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Amendment in Titanium(IV) Chloride and Chalcogenide-Promoted Baylis–Hillman Reaction of Aldehydes with α,β-Unsaturated Ketones

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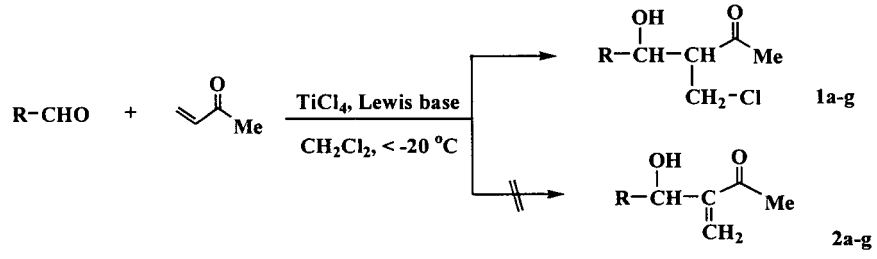
Abstract—The Baylis–Hillman reaction can be drastically affected by the reaction temperature and Lewis base. When the reaction was carried out at $<-20°C$ using methyl sulfide as a Lewis base in the presence of titanium(IV) chloride, the chlorinated compound **1** was obtained as the major product. However, if the reaction was carried out at room temperature (10°C) in the presence of titanium(IV) chloride, the elimination compound **3** was formed as a major product.

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 the reaction products are considerably different from those reported so far. First 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 (Condition A). After adding 20 mol% of dimethyl sulfide (Me_2S) as a Lewis base, the reaction smoothly took place to give the chlorinated product **1a** as the major product, rather than product **2a** which is usually considered as the product of Baylis–Hillman reaction (Scheme 1). For many arylaldehydes having strong electron-withdrawing group on the phenyl ring, the reactions proceed quickly to give **1** with high yields using a catalytic amount of Lewis base (20 mol%) at $-78°C$ (Condition B). However, other arylaldehydes or aliphatic aldehydes need stoichiometric Lewis base and higher temperature ($-20°C$) (Condition C) to give the corresponding product **1** in moderate yields also without formation of **2** (Table 1, entry 5–8). The diphenylthiophosphoramide can also catalyze the reaction (Table 1, entry 9), but the reaction rate is relatively slow. We also confirmed that the compound **1** can be easily completely transformed to compound **2** by treating with triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 2). The purification of **1** by preparative thin layer chromatography (TLC) also caused the



Scheme 1. a: R=*p*-NO_2Ph; b: R=*m*-NO_2Ph; c: R=*p*-CF_3Ph; d: R=*p*-EtPh; e: R=Ph; f: R=*p*-ClPh; g: R=$CH_3(CH_2)_3$.

Keywords: titanium(IV) chloride; Baylis–Hillman reaction; halogenation; *Z*-keto allyl chloride.

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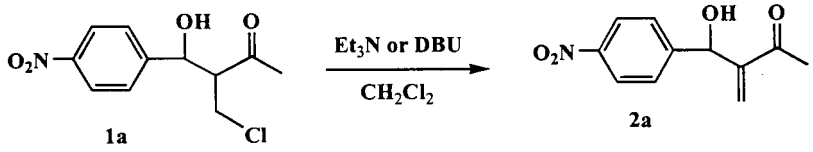
Table 1. Baylis–Hillman reaction of aldehydes with methyl vinyl ketone in the presence of $TiCl_4$ and Lewis base

Entry	R	Lewis base	Conditions	Temp. (°C)	Time (h)	Yield[a] (%)/1
1	*p*-NO_2Ph	none	A[b]	−78	12	–
2	*p*-NO_2Ph	SMe_2	B[c]	−78	12	80
3	*m*-NO_2Ph	SMe_2	B	−78	12	80
4	*p*-CF_3Ph	SMe_2	B	−78	48	81
5	*p*-EtPh	SMe_2	C[d]	−20	72	51
6	Ph	SMe_2	C	−20	72	57
7	*p*-ClPh	SMe_2	C	−20	72	52
8	$CH_3(CH_2)_3$	SMe_2	C	−20	72	32
9	*p*-NO_2Ph	Et_2N–P(=S)Ph_2	B	−78	24	40

