Controlled Microwave-Assisted Amination of Quinolone

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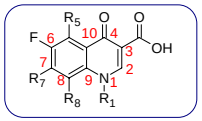
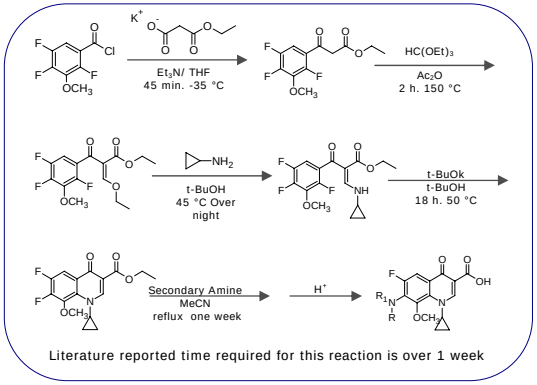
Introduction

The fluoroquinolone antibacterials' represented generically have generated much excitement after the discovery that a fluorine atom at C-6 enhances antibacterial activity. Norfloxacin is generally considered to be the first derivative noted for a significant increase in activity. However, flumequine was the first to demonstrate the advantage of a C-6 fluorine atom. The next entries into this class of antibacterials were ofloxacin, ciprofloxacin, and more recently tosufloxacin, all of which contain a piperazinyl or aminopyrrolidinyl moiety for R_7.



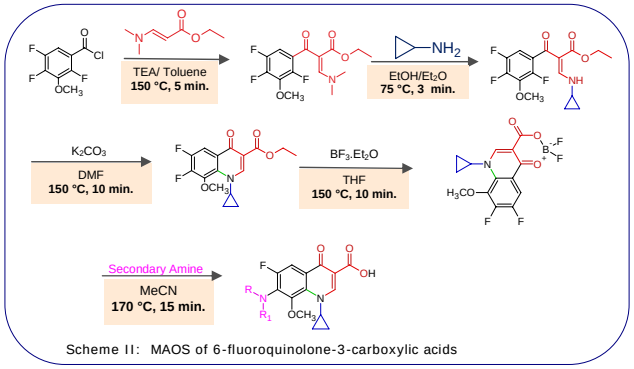
The emergence and alarming spread of bacterial, parasitical and viral strains that are resistant against clinically used drugs, is the driving force behind the ongoing search of new antibacterial and antiviral drugs. The conventional methods of synthesis and isolation any anti-infective agents generally take weeks. The long time required for multi-steps synthesis of these agents makes discovery process of new targets extremely cumbersome. All the literature reported methods of preparations of these class of compounds suffer from many disadvantages like long reaction period, use of strong acids (PPA, H_2SO_4,etc.)/ bases (NaOEt, sodium hydride, potassium 3-aminopropylamide (KAPA), sodium 3-aminopropylamide (NAPA), etc.), dehydrating agents ($ZnCl_2$, $AlCl_3$)[1].



Literature reported time required for this reaction is over 1 week

We have used MAOS for reducing total synthesis time for fluoroquinolones.

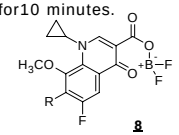
Fluoroquinolone antibacterial are conveniently prepared by the direct amination of 7-halo-6-fluoroquinolone-3-carboxylic acids with piperazine or pyrrolidine derivatives under thermal conditions.
Unlike piperazine derivatives, pyrrolidine derivatives are less reactive towards the quinolone nucleus and in fact (3R,4R)-3,4-diaminopyrrolidine derivatives do not undergo direct amination with quinolone carboxylic acids. However, we could overcome this problem by converting the quinolone carboxylic acid to the corresponding,more reactive, borate ester (Scheme 2).
The retrosynthetic scheme to obtain the targeted 6-fluoroquinoloes starting from commercially available acid chloride (1) is shown in scheme 1. The targeted quinolone is prepared through an intermolecular cyclization of enaminone intermediate (2) prepared using an (N-alkyl) acrylate (route II), this reported method is a milder condition and more efficient than the one depicted in the alternatives route I.



Scheme II: MAOS of 6-fluoroquinolone-3-carboxylic acids

Optimization of the microwave synthesis was performed in a single-mode reactor (sealed vessels) with possibilities for automated dispensing of reaction components and automated vessel transfer. The conditions obtained in the small-scale runs (2-5 ml Vials) was directly applied to larger scale 20 mL vials.

