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Research Article

Synthesis and Characterization of some New 6-substituted-2, 4-di (hetar-2-yl) Quinolines via Micheal Addition - Ring closure Reaction of Schiff base N-(hetar-2-yl) methylene aniline with Hetarylketones

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Abstract

In an attempt to find new bioactive 2,4(-dihetar-2-yl) substituted quinoline derivatives via the reaction of aniline and hetarylchalcone analogues, despite the practical shortcomings the optimum condition was achived in two steps from the reaction of aniline with hetarylaldehyde to give the Schiff base N-(hetar-2-ylmethylene)aniline followed by cyclization with hetarylketones in $ZnCl_2/CH_3COOH$. Subsequent oxidation in acetic acid afforded the substituted quinoline derivatives in excellent yields. The structures of synthetic quinoline derivatives have been characterized by analytical and spectral data.

1.0 Introduction

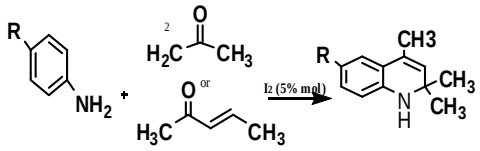
One of the major objectives of organic and medicinal chemistry is the design, synthesis and production of molecules which are having highly therapeutic nature.

The synthesis of quinolines and their derivatives has been of considerable interest because a large number of natural products and drugs contain this heterocyclic unit[1]. Quinolines and their derivatives are receiving increasing importance due to their wide range of biological activities as anti-malarial, anti-bacterial, anti-asthmatic, anti-hypertensive, anti-inflammatory, anti-platelet activity and as tyro-kinase PDGF-RTK inhibiting activity.[2-4]

In addition, quinolines have also been employed in the study of bioorganic and bio-organometallic processes[5]. Due to such a wide range of applicability in medicinal, bioorganic, industrial as well as in the fields of synthetic organic chemistry, there has been increasing interest in the development of efficient methodologies for the synthesis of quinolines[6-9].

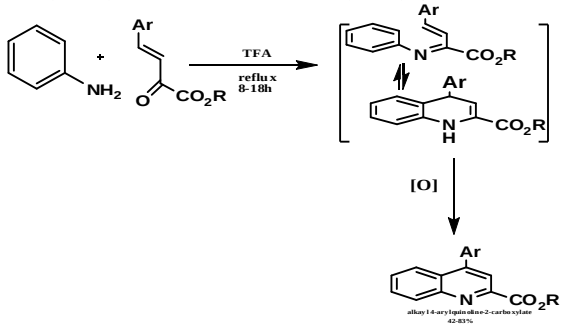
Consequently, various procedures such as the Skraup, Doebner-von Miller, Friedlander and Combes syntheses have been developed for the synthesis of quinoline derivative[10-14].

Various moderators such as acetic or boric acids, ferrous sulfate, thorium, or vanadium or iron oxides have been used to accelerate the reaction and make it higher yielding[15]. The Skraup-Doebner-Von Miller synthesis of quinolines can also be catalyzed by a number of Lewis ($SnCl_4$, $Yb(OTf)_3$, $Sc-(OTf)_3$, $ZnCl_2$, $InCl_3$) and BrÖnsted acids (TsOH, $HClO_4$,Amberlite) in addition to iodine[16].In addition, microwave irradiation in combination with various Lewis acid activators like montmorillonite K-10 as the catalyst has recently been employed with good results[17]. Various substituted anilines have been used in the Skraupquinoline synthesis. For ortho- and para-substituted anilines, the regiochemical outcome is unambiguous. However, the structure of the quinoline products obtained using meta-substituted anilines is unpredictable.[18]



Scheme-1: Doebner and Von Miller with α, β -unsaturated ketone

A reversal of the standard regiochemistry of the Skraup- Doebner-Von Miller was discovered by Later Chen and co-workers. The quinoline synthesis was observed whenanilines were condensed with γ -aryl-β, γ -unsaturated α -ketoestersin refluxing TFA scheme 2. The reaction is proposed to involve1,2-addition of the anilines to γ -aryl-β,γ -unsaturated α -ketoestersto form Schiff's base adducts, followed by cyclizationand oxidation. The products were unambiguously shown to be the 2-carboxy-4-arylquinoline.[19]



Scheme-2: Reversal Skraup-Doebner - Von Miller product

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2.0 Materials and Methods

Melting points were taken on a Boëtius melting point microscope. ^{1}HNMR, analysis was conducted on a Mercury-300BB (300 MHz) instrument in (DMSO-d_6), ^{13}CNMR (75 MHz, DMSO) and Mass spectra on a Jeol JMS.

