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A Practical Synthesis of Morita-Baylis-Hillman Adducts of Aryl Vinyl Ketones Catalyzed by a Proton Donor

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An efficient and practical synthesis of MBH adducts of aryl vinyl ketones was developed using DABCO and 4-nitrophenol as a proton donor. Addition of a proton donor and the use of excess amounts (3.0 equiv) of aldehydes were highly beneficial for the yields of MBH adducts of aryl vinyl ketones.

Key Words : Morita-Baylis-Hillman adducts, Aryl vinyl ketones, Proton donor, 4-Nitrophenol

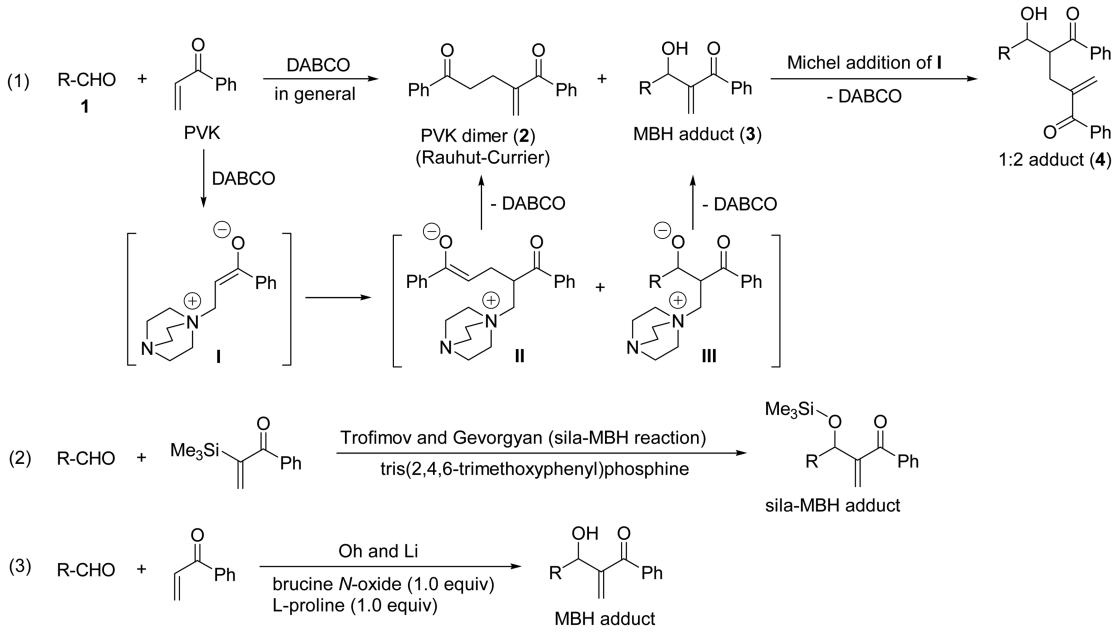
Introduction

The Morita-Baylis-Hillman (MBH) reaction is one of the most powerful methods of carbon-carbon bond-formation.[1] The reaction was shown to be highly efficient with various Michael acceptors such as acrylates, acrylonitriles, and alkyl vinyl ketones.[1] However, the MBH reaction to form the MBH adduct **3** is not efficient with phenyl vinyl ketone (PVK) due to its high reactivity.[2,3] Two major side products **2** and **4** were formed in general, as shown in Scheme 1. The PVK dimer **2** was formed by the Rauhut-Currier reaction via a conjugate addition of the zwitterion **I** to PVK. In addition, the zwitterion **I** can react with the MBH adduct **3** and produced the 1:2 adduct **4**.[2,3a,c]

Previously, Trofimov and Gevorgyan reported the synthesis of MBH adduct of PVK via the sila-MBH reaction using α-silylated aryl vinyl ketone in the presence of a phosphine catalyst (equation 2 in Scheme 1).[3a] Very recently, Oh and Li reported a cooperative catalyst system of proline and brucine *N*-oxide (equation 3 in Scheme 1).[3c] However, both reactions have some limitations to be used generally in a practical sense. For the sila-MBH reaction, a-silylated aryl vinyl ketones and a special catalyst TTMPP (tris(2,4,6-trimethoxyphenyl)phosphine) were required. For the latter method, excess amounts of valuable PVK and an equimolar amount of commercially unavailable brucine *N*-oxide have to be used.

