Multigram Synthesis of *trans*-2-(Trifluoromethyl)cyclopropanamine

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Abstract: 2-(Trifluoromethyl)cyclopropanamine was synthesized. The key step of the synthesis is a transformation of the carboxy group into the trifluoromethyl group by using sulfur tetrafluoride. Twenty gram of the target product was conveniently prepared in a single batch.

Key words: fluorine, trifluoromethyl group, amines, cyclopropyl group, sulfur tetrafluoride

The introduction of small, privileged motifs into compounds with biological activity is a well-known strategy used in medicinal chemistry.[1] The cyclopropyl group, which often has beneficial effects upon biological activity and metabolic stability, is one such privileged motif, the use of which has become increasingly popular in drug design.[2,3] Cyclopropanamine is a small building block, which is often used to provide the pharmacologically relevant compound of interest with the cyclopropyl group.[4] Worth noting is that the cyclopropanamine motif also frequently occurs in drugs (Figure 1).

The trifluoromethyl group is another privileged substructure within medicinal chemistry.[3,5] With this group, the beneficial effect of fluorine substitution is utilized to improve numerous characteristics important to drug molecules. Surprisingly, despite the great potential of cyclopropanamine, to date little is known about the corresponding trifluoromethyl-substituted analogues. For example, 1-(trifluoromethyl)cyclopropanamine (**1**) has received significant attention only in recent years (Figure 2).[6] However, to the best of our knowledge, the synthesis of the isomeric compound 2-(trifluoromethyl)cyclopropanamine (**2**) has remained unknown so far.[7] In this context, herein we report a concise multigram preparation of amine **2**.

The synthesis of amine **2** commenced from dibromide **3** as a starting material (Scheme 1).[8] Slow addition of nitromethane to a stirred suspension of potassium carbonate and dibromide **3** in dimethyl sulfoxide gave cyclopropane **4** in 54% yield.[9] It is important that the time used for nitromethane addition should be as long as possible (up to 12 h), otherwise the yield of product **4** decreases significantly. Next, the ester group in **4** was hydrolyzed with an aqueous mixture of hydrochloric and acetic acids to smoothly provide the corresponding acid **5** in 87% yield.[10] The crucial step of the synthesis, namely the transformation of the carboxy group into the trifluoromethyl group, was successfully performed with the use of sulfur tetrafluoride.[11] Treating acid **5** with 2.5 equivalents of sulfur tetrafluoride in the presence of a catalytic amount of water (to generate HF) at 90 °C for two hours afforded the trifluoromethyl-substituted cyclopropane **6** in 91% yield after distillation. Importantly, several experiments on the fluorination of compound **5** were performed, and each time reproducible results were obtained. Finally, reduction of the nitro group in **6** by the use of aqueous hydrochloric acid with zinc powder completed the synthesis of 2-(trifluoromethyl)cyclopropanamine hydrochloride (**2**·HCl) in 67% yield.

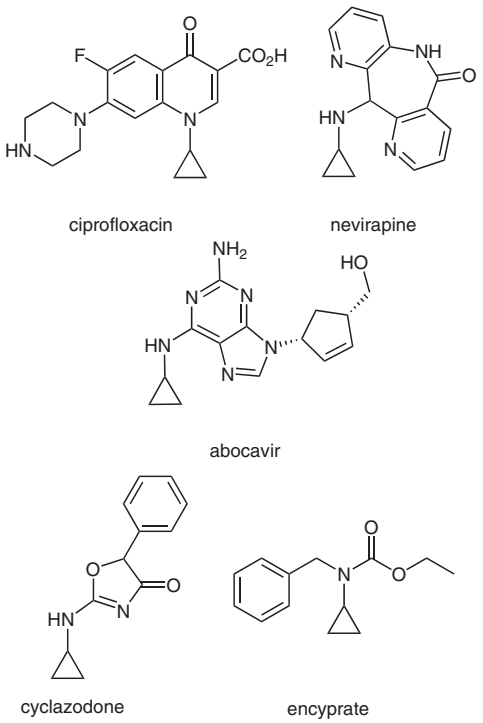

Figure 1 Some marketed drugs possessing the cyclopropanamine moiety: ciprofloxacin (antibiotic, FDA-approved), nevirapine (for treatment of HIV-1 infection, FDA-approved), abocavir (for treatment of HIV-1 infection, FDA-approved), cyclazodone (CNS stimulant), encyprate (antidepressant)

