N-Silylimine of Trifluoropyruvate in the Asymmetric Synthesis of Trifluoroalanine Derivatives

Abstract
Aim. To develop a preparative method for the synthesis of N-trimethylsilylimine of trifluoropyruvate, and study its interaction with acetone under organocatalytic conditions.

Results and discussion. A simple preparative approach to the first representative of N-silylimines of trifluoropyruvate was developed based on the interaction of triphenylphosphinimide and trifluoropyruvic acid methyl ester by the aza-Wittig reaction. It was found that the addition of acetone to N-silylimine occurred in the presence of L- or D-proline and led to the formation of enantiomerically enriched α-amino-γ-oxocarboxylates. The hydrolysis of the ester function resulted in (R)-α-trifluoromethyl aminocarboxylic acid, and the cyclocondensation with isocyanates or 2,5-dimethoxytetrahydrofuran yielded nitrogen-containing heterocycles containing pyrimidine or pyrrolizine nuclei.

Experimental part. The synthetic procedures for the N-silylimine of trifluoropyruvate and its reaction with acetone are provided, along with the transformations of obtained α-amino-γ-oxocarboxylates (hydrolysis, cyclocondensations with isocyanates and 2,5-dimethoxytetrahydrofuran). The structures of the compounds synthesized were proven by 1H, 13C, 19F NMR spectroscopy methods, as well as by the elemental analysis.

Conclusions. A convenient method for the synthesis of N-silylimine of trifluoropyruvate has been developed. Using the example of the Mannich reaction with acetone, it has been demonstrated that N-silylimine of trifluoropyruvate is a convenient substrate for the synthesis of optically active 3,3,3-trifluoroalanine derivatives.

Keywords: asymmetric synthesis; N-silylimine; Mannich reaction; trifluoromethyl; α-amino-γ-oxocarboxylate

A. С. Чередніченко, Ю. В. Рассукана
Інститут органічної хімії Національної академії наук України,
вл. Академіка Кухаря, 5, м. Київ, 02660, Україна

N-силілімін тріфторопірувату в асиметричному синтезі похідних тріфтороаланіну

Анотація
Мета. Розробити препаративний метод для синтезу N-триметилсиліліму ліму тристоропірувату та дослідити закономірності його взаємодії з ацетоном в органокаталітичних умовах.
Результати та їх обговорення. Розроблено простий препаративний підхід до першого представника N-силілімінів тріфторопірувату, який полягає у взаємодії трифенілфосфініміду і метилового естера тріфторопіровиноградної кислоти за схемою реакції аза-Віттіга. Виявлено, що приєднання ацетону до N-силіліміну відбувається в присутності L- або D-проліну і призводить до утворення енантіомерно збагачених α-аміно-γ-оксокарбоксилатів. Гідролізом естерної функції останніх одержано (R)-α-тріфторометил амінокарбонову кислоту, а циклоконденсацією з ізосіанатами та 2,5-диметокситетрагідрофураном синтезовано нітрогеновмісні гетероциклі, що містять піримідинове або піролізинове ядро.
Експериментальна частина. Наведено експериментальні методики синтезу N-силіліміну тріфторопірувату, продуктів його реакції з ацетоном, а також перетворення отриманих α-аміно-γ-оксокарбоксилатів (гідроліз, циклоконденсації з ізосіанатами та 2,5-диметокситетрагідрофураном). Структури усіх отриманих сполук доведено методами ЯМР на ядрах 1H, 13C і 19F, а також елементним алілізом.
Висновки. Розроблено зручний метод синтезу N-силіліміну тріфторопірувату. На прикладі реакції Манніха з ацетоном продемонстровано, що N-силілімін тріфторопірувату є зручним субстратом для синтезу оптично активних похідних 3,3,3-тріфтороаланіну.
Ключові слова: асиметричний синтез; N-силілімін; реакція Манніха; трифторометил; α-аміно-γ-оксокарбоксилат
Introduction

