Synthesis of Isomeric 6-Trifluoromethyl-3-azabicyclo[3.1.0]hexanes: Conformationally Restricted Analogues of 4-Trifluoromethylpiperidine

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Abstract: Two isomeric conformationally restricted analogues of 4-trifluoromethylpiperidine were designed. The synthesis was performed in four steps from commercially available *N*-benzylmaleimide. The key reaction was the [3+2] cycloaddition between trifluoromethyldiazomethane and *N*-benzylmaleimide.

Key words: amines, trifluoromethyl group, cyclopropane, 4-trifluoromethylpiperidine, drug design

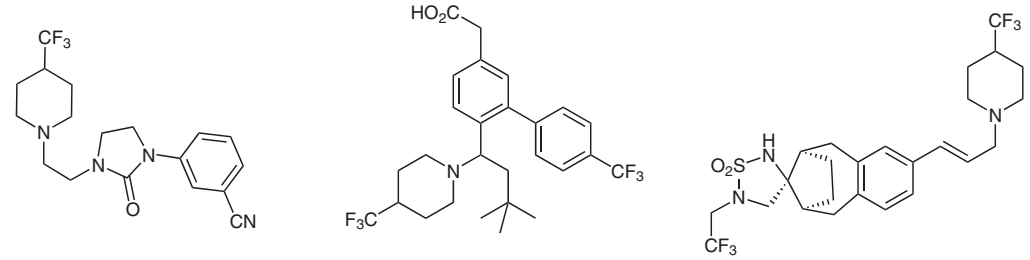
The piperidine motif is historically popular within medicinal chemistry. It is present in more than one hundred FDA-approved drugs.[1] Therefore, substituted piperidine analogues are frequently used in drug discovery projects as common starting materials. Most of them are substituted at the C-4 atom.[2] It is not surprising therefore that 4-trifluoromethylpiperidine has proven to be a valuable building block in drug design.[3] During the last decade it has been successfully used in fifty medicinal projects[4] resulting in more than forty bioactive derivatives.[5] Among them are the potent dopamine D_3 receptor antagonist **1**,[3c,g] the γ-secretase inhibitor **2**,[3b] and the promising nootropic agent **3**,[3a] which have reached preclinical trials (Figure 1). In all cases, the trifluoromethyl group[6] served as a 'metabolically stable lipophilic group,' which was involved in the hydrophobic ligand-protein interactions,[7] increasing thereby the ligand binding efficiency.

Piperidine ring is rather flexible, whereas conformationally restricted compounds are often more efficient and selective ligands for various targets compared to their flexible counterparts, due to fixation of the biologically active conformation.[8] 3-Azabicyclo[3.1.0]hexane fragment is frequently used in drug design as a conformationally restricted analogue of the piperidine motif.[9] Potent antibacterial agent **4**,[9a] selective muscarinic antagonist **5**,[9h] and the launched antimicrobial trovafloxacine[10] are the representative examples of the successful application of this concept (Figure 2).

Given the high pharmacological potential of 4-trifluoromethylpiperidine, its isomeric analogues **6a** and **6b** seem to be interesting for drug discovery (Figure 3). They can be formally considered as 4-trifluoromethylpiperidine, which is 'frozen' at the different conformations by a single C-3–C-5 bond. Importantly, this type of conformational restriction does not bring any elements of chirality to the molecule, preserving its nonchiral structure. In this work, we report on the synthesis of both the compounds **6a** and **6b**.

Retrosynthetic Analysis

Previously, it was shown that substituted trifluoromethylcyclopropanes could be obtained in two steps from trifluoromethyldiazomethane (CF_3CHN_2) and electron-deficient alkenes.[11] This tactic was also adopted by us for



dopamine D_3 antagonist (**1**) GSK, 2009 | γ-secretase modulator (**2**) Biogen, 2011 | nootropic agent (**3**) Merck, 2005

Figure 1 Some pharmacologically relevant derivatives of 4-trifluoromethylpiperidine

