Indian Journal of Chemistry
Vol. 55B, April 2016, pp 517-521

Vilsmeier-Haack reaction: A manifest protocol to synthesise bisquinoline

T R Makhanya[b], P Pitchai*[a], R M Gengan[b] & P S Mohan[c]

[a] PG and Research Department of Chemistry, Government Arts College, Kumbakonam 612 001, India
[b] Department of Chemistry, ML Sultan Campus, Durban University of Technology, Durban 4001, South Africa
[c] Department of Chemistry, School of Chemical Sciences, Bharathiar University, Coimbatore 641 046, India
E-mail: pitchaipandian@gmail.com

Received 28 July 2015; accepted (revised) 23 November 2015

Synthesis of bisquinolines from methyl anthranilate and ethyl acetoacetate is described. This synthesis has been accomplished in three steps. Vilsmeier-Haack reaction is used as a key tool to assemble bisquinoline. Microwave heating during each step of the reaction gives high yield of products in short reaction times.

Keywords: Bisquinolines, Claisen condensation, Vilsmeier-Haack reaction, Schiff base

Several classes and sub-classes of organic molecules are in abundance, however the nitrogen heterocycles are considered as the most highly utilized. It has unlimited structural diversity and immense biological potential for human health as exemplified by the discovery of quinine[1] to combat malaria. However, malaria remains a challenge to mankind because resistant strains of the parasite have evolved. Hence alternative compounds have been investigated and reported to have potent antimalarial activity: bisquinolines such as piperaquine and dequalium are active compounds against chloroquine-resistant strains of malaria[2,3]. Furthermore, bisquinoline displays interesting *in vitro* anti-leishmanial, anti-tumor, anti-protozoal, anti-microbial and anti-trichomoniasis activities[4,5].

There are few strategies for the synthesis of bisquinoline[6-8]: the Friedländer condensation is a common protocol[9,10] whereas the Williamson reaction[3] is also used to a limited extent. This scarcity necessitated a search for alternate routes which could serve as a template for synthesizing complex molecules, if desired. Herein, a three-step reaction scheme including Claisen condensation, Vilsmeier-Haack reaction and Schiff base formation sequentially, were used. Furthermore, the conventional energy source was compared to microwave irradiation; the main benefits of performing reactions under microwave conditions are the significant enhancement of reaction rates, higher product yield as well as conforming to global demands for the use of green technology.

Results and Discussion

Our recent developments on the synthesis of cryptosanguinolentine and other indoloquinoline alkaloids[11-14] sparked our interest in synthesizing bisquinolines particularly with a green concept *i.e.*, *via* microwave irradiation. One of our objectives was to use Vilsmeier-Haack reaction to build starting precursors as lead molecules for more complex target molecules. The Vilsmeier-Haack reaction is not only used to formylate aromatic and aliphatic compounds but is also employed in most of the ring closure reactions to produce considerably higher yield products[15-24].

In the first step of a series of reactions, the starting material 3-acyl-2,4-dihydroxyquinoline **1** was synthesized by microwave irradiation according to our recent report[25] (Scheme I). This reaction was followed by Vilsmeier-Haack reaction to form 3-(3-chloroprop-2-ene-1-al)-2,4-dichloroquinoline **2**; its melting point is 134°C. In this reaction, care must be taken to control the temperature at about 60°C; the literature reaction temperature is not healthy for this component; thereby the product **2** was destroyed significantly on increasing the temperature.

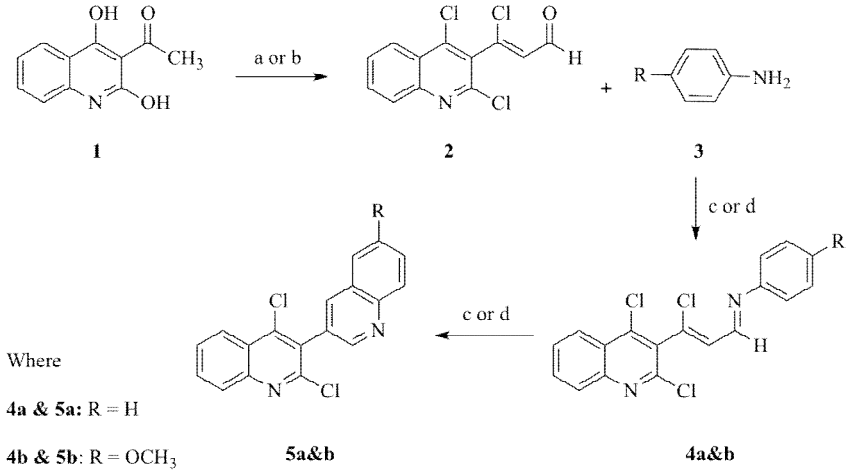
The infrared spectrum shows the aldehyde C-H stretch at 2860 cm^{-1} and the C=O stretch at 1677 cm^{-1}. The aromatic C=N stretch is at 1616 cm^{-1} and C=C stretch occurs at 1556 cm^{-1}. The disappearance of the O-H stretch in the region 3400-3200 cm^{-1}, present in 3-acyl-2,4-dihydroxyquinoline **1** indicates that chlorination was achieved. ^{1}H and ^{13}C NMR spectra show the characteristic aldehydic proton at

