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Abnormal Aza-Baylis–Hillman Reaction of N-Tosylated Imines with Ethyl 2,3-Butadienoate and Penta-3,4-dien-2-one

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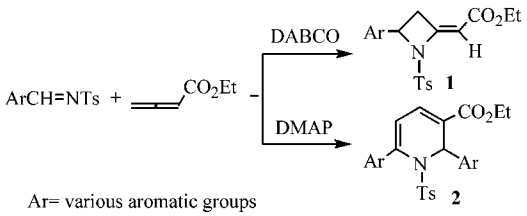
ABSTRACT



The attempted aza-Baylis–Hillman reaction of N-tosylated imines with ethyl 2,3-butadienoate or penta-3,4-dien-2-one gave azetidine derivatives in the presence of DABCO. In the case of the aza-Baylis–Hillman reaction of N-tosylated imines with ethyl 2,3-butandieonate catalyzed by DMAP, novel dihydropyridine derivatives were formed.

Investigation of the Baylis−Hillman reaction has made great progress,[1] including development of 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 a strong Lewis base such as 1,4-diazabicyclo[2,2,2]octane (DABCO) in 1972.[3] During our investigations on the aza-Baylis−Hillman reaction of N-tosylated imines with α,β-unsaturated enones, we found that either "normal" or "abnormal" aza-Baylis−Hillman adducts could be formed depending on the employed Lewis base under otherwise identical conditions.[4] In this paper, we wish to report the unprecedented abnormal aza-Baylis−Hillman reaction of N-tosylated imines with ethyl 2,3-butadienoate or penta-3,4-dien-2-one.[5−7]

In the aza-Baylis−Hillman reaction of N-tosylated imines with ethyl 2,3-butadienoate catalyzed by DABCO and 4-*N*,*N*-dimethylpyridine (DMAP), we found that the "abnormal" aza-Baylis−Hillman adducts **1** and **2**, respectively, were exclusively produced, within short reaction times (Scheme 1).

Scheme 1. Aza-Baylis−Hillman Reaction of N-Tosylated Imines with Ethyl 2,3-Butadienoate

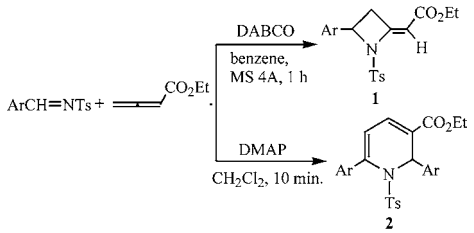


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Table 1. Aza-Baylis−Hillman Reaction of N-Tosylated Imines with Ethyl 2,3-Butadienoate Catalyzed by DABCO in Benzene

entry	Ar	1	% yield[a]
1	C_6H_5	**a**	57[b]
2	C_6H_5	**a**	82
3	*p*-MeC_6H_4	**b**	92
4	*p*-EtC_6H_4[c]	**c**	90
5	p-$MeOC_6H_4$	**d**	75
6	*p*-FC_6H_4	**e**	93
7	*m*-FC_6H_4	**f**	76
8	*p*-ClC_6H_4	**g**	92
9	*p*-BrC_6H_4	**h**	99
10	*o,m*-$Cl_2C_6H_3$	**i**	99
11	*p*-$CF_3C_6H_4$	**j**	85
12	*m*-$NO_2C_6H_4$	**k**	87
13	1-naphthyl	**l**	99
14	3-pyridyl	**m**	42

[a] Isolated yield. [b] In the absence of 4 Å molecular sieve. [c] Reaction was carried out at room temperature for 3 h.