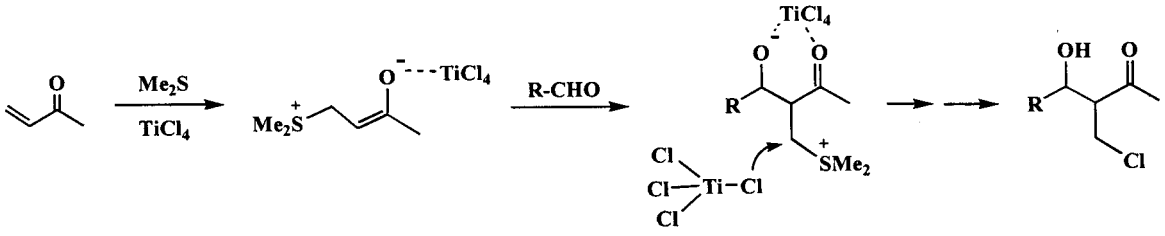
[a] Isolated yields.
[b] Aldehyde/$TiCl_4$=1:1.4.
[c] Aldehyde/$TiCl_4$/Lewis base=1:1.4:0.2.
[d] Aldehyde/$TiCl_4$/Lewis base=1:1.4:1.

transformation of **1** to **2**. Thus, rapid flash column chromatography is necessary in order to obtain the pure product **1**.

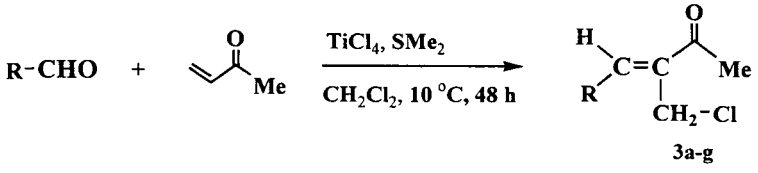
In Scheme 3, we propose a mechanism to explain the formation of product **1**. We believe that the formation of chlorinated compound **1** is the major reaction process in the $TiCl_4$ promoted Baylis–Hillman reaction using Lewis base. In fact, Kataoka also reported partial chlorination in Baylis–Hillman reaction of arylaldehydes with α,β-unsaturated thioesters.[12] But, in his other papers dealing with the Baylis–Hillman reaction of arylaldehydes with α,β-unsaturated ketones, the Baylis–Hillman olefin was obtained as the only product and the formation of chlorinated products were not mentioned at all.[13] This is because they used TLC plates to purify the reaction products. Thus our results are very different from his findings. Based on our results, in the titanium(IV) chloride and chalcogenide-promoted Baylis–Hillman reaction of aldehydes with α,β-unsaturated ketones, the chlorinated product **1** is formed as the only product, and the Baylis–Hillman olefin **2** is derived from the decomposition of **1**.



Scheme 2.



Scheme 3.



Scheme 4. a: R=*p*-NO_2Ph; b: R=*m*-NO_2Ph; c: R=*p*-CF_3Ph; d: R=*p*-EtPh; e: R=Ph; f: R=*p*-ClPh; g: R=$CH_3(CH_2)_8$.

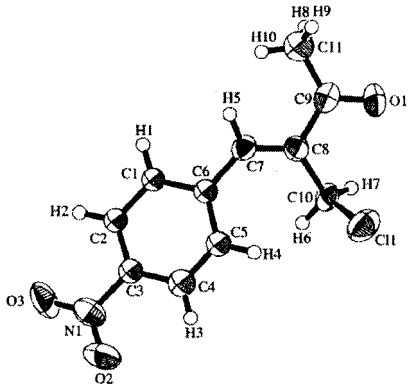


Figure 1. The crystal structure of **3a**.

Table 2. Baylis–Hillman reaction of aldehydes with methyl vinyl ketone in the presence of $TiCl_4$ and 20 mol% of SMe_2

Entry	R	$TiCl_4$ equiv.	Yield[a] (%)/3
1	*p*-NO_2Ph	1.4	62
2	*m*-NO_2Ph	1.4	70
3	*p*-CF_3Ph	1.4	74
4	*p*-EtPh	1.4	47
5	Ph	1.4	50
6	*p*-ClPh	1.4	57
7	$CH_3(CH_2)_8$	1.4	29

[a] Isolated yields.