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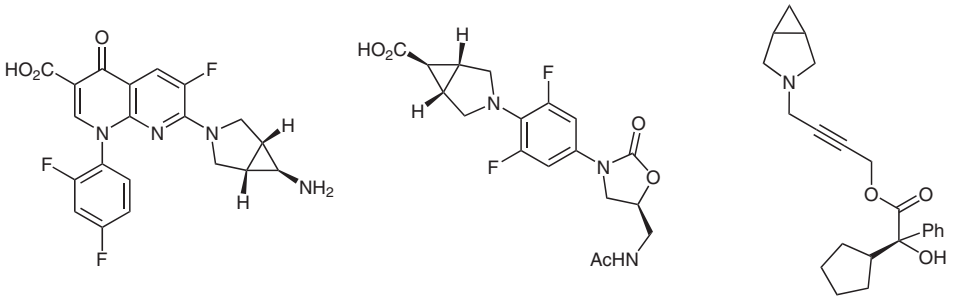


Figure 2 Some biologically active compounds with a 3-azabicyclo[3.1.0]hexane fragment

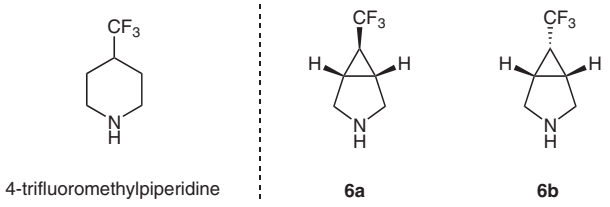
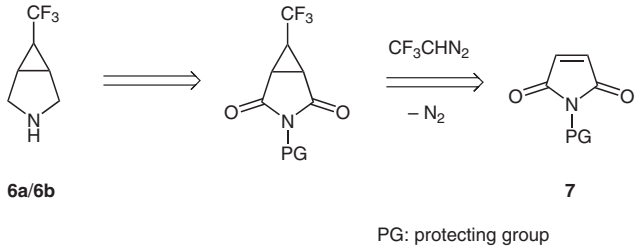


Figure 3 Structure of 4-trifluoromethylpiperidine and amines **6a**, **6b**

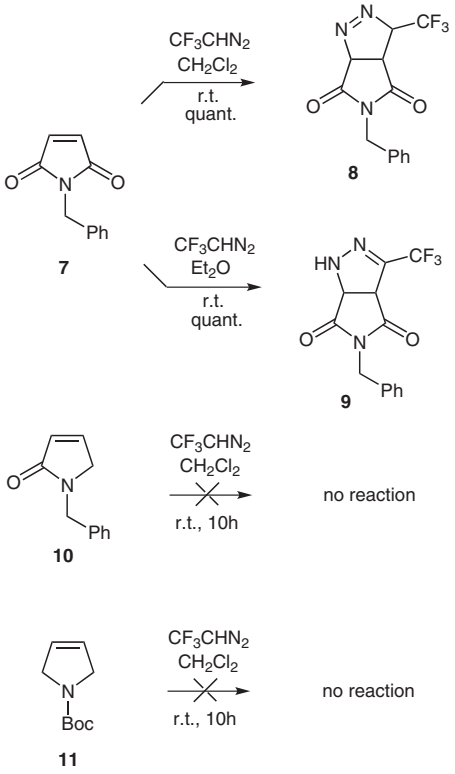
the synthesis of amines **6a** and **6b** (Scheme 1).[12,13] The key step was supposed to be a reaction between electron-deficient maleimide **7** and CF_3CHN_2.[14]



