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Synthesis of (*S*)-(+)-6-Aryl-3-acetyl-6-trifluoromethyl-5,6-dihydropyridin-2(1*H*)-ones

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Abstract—(*S*)-(+)-4-Amino-4-aryl-5,5,5-trifluoropentan-2-ones reacted with ethyl acetoacetate and ethyl trifluoroacetoacetate to give (*S*)-(+)-6-aryl-3-acetyl(or trifluoroacetyl)-6-trifluoromethyl-5,6-dihydropyridin-2(1*H*)-ones.

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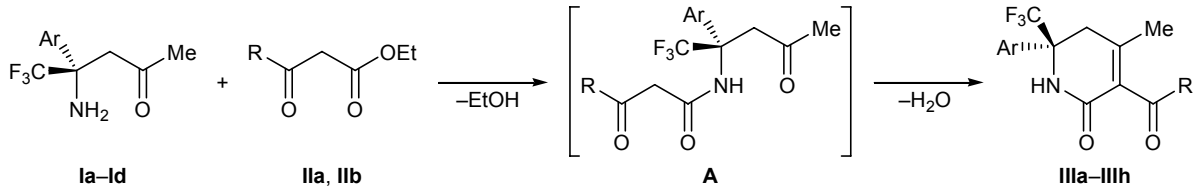
Partly hydrogenated pyridine ring is a structural fragment of molecules of a number of biologically active natural compounds [1–4]; hydrogenated pyridine derivatives are also widely used in agricultural and pharmaceutical chemistry. In particular, some compounds of the 5,6-dihydropyrimidin-2(1*H*)-one series are effective herbicides [5], antiviral [6] and antileukemic agents [7], and biological mediators playing an important role in blood pressure regulation processes [8]. Despite the existence of versatile methods for the synthesis of such compounds, the most convenient procedures are based on intramolecular cyclization of 2-substituted *N*-(3-oxoalkyl)acetamides or their precursors generated *in situ* by the action of bases [9–11]. Taking into account increased researchers' interest [12, 13] in perfluoroalkyl-substituted nitrogen-containing heterocycles, compounds containing a trifluoromethyl group in the α-position with respect to the nitrogen atom [14–16], especially at a chiral carbon center [17, 18] have attracted much attention. Up to now, only a few 6-trifluoromethyl-5,6-dihydropyridin-2(1*H*)-one derivatives have been synthesized by cyclocondensation of "push–pull" enamines with 1-chloro-2,2,2-trifluoroethyl isocyanates [19]. There are no published data on optically active trifluoromethyl-substituted 5,6-dihydropyridin-2(1*H*)-ones.

We have proposed a preparatively convenient procedure for the synthesis of such compounds via cyclization of accessible [20] highly optically pure (*S*)-(+)-4-amino-4-aryl-5,5,5-trifluoropentan-2-ones **Ia**–**Id** with ethyl acetoacetate (**IIa**) and ethyl 4,4,4-trifluoro-3-oxobutanoate (**IIb**) under neutral conditions. By heating the initial reactants in boiling toluene or xylene we obtained the corresponding (*S*)-(+)-3-acetyl-(or trifluoroacetyl)-6-aryl-4-methyl-6-trifluoromethyl-5,6-dihydropyridin-2(1*H*)-ones **IIIa**–**IIIh** in 63–91% yield with an optical purity of 84–91%. `

We previously showed [21] that amines like **I** undergo acylation only by the action of strong electrophiles. Acetoacetic acid esters **IIa** and **IIb** cannot be regarded as such strong electrophiles; however, at elevated temperature they are likely to be converted into reactive α-keto ketenes [22], and the latter react with compounds **Ia**–**Id** to produce *N*-(trifluoro)acetyl-

Scheme 1.



