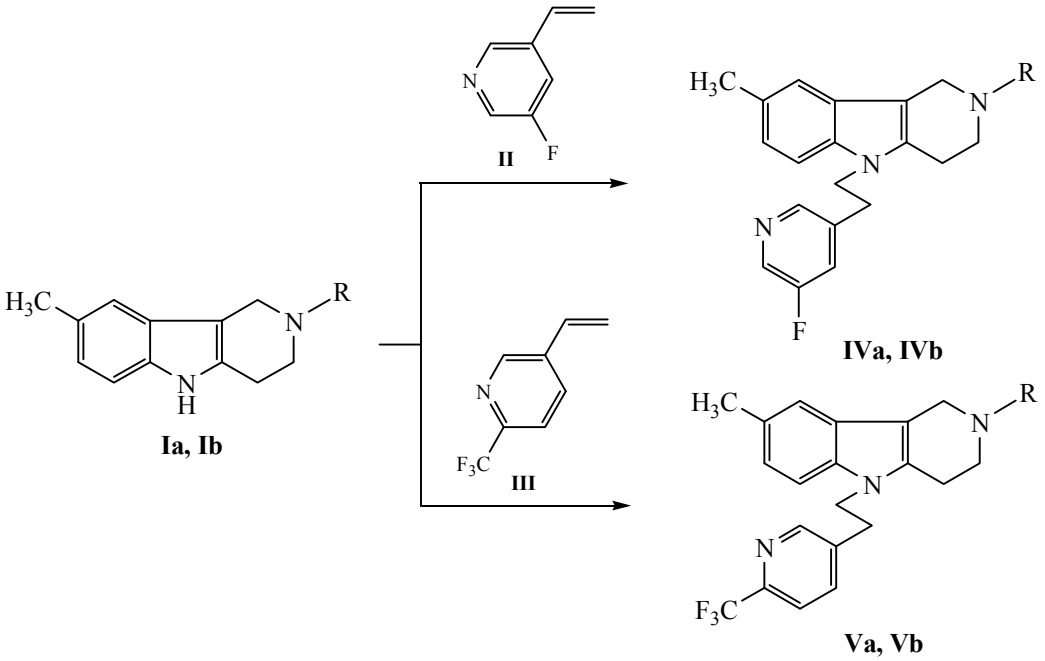
Generally, the main known methods for alkylating gamma-carbolines with vinylpyridines by Michael addition include the use of equimolar amounts of strong bases, for example methoxide or sodium hydride as promoters in DMSO or DMSO–60%-aqueous KOH system [10–12].

In the case of 3-vinyl-5-fluoropyridine and 3-vinyl-6-trifluoromethylpyridine the use of these promoters is not acceptable, since under the reaction conditions (150°C, DMSO) a nucleophilic substitution of the fluorine atom in 3-vinyl-5-fluoropyridine and a destruction of the C–F bond in 3-vinyl-6-trifluoromethylpyridine occur. In this connection, we studied the possibility of using cesium fluoride, which is a source of strong base, fluoride ion [13], as a catalyst for gamma-carbolines alkylation.

It was found that reactions of equimolar amounts of gamma-carbolines **I** and fluorine-containing 3-vinylpyridines **II** or **III** under heating in DMSO at 160°C in the presence of catalytic amounts of CsF afforded substituted 5-[2-(5-fluoropyridin-3-yl)ethyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **IV** or 5-[2-(6-trifluoromethylpyridin-3-yl)ethyl]-2-ethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **V** in yields of 75–80%. In the case of 3-vinyl-5-fluoropyridine **II** or less reactive 3-vinyl-6-trifluoromethylpyridine the reaction time was 6 or 12 h, respectively (Scheme 1).

