Amine and Titanium (IV) Chloride, Boron (III) Chloride or Zirconium (IV) Chloride-Promoted Baylis-Hillman Reactions

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Abstract: The Baylis-Hillman reactions of various aryl aldehydes with methyl vinyl ketone at temperatures below -20°C using Lewis acids such as titanium (IV) chloride, boron (III) chloride or zirconium (IV) chloride in the presence of a catalytic amount of selected amines used as a Lewis bases afford the chlorinated compounds 1 as the major product in very high yields. Acrylonitrile can also undergo the same reaction to give the corresponding chlorinated product in moderate yield. A plausible reaction mechanism is proposed. However, if the reaction was carried out at room temperature (ca. 20°C), then the Z-configuration of the elimination product 3, derived from 1, was formed as the major product.

Keywords: Titanium (IV) chloride; boron (III) chloride; zirconium (IV) chloride; Bayliss-Hillman reaction; halogenation; Lewis base, amine.

Introduction

The Baylis-Hillman reaction and related processes, typically catalyzed by DABCO or tertiary phosphines, have become increasingly important in organic synthesis because the resulting adducts may have several functional groups available for numerous further transformations [1-5]. The major drawbacks
of the Baylis-Hillman reaction are its slow reaction rate and a limited range of useful substrates. To overcome these shortcomings many variations have been devised, such as the use of Lewis acids or various other additives to activate the carbonyl electrophiles [6-10]. Among those Lewis acids examined, TiCl₄ has been successfully used to promote the Baylis-Hillman reaction in the presence of Lewis base catalysts [9,11,12]. During our own investigations of the Baylis-Hillman process we found that many amines are very effective Lewis bases in this interesting reaction and the reaction products differ considerably from those reported so far [13]. Herein we wish to report the full details of the titanium (IV) chloride, boron (III) chloride or zirconium (IV) chloride and amine promoted Baylis-Hillman reactions, along with a plausible reaction mechanism based on the previous findings and our own results.

Results and Discussion

We initially attempted the reaction of \(p\)-nitrobenzaldehyde with methyl vinyl ketone in the presence of TiCl₄ (1.0 eq) at -78 °C. No reaction occurred (Table 1, entry 1). However, after adding 20 mol % (0.20 eq) of triethylamine (Et₃N) as a Lewis base, the reaction took place smoothly to give the chlorinated product 1a, rather than 2a and 3a (usually considered the Baylis-Hillman olefin and trisubstituted alkene) as reported by Kataoka and Li [9, 12], respectively (Scheme 1, Table 1, entry 2). By careful investigation, we found that this reaction was very sensitive to the amounts of both TiCl₄ and amines present in the reaction mixture (Table 1). By means of catalytic amounts of amine and excess amounts of TiCl₄ the reaction proceeded very well. However, using large excesses of amine as a Lewis base, the reaction was completely stopped (Table 1, entry 6). This result suggested that the amine could coordinate to TiCl₄ and that free TiCl₄ acting as a Lewis acid was required to promote the reaction. The amount of TiCl₄ was also crucial for this reaction because using a catalytic amount of TiCl₄, the reaction became very slow and gave low yields of 1a (Table 1, entry 7 and 8). The best reaction conditions were found to be the use of 20 mol % of amine as a Lewis base and 1.4 eq of TiCl₄ as a Lewis acid (Table 1, entry 4).

