# Regioselective synthesis of quinolone antibacterials *via* borate complex of quinolone carboxylic acid

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1-substituted 7-chloro-6-fluoro-4-oxo-1,2-dihydroquinoline-3-carboxylic acids were converted to borate complexes. These compounds were treated with piperazine in presence of triethylamine to afford ciprofloxacin and norfloxacin in high yields.

**Keywords:** quinoline, borate complex, ciprofoxacin, norfloxacin

Ciprofloxacin **(2a**) and norfloxacin (**2b**) are widely used antibiotics in bulk quantities. They are totally synthetic antibacterial agents that have gained acceptance for use in the treatment of various bacterial infections.[1]

**2a** and **2b** can be prepared by substitution of chloro atom of corresponding acid (**1a** and **1b**) with piperazine in the presence of base.[2] In these reactions the unwanted products **3a** and **3b**, resulting from substitution of fluorine atom by piperazine are also formed.

Reaction of **1a** or **1b** with piperazine in water at 150°C gives also the above mixture. The yields for **2a** and **3a** were reported 65% and 10%, respectively.[3] Microwave assisted amination of quinolone carboxylic acids for the expeditious synthesis of fluoroquinolone antibacterials including **2a** and **2b** have been also reported.[4]

Enhancement of halogen activity by chelating of the β-keto acid part of quinolonic acid with boron triacetate have been patented.[5] Although the process claims to have more than 90% yield, actually it never exceeds 75%.[6]

Since the quinolone drugs like ciprofloxacin **2a**, norfloxacin **2b** *etc*. are very useful broad spectrum antibacterial drugs, there is a need to enhance the yield as well as the purity of the aforementioned compounds. Accordingly there is an urgent need for developing an improved process for the preparation of these compounds.

$BF_3.OEt_2$ is a commercially available reagent which has application as a Lewis acid.[7] In order to study the reactivity of piperazine with chlorofluoro–quinolone carboxylic acids **1a** and **1b** and avoid the excess of piperazine, the condensation of piperazine with complex resulting from the reaction of **1a** and **1b** with $BF_3.OEt_2$ was studied. Various conditions varying time, temperature, concentration and a base as a catalyst were studied. Under optimised conditions, using $BF_3.Et_2O$ as chelating agent, $CH_2Cl_2$ as solvent and triethylamine as a base the reaction of **1a** and **1b** with boron trifluoride gave the corresponding complexes (**4a** and **4b**). It was observed that piperazine reacts only at C-7 of these complexes to replace chlorine to afford the boron complexes of ciprofloxacin and norfloxacin (**5a** and **5b**), respectively. Treatment with sodium hydroxide gives the corresponding salts, which were converted to ciprofloxacin **2a** and norfloxacin **2b** in high yields (90% and 92%), respectively (Scheme 2).

In conclusion, we have demonstrated that $BF_3.OEt_2$ serves as a chelating agent for **1a** and **2b**, which regioselectively undergo nucleophilic substitution with piperazine to afford **2a** and **2b** in high yields and high purities.

## Experimental

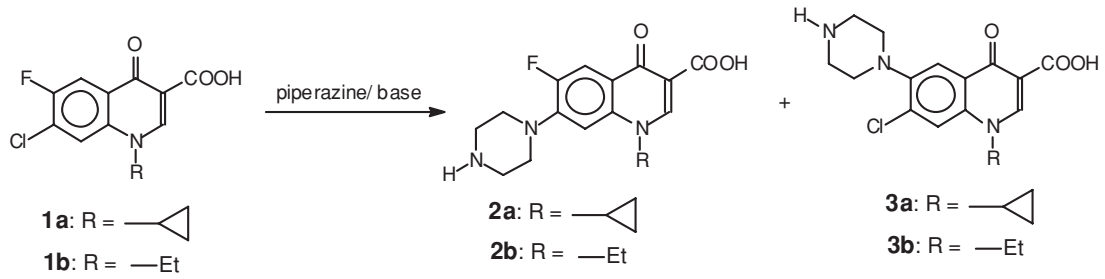
Melting points were measured by using capillary tube method with electro thermal 9100 apparatus. $^1$H NMR and $^{13}$C NMR were recorded on Bruker 500. IR spectra were recorded as KBr discs on a FT-IR Bruker Tensor 27. Mass spectra were measured on Varian CH 7.

