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A Novel Synthesis of Difloxacin Hydrochloride

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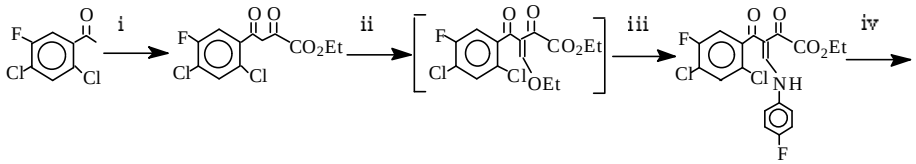
Abstrsact: Difloxacin hydrochloride, one of aryl-fluoro quinolone antibiotic, has been synthesized in seven steps from 2, 4-dichloro-5-fluoroacetophenone *via* oxalylation, ethoxymethylenation, amination, cyclization, hydrolysis, decarbonylation and N-methylpiperazination. Additional four new intermediates are produced.

Keywords: Difloxacin hydrochloride, fluoro quinolone, synthesis.

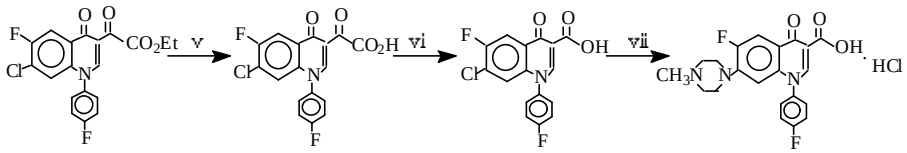
Difloxacin, the third generation of new quinolone antibiotics, has broad-spectrum *in vitro* activity and excellent potency *in vivo* and has been found to be against *gram-positive cocci*, *gram-negative bacteria*, *anaerobe*, *mycoplasm*, *chlamydia*[1,2].

As described previously, high reaction temperature and hazardous reagents are the defects of the methods for preparation of difloxacin[3,4]. We have developed a new synthetic method as shown in the **Scheme**. 2,4-Dichloro-5-fluoro-acetophenone **1** was used as starting material to react with diethyl oxalate in place of diethyl carbonate to give β-keto ester **2**[5] in high yield. It was interesting to note that compound **2** was treated with triethyl orthoformate to afford a new compound **3**, reaction of **3** with *p*-fluoroaniline to form enamino keto ester **4**[6], cyclization of **4** in DMF to give the corresponding carboxylate **5**[7], then hydrolysis with sodium hydroxide to obtain an intermediate **6**[8] which has one more carbonyl than the back bond of difloxacin. Therefore, the key-step was the reaction of the decarbonylization of acid **6** to **7**[9], condensation of **7** with N-methylpiperazine to give difloxacin **8**[10].

Scheme



1 **2** **3** **4**



5 **6** **7** **8**

i. C_2H_5ONa, C_2H_5OH, $(CO_2Et)_2$, 55°C, 3 h, 96.3%; ii. $HC(OEt)_3$, $(CH_3CO)_2O$, 90°C, 1 h; iii. C_2H_5OH, *p*-$FC_6H_4NH_2$, 5~10°C, 10 min, 74.8%; iv. K_2CO_3, DMF, 70°C, 1.5 h, 84.7%; v. NaOH, 70°C, 1.5 h, HCl, 94%; vi. H_2O_2, NaOH, 2 h, 81.3%; vii. DMSO, N-methylpiperazine, 90~100°C, 1 h, 78%.

