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(5*S*)-5-(Trifluoromethyl)pyrrolidin-2-one as a Promising Building Block for Fluoroorganic Chemistry

Andrii V. Bezdudny,[a,b] Anatoliy N. Alekseenko,[a,b] Pavel K. Mykhailiuk,*[a,c] Olga V. Manoilenko,[a] Oleg V. Shishkin,[d] and Yurii M. Pustovit[a,b]

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Pyroglutamic acid smoothly reacts with sulfur tetrafluoride at room temperature to afford enantiomerically pure (5*S*)-5-(trifluoromethyl)pyrrolidin-2-one (92% yield, >99% *ee*). Representative one-step transformations of **1** provided both γ-(*S*)-trifluoromethyl GABA and (2*S*)-2-(trifluoromethyl)-pyrrolidine on a multigram scale.

Introduction

In recent years, fluorinated compounds have received a great deal of interest.[1] The presence of fluorine atoms introduces modifications to the physiological activity of bioactive compounds. Indeed, the small van der Waals radius of fluorine and its high electronegativity have important influences on the physical and chemical properties of a molecule. This led to the discovery of potent medicinal agents,[2] and currently ca. 20% of the marketed pharmaceuticals and ca. 30% of agrochemicals contain at least one fluorine atom.[3] Among all fluorine-containing organic compounds, those possessing the trifluoromethyl group have been the subject of an important area of research since CF_3/H transposition has been recognized as a valuable tool in the blockage of metabolic processes.[4] Moreover, replacement of various functional groups by a trifluoromethyl group has generated potent transition-state-type inhibitors.[5] The importance of trifluoromethyl-substituted compounds is reflected in the ever-increasing research activity in the field of their synthesis.[6] In this context, the development of new synthetic methodologies for facile and practical preparation of optically pure trifluoromethyl-containing synthons from cheap and available starting materials is of particular interest. Herein we report a multigram one-step synthesis of enantiomerically pure (5*S*)-5-(trifluoromethyl)pyrrolidin-2-one (**1**) from (*S*)-pyroglutamic acid. The potential of this novel CF_3-substituted building block has been demonstrated by ordinary one-step transformations into γ-(*S*)-trifluoromethyl GABA (**2**, GABA = γ-aminobutyric acid) and (2*S*)-2-(trifluoromethyl)pyrrolidine (**3**).

[a] Enamine Ltd.,
Oleksandra Matrosova Street 23, Kyiv 01103, Ukraine
Fax: +38-044-537-32-53
E-mail: Pavel.Mykhailiuk@gmail.com
[b] Institute of Organic Chemistry, National Academy of Sciences of Ukraine,
02660 Kyiv-94, Murmanska Street 5, Ukraine
[c] Department of Chemistry, Kyiv National Taras Shevchenko University,
Volodymyrska Street 64, Kyiv 01033, Ukraine
[d] STC, Institute for Single Crystalls, National Academy of Science of Ukraine,
60 Lenina ave., Kharkiv 61001, Ukraine
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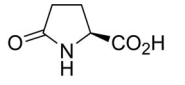
Results and Discussion

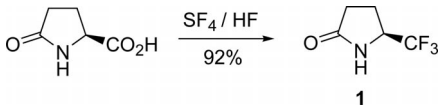
In search of a cheap source of chirality we focused on commercially available (*S*)-pyroglutamic acid (Aldrich 2010: 100 g, 54 USD; Figure 1). Surprisingly, although pyroglutamic acid has emerged as an important and widely used starting material in asymmetric synthesis,[7] its application in the preparation of fluorine-containing compounds has gained much less development so far.[8]



(*S*)-pyroglutamic acid

Figure 1. Structure of (*S*)-pyroglutamic acid.

To the very best of our knowledge, the carboxylic group in pyroglutamic acid has never been converted into the corresponding CF_3 group. To perform this transformation we turned our attention to the well-elaborated SF_4 technique.[9] Indeed, in the presence of anhydrous HF the reaction of pyroglutamic acid with sulfur tetrafluoride (1.1 equiv.) in an autoclave at room temperature for 20 h smoothly afforded pyrrolidone **1** in an excellent yield of 92% (Scheme 1).[10] Importantly, the optical purity of pyroglutamic acid was



1

Scheme 1. Synthesis of compound **1**.

