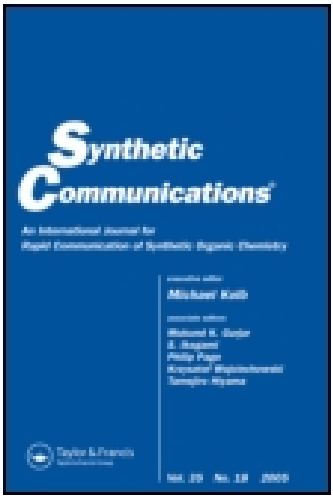


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Facile and Alternative Method for the Synthesis of Mefloquine

M. Suresh Kumar [a] , Y. V. D. Nageshwar [a] & H. M. Meshram [a]

[a] Organic Chemistry Division - I , Indian Institute Of Chemical Technology , Hyderabad, 500 007, INDIA

Published online: 21 Aug 2006.

To cite this article: M. Suresh Kumar , Y. V. D. Nageshwar & H. M. Meshram (1996) A Facile and Alternative Method for the Synthesis of Mefloquine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:10, 1913-1919, DOI: 10.1080/00397919608003544

To link to this article: http://dx.doi.org/10.1080/00397919608003544

SYNTHETIC COMMUNICATIONS, 26(10), 1913-1919 (1996)

A FACILE AND ALTERNATIVE METHOD FOR THE SYNTHESIS OF MEFLOQUINE

M. Suresh Kumar, Y.V.D. Nageshwar and

H.M.Meshram*

Organic Chemistry Division - I,

Indian Institute Of Chemical Technology,

Hyderabad - 500 007, INDIA.

ABSTRACT: A convenient and facile synthesis of Mefloquine, based on sulphoxide-Grignard approach is described.

Mefloquine is a potent antimalarial drug and is given in the chloroquine resistant cases. The first synthesis of Mefloquine is published in 1971[1] and onwards, several synthetic routes have been developed for the preparation of Mefloquine.[2]

IICT Communication No. 3608

*To whom correspondence should be addressed.

Most general route is from 4-bromoquinoline, but there are often serious difficulties in the generation of quinoline carbanion with n-BuLi[3] (-78°). A recent synthesis[4] is based on fluorine ion catalysed Wittig rearrangement but it also involves the use of n-BuLi. Thus in view of the above drawbacks, it is still important to develop simple and convenient method for the preparation of Mefloquine.

In continuation of our work on the process development of Mefloquine,[5] herein we report a new and convenient synthesis of title compound based on sulphoxide-Grignard approach.

The reaction of 2,8-bis(trifluoromethyl)-4-bromoquinoline with p-toluenethiol in presence of potassium hydroxide gives 4-quinoline-p-tolylsulphide in 95% yield[6]. The sulphide is subjected to oxidation with m-CPBA in chloroform at 0° gives sulphoxide in 90% yield.

