

Aza-Morita–Baylis–Hillman reaction of ethyl (arylimino)acetate with methyl vinyl ketone and ethyl vinyl ketone

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Abstract—Aza-Morita–Baylis–Hillman (aza-MBH) reaction of ethyl (arylimino)acetate with methyl vinyl ketone and ethyl vinyl ketone has been investigated. We found that aza-MBH adducts **1** could be formed in the presence of DABCO (30 mol %) and the corresponding adducts **2** could be obtained in the presence of PPh₃ (30 mol %) in moderate to good yields in acetonitrile under mild conditions, respectively.

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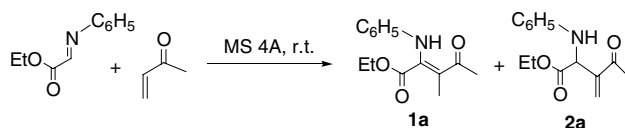
Recently, the aza-Morita–Baylis–Hillman (aza-MBH) reaction of N-sulfonated imines (ArCH=NTs) or N-phosphorated imines [ArCH=NP(O)R₂] with various Michael acceptors such as methyl vinyl ketone and ethyl vinyl ketone has received much attention,¹ and several excellent reaction systems using chiral nitrogen and phosphine Lewis bases such as multifunctional organocatalysts to achieve high enantioselectivities in aza-MBH reaction have been reported.² Therefore, it is interesting to explore a novel type of aza-MBH reaction of other imines with various Michael acceptors. During our ongoing investigation on the aza-MBH reaction, we found that the aza-MBH reaction of ethyl (arylimino)acetate³ with methyl vinyl ketone (MVK) and ethyl vinyl ketone (EVK) afforded different products using 1,4-diazabicyclo[2,2,2]octane (DABCO) and triphenylphosphine (PPh₃) as the Lewis base catalysts under otherwise identical conditions. Herein, we report the initial scope of this finding and present a preliminary mechanistic study revealing the transformation of these two products.

An initial examination was carried out using ethyl (phenylimino)acetate (0.5 mmol) as a substrate in the

aza-MBH reaction with MVK (0.75 mmol) in the presence of DABCO (30 mol %) and molecular sieves 4 Å (100 mg)⁴ without solvent (in a neat condition) at room temperature (20 °C). We found that the corresponding aza-Baylis–Hillman adduct **1a** was obtained in a 55% yield after four days (Table 1, entry 1). In order to improve the yield of **1a**, solvent effects were examined by carrying out the reaction in a variety of solvents such as tetrahydrofuran (THF), 1,2-dichloroethane (DCE), dichloromethane (DCM), *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and so on under otherwise identical conditions (Table 1, entries 2–13). We found that in acetonitrile (CH₃CN), **1a** was obtained in a 76% yield (Table 1, entry 9) and in other solvents, **1a** was obtained in trace to moderate yields even in mixed solvents of CH₃CN and DMF (Table 1, entries 12 and 13). Using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 4-dimethylaminopyridine (DMAP) as the Lewis base catalyst in CH₃CN, **1a** was either obtained in a 12% yield or a disordered reaction was observed (Table 1, entries 14 and 15). These results indicated that the present best reaction conditions for the formation of **1a** are to carry out the reaction in CH₃CN using DABCO as the catalyst. However, using triphenylphosphine (PPh₃) (30 mol %) as a Lewis base catalyst in the reaction, a different aza-MBH adduct **2a** was obtained in a 69% yield after three days in CH₃CN (Table 1, entry 16). Other more nucleophilic tertiary phosphines such as PBu₃, PPh₂Me and PPhMe₂ gave

Keywords: Aza-Morita–Baylis–Hillman; Ethyl (arylimino)acetate; Methyl vinyl ketone; Ethyl vinyl ketone; DABCO; PPh₃.

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Table 1. Aza-MBH reaction of ethyl (phenylimino)acetate with methyl vinyl ketone in the presence of various lewis base catalysts in a variety of solvents^a

