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New discovery in the traditional Baylis-Hillman reaction of arylaldehydes with methyl vinyl ketone

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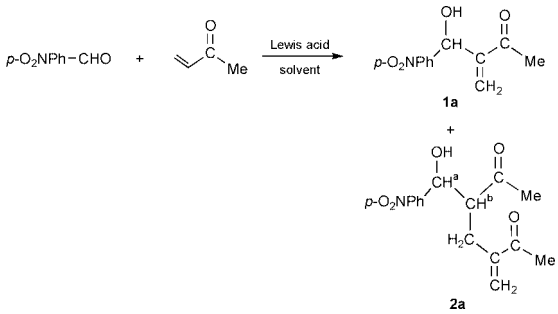
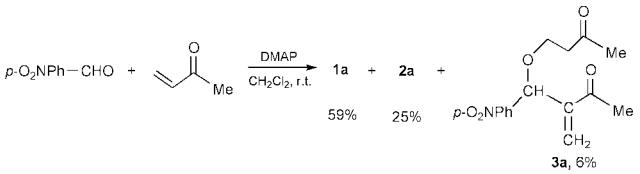
In the Baylis-Hillman reaction of arylaldehydes with methyl vinyl ketone, we found that, besides the normal Baylis-Hillman reaction product 1, the diadduct 2 can also be formed at the same time and the yield of 2 can reach 55% by increasing the amount of methyl vinyl ketone; but for acrylonitrile and methyl acrylate, only the normal Baylis-Hillman adduct was obtained; the substituent's effects were also examined and a plausible reaction mechanism was proposed for the formation of 2.

The Baylis-Hillman reaction has progressed,[1] and now includes a catalytic asymmetric version,[2] since Baylis and Hillman first reported the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of 1,4-diazabicyclo[2,2,2]octane (DABCO) in 1972.[3] However, during our own investigation on this simple and useful reaction,[4] we found that, in the reaction of arylaldehydes with methyl vinyl ketone (MVK) catalyzed by DABCO, the reaction products are not as simple as those reported before. For example, using *p*-nitrobenzaldehyde (1.0 eq.) and MVK (2.0 eq.) as substrates in the presence of catalytic amounts of DABCO (0.1 eq.) in DMSO or DMF, we found that, besides the normal Baylis-Hillman reaction product **1a** compound **2a** was also formed at the same time as a *syn* and *anti* mixture (2 : 3)[5] (Scheme 1, Table 1, entries 1–3). If using *p*-dimethylaminopyridine (DMAP) as a Lewis base in DMSO or DMF, **1a** was exclusively obtained in high yields under the same reaction conditions (Scheme 1, Table 1, entries 4–5). However, in CH_2Cl_2 using DMAP as a Lewis base, **1a** and **2a** were formed along with **3a**, a Michael addition product of **1a** with MVK (Scheme 2).[6] At present, we do not understand why **3a** should be formed in CH_2Cl_2. Increasing the amount of MVK in the reaction system raised the yield of **2a**. Using 4.0 or 8.0 eq. of MVK, the yield of **2a** reached 53 and 55%, respectively (Table 1, entries 6 and 7). The reaction temperature slightly affected the yield of **2a** (Table 1, entries 8 and 9). At higher temperature, the dimer of MVK was formed as well.[7] The formation of **2a** indicates that another important reaction process can operate in the traditional Bayliss-Hillman reaction.

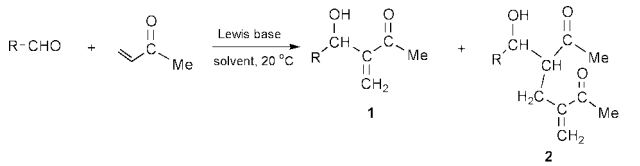


Scheme 1



Scheme 2

For *m*-nitrobenzaldehyde, *p*-bromo or *p*-chlorobenzaldehyde and *trans*-cinnamaldehyde similar results were obtained (Scheme 3, Table 2, entries 3, 9, 11, 16). Using DMAP as a Lewis base, **1** was exclusively formed (Scheme 3, Table 2, entries 4, 10, 12, 17). For benzaldehyde or aliphatic aldehyde, only the corresponding normal Baylis-Hillman adducts **1** were formed under the same reaction conditions (Scheme 3, Table 2,



b: R = *m*-NO_2Ph, **c**: R = *o*-NO_2Ph, **d**: R = *p*-BrPh, **e**: R = *p*-ClPh, **f**: R = Ph, **g**: R = *p*-EtPh, **h**: R = PhCH=CH, **i**: R = $CH_3(CH_2)_3$.

Scheme 3

Table 1 Baylis-Hillman reactions of aldehydes (1.0 eq.) with methyl vinyl ketone (2.0 eq.) in the presence of Lewis base (0.1 eq.)

