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Titanium(IV) Chloride and the Amine-Promoted Baylis–Hillman Reaction

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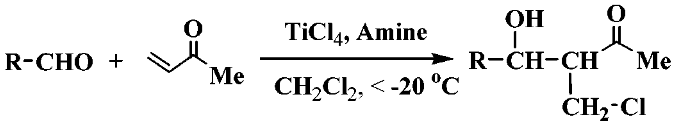
ABSTRACT



In the Baylis–Hillman reaction, we found that, when the reactions of arylaldehydes with methyl vinyl ketone were carried out at <–20 °C using a catalytic amount of amine as a Lewis base in the presence of titanium(IV) chloride, the chlorinated compounds 1 could be obtained as the major product in very high yields for various arylaldehydes. In addition, acrylonitrile could undergo the same reaction to give the corresponding chlorinated product in moderate yield.

The Baylis−Hillman reaction and related processes have become increasingly important in synthetic organic chemistry, because the resulting adducts have an array of multifunctional groups which can be subjected to numerous transformations.[1−5] This carbon−carbon bond formation is typically catalyzed by DABCO or tertiary phosphines. The major drawbacks of the Baylis−Hillman reaction are its slow reaction rate and limited scope of substrates. To overcome these shortcomings, many efforts have been made to use Lewis acids or various other additives to the reaction system in order to activate carbonyl electrophiles.[6−10] Among Lewis acids, $TiCl_4$ has been successfully utilized to promote the Baylis−Hillman reaction in the presence of Lewis base catalysts.[11] During our investigation on the Baylis−Hillman process, we found that many amines are very effective Lewis bases in this interesting reaction and the reaction products are considerably different from those reported so far. First

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[1] For reviews, see: (a) Ciganek, E. *Org. React.* **1997**, *51*, 201. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (c) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.

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[11] (a) Nagaoka, Y.; Yomioka, K. *J. Org. Chem.* **1998**, *63*, 6428. (b) Harrowven, D.; Hannam, J. C. *Tetrahedron* **1999**, *55*, 9341.

[12] Typical reaction procedure: to a solution of triethylamine (10.1 mg, 0.1 mmol, 14.0 uL) in dichloromethane (1.3 mL) was added titanium chloride (0.7 mL, 0.7 mmol) at −78 °C. After the mixture was stirred for 5 min, a solution of *p*-nitrobenzaldehyde (75.5 mg, 0.5 mmol) in dichloromethane (1.0 mL) and methyl vinyl ketone (105.0 mg, 1.5 mmol, 123.0 uL) were added into the reaction solution at −78 °C, respectively. The reaction mixture was kept for 12 h at −78 °C. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (1.0 mL). After filtration, the filtrate was extracted with dichloromethane (5.0 mL × 2) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography to give compound **1a** (105.0 mg, 81%) as a colorless solid (eluent 1/4 ethyl acetate/petroleum ether). Physical data for **1a**: mp 90−91 °C; IR (KBr) ν 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.20 (3H, s, Me), 2.93 (1H, br. s, OH), 3.22−3.38 (1H, m), 3.67 (1H, dd, $J = 11.3, 4.0$ Hz), 3.89 (1H, dd, $J = 11.3, 9.2$ Hz), 5.11 (1H, d, $J = 5.6$ Hz), 7.56 (2H, d, $J = 8.6$ Hz, Ar), 8.25 (2H, d, $J = 8.6$ Hz, Ar); MS (EI) *m/e* 258 (MH^+, 0.60), 208 ($M^+ - 49$, 60), 71 ($M^+ - 186$, 100). Anal. Found: C, 51.64; H, 4.94; N, 5.35. Calcd for $C_{11}H_{12}ClNO_4$: C, 51.27; H, 4.69; N, 5.44.

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of all, we carried out the reaction of *p*-nitrobenzaldehyde with methyl vinyl ketone in the presence of $TiCl_4$ at −78 °C. No reaction occurred. After 20 mol % of triethylamine (Et_3N) was added as a Lewis base, the reaction smoothly took place to give the chlorinated product **1a** as the major product,[12] rather than product **2a**, which is usually considered as the product of the Baylis−Hillman reaction (Scheme 1).