2.1 General Procedure for Synthesis of 2, 6-Dihetaryl quinoline derivatives

2.1.1 Method-I: Micheal addition (chalcone with aniline)

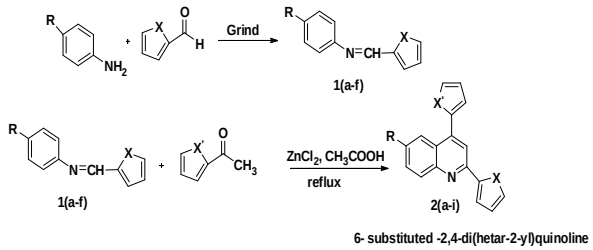
A mixture of aniline (0.05mol), and heterocyclic chalcone(0.05mol) was refluxed in glacial acetic acid in presence of anhydrous zinc chloride for(10-16h). The completion of the reaction was monitored by TLC. The resultant mixture was cooled and rendered basic (pH 8) with 10% $NaHCO_3$, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4. Evaporation left a crude residue which was further purified by flash column chromatography over silica gel (hexane: ethyl acetate: 4:1). The product was obtained in low yield (2-4%).

2.1.2 Method- II: Three components system (without the isolation of schiff base)

A mixture of aniline (0.05mol), hetaryl aldehyde (0.05mol) and Hetarylmethyl ketone (0.05mol) was refluxed in glacial acetic acid in presence of anhydrous zinc chloride for (10-16h). The reaction was monitored by TLC to completion. The resultant mixture was cooled, rendered basic (pH 8) with 10% $NaHCO_3$, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4. Evaporation in vacuo left crude, which was further purified by flash column chromatography over silica gel (hexane: ethyl acetate: 4:1).
The product was obtained in moderate yield (18-36%).

2.1.3 Method-III: Cyclization of the isolated Schiff base with the hetarylketone

Aniline (0.05mol) and, hetaryl aldehyde (0.05mol) were combined and ground using a mortar and pestle. The Schiff base was obtained within 10min as yellow powder. Then a mixture of the Schiff base with the hetarylmethyl ketone was heated in presence of anhydrous zinc chloride and glacial acetic acid for (6-12h), the completion of the reaction was monitored by TLC. The resultant mixture was cooled and rendered basic (pH 8) with 10% $NaHCO_3$, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to leave a crude which was further purified by flash column chromatography over silica gel (hexane :ethyl acetate :: 4:1). The product was obtained in excellent yield (51.7-636%).



1a; R = H, X = O **2a; R = H, X = O, X' = O**
1b; R = OCH_3, X = O **2b; R = OCH_3, X = O, X' = O**
1c; R = Cl, X = O **2c; R = Cl, X = O, X' = O**
1d; R = H, X = S **2d; R = H, X = S, X' = O**
1e; R = OCH_3, X = S **2e; R = OCH_3, X = S, X' = O**
1f; R = Cl, X = S **2f; R = Cl, X = S, X' = O**
2g; R = H, X = S, X' = S
2h; R = OCH_3, X = S, X' = S
2i; R = Cl, X = S, X' = O

Scheme-3: Synthesis of quinoline with isolation of the Schiff base

Table 1: Percentage yields of 6- substituted-2, 4-di (hetar-2-ayl) quinoline

Compounds	2a	2b	2c	2d	2e	2f	2g	2h	2i
Yields%	55.5	51.7	52.9	63.3	55.8	59.1	63.6	60.1	62.1

2.2 Spectral Data

2, 4-di(furan-2-yl)quinoline. [2a]

