An Improved Synthesis of 2-, 3-, and 4-(Trifluoromethyl)cyclohexylamines

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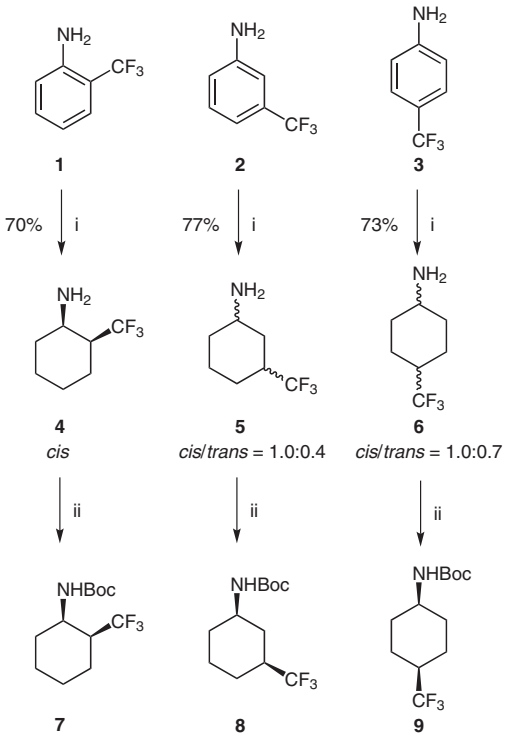
Abstract: An improved synthesis of 2-, 3-, and 4-trifluoromethylcyclohexylamines on a multigram scale via PtO_2-mediated hydrogenation of the corresponding trifluoromethylanilines in trifluoroacetic acid at room temperature under atmospheric pressure is reported. The hydrogenation occurred with a remarkable stereoselectivity favoring the formation of *cis*-isomers.

Key words: trifluoromethyl group, amines, cyclohexyl group, hydrogenation, trifluoroacetic acid

Aminocyclohexane is a pharmacologically potent building block that plays an important role in drug design.[1] Combination of the aminocyclohexane with another privileged substructure, that is, trifluoromethyl group, gives isomeric (trifluoromethyl)cyclohexylamines **4**, **5**, and **6** as shown in Scheme 1. These compounds are presently involved in a number of drug discovery projects.[2] This application resulted in an increase of demand for compounds **4**–**6**.[3] Therefore, the development of an efficient synthetic approach to these isomeric amines is of importance.

One of the most straightforward routes to saturated cycles, such as cyclohexanes, is heterogeneous catalytic hydrogenation.[4] Significant progress has been made in heterogeneous hydrogenation of mono-, bis-, and tricyclic aromatic systems. High-yielding regioselective[5] heterogeneous hydrogenations have been achieved in the case of some bicyclic heteroaromatic compounds. Consequently, the hydrogenation of readily available trifluoromethylanilines **1**–**3**[6] should be a convenient method to the target compounds **4**–**6**. This transformation was mentioned previously in two patents by Bayer and DuPont.[7] The described procedures, however, required the use of 5% Ru/Al_2O_3 as the catalyst and proceeded under extremely harsh conditions (150–175 °C/150–350 bar). On account of such a high reaction temperature and the hydrogen pressure, and hence an increased risk of explosion, the reported protocols cannot be considered as convenient large-scale methods to amines **4**–**6**. A patent by Eli Lilly mentioned the synthesis of compound **5** by hydrogenation of the corresponding aniline **2** in acetic acid using Rh as the catalyst at 50 °C and 4 bar.[8] Further studies on the applicability of this procedure for the preparation of other isomeric (trifluoromethyl)cyclohexylamines were not reported.[9] Therefore, additional optimization of the reaction conditions is necessary. There are several reports in the literature on the reduction of aromatic systems bearing groups or ring heteroatoms capable of protonation in trifluoroacetic acid (TFA) over PtO_2 as the catalyst at atmospheric pressure of hydrogen and ambient temperature.[5,10] The reduction of aniline **1** in trifluoroacetic acid over PtO_2 proceeded smoothly at room temperature and atmospheric pressure of hydrogen. The product **4**[2a] was isolated from the reaction mixture by distillation in 70% yield (Scheme 1).



Scheme 1 Preparation of (trifluoromethyl)cyclohexylamines **4**–**6** and their *N*-Boc derivatives **7**–**9**. *Reagents and conditions*: (i) PtO_2, TFA, H_2 (1.05 bar), r.t.; (ii) a) Boc-anhydride, r.t.; b) crystallization.

