SYNTHESIS OF 3,3-DISUBSTITUTED ACRYLALDEHYDE AND STUDY OF INFLUENCES OF FIELD EFFECTS ON REGIOSELECTIVE NUCLEOPHILIC SUBSTITUTION REACTIONS

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Abstract : A stereoselective S_N2 reaction is reported; reaction of 3-chloro-3-(2,4-dichloroquinolin-3-yl)acrylaldehyde with morpholine in a basic condition yielded 3,3-disubstituted acrylaldehyde. A strong –I effect of heterocyclic aromatic ring facilitates the nucleophilic substitution at the allylic position of acrylaldehyde.

IndexTerms **- 3-chloro-3-(2,4-dichloroquinolin-3-yl)acrylaldehyde, morpholine, stereoselective nucleophilic substitution.**

I. INTRODUCTION

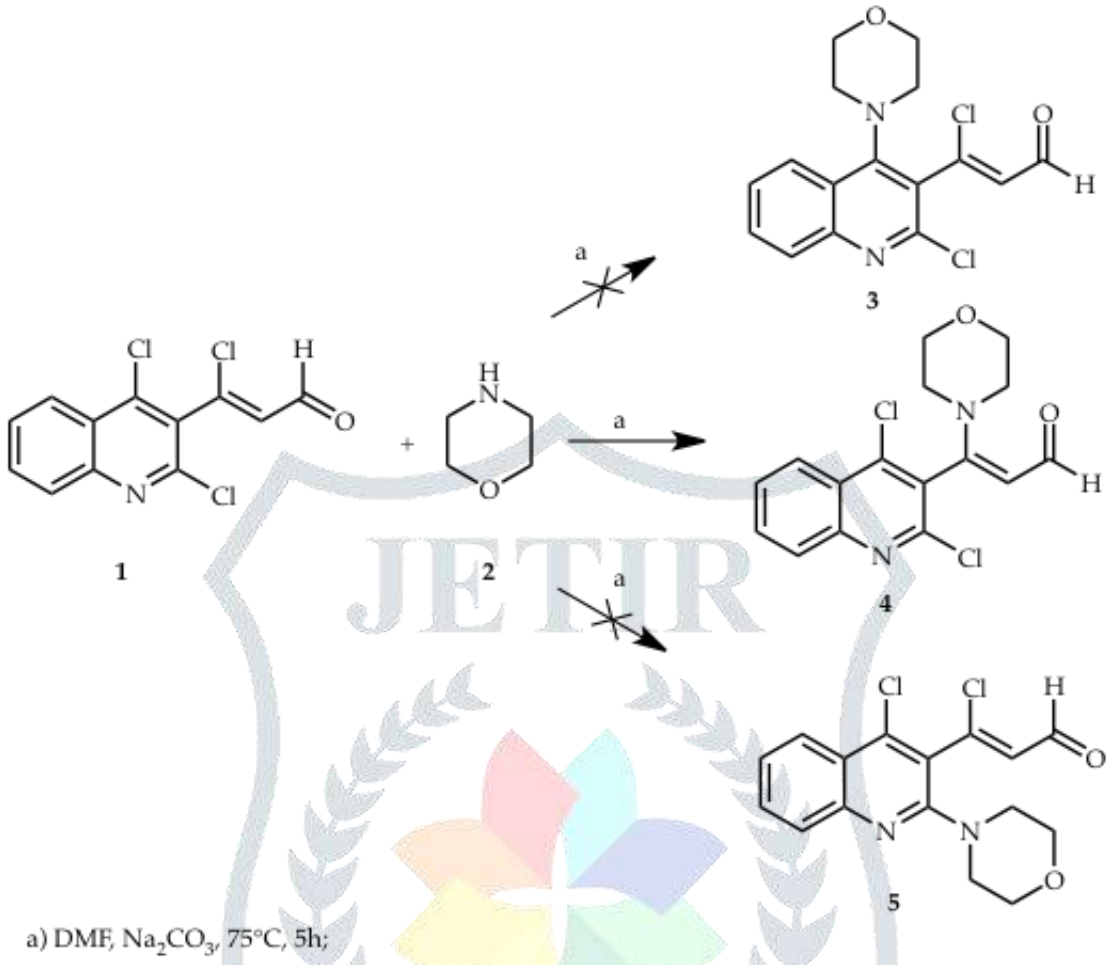
Field effects such as inductive, resonance, hyper conjugation and steric effect (may be called as spatial effect) are nevertheless more important phenomena in the acceleration or hindrance of any type of organic reactions. S_N2 reactions are hindered in tertiary alkyl halides due to the spatial effect; *N*,*N*- dimethylamine is more basic than *N*-methylamine due to the +I effect whereas *N*,*N*,*N*-trimethylamine is less basic than *N*,*N*-dimethylamine due to the spatial effect. The later category was much important that the spatial effect was competed more efficiently than the +I effect of methyl groups.[1] E1 and E2 reactions are stereoselective and Zaitsav's rule was applied- hyper conjugation involved to form more canonical structures and increased the stability of tertiary carbo cations than the secondary and primary.[2] Tosylate ions are strong nucleofuge thereby they can stabilize themselves through resonance and the reaction rate of S_N2 reactions are quite faster.[3] Recent study on the S_N2 reaction of gem difluorinated olefins, enforce to furnish the same on olefins with the other disubstituted olefins.[4]

Quinoline alkaloids with linear chain at 3rd position are quite important in medicinal chemistry to treat rheumatism and viral infection whereas in synthetic organic chemistry as facile precursors for the furano and pyrano quinoline alkaloids like dictamnine and khaplofoline. Dasycarine and preskimmianine are some of the examples for the quinoline alkaloid with a pseudo isoprene unit at 3rd position.[5,6] Our recent reports were anticipated with synthesis of indoloquinolines and naphthyridines by using Vilsmeier Haack, Claisan condensation and Fisher indole procedures.[7-15] Here our scope was archived to study about the reactivity of the acrylaldehyde with the dual electron withdrawing substitution on its allylic position.

