CHEMCOMM Communication
www.rsc.org/chemcomm

Lewis base effects in the Baylis–Hillman reaction of imines with cyclohex-2-en-1-one and cyclopent-2-en-1-one

Min Shi* and Yong-Mei Xu

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China. E-mail: mshi@pub.sioc.ac.cn

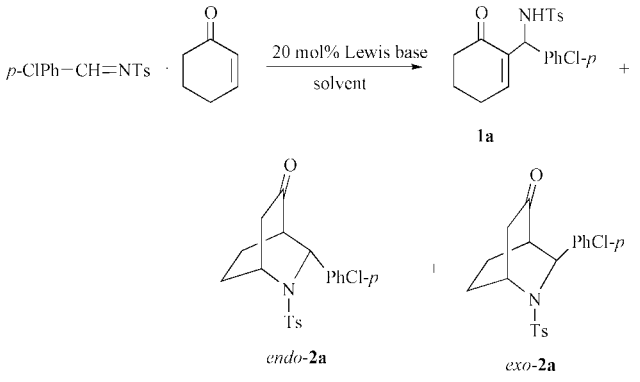
Received (in Cambridge, UK) 5th June 2001, Accepted 5th August 2001
First published as an Advance Article on the web 31st August 2001

In the Baylis–Hillman reaction of *N*-benzylidene-4-methylbenzenesulfonamide with cyclohex-2-en-1-one or cyclopent-2-en-1-one, we found that, in the presence of a catalytic amount of DMAP, the Baylis–Hillman reaction can be greatly accelerated to give the normal Baylis–Hillman adduct 1 or 3 in good or very high yields; moreover, using PBu_3 as a Lewis base in the reaction of *N*-benzylidene-4-methylbenzenesulfonamide with cyclopent-2-en-1-one, the normal Baylis–Hillman adducts 3 could be obtained in very high yields within 5 h, however, using PBu_3 or DBU as a Lewis base in the reaction of *N*-benzylidene-4-methylbenzenesulfonamide with cyclohex-2-en-1-one, besides the normal Baylis–Hillman adduct 1 abnormal Baylis–Hillman adduct 3-aryl-2-[(4-methylphenyl)sulfonyl]-2-azabicyclo[2.2.2]octan-5-one 2 was formed at the same time; the substituent's effects were also examined.

Recently, the Baylis–Hillman reaction has made great progress,[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 strong Lewis base such as 1,4-diazabicyclo-[2.2.2]octane (DABCO) in 1972.[3] During our own investigation on this very simple and useful reaction, we found that the reaction of arylaldehydes with cyclohex-2-en-1-one or cyclopent-2-en-1-one is sluggish under the traditional reaction conditions or even in the presence of $TiCl_4$ as a Lewis acid and amines, SMe_2 or phosphines as Lewis base.[4] Herein we wish to report that, using *N*-benzylidene-4-methylbenzenesulfonamide to replace arylaldehydes, this reaction can be greatly accelerated in the presence of a catalytic amount of Lewis base DMAP and PBu_3. Especially using PBu_3 or DBU as a Lewis base, an unexpected abnormal Baylis–Hillman adduct **2** was formed in the reaction of *N*-benzylidene-4-methylbenzenesulfonamide with cyclohex-2-en-1-one under the same reaction conditions.

The promoters for the reactions of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide with cyclohex-2-en-1-one were systematically examined (Table 1). We found that the solvents, reaction temperatures and Lewis bases played very important roles for this reaction. For example, using 20 mol% of DMAP as a Lewis base in MeOH at 40 °C, the reaction proceeded very well to give the normal Baylis–Hillman adduct **1** in good yield (Table 1, entry 9) even though it cannot promote the same reaction in DMF (Table 1, entry 5). Using 20 mol% of PPh_3 or dppe as a Lewis base, no reactions occurred (Table 1, entry 1–3). However, using PBu_3 or DBU as a Lewis base in MeOH

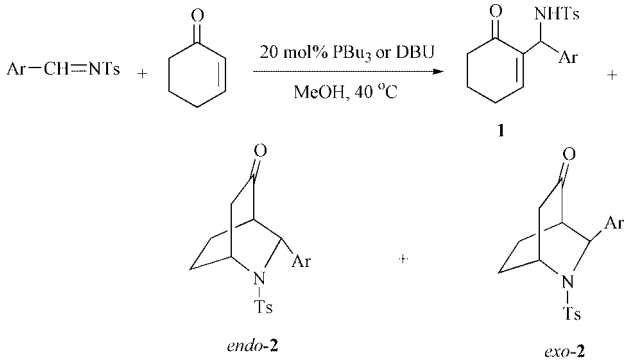
Table 1 Baylis–Hillman reactions of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide (1.0 eq.) with cyclohex-2-en-1-one (1.0 eq.) in the presence of Lewis base (20 mol%)