Results and Discussion

In these contexts, we decided to develop a facile synthetic method of the MBH adducts of aryl vinyl ketones. At the outset of our study, we examined the effect of molar ratio between *p*-nitrobenzaldehyde (**1a**) and PVK in THF in the presence of DABCO (10-30 mol %), as shown in Table 1. As reported in the previous paper,[2a] the 1:2 adduct **4a** (R = *p*-



Scheme 1

Table 1. Optimization of the MBH reaction of PVK with 4-nitrobenzaldehyde (**1a**) and 2-nitrobenzaldehyde (**1b**)[a]

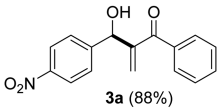
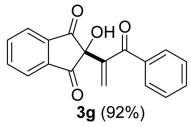
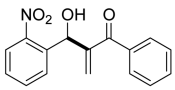
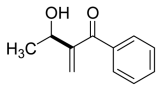
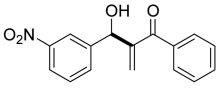
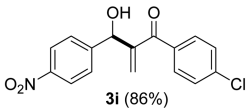
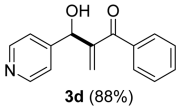
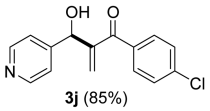
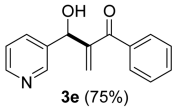
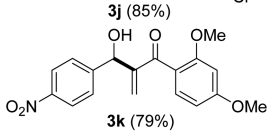
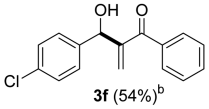
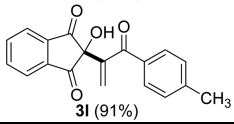
Entry	**1** : PVK	DABCO (Equiv)	Additive (Equiv)	Time (h)	**2** (%)	**3** (%)	**4** (%)
1[b]	1 : 2	0.1	no	60[b]	16[b]	**3a** (0)[b]	**4a** (78)[b]
2	1 : 2	0.1	no	40	15	**3a** (15)	**4a** (55)
3	1 : 1	0.3	no	20	13	**3a** (37)	**4a** (48)
4	2 : 1	0.3	no	20	10	**3a** (70)	**4a** (16)
5	3 : 1	0.3	no	20	< 5	**3a** (72)	**4a** (14)
6	3 : 1	0.5	phenol (0.3)	20	< 5	**3a** (68)	**4a** (17)
7	3 : 1	0.5	4-nitrophenol (0.3)	6	< 5	**3a** (88)	**4a** (< 5)
8	3 : 1	0.5	PEG-3400[c]	20	< 5	**3a** (72)	**4a** (17)
9	3 : 1	0.5	MeOH (5.0)	20	13	**3a** (53)	**4a** (22)
10	3 : 1	0.5	benzoic acid (0.3)	20	< 5	**3a** (86)	**4a** (< 5)
11	3 : 1	0.5	pivalic acid (0.3)	20	< 5	**3a** (82)	**4a** (< 5)
12	3 : 1	0.5	acetaldoxime (0.3)	20	< 5	**3a** (77)	**4a** (13)
13	3 : 1	0.3	no	20	32	**3b** (23)	**4b** (43)
14	3 : 1	0.5	4-nitrophenol (0.3)	12	9	**3b** (68)	**4b** (8)
15	3 : 1	0.5	benzoic acid (0.3)	20	10	**3b** (71)	**4b** (< 5)

[a]Common conditions: THF, rt (**1a** for entries 1-12 and **1b** for entries 13-15). [b]Reported results in Ref. 2a. [c]Arbitray amounts of PEG-3400 were used.