*Difluoro[7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylato-O$^3$,O$^4$]boron.* **4a**: In a round bottomed flask (100 cm$^3$) equipped with stirrer and condenser, compound **1a** (1.5 g, 5.33 mmol) in $CH_2Cl_2$ (30 ml) was prepared. Boran trifluoride in diethyl ether (787 ml, 6.4 mmol) was added to this solution and refluxed for 5 h. The progress of reaction was monitored by TLC using ethyl acetate: heptane (3:1) as eluent. Upon completion, the reaction mixture was cooled down to room temperature. The solid was filtered, washed with a mixture of methanol-water to afford the title compound.

Yield: 1.24 g (71%), m.p. > 250°C; IR $\nu_{max}$ (KBr disc) 1711, 1680, 1533, 1507, 1470, 1125, 1025 cm$^{-1}$; $^1$H NMR, δ ($d_6$-DMSO) 1.5 (m, 4H,), 3.4 (s, 1H,), 8.5 (d, 1H,), 9.0 (d, 1H,), 9.5 (s, 1H,); MS, *m*/*z* 254.

*Difluoro[1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinolene-3-carboxylato-O$^3$,O$^4$]boron.* **5a**: Compound **4a** (0.33 g, 1 mmol), piperazine and triethyl amine (0.202 g, 2 mmol) were stirred in dry DMSO (3 ml) for 3 h. The precipitated solid was filtered, washed with a mixture of methanol and water to afford the title compound.

Yield: 0.36 g (96%), m.p. > 270°C (decomp.); IR $\nu_{max}$ (KBr disc) 1711, 1630, 1585, 1538, 1338 cm$^{-1}$; $^1$H NMR, δ ($d_6$-DMSO) 1.5 (m, 4H,), 3.5 (s, 4H,), 3.85 (s, 4H,), 4.2 (s, 1H,), 7.8 (d, 1H,), 8.1 (d, 1H,), 9.1 (d, 1H,).




**Scheme 1**

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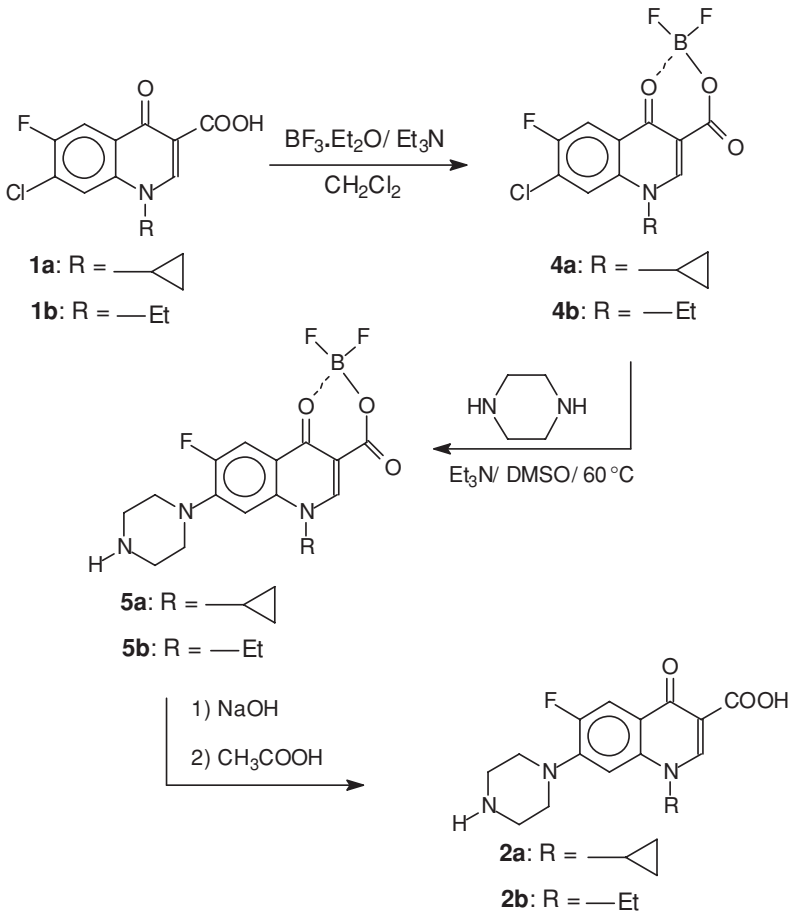


