

Baylis-Hillman Reaction of Arylaldehydes with Phenyl Vinyl Ketone, Phenyl Acrylate, and Phenyl Thioacrylate

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In the *Baylis-Hillman* reaction of aryl aldehydes with phenyl vinyl ketone, we found that the diadduct **4** was exclusively formed, and that the yield of **4** can reach 80% with increasing amounts of phenyl vinyl ketone. But, for phenyl acrylate and phenyl thioacrylate, only the normal *Baylis-Hillman* adduct was obtained. The substituent effects were also examined, and a plausible reaction mechanism was proposed for the formation of **4**.

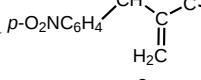
Introduction. – Great progress has made in the execution of the *Baylis-Hillman* reaction [1], for which a catalytic asymmetric version has been published [2], since *Baylis* and *Hillman* first reported in 1972 the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of 1,4-diazabicyclo[2.2.2]octane (DABCO) [3]. However, during our own investigation of 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 equiv.) and MVK (2.0 equiv.) as substrates in the presence of catalytic amounts of DABCO (0.1 equiv.) 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 2:3 mixture of *syn*- and *anti*-isomers (*Scheme 1*) [5], and the substituent effects of arylaldehydes have been extensively examined [5]. This interesting result stimulated us to further examine the influence of the R group of the *Baylis-Hillman* acceptor (C=C–C(O)R) on this reaction. Thus, we synthesized phenyl vinyl ketone (PVK) [6], phenyl acrylate [7], and phenyl thioacrylate [8] as *Baylis-Hillman* acceptors and carefully examined the reaction products formed under the traditional *Baylis-Hillman* reaction conditions.

Results and Discussion. – We found that, in the reaction of *p*-nitrobenzaldehyde (1.0 equiv.) with PVK (1.0 equiv.) in the presence of DABCO (10 mol-%) in DMF, the corresponding *Baylis-Hillman* adduct **3a** (*i.e.*, the normal *Baylis-Hillman* adduct) was not formed at all. The major reaction product was the 1:2 adduct **4a** as a mixture of *syn*- and *anti*-isomers, along with some PVK dimer (*Scheme 2*). Of course, as expected, **4a** was obtained in higher yields when 1.0 equiv. *p*-nitrobenzaldehyde and 2 equiv. of PVK were used in the presence of DABCO (10 mol-%). Results are summarized in *Table 1*. When the reaction was carried out in DMSO, THF, or CH₂Cl₂, similar results were obtained (*Table 1, Entries 1–3*). With DMAP as the *Lewis* base under the same reaction conditions, **4a** was obtained in lower yields (*Table 1, Entries 4 and 5*). Increasing

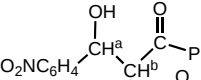
$$p\text{-O}_2\text{NC}_6\text{H}_4\text{—CHO} + \text{CH}_2=\text{C}(\text{Me})\text{C}(\text{OH})\text{Me} \xrightarrow[\text{solvent}]{\text{Lewis base}} p\text{-O}_2\text{NC}_6\text{H}_4\text{—CH}(\text{OH})\text{C}(\text{Me})=\text{CH}_2 \quad \mathbf{1a}$$

$$+ p\text{-O}_2\text{NC}_6\text{H}_4\text{—CH}(\text{OH})\text{CH}(\text{Me})\text{CH}_2\text{C}(\text{Me})=\text{CH}_2 \quad \mathbf{2a}$$

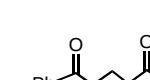
$p\text{-O}_2\text{NC}_6\text{H}_4\text{-CHO} + \text{CH}_2=\text{C}(\text{Ph})\text{C}(\text{O})\text{Ph} \xrightarrow[\text{solvent}]{\text{Lewis base}}$