δ 10.3 and the aldehydic carbon at δ 190.0 respectively. The mass spectrum indicates *m*/*z* at 285 as the molecular ion. The mass spectral fragmentation is postulated as given in Scheme II.

In the third step of the reaction, a mixture of aniline **3a** and **2** was refluxed, as a model reaction, to afford **5a**. Different catalysts and solvents were investigated (Table I). The progress of the reaction was monitored by TLC. The best yield (61%) was obtained in the presence of DMF and K_2CO_3. However, microwave heating of the same mixture at 120°C and 180 W for 5 min gave a higher yield of **4a** (75%). Compound **4a**

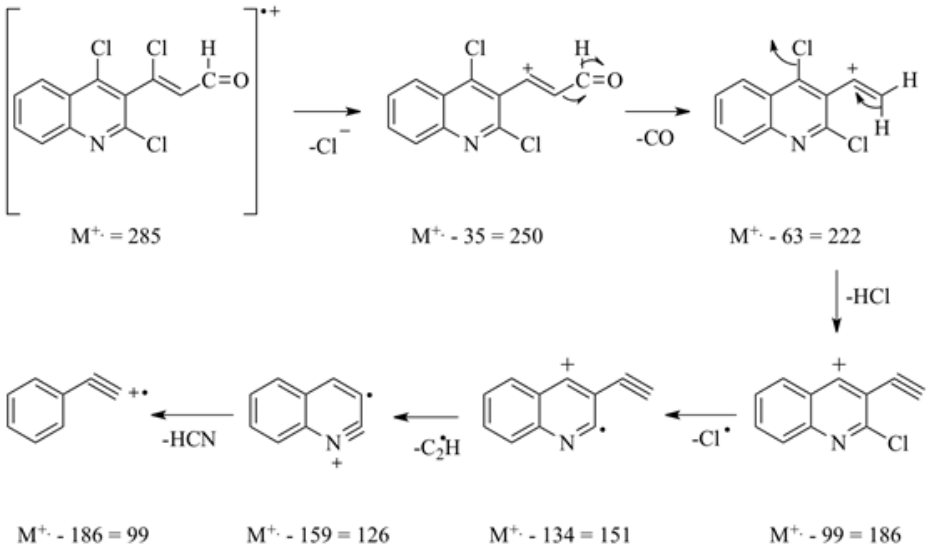
Table I — Catalysts and solvents used for the synthesis of 3-chloro-3-(2,4-dichloroquinolin-3-yl) allylidene-aniline

Method	Reagents/solvents	Reaction Conditions	Yield (%)
1	DMF + K_2CO_3 + aniline	reflux, 4 h	61
2	$CHCl_3$ + HCl + aniline	reflux, 4 h	2
3	PTSA + benzene + aniline	reflux, 4−10 h, Molecular sieve	No product
4	Acetic acid + aniline	reflux, 4 h	48
5	PTSA + ethanol + aniline	reflux, 4 h	42
6	Acetic acid + ethanol + aniline	reflux, 4 h	44



a) DMF, $POCl_3$, 75°C, 17h ; b) DMF, $POCl_3$, 75°C, MWI, 180 watts, 15min.;
c) DMF, K_2CO_3, 120°C, 8h; d) DMF, K_2CO_3, 120°C, MWI, 200 watts, 10 min.