The results are summarized in Table 1 and Table 2. In most cases of the aza-Baylis−Hillman reaction of N-tosylated imines (0.25 mmol) with ethyl 2,3-butadienoate (0.3 mmol) in the presence of DABCO (10 mol %) and 4 Å molecular sieves (100 mg),[8] the corresponding [4-aryl-1-(toluene-4-sulfonyl)azetidin-2-ylidene]acetic acid ethyl esters **1** were produced in good to high yields within 1 h in benzene with (*E*)-configuration (Table 1, entries 2−14).[9] Only for *N*-(*p*-methoxybenzylidene)-4-methylbenzenesulfonamide was a prolonged reaction time required (3 h) (Table 1, entry 5). Other nitrogen Lewis bases such as 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) and triethylamine (Et_3N) showed no catalytic activities for this reaction. However, using DMAP as a Lewis base, we found that the reaction proceeded quickly to produce 2,6-diaryl-1-(toluene-4-sulfonyl)-1,2-dihydropyridine-3-carboxylic acid esters **2** in moderate yields in dichloromethane (DCM) within 10 min (Table 2, entries 1−8).[9]

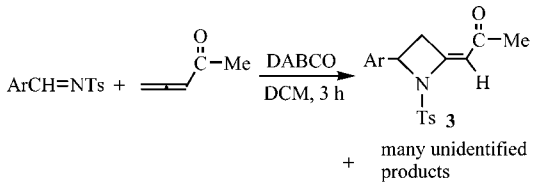
Using penta-3,4-dien-2-one as the substrate, we found that the same reaction also can take place under the same conditions. The results are summarized in Table 3. The corresponding 1-[4-aryl-1-(toluene-4-sulfonyl)azetidin-2-ylidene]propan-2-ones **3** were still obtained as the major products in moderate yields with (*E*)-configuration as well, but along with many unidentified products using DABCO as a Lewis base promoter in DCM (Table 3, entries 1−10).

Table 2. Aza-Baylis−Hillman Reaction of N-Tosylated Imines with Ethyl 2,3-Butadienoate Catalyzed by DMAP

entry	Ar	2	% yield[a]
1	C_6H_5	**a**	60
2	*p*-MeC_6H_4	**b**	44
3	*p*-$MeOC_6H_4$	**c**	30
4	*p*-FC_6H_4	**d**	36
5	*m*-FC_6H_4	**e**	41
6	*p*-ClC_6H_4	**f**	49
7	*p*-BrC_6H_4	**g**	34
8	*p*-$CF_3C_6H_4$	**h**	45
9	*m*-$NO_2C_6H_4$	**i**	31

[a] Isolated yield.

Table 3. Aza-Baylis−Hillman Reaction of N-Tosylated Imines with Penta-3,4-dien-2-one Catalyzed by DABCO



entry	Ar	3	% yield[a]
1	C_6H_5	**a**	43
2	*p*-MeC_6H_4	**b**	38
3	p-MeC_6H_4	**c**	35
4	*p*-FC_6H_4	**d**	34
4	*p*-FC_6H_4	**d**	34
5	*m*-FC_6H_4	**e**	32
6	*p*-ClC_6H_4	**f**	39
7	*p*-BrC_6H_4	**g**	40
8	*m*-$NO_2C_6H_4$	**h**	32
9	*o,m*-$Cl_2C_6H_3$	**i**	31
10	1-naphthyl	**j**	55

[a] Isolated yield.

Their structures were determined by spectroscopic data, microanalyses, and X-ray diffraction. The ORTEP drawings of **2a** and **3d** are shown in Supporting Information.[10]

The mechanism of these unprecedented abnormal aza-Baylis−Hillman reactions has not been unequivocally established, but one plausible explanation is proposed in Scheme 2 on the basis of previous investigations.[1,5−7] The nitrogen Lewis bases DABCO and DMAP act as a nucleophilic trigger and produce the intermediate **A**, which exists as a resonance-stabilized zwitterionic intermediate **A** (enolate) or **B** (allylic carbanion). In the case of DABCO, the allylic carbanion **B** adds to the N-tosylated imine to give the intermediate **C**, which undergoes an intramolecular

(5) Using triphenylphosphine or tributylphosphine as a Lewis base in the reaction of allenoates with N-tosylated imines generates a [3 + 2] cycloaddition to give five-membered pyrrolidine derivatives. (a) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031. (c) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535.

