Microwave enhanced Claisen-Schmidt condensation: A green route to chalcones

Jayant P Singh, Mangalshree Dulawat, Neetu Jaitawat, Sumer S Chundawat, Anju Devpura & Shiv S Dulawat*
Department of Chemistry, B N P G College, M L Sukhadiya University, Udaipur 313 001, India
E-mail: jayantratnawat@gmail.com

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Chalcones have been synthesized under microwave irradiation by Claisen-Schmidt condensation between 4-piperidinoacetophenone and appropriately substituted benzeldehydes using NaOH-Al₂O₃ under solvent free conditions. Neat reactions on microwave irradiation (MWI) under solvent free conditions result in enhancement of yield and reaction rates. High conversion is obtained in absence of solvent. The protocol offers several advantages such as simple procedure, fast reaction rate, mild reaction conditions and excellent yield. Structure elucidation of synthesized compounds has been accomplished by elemental analysis and spectral data. All the compounds have been screened for antimicrobial activity.

Keywords: Chalcones, microwave irradiation, green chemistry, antimicrobial activity

The members of chalcone¹ and flavonoid family have attracted a great deal of interest due to their application as antimicrobial²⁴, anti-inflammatory⁵,⁶ antifungal, antiviral⁷, anti parasitic, antileishmanial⁷, antitubercular⁸-¹¹, and anticancer¹²-¹⁴ pharmacological agents¹⁵,¹⁶. In addition, these compounds are of high interest due to their use as starting materials in the synthesis of a series of heterocyclic compounds like isoxazole, quinolinones, thiadiazines, benzofuranones, benzodiazepines, tetrahydro-2-chromens, flavones, etc.

These areimportant intermediates in many addition reactions of nucleophiles due to inductive polarization of carbonyl group at the β-position. These findings explain the significant interest of scientists in this particular group of compounds.

Several strategies for the synthesis of these systems based on the formation of carbon-carbon bond have been reported. Among them, direct aldol condensation and Claisen-Schmidt condensation¹⁷ still occupy prominent position. The main method for the synthesis of chalcones is the Claisen-Schmidt condensation in the presence of alkaline bases.

Conventional methods present several hurdles, such as toxic reagents, waste disposal problem, strong acidic or basic conditions and low selectivity that pose environmental hazards. In this respect solid phase synthesis under microwave irradiation is considered as an eco-friendly alternative.

Under the frame-work of “Green Chemistry” an environmentally benign solvent free synthesis of chalcones has been developed by condensing 4-piperidinoacetophenone and substituted benzeldehydes using microwave irradiation in the presence of basic alumina as inorganic solid support.

The structures of the various synthesized compounds were assigned on the basis of IR, ¹H NMR, mass spectral data and elemental analysis. These compounds were also screened for their antimicrobial activity.

Results and Discussion

Antimicrobial activity

All the synthesized compounds 5a-h (Scheme I) were screened for their in vitro antibacterial activity at a concentration of 200 µg/mL in DMF against Gram-positive B. subtilis and Gram negative E. coli, K. pneumonia and Pseudomonas bacteria as well as antifungal activity against Candida albicans and Aspergillus fungi by the paper disc diffusion method. The zone of inhibition was measured in mm. Standard drugs Cipro and Fluconazole were used as reference compounds. The zone of inhibition was compared with the standard drugs after 24 hr. of incubation at 25°C. All the compounds 5a-h exhibited moderate to good activity against the test organisms. The results are summarized in Table I.

Experimental Section

All the melting points are uncorrected and were recorded using open ended capillaries. Thin layer chromatography of synthesized compounds was performed on silica gel-G plates using hexane-ethyl acetate (7:3) solvent system and iodine vapour as visualizing agent.