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The reaction was easily scaled up without a decrease in the yield, so that 100 g of the product was conveniently obtained in one synthetic run. Noteworthy, along with product **4**, the formation of side products **4a** and **4b** (Figure 1) was also observed. Alcohol **4a** was isolated from the reaction mixture in 10% yield. GS-MS analysis of the residue after distillation revealed the presence of the mixture of stereoisomeric dicyclohexylamines **4b**. However, compound **4b** was not isolated in its individual state.

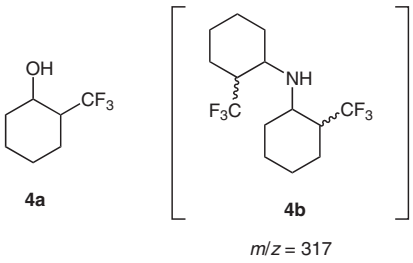

Figure 1 Side products of the hydrogenation of **1**

Reduction of anilines **2** and **3** under the above-mentioned reaction conditions proceeded in a similar manner to afford products **5** and **6** in 77% and 73% isolated yield, respectively.[2c,d,f,11] Like in the case of compound **4**, the formation of the side dicyclohexylamines was observed, while no traces of the corresponding alcohols were detected. Similarly to amine **4**, the scaled up synthesis of both **5** and **6** was subsequently performed to obtain larger quantities (>50 g) of the products in a single batch.

Notably, the reduction of aniline **1** afforded only the *cis*-isomer **4**, as judged by ^{1}H, ^{13}C, ^{19}F NMR, and LC-MS of the product. The *cis*-configuration of amine **4** was unambiguously proved by single crystal X-ray analysis of its Boc derivative **7** (Scheme 1, Figure 2). In contrast to **4**, compounds **5** and **6** were isolated as mixtures of two stereoisomers with *cis*/*trans* ratio of 2.7:1 and 1.4:1, respectively. The stereoisomer ratios were obtained from HPLC analyses while the configuration of the major components was figured out from ^{1}H NMR spectra of *N*-Boc derivatives **8** and **9** (Scheme 1). ^{1}H NMR spectra of crude **8** and **9** recorded in $CDCl_3$ contain two sets of broad singlets corresponding to axial and equatorial NCH protons at about 3.4 and 3.9 ppm, respectively, and axial and equatorial amide protons at about 4.4 and 4.6 ppm, respectively. The relative integral intensities of these sets of singlets fit well with the stereoisomeric ratios obtained for parent amines **5** and **6** by HPLC. The $CDCl_3$ ^{1}H NMR spectrum of compound **7**, that is, the pure *cis*-isomer, contains only one set of broad singlets for its equatorial NCH proton and axial amide proton at 4.1 and 4.7 ppm, respectively. At the same time F_3CCH protons of compounds **7**–**9** are represented as one broad singlet at about 2.3–2.5 ppm. Therefore, it appears that in compounds **7**–**9** chair-chair transition is slow on the NMR timescale; the bulky trifluoromethyl group always assumes the equatorial position while the position of the amide group can vary dependently on the substitution pattern as well as *cis*- or *trans*-configuration. Subsequent repeated crystallization of compounds **8** and **9** from cyclohexane allowed the isolation of their pure *cis*-isomers, which were fully characterized.

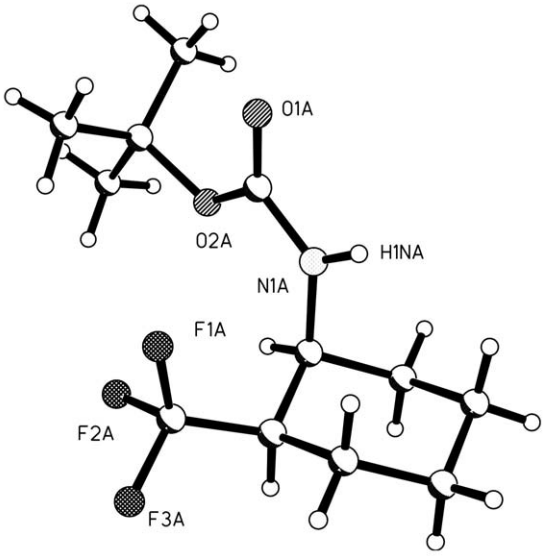

Figure 2 The molecular structure of compound **7** obtained by the single crystal X-ray analysis

In summary, we have optimized the synthesis of isomeric 2-, 3-, and 4-(trifluoromethyl)cyclohexylamines via mild PtO_2 catalyzed hydrogenation of corresponding trifluoromethylanilines. The mild hydrogenation conditions favor the formation of *cis*-isomers of all three trifluorocyclohexylamines. The stereoselectivity, however, decreases from 1,2-substituted **4** to 1,4-substituted **6** isomers. Given the rapid access and scalability of the synthesis, the title compounds can be used as versatile building blocks in organic and medicinal chemistry.