Scheme 1

\[
\text{R-CHO} \quad \xrightarrow{\text{TiCl}_4, \text{Et}_3\text{N}} \quad \text{OH} \quad \text{O} \\
\text{CH}_2\text{Cl}_2, -78 ^\circ \text{C} \quad \text{1a} \\
\text{R= p-NO}_2\text{Ph}
\]
Table 1. Reaction Conditions for the Bayliss-Hillman Reaction of p-Nitrobenzaldehyde with Methyl Vinyl Ketone in the Presence of TiCl4 and Et3N

| Entry | Eq. of Lewis base (Et3N) | Eq. of Lewis acid (TiCl4) | Yielda) [%] 1a |
|-------|--------------------------|---------------------------|-------------|
| 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

For many aryl aldehydes having strongly electron-withdrawing group on the phenyl ring, the reactions proceed quickly to give compounds 1 in high yields using a catalytic amount of Lewis base (20 mol %) at -78°C (Scheme 2, Table 2). However, other aryl aldehydes or aliphatic aldehydes needed higher temperatures (-20°C) to give the corresponding chlorinated product 1 in high to moderate yields. 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 TiCl4 (Table 2).

Scheme 2

\[
\begin{align*}
R-CHO + \text{CH}_2\text{Cl}_2, < -20 ^\circ C &\rightarrow \text{TiCl}_4, \text{Lewis base} & \rightarrow R-\text{CH-CH} \bigg\text{Me} \bigg\text{Me} \\
\text{OH} & & \text{CH}_2\text{-Cl}
\end{align*}
\]

a: p-NO2Ph; b: m-NO2Ph; c: p-CF3Ph; d: Ph; e: p-EtPh; f: p-ClPh; g: CH3(CH2)3.

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 TiCl4 (Table 2). It should be emphasized that in all cases, only one diastereomer was formed during the reaction process based on the \(^1\)H-NMR spectral data evidence. Their relative configurations were confirmed as the syn-form by analysis of the X-ray crystal structure of 1a [13] (Figure 1).
Table 2. Bayliss-Hillman Reaction of Aldehydes with Methyl Vinyl Ketone in the Presence of TiCl₄ and 20 mol% of Lewis Base

| Entry | R          | Lewis base | Temp [°C] | Time [h] | Yielda) [%] |
|-------|------------|------------|-----------|----------|-------------|
| 1     | p-NO₂-Ph   | none       | -78       | 12       | -           |
| 2     | p-NO₂-Ph   | Et₃N       | -78       | 12       | 81          |
| 3     | m-NO₂-Ph   | Et₃N       | -78       | 12       | 88          |
| 4     | p-CF₃-Ph   | Et₃N       | -78       | 48       | 80          |
| 5     | Ph         | Et₃N       | -20       | 48       | 80          |
| 6     | p-Et-Ph    | Et₃N       | -20       | 48       | 72          |
| 7     | p-Cl-Ph    | Et₃N       | -20       | 48       | 70          |
| 8     | CH₃(CH₂)₃  | Et₃N       | -20       | 48       | 45          |
| 9     | p-NO₂-Ph   | Et₂NH      | -78       | 12       | 88          |
| 10    | Ph         | Et₂NH      | -20       | 48       | 71          |
| 11    | p-NO₂-Ph   | DBU        | -78       | 12       | 82          |
| 12    | Ph         | DBU        | -20       | 48       | 65          |

a) isolated yields

Figure 1: Crystal Structure of 1a

Compound 1 can be easily and completely transformed to the compound 2 [14] by treating with an excess amount (2.0 eq) 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) was noted to also cause the transformation of 1 to 2, therefore quick flash column chromatography is required in order to obtain the pure product 1.
Besides methyl vinyl ketone, acrylonitrile underwent the same reaction to give the corresponding chlorinated product \(1h\) in moderate yield in \(\text{CH}_2\text{Cl}_2\) at \(10^\circ\text{C}\) for 5 days (Scheme 4, Table 3, entries 1 and 2), but at -78 \(^\circ\text{C}\), no reaction occurred (entry 3). Raising the reaction temperature to reflux (45\(^{\circ}\text{C}\)) caused a decrease of the yield of \(1h\) (Table 3, entry 4). On the other hand, using methyl acrylate as a Michael acceptor, only trace amounts of chlorinated product were obtained under similar reaction conditions (Scheme 5).
Table 3. Bayliss-Hillman Reaction of p-Nitrobenzaldehyde with Acrylonitrile in the Presence of TiCl₄ and 20 mol % of Amine as Lewis Base

