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Synthesis of pure enantiomers of *cis*- and *trans*-3-(trifluoromethyl)pyroglutamic esters

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Abstract

The addition of the racemic Schiff base ethyl *N*-(diphenylmethylene)glycinate (**2**), from glycine ester, to ethyl-4,4,4-trifluorocrotonate gives, according to the experimental conditions, one or two Michael adducts. Acidic hydrolysis gives the *cis/trans*-3-(trifluoromethyl)pyroglutamates. The enantiomerically pure Schiff base, prepared from chiral 2-hydroxy-3-pinanone and *t*-butyl glycinate, reacts with *trans*-ethyl-4,4,4-trifluorocrotonate to produce four diastereoisomers which may be separated and hydrolysed to give enantiomerically pure *cis*- and *trans*-3-(trifluoromethyl)pyroglutamate.

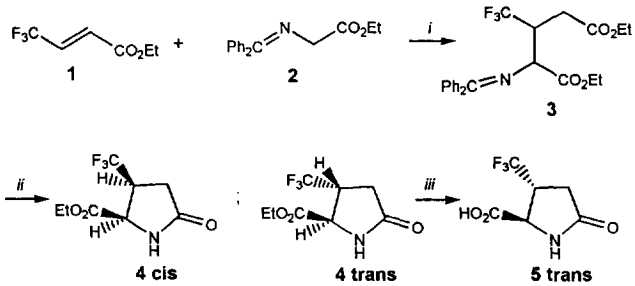
Keywords: *cis, trans*-3-(Trifluoromethyl)pyroglutamate; Enantiomers; NMR spectroscopy; Mass spectrometry; Michael addition

1. Introduction

The synthesis of unusual amino acids is continuing to develop at a tremendous pace and the area of fluorine-containing amino acids takes a most important place in the family of unusual amino acids [1]a. For example, thyrotropin is a tripeptide containing pyroglutamic acid, histidine and proline. Recent research [1]b has shown that this tripeptide regulates a wide variety of biological functions, including the activation of central noradrenergic neurons and related cardiovascular stimulation. The diverse functions suggest the existence of multiple receptors for the tripeptide. So several analogues have been made in which histidine has been replaced by a 2- or 4-trifluoromethyl histidine [2]; these compounds gave a four- to five-fold increase in plasma prolactin level following intra-arterial injection. With the influence of these trifluoromethyl histidines in mind, we decided to prepare the 3-(trifluoromethyl)pyroglutamates.

2. Results and discussion

In preliminary experiments, we tried to prepare racemic 3-(trifluoromethyl)pyroglutamate. Recently, Yamazaki et al. [3] showed that Michael addition of lithium enolates from ketones, esters and amides to ethyl 3-trifluoromethylacrylate



i : LDA, THF -78°C or TEBAC CH_2Cl_2/NaOH aq.
ii : 15 % citric acid, THF
iii : 10 % citric acid, Et_2O, several days

Scheme 1.

proceeds with a high degree of diastereoselectivity at the newly formed carbon-carbon bond. So we decided to attempt the addition of ethyl-4,4,4-trifluorocrotonate (**1**) to the lithium salt of ethyl *N*-(diphenylmethylene)glycinate, obtained by the reaction of lithium diisopropylamide (LDA) and the corresponding glycinate **2** (Scheme 1).

The adduct **3** was a mixture of the two diastereoisomers; no selectivity was observed. Cleavage of the imines **3** was performed with 15% citric acid at room temperature. Under these conditions, a mixture of *cis*- and *trans*-3-(trifluoromethyl)pyroglutamate (**4**) was obtained. NMR data allowed the assignment of the *cis* configuration to the minor diastereoisomer and the *trans* to the major one (*cis*/*trans* = 1:2) (vide infra). We were unable to separate the two diastereoisomers by column chromatography.

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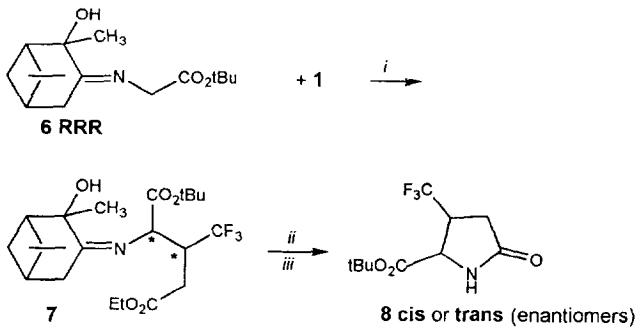

i : LDA, THF -78°C

ii : separation of the four diastereoisomers **7** by column chromatography

iii : 15 % citric acid

Scheme 2.