**Scheme 2**

*1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl) quinoline-3-carboxylic acid. Ciprofloxacin*, **2a**: Compound **5a** (1 g) in 1N sodium hydroxide (10 ml) was refluxed for 1 h. The reaction mixture was cooled to room temperature and was adjusted to pH 7 by addition of acetic acid. The precipitated solid was filtered and washed with a mixture of methanol and water and crystallised from acetic acid to afford pure ciprofloxacin.

M.p. = 256–258°C (255–257°C lit.[8]); $^1$H NMR, δ ($d_6$-DMSO) 1.25 (m, 2H,), 1.45 (m, 2H,), 3.5 (s, 4H,), 3.75 (s, 4H,), 3.8 (s, 1H,), 7.75 (d, *J* = 7Hz, 1H,), 8.0 (d, *J* = 11Hz, 1H,), 8.75 (s, 1H,); $^{13}$C NMR, δ ($CD_3COOD$) 8.2 (t), 36.7 (d), 44.3 (t), 47.2 (t), 107 (d), 112.3 (d), 121 (s), 120.2 (s), 140 (s), 145.5 (s), 145.6 (s), 149 (s), 169.3 (s), 177.2 (s); MS *m*/*z* $M^+$ 331 (30), 287 (85), 245 (100).

Compounds **4b**, **5b** and **2b** were synthesised similarly to **4a**, **5a** and **2a**, respectively.

*Selected data for difluoro[7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylato-$O^3$,$O^4$]boron*, **4b**: Yield: (95%), m.p. 287–289°C; IR $\nu_{max}$ (KBr disc) 1707, 1627, 1319 cm$^{-1}$; $^1$H NMR, δ 1.5 (t, 3H,), 5.0 (q, 2H,), 8.5 (d, 1H,), 8.9 (d, 1H,), 9.5 (s, 1H,).

*Selected data for difluoro[1-ethyl-6-fluoro-4-oxo-7-(piperazyn-1-yl)-1,4-dihydroqinoline-3-carboxylato-$O^3$,$O^4$]boron*, **5b**: Yield: (98%), m.p. 248–250°C; $^1$H NMR, δ ($d_6$-DMSO) 1.5 (t, 3H,), 3.0 (q, 4H,), 3.2 (s, 4H,), 3.3 (s, 1H,), 4.6 (q, 2H,), 7.5 (d, 1H,), 8.2 (d, 1H,), 9.4 (s, 1H,).

*Selected data for 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl) quinoline-3-carboxylic acid. Norfloxacin*, **2b**: Yield: (98%), m.p. 228–229°C (227–228°C lit.[8]); $^1$H NMR, δ ($d_6$-DMSO) 1.5 (t, 3H,), 3.1 (s, 4H,), 3.3 (s, 4H,), 4.60 (q, 2H,), 7.3 (d, 1H,), 8.0 (d, 1H,) 9.1 (s, 1H,), 14.1 (s, 1H).

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