The literature published procedures for synthesis of fluoroquinoline requires over one week time with 15-18% overall yield. Microwave assisted synthesis was used to shorten time required for this multi step synthesis and improve the overall yield.
The introduction of the R_7 substituent through an aromatic nucleophilic substitution of the C-7 fluorine atom onto compound 6 was achieved in good yield under microwave irradiation when this position was activated as boron difluoride derivatives.
The boron trifluoride etherate 7 was prepared under microwave irradiation at 150 °C in 10 minutes [4], at 85% yield.
The literature reported aromatic nucleophilic substitution at C-7 is a very long and time-consuming seven days process [5]. Using microwave irradiation this step was completed in 15 minutes at 170 °C [5]. The major side product of this step is compound 8 in 75:25 ratio (TLC and HPLC). To break the etherate complexe 8, this residue was dissolved in EtOHand triethylamine and stirred at 160 °C for10 minutes. Then solvent was evaporated, the crude residue obtained was poured into 2 N NaOH and filtered. The precipitate was dissolved in DCM and washed with water, dried over Na_2SO_4, filtered and evaporated to afford the final fluoroquinolone in 60-88% yield.



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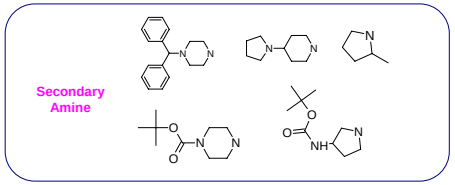
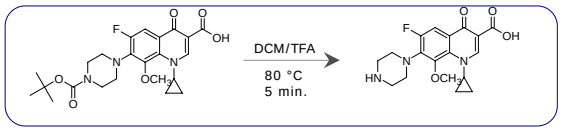
The following amine were reacted with boron trifluoride etherate 7



The Boc- deprotection was achieved using DCM/ TFA 1:1 mixture in 5 minutes at 80 °C. Additions of hexane and evaporations were performed to eliminate excess TFA to result the desired fluoroquinolone in 60-88% yield.



Conventional synthesis requires 386 hrs.
Microwave assisted synthesis requires >1 hr.

In conclusion

We have developed a fast and general method of direct amination of 7-halo-6-fluoroquinolone with piperazine or pyrrolidine derivatives under microwave assisted conditions.
We are confident this methodology will allow for the development of chemical libraries of fluoroquinolone analogues at the fraction of the normal cost and time for biological testing. Microwave heating has shorten the time required for multi step synthesis from week to less than one hour.

1: Kapil Arya* and Manish Agarwal, Bioorganic & Medicinal Chemistry Letters 17 (2007) 86–93
2: John M. Domagala,* Carl L. Heifetz, Marland P. Hutt, Thomas F. Mich, Jeffry B. Nichols, Marjorie Solomon, Donald F. WorthJournal, Medicinal Chemistry, 1988, Vol. 31, No. 5
3: Guillaume Anquetin, Jacques Greiner, Nassira Mahmoudi, Maud Santillana-Hayat, Rafael Gozalbes, Khemais Farhati, Francis Derouin Alexandra Aubry, mmanuelle Cambau, Pierre Vierling, European Journal of Medicinal Chemistry 41 (2006) 1478e1493
Compound 4 (785 mg, 2.37 mmol) in 1:2 EtOH/Et_2O (20 mL) was added to (0.38 mL, 5.48 mmol). After 3 minutes at 75 °C, The reaction mixture was evaporated under reduced pressure to result the pure product 5 at 86% yield.

3: Compound 5 (200 mg, 0.5 mmol) was dissolved in 5mL DMF and K_2CO_3 (220 mg,) was added. Reaction mixture was stirred for 10 min. at 150°C. filtered and 1 ml water was added to the solution then left in refrigerator for 30 min. white needle like precipitate was collated under vacuum filtration. 160 mg, 85.1%TLC: MeOH:DCM 1:9

4: $BF_3.Et_2O$ (MW. 141.93, d. 1.13, 0.75 ml, 5.9 mmol) was added to 4 (180 mg, 0.56 mmol) in suspension in THF (bp 65-67 °C) (10 mL) heated at 150 °C for 10 min., the clear reaction mixture was evaporated under reduced pressure. The crude oily residue was successively washed with Et_2O and water affording 5 as white solid 88%.

5: A solution of 1-(Diphenylmethyl)piperazine(252.35, 0.3 mmol, 76 mg) and 75 (69 mg, 0.2 mmol) in CH_3CN (bp 81-82) (4 mL) was heated in a microwave for 15 min. at 170 °C. After evaporation under reduced pressure, a yellow oil was collected.

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