Synthesis of 4-hydroxy-3-formylideneamino-1\(H\)/methyl/phenylquinolin-2-ones

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Received 26 May 2008 ; accepted (revised) 27 October 2008

An efficient method for the synthesis of 4-hydroxy-3-formylideneamino-1\(H\)/methyl/phenylquinolin-2-ones by the condensation of corresponding 4-hydroxy-3-formyl-1\(H\)/methyl/phenylquinolin-2-one with substituted anilines/aliphatic primary amines is reported. The carboxaldehyde in turn is prepared starting either from substituted anilines or benzoic acid. The structures of compounds are established by the elemental analysis and spectral data.

Keywords: 4-Hydroxy-3-formyl-1\(H\)-quinolin-2-one, Schiff base, 4-hydroxy-3-formylideneamino-1\(H\)-quinolin-2-one

4-Hydroxy-3-substitutedquinolin-2-ones and their analogues have variety of biological activities\(^1\)-\(^3\). 4-Hydroxy-3-formylideneamino-1\(H\)/methyl/phenylquinolin-2-ones generate 4-hydroxy-3-formyl-1\(H\)/methyl/phenylquinolin-2-ones which show anti-viral and anti-hypertensive\(^4\) activities. Owing to the importance of these imines, it is considered worthwhile to prepare a few 4-hydroxy-3-formylideneamino-1\(H\)/methyl/phenylquinolin-2-ones and in this paper the synthesis of thirty two different imines starting from substituted anilines or benzoic acid is reported.

Results and Discussion

The synthetic route for the preparation of imines starting from anthranilic acid, ortho chlorobenzoic acid and aniline is shown in the Scheme I and the compounds in Table I. It involves a linear path via \(N\)-methyl/phenylanlanthranilic acids, 4-hydroxy-1\(H\)/methyl/phenylquinolin-2-ones and 4-hydroxy-3-formyl-1\(H\)/methyl/phenylquinolin-2-ones. Anthranilic acid (0.036 mole) on methylation by DMS (0.070 mole) in presence of 5% of NaOH yield \(N\)-methyl/phenylanlanthranilic acid Ia. The melting point and spectral data obtained matches with that reported in the literature. A new peak in \(^1\)H NMR at \(\delta 3.62\) indicates that anthranilic acid is methylated by DMS. \(N\)-Phenylanlanthranilic acid Ib is prepared by the condensation of ortho chlorobenzoic acid (0.1 mole) with aniline (0.1 mole) in basic medium\(^5\). The structure of the product was confirmed as \(N\)-phenylanlanthranilic acid by its melting point. 4-Hydroxyquinolin-2-one IIa was directly prepared by the condensation of aniline (0.1 mole) with malonic acid (0.1 mole) in presence of POCI\(_3\) (0.3 mole) and ZnCl\(_2\) (0.2 mole, ref. 6). The \(N\)-methylanthranilic acid (0.211 mole) and \(N\)-phenylanlanthranilic acid (0.3 mole) on cyclocondensation with equal amount of acetic anhydride and acetic acid gave 4-hydroxy-1\(H\)/methyl/phenylquinolin-2-one (IIb/IIc, ref. 7,8). The structure of 4-hydroxy-1\(H\)/methyl/phenylquinolin-2-one is elucidated by elemental analysis, melting point and spectral data which coincide with reported literature. Synthesis of 4-hydroxy-3-formyl-1\(H\)/methyl/phenylquinolin-2-one (IIIa,b,c) carried out by Reimer-Tiemann reaction with one equivalent of 4-hydroxy-1\(H\)/methyl/phenylquinolin-2-one (IIa,b,c) (0.0124 mole) using 40 equivalents of CHCl\(_3\) (0.5 mole) and 15% NaOH (ref. 9). The structure of the products was confirmed by the disappearance of vinyl proton of (IIa,b,c) and appearance of aldehyde signal in the offset region at \(\delta 11.2, 10.3\) and 9.4 in IIIa, IIIb and IIIc respectively.