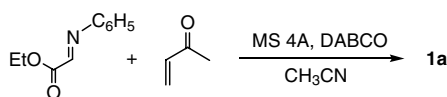
Entry	Solvent	Catalyst	Time (day)	Yield ^b (%)	
				1a	2a
1	Neat	DABCO	4	55	
2	THF	DABCO	4	22	
3	DCE	DABCO	4	Trace	
4	DCM	DABCO	4	Trace	
5	DMF	DABCO	4	36	
6	DMSO	DABCO	4	Trace	
7	Toluene	DABCO	4	19	
8	<i>tert</i> -Amyl-OH	DABCO	4	25	
9	CH ₃ CN	DABCO	4	76	
10	CH ₃ OH	DABCO	4	Disordered	
11	CCl ₄	DABCO	4	Trace	
12	CH ₃ CN:DMF = 1:1	DABCO	4	33	
13	CH ₃ CN:DMF = 4:1	DABCO	4	46	
14	CH ₃ CN	DBU	4	12	
15	CH ₃ CN	DMAP	4	Disordered	
16	CH ₃ CN	PPh ₃	3		69
17	CH ₃ CN	PBu ₃	3		Disordered
18	CH ₃ CN	PPh ₃ Me	3		Disordered
19	CH ₃ CN	PPhMe ₂	3		Disordered

^a Ethyl (phenylimino)acetate (0.5 mmol), methyl vinyl ketone (0.75 mmol), DABCO (0.15 mmol), PPh₃ (0.15 mmol) and solvent (1.5 mL) were used.

^b Isolated yield.

disordered reactions (Table 1, entries 17–19). Using PPh₃ as the Lewis base promoter in neat condition, toluene or THF, **2a** was produced in 40%, 46% and 35% yields, respectively. While in DMF, a disordered reaction was observed. Therefore, acetonitrile is the best solvent for this interesting PPh₃ promoted aza-MBH reaction.

In order to further optimize these conditions, we next examined the aza-MBH reaction of ethyl (phenylimino)acetate with MVK in different ratios of imine with MVK, temperatures and concentrations in CH₃CN. The results are summarized in Tables 2 and 3, respectively.

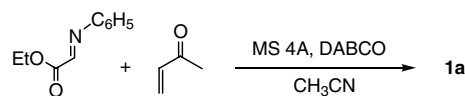
Table 2. Aza-MBH reaction of ethyl (phenylimino)acetate with methyl vinyl ketone in CH₃CN at different temperatures^a

Entry	Molar ratio Imine: MVK	Temperature (°C)	Time (day)	Yield ^b (%) 1a
1	1:1.5	85	2	Disordered
2	1:1.5	rt	4	76
3	1:1.5	0	23	Trace
4	1:3	85	2	Disordered
5	1:3	rt	3	Disordered

^a Ethyl (phenylimino)acetate (0.5 mmol), methyl vinyl ketone (0.75–1.5 mmol), DABCO (0.15 mmol), (0.15 mmol) and acetonitrile (1.5 mL) were used.

^b Isolated yields.

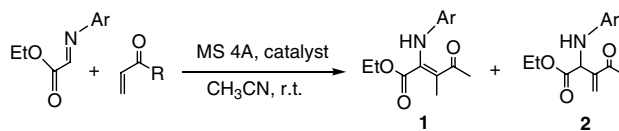
When the reaction was carried out with imine: MVK = 1:1.5 at 85 °C, a disordered reaction was observed. At 0 °C, trace of **1a** was obtained even after a prolonged reaction time (Table 2, entries 1–3). Increasing the amount of MVK did not improve the yield of **1a** at room temperature and at 80 °C (Table 2, entries 4 and 5). When the employed amounts of DABCO was reduced to 20 and 10 mol %, the yields of **1a** decreased to 45% and 38%, respectively (Table 3, entries 1 and 2). Increasing or decreasing the concentrations of substrates in CH₃CN did not improve the yields of **1a**

Table 3. The aza-MBH reaction of ethyl (phenylimino)acetate with methyl vinyl ketone in the presence of various amounts of DABCO and in different concentrations in CH₃CN at room temperature^a

Entry	DABCO (mol %)	Solvent (mL)	Yield ^b (%) 1a
1	20	1.5	45
2	10	1.5	38
3	30	1	34
4	30	2	34
5	30	3	30
6	30	4	28
7	30	5	21

^a Ethyl (phenylimino)acetate (0.5 mmol), methyl vinyl ketone (0.75 mmol) and acetonitrile (1.5–5.0 mL) were used.

^b Isolated yields.

