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Synthesis and spectral Characterization of α, β-Unsaturated KetoneS and Their Dibromo Derivatives

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Abstract :
Reaction of 2-chloro-6-methylquinoline-3-carbaldehyde (1) and 2-hydroxy 5-methyl acetophenone afforded a novel Chalcone (1a). Similarly, some more novel Chalcones (2a-d) were synthesised by condensing benzyloxy benzaldehyde (2) with different substituted 2- hydroxy acetophenones (a-d) by Claisen-Schimidt reaction. Synthesised Chalcones (1a and 2a-d) were then brominated to afford corresponding dibromo chalcone derivatives (3a and 4a-d) respectively. The structures of the newly synthesized chalcones were elucidated by elemental analysis and spectral methods such as IR, 1H NMR and mass spectra.
Keywords: Chalcone, dibromo chalcones, quinoline-3-carbaldehyde, benzyloxy benzaldehyde

Introduction:

Chalcones or α, β-unsaturated ketones are 1, 3-diaryl-2-propen-1-ones, consisting of open chain flavonoids in which two aromatic rings are joined by a three carbon bridge having a keto carbonyl moiety and α, β-unsaturation. Literature survey [1-3] indicates that one of the popular methods for the preparation of chalcone is Claisen-Schimidt condensation of 2-hydroxy acetophenones with appropriate aromatic aldehydes. However, the search for an efficient synthesis for chalcones is still a challenging task. Chalcones are a diverse group of compounds that can be synthesized or obtained from natural sources [4] and have attracted increasing attention due to their numerous pharmacological activities [5] such as antibacterial, antifungal, anticancer, anti-inflammatory, antitubercular, antihyperglycemic [6] and antimalarial agents [7]. The presence of a reactive and unsaturated keto moiety as well as aryl conjugation in chalcones is found to be responsible for their biological activity. Moreover, chalcones provide an opportunity for chemist to synthesize a wide variety of bioactive heterocycles [8-11] due to the presence of α, β-unsaturated carbonyl functionality.

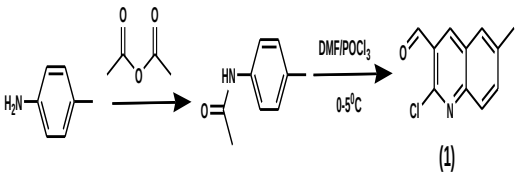
Chalcones can be further brominated by using different brominating agents such as molecular bromine in different organic solvents to get dibromo derivatives [12] having much pharmacological importance. α, β-Dibromo chalcones are valuable synthetic building blocks, which are employed for several types of synthetic transformations, in particular for synthesis of heterocyclic compounds such as pyrazoles, hydroxy pyrazoline and isoxazoles [13] derivatives with antibacterial and antifungal activities [14,15]. Appreciation of these findings motivated us to synthesize chalcones and extend its reaction by brominating them to prepare its dibromo derivative and characterize them by spectral analysis.

Experimental:

The preparation of starting material includes following three steps.

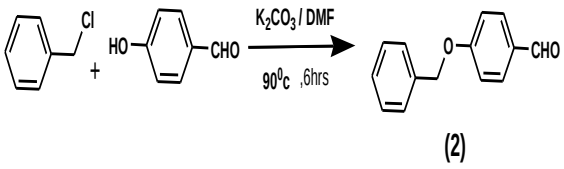
1. **Preparation of 2-chloro-6-methylquinoline-3-carbaldehyde (1):** p-Toluidine was acetylated to obtain corresponding 4-methyl acetanilide, which were then treated with DMF and $POCl_3$ at 0-5˚C according to Vilsmeier-Haeck reaction to afford **1** (Scheme **1**).

Reaction Scheme : 1



2. **Preparation of Benzyloxy benzaldehyde (2):** Benzyloxy benzaldehyde was prepared by treating p-hydroxybenzaldehye and benzylchloride with K_2CO_3 in DMF at 80-90˚C (Scheme **2**).

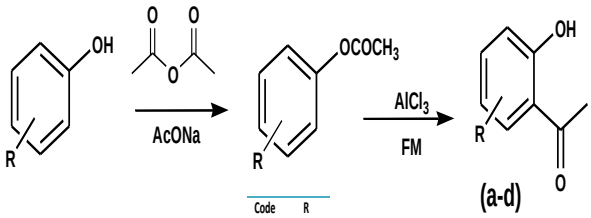
Reaction Scheme : 2



3. **Preparation of substituted acetophenones (a-d):** Substituted acetophenones such as 2-hydroxy 5-

methyl acetophenone **(a),** 2-hydroxy 5-bromo acetophenone **(b),** 2-hydroxy 5-chloro acetophenone **(c),** and 2-hydroxy 3,5-dichloro acetophenone **(d),** were prepared by refluxing substituted phenols such as p-methyl phenol, p-bromophenol, p-chloro phenol, and 3,5-dichloro phenol respectively with acetic anhydride and anhydrous sodium acetate according to known procedure followed by Fries migration of respective phenyl acetate in presence of anhydrous aluminium chloride.

