An efficient synthesis of 2,4-difluoro-3,5-dichlorobenzoic acid

Weiyou Zhou[a,b], Shuitao Yu[a,c], Zhengjun Xia[a,c], Mingguang Zhang[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*

2,4-Difluoro-3,5-dichlorobenzoic acid, as a key intermediate for preparing quinolone-3-carboxylic acids, was synthesised from the commercially available 2,4-difluoro-3-chlorobenzoic acid in excellent yield by a reaction sequence involving nitration, selective reduction, diazotisation and chlorination.

Keywords: quinolone-3-carboxylic acids derivatives , 2,4-difluoro-3,5-dichlorobenzoic acid, synthesis

Since its discovery in 2006, quinolone-3-carboxylic acid derivatives, which are believed to be antibacterial agents, have attracted a great deal of attention due to their high activity and favourable pharmacokinetic properties. 2,3,4,5-Tetrahalogenated benzoic acid derivatives are valuable intermediates in the synthesis of these compounds.[1,2] 2,4-Difluoro-3,5-dichlorobenzoic acid (**1**) is the key intermediate for the synthesis of **2** and **3**,[3] which are potential antibacterial agents. However, there has been only one method for the preparation of the title compound **1** (Scheme 1). Heating tetrachlorobenzoyl chloride (**4**) with potassium fluoride in sulfolane at elevated temperature can give the compound **5**, and the title compound could then be obtained through hydrolysis of **5**. However, the yield of **5** was very low, because 5-chloro-2,3,4-trifluorobenzoyl fluoride was also formed as a co-product in the process.[3,4] To avoid the problem, we have developed a simple and efficient route for the synthesis of 2,4-difluoro-3,5-dichlorobenzoic acid **1** as shown in Scheme 1.

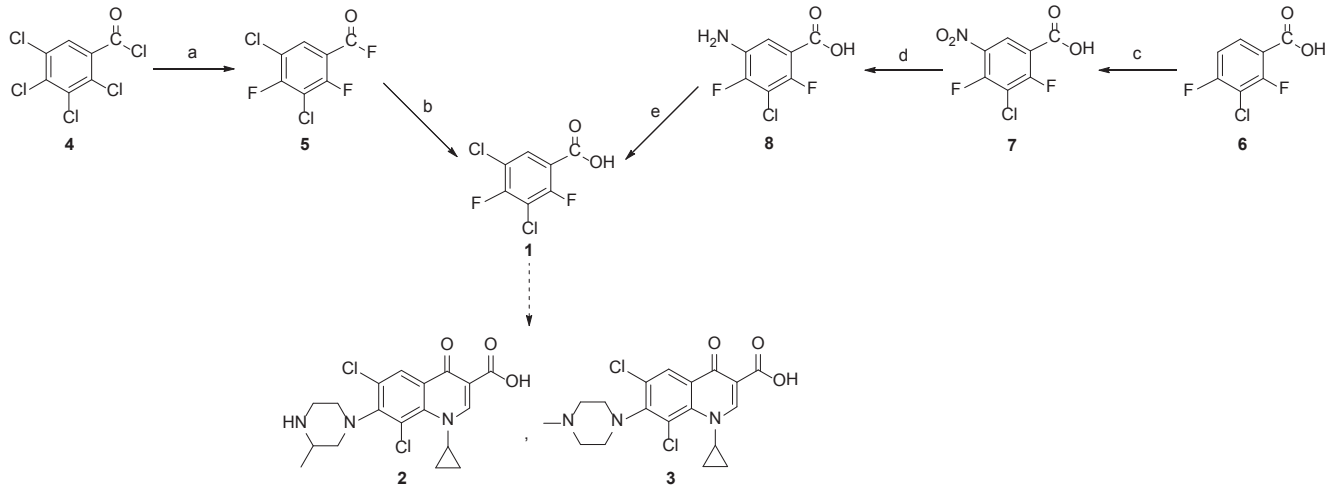
In the preferred route, 2,4-difluoro-3-chlorobenzoic acid (**6**) was chosen as the precusor. Treatment of **6** with concentrated nitric acid provided **7** in a high yield (94.6%) when the water produced in the process was removed by distillation. Compound **7** was reducted by H_2 catalysed by Pd/C to generate 2,4-difluoro-3-chloro-5-aminobenzoic acid (**8**) in moderate yield (87.0%) in an environmentally friendly method.[5] No reduction of the carboxylic acid group to aldehyde nor alcohol was observed. After completion of reduction, compound **8** was converted to the objective compound by diazotisation and chlorination by CuCl/HCl in the final step.[6]

Experimental

All reactions were monitored by TLC. Melting points were determined by the capillary method and are uncorrected. IR spectra were recorded on a NICOLET Impact 410FT-IR instrument. NMR and HRESIMS spectra were recorded on a Bruker Avance 300 NMR spectrometer and an Agilent 6530 Accurate-Mass Q-TOF LC/MS spectrometer, respectively.