3a



4a



PVK dimer

Entry	Lewis base	Solvent	<i>T</i> [°]	Time [h]	Yield [%] ^{a)}	
					4a ^{b)}	PVK dimer
1	DABCO	DMSO	20	60	75	10
2	DABCO	DMF	20	60	88	14
3	DABCO	CH ₂ Cl ₂	20	60	81	12
4	DABCO	THF	20	60	78	16
5	DMAP	DMSO	20	60	65	21
6	DMAP	DMF	20	60	63	20
7	DABCO	DMF ^{c)}	20	60	80	11
8	DABCO	DMF ^{d)}	20	60	60	13
9	PBu ₃	DMF	20	60	trace	36
10	DABCO	DMF	− 30	60	70	8

a) Yield of isolated product. b) *syn/anti* 2 : 3. c) *p*-Nitrobenzaldehyde/PVK 1 : 3. d) *p*-Nitrobenzaldehyde/PVK 1 : 4.

the amounts of PVK did not improve the yields of **4a** (Table 1, Entries 6 and 7). At lower temperature (-30°), **4a** was obtained in 70% yield (Table 1, Entry 9), and, with PBu_3 as the *Lewis* base, only traces of **4a** were obtained. The optimized reaction conditions were found to be 1.0 equiv. arylaldehyde in reaction with 2.0 equiv. PVK in the presence of 10 mol-% DABCO in DMF.

We next investigated the reactions of other arylaldehydes with PVK under the optimized reaction conditions (Scheme 3). With electron deficient arylaldehydes, such as nitrobenzaldehydes or pyridylaldehydes, the reaction proceeded smoothly to give **4** in good yield. However, with *p*-chlorobenzaldehyde or benzaldehyde, only trace amounts of the 1:2 adduct **4** were obtained and the PVK dimer was formed almost exclusively (Scheme 3, Table 2) [7]. In all cases, the normal *Baylis-Hillman* adduct **3** was not formed.

Scheme 3

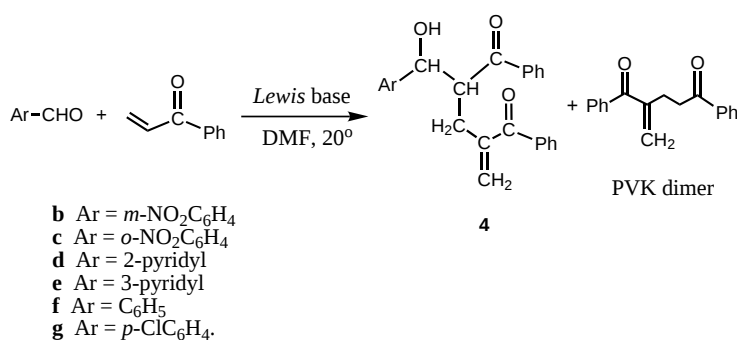


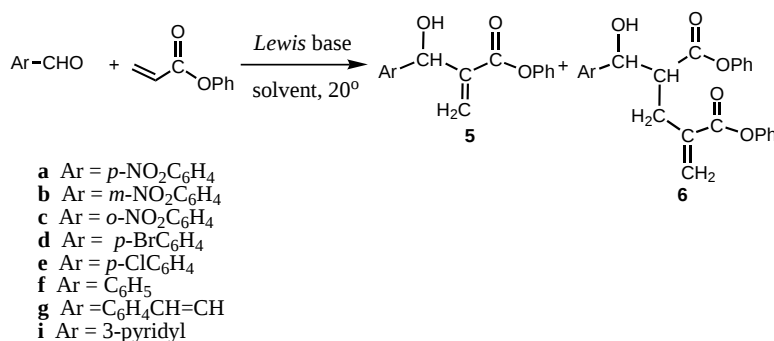
Table 2. Baylis-Hillman Reactions of Arylaldehydes (1.0 equiv.) with PVK (2.0 equiv.) in the Presence of the *Lewis* Base DABCO (0.1 equiv.) in DMF at 20°

Entry	R	Time [h]	Yield [%] ^{a)}	
			4 (syn/anti)	PVK dimer
1	<i>m</i> -NO ₂ C ₆ H ₄	60	76 (2:3)	15
2	<i>o</i> -NO ₂ C ₆ H ₄	60	79 (3:4)	16
3	Pyridin-2-yl	70	82 (3:5)	20
4	Pyridin-3-yl	70	81 (2:3)	16
5	Ph	70	trace	33
6	<i>p</i> -ClC ₆ H ₄	70	trace	29

^{a)} Yield of isolated product.

