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## **Green and efficient synthesis of some new $\alpha$ , $\beta$ -unsaturated ketimines in water under microwave irradiation**

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### **Abstract**

*An environmentally benign and efficient synthesis of some  $\alpha$ ,  $\beta$ -unsaturated ketimines from new substituted 2-hydroxychalcone and different aromatic amines in water under microwave irradiation. This method provides several advantages such as environmental friendliness, simple work-up procedure, short reaction times, non-hazardous and excellent yield of products.*

**Keywords:** 2-hydroxychalcone, substituted aromatic amines,  $\alpha$ ,  $\beta$ -unsaturated ketimines, water, microwave irradiation.

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### **INTRODUCTION**

Chalcones and their derivatives hold a special place among pharmaceutically significant natural products and synthetic compounds [1,2]. The remarkable ability of chalcone nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs [3-5].  $\alpha$ ,  $\beta$ -Unsaturated ketimines, which are obtained from condensation of chalcones and amines, possess various pharmacological properties [6-8]. In both lead identification and lead optimization processes, there is an acute need for new small organic molecules. Conventional methods of organic synthesis are orders of magnitude too slow to satisfy the demand for generation of such compounds. The fields of combinatorial and automated medicinal chemistry have emerged to meet the increasing requirement of new compounds for drug discovery, where speed is of the essence. The synthetic chemical community has been under increased pressure to produce, in an environmentally benign fashion, the myriad of substances required by society in short periods of time, and the best option to accelerate these synthetic processes is to use microwave (MW) technology. The efficiency of MW flash-heating has resulted in dramatic reductions in reaction times (reduced from days and hours to minutes and seconds). The time saved by using the MW heating approach is potentially important in traditional organic synthesis [9-13].

Also, in the context of green chemistry, there are several issues which influence the choice of solvent. It should be relatively nontoxic and relatively non-hazardous (e.g., not flammable or corrosive). The solvent should also be contained, that is, it should not be released to the environment. All these traits are ideally fulfilled by water [14], which is nontoxic, nonflammable, abundantly available, and inexpensive. Moreover, owing to its highly polar character, one can expect novel reactivities and selectivities for organic compounds in water.

To best of our knowledge very less work has been carried out on synthesis of  $\alpha$ ,  $\beta$ -unsaturated ketimines.  $\alpha$ ,  $\beta$ -Unsaturated ketimines were synthesized by condensation of chalcones and aromatic amines in different solvents like ethanol containing few drops of Conc.H<sub>2</sub>SO<sub>4</sub> [15-17], CH<sub>2</sub>Cl<sub>2</sub> in presence of TiCl<sub>4</sub> catalyst [18-20], NaOH [21] or by condensation of anions of enamine phosphine oxides with aldehydes or ketones in THF [22]. However, this method suffers from one or more disadvantages such as harsh reaction condition, unsatisfactory yield, cumbersome product isolation procedure and environmental concern. Therefore, development of improved methods for the synthesis of  $\alpha$ ,  $\beta$ -unsaturated ketimines has acquired relevance to current research.

## RESULTS AND DISCUSSION

As a continuous part of our research work devoted to development of different methodologies in organic chemistry [23-29], herein, first time we would like to report a simple, efficient and green methodology for synthesis of  $\alpha$ ,  $\beta$ -unsaturated ketimines by condensation of 2-hydroxychalcone and substituted aromatic amines in water under microwave irradiation in high yields (85-94%). 2-hydroxychalcone (**3**) was obtained by Claisen-Schmidt condensation of 2-hydroxy-3-iodo-5-chloroacetophenone with 2-hydroxy-5-chlorobenzaldehyde.

In a typical experiment, the reaction of 2-hydroxychalcone (**3**) and substituted aromatic amines (**4**) in water under microwave irradiation to afford the corresponding  $\alpha$ ,  $\beta$ -unsaturated ketimines (**5a-j**). The reaction proceeded rapidly and was completed within 5-8 min. In general, reactions in water are clean, rapid and affords desired product in excellent yields.