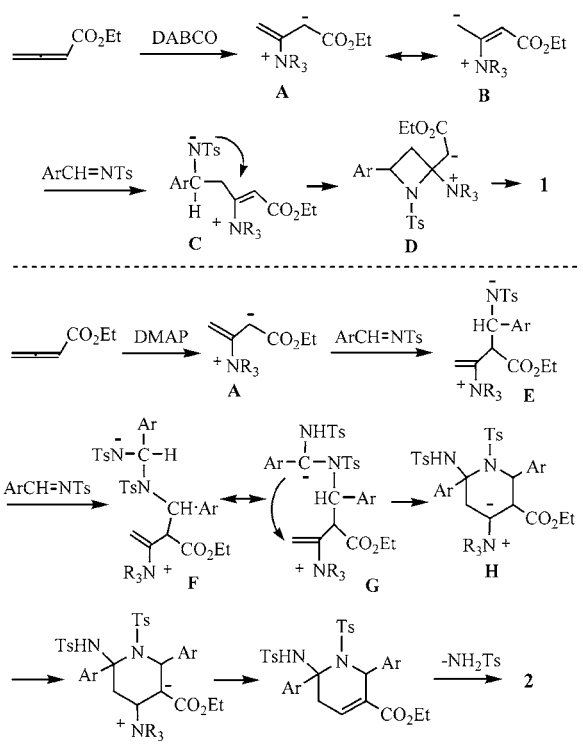
(6) Reaction of 2-methyl-2,3-butadienoate with N-tosylated imines catalyzed by tributylphosphine gave six-membered tetrahydropyridines in high yields. Zhu, X.-F.; Lah, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716.

(7) Baylis−Hillman reaction of aldehydes with ethyl 2,3-butadienonate and penta-3,4-dien-2-one in the presence of DABCO gave the normal Baylis−Hillman adduct. See: Tsuboi, S.; Kuroda, H.; Takatsuka, S.; Fukawa, T.; Sakai, T.; Utaka, M. *J. Org. Chem.* **1993**, *58*, 5952.

(8) MS 4 Å was used to get rid of ambient water or moisture to improve the isolated yields because the employed N-tosylated imines can decompose to the corresponding aldehydes and N-tosylated amines by ambient water or moisture during a prolonged reaction time (Table 1, entries 1−2).

(9) Solvent and Lewis base effects for these abnormal aza-Baylis−Hillman reactions are summarized in Supporting Information.

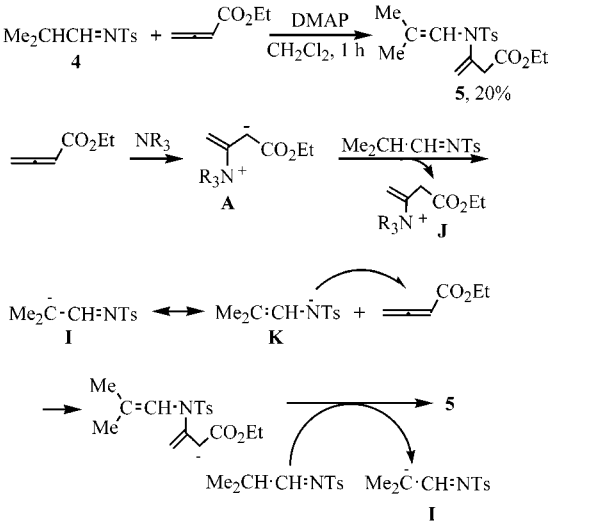
Scheme 2. Plausible Mechanism for the Abnormal Aza-Baylis−Hillman Reaction



nucleophilic attack (Michael type) to give another zwitterionic intermediate **D**. The elimination of NR_3 from **D** affords product **1** and regenerates DABCO. However, in the case of DMAP, the enolate **A** adds to the N-tosylated imine to afford the intermediate **E**, which adds to another N-tosylated imine to give the intermediate **F**. The proton transfer produces the intermediate **G**, and the subsequent intramolecular Michael addition gives the intermediate **H**. Proton-shift and NHTs elimination furnish product **2** and regenerate DMAP.[11]