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preserved during the synthesis, as compound **1** was obtained in >99% *ee*. The structure of compound **1** was confirmed by an X-ray diffraction (Figure 2 and the Supporting Information).

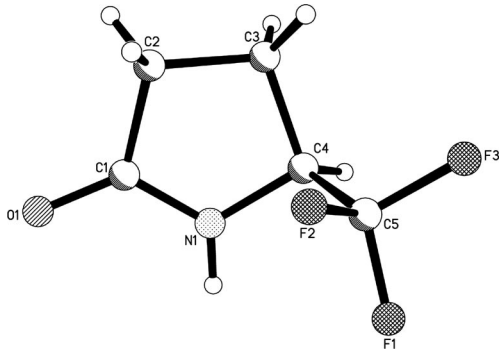
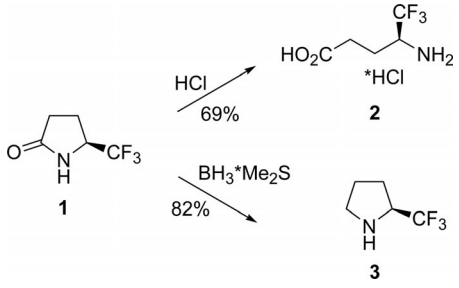


Figure 2. X-ray crystal structure of pyrrolidone **1**.

Worth noting, the synthesis of pyrrolidone **1** was easily scaled up, so that 100 g of the product was conveniently prepared in a single batch. To demonstrate the great potential of optically active trifluoromethyl-substituted synthon **1**, two representative transformations of pyrrolidone **1** were performed (Scheme 2). For example, ordinary acidic hydrolysis of the lactam ring in **1** in aqueous hydrochloric acid afforded amino acid **2** in 69% yield. Compound **2** is an optically active γ-CF_3-substituted analogue of the major inhibitory amino acid transmitter in the central nervous system, γ-aminobutyric acid (GABA).[11] To the very best of our knowledge, this is the first enantioselective synthesis of amino acid **2**.[12]



Scheme 2. Synthesis of compounds **2** and **3**.

An another routine one-step transformation of pyrrolidone **1** – reduction of the amide bond with BH_3·Me_2S complex – provided pyrrolidine **3** in 82% yield (Scheme 2). Indeed, amine **3** was previously prepared by Shustov et al. by treating proline with SF_4, although in a very poor yield of 26%.[13] Moreover, we failed to reproduce this transformation. Obviously, a nitrogen atom in a proline residue must be appropriately protected to avoid reaction of the free amino group with SF_4. Our synthetic strategy, in contrast, allows a two-step multigram preparation of compound **3** from pyroglutamic acid in 75% overall yield.

Conclusions

In summary, we have performed a one-step fluorination of pyroglutamic acid by using sulfur tetrafluoride to obtain (5*S*)-5-(trifluoromethyl)pyrrolidin-2-one (**1**) in 92% yield and >99% *ee*. Following that procedure, 100 g of pyrrolidone **1** was easily prepared in one synthesis run. A huge potential of the novel optically active CF_3-substituted synthon has been demonstrated, as common one-step transformations of pyrrolidone **1** provided optically active γ-(*S*)-trifluoromethyl GABA (**2**) and (2*S*)-2-(trifluoromethyl)-pyrrolidine (**3**). With rapid scalable synthesis, we expect compound **1** to find wide application in the field of fluoroorganic chemistry as a novel fluorine-containing chiral building block.

Experimental Section

General Methods: ^1H, ^{13}C, and ^{19}F NMR spectra were recorded with a Bruker Avance 500 spectrometer at 499.9, 124.9, and 470.3 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS (^1H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. Mass spectra were recorded with an Agilent 1100 LCMSD SL instrument by chemical ionization (CI).