## MATERIALS 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. <sup>1</sup>H NMR spectra were recorded on a Gemini 300-MHz instrument in CDCl<sub>3</sub> as solvent and TMS as an internal standard. The mass spectra were recorded on 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. Microwave irradiation was carried out in a microwave oven (LG Smart Chef MS-255 R operating at 2450 MHz with power output of 900W).

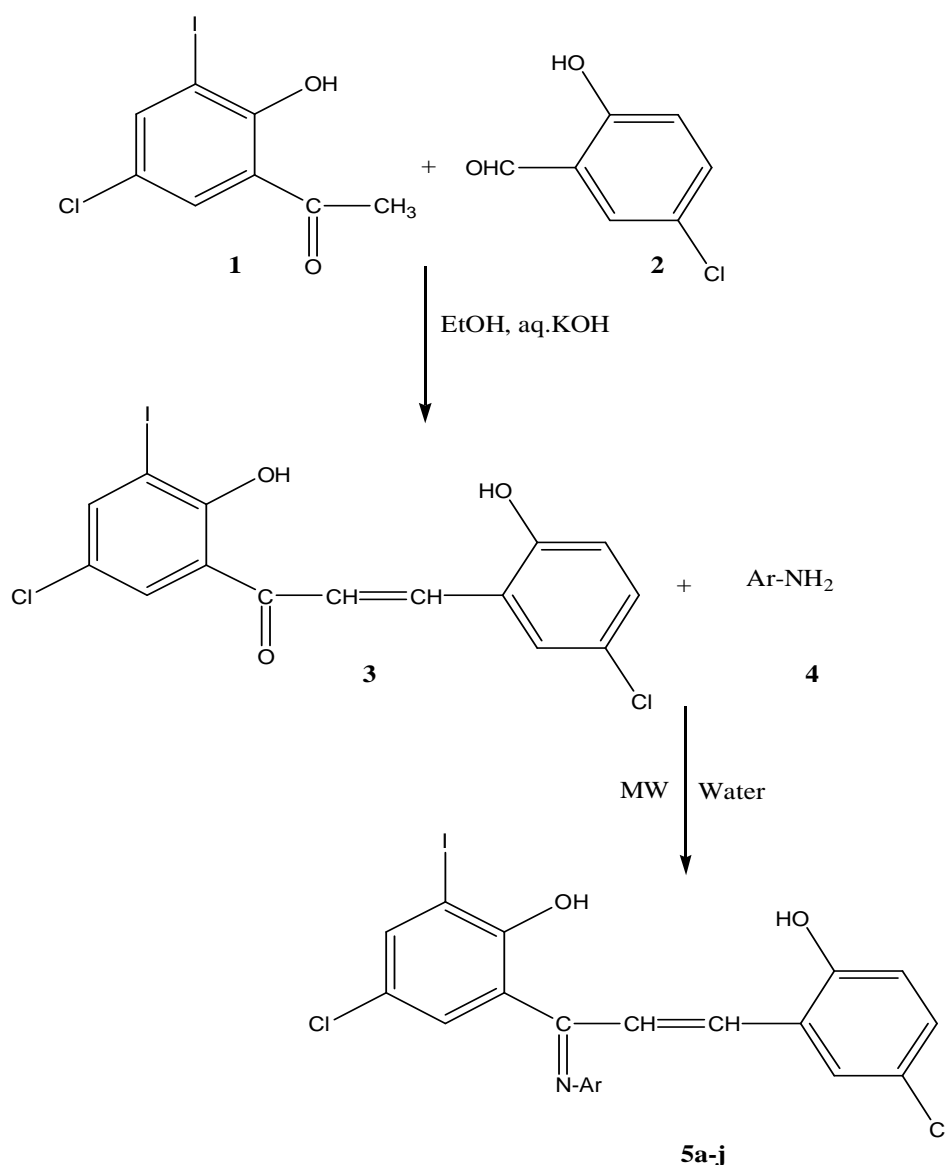
### Synthesis of 1-(2'-hydroxy-3'-iodo-5'-chlorophenyl)-3-(2-hydroxy-5-chlorophenyl)-2-propen-1-one (**3**):

Equimolar quantities of 2-hydroxy-3-iodo-5-chloroacetophenone (0.01mol) and 2-hydroxy-5-chlorobenzaldehyde (0.01mol) were dissolved in ethanol (15ml), under stirring; aq.KOH (10%, 12ml) was added dropwise. The reaction mixture was stirred at room temperature and kept for 12 hr at 50<sup>o</sup>C. The obtained product was diluted with water and acidified with 10% HCl. The separated solid was filtered and recrystallized from acetic acid.