Scheme I



Scheme II

was characterized by IR and ^{1}H NMR. The IR spectrum indicates the imine C-H stretch at 2866 cm^{-1} and the aromatic C-H stretch at 3057 cm^{-1}. The aromatic C=C stretch is at 1488 cm^{-1} and the imine C=N stretch occurs at 1634 cm^{-1}. The ^{1}H NMR spectrum indicates a doublet with a one proton integration at δ 6.25 for olefinic C-H whereas a singlet for one proton integration at δ 6.90 indicates the proton of the carbon α-to nitrogen; two doublets appear at δ 8.0 and δ 7.6 which are characteristic C_5-H and C_8-H, respectively, of the quinolone moiety. An unresolved multiplet for five protons appears at δ 7.25-7.50 for the phenyl protons. The ^{13}C NMR spectrum indicates 17 carbons: δ 158 is assigned to carbon bonded with nitrogen of imine and the C_4-Cl of quinoline is at δ 154.5. The C-Cl of ethylene occurs at δ 150, and C-H ethylene occurs at δ 108. The mass spectrum indicates its molecular ion [$M^{+\cdot}$] signal at *m*/*z* 360. There was no more formation of bisquinoline **5a** even on increasing the refluxing time on conventional and the applied energy on microwave procedure. The above mentioned procedures are also extended for obtaining **4b**. In this case, again the percentage yield of the product was improved by microwave irradiation; also the reaction time was drastically reduced.

In the final step, **4a** and **4b** were used as substrates to synthesize **5a** and **5b**, respectively. In this reaction, DMF and K_2CO_3 were used. Microwave heating at 120°C and 200 W for 10 min gave low yields of 54% and 48% for **5a** and **5b**, respectively. In the case of conventional method with the above conditions, the yield was not being isolated thereby the reaction procedure is declined. Compound **5a** was characterized by ^{1}H NMR: ten quinoline CH protons are found in the aromatic region. The absence of a characteristic C_3-H chemical shift of quinoline in the region δ 6.0 - 6.50 indicates that the third position at both the quinoline rings were occupied and it is considered as a junction point of two different quinoline rings. The mass spectrum indicates its molecular ion [$M^{+\cdot}$] signal at *m*/*z* 320. The ^{1}H NMR spectrum of **5b** indicates a singlet at δ 3.9 for O-CH_3 protons whereas nine quinoline protons appear in the aromatic region.

In conclusion, simple, readily available and economical substrates were used in the synthesis of fresh intermediates and ultimately bisquinolines; this was a three-step reaction requiring diminutive time. Although the yields of the bisquinolines were low, microwave energy proved efficient for generating high yield intermediates.

Experimental Section

All chemicals were purchased from Sigma, South Africa. The progress of reaction was monitored by TLC. TLC plates are pre-coated (thickness 0.25 mm) using aluminium-silica gel with a fluorescent indicator. Individual compounds were isolated by column chromatography over silica gel 60 (Merck particle size 0.040−0.063 mm). Microwave-assisted reactions were conducted using a microwave synthesizer (CEM Discover). ^{1}H and ^{13}C NMR spectra, recorded at 400 MHz, were obtained on a Bruker Ultra Shield Spectrometer. Chemical shifts are reported in parts per million (ppm) relative to the peak of tetramethylsilane as internal standard; *J* values are given in Hz. Infra-red (IR) spectra were recorded on a Perkin-Elmer 100 FT-IR spectrometer. Mass spectrometric data were obtained using a Bruker Micro TOF-Q11 mass spectrometer. Melting points were determined from a Stuart SMP 3 melting point apparatus using open-ended capillary tubes; all melting points are uncorrected.

Preparation of 3-(3-chloroprop-2-ene-1-al)-2,4-dichloroquinoline, 2

Conventional method

Dimethyl formamide (3.85 mL, 0.05 mol) was cooled to 0°C in a flask equipped with a dropping funnel. Phosphoryl chloride (12.97 mL, 0.14 mol) was added drop-wise from the funnel with stirring. The resultant reagent was stirred for a further 30 min at RT and then cooled to 5°C. Then 2.436 g (0.012 mol) 3-acetyl-2,4-dihydroxyquinoline **1** was added and the stirring was continued for further 30 min and then heated over water bath for 17 h. After being subjected to the reaction conditions, the cooled reaction mixture was then poured into crushed ice and neutralized with sodium carbonate solution. The solid 3-(3-chloroprop-2-ene-1-al)-2,4-dichloroquinoline **2** was filtered and dried. The crude product was purified by column chromatography to obtain pure **2**.