Ia–Id **IIa, IIb** **A** **IIIa–IIIh**

I, Ar = Ph (**a**), 4-FC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**); **II**, R = Me (**a**), CF_3 (**b**); **III**, R = Me, Ar = Ph (**a**), 4-FC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**); R = CF_3, Ar = Ph (**e**), 4-FC_6H_4 (**f**), 4-MeC_6H_4 (**g**), 4-$MeOC_6H_4$ (**h**).

acetamides **A**. Unlike *N*-(3-oxoalkyl)acetamides [9–11], intermediate amides **A** undergo thermal intramolecular cyclization in the absence of a base (Scheme 1). The proposed scheme is confirmed by the fact that ethyl cyanoacetate failed to react with amines **I** under analogous conditions.

The described reaction does not involve the chiral carbon center (C^6); therefore, its absolute configuration remains the same as in the initial amine. The presence of a β-dicarbonyl fragment in molecules **III** makes these compounds promising as building blocks for the synthesis of various chiral fused pyridine systems.

The lactam fragment in compounds **IIIa**–**IIIh** gives rise to IR absorption bands at 3200–3220 (N–H) and 1675–1690 cm^{-1} (C=O). Stretching vibrations of the exocyclic acetyl carbonyl group are characterized by absorption at 1705 cm^{-1}, whereas the trifluoroacetyl group absorbs at 1680–1690 cm^{-1}. In the ^1H NMR spectra of **IIIa**–**IIIh** we observed signals from the NH and aromatic protons and two doublets in the region δ 2.97–3.29 ppm due to *AB* spin system formed by methylene protons on C^5. The dihydropyridinone structure of compounds **IIIa**–**IIIh** is also reliably confirmed by the ^{13}C NMR spectra which contained, apart from the characteristic C^2, C^3, and C^4 signals, a singlet from C^5 at δ_C 36–37 ppm and a quartet from C^6 at δ_C 62 ppm, the latter being coupled with fluorine atoms in the trifluoromethyl group ($^2J_{CF}$ = 27.6–28.9 Hz).

EXPERIMENTAL

The ^1H, ^{19}F, and ^{13}C NMR spectra were measured on a Bruker Avance DRX-500 spectrometer at 500.13, 188.14, and 125.75 MHz, respectively, from solutions in $CDCl_3$ using tetramethylsilane (^1H, ^{13}C) and trichlorofluoromethane (^{19}F) as internal references. The IR spectra were recorded from solutions in methylene chloride on a UR-20 spectrometer. The mass spectra were obtained on a PE SCIEX API 150 EX instrument equipped with UV (λ 254 nm) and ELSD detectors. The purity of the products was checked by thin-layer chromatography on Silufol-254 plates using ethyl acetate–hexane (1:5) as eluent. The optical rotations were measured on a Perkin–Elmer 341 polarimeter. The optical purity was determined by ^{19}F NMR spectroscopy with the use of tris[3-(heptafluorobutyryl)-L-camphorato]europium as lanthanide shift reagent.

(*S*)-(+)-3-Acetyl-6-aryl-4-methyl-6-trifluoromethyl-5,6-dihydropyridin-2(1*H*)-ones IIIa–IIIh (*general procedure*). Amino ketone **Ia**–**Id**, 1.6 mmol, was dissolved in 15 ml of anhydrous xylene or toluene, 0.18 ml (1.6 mmol) of ethyl acetoacetate or 0.24 ml (1.6 mmol) of ethyl 4,4,4-trifluoro-3-oxobutanoate, respectively, was added, and the mixture was heated for 4–6 h under reflux. The solvent was distilled off, and the residue was recrystallized from 60% aqueous ethanol (**IIIc**, **IIIe**–**IIIh**) or purified by thin-layer chromatography on silica gel using ethyl acetate–hexane (1:5) as eluent (**IIIa**, **IIIb**, **IIId**).