II. RESULTS AND DISCUSSION

Equimolar mixture of 3-chloro-3-(2,4-dichloroquinolin-3-yl)acrylaldehyde[14] with morpholine was dissolved in DMF and the catalytic amount of sodium carbonate was added. It was assembled in water bath for constant heating at 75°C; the reaction was monitored in regular intervals to ensure the staging and it was found that the conversion was ended up after 5h. The ^{1}H NMR spectrum showed the eight-proton integration at upfield emphasizes that morpholine ring was added to the precursor **1** by substitution. However it was found that there were no substantial changes in the aromatic region. A shift of doublet from δ 6.20 to d 4.84 indicated that the morpholine ring replaced the chlorine atom in the olefinic chain. Eventhough the canonical structures formed due to resonance imply 2nd and 4th position of quinoline ring is

usually electron deficient. But it needs a strong base such as sodamide and *n*-butyllithium to afford nucleophilic substitution.



a) DMF, Na_2CO_3, 75°C, 5h;

Scheme 1

Two electron with drawing groups like a heterocyclic ring and an electronegative chlorine atom at the 3rd carbon of acylaldehyde enforces its electrophilicity and the week nucleophile easily replaces the strong nucleofuge so called chloride ion. It is said to be regioselective. The polar aprotic solvent DMF and the mild base Na_2CO_3 also explored the nature of selectivity. Addition to the above –I effect, spatial effect also employed in this reaction. The substitution at the 2nd and 4th position is also hindered by the presence of a lengthy aliphatic chain at 3rd position of quinoline ring. The broad singlet at δ 12.5 is prompted in ^{1}H-NMR and the carbonyl carbon signal in ^{13}C NMR at δ 196 also supported that there is no change in the aldehydic group. New carbon signals found in upfield at δ 19.63, δ 29.36, δ 31.92 and δ 37.83 are correlated for four carbon atoms of morpholine ring. The data supported that the compound **4** was regioselectively formed and the competition of formation of **3** and **5** are totally absent.

III. CONCLUSION

A regioselective S_N2 reaction on olefinic electron deficient carbon has successfully furnished. Even though 2nd and 4th position of quinoline ring is electropositive, -I effect of electron with drawing group in the olefinic chain increases the selectivity and the steric hindrance of the olefinic chain on the 3rd position restrict the nucleophilic substitution on the respective positions on quinoline.

IV. EXPERIMENTAL

4.1. General

The reagents, solvents and chemicals were purchased on Ranchem Scientifics, Spectrum and Merck India. Melting points are uncorrected and identified through the instrument assembled by Tempo instruments and equipments, India Pvt LTD. IR spectrum was traced from the Perkin-Elmer Paragon 1000 FTIR spectrophotometer as potassium bromide discs unless otherwise indicated. Nuclear Magnetic Resonance spectra were recorded on a Brucker (400 MHz) available at Vellore Institute of Technology, Vellore, India; tetramethyl silane as internal standard and deutrated chloroform as solvent and the *J* values are given in Hz. Column and thin layer chromatography utilized silica gel with the required mesh size and petroleum ether and ethylacetate eluants.

4.2. Synthesis of 3-(2,4-dichloroquinolin-3-yl)-3-morpholinoacrylaldehyde 4

0.001 mole of 3-chloro-3-(2,4-dichloroquinolin-3-yl)acrylaldehyde **1**[14] was in 30 mL of *N*,*N*-dimethyl formamide and 0.001 mole of morpholine was poured with it. 20 mg of sodium carbonate was added to the reaction mixture and was subjected for stirring at room temperature for 10 minute to dissolute the solid particles. Then the round-bottomed flask with the reaction mixture is assembled on a water bath mounded with refluxing unit. After constant reflux at 75°C for 5 hours; the TLC showed the conversion by varying R_f value. The set up was decoupled and cooled in to room temperature. An orange colour solution was poured into a 500 mL ice-bath. It was neutralized with dilute hydrochloric acid and the oily layer was extracted by ethyl acetate. Now the orange pasty mass was purified through column chromatography with petroleum ether and ethyl acetate (95:5) mixture.

4.2.1. Preparation of 3-(2,4-dichloroquinolin-3-yl)-3-morpholinoacrylaldehyde 4

3-chloro-3-(2,4-dihydroxyquinoline-3-yl)acrylaldehyde (**1**)[14] 0.249 g (0.001 mol), morpholine (**2**) (0.001 mol), Yield 1.86 g (75%) as a creamy white solid, m.p.180ºC; IR (KBr) cm^{-1}**:** 3421, 2850, 1629, 1546, 779; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.49 (bs, 1H, CHO), δ 7.183-7.272 (t, 1H, J = 7.6 Hz, quin-H-6), δ 7.331-7.349 (d, 1H, J = 7.2Hz, quin- H-5), δ 7.411-7.460 (t, 1H, J = 7.2 Hz, 1H, quin H-7), δ 7.572-7.590 (d, 1H, quin- H-8), δ 2.574–1.182 (m, 8H, ali-oxazino-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.30, 166.24, 163.32, 141.21, 138.11, 136.71, 131.16, 130.53, 129.44. 128.72, 127.83, 122.21, 120.31, 115.11, 112.77, 37.83, 31.92, 29.36, 19.63.

V. ACKNOWLEDGMENT

The author thanks Vellore Institute of Technology for providing spectral data and S. Sathiyamoorthy thanks UGC, New Delhi for endorsement of the Rajiv Gandhi National Junior Research Fellowship.

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