To obtain one pure diastereoisomer, we decided to use phase-transfer catalysis which generally gives a good yield and good selectivity for mono addition [4]. The reaction was accomplished by simply stirring ester **1** and ketimine **2** in the presence of benzyl triethyl ammonium chloride (TEBAC) at 0 °C in dichloromethane. Under these conditions, only one diastereoisomer of imine **3** was formed; only one signal for the trifluoromethyl group was observed in the NMR spectrum ($\delta = -70.0$ ppm). Acidic cleavage with 15% citric acid (or 1 N HCl) led exclusively to the *trans*-pyroglutamate **4**; hydrolysis of **4**-*trans* by citric acid in ethyl ether over 4 d gave the pure *trans*-trifluoromethyl pyroglutamic acid (**5**).

We then decided to attempt the preparation of enantiomerically pure *cis*- and *trans*-3-(trifluoromethyl)pyroglutamate, by using a chiral imine instead of imine **2**. Yamada et al. [5] have described the asymmetric synthesis of some α-amino acid derivatives by alkylation of the Schiff base obtained from the glycine t-butyl ester and enantiomerically pure 2-hydroxy 3-pinanone. Viallefont et al. [6] demonstrated the interest of this reaction and its usefulness in Michael additions. So we prepared the Schiff base **6** from glycine t-butyl ester and (*RRR*)-2-hydroxy-3-pinanone (Scheme 2).

Michael addition of ethyl-4,4,4-trifluorocrotonate (**1**) in phase-transfer catalysis did not work well; so we used Viallefont conditions (LDA/THF) and obtained a mixture of all four diastereoisomers (63%). From the ^{19}F NMR data of the crude mixture **7**, it was possible to determine the percentage of each compound (52:31:13:4). The mixture was separated by column chromatography and three pure diastereoisomers were obtained. After hydrolysis by citric acid of each diastereoisomer **7**, the major diastereoisomer (52%) gave a *cis*-*t*-butylpyroglutamate **8** which was enantiomerically pure; the second (31%) produced an enantiomer from the *trans*-*t*-butyl pyroglutamate **8**. From the third (13%), we were not able to obtain the other pure **8** *cis*-enantiomer. The minor isomer (4%) gave the other enantiomerically pure *trans*-pyroglutamate **8**.

Experiments from the imine **6**-*SSS* led to a different ratio for these four diastereoisomers. It is interesting to note that under the same hydrolysis conditions [6], the imine **7**, bearing a methyl group instead of trifluoromethyl, led to the corresponding glutamate (no cyclisation to pyroglutamate).

2.1. Determination of the relative configurations of the cis- and trans-3-(trifluoromethyl)glutamates 4 and 8

For the ethyl or *t*-butyl 3-(trifluoromethyl)pyroglutamate diastereoisomers **4** or **8**, the $J_{H_2H_3}$ coupling constants are the same: $J_{H_2H_3} = 8.0$ Hz and $J_{H_2H_3} = 4.0$ Hz. According to the literature [6,7] the larger coupling constant must be attributed to the *cis* isomer and the smaller to the *trans*. As the trifluoromethyl group can introduce steric or electronic interactions and change the conformations, we made an NOE study to be sure of this assignment. Irradiation of the H-2 hydrogen was performed on each isomer **8** and the NOE was observed on the H-3 hydrogen or fluorine atoms. Diastereoisomers **8**, with the largest coupling constant ($J = 8.0$ Hz) produced a positive homo NOE ($H_3[H_2]$: 5%) and a small hereto NOE (F[H_2]: 0.36%). No homo NOE was observed with the other isomer **8** ($J = 4$ Hz), but a positive hereto NOE was recorded (F[H_2]: 1.4%). These NOE values confirm the *cis* and *trans* configurations suggested from the coupling constant: $J_{H_2H_3} = 8$ Hz for the *cis* isomer and $J_{H_2H_3} = 4$ Hz for the *trans*.

3. Experimental details

3.1. General

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AC 200 spectrometer and are reported in δ units (ppm) with tetramethylsilane and $CFCl_3$ as internal standards and $CDCl_3$ and DMSO-d_6 as solvents. 3-(Trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt (TMSP) was used as internal standard when D_2O was the solvent. Mass spectra were taken on a VG AutoSpec (70 eV, EI). Optical rotations were measured with a Perkin-Elmer polarimeter model 141. Melting points were measured on a Büchi apparatus and are reported uncorrected.

