Mild and Efficient Palladium Catalyzed Isomerization of Baylis-Hillman Acetates

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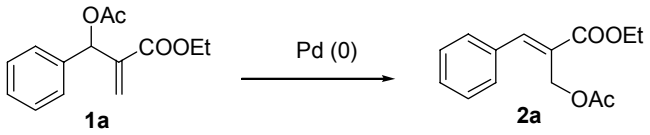
The Baylis-Hillman reaction is one of the powerful carbon-carbon bond forming reaction.[1] The Baylis Hillman adducts and their acetates could be isomerized to give tri-substituted alkenes, cinnamyl alcohols[2] and cinnamyl acetates,[3-9] which are very important because they constituted an important class of synthons for a variety of target molecules. The stereoselective isomerizations of acetates of Baylis Hillman adduct have been reported: TMSOTf,[3] benzyltrimethyl-ammonium fluoride,[4] DABCO,[5] montmorillonite K10 clay,[6] bismuth-triflate,[7] KOAc in ionic liquid[8] and $Yb(OTf)_3$.[9] These reagents have their own drawbacks: longer reaction times, stoichiometric amount of reagents, handling problem due to moisture and air sensitivity. The $Pd(OAc)_2/Ph_3P$ system[10] has also been known to be effective for the isomerization of acetate of Baylis Hillman adduct in acetonitrile under reflux through the [3,3]sigmatropic mechanism.[11] During our study on the development of palladium catalyzed reaction, we found that acetate of Baylis-Hillman adduct **1a** was isomerized to the alkene **2a** stereoselectively and regioselectively in the presence of the catalytic amount of $Pd(Ph_3P)_4$ at room temperature.



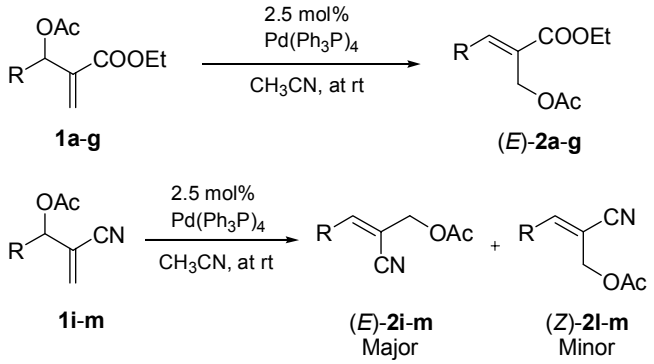
Scheme 1

The isomerization of acetate of Baylis-Hillman adduct **1a** as a model was studied to find the optimum condition using several palladium reagents as a catalyst in variety of solvent systems and the results are summarized in Table 1. The acetate **1a** was found to be isomerized in chloroform at room temperature within 1 h to give tri-substituted alkene **2a** in almost quantitative yield (entry 1). The other solvent systems such as toluene, DMF, THF and CH_3CN showed the similar result (entries 2-5). Only isomerized product spot was observed in the TLC after 1 h in all of solvents listed in Table 1 and only product peaks were observed in the ^1H NMR spectra of the reaction mixture conducted in $CDCl_3$ and CD_3CN for 1 h and 0.5 h respectively: side products and starting material peaks were not observed. Acetonitrile is the choice of solvent due to a little faster reaction rate and personal preference. The isomerization of acetate **1a** was not observed at all after 6 hr stirring when $Pd(OAc)_2$, $Pd(dba)_2$ and Pd/C (10%) without any ligand was used as a catalyst (entries 6-8), while the reaction of acetate **1a** using $Pd(OAc)_2$ in the presence of triphenylphosphine with triethylamine (entry 10) or without triethylamine (entry 11) gave the isomerized product **2a** in almost quantitative yield after 12 h. The reaction of acetate **1a** using $Pd(OAc)_2/PPh_3/Et_3N$ system at room temperature (entry 10) is slower than that catalyzed by $Pd(Ph_3P)_4$. The reaction of acetate **1a** under reflux (entry 11) is faster than that at room temperature (entry 10), while the yield under reflux is lower than that at room temperature due to several side products which was observed in TLC but not

Table 1. Pd-catalyzed isomerization of Baylis-Hillman acetates **1a**[a]

Entry	Pd Cat.	Ligand	Base	Solvent.	Time(h)	Yield[b]
1	$Pd(Ph_3P)_4$	-	-	$CHCl_3$	1	97%
2	$Pd(Ph_3P)_4$	-	-	Toluene	1	96 %
3	$Pd(Ph_3P)_4$	-	-	DMF	1	98 %
4	$Pd(Ph_3P)_4$	-	-	THF	1	96 %
5	$Pd(Ph_3P)_4$	-	-	CH_3CN	0.5	98 %
6	Pd/C (10%)	-	-	CH_3CN	6	No Rexn
7	$Pd(dba)_2$	-	-	CH_3CN	6	No Rexn
8	$Pd(OAc)_2$	-	-	CH_3CN	6	No Rexn
9	$Pd(OAc)_2$	PPh_3		CH_3CN	12	95%
10	$Pd(OAc)_2$	PPh_3	Et_3N	CH_3CN	12	96%
11[c]	$Pd(OAc)_2$	PPh_3	Et_3N	CH_3CN	3	71 %

[a]Reaction conditions: Entries 1-5: substrate **1** (0.4 mmol), $Pd(Ph_3P)_4$ (2.5 mol %), solvent (3 mL), at room temperature under Ar. Entries 9-11: Pd catalyst (5 mol%), ligand (20 mol%), base (3 eq.). [b]Isolated yield. [c]Reflux.



