A practical synthesis of 3-chloro-2,4-difluoro-5-hydroxybenzoic acid

Mingguang Zhang1,2, Zhongbao Bi2, Yunyun Wang1, Yuxun Zhao1, Yang Yang2, Yongqiang Zhu2,3 and Shifa Wang1

Abstract
A new and practical synthesis of 3-chloro-2,4-difluoro-5-hydroxybenzoic acid, a key intermediate for preparing antimicrobial 3-quinolinecarboxylic acid drugs, is synthesized from 2,4-difluoro-3-chlorobenzoic acid. The protocol involves nitration, esterification, reduction of NO2, diazotization, and hydrolysis with a 70% overall yield. The structures of the synthesized compounds are determined by infrared spectroscopy, nuclear magnetic resonance spectroscopy, and high-resolution electrospray ionization mass spectrometry. The advantages of this developed synthetic strategy include an improved overall yield and readily controllable reaction conditions.

Keywords
3-Chloro-2,4-difluoro-5-hydroxybenzoic acid, 3-quinolinecarboxylic acid derivatives, diazotization, hydrolysis, synthesis

Introduction
Synthetic fluoroquinolone (FQ) antibiotics such as nalidixic acid and piromidic acid are effective antibacterial agents for treating infections caused by Gram-negative microorganisms. As a new generation of FQs, 3-quinolinecarboxylic acid derivatives such as norfloxacin, ofloxacin, moxifloxacin, and besifloxacin are well known for their strong antimicrobial activities and broad spectrum of antibacterial activities, including activity against Gram-positive bacteria. Developing new 3-quinolinecarboxylic acid derivatives as novel antibacterial agents with improved activity, superior pharmacokinetic properties, and satisfactory bacterial resistance is important in pharmaceutical research.

1-Cyclopropyl-7-amine-6-hydroxy-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid derivatives have been developed for improving antibacterial effects. The novel antibacterial compounds 2 and 3 have been synthesized from 2,4-difluoro-bromobenzene by aromatic chlorination, carboxylation, nitration, and so on with 11 steps in total. However, the overall procedure is complicated with many reaction steps, and the carboxylation conditions are harsh requiring n-butyllithium below −78 °C. Besides, the reduction of NO2 and the diazotization of NH2 afforded impurities in the target final intermediates that made the purification difficult. In this study, compounds 2 and 3 have been synthesized following the route shown in Scheme 1. 3-Chloro-2,4-difluoro-5-hydroxybenzoic acid (I) was used as the starting material, followed by benzylation, condensation with diethyl malonate, hydrolysis with p-toluenesulfonic acid, condensation with ethyl orthoformate, cyclopropylamine substitution, cyclization, ester hydrolysis, and debenzylation to afford the key quinolone intermediate 1h. Compounds 2 and 3 were prepared by the condensation of 1h with cyclic amines. Overall, the synthetic method is more efficient and does not use n-butyllithium (Scheme 1).

Some FQs are also photolabile compounds which lead to phototoxicity as a side effect. The intrinsic photostability characteristics should be evaluated to demonstrate that light exposure does not result in unacceptable changes. Hydroxylation of FQs at the 6-position is one of the main photodegradation pathways, affording 6-hydroxyciprofloxacin and 6-hydroxy sarafloxacin impurities. For quality

---

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en/us/nam/open-access-at-sage).
control of FQ drug substances, it is necessary to synthesize these impurities, which can be prepared from the derivatives of compound 1. The synthesis of 3-chloro-2,4-difluoro-5-hydroxybenzoic acid (1) was critical for developing new FQs and the quality control of drug substances. However, there is only one reported method for the preparation of the title compound 1 (Scheme 2).\textsuperscript{12} 2,4-Difluoro-1-(methoxymethoxy)benzene (4) was reacted with sec-butyllithium in tetrahydrofuran (THF) at −75°C to give (2,6-difluoro-3-methoxymethoxyphenyl)lithium (5) in 83% yield. 2-Chloro-1,3-difluoro-4-methoxymethoxybenzene (6) was obtained in 82% yield by treating compound 5 with 1,1,2-trichloro-1,2,2-trifluoroethane. Compound 1 could be prepared through Li-substitution and carboxylation of 6 in 75% yield. However, this method uses dangerous alkylithium reagents at extremely low temperatures which limits the large-scale preparation using this route. Furthermore, the overall yield for the synthetic route was only 51%.

