An efficient synthesis of 3,5-dimethoxy-2,4-difluorobenzoic acid

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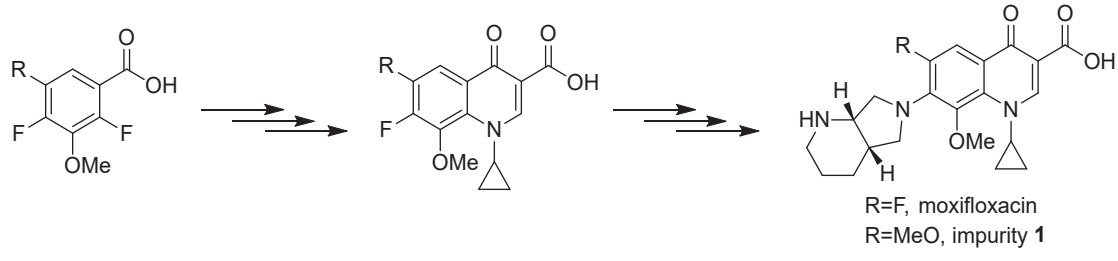
3,5-Dimethoxy-2,4-difluorobenzoic acid, as a key intermediate for preparing an impurity of moxifloxacin, was synthesised from 2,3,4,5-tetrafluorobenzoic acid in moderate yield by nitration, methoxyl substitution, reduction of NO_2, diazotisation and reduction. The structures of the intermediates and the target compound were identified and determined with IR, NMR and HRMS (ESI).

Keywords: 3,5-dimethoxy-2,4-difluorobenzoic acid, moxifloxacin, impurity

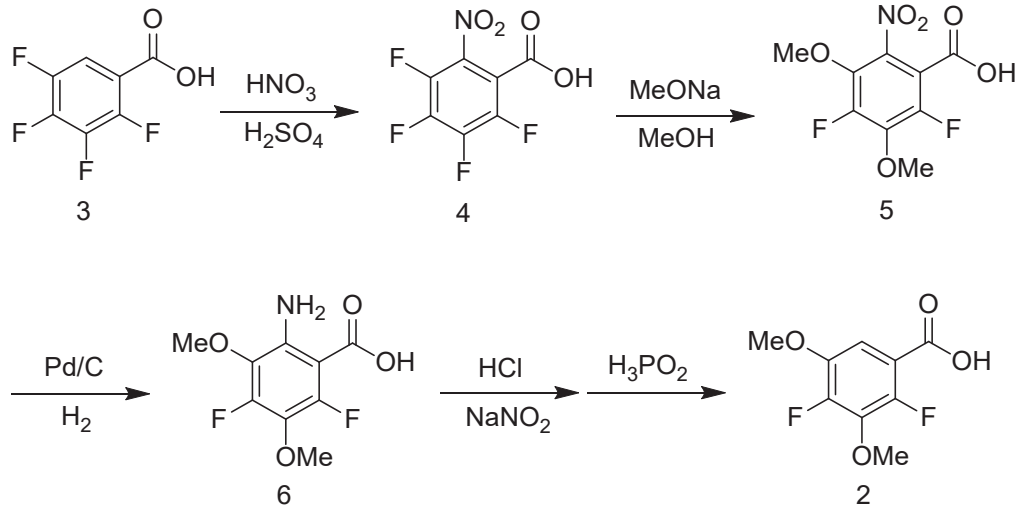
Moxifloxacin hydrochloride is a fourth-generation synthetic fluoroquinolone antibacterial agent developed by Bayer, and was firstly approved by the US FDA in 1999. During the course of our study on preparation of the active pharmaceutical ingredient of moxifloxacin hydrochloride, the content of an impurity, 1-cyclopropyl-6,8-dimethoxy-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**1**), should be controlled.[1] The impurity **1** may be generated from 3,5-dimethoxy-2,4-difluorobenzoic acid (**2**), which may be a trace contaminant of 3-methoxy-2,4,5-trifluorobenzoic acid, the starting material for synthesis of moxifloxacin, as shown in Scheme 1.