On the other hand, if the reaction was carried out at room temperature (10°C), the major reaction product was compound **3** (with *Z*-configuration) rather than **1** (Scheme 4). The *Z*-configuration was confirmed by X-ray analysis (Fig. 1).[14] This reaction was not affected by the Lewis base (Me_2S), and in the presence or absence of Lewis base (Me_2S) the same products were obtained in similar yields. Arylaldehydes with strong electron-withdrawing group on the phenyl ring gave higher yields of **3** (Table 2). Concerning the reaction mechanism, we believe that, at room temperature, the chloride at the titanium metal can directly attack at the vinyl carbon atom combined with dehydration to give compound **3**. Recently, Li reported $TiCl_4$-mediated Baylis–Hillman reaction and aldol reaction without the direct use of a Lewis base.[15] The Baylis–Hillman olefins were obtained when 2-cyclohexene-1-one and 2-cyclopenten-1-one were employed as the substrates at room temperature, whereas β-halogenated aldol products were generated with an α,β-unsaturated *N*-acyl benzoxalinone as the Michael-type acceptor. For methyl vinyl ketone, it is therefore very interesting that compound **3** was obtained as a major product.

In conclusion, we found that the titanium(IV) chloride promoted Baylis–Hillman reaction is not as simple as previously reported. The reaction temperature and presence of Lewis base can drastically effect the reaction product. 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 sulfides and utilize them as chiral ligands to achieve the enantioselective Baylis–Hillman reaction. Work in this direction is currently in progress.

Experimental

General

MPs were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; *J* values are in Hz. Mass spectra were recorded with a HP-5989 instrument and HRMS was measured by a Finnigan MA+ mass spectrometer. Organic solvents were dried by standard methods when necessary. Some of the solid compounds reported in this paper gave satisfactory CHN microanalyses with a Carlo–Erba 1106 analyzer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai $60F_{254}$ silica gel coated plates. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure.

Typical reaction procedure for the preparation of 3-(chloromethyl)-4-hydroxy-4-(4′-nitrophenyl)-2-butanone (1a). To a solution of dimethyl sulfide (6.20 mg, 0.1 mmol, 7.2 μL) in dichloromethane (1.3 mL) was added titanium chloride (0.7 mL, 0.7 mmol) at −78°C. After stirring for 5 min, a solution of *p*-nitrobenzaldehyde (76 mg, 0.5 mmol) in dichloromethane (1.0 mL) and methyl vinyl ketone (105 mg, 1.5 mmol, 123 μL) 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 a flash silica gel column chromatography to give compound **1a** (103 mg, 80%) as a colorless solid (eluent: ethyl acetate/petroleum ether=1/4): mp 90–91°C; IR(KBr) ν 1720 cm^{-1} (C=O); ^{1}H 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); Found: C, 51.64; H, 4.94; N, 5.35%. $C_{11}H_{12}ClNO_4$ requires C, 51.27; H, 4.69; N, 5.44%.

Preparation of 3-(chloromethyl)-4-hydroxy-4-(3′-nitrophenyl)-2-butanone (1b). This compound was prepared in the same manner as that described above. 103 mg, 80%; a colorless oil; IR(KBr) ν 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.20 (3H, s, Me), 2.95 (1H, br. s, OH), 3.20–3.35 (1H, m), 3.66 (1H, dd, *J*=11.3, 3.9 Hz), 3.89 (1H, dd, *J*=11.3, 9.3 Hz), 5.13 (1H, d, *J*=5.6 Hz), 7.54 (1H, t, *J*=7.9 Hz, Ar), 7.69 (1H, d, *J*=7.6 Hz, Ar), 8.2 (1H, d, *J*=7.6 Hz, Ar), 8.25 (1H, s, Ar); MS (EI) *m/e* 257 (M^+, 0.60), 208 (M^+-49, 60), 71(M^+-186, 100); [HRMS (EI) *m/z* 239.0353 (M^+-H_2O). $C_{11}H_{10}O_3NCl$ requires $M-H_2O$, 239.0349].

Preparation of 3-(chloromethyl)-4-hydroxy-4-(4′-trifluoromethylphenyl)-2-butanone (1c). This compound was prepared in the same manner as that described above. 114 mg, 81%; a colorless oil; IR(KBr) ν 1720 cm^{-1}

(C═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.13 (3H, s, Me), 2.65 (1H, br. s, OH), 3.22–3.37 (1H, m), 3.70 (1H, dd, J=10.2, 3.9 Hz), 3.89 (1H, dd, J=10.2, 10.2 Hz), 5.02 (1H, d, J=6.1 Hz), 7.37 (2H, d, J=8.0 Hz, Ar), 7.64 (2H, d, J=8.0 Hz, Ar); MS (EI) *m/e* 280 (M^+, 0.45), 243 (M^+-37, 40), 43 (M^+-237, 100); [HRMS (EI) *m/z* 262.0377 (M^+-H_2O). $C_{12}H_{10}OClF_3$ requires $M-H_2O$, 262.0372].

