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Synthesis of 4-arylidenecyclohexane-1,3-diones from the Baylis–Hillman acetates

Yang Jin Im,[a] Chang Gon Lee,[a] Hyoung Rae Kim[b] and Jae Nyoung Kim[a,*]

[a]*Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea*
[b]*Medicinal Science Division, Korea Research Institute of Chemical Technology, P.O. Box 107, Yusong, Taejon 305-600, Republic of Korea*

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Abstract—Synthesis of 4-arylidenecyclohexane-1,3-dione derivatives was carried out from the Baylis–Hillman acetates. The potential utility of the prepared compounds for the synthesis of cyclohexanedione oxime ether herbicides was examined.

Cyclohexane-1,3-dione derivatives play an important role in organic synthesis due to their usefulness in the preparation of many biologically important compounds.[1] Many herbicides having cyclohexane-1,3-dione backbone such as tralkoxydim, sethoxydim or clethodim are well known.[1] Many methods have been published for the preparation of cyclohexane-1,3-dione moiety.[2] However, synthesis of cyclohexane-1,3-dione derivatives with double bonds at the *exo*-position was not reported in the literature (Scheme 1).[3]

Chamakh and Amri have reported the synthesis of 4-arylidene-2-cyclohexen-1-ones from Baylis–Hillman acetate in ethanol via the tandem three-step process, allylic substitution, deacetylation and cyclization.[4a] Recently, we have published an interesting result from the same reaction, which was carried out in *N*,*N*-dimethylformamide to afford 2-hydroxyacetophenones.[5] As a continuous work, we intended to prepare 2,4-dihydroxyacetophenone derivative **II** in order to prepare multifunctional oxotocopherol-type antioxidant **III** (vide infra, see Scheme 2).[6]

As shown in Scheme 1, the reaction of the Baylis–Hillman acetate **1a**, derived from ethyl acrylate, and 2,4-pentanedione (**2a**) in the presence of potassium carbonate in ethanol at room temperature afforded the corresponding allylic substitution product **3a** and some deacetylated **4a** as a mixture.[4,5] One of the acetyl group was removed by simply elevating the reaction temperature as previously reported.[4a] Whereas, the reaction of **1a** and **2a** in DMF in the presence of K_2CO_3 gave allylic substitution product **3a** without deacetylation in good yield (82%) as expected.[5] However, as shown in Scheme 2, conversion of **3a** into cyclohexane-1,3-dione derivative **I** or resorcinol derivative **II** with various bases was failed. Intractable mixtures of products were observed on TLC. Whereas, the deacetylated compound **4a** can be converted into the corresponding 4-benzylidenecyclohexane-1,3-dione (**5a**) in moderate yield (71%) by using lithium hexamethyldisilizide (LiHMDS) in THF. Thus, we wish to report herein the preparation of 4-arylidenecyclohexane-1,3-dione derivatives for the first time. The results from 2,4-pentanedione (**2a**, entries 1–4) and 3-methyl-2,4-pentanedione (**2b**, entry 5) are summarized in Table 1.

The similar reaction of the Baylis–Hillman acetate **1f**, derived from methyl vinyl ketone, with diethyl malonate (**2c**) gave the similar substitution product **3f**. However, the following decarbethoxylation of **3f** was more difficult than the deacetylation for the above mentioned compounds (for **4a–e**). Thus, in these cases (for **4f** and **4g**) we used the method involving the use of DMAP in refluxing xylene, which was used successfully in our previous paper.[7] The cyclization reaction of **4f** with LiHMDS gave **5a** in a similar yield (entry 6).

As shown in Scheme 1, the reaction mechanism can be postulated as follows. The reaction of the Baylis–Hillman acetates **1** and β-diketone or malonate esters **2**

Keywords: cyclohexane-1,3-dione; herbicides; Baylis–Hillman acetates; antioxidants.

