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An elegant synthesis of indoloquinoline alkaloid cryptotackieine *via* Vilsmeier-Haack approach

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An exclusive approach towards the synthesis of indoloquinoline alkaloid cryptotackiene has been illustrated. Primary starting materials with an established procedure like Vilsmeier-Haack cyclization are used followed by nucleophilic azidation, intra-molecular cyclization and a selective methylation to achieve the target.

Kewwords: 2-Chloro-3-phenylquinoline, cryptotackiene, Vilsmeier-Haack reaction

The past decade literature shows, chemists limit by applying thoughts on single window system towards the target molecule. Now a days, research is moving towards the figures of article instead focusing target molecule. We appear to synthesize indoloquinoline alkaloids a swap for commercially fed anti-malarial such as chloroquine and mefloquine, whilst the usage is increasing significantly[1]. Indoloquinoline alkaloids are largely available on the roots of the West African plant *Cryptolepis sanguinolenta* (Lindl.)[2]. We applied established procedures such as Fischer indole synthesis[3,4], Bucherer reaction[3], photochemical and microwave method[4-8] to synthesize indoloquinolines. Henceforth our thrust is aimed to provide a mechanism for them. Several approaches given by various chemists (cited in our earlier article)[8] are available on studies whereby the procedures are time-consuming and tedious.

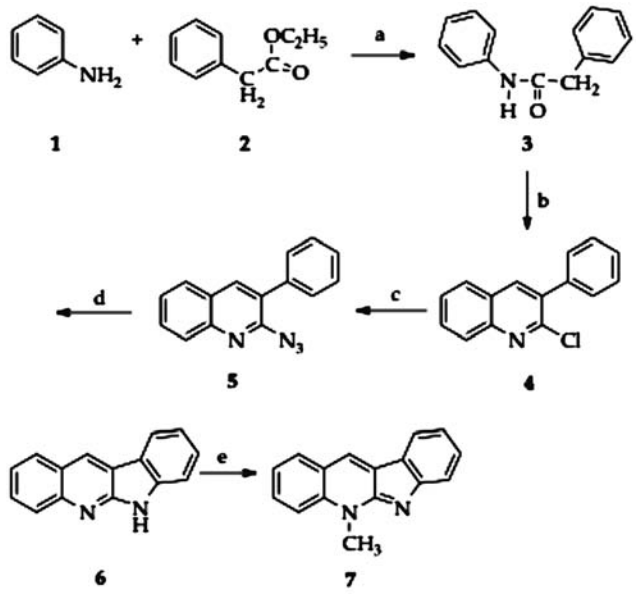
Results and Discussion

Vilsmeier-Haack reaction is an efficient tool to scale up a molecule with an active functional group[9-13]. It was directed for the formylation on active methylene or methyne group[14-16]. It is now extended to cyclisation through and towards heterocyclic system[17,18] (**Scheme I**). We began with the principal starting materials like aniline **1** and 2-phenyl-ethyl ethanoate **2** (obtained through traditional esterification procedure with 2-phenyl-ethanoic acid). An amide formation through a condensation process at 160°C was carried out. The grey crystals were collected and washed with petroleum ether to remove excess of aniline and ester if any. The melting point obtained is 107°C. The IR spectrum showed characteristic vibration of amide carbonyl stretching at 1657 cm^{-1}. A singlet with two proton integration at δ 3.70 and a broad singlet with one proton at δ 7.08 on ^1H NMR are assigned to CH_2 and amide –NH respectively and also the carbonyl carbon of amide is confirmed by obtaining signal at δ 169 on ^{13}C NMR.

Otto-Meth-Cohn[19], an eminent quinoline chemist applied Vilsmeier-Haack reaction to synthesize 2-chloro-3-formylquinoline. Therefore, it was used as a major starting precursor of alkaloids. The second step of our work also involves Vilsmeier-Haack conditions. We followed the above mentioned procedure. Consequently, we reduced the quantity of $POCl_3$ by half. Even if we increase the amount, there is no change in the functional group on the product. The IR vibration of C-Cl stretching at 771 cm^{-1} confirms formation of 2-chloro-3-phenylquinoline, **3**. ^1H NMR further confirms the cyclisation by showing a singlet at δ 8.09 for C_4-H and fading singlet at δ 3.70 of aliphatic CH_2. Likewise, loss of δ 169 signal in ^{13}C NMR confirms the cyclisation (**Scheme II**). Since our aim was to synthesize indoloquinoline moiety, therefore we chose a nucleophilic substitution with sodium azide and acetic acid mixture in ethanol by stirring at RT. The TLC validates the reaction completion; it was followed by the usual work-up procedure and purification through column chromatography yielded rosy red crystals. The difference in melting points of precursor with the product and N=N=N vibration found in IR at 2450 cm^{-1} indicated progress towards the target.