| Entry | Amine  | Temp [°C] | Time [h] | Yield a) [%] |
|-------|--------|-----------|----------|--------------|
| 1     | Et₃N   | 10        | 5        | 37           |
| 2     | DBU    | 10        | 5        | 50           |
| 3     | DBU    | -78       | 3        | 0            |
| 4     | DBU    | 40        | 3        | 16           |

a) isolated yield

To the best of our knowledge, this represents a novel Bayliss-Hillman reaction system because use of a catalytic amount of amine as a Lewis base has never been reported to date for titanium(IV) chloride promoted Bayliss-Hillman reactions. Recently, Aggarwal has reported that using stoichiometric amounts of amine such as DABCO and a catalytic amount of titanium (IV) chloride gave reduced reaction rates, but that use of stoichiometric amounts of amine and a catalytic amount of lanthanide triflates (5 mol%) gave increased rates in the Baylis-Hillman reaction [7]. Our system shows that using excess amounts of titanium (IV) chloride and catalytic amount of amines, the major reaction products in moderate to high yields are the β-chlorinated compounds 1, which can be readily transformed to the Baylis-Hillman olefin 2. Thus the reaction rate of Bayliss-Hillman reaction can be greatly accelerated by means of this reagent system.

We also examined many other metal halides such as PdCl₂, RhCl₃, Cp₂ZrCl₂, ZrCl₄, AlCl₃, TMSCl, SiCl₄, BF₃, BCl₃ and found that BCl₃ and ZrCl₄ also worked as Lewis acids for this reaction, although they are not as effective as TiCl₄. For example, we carried out the Baylis-Hillman reaction using BCl₃ and ZrCl₄ as Lewis acid with Et₃N as a Lewis base under the same reaction conditions as those shown in Scheme 1. The syn-chlorinated products can be also obtained (Scheme 6), but this required longer reaction times (40 h) at -78°C. These results are summarized in Table 4.

Scheme 6

\[
\begin{align*}
R-\text{CHO} + \text{Me-CN} & \xrightarrow{\text{BCl₃ or ZrCl₄, Et₃N, CH₂Cl₂, < -20 °C}} \text{R-CH=CH-Cl} \\
& \quad \quad \quad \quad \quad \quad 1\text{a-e}
\end{align*}
\]
### Table 4. Baylis-Hillman Reaction of Aldehydes with Methyl Vinyl Ketone in the Presence of BCl₃ (1.4 eq.) or ZrCl₄ (1.4 eq) and 20 mol % of Et₃N

| Entry | R           | Lewis acid | Temp [°C] | Time [h] | Yield [a) [%] |
|-------|-------------|------------|-----------|----------|---------------|
| 1     | p-NO₂-Ph    | BCl₃       | -78       | 40       | 64            |
| 2     | m-NO₂-Ph    | BCl₃       | -78       | 42       | 63            |
| 3     | o-NO₂-Ph    | BCl₃       | -78       | 42       | 58            |
| 4     | p-CF₃-Ph    | BCl₃       | -78       | 48       | 42            |
| 5     | Ph          | BCl₃       | -20       | 48       | 34            |
| 6     | p-Cl-Ph     | BCl₃       | -20       | 48       | 45            |
| 7     | p-NO₂-Ph    | ZrCl₄      | -78       | 48       | 57            |
| 8     | p-Cl-Ph     | ZrCl₄      | -78       | 48       | 43            |

[a) isolated yields

In Scheme 7, we propose a tentative mechanism to explain the formation of product 1. In fact, the reactions of trimethylamine and dimethylamine with titanium (IV) chloride had been investigated by Antler and Laubengayer in 1955 [15a]. Chloride ion was detected although the system was complicated. Based on his findings, Periasamy gave a mechanism for the reaction of tertiary amines with TiCl₄ [15b]. Recently many crystal structures of Ti complexes derived from the reaction of TiCl₄ with amines have been disclosed including cationic Ti complexes [15c,d,e].