Preparation of 3-(chloromethyl)-4-hydroxy-4-(4′-ethylphenyl)-2-butanone (1d). This compound was prepared in the same manner as that described above. 62 mg, 51%; a colorless solid; mp 69–71°C; IR(KBr) ν 1720 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (3H, t, J=7.7 Hz), 2.02 (3H, s, Me), 2.15 (1H, br. s, OH), 2.63 (2H, q, J=7.7 Hz), 3.22–3.37 (1H, m), 3.80 (1H, dd, J=10.7, 3.8 Hz), 3.90 (1H, dd, J=10.7, 10.7 Hz), 4.82 (1H, d, J=7.2 Hz), 7.10–7.32 (4H, m, Ar); MS (EI) *m/e* 222 (M^+-18, 1.20), 191 (M^+-49, 20), 135 (M^+-105, 100); [HRMS (EI) *m/z* 240.0908 (M^+). $C_{13}H_{17}O_2Cl$ requires *M*, 240.0917].

Preparation of 3-(chloromethyl)-4-hydroxy-4-phenyl-2-butanone (1e). This compound was prepared in the same manner as that described above. 61 mg, 57%; a colorless oil; IR(KBr) ν 1720 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.02 (3H, s, Me), 2.45 (1H, br. s, OH), 3.22–3.37 (1H, m), 3.78 (1H, dd, J=10.7, 3.8 Hz), 3.90 (1H, dd, J=10.4, 10.4 Hz), 4.84 (1H, d, J=6.9 Hz), 7.10–7.32 (5H, m, Ar); MS (EI) *m/e* 212 (M^+, 1.05), 163 (M^+-49, 60), 107 (M^+-105, 100); [HRMS (EI) *m/z* 212.0594 (M^+). $C_{11}H_{13}O_2Cl$ requires *M*, 212.0604].

Preparation of 3-(chloromethyl)-4-hydroxy-4-(4′-chlorophenyl)-2-butanone (1f). This compound was prepared in the same manner as that described above. 64 mg, 52%; a colorless oil; IR(KBr) ν 1720 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.0 (3H, s, Me), 2.50 (1H, br. s, OH), 3.20–3.32 (1H, m), 3.75 (1H, dd, J=10.7, 3.8 Hz), 3.87 (1H, dd, J=10.7, 10.7 Hz), 4.82 (1H, d, J=6.7 Hz), 7.10–7.32 (4H, m, Ar); MS (EI) *m/e* 246 (M^+, 1.20), 121 (M^+-125, 20), 91 (M^+-155, 100); [HRMS (EI) *m/z* 246.0210 (M^+). $C_{11}H_{12}O_2Cl_2$ requires *M*, 246.0214].

Preparation of 3-(chloromethyl)-4-hydroxy-4-butyl-2-butanone (1g). This compound was prepared in the same manner as that described above. 31 mg, 32%; a colorless oil; IR(KBr) ν 1720 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (3H, t, J=7.1 Hz), 1.10–1.60 (6H, m), 2.08 (1H, s, OH), 2.34 (3H, s, Me), 3.0–3.10 (1H, m), 3.60–3.85 (3H, m); MS (EI) *m/e* 192 (M^+, 0.80), 155 (M^+-37, 30), 43 (M^+-149, 100); [HRMS (EI) *m/z* 192.0908 (M^+). $C_9H_{17}O_2Cl$ requires *M*, 192.0917].

The physical data of the known product 3-[(4′-nitrophenyl)hydroxymethyl]-3-buten-2-one (2a).[9,16] Mp 66–68°C; ^{1}H NMR ($CDCl_3$, 300 MHz) d 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).

