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Journal of Fluorine Chemistry 94 (1999) 7–10

JOURNAL OF FLUORINE CHEMISTRY

Synthesis of fluoro-4-hydroxyquinoline-3-carboxylic acids by the Gould–Jacobs reaction

Elisa Leyva[1,*], Elena Monreal, Alma Hernández

Facultad de Ciencias Químicas, Universidad Autónoma de San Luis Potosí, San Luis Potosí, 78210, Mexico

Received 1 September 1998; accepted 29 September 1998

Abstract

The synthesis of several fluoro-4-hydroxyquinoline-3-carboxylic acids by the Gould–Jacobs reaction is presented. These quinolines are important intermediates for the preparation of antibacterial fluoroquinolones.

Keywords: Synthesis; Fluoroquinolones; Fluoroquinolines; Antibacterial agents

1. Introduction

Since the discovery of the antibacterial penicillium more than 60 years ago, there has been a great deal of interest in finding new natural or synthetic compounds with antibacterial activity. The first quinolones used as antibacterial agents were nalidixic (**1**) and oxolinic (**2**) acids (Scheme 1). However, these quinolones showed activity only against gram-negative microorganisms [1–3]. Subsequent structural modifications on these quinolones have led to new analogues with improved antibacterial potency [4–7]. Common structural features of the more potent, newer generation quinolones (Scheme 1) such as norfloxacin (**3**) and ciprofloxacin (**4**), are a C-6 fluorine and a C-7 cyclic piperazinyl group [8–13].

We have been engaged for several years in the synthesis of fluoroquinolones and fluoroquinolines to study their antimicrobial activity. In this investigation, we present the synthesis of several fluoro-4-hydroxyquinoline-3-carboxylic acids by the Gould–Jacobs reaction [14,15] with some modifications.

2. Results and discussion

Scheme 2 illustrates the sequence of reactions followed. In the first reaction, the commercially available fluoroaniline (**5a–5e**) was reacted with diethyl etoxymethylenemalonate at 100°C, the ethanol produced in the reaction was removed with a light nitrogen flow, to give the corresponding malonate (**6a–6e**). In the second reaction, extreme conditions were required to induce cyclization. The malonate (**6a–6e**) was refluxed with diphenylether at 250°C to give a fluoroester (**7a–7e**). In the last reaction, the ester **7a–7e** was refluxed with an aqueous solution of NaOH to hydrolyze it to the corresponding fluoro-4-hydroxyquinoline-3-carboxylic acid (**8a–8e**). In all the reactions, very good yields were obtained. In all the cyclization reactions, only one compound was obtained, even in the cases in which more than one compound could be produced. These results have important implications for the application of this reaction to the synthesis of fluoroquinolones.

3. Experimental details

3.1. General procedures

All the melting points were recorded on a Fisher Johns apparatus. IR spectra were recorded on a Nicolet 205 FTIR instrument. NMR spectra were obtained on a Bruker AC 200 nuclear magnetic resonance spectrometer. ^{1}H NMR spectra were recorded in ppm from tetramethylsilane and ^{19}F NMR spectra were recorded in ppm from trifluoroacetic acid. The MS spectra were recorded on a AEI MS 902 mass spectrometer 70 eV. All the compounds were purchased from Aldrich.

