A Facile Synthesis of Isomeric *C*-(2,2,2-Trifluoroethyl)anilines

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In memory of Prof. L. M. Yagupolskii - a father of modern fluoroorganic chemistry

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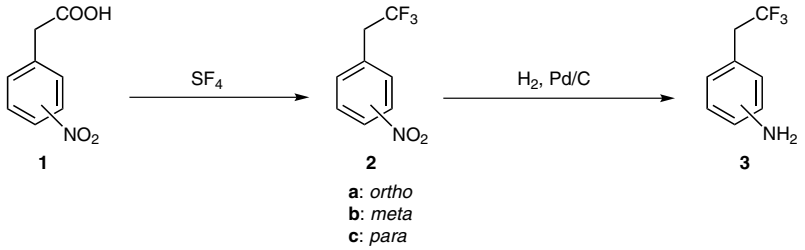
Abstract: Three isomers of *C*-(2,2,2-trifluoroethyl)aniline were prepared on a multigram scale from readily available nitrophenylacetic acids in two steps. First, the carboxy groups of the latter were converted into the trifluoromethyl moieties by treatment with sulfur tetrafluoride. The obtained 2,2,2-trifluoroethyl-substituted nitrobenzenes were reduced catalytically into the corresponding anilines.

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



Scheme 1 The synthesis of isomeric (2,2,2-trifluoroethyl)anilines

2-, 3-, and 4-(2,2,2-Trifluoroethyl)anilines (**3a**–**c**) bearing the privileged trifluoromethyl group[1,2] are presently actively being used as building blocks in many drug discovery programs.[3] These compounds are usually prepared through reduction of the corresponding (2,2,2-trifluoroethyl)nitrobenzenes **2a**–**c**.[3c,d] To our knowledge there is only one report of an alternative preparation of 2-(2,2,2-trifluoroethyl)aniline (**3a**) from aniline and 1-bromo-2,2,2-trifluoroethane.[4] Since the reduction of the majority of nitroaromatic compounds can easily be performed on a large scale, it is the limited synthetic access to **2a**–**c** that hampers the multigram production of the title anilines. There are several reports in the literature describing the preparation of **2a**–**c** on a one-gram or milligram scale. For example, Fuqua et al.[5] described a gram-scale synthesis of 1-nitro-4-(2,2,2-trifluoroethyl)benzene (**2c**) from 4-nitrobenzaldehyde and sodium chlorodifluoroacetate. Another small-scale approach involved copper(I)-catalyzed trifluoromethylation of 4-nitrobenzyl bromide with bis(trifluoromethyl)mercury (Yagupolskii et al.[6]) or (trifluoromethyl)zinc bromide (Kremlev et al.[7]) resulting in **2c**. Similarly, one-gram scale syntheses of 1-nitro-3-(2,2,2-trifluoroethyl)benzene (**2b**) and 1-nitro-4-(2,2,2-trifluoroethyl)benzene (**2c**) were reported by Nguyen et al.[8] and Duan et al.[9] starting from (difluoroethenyl)nitrobenzenes and nitrobenzyl chlorodifluoroacetates, respectively. Milligram-scale syntheses of **2b** and **2c**, contaminated by mono- and difluoroethyl derivatives, from the corresponding nitrobenzyl alcohols and (2,2,2-trichloroethyl)nitrobenzenes were described by Clark et al.[10] and Ando et al.,[11] respectively. Very recently Kawai et al.[12] demonstrated a clean and high-yielding transformation of all three nitrobenzyl bromides into (2,2,2-trifluoroethyl)nitrobenzenes **2a**–**c** by treatment with trifluoromethylsulfonium salts. Nevertheless, like in preceding reports, the latter procedure was performed on a milligram scale.