In addition, the *Baylis-Hillman* reactions with phenyl acrylate or phenyl thioacrylate as the acceptor were also examined (Schemes 4 and 5). With phenyl acrylate as the acceptor, the normal *Baylis-Hillman* adduct **5** was obtained exclusively in most cases (Table 3, Entries 1, 2, and 4–8). Only in the reaction of *o*-nitrobenzaldehyde with phenyl acrylate was diadduct **6c** formed in 29% yield (Table 3, Entry 3). However, with phenyl thioacrylate as a *Baylis-Hillman* acceptor, only in the reaction of *p*-chlorobenzaldehyde with phenyl thioacrylate was the corresponding *Baylis-Hillman*

Scheme 4



Scheme 5

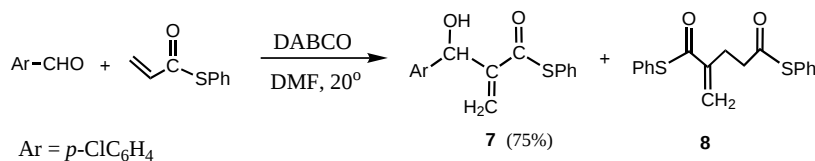


Table 3. Baylis-Hillman Reactions of Arylaldehydes (1.0 equiv.) with Phenyl Acrylate (2.0 equiv.) in the Presence of the Lewis Base DABCO (0.1 equiv.) at 20°

Entry	R	Solvent	Time [h]	Yield [%] ^{a)}	
				5	6
1	<i>p</i> -NO ₂ C ₆ H ₄	DMSO	40	75	0
2	<i>m</i> -NO ₂ C ₆ H ₄	DMF	40	74	0
3	<i>o</i> -NO ₂ C ₆ H ₄	DMF	40	53	29
4	<i>p</i> -BrC ₆ H ₄	DMF	50	78	0
5	<i>p</i> -ClC ₆ H ₄	DMF	50	71	0
6	C ₆ H ₅	DMF	50	79	0
7	C ₆ H ₅ CH=CH	DMF	40	57	0
8	Pyridin-3-yl	DMF	40	78	0

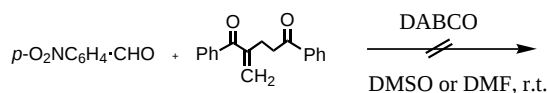
^{a)} Yield of isolated product.

adduct **7** obtained in good yield (Scheme 5). The reactions of other arylaldehydes with phenyl thioacrylate either are very sluggish or gave many unidentified products.

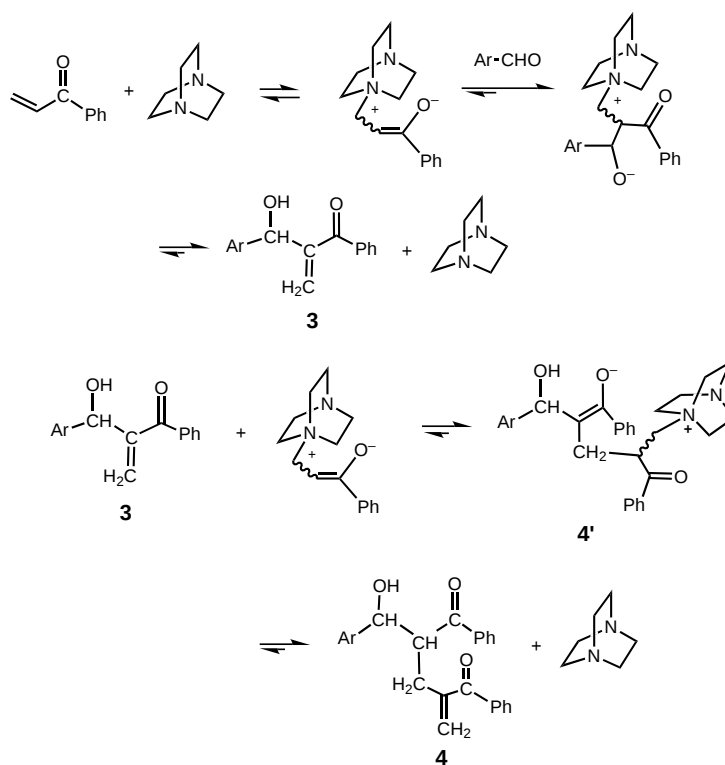
In the traditional *Baylis-Hillman* reaction, in which PVK is used as the acceptor, the exclusive formation of diadduct has never been reported before. To clarify the mechanism for formation of **4**, we carried out reactions of *p*-nitrobenzaldehyde (1.0 equiv.) with PVK dimer (1.0 equiv.) in the presence of catalytic amounts of DABCO (0.1 equiv.). As we found that no reactions occurred under these conditions (Scheme 6), we believe that the diadduct **4** was derived from a second reaction of the normal *Baylis-Hillman* adduct **3** with PVK. In Scheme 7, we formulate a plausible reaction mechanism. Two reactions occur for the traditional *Baylis-Hillman* reaction of