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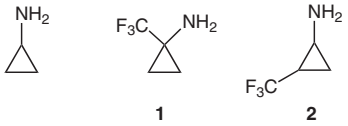
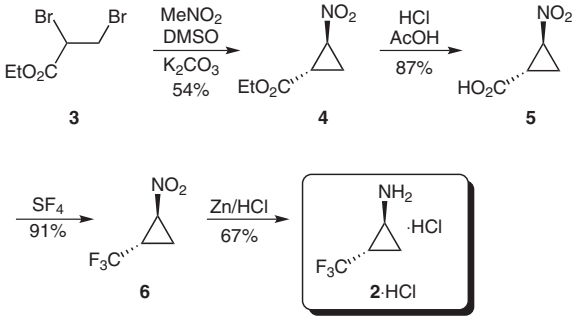


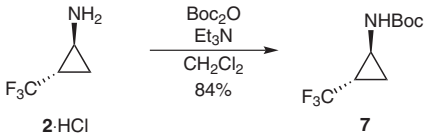
Figure 2 The structures of cyclopropanamine and its trifluoromethyl-substituted analogues **1** and **2**



Scheme 1 Synthesis of amine **2**·HCl

Importantly, the synthesis of **2**·HCl was easily scaled up, so that 20 grams of the product was conveniently prepared in a single batch from dibromide **3**.

To determine the stereoconfiguration of the synthesized compounds, amine **2** was converted into the corresponding Boc-protected derivative **7** (Scheme 2). The *trans* configuration of compound **7** was proven by an X-ray crystallographic analysis (Figure 3).



Scheme 2 Synthesis of compound **7**

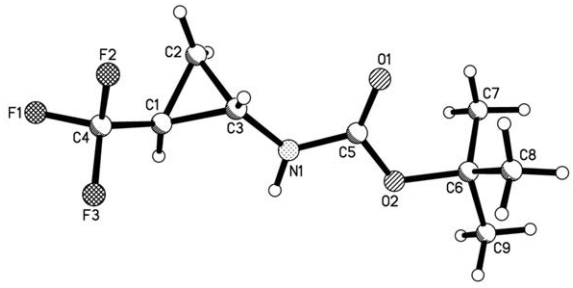


Figure 3 The molecular structure of compound **7** obtained by an X-ray diffraction study

In summary, we have developed a practical synthesis of *trans*-2-(trifluoromethyl)cyclopropanamine (**2**). The key step of the synthesis is a transformation of the carboxy group in cyclopropane **5** into a trifluoromethyl group by using sulfur tetrafluoride. As much as 20 grams of the target amine **2** was conveniently prepared in one synthetic run. Because of its rapid access and scalable synthesis, we believe compound **2** would find wide application within drug design as a novel fluorine-containing building block.

Dibromide **3** was synthesized as reported previously.[8] ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance 500 spectrometer at 499.9 MHz, 124.9 MHz, and 470.3 MHz, respectively. Chemical shifts are reported relative to TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standard. Mass spectra (CI) were recorded on an Agilent 1100 LCMSD SL instrument.

Ethyl *rel*-(1*S*,2*S*)-2-Nitrocyclopropanecarboxylate (4)

$MeNO_2$ (42.2 g, 692 mmol) was added over a period of 12 h to a stirred suspension of dibromide **3** (166.8 g, 642 mmol) and K_2CO_3 (255.4 g, 1.85 mol) in DMSO (310 mL). After the addition had been completed, the reaction mixture was stirred for an additional 16 h at r.t. Thereafter, it was poured into H_2O (3.2 L). The aqueous soln was extracted with Et_2O (3 × 400 mL), and the combined organic extracts were washed with H_2O (2 × 400 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure provided the crude product **4** as a brown oil. The product (~90% purity) was used in the next step without additional purification.

