An alternative approach to synthesis of 3-(2,4-dichloroquinolin-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde using the Vilsmeier Haack reaction

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Abstract
The Vilsmeier Haack reaction is a world-wide strategy in the formylation of aliphatic and aromatic components; this application was further extended to synthesize heterocyclic compounds through cyclisation. Herein we report a simple two step synthesis of pyrazole derivatives by the fusion of quinoline through the Vilsmeier-Haack procedure.

Keywords: Vilsmeier Haack reaction, 3-(2,4-dichloroquinolin-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde and Fisher indole synthesis.

1. Introduction
Pyrazoloquinolines are now showing excellent results against mycobacterium tuberculosis [1-5], cancer [6-7], inflammatory [8-11] and malaria [12]; they are used as fungicide [13] and microbial healer [14, 15]. Our recent research demonstrated the synthesis of indoloquinolines [16] and indolquinoline [17] with the reaction of a key starting material ketone and hydrazine derivatives; though an acid catalysed reaction yielded the targeted products through the formation of a hydrazone in a single step as in the Fisher Indole synthesis. In this work we restricted the cyclization with a mild catalyst and hence isolated the hydrazone which was further treated with the Vilsmeier-Haack reagent to evolve the pyrazoloquinoline type molecule.

Heteroatom directed photo annulations [18, 19], microwave methodologies [20], reactions in water [18-20], Claisen condensation [21], Vilsmeier Haack reaction [16] and Fisher indole synthesis [17] are some of the methodologies adopted by us to develop indoloquinolines and naphthyridines [21].

2. Materials and Methods
Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrophotometer as potassium bromide discs unless otherwise indicated. 1H NMR spectra were obtained on a Brucker (400 MHz) instrument in CDCl3 solutions using tetramethylsilane as an internal standard. J Values are given in Hz. Mass spectra were obtained at the Vellore Institute of Technology, Vellore, Tamil Nadu, India. Column chromatography utilised Merck silica gel 60 and hexane and ethyl acetate as eluants. All the basic chemicals were purchased from Merck (India).

Experimental
Synthesis of 3-(1-(2-phenylhydrazono) ethyl) quinoline-2,4-diol 3
3-Acyl-2,4-dihydroxyquinoline 1 (0.01mole, 2.03g) was weighed and mixed with 3-phenylhydrazine hydrochloride 2 (0.01mole, 1.44g) in methanol and a catalytic amount of glacial acetic acid was added and allowed to reflux at 75°C for 6 hours. The condensed material was then poured into ice-cold water; the precipitate was extracted with ethyl acetate, concentrated and purified through column chromatography with petroleum ether and ethyl acetate mixture (90:10).

Preparation of 3-(1-(2-phenylhydrazono)ethyl)quinoline-2,4-diol 3
Yield 2.34 g (80%); brown in colour; m.p 268°C; IR (KBr, \upsilon_{max}, cm⁻¹): 3161, 3015, 2958, 1664; 1H NMR (400MHz, CDCl3): δ 11.26 (s, 1H, O-H), δ 8.00 (s, 1H, N-H), δ 7.51-7.61 (m, 3H, Ph-C2-H, Ph-C4-H & C6-H), δ 7.17-7.44 (m, 4H, C5, C6, C7 & C8 -H), δ 6.67-6.98(t, 2H, J = 8.10, Ph-C3-H & Ph-C5-H), δ 2.79 (s, 3H, CH3-H); 13C NMR (100 MHz, CDCl3): δ 172.87, 161.84, 150.89, 149.12, 121.91, 140.20, 137.91, 134.71, 132.27, 129.96, 129.86, 127.20, 122.67, 117.00, 116.51, 111.17, 30.99.
Synthesis of 3-(2,4-dichloroquinolin-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde 4

Dimethyl formamide (0.05 mole, 3.85 mL) is cooled to 0°C in a flask equipped with a dropping funnel. Phosphoryl chloride (0.14 mole, 12.97 mL) is added drop wise from the funnel with stirring. The resultant reagent was stirred for a further 30 minutes at room temperature and then cooled to 5°C then 2.93 g (0.01 mole) 3-(1-(2-phenylhydrazono)ethyl)quinoline-2,4-diol 3 is added and the stirring is further continued for 30 minutes and shifted over water bath and heated for 17 hours. After being subjected to the reaction conditions, the reaction mixture was then poured into crushed ice and neutralized with sodium carbonate solution. The solid 3-(2,4-dichloroquinolin-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde 4 was filtered and dried and then purified by column chromatography.