Entry	Lewis base	Solvent	Time/h	Temp./ °C	Yield (%)[a] 1a	endo-2a	exo-2a
1	PPh_3	MeOH	24	20	0	0	0
2	PPh_3–BINOL	THF	48	40	0	0	0
3	dppe–BINOL	THF	72	20	0	0	0
4	PBu_3	DMF	48	40	Trace	0	0
5	DMAP	DMF	36	20	0	0	0
6	DBU	DMF	24	20	0	0	0
7	DABCO	MeOH	36	20	30	0	0
8	PBu_3	MeOH	24	40	20	15	22
9	DMAP	MeOH	24	40	65	0	0
10	DMAP	MeOH	24	20	41	0	0
11	DBU	CH_2Cl_2	24	20	32	10	18
12	DBU	MeOH	24	40	40	10	20

[a] Isolated yields.

Table 2 Baylis–Hillman reactions of *N*-benzylidene-4-methylbenzenesulfonamide (1.0 eq.) with cyclohex-2-en-1-one in the presence of Lewis base (20 mol%)



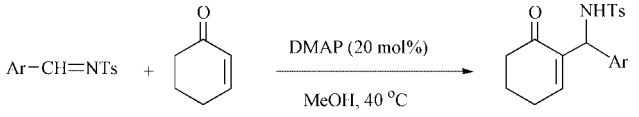
b: Ar= Ph, **c**: Ar= *p*-EtPh, **d**: Ar= *p*-MeOPh, **e**: Ar= *p*-FPh, **f**: Ar= *p*-NO_2Ph.

Entry	Ar	Lewis base	Time/h	Yield (%)[a] 1	endo-2	exo-2
1	Ph	DBU	3	40	12	20
2	Ph	PBu_3	24	16	16	22
3	*p*-EtPh	DBU	3	32	10	18
4	*p*-MeOPh	PBu_3	24	25	25	23
5	*p*-FPh	PBu_3	26	20	19	22
6	*p*-NO_2Ph	PBu_3	24	15	10	25

[a] Isolated yields.

 DOI: 10.1039/b104931n

Table 3 Baylis–Hillman reactions of *N*-benzylidene-4-methylbenzenesulfonamide (1.0 eq.) with cyclohex-2-en-1-one in the presence of Lewis base DMAP (20 mol%)



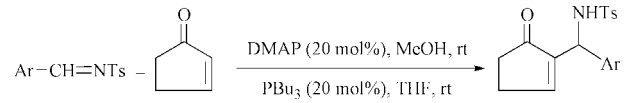
1

b: Ar= Ph, **c**: Ar= *p*-EtPh, **d**: Ar= *p*-MeOPh, **e**: Ar= *p*-FPh, **f**: Ar= *p*-NO_2Ph.

Entry	Ar	Time/h	Yield (%)[a] **1**
1	Ph	24	50
2	*p*-EtPh	24	40
3	*p*-MeOPh	36	30
4	*p*-FPh	24	60
5	*p*-NO_2Ph	24	52

[a] Isolated yields.

Table 4 Baylis–Hillman reactions of *N*-benzylidene-4-methylbenzenesulfonamide (1.0 eq.) with cyclopent-2-en-1-one in the presence of Lewis base DMAP or PBu_3 (20 mol%)



3

a: Ar= Ph, **b**: Ar= *p*-EtPh, **c**: Ar= *p*-MeOPh, **d**: Ar= *p*-Me_2NPh, **e**: Ar= *p*-ClPh, **f**: Ar= *p*-BrPh, **g**: Ar= *p*-NO_2Ph.