The Schiff bases (IV, V and VI) were prepared by following reported method\(^10\) with the condensation of one equivalent of each 4-hydroxy-3-formyl-1\(H\)/methyl/phenylquinolin-2-one (IIIa,b,c) and substituted anilines/aliphatic amines in dichloromethane. The melting points of most of the imines are higher than the melting point of their starting material. The electronic absorption spectral study revealed that formation of Schiff base resulted in bathochromic shift in the longer wavelength absorption band. 4-Hydroxy-3-formyl-methyl-quinolin-2-one IIIb absorbs
at 367 nm (€ 19293) while the absorption spectra of 4-hydroxy-3-formylidene-anilino-1-methylquinolin-2-one Va shows the absorption maximum at 382 nm (€ 9508) in CHCl₃. Thus there is a 15 nm red shift from starting material IIIb. Similarly all the Schiff bases IV, V and VI underwent a red shift of 9-27 nm in their longer wavelength absorption band compared with the respective starting materials (IIIa,b,c). The presence of electron withdrawing nitro group at para position in aniline moiety (Vg and VIg) display a new absorption maximum between 400 and 410 nm while at ortho position no such new absorption maximum was observed. Aliphatic imines (Vm, Vn and VIm) have not shown such bathochromic shifts. The formation of Schiff bases is further proved by the IR spectral studies. The disappearance of $\nu$C=O stretching frequency of aldehydes in the IR spectrum reveals the formation of IV, V and VI. Similar shifts were reported in the IR spectra of N-aryl imines of salicylaldehyde.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'</th>
<th>H, IV (m.p. °C)</th>
<th>CH₃, V (m.p. °C)</th>
<th>Ph, VI (m.p. °C)</th>
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<tr>
<td>1</td>
<td>Ph</td>
<td>IVa (194-95)</td>
<td>Va (148-49)</td>
<td>VIa (154-55, ref.10)</td>
</tr>
<tr>
<td>2</td>
<td>2-NO₂ Ph</td>
<td>IVb (159-60)</td>
<td>Vb (232-33)</td>
<td>VIb (207-08)</td>
</tr>
<tr>
<td>3</td>
<td>4-NO₂ Ph</td>
<td>IVc (259-60)</td>
<td>Ve (&gt;300)</td>
<td>VIe (291-92)</td>
</tr>
<tr>
<td>4</td>
<td>2-CH₃ Ph</td>
<td>IVd (219-20)</td>
<td>Vd (185-86)</td>
<td>VId (179-80)</td>
</tr>
<tr>
<td>5</td>
<td>4-CH₃ Ph</td>
<td>IVe (184-85)</td>
<td>Ve (164-65)</td>
<td>VIe (214-15)</td>
</tr>
<tr>
<td>6</td>
<td>2-OH Ph</td>
<td>-</td>
<td>Vf (191-92)</td>
<td>VI (212-13)</td>
</tr>
<tr>
<td>7</td>
<td>4-OH Ph</td>
<td>-</td>
<td>Vg (262-63)</td>
<td>Vlg (176-77)</td>
</tr>
<tr>
<td>8</td>
<td>2-Cl Ph</td>
<td>-</td>
<td>Vh (191-92)</td>
<td>Vlh (212-13)</td>
</tr>
<tr>
<td>9</td>
<td>3-Cl Ph</td>
<td>-</td>
<td>Vi (159-60)</td>
<td>VII</td>
</tr>
<tr>
<td>10</td>
<td>4-Cl Ph</td>
<td>-</td>
<td>Vj (194-95)</td>
<td>VIj (229-30)</td>
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<tr>
<td>11</td>
<td>2-CN Ph</td>
<td>-</td>
<td>Vk (259-60)</td>
<td>Vlk (254-55)</td>
</tr>
<tr>
<td>12</td>
<td>3-OCH₃ Ph</td>
<td>-</td>
<td>VI (101-02)</td>
<td>VII (229-31)</td>
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<tr>
<td>13</td>
<td>isopropyl</td>
<td>-</td>
<td>Vm</td>
<td>VIm</td>
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<tr>
<td>14</td>
<td>n-butyl</td>
<td>-</td>
<td>Vn</td>
<td>-</td>
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</table>
In $^1H$ NMR spectra of 4-hydroxy-3-formyl-1-methylquinolin-2-one (IIIb), the aldehyde proton gave a signal at $\delta$ 10.30. On formation of imine (-CH=N-) the above signal underwent a diatropic shift resonating at $\delta$ 9.00 in 4-hydroxy-3-formylidene-4'-hydroxyanilino-1-methylquinolin-2-one (Vg), while to $\delta$ 8.40 in 4-hydroxy-3-formylidene-4'-butylamino-1-methylquinolin-2-one (Vn). It is interesting to notice that iminol form is in equilibrium with ketamine in solution which has two coupling vicinal protons. The coupling constants vary between 6.88 and 8.13 Hz. Similar coupling interactions were reported\(^{11}\). The mass spectral fragmentation pattern in the mass spectra of these imines further confirmed the condensation of 4-hydroxy-3-formyl-1H/methyl/phenylquinolin-2-one (IIIa, b, c) with various anilines and other aliphatic primary amines to yield IV/V/VI. The mass spectrum of 4-hydroxy-3-formylidene-2'-nitroanilino-1-methylquinolin-2-one (Vb) intense peak obtained at $m/z$ 323 indicates the molecular ion, shows the presence of odd three nitrogens, 201 is the fragmentation due to the loss of $-\text{NO}_2\text{C}_6\text{H}_4$ and the peak at $m/z$ 175 is attributed to the loss of $-\text{C}=\text{N}-\text{C}_6\text{H}_4\text{NO}_2$ group. Similarly the low intensity fragments at $m/z$ 146, 134, 104 and 77 are derived from the daughter ions and the mass spectral fragmentation of Vb is shown in Scheme II.