The brown residue was subjected to preparative thin layer chromatography (TLC) using hexane: ethyl acetate (4:1). Purification of the crude residue by column chromatography using hexane: ethyl acetate (4:1).
Brown Crystal, m.p. 40-41^{0}C
^{1}HNMR,(300MHZ, DMSO-d_6): δ 6.86- (2H, t, J=6.30 Hz, furanC_4-H, C_4-H) 7.07(1H, d, J=6.30, furanC_3-H), 7.59 (1H, m, J=6.30 Hz, H-furan), 7.70(1H,d. J=7.26 Hz, quinolineC_3-H), 7.60, 7.78,7.98, 8.06 (4H,d. quinoline), 7.86(1H,d. 2- furanC_5-H).
^{13}CNMR (75 MHz, DMSO): δ 157.7, 154.0 (s,CO), 120.0,131.6 ,103.0,124.0, 129.9, 127.0, 158.1, 144.9
Elemental analysis calculated for $C_{17}H_{11}NO_2$: C 78.15, H 4.24, N 5.36, O 12.25
MS:m/z $C_{17}H_{11}NO_2$ (261.27): 262(M^++1, 50.0%)

6-methoxy-2,4-di(furan-2-yl)quinoline. [2b]

Purification of the crude residue was done by column chromatography using hexane: ethyl acetate (4:1) as solvent.
Brown Crystal, m.p. 59-61^{0}C
^{1}HNMR,(300MHZ, DMSO-d_6): δ 3.81(3H, s. J=2.87 Hz, OCH_3), 7.86(2H, d. J=7.38 Hz, 2-furanC_5-H), 6.86, 7.07(2H,t. J=6.30 Hz, 2-furanC_4-H, C_4-H),7.70(1H,d. J=7.26 Hz, quinolineC_3-H), 7.16, 7.30, 7.78, (3H,d, quinoline)
Elemental analysis calculated for $C_{18}H_{13}NO_3$: C 74.22, H 4.50, O 16.48, N 4.81
MS:m/z $C_{18}H_{13}O_3N$ (291.2): 292(M^++1, 49.0%)

6-chloro-2, 4-di (furan-2-yl) quinoline [2c]

Brown Crystal, m.p. 54-55^{0}C
^{1}HNMR, (300MHZ, DMSO-d_6): δ 6.68 (2H, t. J= 6.30Hz, 2-furanC_4-H), 7.07(1H, t. J=6.30Hz, 2-furanC_4-H), 7.86(2H, d. J=7.38Hz, 2-furanC_5-H), 7.70(1H,d. J=7.26 Hz, quinolineC_3-H), 7.65,7.83(2H, d, C_5-H, C_7-H,quinoline), 8.13(1H, d. J=8.05 Hz, quinoline).
Elemental analysiscalculated for $C_{17}H_{10}ClNO_2$: C 69.05, H 3.41, Cl 11.99, N 4.74,
O 10.82. MS: m/z $C_{17}H_{10}ClNO_2$ (295.72): 297(M^++2, 32.4%)

2-(furan-2-yl)-4-(thiophen-2-yl) quinoline [2d]

Brown Crystal, m.p. 65-67^{0}C
^{1}HNMR, (300MHZ, DMSO-d_6): δ 6.68 (1H, t, J=6.30 Hz, 2-furanC_3-H), 7.17(1H, t, J=6.30 Hz, 2-thiophene C_3-H), 7.71(1H, d, J=7.26 Hz, quinoline C_3-H) 7.85 (2H, d, J=6.96 Hz, 2-thiophene C_5-H), 7.86 (2H, d, J=6.96 Hz, 2-furan C_5-H), 7.65-8.06(4H, d, J=7,68 Hz, quinoline)
^{13}CNMR, (75 MHZ, DMSO): δ 142.9(1C, CO), 112,107.1, 154.0, 142.4, 127.6, 128.0, 128.6, 158.1, 144.9, 120.0, 145.8(4C, quinoline), 124.0, 127.0, 129.9, 131.6
Elemental analysis calculated for $C_{17}H_{11}NOS$:C 73.62, H 4.00, N 5.05, O 5.77, S 11.56
MS:m/z$C_{17}H_{11}NOS$ (277): 278(M^++1, 79.4%).