Thus, it is important to develop a more practical and efficient synthetic method for the preparation of compound 1.

**Results and discussion**

Amino hydrolysis of an aryl amine can be used for preparing phenols.\textsuperscript{13–16} As shown in Scheme 3, the retrosynthetic analysis suggests that compound 1 can be synthesized by the hydrolysis of diazonium salt 8, which is the typical method for introducing a hydroxy group into an aromatic ring. Compound 8 could be obtained by the diazotization of compound 9, which occurs rapidly in concentrated sulfuric acid. Compound 9 would be prepared by the reduction of 3-chloro-2,4-difluoro-5-nitrobenzoic acid (10) with hydrogen in the presence of Pd/C, while 10 can be synthesized by the nitration of commercially available 2,4-difluoro-3-chlorobenzoic acid (11).

Based on the retrosynthetic analysis of compound 1, preliminary experiments were performed to verify the feasibility of this scheme. However, the critical intermediate
compound 8 could not be separated from water because of its high solubility. Further optimization was achieved by introducing an ester group into benzoic acid to reduce the solubility. The new synthetic strategy is illustrated in Scheme 4. Compound 1 was obtained by the nitration of 11, which was followed by esterification, reduction of NO2, diazotization, and hydrolysis of 13. The structures of the intermediates and products were characterized by infrared (IR) spectroscopy, 1H nuclear magnetic resonance (NMR) spectroscopy, 13C NMR spectroscopy, and mass spectrometry (MS).

In this new synthetic route, compound 11 was treated with concentrated nitric acid to give 3-chloro-2,4-difluoro-5-nitrobenzoic acid (10) in 94% yield. The nitration of compound 11 was slow because of the electron-withdrawing effects of the F and COOH groups. The reaction required a high temperature and the inclusion of excess concentrated HNO3 as an additive. Following esterification of 10, compound 12 was obtained in a good yield of 86%. The hydrogenation of 12 catalyzed by Pd/C gave ethyl 5-amino-3-chloro-2,4-difluorobenzoate (13) in an excellent yield of 97.0%. Finally, compound 13 was converted into the target compound 1 in 90% yield by diazotization and hydrolysis with H3PO2/H2O in one step.

With optimized reaction conditions in hand, we sought to evaluate the suitable conditions for the reduction of compound 12. 2% Raney Ni and 3 equiv. of hydrazine hydrate (80%) was increased to 4.0 and the reaction temperature was increased to 78°C; the highest yield was 62%, after reacting for 12 h (entries 2 and 3). By further optimizing the additive (entries 4−6), the yield of compound 13 was significantly improved (entry 6, 82%). Compared to Raney Ni and hydrazine hydrate (80%), using 5% Pd/C (66% water) and H2 improved the yield to 72% (entry 7). The additive ratios were also optimized, and the highest yield (97%) was obtained (entries 8−11). On increasing the pressure to 0.8−1.0 MPa, the reactions were complete within 5 h, and the highest yield of 97% was obtained.

In the fourth step, concentrated sulfuric acid was first employed as the solvent for the hydrolysis of compound 13; however, the reaction did not occur. Further experiments showed that compound 1 could be afforded by diazotization with NaNO2 and hydrolysis with 50% H3PO2 to give 13. For optimizing the reaction conditions, the equivalents of NaNO2 and H2SO4 were studied (Table 2). Equivalents of NaNO2 from 1.0 to 1.25 were screened and the results showed that NaNO2 equivalents below 1.2 gave only moderate yields (Table 1, entries 1−3). Subsequently, by decreasing the reaction temperature from 10°C to 0°C, it was found that 1.25 equiv. of NaNO2 in 4.0 equiv. of H2SO4 successfully improved the yield from 57% to 90% (Table 2, entries 4−6).

**Conclusion**

In summary, a novel and practical process for the synthesis of 3-chloro-2,4-difluoro-5-hydroxybenzoic acid (1), a key
intermediate for preparing antimicrobial 3-quinolinecarboxylic acid derivatives, has been developed. The synthetic strategy involved the nitration of 2,4-difluoro-3-chlororobenzoic acid (11), esterification, reduction of NO₂, diazotization, and hydrolysis. Hazardous alkyllithium reagents and low reaction temperatures are avoided to decrease the formation of byproducts. In addition, this new synthetic route has the advantages of readily available reagents and a high overall yield of 70%. The described strategy is also suitable for the synthesis of derivatives of compound 1.

