Preparation of 1,5-Diketones by Addition of Cyclohexanone to Chalcones under Solvent-free Phase Transfer Catalyst Condition

Mustafa CEYLAN*, Hayreddin GEZEGEN
Department of Chemistry, Faculty of Arts and Sciences, Gaziosmanpaşa University, 60250 Tokat-TURKEY
e-mail: mceylan@gop.edu.tr, gezegenh@hotmail.com

Received 26.02.2007

Eight different chalcone-1,5-diketone derivatives (5a-h) were prepared by the reaction of chalcone derivatives (3a-h) with cyclohexanone under the solvent-free phase transfer catalyst condition with moderate to high yields. The mechanistic pathway of the reaction can be explained by the Michael-type addition of cyclohexanone to chalcone derivatives (3a-h).

Key Words: Chalcones, 1,5-Diketones, Solvent-free, Phase Transfer Catalyst, Michael Addition

Introduction

Chalcones, either natural or synthetic, are known to exhibit various biological activities, such as antioxidant, antiinflammatory, antimalarial, antileishmanial, anticancer, and antitumor. In addition, chalcones are very important compounds as a Michael acceptor in organic syntheses. The Michael addition reaction is one of the most fundamental C-C bond-forming reactions in the synthesis of 1,5-dicarbonyl compounds. 1,5-Diketones are extremely important synthetic intermediates in their own right and are desirable starting materials for generating many heterocyclic and polyfunctional compounds.

The solid-state Michael additions have performed well recently. For example, Liu et al. have reported the addition of acetophenone to ferrocenylchalcone as Michael acceptor under the solvent-free condition in which excess amount of acetophenone and NaOH as the catalyst are used. However, there are a few examples related to the addition of cyclic ketones to chalcone derivatives. Herein this kind of reaction is described. It is shown that the 1,5-diketones (5a-h) containing chalcone can be prepared in considerable yield by Michael-type addition of cyclohexanone to chalcone derivatives (3a-h) under solvent-free phase transfer catalyst condition.

*Corresponding author
Results and Discussion

The general synthetic strategy employed to prepare the chalcone derivatives (3a-h) was based on Claisen-Schmidt condensation, which was reported previously.\textsuperscript{17} As shown in Scheme 1 and Table 1, a series of 8 chalcone derivatives (3a-h)\textsuperscript{18–27} were prepared by base catalyzed condensation of appropriately substituted acetophenone with benzaldehyde in yields of 69%-97% (Scheme 1). The structures of all the 8 chalcone derivatives (3a-h) synthesized in this research were established on the basis of IR, $^1$H-NMR, and $^{13}$C-NMR spectral data.

$$\begin{align*}
\text{Acetyl phenone} & \quad + \quad \text{Benzenaldehde} \quad \rightarrow \quad \text{Chalcone} \\
1a & \quad + \quad 2 \quad \rightarrow \quad 3a \\
X & \quad H; \quad b & \quad X = o-Cl; \quad c & \quad m-Cl; \quad d & \quad X = p-Cl; \quad e & \quad X = o-Br \\
f & \quad X = o-OCH_3; \quad g & \quad X = m-OCH_3; \quad h & \quad X = p-OCH_3 \\
\text{NaOH, EtOH} & \quad \text{r.t., 3-4 h.} \\
\end{align*}$$

Scheme 1

The synthesized chalcones derivatives (3a-h) were submitted to the Michael addition reaction. A series of 8 chalcone-1,5-diketones (5a-h) was prepared by base catalyzed addition of cyclohexanone to chalcones (3a-h) under solvent-free phase transfer catalyst condition. In this reaction, chalcone 3 (1 mole), cyclohexanone 4 (2 mole), KOH (6% mole) and PTC (benzyldimethylammonium chloride) (6% mole) were used. After the purification of the crude products, the chalcone-1,5-diketones (5a-h) were obtained in yields of 40%-83% (Scheme 2, Table 1). The advantages of this method are neat conditions, less reaction times, usage of catalytic amount of base.