Scheme 1

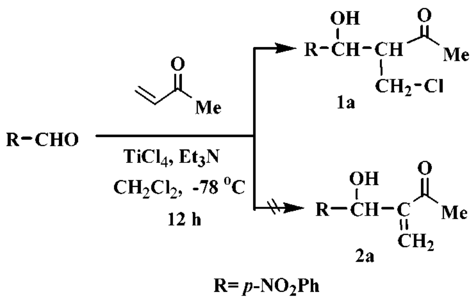


Table 1. Examination of the Reaction Conditions for the Baylis−Hillman Reaction of *p*-Nitrobenzaldehyde with Methyl Vinyl Ketone in the Presence of $TiCl_4$ as a Lewis Acid and Triethylamine as a Lewis Base

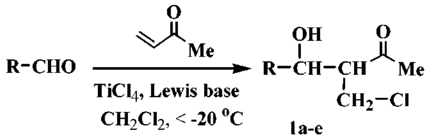
entry	Lewis base Et_3N, equiv	Lewis acid $TiCl_4$, equiv	yield of **1a**,[a] %
1	0	1.4	0
2	0.05	1.4	60
3	0.1	1.4	76
4	0.2	1.4	81
5	1.0	1.4	45
6	6.0	1.4	0
7	0.2	0.4	36
8	0.2	0.8	54

[a] Isolated yields.

The reaction was drastically affected by the amounts of both Lewis acid and Lewis base. By means of a catalytic amount of amine and excess amount of $TiCl_4$ the reaction proceeded very well. However, when a large excess of amine was used as a Lewis base, the reaction was completely stopped (Table 1, entry 6). This result suggested that the amine could coordinate to $TiCl_4$ and free $TiCl_4$ as a Lewis acid was needed to promote the reaction. The amount of $TiCl_4$ was also crucial for this reaction, because with a catalytic amount of $TiCl_4$, the reaction became very slow and gave a low yield of **1a** (Table 1, entries 7 and 8). The best reaction conditions were found to utilize 20 mol % of amine as a Lewis base and 1.4 equiv of $TiCl_4$ as a Lewis acid (Table 1, entry 4).

For many arylaldehydes having a strongly electron-withdrawing group on the phenyl ring, the reactions proceed quickly to give **1** in high yields using a catalytic amount of Lewis base (20 mol %) at −78 °C (Scheme 2 and Table 2).

Scheme 2



a: *p*-NO_2Ph; **b**: *m*-NO_2Ph; **c**: *p*-CF_3Ph; **d**: Ph;
e: *p*-EtPh; **f**: *p*-ClPh; **g**: $CH_3(CH_2)_3$.

Table 2. Baylis−Hillman Reaction of Aldehydes with Methyl Vinyl Ketone in the Presence of $TiCl_4$ and 20 mol % of Lewis Base

entry	R	Lewis base	temp, °C	time, h	yield of **1**,[a] %
1	*p*-NO_2Ph	none	−78	12	0
2	*p*-NO_2Ph	Et_3N	−78	12	81
3	*m*-NO_2Ph	Et_3N	−78	12	88
4	*p*-CF_3Ph	Et_3N	−78	48	80
5	Ph	Et_3N	−20	48	80
6	*p*-EtPh	Et_3N	−20	48	72
7	*p*-ClPh	Et_3N	−20	48	70
8	$CH_3(CH_2)_3$	Et_3N	−20	48	45
9	*p*-NO_2Ph	Et_2NH	−78	12	88
10	Ph	Et_2NH	−20	48	71
11	*p*-NO_2Ph	DBU	−78	12	82
12	Ph	DBU	−20	48	65

[a] Isolated yields.