arylaldehydes with PVK. One is the normal *Baylis-Hillman* reaction, which involves the 1,2-addition of the PVK-derived anion to *p*-nitrobenzaldehyde. Another is the conjugated addition (*Michael* addition) of the anion derived from a second molecule of PVK to **3** via intermediate **4'** (Scheme 7). Compared to MVK, the phenyl group of PVK can significantly stabilize the enolate formed, including the intermediate **4'** (Scheme 7). Thus, the normal *Baylis-Hillman* adduct **3** formed can more easily undertake the next conjugate addition (*Michael* addition) of the anion derived from the second molecule of PVK to afford exclusively the diadduct **4**.

Scheme 6



Scheme 7



Conclusions. – We found that, in the *Baylis-Hillman* reaction of arylaldehydes with PVK, diadduct **4** was exclusively formed and was confirmed to be derived from a second reaction of the normal *Baylis-Hillman* adduct with PVK via a conjugated addition reaction. On the other hand, with phenyl acrylate or phenyl thioacrylate as an acceptor, only the normal *Baylis-Hillman* reaction products were produced. Efforts are

currently underway to elucidate the mechanistic details of this reaction and to determine its scope and limitations.

Experimental Part

General. Commercially obtained reagents were used without further purification. Org. solvents were dried by standard methods when necessary. All reactions were monitored by TLC on *Huanghai GF₂₅₄* silica-gel-coated plates. Flash column chromatography (FC) was carried out with 200–300-mesh silica gel at increased pressure. M.p.: *Yanagimoto* micro-melting-point apparatus; uncorrected. IR: KBr; ν in cm^{-1} . $^1\text{H-NMR}$: *Bruker AM-300* spectrometer; in CDCl_3 ; δ in ppm relative to SiMe_4 as internal standard; J in Hz. MS and HR-MS: *HP-5989* and *Finnigan MA* + mass spectrometer, resp. Some of the solid compounds reported in this paper gave satisfactory CHN microanalyses with a *Carlo-Erba 1106 Analyzer*.

Typical Procedure for the Baylis-Hillman Reaction. To a soln. of DABCO (6 mg, 0.05 mmol) and *p*-nitrobenzaldehyde (76 mg, 0.50 mmol) in DMF (0.50 ml) was added PVK (132 mg, 1.0 mmol), and the mixture was stirred at r.t. for 60 h. The mixture was extracted with CH_2Cl_2 (10.0 ml) and washed with H_2O (3×10.0 ml). The org. layer was dried (anh. MgSO_4), the solvent was removed under reduced pressure, and the residue was purified by FC (SiO_2 ; AcOEt /petroleum ether 1 : 4) to give **4a** (180 mg, 88%, *syn/anti* 2 : 3) and PVK dimer (25 mg, 14%) as a colorless oil. The *syn/anti* ratio of **4a** was determined from the $^1\text{H-NMR}$ spectral data based on the J values of H^a and H^b (Scheme 1); the *anti*-isomer usually has a larger J value (for *anti*-**4a**: $J(\text{H}^a, \text{H}^b) = 4.6$, for *syn*-**4a**: $J(\text{H}^a, \text{H}^b) = 2.8$).