Scheme 1 Retrosynthetic analysis of amines **6a** and **6b**

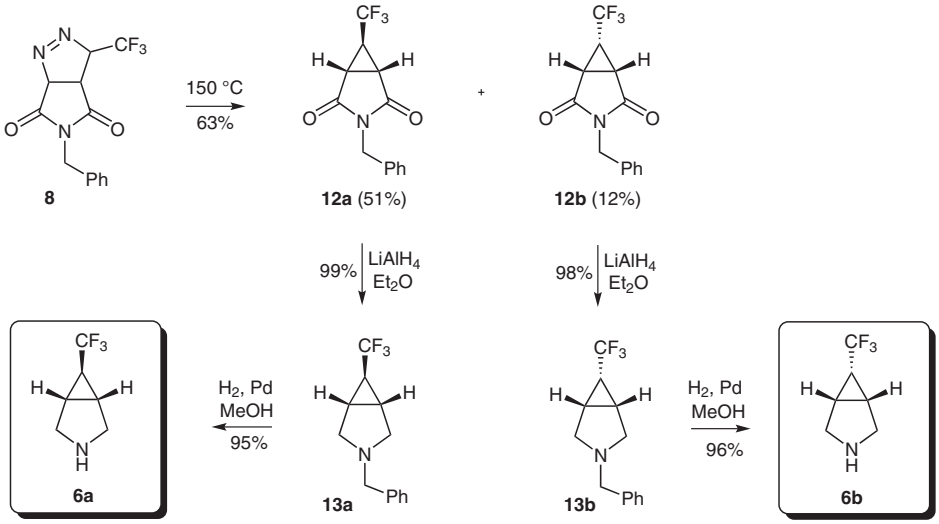
Chemistry

The *N*-benzyl group was chosen to protect the nitrogen atom in compound **7**, because the N–CH_2Ph bond could be subsequently cleaved in quantitative yield by hydrogenolysis. An excess of CF_3CHN_2 (bp 13 °C)[15] was generated by the reaction of commercially available $CF_3CH_2NH_2$·HCl with one equivalent of $NaNO_2$ in water. The formed volatile compound was gradually blown off by an argon stream into a reaction vessel containing the stirred solution of alkene **7** in dichloromethane at room temperature. Indeed, the reaction proceeded smoothly, as judged by TLC and ^{1}H NMR monitoring. No nitrogen evolution was observed, indicating formation of a stable product. After completion of the reaction, the solvent was evaporated under reduced pressure to provide the corresponding Δ^1-pyrazoline **8** in quantitative yield (Scheme 2). It is worth noting that only one stereoisomer of compound **8** was formed. However, the relative configurations of the stereogenic centers were not determined, as these were lost in the next synthesis step. Unexpectedly, the reaction of alkene **7** with CF_3CHN_2 in diethyl ether as the solvent led to quantitative formation of the isomeric Δ^2-pyrazoline **9**. Less active alkenes **10** and **11** did not react with CF_3CHN_2 under the above described conditions.



Scheme 2 Reaction of CF_3CHN_2 with alkenes **7**, **10**, and **11**

The decomposition of pyrazolines **8** and **9** was studied next. Thermal decomposition of pyrazoline **8** was easily performed by heating the compound at 150 °C for one hour. During the reaction a vigorous nitrogen evolution was observed leading to the formation of cyclopropanes **12a**/**12b** (4.3:1.0) in 63% overall yield (Scheme 3). Isomers **12a**/**12b** were easily separated by flash column chromatography. The *trans*-isomer **12a** was obtained as the main reaction product. The pyrazoline **9** was more stable



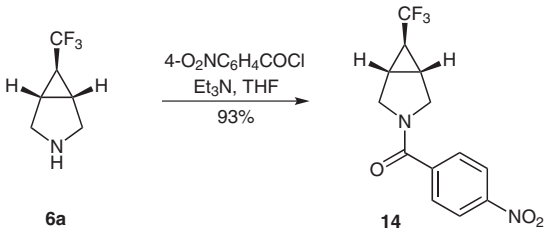
Scheme 3 Synthesis of amines **6a**, **6b**

than compound **8**, and all attempts to perform its thermal decomposition (150–260 °C) led to the formation of the desired product in less than 10% yield.

Reduction of the carbonyl groups in **12a** with $LiAlH_4$ in diethyl ether smoothly gave the N-protected pyrrolidine **13a** in an excellent yield of 99%. Importantly, no cyclopropane ring cleavage was observed. Finally, cleavage of *N*-benzyl group in pyrrolidine **13a** by hydrogenation using 10% palladium on charcoal as the catalyst furnished the target amine **6a** in 95% yield. Again, the cyclopropane ring was stable under the reaction conditions. The isomeric amine **6b** was prepared from amide **12b** following the same synthetic approach in 94% yield over two steps.

