Tetrahedron 64 (2008) 5491–5496

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An efficient synthesis of 3-arylmethyl-7,8-dihydro-6*H*-chromene-2,5-diones from Baylis–Hillman adduct acetates under solvent-free conditions

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ARTICLE INFO

Article history:
Received 23 October 2007
Received in revised form 31 March 2008
Accepted 1 April 2008
Available online 8 April 2008

Keywords:
Baylis–Hillman adducts
α-Pyrone
Solvent free

ABSTRACT

A simple, efficient synthesis of 3-arylmethyl-7,8-dihydro-6*H*-chromene-2,5-dione **4** from Baylis–Hillman adduct acetates derived from aromatic aldehydes and cyclohexane-1,3-diones under solvent-free conditions is described. Interestingly, when Baylis–Hillman adducts derived from aliphatic aldehydes were tested under the similar conditions, the unexpected stereoisomers **5** and **6** were obtained in moderate yields. A plausible mechanism for the formation of **4**–**6** is proposed.

1. Introduction

The α-pyrone moiety is an important structural unit present in many biologically important molecules that show a broad range of biological activities such as anti-HIV,[1] antimicrobial,[2] antifungal,[3] phytotoxic,[3b,4] anti-leukemic,[5] anti-alzheimer,[6] and anti-inflammatory[1b] effects. Moreover a number of α-pyrone derivatives[7] with various biological activities were synthesized. Besides its biological activities, α-pyrone derivatives have been widely used as synthons in organic synthesis.[8] Many methods have been introduced for the synthesis of α-pyrone by traditional approaches or by a process involving transition metal catalyzed reaction. In the past decades, classical methods reported for their preparations are summarized as follows: (1) palladium-catalyzed coupling of 3-halo-(2*Z*)-enoic acids, 3-halo-(2*Z*)-enoates or 2-halobezoic acids with allenylstannanes,[9] alkynes[10] or terminal alkynes[11] and subsequent cyclization; (2) lactonization reaction of various internal alkynes;[12] (3) K_2CO_3-catalyzed Michael addition–lactonization of 1,2-allenic ketones with electron-withdrawing group substituted acetates;[13] (4) nucleophilic addition of active methane compounds to 2-alkynone in the presence of bases.[14] The most disadvantages for some of these methodologies are either low yielding or lacking regioselectivity. As a result, development of simple, efficient and 'green' methodologies for the synthesis of α-pyrone derivatives remains highly desirable.

The Baylis–Hillman reaction is a powerful carbon–carbon bond formation reaction in organic synthesis, and has gained much attention because of its atom economy, selectivity, mild reaction conditions, and provides an unique class of attractive densely functionalized molecules, whose applications in many organic transformation methodologies have been well documented.[15] Owing to its highly synthetic versatility, Baylis–Hillman adducts are also employed as substrates for the preparation of α-pyrone derivatives. Kim and co-workers[16] reported the synthesis of 3,5,6-trisubstituted α-pyrones from Baylis–Hillman adducts and ketones treated with base and trifluoroacetic anhydride. Subsequently, they have also described an attractive synthesis of 3-benzyl-7,8-dihydro-6*H*-chromene derivatives by using Baylis–Hillman adduct acetates as substrates.[17] Despite its elegance, this method has some drawbacks, firstly the reaction mixture should be treated with K_2CO_3 in DMF, after extractive workup, the mixture in *p*-xylene was heated to reflux for 6 h in the presence of DMAP (5.0 equiv) to give α-pyrone derivatives thereafter.

It occurred to us that it would be useful if we would directly convert Baylis–Hillman adduct acetates into the desired 3-substituted-7,8-dihydro-6*H*-chromene-2,5-diones by treatment with an appropriate reagent, if possible under solvent-free conditions. In our ongoing project aimed to synthesize some heterocyclic molecules with Baylis–Hillman adduct acetates, we wish to report a convenient, efficient and 'green' synthesis of 3-substituted-7,8-dihydro-6*H*-chromene-2,5-diones by treatment of Baylis–Hillman adducts and cyclohexane-1,3-diones in the presence of triethylamine under solvent-free conditions.

2. Results and discussions

In our initial study, when we mixed Baylis–Hillman adduct acetate (**1a**) and cyclohexane-1,3-dione (**2a**) in acetone using K_2CO_3

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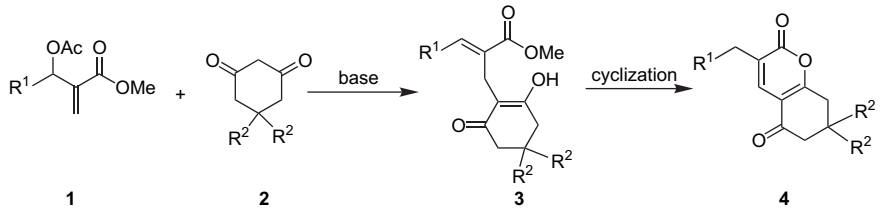
doi:10.1016/j.tet.2008.04.003



Scheme 1.

as base at room temperature for 2 h (Scheme 1), the $S_N2\prime$ type product **3a** was obtained only in 50% yield (Table 1 entry 1), and no desired product **4a** was detected. However, if the similar reaction was performed under refluxing acetone, the yield of product **3a** would be increased to 88% within 25 min (entry 2). When acetonitrile and Et_3N were used as a solvent and a base, respectively, the corresponding product **3d** was obtained in 82% yield (entry 5). Under solvent-free condition, the reaction was completed within 15 min and afforded **3b** with 89% yield (entry 7). In a word, within a short time under refluxing condition, $S_N2\prime$ type products **3** were formed with moderate to good yields. Fortunately, when the reaction time was prolonged to 3 h under refluxing acetone, the desired α-pyrone **4a** was provided in 60% yield. But **3a** could not be converted completely into **4a** even prolonging the reaction time or increasing the amount of K_2CO_3.