For the quality control of moxifloxacin, a reference sample of impurity **1** was required. Compound **2** can be used as the starting material for its synthesis. However, compound **2** is not commercially available and there were few reports on synthesis of compound **2**. One possible way to obtain compound **2** is to use tetrahalogenated benzoic acids as the starting material.[2–4] On treatment of tetrahalogenated benzoic acids with a methoxide reagent, *e.g.* sodium methoxide, the halogen atoms can be substituted by methoxyl groups to obtain anisole derivatives. However, the selectivity of the substitution reaction was very low and resulted in a mixture of mono and multisubstituted products.[5,6] In order to obtain an *ortho*- and *para*-methoxy product selectively, a nitro group was introduced as a directing group.[7] Therefore, compound **2** can be obtained with high selectivity using 2,3,4,5-tetrafluorobenzoic acid (**3**) as starting material followed by nitration, methoxyl substitution, reduction of NO_2, diazotisation and reduction. The synthetic route was illustrated in Scheme 2.

In this sequence, treatment of 2,3,4,5-tetrafluorobenzoic acid (**3**) with concentrated nitric acid and sulfuric acid afforded



Scheme 1



Scheme 2

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6-nitro-2,3,4,5-tetrafluorobenzoic acid (**4**). Because of the electron-withdrawing effects of the F and COOH groups in compound **3**, the nitration reaction of **3** was less efficient and required a high reaction temperature. The yield of compound **4** was 77%. Compound **4** was reacted with sodium methoxide to generate 3,5-dimethoxy-6-nitro-2,4-difluorobenzoic acid (**5**) in 75% yield**.** Hydrogenation of **5** catalysed by Pd/C afforded 3,5-dimethoxy-6-amino-2,4-difluorobenzoic acid (**6**) in excellent yield (96%). After hydrogenation, compound **6** was converted to the target compound **2** by diazotisation and reduction with H_3PO_2/HCl in one step.

Experimental

All reactions were monitored by TLC. Melting points were determined by the capillary method without correction. IR spectra were recorded on Agilent Technologies Cary 630 FTIR instrument. ^{1}H NMR and HRMS (ESI) spectra were recorded on a Bruker Avance 300 NMR spectrometer and an Agilent 6530 Accurate-Mass Q-TOF LC/MS spectrometer respectively.

6-Nitro-2,3,4,5-tetrafluorobenzoic acid (**4**)

A solution of 2,3,4,5-tetrafluorobenzoic acid (**3**) (15.0 g, 77.3 mmol) in concentrated H_2SO_4 (98%, 84.0 g) was added dropwise to a solution of concentrated HNO_3 (65%, 10.5 g) and H_2SO_4 (98%, 15 g) in an ice-bath, the temperature was kept below 50 °C in the addition process. Then the mixture was allowed to stir for another 12 h at 100 °C until TLC (50% EtOAc in hexane) showed that the starting material had disappeared. After the reaction finished, the reaction mixture was cooled to 0 °C and poured into ice-water (150 g) and stirred for another 2 h at 0 °C, filtered and washed with water to afford a white solid (18.3 g). The crude product was purified by recrystallisation from hexane to afford **4**: White solid; yield 14.2 g, 77%; m.p. 138–139 °C; IR (ν_{max}/cm^{-1}): 3056, 2907, 1739, 1565, 1487, 1079, 770; ^{1}H NMR (300 MHz, DMSO-d_6) δ 14.54 (br s, D_2O exchangeable, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.2 (s), 146.3 (d, J_{C-F} = 12.1 Hz), 145.0–141.2 (q, J_{C-F} = 256.6 Hz), 143.8–139.7 (q, J_{C-F} = 257.4 Hz), 133.1 (s), 114.6 (d, J_{C-F} = 18.9 Hz), 109.6 (d, J_{C-F} = 23.4 Hz); HRMS (ESI) calcd for $C_7HF_4NO_4$ [M – COOH]$^-$: 193.9864; found: 193.9869.

3,5-Dimethoxy-6-nitro-2,4-difluorobenzoic acid (**5**)