Assignment of the Stereoconfiguration

To determine stereoconfiguration of the synthesized compounds, acylation of amine **6a** was performed by reaction with 4-nitrobenzoyl chloride to afford the crystalline derivative **14** (Scheme 4). Single crystals of the product were obtained by slow evaporation of a dilute solution in methanol. X-ray diffractional analysis of amide **14** revealed the *trans*-configuration of the pyrrolidine ring and the trifluoromethyl group within the cyclopropane core (Figure 4a).



Scheme 4 Synthesis of amide **14**

Later, *trans*-stereoconfiguration of amine **6a** was additionally confirmed by X-ray diffractional analysis of compound **12a** (Figure 4b). Single crystals of the compound were obtained by slow evaporation of a dilute solution of **12a** in ethyl acetate.

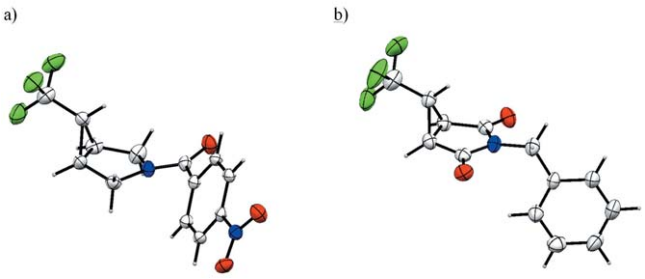


Figure 4 X-ray crystal structures of (a) compound **14**, and (b) compound **12a**

In summary, isomeric 6-trifluoromethyl-3-azabicyclo[3.1.0]hexanes **6a** and **6b** were designed as nonchiral conformationally restricted analogues of pharmacologically relevant 4-trifluoromethylpiperidine. Synthesis of both the compounds was performed in four steps from commercially available *N*-benzylmaleimide (**7**). The key step was a [3+2] cycloaddition between alkene **7** and trifluoromethyldiazomethane. With the reported rapid synthesis, we believe that isomeric amines **6a** and **6b** will find true practical application in drug discovery projects, especially in those where 4-trifluoromethylpiperidine is involved.

Solvents were purified according to standard procedures. All reactions were performed in argon atmosphere. All the other starting materials were provided by Enamine Ltd. Column chromatography was performed using silica gel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on Bruker Avance 500 spectrometer at 499.9 MHz, 470.3 MHz, and 124.9 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal or external (D_2O, TMS) standard. Mass spectra were recorded on Agilent 1100 LCMSD SL instrument by chemical ionization (CI).

Dihydro-5-(phenylmethyl)-3-(trifluoromethyl)pyrrolo[3,4-*c*]pyrazole-4,6(3*H*,5*H*)-dione (8)

A solution of 3,3,3-trifluoroethylamine hydrochloride (54.5 g, 790 mmol, 5 equiv) in H_2O (200 mL) was slowly added (~5–7 h) to a stirred mixture of $NaNO_2$ [106.7 g, 790 mmol, 5 equiv; dissolved in H_2O (200 mL)] and dodecane (200 mL). Upon addition, the formed CF_3CHN_2 was gradually blown off by argon through a drying tube ($MgSO_4$) into a vessel containing a stirred solution of **7** (29.6 g, 158 mmol, 1 equiv) in CH_2Cl_2 (400 mL) at r.t. Thereafter, the solvent was gently removed on a rotary evaporator under vacuum at r.t. to afford crude **8** as a white solid (47.0 g, 158 mmol, ~100%); mp >40 °C (dec.). According to NMR data, the compound was of ~90% purity, and it was used in the next step without additional purification.

^{1}H NMR (500 MHz, DMSO-d_6/TMS): δ = 7.37–7.24 (5 H, m, C_6H_5), 6.41 (1 H, d, $^3J_{H,H}$ = 6.0 Hz, NCHCO), 6.19 (1 H, br s, NCHCF$_3$), 4.55 (1 H, d, $^2J_{H,H}$ = 15.0 Hz, AB system, NC*H*HPh), 4.54 (1 H, d, $^2J_{H,H}$ = 15.0 Hz, AB system, NCH*H*Ph), 3.61 (1 H, m, C*H*CHCF$_3$).