$$\begin{align*}
\text{Chalcone} & \quad + \quad \text{Cyclohexanone} \quad \rightarrow \quad \text{Chalcone-1,5-diketones} \\
3a & \quad + \quad 4 \quad \rightarrow \quad 5a \\
X & \quad H; \quad b & \quad X = o-Cl; \quad c & \quad m-Cl; \quad d & \quad X = p-Cl; \quad e & \quad X = o-Br \\
f & \quad X = o-OCH_3; \quad g & \quad X = m-OCH_3; \quad h & \quad X = p-OCH_3 \\
%6 \text{KOH, %6 PTC} & \quad \text{r.t., 3-4 h.} \\
\end{align*}$$

Scheme 2

It is observed that the Michael-type addition of cyclohexanone to chalcone derivatives (3a-h) can be easily carried out and gives product 5 in satisfactory yield. However, the position of substituents affects the reaction yields. While the high yields were achieved in $m$- and $p$-substituted 5a, c, d, g, h, the low yields were observed to $o$-substituted 5b, e, and f as seen in Table 1. It is assumed that the low yields could be attributed to the steric hindrance of $o$-substituents.

In this series, compounds 5a\textsuperscript{23}, 5d\textsuperscript{28} and 5h\textsuperscript{29} are known in the literature. The structures of other 1,5-diketones (5b, c, e, f and g) were determined on the basis of spectral data ($^1$H-, $^{13}$C-NMR, IR, MS, and elemental analysis). In the $^1$H-NMR spectrum of 5a-h, the protons of PhCOCH$_2$ gave an AB system that is characteristic signals for these compounds. While, part A of the AB system is shown as a doublet of doublet at $\delta = 3.50 - 3.42$ ($J = 15.7-16.7, 3.9-4.5$ Hz) and that of part B as a doublet of doublet at $\delta = 3.23-3.15$ ($J = 15.7-16.7, 9.5-9.6$ Hz). In addition, all spectral data are consistent with the titled compounds.
Table 1. Prepared 1,5-diketones.

<table>
<thead>
<tr>
<th>Reagents</th>
<th>Products</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="3a" /></td>
<td><img src="image" alt="5a" /></td>
<td>83</td>
<td>146-148°</td>
</tr>
<tr>
<td><img src="image" alt="3b" /></td>
<td><img src="image" alt="5b" /></td>
<td>65</td>
<td>120-124</td>
</tr>
<tr>
<td><img src="image" alt="3c" /></td>
<td><img src="image" alt="5c" /></td>
<td>75</td>
<td>107-109</td>
</tr>
<tr>
<td><img src="image" alt="3d" /></td>
<td><img src="image" alt="5d" /></td>
<td>72</td>
<td>113-116</td>
</tr>
<tr>
<td><img src="image" alt="3e" /></td>
<td><img src="image" alt="5e" /></td>
<td>63</td>
<td>120-122</td>
</tr>
<tr>
<td><img src="image" alt="3f" /></td>
<td><img src="image" alt="5f" /></td>
<td>40</td>
<td>108-111</td>
</tr>
<tr>
<td><img src="image" alt="3g" /></td>
<td><img src="image" alt="5g" /></td>
<td>78</td>
<td>89-92</td>
</tr>
<tr>
<td><img src="image" alt="3h" /></td>
<td><img src="image" alt="5h" /></td>
<td>78</td>
<td>128-130</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield.

<sup>b</sup>Lit., 148-149 °C.
Experimental

$^1$H and $^{13}$C-NMR spectra were recorded with a Varian Gemini 200 MHz and an AC Bruker 400 MHz. As internal standards served TMS ($\delta$ 0.00) for $^1$H-NMR and CDCl$_3$ ($\delta$ 77.0) for $^{13}$C-NMR spectroscopy. J values were given in Hz. IR spectra were recorded on a Jasco FT/IR-430 spectrometer. Mass spectra were taken with a Thermo Finnigan Trace GC/Trace DSQ/A1300, (EI Quadrupole, 70 eV) equipped with a SGE-BPX5 MS capillary column (30 m x 0.25 mm i.d., 0.25 µm). Elemental analyses were obtained using a LECO CHNS 932 elemental analyzer. Melting points were measured on an Electrothermal 9100 apparatus.

