Tetrahedron Vol 47, No 36, pp 7609-7614, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00
Pergamon Press plc

A STRAIGHTFORWARD AND HIGH YIELDING SYNTHESIS OF MEFLOQUINE -II.

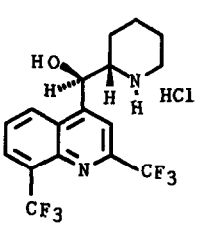
Solange Adam
Pharmaceutical Research Department
F. Hoffmann-La Roche AG.CH-4002 Basel (Switzerland)

(*Received in Germany* 28 *June* 1991)

Summary *A new practical and high yielding synthesis of mefloquine (1) is described Heteroarylation of 2-pyridylacetonitrile (2) gave the key intermediate 2-pyridyl-4-quinolylacetonitrile 4, which, on reaction with m-chloroperbenzoic acid, gave unexpectedly the cyanhydrine 5 The later, after base treatment afforded quantitatively the ketone 6*

Introduction

Several years ago (1977) we were interested in developing new synthetic routes to mefloquine (1), a highly active blood schizontocide against multi-drug resistant falciparum malaria.
In the preceding paper[1] we reported on its synthesis via fluoride ion-catalysed Wittig rearrangement. Unfortunately, one step in the synthesis has to be performed at -78°C precluding its use on the plant scale. In this article we describe a new practical and high yielding route to this potent antimalarial agent[2] which has been launched under the name Lariam^{R} (F. Hoffmann-La Roche).



mefloquine

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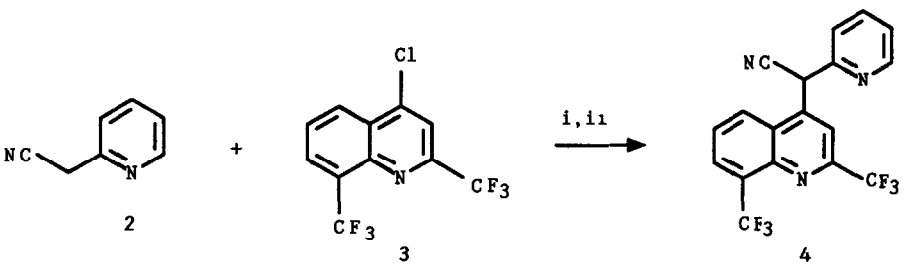
Results and Discussion

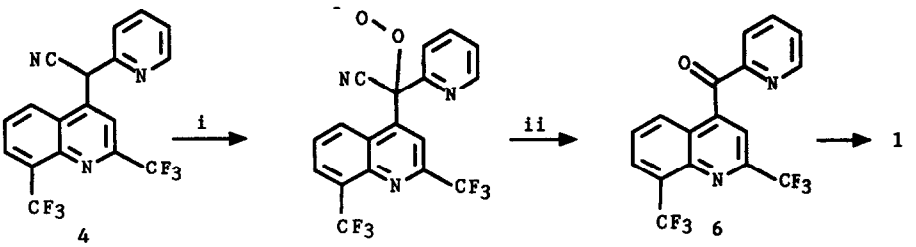
The base-catalysed oxidative decyanation of secondary nitriles has been shown to be a viable way to preparing ketones in relative fair yields.[3,4] Furthermore, we have shown that the combination of powdered KOH and air is a very efficient and powerful oxiding system.[1] Therefore our interest focused on the potential application of this oxidation to the 4-quinolyl-2-pyridylacetonitrile 4 (Scheme 1), which is as we found, readily available from 2-pyridyl acetonitrile[5] (2) and the 4-chloroquinoline 3 in 91% yield.



Scheme 1 Reagents i)NaH,toluene, DMF, 0-5° C , 1h
ii)chloroquinoline, 5-10° C, 2h

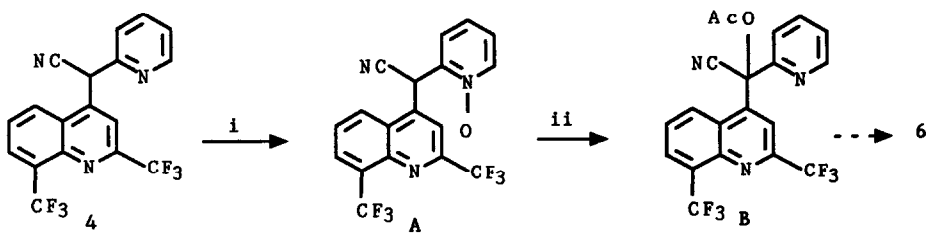
The nitrile 4 was then treated with 2.7 equivalents of powdered KOH in acetonitrile under aerobic conditions for several hours at room temperature. Following the addition of the base the already light rosa-coloured solution turned deep red. But surprisingly, only traces of the ketone 6 were detectable after 6 hours . The oxidation did go to completion but after more than 3 days at room temperature. The colour of the reaction mixture changed from red to yellow, this change indicating the end of the oxidation process. Probably, the red anion is trapped by oxygen to give as shown in Scheme 2, a peroxy intermediate which may disproportionate following the pathways already described.[1,3] In MeOH the reaction also proceeded with extreme sluggishness.