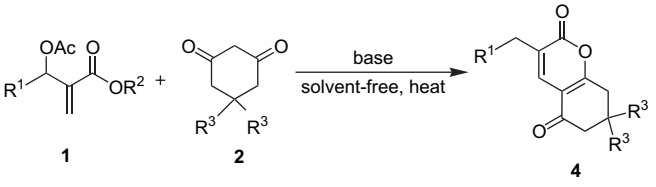
To optimize this reaction, the same reaction was carried out in various solvents including ethanol, acetonitrile, and under solvent-free conditions in the presence of several bases. The results are summarized in Table 1. When DMAP was used as base in refluxing acetone or under solvent-free condition, product **4** was obtained in poor yield (entries 8 and 9). It was found that under refluxing condition, ethanol resulted in poor yield (entry 16), acetonitrile brought higher yield (entries 14 and 15), and the highest yield (80%) was obtained under solvent-free condition (entries 17). The solvent-free condition might be benefit to increasing the reaction efficiency in two ways: (1) driving the reaction toward the desired α-pyrone products by achieving high concentration of reactants; (2) removing the other volatile products like alcohols, and facilitating completion of the reaction.[18]

With the optimal reaction condition in hand, we then successfully transformed a representative class of Baylis–Hillman adduct acetates into 3-substituted-7,8-hydro-6*H*-chromene-2,5-dione derivatives and the full results are summarized in Table 2 (Scheme 2).

Table 2
Synthesis of 3-arylmethyl-7,8-hydro-6*H*-chromene-2,5-dione **4** from Baylis–Hillman adduct acetates under solvent-free conditions[a]

Entry	R^1	R^2	R^3	Time (h)	Yield (%)[b]
1	Phenyl	Me	H	2.5	80 (**4a**)
2	Phenyl	Et	H	6	71 (**4a**)
3	3-Nitrophenyl	Me	H	2	91 (**4b**)
4	2-Chlorophenyl	Me	H	2	88 (**4c**)
5	2-Chloro-6-fluorophenyl	Me	H	3.5	82 (**4d**)
6	4-Fluorophenyl	Me	H	2.5	84 (**4e**)
7	Furan-2-yl	Me	H	5	80 (**4f**)
8	4-Methylthiazol-5-yl	Me	H	2.5	89 (**4g**)
9	Phenyl	Me	Me	2	79 (**4h**)
10	3-Nitrophenyl	Me	Me	2	89 (**4i**)
11	3-Nitrophenyl	Et	Me	4.5	85 (**4i**)
12	2-Chlorophenyl	Me	Me	2	89 (**4j**)
13	2-Chlorophenyl	Et	Me	5	82 (**4j**)
14	2-Chloro-6-fluorophenyl	Me	Me	4	80 (**4k**)
15	4-Fluorophenyl	Me	Me	3	82 (**4l**)
16	Furan-2-yl	Me	Me	5.5	78 (**4m**)
17	4-Methylthiazol-5-yl	Me	Me	2.5	90 (**4n**)
18	3,4-(Methylenedioxy)phenyl	Me	Me	7	63 (**4o**)

[a] All reactions were carried out on a 1 mmol scale of Baylis–Hillman adduct acetates with cyclic β-diketone derivatives (1.2 mmol) in the presence of Et_3N (1.2 mmol) at 90 °C under solvent-free conditions.
[b] Isolated yield based on Baylis–Hillman adduct acetates.

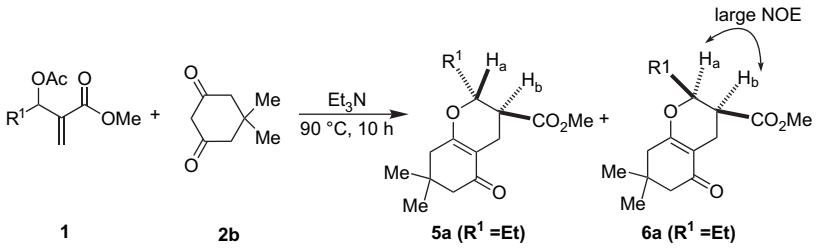


Scheme 2.

Table 1
Synthesis of (*E*)-methyl 2-((2-hydroxy-4,4-disubstituted-6-oxocyclohex-1-enyl)methyl)-3-arylmethylacrylate **3** and 3-benzyl-7,8-hydro-6*H*-chromene-2,5-dione (**4a**) from Baylis–Hillman adduct acetate (**1**) and cyclohexane-1,3-diones (**2**) under various conditions