The development of new synthetic approaches to fluorine-containing derivatives of α-aminocarboxylic acids has remained an urgent task over the past few decades, considering the wide spectrum of their biological action and, as a result, their increasingly expanding application in drug design [1–4]. However, modern requirements for the design of biologically active molecules containing a stereogenic center demand the synthesis of both enantiomeric forms. Therefore, the development of synthetic methods for non-racemic fluorinated amino acids derivatives is a particular task. Imines of trifluoropyruvate have already proven themselves as convenient precursors of acyclic and heterocyclic amino acids, including enantiomerically enriched ones [5–7]. Thus, we have recently demonstrated that asymmetric functionalization of enantiomerically pure N-(tert-butylsulfinyl)imines of trifluoropyruvate allows obtaining non-racemic derivatives of trifluoroalanine [8]. However, for synthesizing optically active compounds, it is also possible to apply the strategy of functionalization of non-chiral imines using the asymmetric catalysis. The organocatalytic Mannich reaction of acetone with acyclic and heterocyclic polyfluoroalkyl imines has already become a convenient tool for constructing a C-C bond near the stereogenic azomethine carbon atom, and obtaining optically active compounds. Moreover, we previously showed that the organocatalytic addition of acetone to NH-imino phosphonates, phosphorus analogs of iminocarboxylates, proceeds with high chemo- and enantioselectivity [9, 10].

At the same time, in recent years, the use of silyl derivatives in organic synthesis has expanded, and “silyl” strategies for the synthesis of many classes of compounds have been developed. N-Silylimines are synthetic equivalents of unprotected NH-imines and can serve as convenient synthons for obtaining amino acids derivatives with a free amino function. An important advantage of N-silylimines is the ease of their conversion into N-unprotected amino acids derivatives since the silyl group is usually removed while treating the reaction mixture. Nevertheless, as far as we know, N-silylated imines of trifluoropyruvate have remained unknown to date. In this work, we proposed a simple method for the synthesis of N-trimethylsilylimine of trifluoropyruvate and studied its behavior in the proline-catalyzed Mannich reaction with acetone.

Results and discussion

To develop a synthetic approach to methyl α-(N-trimethylsilylimino)trifluoropropionate (4), we employed a strategy that was previously successfully used to obtain the “parent” NH-imine of trifluoropyruvate [11]. The method consists in the interaction of commercially available methyl trifluoropyruvate (1) with N-(trimethylsilyl)triphenylphosphinimine (2) yielded from silyl azide and triphenylphosphine by the Staudinger reaction (Scheme 1).

Condensation of ketone 1 with phosphinimide 2 proceeds in several steps, resulting in the formation of the desired iminocarboxylate 4. Spectral monitoring of the reaction mixture by NMR on the fluorine and phosphorus nuclei indicated that initially nucleophilic addition of the =NSiMe3 group of compound 2 to the highly polarized C=O bond of ketoester 1 occurred, giving phosphazacarboxylate 3. Thus, the signal in the
Scheme 2. Proline-catalyzed Mannich reaction of imine 4 with acetone

Scheme 3. Synthesis of α-aminocarboxylic acid (R)-6

Figure. Possible intermediate of iminophosphorane 3 transformation into imine 4

$^{31}$P NMR spectra of compound 3 appears in the region expected for iminophosphoranes (3.5 ppm), and the chemical shift in $^{31}$P NMR (−80.04 ppm) indicates the location of the trifluoromethyl group and the siloxy function at the sp$^3$-hybridized carbon atom. Iminophosphorane 3 is stable at room temperature, but when heated or distilled it easily eliminates triphenylphosphine oxide and transforms into imine 4 – the first representative of N-silylimines of trifluoropyruvate. It is most likely that the rearrangement 3 → 4 involves 1,3-O,N migration of the trimethylsilyl group followed by the elimination of triphenylphosphine oxide from the classical intermediate of the aza-Wittig reaction – oxazaphosphetane A (Figure).

