# Practical Enantioselective Synthesis of a 3-Aryl-3-Trifluoromethyl-2-Aminopropanol Derivative

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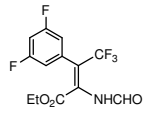
## Supporting Information

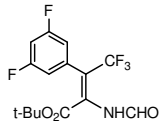
### Experimental

#### (*Z*)-Ethyl 3-(3,5-difluorophenyl)-4,4,4-trifluoro-2-formamidobut-2-enoate (3a)



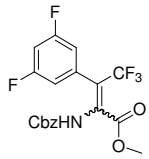

Potassium t-butoxide (95%; 0.811 g, 6.86 mmol) is suspended in 5 mL dry THF. The suspension is cooled to –78°C. A solution of ethyl isocyanoacetate (95% pure; 0.79 mL, 6.86 mmol) dissolved in 1.5 mL THF is then added dropwise. After the addition, the mixture is stirred at –78°C for 30 minutes. A solution of ketone **1** (1.441 g, 6.86 mmol) dissolved in 2 mL THF is then added dropwise to the mixture, and the reaction is allowed to stir for 1 hour at –78°C. The cooling bath is removed, and the mixture allowed to warm at room temperature for 2 hours. 1N HCl (6.9 mL) is added, and the mixture is stirred for 30 minutes at room temperature. The THF layer is decanted and retained, and the aqueous phase is extracted twice with methylene chloride. The combined organic phase is dried ($Na_2SO_4$) and evaporated. The crude material is chromatographed on silica gel using EtOAc/methylene chloride in a gradient elution (0-3% EtOAc) to afford 1.749 g of the title product as a single isomer (79% yield). $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.81 (t, *J* = 7.2 Hz, 3H), 3.81-3.86 (q, *J* = 7.1 Hz, 2H), 6.96-7.04 (m, 2H), 7.32-7.38 (m, 1H), 8.19 (s, 1H), 10.54 (s, 1H). MS (*m/z*, negative ESI, for M-H): 322.

#### (*Z*)-*tert*-Butyl 3-(3,5-difluorophenyl)-4,4,4-trifluoro-2-formamidobut-2-enoate (3b)



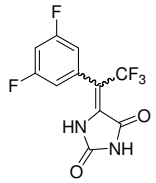

Potassium t-butoxide (95%; 0.494 g, 4.18 mmol) is suspended in 5 mL dry THF. The suspension is cooled to –78°C. A solution of t-butyl isocyanoacetate (95% pure; 0.61 mL, 4.18 mmol) dissolved in 1.5 mL THF is then added dropwise. After the addition, the mixture is stirred at –78°C for 30 minutes. A solution of ketone **1** (0.878 g, 4.18 mmol) dissolved in 1.5 mL THF is then added dropwise to the mixture, and the reaction is allowed to stir for 1 hour at –78°C. The cooling bath is removed, and the mixture allowed to warm at room temperature for 2 hours and 15 minutes. 1N HCl (4.2 mL) is added, and the mixture is stirred for 10 minutes at room temperature. The THF layer is decanted and retained, and the aqueous phase is extracted twice with methylene chloride. The combined organic phase is dried ($Na_2SO_4$) and evaporated. The crude material is chromatographed on silica gel using EtOAc/methylene chloride in a gradient elution (1-6% EtOAc) to afford 0.996 g of the title product as a single isomer (68% yield). $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.08 (s, 9H), 6.99-7.04 (m, 2H), 7.35-7.40 (m, 1H), 8.17 (s, 1H), 10.42 (s, 1H). MS (*m/z*, negative ESI, for M-H): 350.