Many aliphatic N-tosylated imines are, in general, labile. We synthesized a relatively stable aliphatic N-tosylated imine **4** according to the literature[12] and used it in this reaction

Scheme 3. Aza-Baylis−Hillman Reaction of Aliphatic N-Tosylated Imine **4** with Ethyl 2,3-Butadienoate



catalyzed by DMAP. However, we found that the corresponding 3-[(2-methylpropenyl)(toluene-4-sulfonyl)amino]-but-3-enoic acid ethyl ester **5** was produced in this reaction in 20% yield (Scheme 3). A mechanism is shown below. The allylic H of **4** is abstracted by intermediate **A** to give intermediates **I** and **J**. The intermediate **I** can produce another more stable anion **K**. The reaction between intermediate **K** and **4** furnishes product **5**.

In this paper, we disclose the unprecedented "abnormal" aza-Baylis−Hillman reactions of N-tosylated imines with ethyl 2,3-butadienoate or penta-3,4-dien-2-one by means of different nitrogen Lewis bases under mild conditions. Most of these aza-Baylis−Hillman reactions reached completion at 20 °C within 10 min to 3 h, giving the unexpected "abnormal" aza-Baylis−Hillman adducts **1**, **2**, or **3** in moderate to excellent yields. The importance of this finding was exemplified by their expedient formal [2 + 2] and [4 + 2] annulation reactions with N-tosylated imines to give the azetidine and dihydropyridine derivatives under mild conditions.[13] Efforts are underway to elucidate the mechanistic details and Lewis base effects of this abnormal aza-Baylis−Hillman reaction.

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Supporting Information Available: ^{13}C and ^{1}H NMR spectral and analytic data for compounds **1**−**3** and ORTEP structures for **2a** and **3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Crystal data of **2a** have been deposited in CCDC as deposition number 211894. Empirical formula: $C_{27}H_{25}NO_4S$. Formula weight: 459.54; Crystal color, habit: colorless, prismatic. Crystal dimensions: 0.468 × 0.375 × 0.245 mm. Crystal system: triclinic. Lattice type: primitive. Lattice parameters: a = 7.6675(8) Å, b = 13.8140(15) Å, c = 22.914(3) Å, α = 92.491(2)°, β = 93.885(2)°, γ = 98.992(2)°, V = 2388.1(4) Å^3. Space group: P-1. Z = 4. D_{calcd} = 1.278 g/cm^3. F_{000} = 968. Diffractometer: Rigaku AFC7R. Residuals: R, R_w = 0.0605, 0.1271. The crystal data of **3d** have been deposited in CCDC as deposition number 211895. Empirical formula: $C_{19}H_{18}NO_3FS$. Formula weight: 359.40. Crystal color, habit: colorless, prismatic. Crystal dimensions: 0.478 × 0.237 × 0.226 mm. Crystal system: monoclinic. Lattice type: primitive. Lattice parameters: a = 6.3576(9) Å, b = 8.9534(13) Å, c = 31.589(5) Å, α = 90°, β = 91.829(3)°, γ = 90°, V = 1797.2(4) Å^3. Space group: $P2(1)/n$. Z = 4. D_{calcd} = 1.328 g/cm^3. F_{000} = 752. Diffractometer: Rigaku AFC7R. Residuals: R, R_w = 0.0568, 0.1278.

(11) We believe that the nitrogen Lewis bases DABCO and DMAP should have different catalytic abilities in the Baylis−Hillman reaction as the promoters because they have different nucleophilicities and basicities. At the present stage, we cannot give a clear-cut explanation of this interesting Lewis base effect.

(12) Chemla, F.; Hebbe, V.; Normant, J. F. *Synthesis* **2000**, *1*, 75.

(13) Reaction of methylallene with N-tosylated imines gives alkylideneazetidines in 3% yield at 130 °C. See: Baumann, H.; Duthaler, R. O. *Helv. Chem. Acta* **1988**, *71*, 1025. The reaction of ketenes with imines gives azetidinones and 2:1 adducts. See: Mukerjee, A. K.; Srivastava, R. C. *Synthesis* **1973**, 327.