(5*S*)-5-(Trifluoromethyl)pyrrolidin-2-one (1): A mixture of (*S*)-pyroglutamic acid (96.8 g, 0.75 mol), anhydrous HF (50 mL), and SF_4 (178 g, 1.65 mol) was kept in a stainless steel autoclave at 20 °C for 20 h. The gaseous products were removed (under a good fume-hood), and the content was poured into ice (500 g). The mixture was neutralized with 10% aqueous ammonia, concentrated to 2/3 of its volume, and left to stand in a refrigerator at 5 °C for 8 h. The crystalline product was filtered off and crystallized from water (300 mL) to obtain (*S*)-**1** (106.0 g, 0.69 mol, 92% yield) as a white solid. M.p. 107–108 °C. $[\alpha]_D^{20}$ = –5.5 (*c* = 1.20, MeOH). ^1H NMR (500 MHz, $CDCl_3$, Me_4Si): δ = 7.54 (br. s, 1 H, N*H*), 4.09 (m, 1 H, NC*H*CF_3), 2.52 (m, 1 H, C*H*H), 2.34 (m, 2 H, CH_2), 2.24 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, Me_4Si): δ = 178.88 (s, N*C*=O), 125.23 (q, $^1J_{C,F}$ = 280.0 Hz, *C*F_3), 55.15 (q, $^2J_{C,F}$ = 32.0 Hz, N*C*HCF$_3$), 28.53 (s, *C*H$_2$), 20.52 (q, $^3J_{C,F}$ = 2.0 Hz, *C*H$_2$CHCF$_3$) ppm. ^{19}F NMR (477 MHz, $CDCl_3$, $CFCl_3$): δ = –79.2 (d, $^3J_{F,H}$ = 7.0 Hz, C*F*$_3$) ppm. MS: *m*/*z* = 154 [M + 1]. $C_5H_6F_3NO$ (153.10): calcd. C 39.23, H 3.95, N 9.15; found C 39.01, H 3.61, N 9.31. Crystals of **1** suitable for X-ray diffraction were obtained by slow evaporation of a diluted solution of **1** in cyclohexane.

(*S*)-4-Amino-5,5,5-trifluoropentanoic Acid Hydrochloride (2): A suspension of lactam **1** (5.0 g, 32 mmol) in 6 N aq. HCl was heated at reflux for 12 h. The solvent was evaporated in vacuo. The formed residue was crystallized from acetone/hexane to give pure amino acid **2**·HCl (4.5 g, 22 mmol, 69% yield) as a white solid. M.p. 153–154 °C. $[\alpha]_D^{20}$ = –8.8 (*c* = 1.13, MeOH). ^1H NMR (500 MHz, D_2O, Me_4Si): δ = 4.12 (q, $^3J_{H,F}$ = 6.2 Hz, 1 H, C*H*CF$_3$), 2.58 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_2COOH), 2.19 (m, 1 H, C*H*H), 2.04 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 175.94 (s, *C*OOH), 123.75 (q, $^1J_{C,F}$ = 278.8 Hz, *C*F_3), 51.65 (q, $^2J_{C,F}$ = 32.5 Hz, N*C*HCF$_3$), 29.09 (s, *C*H$_2$COOH), 21.72 (s, *C*H$_2$) ppm. ^{19}F NMR (477 MHz, $CDCl_3$, $CFCl_3$): δ = –83.4 (d, $^3J_{F,H}$ = 7.2 Hz, C*F*$_3$) ppm. $C_5H_9ClF_3NO_2$ (207.58): calcd. C 28.93, H 4.37, N 6.75; found C 28.71, H 4.21, N 6.96.