						Yield (%)[a]	
Entry	R	Lewis base	Solvent	Temp./°C	Time/h	**1a**	**2a**[e]
1	*p*-NO_2Ph	DABCO	DMSO	20	40	60	20
2	*p*-NO_2Ph	DABCO	DMF	20	40	63	23
3	*p*-NO_2Ph	DABCO	CH_2Cl_2	20	40	61	34
4	*p*-NO_2Ph	DMAP	DMSO	20	40	85	0
5	*p*-NO_2Ph	DMAP	DMF	20	40	83	0
6	*p*-NO_2Ph	DABCO	DMF[b]	20	60	41	53
7	*p*-NO_2Ph	DABCO	DMF[c]	20	60	41	55
8	*p*-NO_2Ph	DABCO	DMF[b]	−30	60	54	40
9[d]	*p*-NO_2Ph	DABCO	DMF[b]	70	60	37	56

[a] Isolated yields. [b] Mole ratio of aldehyde : MVK = 1 : 4. [c] Mole ratio of aldehyde : MVK = 1 : 8. [d] Dimer of MVK was formed. [e] *syn* : *anti* = 2 : 3.

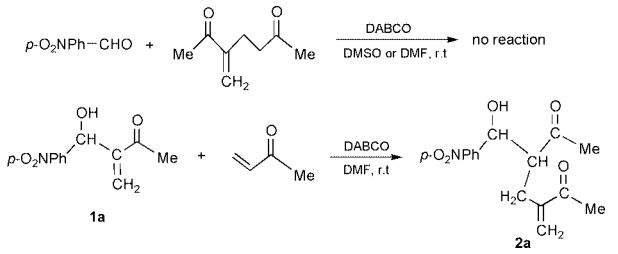
Table 2 Baylis-Hillman reactions of aldehydes (1.0 eq.) with methyl vinyl ketone (2.0 eq.) in the presence of Lewis base (0.1 eq.)

					Yield (%)[a]	
Entry	R	Lewis base	Solvent	Time	**1**	**2**[d]
1	*m*-NO_2Ph	DABCO	DMSO	20	50	27
2	*m*-NO_2Ph	DABCO	DMF	20	50	27
3	*m*-NO_2Ph	DABCO	DMF[b]	20	50	41
4	*m*-NO_2Ph	DMAP	DMF	20	87	0
5	*o*-NO_2Ph	DABCO	DMF	50	83	0
6	*o*-NO_2Ph	DMAP	DMF	20	83	0
7	*o*-NO_2Ph	DMAP	CH_2Cl_2	40	81	0
8	*p*-BrPh	DABCO	DMF	140	57	25
9	*p*-BrPh	DABCO	DMF[b]	80	51	36
10	*p*-BrPh	DMAP	DMF	120	88	0
11	*p*-ClPh	DABCO	DMF[b]	160	62	33
12	*p*-ClPh	DMAP	DMF	60	67	0
13	Ph	DABCO	DMF	90	73	0
14	Ph	DMAP	DMF	130	54	0
15	*p*-EtPh	DMAP	DMF	7d	0	0
16	PhCH=CH	DABCO	DMF[b]	60	57	24
17	PhCH=CH	DMAP	DMF[b]	49	60	0
18[c]	$CH_3(CH_2)_3$	DABCO	DMF[b]	49	15	0

[a] Isolated yields. [b] Mole ratio of aldehyde : MVK = 1 : 4. [c] Dimer of MVK was formed. [d] *syn* : *anti* = 2 : 3.

entries 13, 18) and for *p*-ethylbenzaldehyde, no reaction occurred at all (Scheme 3, Table 2, entry 15). But surprisingly we found that, for *o*-nitrobenzaldehyde, the Baylis-Hillman adduct **1** was produced as the single product (Table 2, entries 4–6). This result suggested that the *o*-nitro group on the phenyl ring could block out the further reaction of **1** with MVK.

In the traditional Baylis-Hillman reaction for simple methyl vinyl ketone (MVK), this phenomenon has never been reported before. Only in the reaction of dicarbonyl compounds with acrylonitrile in the presence of DABCO, the diadduct, which was thought to be derived either from reaction of acrylonitrile dimer with starting material or from the conjugated addition of the anion derived from a second molecule of acrylonitrile to the Baylis-Hillman adduct, was obtained as a minor product.[8] In order to clarify the mechanism for the formation of **2a**, we carried out the reactions of **1a** (1.0 eq.) with MVK (2.0–8.0 eq.) and *p*-nitrobenzaldehyde (1.0 eq.) with MVK dimer (1.0 eq.) in the presence of catalytic amounts of DABCO (0.1 eq.), respectively (Scheme 4). We found that **2a** was indeed formed



Scheme 4

from the reaction of **1a** with methyl vinyl ketone (MVK) in the presence of catalytic amounts of DABCO (0.1 eq.) as a *syn* and *anti* mixture (2 : 3), but that no reactions occurred between *p*-nitrobenzaldehyde and MVK dimer under the same reaction conditions (Scheme 4). The yield of **2a** can reach 41 or 48% if using 4.0 or 8.0 eq. of MVK, respectively. Thus, we can conclude that two reactions occur for the traditional Baylis-Hillman reaction of aryaldehydes with MVK. One is the normal Baylis-Hillman reaction which is the 1,2-addition of the anion derived from MVK to *p*-nitrobenzaldehyde. The other is the conjugated addition (Michael addition) of the anion derived from a second molecule of MVK to **1**.