In an effort to decrease the reaction time,air or oxygen was bubbled into the solutions without much success. The use of other solvents and bases was also investigated without further improvement. Because these efforts were largely futile they will not be described here.



Scheme 2 Reagents i) base, air or O_2, ii) rt, > 3 days

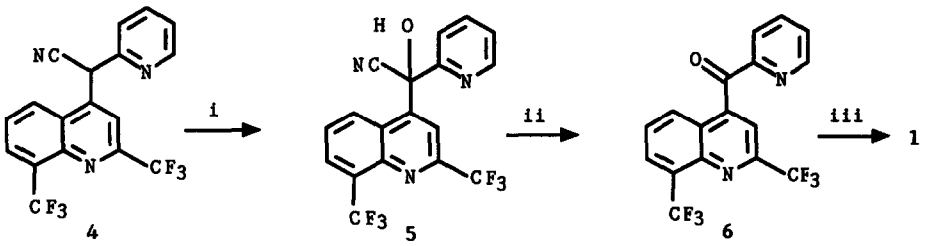
Although the preparation of mefloquine by this autoxidative route was novel, the synthetic utility appeared to be limited, so attention was turned to the alternative approach depicted in Scheme 3.



Scheme 3. Reagents i) oxidation, ii) Ac_2O

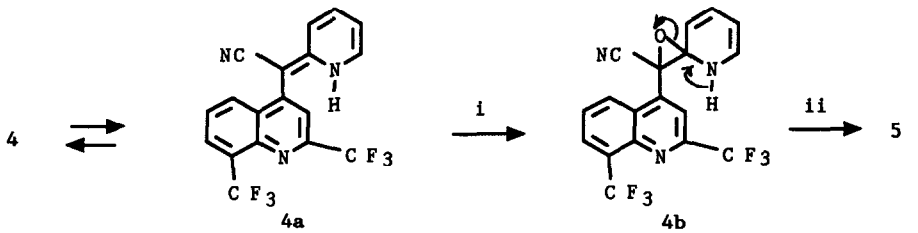
Plainly said,the basic idea was to prepare first the N-oxide **A** , then, to affect its rearrangement to the corresponding α-acetate **B** via the well known N-oxide rearrangement which occurs in the presence of acetic anhydride.[6] The nitrile 4 then, was treated at room temperature with one equivalent of m-chloroperbenzoic acid in ether and under these conditions a sole product was formed. Interestingly, it turned out that instead the N-oxide **A**, the compound in hands was the cyanhydrine 5 which was isolated quantitatively as colourless crystals! (Scheme 4).

In Scheme 5 is given a reasonable mechanism for this oxidation: the exocyclic double bond of 4a is electron rich and 4a reacts quickly with the peracid to give the epoxide 4b which rearranges rapidly to the cyanhydrine 5. The fact that the corresponding 4-quinolylphenyl-acetonitrile 7 did not react when submitted to the same reaction

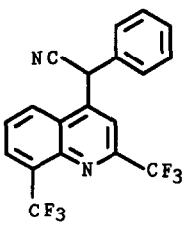


Scheme 4 Reagents i)m-chloroperbenzoic acid, ii) base, iii) H_2, P_tO_2

conditions points to the involvement, of the pyridine nitrogen during this oxidation (e.i. Scheme 5). No further attempts were made to clarify the mechanism of this odd oxydation. Treatment of 5 with sodium hydroxide yielded the ketone 6 quantitatively.



Scheme 5 i) 1 equiv m-chloroperbenzoic acid, rt, min ii) rear



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Because of the limited use of m-chloroperbenzoic in the plant,we explored the combination H_2O_2 and acetic acid (CH_3CO_2H).[7] These conditions proved to be a mild and high-yielding alternative to the costly peracid, the ketone 6 was obtained directly in 95% yield. The temperature and the reaction time proved to be critical parameters

for this conversion. With longer reaction times or higher temperatures the ketone was formed along with its N-oxide. Finally, catalytic hydrogenation of 6 as already described,[1] gave mefloquine (1) in 80% yield along with the threo isomer.

Conclusion

The mild conditions described above combined with the high yields obtained at each step make this approach a viable alternative to the already known synthetic pathways leading to mefloquine (1).