Trifluoromethylanilines **1**–**3** were purchased from commercial sources. ^{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 in ppm downfield from TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. Mass spectra were recorded on a GC/MS instrument by electronic ionization (EI).

Catalytic Hydrogenation of Trifluoromethylanilines; General Procedure

PtO_2 (6 g) was added portionwise to a degassed solution of the corresponding trifluoromethylaniline **1**–**3** (80.1 g, 0.5 mol) in TFA (200 mL). A H_2 pressure of ca. 1.05 bar was applied; and the reaction mixture was shaken at r.t. After ca. 60–80 h, the reaction was stopped. The catalyst was filtered off, and the solvent and **4a** (in the case of **1**) were removed under reduced pressure. The residue was triturated 5–10 min with hot 40% aq NaOH (200 mL) and the organic fraction was extracted with Et_2O (3 × 100 mL). The Et_2O solution was dried over NaOH plates and the solvent was removed under reduced pressure. The crude products were purified by distillation under atmospheric pressure.

2-(Trifluoromethyl)cyclohexylamine (4)
Isolated as a pure *cis*-isomer; yield 58.2 g (70%); yellow oil; bp 150–151 °C/760 Torr.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (br s, 2 H, NH_2), 1.15–1.21 (m, 1 H, CH), 1.38–1.73 (m, 7 H, CH), 1.89–2.20 (m, 1 H, CH), 3.36–3.38 (br s, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.89, 18.89, 24.81, 33.23, 44.44 (q, $^3J_{CF}$ = 2.5 Hz), 45.70 (q, $^2J_{CF}$ = 24 Hz), 127.53 (q, $^1J_{CF}$ = 279 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.08 (br s, CF_3).

GS-MS: *m*/*z* = 167 (M^+).

2-(Trifluoromethyl)cyclohexanol (4a)
The compound was obtained as a side product during the synthesis of amine **4**. After the hydrogenation had been stopped, the catalyst was filtered off, the solvent and **4a** were collected under vacuum at 10 mm Hg in a trap cooled down to –10 °C. An excess of H_2O was added and the formed suspension was extracted with Et_2O (3 × 50 mL). The combined Et_2O extracts were washed with aq $NaHCO_3$ (100 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was subjected to distillation under atmospheric pressure to provide pure alcohol **4a** as a 95:5 mixture of stereoisomers; yield: 8.3 g (10%); colorless oil; bp 157–158 °C/760 Torr. Signals of the main isomer are listed below.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.16–1.36 (m, 1 H, CH), 1.37–1.55 (m, 2 H, CH), 1.59–1.95 (m, 5 H, CH), 1.99–2.17 (m, 2 H, CH + OH), 4.23–4.36 (br m, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.88, 19.15 (q, $^3J_{CF}$ = 2 Hz), 24.63, 32.58, 45.95 (q, $^2J_{CF}$ = 24 Hz), 63.91 (q, $^3J_{CF}$ = 3 Hz), 128.52 (q, $^1J_{CF}$ = 280 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.22 (br s, CF_3).

GS-MS: *m*/*z* = 168 (M^+).

3-(Trifluoromethyl)cyclohexylamine (5)
Isolated as a mixture of *cis*- and *trans*-isomers (*cis*/*trans* ratio 2.7:1 as revealed by HPLC and ^{19}F NMR); yield: 64 g (77%); yellowish oil; bp 158–159 °C/760 Torr.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.10 (br s, CF_3, major), –73.40 (br s, CF_3, minor).

GS-MS: *m*/*z* = 167 (M^+).

4-(Trifluoromethyl)cyclohexylamine (6)
Isolated as a mixture of *cis*- and *trans*-isomers (*cis*/*trans* ratio 1.4:1 as revealed by HPLC and ^{19}F NMR); yield: 60.7 g (73%); yellowish oil; bp 158–160 °C/760 Torr.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.10 (br s, CF_3, major), –73.40 (br s, CF_3, minor).

