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Arylation of the Baylis-Hillman Adducts

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Abstract *: Palladium catalyzed arylation of the Baylis-Hillman adducts, methyl 3-hydroxy-2-methylenealkanoates, has been described.*

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.[1-3] 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.[4-6] Also the Heck reaction of α, β-unsaturated esters has been well documented to produce arylated α, β-unsaturated esters.[7,8] However the Heck reaction *i.e.* arylation of alkenes possessing both allylic alcohol and α, β-unsaturated ester moieties in which carbon-carbon double bond is an integral part of both allyl alcohol and α, β-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 α, β-unsaturated ester moieties.[9-18] As a part of our research program on the Baylis-Hillman reaction,[15-18] 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

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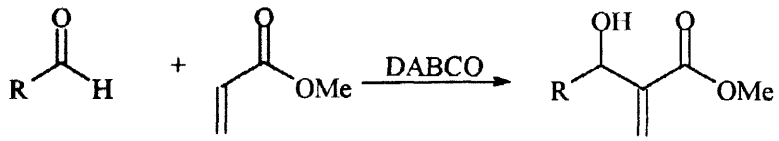

(eq.1)

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Table 1: Arylation of the Baylis-Hillman Adducts[a]

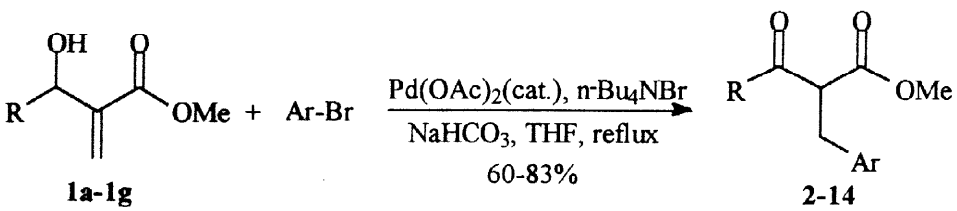
Substrate	R	Ar	Time (h)	Product	Yield[b] (%)
1a	Ph	Ph	10	**2**[c]	81
1a	Ph	4-$CH_3C_6H_4$	10	**3**	76
1a	Ph	α-Naphthyl	7	**4**	83
1b	4-i-$C_3H_7C_6H_4$	Ph	10	**5**[c]	75
1b	4-i-$C_3H_7C_6H_4$	4-$CH_3C_6H_4$	10	**6**[c]	76
1b	4-i-$C_3H_7C_6H_4$	α-Naphthyl	8	**7**[c]	82
1c	2-$OCH_3C_6H_4$	Ph	18	**8**[c]	67
1d	4-$CH_3C_6H_4$	Ph	12	**9**[c]	80
1e	4-ClC_6H_4	Ph	8	**10**[c]	60
1f	i-C_3H_7	Ph	10	**11**[d]	61
1f	i-C_3H_7	4-$CH_3C_6H_4$	7	**12**[d]	76
1g	n-C_5H_{11}	Ph	9	**13**[d]	64
1g	n-C_5H_{11}	α-Naphthyl	7	**14**[d]	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, ^{1}H NMR, ^{13}C NMR, mass spectral and elemental analysis.
d) ^{1}H NMR and ^{13}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 $Pd(OAc)_2$ (2 mol%), $NaHCO_3$ (2.5 mM) and n-Bu_4NBr (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 ≈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).



1a-1g **2-14** (eq.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 CH_2Cl_2. ^1H NMR (200 MHz) and ^{13}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 (3mL) was refluxed for 7-18 hours (as mentioned in the Table 1) in the presence of $Pd(OAc)_2$ (2 mol%, 0.02 mM, 4.5 mg), $NaHCO_3$ (2.5 mM, 210 mg) and n-Bu_4NBr (1 mM, 322 mg). Then the reaction mixture was cooled, diluted with water and extracted with ether. The organic layer was dried over anhydrous Na_2SO_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 ≈5% impurities and were further purified by preparative HPLC (Shim-pack PREP-ODS column) using methanol as solvent. The compounds **12-14** contain ≈5-8% impurities as indicated by ^{1}H NMR and ^{13}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) νmax/cm^{-1}: 1685, 1741; ^{1}H NMR: δ 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}C NMR: δ 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 $C_{17}H_{16}O_3$: 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) νmax/cm^{-1}: 1687, 1741; ^{1}H NMR: δ 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}C NMR:δ 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 $C_{18}H_{18}O_3$: 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 (CH_2Cl_2) νmax/cm^{-1}: 1676, 1738; ^{1}H NMR: δ 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}C NMR: δ 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 $C_{21}H_{18}O_3$: 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) νmax/cm^{-1}: 1682, 1741; ^{1}H NMR: δ 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}C NMR:δ 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 $C_{20}H_{22}O_3$: 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) νmax/cm^{-1}: 1682, 1741; ^{1}H NMR:δ 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}C NMR:δ 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 $C_{21}H_{24}O_3$: 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) vmax/cm^{-1}: 1682, 1739; ^{1}H NMR: δ 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}C NMR: δ 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 $C_{24}H_{24}O_3$: 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) vmax/cm^{-1}: 1672, 1739; ^{1}H NMR: δ 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}C NMR: δ 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 $C_{18}H_{18}O_4$: 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) vmax/cm^{-1}: 1682, 1741; ^{1}H NMR: δ 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}C NMR: δ 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 $C_{18}H_{18}O_3$: 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) vmax/cm^{-1}: 1687, 1741; ^{1}H NMR: δ 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}C NMR: δ 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 $C_{17}H_{15}O_3Cl$: 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) vmax/cm^{-1}: 1714, 1743; ^{1}H NMR: δ 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}C NMR: δ 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) vmax/cm^{-1}: 1714, 1745; ^{1}H NMR: δ 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}C NMR: δ 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) vmax/cm^{-1}: 1716, 1743; ^{1}H NMR: δ 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}C NMR: δ 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) vmax/cm^{-1}: 1716, 1745; ^{1}H NMR: δ 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}C NMR: δ 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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