* Corresponding author. Fax: +82-62-5303389; e-mail: kimjn@chonnam.chonnam.ac.kr

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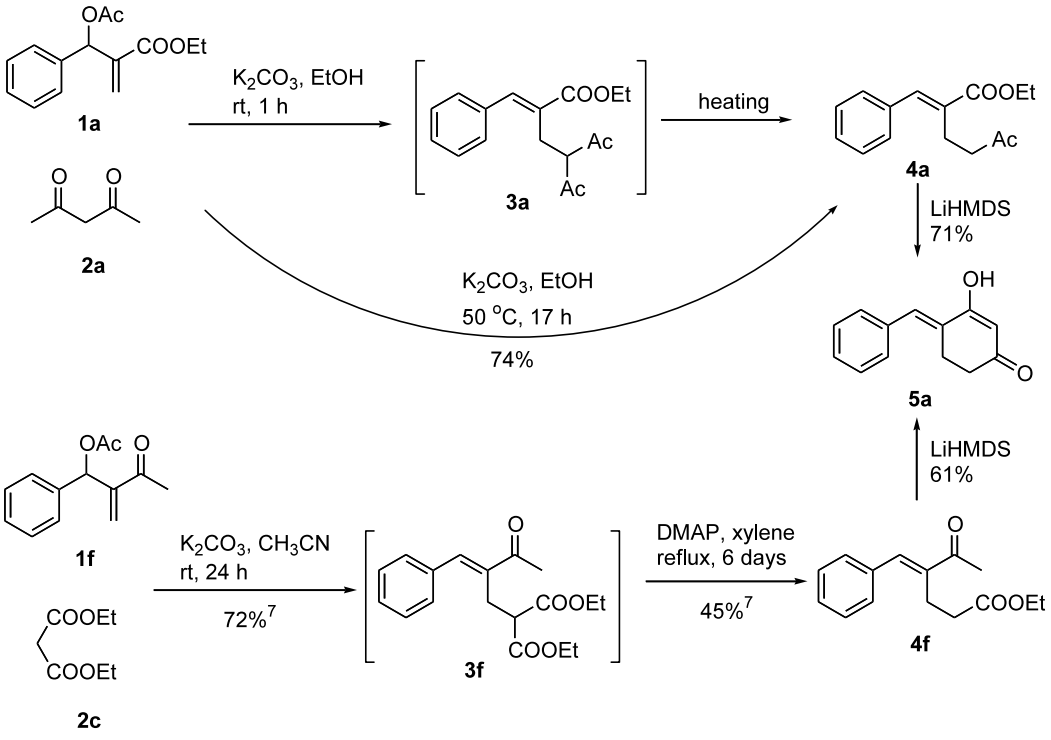
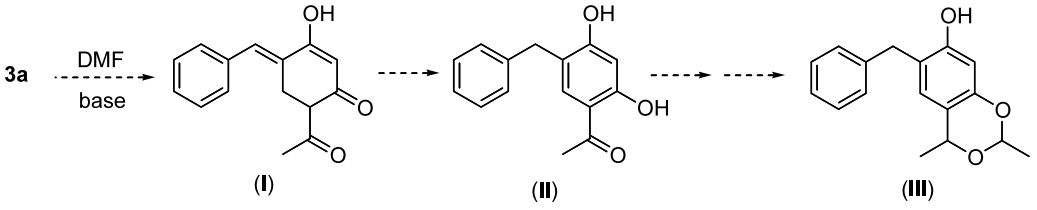


Scheme 1.



Scheme 2.

afforded the corresponding allylic substitution products **3**. From these compounds we could prepare the desired starting materials **4** either (i) by simply heating in ethanol in the presence of K_2CO_3, or (ii) by the DMAP catalyzed thermal decarbethoxylation. Finally, treatment of **4** with LiHMDS (THF, 0°C to rt) afforded the desired 4-arylidenecyclohexane-1,3-diones **5**.

As shown in Scheme 3, 4-benzylidenecyclohexane-1,3-dione (**5a**) could be converted into *O*-acetylated derivative **6** in good yield (95%). The structure of **6** was confirmed by NOE as shown. Migration of the acetyl group to carbon from oxygen was performed by DMAP as previously reported in a similar system to give **7** in 42% yield.[8] Synthesis of the potential oxime ether herbicide **8** was carried out with *O*-ethylhydroxylamine hydrochloride in 92% yield.[9] Further transformation of **7** into other oxime ether herbicides and the study on their herbicidal activity are underway.

