Microwave assisted Perkin reaction for the synthesis of α-arylidine-γ-phenyl-Δ, β, γ-butenolides

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Perkin condensation with subsequent intramolecular lactonisation as one pot synthesis of α-arylidine-γ-phenyl-Δ, β, γ-butenolides have been studied under microwave irradiation. The butenolides are cleaved to give keto acids, which are the precursors of pericarbonyl lactone lignans possessing variety of biological activities. Syntheses of butenolides have been carried out using pyridine as a catalyst under microwave conditions. The generality of this protocol has been demonstrated by synthesizing a variety of substituted butenolides in excellent yields, short reaction time and with good purity compared to those under classical thermal conditions. All the products have been characterized by their IR, 1H NMR and UV spectral values.

Keywords: Perkin reaction, microwave irradiation, pericarbonyl lactone lignan, butenolides, aromatic aldehydes

Pericarbonyl lactone lignans attracted special attention of organic chemists because they have wide range of therapeutic properties like anti-inflammatory4, antibacterial5, antioxidant6, anti-cancer7, CNS depressants8, immunomodulatory9,10, etc. The broad spectrum of biological activities has made them privileged structures in combinatorial drug discovery. The Perkin condensation reaction is the most straightforward and atom-economic route for the synthesis of these lignans8.

In reported methods, the Perkin condensation reactions were carried out by conventional heating for three hour reflux9,10. These traditional heating techniques were however, rather slow and a temperature gradient can develop within the sample. In addition, local overheating can lead to product, substrate and reagent decomposition. Therefore microwave heating was carried out to overcome the above mentioned disadvantages, as in microwave dielectric radiation passes through the walls of the vessel and heats only the reactants and reagents, not the reaction vessel itself, which can lead to less by-products and/or decomposition products.

In continuation of our interest on microwave assisted organic transformations11-13, we have reported herein an efficient Perkin reaction in the microwave oven by employing pyridine as a catalyst. The butenolide formed in the Perkin reaction was then cleaved easily with alcoholic sodium carbonate to give the keto acid which was identified as α-arylidine-β-benzoyl propionic acid14,15 containing the required skeleton to prepare pericarbonyl lactone lignan16.

Experimental Section
All the chemicals and reagents were of LR or AR grade and procured from S.D. Fine Chem Ltd. (Mumbai), Loba Chemie, Mumbai, E. Merck (India) Ltd., and used as received. IR spectra were recorded on a Perkin-Elmer FT spectrophotometer in KBr disc, 1H NMR were recorded on a Varian 300 MHz spectrometer in CDCl3 as a solvent and TMS as an internal standard. Melting points were recorded on a melting point apparatus with capillary tubes and are uncorrected. Analytical TLC was performed on glass slides coated with silica gel G/UV-254 of 0.2 mm thickness. Elemental analysis data were recorded using Thermo Finnegan FLASH EA 1112 CHN analyzer. For the microwave irradiation experiments, a conventional (unmodified) house hold microwave oven equipped with a turntable was used (LG Smart Chef MS-255r operating at 2450 MHz having maximum output of 800 W).

General Procedure
Synthesis of α-arylidine-γ-phenyl-Δ, β, γ-butenolide
The reaction mixture of β-benzoyl propionic acid (1 g), aryl aldehyde (1 g), acetic anhydride (1 mL) and two drops of pyridine were taken in 250 mL beaker. It was mixed properly with the help of glass rod. An inverted funnel was placed over the rim of the beaker and irradiated in a microwave oven at 800 W for 14-15 min while monitoring the reaction with the help of TLC. After the completion of the reaction, the immediate temperature of the reaction mixture was recorded using the thermometer, which was found to be 55°C. The hot reaction mixture was poured in cold water with stirring and then acidified with conc. HCl. The yellow mass obtained was filtered and crystallized from benzene to give α-arylidine-γ-phenyl-Δ, β, γ-butenolide.
Adopting the above described method, five different substituted butenolides (3a-e) were identified and characterized (Table I).

Cleavage of butenolide to α-arylidine-β-benzoyl propionic acid 14,15

α-Arylidine-γ-phenyl-Δβ,γ-butenolide (1 g) was cleaved easily with alcoholic sodium carbonate solution [prepared by dissolving 1 g anhydrous sodium carbonate (Na₂CO₃) in 4 mL methanol and 6 mL water]. The resulting mixture was filtered, cooled and acidified with conc. HCl to get a brown precipitate which was crystallized from aq. methanol and was identified as α-arylidine-β-benzoyl propionic acid.

Adopting the above described method, five different substituted α-arylidine-β-benzoyl propionic acids (4a-e) were identified and characterized (Scheme I).

Result and Discussion

Perkin condensation is a prelude to the development of pericarbonyl lactone system. It consists of two steps-butenolide formation followed by the formation of keto acid which was identified as α-arylidine-β-benzoyl propionic acid. It was envisaged to use β-benzoyl propionic acid system as it has two reactive methylene groups and a carboxylic functional group which could lead to the basic skeleton of 1-phenylnapththalene lignans. The carboxyl group would yield a part of furan ring and the oxo group could be reduced.

To start our investigation, we performed the study of the butenolide formation under microwave irradiation by the condensation of aryl aldehyde, β-benzoyl propionic acid and acetic anhydride using pyridine as a catalyst (Scheme I). Microwave irradiation proved to be extremely useful for promoting and simplifying of Perkin condensation reaction. The reaction time is 12 times shorter than at conventional heating and the yields of isolated products are 8-15% higher.

