Green approach for the synthesis of some new α,β-unsaturated ketimines under water suspension

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ABSTRACT. An environmentally benign and efficient synthesis of some α,β-unsaturated ketimines from new 2-hydroxychalcone and different aromatic amines under water suspension. The remarkable advantages offered by this method are environmentally friendly, short reaction times, non-hazardous, simple work-up procedure and good to excellent yields of products.

Keywords: 2-hydroxychalcone; substituted aromatic amines; unsaturated ketimines; water suspension; green chemistry

Introduction

An environmentally friendly chemical process is the vital part of the current chemical research and development [1]. Recently, environmentally benign approaches have been developed using solvent-free conditions [2-4]. However, organic reactions in aqueous media have attracted much attention in synthetic organic chemistry, not only because water is one of the most abundant, cheap, and environmentally friendly solvent, but also because water exhibits unique reactivity and selectivity, which is different from those in conventional organic solvents [5-9]. The synthesis and assaying of biological activity of imines have considerable interest in recent decades [10]. Imines [11], both aldimines and ketimines due to presence of carbon-nitrogen bond in their molecules, provides a potential site for chemical [12-13] as well as biological [14-15] activity, but very less work has been carried out on synthesis of α,β-unsaturated ketimines.

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Therefore, we focus on developing the novel procedure for synthesis of α,β-unsaturated ketimines by condensation of substituted 2-hydroxychalcone and different aromatic amines under water suspension.

α,β-Unsaturated ketimines are chalcone Schiff’s bases possess various pharmacological properties [16-18]. To best of our knowledge very less work has been carried out on synthesis of α,β-unsaturated ketimines. α,β-Unsaturated ketimines were synthesized by condensation of chalcones and aromatic amines in different solvents like ethanol containing few drops of conc. H2SO4 [19, 20], CH2Cl2 in presence of TiCl4 catalyst [21-23] or by condensation of anions of enamine phosphine oxides with aldehydes or ketones in THF [24]. However, although each of the above methods has its own merits, they are plagued by the limitations of low yield, use of toxic organic solvents, and the requirements of excess of reagents/catalysts, special apparatus, and harsh reaction conditions. Therefore, development of improved method for the synthesis of α,β-unsaturated ketimines has acquired relevance to current research

**Material and Methods**

Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrometer. 1HNMR spectra were recorded on a Gemini 300-MHz instrument in CDCl3 as solvent and TMS as an internal standard. The mass spectra were recorded on EI-SCHIMADJU-GC-MS Mass spectrometer. Elemental analysis was carried out on a Carlo Erba 1108 analyzer. The purity of products was checked by thin-layer chromatography (TLC) on silica-gel.

**Synthesis of 1-(2′-hydroxy-3′-iodo-5′-methylphenyl)-3-(2-hydroxy-4-methyl-5-chlorophenyl)-2-propen-1-one (3)**

Equimolar quantities of 2-hydroxy-3-iodo-5-methylacetophenone (0.01 mol) and 2-hydroxy-4-methyl-5-chlorobenzaldehyde (0.01 mol) and solid pallets of KOH (0.02 mol) were taken in mortar and grind for five minute. On completion of grinding as monitored by TLC, the obtained solid mixture was diluted with cold water, neutralized by dil. HCl and recrystallized from acetic acid. Red-Orange crystals; M.P. 148-150 °C; Yield 90%; IR (KBr): 3345 (-OH), 1680 (-C=O), 1610, 1590 cm⁻¹. 1HNMR (CDCl3) δ: 2.20 (s, 3H, CH3), 2.35 (s, 3H, CH3), 6.56 (d,1H, Hα), 7.23 (d,1H, Hβ), 7.75-7.98 (m, 4H, Ar-H), 8.18 (s, 1H, OH), 13.05 (s, 1H, OH). MS: m/z = 428.5 [M⁺]. Anal. Calcd. For C17H14O3I: C, 47.60; H, 3.26; X(I, Cl), 37.92. Found: C, 47.81; H, 3.38; X(I, Cl), 38.03.

