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AN EXPEDIENT AND HIGH YIELDING SYNTHESIS OF MEFLOQUINE, VIA FLUORIDE ION-CATALYZED WITTIG REARRANGEMENT I.

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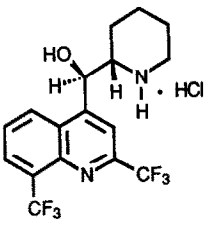
Summary: Starting from readily accessible materials, a short and efficient synthesis of mefloquine 1 is described. In the presence of fluoride ion and air, the carbinol 6, arising from the Wittig rearrangement was found to be rapidly and quantitatively converted to the ketone 8.

Introduction

Mefloquine 1, registered under the name Lariam® (F.Hoffmann-La Roche) is a highly active blood schizontocide against multi-drug resistant falciparum malaria.[1] The first synthesis of this (±)2,8-bis(trifluoromethyl)-α-(2-piperidyl)-4-quinoline methanol, was published in 1971.[2] Several years ago we were interested in developing new synthetic routes to this potent antimalarial agent.[3]



mefloquine

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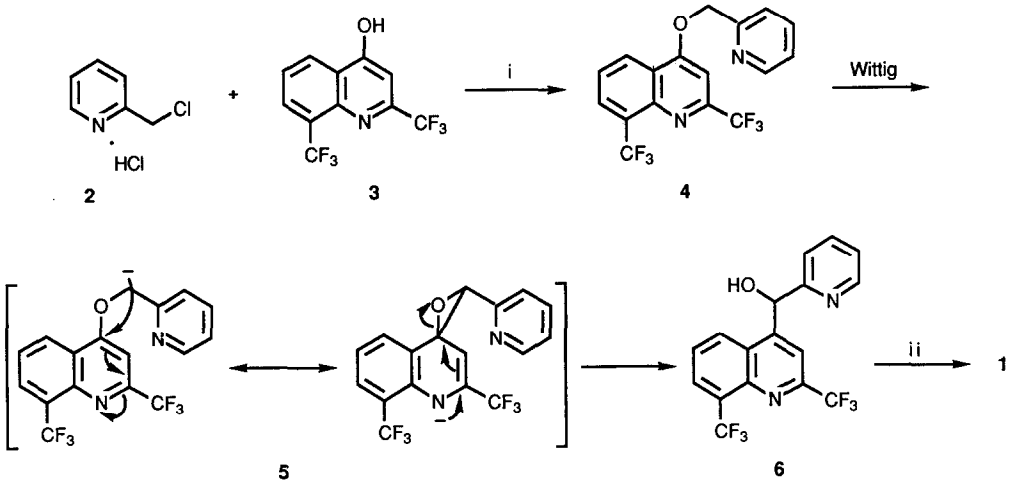
Results and Discussion

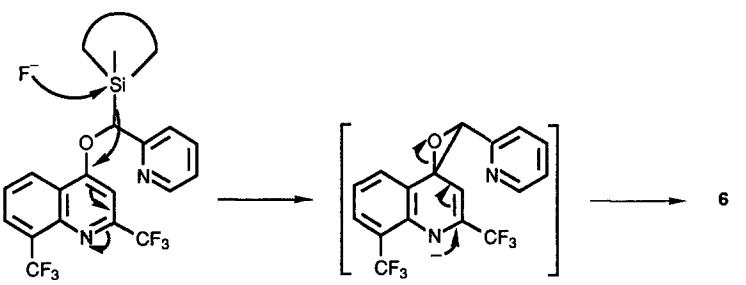
The Wittig rearrangement of aryl ethers to arylcarbinols is well documented.[4,5] Therefore our interest focussed on the potential application of this reaction to the quinolyl ether 4 which is, as we found, readily available from 2-chloromethyl pyridine[6] 2 and 4-hydroxy quinoline[2] 3 in 90% yield (Scheme 1). The ether 4 was then subjected to the action of strong bases like phenyl-lithium, n-butyllithium or $NaNH_2$ in tetrahydrofuran (THF) or benzene at varying temperatures, ranging from -78°C to 60°C, but the deeply coloured mixtures gave only decomposition and tar

products, upon quenching and usual work-up in every case. Yet, when the ether 4 was treated with NaH in THF or DMF, the carbinol 6 was isolated in low yield (~ 10%). This later result led us to consider milder conditions for the generation of the putative carbanion intermediate 5.