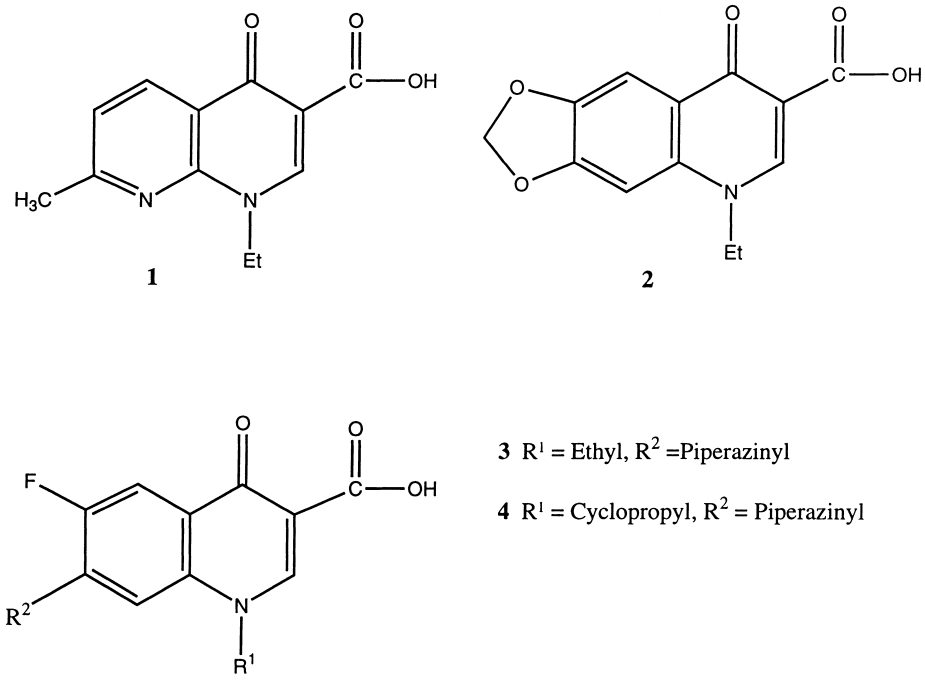
3.1.1. Malonates (**6a–6e**)

The corresponding fluoroaniline **5a–5e** (0.02 mols) was reacted with diethyl ethoxymethylenemalonate

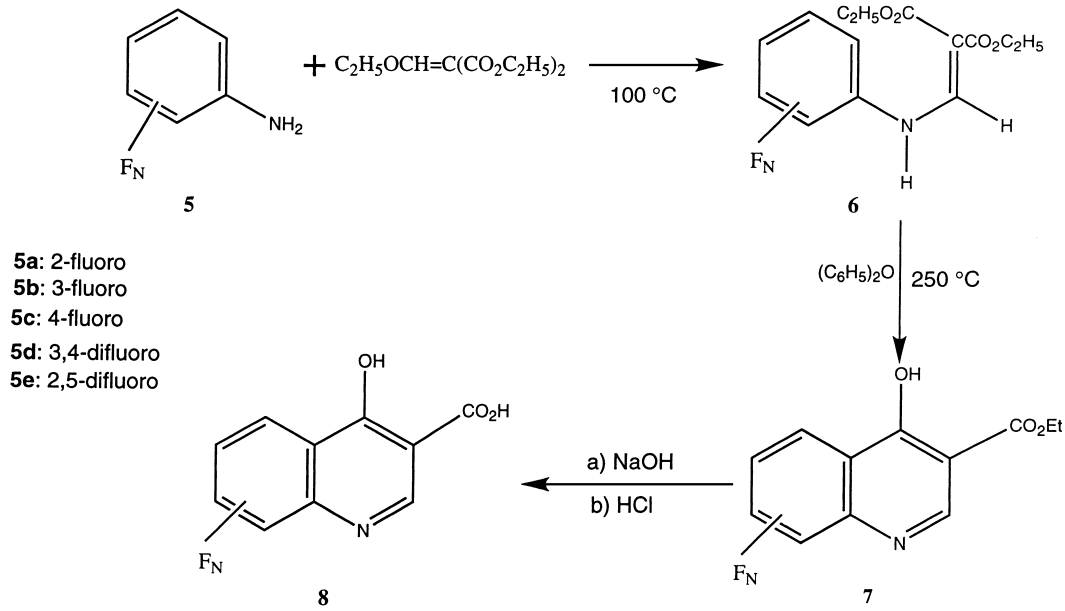
*Corresponding author.

[1]Present address: Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095-1569, USA (on leave from UASLP).

0022-1139/99/$ – see front matter
PII: S0022-1139(98)00310-8



Scheme 1.