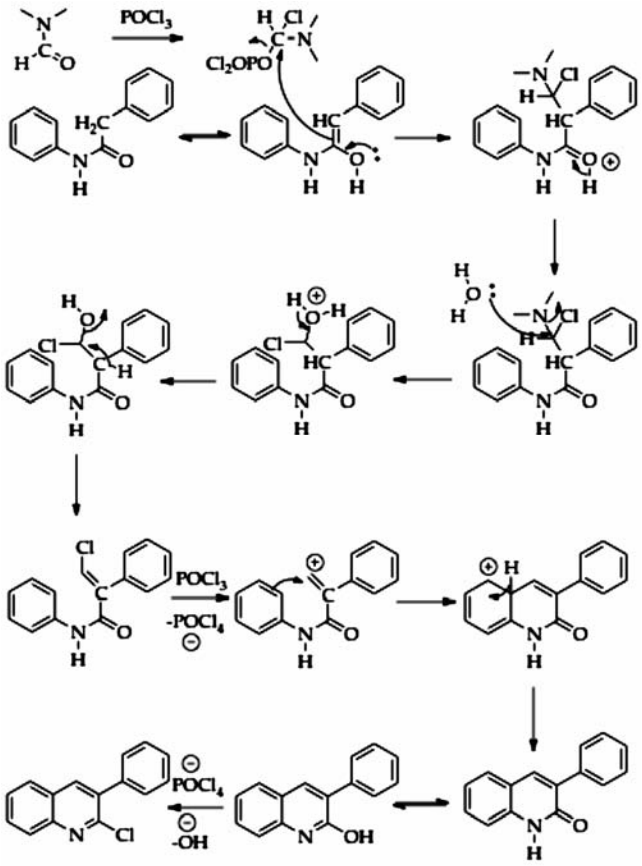
Finally we unrestricted the cyclisation by refluxing at super heating temperatures using 1,2-dichlorobenzene as solvent. The reaction is completed after 5 h heating. After the purification, *N*-methylation is carried out with dimethyl sulphate and the spectra of both the compounds were correlated with the earlier reports[20,21].

In conclusion, a convenient and highly efficient protocol – Vilsmeier-Haack reaction for the synthesis of indoloquinoline alkaloid cryptotackiene has been established. Moreover, high yields of the products,



a) 160°C, 6h; b) DMF, $POCl_3$, 70°C, 24h; c) NaN_3, AcOH, EtOH, rt, 5h; d) 1,2-dichlorobenzene, 180°C, 5h; e) Me_2SO_4, DMF, 150°C, 6h.

Scheme I



Scheme II — Vilsmeier-Haack mechanism for the formation of 2-chloro-3-phenylquinoline **4**

short reaction times, inexpensive and non-toxic reagents are noteworthy advantages for this method.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrophotometer as KBr discs unless otherwise indicated. ^{1}H NMR spectra were obtained on a Bruker (600 MHz) or a Bruker (500 MHz) or a Bruker (400 MHz) or a Bruker (300 MHz) instrument in either $CDCl_3$ or DMSO-d_6 solutions using tetramethylsilane as an internal standard. *J* values are given in Hz. Column chromatography was performed over Merck silica gel 60 with hexane and ethyl acetate as eluants. All the basic chemicals were purchased from S. D. Fine Chemicals (India).

Synthesis of 2-phenyl-ethyl ethanoate, 2: 2-Phenyl-ethanoic acid (0.1 mol) was dissolved in dry ethanol and 3 drops of concentrated H_2SO_4 was added. Then the reaction mixture was heated at 75°C for 3 h. All the solvents were evaporated. Then the reaction mass was poured into 1000 mL of ice-cold water, followed by layer separation. The organic layer was then collected and dried over anhyd. Na_2SO_4. Yield 12 mL (95%); IR(KBr): 3085, 3060, 2982, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.22-7.30 (m, 5H, Ar-H), 4.08-4.13 (quart, 2H, *J* = 7.2 Hz, OC*H*$_2$-H), 3.57 (s, 3H, COC*H*$_2$-H), 1.19-1.22 (t 3H, *J* = 7.2 Hz, C*H*$_3$-H); ^{13}C NMR ($CDCl_3$): δ 176.37, 171.80, 134.23, 133.72, 129.46, 128.67, 128.63, 127.29, 127.12, 60.92, 41.48, 14.23.