Entry	R	Lewis base	Time/h	Yield (%)[a] **3**
1	Ph	DMAP	24	75
2	Ph	PBu_3	5	70
3	*p*-EtPh	DMAP	24	82
4	*p*-EtPh	PBu_3	6	85
5	*p*-MeOPh	PBu_3	6	90
6	*p*-Me_2NPh	PBu_3	6	90
7	*p*-ClPh	PBu_3	5	99
8	*p*-ClPh	DMAP	24	54
9	*p*-BrPh	PBu_3	5	83
10	*p*-NO_2Ph	DMAP	24	80
11	*p*-NO_2Ph	PBu_3	5	90

[a] Isolated yields.

at 40 °C, an unexpected adduct **2** (*endo–exo*-mixture) (abnormal Baylis–Hillman adduct) was obtained along with the formation of **1** (Table 1, entry 8, 11 and 12). For other *N*-benzylidene-4-methylbenzenesulfonamides using PBu_3 or DBU as a Lewis base in MeOH, similar results were obtained under the optimized reaction conditions (Table 2). We believe that **2** is produced stepwise *via* an aldol condensation reaction of the enolate derived from cyclohex-2-en-1-one in the presence of Lewis base to imine and an intramolecular conjugated addition (Michael addition) of the formed anion to α,β-unsaturated ketone moiety. The structures of **1** and **2** were determined by spectral data.[5] The crystal structure of *endo*-**2d** was established by X-ray analysis.[6,7]

Meanwhile, we also examined the reaction of other *N*-benzylidene-4-methylbenzenesulfonamides with cyclohex-2-en-1-one using DMAP as a Lewis base (Table 3). Only normal Baylis–Hillman products **1** were formed in moderate yields.

On the other hand, for the reaction of *N*-benzylidene-4-methylbenzenesulfonamides with cyclopent-2-en-1-one, we surprisingly found that the normal Baylis–Hillman products **3** can be exclusively obtained using DMAP or PBu_3 as a Lewis base under the same reaction conditions (Table 4). No abnormal adducts were formed and the Baylis–Hillman adducts **3** were obtained in very high yields. The reaction rates are much faster than those of cyclohex-2-en-1-one under the same conditions. Especially using PBu_3 as a Lewis base at rt, products **3** can reach to 90% within 5 h. In some cases, the reactions proceeded quantitatively.

In conclusion, we found that, in the Baylis–Hillman reaction of *N*-benzylidene-4-methylbenzenesulfonamides with cyclohex-2-en-1-one or cyclopent-2-en-1-one, the Lewis bases and solvents can significantly affect the reaction. Using PBu_3 or DBU as a Lewis base in the reaction of *N*-benzylidene-4-methylbenzenesulfonamides with cyclohex-2-en-1-one, the abnormal Baylis–Hillman adduct was formed, along with the normal Baylis–Hillman adduct. Efforts are underway to elucidate the mechanistic details of this reaction and to disclose the scope and limitations of this reaction. Works along this line are currently in progress.

We thank the State Key Project of Basic Research (Project 973) (No. G2000048007) and the National Natural Science Foundation of China (20025206) for financial support. We also thank the Inoue Photochirogenesis Project (ERATO, JST) for chemical reagents.

Notes and references

1 E. Ciganek, *Org. React.*, 1997, **51**, 201.

2 Y. Iwabuchi, M. Nakatani, N. Yokoyama and S. Hatakeyama, *J. Am. Chem. Soc.*, 1999, **121**, 10219.

3 (*a*) A. B. Baylis and M. E. D. Hillman, *Ger. Offen.*, 1972, **2**, 155, 113; *Chem. Abstr.*, 1972, **77**, 34174q; M. E. D. Hillman and A. B. U. S. Baylis, 1973, 3,743,669; (*b*) K. Morita, Z. Suzuki and H. Hirose, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 2815.

4 (*a*) M. Shi, J.-K. Jiang and Y.-S. Feng, *Org. Lett.*, 2000, **2**, 2397; (*b*) M. Shi and Y.-S. Feng, *J. Org. Chem.*, 2001, **66**, 406; (*c*) M. Shi, J.-K. Jiang, S.-C. Cui and Y.-S. Feng, *J. Chem. Soc., Perkin Trans. 1*, 2001, 390; (*d*) M. Shi and J.-K. Jiang, *Tetrahedron*, 2000, **56**, 4793; (*e*) M. Shi, C.-Q. Li and J.-K. Jiang, *Chem. Commun.*, 2001, 833.