6-methoxy-2-(furan-2-yl)-4-(thiophen-2-yl)quinoline. [2e]

Brown Crystal, m.p. 90-92^{0}C
^{1}HNMR, (300MHZ, DMSO-d_6): δ 3.81(3H, s, J=2.87, OCH_3), 6.68, 707(2H, t, J=6.30Hz, 2-furanC_3-H, C_4-H), 7.17-7.31(3H, m, J=6.69Hz), 7.69(1H, d, J=7.20Hz, 2-thiopheneC_5-H), 7.71(1H, d, 7.726Hz, quinolineC_3-H), 7.85(1H, m, J=6.69Hz thiopheneC_3-H), 7.86(1H, m, 2-furanC_5-H), 7.05, 7.19(2H, d, J=8.05Hz, quinoline, 7.79(1H, d, J=8.05Hz, quinoline)

Elemental analysis calculated for $C_{18}H_{13}NO_2S$: C 70.34, H 4.26, N 4.56, O 10.41, S 10.43
MS:m/z$C_{18}H_{13}ClNOS$ (307): 307(M^+, 45.6%), 308 (19.1%)

6-chloro-2-(furan-2-yl)-4-(thiophen-2-yl)quinoline. [2f]

Brown Crystal, m.p. 86-88^{0}C
^{1}HNMR, (300MHZ, DMSO-d_6): δ 6.68-7.07(2H, t. J=6.30Hz, 2-furanC_3-H, C_4-H), 7.17(1H, t, J=6.69Hz, 2-thiopheneC_4-H), 7.69(1H, m, J=7.20Hz,2-thiophene), 7.64(1H, m. J=7.68Hz, quinoline), 7.71(1H, d, J=7.26Hz, quinolineC_3-H), 7.64,7.82(2H, d, J=7.61,quinoline), 7.85(1H,t, J=6.96Hz, 2-thioheneC_3-H), 7.86(1H, m, J=7.38Hz, 2-furanC5-H),8.11(1H,d, J=8.05Hz, quinoline)
Elemental analysis calculated for $C_{17}H_{10}ClNOS$: C 65.49, H 3.23, Cl 11.37, N 4.49, O 5.13, S 10.28 .MS:m/z$C_{17}H_{10}ClNOS$ (311): 312(M^++1, 66.6%), 313 (11.1%)

2, 4-di (thiophen-2-yl)quinoline. [2g]

Yellow Crystal, m.p. 108-110^{0}C
^{1}HNMR, (300MHZ, DMSO-d_6): δ 7.17, 7.40(2H, t, J=6.30 Hz, 2-thiopheneC4-H, C4-H), 7.85(1H, t, J=6.30Hz, 2-thiopheneC4-H), 7.69(1H, d, J=7.20 Hz, 2- thiopheneC_5-H), 7.73(1H, d, J=7.26 Hz, quinolineC_3-H), 7.68,7.80,(2H, d, quinoline), 8.06,8.13(2H,d, quinoline)
^{13}CNMR (75 MHz, DMSO): δ 142.4, 141.9(2C, s. J=125.6 2-thiophene C-S), 118.9, 144.9, 145.8, 158.1, 127.6, 128.0, 128.6, 103.0, 127.0, 129.9, 131.6
Elemental analysis calculated for $C_{17}H_{11}NS_2$: C 69.59, H 3.78, N 4.77, S 21.86;
MS:m/z $C_{17}H_{11}NS_2$(293): 294 (M^++1, 55.0 %)

6-methoxy-2,4-di(thiophen-2-yl)quinoline. [2h]

Yellow crystal, m.p. 123-124^{0}C
^{1}HNMR, (300MHZ, DMSO-d_6 DMSO-d_6): δ 3.81(3H, s, J=2.87Hz, OCH_3), 7.17 (2H, t, J=6.30 Hz, 2-thiophene, C_4-H), 7.31-7.40(2H, m, J=6.69Hz), 7.69(2H, d, J=7.20 Hz, 2- thiopheneC_5-H), 7.85(2H, d, J=6.96 Hz, 2- thiopheneC_3-H), 7.73(1H, d, J=7.26 Hz, C_3-H quinoline), 7.81(1H, d, J=8.05Hz, quinoline), 7.17,7.31(2H, d, J=8.05Hz, quinoline).Elemental analysis calculated for $C_{18}H_{13}NOS_2$: C 66.84, H 4.05, N 4.33, O 4.95, S 19.8. MS:m/z $C_{18}H_{13}ONS_2$ (323.43): 324(M^++1, 60.9%)