Synthesis of *N*-phenyl-benzylamide, 3: 2-Phenyl-ethyl ethanoate **2** (0.1 mol) was measured out and mixed with 0.1 mol of aniline **1** and was heated directly at 130°C for 6 h. The solid which appeared was further purified by washing with chloroform and petroleum ether mixture, 85% yield of *N*-phenyl-benzyl-amide **3** was obtained. Yield 2.82 g (85%); m.p. 107°C; IR(KBr): 3284, 3059, 1657 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.12-7.42 (m, 10H, (benzyl)-Ar-H (anilino)-Ar-H), 7.06-7.10 (bs, 1H,-*NH*-H), 3.74 (s, 2H, COC*H*$_2$-H); ^{13}C NMR ($CDCl_3$): δ 169.11, 137.61, 134.43, 129.58, 129.30, 128.98, 128.50, 127.75, 124.51, 119.84, 44.90.

Synthesis of 2-chloro-3-phenylquinoline, 4: Dimethyl formamide (3.85 mL, 0.05 mol) was cooled to 0°C in a flask equipped with a dropping funnel. $POCl_3$ (12.97 mL, 0.14 mol) was added drop-wise from a dropping funnel with stirring. The resultant reagent was stirred for a further 30 min at RT and then cooled to 5°C. Thereafter, *N*-phenyl-benzylamide **3** (2.1 g, 0.012 mol) was added and the stirring was further continued for 30 min; the reaction set-up was shifted to a

water bath and reflexed for 24 h. After being subjected to the reaction conditions, the cooled reaction mixture was poured into crushed ice and neutralized with Na_2CO_3 solution. The solid 2-chloro-3-phenylquinoline **4** was filtered, dried and then purified by column chromato-graphy. Yield 2.22 g (65%); m.p. 134°C; ^{1}H NMR ($CDCl_3$): δ 8.09 (m, 2H, C_4 and C_8-H), 7.82 (d, 1H, *J* = 8.0 Hz, C_5-H), 7.73 (t, 1H, *J* = 8.5 Hz, C_7-H), 7.56(t, 1H, *J* = 7.0 Hz, C_6-H), 7.39-7.51 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 149.50, 146.58, 139.16, 137.44, 134.86, 130.66, 129.68, 128.36, 128.04, 127.98, 127.58, 127.47, 127.26, 123.56.

Synthesis of 2-triazo-3-phenylquinoline, 5: 2-Chloro-3-phenyl quinoline **4** (0.01 mol, 2.39 g) was dissolved in DMF and 0.1 mol of sodium azide (0.650 g) was added to it. The initial colour of the mixture was yellow; it was allowed to stir at 40°C for 30 min. About 1 mL of acetic acid was poured into the reaction mixture and stirring was extended for another 3 h until the colour changed to rosy red. The reaction completion was noted through TLC. The mixture was then poured into ice-cold water, filtered, dried and purified by recystallisation from chloroform. Yield: 1.98 g (90%); m.p. 153°C; ^{1}H NMR ($CDCl_3$): δ 8.69 (d, 1H, *J* = 8.5 Hz, C_8-H), 8.16 (d, 2H, *J* = 8.5 Hz, Ph-C_2 and C_6-H), 8.06 (s, 1H,C_4–H), 8.00 (d, 1H, *J* = 8.0 Hz, C_5-H), 7.84 (t, 1H, *J* = 8.5 Hz, C_7-H), 7.71 (t, 1H, *J* = 8.5 Hz, C_6-H), 7.56 (t, 2H, *J* = 8.0 Hz, Ph-C_3 and C_5-H), 7.51 (t, 1H, *J* = 8.0 Hz, Ph-C_4-H); ^{13}C NMR ($CDCl_3$): δ 147.34, 138.84, 133.88, 130.71, 129.96, 129.67, 129.59, 129.53, 129.02, 128.96, 128.56, 128.31, 126.61, 124.40, 116.84.

Synthesis of indolo[2,3-*b*]quinoline, 6: 2-Triazo-3-phenylquinoline **5**: 2.46 g (0.01 mol); Yield 2.017 g (80%).

Synthesis of 5-methyl-5*H*-indolo[2,3-b]quinoline, 7: Indolo[2,3-*b*]quinoline **6**: 2.18 g (0.01 mol); Yield 1.92 g (88%).

The synthetic procedures were used as such based on earlier reports and the spectral data coincided with compounds **6** and **7**[20,21].

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