In this work we report a straightforward two-step preparation of (2,2,2-trifluoromethyl)anilines **3a**–**c** on a multigram scale. As shown in Scheme 1, the synthesis starts from readily available nitrophenylacetic acids **1a**–**c**. Treatment of the latter with three equivalents of sulfur

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tetrafluoride[13,14] at room temperature for three days afforded (2,2,2-trifluoroethyl)nitrobenzenes **2a–c** in good to high yields. Finally, palladium-on-carbon mediated hydrogenation of the nitro groups in **2a–c** furnished the target (2,2,2-trifluoroethyl)anilines **3a–c** in near quantitative yields. Both synthetic steps were carried out with batch sizes of 50–100 grams.

To conclude, we have developed a reliable two-step procedure for the multigram-scale preparation of isomeric *C*-(2,2,2-trifluoroethyl)anilines. Inasmuch as the latter are important building blocks in medical research, our method would stimulate a more active involvement of the title compounds in ongoing drug discovery programs.

Solvents were purified according to standard procedures. 2-Nitrophenylacetic acid (**1a**) and 4-nitrophenylacetic acid (**1c)** were purchased from Linsai Trade; 3-nitrophenylacetic acid was purchased from Daming Ruiheng Chemical Co, Ltd. All other materials were purchased from Aldrich and Enamine. Melting points are uncorrected. ^{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 376 MHz, respectively. Chemical shifts are reported downfield from TMS (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F) as internal standards. Mass spectra were recorded on an Agilent 1100 LC MSD SL instrument with chemical ionization (APCI) mode. Elemental analyses were carried out on a LECO CHN-900 analyzer.

(2,2,2-Trifluoroethyl)nitrobenzenes 2a–c; General Procedure
Nitrophenylacetic acid (90.5 g, 0.5 mol) was placed in 500-mL stainless steel autoclave, which was then evacuated, cooled with liquid N_2, and charged with SF_4 (162 g, 1.5 mol). The autoclave was kept at r.t. for 72 h. The gaseous products were vented off, the residue was dissolved in CH_2Cl_2, poured onto ice and triturated with concd NH_4OH (200 mL). After 2 h the mixture was filtered, the organic phase was separated, dried (Na_2SO_4), and concentrated on a rotary evaporator. The crude product was subjected to vacuum distillation.

1-Nitro-2-(2,2,2-trifluoroethyl)benzene (2a)
Yield: 43.1 g (42%); mp 21–22 °C; bp 63–65 °C/0.13 mbar.

^{1}H NMR (500 MHz): δ = 3.91 (q, $^3J_{HF}$ = 10.4 Hz, 2 H), 7.47 (d, $^3J_{HH}$ = 7.6 Hz, 1 H), 7.52 (t, $^3J_{HH}$ = 8.2 Hz, 1 H), 7.62 (t, $^3J_{HH}$ = 7.6 Hz, 1 H), 8.00 (d, $^3J_{HH}$ = 8.2 Hz, 1 H).

^{13}C NMR (125 MHz): δ = 36.25 (q, $^2J_{CF}$ = 30.7 Hz), 124.67 (q, $^3J_{CF}$ = 3 Hz), 125.21 (q, $^1J_{CF}$ = 277.7 Hz), 125.34, 129.55, 133.23, 133.4, 149.93.

^{19}F NMR (376 MHz): δ = –65.58 (t, $^3J_{FH}$ = 10.4 Hz).

LC-MS: *m*/*z* = 205 (M^+).

Anal. Calcd for $C_8H_6F_3NO_2$: C, 46.84; H, 2.95; N, 6.83. Found: C, 46.56; H, 3.18; N, 6.64.

1-Nitro-3-(2,2,2-trifluoroethyl)benzene (2b)
Yield: 79.4 g (78%); mp 45–46 °C; bp 90–92 °C/0.2 mbar.

^{1}H NMR (500 MHz): δ = 3.48 (q, $^3J_{HF}$ = 10.4 Hz, 2 H), 7.55 (t, $^3J_{HH}$ = 7.9 Hz, 1 H), 7.63 (d, $^3J_{HH}$ = 7.9 Hz, 1 H), 8.18 (s, 1 H), 8.21 (d, $^3J_{HH}$ = 7.9 Hz, 1 H).