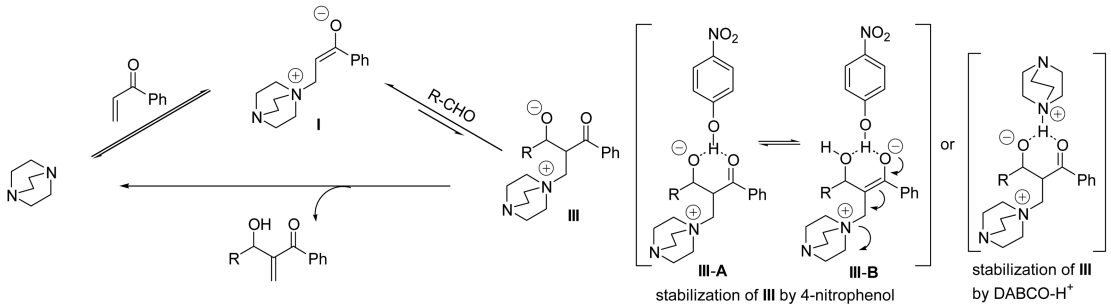
nitrophenyl) was formed as a major product along with appreciable amount of a PVK dimer **2** when we used **1a**:PVK = 1:2 ratio (entries 1-2). When the amount of **1a** increased gradually to 3.0 equiv, the yield of MBH adduct **3a** increased also to 72% (entries 3-5). Although the yield (72%, entry 5) was not high, we think the reaction condition would be more beneficial than the previous methods.[3] Thus we carried out the reaction of 2-nitrobenzaldehyde (**1b**) under the same reaction conditions (**1b**:PVK = 3:1); however, the reaction afforded the MBH adduct **3b** in low yield (23%) along with a PVK dimer **2** (32%) and the corresponding 1:2 adduct **4b** (43%),[2a,3c] as shown in entry 13.

We think the yields of MBH adducts could be increased by reducing the formations of a PVK dimer and 1:2 adduct by completion of the reaction in a short time. Thus we decided to examine the effect of a proton donor such as phenol in order to facilitate the MBH reaction. Such a rate-increasing effect of a proton donor has been reported by us[4] and other

Table 2. Synthesis of MBH adducts of aryl vinyl ketones[a]

Entry	Time (h)	Product (%)	Entry	Time (h)	Product (%)
1	6	 **3a** (88%)	7	6	 **3g** (92%)
2	12	 **3b** (68%)	8	10	 **3h** (69%)[c]
3	8	 **3c** (84%)	9	6	 **3i** (86%)
4	18	 **3d** (88%)	10	6	 **3j** (85%)
5	12	 **3e** (75%)	11	6	 **3k** (79%)
6	18	 **3f** (54%)[b]	12	6	 **3l** (91%)

[a]Conditions: aldehyde (1.2 mmol), aryl vinyl ketone (0.4 mmol), 4-nitrophenol (30 mol %), DABCO (50 mol %), THF, rt. [b]Conditions: 4-nitrophenol (50 mol %) and DABCO (100 mol %) were used. Under the typical conditions the yield was 39%. [c]10.0 equiv of acetaldehyde was used.



Scheme 2

groups.[5,6] Thus, we examined the reaction of **1a** in the presence of a proton donor, and the results are summarized in the Table 1 (entries 6-12, 14 and 15). As shown, the effect of phenol (entry 6), PEG-3400 (entry 8), MeOH (entry 9), and acetaldoxime (entry 12) were negligible. When we used 4-nitrophenol as an additive (entry 7), the yield of **3a** increased to 88%. In addition, the reaction of 2-nitrobenzaldehyde gave the corresponding MBH adduct **3b** in an increased yield (68%, entry 14). It is interesting to note that the addition of benzoic acid (entry 10) or pivalic acid (entry 11) also increased the yield of **3a** to some extent (*vide infra*). The reaction of **1b** in the presence of benzoic acid (entry 15) also afforded a good yield of **4b** (71%).

Encouraged by the successful results, we carried out the MBH reactions of aryl vinyl ketones with various aldehydes and ninhydrin in the presence of DABCO (0.5 equiv) and 4-nitrophenol (0.3 equiv), and the results are summarized in Table 2. The reactions of 3-nitrobenzaldehyde, 4-pyridinecarbaldehyde, and 3-pyridinecarbaldehyde afforded good yields of MBH adducts **3c-e** (entries 3-5), while the reaction of 4-chlorobenzaldehyde gave low yield (39%) of **3f**. The yield of **3f** increased to 54% by using 50 mol % of 4-nitrophenol and 100 mol % of DABCO (entry 6). The reactions of ninhydrin (entry 7) and acetaldehyde (entry 8) also produced **3g** and **3h** in good yields (69-92%). The reactions with 4-chlorophenyl vinyl ketone (entries 9 and 10), 2,4-dimethoxyphenyl vinyl ketone (entry 11), and 4-methylphenyl vinyl ketone (entry 12) afforded the corresponding MBH adducts **3i-l** in good yields (79-91%).