6-chloro-2,4di(thiophen-2-yl)quinoline

Yellow Crystal, m.p. 119-120^{0}C
^{1}HNMR, (300MHz, DMSO-d_6): δ7.17 (2H, t, J=6.30 Hz, 2-thiophene, C_4-H), 7.40(1H, m, J=6.96Hz), 7.64-7.69 (3H, m, J=7.20Hz), 7.73(1H, d, J=7.26 Hz, C_3-H quinoline) 7.68,7.86 (2H, d, J=7.61Hz, quinoline), 8.16(1H, d, J=8.05Hz, CH-quinoline)
Elemental analysis calculated for $C_{17}H_{10}ClNS_2$: C 62.28, H 3.07, Cl 10.81, N 4.27, S 19.56
MS:m/z $C_{17}H_{10}ClNS_2$ (327.): 328(M^++1, 41.1%)

3.0 Results and Discussion

3.1 Micheal Addition (chalcone with aniline)

In view of the interest in the Skraup-Doebner-Von Miller quinoline synthesis, it is not surprising that many mechanistic studies are already on record. Skraup himself suggested that aldehyde anils underwent direct acid-catalyzed closure to quinolines. To accommodate this fact, KÖnig proposed a modification of a mechanism first suggested by Bischler which involves the 3-anilinopropanal imine as the key intermediate (figure 1) [20]. KÖnig's mechanistic proposal was subsequently supported by deuterium-labeling experiments[21].
These studies showed conclusively that anils cannot undergo direct closure but must either revert to the *α*-anilino carbonyl compounds and cyclize or react via the conjugate adducts. However, in 1989, Eisch showed that under anhydrous conditions, in the absence of free anilines, isolated aldehyde anils undergo a rearrangement via 1, 3-diazetidinium ions to afford 2-substituted quinolines[22].

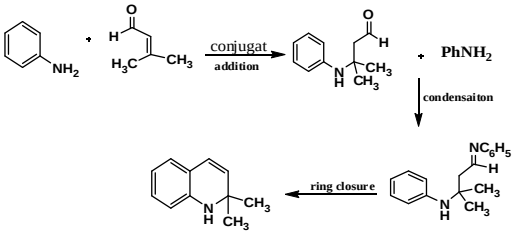


Figure-1: Doebner and Von Miller mechanism for the synthesis of Quinoline

3.2 The Schiff Base Formation

Schiff bases that contain aryl substituent, with effective congugation, are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstabe and readily polymerizable[23].
The generally accepted mechanism for this reaction was proposed by Snell and Braunstein [24, 25]. It consists of the addition of the amine to a carbonyl compound to give an intermediate carbinolamine that loses one molecule of water to produce the imine.[26] Although carbinolamines have proved to be difficult to observe in studies of Schiff base formation, experimental evidence supported the occurrence of such intermediate and the location of the rate-limiting step of the whole reaction is in its dehydration[27-29]. Quantum mechanics calculations onto a reactive system provided a detailed description of the intermediates and transition state geometries involved in the reaction.
A molecular complex consisting of hetarylaldehyde, para-methoxy-aniline and one water molecule was chosen as model compound to study the Schiff base formation. The purpose of including one water molecule in the model molecular complex was not the simulation of water solvation environment but its consideration as reactive species for the processing of the reaction.
In the present study Restricted Hartree-Fock (RHF) calculations were performed with the Gaussian03, software packages, running in an Intel Pentum (R) 1.86 GB personal computer.