Acknowledgements

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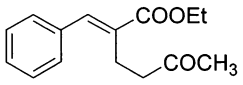
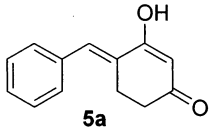
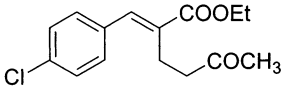
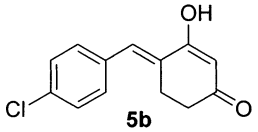
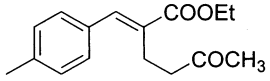
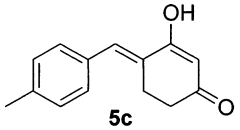
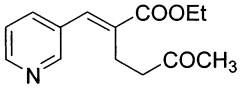
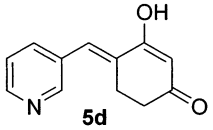
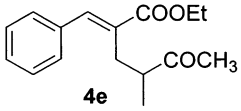
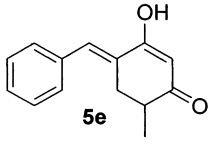
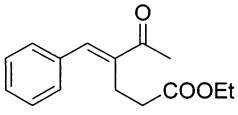
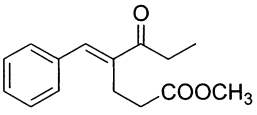
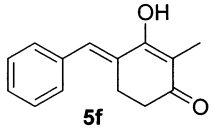
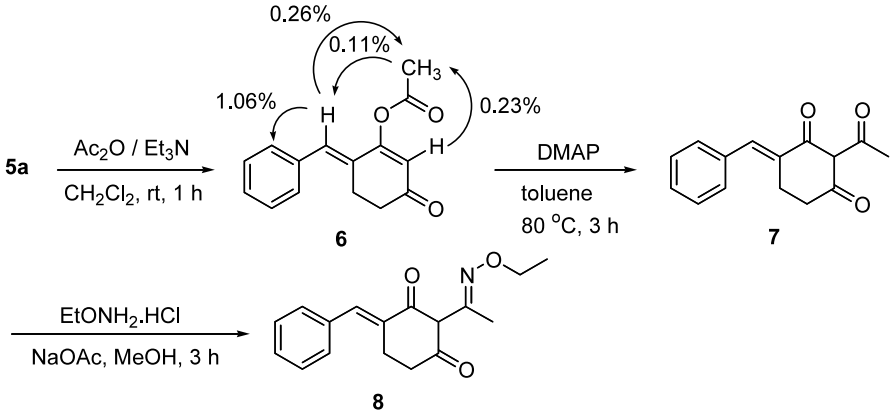
Table 1. Synthesis of 4-arylidenecyclohexane-1,3-diones **5**

entry	substrate **4**[a]	conditions	product **5**	yield (%)
1	 **4a**	LiHMDS / THF 0 °C → rt, 20 h	 **5a**	71
2	 **4b**	LiHMDS / THF 0 °C → rt, 23 h	 **5b**	52
3	 **4c**	LiHMDS / THF 0 °C → rt, 23 h	 **5c**	51
4	 **4d**	LiHMDS / THF 0 °C → rt, 17 h	 **5d**	62
5	 **4e**	LiHMDS / THF 0 °C → rt, 20 h	 **5e**	73
6	 **4f**	LiHMDS / THF 0 °C → rt, 4 h	**5a**	61
7	 **4g**	LiHMDS / THF 0 °C → rt, 20 h	 **5f**	47

[a]Starting materials were prepared according to the reported procedures.[4,5,7]



Scheme 3.

