Vilsmeier-Haack reaction on quinaldines

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The study of the Vilsmeier-Haack reaction on 4-hydroxyquinaldines resulted with the preparation of rarely existing 4-chloro-3-formyl-2(vinyl-1-ol)-quinolines. Currently there has been relentless interest towards the use of Vilsmeier-Haack Reagent in organic synthesis of several nitrogen and oxygen heterocycles. It is proved to be a mild and efficient method for the formylation of reactive aromatic and hetero aromatic substrates. Its versatility has been further extended as an activating agent for acylhalo addition and ring annulation. Besides the aromatic formylation a wide variety of carbonyl compounds activated methyl and methylene groups and oxygen, nitrene neucleophiles efficiently react with Vilsmeier-Haack reagent to yield the corresponding iminium salts. The intramolecular cyclisation potential of halomethyleneiminium salts formed under Vilsmeier condition and microwave induced Vilsmeier conditions were studied and reported.\textsuperscript{11} There has been instances in which chloromethyleneiminium salt reacts with active methyl groups followed by intramolecular cyclisation by the nucleophilic attack of adjacent group. Based on the above facts, it is very much evident that the reactive intermediate involved in Vilsmeier-Haack reaction are the halomethyleneiminium salts derived from the respective formamidines. The classical Vilsmeier-Haack reactions involves electrophilic substitution of an activated aromatic ring with a halomethyleneiminium salt to yield the corresponding iminium species, which facilitates easy entry in to large number of novel heterocyclic systems.

The capability of the reagent to generate a broad spectrum of iminium species has now been explored to hitherto non-existing vinyl alcohol intermediate. We reached this end, when a synthetic strategy was manipulated for the construction of \([c]\) annelated nitrogen and oxygen heterocycles through a prominent intermediate 4-chloro-3-formyl quinaldines, which could be thought of obtainable from Vilsmeier-Haack reaction of 4-hydroxyquinaldines.

Results and Discussion

We envisaged that the Vilsmeier-Haack reaction on 4-hydroxyquinaldines 4, which was prepared from aniline 1 and ethyl acetoacetate 2 and by subsequent cyclization of the \(\alpha\)-anilino crotonates 3 would provide an efficient intermediate for the preparation of several substituted \(\beta\) annelated heterocyclic compounds. The reaction was carried out at 100°C for 15-20 hr, using the Vilsmeier-Haack reagent derived from phosphorus oxychloride-dimethyl formamide in situ against 4-hydroxyquinaldines. Indeed, the reaction proceeded uneventfully and a mixture of products were obtained. These were isolated using silica gel column chromatography. The analytical and spectroscopic data confirmed the products as 4-chloro-3-formyl-2(vinyl-1-ol)-quinoline 5, 4-hydroxy-3-formyl quinaldine 6 and 4-chloroquinaldine 7 in good yields. Thus, the treatment of Vilsmeier Reagent at 100°C provided an efficient and facile method for the generation of quinoline vinyl alcohol. The time taken for each reaction and their yields are shown in Scheme I and Table I.

The Vilsmeier-Haack reagents are normally applied for the formylation of aromatic and heteroaromatic compounds. It is the chloromethyleneiminium species \(10\) responsible for the formylation. As in our reaction, the chloromethyleneiminium species \(10\) obtained in situ from phosphorus oxychloride-dimethyl formamide reacts with the active methyl group of 4-hydroxyquinaldines to yield 11. The second formylation occurs at the C-H moiety of the quinaldine leading to an iminium species 12. (Scheme II)
Scheme I

(i) dil. HCl (1:1), rt (ii) Ph$_3$O, 240°C, (iii) Vilsmeier-Haack Reagent (DMF-POCl$_3$), 100°C

1, 3-7: a) $R_1=R_2=R_3=R_4=H$
   b) $R_1=CH_3$, $R_2=R_3=R_4=H$
   c) $R_2=CH_3$, $R_1=R_3=R_4=H$
   d) $R_3=Cl$, $R_1=R_2=R_4=H$
   e) $R_1=R_4=CH_3$, $R_2=R_3=H$

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<th>$R_2$</th>
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<th>$R_4$</th>
<th>Reaction time (hr)</th>
<th>Yields$^b$ (%)</th>
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<td>CH$_3$</td>
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$^a$ All reactions were carried out at 100°C
$^b$ isolated yields after column chromatography on silica gel.
Simultaneously these iminium salts having the special capability to replace the hydroxyl group at an asymmetric carbon atom by chlorine, bromine etc., might have led to the formation of 4-chloroquinaldine 7 in minor yields and also in the conversion of hydroxy moiety to the chloro moiety in case of 4-chloro-3-formyl-2(vinyl-1-ol)quinoline 5. In the case of 4-hydroxyquinaldine 1a and 8-methyl-4-hydroxyquinaldine 1b the reaction is completed within 15 hr. But in the case of 5,8-dimethyl-4-hydroxyquinaldine 1e, the time taken is 20 hr for the completion of the reaction, which is monitored by the TLC studies.