Scheme 2.

(0.0216 mols) at 100°C for 80 min. During this time, a light nitrogen flow was introduced to the reaction mixture to remove the ethanol formed. Then, hexane was added to dissolve the product. The reaction mixture was warmed (100°C) and allowed to cool to room temperature to give the corresponding malonate **6a–6e** as a white crystalline compound. We found that the yields on this reaction were improved upon the removal of the ethanol produced. We also found that the resulting malonate **6a–6e** was easily purified with hexane.

3.1.2. Cyclization

Diphenylether (14 ml) was heated in an oil bath at 250°C and the malonate **6a–6e** (0.012 mols) was slowly added. The mixture was kept under reflux for one hour. During this time, vapors evolved and a white solid formed. The solid was

filtered and washed with hexane to remove the excess of diphenylether. The corresponding ester **7a–7e** was obtained as a white solid.

3.1.3. Hydrolysis

Each fluoroester **7a–7e** was refluxed with an aqueous solution of NaOH (10%) for 1 h. The mixture was cooled to room temperature and was acidified with a solution of HCl (10%) to give the corresponding acid **8a–8e** as a white precipitate.

3.2. Preparation of 8-fluoro-4-hydroxyquinoline-3-carboxylic acid (**8a**)

Following the general procedure, **6a** was obtained as a crystalline white solid (92%) with m.p. 80–81°C, IR (KBr) 1686 cm^{-1} (ester); ^1H NMR (CD_3COCD_3) δ (ppm): 1.24 (3H, t, CH_3), 1.30 (3H, t, CH_3), 4.20 (2H, C, CH_2), 4.24 (2H, C, CH_2), 7.26 (3H, m, aromatic H), 7.60 (1H, m, aromatic H), 8.55 (1H, d, vinyl H), 11.02 (1H, d, NH); MS (EI, 70 eV) *m/z*: 281 (100%); 235 (87%), 207 (15%), 190 (26%), 162 (27%), 122 (31%), 95 (18%).

Refluxing **6a** with diphenylether gave **7a** as a white solid (65%) with m.p. 202–203°C; IR (KBr) 1719 cm^{-1} (ester). The solid was washed with hexane and used in the next reaction. **7a** was hydrolyzed with NaOH and the resulting solution was precipitated with HCl to give the corresponding acid **8a** as a white solid (96%) with m.p. 263°C; IR (KBr) 1714 cm^{-1} (COOH); ^1H NMR (DMSO-D_6) δ (ppm): 7.59 (1H, m, $J_{H-F} = 13$ Hz, $J_{H-H} = 7$ Hz , $J_{H-H} = 3$ Hz, aromatic H), 7.84 (1H, m, $J_{H-H} = 9$ Hz, $J_{H-F} = 5$ Hz, aromatic H), 8.10 (1H, m, $J_{H-H} = 5$ Hz,, $J_{H-H} = 8$ Hz, aromatic H), 8.66 (1H, S, aromatic H), 15 (1H, broad S, COOH); ^{19}F NMR (DMSO-D_6) δ (ppm): −49.7 (m, aromatic F); MS (EI, 70 eV) m/z: 207 (40%), 189 (100%), 161 (12%), 133 (38%), 107 (24%), 94 (10%); exact mass for $C_{10}H_6NO_3F$ 207.0331 . Found: 207.0332.

3.3. Preparation of 7-fluoro-4-hydroxyquinoline-3-carboxylic acid (**8b**)

Following the general procedure, **6b** was obtained as a crystalline white solid (65%) with mp 44–45°C; IR (KBr) 1689 cm^{-1} (ester); ^1H NMR (CD_3COCD_3) δ (ppm): 1.22 (3H, t, CH_3), 1.26 (3H, t, CH_3), 4.18 (2H, C, CH_2), 4.22 (2H, C, CH_2), 6.86 (1H, m, aromatic H), 7.22 (2H, m, aromatic H), 7.42 (1H, m, aromatic H), 8.47 (1H, d, vinyl H), 10.82 (1H, d, NH); MS (EI, 70 eV) *m/z*: 281 (100%), 235 (78%), 207 (13%), 190 (23%), 162 (34%), 122 (35%), 95 (33%).