**Scheme II** — Mass spectral fragmentation of 4-Hydroxy-3-formylidene-2'-nitroanilino-1-methylquinolin-2-one (Vb)

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**Experimental Section**

All the chemicals were purchased from Loba chemicals. The reagents and solvents were analytical grade and were used without further purification unless otherwise mentioned. Carbon, hydrogen and nitrogen were determined by Perkin-Elmer 240c instrument, IR spectra were recorded as KBr pellet on a Perkin-Elmer-1700 spectrophotometer. Electronic absorbance spectra were recorded on a Shimadzu UV-365 spectrophotometer. $^1H$ NMR spectra were measured on a Varian INOVA-500 spectrometer. Melting points were recorded on a Polmon MP 96.

**Synthesis of N-methylantranilic acid**

N-Methylantranilic acid was prepared by reported method\(^7\). Anthranilic acid 5 g (0.036 mole) was dissolved in 13 mL of 5% sodium hydroxide. To this clear solution 1.6 mL (0.070 mole) of dimethyl sulphate was added and stirred for an hr. The reaction-mixture was filtered and washed with cold water and dried. It was recrystallized from ethanol. Yield: 3.5 g (65%); m.p. 187-89°C; ESI-MS, $m/z$: 151; $^1H$ NMR (CDCl$_3$): $\delta$ 3.62 (s, 3H, -NH-CH$_3$), 6.81 (d, 2H, Ar-H, $J = 7.6$ Hz), 7.61 (t, 1H, Ar-H, $J = 7.8$ Hz), 8.11 (d, 1H, Ar-H, $J = 7.2$ Hz), 9.10 (br s, 2H,
-CO₂H and -NH-Me); IR (KBr): 3380 (N-H), 2968 (C-H), 1675 (C=O), 1580 cm⁻¹ (C=C).

**Synthesis of N-phenylantranilic acid**

15.6 g (0.1 mole) of ortho chlorobenzoic acid, 9.3 g (0.1 mole) of aniline, 13.8 g (0.1 mole) of potassium carbonate and 0.5 g (0.006 mole) of cupric oxide were dissolved in 100 mL of N,N-dimethyl formamide. The reaction-mixture was heated at 80°C on water-bath for 6 hr. After completion of the reaction, the contents were poured into ice-cold water and the unreacted aniline was removed under steam distillation and the residual solution contained potassium N-phenyl anthranilate. Residual solution was extracted with ether and the aqueous layer was acidified with dilute hydrochloric acid. The solid was treated with 10% sodium hydroxide solution, filtered and the filtrate on acidification with hydrochloric acid gave 4-hydroxy-quinolin-2-one (IIa). Yield: 13 g (81%); m.p. >300°C; ESI-MS, m/z: 213; ¹H NMR (CDCl₃): δ 4.76 (br s, 1H, -NH), 6.73 (dd, 1H, Ar-H, J₁ = 7.2 Hz and J₂ = 7.7Hz), 7.22-7.55 (m, 7H, Ar-H), 7.93 (d, 1H, Ar-H, J = 8.3Hz), 9.21 (br s, 1H, COOH); IR (KBr): 3379 (N-H), 3005 (Ar-H), 1669 (C=O), 1580 cm⁻¹ (C=C).

