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A PRACTICAL SYNTHESIS OF FLUOROQUINOLONE ANTIBIOTIC MOXIFLOXACIN

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Abstract

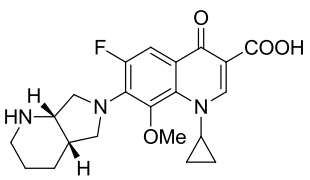
The fluoroquinoloneantibiotic has been used in clinical practice since the 1980s, primarily for the treatment infections caused by Gram-negative bacteria. Moxifloxacin, a fourth-generation fluoroquinolone antibiotic developed by pharmaceutical company Bayer AG, exhibit broad spectrum of activity against Gram-negative, Gram-positive bacteria as well as anaerobia. Moxifloxacin is used for community-acquired respiratory tract infections, sinusitis, acute exacerbations of chronic bronchitis and pneumonia, and skin structure infections. We have described the synthesis of moxifloxacin using difluoroboron complex. In this paper, a practical synthesis of moxifloxacin using acetoxyboronate complexwas reported.

Keywords. Fluoroquinolone, antibiotic, moxifloxacin.

1. INTRODUCTION

The fluoroquinoloneantibiotic have been used in clinical practice since the 1980s, primarily for the treatment infections caused by Gram-negative bacteria [1]. Recently, new fluoroquinolone derivatives have been developed with enhanced activity against Gram-positive microbes as well as anaerobia.

Moxifloxacin, a fourth generation fluoroquinolone antibiotic developed by pharmaceutical company Bayer AG, reached the market in 1999 under brand name Avelox [2]. FDA approved Moxifloxacin for the treatment of community-acquired respiratory tract infections, sinusitis, chronic bronchitis and pneumonia, and skin structure infections. In addition, Moxifloxacin has been used in clinical for multi-drug resistance tuberculosis [3].



Moxifloxacin

We have reported the synthesis of fluoroquinolonering and the side chain amine [4-5]. The synthesis of Moxifloxacin using difluoroboron complex was described [6]. In this study, we reported a practical synthesis of moxifloxacin *via* acetoxyboronate complex. In this reaction, the side chain amine reacted with the complex regioselectively and Moxifloxacin was obtained with better yield compared to the previous synthetic route.

2. MATERIALS AND METHODS

All chemicals were used as received from commercial sources without further purification.

Melting point were recorded on a EZ-Melt thermometer. ^{1}H and ^{13}C-NMR spectra were recorded on a BrukerAvance 500 (500 MHz, ^{1}H; 125 MHz ^{13}C) spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) or the internal solvent signal of deuterated solvents (^{13}C and ^{1}H). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet) and dd (double doublet). Coupling constants *J* are reported in Hertz. The mass spectra were recorded with a Agilent 1260 MS instrument. For thin layer chromatography, analytical TLC plates (70-230 mesh silica gel

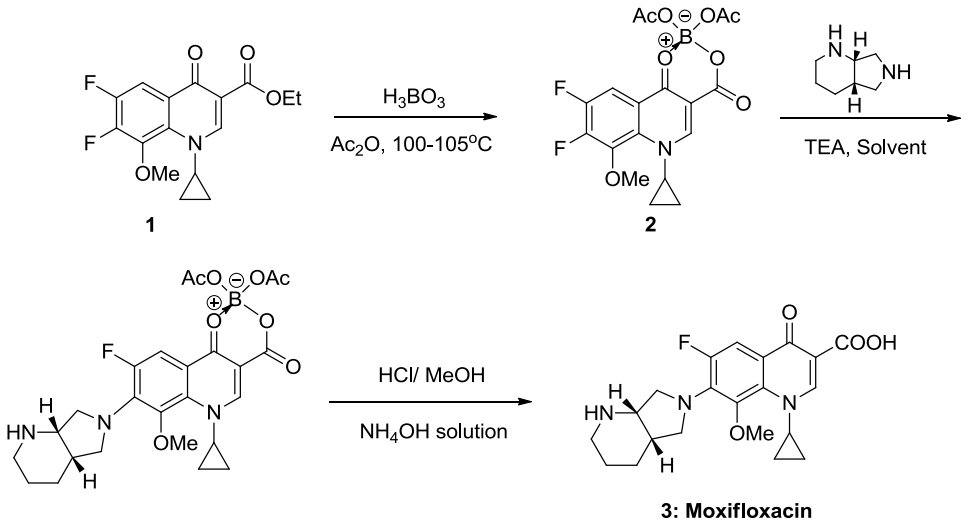
(Merck) were used. Visualization was accomplished with UV (254 nm).

