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SHORT COMMUNICATIONS

Synthesis of Chiral 3-Aryl-1-methyl-3-trifluoromethyl-3*H*-pyrrolizines

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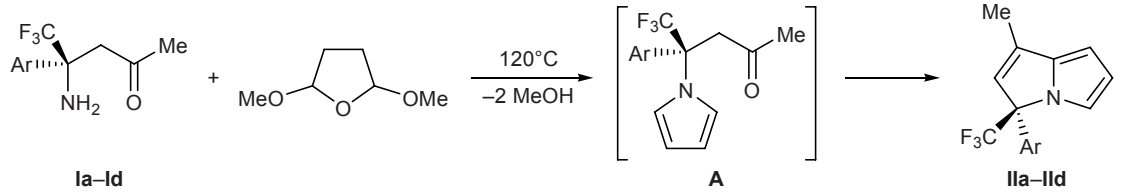
Pyrrolizines [1] are fused heterocyclic compounds with a bridgehead nitrogen atom and are important from both synthetic and biological viewpoints. Derivatives of 3*H*-pyrrolizine are key intermediates in total syntheses of antitumor mitomycin antibiotics [2–5] and their metabolites [6, 7]. Therefore, search for new ways and versions of synthesis of 3*H*-pyrrolizine derivatives attracts persistent interest. Taking into account pharmacological effects resulting from introduction of a trifluoromethyl group into organic molecules [8, 9], compounds containing a CF_3 group at a chiral carbon atom become especially significant [10, 11].

In the present communication we report on a one-step synthetic approach to new optically active trifluoromethyl-substituted 3*H*-pyrrolizines on the basis of accessible chiral synthons, (–)-(4*S*)-4-amino-4-aryl-5,5,5-trifluoropentan-2-ones **Ia**–**Id** which were obtained by us previously [12]. By heating compounds **Ia**–**Id** with 1,5-dimethoxytetrahydrofuran in boiling acetic acid we synthesized the corresponding (–)-(3*S*)-3-aryl-1-methyl-3-trifluoromethyl-3*H*-pyrolizines **IIa**–**IId** in 67–89% yield with an optical purity of 72–87%. The most probable mechanism of their formation involves intermediate β-pyrrolyl ketones **A** [13] which undergo intramolecular electrophilic cyclization at the α-carbon atom of the pyrrole ring.

(–)-(3*S*)-3-Aryl-1-methyl-3-trifluoromethyl-3*H*-pyrrolizines IIa–IId (*general procedure***).** 1,5-Dimethoxytetrahydrofuran, 0.21 g (1.6 mol), was added to a solution of 1.6 mmol of (–)-(4*S*)-4-amino-4-aryl-5,5,5-trifluoropentan-2-one **Ia**–**Id** in 10 ml of acetic acid, and the mixture was heated for 30–40 min under reflux. The mixture was evaporated, 30 ml of water and 60 ml of diethyl ether were added to the residue, and the organic phase was separated, dried over anhydrous sodium sulfate, filtered, and evaporated.

(–)-(3*S*)-1-Methyl-3-phenyl-3-trifluoromethyl-3*H*-pyrrolizine (IIa). Yield 89%, viscous oily substance, R_f 0.70, $[\alpha]_D^{20}$ = –345.83 (*c* = 1.8, MeOH), *ee* 72%. ^{1}H NMR spectrum, δ, ppm: 2.10 s (3H, CH_3), 6.03 s (1H, 5-H), 6.10 d (1H, 7-H, *J* = 2.5 Hz), 6.40 d (1H, 6-H, *J* = 2.5 Hz), 7.01 s (1H, 2-H), 7.32–7.39 m (5H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 12.49 (CH_3), 73.8 q (C^3, J_{CF} = 30.1 Hz), 99.21 (C^6), 113.34 (C^7), 118.20 (C^2), 124.7 q (CF_3, J_{CF} = 283.6 Hz), 124.92 (C^5), 126.65 ($C^{4'}$), 128.63 ($C^{2'}$, $C^{6'}$), 128.87 ($C^{3'}$, $C^{5'}$), 134.06 (C^1), 134.87 ($C^{1'}$), 142.30 (C^8). ^{19}F NMR spectrum: δ_F –75.01 ppm, s. Found, %: C 68.56; H 4.64; N 5.48. *m*/*z* 264 $[M + 1]^+$. $C_{15}H_{12}F_3N$. Calculated, %: C 68.44; H 4.59; N 5.32. *M* 263.26.