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9. Typical procedure for the synthesis of 4-benzylidenecyclohexane-1,3-dione (**5a**). To a stirred solution of LiHMDS (1.9 mL, 1.9 mmol, 3.1 equiv.) at 0°C was added dropwise a solution of **4a** (149 mg, 0.61 mmol) in dry THF (2 mL) during 5 min. After the addition, the reaction mixture was warmed to room temperature slowly and stirred further for 20 h. The reaction mixture was poured into cold HCl solution and extracted with ethyl acetate. After usual workup and column chromatographic purification (hexane/ethyl acetate, 1:1) we could obtain the desired compound **5a** as a white solid, 87 mg (71%). The compound **5a** existed as an enol form in DMSO-d_6 based on its ^{1}H NMR spectrum. ^{13}C NMR spectra of cyclohexane-1,3-dione derivatives were very complex as reported,[10] and we did not assign them. Mp 163–164°C; IR (KBr) 3448, 2947, 1612, 1219 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.42 (t, $J=6.9$ Hz, 2H), 2.98 (t, $J=6.9$ Hz, 2H), 3.00 (br s, 1H), 5.62 (s, 1H), 7.03–7.42 (m, 6H); Mass (70 eV) m/z (rel. intensity) 102 (20), 115 (48), 129 (55), 157 (17), 199 (100), 200 (M$^+$, 98). Selected spectroscopic data of other compounds are as follows:

5b: mp 176–177°C; IR (KBr) 2968, 2683, 1606, 1529, 1223 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.30 (t, $J=6.3$ Hz, 2H), 2.85 (t, $J=6.3$ Hz, 2H), 5.43 (s, 1H), 7.25 (s, 1H), 7.43 (s, 4H), 11.26 (br s, 1H).

5c: mp 164–165°C; IR (KBr) 3448, 2958, 2721, 2513, 1595, 1223 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.31 (t, $J=6.6$ Hz, 2H), 2.33 (s, 3H), 2.90 (dd, $J=6.6$ and 1.8 Hz, 2H), 5.42 (s, 1H), 7.21–7.34 (m, 5H), 11.15 (br s, 1H); Mass (70 eV) m/z (rel. intensity) 115 (31), 128 (31), 129 (37), 143 (22), 157 (15), 199 (100), 214 (M$^+$, 26).

5d: IR (KBr) 3448, 2519, 1655, 1643 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.36 (t, $J=6.9$ Hz, 2H), 2.90 (dd, $J=6.9$ and 1.5 Hz, 2H), 5.64 (s, 1H), 7.34 (s, 1H), 7.90–7.97 (m, 1H), 8.40–8.47 (m, 1H), 8.75–8.78 (m, 1H), 8.93 (s, 1H).

5e: mp 163–164°C; IR (KBr) 2519, 1597, 1523, 1219 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.99 (d, $J=6.6$ Hz, 3H), 2.32–2.40 (m, 1H), 2.53–2.62 (m, 1H), 2.98–3.06 (m, 1H), 5.37 (s, 1H), 7.29–7.42 (m, 6H); Mass (70 eV) m/z (rel. intensity) 102 (25), 115 (44), 129 (57), 143 (18), 213 (100), 214 (M$^+$, 92).

5f: mp 205–206°; IR (KBr) 2954, 1635, 1558, 1149, 1095 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.71 (s, 3H), 2.41 (t, $J=6.6$ Hz, 2H), 2.85 (td, $J=6.6$ and 1.5 Hz, 2H), 7.25–7.43 (m, 6H); Mass (70 eV) m/z (rel. intensity) 115 (49), 129 (57), 213 (96), 214 (M$^+$, 100).

8: pale yellow oil; IR (KBr) 3448, 1655, 1624, 1539 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, $J=7.0$ Hz, 3H), 2.38 (s, 3H), 2.49 (t, $J=7.0$ Hz, 2H), 2.96 (t, $J=7.0$ Hz, 2H), 4.18 (q, $J=7.0$ Hz, 2H), 7.32–7.41 (m, 5H), 7.60 (s, 1H), 14.42 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.32, 15.04, 24.59, 37.82, 70.17, 109.29, 128.19, 128.44, 129.50, 130.72, 133.64, 135.97, 160.27, 172.18, 195.75.
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