^{13}C NMR (125 MHz, DMSO-d_6/TMS): δ = 173.45 (s, NCO), 169.12 (s, NCO), 135.72 (s, C, Ph), 128.96 (s, CH, Ph), 128.17 (s, CH, Ph), 128.10 (s, CH, Ph), 123.53 (q, $^1J_{C,F}$ = 278.8 Hz, CF$_3$), 96.48 (s, N*C*HCO), 90.81 (q, $^2J_{C,F}$ = 27.5 Hz, *C*HCF$_3$), 42.71 (s, *C*H$_2$Ph), 38.91 (s, CH*C*HCO).

^{19}F NMR (470 MHz, DMSO-d_6/CFCl$_3$): δ = –72.17 (d, $^2J_{F,H}$ = 9.4 Hz, CF$_3$).

MS: *m*/*z* = 269 (M – 28)$^+$.

Dihydro-5-(phenylmethyl)-3-(trifluoromethyl)pyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (9)

A solution of 3,3,3-trifluoroethylamine hydrochloride (5.5 g, 79 mmol, 5 equiv) in H_2O (20 mL) was slowly added (~5–7 h) to a stirred mixture of $NaNO_2$ (10.7 g, 79 mmol, 5 equiv; dissolved in H_2O (20 mL)] and dodecane (20 mL). Upon addition, the formed CF_3CHN_2 was gradually blown off by argon through a drying tube ($MgSO_4$) into a vessel containing a stirred solution of **7** (3.0 g, 15.8 mmol, 1 equiv) in Et_2O (40 mL) at r.t. Thereafter, the solvent was gently removed on a rotary evaporator under vacuum at r.t. to give pure **9** as a white solid (4.7 g, 15.8 mmol, ~100%); mp 116 °C.

^{1}H NMR (500 MHz, CDCl$_3$/TMS): δ = 7.31 (5 H, s, C_6H_5), 6.95 (1 H, br s, NH), 4.84 (1 H, d, $^3J_{H,H}$ = 10.5 Hz, COC*H*NH), 4.70 (1 H, d, $^2J_{H,H}$ = 14.0 Hz, NC*H*HPh), 4.64 (1 H, d, $^2J_{H,H}$ = 14.0 Hz, NCH*H*Ph), 4.40 (1 H, d, $^3J_{H,H}$ = 10.5 Hz, COC*H*NH).

^{13}C NMR (125 MHz, CDCl$_3$/TMS): δ = 174.01 (s, NCO), 170.57 (s, NCO), 135.15 (q, $^2J_{C,F}$ = 38.8 Hz, *C*CF$_3$), 134.61 (s, C, Ph), 128.86 (s, CH, Ph), 128.70 (s, CH, Ph), 128.43 (s, CH, Ph), 119.76 (q, $^1J_{C,F}$ = 268.8 Hz, CF$_3$), 63.54 (s, *C*HCO), 51.31 (s, *C*HCO), 43.24 (s, *C*H$_2$Ph).

^{19}F NMR (470 MHz, DMSO-d_6/CFCl$_3$): δ = –64.99 (s, CF$_3$).

MS: *m*/*z* = 269 (M – 28)$^+$.

***trans*-3-Benzyl-6-(trifluoromethyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (12a) and *cis*-3-Benzyl-6-(trifluoromethyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (12b)**

Compound **8** (15.1 g, 51.0 mmol) was heated in an oil bath under vacuum (20 mmHg) at 150 °C during 1 h; an exothermic evolution of N_2 was observed. The formed crude **12a**/**12b** mixture was dissolved in CH_2Cl_2 (500 mL), triturated with 5% aq $KMnO_4$ (500 mL), washed with H_2O (150 mL), dried ($MgSO_4$), and evaporated. The obtained residue was purified by flash column chromatography. Elution with hexane–EtOAc mixture (2:1) afforded first **12a** (7.0 g, 26.0 mmol, 51%) as a white solid; mp 114–116 °C; R_f = 0.4 (hexanes–EtOAc, 2:1). Crystals of compound **12a** suitable for X-ray structural analysis were obtained by slow evaporation of a dilute solution of **12a** in EtOAc.