**(*E, Z*)-Methyl 2-(benzyloxycarbonylamino)-3-(3,5-difluorophenyl)-4,4,4-trifluorobut-2-enoate (11)**



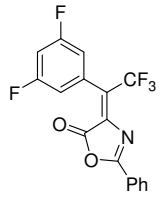

To a solution of methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate (378 mg, 1.1 mmol, 97% pure) in dichloromethane, DBU (0.183 mL, 1.2 mmol) was added. The mixture was stirred at room temperature for 10 min. A solution of 1-(3,5-difluorophenyl)-2,2,2-trifluoroethanone (210 mg, 1 mmol) in dichloromethane (1 mL) was added. The mixture was stirred at room temperature for 18 h, diluted with EtOAc, washed with 2N HCl, $NaHCO_3$ solution, brine, dried over $MgSO_4$ and concentrated to afford crude product as a mixture of isomers as judged by HPLC and LCMS. Flash chromatography on silica gel (hexane-EtOAc, 9:1) afforded 131 mg of the title product as a 2:1 mixture of isomers. $^1$H NMR (300 MHz, $CDCl_3$, for 2:1 mixture of isomers), δ: 7.42-7.27 (m, 8 H), 6.96 - 6.76 (m, 4.5 H), 6.2 (s, 1 H; major isomer), 5.18 (s, 1 H, minor isomer), 5.09 (s, 2 H, major isomer), 3.92 (s, 3 H, major isomer), 3.53 (s, 1.5 H, minor isomer). $^{19}$F NMR (282 MHz, $CDCl_3$, for 2:1 mixture of isomers), δ: -58.4 (s, 1.5 H, minor isomer), -59.6 (s, 3 H, major isomer), -106.8 (s, 2 H, major isomer), -109.4 (s, 1 H, minor isomer). MS (*m/z*, positive ESI, for M+Na): 438. MS (*m/z*, negative ESI, for M-H): 414.

**(*E, Z*)-5-(1-(3,5-difluorophenyl)-2,2,2-trifluoroethylidene)imidazolidine-2,4-dione (12)**



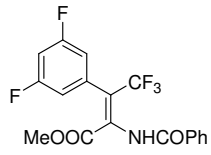
A solution of LiOH monohydrate (50 mg, 1.2 mmol) in 0.5 mL of water was added to a mixture of diethyl 2,5-dioxoimidazolidin-4-ylphosphonate[i] (283 mg, 1.2 mmol) and 95:5 EtOH-water (4 mL). 1-(3,5-Difluorophenyl)-2,2,2-trifluoroethanone (210 mg, 1 mmol) was added. The mixture was stirred at room temperature for 4 d then diluted with water. 2N HCl was added. Organic solvents were distilled off in vacuum. The residue was diluted with 2N HCl and extracted with EtOAc. The EtOAc solution was dried over $MgSO_4$ and concentrated to afford 220 mg of the title product (2:1 mixture of isomers as judged by HPLC and LCMS). $^1$H NMR (300 MHz, $CDCl_3$, for 2:1 mixture of isomers), δ: 9.18 (s, 0.5 H, minor isomer), 9.07 (s, 1 H, major isomer), 8.63 (s, 1 H, major isomer), 8.04 (s, 0.5 H, minor isomer), 7.0 - 6.74 (m, 4.5 H). MS (*m/z*, positive ESI, for M+H): 293.

**(*Z*)-4-(1-(3,5-Difluorophenyl)-2,2,2-trifluoroethylidene)-2-phenyloxazol-5(4H)-one (13)**



To a suspension of N-benzoylglycine (183 mg, 1 mmol, 98% pure) in acetic anhydride (1.5 mL) $K_2CO_3$ (69 mg) was added, followed by 1-(3,5-difluorophenyl)-2,2,2-trifluoroethanone (210 mg, 1 mmol). The mixture was stirred at room temperature for 18 h then poured into water. The resultant suspension was stirred at room temperature for 18 h. The precipitated solid was filtered, washed with water, and dried in air to afford 273 mg of the title product. $^1$H NMR (300 MHz, $CDCl_3$), δ: 8.22-8.17 (m, 2 H), 7.74-7.66 (m, 1 H), 7.61-7.51 (m, 2 H), 7.01 - 6.85 (m, 3 H). $^{19}$F NMR (282 MHz, $CDCl_3$), δ: -60.6 (s, 3 H), -109.47 (s, 2 H). MS (*m/z*, positive ESI, for M+H): 354.