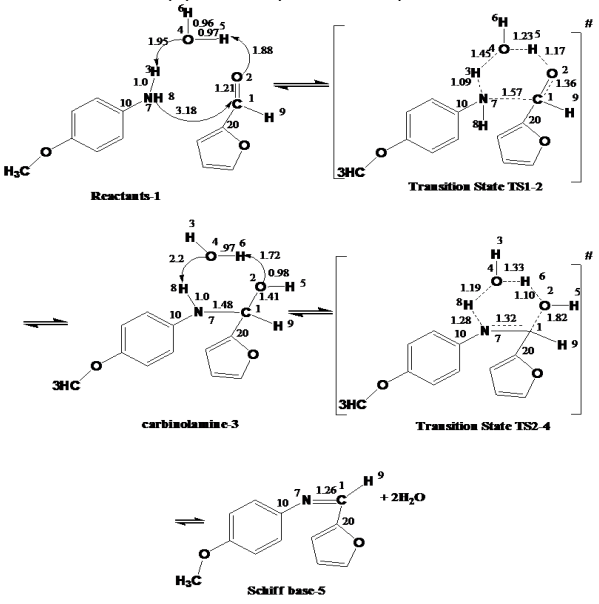
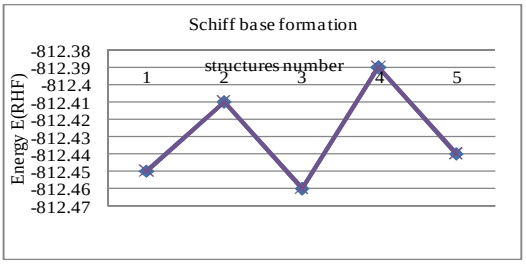


Figure 2: Mechanism of Schiff base formation between para-methoxy-aniline and furaldehyde

The mechanism of the Schiff base formation reactions of para-methoxy-aniline with furaldehyde involves two steps, namely: (1) formation of carbinolamine (1-3 in figure 2) and (2) dehydration of the carbinolamine to give the imine (3-5 in figure 2), figure 2 shows the atoms directly involved in the reaction and the overall process.
Figure 1 shows the energy profiles forthe process in the gas phase with RHF/3-21G.

Tables 3 and 4 show the relative energies, ΔHº, ΔGº and ΔSº data for the structures involved.

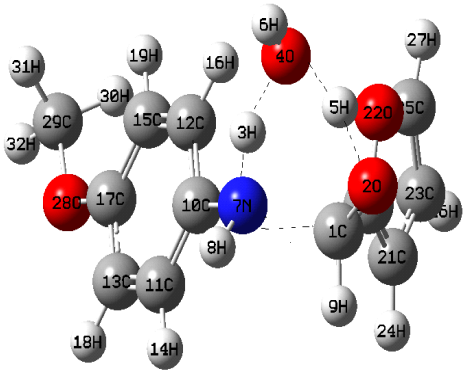


1= Reactant, 2= TS1, 3= Intermediate, 4= TS2, 5= Product
Figure 3: Energy profile for the reaction. Energy is in a.u.

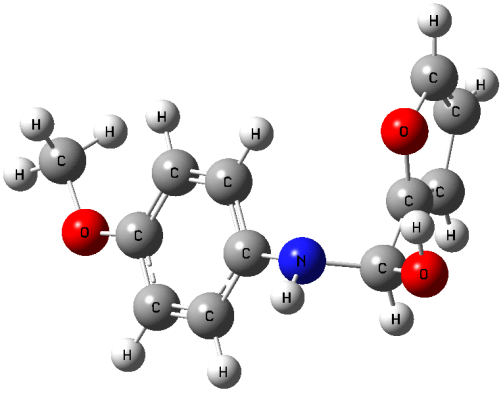
Table 2: Energies (RHF) for each of the structures of the reaction path from the standard thermochemistry output of a frequency calculation a

Structure	E(RHF)
1[a]	-812.450285
2[b]	-812.416005
3[c]	-812.462736
4[d]	-812.392964
5[f]	-812.446041