(*S*)-(+)-3-Acetyl-4-methyl-6-phenyl-6-trifluoromethyl-5,6-dihydropyridin-2(1*H*)-one (IIIa). Yield 76%, mp 113–115°C, $[\alpha]_D^{20}$ = +37.4° (*c* = 0.98, MeOH). IR spectrum, ν, cm^{-1}: 3210 (NH); 1705, 1685 (C=O). ^1H NMR spectrum, δ, ppm: 1.98 s (3H, CH_3), 2.34 s (3H, CH_3), 3.02 d (1H, CH_2, *J* = 18.0 Hz), 3.20 d (1H, CH_2, *J* = 18.0 Hz), 7.11 s (1H, NH), 7.42–7.44 m (3H, H_{arom}), 7.50–7.53 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.06 (CH_3), 31.39 (CH_3), 36.93 (C^5), 62.30 q (C^6, *J* = 27.6 Hz), 124.93 q (CF_3, *J* = 285.4 Hz), 126.15, 129.00, 129.38, 132.20 (C_{arom}), 135.94 (C^4), 149.08 (C^3), 164.31 (C^2), 200.64 (C=O). ^{19}F NMR spectrum: δ_F –78.76 ppm. Mass spectrum: *m*/*z* 298 $[M]^+$. Found, %: C 60.58; H 4.77; N 4.73. $C_{15}H_{14}F_3NO_2$. Calculated, %: C 60.60; H 4.75; N 4.71. *M* 297.3.

(*S*)-(+)-3-Acetyl-6-(4-fluorophenyl)-4-methyl-6-trifluoromethyl-5,6-dihydropyridin-2(1*H*)-one (IIIb). Yield 63%, mp 110–113°C, $[\alpha]_D^{20}$ = +23.2° (*c* = 1.0, MeOH). IR spectrum, ν, cm^{-1}: 3200 (NH); 1705, 1675 (C=O). ^1H NMR spectrum, δ, ppm: 1.98 s (3H, CH_3), 2.33 s (3H, CH_3), 2.98 d (1H, CH_2, *J* = 18.0 Hz), 3.19 d (1H, CH_2, *J* = 18.0 Hz), 7.10–7.13 m (2H, H_{arom}), 7.46 s (1H, NH), 7.50–7.52 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.08 (CH_3), 31.38 (CH_3), 36.89 (C^5), 62.02 q (C^6, *J* = 27.6 Hz), 115.94, 116.11, 128.22, 128.29, 131.76 (C_{arom}), 127.06 q (CF_3, *J* = 285.4 Hz), 132.24 (C^4), 148.99 (C^3), 164.09 d ($C^{4'}$, *J* = 248.9 Hz), 164.42 (C^2), 200.50 (C=O). ^{19}F NMR spectrum, δ_F, ppm: –77.19, –78.95, –112.71. Mass spectrum: *m*/*z* 316 $[M]^+$. Found, %: C 57.13; H 4.14; N 4.43. $C_{15}H_{13}F_4NO_2$. Calculated, %: C 57.15; H 4.16; N 4.44. *M* 315.3.

(*S*)-(+)-3-Acetyl-4-methyl-6-(4-methylphenyl)-6-trifluoromethyl-5,6-dihydropyridin-2(1*H*)-one (IIIc). Yield 90%, mp 145–147°C, $[\alpha]_D^{20}$ = +2.0° (*c* = 1.0, MeOH). IR spectrum, ν, cm^{-1}: 3210 (NH); 1705, 1690 (C=O). ^1H NMR spectrum, δ, ppm: 1.94 s (3H, CH_3), 2.34 s (3H, CH_3), 2.36 s (3H, CH_3), 2.97 d (1H, CH_2, *J* = 17.5 Hz), 3.14 d (1H, CH_2, *J* = 17.5 Hz), 6.54 s (1H, NH), 7.24 d (2H, H_{arom}, *J* = 8.0 Hz), 7.38 d (2H_{arom}, *J* = 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.99 (CH_3), 21.08 (CH_3), 31.39 (CH_3), 36.80 (C^5),

62.09 q (C^6, J = 27.6 Hz), 124.78 q (CF_3, J = 284.2 Hz), 126.20, 129.62, 132.18, 132.94 (C_{arom}), 139.30 (C^4), 149.28 (C^3), 164.70 (C^2), 200.79 (C=O). ^{19}F NMR spectrum: δ_F –78.96 ppm. Mass spectrum: m/z 312 $[M]^+$. Found, %: C 61.70; H 5.23; N 4.48. $C_{16}H_{16}F_3NO_2$. Calculated, %: C 61.73; H 5.18; N 4.50. M 311.3.