**(*Z*)-Methyl 2-benzamido-3-(3,5-difluorophenyl)-4,4,4-trifluorobut-2-enoate (14)**



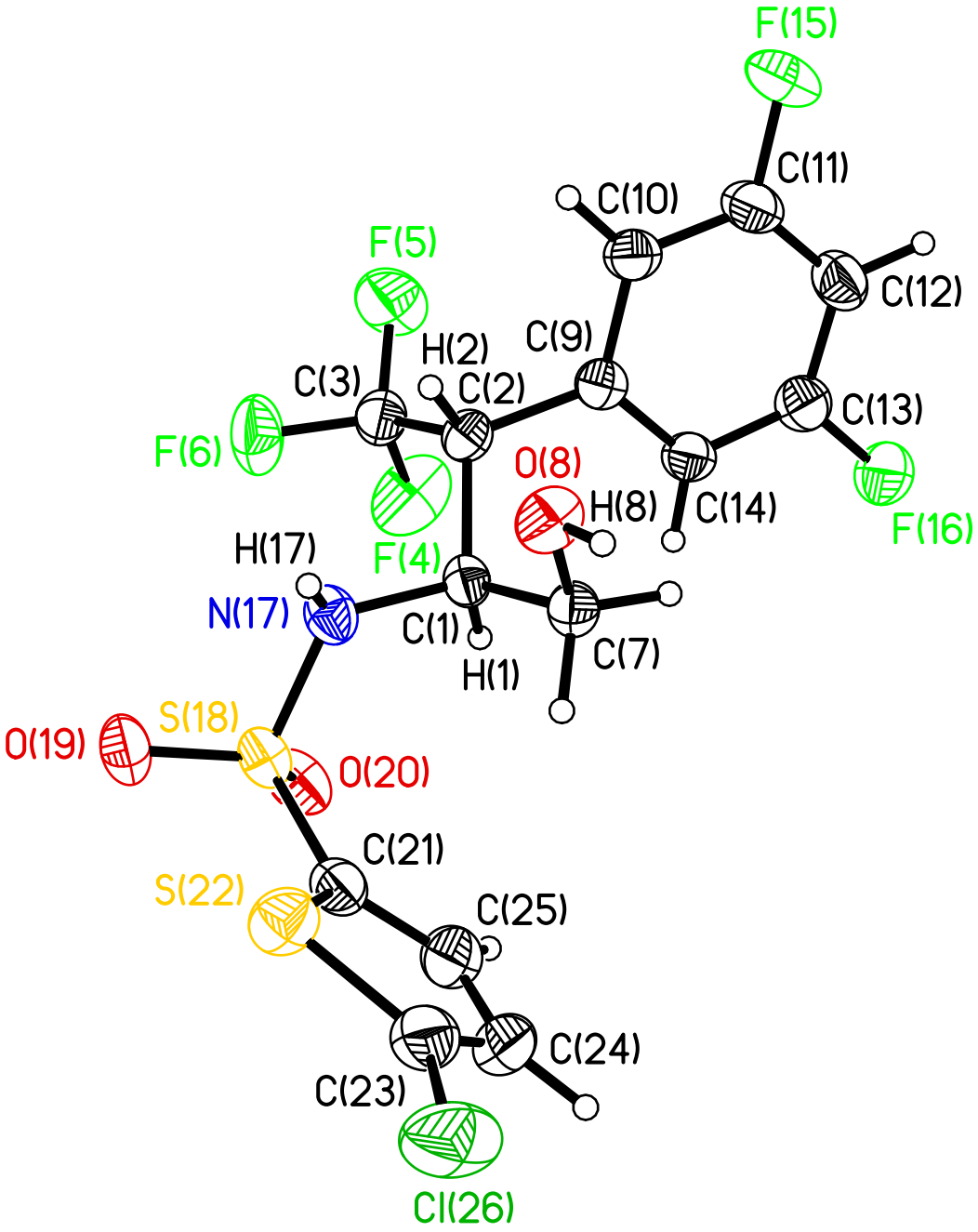
A mixture of (*Z*)-4-(1-(3,5-Difluorophenyl)-2,2,2-trifluoroethylidene)-2-phenyloxazol-5(4H)-one **13** (273 mg, 0.77 mmol), NaOAc (70 mg, 0.85 mmol) and MeOH (4 mL) was stirred at room temperature for 2 h then concentrated in vacuum. The residue was dissolved in EtOAc, washed with water, brine, dried over $MgSO_4$ and concentrated to afford 250 mg of the title product as a yellow solid. $^1$H NMR (300 MHz, $CDCl_3$), δ: 8.46 (s, 1 H), 7.88 – 7.80 (m, 2 H), 7.68 – 7.60 (m, 1 H), 7.57 – 7.49 (m, 2 H), 6.92 – 6.82 (m, 3 H), 3.61 (s, 3 H). $^{19}$F NMR (282 MHz, $CDCl_3$), δ: -58.23 (s, 3 H), -109.28 (s, 2 H). MS (*m/z*, positive ESI, for M+H): 385.