5 Spectral data for **1e**: mp 132–133 °C; IR (KBr) ν 1652 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.52–1.75 (1H, m), 1.76–2.0 (1H, m), 2.07–2.20 (2H, m, CH_2), 2.20–2.50 (2H, m, CH_2), 2.46 (3H, s, CH_3), 5.07 (1H, d, J = 9.4 Hz, NH), 5.98 (1H, d, J = 9.4 Hz, CH), 6.83 (1H, t, J = 4.0 Hz, =CH), 6.95 (2H, t, J = 8.6 Hz, Ar), 7.10–7.20 (2H, m, Ar), 7.23 (2H, d, J = 8.3 Hz, Ar), 7.65 (2H, d, J = 8.3 Hz, Ar); MS (EI) *m/e* 278 (M^+ − 95, 1.5), 218 (M^+ − 155, 100); [Found: C, 64.42; H, 5.37; N, 3.59%. $C_{20}H_{20}NFO_3S$ requires C, 64.32; H, 5.40; N, 3.75%]. Spectral data for *endo*-**2e**: mp 163–164 °C; IR (KBr) ν 1728 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.50–2.0 (4H, m, CH_2), 2.02–2.50 (2H, m, CH_2), 2.43 (3H, s, CH_3), 2.46 (1H, dd, J = 5.4, 3.0 Hz), 4.46–4.51 (1H, m, CH), 5.07 (1H, s, CH), 7.17 (2H, t, J = 9 Hz, Ar), 7.20–7.40 (4H, m, Ar), 7.60 (2H, d, J = 8.2 Hz); MS (EI) *m/e* 373 (M^+). [Found: C, 64.55; H, 5.21; N, 3.57%. $C_{20}H_{20}NFO_3S$ requires C, 64.32; H, 5.40; N, 3.75%]. Spectral data for *exo*-**2e**: mp 186–187 °C; IR (KBr) ν 1726 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.50–1.80 (1H, m), 1.80–2.10 (3H, m, CH_2), 2.35 (1H, dd, J = 21.9, 3.2 Hz, CH), 2.40 (3H, s, CH_3), 2.40 (1H, dd, J = 5.4, 3.0 Hz), 2.70 (1H, dd, J = 21.9, 3.2 Hz, CH), 4.49–4.52 (1H, m, CH), 4.97 (1H, d, J = 2.2 Hz, CH), 6.91 (2H, t, J = 9.0 Hz, Ar), 7.0–7.18 (2H, m, Ar), 7.25 (2H, d, J = 8.2 Hz, Ar), 7.60 (2H, d, J = 8.2 Hz, Ar); MS (EI) *m/e* 373 (M^+). [Found: C, 64.11; H, 5.38; N, 3.71%. $C_{20}H_{20}NFO_3S$ requires C, 64.32; H, 5.40; N, 3.75%]

6 Crystal data for *endo*-**2d**: Empirical Formula: $C_{21}H_{23}O_4NS$; Formula Weight: 385.48; Crystal Color, Habit: colorless, prismatic; Crystal Dimensions: 0.20 × 0.20 × 0.30 mm; Crystal System: orthorhombic; Lattice Type: Primitive; Lattice Parameters: a = 7.935(3), b = 10.593(3), c = 22.562(2) Å, V = 1896(1) $Å^3$; Space group: $Pna2_1$ (#33); Z = 4; D_{calc} = 1.350 g cm^{-3}; F_{000} = 816.00; μ(MoKα) = 1.98 cm^{-1}; Diffractometer: Rigaku AFC7R; Residuals: *R*; *Rw*: 0.062, 0.063. CCDC 165558. See http://www.rsc.org/suppdata/cc/b1/b104931n/ for crystallographic files in .cif or other electronic format.

7 Spectral data for **3c**: mp 118–120 °C; IR (KBr) ν 1684 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.0–2.20 (1H, m), 2.20–2.40 (2H, m, CH_2), 2.38 (3H, s, CH_3), 2.43–2.52 (1H, m, CH), 3.73 (3H, s, OCH_3), 5.20 (1H, d, J = 8.4 Hz, NH), 5.92 (1H, d, J = 8.4 Hz, CH), 6.72 (2H, d, J = 8.7 Hz, Ar), 7.05 (2H, d, J = 8.7 Hz, Ar), 7.18 (2H, d, J = 8.2 Hz, Ar), 7.33 (1H, t, J = 3.0 Hz, =CH), 7.58 (1H, d, J = 8.2 Hz, Ar); MS (EI) *m/e* 371 (M^+). [Found: C, 64.60; H, 5.60; N, 3.53%. $C_{20}H_{21}NO_4S$ requires C, 64.67; H, 5.70; N, 3.77%]