Reports from the literature support the notion that a C-SiR_3 moiety is a protected carbanion which may be easily unmasked, for example with catalytic amounts of fluoride ion.[7-9] From the mechanistic point of view then, introduction of a -SiR_3 substituent onto 4 ought to facilitate the rearrangement (Scheme 2).

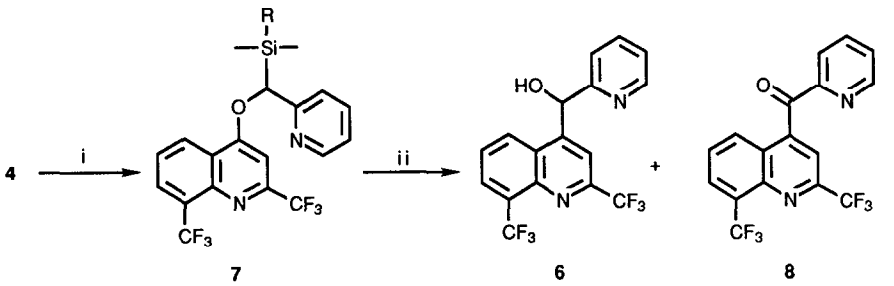


Scheme 1: Reagents: i) NaH, DMF, 0°C⟶110°C; ii) H_2, PtO_2, EtOH, MeOH, H^+.



Scheme 2

Therefore, the silylated derivatives 7a and 7b were synthesized as shown in Scheme 3. Treatment of 4 with n-butyllithium, at -78°C, in THF gave rise to the deep green coloured anion, which was subjected to silylation either with trimethylchlorosilane (TMCS) or t-butyldimethylchlorosilane (TBDMSCl), affording after flash chromatography 7a and 7b respectively, as oils in 70% yield. Treatment of either 7a or 7b (Scheme 3) with catalytic amounts of TBAF (0.2 - 0.5 equiv.) in acetonitrile at room temperature generated a deeply green-coloured solution. The starting material disappeared rapidly, as shown by tlc, affording quantitatively a mixture of the expected carbinol 6 and what was shown to be the ketone 8.

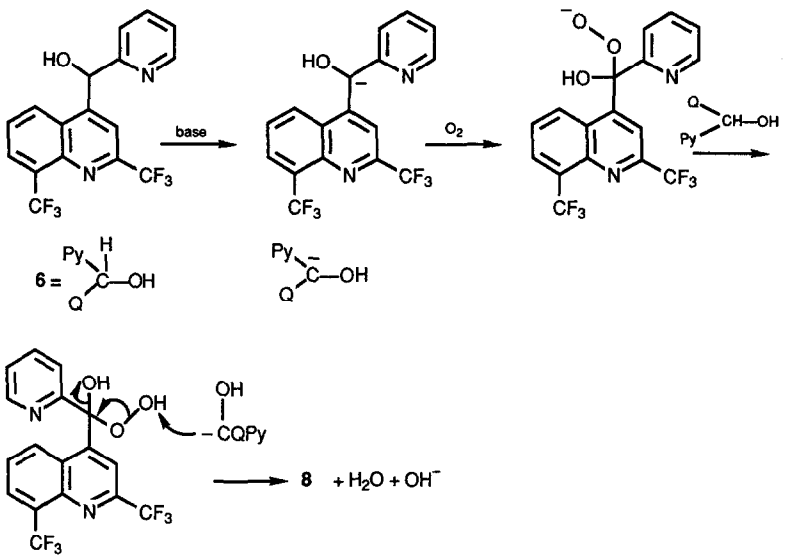


Scheme 3: Reagents: i) n-BuLi, –78°C, THF, 1 h, trialkylchlorosilane derivative, ii) TBAF, acetonitrile, rt.
7a: R = CH_3 **7b**: R = t-C_4H_9

Interestingly, the amounts of the ketone 8 varied with: i) the quantity of TBAF, ii) the reaction time, and iii) with the speed of stirring!