(–)-(3*S*)-3-(4-Fluorophenyl)-1-methyl-3-trifluoromethyl-3*H*-pyrrolizine (IIb). Yield 83%, viscous oily substance, R_f 0.80, $[\alpha]_D^{20}$ = –338.27 (*c* = 1.6, MeOH), *ee* 75%. ^{1}H NMR spectrum, δ, ppm: 2.11 s (3H, CH_3), 6.01 s (1H, 5-H), 6.11 d (1H, 7-H, *J* = 2.5 Hz), 6.41 d (1H, 6-H, *J* = 2.5 Hz), 6.99 s (1H, 2-H), 7.07 t (2H,



Ia–Id **A** **IIa–IId**

Ar = Ph (**a**), 4-FC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**).

H_{arom}, J = 8.5 Hz), 7.31 t (2H, H_{arom}, J = 8.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 12.46 (CH_3), 73.3 q (C^3, J_{CF} = 31.4 Hz), 99.47 (C^6), 113.63 (C^7), 115.68 ($C^{3'}$), 115.94 ($C^{5'}$), 118.01 (C^5), 124.6 q (CF_3, J_{CF} = 284.1 Hz), 124.84 (C^2), 128.67 ($C^{2'}$, $C^{6'}$), 129.95 (C^1), 135.94 ($C^{1'}$), 142.26 (C^8), 163.7 d ($C^{4'}$, J_{CF} = 248.9 Hz). ^{19}F NMR spectrum, δ_F, ppm: –75.14 s, –114.162 s. Found, %: C 64.18; H 4.14; N 5.08. m/z 282.4 $[M + 1]^+$. $C_{16}H_{14}F_3NO$. Calculated, %: C 64.06; H 3.94; N 4.98; M 281.26

(–)-(3*S*)-1-Methyl-3-(4-methylphenyl)-3-trifluoromethyl-3*H*-pyrrolizine (IIc). Yield 67%, viscous oily substance, R_f 0.78, $[\alpha]_D^{20}$ = –292.97 (c = 0.26, MeOH), *ee* 81%. ^1H NMR spectrum, δ, ppm: 2.09 s (3H, CH_3), 2.35 s (3H, CH_3), 6.02 s (1H, 5-H), 6.09 d (1H, 7-H, J = 2.5 Hz), 6.40 d (1H, 6-H, J = 2.5 Hz), 7.01 s (1H, 2-H), 7.15–7.23 m (4H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 12.50 (1-CH_3), 21.02 (4′-CH_3), 73.6 q (C^3, J_{CF} = 30.1 Hz), 99.09 (C^6), 113.23 (C^7), 118.14 (C^2), 124.7 q (CF_3, J_{CF} = 284.1 Hz), 125.17 (C^5), 126.55 ($C^{2'}$, $C^{6'}$), 129.57 ($C^{3'}$, $C^{5'}$), 131.03 (C^1), 135.53 ($C^{1'}$), 138.59 ($C^{4'}$), 142.29 (C^8). Found, %: C 69.66; H 5.24; N 5.19. m/z 278 $[M + 1]^+$. $C_{16}H_{14}F_3N$. Calculated, %: C 69.31; H 5.09; N 5.05. M 277.29.