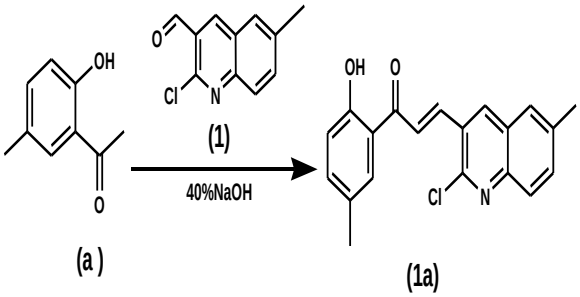
Reaction Scheme : 3



Code	R
a	5-CH_3
b	5-Br
c	5-Cl
d	3,5-Cl_2

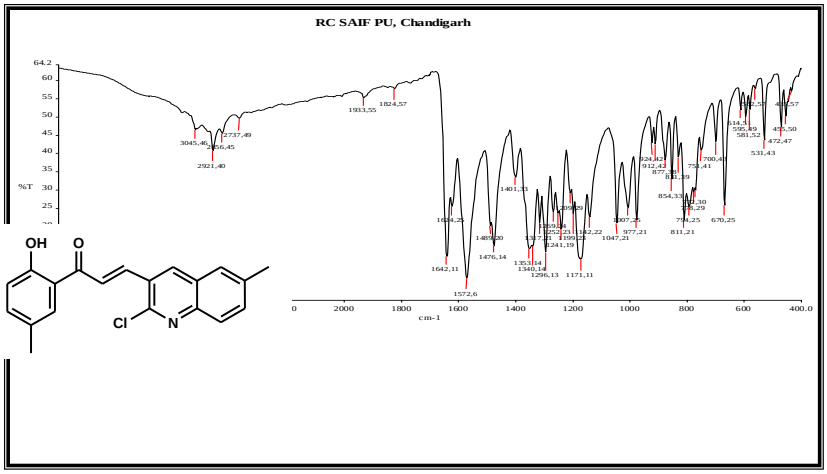
General procedure for Synthesis of Chalcones (1a and 2a-d): a (10mmole) and **1**(10mmole) were dissolved in minimum quantity of ethanol and heated till the solid get dissolved. Aqueous 40% sodium hydroxide solution (10 mL) was added drop wise with constant stirring. The mixture was further stirred mechanically at room temperature to obtain dark orange mass and kept overnight. Then it was acidified by 1:1 hydrochloric acid. The solid obtained was filtered, washed and recrystallized to get **1a** (Scheme **4**).

Reaction Scheme : 4



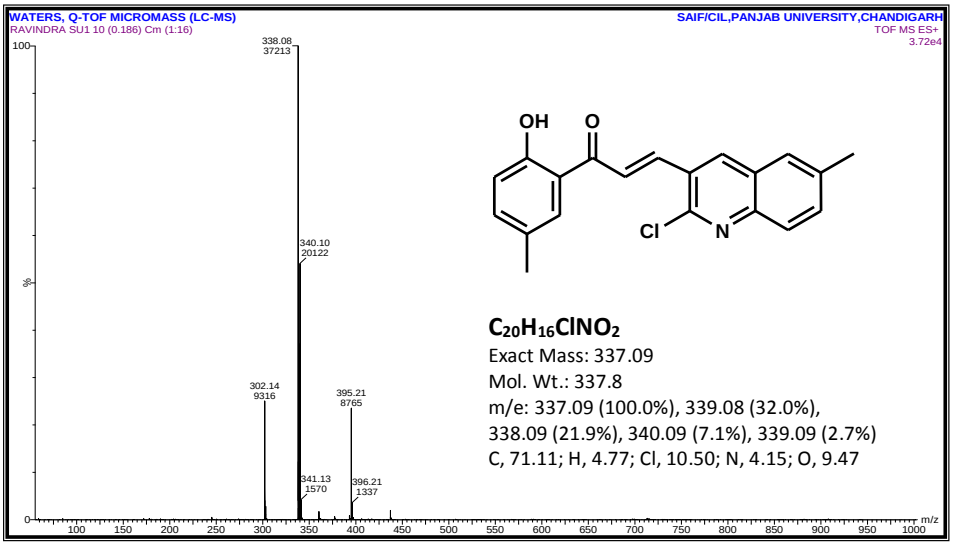
(E)-3-(2-chloro-6-methylquinolin-3-yl)-1-(2-hydroxy-5-methylphenyl) prop-2-en-1-one (1a): Yellowish crystals, MP: 210-212°C, Yield: 79%, Recrystallizing solvent: CH_3COOH, MF: $C_{20}H_{16}ClNO_2$ IR**:** 3045 (ArH), 2856, 2921 (CH_3), 1642 (C=O), 1476, 1489 (C=C), 1572 (C=N) ^{1}H NMR: 2.3594 (s, 3H, -CH_3), 2.5653 (s, 3H, -CH_3), 12.2193 (b, 1H, -OH), 6.9130 - 9.1623 (m, 9H, ArH) MS: 338 $[M+H]^+$ Calculated: C, 71.11; H, 4.77; N,4.15 Found: C, 69.82; H, 4.76; N,3.81.