Entry	R^1	R^2	Conditions	Time	Yield of **3**[a] (%)	Yield of **4**[a] (%)
1	Phenyl	H	K_2CO_3 (0.6 equiv), acetone, rt	120 min	50 (**3a**)	—
2	Phenyl	H	K_2CO_3 (0.6 equiv), acetone, reflux	25 min	88 (**3a**)	—
3	Phenyl	CH_3	K_2CO_3 (0.6 equiv), acetone, reflux	25 min	87 (**3b**)	—
4	Furan-2-yl	H	K_2CO_3 (0.6 equiv), acetone, reflux	25 min	80 (**3c**)	—
5	Furan-2-yl	CH_3	Et_3N (1.2 equiv), acetonitrile, reflux	20 min	82 (**3d**)	—
6	Ethyl	CH_3	Et_3N (1.2 equiv), solvent-free, 60 °C	120 min	78 (**3e**)	—
7	Phenyl	CH_3	Et_3N (1.2 equiv), solvent-free, 90 °C	15 min	89 (**3b**)	—
8	Phenyl	CH_3	DMAP (1.2 equiv), acetone, reflux	2.5 h	60 (**3b**)	11 (**4b**)
9	Phenyl	CH_3	DMAP (1.2 equiv), solvent-free, 90 °C	2 h	32 (**3b**)	48 (**4b**)
10	Phenyl	H	K_2CO_3 (0.6 equiv), acetone, reflux	3 h	20 (**3a**)	60 (**4a**)
11	Phenyl	H	K_2CO_3 (0.6 equiv), acetone, reflux	12 h	21 (**3a**)	61 (**4a**)
12	Phenyl	H	K_2CO_3 (1.2 equiv), acetone, reflux	4 h	23 (**3a**)	62 (**4a**)
13	Phenyl	H	Et_3N (1.2 equiv), acetone, reflux	3.5 h	21 (**3a**)	65 (**4a**)
14	Phenyl	H	K_2CO_3 (0.6 equiv), acetonitrile, reflux	2.5 h	12 (**3a**)	78 (**4a**)
15	Phenyl	H	Et_3N (1.2 equiv), acetonitrile, reflux	2.5 h	14 (**3a**)	73 (**4a**)
16	Phenyl	H	Et_3N (1.2 equiv), ethanol, reflux	10.5 h	34 (**3a**)	43 (**4a**)
17	Phenyl	H	Et_3N (1.2 equiv), solvent-free, 90 °C	2.5 h	10 (**3a**)	80 (**4a**)

[a] Isolated yield.



Scheme 3.

As a result, the desired α-pyrones were obtained in good to excellent yields. The presence of electron-withdrawing or electron-donating groups has obviously influenced the rate and efficiency of the reaction. The substrates with electron-donating groups resulted in lower yield and needed longer reaction time (Table 2, entry 18), while the substrates with electron-withdrawing groups (entries 3, 4, and 10–13) afforded the corresponding products in good yield. On the other hand, ethyl ester in substrates **1** gave lower yields than that of methyl ester probably due to higher steric effect of the former (entries 1 and 2).

Interestingly, when the Baylis–Hillman adducts **1** (R^1=Et) derived from propionaldehyde and methyl acrylate were used as the substrates (Scheme 3), the unexpected products **5a** and **6a** were obtained with the ratio of about 1:2, which were confirmed by their spectroscopic data: ^{1}H, ^{13}C, DEPT, NOE, IR, HRMS, and MS experiments. ^{1}H NMR spectra showed two typical chemical shifts of H_a (4.08 ppm) and H_b (2.94 ppm) in compound **6a**. It was found that large NOE existed between H_a and H_b in compound **6a** (Scheme 3), while in the case of **5a**, no evident NOE was observed. Thus we presumed that compound **6a** should be cis-isomer while compound **5a** should be trans-isomer.[19]

And we also found that when other Baylis–Hillman adducts derived from aliphatic aldehydes and methyl acrylate were used, the similar results were obtained (Table 3).

Table 3
Synthesis of methyl 2-substituted-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-3-carboxylates **5** and **6** from Baylis–Hillman adduct acetates under solvent-free conditions[a]

Entry	R^1	Time (h)	Yield of **5**[a] (%)	Yield of **6**[a] (%)
19	Ethyl	10	12 (**5a**)	25 (**6a**)
20	*n*-Butyl	4.5	10 (**5b**)	21 (**6b**)
21	*i*-Butyl	4.5	11 (**5c**)	23 (**6c**)

[a] Isolated yield.

From the above results, a possible mechanism for the formation of compounds **4**–**6** from Baylis–Hillman adduct acetates and cyclic β-diketone derivatives can be summarized as shown in Scheme 4. The formation of compounds **5a** and **6a** might include two-step successive reaction: $S_N2\prime$ substitution–cyclization and 1,4-addition. Firstly, the reaction of Baylis–Hillman acetates **1** with cyclic β-diketone derivatives **2** in the presence of bases gives $S_N2\prime$ products **3**, followed by 1,4-addition to the corresponding stereoisomers **5a** and **6a**.