Yield: 55.2 g (348 mmol; 54%); brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.57 (m, 1 H, C*H*NO_2), 4.17 (q, *J* = 7.0 Hz, 2 H, OC*H*$_2$CH$_3$), 2.69 (m, 1 H, C*H*CO_2Et), 2.03 (m, 1 H, C*H*H), 1.70 (q, *J* = 7.0 Hz, 1 H, CH*H*), 1.26 (t, *J* = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$).

***rel*-(1*S*,2*S*)-2-Nitrocyclopropanecarboxylic Acid (5)**

A suspension of ester **4** (53.2 g, 335 mmol) in AcOH (46 mL) and 12 N aq HCl (46 mL) was stirred at 90 °C for 2 h. The solvent was evaporated under vacuum. The residue was recrystallized from AcOH to provide acid **5**.

Yield: 38.1 g (291 mmol; 87%); white solid.

Analytical data are identical to those previously described.[9]

***rel*-(1*S*,2*S*)-1-Nitro-2-(trifluoromethyl)cyclopropane (6)**

A mixture of acid **5** (34.0 g, 0.26 mol), H_2O (1 mL), and SF_4 (70.0 g, 0.64 mol) was kept in a stainless steel autoclave at 90 °C for 2 h. Then the gaseous products were removed (under a good fumehood), and the content was poured into ice (1000 g). The mixture was neutralized with 10% aq NH_3. The organic layer was separated, dried ($MgSO_4$), and purified by distillation (68–70 °C/50 Torr); this gave pure product **6**.

Yield: 36.6 g (236 mmol, 91%); colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.52 (m, 1 H, C*H*NO_2), 2.76 (m, 1 H, C*H*CF_3), 2.03 (m, 1 H, C*H*H), 1.62 (q, *J* = 7.5 Hz, 1 H, CH*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 123.25 (q, $^1J_{CF}$ = 270.0 Hz, *C*F_3), 54.93 (s, *C*HNO_2), 24.35 (q, $^2J_{CF}$ = 38.8 Hz, *C*HCF_3), 12.78 (q, $^3J_{CF}$ = 2.5 Hz, *C*H$_2$).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –67.54 (d, $^3J_{FH}$ = 9.5 Hz, C*F*$_3$).

MS (CI): *m*/*z* = 155 [M$^+$].

***rel*-(1*S*,2*S*)-2-(Trifluoromethyl)cyclopropanamine Hydrochloride (2·HCl)**

Cooled by ice water, compound **6** (36.0 g, 232 mmol) was dissolved in *i*-PrOH (200 mL) and treated with 6 N aq HCl (1000 mL). Zn dust (102.8 g, 1.58 mmol, 7 equiv) was added slowly, so that the temperature of the reaction mixture did not exceed 40 °C. The reaction mixture was thereafter stirred at r.t. for 12 h. The suspension was collected by filtration. The filtrate was quenched by an addition of sat. aq $NaHCO_3$ (1200 mL). The aqueous phase was extracted with Et_2O (3 × 300 mL). The combined organic extracts were dried ($MgSO_4$) and filtered. An excess of gaseous anhyd HCl was bub-

bled through the organic layer. The precipitate (**2**·HCl) was collected by filtration and dried under vacuum.

Yield 25.6 g (159 mmol, 67%); white solid; mp 193 °C (dec).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.91 (br s, 3 H, NH_3^+), 2.96 (br s, 1 H, CHNH_3^+), 2.45 (m, 1 H, CHCF_3), 1.42 (m, J = 7.5 Hz, 1 H, CHH), 1.23 (dd, J = 8.0, 1 H, 6.5 Hz, CHH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 125.55 (q, $^1J_{CF}$ = 268.8 Hz, CF$_3$), 25.12 (d, $^3J_{CF}$ = 3.8 Hz, CHNH$_3^+$), 18.05 (q, $^2J_{CF}$ = 37.5 Hz, CHCF$_3$), 7.55 (s, CH$_2$).