Imine 4 is a yellow liquid that can be easily distilled at atmospheric pressure (b. p. 126–128 °C), and is stable in an inert atmosphere. The most characteristic for the structural identification of iminocarboxylate 4 is the position and multiplicity of the signal of azomethyne carbon atom in the $^{13}$C NMR spectrum (150.7 ppm, q, $^3J_{CF} = 37.3$ Hz), which confirms the presence of the CF$_3$C=N fragment, along with the presence of a singlet signal of the CH$_3$Si-group carbons (−0.1 ppm). Noteworthy, in contrast to NH-imine of trifluoropyruvate, which exists as a mixture of E- and Z-isomers, there is only one set of signals observed in the $^1$H, $^{31}$P NMR spectra for its N-silylated analogue 4 [11, 12].

It was found that iminocarboxylate 4 also underwent the Mannich reaction with acetone in the presence of L- or D-proline (Scheme 2).

Addition of acetone to the C=N bond of imine 4 proceeded at room temperature in DMOSO and was completed within 24 hours.

Enantiomerically enriched α-amino-γ-oxocarboxylates (R)-5 and (S)-5 with a free amino group were isolated after treating the reaction mixture with water; further treatment with the hydrochloride solution in diethyl ether allowed to obtain the corresponding hydrochlorides, which were more suitable for storage.

Considering the fact that the interaction of iminocarboxylate 4 and iminophosphonates [9] with acetone occurs under the same conditions, it can be assumed that the absolute configuration of the newly formed stereocenter of compound 5 is identical to the structure of (R)-2-amino-1,1,1-trifluoro-4-oxopentyl-2-phosphonate determined in our laboratory earlier [9, 10].

A separate task in the asymmetric synthesis is to determine the enantiomeric purity of the non-racemic compounds obtained. Previously, we found that the chiral solvating agent (CSA) – tert-Bu(PH)P(SiOH) – was effective in identifying the ee of phosphoryl analogues of compounds 5 [9, 10]. It was determined that this CSA could also be applied to aminocarboxylates 5. Thus, in the ratio of 3:1 of carboxylate (R)-5 and CSA, a clear separation of the signals was observed in the $^{31}$P NMR spectra (C$_6$D$_6$) (Δδ ~0.1 ppm), which allowed to detect ee of optically active ketocarboxylates 5. It turned out that the enantioselectivity of the acetone addition to iminocarboxylates was significantly lower compared to iminophosphonates, and reached about 35%. Unfortunately, our attempts to improve the enantiomeric excess of the products by increasing the amount of proline (1 equiv) or by performing the reaction at lower temperatures (5 °C) in no way affected the stereochemical result of the interaction.

γ-Ketoester 5 contains several functional groups, which make it an attractive synthon for the synthesis of non-racemic trifluoralanine derivatives, both acyclic and heterocyclic.

The presence of an amino acid fragment in the molecule also allows applying compound 5 to the peptide synthesis; therefore, it is of great
importance to perform hydrolysis of the ester function. It is worth noting that compounds containing a carboxylate group near the quaternary carbon atom often undergo decarboxylation during hydrolysis. However, it was found that hydrolysis of the ester function of aminocarboxylate (R)-5 proceeded smoothly by the sequential treatment with sodium hydroxide and a diluted hydrochloric acid solution (1 M), leading to the formation of amino acid (R)-6 isolated as hydrochloride (Scheme 3).

The presence of the amino group and the keto function in carboxylates is a prerequisite for the design of various heterocyclic systems on their basis. Hence, the cyclocondensation of carboxylate (R)-5 with aryl isocyanates occurs when heating the substrate/reagent mixture at 125 °C (Scheme 4). As a result, optically enriched 4-trifluoromethyl dihydropyrimidinones (R)-7 were obtained with moderate yields. Further hydrolysis of the ester group was carried out at room temperature by the treatment with LiOH and sequential treatment of the reaction mixture with 1 M hydrochloric acid solution.

Cyclocondensation of aminoketone (R)-5 with 2,5-dimethoxytetrahydrofuran led to non-racemic trifluoromethylated pyrrolizine (R)-9. The reaction proceeded under heating in acetic acid within 8 hours (Scheme 5).