Refluxing **6b** with diphenylether gave **7b** as a white solid (60%) with mp 263–265°C; IR (KBr) 1738 cm^{-1} (ester). The solid was washed with hexane and used in the next reaction. **7b** was hydrolyzed with NaOH and the resulting solution was precipitated with HCl to give the corresponding acid **8b** as a white solid (90%) with m. p. 245–246°C; IR (KBr) 1706 cm^{-1} (COOH); ^1H NMR (DMSO-D_6) δ (ppm): 7.46 (1H, m, $J_{H-F} = 10$ Hz, $J_{H-H} = 5$ Hz, aromatic H), 7.58 (1H, m, $J_{H-H} = 8$ Hz, $J_{H-F} = 5$ Hz, aromatic H), 8.26 (1H, dd, $J_{H-F} = 10$ Hz, $J_{H-H} = 5$ Hz), 8.8 (1H, S, aromatic H), 13.6 (1H, broad S, COOH); ^{19}F NMR (DMSO-D_6) δ −44.2 (m, aromatic F); MS (EI, 70 eV) *m/z*: 207 (34%), 189 (59%), 161 (5%), 133 (28%), 107 (28%), 94 (10%); exact mass for $C_{10}H_6NO_3F$ 207.0331. Found: 207.0332.

3.4. Preparation of 6-fluoro-4-hydroxyquinoline-3-carboxylic acid (**8c**)

Following the general procedure, **6c** was obtained as a crystalline solid (75%) with m.p. 69–70°C; IR (KBr) 1685 cm^{-1} (ester); ^1H NMR (CD_3COCD_3) δ 1.22 (3H, t, CH_3), 1.26 (3H, t, CH_3), 4.20 (2H, C, CH_2), 4.24 (2H, C, CH_2), 7.24 (2H, m, aromatic H), 7.74 (2H, m, aromatic H), 8.44 (1H, d, vinyl H), 10.86 (1H, d, NH); MS (EI, 70 eV) *m/z*: 281 (100%), 235 (82%), 207 (10%), 190 (26%), 162 (53%), 122 (31%), 95 (33%).

Refluxing **6c** with diphenylether gave **7c** as a white solid (60%) with m.p. 273–275°C; IR (KBr) 1728 cm^{-1} (ester). The solid was washed with hexane and used in the next reaction. **7c** was hydrolyzed with NaOH and the resulting solution was precipitated with HCl to give the corresponding acid **8c** as a white solid (70%) with m.p. 287°C; IR (KBr) 1680 cm^{-1} (COOH); ^1H NMR (DMSO-D_6), 7.91 (3H, m, aromatic H). 8.9 (1H, S, aromatic H), 15 (1H, broad S, COOH); ^{19}F NMR (DMSO-D_6) δ −34.8 (m, aromatic F); MS (EI, 70 eV), *m/z*: 207 (40%), 189 (100%), 161 (12%). 133 (38%), 107 (24%), 94 (10%); exact mass for $C_{10}H_6NO_3F$ 207.0331. Found: 207.0332.

3.5. Preparation of 6,7-difluoro-4-hydroxyquinoline-3-carboxylic acid (**8d**)

Following the general procedure, **6d** was obtained as a crystalline slightly pink solid (85%) with m. p. 76–77°C; IR (KBr) 1739 cm^{-1} (ester), 1688 cm^{-1} (ester); ^1H NMR (CD_3COCD_3) δ (ppm): 1.2 (3H, t, CH_3), 1.26 (3H, t, CH_3), 4.18 (2H, C, CH_2), 4.24 (2H, C, CH_2), 7.26 (1H, m, aromatic H), 7.40 (1H, m, aromatic H), 7.44 (1H, m, aromatic H), 8.40 (1H, d, vinyl H), 10.82 (1H, d, NH); MS (EI, 70 eV) *m/z*: 299 (100%), 253 (76%), 225 (13%), 208 (14%), 180 (53%), 140 (23%), 113 (19%).

