AN EXPEDITIOUS SYNTHESIS OF QUINOLONE ANTIBACTERIALS

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Abstract: A facile and rapid synthesis of ciprofloxacin under microwave irradiation is described. The product ciprofloxacin was isolated and the impurity was characterized as the product of substitution of fluorine instead of chlorine in acid **1**. Similarly norfloxacin was synthesized.

Quinolones represent a large family of synthetic antibacterial agents, which inhibits the two important bacterial enzymes and are characterized by a broad spectrum antibacterial activity (1). The fluoro derivatives of these compounds are the latest addition to the therapeutic agents that are presently used in clinical practice to fight Mycobacterium tubercular infections (2).

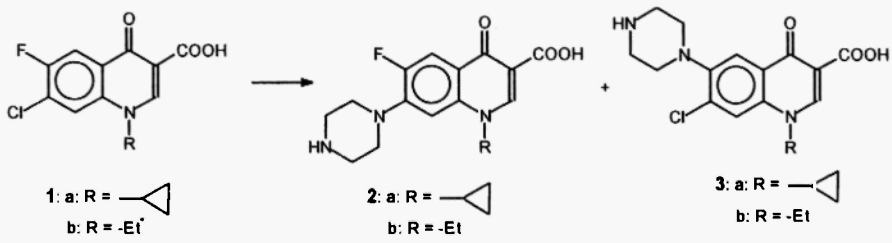
Among them ciprofloxacin **2a** and norfloxacin **2b** are widely used antibiotics in bulk quantities. In fact **2a** is the most widely used as third generation quinolone antibiotic in the world and is superior to chloroamphenicol, aminoglycosides and cephalosporin and commonly used for curing enteric fever, septicaemici, bronchopeneiemonia aestrogelitis, prostates and non-genococial arethritis (3).

2a and **2b** are commonly prepared by the substitution reaction of an appropriate acid **1a** and **1b** with piperazine (4). Use of borate or fluoroborate complex of quinolone carboxylic acid in order to obtain fluoro derivative **2a** and **2b** predominantly have been also reported (5).

Application of the microwave heating technique is currently under extensive examination (6). As a part of our on going research program to develop chemical transformation under microwave irradiation (7), in this communication we report an efficient, rapid and selective synthesis of quinolone antibacterials, ciprofloxacin **2a** and norfloxacin **2b**.

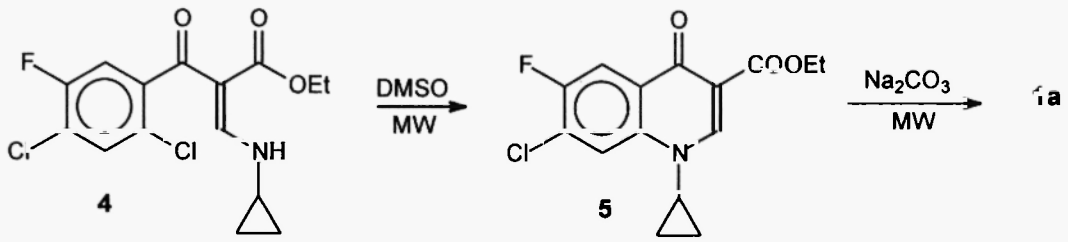
Results and Discussions

In order to study the reactivity of piperazine with chloro-fluoro-quinolone carboxylic acid (1a and 1b) and avoid the excess of piperazine and solvents which are normally employed (DMF, DMSO or DMAC), the substitution of piperazine with **1a** and **1b** in water has been studied (3). Even under optimized conditions, it was observed that piperazine reacts at both positions C-6 (substitution of fluorine) afford **2a** and **2b** and C-7 (substitution of chlorine) to give **3a** and **3b** (Scheme-1)



Scheme-1

Prompted by stringent environmental protection laws in recent years, there have been increasing emphasis on the use and design of eco-friendly reagents, solid state and solvent free reactions (8). At first we tried to cyclize 2-(2,4-dichloro-5-fluorobenzoyl-3-cyclopropylamine-ethylacrylate 4 to ester of 1-cyclopropyl-6-fluoro-7-chloro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid **5** under microwave irradiation in solventless system, which did not go to completion. However, when we used DMSO as solvent in open vessel, reaction completed in four minutes in 90% yield to afford **5**. Compound **5** was hydrolyzed to the corresponding acid **1a** under microwave irradiation in sodium carbonate solution (Scheme-2).



Scheme-2

Microwave assisted synthesis of **2a** and **2b** involves irradiation of mixture of **1a** and **1b** (9) and excess of piperazine in DMSO using a household microwave oven. The progress of reaction was monitored by TLC. Both reactions were completed in ten minutes in high yields. Under thermal condition reaction of piperazine with **1a** has been completed after refluxing 18 hrs in pyridine in 69% yield (9).