In fact, it turned out that when a solution of the carbinol 6, in acetonitrile, was treated in an open-vessel with TBAF, a green coloration appeared and after a few minutes or hours, depending on the amount of TBAF, 6 was completely oxidized to 8. The remarkable ease of oxidation of 6 must be due to the attack of oxygen on the carbanion, which results from the removal of the acidic hydrogen on the carbinol by the strong base F^-. Considering the electrophilic nature of oxygen, in Scheme 4 is outlined a reasonable mechanism for this oxydation. It should be noted in this context that carbanions generated under certain phase transfer conditions or in the presence of crown ethers are rapidly oxidized by air.[10] An alternative radical process could also be operative. It is then clear that the oxidation rate is enhanced by rapid stirring, which presumably increases oxygen absorption.

Attempts to promote the oxidation with other fluorides like NaF, KF and NH_4F met with failure, CsF gave only traces of the ketone. - In THF, the reaction was slower. As expected, protic solvents like methanol retard the reaction considerably.



Scheme 4

Substitution of powdered KOH for TBAF, in acetonitrile, also favored the oxidation, although in this case the reaction had to be worked-up immediately in order to prevent the decomposition of the ketone. With KOH, the reaction could also be run in methanol, in this case the reaction mixture remained colourless and the oxidation proceeded with extreme sluggishness.

We observed, but did not quantify, the formation of acetamide in the reactions performed in acetonitrile, suggesting a possible participation of the solvent.

Catalytic hydrogenation[2] of 8 finally gave mefloquine 1 in 80% yield along with the threo isomer (Scheme 1).

Conclusion

The mild conditions described above for the synthesis of 6, starting from 4, make this approach an excellent alternative to the already known synthetic pathways leading to such heterocyclic diaryl carbinols. - We are investigating the scope and potential of this fluoride ion-catalyzed Wittig rearrangement by extending it to other substrates.

EXPERIMENTAL

The methods were the same as described[11], unless otherwise quoted.

4-(2-Pyridylmethoxy)-2,8-bis(trifluoromethyl)quinoline (4)

A suspension of 3 (6.4 g, 22.76 mmol) in a dry flask under argon in toluene and anhyd DMF (50 ml) was treated with NaH (1.5 g, 50 mmol). The mixture was stirred for 10 min at room temperature. To the yellow light suspension, 2 was added in portions in 15 min. The pink mixture was warmed to 110°C and stirred for 20 h at this temperature. The suspension was cooled to 0°C, treated with water and extracted with ethyl ether. The organic extract was washed with water, dried and evaporated to provide a crystalline residue which was recrystallized from ethyl ether to give 4 (7.5 g, 20.4 mmol, 90%) as white needles. - ^{1}NMR, 5.55 (s, OCH_2), 7.3 (s, H_3), ~7.2-8.82 (m, Ar). - MS, m/e 372 (M), 353 (M-F), 303 ($M-CF_3$).

4-[(tert-Butyldimethylsilyl)(2-pyridyl)methoxy]-2,8-bis(trifluoromethyl) quinoline (7b)

A cooled (-78°C), stirred solution of 4 (1.42 mmol) in 20 ml THF was treated under Ar with 3 equiv. of commercially available BuLi (2,2 N in hexane, Fluka) for 10 min (-78°). After 1 h the deep green solution was treated with a solution of TBDMSCl (3 equiv.) in 20 ml THF which was added dropwise over 15 min. After 1 h the reaction was allowed to warm to room temperature and stirring was continued overnight.
The red solution was quenched with cold aqueous THF and evaporated under vacuum to remove most of the THF and the residue was extracted with ethyl ether. The combined ether extracts were washed with water, dried, filtered and evaporated to provide an oil. The crude product was rapidly chromatographed on silica gel using EtOAc in hexane as eluting solvent to give 0.5 g of 7b as an oil. - ^{1}HNMR (250 MHz, $CDCl_3$) δ = 0.15 [s, $Si(CH_3)_2$], 0.93 (s, Si-t-C_4H_9), 6.56 (s, O-CH), ~7.15 (m, H'_5), 7.48 (~d, H'_3), ~7.65 (m, H'_4, H_6), ~8.09 (~d, H_7), 8.29 (s, H_3), ~8.47 (m, H'_6), ~8.7 (~d, H_5) ppm. MS, m/e, 486 (M), 471 ($M-CH_3$), 429 (M-t-butyl), - IR, 1310, 838, 777, Si-trialkyl.