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**Scheme 7**

\[
\text{Et}_3\text{N} + \text{TiCl}_4 \rightarrow (\text{Et}_3\text{N}-\text{TiCl}_3)^+ \rightarrow \text{R-CHO} \rightarrow \text{product}
\]
The reaction mechanism proposed in Scheme 7 is based on those previous findings and the results of our own investigations as shown in Table 1. We believe that amine can strongly coordinate to the Ti metal center of TiCl₄ to give an ionic metal complex containing chloride ion. This reaction is related with the attack of chloride ion on the methyl vinyl ketone in a Michael addition fashion (Scheme 7). Using BCl₃ or ZrCl₄ as a Lewis acid, the reactions would proceed via the same mechanism. Thus, the formation of chlorinated compound 1 is a major reaction process in the TiCl₄, BCl₃, and ZrCl₄ and Lewis base amine promoted Baylis-Hillman reaction.

**Figure 2:** The chiral Lewis bases used for the Bayliss-Hillman reaction

We also examined the catalytic enantioselective Baylis-Hillman reaction using chiral amines or aminoalcohols as chiral Lewis bases for this reaction (Scheme 8). The enantiomeric excesses achieved were determined by chiral HPLC analysis of 1a or 2a after treating with DBU or Et₃N. In Figure 2, we
show the chiral Lewis bases used for this reaction. These chiral ligands (A-L) were either prepared by us according to the known synthetic methods or purchased from Aldrich. For sterically bulky amines, the reaction is relatively slow and longer reaction times are required, but in all cases, the achieved enantiomeric excesses were only about 10~20%. We believe that this is related to the mechanism shown in Scheme 7 because the reaction is via separated ionic intermediates and the chiral centers are far away from the aldol reaction center. These results partially support our proposed reaction mechanism (Scheme 7).

On the other hand, by carrying out this reaction at room temperature (about 20 °C), we confirmed that the elimination product 3 was the only product under the same reaction conditions (Scheme 9, Table 5, entries 3-10).

**Table 5.** Bayliss-Hillman Reaction of Aldehydes with Methyl Vinyl Ketone in the Presence of 1.4 eq. of TiCl₄ and 0.20 eq. of Et₃N at Room Temperature

| Entry | R           | Time [h] | Yielda) (%) |
|-------|-------------|----------|-------------|
| 1     | p-NO₂-Ph    | 6        | 30b)        |
| 2     | p-NO₂-Ph    | 6        | 50          |
| 3     | p-NO₂-Ph    | 24       | 92          |

**Scheme 8**

\[
p-\text{NO}_2\text{Ph}-\text{CHO} + \overset{\text{TiCl}_4,\text{ Lewis base}}{\text{CH}_2\text{Cl}_2, < -20 °C}} \rightarrow p-\text{NO}_2\text{Ph}-\underset{\text{CH}_2\text{Cl}_2}{\text{CH-CH}}\underset{\text{Me}}{\text{Me}} 1a
\]

**Scheme 9**

\[
R-\text{CHO} + \overset{\text{TiCl}_4,\text{Et}_3\text{N}}{\text{CH}_2\text{Cl}_2, 20 °C}} \rightarrow R-\underset{\text{CH}_2\text{Cl}}{\text{C=O}} 3
\]
This reaction was first disclosed by Li and coworkers. They reported that in the presence of stoichiometric or nonstoichiometric TiX₄, compound 3 could be formed in its Z-configuration [12]. Later we also reported that 3 could be exclusively obtained in the TiCl₄ and chalcogenide promoted Baylis-Hillman reaction at room temperature (20°C) [16]. The Z-configuration has been confirmed by X-ray analysis (Figure 3) [16].