GS-MS: *m*/*z* = 167 (M^+).

Amides 7–9; General Procedure
Boc_2O (65.4 g, 0.3 mol) was added to a solution of amine **4**–**6** (50 g, 0.3 mol) in CH_2Cl_2 (500 mL) at 0 °C. The mixture was stirred at r.t. for 4 h and then triturated with 5% aq HCl (300 mL). The organic phase was separated, washed with H_2O (2 × 300 mL), and dried (Na_2SO_4). Evaporation of the solvent provided the residue, which was recrystallized (repeatedly, if necessary) from cyclohexane to afford pure products.

2-(Trifluoromethyl)cyclohexylcarbamic Acid *tert*-Butyl Ester (7)
Yield: 68 g (85%); colorless solid; mp 84–86 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.22–1.29 (m, 1 H, HC*H*), 1.35–1.43 (m, 1 H, HC*H*), 1.41 (s, 9 H, CH_3), 1.46–1.49 (m, 1 H, HC*H*), 1.52–1.59 (m, 3 H, HC*H*), 1.65–1.68 (m, 1 H, HC*H*), 1.75–1.84 (m, 1 H, HC*H*), 2.42 (m, 1 H, F_3CCH), 4.13 (m, 1 H, HNC*H*), 6.97 (d, $^3J_{HH}$ = 10 Hz, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.71, 19.98, 24.32, 28.70, 31.30, 43.39 (q, $^2J_{CF}$ = 24 Hz), 44.17, 78.19, 127.74 (q, $^1J_{CF}$ = 279 Hz), 155.37.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –69.09 (s, CF_3).

GS-MS: *m*/*z* = 267 (M^+).

X-ray Diffraction Study[12]
The crystals suitable for an X-ray diffractional study were obtained by a slow evaporation of a diluted solution of **7** in cyclohexane. Single crystal X-ray analysis was performed on the Xcalibur-3 diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scanning, $2\Theta_{max}$ = 60°). The structure was solved by direct method using SHELXTL package.

Crystal data for **7**: $C_{12}H_{20}F_3NO_2$, colorless crystals, crystal dimensions 0.20 × 0.30 × 0.30 mm, M_r = 267.29; monoclinic, space group $P2_1/c$, *a* = 32.732(1), *b* = 12.2259(4), *c* = 21.7756(8) Å, *β* = 96.211(3)°, *V* = 8662.8(5) Å^3, *ρ* = 1.230 g·cm^{-1}, *Z* = 24, μ(MoK_α) = 0.108 $_{MM}^{-1}$, *T* = 198(2) K, *F*(000) = 3408. 67750 reflections collected, of which 15225 were unique, R_{int} = 0.058; wR_2 = 0.259 (14809 reflections), R_1 = 0.085 [8316 reflections, F>4σ(*F*), *S* = 1.033].

3-(Trifluoromethyl)cyclohexylcarbamic Acid *tert*-Butyl Ester (8)
Yield 48 g (60%); colorless solid; mp 96–97 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.05–1.15 (m, 2 H, CH), 1.20–1.25 (m, 1 H, CH), 1.33–1.39 (m, 1 H, CH), 1.41 (s, 9 H, CH_3), 1.89–1.92 (m, 2 H, CH), 1.98–2.03 (m, 1 H, CH), 2.04–2.15 (m, 1 H, CH), 2.23–2.26 (m, 1 H, CH), 3.48 (br s, 1 H, CH), 4.44 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.56, 24.15, 32.11, 32.72, 41.25 (q, $^2J_{CF}$ = 26 Hz), 48.56, 127.11 (q, $^1J_{CF}$ = 278 Hz), 155.03.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.21 (d, $^3J_{HF}$ = 11 Hz, CF_3).

GS-MS: *m*/*z* = 267 (M^+).

4-(Trifluoromethyl)cyclohexylcarbamic Acid *tert*-Butyl Ester (9)
Yield 33 g (42%); colorless solid; mp 126–127 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08–1.51 (m, 1 H, CH), 1.40 (s, 9 H, CH_3), 1.44–1.62 (m, 3 H, CH), 1.78–1.82 (m, 2 H, CH), 1.85–1.88 (m, 1 H, CH), 1.97–2.00 (m, 1 H, CH), 2.11–2.14 (m, 1 H, CH), 3.83 (br s, 1 H, CH), 4.65 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.05, 24.03, 28.42, 28.85, 31.89, 41.09 (q, $^2J_{CF}$ = 26 Hz), 48.96, 127.15 (q, $^1J_{CF}$ = 278 Hz), 155.20.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –74.09 (d, $^3J_{HF}$ = 11 Hz, CF_3).