Table 4. The aza-MBH reaction of a variety of ethyl (arylimino)acetate with methyl vinyl ketone in CH₃CN in the presence of DABCO and PPh₃ at room temperature^a

Entry	Ar	Catalyst	R	Time (day)	Yield ^b (%)	
					1	2
1	<i>p</i> -CH ₃ C ₆ H ₄	DABCO PPh ₃	Me	3	1b , 34	
			Me	2		
2	<i>p</i> -BrC ₆ H ₄	DABCO PPh ₃	Me	2	1c , 64	
			Me	4		
3	<i>p</i> -ClC ₆ H ₄	DABCO PPh ₃	Me	4	1d , 70	
			Me	4		
4	<i>m</i> -CH ₃ C ₆ H ₄	DABCO PPh ₃	Me	3	1e , 63	
			Me	3		
5	<i>m</i> -CF ₃ C ₆ H ₄	DABCO PPh ₃	Me	2	1f , 85	
			Me	2		
6	<i>p</i> -Cl, <i>o</i> -CH ₃ C ₆ H ₃	DABCO PPh ₃	Me	4	1g , 75	
			Me	3		
7	<i>p</i> -CH ₃ C ₆ H ₄	DABCO PPh ₃	Et	4	1h , 51	
			Et	4		
8	<i>m</i> -CH ₃ C ₆ H ₄	DABCO PPh ₃	Et	4	1i , 72	
			Et	3		
9	<i>p</i> -Cl, <i>o</i> -CH ₃ C ₆ H ₃	DABCO PPh ₃	Et	4	1j , 50	
			Et	3		

^a Ethyl (arylimino)acetate (0.5 mmol), methyl vinyl ketone (0.75 mmol), DABCO (0.15 mmol), PPh₃ (0.15 mmol) and solvent (1.5 mL) were used.

^b Isolated yields.

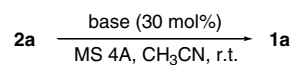
under otherwise identical conditions (Table 3, entries 4–7). Thus, this aza-MBH reaction should be carried out in CH₃CN at room temperature (20 °C) with a ratio of imine:MVK = 1:1.5.

Under these optimized reaction conditions, we next carried out this interesting aza-MBH reaction of a variety of ethyl (arylimino)acetate with MVK in CH₃CN in the presence of DABCO and PPh₃ at room temperature. The results are summarized in Table 4. As can be seen from Table 4, the corresponding aza-MBH adducts **1b–j** and **2b–j** were obtained in moderate to good yields in the presence of DABCO (30 mol %) and PPh₃ (30 mol %) in CH₃CN, respectively (Table 4, entries 1–6). For sterically encumbered ethyl (arylimino)acetate, the corresponding aza-Baylis–Hillman adducts **1g** and **2g** were obtained in 75% and 52% yields in the presence of DABCO (30 mol %) and PPh₃ (30 mol %), respectively (Table 4, entry 6). Using EVK as a Michael acceptor, similar results were obtained (Table 4, entries 7–9). However, using methyl acrylate (R = OMe) or acrolein (R = H) as a Michael acceptor, no reaction occurred under identical conditions.

Since adducts **1** are a kind of ‘abnormal’ products⁵ in aza-MBH reaction, it is necessary to confirm the pathway for the formation of **1** in the presence of DABCO. Thus, several control experiments were carried out for the transformation of **2a** to **1a** in the presence of various bases. We found that in the presence of DABCO (30 mol %) and Et₃N (30 mol %), **2a** could be transformed to **1a** in 90% and 52% yields, respectively, under

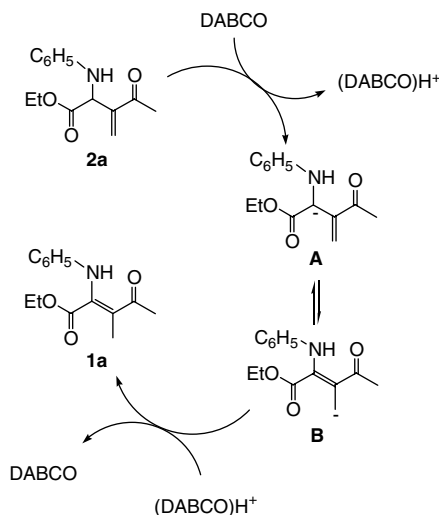
the standard reaction conditions (Scheme 1). ^tPr₂NEt, a non-nucleophilic and weak base, is less effective in the transformation. In addition, disordered reactions were observed in the presence of strong base DBU and inorganic base K₂CO₃ (Scheme 1). On the basis of the above results, we believe that adducts **1** are derived from the normal aza-MBH adducts **2** during the reaction using DABCO as a Lewis base catalyst. A plausible mechanism is shown in Scheme 2. DABCO abstracts a proton from **2a** to give intermediate **A**, which is in equilibrium with intermediate **B**. The reprotonation of **B** with (DABCO)H⁺ produces **1a** (Scheme 2).