Typical reaction procedure for the preparation of 3-(chloromethyl)-4-(4′-nitrophenyl)-3-buten-2-one (3a). To a solution of dimethyl sulfide (6.20 mg, 0.1 mmol, 7.2 μL) in dichloromethane (1.3 mL) was added titanium chloride (0.7 mL, 0.7 mmol) at room temperature. After stirring for 5 min, a solution of *p*-nitrobenzaldehyde (76 mg, 0.5 mmol) in dichloromethane (1.0 mL) and methyl vinyl ketone (105 mg, 1.5 mmol, 123 μL) were added into the reaction at room temperature. The reaction mixture was kept for 48 h at room temperature. 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 **3a** (74 mg, 62%) as a colorless solid (eluent: ethyl acetate/petroleum ether=1/8): mp 134–136°C; IR(KBr) ν 1640 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$, 300 Hz) δ 2.55 (3H, s, Me), 4.38 (2H, s, CH_2), 7.69 (1H, s), 7.75 (2H, d, J=8.6 Hz, Ar), 8.35 (2H, d, J=8.6 Hz, Ar); MS (EI) *m/e* 239 (M^+, 0.40), 222 (M^+-17, 40), 115 (M^+-124, 100); Found: C, 54.94; H, 3.92; N, 5.87%. $C_{11}H_{10}ClNO_3$ requires C, 55.13; H, 4.21; N, 5.84%.

Preparation of 3-(chloromethyl)-4-(3′-nitrophenyl)-3-buten-2-one (3b). This compound was prepared in the same manner as that described above. 84 mg, 70%; a colorless solid; mp 130–132°C; IR(KBr) ν 1640 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.55 (3H, s, Me), 4.40 (2H, s, CH_2), 7.70 (1H, s), 7.71 (1H, t, J=7.7 Hz, Ar), 7.96 (1H, d, J=7.7 Hz, Ar), 8.30 (1H, dd, J=8.2, 1.3 Hz, Ar), 8.44 (1H, s, Ar); MS (EI) *m/e* 239 (M^+, 60), 222 (M^+-17, 50), 115 (M^+-124, 50), 43 (M^+-196, 100); [HRMS (EI) *m/z* 239.0351 (M^+). $C_{11}H_{10}ClNO_3$ requires *M*, 239.0349].

Preparation of 3-(chloromethyl)-4-(4′-trifluoromethylphenyl)-3-buten-2-one (3c). This compound was prepared in the same manner as that described above. 97 mg, 74%; a colorless solid; mp 43–45°C; IR(KBr) ν 1640 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.54 (3H, s, Me), 4.39 (2H, s, CH_2), 7.70 (1H, s), 7.60–7.76 (4H, m, Ar); MS (EI) *m/e* 262 (M^+, 100), 193 (M^+-69, 70), 183 (M^+-79, 50), 115 (M^+-147, 40); [HRMS (EI) *m/z* 262.0381 (M^+). $C_{12}H_{10}ClF_3O$ requires *M*, 262.0372].

Preparation of 3-(chloromethyl)-4-(4′-ethylphenyl)-3-buten-2-one (3d). This compound was prepared in the same manner as that described above. 52 mg, 47%; a colorless oil; IR(KBr) ν 1640 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (3H, t, J=7.1 Hz), 2.51 (3H, s, Me), 2.67 (2H, q, J=7.1 Hz), 4.48 (2H, s, CH_2), 7.31 (2H, d, J=8.0 Hz), 7.55 (2H, d, J=8.0 Hz), 7.69 (1H, s); MS (EI) *m/e* 222 (M^+, 30), 193 (M^+-29, 100), 128 (M^+-94, 40); [HRMS (EI) *m/z* 222.0809 (M^+). $C_{13}H_{15}ClO$ requires *M*, 222.0811].

Preparation of 3-(chloromethyl)-4-phenyl-3-buten-2-one (3e). This compound was prepared in the same manner as that described above. 49 mg, 50%; a colorless oil; IR(KBr) ν 1640 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.52 (3H, s, Me), 4.46 (2H, s, CH_2), 7.31–7.50 (3H, m, Ar), 7.51–7.61 (2H, m, Ar), 7.71 (1H, s); MS (EI) *m/e* 194 (M^+, 100), 115 (M^+-79, 40), 43 (M^+-151, 40); [HRMS (EI) *m/z* 194.0498 (M^+). $C_{11}H_{11}ClO$ requires *M*, 194.0492].

Preparation of 3-(chloromethyl)-4-(4′-chlorophenyl)-3-buten-2-one (3f). This compound was prepared in the same manner as that described above. 65 mg, 57%; a colorless solid; mp 87–89 °C; IR(KBr) ν 1640 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.51 (3H, s, Me), 4.42 (2H, s, CH_2), 7.46 (2H, d, J=8.6 Hz), 7.54 (2H, d, J=8.6 Hz), 7.69 (1H, s); MS (EI) *m/e* 228 (M^+, 20), 193 (M^+-35, 40), 149 (M^+-79, 40), 115 (M^+-113, 40), 43 (M^+-185, 100); [HRMS (EI) *m/z* 228.0110 (M^+). $C_{11}H_{10}Cl_2O$ requires *M*, 228.0109].