General procedure for preparation of 1,5-diketones 5a-h

To a mixture of chalcone 1a (10 mmol) and cyclohexanone 4 (20 mmol) solid KOH (0.6 mmol) and PTC (0.6 mmol) were added and stirred for 3 or 4 h at room temperature. Then, the mixture was extracted with CHCl$_3$ (20 mL) and dried over Na$_2$SO$_4$. After the solvent removed in vacua, the product was precipitated in CCl$_4$/hexane (3:1).

2-(3-oxo-1,3-diphenylpropyl) cyclohexanone (5a): Yield: 83%; colorless solid; mp 146-148 °C (CCl$_4$/hexane, 3:1). $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ = 7.93-7.89 (m, 2H), 7.55-7.41 (m, 3H), 7.37-7.13 (m, 5H), 3.78-3.68 (m, 1H), 3.50 A part of AB system (dd, 1H, J = 16.2, 4.1 Hz), 3.23 B part of AB system (dd, 1H, J = 16.2, 9.5 Hz), 2.75-2.68 (m, 1H), 2.53-2.32 (m, 2H), 2.01-1.94 (m, 1H), 1.79-1.51 (m, 4H), 1.49-1.24 (m, 1H). $^{13}$C-NMR (50 MHz, CDCl$_3$): $\delta$ = 215.6, 200.8, 144.1, 139.1, 134.8, 130.4 (2C), 130.4 (2C), 130.3 (2C), 130.2 (2C), 128.6, 57.8, 46.2, 44.3, 43.1, 34.5, 30.5, 26.1. IR (KCl): 3056, 33025, 2939, 2918, 2854, 1705, 1691, 1431, 1369, 1122, 1072, 972, 721, 567 cm$^{-1}$. MS m/z (relative intensity): 306.5 (M$^+$, 1), 287.5 (3), 209.3 (7), 187.2 (98), 105.0 (100), 77.0 (79). Anal. Calcd for C$_{21}$H$_{22}$O$_2$: C 82.32, H 7.24; found: C 81.98, H 7.22.

2-(3-(2-chlorophenyll)-3-oxo-1-phenylpropyl) cyclohexanone (5b): Yield: 65%; colorless solid; mp 121-124 °C (CCl$_4$/hexane, 3:1). $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ = 7.43-7.11 (m, 9H), 3.71-3.59 (m, 1H), 3.46 (dd, 1H, J = 16.6, 4.5 Hz), 3.23 (dd, 1H, J = 16.6, 9.5 Hz), 2.72-2.60 (m, 1H), 2.55-2.12 (m, 8H). $^{13}$C-NMR (50 MHz, CDCl$_3$): $\delta$ = 215.2, 203.8, 143.7, 141.5, 132.7, 133.3, 132.2 (2C), 130.9, 130.5, 130.4 (2C), 128.7, 128.6, 57.7, 50.2, 44.2, 43.0, 34.2, 30.4, 26.0. IR (KCl): 3058, 3026, 2933, 2918, 2854, 1705, 1691, 1431, 1369, 1122, 1072, 972, 721, 567 cm$^{-1}$. MS m/z (relative intensity): 340.7 (M$^+$, 2), 322.5 (6), 293.4 (15), 243.3 (100), 187.3 (81), 139.0 (61), 77.1 (3). Anal. Calcd for C$_{21}$H$_{22}$ClO$_2$: C 74.00, H 6.21; found: C 73.74, H 6.23.

2-(3-(3-chlorophenyll)-3-oxo-1-phenylpropyl) cyclohexanone (5c): Yield: 75%; colorless solid; mp 107-109 °C (CCl$_4$/hexane, 3:1). $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ = 7.87-7.79 (m, 2H), 7.50-7.14 (m, 7H), 3.72-3.62 (m, 1H), 3.50 (dd, 1H, J = 16.1, 3.9 Hz), 3.17 (dd, 1H, J = 16.1, 9.6 Hz), 2.79-2.66 (m, 1H), 2.55-2.39 (m, 2H), 2.02-1.98 (m, 1H), 1.83-1.52 (m, 4H), 1.28-1.22 (m, 1H). $^{13}$C-NMR (50 MHz, CDCl$_3$): $\delta$ = 215.5, 199.4, 143.8, 140.6, 136.7, 134.7, 131.8, 130.5 (2C), 130.3, 130.2 (2C), 128.7, 128.3, 57.7, 46.5, 44.4, 43.2, 34.6, 30.6, 26.3. IR (KCl): 3066, 3030, 2941, 2922, 2850, 1707, 1683, 1413, 1363, 1226, 1215, 1124, 700, 569 cm$^{-1}$. MS m/z (relative intensity): 340.7 (M$^+$, 1), 322.5 (3), 293.3 (10), 243.3 (62), 187.2 (100), 139.1 (40), 77.1 (35). Anal. Calcd for C$_{21}$H$_{22}$ClO$_2$: C 74.00, H 6.21; found: C 73.86, H 6.25.