The IR spectra were recorded on Digilab FTS-14 or Perkin-Elmer 157P spectrophotometer in KBr (νmax in cm⁻¹). ¹H NMR was recorded on acetone-d₆ on a
**Varian CFT-20 or Brucker DRX-300 (300 MHz) spectrometer using TMS as internal standard (chemical shift in $\delta$ ppm). FAB mass spectra were recorded on Jeol SX-102 spectrometer. All compounds gave satisfactory elemental analysis and spectral data. All the reactions were carried out in a domestic microwave oven (Kenstar, output energy 1200 W, frequency 2450 MHz, Model No. MO9760). 4-Piperidinoacetophenone 3 was synthesized in-house under MWI.**

**Synthesis of 4-piperidinoacetophenone 3**

Synthesis of 4-piperidinoacetophenone 3 was performed using 4-fluoroacetophenone 1 (0.02 mol) and piperidine 2 (0.017 mol) using $\text{K}_2\text{CO}_3$ (0.017 mol) and DMSO (15 mL) under microwave irradiation at 25% microwave power (300 W) for a period of 5 min. On completion of reaction (TLC), the reaction mixture was treated with ice-cold water to obtain the precipitate of the product 3 leaving behind $\text{K}_2\text{CO}_3$ dissolved in water. The product was filtered, washed with water and purified by recrystallization from $n$-heptane to afford analytical samples of compound 3.

**General procedure for synthesis of chalcones, 5a-h**

**Method (A)**

**Conventional solution phase**

A solution of 4-piperidinoacetophenone 3 (0.01 mol) and different substituted benzenaldehyde 4a-h

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**Table I — Antimicrobial activity of compounds 5a-h (zone of inhibition in mm)**

<table>
<thead>
<tr>
<th>Compd</th>
<th>B. subtilis</th>
<th>K. pneumonia</th>
<th>E. coli</th>
<th>Pseudomonas</th>
<th>C. albicans</th>
<th>Aspergillus</th>
</tr>
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<tbody>
<tr>
<td>5a</td>
<td>16</td>
<td>13</td>
<td>13</td>
<td>26</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>5b</td>
<td>13</td>
<td>12</td>
<td>12</td>
<td>24</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>5c</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>25</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>5d</td>
<td>16</td>
<td>14</td>
<td>12</td>
<td>23</td>
<td>10</td>
<td>12</td>
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<tr>
<td>5e</td>
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<td>10</td>
<td>12</td>
<td>23</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>5f</td>
<td>16</td>
<td>23</td>
<td>16</td>
<td>32</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>5g</td>
<td>12</td>
<td>21</td>
<td>18</td>
<td>23</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>5h</td>
<td>13</td>
<td>19</td>
<td>19</td>
<td>23</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Cipro (Std.)</td>
<td>36</td>
<td>32</td>
<td>32</td>
<td>35</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Flucanazole (Std.)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Control (DMF)</td>
<td>00</td>
<td>00</td>
<td>00</td>
<td>00</td>
<td>00</td>
<td>00</td>
</tr>
</tbody>
</table>
NOTES

(0.01 mol) in ethanol (25 mL) was stirred at RT for a period specified as in Table II in the presence of 30% NaOH solution (8 mL). After that, the sodium salt of chalcone was decomposed by ice cold 2N HCl (2-3 mL). The separated chalcone was filtered, washed with water (2 × 50 mL) and purified by recrystallization from ethanol to afford analytical samples of compounds 5a-h.

Method (B)

One pot solution phase MWI (Aq. NaOH)

To a solution of 4-piperidinoacetophenone 3 (0.01 mol), substituted benzeldehydes 4a-h (0.01 mol) in ethanol (25 mL) was added into a 100 mL Borosil flask fitted with a funnel as a loose top. NaOH solution (40%, 3 mL) was added and the reaction mixture was subjected to microwave irradiation at 25% microwave power (300 W) for a period specified as in Table II with short interval of 30 sec to 1 min to avoid excessive evaporation of solvent. The reaction mixture was cooled and neutralized with 2N HCl (2-3 mL). The separated product was filtered, washed with water (2 × 50 mL) and purified by recrystallization from ethanol to afforded analytical samples of compounds 5a-h.

Method (C)

One pot solid phase MWI (Basic alumina)

A mixture of 4-piperidinoacetophenone 3 (0.01 mol) and substituted benzeldehydes 4a-h (0.01 mol) was dissolved in ethanol (10 mL) and taken in a 100 mL Borosil flask. To this basic alumina (4.0 g) was added and the reactants were properly mixed with the help of a glass rod. The adsorbed material was dried in air and irradiated inside the microwave oven at low power level (30%) for a period specified as in Table II. On completion of reaction (TLC), the reaction mixture was treated with ice-cold water to obtain the precipitate of the product 5a-h leaving behind K$_2$CO$_3$ dissolved in water. The product was filtered, washed with water and purified by recrystallization from ethanol to afforded analytical samples of compounds 5a-h.