**(3):1-(2'-hydroxy-3'-iodo-5'-chlorophenyl)-3-(2-hydroxy-5-chlorophenyl)-2-propen-1-one:**  
**IR (KBr):** 3347 (-OH), 1678(-C=O), 1610, 1591  $\text{cm}^{-1}$ ;  **$^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ :** 6.57 (d, 1H,  $\text{H}_\alpha$ ), 87.25 (d, 1H,  $\text{H}_\beta$ ), 7.55-7.90 (m, 5H, Ar-H), 8.15 (s, 1H, OH), 13.02 (s, 1H, OH); **MS:**  $m/z = 435$  [ $\text{M}^+$ ]; Anal. Calcd. For  $\text{C}_{15}\text{H}_9\text{O}_3\text{ICl}_2$ : C, 41.37; H, 2.06; X, 45.51. Found: C, 41.48; H, 2.13; X, 45.60.

### Typical Procedure for synthesis of $\alpha$ , $\beta$ -unsaturated ketimines:

A mixture of 1-(2'-hydroxy-3'-iodo-5'-chlorophenyl)-3-(2-hydroxy-5-chlorophenyl)-2-propen-1-one (0.001mol) and substituted aromatic amine (0.001mol) in water (10 ml) were taken in Erlen Meyer flask capped with a funnel. This was subjected to microwave irradiated for sufficient interval of time using resting intervals of 2 min. after every 10 sec. of irradiation. The total period of microwave irradiation (160W) was 3-5 min. (Table-1). The progress of reaction was monitored by TLC. After completion of reaction, the reaction content cooled to room temperature. Then the separated solid was filtered and recrystallized from ethyl alcohol.



Schme1: Synthesis of  $\alpha$ ,  $\beta$ -unsaturated ketimines

**Table-1: Synthesis of  $\alpha$ ,  $\beta$ -unsaturated ketimines in water under Microwave Irradiation**

Entry	Ar	Time (min.)	Yield (%)	Melting Point ( $^{\circ}$ C)
5a	C <sub>6</sub> H <sub>5</sub>	5	87	72
5b	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	4	90	75
5c	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	5	85	95
5d	4-Cl-C <sub>6</sub> H <sub>4</sub>	4	89	86
5e	4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	4	94	71
5f	3-Cl-C <sub>6</sub> H <sub>4</sub>	5	90	66
5g	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	3	91	62
5h	4-Br-C <sub>6</sub> H <sub>4</sub>	5	94	120
5i	2-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	4	88	79
5j	3-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	5	85	74

**Spectroscopic data of synthesized compounds:**

**(5a):2[1-(phenylimino)-3-(5-chloro-2-hydroxyphenyl)allyl]-4-chloro-6-iodophenol:** IR (KBr): 3285 (-OH), 1630 (-C=N), 1608, 1585 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>)  $\delta$ : 6.66 (d, 1H, H <sub>$\alpha$</sub> ),  $\delta$ 7.10 (d, 1H, H <sub>$\beta$</sub> ), 7.30-8.19 (m, 10H, Ar-H), 8.33 (s, 1H, OH), 12.95 (s, 1H, OH); MS: m/z = 510 [M<sup>+</sup>]; Anal. Calcd. For C<sub>21</sub>H<sub>14</sub>O<sub>2</sub>ICl<sub>2</sub>N: C, 49.41; H, 2.74; X, 38.82; N, 2.74. Found: C, 49.53; H, 2.79; X, 38.89; N, 2.81.