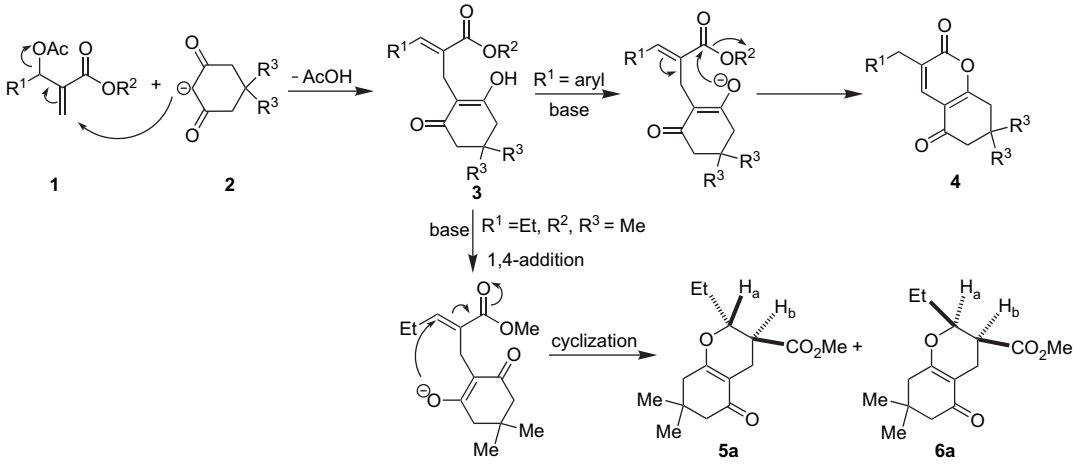
3. Conclusion

We have developed a simple, efficient, and 'green' method for the synthesis of various α-pyrone derivatives from Baylis–Hillman acetates (derived from aromatic aldehydes and acrylate esters) and cyclic β-diketone derivatives under solvent-free conditions. The major advantages of the present process are solvent-free conditions, simple experimental procedure, high yields, short reaction time, and easy workup.

4. Experimental

4.1. General

Starting materials and solvents were purchased from common commercial sources and were used without additional purification. Melting points were determined with a Büchi B-540 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet Aviatar-370 spectrometer using samples as neat liquids or as KBr plates. Mass spectra were measured with Thermo Finnigan LCQ-Advantage spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS, δ=0) as an internal standard at ambient temperature on a Varian-400 MHz spectrometer at 400 and 100 MHz. Elemental analyses were carried out on a Vario EL III instrument. High-resolution mass



Scheme 4.

spectral (HRMS) analyses were measured on an APEX (Bruker) mass III spectrometer using ESI (electrospray ionization) techniques.

4.2. General procedure for the preparation of (*E*)-methyl 2-[(2,6-dioxocyclohexyl)methyl]-3-arylmethylacrylate (3)

To a magnetically stirred solution of Baylis–Hillman adduct acetates (1 mmol) and cyclic β-diketones (1.2 mmol) in acetone (8 mL), K_2CO_3 (1.2 mmol) was added at room temperature. The mixture was then heated under reflux, until TLC monitoring indicated complete consumption of the Baylis–Hillman acetates. The reaction mixture was then filtered and evaporated to furnish the crude product, which was purified by column chromatography (silica gel, 3:2→4:1 v/v hexane/ethyl acetate gradient elution) to give the pure product.

*4.2.1. (E)-Methyl 2-((2-hydroxy-6-oxocyclohex-1-enyl)methyl)-3-phenylacrylate (**3a**)*[17]

White solid; mp 98–99 °C; IR (KBr): ν_{max} 1710, 1556, 1344, 1271, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.74 (br s, 1H), 7.75 (s, 1H), 7.61 (d, J=7.2 Hz, 2H), 7.44–7.34 (m, 3H), 3.86 (s, 3H), 3.51 (s, 2H), 2.40–2.28 (m, 4H), 1.86–1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.5, 172.4, 142.3, 135.4, 129.6, 129.5 (CH×2), 128.6, 128.4, 128.3 (CH×2), 113.0, 52.9, 39.7, 29.6, 20.2, 18.0; MS m/z (%) 286 (M^+, 18), 254 (100). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.26; H, 6.40.

*4.2.2. (E)-Methyl 2-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)methyl)-3-phenylacrylate (**3b**)*

White solid; mp 138–140 °C; IR (KBr): ν_{max} 1709, 1562, 1351, 1313, 1251, 1204 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.68 (br s, 1H), 7.71 (s, 1H), 7.59 (d, J=8.0 Hz, 2H), 7.42–7.33 (m, 3H), 3.84 (s, 3H), 3.54 (s, 2H), 2.24–2.16 (m, 4H), 0.95 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.0, 172.3, 141.9, 135.2, 129.5, 129.2 (CH×2), 128.6, 128.2 (CH×2), 127.9, 111.8, 52.8, 50.5, 43.5, 31.2, 28.1 (CH_3×2), 20.5; MS m/z (%) 315 (M^++1, 30), 314 (M^+, 19), 282 (100). Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.48; H, 7.18.

*4.2.3. (E)-Methyl 3-(furan-2-yl)-2-((2-hydroxy-6-oxocyclohex-1-enyl)methyl)acrylate (**3c**)*

White solid; mp 142–143 °C; IR (KBr): ν_{max} 1717, 1620, 1542, 1378, 1253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.99 (br s, 1H), 7.59 (d, J=1.6 Hz, 1H), 7.50 (s, 1H), 7.16 (d, J=3.2 Hz, 1H), 6.55 (dd, J=3.2, 1.6 Hz, 1H), 3.84 (s, 3H), 3.67 (s, 2H), 2.48–2.40 (m, 2H), 2.36–2.30 (m, 2H), 1.91–1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.5, 174.0, 172.6, 150.7, 144.6, 128.6, 124.5, 117.2, 113.1, 112.4, 52.9, 36.9, 29.7, 21.5, 20.2; MS m/z (%) 276 (M^+, 22), 244 (100). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.18; H, 5.80.

*4.2.4. (E)-Methyl 3-(furan-2-yl)-2-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)methyl)acrylate (**3d**)*

White solid; mp 163–164 °C; IR (KBr): ν_{max} 1716, 1628, 1548, 1370, 1350, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.89 (br s, 1H), 7.59 (d, J=1.6 Hz, 1H), 7.49 (s, 1H), 7.18 (d, J=3.2 Hz, 1H), 6.54 (dd, J=3.2, 1.6 Hz, 1H), 3.84 (s, 3H), 3.68 (s, 2H), 2.35–2.27 (m, 2H), 2.17–2.09 (m, 2H), 1.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9, 172.6, 169.2, 150.6, 144.6, 128.5, 124.6, 117.2, 112.5, 111.9, 52.9, 50.6, 43.3, 31.2, 28.2 (CH_3×2), 21.2; MS m/z (%) 304 (M^+, 18), 272 (100). Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.01; H, 6.58.