12a

^{1}H NMR (500 MHz, CDCl$_3$/TMS): δ = 7.33 (5 H, m, C_6H_5), 4.55 (2 H, s, NC*H*$_2$Ph), 2.81 (2 H, d, $^3J_{H,H}$ = 3.0 Hz, CH), 2.56 (1 H, m, CHCF$_3$).

^{13}C NMR (125 MHz, CDCl$_3$/TMS): δ = 170.96 (s, NCO), 135.29 (s, C, Ph), 128.87 (s, CH, Ph), 128.67 (s, CH, Ph), 128.28 (s, CH, Ph), 122.15 (q, $^1J_{C,F}$ = 271.3 Hz, CF$_3$), 42.26 (s, *C*H$_2$Ph), 31.25 (d, $^2J_{C,F}$ = 38.8 Hz, *C*HCF$_3$), 31.25 (d, $^3J_{C,F}$ = 1.3 Hz, *C*HCHCF$_3$).

^{19}F NMR (470 MHz, CDCl$_3$/CFCl$_3$): δ = –69.05 (d, $^2J_{F,H}$ = 4.7 Hz, CF$_3$).

MS: *m*/*z* = 269 (M)$^+$.

Anal. Calcd for $C_{13}H_{10}F_3NO_2$: C, 58.00; H, 3.74; N, 5.20. Found: C, 58.35; H, 3.47; N, 5.32.

12b

Further elution gave isomer **12b** (1.6 g, 5.9 mmol, 12%) as a white solid; mp 114–116 °C; R_f = 0.3 (hexanes–EtOAc, 2:1).

^{1}H NMR (500 MHz, CDCl$_3$/TMS): δ = 7.40–7.32 (5 H, m, C_6H_5), 4.54 (2 H, s, NC*H*$_2$Ph), 2.82 (2 H, d, $^3J_{H,H}$ = 9.0 Hz, CH), 2.49 (1 H, m, CHCF$_3$).

^{13}C NMR (125 MHz, CDCl$_3$/TMS): δ = 169.84 (s, NCO), 135.03 (s, C, Ph), 129.16 (s, CH, Ph), 128.61 (s, CH, Ph), 128.09 (s, CH, Ph), 123.21 (q, $^1J_{C,F}$ = 273.8 Hz, CF$_3$), 42.93 (s, *C*H$_2$Ph), 32.86 (d, $^2J_{C,F}$ = 38.8 Hz, *C*HCF$_3$), 24.91 (d, $^3J_{C,F}$ = 1.3 Hz, *C*HCHCF$_3$).

^{19}F NMR (470 MHz, CDCl$_3$/CFCl$_3$): δ = –60.21 (d, $^2J_{F,H}$ = 4.7 Hz, CF$_3$).

MS: *m*/*z* = 269 (M)$^+$.

Anal. Calcd for $C_{13}H_{10}F_3NO_2$: C, 58.00; H, 3.74; N, 5.20. Found: C, 58.24; H, 3.65; N, 5.53.

***trans*-3-Benzyl-6-(trifluoromethyl)-3-azabicyclo[3.1.0]hexane (13a)**

A solution of compound **12a** (6.05 g, 22.5 mmol) in anhyd Et_2O (50 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (2.13 g, 56.1 mmol) in anhyd Et_2O (50 mL). The formed suspension was heated at reflux for 3 h. The reaction mixture was cooled to r.t. and H_2O (3 mL) was added dropwise. The solution was evaporated under vacuum and H_2O (50 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and evaporated under vacuum to give product **13a** (5.37 g, 22.3 mmol, 99%) as an oil. The material was sufficiently pure to be used in the next step without additional purification.

