

## Research Article

# Efficient Knoevenagel Condensation Reactions Catalyzed by Activated Gel Zirconium(IV) Oxide

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The condensation reaction has been carried out very conveniently to obtain the corresponding substituted 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) in excellent yields. The reaction conditions are very mild and applicable to various aldehydes as well as active methylene compounds.

## 1. Introduction

In past decades, several carbon-carbon bond-forming reactions have been discovered, and their applications in organic chemistry have also been well documented in the literature [1–6]. Base-catalyzed transformations are frequently used both on small scale as well as large scale in organic synthesis, for example, in Aldol [7], Knoevenagel [8], Henry [9], and Michael [10] reactions. To catalyze these processes, organic amines, alkali alkoxides, and alkali hydroxides are commonly used as a homogeneous phase with the reagents. Although effective, these reagents are difficult to separate and, in many cases, are not recycled. To alleviate this problem, solid basic catalysts have been developed utilizing either inorganic solid materials, such as base metal oxides and carbonates, or by supporting organic bases, for example, amines, on inorganic or polymeric supports. This approach has attracted intense interest and has been reviewed extensively [11, 12]. Effective heterogeneous base catalysis have been found for Aldol [13–15], Knoevenagel [16–18], Henry [19, 20], and Michael [21] reactions, and, in many, cases the solid base is recyclable [22]. Chalcones are the main precursors for the biosynthesis of flavonoids, which are frequent components of the human diet [23]. Recently, studies on biological evaluation of chalcones revealed some to be anticancer [24, 25], anti-inflammatory [26, 27], antimitotic [28], antitubercular [29], cardiovascular [30], cell differentiation inducing [31], nitric oxide regulation modulatory [32], and antihyperglycemic agents [33]. Of

the many methods available for the synthesis of chalcones, the most widely used is the base-catalyzed Claisen-Schmidt reaction in which the condensation of a ketone with an aldehyde is carried out in the presence of aq. NaOH [34], KOH [35], Ba(OH)<sub>2</sub> [36, 37], hydrotalcites [38], LiHDMS [39], and calcined NaNO<sub>3</sub>/natural phosphates [40]. The acid-catalyzed methodologies include the use of AlCl<sub>3</sub> [40], dry HCl [41], Zn(bpy)(OAc)<sub>2</sub> [42], TiCl<sub>4</sub> [43], CpZrH<sub>2</sub>/NiCl<sub>2</sub> [44], Zeolites [45], RuCl<sub>3</sub> [46], and Selectfluor [47].

## 2. Experimental

Aldehydes were distilled before use. Melting points were determined using a Linkman HF591 heating stage, used in conjunction with a TC92 controller, and reuncorrected. NMR spectra were recorded using a Bruker DRX500 machine at room temperature. <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured using deuteriochloroform as solvent, and chemical shifts were measured relative to residual solvent as an internal standard and are expressed in parts per million (δ). Mass spectra were obtained using a Micro Mass LCT machine in ES or EI mode. Infrared spectra were measured on a Perkin Elmer Paragon 100 FT-IR spectrometer.

*2.1. Typical Procedure for 2,2'-(Phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (3a).* A mixture of benzaldehyde (**1**) (1 mmol) dimedone (**2**) (1 mmol), ZrOCl<sub>2</sub>·THF (0.048 g, 0.15 mmol), and sodium amide (0.005 g,

0.15 mmol) was added at room temperature. The solution was stirred for 20 min at room temperature. After dilution with moist ether (10 mL), the solution was washed with water (3 × 20 mL) to discharge the colour and the ZrOCl<sub>2</sub> and sodium amide. The ethereal solution obtained after extraction was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The crude mixture was passed through a silica gel column chromatography to afford desired product (**3a**).

2.2. 2,2'-((Phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3a**). FT-IR (KBr)  $\nu_{\max}$  3435, 3093, 2982, 1721 (C=O), 1558, 1441, 1366, 1237, 919, 855 and 821 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.10 (s, 6H), 1.24 (s, 6H), 2.38 (m, 8H), 5.54 (s, 1H), 7.29 (ddd, J = 8.5, 2.5 and 1.5 Hz, 1H), 7.32 (m, J = 8.5 Hz, 2H) and 7.36 (dd, J = 8.5 and 1.5 Hz, 2H), 11.89 (s, ex. with D<sub>2</sub>O, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  27.4, 29.64, 31.40, 32.72, 46.43, 47.40, 115.57, 125.83, 126.75, 128.20, 138.2, 196.42 (C=O), 190.13 (C=O); (EI) Found: M<sup>+</sup>, 368.2005, C<sub>23</sub>H<sub>28</sub>O<sub>4</sub> requires M<sup>+</sup>, 368.3202; LRMS m/z (EI): 368 (M<sup>+</sup>, 93%), 293 (M-C<sub>6</sub>H<sub>5</sub>, 45%). Elemental analysis: found (%): C, 75.12; H, 7.86. Calcd. for C<sub>23</sub>H<sub>28</sub>O<sub>4</sub>: C, 74.97; H, 7.66.

