

## Arylation of the Baylis-Hillman Adducts

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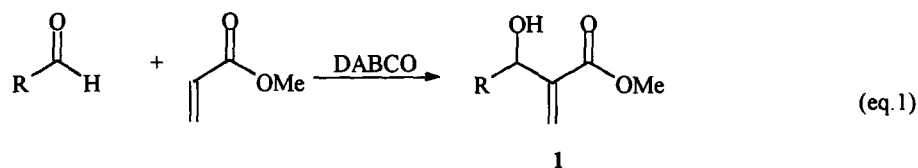
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**Abstract:** Palladium catalyzed arylation of the Baylis-Hillman adducts, methyl 3-hydroxy-2-methylenealkanoates, has been described. © 1998 Elsevier Science Ltd. All rights reserved.

In recent years there has been much focus and emphasis on the Heck reaction for the construction of carbon-carbon bond at the vinylic position involving palladium catalyzed coupling of haloarenes and haloalkenes with alkenes.<sup>1-3</sup> A variety of substituted and functionalized alkenes have been successfully arylated or alkenylated *via* the Heck reaction to produce synthetically useful molecules. The Heck reaction *i.e.* arylation of allylic alcohols has been well studied to provide arylated saturated carbonyl compounds or arylated allyl alcohols by changing the reaction conditions.<sup>4-6</sup> Also the Heck reaction of  $\alpha$ ,  $\beta$ -unsaturated esters has been well documented to produce arylated  $\alpha$ ,  $\beta$ -unsaturated esters.<sup>7,8</sup> However the Heck reaction *i.e.* arylation of alkenes possessing both allylic alcohol and  $\alpha$ ,  $\beta$ -unsaturated ester moieties in which carbon-carbon double bond is an integral part of both allyl alcohol and  $\alpha$ ,  $\beta$ -unsaturated ester moieties, has not been studied. Such a study is highly desirable and will be useful as this will further expand the scope of the Heck reaction in synthetic organic chemistry. The Baylis-Hillman reaction provides an easy access for such interesting class of alkenes having both allyl alcohol and  $\alpha$ ,  $\beta$ -unsaturated ester moieties.<sup>9-18</sup> As a part of our research program on the Baylis-Hillman reaction,<sup>15-18</sup> we herein report the Heck reaction *i.e.* arylation of the Baylis-Hillman adducts, methyl 3-hydroxy-2-methylenealkanoates (obtained *via* the DABCO catalyzed coupling of methyl acrylate with aldehydes (Equation 1) ) under the influence of palladium acetate, thus providing a very simple and convenient methodology for the synthesis of methyl 2-(arylmethyl)-3-oxoalkanoates, an important and useful class of synthons.

We have first examined the reaction between methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**1a**) and bromobenzene under the catalytic influence of palladium acetate. The best results were obtained when a

Table 1: Arylation of the Baylis-Hillman Adducts<sup>a</sup>

Substrate	R	Ar	Time (h)	Product	Yield <sup>b</sup> (%)
1a	Ph	Ph	10	2 <sup>c</sup>	81
1a	Ph	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	10	3	76
1a	Ph	α-Naphthyl	7	4	83
1b	4-i-C <sub>3</sub> H <sub>7</sub> C <sub>6</sub> H <sub>4</sub>	Ph	10	5 <sup>c</sup>	75
1b	4-i-C <sub>3</sub> H <sub>7</sub> C <sub>6</sub> H <sub>4</sub>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	10	6 <sup>c</sup>	76
1b	4-i-C <sub>3</sub> H <sub>7</sub> C <sub>6</sub> H <sub>4</sub>	α-Naphthyl	8	7 <sup>c</sup>	82
1c	2-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Ph	18	8 <sup>c</sup>	67
1d	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Ph	12	9 <sup>c</sup>	80
1e	4-ClC <sub>6</sub> H <sub>4</sub>	Ph	8	10 <sup>c</sup>	60
1f	i-C <sub>3</sub> H <sub>7</sub>	Ph	10	11 <sup>d</sup>	61
1f	i-C <sub>3</sub> H <sub>7</sub>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	7	12 <sup>d</sup>	76
1g	n-C <sub>5</sub> H <sub>11</sub>	Ph	9	13 <sup>d</sup>	64
1g	n-C <sub>5</sub> H <sub>11</sub>	α-Naphthyl	7	14 <sup>d</sup>	79

a) All reactions were carried out in 1mM scale in THF at reflux temperature for 7–18 h.

b) Yields of the products obtained after column chromatography ( using 5% EtOAc in hexane. silica gel ). The molecules 2, 3, 5–14 were obtained as colorless liquids and the molecule 4 was obtained as a colorless solid.