Refluxing **6d** with diphenylether gave **7d** as a white solid (80%) with m.p. 238–239°C; IR (KBr) 1698 cm^{-1} (ester). The solid was washed with hexane and used in the next reaction. **7d** was hydrolyzed with NaOH and the resulting solution was precipitated with HCl to give the corresponding acid **8d** as a white solid (95%) with m.p. 276–278°C; IR (KBr) 1712 cm^{-1} (COOH); ^1H NMR (DMSO-D_6), δ (ppm): 7.88 (1H, m, $J_{H-H} = 11$ Hz, $J_{H-F} = 6$, $J_{H-F} = 3$ Hz, aromatic H), 8.17 (1H, m, $J_{H-H} =$ Hz, $J_{H-F} = 10$ Hz, $J_{H-F} =$ 2 Hz, aromatic H), 8.9 (1H, S, aromatic H), 13.75 (H, broad S, COOH); ^{19}F NMR (DMSO-D_6) δ (ppm): −48.44 (1F,m, aromatic F), −58.78 (1F,m,aromatic F); MS (EI, 70 eV) *m/z*:

225 (36%), 207 (100%), 179 (12%), 151 (53%),125 (34%), 112 (17%); exact mass for $C_{10}H_5NO_3F_2$ 225.0237. Found: 225.0237.

3.6. Preparation of 5,8-difluoro-4-hydroxyquinoline-3-carboxylic acid (**8e**)

Following the general procedure, **6e** was obtained as a white crystalline solid (75%) with m.p. 88°C; IR (KBr) 1720 cm^{-1} (ester); ^1H NMR (CD_3COCD_3) δ 1.20 (3H, t, CH_3), 1.22 (3H, t, CH_3), 4.20 (2H, C, CH_2), 4.24 (2H, C, CH_2), 7.24 (1H, m, aromatic H), 7.42 (1H, m, aromatic H), 8.49 (1H, d, vinyl H), 11.08 (1H, d, NH); MS (EI, 70 eV) *m/z*: 299 (79%), 253 (86%), 225 (10%), 208 (12%), 180 (67%), 140 (20%), 113 (10%).

Refluxing **6e** with diphenylether gave **7e** as a white solid (65%) with mp 220–221°C; IR (KBr) 1720 cm^{-1} (ester). The solid was washed with hexane and used in the next reaction. **7e** was hydrolyzed with NaOH and the resulting solution was precipitated with HCl to give the corresponding acid **8e** as a white solid (98%) with m.p. 308–310°C; IR (KBr) 1720 cm^{-1} (COOH); ^1H NMR (DMSO-D_6), δ 7.33 (1H, m, $J_{H-H} = 9$ Hz, $J_{H-F} = 12$, $J_{H-F} = 4$ Hz, aromatic H), δ 7.84 (1H, m, $J_{H-H} = 9$ Hz, $J_{H-F} = 10$ Hz, $J_{H-F} = 4$ Hz, aromatic H), 8.6 (1H, S, aromatic H), 14.9 (H, broad S, COOH); ^{19}F NMR (DMSO-D_6) δ (ppm): −37 (1F, m, aromatic F), −53 (IF, m, aromatic); MS (EI, 70 eV) *m/z*: 225 (49%), 207 (74%), 179 (10%), 151 (33%),125 (45%), 112 (24%); exact mass for $C_{10}H_5NO_3F_2$ 225.0237 g. Found: 225.0237.

Acknowledgements

Financial Support by CONACyT (Grant 0762-M9109) and UASLP (C98-FAI-06-6.42) is gratefully acknowledged. We thank Prof. Miguel Garcia-Garibay from the University of California at Los Angeles for help with the MS measurements.

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