5-Nitro-2,4-difluoro-3-chlorobenzoic acid (**7**): A stirred solution of 2,4-difluoro-3-chlorobenzoic acid (**6**) (15 g, 77.9 mmol) in concentrated H_2SO_4 (98%, 49.5 g) was treated dropwise with the mixture of concentrated HNO_3 (65%, 9.0 g) and H_2SO_4 (98%, 9.3 g) for 1h at 90 ℃. 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 (12 g) was added. The precipitate was separated by centrifugation and dried between 40–45 ℃ for 18 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 yellow solid **7** (17.5 g) in 94.6% yield. m.p. 123–124 ℃. IR ν (cm^{-1}): 3267, 3053, 1689, 1529, 1319, 891. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.9 (br s, 1H), 8.57(t, J= 8.19 Hz, 1H), 8.57 (t, J= 7.83 Hz, 1H, D_2O exchangeable).^{13}C NMR (300 MHz, DMSO-d_6): δ 161.9–162.0 (d, $J_{C\text{-}F}$= 13.1 Hz), 158.5–162.2 (q, $J_{C\text{-}F}$= 267.8 Hz), 152.6.–156.2 (q, $J_{C\text{-}F}$= 268.5 Hz), 133.8–134.0 (q, $J_{C\text{-}F}$= 7.1 Hz), 127.4 (d, $J_{C\text{-}F}$= 1.5 Hz), 116.7–116.9 (q, $J_{C\text{-}F}$= 12.0 Hz), 112.9–113.4 (q, $J_{C\text{-}F}$= 22.5 Hz). HRESIMS calcd for $C_7H_2ClF_2NO_4$ $[M\text{-}H]^-$ 235.9562; found 235.9566.

2,4-Difluoro-3-chloro-5-aminobenzoic acid (**8**): Compound **7** (17.1 g, 72.0 mmol), Pd/C (10%, 1.71 g), and methanol (180 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



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

a balloon of H_2 at room temperature for 6.5 h under a pressure of 0.6 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 **8** (13.0 g) in 87.0% yield. m.p. 156–157 ℃. IR ν (cm^{-1}): 3473, 3128, 3279, 3041, 1673, 1348, 883. ^{1}H NMR (300 MHz, DMSO-d_6): 13.1(1H, s), 7.31 (1H, br s, CH), 6.51(2H, s). ^{13}C NMR (500 MHz, DMSO-d_6): δ 167.2, (d, $J_{C\text{-}F}$ = 3.8 Hz), 151.0–153.0 (d, $J_{C\text{-}F}$ = 250.0 Hz), 150.6–152.6 (d, $J_{C\text{-}F}$ = 250.0 Hz), 135.1–135.2 (q, $J_{C\text{-}F}$ = 12.5 Hz), 117.9 (d, $J_{C\text{-}F}$ = 6.3 Hz), 117.5–117.6 (q, $J_{C\text{-}F}$ = 10.0 Hz), 112.1–112.5 (q, $J_{C\text{-}F}$ = 18.8 Hz). HRESIMS calcd for $C_7H_2ClF_2NO_4$ $[M\text{-}H]^-$ 205.9820; found 205.9825.

2,4-Difluoro-3,5-dichlorobenzoic acid (**1**): A mixture of compound **8** (12.0 g, 57.8 mmol), concentrated hydrochloric acid (72.0 g), water (72.0 g), CuCl (21.3 g, 215.2 mmol) and dichloromethane (174.0 g) was stirred at 0 ℃. To this emulsion a solution of $NaNO_2$ (5.1 g, 73.9 mmol) in water (72.0 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 × 30 mL) and the combined organic phases were washed with $Na_2S_2O_4$ solution (10%, 2 × 24 mL), HCl solution (5%, 2 × 24 mL), decolourised with activated carbon 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 (6 mL) and ethyl acetate (3 mL), and then dried between 50 and 55 ℃ for 7.5 h. The compound was obtained as a white solid (3.8 g, 12.9%). m.p. 155–156 ℃. IR ν (cm^{-1}): 3295, 3061, 1659, 852. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.9 (br s, 1 H), 7.98–8.03 (t, *J*= 7.71 Hz, 1H), 7.95–8.00 (t, *J*= 7.71 Hz, 1H, D_2O exchangeable). ^{13}C NMR (300 MHz, DMSO-d_6): δ =162.4–162.5 (d, $J_{C\text{-}F}$ = 3.8 Hz), 154.6–158.1 (q, $J_{C\text{-}F}$ = 264.0 Hz), 154.4–157.8 (q, $J_{C\text{-}F}$ = 252.8 Hz), 131.2 (d, $J_{C\text{-}F}$ = 2.3 Hz), 117.4–117.6 (q, $J_{C\text{-}F}$ = 11.6 Hz) , 116.3–116.6 (q, $J_{C\text{-}F}$ = 18.0 Hz), 111.4–111.9 (q, $J_{C\text{-}F}$ = 20.3 Hz). HRESIMS calcd for $C_7H_2Cl_2F_2O_2$ $[M\text{-}H]^-$ 224.9322; found 224.9326.

Received 1 March 2015; accepted 8 April 2015
Paper 1503223 doi: 10.3184/174751915X14295255352061
Published: 08 May 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 E. Klauke, U. Petersen and K. Grohe, DE3420796, 1985-12-05.
5 L.Y. Li, H.X. Zhao, J.Y. Wang and R.H. Wang, *ACSNano*, 2014, **8**, 5352.
6 D.S.N. Parker, B.B. Dangi, R.I. Kaiser, A. Jamal, M.N. Ryazantsev, K. Morokuma, A. Korte and W. Sander, *J. Phy. Chem. A*, 2014, **118**, 2709.