(*S*)-(+)-3-Acetyl-6-(4-methoxyphenyl)-4-methyl-6-trifluoromethyl-5,6-dihydropyridin-2(1*H*)-one (IIId). Yield 71%, mp 105–107°C, $[\alpha]_D^{20}$ = +48.5° (c = 0.79, MeOH). IR spectrum, ν, cm^{-1}: 3210 (NH); 1705, 1695 (C=O). ^1H NMR spectrum, δ, ppm: 1.97 s (3H, CH_3), 2.33 s (3H, CH_3), 2.97 d (1H, CH_2, J = 17.5 Hz), 3.16 d (1H, CH_2, J = 17.5 Hz), 3.83 s (3H, CH_3O), 6.94 d (2H, H_{arom}, J = 7.5 Hz), 7.41 d (2H_{arom}, J = 7.5 Hz), 7.41 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 21.08 (CH_3), 31.40 (CH_3), 36.88 (C^5), 61.92 q (C^6, J = 27.6 Hz), 114.26, 127.52, 127.67, 160.15 (C_{arom}), 124.80 q (CF_3, J = 284.0 Hz), 132.18 (C^4), 149.21 (C^3), 164.53 (C^2), 200.77 (C=O). ^{19}F NMR spectrum: δ_F –79.08 ppm. Mass spectrum: m/z 328 $[M]^+$. Found, %: C 58.72; H 4.95; N 4.25. $C_{16}H_{16}F_3NO_3$. Calculated, %: C 58.71; H 4.93; N 4.28. M 327.3.

(*S*)-(+)-4-Methyl-6-phenyl-3-trifluoroacetyl-6-trifluoromethyl-5,6-dihydropyridin-2(1*H*)-one (IIIe). Yield 87%, mp 115–117°C, $[\alpha]_D^{20}$ = +37.7 (c = 1.15, MeOH). IR spectrum, ν, cm^{-1}: 3210 (NH); 1680, 1675 (C=O). ^1H NMR spectrum, δ, ppm: 2.02 s (3H, CH_3), 3.15 d (1H, CH_2, J = 18.0 Hz), 3.29 d (1H, CH_2, J = 18.0 Hz), 7.42–7.51 m (5H, H_{arom}), 8.22 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 21.02 (CH_3), 37.07 (C^5), 62.63 q (C^6, J = 28.9 Hz), 115.04 q (CF_3, J = 291.7 Hz), 124.72 q (CF_3, J = 284.2 Hz), 126.26, 126.98, 129.01, 129.55 (C_{arom}), 135.10 (C^3), 155.36 (C^4), 163.69 (C^2), 184.79 q (C=O, J = 38.9 Hz). ^{19}F NMR spectrum, δ_F, ppm: –77.16, –78.77. Mass spectrum: m/z 352 $[M]^+$. Found, %: C 51.31; H 3.16; N 3.99. M 351.2.

(*S*)-(+)-6-(4-Fluorophenyl)-4-methyl-3-trifluoroacetyl-6-trifluoromethyl-5,6-dihydropyridin-2(1*H*)-one (IIIf). Yield 68%, viscous oily substance, $[\alpha]_D^{20}$ = +57.3° (c = 1.02, MeOH). IR spectrum, ν, cm^{-1}: 3200 (NH); 1680, 1675 (C=O). ^1H NMR spectrum, δ, ppm: 2.02 s (3H, CH_3), 3.09 d (1H, CH_2, J = 18.0 Hz), 3.27 d (1H, CH_2, J = 18.0 Hz), 7.14 d (2H, H_{arom}, J = 7.5 Hz), 7.55 d (2H, H_{arom}, J = 7.5 Hz), 8.25 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 21.03 (CH_3), 37.12 (C^5), 62.28 q (C^6, J = 27.6 Hz), 114.23, 114.33, 126.95, 127.54 (C_{arom}), 116.21 q (CF_3, J = 291.7 Hz), 124.75 q (CF_3, J = 284.1 Hz), 155.11 (C^3), 160.30 (C^4), 162.08 d ($C^{4'}$, J = 296.7 Hz), 169.75 (C^2), 184.89 q (C=O, J = 38.9 Hz). ^{19}F NMR spectrum, δ_F, ppm: –77.18, –78.98, –112.71. Mass spectrum: m/z 370 $[M]^+$. Found, %: C 48.82; H 2.70; N 3.81. $C_{15}H_{10}F_7NO_2$. Calculated, %: C 48.79; H 2.73; N 3.79. M 369.2.