2-(3-(4-chlorophenyll)-3-oxo-1-phenylpropyl) cyclohexanone (5d): Yield: 72%; colorless solid; mp 113-116 °C (CCl$_4$/hexane, 3:1). $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ = 7.94-7.83 (m, 2H), 7.42-7.29 (m, 2H), 7.27-7.12 (m, 5H), 3.68-3.61 (m, 1H), 3.54 (dd, 1H, J = 15.8, 4.0 Hz), 3.15 (dd, 1H, J = 15.8,
2-(3-(2-bromophenyl)-3-oxo-1-phenylpropyl) cyclohexanone (5e): Yield: 63%; colorless solid; mp 120-122 °C (CCl₄-hexane, 3:1). ¹H-NMR (200 MHz, CDCl₃): δ = 7.53-7.49 (m, 1H), 7.31-7.09 (m, 8H), 3.72-3.60 (m, 1H), 3.46 (dd, 1H, J = 16.7, 4.4 Hz), 3.21 (dd, 1H, J = 16.7, 9.5 Hz), 2.73-2.32 (m, 1H), 2.55-2.32 (m, 2H), 1.98-1.83 (m, 1H), 1.80-1.49 (m, 4H), 1.32-1.22 (m, 1H). ¹³C-NMR (50 MHz, CDCl₃): δ = 215.2, 204.5, 143.6, 143.6, 135.5, 133.3, 130.5 (2C), 130.5 (2C), 130.3 (2C), 128.7, 57.8, 46.4, 44.5, 43.4, 34.7, 30.6, 26.3. IR (KCl): 3057, 3024, 2939, 2918, 2852, 1707, 1685, 1589, 1446, 1398, 1215, 1095, 982, 816, 696, 57 cm⁻¹. MS m/z (relative intensity): 340.6 (M⁺, 1), 322.5 (1), 293.0 (6), 243.3 (60), 187.2 (100), 139.0 (49), 77.1 (2). Anal. Calcld. for C₂₁H₂₁ClO₂ (340.44): C 74.00, H 6.21; found: C 73.68, H 6.26.

2-(3-(2-methoxyphenyl)-3-oxo-1-phenylpropyl) cyclohexanone (5f): Yield: 40%; colorless solid; mp 108-111 °C (CCl₄-hexane, 3:1). ¹H-NMR (200 MHz, CDCl₃): δ = 7.43-7.41 (m, 2H), 7.38-7.12 (m, 5H), 6.95-6.85 (m, 2H), 3.83 (s, 3H), 3.80-3.68 (m, 1H), 3.38-3.34 (m, 2H), 2.72-2.28 (m, 3H), 1.95-1.42 (m, 6H). ¹³C-NMR (50 MHz, CDCl₃): δ = 215.4, 203.23, 160.1, 144.5, 134.9, 132.1, 130.9, 130.6 (2C), 130.2 (2C), 128.3, 122.5, 113.3, 57.9, 57.5, 50.8, 43.8, 42.6, 33.8, 30.3, 25.6. IR (KCl): 3058, 3026, 2952, 2854, 1703, 1666, 1433, 1433, 1284, 1242, 1022, 752, 698, 567 cm⁻¹. MS m/z (relative intensity): 336.6 (M⁺, 0.5), 318.5 (41), 239.3 (42), 187.3 (12), 135.0 (100), 77.0 (9). Anal. Calcld. for C₂₂H₂₃BrO₂ (385.29): C 65.46, H 5.49; found: C 65.03, H 5.93.