In conclusion, we have demonstrated the importance of the iminium species in Vilsmeier-Haack Reaction on 4-hydroxyquinaldines 1a-e resulting in the formation of an efficient vinyl intermediate 4-chloro-3-formyl-2(vinyl-1-ol)quinoline 5, 3-formyl-4-hydroxy quinaldine 6 and 4-chloroquinaldine 7 which paves a path for the construction of newer nitrogen and oxygen heterocycles such as diazepines, diazocines etc., of biological importance.

**Experimental Section**

Thin layer chromatography was used to access the reactions and the purity of products. Melting Points were determined on a Boetius Microheating Table and Mettler-FP5 Melting apparatus and are uncorrected. IR spectra were recorded in Shimadzu – 8201FT instrument in KBr disc (νmax in cm⁻¹) and only noteworthy absorption levels (reciprocal centimetre) are listed. ¹H NMR spectra were recorded in a AMX-400 MHz spectrometer in CDCl₃ solution (chemical shifts are expressed in δ/ppm relative to TMS), coupling constants (J) in Hz and signal multiplicities are represented by bs (broad singlet), s (singlet), d (doublet), t (triplet) and m (multiplet). ¹³C NMR were also recorded on the same AMX-400 MHz spectrometer with tetra methyl silane (TMS) as internal standard. Mass spectra were recorded on a Jeol-D-300 mass spectrometer. CHN analyses were carried out on a Carlo Erba 106 and Perkin-Elmer Model 240 analysers.

**Vilsmeier-Haack reaction on 4-hydroxyquinaldine.** The Vilsmeier reagent was prepared by
taking N,N-dimethylformamide (3.86 mL, 0.05 mole) in a round-bottomed flask in an ice cold condition (0–5°C) with constant stirring. To this, phosphorus oxychloride (13.04 mL, 0.014 mole) was added dropwise for a period of 30 min and the resultant mixture was stirred for a further 1 hr. The appropriate 4-hydroxyquinolines 4a-e were added to the Vilsmeier reagent and stirred for further 30 min and the reaction mixture was kept in a water bath at 100°C for the stipulated period of time. After the reaction was completed as inferred through TLC, the reaction mixture was poured onto 500 g of crushed ice with constant manual stirring. It was kept aside for overnight. After neutralizing the above with 4 N NaOH, the precipitate obtained was washed well with water and extracted using ethyl acetate. The combined organic layers were then collected and dried over anhyd. Na2SO4. The silica gel chromatography of the reaction mixture afforded three products 5, 6 and 7 at pet.ether(100), pet.ether-ethyl acetate(94:6) and pet.ethyl-ethyl acetate(85:15) respectively. The products were recrystallized with methanol.

3-Formyl-3-formyl-2-(vinyl-1-ol)quinoline 5a: 1H NMR (CDCl3, 400 MHz): δ 7.7(d, 1H, C5-H, J = 8.1 Hz), 7.6(t, 1H, C7-H, J = 8.3 Hz), 7.9(t, 1H, C6-H, J = 7.3 Hz), 8.2(d, 1H, C3-H, J = 8.3 Hz), 9.2(s, 1H, C7-CHO), 9.4 & 9.6(2s, 2H, vinylic protons), 16.5(bs, vinylic–OH, D2O Exchangeable); 13C NMR (CDCl3, 400 MHz): δ 192.419, 189.332, 189.08, 146.24, 137.30, 135.90, 133.32, 126.93, 125.21, 122.61, 119.32, 118.99; MS(70 eV, m/z, M+) : 233, (M+2): 235; IR: 3438, 1664, 1595. Anal. Found: C: 61.62; H: 3.38; N: 5.92. Calcd. for C11H12O2NCl: C: 61.69; H: 3.45; N: 5.99; mp: 155°C.

3-Formyl-4-hydroxyquinoline 6a: 1H NMR (CDCl3, 400 MHz): δ 7.6(t, 1H, C7-H, J = 7.3 Hz), 7.5(t, 1H, C6-H, J = 7.6 Hz), 7.5(d, 1H, C3-H, J = 7.14 Hz), 7.3(s, 1H, C1-H), 8.1(d, 1H, C5-H, J = 8.2 Hz), 7.7(t, 1H, C7-H, J = 7.54 Hz), 7.9(t, 1H, C6-H, J = 7.82 Hz), 7.5(d, 1H, C3-H, J = 8.14 Hz); IR: 1590. mp: 65°C.