2.3. 2,2'-((4-Chlorophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3b**). FT-IR (KBr)  $\nu_{\max}$  3456, 3100, 2978, 1719 (C=O), 1550, 1453, 1355, 1264, 918, 850 and 825 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  0.85 (s, 6H), 1.22 (s, 6H), 2.40 (m, 8H), 5.55 (s, 1H), 7.02 (d, J = 8.03 Hz, 1H), 7.24 (m, J = 8.03 Hz, 2H) and 11.87 (s, ex. with D<sub>2</sub>O, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  27.39, 29.59, 31.40, 32.38, 46.39, 47.01, 115.31, 128.18, 131.55, 136.68, 189.42 (C=O), 190.63 (C=O); (EI) Found: M<sup>+</sup>, 402.3805, C<sub>23</sub>H<sub>27</sub>ClO<sub>4</sub> requires M<sup>+</sup>, 402.1678; LRMS m/z (EI): 402 (M<sup>+</sup>, 86%), 325 (M-C<sub>6</sub>H<sub>5</sub>, 45%). Elemental analysis: found (%): C, 68.88; H, 6.86; Cl, 8.91. Calcd. for C<sub>23</sub>H<sub>27</sub>ClO<sub>4</sub>: C, 68.56; H, 6.75; Cl, 8.80.

2.4. 2,2'-((3-Nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3c**). FT-IR (KBr)  $\nu_{\max}$  3356, 3103, 2965, 1704 (C=O), 1555, 1450, 1345, 1254, 967, 835 and 811 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.10 (s, 6H), 1.41 (s, 6H), 2.38 (m, 8H), 4.66 (s, 1H), 7.41–7.56 (m, 4H) and 12.01 (s, ex. with D<sub>2</sub>O, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  27.32, 29.67, 31.41, 32.90, 47.01, 128.99, 132.93, 144.04, 151.32, 184.47 (C=O), 190.88 (C=O); (EI) Found: M<sup>+</sup>, 413.1805, C<sub>23</sub>H<sub>27</sub>NO<sub>6</sub> requires M<sup>+</sup>, 413.1618; LRMS m/z (EI): 413 (M<sup>+</sup>, 56%), 336 (M-C<sub>6</sub>H<sub>5</sub>, 45%). Elemental analysis: found (%): C, 66.91; H, 6.86; N, 3.41. Calcd. for C<sub>23</sub>H<sub>27</sub>NO<sub>6</sub>: C, 66.81; H, 6.58; N, 3.39.

2.5. 2,2'-((4-Nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3d**). FT-IR (KBr)  $\nu_{\max}$  3397, 3096, 2923, 1705 (C=O), 1551, 1455, 1355, 1250, 927, 825 and 819 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.01 (s, 6H), 1.23 (s, 6H), 1.98 (m, 8H), 4.56 (s, 1H), 7.52–7.98 (m, 4H), and 12.11 (s, ex. with D<sub>2</sub>O, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  25.23, 26.45, 30.31, 31.98, 47.01, 114.79, 120.90, 122.22, 128.99, 132.93, 134.94, 145.23, 148.37, 189.73 (C=O), 198.8

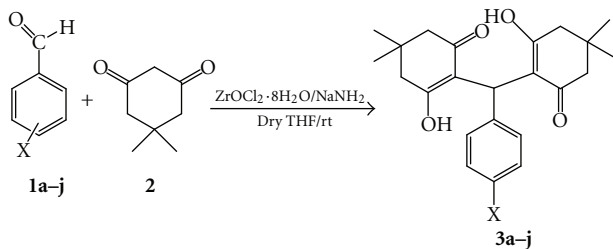
(C=O); (EI) found: M<sup>+</sup>, 413.1805, C<sub>23</sub>H<sub>27</sub>NO<sub>6</sub> requires M<sup>+</sup>, 413.1618; LRMS m/z (EI): 413 (M<sup>+</sup>, 66%), 336 (M-C<sub>6</sub>H<sub>5</sub>, 55%). Elemental analysis: found (%): C, 66.91; H, 6.86; N, 3.41. Calcd. for C<sub>23</sub>H<sub>27</sub>NO<sub>6</sub>: C, 66.81; H, 6.58; N, 3.39.