IR spectra of 1a



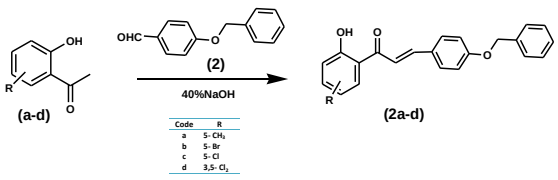
^{1}H NMR spectra of 1a

Mass spectra of 1a



Similarly, **2a-d** were synthesised from **a-d** by extending the same procedure followed for **1a** (Scheme **5**).

Reaction Scheme : 5



(2*E*)-3-[4-(benzyloxy)phenyl]-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (2a): Orange colour, MP:131°-133°C, Yield: 84.00% Recrystallizing solvent: CH_3COOH, MF: $C_{23}H_{20}O_3$, ^1H NMR: 2.3518 (s, 3H, $-CH_3$), 2.5232 (s, 2H, $-CH_2$), 12.2267 (b, 1H, -OH), 6.8346 – 8.9928 (m, 14H, ArH) MS: 345 $[M+H]^+$, Calculated: C, 80.21; H, 5.85; Found: C, 80.43; H, 5.91.

(2*E*)-3-[4-(benzyloxy)phenyl]-1-(5-bromo-2-hydroxyphenyl)prop-2-en-1-one (2b): Orange colour, MP:141°-143° Yield: 91.88% Recrystallizing solvent: CH_3COOH, MF:$C_{22}H_{17}O_3Br$. ^1H NMR: 2.5196 (s, 2H, $-CH_2$), 12. 4001 (b, 1H, -OH), 6.8357– 9.5181 (m, 14H, ArH) MS: 409 $[M]^+$, Calculated: C, 64.56; H, 4.19 Found: C, 64.54; H, 4.25.

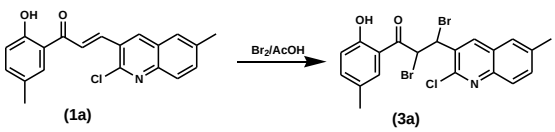
(2*E*)-3-[4-(benzyloxy)phenyl]-1-(5-chloro-2-hydroxyphenyl)prop-2-en-1-one (2c): Orange colour, MP:135°-136°C, Yield: 88.56%, Recrystallizing solvent: CH_3COOH, MF: $C_{22}H_{17}O_3Cl$. ^1H NMR: 2.4999 (s, 2H, $-CH_2$), 12. 3564 (b, 1H, -OH), 6.8132–9.5012 (m, 14H, ArH) MS: 366 $[M+H]^+$, Calculated: C, 72.43; H, 4.70; Found: C, 72.41; H, 4.65.

(2*E*)-3-[4-(benzyloxy)phenyl]-1-(3,5-dichloro-2-hydroxyphenyl)prop-2-en-1-one(2d): Orange colour, MP:163°-165°C, Yield: 71.16%, Recrystallizing solvent: CH_3COOH, MF:$C_{22}H_{16}O_3Cl_2$, ^1H NMR: 2.5881 (s, 2H, $-CH_2$), 12. 5144 (b, 1H, -OH), 6.8762 – 9.4357 (m, 13H, ArH) MS: 399 $[M]^+$, 422 $[M+Na]^+$,

Calculated: C, 66.18; H, 4.04; Found: C, 66.33; H, 4.01.

Preparation of 2,3-dibromo-3-(2-chloro-6-methylquinolin-3-yl)-1-(2-hydroxy-5-methylphenyl)propan-1-one (3a): Chalcone (**1a**, 0.01M) was added to acetic acid (5mL) and then Br_2 solution (25%, 3.4ml) was added drop wise with vigorous stirring. Solid was separated out and reaction mixture was allowed to stand at room temperature for 30 minutes, product so obtained was filtered, washed and re-crystallized to get **3a** (Scheme **6**).