^{13}C NMR (125 MHz): δ = 39.86 (q, $^2J_{CF}$ = 30.7 Hz), 123.29, 125.10, 125.19 (q, $^1J_{CF}$ = 277 Hz), 129.77, 132.05 (q, $^3J_{CF}$ = 3 Hz), 136.20, 148.46.

^{19}F NMR (376 MHz): δ = –66.29 (t, $^3J_{FH}$ = 10.4 Hz).

LC-MS: *m*/*z* = 205 (M^+).

Anal. Calcd for $C_8H_6F_3NO_2$: C, 46.84; H, 2.95; N, 6.83. Found: C, 46.72; H, 3.11; N, 6.79.

1-Nitro-4-(2,2,2-trifluoroethyl)benzene (2c)
Yield: 92.3 g (90%); mp 66–67 °C; bp 95–97 °C/0.2 mbar.

^{1}H NMR (500 MHz): δ = 3.49 (q, $^3J_{HF}$ = 10.4 Hz, 2 H), 7.48 (d, $^3J_{HH}$ = 8.4 Hz, 2 H), 8.22 (d, $^3J_{HH}$ = 8.4 Hz, 2 H).

^{13}C NMR (125 MHz): δ = 39.97 (q, $^2J_{CF}$ = 30.3 Hz), 123.82, 125.12 (q, $^1J_{CF}$ = 277 Hz), 131.16, 137.26 (q, $^3J_{CF}$ = 2.7 Hz), 147.96.

^{19}F NMR (376 MHz): δ = –66.00 (t, $^3J_{FH}$ = 10.4 Hz).

LC-MS: *m*/*z* = 205 (M^+).

Anal. Calcd for $C_8H_6F_3NO_2$: C, 46.84; H, 2.95; N, 6.83. Found: C, 46.70; H, 3.07; N, 6.68.

***C*-(2,2,2-Trifluoroethyl)anilines 3a–c; General Procedure**
A soln of nitro compound **2** (97 g, 0.473 mol) in MeOH (500 mL) was stirred under atmosphere of H_2 at r.t. and ambient pressure in the presence of 10% Pd/C (10 g) until consumption of H_2 ceased. The catalyst was filtered off and the filtrate was concentrated and distilled under vacuum.

2-(2,2,2-Trifluoroethyl)aniline (3a)
Yield: 78.7 g (95%); mp 46–47 °C; bp 73–75 °C/16 mbar.

^{1}H NMR (500 MHz): δ = 3.34 (q, $^3J_{HF}$ = 11.0 Hz, 2 H), 3.69 (br s, 2 H), 6.74 (d, $^3J_{HH}$ = 7.9 Hz, 1 H), 6.80 (t, $^3J_{HH}$ = 7.4 Hz, 1 H), 7.15 (m, 2 H).

^{13}C NMR (125 MHz): δ = 35.94 (q, $^2J_{CF}$ = 30.0 Hz), 115.51 (q, $^3J_{CF}$ = 3 Hz), 117.09, 119.42, 126.48 (q, $^1J_{CF}$ = 277.7 Hz), 129.42, 132.42, 145.41.

^{19}F NMR (376 MHz): δ = –65.62 (t, $^3J_{FH}$ = 10.4 Hz).

LC-MS: *m*/*z* = 176 ($M + H^+$).

Anal. Calcd for $C_8H_8F_3N$: C, 54.86; H, 4.60; N, 8.00. Found: C, 54.74; H, 4.75; N, 7.69.

3-(2,2,2-Trifluoroethyl)aniline (3b)
Yellowish oil; yield: 75.4 g (91%); bp 91–92 °C/16 mbar.

^{1}H NMR (500 MHz): δ = 3.29 (q, $^3J_{HF}$ = 11.0 Hz, 2 H), 3.71 (br s, 2 H), 6.63 (s, 1 H), 6.68 (d, $^3J_{HH}$ = 7.8 Hz, 1 H), 6.71 (d, $^3J_{HH}$ = 7.8 Hz, 1 H), 7.16 (t, $^3J_{HH}$ = 7.8 Hz, 1 H).