Preparation of 3-(chloromethyl)-4-nonyl-3-buten-2-one (3g). This compound was prepared in the same manner as that described above. 52 mg, 29%; a colorless oil; IR(KBr) ν 1640 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (3H, t, J=7.1 Hz, Me), 1.10–1.40 (12H, m, CH_2), 1.40–1.60 (2H, m, CH_2), 2.36 (3H, s, Me), 2.34 (2H, td, J=7.6, 7.6 Hz), 4.32 (2H, s, CH_2), 6.85 (1H, t, J=7.6 Hz); MS (EI) *m/e* 244 (M^+, 20), 209 (M^+-35, 40), 109 (M^+-135, 70), 43 (M^+-201, 100); [HRMS (EI) *m/z* 244.1596 (M^+). $C_{14}H_{25}ClO$ requires *M*, 244.1594].

Crystallography

A suitable single crystal with 0.20×0.20×0.30 mm^3 dimensions obtained by recrystallization of **3a** from CH_2Cl_2/petroleum ether (1/6) was mounted at the top of a glass capillary. Crystal data have been given in the references and notes.[14] Data were collected on a Rigaku AFC7R diffractometer with graphite-monochromated Mo-Kα radiation λ= 0.71069 Å using the $\omega-2\theta$ technique at 20°C. A total of 2525 unique reflection was collected. The data were collected for Lorentz polarization effects. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically by full-matrix least squares. All hydrogen atoms were included in calculated position. All calculations were performed using the TEXSAN crystallographic software package. Final R and R_w values were 0.066 and 0.061 for 1110 observed reflection. This crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC 142973.

Acknowledgements

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References

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.
2. Brzezinski, L. J.; Rafel, S.; Leahy, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 4317.
3. Marko, I. E.; Giles, P. G.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015.
4. Richter, H.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 2729.
5. Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1999**, 2533.
6. Kunidig, E. P.; Xu, L. H.; Romanens, P.; Bernardinelli, G. *Tetrahedron Lett.* **1993**, *34*, 7049.
7. Aggarwal, V.; Mereu, A.; Tarver, G. J.; MaCague, R. *J. Org. Chem.* **1998**, *63*, 7183.
8. Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539.
9. Kataoka, T.; Iwama, T.; Tsujiyama, S.-I.; Iwamura, T.; Watanaba, S.-I. *Tetrahedron* **1998**, *54*, 11813.
10. Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1999**, *40*, 1509.
11. (a) Nagaoka, Y.; Yomioka, K. *J. Org. Chem.* **1998**, *63*, 6428. (b) Harrowven, D.; Hannam, J. C. *Tetrahedron* **1999**, *55*, 9341.
12. Kataoka, T.; Iwama, T.; Kinoshita, S.; Tsujiyama, Y.; Iwamura, T.; Watanabe, S. *Synlett* **1999**, 197.
13. (a) Kataoka, T.; Iwama, T.; Tsujiyama, S.; Kanematsu, K.; Iwamura, T.; Watanabe, S. *Chem. Lett.* **1999**, 257. (b) Kataoka, T.; Iwama, T.; Tsujiyama, S. *Chem. Commun.* **1998**, 197.
14. The crystal data of **3a**: empirical formula: $C_{22}H_{20}N_2O_6Cl_2$; Formula weight: 479.32; crystal color, habit: colorless, prismatic; crystal dimensions: 0.20×0.20×0.30 mm^3; Crystal system: monoclinic; lattice type: primitive; lattice type: a=7.524(2) Å, b=17.541(3) Å, c=17.07(1) Å, β=98.64(4)°, V=2227(1) $Å^3$; space group: $P2_1/n$ (#14); Z value=4; D_{calc}=1.429 g/cm^3; F_{000}=992.00; μ(MoKα)=3.33 cm^{-1}; R=0.066, R_w=0.061.
15. Li, G.; Wei, H.-X.; Gao, J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1.
16. Iwama, T.; Tsujiyama, S.-I.; Kinoshita, H.; Kanamatsu, K.; Tsurukami, Y.; Iwamura, T.; Watanabe, S.-I.; Kataoka, T. *Chem. Pharm. Bull.* **1999**, *47*, 956.