Microwave assisted rapid synthesis of 3-alkoxy-2-cyclohexen-1-ones from 1,3-cyclohexanedione

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Synthesis of 3-alkoxy-2-cyclohexen-1-ones from 1,3-cyclohexanedione with various alcohols has been achieved under microwave irradiation conditions within 7 min.

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3-Alkoxy-2-cyclohexenones are of great synthetic interest as they are precursors for many transformations. The utility of these substrates is multifaceted. These may be further functionalised or used as such as synthons for extensive applications. 3-Alkoxy-2-cycloalkenones are derived from β-cyclohexadiene. Hence, this conversion assumes importance for the construction of synthetic intermediates.

3-Alkoxy-2-cycloalkenones have been largely reported to have great synthetic utility. Their alkyla-
tion and subsequent reduction followed by hydrolysis and dehydration yields 4-alkylated-2-cyclo-
hexenones. 3-Alkoxy-2-cycloalkenones on treatment with organo-metallic reagents followed by hydrolysis and dehydration offer a variety of 3-substituted 2-cyclohexenones. Further, they may act as dienophiles in Diels-Alder reactions. 4a has been used as synthetic precursor for the synthesis of 2-aryl and 2-alkenyl-3-alkoxy-cyclohexenones and optically active cyclohexenones that serve as starting material for many terpenoids. In addition, regiospecific synthesis of functionalized bicyclic[2.2.2]octenones and tricyclo[llicinone, a neurotrophic substance have also been carried out using 4b as the synthon.

Microwave irradiation technique shows considerable acceleration to this reaction considerably. In a typical example, a solution of 1, ethanol and p-TsOH in toluene was subjected to microwave irradiation in a domestic microwave oven (Kelvinator - India, 700 watts, 2450 MHz frequency) for 7 min and the reaction was found to be complete as shown by TLC (Scheme I). Reactions with other alcohols were also carried out and all the reactions proceeded to completion within 7 min providing clean products of 3-alkoxy-2-cyclohexen-1-one in good yields (Table I). To generalize this reaction, dimedone was treated with a few alcohols. However, the reactions were incomplete with toluene as the medium. Therefore, a solvent with higher dielectric constant (chlorobenzene) was chosen, as it would be more suitable for dimedone reaction. Solvents with higher polarity have been known to accelerate product formation. Thus, the reaction proceeded well with chlorobenzene as the solvent and 3-alkoxy-5,5-dimethyl-2-cyclohexenones were formed in excellent yields. The reactions were generally carried out in small scale. However, the reaction of 1 with isopropanol was also carried out in 5 g scale to test the viability of the synthetic methodology for scale up and the same reactions take longer periods (6-8 hr) for completion. Hence, an attempt was made under microwave irradiation conditions. Microwave irradiation has been widely accepted as a catalytic tool by synthetic chemists. The advantages of using the microwave technique is that it offers quicker and cleaner reactions compared to conventional thermal reactions. The solvents with higher dielectric constants are superheated and the reactions take place rapidly.

Results and discussion

The microwave irradiation technique has been found to accelerate and increase the yields of this reaction considerably. In a typical example, a solution of 1, ethanol and p-TsOH in toluene was subjected to microwave irradiation in a domestic microwave oven (Kelvinator - India, 700 watts, 2450 MHz frequency) for 7 min and the reaction was found to be complete as shown by TLC (Scheme I). Reactions with other alcohols were also carried out and all the reactions proceeded to completion within 7 min providing clean products of 3-alkoxy-2-cyclohexen-1-one in good yields (Table I). To generalize this reaction, dimedone was treated with a few alcohols. However, the reactions were incomplete with toluene as the medium. Therefore, a solvent with higher dielectric constant (chlorobenzene) was chosen, as it would be more suitable for dimedone reaction. Solvents with higher polarity have been known to accelerate product formation. Thus, the reaction proceeded well with chlorobenzene as the solvent and 3-alkoxy-5,5-dimethyl-2-cyclohexenones were formed in excellent yields. The reactions were generally carried out in small scale. However, the reaction of 1 with isopropanol was also carried out in 5 g scale to test the viability of the synthetic methodology for scale up and the same reactions take longer periods (6-8 hr) for completion. Hence, an attempt was made under microwave irradiation conditions. Microwave irradiation has been widely accepted as a catalytic tool by synthetic chemists. The advantages of using the microwave technique is that it offers quicker and cleaner reactions compared to conventional thermal reactions. The solvents with higher dielectric constants are superheated and the reactions take place rapidly.

Scheme I
proceeded within 7 min as expected.

**Conclusion**

We have shown that the useful synthetic intermediate 3-alkoxy-2-cyclohexenones can be synthesized from 1,3-diketones in a very rapid and clean method with excellent yields under microwave irradiation conditions.

**Experimental Section**

Toluene and chlorobenzene were dried under calcium hydride and distilled before use. Alcohols were dried and distilled prior to use. The reactions were carried out in a domestic microwave oven (T-23 model, Kelvinator-India, 700 watts, 2450 MHz frequency). Analytical thin layer chromatography was performed on pre-coated plastic silica gel plates of 0.25 mm thickness containing PF 254 indicator (Merck, Darmstadt). IR spectra were recorded neat on a Perkin-Elmer RX I FT-IR spectrometer. 1H and 13C NMR spectra were recorded in CDCl3 on a 300 MHz Bruker spectrometer (chemical shifts in δ, ppm) using TMS as an internal standard.