**Experimental**

2,4-Difluoro-3-chlororobenzoic acid (11) was purchased from Aladdin (Shanghai) with 98% purity. Unless otherwise mentioned, all solvents, reagents, and materials were purchased from commercial suppliers and used without further purification. All reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (GF-254; Qingdao Ocean Chemical Company, China) and products were purified by silica gel column chromatography (200–300 mesh; Qingdao Marine Chemical Industry Corporation, China). Melting points (m.p.) were determined on a YRT-3 melting point apparatus using the capillary method without correction. IR spectra were obtained on a Avatar 330FT-IR (Thermo Nicolet) spectrometer, using the attenuated total reflectance (ATR) method. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance DPX 300 MHz instrument in CDCl₃ or DMSO-d₆ with tetramethylsilane (TMS) as an internal reference. Chemical shifts (δ) are reported in parts per million (ppm). High-resolution mass spectra (HRMS) were obtained from Agilent 1100 LC/MS Spectrometry Services.

### Table 1. Optimization of the reduction reaction conditions.

| Entry | Additive (w/w, equiv., H₂ pressure)a | Solvent | Temperature (°C) | Time (h) | Yield (%)b |
|-------|-------------------------------------|---------|------------------|---------|------------|
| 1     | Raney Ni (0.02), NH₂NH₂ (3.0)       | Ethanol | 60               | 9       | 45         |
| 2     | Raney Ni (0.02), NH₂NH₂ (4.0)       | Ethanol | 70               | 9       | 53         |
| 3     | Raney Ni (0.03), NH₂NH₂ (4.0)       | Ethanol | 78               | 12      | 62         |
| 4     | 5% Pd-C (0.02), NH₂NH₂ (3.0)        | Ethanol | 60               | 9       | 63         |
| 5     | 5% Pd-C (0.02), NH₂NH₂ (3.0)        | Methanol| 68               | 9       | 75         |
| 6     | 5% Pd-C (0.03), NH₂NH₂ (4.0)        | Methanol| 68               | 9       | 82         |
| 7     | 5% Pd-C (0.02), H₂ (0.1 MPa)        | Ethanol | 60               | 9       | 72         |
| 8     | 5% Pd-C (0.03), H₂ (0.1 MPa)        | Ethanol | 78               | 6       | 85         |
| 9     | 5% Pd-C (0.02), H₂ (0.5 MPa)        | Methanol| 30               | 5       | 93         |
| 10    | 5% Pd-C (0.02), H₂ (0.8 MPa)        | Methanol| 40               | 5       | 97         |
| 11    | 5% Pd-C (0.03), H₂ (1 MPa)          | Methanol| 40               | 5       | 97         |

aEntries 1–3: Raney Ni (w/w); entries 4–11: 5% Pd-C (dry weight/w).
bIsolated yield.

### Table 2. Optimization of the diazotization and hydrolysis reaction conditions.a

| Entry | NaNO₂ (equiv.) | H₂SO₄ (equiv.) | Temperature (°C) | Time (h) | Yield (%)b |
|-------|----------------|---------------|------------------|---------|------------|
| 1     | 1.0            | 2.5           | 10               | 4       | 48         |
| 2     | 1.0            | 3.0           | 10               | 3       | 50         |
| 3     | 1.2            | 3.0           | 5                | 3       | 57         |
| 4     | 1.25           | 3.0           | 5                | 3       | 63         |
| 5     | 1.25           | 4.0           | 0                | 2       | 89         |
| 6     | 1.25           | 4.0           | 0                | 2.5     | 90         |

aCompound 13 (10 mmol), H₂O (50 mL), 50% H₃PO₂ (30 mmol).
bIsolated yield.