In the MBH reaction, the reaction could be accelerated by increasing the amount of enolate **I**, activation of the aldehyde, or stabilization of the zwitterion **III**. As shown in Scheme 2, a stabilization of the intermediate **III** with 4-nitrophenol would facilitate the formation of **III** as well as the departure of a DABCO moiety, and this increase the whole MBH reaction rate.[5a,d-f,7] In these contexts, various proton donors[5,6] and Lewis acids[5i-k] have been known to increase the reaction rate by stabilizing the zwitterion **III**. Thus, an increase of reaction rate by using 4-nitrophenol is beneficial for the increase of yield of a MBH adduct. In addition, a rapid consumption of PVK is also important in order to prohibit the formation of unwanted 1:2 adduct by using aldehyde/PVK in a 3:1 molar ratio. As noted above, the addition of carboxylic acid derivatives (entries 10, 11, and 15 in Table 1) also increased the reaction rate, and a proton donor in these cases might be a protonated DABCO.[8]

In summary, we disclosed an efficient and practical synthesis of MBH adducts of aryl vinyl ketones using DABCO and 4-nitrophenol as a proton donor. Addition of a proton donor and the use of excess amounts (3.0 equiv) of aldehydes were highly beneficial for the yields of MBH adducts of aryl vinyl ketones.

Experimental Section

Typical Procedure for the Synthesis of 3a. Aryl vinyl ketones were prepared before use from 3-chloro-1-aryl-propan-ones by treatment with KOAc in EtOH (reflux, 3 h) as reported.[9] A solution of 4-nitrobenzaldehyde (**1a**, 181 mg, 1.2 mmol), PVK (53 mg, 0.4 mmol), DABCO (22 mg, 50 mol %), and 4-nitrophenol (17 mg, 30 mol %) in THF (1.5 mL) was stirred at room temperature for 6 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/Et_2O/CH_2Cl_2, 25:5:1) compound **3a** was obtained as pale yellow oil, 100 mg (88%). Other MBH adducts **3b-l** were synthesized similarly, and the selected spectroscopic data of **3d-l** are as follows. MBH adducts **3a-c**[3c] were known compounds, and the spectroscopic data were identical with the reported.

Compound 3d: 88%; pale yellow oil; IR (film) 3433, 1703, 1674, 1597, 1449, 1410 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.94 (br s, 1H), 5.78 (s, 1H), 5.85 (s, 1H), 6.15 (d, J = 0.9 Hz, 1H), 7.37-7.44 (m, 4H), 7.52-7.58 (m, 1H), 7.65-7.68 (m, 2H), 8.47 (dd, J = 4.8 and 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 72.28, 121.43, 127.55, 128.36, 129.45, 132.90, 136.95, 148.03, 149.49, 151.20, 197.64; ESIMS *m/z* 262 (M^++Na). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.61; H, 5.54; N, 5.59.

Compound 3e: 75%; colorless oil; IR (film) 3399, 1653, 1596, 1427, 1330 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.00 (br s, 1H), 5.83 (s, 1H), 5.86 (s, 1H), 6.19 (s, 1H), 7.25 (dd, J = 8.4 and 4.8 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.67 (d, J = 7.2 Hz, 2H), 7.79-7.82 (m, 1H), 8.40 (dd, J = 4.8 and 1.2 Hz, 1H), 8.58 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 71.22, 123.47, 126.98, 128.31, 129.43, 132.78, 134.58, 137.02, 137.53, 148.09, 148.44, 148.56, 197.54; ESIMS *m/z* 262 (M^++Na). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.38; H, 5.60; N, 5.72.

Compound 3f: 54%; colorless oil; IR (film) 3443, 1651,

1597, 1447, 1333 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.65 (d, *J* = 5.4 Hz, 1H), 5.74 (d, *J* = 5.4 Hz, 1H), 5.79 (s, 1H), 6.07 (d, *J* = 0.9 Hz, 1H), 7.28-7.32 (m, 2H), 7.35-7.39 (m, 2H), 7.41-7.44 (m, 2H), 7.51-7.57 (m, 1H), 7.65-7.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 73.31, 126.93, 127.84, 128.30, 128.58, 129.49, 132.84, 133.43, 137.00, 139.81, 148.37, 198.08; ESIMS *m/z* 295 (M^++Na), 297 (M^++Na+2). Anal. Calcd for $C_{16}H_{13}ClO_2$: C, 70.46; H, 4.80. Found: C, 70.77; H, 4.93.