2-(3-(3-methoxyphenyl)-3-oxo-1-phenylpropyl) cyclohexanone (5g): Yield: 78%; colorless solid; mp 89-92 °C (CCl₄-hexane, 3:1). ¹H-NMR (200 MHz, CDCl₃): δ = 7.55-7.43 (m, 2H), 7.42-7.01 (m, 7H), 3.81 (s, 3H), 3.78-3.66 (m, 1H), 3.50 (dd, 1H, J = 16.1, 4.0 Hz), 3.20 (dd, 1H, J = 16.1, 9.6 Hz), 2.79-2.55 (m, 1H), 2.52-2.38 (m, 2H), 1.99-1.56 (m, 5H), 1.28-1.22 (m, 1H). ¹³C-NMR (50 MHz, CDCl₃): δ = 215.5, 200.6, 161.7, 143.9, 134.0, 131.4, 130.5 (2C), 130.4 (2C), 128.6, 122.8, 121.5, 114.5, 57.8, 57.4, 44.4, 43.3, 34.5, 30.6, 26.2. IR (KCl): 3058, 3028, 2931, 2912, 2852, 1709, 1678, 1581, 1431, 1259, 1049, 987, 700, 573 cm⁻¹. MS m/z (relative intensity): 336.5 (M⁺, 10), 318.5 (6), 239.4 (100), 187.2 (89), 150.0 (77), 135.1 (71), 77.1 (13). Anal. Calcld. for C₂₂H₂₄O₃ (336.42): C 78.54, H 7.19; found: C 78.15, H 7.48.

2-(3-(4-methoxyphenyl)-3-oxo-1-phenylpropyl) cyclohexanone (5h): Yield: 68%; colorless solid; mp 128-130 °C (CCl₄-hexane, 3:1). ¹H-NMR (400 MHz, CDCl₃): δ = 7.91-7.89 (m, as brd., 2H,J = 8.8 Hz, AA’ part of AA’XX’ system, 7.26-7.23 (m, 2H), 7.18-7.14 (m, 3H), 6.91-6.87 (m, as brd., 2H,J = 8.8 Hz, XX’ part of AA’XX’ system), 3.84 (s, 3H), 3.75-3.69 (dt, J = 9.8, 4.4 Hz, 1H), 3.42 (dd, 1H, J = 15.7, 4.0 Hz), 3.16 (dd, 1H, J = 15.7, 9.5 Hz), 2.75-2.69 (dt, J = 9.8, 5.1 Hz, 1H), 2.55-2.48 (m, 1H), 2.42-2.35 (1H), 2.00-1.93 (m, 1H), 1.80-1.72 (m, 2H), 1.68-1.61 (m, 1H), 1.59-1.50 (m, 1H), 1.31-1.26 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ = 213.9, 197.5, 163.5, 142.3, 130.7 (2C), 133.4, 127.5 (2C), 128.6 (2C), 126.8, 113.8 (2C), 56.1, 55.6, 44.1, 42.5, 41.5, 32.6, 28.7, 24.2. IR (KCl): 3057, 3026, 2933, 2852, 1707, 1672, 1603, 1420, 1255, 1167, 984, 816, 698, 565 cm⁻¹. MS m/z (relative intensity): 336.4 (M⁺, 4), 318.5 (2.5), 239.3 (43), 187.2 (5), 150.1 (100), 135.0 (61), 77.0 (2). Anal. Calcld. for C₂₂H₂₄O₃ (336.42): C 78.54, H 7.19; found: C 78.30, H 7.18.
Conclusion

In conclusion, the Michael addition of cyclohexanone to chalcone derivatives \(3a-h\) under solvent-free phase transfer catalyst condition is a fast, mild, cheap and simple method to prepare chalcone-1,5-diketones (\(5a-h\)). Products are isolated by reasonably high yields with simple extraction into organic solvent.

Acknowledgements

The authors are indebted to the Gaziosmanpaşa University (Grant BAP-2005-31) and the Scientific and Technical Research Council of Turkey (Grant TUBITAK-106T103) for financial support of this work. Furthermore, we thank Dr. Cavit Kazaz and Dr. Hamdullah Kılıc (Atatürk University) for NMR, Mass spectra and elemental analysis.

References

Preparation of 1,5-Diketones by Addition of Cyclohexanone to..., *M. CEYLAN, H. GEZEGEN*