Preparation of 3-(2,4-dichloroquinolin-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde 4

Yield 2.57 g (70%); m.p 94°C; IR (KBr, νmax, cm⁻¹): 3070, 3013, 2960, 2845, 1682, 776, 756; ¹H NMR (400MHz, CDCl₃): δ 10.30 (s, 1H, -CHO-H), δ 7.25-7.87 (m, 15H, 2 x ph-H, pyra-H, C₄, C₅, C₆, C₇ & C₈ –H); ¹³C NMR (100 MHz, CDCl₃): δ 181.10, 162.74, 154.19, 138.85, 138.07, 136.28, 132.33, 141.32, 130.41, 129.92, 129.48, 129.12, 129.00, 128.83, 128.49, 128.10, 127.62, 126.62, 126.23, 125.77, 123.88, 123.76, 122.84, 120.39, 116.23.

3. Result and discussion

In the current research investigation we synthesised 3-(2,4-dichloroquinolin-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde 4 in two steps (scheme 1). We chose 3-acyl-2,4-dihydroxy quinoline 1 as a starting precursor since we have this prepared in bulk. We dissolved 1 in methanol with an equivalent amount of phenylhydrazine hydrochloride 2. A few drops of acetic acid was added to initiate the reaction and then the mixture was refluxed. After 30 minutes, analysis by thin layer chromatography showed the appearance of a new spot. After six hours the reaction mixture was poured into an ice-cold water; the brownish precipitate was filtered, dried and purified through column chromatography; the yield was 80% and m.p is 268°C. The identity of 3 was established by analysis via FTIR: disappearance of the characteristic stretching of C=O at 1730 cm⁻¹ and an appearance of C=N stretching at 1664 cm⁻¹. Furthermore the disappearance of carbonyl carbon signal at δ175 from the ¹³C NMR spectrum confirmed the functional group modification. On comparing the ¹H NMR spectrum of 3 with 1, it was observed that three proton singlet was unchanged at δ 2.79; an appearance of a one proton singlet at δ 8.00 for N-H proton, a triplet for two protons at δ 6.68 for Ph-C₃-H & Ph-C₅-H and a three proton multiplet from δ 7.51-7.61 for Ph-C₂-H, Ph-C₄-H & C₆-H confirmed the condensation reaction and the product 3.

In the second step, we used the Vilsmeier Haack reaction as in our earlier reports [16]. After working up the mixture, it was purified with column chromatography in petroleum ether: ethyl acetate mixture to give 4 in 70% yield it melted at 95°C. Analysis by FTIR showed the C=O stretching of an aldehyde group at 1682 cm⁻¹; the aldehydic C-H stretching at 2845 cm⁻¹; C=N stretching at 1682 cm⁻¹ and C-Cl stretching at 756 cm⁻¹ and 776 cm⁻¹. In the ¹H NMR spectrum, the phenolic O-H group was absent but a one proton singlet at δ 10.30 was present. The characteristic signal of aldehydic carbon at δ 190 in ¹³C NMR spectrum and disappearance of CH₃ carbon signal at δ 23 thereby conforming the identity of 4.

4. Conclusion

A two-step method offers an excellent synthetic way to afford a pyrazolo quinoline; the spectral data helps to elucidate the structures of synthesized molecules. This reaction protocol shows that the Vilsmeier Haack reaction is more useful for the cyclization of heterocycles.

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6. References