However, other arylaldehydes or aliphatic aldehydes need a higher temperature (−20 °C) to give the corresponding chlorinated product **1** in high or moderate yield (Scheme 2 and Table 2). Moreover, we found that, besides triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and diethylamine were also very effective Lewis bases for this reaction in the presence of $TiCl_4$ (Table 2). All cases shown in Table 1 only needed a catalytic amount of amine (20 mol %) to bring the reaction to completion in the presence of $TiCl_4$ (Table 2). In the meantime, it should be emphasized that, in all cases, only one diastereomer was formed during the reaction process, on the basis of the ^{1}H NMR spectral data. Their relative configurations were confirmed as the *anti* form by an X-ray analysis of the crystal structure of **1a**[13] (Figure 1). Compound **1** can be easily and completely transformed to

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(13) Crystal data for **2a**: empirical formula, $C_{11}H_{12}ClNO_4$; formula weight, 257.67; crystal color, habit: colorless, column; crystal dimensions, 0.28 × 0.30 × 0.18 mm; crystal system, orthorhombic; lattice type, primitive; lattice parameters, $a = 10.615(1)$ Å, $b = 14.277(1)$ Å, $c = 7.838(1)$ Å, $V = 1187.8(3)$ Å^3; space group, $P2_12_12_1$ (No. 19); $Z = 4$; $D_{calcd} = 1.441$ g/cm^3; $F_{000} = 536.00$; μ(Mo Kα) = 3.23 cm^{-1}; residuals, $R = 0.065$, $R_w = 0.052$.

(14) Physical data for the known compound **2a**:[9] mp 66−68 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.36 (3H, s, Me), 3.26 (1H, br s, OH), 5.68 (1H, s), 6.05 (1H, s), 6.28 (1H, s), 7.56 (2H, d, $J = 8.6$ Hz, Ar), 8.19 (2H, d, $J = 8.6$ Hz, Ar).

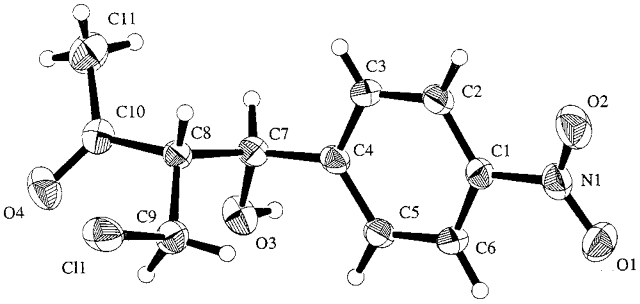
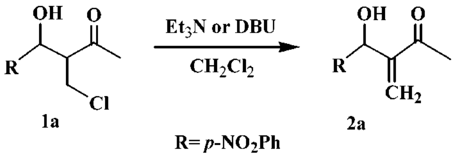


Figure 1. Crystal structure of **1a**.

compound **2**[14] by treatment with an excess amount (2.0 equiv) of triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 3). The purification of **1** by preparative thin-layer chromatography (TLC) would also cause the transformation of **1** to **2**. Thus, rapid flash column chromatography is necessary in order to obtain the pure product **1**.

Scheme 3



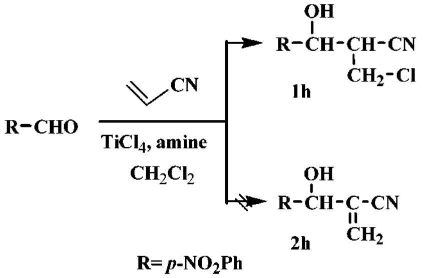
In addition to methyl vinyl ketone, acrylonitrile underwent the same reaction to give the corresponding chlorinated product **1h** in moderate yield in dichloromethane at 10 °C for 5 days (Table 3, entry 1 and 2). However, at −78 °C, no reaction occurred (entry 3). Raising the reaction temperature to reflux (45 °C) caused a decrease in the yield of **1h** (Scheme 4 and Table 3, entry 4). On the other hand, using methyl acrylate as a Michael acceptor, only a trace amount of chlorinated product was obtained under similar reaction conditions (Scheme 5).