2.6. 2,2'-((2,4-Dinitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3e**). FT-IR (KBr)  $\nu_{\max}$  3453, 3114, 2925, 1701 (C=O), 1565, 1456, 1332, 1245, 915, 826, and 808 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.05 (s, 6H), 1.31 (s, 6H), 2.24 (m, 8H), 4.56 (s, 1H), 7.65–8.20 (m, 4H), and 12.43 (s, ex. with D<sub>2</sub>O, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  26.30, 28.66, 30.40, 32.91, 45.01, 108.65, 114.65, 124.02, 128.56, 131.53, 132.74, 142.33, 144.37, 187.98 (C=O), 192.76 (C=O); (EI) found: M<sup>+</sup>, 458.1805, C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>8</sub> requires M<sup>+</sup>, 458.1709; LRMS m/z (EI): 458 (M<sup>+</sup>, 75%), 386 (M-C<sub>6</sub>H<sub>5</sub>, 65%). Elemental analysis: found (%): C, 60.34; H, 5.83; N, 6.21. Calcd. for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>8</sub>: C, 60.26; H, 5.72; N, 6.11.

2.7. 2,2'-((4-Fluorophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3f**). FT-IR (KBr)  $\nu_{\max}$  3523, 3115, 2865, 1706 (C=O), 1535, 1433, 1298, 1222, 950, 838 and 816 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.02 (s, 6H), 1.23 (s, 6H), 2.42 (m, 8H), 4.86 (s, 1H), 7.02 (d, J = 8.01 Hz, 2H), 7.24 (d, J = 8.01 Hz, 2H), and 11.98 (s, ex. with D<sub>2</sub>O, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  27.32, 29.67, 31.41, 32.92, 47.01, 56.87, 112.65, 138.93, 141.94, 146.33, 156254 (d, J = 285.5 Hz, CF), 188.27 (C=O), 191.88 (C=O); (EI) Found: M<sup>+</sup>, 386.1911, C<sub>23</sub>H<sub>27</sub>FO<sub>4</sub> requires M<sup>+</sup>, 386.1904; LRMS m/z (EI): 386 (M<sup>+</sup>, 76%), 309 (M-C<sub>6</sub>H<sub>5</sub>, 45%). Elemental analysis: found (%): C, 71.56; H, 7.12. Calcd. for C<sub>23</sub>H<sub>27</sub>FO<sub>4</sub>: C, 71.48; H, 7.04.

2.8. 2,2'-((4-(Trifluoromethyl)phenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3g**). FT-IR (KBr)  $\nu_{\max}$  3556, 3121, 2865, 1698 (C=O), 1550, 1420, 1376, 1244, 927, 865, and 831 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.12 (s, 6H), 1.29 (s, 6H), 2.28 (m, 8H), 4.76 (s, 1H), 7.41–7.56 (m, 4H), and 12.37 (s, ex. with D<sub>2</sub>O, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  27.39, 29.59, 31.40, 32.38, 46.31, 47.01, 115.31, 123.54, 126.11 (q, J = 283.4 Hz, CF<sub>3</sub>), 131.55, 136.68, 148.98, 184.57 (C=O), 190.88 (C=O); (EI) found: M<sup>+</sup>, 436.1905, C<sub>24</sub>H<sub>27</sub>F<sub>3</sub>O<sub>4</sub> requires M<sup>+</sup>, 436.1910; LRMS m/z (EI): 436 (M<sup>+</sup>, 86%), 359 (M-C<sub>6</sub>H<sub>5</sub>, 35%). Elemental analysis: found (%): C, 66.01; H, 6.26. Calcd. for C<sub>24</sub>H<sub>27</sub>F<sub>3</sub>O<sub>4</sub>: C, 66.04; H, 6.24.

2.9. 2,2'-((4-Methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3h**). FT-IR (KBr)  $\nu_{\max}$  3421, 3098, 2876, 1717 (C=O), 1552, 1450, 1362, 1291, 951, 835, and 823 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.15 (s, 6H), 1.51 (s, 6H), 2.54 (m, 8H), 4.78 (s, 1H), 7.41–7.56 (m, 4H), and 11.76 (s, ex. with D<sub>2</sub>O, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  28.43, 30.67, 32.61, 33.93, 49.02, 116.65, 122.91, 122.22, 128.99, 132.93, 134.94, 145.23, 148.37, 181.37 (C=O), 189.78 (C=O); (EI) found: M<sup>+</sup>, 398.2111, C<sub>24</sub>H<sub>30</sub>O<sub>5</sub> requires M<sup>+</sup>, 398.2103; LRMS m/z (EI): 398 (M<sup>+</sup>, 46%), 321 (M-C<sub>6</sub>H<sub>5</sub>, 55%). Elemental analysis: found (%): C, 72.43; H, 7.64. Calcd. for C<sub>24</sub>H<sub>30</sub>O<sub>5</sub>: C, 72.34; H, 7.59.