In conclusion, we found that in the Baylis-Hillman reaction of arylaldehydes with methyl vinyl ketone, besides the normal Baylis-Hillman adduct **1**, diadduct **2** was also formed and was confirmed to be derived from the further reaction of **1** with MVK *via* a conjugated addition reaction. Efforts are underway to elucidate the mechanistic details of this reaction and to disclose the scope and limitations of this reaction. Work along this line is currently in progress.

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5 The *syn* and *anti* ratio of **2a** was determined by the ^{1}H NMR spectral data based on the *J* value of H^a and H^b (Scheme 1) because the *anti*-isomer usually has bigger *J* value (for *anti*-**2a**: JH^aH^b = 6.3 Hz, for *syn*-**2a**: JH^aH^b = 2.8 Hz). The spectral data of **1a**: mp 76–77 °C; IR (KBr) ν 1658 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.37 (3H, s, Me), 3.34 (1H, d, *J* = 5.3 Hz, OH), 5.69 (1H d, *J* = 5.3 Hz), 6.04 (1H, s), 6.28 (1H, s), 7.56 (2H, d, *J* 8.6 Hz, Ar), 8.25 (2H, d, *J* 8.6 Hz, Ar); MS (EI) *m*/*z* 220 (M^+ − 1, 20.9), 204 (M^+ − 17, 100), 174 (M^+ − 47, 88.1). The spectral data of *anti*-**2a**: a colorless oil; IR (KBr) ν 1709 and 1676 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.07 (3H, s, Me), 2.37 (3H, s, Me), 2.52 (1H, dd, *J* = 13.8, 5.2 Hz, CH), 2.60 (1H, dd, *J* = 13.8, 7.9 Hz, CH), 3.15–3.25 (1H, m, CH), 3.76 (1H, d, *J* = 7.4 Hz, OH), 4.80 (1H, t, *J* = 6.3 Hz, CH), 5.92 (1H, s), 6.12 (1H, s), 7.55 (2H, d, *J* = 9.4 Hz, Ar), 8.22 (2H, d, *J* = 9.4 Hz, Ar); MS (EI) *m*/*z* 274 (M^+ − 18, 13.2), 232 (M^+ − 59, 24.5), 97 (M^+ − 194, 44), 43 (M^+ − 248, 100). The spectral data of *syn*-**2a**: a colorless oil; IR (KBr) ν 1709 and 1676 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.04 (3H, s, Me), 2.25 (3H, s, Me) 2.52 (1H, dd, *J* = 13.8, 5.2 Hz, CH) 2.60 (1H, dd, *J* = 13.8, 7.9 Hz, CH), 3.15–3.25 (1H, m, CH), 3.67 (1H, d, *J* = 2.8 Hz, OH), 5.0 (1H, t, *J* = 2.8 Hz, CH), 5.73 (1H, s), 5.97 (1H, s), 7.53 (2H, d, *J* = 9.4 Hz, Ar), 8.20 (2H, d, *J* = 9.4 Hz, Ar); MS (EI) *m*/*z* 274 (M^+ − 18, 13.2), 232 (M^+ − 59, 24.5), 97 (M^+ − 194, 44), 43 (M^+ − 248, 100).

6 The spectral data of **3a**: a colorless oil; IR (KBr) ν 1712 and 1675 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.15 (3H, s, Me), 2.78 (3H, s, Me), 2.69 (2H, t, *J* = 7.2 Hz, CH_2), 3.50–3.62 (1H, m, CH), 3.62–3.74 (1H, m, H), 5.4 (1H, s), 6.23 (1H, s), 7.53 (2H, d, *J* = 9.4 Hz, Ar), 8.20 (2H, d, *J* = 9.4 Hz, Ar); MS (EI) *m*/*z* 291 (M^+, 3.2), 274 (M^+ − 18, 10.5), 72 (M^+ − 219, 24.2), 43 (M^+ − 248, 100).

7 Dimer could be obtained from methyl vinyl ketone in the presence of DABCO. The ^{1}H NMR data of dimer: IR (KBr) ν 1714 and 1676 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.07 (3H, s, Me), 2.29 (3H, s, Me), 2.40–2.54 (4H, m, CH_2), 5.80 (1H, s, CH), 6.0 (1H, s, CH); MS (EI) *m*/*z* 141 (MH^+, 0.84), 125 (M^+ − 15, 60), 97 (M^+ − 43, 100), 43 (M^+ − 97, 100).

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