^{13}C NMR (125 MHz): δ = 40.10 (q, $^2J_{CF}$ = 29.3 Hz), 114.71, 116.62, 120.23, 125.89 (q, $^1J_{CF}$ = 277 Hz), 129.50, 131.19 (q, $^3J_{CF}$ = 3 Hz), 146.69.

^{19}F NMR (376 MHz): δ = –66.15 (t, $^3J_{FH}$ = 11.0 Hz).

LC-MS: *m*/*z* = 176 ($M + H^+$).

Anal. Calcd for $C_8H_8F_3N$: C, 54.86; H, 4.60; N, 8.00. Found: C, 54.70; H, 4.78; N, 7.86.

4-(2,2,2-Trifluoroethyl)aniline (3c)
Yield: 80.3 g (97%); mp 45–46 °C; bp 108–110 °C/18.6 mbar.

^{1}H NMR (500 MHz): δ = 3.23 (q, $^3J_{HF}$ = 10.9 Hz, 2 H), 3.55 (br s, 2 H), 6.65 (d, $^3J_{HH}$ = 8.3 Hz, 2 H), 7.06 (d, $^3J_{HH}$ = 8.3 Hz, 2 H).

^{13}C NMR (125 MHz): δ = 39.44 (q, $^2J_{CF}$ = 29.7 Hz), 115.16, 119.85 (q, $^3J_{CF}$ = 2.7 Hz), 126.08 (q, $^1J_{CF}$ = 276.3 Hz), 131.11, 146.33.

^{19}F NMR (376 MHz): δ = –66.99 (t, $^3J_{FH}$ = 10.9 Hz).

LC-MS: *m*/*z* = 176 ($M + H^+$).

Anal. Calcd for $C_8H_8F_3N$: C, 54.86; H, 4.60; N, 8.00. Found: C, 54.67; H, 4.73; N, 7.82.

References

(1) For recent reviews and relevant reports, see: (a) Mikami, K.; Fustero, S.; Sánchez-Roselló, M.; Aceña, J. L.; Soloshonok, V. A.; Sorochinsky, A. E. *Synthesis* **2011**, 3045. (b) Sorochinsky, A. E.; Soloshonok, V. A. *J. Fluorine Chem.* **2010**, *131*, 127. (c) O'Hagan, D. *J. Fluorine Chem.*

2010, *131*, 1071. (d) Artamonov, O. S.; Mykhailiuk, P. K.; Voievoda, N. M.; Volochnyuk, D. M.; Komarov, I. V. *Synthesis* **2010**, 443. (e) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (f) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4360. (g) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, 317. (h) Kirsch, P. *Modern Fluoroorganic Chemistry;* Wiley-VCH: Weinheim, **2004**.

(2) Of ca. 1350 small-molecule FDA-approved drugs, 43 contain the trifluoromethyl group. See: Wishart, D. S.; Knox, C.; Guo, A. C.; Cheng, D.; Shrivastaya, S.; Tzur, D.; Gautam, B.; Hassanali, M. *Nucleic Acids Res.* **2008**, *36*, D901.