The compounds synthesized by the above procedure were found to be identical to those obtained by method A, B, C and D on the basis of their m.p. and IR spectra. The characterization data of synthesized compounds 5a-h as well as compound 3 are given below.

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>m.p. (°C)</th>
<th>Method-A (hr)/b</th>
<th>Method-B (min)/b</th>
<th>Method-C (min)/b</th>
<th>Method-D (min)/b</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>4-OCH$_3$</td>
<td>144</td>
<td>5/81</td>
<td>5/86</td>
<td>2/97</td>
<td>3/91</td>
</tr>
<tr>
<td>5b</td>
<td>3,4-OCH$_3$</td>
<td>155</td>
<td>7/79</td>
<td>5/82</td>
<td>2/92</td>
<td>3/88</td>
</tr>
<tr>
<td>5c</td>
<td>3,4-OCH$_3$</td>
<td>158</td>
<td>7/77</td>
<td>5/81</td>
<td>3/90</td>
<td>3/82</td>
</tr>
<tr>
<td>5d</td>
<td>3-NO$_2$</td>
<td>177</td>
<td>4/83</td>
<td>3/88</td>
<td>2/93</td>
<td>2/86</td>
</tr>
<tr>
<td>5e</td>
<td>4-N(CH$_3$)$_2$</td>
<td>200</td>
<td>10/67</td>
<td>6/79</td>
<td>4/86</td>
<td>4/80</td>
</tr>
<tr>
<td>5f</td>
<td>4-OH</td>
<td>190</td>
<td>12/71</td>
<td>5/81</td>
<td>3/91</td>
<td>5/78</td>
</tr>
<tr>
<td>5g</td>
<td>2-Cl</td>
<td>108</td>
<td>12/62</td>
<td>6/76</td>
<td>5/88</td>
<td>4/74</td>
</tr>
<tr>
<td>5h</td>
<td>4-Cl</td>
<td>186</td>
<td>12/68</td>
<td>6/79</td>
<td>5/89</td>
<td>5/83</td>
</tr>
</tbody>
</table>

a = Time (min) and b = Yield (%)
5a: Yellow crystals, m.p. 144°C. Anal. Caled for C_{21}H_{28}NO_3 (321.4): C, 78.47; H, 7.21. Found: C, 77.82; H, 6.92%. \(^1\)H NMR (acetone-d_6): δ 1.62-2.76 (m, piperidine-H), 3.87 (3H, s, -OCH_3), 6.92-8.10 (m, Ar-H), 7.60 (1H, d, -CO-CH=), 8.02 (1H, d, =CH-Ar); IR (KBr): 3061 (Ar-H), 1655 (C=O), 1596, 1507, 1461, 1420 (C=C/Ar), 1015 (CH=CH trans), 817, 720, 678 cm\(^{-1}\) (substituted phenyl); MS (EI): m/z 322 (M+1), 321 (M\(^+\)), 291, 207, 132, 78.

5b: Yellow crystals, m.p. 155°C. Anal. Caled for C_{22}H_{30}NO_3 (351.44): C, 75.19; H, 7.17. Found: C, 74.96; H, 7.01%. \(^1\)H NMR (acetone-d_6): δ 1.64-2.72 (m, piperidine-H), 3.84, 3.82 (6H, s, -OCH_3), 6.90-8.04 (m, Ar-H), 7.35 (1H, d, -CO-CH=), 8.13 (1H, d, =CH-Ar); IR (KBr): 3054 (Ar-H), 1658 (C=O), 1600, 1509, 1458 (C=C/Ar), 996, 954 (CH=CH trans), 893, 770, 724, 632 cm\(^{-1}\) (substituted phenyl); MS (EI): m/z 352 (M+1), 351 (M\(^+\)), 321, 290, 215, 132, 78, 65, 53.

