An efficient synthesis of 5-chloro-2, 3, 4-trifluorobenzoic acid

Shuitao Yu[a,c], Weiyou Zhou[a,b], Zhengjun Xia[a,c], Song Lin[a,c] and Zaixin Chen[a,c*]

[a]*Yabang Medical Research Institute, Changzhou 213145, P.R. China*
[b]*Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology, Changzhou University, Changzhou 213164, P.R. China*
[c]*Jiangsu Novel Quinolone Antibacterial Drugs Engineering Research Center, Changzhou 213145, P.R. China*

5-Chloro-2, 3, 4-trifluorobenzoic acid, a key intermediate for preparing quinolone-3-carboxylic acid derivatives, was synthesised from the commercially available 2, 3, 4, 5-trifluorobenzoic acid in excellent yield by a reaction sequence involving nitration, selective reduction, diazotisation and chlorination.

Keywords: quinolone-3-carboxylic acids derivatives, 5-chloro-2, 3, 4-trifluorobenzoic acid

Quinolone-3-carboxylic acids derivatives have recently attracted attention due to their high activity and favourable pharmacokinetic properties as antibacterial agents. 5-Chloro-2, 3, 4-trifluorobenzoic acid derivatives are valuable intermediates for the synthesis of these compounds[1,2] such as compound **1**.[3] However, there is only one method for the preparation of the title compound **2** (Scheme 1) using tetrachlorobenzoyl chloride (**3**) as the starting matierial. Heating compound **3** with potassium fluoride in sulfolane at elevated temperature resulted in the product but the yield was low, because 2, 4-difluoro-3, 5-dichloro benzoyl fluoride was also formed as a byproduct.[3] This is unattractive for the large-scale synthesis of **2** due to the low yield. Consequently, we have developed a simple and efficient route for the preparation of 5-chloro-2, 3, 4-trifluorobenzoic acid. The synthetic route is shown in Scheme 1.

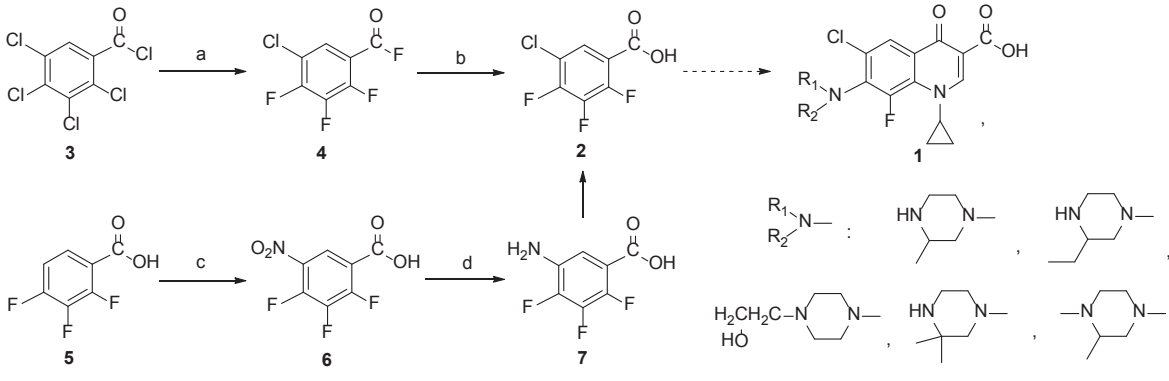
2, 3, 4-Trifluorobenzoic acid (**5**) was treated with concentrated nitric acid and sulfuric acid to give **6** in a high yield (97.1%) when the water produced in the process was removed by distillation. Compound **6** was reduced with H_2 catalysed by Pd/C to generate 2, 3, 4-trifluoro-5-aminobenzoic acid (**7**) in high yield (98.2%) and in an environmentally friendly method.[4] No reduction of the carboxylic acid group to an aldehyde or alcohol was observed. After completion of the reduction, compound **7** was converted to the required compound (**2**) by diazotisation and chlorination with CuCl/HCl in the final step.[5]

Experimental

All reactions were monitored by TLC. Melting points were determined by the capillary method without correction. IR spectra were recorded on NICOLET Impact 410FT-IR instrument. NMR and HRESIMS spectra were recorded on a Bruker Avance 300 NMR spectrometer and a Agilent 6530 Accurate-Mass Q-TOF LC/MS spectrometer, respectively.

5-Nitro-2,3,4-trifluorobenzoic acid (**6**): A stirred solution of 2, 3, 4-trifluorobenzoic acid (**5**) (10 g, 56.8 mmol) in concentrated H_2SO_4 (98%, 33.0 g) was treated dropwise with the mixture of concentrated HNO_3 (65%, 6.0g) and H_2SO_4 (98%, 6.3g) for 3.5 h between 90 and 95 °C. The reaction progress was monitored by TLC (30% ethyl acetate in hexane). After completion of the reaction, the reaction mixture was cooled to room temperature and ice-water (50g) was added. The precipitation was separated by centrifugation and dried between 50 and 55 °C for 8 h. The crude product was purified by column chromatography using 20% ethylacetate:hexane as eluent. The solvent was removed under reduced pressure to afford a white solid **6** (12.2 g) in 97.1% yield; m.p. 125–126 ℃. IR (KBr) /cm^{-1}: 3258, 3047, 1681, 1479, 1238, 887. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.9 (br s, 1H), 8.39–8.44 (q, J= 7.29 Hz, 1 H), 8.42 (s, 1H, D_2O exchangeable). ^{13}C NMR(DMSO-d_6, 300 MHz): δ 162.0 (s), 151.9–155.6 (m, $J_{C\text{-}F}$ = 268.9 Hz), 146.0–149.9 (m, $J_{C\text{-}F}$ = 269.6 Hz), 139.0–142.8 (m, $J_{C\text{-}F}$ = 251.6 Hz), 133.5 (s) , 116.6–116.8 (q, $J_{C\text{-}F}$ = 9.0 Hz), 112.9 (d, $J_{C\text{-}F}$ = 2.3 Hz). HRESIMS calcd for $C_7HF_3NO_4$ [M–H]$^-$ 219.9858; found 219.9863.