GS-MS: *m*/*z* = 267 (M^+).

References

(1) There are 1148 N-substituted derivatives of cyclohexanamine in the 'MDL Drug Data Report' database.
(2) For the use of amines **4**, **5**, and **6** within contemporary drug discovery programs, see: (a) Inoue, T.; Hatanaka, K.; Sasaki, H.; Takahashi, F.; Higashi, Y.; Hondo, T.; Sawada, H.; Okimoto, A.; Mukoyoshi, K.; Tanaka, A.; Shirakami, S.; Nakajima, Y.; Tojo, T.; Morita, M. Patent WO2007/7919 A2, **2007**. (b) Weigand, S.; Bischoff, H.; Dittrich-Wengenroth, E.; Heckroth, H.; Lang, D.; Vaupel, A.; Woltering, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4619. (c) Aquila, B.; Lyne, P.; Pontz, T. US Patent 2009/170849, **2009**. (d) Rehwinkel, H.; Hoelscher, P.; Jaroch, S.; Suelzle, D.; Hillmann, M.; Burton, G. A.; Macdougall, F. US Patent 2004/6075 A1, **2004**. (e) Priepke, H.; Doods, H.; Kuelzer, R.; Pfau, R.; Stenkamp, D.; Roenn, R.; Pelcman, B. Patent

WO2011/48004 A1, **2011**. (f) Stewart, A. J. W.; Bloxham, J.; Dupree, T. B.; Hanrahan, P. E.; Procter, M. J.; Smyth, D.; Schofield, K. L.; Sambrook-Smith, C. P.; Krulle, T. M.; Fry, P. T.; Bradley, S. E. Patent WO 2008/142454 A1, **2008**. (g) Flohr, A.; Jakob-Roetne, R.; Norcross, R. D.; Riemer, C. US Patent 2004/242576 A1, **2004**.

(3) Since 2006 Enamine Ltd. has received 46 requests for providing amine **4**, 59 for **5**, and 119 for **6**.

(4) (a) Rylander, R. N. *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, **1967**. (b) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley: New York, **2001**.

(5) (a) Vierhapper, F. M.; Eliel, E. L. *J. Org. Chem.* **1975**, *40*, 2729. (b) Hönel, M.; Vierhapper, F. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1933. (c) Hönel, M.; Vierhapper, F. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2607. (d) Hönel, M.; Vierhapper, F. M. *Monatsh. Chem.* **1984**, *115*, 1219.

(6) Prices quoted in the ABCR catalogue (2011) for 100 g of the compounds: aniline **1**: € 16; **2**: € 12; **3**: € 205.

(7) (a) Ploeg, H. L. US Patent Application 3933815, **1976**. (b) Ziemann, H.; Alles, H.-U. German Patent DE2630562 A1, **1978**.

(8) Campbell, J. B.; Gerald, F. S.; Turner, W. W. US Patent Application 5135955, **1992**.

(9) In all experiments described in refs. 7 and 8, a statistical mixture of *cis*- and *trans*-isomers of **4**–**6** was obtained.

(10) (a) Zalesskaya, I. M.; Blakitnyi, A. N.; Saenko, E. P.; Fialkov, Yu. A.; Yagupolskii, L. M. *J. Org. Chem. USSR (Engl. Transl.)* **1980**, *16*, 1031. (b) Alexeenko, A. N.; Nazaretian, V. P. *J. Fluorine Chem.* **1994**, *69*, 241. (c) Skupinska, K. A.; Mcearchern, E. J.; Skerlj, R. T.; Bridger, G. J. *J. Org. Chem.* **2002**, *67*, 7890.

(11) Preparation of compounds **5** and **6** by other methods is mentioned in: (a) Della, E. W. *Aust. J. Chem.* **1970**, *23*, 2471. (b) Baldry, K. W.; Robinson, M. J. T. *Tetrahedron* **1977**, *33*, 1663. (c) Shukla, D.; Welter, T. R. Patent WO 2009/126203, **2009**.

(12) The final atomic coordinates, and crystallographic data for compound **7** have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk]. They are available on request quoting the deposition number CCDC 857234.