The synthesized compounds **IVa**, **IVb, Va**, and **Vb** were colorless crystalline substances whose composition and structure were proved by elemental analysis and ^{1}H, ^{19}F NMR spectroscopy. In the ^{1}H NMR spectra of compounds **IV** and **V** there were triplet signals of the ethylene spacer linking gamma-carboline and pyridine moieties (3.01–3.05 and 4.16–4.21 ppm). The signals of fluorine atom of the pyridine ring of **IV** appeared at –47.46 and –48.22 ppm. The signals of CF_3-group of the pyridine ring of **V** were observed at 9.59 and 10.01 ppm.

Scheme 1.



IV, **V**: R = CH_3 (**a**), C_2H_5 (**b**).

In summary, we developed an original method of CsF-catalyzed alkylation of gamma-carbolines by fluorine-containing 3-vinylpyridines. This synthetic approach can be successfully used in obtaining both known and potential neuroprotective agents in a series of fluorine-containing gamma-carbolines.

EXPERIMENTAL

^{1}H (200.13 MHz) and ^{19}F (188.29 MHz) NMR spectra were recorded on a Bruker DPX 200 instrument, internal reference TMS or external reference CF_3COOH, respectively. Melting points were determined in glass capillaries.

Gamma-carbolines **Ia** and **Ib** were prepared as described in [14]. Vinyl pyridines **II** and **III** were obtained by the procedure reported in [15].

2,8-Dimethyl-5-[2-(5-fluoropyridin-3-yl)ethyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (IVa). A mixture of 1 mmol of **Ia**, 1 mmol of **II**, 0.1 g of CsF, and 0.02 g of hydroquinone in 1.5 mL of DMSO was heated with stirring at 150–160°C for 6 h. Then DMSO was removed in a vacuum at 3 mmHg. The product was extracted from the residue by CH_2Cl_2, evaporated, and chromatographed on silica gel (60 μm) eluting with MeOH–$CHCl_3$ mixture (1 : 10). Yield 0.26 g (80%), mp 103–104°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.41 s (3H, Me), 2.49–2.56 m (5H, CH_2 + MeN), 2.71 t (2H, CH_2, $^3J_{HH}$ 6.1 Hz), 3.02 t (2H, CH_2, $^3J_{HH}$ 6.1 Hz), 3.63 s (2H, CH_2), 4.21 t (2H, CH_2, $^3J_{HH}$ 6.1 Hz), 6.88 d. t (1H, CH_{Py}, $^3J_{HF}$ 9.1, $^4J_{HH}$ 1.9 Hz), 6.98 d (1H, CH_{Ind}, $^3J_{HH}$ 8.4 Hz), 7.10 d (1H, CH_{Ind}, $^3J_{HH}$ 8.4 Hz), 7.21 s (1H, CH_{Ind}), 8.13 t (1H, CH_{Py}, $^4J_{HH}$ 1.9 Hz), 8.32 d (1H, CH_{Py}, $^4J_{HH}$ 1.9 Hz). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: –47.46 d (CF_{Ar}, $^3J_{FH}$ 9.1 Hz). Found, %: C 74.47; H 6.63; N 12.76. $C_{20}H_{22}FN_3$. Calculated, %: C 74.28; H 6.86; N 12.99.

8-Methyl-5-[2-(5-fluoropyridin-3-yl)ethyl]-2-ethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (IVb) was prepared similarly. Yield 2.6 g (77%), mp 93–95°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.20 t (3H, Me, $^3J_{HH}$ 6.2 Hz), 2.46 m (5H, CH_2 + MeN), 2.63 m (2H, CH_2), 2.76 m (2H, CH_2), 3.01 t (2H, CH_2, $^3J_{HH}$ 6.3 Hz), 3.67 s (2H, CH_2), 4.20 t (2H, CH_2, $^3J_{HH}$ 6.3 Hz), 6.88 d. t (1H, CH_{Py}, $^3J_{HF}$ 9.1, $^4J_{HH}$ 1.9 Hz), 6.97 d (1H, CH_{Ind}, $^3J_{HH}$ 8.4 Hz), 7.10 d (1H, CH_{Ind}, $^3J_{HH}$ 8.4 Hz), 7.23 s (1H, CH_{Ind}), 8.16 t (1H, CH_{Py}, $^4J_{HH}$ 1.9 Hz), 8.32 d (1H, CH_{Py}, $^4J_{HH}$ 1.9 Hz). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: –48.22 d ($^3J_{FH}$ 9 Hz). Found, %: C 74.56; H 7.03; N 12.67. $C_{21}H_{24}FN_3$. Calculated, %: C 74.75; H 7.17; N 12.45.