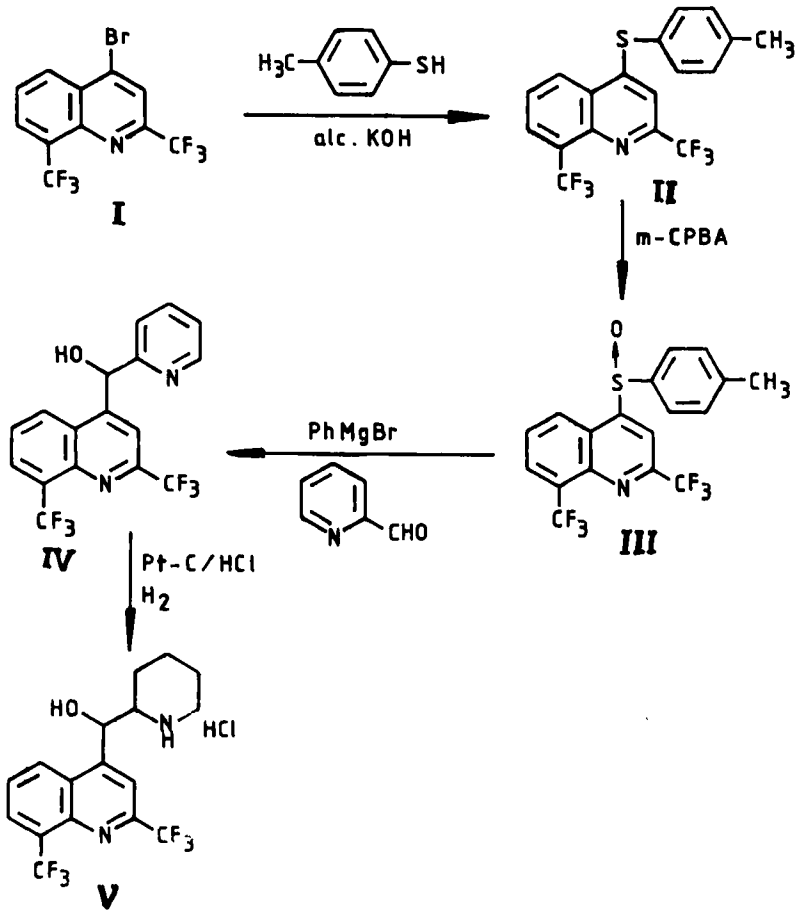
It is well established in literature that sulphoxide moiety is easily unmasked with PhMgBr to generate the corresponding Grignard reagent[7]. So we have utilised the potent application of this reaction to quinolyl-p-tolylsulphoxide. The addition of THF solution of 2,8-bis(trifluoromethyl)-p-tolylsulphoxide to the PhMgBr at 0° to room temperature and in situ

addition of pyridine 2- carboxaldehyde gives corresponding carbinol in 55% yield. Carbinol on hydrogenation gives Mefloquine hydrochloride.

EXPERIMENTAL:

Mass spectra were recorded on VG Micromass 7070H spectrometer. ^1H NMR spectra were recorded on a Gemini 200 MHz spectrometer using TMS as internal standard. IR spectra were recorded on Nicolet 740 FT-IR spectrometer. Column chromatography was carried out using E-Merck silica gel . All solvents were dried prior to use.

1) Preparation of 2,8-bis(trifluoromethyl)-4-quinolyl p-tolylsulphide (II): Potassium hydroxide (0.05g,0.01mole) is dissolved in ethanol (20 ml) to which p-toluenethiol (1.24 g.,0.01mole) is added. The mixture is heated to 60^o and methanolic solution of 4-bromoquinoline (3.43 g.,0.01mole) is added dropwise over a period of 10 minutes. It is stirred at the same temperature for 2 hours. Reaction mixture is poured into water and extracted with ether(2x50). The ether layer is washed with 10% KOH(10 ml) and dried over anhydrous sodium sulphate. The solvent is evaporated to afford crude product which is crystallised from hexane-ether(1:1) to give compound II(3.6g.) in 95% yield.M.P. $98-100^o$.MS:M^+ 387. ^1H NMR:($CDCl_3$): δ2.4(3H,s),



Scheme

7.0(1H,s), 7.3(2H,d),7.4(2H,d), 7.6(1H,t), 8.1(1H,d), 8.4(1H,d).IR:(KBr cm^{-1}): 650(C-S), 1600, 1585, 1515 (C-C),1305,1140(C-F).

2) Preparation of 2,8-bis(trifluoromethyl)-4-quinolyl-p-tolylsulphoxide(III): To a cold(0^{o}) solution of compound **II** (3.87g,0.01mole) in chloroform ,m-CPBA (1.89g.,0.01mole) is added in portions over a period of 20 minutes. Reaction mixture is stirred at room temperature for 12 hours and poured into water. It is extracted with chloroform (2X50ml), organic layer washed with 10% sodium bicarbonate solution (50ml) and dried over anhydrous sodium sulphate .The solvent is removed under reduced pressure to give compound IV(3.82g. in 90% yield as white solid.M.P:141-143^{o}.MS:M^{+}403.