(3) (a) Zhu, G.-D.; Gong, J.; Gandhi, V. B.; Woods, K.; Luo, Y.; Liu, X.; Guan, R.; Klinghofer, V.; Johnson, E. F.; Stoll, V. S.; Mamo, M.; Li, Q.; Rosenberg, S. H.; Giranda, V. L. *Bioorg. Med. Chem.* **2007**, *15*, 2441. (b) Gujjar, R.; Mazouni, F. E.; White, K. L.; White, J.; Creason, S.; Shackleford, D. M.; Deng, X.; Charman, W. N.; Bathurst, I.; Burrows, J.; Floyd, D. M.; Matthews, D.; Buckner, F. S.; Charman, S. A.; Phillips, M. A.; Rathod, P. K. *J. Med. Chem.* **2011**, *54*, 3935. (c) Jimonet, P.; Audiau, F.; Barreau, M.; Blanchard, J.-C.; Boireau, A.; Bour, Y.; Coléno, M.-A.; Doble, A.; Doerflinger, G.; Huu, D. H.; Donat, M.-H.; Duchesne, J. M.; Ganil, P.; Guérémy, C.; Honoré, E.; Just, B.; Kerphirique, R.; Gontier, S.; Hubert, P.; Laduron, P. M.; Le Blevec, J.; Meunier, M.; Miquet, J.-M.; Nemecek, C.; Pasquet, M.; Piot, O.; Pratt, J.; Rataud, J.; Reibaud, M.; Stutzmann, J.-M.; Mignani, S. *J. Med. Chem.* **1999**, *42*, 2828. (d) Xu, H.; Maga, J.; Focher, F.; Smith, E. R.; Spadari, S.; Gambino, J.; Wright, G. E. *J. Med. Chem.* **1995**, *38*, 39. (e) Audiau, F.; James, C. US 5,236,940, **1993**.

(4) Dupré, V. M.; Pechmèze, J. P. E.; Sureau, R. F. M. FR 2,265,739, **1974**.

(5) Fuqua, S. A.; Duncan, W. G.; Silverstein, R. M. *J. Org. Chem.* **1965**, *30*, 1027.

(6) Kondratenko, N. V.; Vechirko, E. P.; Yagupolskii, L. M. *Synthesis* **1980**, 932.

(7) Kremlev, M. M.; Tyrra, W.; Mushta, A. I.; Naumann, D.; Yagupolskii, Y. L. *J. Fluorine Chem.* **2010**, *131*, 212.

(8) Nguyen, B. V.; Burton, D. J. *J. Org. Chem.* **1997**, *62*, 7758.

(9) Duan, J.-X.; Chen, Q.-Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 725.

(10) Clark, J. H.; McClinton, M. A.; Blade, R. J. *J. Fluorine Chem.* **1992**, *59*, 257.

(11) Ando, A.; Miki, T.; Kumadaki, I. *J. Org. Chem.* **1988**, *53*, 3637.

(12) Kawai, H.; Furukawa, T.; Nomura, Y.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2011**, *13*, 3596.

(13) For comprehensive reviews on the use of SF_4 in organic synthesis, see: (a) Burmakov, A. I.; Kunishenko, B. V.; Alekseeva, L. A.; Yagupolskii, L. M. In *New Fluorinating Agents in Organic Synthesis;* German, L.; Zemskov, S. V.; Alekseeva, L. A., Eds.; Springer: Berlin, **1989**. (b) Dmowski, W. *Houben Weyl, Methods of Organic Chemistry,* Vol. E10a; Baasner, B.; Hagemann, H.; Tatlow, J. C., Eds.; Thieme: Stuttgart, **1999**, 321.

(14) Our contributions in this field: (a) Radchenko, D. S.; Mykhailiuk, P. K.; Bezdudny, A. V.; Komarov, I. V. *Synlett* **2009**, 1827. (b) Sibgatulin, D. A.; Bezdudny, A. V.; Mykhailiuk, P. K.; Voievoda, N. M.; Kondratov, I. S.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2010**, 1075. (c) Bezdudny, A. V.; Klukovsky, D.; Mykhailiuk, P. K.; Shishkin, O. V.; Pustovit, Y. M. *Synthesis* **2011**, 119. (d) Bezdudny, A. V.; Alekseenko, A. N.; Mykhailiuk, P. K.; Manoilenko, O. V.; Shishkin, O. V.; Pustovit, Y. M. *Eur. J. Org. Chem.* **2011**, 1782. (e) Gerus, I. I.; Mironetz, R. X.; Kondratov, I. S.; Bezdudny, A. V.; Dmytriv, Y. V.; Shishkin, O. V.; Starova, V. S.; Zaporozhets, O. A.; Tolmachev, A. A.; Mykhailiuk, P. K. *J. Org. Chem.* **2012**, *77*, 47.