**(5b):2[1-(4-Nitro-phenylimino)-3-(5-chloro-2-hydroxyphenyl)allyl]-4-chloro-6-iodophenol:** IR (KBr): 3290 (-OH), 1641 (-C=N), 1608, 1587 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>)  $\delta$ : 6.62 (d, 1H, H <sub>$\alpha$</sub> ),  $\delta$ 7.12 (d, 1H, H <sub>$\beta$</sub> ), 7.27-7.99 (m, 9H, Ar-H), 8.34 (s, 1H, OH), 12.91 (s, 1H, OH); MS: m/z = 548.5 [M<sup>+</sup>]; Anal. Calcd. For C<sub>23</sub>H<sub>18</sub>O<sub>2</sub>IClN<sub>2</sub>: C, 50.31; H, 3.28; X, 29.62; N, 5.10. Found: C, 50.40; H, 3.22; X, 29.70; N, 5.18.

**(5c):2[1-(3-Nitro-phenylimino)-3-(5-chloro-2-hydroxyphenyl)allyl]-4-chloro-6-iodophenol:** IR (KBr): 3294 (-OH), 1645 (-C=N), 1608, 1585 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>)  $\delta$ : 2.22 (s, 3H, CH<sub>3</sub>), 2.30 (s, 3H, CH<sub>3</sub>), 6.64 (d, 1H, H <sub>$\alpha$</sub> ),  $\delta$ 7.10 (d, 1H, H <sub>$\beta$</sub> ), 7.22-8.04 (m, 9H, Ar-H), 8.30 (s, 1H, OH), 12.90 (s, 1H, OH); MS: m/z = 548.5 [M<sup>+</sup>]; Anal. Calcd. For C<sub>23</sub>H<sub>18</sub>O<sub>2</sub>IClN<sub>2</sub>: C, 50.31; H, 3.28; X, 29.62; N, 5.10. Found: C, 50.42; H, 3.20; X, 29.68; N, 5.17.

**(5d):2[1-(4-Chloro-phenylimino)-3-(5-chloro-2-hydroxyphenyl)allyl]-4-chloro-6-iodophenol:** IR (KBr): 3292 (-OH), 1647 (-C=N), 1600, 1581 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>)  $\delta$ : 6.71 (d, 1H, H <sub>$\alpha$</sub> ),  $\delta$ 7.15 (d, 1H, H <sub>$\beta$</sub> ), 7.30-8.05 (m, 9H, Ar-H), 8.30 (s, 1H, OH), 12.92 (s, 1H, OH); MS: m/z = 544.5 [M<sup>+</sup>]. Anal. Calcd. For C<sub>21</sub>H<sub>13</sub>O<sub>2</sub>ICl<sub>3</sub>N: C, 46.28; H, 2.38; X, 42.88; N, 2.57. Found: C, 46.22; H, 2.43; X, 42.82; N, 2.61.

**(5e):2[1-(4-Methoxy-phenylimino)-3-(5-chloro-2-hydroxyphenyl)allyl]-4-chloro-6-iodophenol:** IR (KBr): 3299 (-OH), 1650 (-C=N), 1611, 1588 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>)  $\delta$ : 3.47 (s, 3H, OCH<sub>3</sub>), 6.65 (d, 1H, H <sub>$\alpha$</sub> ),  $\delta$ 7.17 (d, 1H, H <sub>$\beta$</sub> ), 7.32-8.11 (m, 9H, Ar-H), 8.32 (s, 1H, OH), 13.02 (s, 1H, OH); MS: m/z = 540 [M<sup>+</sup>]; Anal. Calcd. For C<sub>22</sub>H<sub>16</sub>O<sub>3</sub>ICl<sub>2</sub>N: C, 48.88; H, 2.96; X, 36.66; N, 2.59. Found: C, 48.99; H, 3.02; X, 36.72; N, 2.65.

**(5f):2[1-(3-Chloro-phenylimino)-3-(5-chloro-2-hydroxyphenyl)allyl]-4-chloro-6-iodophenol:** IR (KBr): 3290 (-OH), 1649 (-C=N), 1600, 1583 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>)  $\delta$ : 6.74 (d, 1H, H <sub>$\alpha$</sub> ),  $\delta$ 7.18 (d, 1H, H <sub>$\beta$</sub> ), 7.35-8.07 (m, 9H, Ar-H), 8.26 (s, 1H, OH), 12.95 (s, 1H, OH); MS: m/z =

544.5 [M<sup>+</sup>]. Anal. Calcd. For C<sub>21</sub>H<sub>13</sub>O<sub>2</sub>ICl<sub>3</sub>N: C, 46.28; H, 2.38; X, 42.88; N, 2.57. Found: C, 46.20; H, 2.44; X, 42.82; N, 2.63.