**Synthesis of 4-hydroxy-quinolin-2-one IIa**

A mixture of aniline 9.3 g (0.1 mole) and malonic acid 10.4 g (0.1 mole) was heated at 100°C for 1 hr. with phosphoryl chloride 46 g (0.3 mole) and anhydrous zinc chloride 27.3 g (0.2 mole). The mixture was maintained at 80°C on a water-bath. At 4°C and stirred. Subsequently the temperature inside the flask was maintained at 80°C on a water-bath. Stirring was continued for 12 hr, and the reaction-mixture was cooled to RT. The orange coloured liquid was acidified with dilute sulphuric acid. It was extracted with ethyl acetate and dried with anhydrous sodium sulphate. Ethyl acetate was removed under vacuum and the solid obtained was purified by column chromatography (SiO₂) in hexane, ethyl acetate (7:3) mixture. IIIa: Yield: 0.91 g (39%); m.p. >350°C; ESI-MS, m/z: 189. IIIb: Yield: 0.93 g (37%); m.p. 176°C; ESI-MS, m/z: 203. IIIc: Yield: 1.15 g (35%); m.p. 234-35°C; ESI-MS, m/z: 265.

**General procedure for the synthesis of 4-hydroxy-3-formylideneanilinoquinolin-2-ones (IV/V/VI)**

To a solution of aldehyde (0.1 mmole) (IIIA/IIIb/IIIc) in dichloromethane, aniline or substituted aniline or aliphatic amine (0.1 mole) was added and the reaction-mixture was stirred for 8 hr. The residue obtained on evaporation of the solvent was purified by column chromatography (SiO₂) using pet ether, ethyl acetate (9:1 v/v) as eluent to give Schiff base up to 96% yield as bright yellow solid.

- **4-Hydroxy-3-formyldiene-anilinoquinolin-2-one IVa:**
  ¹H NMR (CDCl₃): δ 6.70 (s, 1H, -NH), 7.20-7.60 (m, 9H, Ar-H), 8.20 (s, 1H, -OH), 9.00 (d, 1H, -CH=N- , J = 7.62 Hz); ESI-MS, m/z: 264; UV (CHCl₃)
λ max: 370 (14960), 245 nm (ε 13950); Anal. Calcd. for C_{18}H_{12}N_{2}O_{2}: C, 72.65; H, 4.51; N, 10.33. Found: C, 72.72; H, 4.58; N, 10.60%.

4-Hydroxy-3-formylidene-2'-nitroanilinoquinolin-2-one Vb: ¹H NMR (CDCl₃): δ 6.00 (s, 1H, -NH₃), 6.80 (m, 1H, Ar-H), 7.20-7.60 (m, 7H, Ar-H), 8.20 (s, 1H, -OH), 9.00 (d, 1H, -CH=N-, J = 8.12 Hz); UV (CHCl₃): 380 (11033), 346 (7662), 249 nm (ε 20819); Anal. Calcd. for C_{18}H_{13}N₃O₂: C, 73.98; H, 5.49; N, 9.50%. Found: C, 72.72; H, 4.58; N, 10.60%.

4-Hydroxy-3-formylidene-2'-ethylanilinoquinolin-2-one IVa: ¹H NMR (CDCl₃): δ 3.62 (s, 3H, -N-CH₃), 7.20-7.60 (m, 1H, Ar-H), 7.62 (d, 1H, Ar-H, J = 7.66 Hz), 8.22-8.40 (s, 1H, -OH), 9.22 (d, 1H, -CH=N-, J = 7.94 Hz); UV (CHCl₃): 398 (20741), 346 (12741), 258 nm (ε 18458); IR (KBr): 1655 (C=O), 1601 cm⁻¹ (C=N).