^{19}F NMR (377 MHz, DMSO-d_6): δ = –60.72 (d, $^3J_{FH}$ = 7.5 Hz, CF_3).

tert-Butyl *rel*-(1*S*,2*S*)-*N*-[2-(Trifluoromethyl)cyclopropyl]carbamate (7)

Boc_2O (1.66 g, 7.6 mmol) was added to a suspension of amine **2**·HCl (1.23 g, 7.6 mmol) and Et_3N (1.62 g, 16.0 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred at r.t. for 12 h. H_2O (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction mixture. The organic phase was separated, washed with H_2O (5 mL) and dried (Na_2SO_4). Evaporation of the solvent provided the residue, which was recrystallized (benzene–hexane) to afford pure product **7**.

Yield: 1.44 g (6.4 mmol, 84%); white solid; mp 64 °C.

The crystals suitable for an X-ray diffractional study were obtained by a slow evaporation of a diluted soln of **7** in cyclohexane.

Main Atropisomer of 7

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.93 (br s, 1 H, NH), 2.87 (br s, 1 H, CHNH), 1.68 (br s, 1 H, CHCF_3), 1.17 (d, J = 6.0 Hz, 1 H, CHH), 1.05 (br s, 1 H, CHH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.95 (s, NC=O), 125.21 (q, $^1J_{CF}$ = 270.0 Hz, CF$_3$), 80.34 [br s, OC(CH$_3$)$_3$], 28.26 [s, OC(CH$_3$)$_3$], 26.35 (br s, CH, c-Pr), 21.95 (br s, CH, c-Pr), 10.31 (br s, CH$_2$, c-Pr).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –66.77 (d, $^3J_{FH}$ = 3.8 Hz, CF_3).

MS (CI): m/z = 225 [M$^+$].

X-ray Diffraction Study of 7

The molecule of compound **7** contains two chiral centers (at the C1 and C3 atoms), which have identical configurations (*S*,*S* or *R*,*R*, accordingly). Compound **7** crystallizes in a noncentrosymmetric space group; however, the absence of heavy atoms does not allow the unambiguous determination of the configuration of the chiral centers. The substituents at the C1 and C3 atoms occupy *trans* positions relative to the plane of the propane ring [the C4–C1–C3–N1 torsion angle is 138.2(1)°]. The trifluoromethyl group is turned in such a way that the C4–F1 bond is orthogonal to the propane ring [the C2–C1–C4–F1 torsion angle is 87.3(1)°], which leads to the appearance of an H3···F2 intramolecular shortened contact (the distance between the atoms is 2.49 Å; cf. van der Waals radii sum 2.57 Å). The planar carbamide fragment of the substituent at the C3 atom is turned relatively to the C2–C3 bond of the ring [the C5–N1–C3–C2 torsion angle is 100.3(1)°]. The *tert*-butyl group has an *ap* conformation with respect to the N1–C5 bond and is turned in such way that the C6–C9 bond is antiperiplanar to the C5–O2 bond [the C6–O2–C5–N1 and C5–O2–C6–C9 torsion angles are 175.9(1)° and 179.8(1)°, respectively].

In the crystal phase, the molecules **7** form infinite chains along the [100] crystallographic direction owing to the formation of the N1–H···O1′ (1 + x, y, z) intermolecular hydrogen bond (H···O 2.08 Å, N–H···O 163°). A C2–H···F2′ (x, –y, –0.5 + z) intermolecular hydrogen bond (H···F 2.49 Å, C–H···F 156°) is observed in the crystal phase.

The colorless crystals of **7** ($C_9H_{14}NO_2F_3$) are monoclinic. At 100 K, a = 5.1064(2), b = 20.0360(7), c = 10.4797(4) Å, β = 98.768(3)°, V = 1059.67(7) Å^3, M_r = 225.21, Z = 4, space group Cc, d_{calc} = 1.412 g·cm^{-3}, μ(Mo Kα) = 0.133 mm^{-1}, F(000) = 472. Intensities of 5557 reflections (2502 independent, R_{int} = 0.014) were measured on the 'Xcalibur-3' diffractometer (graphite monochromated Mo Kα radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 60°). The structure was solved by direct methods using the SHELXTL package.[12] Positions of the hydrogen atoms were located from electron density difference maps and refined by using isotropic approximation. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 2484 reflections was converged to wR_2 = 0.062 [R_1 = 0.024 for 2314 reflections with $F > 4\sigma(F)$, S = 1.011]. CCDC 791009 contains the supplementary crystallographic data for **7**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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