Preparation of complex 2: 1-Cycloropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-(O^3, O^4)-*bis*-(Acyloxy-O)borate.

The mixture of boric acid (15 g, 0.24 mol) and acetic anhydride (160 mL) was heated to 80^{o}C for 1 hour and then was cooled down to about 60-70 ^{o}C. Ethyll-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate (50 g, 0.155 mol) is added under stirring. The temperature is then raised and maintained for 1 hour in the range of 100^{o}Cto 105^{o}C. Chilled water (500 ml) is added and the reaction mixture was maintained for 2 hrs at 0^{o}Cto 5^{o}C. The boron acetate complex was filtered, washed with water (500 ml) and dried at 50 ^{o}Cto 55^{o}Cunder vacuum to constant weight. The dry weight is 63 g corresponding to yield of 96%.

White powder; mp: 113-114^{o}C; ^{1}H-NMR (500MHz, $CDCl_3$) δ (ppm): 9.19 (s, 1H, H-2); 8.07 (t, *J* = 9 Hz, 1H, H-5); 4.37 (m, 1H, C<u>H</u>-N); 4.19 (s, 3H, OC<u>H</u>$_3$); 2.01 (s, 6H, CH_3), 1.29-1.27 (m, 2H, C<u>H</u>$_2$-cyclopropyl); 1.21(m, 2H, C<u>H</u>$_2$-cyclopropyl). ^{13}C-NMR (125MHz, $CDCl_3$) δ (ppm): 172.9; 172.9; 170.3; 153.7; 151.5 (C-F, *J* = 125 Hz); 150.4; 149.2 (C-F, *J* = 125 Hz); 141.5, 133.3; 119.5; 109.0; 107.2; 63.4; 43.3; 23.0; 9.4; 9.4. ESI-MS m/z: $[M+H]^+$: 424.

Synthesis of Moxifloxacin 3: The acetoxyboronate complex **2** (50.0 g, 0.118 mol) was suspended in solvent (200 ml). (*S*,*S*)-2,8-diazabicyclo-(4,3,0)-nonane (16.3 g, 0.13 mol) diluted with 50 ml solvent was slowly added followed by triethylamine (24.5 ml, 0.177 mol). The reaction mixture were stirred at certain temperature. After reaction was over, solvent was removed and methanol (200.0 ml) was added. pH was adjusted to 1.0-2.0 using hydrochloric acid and the reaction mixture was stirred at 10-15 ^{o}C for 2 hours. After the completion of the reaction, the mixture was concentrated to residue. Purified water 500.0 ml was added and pH was adjusted to 7.5-8.0 using aquaeous ammonia under stirring. The mixture was extracted with dichloromethane. The combined organic extracts was dried over sodium sulfate, concentrated under vacuum to afford moxifloxacin base as a yellow powder.mp: 206-208 ^{o}C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 8.62 (s, 1H, H-2); 7.60 (d, *J* = 14.5 Hz, 1H, H-5); 4.12-4.10 (m, 1H, H-13); 3.98-3.94 (m, 1H); 3.88-3.86 (m, 1H); 3.54 (s, 3H, H-12); 3.37-3.23 (m, 3H); 2.88-2.86 (m, 1H); 2.54-2.51(m, 1H); 2.24 (m, 1H); 1.73- 1.59 (m, 3H); 1.41 (m, 1H); 1.21-1.17 (m, 1H); 1.13-1.08 (m, 1H); 1.02-0.96 (m, 1H); 0.89-0.84 (m, 1H). ^{13}C-NMR (125MHz, DMSO-d_6) δ (ppm): 175.8; 165.9; 153.7; 149.9; 140.2; 137.3; 134.5; 116.4; 106.3; 106.1; 61.1; 58.5; 56.0; 52.1; 44.4; 40.6; 36.3; 22.9; 21.5; 9.6; 8.1. ESI-MS m/z: $[M-H]^-$: 400.