■ Conclusions

A convenient method for the synthesis of N-silylimine of trifluoropyruvate has been developed based on the aza-Wittig reaction of methyl trifluoropyruvate with N-silyl triphenylphosphinimide. It has been determined that N-trimethylsilylimine of trifluoropyruvate undergoes an organocatalytic Mannich reaction with acetone in the presence of L- or D-proline, which leads to the enantiomerically enriched multifunctional aminoketones. Their utility for obtaining non-racemic derivatives of trifluoroalanine was disclosed.

■ Experimental part

NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer [operating frequencies 500 MHz (1H), 125 MHz (13C), and 470 MHz (19F)]; a Varian Unity Plus 400 instrument [operating frequencies 400 MHz (1H), 100 MHz (13C) and 376.5 MHz (19F)]; a Mercury Varian Unity Plus 300 instrument [operating frequencies 300 MHz (1H) and 76 MHz (13C)]; a Mercury VX 200 Varian instrument [operating frequency 188 MHz (19F)]. Chemical shifts were reported relative to the internal TMS (1H, 13C) or CFCl3 (19F) standards. The optical rotation was measured on an Anton Paar MCP 300 polarimeter (the sample cell path length 100 mm, wavelength 589 nm). The solvents were dried according to the standard procedures. The starting materials were purchased from Merck, Fluka, and Enamine Ldt. Melting points were uncorrected. TLC was performed using silica gel Kieselgel Merck 60 (400–630 mesh) as the stationary phase. The elemental analysis was performed in the analytical laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine.
Methyl 3,3,3-trifluoro-2-((trimethylsilyl)-imino)propanoate (4)

To the solution of triphenylphosphine (25 g, 95 mmol) in anhydrous toluene (50 mL), trimethylsilyl azide (16.5 g, 19 mL, 0.14 mol) was added while stirring. The mixture was refluxed until evolution of gas ceased (approx. 6 h, monitored by $^{31}$P NMR), then the solvent was removed under reduced pressure. The residue was dissolved in Et$_2$O (140 mL) and cooled to 0°C, then methyl trifluoropryvuate (14.8 g, 9.7 mL, 95 mmol) was added dropwise, and the mixture was allowed to warm to room temperature. According to $^{31}$P and $^{19}$F NMR data, there are signals of imine 4 and phosphinimide $^3$ in a ratio of ~1:12. The spectroscopic characteristics of imide 3 (Et$_2$O) are as follows: $^{19}$F NMR, $\delta$, ppm: $-80.04$; $^{31}$P NMR, $\delta$, ppm: 3.5. The solvent was evaporated in vacuo, the residue was distilled at atmospheric pressure to obtain imine 4 as a yellow oil.

Yield – 10.3 g (48%). B. p. 126–128 °C. Anal. Calcd for C$_{11}$H$_{16}$F$_3$NO$_5$: %: C 37.00; H 5.32; N 6.16. Found, %: C 37.12; H 5.30; N 6.09. $^1$H NMR (300 MHz, C$_6$D$_5$), $\delta$, ppm: 0.35 (9H, s, SiCH$_3$); 3.37 (3H, s, OCH$_3$); 4.4 mmol) and acetone (1.3 g, 1.6 mL, 22 mmol) in anhydrous DMSO (3.5 mL), L-proline (0.051 g, 0.44 mmol) was added, and the mixture was stirred at room temperature for 24 h. Then the mixture was diluted with water (10 mL) and extracted with Et$_2$O (4×20 mL). The organic phases were collected and mixed with 15% HCl solution (15 mL) while stirring, the aqueous layer was separated and neutralized with NaHCO$_3$. The product was extracted with Et$_2$O (3×15 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo to give 5 as a yellowish oil.