2,8-Dimethyl-5-[2-(6-trifluoromethylpyridin-3-yl)ethyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole

(Va). A mixture of 1 mmol of **Ia**, 1 mmol of **III**, 0.1 g of CsF and 0.02 g of hydroquinone in 1.5 mL of DMSO was heated with stirring at 150–160°C for 12 h. Then DMSO was removed in a vacuum at 3 mmHg. The product was extracted from the residue by CH_2Cl_2, evaporated, and chromatographed on silica gel (60 μm) eluting with MeOH–$CHCl_3$ mixture (1 : 15). Yield 2.8 g (75%), mp 94–96°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.24 t (2H, CH_2, $^3J_{HH}$ 5.3 Hz), 2.39 s (3H, Me), 2.42 s (3H, MeN), 2.53 t (2H, CH_2, $^3J_{HH}$ 5.3 Hz), 3.03 t (2H, CH_2, $^3J_{HH}$ 6.5 Hz), 3.47 s (2H, CH_2), 4.16 t (2H, CH_2, $^3J_{HH}$ 6.5 Hz), 6.82 d (1H, CH_{Py}, $^3J_{HH}$ 8.5 Hz), 6.93 d (1H, CH_{Ind}, $^3J_{HH}$ 6.5 Hz), 6.97 d (1H, CH_{Py}, $^3J_{HH}$ 8.5 Hz), 7.07 br.s (1H, CH_{Ind}), 7.36 d (1H, CH_{Ind}, $^3J_{HH}$ 6.5 Hz), 8.34 br.s (1H, CH_{Py}). ^{19}F NMR spectrum ($CDCl_3$): δ_F 9.59 ppm. Found, %: C 67.72; H 6.13; N 10.98. $C_{21}H_{22}F_3N_3$. Calculated, %: C 67.55; H 5.94; N 11.25.

8-Methyl-5-[2-(6-trifluoromethylpyridin-3-yl)-ethyl]-2-ethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*] indole (Vb) was prepared similarly. Yield 3.0 g (77%), mp 81–83°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.19 t (3H, Me, $^3J_{HH}$ 7.3 Hz), 2.34–2.50 m (5H, CH_2 + MeN), 2.55–2.66 m (2H, CH_2), 2.72 t (2H, CH_2, $^3J_{HH}$ 5.6 Hz), 3.05 t (2H, CH_2, $^3J_{HH}$ 5.9 Hz), 3.65 s (2H, CH_2), 4.19 t (2H, CH_2, $^3J_{HH}$ 5.9 Hz), 6.94 d (1H, CH_{Py}, $^3J_{HH}$ 8.5 Hz), 7.04 d (1H, CH_{Py}, $^3J_{HH}$ 8.5 Hz), 7.21 br.s (1H, CH_{Ind}), 7.24 d (1H, CH_{Ind}, $^3J_{HH}$ 7.1 Hz), 7.46 d (1H, CH_{Ind}, $^3J_{HH}$ 7.1 Hz), 8.37 br.s (1H, CH_{Py}). ^{19}F NMR spectrum ($CDCl_3$): δ_F 10.01 ppm. Found, %: C 68.41; H 6.03; N 10.66. $C_{22}H_{24}F_3N_3$. Calculated, %: C 68.20; H 6.24; N 10.85.

ACKNOWLEDGMENTS

This work was financially supported by the Russian Foundation for Basic Research (grant no. 14-03-00491-a) and the Department of Chemistry and Material Sciences of the Russian Academy of Sciences in the frame of the Program “Fundamental sciences to medicine.”

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