**Single Crystal X-ray Analysis of 5-Chlorothiophene-2-sulfonic Acid [(1*S*,2*R*)-2-(3,5-Difluorophenyl)-3,3,3-trifluoro-1-hydroxymethylpropyl]amide (1)**

Crystals were grown by dissolving 5 mg of **1** in 0.5 mL of $Et_2O$, and then diluting that solution with 1 mL of toluene. The combined total was left at room temperature to evaporate slowly resulting in a batch of colorless needles. One of the needles was isolated, cut to 0.26 mm x 0.26 mm x 0.32 mm in size, mounted on a glass fiber with silicone grease and then transferred to a Nonius KappaCCD diffractometer equipped with an MSC X-stream cryosystem and Mo Kα radiation (λ = 0.71073 Å) for the analysis. Crystal Data for **1**: $C_{14}H_{11}ClF_5NO_3S_2$, FW = 435.81, Orthorhombic, $P2_12_12_1$ (No. 19), a = 5.3576 (1) Å, b = 11.9067 (2) Å, c = 27.0616 (5) Å, alpha = 90°, beta = 90°, gamma = 90°, V = 1726.30 (5) Å$^3$, Z = 4 and T = 200(2) K.

The structure was solved by direct methods and refined by full-matrix least-squares on $F^2$ using SHELXTL. Refinement Results for **1**: $R(F) = 0.0557$, $wR(F^2) = 0.1087$, and $S = 1.067$ for 3741 reflections with $I > 2\sigma(I)$, and $R(F) = 0.0865$, $wR(F^2) = 0.1307$, and $S = 1.095$ for 5057 unique reflections and 279 parameters. The Flack absolute structure parameter refined to x = -0.09 (8) indicating that the collected intensity data is of sufficient quality to unequivocally establish that the absolute structure is indeed 5-Chlorothiophene-2-sulfonic Acid [(1*S*,2*R*)-2-(3,5-Difluorophenyl)-3,3,3-trifluoro-1-hydroxymethylpropyl]amide. For comparison, the refinement of the inverted molecule having the wrong absolute structure, i.e. (1*R*,2*S*), gave $R(F) = 0.0567$, $wR(F^2) = 0.1136$, and $S = 1.055$ for 3741 reflections with $I > 2\sigma(I)$, and $R(F) = 0.0874$, $wR(F^2) = 0.1366$, and $S = 1.082$ for 5057 unique reflections and 279 parameters. The Flack parameter based on the wrong absolute structure was 1.06 (8).

Additional experimental and refinement details including all coordinates and atomic displacement parameters, and bond distances and angles are available in CIF format. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre by requesting CCDC 743622 via www.ccdc.cam.ac.uk/data_request/cif.




[i] Meanwell, N. A.; Roth, H. R.; Smith, E. C. R.; Wedding, D. L.; Wright, J. J. K. *J. Org. Chem.* **1991**, *56*, 6897