Scheme 2

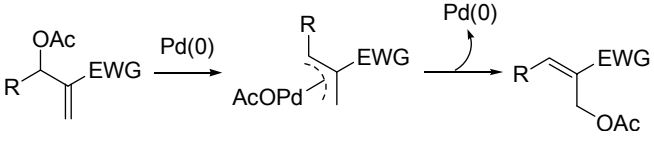
Table 2. Isomerization of various Acetates of the Baylis-Hillman Adducts

Entry	Reactant **1**	R	EWG	Time (h)	Yield[a] (%)
1	**1a**	C_6H_5	COOEt	1	92
2	**1b**	3-$NO_2C_6H_5$	COOEt	3	82
3	**1c**	4-$NO_2C_6H_5$	COOEt	1	92
4	**1d**	4-BrC_6H_5	COOEt	1	90
5	**1e**	4-$CH_3C_6H_5$	COOEt	1	96
6	**1f**	4-$MeOC_6H_5$	COOEt	1	99
7	**1g**	Furyl	COOEt	1	93
8	**1h**	C_6H_5	COMe	2	98
9	**1i**	C_6H_5	CN	2	86
10	**1j**	4-$MeOC_6H_5$	CN	2	94
11	**1k**	3-$NO_2C_6H_5$	CN	1	86
12	**1l**	4-BrC_6H_5	CN	2	70(16)[b]
13	**1m**	4-$NO_2C_6H_5$	CN	3	80(10)

[a]Isolated yield. [b]Yields in parentheses are those for (*Z*)-isomer.

characterized. Therefore, $Pd(Ph_3P)_4$ in acetonitrile at room temperature is the choice of reaction condition.

Our optimum condition was applied to a variety of acetates of Baylis-Hillman adducts **1** to understand the scope and the generality of the $Pd(Ph_3P)_4$ catalyzed isomerization and the results are listed in the Table 2. The isomerizations of all acetates **1** under our condition are very efficient and fast. Starting material was not observed in TLC and the isolated yields are excellent in all of the cases. The stereochemistry of the products **2** was assigned on the basis of the ^{1}H NMR values of the olefinic protons and methylene protons by comparison with the literature values.[12] The reaction of acetates **1** gave only (*E*) stereoisomer of alkenes **2** except for two substrates. Some acetates with nitrile group (**1m** and **1n**) gave the corresponding (*E*)-alkenes as a major products and the corresponding (*Z*) isomers as a minor products. (entries 12 and 13)



Scheme 3

The proposed mechanism is the formation of π-allyl-palladium intermediates[13] by the oxidative addition of allyl acetate **1** to palladium followed by the reductive elimination to give thermodynamically stable tri-substituted alkenes **2**.

In conclusion, acetates of the Baylis-Hillman adducts **1** were isomerized into the corresponding thermodynamically stable tri-substituted alkenes **2** in the presence of 2.5 mole % of $Pd(Ph_3P)_4$ as a catalyst under argon atmosphere in almost quantitative yields. The isomerization reaction is simple, fast and efficient.

Experimetal Section

General Procedure. To the Baylis-Hillman acetates **1** (0.2 mmol) in acetonitrile (3 mL) was added 2.5 mol% of $Pd(PPh_3)_4$ and the resulting solution was stirred at room temperature under argon atmosphere for the time mentioned in Table 2. The reaction mixture was concentrated and purified by column chromatography (silica gel, 230-400 mesh, 7:1 = hexane/EtOAc) to give the corresponding products **2**.

(**2a**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31-1.36 (t, 3H, *J* = 6.9 Hz), 2.09 (s, 1H), 4.27-4.33 (q, 2H, *J* = 6.9 Hz), 4.95 (s, 2H), 7.38 (m, 5H), 7.97 (s, 1H). IR (neat): 2985, 1793, 1708, 1639, 1446, 1369, 1222, 1114, 1022, 960 cm^{-1}

(**2b**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, 3H, *J* = 6.9 Hz), 2.14 (s, 3H), 4.30-4.37 (q, 2H, *J* = 6.9 Hz), 4.90 (s, 2H), 7.61-7.69 (m, 2H), 7.97 (s, 1H), 8.30 (m, 2H). IR (neat): 2923, 1739, 1712, 1531, 1469, 1349, 1222, 1114, 1022, 964, 929, 809 cm^{-1}

(**2c**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3H, *J* = 7.2 Hz), 2.09 (s, 3H), 4.32 (q, 2H, *J* = 6.9 Hz), 4.91 (s, 2H), 7.55 (d, 2H, *J* = 7.8 Hz), 7.96 (s, 1H), 8.27 (d, 2H, *J* = 7.8 Hz).