Yield – 0.7 g (75%). $[\alpha]_D^{20}$ = $-3.63$ (c 0.25, CH$_2$Cl$_2$). Anal. Calcd for C$_{11}$H$_{16}$F$_3$NO$_5$: %: C 39.44; H 4.73; N 6.57. Found, %: C 39.51; H 4.70; N 6.52. $^1$H NMR (400 MHz, CDCl$_3$), $\delta$, ppm: 2.18 (3H, s, CH$_3$); 2.35 (2H, br. s, NH$_2$); 2.86 (1H, d, $^3$J$_{NH}$ = 18 Hz, CH$_3$); 3.37 (1H, d, $^3$J$_{NH}$ = 18 Hz, CH$_3$); 3.76 (3H, s, OCH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$), $\delta$, ppm: 30.34 (s, CH$_3$); 45.28 (s, CH$_3$); 53.54 (s, OCH$_3$); 62.69 (q, $^2$J$_{CF}$ = 27.3 Hz, CCF$_3$); 124.11 (q, $^1$J$_{CF}$ = 284.6 Hz, CF$_3$);

169.77 (s, COOME); 207.91 (s, C=O). $^{19}$F NMR (376.5 MHz, CDCl$_3$), $\delta$, ppm: $-78.92$ (s).

*(R)-methyl 2-amino-4-oxo-2-(trifluoromethyl)pentanoate hydrochloride ((R)-5$^*$HCl)

To the solution of amine (R)-5 (1.5 g, 7 mmol) in Et$_2$O (10 mL), a saturated solution of HCl in Et$_2$O (5 mL) was added dropwise at room temperature. After the precipitate was formed, the solution was decanted; the precipitate was triturated with a mixture of Et$_2$O/hexane (3:1, 15 mL) and collected by filtration to obtain compound 5 as a hydrochloride.

Yield – 1.2 g (68%). M. p. 146–147 °C. $[\alpha]_D^{20}$ = $-18.05$ (c 0.25, MeOH). Anal. Calcd for C$_{19}$H$_{18}$ClF$_5$NO$_3$: %: C 33.68; H 4.64; Cl 14.20; N 5.92. Found, %: C 33.70; H 4.60; Cl 14.51; N 5.56. $^1$H NMR (300 MHz, DMSO-d$_6$), $\delta$, ppm: 2.21 (3H, s, CH$_3$); 3.57 (1H, d, $^3$J$_{HH}$ = 18.5 Hz, CH$_3$); 3.65 (1H, d, $^3$J$_{HH}$ = 18.5 Hz, CH$_3$); 3.81 (3H, s, OCH$_3$); 7.42 (3H, br. s, NH$_2$HCl). $^{13}$C NMR (125 MHz, DMSO-d$_6$), $\delta$, ppm: 29.55 (s, CH$_3$); 43.37 (s, CH$_3$); 54.31 (s, OCH$_3$); 61.2 (q, $^2$J$_{CF}$ = 28 Hz, CCF$_3$); 122.64 (q, $^1$J$_{CF}$ = 286 Hz, CF$_3$); 164.78 (s, COOME); 203.5 (s, C=O). $^{19}$F NMR (188 MHz, DMSO-d$_6$), $\delta$, ppm: $-73.61$ (s).

(S)-methyl 2-amino-4-oxo-2-(trifluoromethyl)pentanoate hydrochloride ((S)-5$^*$HCl) was obtained from amine (S)-5 (0.4 g, 1.9 mmol). Yield – 0.3 g (64%). $[\alpha]_D^{20}$ = +14.26 (c 0.25, MeOH). Other physicochemical characteristics are identical to (R)-5$^*$HCl.

*(R)-2-amino-4-oxo-2-(trifluoromethyl)pentanoic acid hydrochloride ((R)-6$^*$HCl)

To the solution of aminocarboxylate (R)-5$^*$HCl (0.4 g, 1.6 mmol) in MeOH (8 mL), the solution of NaOH (0.1 g, 4 mmol) in H$_2$O (4 mL) was added in one portion. The mixture was stirred at room temperature overnight, and then 1 M hydrochloric acid solution was added dropwise until pH 1–2. The mixture was concentrated in vacuo to dryness, and triturated with MeOH (10 mL). The inorganic precipitate was filtered off. The filtrate was concentrated under reduced pressure to give carboxylic acid (R)-6$^*$HCl as an ivory powder.