X=H, 4-Cl, 3-NO<sub>2</sub>, 4-NO<sub>2</sub>, 2,4-(NO<sub>2</sub>)<sub>2</sub>, 4-F, 4-CF<sub>3</sub>, 4-OCH<sub>3</sub>, 4-CH<sub>3</sub>, 4-Br

**SCHEME 1:** The Knoevenagel condensation between substituted benzaldehydes (**1a-j**) and dimedone (**2**) in presence of ZrOCl<sub>2</sub>·8H<sub>2</sub>O/NaNH<sub>2</sub> as catalysis to yield the product (**3a-j**).

**2.10.** 2,2'-(*p*-Tolylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3i**). FT-IR (KBr)  $\nu_{\max}$  3427, 3111, 2901, 1707 (C=O), 1495, 1450, 1345, 1264, 943, 835 and 819 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.04 (s, 6H), 1.21 (s, 6H), 2.21 (m, 8H), 4.51 (s, 1H), 7.32–7.546 (m, 4H), and 11.12 (s, ex. with D<sub>2</sub>O, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  26.31, 26.67, 30.31, 31.9, 46.11, 112.79, 119.90, 121.62, 124.99, 131.73, 134.94, 141.23, 148.37, 182.07 (C=O), 189.08 (C=O); (EI) found: M<sup>+</sup>, 382.4970, C<sub>24</sub>H<sub>30</sub>O<sub>4</sub> requires M<sup>+</sup>, 382.4906; LRMS m/z (EI): 382 (M<sup>+</sup>, 43%), 305 (M–C<sub>6</sub>H<sub>5</sub>, 45%). Elemental analysis: found (%): C, 75.64; H, 8.04. Calcd. for C<sub>24</sub>H<sub>30</sub>O<sub>4</sub>: C, 75.36; H, 7.91.

**2.11.** 2,2'-((4-Bromophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**3j**). FT-IR (KBr)  $\nu_{\max}$  3453, 3121, 2908, 1710 (C=O), 1567, 1444, 1376, 1254, 917, 835, and 821 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.13 (s, 6H), 1.53 (s, 6H), 2.62 (m, 8H), 4.76 (s, 1H), 7.65–7.87 (m, 4H), and 11.75 (s, ex. with D<sub>2</sub>O, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  24.33, 28.76, 31.31, 32.9, 47.04, 115.81, 121.91, 122.02, 128.99, 132.93, 134.94, 145.23, 148.37, 187.79 (C=O), 190.69 (C=O); (EI) found: M<sup>+</sup>, 446.1201, C<sub>23</sub>H<sub>27</sub>BrO<sub>4</sub> requires M<sup>+</sup>, 446.1128; LRMS m/z (EI): 446 (M<sup>+</sup>, 56%), 336 (M–C<sub>6</sub>H<sub>5</sub>, 45%). Elemental analysis: found (%): C, 61.82; H, 5.96; Br, 17.474. Calcd. for C<sub>23</sub>H<sub>27</sub>BrO<sub>4</sub>: C, 61.75; H, 6.08; Br, 17.86.

### 3. Results and Discussion

In our continued interest, in the Knoevenagel condensations and its application in the synthesis of bioactive molecules, we report here a very simple and highly efficient method for the condensation of various aromatic (**1**) with active methylene compound (**2**), for example, dimedone, in the presence of ZrOCl<sub>2</sub>/NaNH<sub>2</sub> as catalysis in THF at room temperature with stirring (Scheme 1).

It was exciting to observe that all the reactions occurred rapidly and were complete in just a few minutes giving excellent yields of the Knoevenagel products (**3**) (Table 1).

To determine the appropriate concentration of the catalyst zirconium oxychloride/sodium amide, we investigated the model reaction at different concentration of zirconium oxychloride/sodium amide such as 5, 10, 15, and 20 mol%.