*4.2.5. (E)-Methyl 2-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)methyl)pent-2-enoate (**3e**)*

Viscous oil; IR (film): ν_{max} 2959, 2873, 1716, 1672, 1611, 1439, 1375, 1297 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.26 (br s, 1H), 6.87 (t, J=8.0 Hz, 1H), 3.80 (s, 3H), 3.27 (s, 2H), 2.56 (td, J=8.0, 6.0 Hz, 2H), 2.32 (s, 2H), 2.19 (s, 2H), 1.03 (t, J=6.0 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 172.4, 172.1, 149.5, 128.2, 111.9, 52.7, 50.7, 43.2, 31.3, 28.1 (CH_3×2), 32.4, 19.3, 13.1; MS m/z (%) 265 (M^+−1, 100), 264 (40), 233 (30). HRMS (ESI, m/z) calcd for $C_{15}H_{22}O_4$ $(M+H)^+$ 267.1598, found 267.1595.

4.3. General procedure for the preparation of 3-arylmethyl-7,8-dihydro-6*H*-4,5-dione derivatives

A magnetically stirred mixture of Baylis–Hillman acetates (1 mmol), cyclic β-diketones (1.2 mmol), and Et_3N (1.2 mmol) was heated at 80–90 °C, and the reaction was monitored by TLC. The reaction mixture was then cooled to room temperature, treated with brine (10 mL) and dichloromethane (10 mL), and the separated aqueous phase was extracted with dichloromethane (2×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a yellow oil, which was purified by column chromatography (silica gel, 2:1→6:1 v/v hexane/ethyl acetate gradient elution) to give the pure product.

*4.3.1. 3-Benzyl-7,8-dihydro-6H-chromene-2,5-dione (**4a**)*[17]

Viscous oil; IR (film): ν_{max} 1736, 1681, 1635, 1584, 1396 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.33–7.29 (m, 2H), 7.27–7.24 (m, 3H), 3.77 (s, 2H), 2.83 (t, J=6.4 Hz, 2H), 2.52 (t, J=6.4 Hz, 2H), 2.18–2.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 172.1, 161.1, 137.4, 135.4, 129.0 (CH×2), 128.6 (CH×2), 127.0, 126.8, 114.6, 36.5, 36.3, 27.7, 20.3; MS m/z (%) 225 (M^++1, 22), 254 (M^+, 100). HRMS (ESI, m/z) calcd for $C_{16}H_{14}O_3$ $(M+H)^+$ 255.1023, found 255.1026.

*4.3.2. 3-(3-Nitrobenzyl)-7,8-dihydro-6H-chromene-2,5-dione (**4b**)*

White solid; mp 143–144 °C; IR (KBr): ν_{max} 1730, 1715, 1667, 1633, 1579, 1528, 1400, 1352 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J=7.2 Hz, 1H), 8.10 (s, 1H), 7.65 (s, 1H), 7.63 (d, J=7.2 Hz, 1H), 7.51–7.47 (m, 1H), 3.88 (s, 2H), 2.86 (t, J=6.4 Hz, 2H), 2.56 (t, J=6.4 Hz, 2H), 2.18–2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 172.9, 160.7, 148.3, 139.5, 136.4, 135.3, 129.5, 125.3, 123.7, 122.0, 114.5, 36.4, 36.2, 27.7, 20.2; MS m/z (%) 299 (M^+, 48), 282 (100). Anal. Calcd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.24; H, 4.55; 4.77.

*4.3.3. 3-(2-Chlorobenzyl)-7,8-dihydro-6H-chromene-2,5-dione (**4c**)*

Viscous oil; IR (film): ν_{max} 1732, 1682, 1635, 1584, 1396 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.37 (m, 2H), 7.33–7.31 (m, 1H), 7.24–7.22 (m, 2H), 3.90 (s, 2H), 2.84 (t, J=6.4 Hz, 2H), 2.51 (t, J=6.4 Hz, 2H), 2.17–2.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 172.1, 160.9, 135.5, 134.7, 134.2, 131.5, 129.6, 128.5, 127.0, 124.9, 114.5, 36.4, 33.7, 27.6, 20.1; MS m/z (%) 289 (M^++1, 30), 287 (M^+−1, 100). HRMS (ESI, m/z) calcd for $C_{16}H_{13}ClO_3$ $(M+H)^+$ 289.0633, found 289.0632.

*4.3.4. 3-(2-Chloro-6-fluorobenzyl)-7,8-dihydro-6H-chromene-2,5-dione (**4d**)*

White solid; mp 86–87 °C; IR (KBr): ν_{max} 1737, 1682, 1638, 1584, 1396 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28–7.25 (m, 2H), 7.17 (s, 1H), 7.07–7.02 (m, 1H), 3.95 (s, 2H), 2.86 (t, J=6.4 Hz, 2H), 2.52 (t, J=6.4 Hz, 2H), 2.17–2.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 171.9, 161.6 (d, J=247.9 Hz), 160.8, 135.8, 134.2, 129.2 (d, J=9.1 Hz), 125.6, 124.1, 123.0 (d, J=18.2 Hz), 114.6, 114.3 (d, J=22.0 Hz), 36.5, 27.8, 26.7, 20.3; MS m/z (%) 307 (M^++1, 7), 271 (100). Anal. Calcd for $C_{16}H_{12}ClFO_3$: C, 62.65; H, 3.94. Found: C, 62.58; H, 3.87.