2: Yield 2.22 g (65%). m.p.134°C. IR(KBr): 3453, 2860, 1677, 1616, 1556, 828, 764, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.3 (d, *J* = 8.0 Hz, 1H, -CHO), 8.26 (d, *J* = 7.1 Hz, 1H, H-5), 8.00 (d, 1H, *J* = 7.1 Hz, H-8), (7.86, t, *J* = 7.1 Hz, 1H, H-7), 7.71(t, 1H, H-6), 6.73 (d, *J* = 8.0 Hz, 1H, H-2′); ^{13}C NMR (400 MHz, $CDCl_3$): δ 190.0, 147.7, 146.9, 144.7, 143.1, 133.8, 132.4, 131.9, 131.6, 128.9, 128.7, 128.2, 124.9, 124.8, 121.1; EI-MS: *m*/*z* 285 ($M^{+\cdot}$).

Microwave method

The reaction mixture after being stirred at RT was transferred to the microwave unit. The appearance of the reaction mixture was a pale yellow colloidal suspension; after 15 min of stirring the reaction mixture became a clear red solution. After cooling to RT, the reaction mixture was poured into 1000 mL cold water and subsequently neutralized with Na_2CO_3. By this method the yield was 72%. The physical data match the product obtained in the conventional method.

Synthesis of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-anilines 4a and 4b

Dimethyl formamide (15 mL, 0.05 mol) was mixed with aniline and aniline derivatives **3a**, **3b** (1.4318 g, 0.005 mol), **2** (1 mL, 0.01 mol) and K_2CO_3 (1.3821 g, 0.01 mol), separately. The mixture was heated under microwave conditions at 120°C and 180 W for 5 min. The mixture was cooled and poured into crushed ice. The crude solid was filtered and dried. The product was purified by column chromatography using petroleum ether and ethyl acetate (80:20) as eluent.

4a: Yield 1.75g (61%). m.p.95.7°C. IR(KBr): 3057, 3027, 2866, 1634, 1579, 1554, 1488 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.7 Hz, 1H, C_5-H), 7.70 (d, *J* = 7.4 Hz, 1H, C_8-H), 7.30-7.50 (m, 1H, C_7-H), 7.25 (m, 1H, C_6-H), 7.13 (m, 2H, Ph-C_3 and C_5-H), 7.0 (m, 1H, Ph-C_4-H), 6.90 (d, *J* = 7.2 Hz, 2H, Ph-C_2 and C_6-H), 6.68 (d, *J* = 7.2 Hz, 1H, *N*-α-H), 6.25 (d, *J* = 7.4 Hz, 1H, *N*-β-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 158.1, 155.2, 149.6, 149.3, 146.7, 142.1, 132.3, 130.5, 128.6, 124,3, 127.4, 123.7, 123.2, 121.9, 121.2, 120.5, 110.3, 108.1; EI-MS: *m*/*z* 360 ($M^{+\cdot}$).

4b. Yield 1.01g (45 %). m.p.106°C; IR(KBr): 2991, 2832, 1633, 1584, 1457, 1438, 1344, 1280, 1238, 1167, 1105, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.3 Hz, 1H, C_5-H), 7.70 (d, *J* = 8.9 Hz, 1H, C_8-H), 7.50 (m,1H, C_7-H), 7.45 (m,1H, C_6-H), 6.90-7.07 (m, 4H, Ph-C_2, C_3, C_5 and C_6-H), 6.80 (d, *J* = 7.2 Hz, 1H, *N*-α-H), 6.02 (d, *J* = 7.9 Hz, 1H, *N*-β-H), 3.98 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 160.0, 158.0, 157.0, 155.0, 150.0, 146.7, 145.4, 132.0, 130.5, 129.0, 128.6, 125.7, 123.2, 120.5, 118.1, 109.0,108.1, 105.9, 55.0.

Synthesis of 2, 4-dichloro-3, 4′-biquinoline 5a and 5b

Dimethyl formamide (15 mL, 0.05 mol) was mixed with **4a** or **4b** (1.9 g, 0.01 mol) and K_2CO_3 (1.3821 g, 0.01 mol). The mixture was heated under microwave conditions at 120°C and 200 W for 10 min. The mixture was cooled and poured into crushed ice. The crude solid was filtered, dried and purified by column chromatography using petroleum ether and ethyl acetate (85:15) as eluent.