A solution of compound **4** (14.0 g, 58.6 mmol) and methanol (250 mL) was stirred in an ice-bath, sodium methoxide (7.5 g) was added in portions, after the addition was complete, the mixture was warmed to room temperature and stirred for 3 h when TLC (25% EtOAc, 5% AcOH in hexane) showed that the starting material had disappeared. The solution was adjusted to neutral pH with acetic acid. The solvent was removed under reduced pressure to afford a yellow solid, which was recrystallised from EtOAc to afford **5**: Light yellow solid; yield 11.5 g, 75%; m.p. 127–129 °C; IR (ν_{max}/cm^{-1}) KBr: 3147, 2961, 2361, 1602, 1540, 1372, 1023, 853; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.9 (s, 3H), 4.0 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.2 (s), 148.7–145.2 (q, J_{C-F} = 248.3 Hz), 137.3 (s), 139.4–136.7 (q, J_{C-F} = 162.3 Hz), 123.1 (d, J_{C-F} = 24.2 Hz), 112.3 (d, J_{C-F} =18.9 Hz), 108.6 (d, J_{C-F} = 24.9 Hz), 63.1 (d, J_{C-F} = 4.5 Hz), 62.1 (s); HRMS (ESI) calcd for $C_9H_7F_2NO_6$ [M – COOH]$^-$: 218.0265; found: 218.0268.

3,5-Dimethoxy-6-amino-2,4-difluorobenzoic acid (**6**)

Compound **5** (11.0 g, 41.8 mmol), Pd/C (10%, 1.1 g), and methanol (120 mL) were placed in an autoclave (250 mL). H_2 was purged into the autoclave three times to remove air, and the reaction mixture was stirred at 30 °C for 7 h under a pressure between 2.0 and 2.2 MPa. After the reaction, the resultant mixture was transferred into a tube and filtered to recover the catalyst. The solvent was removed under reduced pressure to afford **7**: grey solid; yield 9.4 g, 96%; m.p. 179–181 °C; IR (ν_{max}/cm^{-1}) KBr: 3516, 3450, 3348, 2948, 1681, 1469, 1270, 1003, 709; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.42 (br s, D_2O exchangeable, 2H), 3.79 (s, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.9 (s), 154.02–153.6 (q, J_{C-F} = 24.2 Hz), 150.7–150.3 (q, J_{C-F} = 21.1 Hz), 141.8–141.6 (t, J_{C-F} = 6.0 Hz), 130.5–130.3 (t, J_{C-F} = 11.3 Hz), 126.0–125.6 (t, J_{C-F} = 17.4 Hz), 97.8 (d, J_{C-F} = 12.8 Hz), 62.3 (s), 60.8 (d, J_{C-F} = 3.0 Hz); HRMS (ESI) calcd for $C_9H_9F_2NO_4$ [M – H]$^-$: 232.0421; found: 232.0425.

3,5-Dimethoxy-2,4-difluorobenzoic acid (**2**)

A mixture of compound **6** (9.0 g, 38.6 mmol) and water (100 mL) was cooled to 0 °C and concentrated hydrochloric acid (29.7 g) was added dropwise the temperature was kept below 5 °C, and a white solid precipitated in the process. The mixture was stirred for 30 minutes. A solution of $NaNO_2$ (4.0 g, 57.9 mmol) in water (25 mL) was added dropwise to this cold emulsion. Stirring was continued for another 30 minutes, the reaction mixture turned to clear solution. Then a solution of hypophosphorous acid (14 mL) and water (30 mL) was added dropwise below 5 °C for nearly 1 h. The mixture was stirred for a further 1 h. The reaction was monitored by TLC (25% EtOAc, 5% AcOH in hexane). The reaction mixture was extracted with dichloromethane (2 × 300 mL) and the combined organic phases were decolourised with activated charcoal and dried over anhydrous 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 and EtOAc (12 mL, 5:1), and dried between 50 and 55 °C for 5 h to obtain **2**: White solid; yield 6.1 g, 72%; m.p. 161–163 °C; IR (ν_{max}/cm^{-1}) KBr: 2967, 1703, 1610, 1482, 1140, 922; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.85 (br s, 1H, D_2O exchangeable), 7.31 (q, J = 6.72 Hz, 1H), 4.05 (s, 1H), 3.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 (s), 153.1–149.6 (q, J_{C-F} = 258.9 Hz), 151.5–148.0 (q, J_{C-F} = 258.1 Hz), 144.5–144.6 (d, J_{C-F} = 9.8 Hz), 138.3–138.0 (t, J_{C-F} = 11.3, 15.8 Hz), 112.6–112.5 (t, J_{C-F} = 3.8, 4.5 Hz), 108.3 (d, J_{C-F} = 2.3 Hz), 62.1 (s), 56.6 (s); HRMS (ESI) calcd for $C_9H_8F_2O_4$ [M – H]$^-$: 217.0312; found: 217.0316.

Electronic Supplementary Information

The ESI {HRMS (ESI) spectra} is available through: stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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