Yield – 0.35 g (92%). M. p. 201–202 °C (dec.). $[\alpha]_D^{20}$ = $-7.28$ (c 0.5, MeOH). Anal. Calcd for C$_{19}$H$_{18}$ClF$_5$NO$_3$: %: C 30.59; H 3.85; Cl 15.05; N 5.92. Found, %: C 30.52; H 3.90; Cl 15.30; N 5.82. $^1$H NMR (300 MHz, DMSO-d$_6$), $\delta$, ppm: 2.19 (3H, s, CH$_3$); 3.48 (1H, d, $^3$J$_{HH}$ = 20.2 Hz, CH$_3$); 3.54 (1H, d, $^3$J$_{HH}$ = 20.2 Hz, CH$_3$); 7.9 (3H, br. s, NH$_2$HCl). $^{13}$C NMR (125 MHz, DMSO-d$_6$), $\delta$, ppm: 29.92 (s, CH$_3$); 43.65 (s, CH$_3$); 61.41 (q, $^2$J$_{CF}$ = 26 Hz, CCF$_3$); 124.1 (q, $^1$J$_{CF}$ = 285 Hz, CF$_3$); 166.68 (s, COOH); 204.11 (s, C=O). $^{19}$F NMR (188 MHz, DMSO-d$_6$), $\delta$, ppm: $-73.68$ (s).
(R)-Methyl 1-(4-chlorophenyl)-6-methyl-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydro-
pyrimidine-4-carboxylate ((R)-7a)

A mixture of aminocarboxylate (R)-5 (0.5 g, 2.3 mmol) and 4-chlorophenylisocyanate (0.36 g, 0.3 mL, 2.3 mmol) was heated at 120–125°C for 24 h. Then the mixture was cooled down to room temperature and the residue was purified by TLC (R<sub>f</sub> = 0.35 (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1:25)), triturated with Et<sub>2</sub>O (5 mL), and the precipitate was collected by filtration to obtain 7a as a light brown powder.

Yield – 0.29 g (36%). M. p. > 175 °C (dec.).

[a]<sub>D</sub><sup>20</sup> = +6.1 (c 0.25, MeOH). Anal. Calcled for C<sub>15</sub>H<sub>11</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>3</sub>: %: C 52.63; H 3.98; N 10.31. Found, %: C 52.83; H 4.28; N 8.18. 1H NMR (400 MHz, CDCl<sub>3</sub>), ppm: 1.64 (3H, s, CH<sub>3</sub>); 3.81 (3H, s, OCH<sub>3</sub>); 3.90 (3H, s, OCH<sub>3</sub>); 4.98 (1H, s, CH); 5.98 (1H, s, NH). 13C NMR (125 MHz, CDCl<sub>3</sub>), ppm: 19.96 (s, CH<sub>3</sub>); 106.25 (s, C=O); 113.95 (s, C=O); 122.51 (q, J<sub>CF</sub> = 29 Hz, CF<sub>3</sub>); 129.02 (s, C=O); 133.15 (s, C=O); 148.10 (s, H<sub>CCl</sub>=); 162.76 (s, COOMe). 19F NMR (376.5 MHz, CDCl<sub>3</sub>), ppm: –80.54 (s).

**Methyl (R)-1-(4-methoxyphenyl)-6-methyl-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydro-
pyrimidine-4-carboxylate ((R)-7b)**

A mixture of aminocarboxylate (R)-5 (1 g, 4.7 mmol) and 4-methoxyphenylisocyanate (0.69 g, 0.6 mL, 4.7 mmol) was heated at 120–125°C for 24 h. Then the mixture was cooled down to room temperature and triturated with Et<sub>2</sub>O (5 mL). The precipitate was collected by filtration to obtain carboxylic acid (R)-7b as a brown powder.