^{1}H NMR: ($CDCl_3$):δ 2.3 (3H,s), 7.3(2H,d),7.3(2H,d), 7.7(1H,t), 8.2(1H,d), 8.3(1H,d). IR: (KBr, cm^{-1}) 1050 (S-O), 1600, 1585, 1515(C-C), 1305, 1140(C-F).

3) Preparation of 2,8-bis(trifluoromethyl)-2,2'-pyridyl methanol(IV): A mixture of bromobenzene(1.57g. 0.01mole), Mg powder(0.24g. 0.01mole) and catalytic amount of ethylbromide is stirred in dry THF (50ml) for 45 minutes at room temperature, untill a clear solution is obtained.THF solution (25ml) of compound **III**(4.3g. 0.01mole)is added drop wise to the above solution over a period of 5 minutes.The mixture is

stirred at 40° for 1 hour, cooled to 0° and then pyridine 2-carboxaldehyde(1.07g. 0.01mole) is added drop wise over a period of 5 minutes. Further the reaction mixture is stirred at room temperature for another 3 hours and poured into the saturated ammonium chloride solution (50ml).It is extracted with ether(2x50ml) and dried over anhydrous sodium sulphate. After evaporation of solvent , the crude product is chromatographed on silica gel using DCM-Hexane(1:1) as eluent to give compound **IV**(2.04g) in 55% yield.

M.P.141°.MS:M^+372 ^1H NMR ($CDCl_3$):δ 5.1(-OH,s), 6.4(1H,s), 7.0(1H,d), 7.3(1H,dd), 7.6(2H,q), 7.9(1H,d), 8.1(1H,d), 8.4(1H,d), 8.7(1H,d). IR: (KBr cm^{-1}): 3340(O-H), 1600, 1585, 1515(C-C), 1305, 1140(C-F).

4)Preparation of 2'-piperidyl-2,8-bis(trifluoromethyl) -4-quinoline methanol (Mefloquine hydro chloride)(V): A mixture of compound **IV** (3.72g, 0.01mole),Pt-C(5%) (3.72g, 0.01mole), HCl(5ml) and ethanol (50ml) is stirred at room temperature for 6 hours under hydrogen atmosphere. The catalyst is removed by filtration and the filtrate is concentrated to dryness. The solid obtained is crystalised from acetonitrile to afford compound **V** in 80% yield(3.2g.).M.P. 245°.MS M^+: 412. ^1H NMR (DMSO-D6):δ 1.6-3.2(9H,m), 6.0(1H,d), 6.7 (1H,brd), 7.8(1H,d), 8.0(1H,s), 8.2(1H,d), 8.9(1H,d). IR:(KBr cm^-

[1]) 3240(O-H) , 3100-2500(N-H), 1600, 1585, 1515(C-C), 1305, 1140(C-F).

Acknowledgement:

Authors thank Dr.J.S.Yadav, Head, Organic Division-I for his constant encouragement and one of the authors (M.S.K.) thanks CSIR for a Fellowship(JRF).

References:

1) Lutz,R.E.; Patel,A.R.; Ohnacht,C.J., J.Med.Chem. **1971**,14,926.

2) Adam - Molina,S., Eur.pat.Appl.E.P.103,259,**1984**. C.A 101,P38364p, 1984.

3) Adam,S., Tetrahedron **1989**,45,1409.

4) Grethe,G; Mitt,T., Ger. Offen 2,806,909,**1978**. C.A 90 P22838q, 1979.

5) Nageshwar,Y.V.D.; Meshram,H.M.; Sattur,P.B., Patent: CSIR(INDIA),Pat.Nos: 170910, 170915, 170917, 170918, 171110, 171290.

6) Ipatieff,V.N.; Pines,H.; Friedman,B.S., J.Am.Chem. Soc.**193**8,60,2731.

7) Furukawa,N., Tetrahedron Lett.**1987**,28,5848.

(Received in the UK 1st November 1995)