4-[(2-Pyridyl)trimethylsilyl)methoxy]-2,8-bis(trifluoromethyl)quinoline (7a)

Preparation following the above procedure. - ^{1}H NMR (90 MHz, $CDCl_3$) δ = 0.1 [s, $Si(CH_3)_3$], 6.58 (s, O-CH), ~7-8.8 (m, Ar) ppm.

General procedure for the Wittig rearrangement

To a stirred solution of 7b (0.1 g, 0.20 mmol) in acetonitrile was added TBAF (0.03 g) at room temperature yielding a deep green-coloured solution. As shown by tlc the starting material disappeared rapidly (10 min). The solvent was evaporated and the residue was chromatographed on silica gel (EtOAc-hexane, 3-7) to give 6 (35 mg, 0.09 mmol, 45%) and 8 (30 mg, 0.08 mmol, 40%). - These compounds were identical with samples obtained by other routes.

Procedures for the base catalyzed oxidations of 6

(A) TBAF in acetonitrile: A solution of 6 (0.1 g) in acetonitrile (5 ml) open to the atmosphere, was treated under vigorous stirring with TBAF (0.04 g). The coloured mixture was kept at rt overnight. After evaporation the residue was taken up in ethyl ether and filtrated over a plug of silica gel, the ketone 8 was isolated quantitatively.

(B) KOH in acetonitrile: 6 (0.1 g) was treated under the same conditions as above with powdered KOH (0.025 g), the solution was more intensively coloured (green) as in the preceding example. The end of the oxidation was characterized by a persistent yellowish colour. The ketone was isolated quantitatively as above after 2 h.

6 (0.2 g) was treated with powdered KOH (0.07 g) as above, after 5 min the oxidation was almost complete. Isolation of the ketone 8 in over 90% yield.

(±)2,8-Bis(trifluoromethyl)-α-(2-piperidyl)-4-quinoline methanol (1)

This was prepared by catalytic hydrogenation of 8 (3.70 g, 10 mmol) in 40 ml EtOH and 30 ml MeOH, containing HCl (12 mmol) over PtO_2 (0.5 g) at normal pressure for 5.5 h. The mixture was filtered and the filtrate was then evaporated. The crystalline residue was recrystallized (EtOH-acetone) to give 3.4 g 1 (8 mmol, 80%), m.p. 261-263°C.

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REFERENCES

1. World Health Organization: Development of Mefloquine as an Antimalarial Drug. Bull. W. H. O. (1983), 61, 169-178.
2. Lutz, R.E.; Patel A.R.; Ohnmacht, C.J. J. Med. Chem. 1971, 14, 926-928
3. Adam, S. (F.Hoffmann-La Roche) C.A. 1984, 101, 38364P, Eur. Pat. Appl. 103259, 1982.
4. Cram, D.J. "Fundamentals of Carbanion Chemistry", Academic Press, New York, 1965, 230-233.
5. March, J. Advanced Organic Chemistry, McGraw-Hill Book Co., New York, 1977, 1015-1016.
6. Available from Fluka.
7. Nakamura, E.; Kuwajima, I. Angew. Chem., Int. Ed. Engl., 1976, 15, 498
8. Chan, T.H. Acc. Chem. Res., 1977, 10, 442-448 and references cited therein.
9. (a) Hosomi, A.; Shirahata, A.; Sakurai, H. Tetrahedron Lett., 1978, 19, 3043-3046. (b) Saskar, T.K.; Adersen, N.H. Ibid., 1978, 19, 3513-3816.
10. Sepp, D.T.; Scherer, K.V.; Weber, W.P. Tetrahedron Lett., 1974, 15 2983-2984.
11. Adam, S.; Schönholzer, P.; Arnold, W. Tetrahedron, 1983, 39, 2485-2491.