5a. Yield 0.30g (54%). Since the sample was a paste, no melting point was measured. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J* = 8.4 Hz, 1H, $C_{2'}$-H), 8.25 (d, *J* = 8.2 Hz, 1H, $C_{5'}$-H), 8.15 (t, *J* = 8.5 Hz, 1H, $C_{7'}$-H), 8.06 (d, *J* = 7.8 Hz, 1H, $C_{8'}$-H), 7.90 (d, *J* = 8.4 Hz, 1H, C_5-H), 7.8 (m, 2H, $C_{6'}$ and C_6-H), 7.60-7.75 (m, 1H, C_7-H), 6.9 (d, *J* = 6.8 Hz, 1H, $C_{3'}$-H); EI-MS: *m*/*z* 320 ($M^{+\cdot}$).

5b. Yield 0.20g (48 %). Since the sample was a paste, no melting point was measured. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 8.3 Hz, 1H, $C_{2'}$-H), 8.30 (d, *J* = 8.4 Hz, 1H, $C_{8'}$-H), 7.85 (m, 2H, $C_{5'}$ and C_5-H), 7.75 (m, 1H, C_6-H), 7.60-7.70 (m, 1H, $C_{7'}$ and C_7-H), 6.9 (d, 1H, $C_{3'}$-H), 3.83 (s, 3H, OCH_3-H).

Acknowledgements

The authors are grateful for financial support from the National Research Foundation (NRF) and the Durban University of Technology.

References

1 Wolf R, Wolf D & Ruocco V, *Clinics in Dermatology*, 18 (2000) 17.
2 Praveen K B, Venkataraman S, Meera R & Devi P, *Int J Chem Sci*, 1 (2011) 69.
3 Wentao G, Yang L & Songtao W, *Res Chem Intermed*, 40 (2014) 669.
4 Kareme C, Fanello C I, Overmeir C V, Vangeertruyden J P, Doren W V, Ngamije D & Alessandro D U, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 100 (2006) 1105.
5 Kaur K, Jain M, Reddy R P & Jain R, *Eur J Med Chem*, 45 (2010) 3245.
6 Heerden L, Cloete T T, Breytenbach J W, De Kock C, Smith P J, Breytenbach J C & David D N, *Eur J Med Chem*, 55 (2012) 335.
7 Sai L, Qiang H, Yajing L, Xiaolong Z, Shuang L, Chao H & Ping G, *Eur J Med Chem*, 64 (2013) 62.
8 Raynes K, Foley M, Tilley L & Deady L W, *Biochem Pharmacol*, 52 (1996) 551.
9 Li Y, Gao W & Beilstein J, *Org Chem*, 6 (2010) 966.
10 Bhowmik P K, Nedeltchev A K, Haesook H, Soo J-T, Jae Koh J, Senthilkumar L & Umadevi P, *J Photochem Photobiol A*, 45 (2014) 283.
11 Dhanabal T, Sangeetha R & Mohan P S, *Tetrahedron*, 62 (2006) 6258.
12 Pitchai P, Mohan P S & Gengan R M, *Indian J Chem*, 48B (2009) 692.
13 Gengan R M, Pitchai P, Chandraprakash K & Mohan P S, *Molecules*, 15 (2010) 3171.

14 Pitchai P, Uvarani C, Makhanya T R, Gengan R M & Mohan P S, *Res & Revs: J Chem*, 3(4) (2014) 60.
15 Cohn O M & Narine A B, *Tetrahedron Lett*, 23 (1978) 2045.
16 Khan A K & Shoeb A, *Indian J Chem*, 24B (1985) 62.
17 Lawrence B, McGuire M & G Freeman A, *J Heterocycl Chem*, 20 (1983) 41.
18 Seshadry S, *J Sci Ind Res*, 32 (1973) 128.
19 Martin & Poignant, *J Chem Soc Perkin Trans*, 2 (1972) 1964.
20 Dinakaran K & Perumal P T, *Indian J Chem*, 39B (2000) 135.
21 Reddy M P & Krishna Rao G S, *J Org Chem*, 46 (1981) 5731.
22 Katritzky A R & Charles M, *J Am Chem Soc*, 105 (1983) 3279.
23 Vattoly J, Majo & Perumal P T, *J Org Chem*, 63 (1998) 7136.
24 Akila S, Majo V J & Balasubramanian K, *Indian J Chem*, 41B (2002) 647.
25 Pitchai P, Uvarani C, Gengan R M & Mohan P S, *Indian J Chem*, 52B (2013) 776.