3. RESULTS AND DISCUSSION

We firstly started our study by the preparation of acetoxyboronate complex of fluoroquinoline ring.The reaction of boric acid with acetic anhydride formed the triacetoxyboronate, that was treated withethyll-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylate to produce the desired complex just for 2hrs [7]. Compared to the previous report of difluoroboron complex, that was obtained in 84% yield in 18 hrs reaction with $BF_3.Et_2O$ [6], this method has many advantages. The reaction used low-cost reagents like boric acid and acetic anhydride, the complex was obtained in a

better yield (96 %) than that of difluoroboron one and in a reduced time (only 2-3hrs).The ^{1}H-NMR showed the signals of protons of fluoroquinolone ring at δ_H 9.19 (s, 1H,H-2), 8.07 (t, 1H, H-5), 4.38 (m, 1H, N-C<u>H</u>) and 1.43-1.28 (m, 4H, C<u>H</u>$_2$-cyclopropyl ring). Moreover, a signal of two new acetyl groups attached to boron was found at δ_H 2.01 ppm while the peak of ethyl ester group disappeared. The molecular ion peak $[M+H]^+$ was found at 424 in the ESI-MS spectrum.Therefore, the acetoxyboronate complex structure was confirmed by the spectroscopy data.

Next, the condition of the coupling reaction between the side chain amine and the acetoxyboronate complex was investigated. Like the difluoroboron complex, the side chain amine reacted regioselectively at C-7 position of the fluoroquinolinering. The solvents and the temperature of the reaction were varied. The results were shown in the table 1.

Table 1: Yields of the coupling reaction at different conditions

No	Solvent	Temp., ^{o}C	Time	Yield, %
1	MeCN	80	30 min	64.5
2	MeOH	80	40 min	58.7
3	EtOH	80	40 min	60.3
4	Toluene	80	2 h	51.1
5	MeCN	50	1 h	68.7
6	MeCN	25	2.5 h	73.5

Different solvents like MeOH, EtOH, acetonitrile and toluene was selected for the investigation. The reaction mixture of the complex, amine and triethylamine was heated at 80^{o}C. Reaction using acetonitrile as the solvent gave the best result, Moxifloxacin was obtained in 64.5 % yield.

Then the temperature of the reaction using acetonitrile as the solvent was varied. At lower temperature, the reaction required longer time as expected but gave better yields. This result is consistent with our reported paper [6], the reaction of the acetoxyboronate complex using solvent acetonitrile and at room temperature afforded moxifloxacin base with highest yield of 73.5 %. The yield of this method is slightly higher than that of previous synthetic route using difluoroboron complex (67.8 %). The structure of Moxifloxacin was confirmed by IR, NMR and MS data and identical with the previously reported literature [6, 8].

4. CONCLUSION

In summary, Moxifloxacin base was obtained from fluoroquinolinering *via* acetoxyboronate complex with 70 % overall yield. This method gave the desired moxifloxacin with better yield than that of difluoroboron complex (60 %). In adition, the preparation of the acetoxyboronate complex is more effective, using low-cost chemical reagents, a shorter time and better yield. This synthetic route was successfully applied to prepare Moxifloxacin in large scale.

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