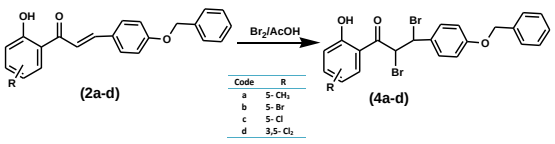
Reaction Scheme : 6



2,3-dibromo-3-(2-chloro-6-methylquinolin-3-yl)-1-(2-hydroxy-5-methylphenyl)propan-1-one (3a) : Pale yellow colour, MP:148-150°C Yield: 75%, Recrystallizing solvent: Ethanol, MF: $C_{20}H_{16}Br_2ClNO_2$. ^1H NMR: 2.3475 (s, 3H, -CH_3), 2.4989 (s, 3H, -CH_3), 12.1356 (b, 1H, -OH), 5.6523 (d, 1H, H_β, *J*=11.24), 6.2084 (d, 1H, H_α, *J*=11.24), 6.5695 - 9.8739 (m, 7H, ArH) MS: 498 $[M+H]^+$, Calculated: C, 48.47; H, 2.85; N, 2.83; Found: C, 48.54; H, 2.76; N, 2.80.

Similarly, **4a-d** were synthesised from **2a-d** by extending the same procedure followed for **3a** (Scheme **7**).

Reaction Scheme : 7



3-(4-(benzyloxy)phenyl)-2,3-dibromo-1-(2-hydroxy-5-methylphenyl) propan-1-one (4a) : Pale yellow colour, MP:143-145°C, Yield: 51.09%, Re crystallizing solvent: CH_3COOH, MF: $C_{23}H_{20}Br_2O_3$.

3-(4-(benzyloxy)phenyl)-2,3-dibromo-1-(2-hydroxy-5-bromophenyl) propan-1-one (4b) : Orange colour, MP:124-126°C, Yield: 61.69%, Re crystallizing solvent: CH_3COOH, MF: $C_{22}H_{17}Br_3O_3$.

3-(4-(benzyloxy)phenyl)-2,3-dibromo-1-(2-hydroxy-5-chlorophenyl) propan-1-one (4c) : Yellowish colour, MP:130-132°C, Yield: 54.64%, Re crystallizing solvent: CH_3COOH, MF: $C_{22}H_{17}O_3ClBr_2$.

3-(4-(benzyloxy)phenyl)-2,3-dibromo-1-(2-hydroxy-3,5-dichlorophen yl) propan-1-one (4d) : Yellowish colour, MP:168-170°C, Yield: 61.46% Re crystallizing solvent: CH_3COOH, MF: $C_{22}H_{16}Br_2Cl_2O_3$.

Results and Discussion:

The synthesis of the novel chalcones (**1a** and **2a-d**) and its dibromo derivatives (**3a** and **4a-d**) are described in reaction schemes. The identities of the chalcones have been established on the basis of their elemental analysis and spectral data such as IR, ^1H NMR and Mass spectral studies [16].

The reaction of 2-chloro-6-methylquinoline-3-carbaldehyde **(1)** with 2-hydroxy 5-methyl acetophenone in presence of 40% NaOH afforded (**1a**) by Claisen-Schimidt condensation. $FeCl_3$ test for **1a** gave violet colouration showing the presence of phenolic –OH. The IR spectra of **1a** showed stretching bands at 1572 cm^{-1} due to C=N and at 1642 cm^{-1} for C=O. Similarly the ^1H NMR spectrum showed a singlet at δ 12.2193 ppm for one –OH proton, a singlet at δ 2.3594 ppm for three protons of one CH_3 and another singlet at δ 2.5653 ppm for three protons of another CH_3, a multiplet in the range of δ 6.9130 to 9.1623 ppm due to nine protons confirms the formation of **1a** which was further confirmed by mass spectrum with a molecular ion peak at *m/z* 338 $[M+H]^+$ and 360 $[(M+Na)^+]$ is in agreement with the molecular formula $C_{20}H_{15}NO_2Cl$ (Scheme **4**).

Extending the reaction, Chalcones **1a** and **2a-d** were further brominated by using molecular bromine in acetic acid to get dibromo derivatives **3a** and **4a-d** respectively. ^1H NMR spectrum of **3a** showed one doublet at δ 5.6523 ppm for H_β proton while another doublet at δ 6.2084 ppm for H_α proton confirms the addition of bromine to form **3a.** Similarly, its mass spectrum gave a $[M+H]^+$ peak at *m/z* 498, confirms the molecular formula $C_{20}H_{16}Br_2ClNO_2$.

Conclusion:

In conclusion, we have synthesised Chalcones **(1a** and **2a-d)** in the sufficient quantities by refluxing substituted aldehydes with substituted ketones. Simultaneously, extended their reactions to afford dibromo derivatives **(3a** and **4a-d)** in good yields and confirmed their structures on the basis of spectral and the elemental analysis data.

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