The carbanion formation at the α-carbon 12 is likely to be stabilized by a phenyl conjugated double bond on one side and a characteristic anhydride unit of the Perkin condensation on the other side. It is observed that 13 on treatment with acetic anhydride cyclizes quantitatively to the lactone 3, undoubtedly through the intermediate 15 (Scheme III).

To extend the scope of reaction and to generalize the procedure, the reaction of β-benzoyl propionic acid 1 was carried out with a series of aryl aldehydes [veratraldehyde 2a, pipernol 2b, vanillin 2c, 3,4,5 trimethoxy-benzaldehyde 2d and benzaldehyde 2e] to obtain the corresponding butenolides 3a-e. The lactone rings of butenolides were then opened with alcoholic sodium carbonate to give the corresponding α-arylidine-β-benzoyl propionic acids 4a-e, which latter undergo cyclization to give pericarbonyl lactone system under the catalysis of sulphamic acid as a green catalyst (Scheme II). It has been reported that for the system of the above type 4 to undergo cyclization, the presence of aldehydes having hydroxy, methoxy or methylenedioxy groups at para position 19 to the cyclization site in the aromatic ring is essential. Therefore, the reactions are restricted to aldehydes possessing such groups.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Butenolide</th>
<th>Formula</th>
<th>Elemental Analysis</th>
<th>UV λmax nm (log ε)</th>
<th>IR (cm⁻¹)</th>
<th>NMR (δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Observed (%)</td>
<td>C</td>
<td>H</td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>3a</td>
<td>C₁₉H₁₆O₄</td>
<td>74.86 5.26</td>
<td>74.81</td>
<td>5.23</td>
<td></td>
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<tr>
<td>2</td>
<td>3b</td>
<td>C₁₈H₁₂O₄</td>
<td>73.37 4.55</td>
<td>73.48</td>
<td>4.59</td>
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<tr>
<td>3</td>
<td>3c</td>
<td>C₁₈H₁₄O₄</td>
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<td>70.32</td>
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<tr>
<td>4</td>
<td>3d</td>
<td>C₂₁H₁₉O₄</td>
<td>75.27 5.15</td>
<td>75.25</td>
<td>5.11</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>C₁₇H₁₂O₂</td>
<td>82.26 4.81</td>
<td>82.25</td>
<td>4.83</td>
<td></td>
</tr>
</tbody>
</table>

*In compd 3a-e, the δ values of 1H (d) of Ar-C=H are slightly less due to anisotropic effect.
Scheme I — Cyclization reactions to achieve 1-Phenylnaphthalene lactone/Pericarbonyl lactone

$$\text{β-benzoyl propionic acid} \quad 1$$

$$\text{Perkin Reaction}$$

$$\text{α-arylidine-γ-phenyl-Δ,β,γ-butenolide} \quad 3$$

$$\text{Na}_2\text{CO}_3$$

$$\text{α-arylidine-β-benzoyl propionic acid} \quad 4$$

Scheme II

$$\text{α-arylidine-β-benzoyl propionic acid} \quad 4$$

$$\text{α-arylidine-β-methylene-β-benzoyl propionic acid} \quad 5$$

Pericarbonyl lactone

**Substitutions**

a: \( R_1 = R_2 = -\text{OCH}_3, R_3 = \text{H} \)

b: \( R_1 = R_2 = -\text{O-CH}_2\text{-O}, R_3 = \text{H} \)

c: \( R_1 = -\text{OCH}_3, R_2 = -\text{OH}, R_3 = \text{H} \)

d: \( R_1 = R_2 = R_3 = -\text{OCH}_3 \)

e: \( R_1 = R_2 = R_3 = \text{H} \)
Scheme III

**Table II** — Comparative data on conventional and microwave assisted synthesis of butenolides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Products</th>
<th>Time (min)</th>
<th>Yield(^*) (%)</th>
<th>m.p. (°C)</th>
<th>Found</th>
<th>Lit.(^{11})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Butenolide</td>
<td>Conv. MW</td>
<td>Conv. MW</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3a</td>
<td>180</td>
<td>15</td>
<td>73</td>
<td>88</td>
<td>122-24</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>180</td>
<td>14.5</td>
<td>85</td>
<td>95</td>
<td>165-66</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>180</td>
<td>15</td>
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<td>95</td>
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<tr>
<td>4</td>
<td>3d</td>
<td>180</td>
<td>14.5</td>
<td>88</td>
<td>96</td>
<td>165-69</td>
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<tr>
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<td>3e</td>
<td>180</td>
<td>14.2</td>
<td>70</td>
<td>78</td>
<td>150-53</td>
</tr>
</tbody>
</table>

Conv. = Burner (previous work)
MW = Microwave oven (present work)
When the reaction time and yields of conventional methodology were compared with our microwave assisted procedure (Table II), it is found that ours is more convenient over that of conventional, in terms of considerable reduction in reaction time, improved yields and facile nature of the reaction.

**Conclusion**

In summary, the alternative MW-assisted method was found to be a viable alternative to the presently existing conventional procedure to produce the butenolides which further lead to pericarbonyl lactone systems.

**Acknowledgement**

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**References**