**Typical procedure for synthesis of α,β-unsaturated ketimines**

A mixture of 1-(2′-hydroxy-3′-iodo-5′-methylphenyl)-3-(2-hydroxy-4-methyl-5-chlorophenyl)-2-propen-1-one (0.01 mol) and substituted aromatic amine (0.01 mol)
was stirred at room temperature in water (20 mL) for an appropriate time (Table 1). The progress of reaction was monitored by TLC. After completion of reaction, the separated solid was filtered and recrystallized from ethyl alcohol.

**Spectroscopic data of synthesized compounds**

5a: Pale yellow crystals. IR (KBr): 3282 (-OH), 1605 (-C=N), 1583 cm⁻¹. ¹HNMR (CDCl₃) δ: 2.22 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 6.67 (d, 1H, Hα), 7.10 (d, 1H, Hβ), 7.29-8.05 (m, 9H, Ar-H), 8.35 (s, 1H, OH), 12.96 (s, 1H, OH). MS: m/z = 503.5 [M⁺]. Anal. Calcd. For C₂₃H₁₉O₂IClN: C, 54.81; H, 3.40; X(I, Cl), 36.76; N, 2.67. Found: C, 50.41; H, 3.20; X(I, Cl), 32.27; N, 2.78.

5b: Dark yellow crystals. IR (KBr): 3290 (-OH), 1608 (-C=N), 1583 cm⁻¹. ¹HNMR (CDCl₃) δ: 2.20 (s, 3H, CH₃), 2.31 (s, 3H, CH₃), 6.64 (d, 1H, Hα), 7.12 (d, 1H, Hβ), 7.25-7.99 (m, 8H, Ar-H), 8.33 (s, 1H, OH), 12.90 (s, 1H, OH). MS: m/z = 548.5 [M⁺]. Anal. Calcd. For C₂₃H₁₈O₂IClN₂: C, 50.31; H, 3.28; X(I, Cl), 29.62; N, 5.10. Found: C, 50.40; H, 3.22; X(I, Cl), 29.70; N, 5.18.

5c: Dark yellow crystals. IR (KBr): 3294 (-OH), 1608 (-C=N), 1585 cm⁻¹. ¹HNMR (CDCl₃) δ: 2.22 (s, 3H, CH₃), 2.30 (s, 3H, CH₃), 6.64 (d, 1H, Hα), 7.10 (d, 1H, Hβ), 7.22-8.04 (m, 8H, Ar-H), 8.30 (s, 1H, OH), 12.90 (s, 1H, OH). MS: m/z = 548.5 [M⁺]. Anal. Calcd. For C₂₃H₁₈O₂IClN₂: C, 50.31; H, 3.28; X(I, Cl), 29.62; N, 5.10. Found: C, 50.42; H, 3.20; X(I, Cl), 29.68; N, 5.18.

5d: Light yellow crystals. IR (KBr): 3295 (-OH), 1603 (-C=N), 1600, 1582 cm⁻¹. ¹HNMR (CDCl₃) δ: 2.25 (s, 3H, CH₃), 2.37 (s, 3H, CH₃), 6.70 (d, 1H, Hα), 7.16 (d, 1H, Hβ), 7.30-8.0 (m, 8H, Ar-H), 8.36 (s, 1H, OH), 12.94 (s, 1H, OH). MS: m/z = 537 [M⁺]. 539 [M+H⁺]. Anal. Calcd. For C₂₃H₁₈O₂ICl₂N: C, 51.30; H, 3.34; X(I, Cl), 36.80; N, 2.60. Found: C, 50.41; H, 3.40; X(I, Cl), 36.76; N, 2.67.

5e: Faint yellow. IR (KBr): 3299 (-OH), 1605 (-C=N), 1611, 1588 cm⁻¹. ¹HNMR (CDCl₃) δ: 2.27 (s, 3H, CH₃), 2.38 (s, 3H, CH₃), 3.45 (s, 3H, OCH₃), 6.64 (d, 1H, Hα), δ7.14 (d, 1H, Hβ), 7.25-8.05 (m, 8H, Ar-H), 8.30 (s, 1H, OH), 12.96 (s, 1H, OH). MS: m/z = 533.5 [M⁺]. Anal. Calcd. For C₂₄H₂₂O₃IClN: C, 53.98; H, 3.93; X, (I, Cl), 30.45; N, 2.62. Found: C, 54.09; H, 4.01; X (I, Cl), 30.52; N, 2.66.