In summary, we have presented an interesting aza-MBH reaction of ethyl (arylimino)acetate with MVK and EVK under mild conditions.⁶ We found that aza-MBH adducts **1** could be formed in the presence of DABCO (30 mol %) and the corresponding adducts **2** could be obtained in the presence of PPh₃ (30 mol %) in moderate to good yields in acetonitrile under mild conditions. Efforts are in progress to further confirm the mechanistic details of this aza-MBH reaction and to understand its scope and limitations.



bases: DABCO, 90%; Et₃N, 52%; ^tPr₂NEt, 4%; DBU, disordered; K₂CO₃, disordered.

Scheme 1. Transformation of **2a** to **1a** in the presence of various bases.



Scheme 2. Mechanism of the transformation of **2a** to **1a** in the presence of DABCO.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2006.08.131](https://doi.org/10.1016/j.tetlet.2006.08.131).

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- The yield of the aza-Baylis–Hillman adduct can be improved in the presence of molecular sieves 4 Å to get rid of the moisture, since part of the imine will be decomposed by ambient moisture during the reaction.
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- General reaction procedure. To a mixture of ethyl (arylimino)acetate (0.5 mmol), methyl vinyl ketone (0.75 mmol), DABCO (0.15 mmol), 4 Å molecular sieves (100 mg) was added solvent (1.5 mL), and the solution was stirred under argon atmosphere at room temperature for the required time indicated in the tables. After the reaction, solution was concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/18) to afford the corresponding pure product **1**.

Compound **1a**: A yellow oil. IR (KBr): ν 3383, 2982, 2935, 1736 (C=O), 1568, 1501, 1260, 974 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz, TMS): δ 1.09 (t, $J = 7.2$ Hz, 3H, CH_3), 1.92 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.16 (q, $J = 7.2$ Hz, 2H, CH_2), 7.03 (d, $J = 8.1$ Hz, 2H, Ar), 7.11 (t, $J = 7.8$ Hz, 1H, Ar), 7.25–7.30 (m, 2H, Ar), 12.15 (s, 1H, NH). ^{13}C NMR (CDCl_3 , 75 MHz): δ 13.5, 14.7, 28.9, 61.7, 101.4, 121.8, 124.7, 129.1, 139.6, 148.1, 164.3, 200.9. MS (EI) m/z 247 (M^+ , 15.71), 174 ($\text{M}^+ - 73$, 74.86), 132 ($\text{M}^+ - 115$, 33.88), 130 ($\text{M}^+ - 117$, 24.54), 104 ($\text{M}^+ - 143$, 78.70), 93 ($\text{M}^+ - 154$, 38.63), 77 ($\text{M}^+ - 170$, 100), 51 ($\text{M}^+ - 196$, 46.34). HRMS (EI) calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_3$ requires 247.1208, found: 247.1216.

To a mixture of ethyl (arylimino)acetate compound (0.5 mmol), methyl vinyl ketone (0.75 mmol), PPh_3 (0.15 mmol), 4 Å molecular sieves (100 mg) was added solvent (1.5 mL), and the solution was stirred under argon atmosphere at room temperature for the required time indicated in the tables. After the reaction solution was concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/18) to afford the corresponding pure product **2**.

Compound **2a**: A yellow oil. IR (KBr): ν 3394, 2923, 2852, 1737 (C=O), 1680, 1603, 1506, 751 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz, TMS): δ 1.24 (t, $J = 7.2$ Hz, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.20 (q, $J = 7.2$ Hz, 2H, CH_2), 5.14 (s, 1H, CH), 6.14 (s, 1H, =CH), 6.17 (s, 1H, =CH), 6.58 (d, $J = 7.8$ Hz, 2H, Ar), 6.74 (t, $J = 7.5$ Hz, 1H, Ar), 7.16 (t, $J = 7.8$ Hz, 2H, Ar). ^{13}C NMR (CDCl_3 , 75 MHz): δ 14.0, 26.1, 55.9, 61.8, 113.4, 118.2, 126.7, 129.2, 145.5, 145.6, 171.0, 198.4. MS (EI) m/z 247 (M^+ , 6.98), 174 ($\text{M}^+ - 73$, 100), 132 ($\text{M}^+ - 115$, 33.27), 130 ($\text{M}^+ - 117$, 51.12), 77 ($\text{M}^+ - 170$, 35.16), 57 ($\text{M}^+ - 190$, 17.44), 55 ($\text{M}^+ - 192$, 19.21), 43 ($\text{M}^+ - 204$, 99.19). HRMS (EI) calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_3$ requires 247.1208, found: 247.1220.