Table 3. Baylis−Hillman Reaction of *p*-Nitrobenzaldehyde with Acrylonitrile in the Presence of $TiCl_4$ and 20 mol % of Amines as Lewis Bases

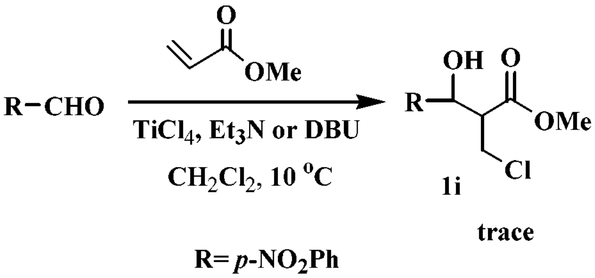
entry	amine	temp, °C	time, days	yield,[a] %
1	Et_3N	10	5	37
2	DBU	10	5	50
3	DBU	−78	3	0
4	DBU	40	3	16

[a] Isolated yield.

Scheme 4



Scheme 5



To the best of our knowledge, this is a novel Baylis−Hillman reaction system, because using a catalytic amount of amine as a Lewis base has not been reported so far in the titanium(IV) chloride promoted Baylis−Hillman reactions. Recently, Aggarwal reported that using stoichiometric amounts of an amine such as DABCO and a catalytic amount of titanium(IV) chloride gave reduced rate, but using a catalytic amount of lanthanide triflates (5 mol %) gave an increased rate in the Baylis−Hillman reaction.[7] Our system shows that, using excess amounts of titanium(IV) chloride and a catalytic amount of amines, the major reaction products are β-chlorinated compounds **1** in moderate to high yields, which can be readily transformed to the Baylis−Hillman olefin **2**. Thus, the reaction rate of the Baylis−Hillman reaction can be greatly enhanced by means of this reaction system.

In Scheme 6, we tentatively proposed the mechanism to explain the formation of product **1**. The reactions of trimethylamine and dimethylamine with titanium(IV) chloride were investigated by Antler and Laubengayer in 1955.[15a] Chloride ion was detected, although the system was complicated. According to his finding, Periasamy determined a mechanism in the reaction of tertiary amines with $TiCl_4$.[15b] The reaction mechanism proposed in Scheme 6 was based on those previous findings and the results of our own investigations shown in Table 1. We believe that amine can strongly coordinate to the Ti metal center of $TiCl_4$ to give an ionic metal complex having a chloride ion. This reaction is related to the attack of chloride ion at the methyl vinyl ketone (Scheme 6). In fact, the formation of chlorinated

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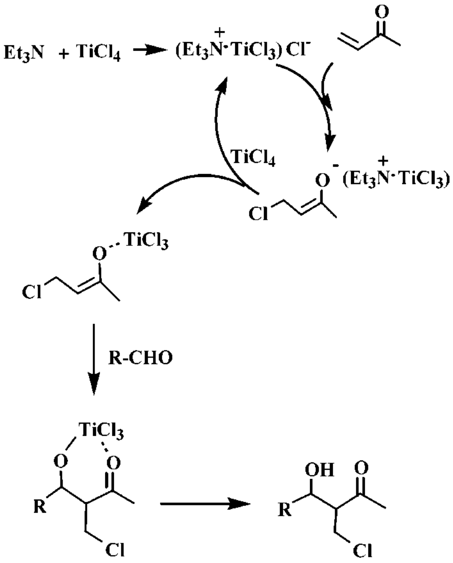
[15] (a) Antler, M.; Laubengayer, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5250. (b) Bharathi, P.; Periasamy, M. *Org. Lett.* **1999**, *1*, 857.

Scheme 6



compound **1** is a major reaction process in the $TiCl_4$ and Lewis base promoted Baylis–Hillman reaction.

In conclusion, we have discovered a novel reaction system of the Baylis–Hillman reaction using a catalytic amount of amine as a Lewis base and an excess amount of titanium(IV) chloride as a Lewis acid. Efforts are underway to elucidate the mechanistic details of this reaction and to disclose the scope and limitations of this reaction. Moreover, we are planning to synthesize chiral amines and utilize them as chiral ligands to achieve the catalytic enantioselective Baylis–Hillman reaction shown in Scheme 1. Work in this direction is currently in progress.

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Supporting Information Available: Text giving the physical data for products **1b**–**h** and electronic files giving CIF data for **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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