4-Hydroxy-3-formylidene-2'-anilino-1-methylquinolin-2-one Va: ¹H NMR (CDCl₃): δ 3.62 (s, 3H, -N-CH₃), 7.20-7.70 (m, 9H, Ar-H), 8.20-8.30 (s, 1H, -OH), 9.02 (d, 1H, -CH=N-, J = 7.16 Hz); UV (CHCl₃): 376 (8008), 249 nm (ε 19466); ESI-MS, m/z: 278.

4-Hydroxy-3-formylidene-2'-nitroanilino-1-methylquinolin-2-one Vb: ¹H NMR (CDCl₃): δ 3.62 (s, 3H, -N-CH₃), 7.20-7.70 (m, 9H, Ar-H), 7.62 (d, 1H, Ar-H, J = 7.66 Hz), 8.22-8.40 (s, 1H, -OH), 9.22 (d, 1H, -CH=N-, J = 7.94 Hz); UV (CHCl₃): 384 (64567), 253 nm (ε 58658); IR (KBr): 1655 (C=O), 1599 cm⁻¹ (C=N); ESI-MS, m/z (%): 323 (100), 201 (70), 175 (13), 146 (11), 134 (12), 104 (21), 77 (18).

4-Hydroxy-3-formylidene-2'-anilino-1-methylquinolin-2-one Vd: ¹H NMR (CDCl₃): δ 1.40 (d, 6H, -CH₃, J = 4.18 Hz), 3.58 (s, 3H, -N-CH₃), 3.74-3.82 (m, 1H, -CH (CH₃)), 7.12-7.20 (m, 2H, Ar-H), 7.48-7.60 (t, 2H, Ar-H, J = 7.88 Hz), 8.20-8.42 (s, 1H, -OH), 9.00 (d, 1H, -CH=N-, J = 8.21 Hz); UV (CHCl₃): 346 (33251), 333 nm (ε 26705); IR (KBr): 1653 (C=O), 1606 cm⁻¹ (C=N).

4-Hydroxy-3-formylideneanilino-1-phenylquinolin-2-one Vla: ¹H NMR (CDCl₃): δ 7.12-7.48 (m, 13H, Ar-H), 7.56 (t, 1H, Ar-H, J = 8.18 Hz), 8.22 (s, 1H, -OH), 9.04 (d, 1H, -CH=N, J = 6.98 Hz); UV (CHCl₃): 382 (20314), 256 nm (ε 16190); IR (KBr): 1655 (C=O), 1607 cm⁻¹ (C=N).

4-Hydroxy-3-formylidene-2'-nitroanilino-1-phenylquinolin-2-one Vb: ¹H NMR (CDCl₃): δ 6.52 (d, 1H, Ar-H, J = 7.64 Hz), 7.20 (t, 1H, Ar-H, J = 7.72 Hz), 7.28-7.46 (m, 8H, Ar-H), 7.52-7.84 (m, 3H, Ar-H), 8.26-8.40 (s, 1H, -OH), 9.08 (d, 1H, -CH=N-, J = 7.38 Hz); UV (CHCl₃): 396 (21836), 344 (13552), 254 nm (ε 19263); IR (KBr): 1662 (C=O), 1598 cm⁻¹ (C=N); Anal. Calcd. for C_{18}H_{13}N₃O₂: C, 68.57; H, 3.92; N, 10.90. Found: C, 68.51; H, 3.90; N, 10.81%.

4-Hydroxy-3-formylidene-2'-anilino-1-methylquinolin-2-one Vdb: ¹H NMR (CDCl₃): δ 1.52 (d, 6H, -CH₃, J = 4.26 Hz), 2.64 (m, 1H, -CH (CH₃)), 6.62 (d, 1H, Ar-H, J = 7.39 Hz), 7.22-7.80 (m, 8H, Ar-H), 8.64-8.68 (s, 1H, -OH), 9.00-9.20 (d, 1H, -CH=N-, J = 7.94 Hz).

Acknowledgement

The authors (P V and A M) would like to thank the Director, Indian Institute of Chemical Technology, for spectral data and the Head, Department of Chemistry, Osmania University for providing necessary facilities.

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