**(5g):2[1-(4-Methyl-phenylimino)-3-(5-chloro-2-hydroxyphenyl)allyl]-4-chloro-6-iodophenol:** IR (KBr): 3288 (-OH), 1652 (-C=N), 1610, 1586 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ: 2.35 (s, 3H, CH<sub>3</sub>), 6.67 (d, 1H, H<sub>α</sub>), δ7.17 (d, 1H, H<sub>β</sub>), 7.30-8.10 (m, 9H, Ar-H), 8.37 (s, 1H, OH), 13.10 (s, 1H, OH); MS: m/z = 524 [M<sup>+</sup>]; Anal. Calcd. For C<sub>22</sub>H<sub>16</sub>O<sub>2</sub>ICl<sub>2</sub>N: C, 50.38; H, 3.05; X, 37.78; N, 2.67. Found: C, 55.45; H, 3.09; X, 37.83; N, 2.74.

**(5h):2[1-(4-Bromo-phenylimino)-3-(5-chloro-2-hydroxyphenyl)allyl]-4-chloro-6-iodophenol:** IR (KBr): 3288 (-OH), 1640 (-C=N), 1609, 1583 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ: 6.67 (d, 1H, H<sub>α</sub>), δ7.10 (d, 1H, H<sub>β</sub>), 7.33-8.14 (m, 9H, Ar-H), 8.33 (s, 1H, OH), 13.02 (s, 1H, OH); MS: m/z = 589 [M<sup>+</sup>]; Anal. Calcd. For C<sub>21</sub>H<sub>13</sub>O<sub>2</sub>ICl<sub>2</sub>BrN: C, 42.78; H, 2.20; X, 47.19; N, 2.37. Found: C, 42.74; H, 2.24; X, 47.13; N, 2.40.

**(5i):2[1-(2-Methyl-phenylimino)-3-(5-chloro-2-hydroxyphenyl)allyl]-4-chloro-6-iodophenol:** IR (KBr): 3285 (-OH), 1655 (-C=N), 1613, 1586 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ: 2.37 (s, 3H, CH<sub>3</sub>), 6.69 (d, 1H, H<sub>α</sub>), δ7.20 (d, 1H, H<sub>β</sub>), 7.34-8.08 (m, 9H, Ar-H), 8.40 (s, 1H, OH), 13.16 (s, 1H, OH); MS: m/z = 524 [M<sup>+</sup>]; Anal. Calcd. For C<sub>22</sub>H<sub>16</sub>O<sub>2</sub>ICl<sub>2</sub>N: C, 50.38; H, 3.05; X, 37.78; N, 2.67. Found: C, 55.47; H, 3.10; X, 37.85; N, 2.74.

**(5j):2[1-(3-Methoxy-phenylimino)-3-(5-chloro-2-hydroxyphenyl)allyl]-4-chloro-6-iodophenol:** IR (KBr): 3305 (-OH), 1652 (-C=N), 1611, 1588 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ: 3.50 (s, 3H, OCH<sub>3</sub>), 6.67 (d, 1H, H<sub>α</sub>), δ7.19 (d, 1H, H<sub>β</sub>), 7.35-8.15 (m, 9H, Ar-H), 8.30 (s, 1H, OH), 13.0 (s, 1H, OH); MS: m/z = 540 [M<sup>+</sup>]; Anal. Calcd. For C<sub>22</sub>H<sub>16</sub>O<sub>3</sub>ICl<sub>2</sub>N: C, 48.88; H, 2.96; X, 36.66; N, 2.59. Found: C, 49.00; H, 3.01; X, 36.70; N, 2.67.

## 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 in water using microwave irradiation. The present method contribute to the dream of green technology due to shorter reaction time, simple work-up procedure; high yield (85-94%), environmentally friendly as it does not use any auxiliary or organic solvent.

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