3.2. Diethyl N-(diphenylmethylene)-2-(trifluoromethyl)glutamate (3)

To prepare this compound 2.67 g (10.0 mmol) of *N*-(diphenylmethylene)glycine ethyl ester (**2**) were added under nitrogen at −78 °C to a stirred solution of LDA (12.0 mmol) in 20 ml of dry tetrahydrofuran. After 30 min, 1.5 ml (1.68 g, 10.0 mmol) of ethyl-4,4,4-trifluoro-*trans*-2-butenoate (**1**) was added and the mixture stirred for 1 h at −78 °C and then allowed to warm up to room temperature. Saturated ammonium chloride solution (7 ml) was added, followed by extraction with diethyl ether (3×70 ml), drying over sodium sulphate and evaporation of the solvents in vacuum (30 °C) to give a yellow residue, which was filtered

over silica (*n*-pentane/diethyl ether 1:1, 1% triethylamine) to give a colourless oil containing two isomeric compounds **3**, which were not separable by chromatography. Yield:2.78 g (65%).

^{19}F NMR ($CDCl_3$) δ: −68.12 (d, J_{HF} = 10.8 Hz); −70.17 (J_{HF} = 7.7 Hz) (mixture of the two diastereoisomers) ppm. The major isomer **3** (δ = −70.17 ppm) was obtained as a pure diastereoisomer by phase-transfer catalysis; all its analytical data are given later elsewhere (cf. glutamate **3** obtained by phase-transfer catalysis).

3.3. Ethyl 3-(trifluoromethyl) pyroglutamate (4) (cis/trans)

The Michael adduct **3** (mixture of two isomers) (2.0 g, 4.6 mmol) was dissolved in 5 ml of tetrahydrofuran and stirred for 5 d with 6 ml of 15% aqueous citric acid at room temperature. After the starting material had disappeared (TLC), the solvent was evaporated and the aqueous solution extracted with benzene (3 × 10 ml). After removing the solvent, the residue was crystallised from *n*-hexane/chloroform to give a mixture of *cis*- and *trans*-**4** yield, 0.57 g (55%). The isomers could not be separated.

^{19}F NMR ($CDCl_3$) δ: *cis*-(**4**): −69.04 (d, $^3J_{HF}$ = 7.8 Hz); *trans*-(**4**): −73.66 (d, $^3J_{HF}$ = 11.2 Hz) ppm. Analytical data for *trans*-(**4**) are given elsewhere.

cis-(**4**): ^{1}H NMR ($CDCl_3$) δ: 1.30 (t, ^3J = 7.3 Hz, 3 H); 2.53 (dd, ^2J = 16.7 Hz, ^3J = 9.0 Hz, 1H); 2.67 (dd, ^2J = 16.7 Hz, ^3J = 10.5 Hz, 1H); 3.43 (m, 1H); 4.25 (q, ^3J = 7.1 Hz, 2H); 4.40 (d, ^3J = 8.0 Hz, 1H); 7.00 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ: 13.81, 29.70, 44.77 (q, $^2J_{CF}$ = 30.6 Hz); 55.13, 62.40, 124.87 (q, $^1J_{CF}$ = 277.5 Hz); 169.14; 175.17 ppm. MS: 225 (M^+, 3%); 152 ($M^+ - CO_2Et$, 100%).

3.4. Glutamate 3 (by phase-transfer catalysis)

N-(Diphenylmethylene)glycine ethyl ester (**2**) (1.87 g, 7.0 mmol), 0.3 g of benzyl triethyl ammonium chloride, 10 ml of a 10% solution of sodium hydroxide in water and 10 ml of dichloromethane were stirred for 15 min at 0 °C and then 1.05 ml (1.18 g, 7.0 mmol) of ethyl-4,4,4-trifluoro-*trans*-2-butenoate (**1**) added. The whole two-phase system was stirred vigorously for 90 min at 0 °C. The reaction mixture was diluted with water/dichloromethane (100 ml/50 ml) and the aqueous layer extracted three times with 30 ml of dichloromethane. The combined organic layers were washed with water (2 × 30 ml), saturated sodium chloride (30 ml) and dried over sodium sulphate. The solvent was evaporated in vacuum (30 °C) and the residue purified by column chromatography (*n*-pentane/diethyl ether 8:1; 1% triethylamine) to give 2.55 g (84%) of **3** as a colourless oil.