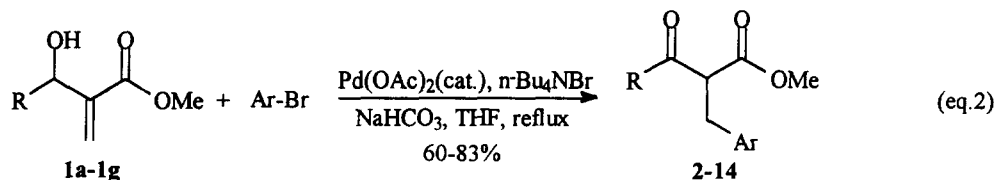
c) The molecules 2, 5–10 contain ≈5% impurity and were further purified by preparative HPLC (Shim-pack PREP-ODS column, methanol). All these compounds 2–10 gave satisfactory IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, mass spectral and elemental analysis.

d) <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra show that these molecules contain ≈5–8% impurity.

solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (1a) (1 mM) and bromobenzene (2 mM) in THF (3 mL) was refluxed for 10h in the presence of Pd(OAc)<sub>2</sub> (2 mol%), NaHCO<sub>3</sub> (2.5 mM) and n-Bu<sub>4</sub>NBr (1 mM), thus providing methyl 2-benzyl-3-oxo-3-phenylpropanoate (2) after column chromatography (5%

EtOAc in hexane, silica gel) in 81% yield. This molecule is contaminated with  $\approx 5\%$  impurity. However purification by preparative HPLC (Shim-pack PREP-ODS column using methanol as solvent) provided the pure methyl 2-benzyl-3-oxo-3-phenylpropanoate (**2**).

Encouraged by this result we have subjected a variety of the Baylis-Hillman adducts to arylation using various aryl bromides which produced the desired methyl 2-(arylmethyl)-3-oxoalkanoates (Table 1, Equation 2).



In conclusion, the arylation of the Baylis-Hillman adducts, methyl 3-hydroxy-2-methylenealkanoates, provides an easy access to methyl 2-(arylmethyl)-3-oxoalkanoates, an important class of organic synthons, thus highlighting the importance and applications of both the Heck and Baylis-Hillman reactions.

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## EXPERIMENTAL

The melting points were recorded on Superfit melting point apparatus and are uncorrected. IR spectra were recorded on Jasco-FT-IR model 5300 spectrometer using samples as neat liquid or solution in  $\text{CH}_2\text{Cl}_2$ .  $^1\text{H}$  NMR (200 MHz) and  $^{13}\text{C}$  NMR (50 MHz) spectra were recorded on Bruker-AC-200 spectrometer using chloroform- $d$  as solvent and tetramethylsilane (TMS,  $\delta = 0$  ppm) as internal standard. Mass spectra were recorded on micromass VG 7070H instrument. Elemental analyses were performed on Perkin-Elmer 240C-CHN analyser. HPLC analyses were performed on Shimadzu LC-10AD instrument equipped with SPD-10A UV-VIS detector using Shim-pack PREP-ODS column and methanol as solvent.

### General Procedure for the preparation of methyl 2-arylmethyl-3-oxo-alkanoates (**2-14**):

A solution of methyl 3-hydroxy-2-methylenealkanoate (**1**) (1 mM) and aryl bromide (2 mM) in THF (3 mL) was refluxed for 7-18 hours (as mentioned in the Table 1) in the presence of  $\text{Pd}(\text{OAc})_2$  (2 mol%, 0.02 mM, 4.5 mg),  $\text{NaHCO}_3$  (2.5 mM, 210 mg) and  $n\text{-Bu}_4\text{NBr}$  (1 mM, 322 mg). Then the reaction mixture was cooled, diluted with water and extracted with ether. The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and solvent

was evaporated. The crude product obtained was purified by column chromatography (5% EtOAc in hexane, silica gel). The molecules 2, 5-11 contain  $\approx 5\%$  impurities and were further purified by preparative HPLC (Shim-pack PREP-ODS column) using methanol as solvent. The compounds 12-14 contain  $\approx 5\text{--}8\%$  impurities as indicated by  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectral analysis. Attempts to further purification of the molecules 12-14 by preparative HPLC were not successful.