Data of *syn*-2-[(Hydroxy)(4-nitrophenyl)methyl]-4-methylidene-1,5-diphenylpentane-1,5-dione (syn-4a): IR: 1649, 1668 ($\text{C}=\text{O}$). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): 2.86–2.93 (*m*, CH_2); 4.09 (*d*, $J = 2.6$, OH); 4.20–4.30 (*m*, CH); 5.16 (*dd*, $J = 2.8, 2.6$, CH); 5.55 (*s*, 1 H); 5.82 (*s*, 1 H); 7.20–7.60 (*m*, 10 arom. H); 7.87 (*d*, $J = 8.6$, 2 arom. H); 8.10 (*d*, $J = 8.6$, 2 arom. H). EI-MS: 397 (0.2, $[M - 18]^+$), 378 (0.2, $[M - 37]^+$), 159 (50.1, $[M - 256]^+$), 105 (100, $[M - 310]^+$). EI-HR-MS: 415.1411 (M^+ , $\text{C}_{25}\text{H}_{21}\text{NO}_5$, calc. 415.1420).

Data of *anti*-4a: IR: 1649, 1668 ($\text{C}=\text{O}$). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): 2.93–3.10 (*m*, CH_2); 4.30–4.40 (*m*, CH); 4.42 (*d*, $J = 8.2$, OH); 5.06 (*dd*, $J = 8.2, 4.6$, CH); 5.74 (*s*, 1 H); 6.07 (*s*, 1 H); 7.20–7.60 (*m*, 10 arom. H); 7.87 (*d*, $J = 8.6$, 2 arom. H); 8.10 (*d*, $J = 8.6$, 2 arom. H). EI-MS: 397 (0.2, $[M - 18]^+$), 378 (0.2, $[M - 37]^+$), 159 (50.1, $[M - 256]^+$), 105 (100, $[M - 310]^+$). EI-HR-MS: 415.1411 (M^+ , $\text{C}_{25}\text{H}_{21}\text{NO}_5$, calc. 415.1420).

PVK Dimer could be obtained as a colorless oil from PVK in the presence of DABCO. IR: 1650, 1680 ($\text{C}=\text{O}$). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): 2.91 (*t*, $J = 7.3$, CH_2); 3.23 (*t*, $J = 7.3$ Hz, CH_2); 5.67 (*s*, 1 H); 5.96 (*s*, 1 H); 7.30–7.55 (*m*, 6 arom. H); 7.70–7.75 (*m*, 2 arom. H); 7.90–8.0 (*m*, 2 arom. H). EI-MS: 264 (1.0, M^+), 159 (63.8, $[M - 105]^+$), 105 (100, $[M - 159]^+$), 77 (54.2, $[M - 187]^+$). EI-HR-MS: 264.1142 (M^+ , $\text{C}_{18}\text{H}_{16}\text{O}_2$, calc. 264.1150).

Data of 2-[(Hydroxy)(4-nitrophenyl)methyl]-1-phenoxyprop-2-en-1-one (5a): Colorless oil. IR: 1723 ($\text{C}=\text{O}$). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): 3.28 (*d*, $J = 5.6$, OH); 5.75 (*d*, $J = 5.6$, CH); 6.12 (*s*, 1 H); 6.68 (*s*, 1 H); 6.98–7.10 (*m*, 2 arom. H); 7.20–7.35 (*m*, 1 arom. H); 7.34–7.50 (*m*, 2 arom. H); 7.63 (*d*, $J = 8.5$, 2 arom. H); 8.23 (*d*, $J = 8.5$, 2 arom. H). EI-MS: 281 (6.0, $[M - 18]^+$). EI-HR-MS: 299.0788 (M^+ , $\text{C}_{16}\text{H}_{13}\text{NO}_5$, calc. 299.0794).

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