^{1}H NMR ($CDCl_3$) δ: 1.21 (t, CH_3, ^3J = 7.1 Hz); 1.22 (t, CH_3, ^3J = 7.1 Hz); 2.82 (dd, 1 H, ^2J = 17.1 Hz, ^3J = 6.6 Hz); 3.18 (dd, 1 H, ^2J = 17.1 Hz, ^3J = 5.7 Hz); 3.75 (m, 1 H); 4.04-4.24 (m, $2CH_2$); 4.47 (d, CH, ^3J = 2.6 Hz, 1 H); 7.14-7.80 (m, 10 H) ppm. ^{19}F NMR ($CDCl_3$) δ: −70.00 (d, CF_3, J_{HF} = 7.8 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 14.06 (s, CH_3); 14.11 (s, CH_3); 30.23 (s, CH_2CO); 42.95 (q, CF_3CHCH_2, $^2J_{CF}$ = 25.7 Hz); 61.01 (s, CH_2CH_3); 61.79 (s, CH_2CH_3); 62.56 (s, CH–N=); 127.98 (q, CF_3, J_{CF} = 280.7 Hz); 127.60 (s, arom. C); 128.10 (s, arom. C); 128.56 (s, arom. C); 128.95 (s, arom. C); 129.05 (s, arom. C); 130.78 (s, arom. C); 169.53 (s, C=O); 171.07 (s, C=O); 172.52 (s, C=N) ppm. MS: 435 (M^+, 28); 406 (14); 390 (63); 362 (99); 361 (48); 348 (28); 288 (57); 266 (52); 193 (78); 165 (100); 105 (24); 104 (24); 77 (27).

3.5. Ethyl trans-3-(trifluoromethyl)pyroglutamate (4)

The Michael adduct (PTC reaction) was deprotected and cyclised by citric acid (see above) to give the pure *trans*-(**4**) in 55% yield; m.p. 97 °C (colourless needles, from benzene).

^{1}H NMR (D_2O/TMSP) δ: 1.30 (t, CH_3, ^3J = 7.1 Hz); 2.61 (dd, 1 H, ^2J = 18.3 Hz, ^3J = 4.3 Hz); 2.84 (dd, 1 H, $^2J_{AM}$ = 18.3 Hz, $^3J_{AX}$ = 10.1 Hz); 3.63 (m, 1 H); 4.29 (q, CH_2); 4.61 (d, 1 H, ^3J = 3.4 Hz) ppm. ^{19}F NMR (D_2O) δ: −72.48 (d, $^3J_{FH}$ = 10.2 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ:14.03 (s, CH_3); 29.53 (s, CH_2CO); 41.04 (CF_3CH, $^2J_{CF}$ = 30.6 Hz); 55.35 (s, CHNH); 62.67 (s, CH_2CH_3); 131.64 (q, CF_3, J_{CF} = 277.5 Hz); 169.68 (s, C=O); 174.48 (s, C=O) ppm. MS:225 (M^+, 4); 152 (100); 132 (6); 124 (5); 104 (7). Analysis: Calc. for $C_8H_{10}NO_3F_3$: C, 42.67; H, 4.47; N 6.22%. Found: C, 41.96; H, 4.27; N, 6.07%.

3.6. trans-3-(Trifluoromethyl)pyroglutamic acid (5)

A solution of **4**-*trans* (0.45 g, 2.0 mmol) in 2 ml of diethyl ether was stirred for 4 d with 2 ml of 10% aqueous citric acid at room temperature. The aqueous layer was extracted with benzene (5 × 10 ml) and the combined organic layers dried over sodium sulphate. After the addition of *n*-pentane, the acid crystallised at −10 °C. Yield 0.23 g (58%); m.p. 174 °C (colourless crystals).

^{1}H NMR (DMSO-d_6) δ: 2.24 (dd, 1 H, ^2J = 17.7 Hz, ^3J = 4.1 Hz); 2.63 (dd, 1 H, ^2J = 17.4 Hz, ^3J = 10.2 Hz); 3.49 (m, 1 H); 4.13 (d, 1 H, ^3J = 3.1 Hz) ppm. ^{19}F NMR (DMSO-d_6) δ: −71.89 (d, $^3J_{FH}$ = 11.3 Hz) ppm. ^{13}C NMR (DMSO-d_6) δ: 29.21 (s, CH_2CO); 54.56 (s, $CHCO_2H$); 126.90 (q, CF_3, J_{CF} = 277.7 Hz); 171.96 (s, C=O); 173.64 (s, C=O) ppm. MS: 197 (M^+, 2); 152 (100); 104 (27); 77 (24).