**Methyl 2-benzyl-3-oxo-3-phenylpropanoate (2):**

Yield: 81%; IR (neat)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1685, 1741;  $^1\text{H}$  NMR:  $\delta$  3.33 (d, 2H,  $J = 7.0$  Hz), 3.63 (s, 3H), 4.64 (t, 1H,  $J = 7.0$  Hz), 7.11-7.62 (m, 8H), 7.89-8.05 (m, 2H);  $^{13}\text{C}$  NMR:  $\delta$  34.83, 52.40, 55.82, 126.61, 128.50, 128.59, 128.68, 128.82, 133.51, 136.13, 138.32, 169.66, 194.39; MS ( $m/z$ ): 268 ( $M^+$ ); Analysis calculated for  $\text{C}_{17}\text{H}_{16}\text{O}_3$ : C, 76.09; H, 6.01; found: C, 76.15; H, 6.03.

**Methyl 2-(4-methylphenyl)methyl-3-oxo-3-phenylpropanoate (3):**

Yield: 76%; IR (neat)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1687, 1741;  $^1\text{H}$  NMR:  $\delta$  2.27 (s, 3H), 3.28 (d, 2H,  $J = 7.0$  Hz), 3.62 (s, 3H), 4.61 (t, 1H,  $J = 7.0$  Hz), 7.01-7.63 (m, 7H), 7.94 (d, 2H,  $J = 7.2$  Hz);  $^{13}\text{C}$  NMR:  $\delta$  20.97, 34.46, 52.43, 56.04, 128.72, 129.23, 133.52, 135.28, 136.15, 169.77, 194.47; MS ( $m/z$ ): 282 ( $M^+$ ); Analysis calculated for  $\text{C}_{18}\text{H}_{18}\text{O}_3$ : C, 76.57; H, 6.42; found: C, 76.36; H, 6.45.

**Methyl 2-(naphth-1-ylmethyl)-3-oxo-3-phenylpropanoate (4):**

Yield: 83%; M. P: 68-70°C; IR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1676, 1738;  $^1\text{H}$  NMR:  $\delta$  3.63 (s, 3H), 3.82 (d, 2H,  $J = 6.8$  Hz), 4.83 (t, 1H,  $J = 6.8$  Hz), 7.17- 8.19 (m, 12H);  $^{13}\text{C}$  NMR:  $\delta$  31.81, 52.50, 54.59, 123.16, 125.41, 125.59, 126.27, 127.25, 127.53, 128.53, 128.61, 129.00, 131.63, 133.47, 133.93, 134.14, 136.26, 169.88, 194.54; MS ( $m/z$ ): 318 ( $M^+$ ); Analysis calculated for  $\text{C}_{21}\text{H}_{18}\text{O}_3$ : C, 79.22; H, 5.69; found: C, 79.26; H, 5.67.

**Methyl 2-benzyl-3-(4-(1-methylethyl)phenyl)-3-oxopropanoate (5):**

Yield: 75%; IR (neat)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1682, 1741;  $^1\text{H}$  NMR:  $\delta$  1.24 (d, 6H,  $J = 6.8$  Hz), 2.92 (sept, 1H,  $J = 6.8$  Hz), 3.32 (m, 2H), 3.63 (s, 3H), 4.63 (t, 1H,  $J = 7.2$  Hz), 7.12- 7.35 (m, 7H), 7.89 (d, 2H,  $J = 8.4$  Hz);  $^{13}\text{C}$  NMR:  $\delta$  23.61, 34.31, 34.95, 52.50, 55.93, 126.66, 126.91, 128.58, 128.94, 129.02, 134.07, 138.62, 155.26, 169.91, 193.93; MS ( $m/z$ ): 310 ( $M^+$ ); Analysis calculated for  $\text{C}_{20}\text{H}_{22}\text{O}_3$ : C, 77.39; H, 7.14; found: C, 77.45; H, 7.18.