**General procedure**

To a solution of 1,3-cyclohexanedione 1 or 2 (0.892 mmole) in dry toluene or chlorobenzene (7 mL), appropriate alcohol (1.78 mmole) and p-TsOH (0.0284 mmole) were added and the reaction mixture was irradiated in a microwave oven for 7 min with intermittent cooling. After the reaction was complete, the reaction mixture was washed with 10% aqueous NaOH solution followed by washing with water until the aqueous washings are neutral. The organic layer was then dried over anhydrous Na2SO4, concentrated under reduced pressure and purified by column chromatography (Table I). The products were purified by column chromatography (Table I). The products were

<table>
<thead>
<tr>
<th>Compd</th>
<th>1H NMR (CDCl3) (δ, ppm)</th>
<th>13C NMR (CDCl3) (δ, ppm)</th>
<th>Mass (M⁺)</th>
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<tbody>
<tr>
<td>4a</td>
<td>5.38 (s, 1H), 3.70 (s, 3H), 2.33-2.44 (m, 4H), 1.94-2.03 (m, 2H)</td>
<td>200.2, 179.1, 102.7, 56.0, 37.1, 31.3, 21.6</td>
<td>126</td>
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<tr>
<td>4b</td>
<td>5.36 (s, 1H), 3.9 (q, 2H, J=6.8Hz), 2.34-2.45 (m, 4H), 1.97-2.02 (m, 2H), 1.37 (t, 3H, J=7.3Hz)</td>
<td>200.4, 178.5, 102.5, 64.3, 39.8, 36.6, 21.1, 14.1</td>
<td>140</td>
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<td>4c</td>
<td>5.35 (s, 1H), 4.42-4.45 (m, 1H), 2.33-2.39 (m, 4H), 1.95-1.99 (m, 2H), 1.30 (d, 6H, J=6.35Hz)</td>
<td>200.0, 177.0, 102.9, 70.9, 36.6, 29.5, 21.6, 21.1</td>
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<td>4d</td>
<td>5.33 (s, 1H), 4.10 (t, 2H, J=5.4Hz), 3.79 (t, 2H, J=5.7Hz), 2.47 (t, 2H, J=6.26Hz), 2.38 (t, 2H, J=7.3Hz), 1.96-2.05 (m, 2H)</td>
<td>200.1, 178.1, 103.4, 68.4, 41.6, 37.1, 29.2, 21.6</td>
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<td>4e</td>
<td>5.35 (s, 1H), 3.96 (t, 2H, J=4.4Hz) 3.69 (t, 2H, J=4.6Hz), 3.42 (s, 3H), 2.45 (t, 2H, J=6.2Hz), 2.35 (t, 2H, J=6.4Hz), 1.93-2.02 (m, 2H)</td>
<td>199.7, 177.7, 102.8, 70.9, 67.5, 59.0, 36.6, 30.8, 21.1</td>
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<td>4f</td>
<td>5.91-6.04 (m, 1H), 5.30-5.42 (m, 4H), 4.40 (d, 2H, J=5.4Hz), 2.33-2.42 (m, 4H), 1.96-2.03 (m, 2H)</td>
<td>200.5, 178.3, 132.2, 119.8, 108.3, 75.9, 69.9, 37.5, 31.8, 22.0</td>
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<td>4g</td>
<td>5.36 (s, 1H), 3.83 (t, 2H, J=6.4Hz), 2.33-2.45 (m, 4H), 1.96-2.00 (m, 2H), 1.68-1.71 (m, 4H), 0.95 (t, 3H, J=7.3Hz)</td>
<td>200.2, 178.5, 101.8, 68.3, 36.6, 30.5, 29.0, 21.2, 19.1, 17.4</td>
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<td>4h</td>
<td>5.34 (s, 1H), 4.17-4.25 (m, 1H), 3.74-3.93 (m, 4H), 2.31-2.47 (m, 4H), 1.88-2.00 (m, 4H), 1.59-1.70 (m, 2H)</td>
<td>199.5, 177.7, 103.7, 70.9, 37.1, 29.4, 21.0</td>
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<td>4i</td>
<td>5.33 (s, 1H), 3.83-4.12 (m, 1H), 3.43-3.55 (m, 4H), 2.34-2.45 (m, 4H), 1.95-2.00 (m, 2H), 1.52-1.60 (m, 2H), 1.32-1.44 (m, 2H), 0.96-1.01 (m, 2H)</td>
<td>199.9, 177.8, 101.9, 75.5, 69.6, 68.3, 36.5, 29.4, 28.7, 27.6, 25.5, 21.0</td>
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<td>4j</td>
<td>7.25-7.31 (m, 5H), 5.41 (s, 1H), 4.80 (s, 2H), 2.39 (t, 2H, J=6.2Hz), 2.29 (t, 2H, J=6.3Hz), 1.88-1.96 (m, 2H)</td>
<td>200.3, 178.1, 135.0, 128.9, 128.8, 127.3, 103.7, 70.9, 37.1, 29.4, 21.0</td>
<td>202</td>
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</table>
then analysed using FT-IR, $^1$H NMR, $^{13}$C NMR and GC-MS and the values are reported in Table II.

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References