5f: Pale yellow crystals. IR (KBr): 3290 (-OH), 1608 (-C=N), 1599, 1580 cm⁻¹. ¹HNMR (CDCl₃) δ: 2.25 (s, 3H, CH₃), 2.34 (s, 3H, CH₃), 6.67 (d, 1H, Hα), 7.13 (d, 1H, Hβ), 7.32-8.10 (m, 8H, Ar-H), 8.35 (s, 1H, OH), 12.97 (s, 1H, OH). MS: m/z = 537 [M⁺]. Anal. Calcd. For C₂₃H₁₈O₂ICl₂N: C, 51.30; H, 3.34; X(I, Cl), 36.80; N, 2.60. Found: C, 50.40; H, 3.40; X(I, Cl), 36.75; N, 2.65.

5g: Faint yellow crystals. IR (KBr): 3300 (-OH), 1608 (-C=N), 1586 cm⁻¹. ¹HNMR (CDCl₃) δ: 2.29 (s, 6H, 2xCH₃), 2.40 (s, 3H, CH₃), 6.67 (d, 1H, Hα), 7.15 (d, 1H, Hβ), 7.30-8.04 (m, 8H, Ar-H), 8.36 (s, 1H, OH), 12.94 (s, 1H, OH). MS: m/z = 503.5 [M⁺]. Anal. Calcd. For C₂₃H₁₈O₂IClN: C, 54.81; H, 3.40; X(I, Cl), 32.27; N, 2.78. Found: C, 50.40; H, 3.20; X(I, Cl), 32.39; N, 2.86.
7.28-8.02 (m, 8H, Ar-H), 8.33 (s, 1H, OH), 12.98 (s, 1H, OH). MS: m/z = 517.5 [M⁺].
Anal. Calcd. For C₂₄H₂₁O₂IClN: C, 55.65; H, 4.05; X(I, Cl), 31.40; N, 2.70. Found: C, 55.57; H, 3.98; X(I, Cl), 31.33; N, 2.74.

**5h**: Redish-yellow crystals. IR (KBr): 3288 (-OH), 1609 (-C=O), 1583 cm⁻¹. ¹H NMR (CDCl₃): δ: 2.25 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 6.67 (d, 1H, Hα), 7.10 (d, 1H, Hβ), 7.30-8.06 (m, 8H, Ar-H), 8.33 (s, 1H, OH), 13.02 (s, 1H, OH). MS: m/z = 582.5 [M⁺]. Anal. Calcd. For C₂₃H₁₉O₂IClBrN: C, 47.38; H, 3.09; X(I, Cl, Br), 41.63; N, 2.40. Found: C, 47.45; H, 3.05; X(I, Cl, Br), 41.71; N, 2.35.

**5i**: Faint yellow crystals. IR (KBr): 3303 (-OH), 1609 (-C=O), 1580 cm⁻¹. ¹H NMR (CDCl₃): δ: 2.29 (s, 6H, 2xCH₃), 2.42 (s, 3H, CH₃), 6.69 (d, 1H, Hα), 7.15 (d, 1H, Hβ), 7.31-8.05 (m, 8H, Ar-H), 8.29 (s, 1H, OH), 12.96 (s, 1H, OH). MS: m/z = 517.5 [M⁺]. Anal. Calcd. For C₂₄H₂₁O₂IClN: C, 55.65; H, 4.05; X(I, Cl), 31.40; N, 2.70. Found: C, 55.57; H, 3.98; X(I, Cl), 31.33; N, 2.74.

**5j**: Pale yellow crystals. IR (KBr): 3295 (-OH), 1605 (-C=O), 1585 cm⁻¹. ¹H NMR (CDCl₃): δ: 2.27 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 3.47 (s, 3H, OCH₃), 6.66 (d, 1H, Hα), 7.14 (d, 1H, Hβ), 7.28-8.0 (m, 8H, Ar-H), 8.36 (s, 1H, OH), 12.95 (s, 1H, OH). MS: m/z = 533.5 [M⁺]. Anal. Calcd. For C₂₄H₂₃O₂IClN: C, 53.98; H, 3.93; X(I, Cl), 30.45; N, 2.62. Found: C, 54.07; H, 3.99; X(I, Cl), 30.50; N, 2.67.