*4.3.5. 3-(4-Fluorobenzyl)-7,8-dihydro-6H-chromene-2,5-dione (**4e**)*

White solid; mp 135–136 °C; IR (KBr): ν_{max} 1731, 1677, 1639, 1591, 1507, 1395 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 1H),

7.23–7.20 (m, 2H), 7.01–6.97 (m, 2H), 3.74 (s, 2H), 2.84 (t, *J*=6.4 Hz, 2H), 2.53 (t, *J*=6.4 Hz, 2H), 2.17–2.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 172.3, 161.8 (d, *J*=243.4 Hz), 161.0, 135.4, 133.1, 130.5 (d, *J*=8.3 Hz, CH×2), 126.8, 115.5 (d, *J*=21.2 Hz, CH×2), 114.6, 36.5, 35.6, 27.7, 20.3; MS *m*/*z* (%) 271 (M^+−1, 100), 243 (78). Anal. Calcd for $C_{16}H_{13}FO_3$: C, 70.58; H, 4.81. Found: C, 70.53; H, 4.87.

4.3.6. 3-(Furan-2-ylmethyl)-7,8-dihydro-6H-chromene-2,5-dione (**4f**)

Viscous oil; IR (film): ν_{max} 1736, 1682, 1635, 1584, 1397 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.33 (d, *J*=1.6 Hz, 1H), 6.31 (dd, *J*=3.2, 1.6 Hz, 1H,), 6.17 (d, *J*=3.2 Hz, 1H), 3.79 (s, 2H), 2.84 (t, *J*=6.4 Hz, 2H), 2.53 (t, *J*=6.4 Hz, 2H), 2.17–2.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 172.3, 160.7, 150.5, 141.9, 135.8, 123.9, 114.5, 110.4, 107.5, 36.4, 28.5, 27.7, 20.2; MS *m*/*z* (%) 245 (M^++1, 27), 244 (M^+, 100). HRMS (ESI, *m*/*z*) calcd for $C_{14}H_{12}O_4$ $(M+H)^+$ 245.0816, found 245.0817.

4.3.7. 3-((4-Methylthiazol-5-yl)methyl)-7,8-dihydro-6H-chromene-2,5-dione (**4g**)

White solid; mp 118–119 °C; IR (KBr): ν_{max} 1737, 1713, 1673, 1638, 1585, 1397, 1372; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.53 (s, 1H), 3.92 (s, 2H), 2.86 (t, *J*=6.4 Hz, 2H), 2.54 (t, *J*=6.4 Hz, 2H), 2.43 (s, 3H), 2.17–2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 172.5, 160.7, 150.6, 150.5, 135.5, 126.2, 125.3, 114.6, 36.5, 27.8, 26.8, 20.3, 14.9. MS *m*/*z* (%) 275 (M^++1, 40), 177 (100). Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.09. Found: C, 61.05; H, 4.82; N, 5.01.

4.3.8. 3-Benzyl-7,7-dimethyl-7,8-dihydro-6H-chromene-2,5-dione (**4h**)[17]

White solid; mp 141–143 °C; IR (KBr): ν_{max} 1717, 1675, 1633, 1583, 1400 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.31–7.25 (m, 5H), 3.76 (s, 2H), 2.68 (s, 2H), 2.38 (s, 2H), 1.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 170.8, 161.4, 137.4, 135.1, 129.1 (CH×3), 128.7 (CH×2), 126.8, 113.6, 50.4, 41.4, 36.3, 32.6, 28.2 (CH_3×2); MS *m*/*z* (%) 281 (M^+−1, 42), 265 (100). Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.51; H, 6.38.

4.3.9. 3-(3-Nitrobenzyl)-7,7-dimethyl-7,8-dihydro-6H-chromene-2,5-dione (**4i**)

White solid; mp 150–152 °C; IR (KBr): ν_{max} 1737, 1670, 1633, 1584, 1530, 1398, 1353 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$:) δ 8.12 (s, 1H), 8.11 (d, *J*=6.4 Hz, 1H), 7.63 (d, *J*=6.4 Hz, 1H), 7.62 (s, 1H), 7.52–7.48 (m, 1H), 3.88 (s, 2H), 2.72 (s, 2H), 2.41 (s, 2H), 1.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 171.5, 161.0, 148.2, 139.4, 135.9, 135.3, 129.4, 125.1, 123.7, 121.9, 113.4, 50.2, 41.3, 36.1, 32.6, 28.1 (CH×2); MS *m*/*z* (%) 326 (M^+−1, 50), 294 (100). Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 66.01; H, 5.19; N, 4.20.

4.3.10. 3-(2-Chlorobenzyl)-7,7-dimethyl-7,8-dihydro-6H-chromene-2,5-dione (**4j**)

White solid; mp 107–108 °C; IR (KBr): ν_{max} 1738, 1682, 1589, 1397 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.38 (m, 2H), 7.34–7.32 (m, 1H), 7.25–7.23 (m, 2H), 3.90 (s, 2H), 2.71 (s, 2H), 2.38 (s, 2H), 1.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 170.7, 161.4, 135.3, 134.8, 134.4, 131.7, 129.8, 128.6, 127.3, 124.9, 113.6, 50.4, 41.4, 33.8, 32.6, 28.3 (CH_3×2); MS *m*/*z* (%) 317 (M^++1, 7), 281 (100). Anal. Calcd for $C_{18}H_{17}ClO_3$: C, 68.25; H, 5.41. Found: C, 68.20; H, 5.35.

