CONVENIENT ONE POT SYNTHESIS OF SOME FLUOROQUINOLONES IN AQUEOUS MEDIA

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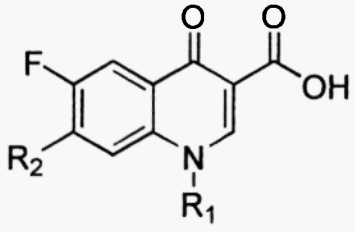
Abstract: A one pot synthetic strategy for the preparation of fluoroquinolones from **1** is introduced. Product **3** was condensed with piperazine in an aqueous media to produce pharmaceutical grade ciprofloxacin in 86% yield. The method was extended to the synthesis of some other fluoroquinolones with pharmaceutical grade quality.

Keyword: Ciprofloxacin, enrofloxacin, norfloxacin, pefloxacin, fluoroquinolones.

Introduction

Fluoroquinolones are synthetic antibiotics (1-7), which contain a quinolone structure and are effective on a wide range of Gram-positive and Gram-negative bacteria. They interrupt the production of bacteria DNA through DNA gyrase inhibition (8). Recently, more highly effective broad-spectrum antibacterial agents containing fluorine atom at C-6 have been synthesized. Solid phase synthesis (9-10) and microwave preparation (11-12) of some examples are also reported. Some general examples are ciprofloxacin (13), norfloxacin (14), enrofloxacin (15), and pefloxacin (16) with the structures illustrated in Scheme-1.



Ciprofloxacin: R^1=cyclopropyl, R^2= 1-piperazinyl; enrofloxacin: R^1=cyclopropyl, R^2= 4-ethyl-1-piperazinyl; norfloxacin: $R^1 = C_2H_5$, R^2= 1-piperazinyl; pefloxacin: $R^1 = C_2H_5$, R^2 = 4-methyl-1- piperazinyl

Scheme-1

Results and Discussions

Several synthetic routes have been reported so far for the synthesis of such structures (17-19). The present research focused on the optimization of fluoroquinolones synthetic approach for further convenient industrial production of such compounds. In this work, a decrease in the number of steps of the reactions has been achieved and the condensation of the required carboxylic acids with piperazine derivatives in the key step is conducted in water media (Scheme-2). This methodology optimizes the process, from temperature, concentration, yields, and reaction time points of view.

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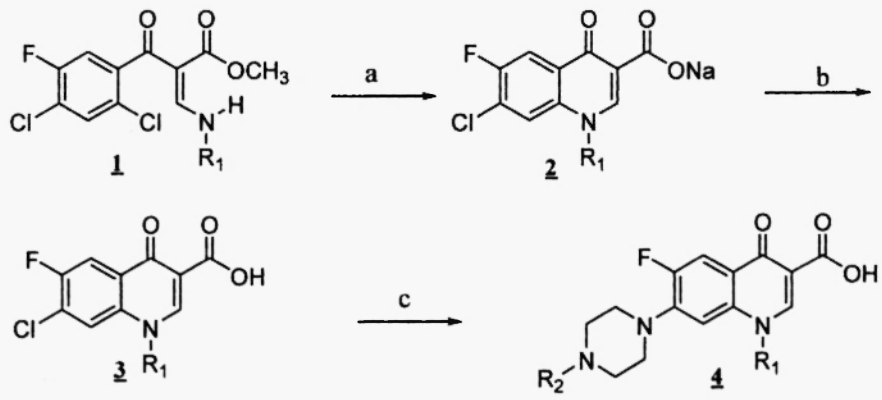


A: toluene, NaOH, 110 °C, 4 hrs; b: vacuum distillation, H^+/H_2O; c: piperazine (or 1-alkyl piperazine), 115 °C, 14 hrs.

Scheme-2

Compound 1 is the starting material which is made by the method reported by Grohe and co-workers (18). Cyclization and hydrolysis of the esters are carried out in the presence of excessive NaOH in refluxing toluene or dioxane. Removal of the solvent followed by acidification of the residual yields the required carboxylic acid 3. Subsequent condensation of 3 with piperazine derivatives in aqueous media furnishes the production of the desired fluoroquinolone derivative 4 in yields above 85% along with minor side product 5. The results are summarized in the Table.

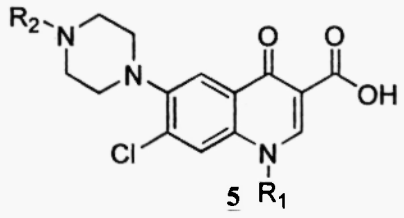
Table: Results of the condensation reactions of 3.

R1	R2	Temperature (°C)	Time (h)	yield
	H	115	14	86%
	C_2H_5	112	12	89%
—Et	H	114	15	85%
—Et	CH_3	110	12	90%

Experimental

To 60 g (181 mmol) of ester 1 (R^1=cyclopropyl) in toluene was added NaOH (18g, 450 mmol) and the mixture was refluxed for 4 h. The solvent was removed under reduced pressure, the residue was mixed with excessive amount of water, and the mixture was acidified by dilute HCl. The solid phase was separated by filtration and was added to a refluxing solution of piperazine (45 g, 523 mmol) in 100 mL water in a 250 mL flask. The mixture was refluxed for 1 h under atmospheric pressure. The solvent volume was reduced to 50 mL and refluxing continued for another 14 h at 115 °C. The course of the reaction was monitored by HPLC method. The

suspension was diluted by 200 mL water and the pH of the mixture was adjusted at 7 before filtration of the precipitates. Analysis by HPLC showed the formation of ciprofloxacin and its related isomer 5 in a ratio of 6.7/1. The two products were separated by treating their solid mixture with a 1:2 (v/v) solution of H_2O/CH_3OH at pH=1, the conditions under which compound 5 dissolves and pure solid ciprofloxacin hydrochloride (59 g, 86%) is precipitated. The structure of the product is confirmed by H-NMR, MS and IR spectra.



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Conclusions

The present method illustrates that the cyclization and hydrolysis of esters of type 1 can be accomplished in solvents with low dielectrical constant and higher boiling points than 100 oC such as toluene or dioxane. The product of the first part, 3, without any purification requirement can be condensed directly by piperazine to give ciprofloxacin. Synthesis of similar structures using the present method has been successful and more examples are underway.

Acknowledgements

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