3-Chloro-2,4-difluoro-5-nitrobenzoic acid (10)

A solution of concentrated HNO₃ (65%, 15.0 g) and H₂SO₄ (98%, 8.0 g) was added dropwise to 2,4-difluoro-3-chlororobenzoic acid (11) (15.0 g, 78.13 mmol) and concentrated
H₂SO₄ (98%, 32.0 g) at ice-bath temperature. The temperature was kept below 20°C during the addition process. After the addition was complete, the mixture was stirred for 2 h at 70–75°C until TLC (40% ethyl acetate in hexane) showed the starting materials had disappeared. The mixture was cooled to room temperature, poured into ice-water (180 g), stirred for another 1 h at 0–5°C, filtered, and washed with water to afford a gray solid. The crude product was purified by recrystallization from hexane to afford 10 as a white solid (17.38 g, 94%); m.p. 122–124°C, (123–124°C); 17 IR (KBr)/cm⁻¹: 3656, 3506, 3257, 3048, 1698, 1597, 1495, 1459, 1088, 932; 1H NMR (300 MHz, DMSO-d₆): δ = 160.9 (d, J = 7.2 Hz, 1 H), 160.3 (dd, J = 218.4, 2.7 Hz), 154.4 (dd, J = 218.1, 3.7 Hz), 139.2, 127.4, 116.8 (dd, J = 12.1, 4.1 Hz), 113.2 (t, J = 22.5 Hz); HRMS (ESI): m/z [M–H]⁻ calcd for C₁₀H₉ClF₂NO₂: 235.9562; found: 235.9559.

Ethyl 3-chloro-2,4-difluoro-5-nitrobenzoate (12)

A mixture of compound 10 (12.0 g, 50.6 mmol), ethanol (200 mL), and H₂SO₄ (98%, 7.5 g) was stirred under reflux for 3 h until the starting materials had disappeared (TLC detection, 10% ethyl acetate, 90% hexane). After cooling, the solvent was removed under reduced pressure, the residue cooled to 5°C, and the pH value was adjusted to neutral with 10% sodium carbonate solution (70 mL). The mixture was extracted twice with ethyl acetate (60 mL × 2) and the combined organic layer was dried with Na₂SO₄. The solvent was removed on a rotary evaporator and the crude product was purified by column chromatography using 5% ethyl acetate:9% petroleum ether as an eluent. The solvent was washed with a mixture of hexane (10 mL) and ethyl acetate (2 mL), and then dried between 50 and 55°C for 5 h. The product was obtained as a white solid (18.4 g, 90%); m.p. 115.2–115.9°C, (116–118°C); 13C NMR (300 MHz, CDCl₃): δ = 161.9 (d, J = 3.8 Hz), 160.3 (dd, J = 218.4, 2.7 Hz), 154.4 (dd, J = 218.1, 3.7 Hz), 139.2, 127.4, 116.8 (dd, J = 12.1, 4.1 Hz), 113.2 (t, J = 22.5 Hz); HRMS (ESI): m/z [M–H]⁻ calcd for C₁₀H₇ClF₂NO₂: 235.9562; found: 235.9559.

Ethyl 5-amino-3-chloro-2,4-difluorobenzoate (13)

Compound 12 (10.0 g, 37.73 mmol), Pd/C (10%, 0.2 g), and methanol (100 mL) were placed in an autoclave (250 mL). H₂ was purged into the autoclave three times to remove air, and the reaction mixture was stirred at 40°C for 5 h under a pressure between 0.8 and 1.0 MPa. After the reaction was complete, the resulting mixture was transferred to a tube and filtered to recycle the catalyst. The solvent was removed under reduced pressure to afford 13 as a gray solid (8.6 g, 97%); m.p. 115.2–115.9°C; IR (KBr)/cm⁻¹: 3431, 3410, 3351, 3216, 3072, 3011, 2972, 1713, 1496, 1284, 1018, 779; 1H NMR (300 MHz, CDCl₃): δ = 7.27 (m, 1 H), 4.37 (q, J = 7.1 Hz, 2 H), 3.76 (s, 2 H, D₉O exchangeable), 1.38 (t, J = 7.1 Hz, 3 H); 13C NMR (75 MHz, CDCl₃): δ = 163.4 (d, J = 4.3 Hz), 150.9 (d, J = 253.5 Hz), 149.9 (d, J = 248.9 Hz), 131.3 (dd, J = 12.8, 3.1 Hz), 115.8 (d, J = 5.4 Hz), 115.3 (dd, J = 10.9, 3.7 Hz), 111.2 (dd, J = 22.9, 18.6 Hz), 61.6, 14.0; HRMS (ESI): m/z [M–H]⁻ calcd for C₁₀H₇ClF₂NO₂: 236.0133; found: 236.0128.