3.7. Schiff base 6

This was prepared from glycine t-butyl ester and (*RRR*)-2-hydroxy-3-pinanone as described in the literature [5,6].

3.8. Synthesis of the Michael adduct 7

A 2 M solution of LDA (18.0 mmol) in tetrahydrofuran (9.0 ml) was added under a nitrogen atmosphere at −78 °C to 2.20 g (7.8 mmol) of the imine **6** (*SSS* or *RRR*) in 50 ml of dry tetrahydrofuran. The mixture was stirred for 45 min and 1.15 ml (1.3 g, 7.8 mmol) of ethyl-4,4,4-trifluoro-*trans*-

2-butenoate (**1**) added. After reaction for 4 h, the mixture was warmed to room temperature and hydrolysed with 40 ml of saturated ammonium chloride. The aqueous layer was extracted with diethyl ether (4×100 ml), the combined organic layers dried over sodium sulphate, evaporated in vacuum (30 °C) and the residue filtered over silica (*n*-pentane/diethyl ether) to give 2.2 g (63%) of a colourless oil containing all four possible diastereoisomers **7** in the ratio 52:13:31:4. These figures are for the *RRR* enantiomer; the *SSS* case gave complementary results. The separation of the diastereoisomers was carried out by simple column chromatography with a gradient eluent (starting with *n*-pentane and 1% of triethylamine, diethyl ether being added progressively). Three of the four compounds could be obtained pure as colourless oils.

^{1}H NMR ($CDCl_3$) δ: (a) 4.41 (d, $^3J_{HH}$=4.9 Hz); (b) not pure; (c) 4.54 (d, $^3J_{HH}$=2.6 Hz); (d) 4.38 (d, $^3J_{HH}$=5.1 Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: (a) −66.87 (d, $^3J_{HF}$=7.4 Hz); (b) −67.31 (d, $^3J_{HF}$=8.2 Hz); (c) −70.48 (d, $^3J_{HF}$=8.3 Hz); (d) −70.62 (d, $^3J_{HF}$=10.8 Hz) ppm.

3.9. t-Butyl 3-(trifluoromethyl)pyroglutamate (8) (cis and trans)

Each of the Schiff bases **7** was dissolved in 7 ml of tetrahydrofuran and stirred for 4 d with 6 ml of 15% citric acid at room temperature. The solvent was evaporated in vacuum (30 °C) and the citric acid solution extracted with benzene (3×10 ml). The organic layer was dried over sodium sulphate and evaporated. The residue could be recrystallised from *n*-hexane/chloroform to give slightly yellowish or colourless crystals. Yield, 45%-55%.

cis-(**8**): m.p. 158 °C. ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 9 H, ^{t}-Bu); 2.52 (dd, 1 H, ^2J=16.7 Hz, ^3J=8.9 Hz); 2.65 (dd, 1 H, ^2J=16.7 Hz, ^3J=9.5 Hz); 3.39 (m, 1 H); 4.28 (d, 1 H, $^3J_{HH}$=8.0 Hz, 1 H); 6.81 (m, 1 H, N H) ppm. ^{19}F NMR ($CDCl_3$) δ: −68.29 (d, $^3J_{FH}$=7.5 Hz) ppm. MS: 152 (61); 57 (100); 41 (35). $[\alpha]_{589}^{25}$= +35.8° (c=0.1, $CHCl_3$).

trans-(**8**): m.p. 142 °C. ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 9 H, ^{t}Bu); 2.55 (dd, 1 H, ^2J=17.9 Hz, ^3J=5.7 Hz); 2.67 (dd, 1 H, ^2J=17.8 Hz, ^3J=10.1 Hz); 3.37 (m, 1 H); 4.20 (d, 1 H, ^3J=4.0 Hz); 6.48 (m, 1 H, NH) ppm. ^{19}F NMR ($CDCl_3$) δ: −73.49 (d, $^3J_{FH}$=8.8 Hz) ppm. MS: 152 (60); 57 (100); 41 (23). $[\alpha]_{589}^{25}$= −20.8° (c=0.1, $CHCl_3$); $[\alpha]_{589}^{25}$= +27.1° (c=0.1, $CHCl_3$).

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