EXPERIMENTAL

The methods were the same as described,[8] unless otherwise quoted. 4-Hydroxy-2,8-bis(trifluoromethyl)quinoline was prepared in two steps according to the literature.[9]

4-Chloro-2,8-bis(trifluoromethyl)quinoline (3)
Phosphoryl chloride ($POCl_3$, 43.1 g, 0.28 mol) was preheated at 60°C and under stirring the 4-hydroxy-2,8-bis(trifluoromethyl)quinoline (79.3 g, 0.28 mol) was added in portions over 20 min. The mixture was warmed at 110°C and stirred at this temp. for 2 h. After cooling at 60°C, the reaction mixture was poured under stirring onto 200 g ice. The crystalline suspension was extracted with ethyl ether. The organic extract was washed with saturated $NaHCO_3$ solution, water, dried, filtered then evaporated to provide a crystalline residue which was recrystallised in ethers to give 71 g of 3 (0.237 mol, 85%) as yellowish crystals, m.p. 49-51°C.

α-(2-Pyridyl)-2,8-bis(trifluoromethyl)-4-quinolylacetonitrile (4)
A cooled (0°C-5°C), stirred suspension of NaH (18.9 g, 0.45 mol, 55-60% dispersion in mineral oil) in toluene (300 ml) and DMF (150 ml) was treated under Ar with a solution of 2-pyridylacetonitrile (28 g, 0.237 mol) in toluene (120 ml) and DMF (25 ml) for 30 min. The resulting yellow-brown-coloured suspension was stirred for 1h at the same temperature. A solution of 3 (71 g, 0.237 mol) in toluene (120 ml) and DMF (25 ml) was then added dropwise over 1h. The deep red-coloured mixture was stirred for 2h at 5°C-10°C. The deep-coloured mixture was then quenched by the dropwise addition of 250 ml cold water and extracted with ethyl acetate. The organic extract was washed with water, brine, dried, filtered and evaporated to provide a crystalline residue (100 g) which was taken-up in 100 ml ether, 100 ml isopropyl ether followed by the addition of 500 ml petroleum ethers to give 82.5 g(0.216 mol, 91% yield) of 4 as light beige coloured crystals, m.p. 189-191°C. - ^{1}H NMR ($DMSOd_6$) δ 7.11 (s, CH-CN), 8.34 (s, CH=C-CF_3), ~ 7.3-8.8 (m, Ar). - MS, m/e 381 (M), 354 (M-HCN).

α-Hydroxy-α-(2-pyridyl)-2,8-bis(trifluoromethyl)-4-quinolylacetonitrile (5)
A stirred solution of m-chloroperbenzoic acid (0.956 g , 5 mmol) in 100 ml Et_2O was treated portionwise over 5 min at room temp. with 4

(1.905 g, 5 mmol). After 40 min at the same temp. the reaction was finished. The solution was washed with a cold saturated solution of sodium bicarbonate, then with water, dried, filtered and evaporated to give 5 as colourless crystals which were recrystallised from ethyl ether - petroleum ether to give 1.8 g of 5 (4.53 mmol, 91% yield), m.p. 107-109°C. - ^{1}H NMR (DMSOd_6) δ 6.39 (broad s, OH), ~ 7.7-8.5 (m, Ar). - MS, m/e 370 (M-HCN). - MA calculated: C 54.42, H 2.28, N 10.58; found: C 54.37, H 2.40, N 10.61.

2-Pyridyl-2,8-bis-(trifluoromethyl)-4-quinolylketone (6)
CAUTION: in both methods **HCN** is liberated, therefore these reactions are to be performed in a good ventilated hood, the aqueous phases treated under cooling with NaOCl solution to convert HCN to less harmful HCNO.

A) From the cyanhydrine 5 via base hydrolysis: The cyanhydrine was prepared as above on a 50 mmole scale, at the end of the oxidation reaction, the reaction mixture was treated dropwise under stirring with aqueous NaOH (300ml, 0.1N). After stirring for 10 min at room temperature the organic phase was separated (CAUTION) and washed with water, dried, filtered and concentrated. The crystalline residue was recrystallised from ether-petroleum ether to give 17.9 g of the ketone 6 (48.3 mmol, 97% yield). The compound was identical with samples obtained by other routes.

B) From the nitrile 4: To a stirred suspension of 4 (38.1 g, 0.1 mol) in acetic acid (175 ml) was added H_2O_2 (75 ml of a 30% solution) dropwise at room temp.. The stirred suspension was then placed in a preheated (75°C) oil bath. After 20 min, at the intern temperature of 70°C a clear solution was obtained, after 35 min the ketone 6 began to crystallise. After 60 min, at this temperature the reaction was finished (tlc) and rapidly cooled under stirring at room temp.. The crystalline suspension was then poured under stirring (CAUTION) onto 300 g ice, then cooled at -15°C and stirred for 15 min at this temperature. The light rosa-coloured crystals were filtered off and washed with water still pH=5. The crystals were dissolved in 600 ml ethyl ether, the yellow solution was then dried, treated with 10 g of bleaching earth, filtered and evaporated to give 35.3 g (0.095 mol, 95% yield) of 6 as a crystalline residue (homogene on tlc) which was used in the next step without further purification to give mefloquine in 80% yield as already described.[1,9]

Acknowledgement - Our thanks are due to our colleagues of Hoffmann-La Roche Central Research for spectral data and elemental analyses.

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