5c: Yellow crystals, m.p. 158°C. Anal. Caled for C_{21}H_{27}NO_2 (341.46): C, 72.42; H, 7.13. Found: C, 72.01; H, 6.94%. \(^1\)H NMR (acetone-d_6): δ 1.60-2.69 (m, piperidine-H), 3.85 (9H, s, -OCH_3), 7.1-8.08 (m, Ar-H), 7.05 (1H, d, -CO-CH=), 7.98 (1H, d, =CH-Ar); IR (KBr): 3040 (Ar-H), 1650 (C=O), 1606, 1502, 1481 (C=C/Ar), 1026, 966 (CH=CH trans), 878, 864, 787, 706 cm\(^{-1}\) (substituted phenyl); MS (EI): m/z 382 (M+1), 381 (M\(^+\)), 350, 321, 290, 207, 136, 80, 60, 45.

5d: Orange crystals, m.p. 177°C. Anal. Caled for C_{20}H_{29}NO_3 (336.38): C, 71.41; H, 5.99. Found: C, 71.07; H, 5.42%. \(^1\)H NMR (acetone-d_6): δ 1.59-2.62 (m, piperidine-H), 7.04-7.96 (m, Ar-H), 7.35 (1H, d, -CO-CH=), 8.13 (1H, d, =CH-Ar); IR (KBr): 3052 (Ar-H), 1645 (C=O), 1595, 1505, 1462 (C=C/Ar), 1320 (Ar-NO_2), 1009 (CH=CH trans), 818, 731, 670, 610 cm\(^{-1}\) (substituted phenyl); MS (EI): m/z 336 (M\(^+\)), 290, 277, 190, 118, 103, 78, 65, 26.

5e: Yellow crystals, m.p. 200°C. Anal. Caled for C_{22}H_{30}O_2 (343.45): C, 79.0; H, 7.84. Found: C, 78.63; H, 7.21%. \(^1\)H NMR (acetone-d_6): δ 1.49-2.60 (m, piperidine-H), 2.82 (6H, s, ter.-amine-H), 7.11-8.0 (m, Ar-H), 7.25 (1H, d, -CO-CH=), 8.0 (1H, d, =CH-Ar); IR (KBr): 3068 (Ar-H), 1661 (C=O), 1599, 1501, 1454 (C=C/Ar), 998, 956 (CH=CH trans), 878, 864, 787, 704 cm\(^{-1}\) (substituted phenyl); MS (EI): m/z 335 (M+1), 334 (M\(^+\)), 321, 305, 287, 208, 130, 77, 68, 24.

5f: Orange crystals, m.p. 190°C. Anal. Caled for C_{20}H_{28}NO_2 (307.39): C, 78.15; H, 6.89. Found: C, 78.00; H, 6.19%. \(^1\)H NMR (acetone-d_6): δ 1.54-2.70 (m, piperidine-H), 6.87-8.07 (m, Ar-H), 7.40 (1H, d, -CO-CH=), 8.16 (1H, d, =CH-Ar), 8.36 (1H, phenolic H); IR (KBr): 3292 (Ar-OH), 3062 (Ar-H), 1650 (C=O), 1590, 1516, 1490, 1454 (C=C/Ar), 1005 (CH=CH trans), 818, 735, 690, 625 cm\(^{-1}\) (substituted phenyl); MS (EI): m/z 308 (M+1), 305 (M-2), 290, 206, 131, 116, 77, 41, 30.

5g: Yellow crystals, m.p. 108°C. Anal. Caled for C_{20}H_{28}ClNO (325.83): C, 73.72; H, 6.19. Found: C, 73.28; H, 5.94%. \(^1\)H NMR (acetone-d_6): δ 1.64-2.68 (m, piperidine-H), 7.11-8.2 (m, Ar-H), 6.98 (1H, d, -CO-CH=), 7.98 (1H, d, =CH-Ar); IR (KBr): 3060 (Ar-H), 1654 (C=O), 1602, 1498, 1487 (C=C/Ar), 1005 (CH=CH trans), 849, 772, 701 cm\(^{-1}\) (substituted phenyl); MS (EI): m/z 327 (M+1), 326 (M\(^+\)), 293, 207, 125, 104, 77, 41, 30.

Conclusion

The proposed microwave-assisted methodology on inorganic solid support provides an easier, facile, practically convenient and eco-friendly one-pot synthesis of bio-active chalcones 5a-h as compared to existing conventional methods. Significant antimicrobial activity was observed with compound 5f against bacteria and fungi.

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References