^{1}H NMR (500 MHz, CDCl$_3$/TMS): δ = 7.36–7.25 (5 H, m, C_6H_5), 3.63 (2 H, s, NC*H*$_2$Ph), 3.05 (2 H, d, $^2J_{H,H}$ = 9.0 Hz, NC*H*HCH), 2.40 (2 H, d, $^2J_{H,H}$ = 9.0 Hz, NCH*H*CH), 2.05 (1 H, m, CHCF$_3$), 1.78 (2 H, s, CH of cyclopropane).

^{19}F NMR (470 MHz, CDCl$_3$/CFCl$_3$): δ = –68.07 (d, $^2J_{F,H}$ = 9.4 Hz, CF$_3$).

MS: *m*/*z* = 241 (M)$^+$.

***cis*-3-Benzyl-6-(trifluoromethyl)-3-azabicyclo[3.1.0]hexane (13b)**

Compound **13b** was prepared from **12b** (1.20 g, 4.5 mmol) following the same experimental procedure used in the synthesis of **13a**; yield: 1.05 g (4.4 mmol, 98%); oil.

^{1}H NMR (500 MHz, CDCl$_3$/TMS): δ = 7.30 (5 H, m, C_6H_5), 3.65 (2 H, s, NC*H*$_2$Ph), 3.20 (2 H, d, $^2J_{H,H}$ = 9.5 Hz, NC*H*HCH), 2.55 (2 H, d, $^2J_{H,H}$ = 9.5 Hz, NCH*H*CH), 1.78 (2 H, d, *J* = 8.0 Hz, CH of cyclopropane), 1.51 (1 H, m, CHCF$_3$).

^{13}C NMR (125 MHz, CDCl$_3$/TMS): δ = 139.34 (s, C, Ph), 128.44 (s, CH, Ph), 128.09 (s, CH, Ph), 126.80 (s, CH, Ph), 127.21 (q, $^1J_{C,F}$ = 273.8 Hz, CF$_3$), 58.93 (s, *C*H$_2$Ph), 52.25 (s, C*H*$_2$NCH$_2$Ph), 23.52 (d, $^2J_{C,F}$ = 37.5 Hz, *C*HCF$_3$), 22.01 (s, *C*HCHCF$_3$).

^{19}F NMR (470 MHz, $CDCl_3$/$CFCl_3$): δ = –56.28 (d, $^2J_{F,H}$ = 9.4 Hz, CF_3).

MS: *m*/*z* = 241 $(M)^+$.

***trans*-6-(Trifluoromethyl)-3-azabicyclo[3.1.0]hexane Hydrochloride (6a·HCl)**

Compound **13a** (5.0 g, 20.7 mmol) was added to a sat. solution of anhyd HCl in MeOH (50 mL). The suspension was evaporated under vacuum to provide pure **13a**·HCl. The compound was dissolved in MeOH (50 mL) and the formed solution was hydrogenated for 12 h (50 atm, 35 °C) using 10% Pd/C (50 mg) as a catalyst. The reaction mixture was filtered off, the filtrate was evaporated under vacuum, and Et_2O (20 mL) was added to the residue. The resulting white solid was collected by filtration to give pure **6a**·HCl (3.7 g, 19.7 mmol, 95%); white solid; mp >200 °C.

^{1}H NMR (500 MHz, D_2O/TMS): δ = 3.52 (4 H, br s, NCH_2), 2.58 (2 H, br s, CH), 1.73 (1 H, m, $CHCF_3$).

^{13}C NMR (125 MHz, D_2O/TMS): δ = 124.82 (q, $^1J_{C,F}$ = 270.0 Hz, CF_3), 47.15 (s, NCH_2), 21.41 (d, $^2J_{C,F}$ = 36.3 Hz, *C*HCF_3), 22.01 (d, $^3J_{C,F}$ = 1.3 Hz, *C*HCHCF_3).

^{19}F NMR (470 MHz, D_2O/$CFCl_3$): δ = –68.39 (d, $^2J_{F,H}$ = 4.7 Hz, CF_3).

Anal. Calcd for $C_6H_9ClF_3N$: C, 38.42; H, 4.84; N, 7.47. Found: C, 38.35; H, 4.97; N, 7.32.