(–)-(3*S*)-3-(4-Methoxyphenyl)-1-methyl-3-trifluoromethyl-3*H*-pyrrolizine (IId). Yield 89%, viscous oily substance, R_f 0.79, $[\alpha]_D^{20}$ = –417.20 (c = 0.33, MeOH), *ee* 87%. ^1H NMR spectrum, δ, ppm: 2.09 s (3H, CH_3), 3.80 s (3H, CH_3O), 6.02 s (1H, 5-H), 6.08 d (1H, 7-H, J = 2.5 Hz), 6.39 d (1H, 6-H, J = 2.5 Hz), 6.91 d (2H, H_{arom}, J = 8.0 Hz), 7.00 s (1H, 2-H), 7.27 d (2H, H_{arom}, J = 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 12.48 (CH_3), 55.31 (CH_3O), 73.40 q (C^3, J_{CF} = 30.1 Hz), 55.31 (C^6), 99.08 (C^7), 113.25 (C^2), 114.23 ($C^{3'}$, $C^{5'}$), 118.04 (C^5), 124.7 q (CF_3, J_{CF} = 282.9 Hz), 125.17 (C^1), 127.99 ($C^{2'}$, $C^{6'}$), 135.43 ($C^{1'}$), 142.26 (C^8), 159.74 ($C^{4'}$). ^{19}F NMR spectrum: δ_F –75.34 ppm, s. Found, %: C 65.67; H 4.94; N 4.88. m/z 294 $[M + 1]^+$. $C_{16}H_{14}F_3NO$. Calculated, %: C 65.52; H 4.81; N 4.78. M 293.29.

The ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer at 500.13, 188.14, and 125.75 MHz, respectively, using $CDCl_3$ as solvent; the chemical shifts were determined relative to tetramethylsilane (^1H, ^{13}C) and CCl_3F (^{19}F) as internal standards. The mass spectra were obtained on a Perkin–Elmer SCIEX API 150 instrument equipped with UV (λ 254 nm) and ELSD detectors. The purity of the products was checked by TLC on Silufol UV-254 plates using ethyl acetate–hexane (3 : 1) as eluent. The optical rotations were measured on a Perkin–Elmer 341 polarimeter. The optical purity was determined by ^{19}F NMR spectroscopy using tris[3-(heptafluorobutyryl)-L-camphorato]europium as lanthanide shift reagent.

REFERENCES

1. Flitsch, W. and Jones, G., *Adv. Heterocycl. Chem*., 1984, vol. 37, p. 1.
2. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2000, vol. 2, p. 439.
3. Nakatsubo, F., Cocuzza, A.J., Keeley, D.E., and Kishi, Y., *J. Am. Chem. Soc*., 1977, vol. 99, p. 4835.
4. Nakatsubo, F., Fukuyama, T., Cocuzza, A.J., and Kishi, Y., *J. Am. Chem. Soc*., 1977, vol. 99, p. 8115.
5. Fukuyama, T. and Yang, L., *J. Am. Chem. Soc*., 1987, vol. 109, p. 7881.
6. Shaw, K.J., Luli, J.R., and Rapoport, H., *J. Org. Chem*., 1985, vol. 50, p. 4515.
7. Rebek, J.J., Shaber, S.H., Shue, Y-K., Gernet, J.C., and Zimmerman, S., *J. Org. Chem*., 1984, vol. 49, p. 5164.
8. Filler, R. and Kobayashi, Y., *Biomedicinal Aspects of Fluorine Chemistry*, Tokyo: Kodansha, 1982, p. 246.
9. Filler, R., Kobayashi, Y., and Yagupolski, L.M., *Organofluorine Compounds in Medicinal Chemistry and Biomedicinal Applications*, Amsterdam: Elsevier, 1993, p. 386.
10. Corbet, J.W., Ko, S.S., Rodgers, J.D., Jeffrey, S., Bacheler, L.T., Klabe, R.M., Diamond, S., Lai, C.-M., Rabel, S.R., Saye, J.A., Adams, S.P., Trainor, G.L., and Anderson, P.S., *Antimicrob. Agents Chemother*., 1999, vol. 43, p. 2893.
11. Magnus, N.A., Confalone, P.N., Storace, L., Patel, M., Wood, C.C., Davis, W.P., and Parsons, R.L., Jr., *J. Org. Chem*., 2003, vol. 68, p. 754.
12. Sukach, V.A., Golovach, N.M., Pirozhenko, V.V., Rusanov, E.B., and Vovk, M.V., *Tetrahedron: Asymmetry*, 2008, vol. 19, p. 761.
13. Josey, A.D. and Jenner, E.L., *J. Org. Chem*., 1962, vol. 27, p. 2466.