4.3.11. 3-(2-Chloro-6-fluorobenzyl)-7,7-dimethyl-7,8-dihydro-6H-chromene-2,5-dione (**4k**)

White solid; mp 130–131 °C; IR (KBr): ν_{max} 1740, 1684, 1584, 1390, 1369 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.24 (m, 2H), 7.14 (s, 1H), 7.07–7.04 (m, 1H), 3.96 (s, 2H), 2.72 (s, 2H), 2.37 (s, 2H), 1.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 170.6, 161.6 (d, *J*=248.0 Hz), 161.2, 135.8, 133.9, 129.2 (d, *J*=9.9 Hz), 125.5, 123.9, 122.9 (d, *J*=19.0 Hz), 114.2 (d, *J*=22.8 Hz), 113.5, 50.4, 41.4, 32.6, 28.2 (CH_3×2), 26.6; MS *m*/*z* (%) 335 (M^++1, 4), 299 (100). Anal. Calcd for $C_{18}H_{16}ClFO_3$: C, 64.58; H, 4.82. Found: C, 64.53; H, 4.76.

4.3.12. 3-(4-Fluorobenzyl)-7,7-dimethyl-7,8-dihydro-6H-chromene-2,5-dione (**4l**)

White solid; mp 138–139 °C; IR (KBr): ν_{max} 1713, 1676, 1634, 1582, 1508, 1399; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.24–7.21 (m, 2H), 7.02–6.98 (m, 2H), 3.74 (s, 2H), 2.69 (s, 2H), 2.39 (s, 2H), 1.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 170.9, 161.8 (d, *J*=243.4 Hz), 161.3, 135.2, 133.0, 130.6 (d, *J*=8.0 Hz, CH×2), 126.7, 115.5 (d, *J*=21.2 Hz, CH×2), 113.6, 50.4, 41.4, 35.6, 32.7, 28.3 (CH_3×2); MS *m*/*z* (%) 300 (M^+, 15), 299 (M^+−1, 100). Anal. Calcd for $C_{18}H_{17}FO_3$: C, 71.99; H, 5.71. Found: C, 71.90; H, 5.65.

4.3.13. 3-(Furan-2-ylmethyl)-7,7-dimethyl-7,8-dihydro-6H-chromene-2,5-dione (**4m**)

Viscous oil; IR (film): ν_{max} 1731, 1675, 1643, 1398 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.35 (d, *J*=0.8 Hz, 1H), 6.33 (dd, *J*=3.2, 0.8 Hz, 1H,), 6.19 (d, *J*=3.2 Hz, 1H), 3.81 (s, 2H), 2.71 (s, 2H), 2.40 (s, 2H), 1.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 171.0, 161.2, 150.4, 150.3, 142.0, 135.6, 123.8, 113.6, 110.5, 107.7, 50.4, 41.4, 32.7, 28.6, 28.2 (CH_3×2); MS *m*/*z* (%) 273 (M^++1, 23), 272 (M^+, 100). HRMS (ESI, *m*/*z*) calcd for $C_{16}H_{16}O_4$ $(M+H)^+$ 273.1129, found 273.1126.

4.3.14. 7,7-Dimethyl-3-((4-methylthiazol-5-yl)methyl)-7,8-dihydro-6H-chromene-2,5-dione (**4n**)

White solid; mp 123–124 °C; IR (KBr): ν_{max} 1725, 1679, 1633, 1581, 1397, 1369 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.50 (s, 1H), 3.92 (s, 2H), 2.72 (s, 2H), 2.43 (s, 3H), 2.41 (s, 2H), 1.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 171.1, 160.9, 150.4, 150.3, 135.0, 125.9, 124.8, 113.3, 50.2, 41.2, 32.5, 28.1 (CH_3×2), 26.6, 14.8; MS *m*/*z* (%) 304 (M^++1, 40), 205 (100), 149 (41). Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.36; H, 5.87; N, 4.66.

4.3.15. 3-(Benzo[d][1,3]dioxol-5-ylmethyl)-7,7-dimethyl-7,8-dihydro-6H-chromene-2,5-dione (**4o**)

White solid; mp 109–110 °C; IR (KBr): ν_{max} 1726, 1675, 1636, 1588, 1499, 1487, 1397 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (s, 1H), 6.76–6.69 (m, 3H), 5.94 (s, 2H), 3.68 (s, 2H), 2.69 (s, 2H), 2.38 (s, 2H), 1.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 170.8, 161.4, 147.8, 146.4, 135.0, 130.9, 127.0, 122.2, 113.6, 109.5, 108.4, 100.9, 50.4, 41.4, 36.0, 32.6, 28.3 (CH_3×2); MS *m*/*z* (100%) 327 (M^++1, 21), 326 (M^+, 100). Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 67.79; H, 5.60.

4.3.16. Methyl 2-ethyl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-3-carboxylate (**5a**)

Viscous oil; IR (film): ν_{max} 2957, 2880, 1737, 1631, 1437, 1396, 1224, 1167, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10–4.05 (m, 1H), 3.71 (s, 3H), 2.64–2.56 (m, 2H), 2.49–2.39 (m, 1H), 2.29–2.19 (m, 4H), 1.73–1.58 (m, 2H), 1.07 (s, 6H), 1.03 (t, *J*=8.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 173.3, 168.8, 108.5, 78.3, 52.0, 50.4, 42.0, 41.9, 32.1, 28.2, 27.8, 25.9, 21.0, 9.2; MS *m*/*z* (100%) 265 (M^+−1, 30), 264 (68), 233 (100), 189 (30). HRMS (ESI, *m*/*z*) calcd for $C_{15}H_{22}O_4$ $(M+H)^+$ 267.1598, found 267.1596.