Yield – 0.64 g (40%). M. p. 145–146 °C. [α]<sub>D</sub><sup>20</sup> = +17.6 (c 0.25, MeOH). Anal. Calcled for C<sub>16</sub>H<sub>15</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>3</sub>, %: C 52.33; H 4.39; N 8.14. Found, %: C 52.38; H 4.36; N 8.18. 1H NMR (300 MHz, CDCl<sub>3</sub>), ppm: 1.64 (3H, s, CH<sub>3</sub>); 3.81 (3H, s, OCH<sub>3</sub>); 3.90 (3H, s, OCH<sub>3</sub>); 4.98 (1H, s, CH); 5.98 (1H, s, NH). 13C NMR (125 MHz, CDCl<sub>3</sub>), ppm: 19.96 (s, CH<sub>3</sub>); 106.25 (s, C=O); 113.95 (s, C=O); 122.51 (q, J<sub>CF</sub> = 29 Hz, CF<sub>3</sub>); 129.02 (s, C=O); 133.15 (s, C=O); 148.10 (s, H<sub>CCl</sub>=); 162.76 (s, COOMe). 19F NMR (376.5 MHz, CDCl<sub>3</sub>), ppm: –80.54 (s).

(R)-1-(4-chlorophenyl)-6-methyl-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydro-
pyrimidine-4-carboxylic acid ((R)-9)

A solution of LiOH (20 mg, 0.8 mmol) in H<sub>2</sub>O (2.5 mL) was added in one portion to a solution of carboxylate (R)-7a (0.13 g, 0.4 mmol) in MeOH (5 mL). The resulting mixture was stirred at room temperature overnight, the solvent was evaporated, and the aqueous layer was washed with MTBE (2×5 mL), neutralized with 1 M hydrochloric acid solution and extracted with EtOAc (3×15 mL). Organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to give carboxylic acid (R)-9 as a pale yellow powder.

Yield – 0.11 g (92%). M. p. 109–110 °C. [α]<sub>D</sub><sup>20</sup> = +30.25 (c 0.25, MeOH). Anal. Calcled for C<sub>16</sub>H<sub>15</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>3</sub>, %: C 46.65; H 3.01; Cl 10.59; N 8.37. Found, %: C 46.57; H 3.11; Cl 11.12; N 8.35. 1H NMR (300 MHz, DMSO-d<sub>6</sub>), ppm: 1.57 (3H, s, CH); 4.96 (1H, s, CH); 7.21 (2H, d, J<sub>HH</sub> = 8.4 Hz, ArH); 7.48 (2H, d, J<sub>HH</sub> = 8.4 Hz, ArH); 8.43 (1H, s, NH). 13C NMR (125 MHz, CDCl<sub>3</sub>), ppm: 19.63 (s, CH<sub>3</sub>); 63.09 (q, J<sub>CF</sub> = 31 Hz, CF<sub>3</sub>); 91.71 (s, CH); 122.68 (q, J<sub>CF</sub> = 288 Hz, CF<sub>3</sub>); 129.03; 130.21; 134.34 (s, C=C); 139.44 (s, H<sub>CCl</sub>=); 153.77 (s, C=O); 167.91 (s, COO). 19F NMR (188 MHz, DMSO-d<sub>6</sub>), ppm: –76.95 (s).
(0.62 g, 0.61 mL, 4.7 mmol) was added. The mixture was heated at 125–130 °C for 8 h. Acetic acid was evaporated in vacuo, the residue was dissolved in EtOAc (40 mL), washed with a saturated solution of NaHCO3 (10 mL) and brine (2×10 mL), dried over Na2SO4 and concentrated in vacuo to obtain a crude product, which was purified by TLC (Rf = 0.2 (MeOH/CHCl3 1:100)) to give 9 as a brown oil.

Yield – 0.64 g (56%). [α]D20 = +111.26 (c 0.5, CH2Cl2). Anal. Calcd for C11H10F3NO2, %: C 53.88; H 4.11; N 5.71. Found, %: C 53.72; H 4.05; N 5.79. 1H NMR (300 MHz, CDCl3), δ, ppm: 2.11 (3H, d, JHH = 1.5 Hz, CH3); 3.86 (3H, s, OCH3); 73.12 (q, JCF = 31.4 Hz, CF3); 99.52 (s, CH); 112.81; 117.94; 118.52 (s, CHα); 122.23 (q, JCF = 283.9 Hz, CF3); 138.65; 141.17 (s, Cα); 164.15 (s, C=O). 19F NMR (188 MHz, CDCl3), δ, ppm: –74.46 (s).

### References