Compound 3g: 92%; white solid, mp 105-106 °C; IR (KBr) 3433, 1749, 1715, 1645, 1595, 1337, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.95 (s, 1H), 6.30 (s, 1H), 6.83 (s, 1H), 7.37-7.42 (m, 2H), 7.51-7.57 (m, 1H), 7.63-7.67 (m, 2H), 7.85-7.91 (m, 2H), 8.01-8.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 77.09, 124.27, 128.35, 129.45, 132.17, 132.93, 136.09, 141.09, 144.69, 196.07, 197.10 (1 carbon is overlapped); ESIMS *m/z* 315 (M^++Na). Anal. Calcd for $C_{18}H_{12}O_4$: C, 73.97; H, 4.14. Found: C, 74.14; H, 4.03.

Compound 3h: 69%; colorless oil; IR (film) 3443, 1649, 1595, 1449, 1337, 1292 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (d, *J* = 6.6 Hz, 3H), 3.18 (br s, 1H), 4.86 (q, *J* = 6.6 Hz, 1H), 5.71 (s, 1H), 6.12 (s, 1H), 7.44-7.50 (m, 2H), 7.55-7.61 (m, 1H), 7.76-7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.99, 67.62, 124.93, 128.25, 129.48, 132.64, 137.40, 150.36, 198.70; ESIMS *m/z* 199 (M^++Na). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.69; H, 6.92.

Compound 3i: 86%; pale yellow oil; IR (film) 3474, 1651, 1587, 1520, 1346 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.72 (d, *J* = 5.7 Hz, 1H), 5.85 (d, *J* = 5.7 Hz, 1H), 5.86 (s, 1H), 6.13 (d, *J* = 1.2 Hz, 1H), 7.40 (dt, *J* = 9.0 and 2.1 Hz, 2H), 7.59-7.65 (m, 4H), 8.19 (dt, *J* = 9.0 and 2.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 73.10, 123.69, 127.19, 127.86, 128.80, 130.84, 134.98, 139.65, 147.36, 147.58, 148.54, 196.46; ESIMS *m/z* 340 (M^++Na), 342 (M^++Na+2). Anal. Calcd for $C_{16}H_{12}ClNO_4$: C, 60.48; H, 3.81; N, 4.41. Found: C, 60.52; H, 3.98; N, 4.29.

Compound 3j: 85%; white solid, mp 108-110 °C; IR (KBr) 3416, 1703, 1674, 1589, 1406 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.38 (br s, 1H), 5.80 (s, 1H), 5.81 (s, 1H), 6.16 (s, 1H), 7.36 (d, *J* = 6.0 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 8.43 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 71.71, 121.50, 127.02, 128.70, 130.80, 135.20, 139.38, 148.18, 149.35, 151.35, 196.11; ESIMS *m/z* 296 (M^++Na), 298 (M^++Na+2). Anal. Calcd for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; N, 5.12. Found: C, 65.84; H, 4.67; N, 5.01.

Compound 3k: 79%; colorless oil; IR (film) 3439, 1645, 1605, 1520, 1346 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.73 (s, 3H), 3.83 (s, 3H), 4.04 (d, *J* = 6.3 Hz, 1H), 5.78 (d, *J* = 6.3 Hz, 1H), 5.79 (s, 1H), 6.00 (d, *J* = 0.6 Hz, 1H), 6.43 (d, *J* = 2.1 Hz, 1H), 6.47 (dd, *J* = 8.7 and 2.1 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.60-7.65 (m, 2H), 8.15-8.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.44 (2C), 73.15, 98.68, 104.49, 120.28, 123.33, 127.27, 127.76, 132.16, 147.07, 149.28, 159.59, 163.77, 197.26 (1 carbon is overlapped); ESIMS *m/z* 366 (M^++Na). Anal. Calcd for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08. Found: C, 63.20; H, 5.17; N, 4.03.

Compound 3l: 91%; white solid, mp 165-166 °C; IR (KBr) 3428, 1749, 1715, 1643, 1605, 1337 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 3.58 (br s, 1H), 6.28 (s, 1H), 6.77 (s, 1H), 7.19-7.22 (m, 2H), 7.55-7.59 (m, 2H), 7.85-7.91 (m, 2H), 8.02-8.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.62, 77.18, 124.29, 129.08, 129.71, 131.32, 133.40, 136.09, 141.16, 143.98, 144.76, 195.67, 197.03; ESIMS *m/z* 329 (M^++Na). Anal. Calcd for $C_{19}H_{14}O_4$: C, 74.50; H, 4.61. Found: C, 74.69; H, 4.90.

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