Unlike thermal reaction, microwave reactions are very fast (10 min), the isolation of product is very simple and the product does not require any further purification. The yield of reaction is also high (77%).

In summary, a facile, rapid and high yielding synthesis of ciprofloxacin and norfloxacin under microwave irradiation has been developed. By development of use of microwave oven at industrial level, we hope this methodology find application in pilot plant.

Experimental

Melting points were determined on a Reichert apparatus and are uncorrected. IR spectra were recorded on a FT, Bruker Tensor 27 using KBr discs. ^{1}HNMR spectra were recorded on a Bruker (500 MHz) instrument using TMS as internal standard.

Synthesis of 1-cyclopropyl-6-fluoro-7-chloro-4-oxo-1,4-dihydro-quinoline-3-ethyl ester 5

A mixture of compound 4 (0.1 g, 0.03 mmol), sodium carbonate (0.05 g, 0.04 mmol) and DMSO (1 mL) in a beaker was placed in a household microwave oven at power of 1000 W for 4 min. To the crude, chloroform (10 mL) was added. The reaction mixture was filtered off and the filtrate was evaporated to dryness under reduced pressure. Yield: 0.09 g (90%); mp: 225-6 C (lit.: 224-5 C[10]); ^{1}HNMR δ ($CDCl_3$) 1.1-1.5 (m, 4H, 2 CH_2 cyclopropyl), 1.4 (t, 3H, Me), 3.2-3.5 (m, 1H, CH cyclopropyl), 3.4 (q, 2H, CH_2), 7.8 (d, J = 9 Hz, 1H, aromatic), 8.2 (d, J = 8.5, 1H, aromatic), 8.55 (s, 1H, CH); IR, $\tilde{\upsilon}$ (KBr disc) 1730, 1700, 1610, 1549, 1476, 1250 cm^{-1}.

Synthesis of 1a

Ester **5** (0.1 g, 0.03 mmol) was dissolved in aqueous Na_2CO_3 (0.2 g) in water (1 mL) in a beaker. The beaker was placed in a household microwave at power of 300 W for 10 min. After completion of reaction $CHCl_3$ (10 mL) was added. The mixture was filtered off and the filtrate evaporated to dryness under reduced pressure to afford **1a**. Yield: 0.08 g (88%); mp: 245-6 C (lit.: 246-7 C[10]); ^{1}HNMR δ (d6-DMSO) 1.1-1.4 (m, 4H, 2 CH_2 cyclopropyl), 3.6-4.0 (m, 1H, CH cyclopropyl), 8.2 (d, J = 9 Hz, 1H, aromatic), 8.5 (d, J = 8.5, 1H, aromatic), 8.75 (s, 1H, CH), 14.5 (s, broad, 1H, COOH); IR, $\tilde{\upsilon}$ (KBr disc) 1726, 1613, 1444, 1183, 1024, 743 cm^{-1}; MS, m/z, M+ 281 (25), 239 (65), 237 (90), 236 (52), 222 (27), 208 (36), 41 (100).

Synthesis of ciprofloxacin 2a

Acid **1a** (0.1 g, 0.04 mmol) and piperazine (0.06 g, 0.75 mmol) were mixed in a beaker. The beaker was placed in a household microwave oven at power 400 W for four intervals of 5 minutes. After completion of reaction, water (2 mL) was added, the mixture was adjusted to pH 7 by 10% hydrochloric acid and cooled. The precipitated solid was collected by filtration, washed with water at dissolved in 4% hydrochloric acid (2 mL) at 80 C. After treatment with charcoal, the solution was cooled. The resulting crystal was collected by filtration and washed with ethanol to give ciprofloxacin hydrochloride. Yield 0.1 g (78%), mp.: > 300 C (lit.: 308-10[11]).

Synthesis of norfloxacin

Acid **1b** (0.1 g, 0.031 mmol) and piperazine (0.06 g, 0.75 mmol) were mixed in a beaker. The beaker was placed in a household microwave oven for four intervals of 5 minutes. After completion of reaction, water (2 mL) was added, the mixture was adjusted to pH 7 by 10% hydrochloric acid and cooled to 0 C. The precipitated solid was collected by filtration, washed with water at dissolved in 4% hydrochloric acid (2 mL) at 80 C. After treatment with charcoal, the solution was cooled. The resulting crystal was collected by filtration and washed with ethanol to give ciprofloxacin hydrochloride. Yield 0.8 g (66%), mp.: 220-1 C (lit.: 221[4c]).

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