***cis*-6-(Trifluoromethyl)-3-azabicyclo[3.1.0]hexane Hydrochloride (6b·HCl)**

Compound **6b**·HCl was prepared from **13b** (1.00 g, 4.1 mmol) following the same experimental procedure used in the synthesis of **6a**; yield: 0.74 g (4.0 mmol, 96%); white solid; mp >200 °C.

^{1}H NMR (500 MHz, D_2O/TMS): δ = 3.77 (2 H, d, $^2J_{H,H}$ = 13.0 Hz, NCH*H*CH), 3.53 (2 H, d, $^2J_{H,H}$ = 13.0 Hz, NCH*H*CH), 2.37 (2 H, br s, CH), 2.02 (1 H, m, $CHCF_3$).

^{13}C NMR (125 MHz, D_2O/TMS): δ = 126.93 (q, $^1J_{C,F}$ = 271.3 Hz, CF_3), 45.82 (s, NCH_2), 25.01 (d, $^2J_{C,F}$ = 35.0 Hz, *C*HCF_3), 23.15 (d, $^3J_{C,F}$ = 1.3 Hz, *C*HCHCF_3).

^{19}F NMR (470 MHz, D_2O/$CFCl_3$): δ = –59.37 (d, $^2J_{F,H}$ = 9.4 Hz, CF_3).

Anal. Calcd for $C_6H_9ClF_3N$: C, 38.42; H, 4.84; N, 7.47. Found: C, 38.30; H, 4.99; N, 7.63.

***trans*-3-(4-Nitrobenzoyl)-6-(trifluoromethyl)-3-azabicyclo[3.1.0]hexane (14)**

Et_3N (0.45 mL, 3.21 mmol) was added to a solution of **6a**·HCl (200 mg, 1.07 mmol) in THF (5 mL) under stirring at 0 °C. A solution of 4-nitrobenzoyl chloride (218 mg, 1.18 mmol) in THF (5 mL) was added dropwise, while keeping the reaction temperature below 5 °C. The reaction mixture was stirred at r.t. for 2 h and then evaporated under vacuum. EtOAc (30 mL) was added, and the organic layer was washed with 15% aq citric acid (1 × 10 mL), sat. aq $NaHCO_3$ (1 × 10 mL), and brine (1 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated under vacuum. The residue was recrystallized from Et_2O–hexane (1:4) to afford the pure amide **14** (298 mg, 1.00 mmol, 93%) as a white solid; mp 90 °C.

^{1}H NMR (500 MHz, DMSO-d_6/TMS): δ = 8.28 (2 H_{arom}, d, $^3J_{H,H}$ = 8.0 Hz), 7.75 (2 H_{arom}, d, $^3J_{H,H}$ = 8.0 Hz), 4.00 (1 H, d, $^2J_{H,H}$ = 12.5 Hz, NCH*H*CH), 3.67 (2 H, m, NCH*H*CH), 3.45 (2 H, the signals are hidden by the signal of residual water, NCH_2), 2.11 (1 H, m, C*H*CH*C*F_3), 2.06 (1 H, m, C*H*CH*C*F_3), 1.96 (1 H, m, $CHCF_3$).

^{13}C NMR (125 MHz, DMSO-d_6/TMS): δ = 167.78 (s, C=O), 148.40 (s, C_{arom}), 143.32 (s, C_{arom}), 129.90 (s, CH_{arom}), 126.51 (q, $^1J_{C,F}$ = 267.5 Hz, CF_3), 124.03 (s, CH_{arom}), 50.02 (s, NCH_2), 47.32 (s, NCH_2), 21.90 (q, $^2J_{C,F}$ = 35.0 Hz, *C*HCF_3), 20.26 (br s, *C*HCHCF_3), 18.84 (br s, *C*HCHCF_3).

^{19}F NMR (470 MHz, DMSO-d_6/$CFCl_3$): δ = –62.70 (d, $^2J_{F,H}$ = 9.4 Hz, CF_3).

Crystals of compound **14** suitable for X-ray structural analysis were obtained by slow evaporation of a dilute solution of **14** in MeOH.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are copies of NMR spectra and crystallographic data for compounds **12a** and **14**.

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