3-Chloro-2,4-difluoro-5-hydroxybenzoic acid (I)

A mixture of compound 13 (2.35 g, 10 mmol) and H₂O (45 mL) was cooled to 0°C, concentrated sulfuric acid (98%, 4.0 g) was added dropwise, and the temperature was kept below 5°C. A white solid precipitated during the process, and the mixture was stirred for 30 min. To this emulsion, a solution of NaNO₂ (0.86 g, 12.5 mmol) in H₂O (5.0 mL) was added dropwise to the cooled reaction mixture. Stirring was continued for another 30 min during which the reaction mixture became a clear solution. A solution of 50% hypophosphorous acid (3.96 g, 30 mmol) was added dropwise below 0°C, and the mixture was stirred at 0°C for 2.5 h. Then, the pH of the reaction mixture was adjusted to 9–10 with 30% NaOH and stirred for another 1 h at 50°C (the reaction was monitored by TLC [25% ethyl acetate, 5% acetic acid in hexane]). The reaction mixture was cooled to room temperature and extracted with dichloromethane (2 × 300 mL), and the combined organic phases were decolorized with activated charcoal and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure to afford a white solid. The crude product was washed with a mixture of hexane (10 mL) and ethyl acetate (2 mL), and then dried between 50 and 55°C for 5 h. The product was obtained as a white solid (1.87 g, 90%); m.p. 194.7–195.9°C, (195–197°C); 1H NMR (400 MHz, CDCl₃): δ = 13.47 (br, s, 1 H, D₉O exchangeable), 10.66 (br, s, 1 H, D₉O exchangeable), 7.43 (dd, J = 9.09, 7.32 Hz, 1 H); 13C NMR (300 MHz, CDCl₃): δ = 163.6 (d, J = 3.6 Hz), 150.2 (d, J = 252.9 Hz), 149.7 (d, J = 252.4 Hz), 141.8 (dd, J = 11.6, 2.9 Hz), 117.1 (d, J = 4.3 Hz), 115.5 (dd, J = 11.1, 3.8 Hz), 110.4 (dd, J = 22.9, 18.4 Hz); 19F NMR (376 MHz, CDCl₃): δ = −122.5, −127.6; HRMS (ESI): m/z [M–H]⁻ calcd for C₁₀H₇ClF₂O₃: 206.9661; found: 206.9672.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Natural National Science Foundation of China (No. 31470592).

ORCID iD

Shifa Wang https://orcid.org/0000-0001-8578-9845
Supplemental material
Supplemental material for this article is available online.

References
1. Gore J, Bryant Z, Stone MD, et al. Nature 2006; 439: 100.
2. Deschenes J and Blondeau J. Can J Ophthalmol 2015; 50: 184.
3. Hu YQ, Xu Z, Qiang M, et al. J Heterocyclic Chem 2018; 55: 187.
4. Chen YL, Fang KC, Sheu JY, et al. J Med Chem 2001; 44: 2374.
5. Anquetin G, Rouquayrol M, Mahmoudi N, et al. Bioorg Med Chem Lett 2004; 14: 2773.
6. Sobhi M. Prot Met Phys Chem 2014; 50: 825.
7. Natalini B, Sardella R, Massari S, et al. Talanta 2011; 85: 1392.
8. Benoit L, Hu X, Eric Almstead J, et al. WO2004014893, 2004.
9. Benoit L, Kim AJ and Jeffrey G. US2002049192, 2002.
10. Ge LK, Chen JW, Wei XX, et al. Environ Sci Technol 2010; 44: 2400.
11. Guo HG, Gao NY and Chu WH. Environ Sci Pollut Res 2013; 20: 3202.
12. Marzi E, Gorecka J and Schlosser M. Synthesis 2004; 1609.
13. Robin F, Robert WC and Andrew DM. Org Process Res Dev 2003; 7: 762.
14. Sayyed IA, Panse DG, Bhawal BM, et al. Synth Commun 2000; 30: 2533.
15. Takuwa T, Minowa T, Onishi JY, et al. Bull Chem Soc Jpn 2004; 77: 1717.
16. Van Es T, Staskun B and Piggott AM. S Afr J Chem 2006; 59: 101.
17. Zhou WY, Yu ST, Xia ZJ, et al. J Chem Res 2015; 39: 277.