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Microwave assisted amination of quinolone carboxylic acids: an expeditious synthesis of fluoroquinolone antibacterials

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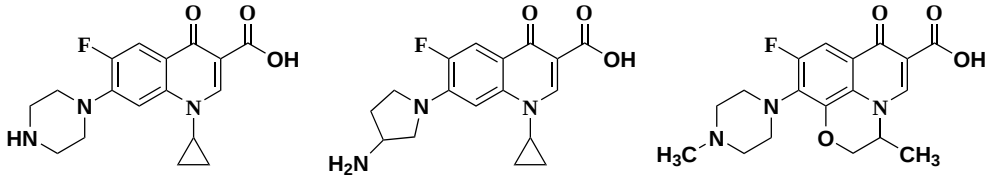
Abstract—A facile amination of quinolone carboxylic acids to fluoroquinolone antibacterials under microwave irradiation is described.

The fluoroquinolones such as ciprofloxacin, norfloxacin and sporfloxacin are totally synthetic antibacterial agents that have gained wide acceptance for use in the treatment of various bacterial infections.[1] Their mode of action is believed to involve inhibition of bacterial DNA gyrase, an enzyme essential for DNA replication.[2] Moreover, recent studies have identified some quinolones which also inhibit mammalian topoisomerase-II as potential lead compounds in the development of anticancer drugs.[3] In addition, very recently, it has been reported that fluoroquinolone antibacterials having the pyridone carboxylic acid skeleton at the N-1 position, show anti-HIV activity.[4] In general, piperazine or 3-aminopyrrolidine derivatives at the C-7 position of the quinolone nucleus have significant biological activity (Scheme 1). Knowing of the increasing incidence of bacterial resistance to a large number of antibacterial agents[5] coupled with the desire to make more potent broad spectrum quinolone antibacterials, we embarked on the synthesis of chemically modified quinolones and subsequently reported novel fluoroquinolone antibacterials having chiral 3,4-diaminopyrrolidine derivatives at the C-7 position.[6]

Fluoroquinolone antibacterials are conveniently prepared by the direct amination of 7-halo-6-fluoroquinolone-3-carboxylic acids with piperazine or pyrrolidine derivatives under thermal conditions. Unlike piperazine derivatives, pyrrolidine derivatives are less reactive towards the quinolone nucleus and in fact (3*R*,4*R*)-3,4-diaminopyrrolidine derivatives do not undergo direct amination with quinolone carboxylic acids.[6] However, we could overcome this problem by converting the quinolone carboxylic acid to the corresponding, more reactive, borate ester (Scheme 2).[7] Hence, the ideal approach would be the direct amination of quinolone carboxylic acids under mild reaction conditions which would allow us to generate diverse chemical libraries[8] for biological screening. In this communication we report a facile and general method for the direct amination of quinolone carboxylic acids with less reactive amines under microwave conditions.[9]

Microwave assisted synthesis of fluoroquinonolone antibacterials involves irradiation of a mixture of the 7-halo-6-fluoroquinolone carboxylic acid **1**[10] and an excess of the amine **2** in DMSO using an unmodified



Scheme 1.

Keywords: fluoroquinolone; antibacterial; amination; microwave.

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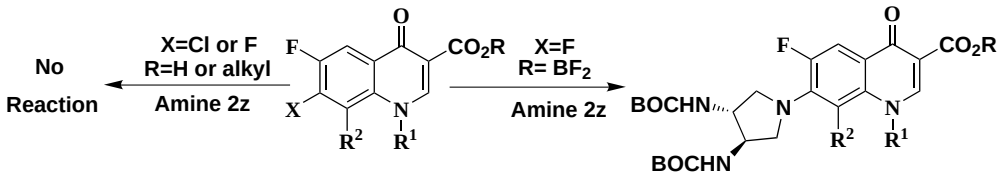
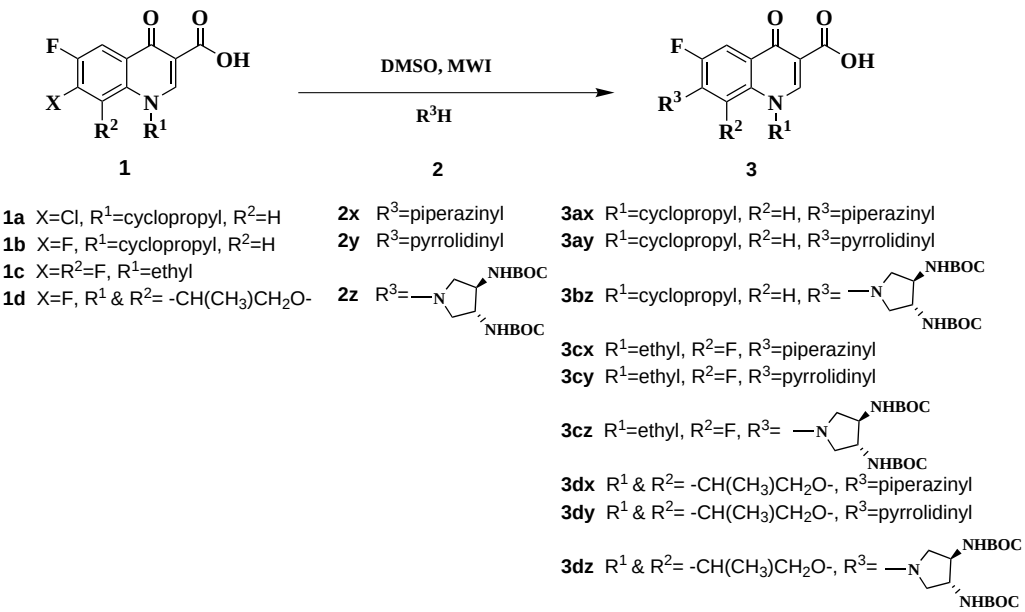