**Results and Discussion**

In continuation of earlier research work devoted towards development of green chemistry and development of new synthetic methodologies in organic chemistry [25] herein, we report a simple, efficient and environmentally benign procedure for synthesis of some new α,β-unsaturated ketimines from condensation of 2-hydroxychalcone with substituted aromatic amines in water suspension with high yields (Scheme 1).

![Scheme 1](image-url)
The starting α,β-unsaturated carbonyl compound was synthesized by Claisen-Schmidt condensation between 2-hydroxy-3-iodo-5-methylacetophenone and 2-hydroxy-4-methyl-5-chlorobenzaldehyde in the presence of solid KOH in combination with grinding at room temperature under solvent-free environment afforded 1-(2′-hydroxy-3′-iodo-5′-methylphenyl)-3-(2-hydroxy-4-methyl-5-chlorophenyl)-2-propen-1-one (3).

Recently various method have been developed for the synthesis α,β-unsaturated ketimines which involves use of hazardous solvent and costly chemicals/catalyst [19-23]. With the increasing environmental concerns and regulatory constrains faced in the chemical and pharmaceutical industries, development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic chemical research [26]. Thus utilization of non-toxic chemicals, renewable materials and solvent-free conditions are the key issues of green synthetic strategy. This observation led to increased our interest to synthesize α,β-unsaturated ketimines from condensation of 2-hydroxychalcone with substituted aromatic amines in water suspension media. In a typical experimental procedure, the reaction was carried out between 2-hydroxychalcone (3) and substituted aromatic amines (4) under water suspension media afforded corresponding α,β-unsaturated ketimines (5a-j).

The reaction proceeded rapidly and completed within 41-60 min. The products were confirmed by the absence of carbonyl band of the reactant (3) in IR spectra, and the presence of an imine ν(C=N) band within 1590-1610 cm⁻¹ region. In the ¹H NMR spectra characteristic doublet signals appeared near δ 6.60 and 7.15 ppm due to α,β-unsaturated protons. In IR spectra, appearance of C=N absorption band and disappearance of >C=O band is focusing point.

The notable advantages of present protocol are neat reaction conditions, no need of any catalyst, environmentally eco-friendly and reaction were take place in water suspension giving quantitative yields (79-93%) of products (see Table 1) in comparison to traditional methods [13, 14].

Table 1. Synthesis of α,β-unsaturated ketimines under water suspension (5a-j)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Time (min.)</th>
<th>Yield (%)</th>
<th>Melting Point (°C)</th>
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<tbody>
<tr>
<td>5a</td>
<td>C₆H₅</td>
<td>57</td>
<td>87</td>
<td>67-69</td>
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<tr>
<td>5b</td>
<td>4-NO₂-C₆H₄</td>
<td>60</td>
<td>88</td>
<td>79-80</td>
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<td>3-NO₂-C₆H₄</td>
<td>52</td>
<td>79</td>
<td>85-87</td>
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<tr>
<td>5d</td>
<td>4-Cl-C₆H₄</td>
<td>53</td>
<td>86</td>
<td>70-73</td>
</tr>
<tr>
<td>5e</td>
<td>4-OCH₃-C₆H₄</td>
<td>41</td>
<td>91</td>
<td>81-83</td>
</tr>
<tr>
<td>5f</td>
<td>3-Cl-C₆H₄</td>
<td>49</td>
<td>85</td>
<td>75-77</td>
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<tr>
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<td>4-CH₃-C₆H₄</td>
<td>44</td>
<td>81</td>
<td>69-72</td>
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<tr>
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<td>48</td>
<td>90</td>
<td>131-133</td>
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<tr>
<td>5i</td>
<td>2-CH₃-C₆H₄</td>
<td>47</td>
<td>87</td>
<td>73-75</td>
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<tr>
<td>5j</td>
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<td>55</td>
<td>93</td>
<td>97-98</td>
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</table>

Conclusion
In conclusion, we have first time reported a simple and efficient synthesis for α,β-unsaturated ketimines from 2-hydroxychalcone and substituted aromatic amines under water suspension. The notable merits of the present method are shorter reaction time, simple work-up procedure; high yield (79-93%), environmentally friendly as it does not use any auxiliary or organic solvent.

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**References and Notes**