5-Amino-2,3,4-trifluorobenzoic acid (**7**): Compound **6** (12.0 g, 54.3 mmol), Pd/C (10%, 1.2g), and methanol (120 mL) were placed in a autoclave (250 mL). The autoclave was purged with H_2 three times to remove air, and the reaction mixture was stirred with a balloon of H_2 at room temperature for 6.0 h under a pressure between 1.0 and 1.2 MPa. After the reaction, the resultant mixture was transferred into a tube and the solid was separated by centrifugation. The solvent was removed under reduced pressure to afford a white solid **7** (10.2 g) in 98.2% yield; m.p. 157–158 ℃. IR (KBr) /cm^{-1}: 3465, 3117, 3265, 3031, 1685, 1335, 872. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.89 (br s, 2H), 7.15–7.21 (m, J= 8.01 Hz, 1 H). ^{13}C NMR(DMSO-d_6, 300 MHz): δ 164.0–164.1 (t, $J_{C\text{-}F}$ = 3.0 Hz), 140.1–143.5 (m, $J_{C\text{-}F}$ = 246.8 Hz), 140.0–143.4 (m, $J_{C\text{-}F}$ = 234.0 Hz), 138.4–142.0 (m, $J_{C\text{-}F}$ = 243.4 Hz), 132.9–133.0 (d, $J_{C\text{-}F}$ = 9.8 Hz) , 115.7–115.9 (q, $J_{C\text{-}F}$ = 7.9 Hz), 111.6–111.7 (q, $J_{C\text{-}F}$ = 5.3 Hz). HRESIMS calcd for $C_7H_3F_3NO_2$ [M–H]$^-$ 190.0116; found 190.0121.



Scheme 1 Reagents and conditions: (a) KF, sulfolane; (b) hydrolysis; (c) HNO_3 (65%), H_2SO_4 (98%); (d) H_2, Pd/C; (e) HCl/$NaNO_2$, CuCl.

* Correspondent. E-mail: zaixin-chen@163.com

5-Chloro-2,3,4-trifluorobenzoic acid (**2**): A mixture of compound **7** (10.0 g, 52.3 mmol), concentrated hydrochloric acid (47.6 g), water (119.0 g), CuCl (27.5 g, 277.8 mmol) and dichloromethane (107 mL) was stirred at 0 ℃. To this emulsion a solution of $NaNO_2$ (4.8 g, 69.6 mmol) in water (56.0 mL) was added dropwise to the cooled reaction mixture. The reaction mixture was stirred for another 4 hours at room temperature. The reaction progress was monitored by TLC (30% ethyl acetate in hexane). The reaction mixture extracted with dichloromethane (2 × 20 mL) and the combined organic phases were washed with $Na_2S_2O_4$ solution (10%, 2 × 20 mL), HCl solution (5%, 2 × 20 mL), decolourised with activated charcoal and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford a white solid. The crude product was washed with a mixture of hexane (5 mL) and ethyl acetate (2 mL), and then dried between 50 and 55 ℃ for 5 h. The product (**2**) was obtained as a white solid (7.1 g, 64.5%); m.p. 155–156 ℃. IR (KBr) /cm^{-1}: 3297, 3085, 1660, 873. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.4 (br s, 1H), 7.87–8.07 (t, J= 7.8 Hz, 1H), 8.01–8.08 (t, J= 7.8 Hz, 1H, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 300 MHz): δ 162.5 (s), 148.3–150.5 (m, $J_{C\text{-}F}$ = 261.3 Hz), 148.2–150.3 (m, $J_{C\text{-}F}$ = 275.6 Hz), 139.4–141.6 (m, $J_{C\text{-}F}$ = 275.0 Hz), 126.2 (d, $J_{C\text{-}F}$ = 2.5 Hz) , 116.3–116.4 (m, $J_{C\text{-}F}$ = 14.9 Hz), 112.7 (t, $J_{C\text{-}F}$ = 30.0 Hz). HRESIMS calcd for $C_7HClF_3O_2$ $[M–H]^-$ 208.9617; found 208.9623.

Received 3 May 2015; accepted 19 May 2015
Paper 1503341 doi: 10.3184/174751915X14322269913981
Published online : 4 June 2015

References

1 Z.F. Zhang, A.Z. Yu and W.C. Zhou, *Bioorg. Med. Chem.*, 2007, **15**, 7274.
2 Y. Zhi, L.X. Gao, Y. Jin, C.L. Tang, J.Y. Li, J. Li and Y.Q. Long, *Bioorg. Med. Chem.*, 2014, **22**, 3670.
3 E. Klauke, U. Petersen and K. Grohe, US5072038, 1991-12-10.
4 L.Y. Li, H.X. Zhao, J.Y. Wang and R.H. Wang, *ACSNano*, 2014, **8**, 5352.
5 D.S.N. Parker, B.B. Dangi, R.I. Kaiser, A. Jamal, M.N. Ryazantsev, K. Morokuma, A. Korte and W. Sander, *J. Phys. Chem. A*, 2014, **118**, 2709.