References and notes

1. A. L. Barry, C. Thornsberry, R. N. Jones, *et al*., *Antimicrobial Agents and Chemotherapy*, **1986**, *29* (1), 40.
2. B. R. Smith, J. L. Lefrock, J. B. Donato, *et al.*, *Antimicrobial Agents and Chemotherapy*, **1986**, *29* (2), 355.
3. H. Y. Guo, Z. M. Tian, L. Y. Sun, *et al*., *Chinese Journal of Pharmaceuticals*, **1992**, *23* (12), 529.
4. D. T. W. Chu, P. B. Fernandes, A. K. Claibrone, *et al*., *J. Med. Chem.*, **1985**, *28*, 1558.
5. Compound **2**: White needle-like crystal. mp: 133.1~134.2°C. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.4 (t, 3H, J=7.0Hz, CH_3), 4.4 (q, 2H, J=7.0Hz, CH_2), 7.0 (s, 1H, conjugated olefinic H), 7.5~7.6 (m, 2H, Ar-H), 14.5 (br, 1H, conjugated hydroxyl H); IR (KBr, cm^{-1}): 3466, 3098, 3051, 2987, 1746, 1660, 1637, 1610, 1585, 1544, 1440; MS (*m/z*): 306 (M^+, 2%), 271 (M^+-Cl, 21%), 233 (M^+-CO_2Et, 100%), 206 (M^+-$COCO_2$Et, 2.7%), 191 (M^+-2Cl-OEt, 24.6%); Anal. Calcd for $C_{12}H_9Cl_2FO_4$: C, 46.93; H, 2.95. Found: C, 47.02; H, 3.02.
6. Compound **4**: White solid. mp: 149.5~150.5°C. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.3~1.4 (t, 3H, J=7.0Hz, CH_3); 4.0~4.3 (q, 2H, J=7.0Hz, CH_2); 7.1 (d, 1H, J=6.0Hz, olefinic-H); 7.3~7.4 (m, 2H, Ar-H); 7.6~7.8 (m, 2H, Ar-H); 8.7(m, 2H, Ar-H); 12.4~12.8 (br, 1H, NH); IR (KBr, cm^{-1}): 3450, 3168, 3077, 2977, 1736, 1655, 1619, 1261; MS (*m/z*): 428 (M, 1.6%); 354 (M-CO_2Et, 59.2%); 318 (M-CO_2Et-Cl, 29.4%); 290 (M-$COCO_2$Et, 3.3%); 191 (M-CCHNHC$_6$H$_4$F-$COCO_2$Et, 100%); Anal. Calcd for $C_{19}H_{14}Cl_2F_2NO_4$: C, 53.29; H, 3.06; N, 3.27. Found: C, 53.44; H, 3.02; N, 3.34.
7. Compound **5**: White solid. mp: 213~214°C. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.4~1.5 (t, 3H, J=7.0Hz, CH_3); 4.5 (q, 2H, J=7.0Hz, CH_2); 7.1 (d, 1H, J=6.0Hz, olefinic-H); 7.4~7.5 (m, 2H, Ar-H); 7.7~7.8 (m, 2H, Ar-H); 8.2 (m, 1H, Ar-H); 8.4 (s, 1H, Ar-H); IR (KBr, cm^{-1}): 3052, 2988, 1736, 1678, 1619, 1264; MS (*m/z*): 392 (M, 2.0%); 363 (M-Et, 4.5%); 334 (M-Et-CO, 5.7%); 318 (M-CO_2Et, 100%); 291 (M-CO CO_2Et, 17.1%); Anal. Calcd for $C_{19}H_{13}ClF_2NO_4$: C, 58.20; H, 3.09; N, 3.57. Found: C, 58.27H, 3.05; N, 3.54.
8. Compound **6**: White solid. mp: 243.5~244°C. ^{1}H-NMR ($CDCl_3$, δ ppm): 7.2 (d, 1H, J=6.0Hz, olefinic-H); 7.5~7.6 (m, 2H, Ar-H); 7.7~7.8 (m, 2H, Ar-H); 8.1 (m, 1H, Ar-H); 8.5 (s, 1H, Ar-H); 13.9 (br, 1H, hydroxyl-H); IR (KBr, cm^{-1}): 3455, 3089, 3038, 1744, 1679, 1610, 1265; MS (*m/z*): 364 (M, 10.84%); 335 (M-CO, 1.4%); 318 (M-COOH, 85.2%); 291 (M-COCOOH, 100%); Anal. Calcd for $C_{17}H_9ClF_2NO_4$: C, 56.14; H, 2.22; N, 3.85. Found: C, 55.95; H, 2.11; N, 3.90.
9. Compound **7**: White solid. mp: 260~263°C. ^{1}H-NMR ($CDCl_3$, δ ppm): 7.3 (d, 1H, J=6.0Hz, olefinic-H); 7.5~7.6 (m, 2H, Ar-H); 7.7~7.8 (m, 2H, Ar-H); 8.3 (m, 1H, Ar-H); 8.8 (s, 1H, Ar-H); 14.5 (br, 1H, hydroxyl-H); MS (*m/z*): 335 (M, 2.67%); 318 (M-OH, 2.86%); 291 (M-COOH, 100%).
10. Compound **8**: White solid. mp: 276~278°C. MS (*m/z*): 399 (M^+-HCl, 28.6%); 355 (M^+-HCl-CO_2, 100%). It was the same as the document reported[4].

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