4-Chloroquinoline 7a: 1H NMR (CDCl3, 400 MHz): δ 2.5(s, 3H, CH3), 7.3(s, 1H, C1-H), 8.1(d, 1H, C5-H, J = 8.2 Hz), 7.7(t, 1H, C7-H, J = 7.54 Hz), 7.9(t, 1H, C6-H, J = 7.82 Hz), 7.5(d, 1H, C3-H, J = 8.14 Hz); IR: 1590. mp: 65°C.
4,6-Dichloro-3-formyl-2-(vinyl-1-ol)quinoline 5d: 
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.3(d, 1H, C$_7$-H, $J$ = 7.68 Hz), 7.5(d, 1H, C$_6$-H, $J$ = 7.96 Hz), 8.1(s, 1H, C$_5$-H), 9.2(s, 1H, C$_5$-CHO), 9.3 & 9.5(2s, 2H, vinylic protons), 16.5(bs, vinylic–OH, D$_2$O Exchangeable); 
$^{13}$C NMR(CDCl$_3$, 400 MHz): $\delta$ 192.27, 189.26, 189.08, 133.90, 133.21, 129.80, 129.04, 124.41, 121.13, 120.86, 119.87, 118.34; MS(70 eV, m/z, M$^+$): 267, (M+2): 269, (M+4): 271; IR: 3510, 1702, 1610.

Anal. found: C, 53.71; H, 2.65; N, 5.22. Calcd. for C$_{12}$H$_8$O$_2$NCl: C, 53.76; H, 2.63; N, 5.26; mp. 180°C.

6-Chloro-3-formyl-4-hydroxyquinidine 6d: 
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.5(s, 3H, CH$_3$), 7.4(d, 1H, C$_7$-H, $J$ = 7.96 Hz), 7.7(d, 1H, C$_6$-H, $J$ = 7.64 Hz), 8.2(s, 1H, C$_5$-H), 9.4(s, 1H, CHO), 14.2(bs, 1H, OH); MS(70 eV, m/z, M$^+$): 221; IR: 3480, 1715, 1595.

Anal. found: C, 59.52; H, 3.57; N, 6.27. Calcd. for C$_{14}$H$_{12}$O$_2$NCl: C, 59.61; H, 3.64; N, 6.32; mp. 230°C.

4,6-Dichloroquinidine 7d: 
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.4(s, 3H, CH$_3$), 7.4(s, 1H, C$_7$-H), 7.7-8.0(m, 3H, Ar-H); IR: 1575. mp. 74°C.

4-Chloro-5,8-dimethyl-3-formyl-2-(vinyl-1-ol)quinoline 5e: 
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.6(s, 6H, 2xCH$_3$), 7.6(d, 1H, C$_6$-H, $J$ = 7.46 Hz), 7.9(d, 1H, C$_5$-H, $J$ = 7.96 Hz), 9.3(s, 1H, -CHO), 9.4 & 9.5(2s, 2H, vinylic protons), 16.5(bs, vinylic–OH, D$_2$O Exchangeable); 
$^{13}$C NMR(CDCl$_3$, 400 MHz): $\delta$ 192.34, 189.38, 189.07, 144.34, 136.38, 133.86, 130.95, 127.54, 126.01, 123.11, 122.45, 118.60, 19.80, 18.95; MS(70 eV, m/z, M$^+$): 261 (M+2): 263; IR: 3525, 1680, 1595.

Anal. found: C, 64.21; H, 4.57; N, 5.28. Calcd. for C$_{14}$H$_{12}$O$_2$NCl: C, 64.25; H, 4.62; N, 5.35; mp. 170°C.

3-Formyl-4-hydroxy-5,8-dimethylquinidine 6e: 
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.7(s, 9H, 3xCH$_3$), 7.5(d, 1H, C$_5$-H, $J$ = 7.84 Hz), 7.7(d, 1H, C$_6$-H, $J$ = 7.68 Hz), 9.2(s, 1H, CHO), 14.5(bs, 1H, OH); MS(70 eV, m/z, M$^+$): 215; IR: 3510, 1702, 1610. Anal. found: C, 72.47; H, 6.01; N, 6.42. Calcd. for C$_{14}$H$_{12}$O$_2$N: C, 72.54; H, 6.09; N, 6.51; mp. 155°C.

4-Chloro-5,8-dimethylquinidine 7e: 
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.6(s, 9H, 3xCH$_3$), 7.4(s, 1H, C$_7$-H), 7.6-7.8(m, 2H, Ar-H); IR: 1580. mp. 80°C.

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References