4.3.17. Methyl 2-ethyl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-3-carboxylate (**6a**)

Viscous oil; IR (film): ν_{max} 2957, 2880, 1738, 1628, 1437, 1396, 1217, 1165, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.22–4.18 (m, 1H), 3.69 (s, 3H), 2.97–2.92 (m, 1H), 2.50–2.48 (m, 2H), 2.29–2.22 (m, 4H), 1.69–1.63 (m, 1H), 1.55–1.50 (m, 1H), 1.07 (s, 6H), 1.02 (t, *J*=7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 171.6, 168.6, 108.4, 78.0, 51.7, 50.4, 42.1, 40.2, 32.1, 28.5, 27.7, 23.8, 18.8, 10.2; MS

m/*z* (100%) 265 (M^+-1, 36), 233 (100), 217 (50), 189 (80). HRMS (ESI, *m*/*z*) calcd for $C_{15}H_{22}O_4$ $(M+H)^+$ 267.1598, found 267.1595.

4.3.18. Methyl 2-butyl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-3-carboxylate (**5b**)

Viscous oil; IR (film): ν_{max} 2958, 2881, 1737, 1632, 1437, 1396 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.15–4.11 (m, 1H), 3.71 (s, 3H), 2.63–2.55 (m, 2H), 2.44–2.41 (m, 1H), 2.27–2.23 (m, 4H), 1.62–1.58 (m, 2H), 1.51–1.50 (m, 1H), 1.39–1.32 (m, 3H), 1.07 (s, 6H), 0.91 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 173.6, 168.6, 108.5, 76.8, 52.0, 50.5, 42.4, 42.1, 32.6, 32.1, 28.7, 27.9, 27.1, 22.4, 21.0, 13.9; MS *m*/*z* (100%) 295 (M^++1, 100). HRMS (ESI, *m*/*z*) calcd for $C_{17}H_{26}O_4$ $(M+H)^+$ 295.1911, found 295.1913.

4.3.19. Methyl 2-butyl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-3-carboxylate (**6b**)

Viscous oil; IR (film): ν_{max} 2957, 2881, 1737, 1627, 1436, 1396 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.31–4.28 (m, 1H), 3.69 (s, 3H), 2.94–2.90 (m, 1H), 2.50–2.48 (m, 2H), 2.28–2.23 (m, 4H), 1.63–1.61 (m, 1H), 1.46–1.44 (m, 2H), 1.39–1.32 (m, 3H), 1.07 (s, 6H), 0.91 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 171.8, 168.5, 108.5, 74.7, 51.8, 50.5, 42.2, 40.8, 39.2, 32.3, 28.5, 27.9, 24.8, 23.2, 21.8, 18.6; MS *m*/*z* (100%) 295 (M^++1, 100). HRMS (ESI, *m*/*z*) calcd for $C_{17}H_{26}O_4$ $(M+H)^+$ 295.1911, found 295.1913.

4.3.20. Methyl 2-isobutyl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-3-carboxylate (**5c**)

Viscous oil; IR (film): ν_{max} 2957, 2882, 1736, 1625, 1438, 1397 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.25–4.21 (m, 1H), 3.71 (s, 3H), 2.57–2.53 (m, 2H), 2.48–243 (m, 1H), 2.30–2.20 (m, 4H), 1.91–1.86 (m, 1H), 1.62–1.56 (m, 1H), 1.33–1.25 (m, 1H), 1.05 (d, J=11.5 Hz, 6H), 0.94 (t, J=6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 173.3, 168.6, 108.5, 75.6, 52.0, 50.5, 42.8, 42.1, 32.1, 28.7, 27.9, 24.4, 23.4, 21.6, 20.8; MS *m*/*z* (100%) 295 (M^++1, 100). HRMS (ESI, *m*/*z*) calcd for $C_{17}H_{26}O_4$ $(M+H)^+$ 295.1911, found 295.1909.

4.3.21. Methyl 2-isobutyl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-3-carboxylate (**6c**)

Viscous oil; IR (film): ν_{max} 2958, 2880, 1737, 1627, 1436, 1396 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.45–4.41 (m, 1H), 3.70 (s, 3H), 2.91–2.87 (m, 1H), 2.52–2.44 (m, 2H), 2.27–2.23 (m, 4H), 1.82–1.80 (m, 1H), 1.60–1.54 (m, 1H), 1.22–1.17 (m, 1H), 1.06 (s, 6H), 0.94 (t, J=5.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 171.8, 168.5, 108.5, 74.7, 51.8, 50.5, 42.2, 40.8, 39.2, 32.3, 28.5, 27.9, 24.8, 23.2, 21.8, 18.6; MS *m*/*z* (100%) 295 (M^++1, 100). HRMS (ESI, *m*/*z*) calcd for $C_{17}H_{26}O_4$ $(M+H)^+$ 295.1911, found 295.1910.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 20476098 and No. 20676123) for financial support.

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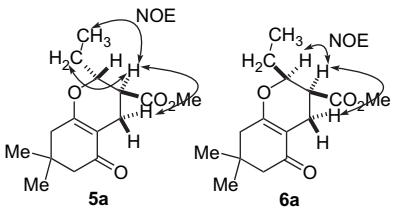

Representative NOE effects observed during the NMR investigation of the two isomeric products **5a** and **6a**.