**Methyl 2-(4-methylphenyl)methyl-3-(4-(1-methylethyl)phenyl)-3-oxopropanoate (6):**

Yield: 76%; IR (neat)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1682, 1741;  $^1\text{H}$  NMR:  $\delta$  1.25 (d, 6H,  $J = 6.8$  Hz), 2.28 (s, 3H), 2.93 (sept, 1H,  $J = 6.8$  Hz), 3.28 (m, 2H), 3.64 (s, 3H), 4.60 (t, 1H,  $J = 7.0$  Hz), 7.01-7.39 (m, 6H), 7.89 (d, 2H,  $J = 8$  Hz);  $^{13}\text{C}$  NMR:  $\delta$  21.03, 23.62, 34.31, 34.54, 52.48, 56.09, 126.90, 128.79, 129.03, 129.27, 134.08, 135.53, 136.16, 155.23, 169.98, 194.00; MS ( $m/z$ ): 324 ( $M^+$ ); Analysis calculated for  $\text{C}_{21}\text{H}_{24}\text{O}_3$ : C, 77.75; H, 7.45; found: C,

77.65; H, 7.42.

**Methyl 3-(4-(1-methylethyl)phenyl)-2-(naphth-1-ylmethyl)-3-oxopropanoate (7):**

Yield: 82%; IR (neat)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1682, 1739;  $^1\text{H}$  NMR:  $\delta$  1.22 (d, 6H,  $J=7.0$  Hz), 2.91 (m, 1H), 3.63 (s, 3H), 3.80 (d, 2H,  $J=7.2$  Hz), 4.81 (t, 1H,  $J=7.2$  Hz), 7.15–8.08 (m, 11H);  $^{13}\text{C}$  NMR:  $\delta$  23.57, 31.90, 34.28, 52.51, 54.71, 123.33, 125.51, 125.63, 126.29, 126.82, 127.33, 127.55, 128.95, 129.05, 131.81, 134.08, 134.30, 134.44, 155.18, 170.10, 194.09; MS ( $m/z$ ): 360 ( $M^+$ ); Analysis calculated for  $\text{C}_{24}\text{H}_{24}\text{O}_3$ : C, 79.97; H, 6.71; found: C, 80.21; H, 6.68.

**Methyl 2-benzyl-3-(2-methoxyphenyl)-3-oxopropanoate (8):**

Yield: 67%; IR (neat)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1672, 1739;  $^1\text{H}$  NMR:  $\delta$  3.27 (m, 2H), 3.64 (s, 3H), 3.85 (s, 3H), 4.67 (t, 1H,  $J=6.8$  Hz), 6.85–7.70 (m, 9H);  $^{13}\text{C}$  NMR:  $\delta$  34.61, 52.02, 55.24, 60.10, 111.49, 120.86, 126.32, 126.90, 128.28, 128.88, 131.04, 134.17, 138.99, 158.31, 170.41, 196.03; MS ( $m/z$ ): 298 ( $M^+$ ); Analysis calculated for  $\text{C}_{18}\text{H}_{18}\text{O}_4$ : C, 72.47; H, 6.08; found: C, 72.24; H, 6.10.

**Methyl 2-benzyl-3-(4-methylphenyl)-3-oxopropanoate (9):**

Yield: 80%; IR (neat)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1682, 1741;  $^1\text{H}$  NMR:  $\delta$  2.39 (s, 3H), 3.31 (m, 2H), 3.62 (s, 3H), 4.62 (t, 1H,  $J=7.2$  Hz), 7.15–7.30 (m, 7H), 7.85 (d, 2H,  $J=8$  Hz);  $^{13}\text{C}$  NMR:  $\delta$  21.60, 34.89, 52.41, 55.80, 126.61, 128.52, 128.82, 128.85, 129.43, 133.72, 138.51, 144.52, 169.83, 193.95; MS ( $m/z$ ): 282 ( $M^+$ ); Analysis calculated for  $\text{C}_{18}\text{H}_{18}\text{O}_3$ : C, 76.57; H, 6.42; found: C, 76.65; H, 6.39.