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(2*S*)-2-(Trifluoromethyl)pyrrolidine (3): Pyrrolidone (*S*)-**1** (30.6 g, 0.20 mol) was dissolved in dry THF under an atmosphere of argon, and the solution was cooled in an ice bath. $BH_3{\cdot}Me_2S$ (45.6 g, 57 mL, 0.60 mol) was added to the solution over 1 h. The mixture was then stirred at reflux for 2 h, cooled to –20 °C, and treated with a saturated solution of HCl in methanol (200 mL). *CAUTION: Vigorous evolution of gas.* After the addition, the mixture was kept at –20 °C for 1 h and then warmed to room temperature. The volatile products were removed in vacuo, and the residue was dissolved in dry toluene and heated to 60–70 °C. The solvent was then removed under reduced pressure. The latter procedure was repeated three times, and the residue was dried under high vacuum at 60 °C. The hydrochloride of (*S*)-**3** obtained in this way was treated with a 40% aqueous NaOH (100 mL), and the product was distilled at atmospheric pressure. The distillate was redistilled from NaOH pellets to obtain (*S*)-**3** (22.8 g, 0.16 mol, 82% yield) as a colorless liquid. B.p. 86–92 °C. $[\alpha]_D^{20}$ = +9.3 (*c* = 1.17, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ = 3.66 (m, 1 H, NC*H*CF_3), 3.03 (t, $^3J_{H,H}$ = 6.0 Hz, 2 H, NCH_2), 2.03–1.86 (m, 4 H, N*H*, CH_2, C*H*H), 1.77 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, Me_4Si): δ = 126.92 (q, $^1J_{C,F}$ = 277.5 Hz, *C*F_3), 58.66 (q, $^2J_{C,F}$ = 28.8 Hz, N*C*HCF_3), 47.07 (s, N*C*H_2), 25.82 (q, $^3J_{C,F}$ = 1.3 Hz, *C*H_2CHCF_3), 25.54 (s, *C*H_2) ppm. ^{19}F NMR (477 MHz, $CDCl_3$, $CFCl_3$): δ = –77.3 (d, $^3J_{F,H}$ = 5.2 Hz, C*F*$_3$) ppm. MS: *m*/*z* = 139. $C_5H_8F_3N$ (139.12): calcd. C 43.17, H 5.80, N 10.07; found C 43.31, H 5.95, N 9.81.

X-ray Diffraction Study of (5*S*)-5-(trifluoromethyl)pyrrolidin-2-one (1): The pyrrolidone ring adopts an envelope conformation. The deviation of the C3 atom from the mean plane of the remaining atoms of the ring is –0.34 Å. The trifluoromethyl group occupies the axial position and is turned in such way that the C5–F3 bond is antiperiplanar relative to the N1–C4 bond (the C1–N1–C4–C5 and N1–C4–C5–F3 torsion angles are 106.6(3) and 179.6(2)°, respectively). In the crystal phase, molecules of **1** form infinite chains (Figure 1, Supporting Information) along the [0 1 0] crystallographic direction due to the formation of N1–H1N···O1′ (0.5 – *x*, 0.5 + *y*, 1 –*z*) intermolecular hydrogen bonds (H···O 1.96 Å, N–H···O 168°). Crystals of **1** ($C_5H_6F_3NO$) are monoclinic. At 100 K *a* = 9.378(3) Å, *b* = 6.972(2) Å, *c* = 10.461(3) Å, β = 113.40(3)°, *V* = 627.7(3) Å^3, M_r = 153.11, *Z* = 4, space group C_2, $d_{calcd.}$ = 1.620 g/cm^3, μ (Mo-K_α) = 0.171 mm^{-1}, *F*(000) = 312. Intensities of 2052 reflections (1457 independent, R_{int} = 0.050) were measured with an Xcalibur-3 diffractometer (graphite monochromated Mo-K_α radiation, CCD detector, ω-scanning, $2\Theta_{max}$ = 60°). The structure was solved by direct methods by using the SHELXTL package.[14] The positions of the hydrogen atoms were located from electron density difference maps and refined by riding model with U_{iso} = 1.2 U_{eq} of the carrier atom. The hydrogen atom forming the intermolecular hydrogen bond was refined in isotropic approximation. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms by using 1434 reflections was converged to wR_2 = 0.031 [R_1 = 0.037 for 578 reflections with $F > 4\sigma(F)$, S = 0.624]. CCDC-776859 (for **1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra, determination of the optical purity of compounds **1**–**3**, and X-ray diffraction study of compound **1**.

Acknowledgments

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