A New Short and Efficient Strategy for the Synthesis of Quinolone Antibiotics

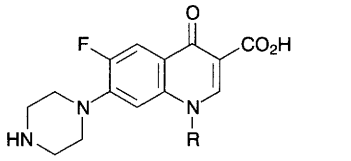
Andrew Jackson and Otto Meth-Cohn†

Chemistry Department, University of Sunderland, Sunderland, UK SR1 3SD

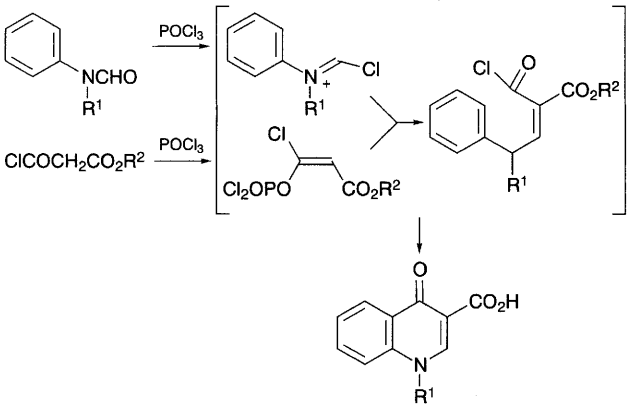
A simple protocol for the synthesis of quinolone antibiotics is exemplified for the synthesis of norfloxacin; 3-chloro-4-fluoroaniline with triethyl orthoformate is transformed into its *N*-ethyl-*N*-formyl derivative which reacts with methyl malonyl morpholide and phosphoryl chloride at 100 °C to give 6-fluoro-7-chloro-1-ethylquinol-4-one-3-carboxylic acid, which has previously been converted into norfloxacin by the action of piperazine.

The quinoline antibiotics, a very important alternative to β-lactams, tetracyclines and aminoglycosides, operate as DNA gyrase inhibitors against all types of Gram-negative bacteria.[1] The 6-fluoro-7-piperazinylquinolin-4-one-3-carboxylic acids have become the major drugs in this group, *e.g.* norfloxacin **1** and ciprofloxacin **2**. The Bayer synthesis for ciprofloxacin is long and costly; an expensive starting material is required and thus leads to a high priced drug. Herein we disclose a novel, simple approach exemplified by the three-step synthesis of norfloxacin.

We have demonstrated elsewhere the value of the Vilsmeier reaction in the synthesis of quinolines.[2] In particular, quinolinium salts are generated by the interaction of *N*-substituted formanilides, phosphoryl chloride and an electrophilic alkene precursor.[3] When methyl or ethyl malonyl chloride are used as the 'electrophilic alkene' (presumably by way of the 'enol' tautomer) a 4-chloro-quinolinium-3-carboxylate is produced which is readily transformed into a 4-quinolone by boiling in aqueous acid or by the action of a base (Scheme 1). This short, high yielding reaction is ideal for application to the synthesis of quinolone antibiotics.



1 R = Et, Norfloxacin
2 R = cyclopropyl, Ciprofloxacin

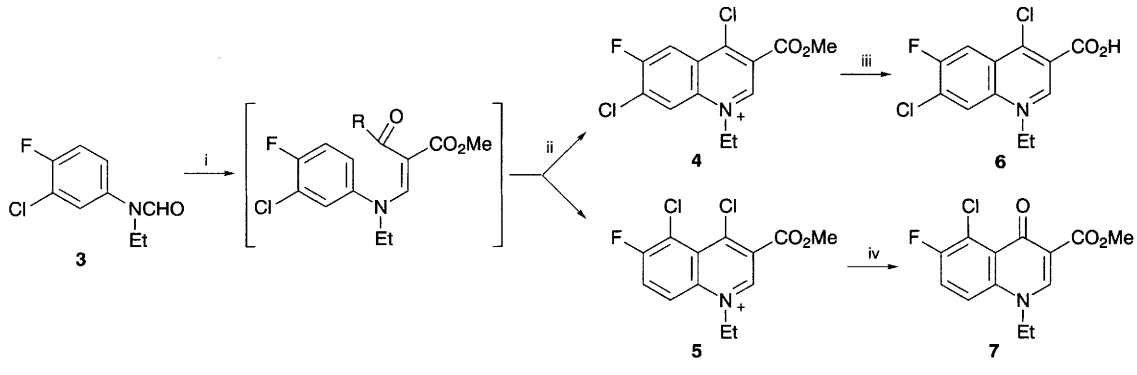


Scheme 1

3-Chloro-4-fluoroaniline is readily converted into 3-chloro-4-fluoro-*N*-ethylformanilide **3** by the action of triethyl orthoformate and catalytic sulfuric acid.[4] This unsymmetrically substituted formanilide is capable of cyclising either *ortho* or *para* to the chlorine substituent. On treatment with methyl malonyl chloride and phosphoryl chloride at 80 °C, a vigorous reaction ensued and after removal of the excess of phosphoryl chloride *in vacuo* and addition of water, a precipitate rapidly formed which proved to be pure methyl 1-ethyl-5-chloro-6-fluoro-4-quinolone-3-carboxylate **7** in 40% yield. It is evident that the 5-chloro-substituent sufficiently activates the hydrolysis of the 4-chloroquinolinium salt **5** to effect a kinetic separation of the two isomeric cyclisation products (Scheme 2). The intermediate salt **4** can be isolated at its hexafluorophosphate by addition of ammonium hexafluorophosphate to the aqueous solution. Alternatively, when this solution is boiled the required quinolone (**6**) is produced (41%).

By utilising the sterically more disciminating 'alkene' precursor, methyl malonyl morpholide (R = morpholino) in place of methyl malonyl chloride, a totally regiospecific reaction is observed giving solely the required quinolone **6** in 76% yield when the cyclisation was conducted in $POCl_3$ at 100 °C. Similarly, use of *N*-formyldiarylamines produces the important *N*-arylquinolones, another important type of quinolone antibiotic.

Received, 6th March 1995; Com. 5/02217G



Scheme 2 *Reagents and conditions*: i, $POCl_3$, $RCOCH_2CO_2Me$, 80 °C; ii, NH_4PF_6; iii, heat, H^+; iv, H_2O

Footnote

† E-mail: otto.meth-cohn@sunderland.ac.uk

References

1 For a review see: K. Grohe, *Chem. Br.*, 1993, 34.
2 For reviews see: O. Meth-Cohn and B. Tamowski, *Adv. Heterocycl. Chem.*, 1981, **31**, 207; O. Meth-Cohn, *Heterocycles*, 1993, **35**, 539.
3 O. Meth-Cohn and D. L. Taylor, *Tetrahedron Lett.*, 1993, **34**, 3629.
4 R. M. Roberts and P. J. Vogt, *Org. Synth., Coll. Vol. IV*, 420.