IR (neat): 2923, 2217, 1739, 1708, 1635, 1596, 1519, 1346, 1222, 1110, 1022, 852 cm^{-1}

(**2d**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, 3H, *J* = 7.2 Hz), 2.09 (s, 3H), 4.31 (q, 2H, *J* = 6.9 Hz), 4.92 (s, 2H), 7.23 (d, 2H, *J* = 8.1 Hz), 7.53 (d, 2H, *J* = 8.1 Hz), 7.88 (s, 1H). IR (neat): 2915, 1739, 1712, 1639, 1585, 1488, 1369, 1222, 1114, 1072, 1022, 960, 840, 813 cm^{-1}

(**2e**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, 3H, *J* = 7.2 Hz), 2.10 (s, 3H), 2.38 (s, 3H), 4.31 (q, 2H, *J* = 7.8 Hz), 4.97 (s, 2H), 7.23 (m, 4H), 7.95 (s, 1H). IR (neat): 2927, 1739, 1708, 1635, 1511, 1457, 1369, 1222, 1110, 1022, 960, 921, 813 cm^{-1}

(**2f**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, 3H), 2.11 (s, 3H), 3.84 (s, 3H), 4.30 (q, 2H, *J* = 7.8 Hz), 4.99 (s, 2H), 6.94 (d, 2H, *J* = 9.0 Hz), 7.36 (d, 2H, *J* = 9.0 Hz), 7.93 (s, 1H). IR (neat): 2927, 1739, 1704, 1604, 1511, 1465, 1369, 1303, 1222, 1176, 1106, 1022, 960, 829 cm^{-1}

(**2g**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, 3H, *J* = 6.9 Hz), 2.06 (s, 3H), 4.29 (q, 2H, *J* = 7.2 Hz), 5.24 (s, 2H), 6.51 (s, 1H), 6.74 (s, 1H), 7.60 (d, 2H, *J* = 8.7 Hz). IR (neat): 2927, 1731, 1704, 1631, 1469, 1369, 1230, 1207, 1110, 1022, 960, 929, 883 cm^{-1}

(**2h**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.46 (s, 3H), 4.92 (s, 2H), 7.39 (m, 5H), 7.77 (s, 1H). IR (neat): 2927, 1735, 1658, 1627, 1523, 1411, 1353, 1299, 1222, 1103, 1025, 979, 948, 890, 806 cm^{-1}

(**2i**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 4.82 (s, 2H), 7.23 (s, 1H), 7.45 (m, 3H), 7.79 (m, 2H). IR (neat): 2923, 2854, 2217, 1743, 1623, 1450, 1369, 1218, 1029 cm^{-1}

(**2j**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H), 3.86 (s, 3H), 4.79 (s, 2H), 6.96 (d, 2H, J = 9.0 Hz), 7.14 (s, 1H), 7.80 (d, 2H, J = 9.0 Hz). IR (neat): 2927, 2850, 2213, 1739, 1600, 1511, 1457, 1373, 1307, 1257, 1218, 1180, 1025, 971, 902, 829 cm^{-1}

(**2k**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3H), 4.86 (s, 2H), 7.30 (s, 1H), 7.57-7.69 (t, 1H, J = 7.8 Hz), 8.20-8.31 (m, 2H), 8.50 (s, 1H). IR (neat): 2923, 2850, 2221, 1743, 1612, 1531, 1438, 1349, 1218, 1033, 914, 825 cm^{-1}

(**2l**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) (*E*) - δ 2.16 (s, 3H), 4.84 (s, 2H), 7.16 (d, 2H, J = 7.5 Hz), 7.37 (s, 1H), 7.57 (d, 2H, J = 7.5 Hz). (*Z*) - δ 2.15 (s, 3H), 4.80 (s, 2H), 7.16 (s, 1H), 7.59 (d, 2H, J = 7.5 Hz), 7.64 (d, 2H, J = 7.5 Hz). IR (neat): 2923, 2850, 2217, 1743, 1627, 1585, 1488, 1369, 1214, 1072, 1029, 898, 817 cm^{-1}

(**2m**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) (*E*) - δ 2.18 (s, 3H), 4.86 (s, 2H), 7.25 (s, 1H), 7.92 (d, 2H, J = 9.0 Hz), 8.29 (d, 2H, J = 8.4 Hz). (*Z*) - δ 2.18 (s, 1H), 4.86 (s, 2H), 7.30 (s, 1H), 7.94 (d, 2H, J = 7.8 Hz), 8.29 (d, 2H, J = 8.4 Hz). IR (neat): 2923, 2850, 2221, 1743, 1596, 1519, 1346, 1218, 1110, 1033, 906, 848 cm^{-1}

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