Scheme 2.

domestic microwave oven (Scheme 3).[11] A beaker of water was kept near the reaction vessel to serve as a 'heat sink' to provide fine control of the temperature of the reaction mixture.[12] The reaction mixtures were continuously exposed to microwave irradiation for no more than 10 min. In the case of reactions requiring longer time, after regular intervals they were exposed again to microwave irradiation. Unlike conventional methods,[13] these reactions are very facile (8–35 min), the isolation procedure is very simple and the product does not require any further purification. After completion of the reaction, the mixture was cooled to room temperature and then triturated with water. The triturated mixture was allowed to stand at 0°C for 1 h to complete the separation of product and then filtered to give the pure fluoroquinolone **3** in very good yields. In the case of entries 1, 4 and 7, better yields were obtained by removing DMSO under vacuum followed by triturating the residue with aqueous isopropanol. The purity of the isolated product was found to be very high by HPLC (>92%).[14] The reaction times and yields are shown in Table 1. Although, both piperazine **2x** and pyrrolidine **2y** underwent facile aromatic nucleophilic substitution with 7-fluoro- as well as 7-chloroquinolone-3-carboxylic acids **1a–d** under microwave conditions, the rate of reaction of piperazine **2x** was found to be faster than pyrrolidine **2y**. Chiral (3*R*,4*R*)-3,4-diaminopyrrolidine derivative **2z**, derived from L(+)-tartaric acid,[6] reacted readily with 6,7-difluoroquinolone-3-carboxylic acids **1b–d**, however the reaction of **2z** with the 7-chloro-6-fluoroquinolone-3-carboxylic acid **1a** was found to be very slow and resulted in the isolation of impure product.

Typical experimental procedure: A mixture of 1-ethyl-6,7,8-trifluoro-4-oxo-1,4-dihydro quinoline-3-carboxylic acid **1c** (100 mg, 0.37 mmol) and (3*R*,4*R*)-3,4-diamino pyrrolidine **2z** (212 mg, 0.78 mmol) in DMSO (1.5 mL) was irradiated in an unmodified domestic microwave oven at power setting 2 for 20 min (2×10 min pulse).[11] The reaction mixture was cooled to room temperature, triturated with water (3 mL), allowed to stand at 0°C for 1 h and then filtered. The solid was washed with water (2 mL) and dried under high vacuum to afford pure fluoroquinolone **3cz**[6] (165 mg, 85%) as an off white solid, mp 254–256°C.

In conclusion, we have developed a facile and general synthesis of fluoroquinolone antibacterial agents by direct amination of 7-halo-6-fluoroquinolone-3-carboxylic acids in excellent yields, under microwave conditions. We are confident this methodology will allow us to develop chemical libraries of fluoroquinolone analogues at the fraction of the normal cost and time for biological testing.



Scheme 3.

Table 1. Microwave assisted synthesis of fluoroquinolones

Entry	Substrate	Amine (equiv.)	Time (min)	Product[a]	Yield[b] (%)	Purity[c] (%) (HPLC)
1	**1a**	**2x** (3.5)	10+10	**3ax**	84	99.84
2	**1a**	**2y** (3.0)	10+10+10+5	**3ay**	78	98.95
3	**1b**	**2z** (2.5)[d]	10+10+10+5	**3bz**	83	92.74
4	**1c**	**2x** (3.5)	8	**3cx**	81	96.54
5	**1c**	**2y** (5.0)	8	**3cy**	82	96.85
6	**1c**	**2z** (2.1)	10+10	**3cz**	85	99.47
7	**1d**	**2x** (3.5)	10+5	**3dx**	75	98.79
8	**1d**	**2y** (5.0)	10+5	**3dy**	87[e]	96.98
9	**1d**	**2z** (2.1)	10+10+10+5	**3dz**	94[e]	92.08

[a] All the products gave satisfactory spectral data.
[b] Isolated yields.
[c] For HPLC conditions see Ref. 14.
[d] Reaction was carried out in presence of 3 equiv. of Hunig base.
[e] Reaction mixture was extracted with CH_2Cl_2 after adding water.

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14. HPLC Conditions: Column: Inertsil ODS-2, 25 cm, 4.6 mm, 5μ (GL sciences); flow rate: 1.0 mL/min; temperature: 35°C; mobile phase: 45% buffer solution (to a solution of 0.05 M sodium lauryl sulfate was added 0.1% triethylamine and the pH of the solution was adjusted to 3.0 using 0.1 M phosphoric acid) in acetonitrile; sample concentration: 0.1 mg/mL in acetonitrile.