**Methyl 2-benzyl-3-(4-chlorophenyl)-3-oxopropanoate (10):**

Yield: 60%; IR (neat)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1687, 1741;  $^1\text{H}$  NMR:  $\delta$  3.32 (d, 2H,  $J=7.2$  Hz), 3.64 (s, 3H), 4.58 (t, 1H,  $J=7.6$  Hz), 7.16–7.47 (m, 7H), 7.86 (m, 2H);  $^{13}\text{C}$  NMR:  $\delta$  34.80, 52.53, 55.88, 126.73, 128.57, 128.83, 129.02, 130.02, 134.56, 138.15, 140.07, 169.41, 193.24; MS ( $m/z$ ): 302 ( $M^+$ ); Analysis calculated for  $\text{C}_{17}\text{H}_{15}\text{O}_3\text{Cl}$ : C, 67.44; H, 4.99; found: C, 67.31; H, 5.01.

**Methyl 2-benzyl-4-methyl-3-oxopentanoate (11):**

Yield: 61%; IR (neat)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1714, 1743;  $^1\text{H}$  NMR:  $\delta$  0.86 (d, 3H,  $J=6.8$  Hz), 1.04 (d, 3H,  $J=6.8$  Hz), 2.60 (m, 1H), 3.15 (d, 2H,  $J=7.4$  Hz), 3.68 (s, 3H), 3.95 (t, 1H,  $J=7.4$  Hz), 7.05–7.36 (m, 5H);  $^{13}\text{C}$  NMR:  $\delta$  17.67, 17.76, 34.51, 41.33, 52.34, 58.54, 126.67, 128.55, 128.92, 138.42, 169.54, 208.29.

**Methyl 2-(4-methylphenyl)methyl-4-methyl-3-oxopentanoate (12):**

Yield: 76%; IR (neat)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1714, 1745;  $^1\text{H}$  NMR:  $\delta$  0.89 (d, 3H,  $J=6.8$  Hz), 1.05 (d, 3H,  $J=6.8$  Hz), 2.29 (s, 3H), 2.60 (m, 1H), 3.11 (d, 2H,  $J=7.2$  Hz), 3.68 (s, 3H), 3.93 (t, 1H,  $J=7.2$  Hz), 7.05 (m, 4H);  $^{13}\text{C}$  NMR:  $\delta$  17.65, 17.73, 20.94, 34.06, 41.25, 52.25, 58.57, 128.70, 129.16, 135.21, 136.09, 169.55, 208.37.

**Methyl 2-benzyl-3-oxooctanoate (13):**

Yield: 64%; IR (neat)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1716, 1743;  $^1\text{H}$  NMR:  $\delta$  0.83 (t, 3H,  $J=6.8$  Hz), 1.05–1.62 (m, 6H), 2.18–2.61 (m, 2H), 3.15 (d, 2H,  $J=7.6$  Hz), 3.68 (s, 3H), 3.80 (t, 1H,  $J=7.6$  Hz), 7.05–7.36 (m, 5H);  $^{13}\text{C}$  NMR:  $\delta$  13.74, 22.26, 22.89, 30.99, 34.10, 42.75, 52.21, 60.30, 126.57, 128.48, 128.72, 138.22, 169.51, 204.54.

**Methyl 2-(naphth-1-ylmethyl)-3-oxooctanoate (14):**

Yield: 79%; IR (neat)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1716, 1745;  $^1\text{H}$  NMR:  $\delta$  0.82 (t, 3H,  $J=6.6$  Hz), 1.00–1.55 (m, 6H), 2.10–2.58 (m, 2H), 3.67 (m, 5H), 4.00 (t, 1H,  $J=7.6$  Hz), 7.25–8.05 (m, 7H);  $^{13}\text{C}$  NMR:  $\delta$  13.78, 22.29, 22.90, 30.99, 31.20, 43.02, 52.37, 59.06, 123.16, 125.44, 125.64, 126.27, 127.26, 127.56, 129.01, 131.50, 133.96, 134.10, 169.79, 204.83.

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