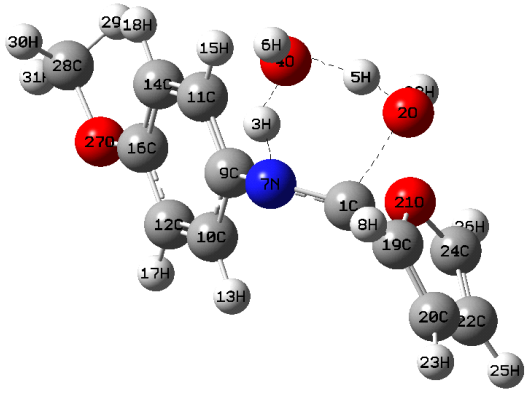
The Optimization structures of six-member ring transitions states TS1, TS2 and carbinolamine intermediate 3 of the above reaction calculated by RHF/3-21G. [30]



Transition state -TS1



Intermediate carbinolamine -3



Transition state -TS2

TS1, TS2 and carbinolamine intermediate 3 of the above reaction calculated by RHF/3-21G.

Figure 4: Optimized structures of six-membered ring transitions states

Table 3: Calculated energies of reactants, six-membered ring transition states, carbinolamine and products using RHF/3-21G in kcal mol^{-1}[a,b]

Compound	ΔE kcal mol^{-1}	ΔG kcal mol^{-1}	ΔH kcal mol^{-1}	ΔS kcal mol^{-1}
1[c]	0	0	0	0
TS1-2[d]	21.51	26.17	1.14	-0.35
3[e]	-7.81	5.44	-7.71	-0.17
TS2-4[f]	43.78	20.73	8.71	0.17
5[g]	10.47	7.55	18.95	0.16

[a]All structures were fully optimized. Cartesian coordinates of all structures are available as supplementary material.
[b] Energies reported relative to the sum of energies of separated reactants.
[c,d,e,f,g] Reactants, cyclic transition state-TS1, intermediate, cyclic transition state-TS2 and product respectively (refer to figure 2).

3.3 The Cyclization of the Schiff Base

The above mentioned Schiff bases were allowed to react with hetarylketone in presence of hydrochloric acid with absolute alcohol it has given the product in very low yield; on replacement of absolute alcohol by glacial acetic acid and anhydrous zinc chloride it has given the product in excellent yield, and having identical melting point. A cyclized structure was assigned to the product quinolines and their derivatives respectively supported by elemental analysis and nuclear magnetic resonance.

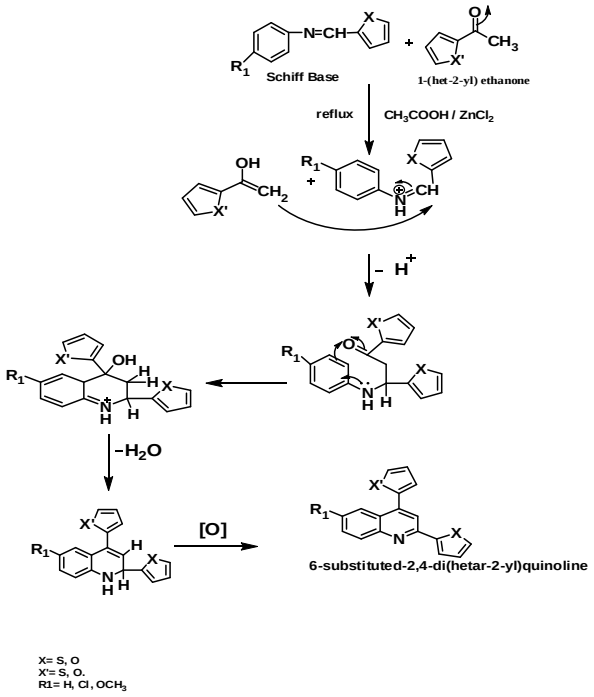


Figure 5: Mechanism of the synthesis of 6-subetituted-2-4-di (hetar-2-yl) quinoline via the Schiffbase cyclization

4.0 Conclusion

In conclusion a new acid catalyzed ($ZnCl_2/CH_3COOH$) synthesis of 6-substituted-2, 4-di (hetar-2-yl) quinolines via cyclization of Schiff base N-(hetar-2-ylmethylene) aniline with the appropriate ketone is described. This method provides the products in good to excellent yields and selectivity's in short reaction times from commercially available and inexpensive starting materials. In addition to efficiency, the solvent-free reaction in the isolation of the Schiff base has limited energy consumption, waste-free nature, makes the process an active green synthesis of the desired molecules.

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