**TABLE 1:** Reaction time, yields, and melting points of the products (**3a-j**).

Entry	X	Time (min)	Yield (%) <sup>a</sup>	Mp (°C)
1	H	20	88	188-189
2	4-Cl	25	83	144-145
3	3-NO <sub>2</sub>	20	90	151-152
4	4-NO <sub>2</sub>	10	96	162-163
5	2,4-(NO <sub>2</sub> ) <sub>2</sub>	5	97	172-173
6	4-F	15	90	183-184
7	4-CF <sub>3</sub>	10	98	133-134
8	4-OCH <sub>3</sub>	25	90	166-167
9	4-CH <sub>3</sub>	30	91	178-179
10	4-Br	30	91	184-185

Reaction conditions: **1** (1 mmol), **2** (1 mmol), ZrOCl<sub>2</sub>·8H<sub>2</sub>O/NaNH<sub>2</sub> (15 mol %), in THF (5 mL) at 25°C.

<sup>a</sup>Isolated yield.

**TABLE 2:** Effect of concentrations of catalyst.

Entry	ZrOCl <sub>2</sub> ·8H <sub>2</sub> O (mol %)	Yield (%) <sup>a</sup>
1	5	35
2	10	65
3	15	88
4	20	88

Reaction conditions: **1a** (1 mmol), **2** (1 mmol), ZrOCl<sub>2</sub>·8H<sub>2</sub>O/NaNH<sub>2</sub> (15 mol %), in THF (5 mL) at 25°C.

<sup>a</sup>Isolated yields.

**TABLE 3:** Effect of temperature.

Entry	Temperature (°C)	Yield (%) <sup>a</sup>
1	0	35
2	5	45
3	10	48
4	15	55
5	20	60
6	25	88
7	35	75
8	40	68

Reaction condition: **1a** (1 mmol), **2** (1 mmol), ZrOCl<sub>2</sub>·8H<sub>2</sub>O/NaNH<sub>2</sub> (15 mol %), in THF (5 mL).

<sup>a</sup>Isolated yield.

The product was found in 35%, 65%, 88%, and 88% yield, respectively. This indicates that 15 mol% of zirconium oxychloride/sodium amide is sufficient to carry out the reaction smoothly (Table 2).

The temperature of 25°C was chosen as optimum temperature. Any further increase in the temperature failed to enhance the reaction rate substantially, while lowering the temperature below 25°C did show down the reaction rate (Table 3).

In order to evaluate the effect of solvent, various solvents such as dichloromethane, chloroform, ethyl acetate, methanol, water, and tetrahydrofuran were used for the

TABLE 4: Screening of solvents.

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%) <sup>a</sup>
1	Dichloromethane	25		—
2	Chloroform	25		Trace
3	Ethyl acetate	25		Trace
4	Methanol	25		Trace
5	Water	25		Trace
6	Tetrahydrofuran (dry)	25		88

Reaction condition: **1a** (1 mmol), **2** (1 mmol), ZrOCl<sub>2</sub>·8H<sub>2</sub>O/NaNH<sub>2</sub> (15 mol %), in solvent (5 mL) at 25°C.

<sup>a</sup>Isolated yields.

model reaction in the presence of zirconium oxychloride/sodium amide. Surprisingly, use of dichloromethane stopped the reaction at the Knoevenagel condensation step and no further reaction took place (TLC). Reaction in chloroform, ethyl acetate, methanol, and water resulted in moderate yields trace, whereas water brought the reaction to completion efficiently to furnish the product in excellent 88% yield (Table 4, entry 6).

#### 4. Conclusion

In summary, we have developed an expedient and clean protocol for the synthesis of substituted 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) derivatives. This method has the advantages of a wide scope of substrates, operational simplicity, easy work-up procedures, shorter reaction times, and high yields.

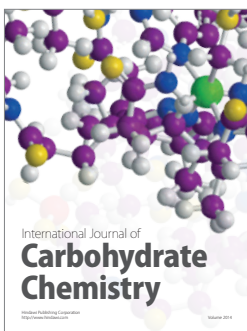
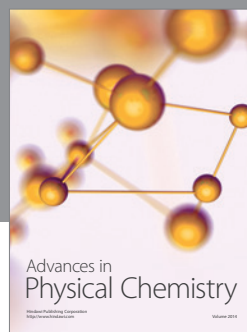
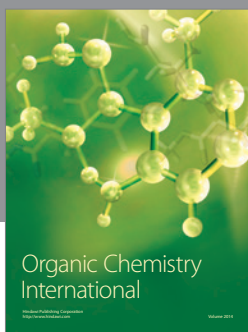
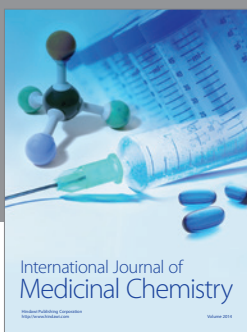
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