(*S*)-(+)-4-Methyl-6-(4-methylphenyl)-3-trifluoroacetyl-6-trifluoromethyl-5,6-dihydropyridin-2(1*H*)-one (IIIg). Yield 91%, mp 164–166°C, $[\alpha]_D^{20}$ = +65.9° (c = 1.39, MeOH). IR spectrum, ν, cm^{-1}: 3220 (NH); 1685, 1680 (C=O). ^1H NMR spectrum, δ, ppm: 1.99 s (3H, CH_3), 2.37 s (3H, CH_3), 3.04 d (1H, CH_2, J = 18.0 Hz), 3.29 d (1H, CH_2, J = 18.0 Hz), 7.25 d (2H, H_{arom}, J = 7.8 Hz), 7.38 d (2H, H_{arom}, J = 7.8 Hz), 7.81 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 20.96 (CH_3), 37.06 (C^5), 62.45 q (C^6, J = 27.6 Hz), 115.05 q (CF_3, J = 291.1 Hz), 124.76 q (CF_3, J = 284.1 Hz), 126.15, 126.97, 129.66, 132.12 (C_{arom}), 139.55 (C^3), 155.37 (C^4), 163.71 (C^2), 184.91 q (C=O, J = 38.9 Hz). ^{19}F NMR spectrum, δ_F, ppm: –77.08, –79.01. Mass spectrum: m/z 366 $[M]^+$. Found, %: C 52.63; H 3.62; N 3.87. $C_{16}H_{13}F_6NO_2$. Calculated, %: C 52.61; H 3.59; N 3.83. M 365.3.

(*S*)-(+)-6-(4-Methoxyphenyl)-4-methyl-3-trifluoroacetyl-6-trifluoromethyl-5,6-dihydropyridin-2(1*H*)-one (IIIh). Yield 73%, mp 118–120°C, $[\alpha]_D^{20}$ = +16.5° (c = 1.0, MeOH). IR spectrum, ν, cm^{-1}: 3210 (NH); 1690, 1680 (C=O). ^1H NMR spectrum, δ, ppm: 2.02 s (3H, CH_3), 3.10 d (1H, CH_2, J = 17.5 Hz), 3.29 d (1H, CH_2, J = 17.5 Hz), 3.84 s (3H, CH_3O), 6.96 d (2H, H_{arom}, J = 7.5 Hz), 7.46 d (2H, H_{arom}, J = 7.5 Hz), 8.39 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 21.00 (CH_3), 37.07 (C^5), 55.32 (CH_3O), 62.25 q (C^6, J = 27.6 Hz), 114.18, 114.27, 126.91, 127.63 (C_{arom}), 116.20 q (CF_3, J = 291.7 Hz), 124.76 q (CF_3, J = 284.1 Hz), 155.58 (C^3), 160.28 (C^4), 163.84 (C^2), 184.91 q (C=O, J = 38.9 Hz). ^{19}F NMR spectrum, δ_F, ppm: –77.11, –79.13. Mass spectrum: m/z 382 $[M]^+$. Found, %: C 50.44; H 3.41; N 3.71. $C_{16}H_{13}F_6NO_3$. Calculated, %: C 50.40; H 3.44; N 3.67. M 381.3.

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