**Figure 3: Crystal Structure of 3a**

We now wish to report that in the initial reaction stage, the presence of Lewis base can still significantly speed up this reaction (Table 5, entry 1 and 2). In order to clarify the formation of 3, we treated 1a and 2a directly with TiCl₄ in dichloromethane at room temperature. We found that 1a can be transformed to 3a within 6 h, whereas the reaction of 2a with TiCl₄ was much slower (Scheme 10). These
results strongly suggest that 3a is derived directly from 1a formed first in the reaction. Thus, we conclude that, at room temperature, the chlorinated products 1 could be formed either in the absence or in the presence of Lewis base, but they are rapidly transformed to the elimination product 3 exclusively.

![Scheme 10](image)

**Conclusions**

We have found that TiCl₄, BCl₃ or ZrCl₄ and amine promoted Baylis-Hillman reaction is a very efficient reaction system for producing chlorinated compounds 1. The amine compounds are good Lewis bases and TiCl₄, BCl₃ and ZrCl₄ are good Lewis acids for this reaction. The reaction temperatures, the amount of Lewis acid, and the amount of Lewis base can drastically affect the reaction products and reaction rates. The relative activities of different Lewis acids for this reaction are TiCl₄ > BCl₃ > ZrCl₄ and the best combination of Lewis acid and Lewis base for this reaction is TiCl₄ (1.4 eq) with NEt₃ (0.2 eq). The relative configuration of 1 was not affected by the Lewis acids (TiCl₄, BCl₃ or ZrCl₄) used at all. The reaction was initiated by chloride ion attacking at the Michael acceptor of the α,β-unsaturated ketone. The chloride ion was produced by coordination of Lewis bases (NEt₃) to Lewis acids such as TiCl₄, BCl₃, and ZrCl₄. Undoubtedly compound 3 was derived mainly from 1. Efforts are underway to elucidate the full mechanistic details of this reaction and to disclose the scope and limitations of this reaction. Work along this line are currently in progress.

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Experimental Section

General

Melting points are uncorrected. $^1$H- and $^{13}$C-NMR spectra were recorded on a Bruker AMX-300 spectrometer at 300 MHz and 75 MHz, respectively. Mass spectra were recorded by the EI method and HRMS was measured by a Finnigan MA+ mass spectrometer. Organic solvents used were dried by standard methods when necessary. All solid compounds reported in this paper gave satisfactory CHN microanalyses. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF$_{254}$ silica gel coated plates. Flash Column Chromatography was carried out using 300-400 mesh silica gel at increased pressure.

Typical procedure for the preparation of compounds 1a-h and 2a: 3-(Chloromethyl)-4-hydroxy-4-(4'-nitrophenyl)-2-butanone (1a).

To a solution of triethylamine (10.1 mg, 0.1mmol, 14.0 µL) in CH$_2$Cl$_2$(1.3 mL) was added titanium tetrachloride (0.7 mL, 0.7 mmol) at -78 °C. After stirring for 5 min, a solution of p-nitrobenzaldehyde (75.5 mg, 0.5 mmol) in CH$_2$Cl$_2$ (1.0 mL) and methyl vinyl ketone (105.0 mg, 1.5 mmol, 123.0 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 CH$_2$Cl$_2$ (5.0 mL x 2) and dried over anhydrous MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by a flash chromatography (silicagel, eluent 1:4 ethyl acetate/petroleum ether) to give compound 1a (105.0 mg, 81%) as a colorless solid, mp 90-91 °C; IR (KBr) ν 1720 cm$^{-1}$; $^1$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); Anal. 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%.

3-(Chloromethyl)-4-hydroxy-4-(3'-nitrophenyl)-2-butanone (1b).

Colorless oil, 113 mg (88%); 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$_2$O). C$_{11}$H$_{10}$O$_3$NCl requires M-H$_2$O, 239.0349].

3-(Chloromethyl)-4-hydroxy-4-(4'-trifluoromethylphenyl)-2-butanone (1c).

Colorless oil, 112 mg (80%); 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
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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⁺-H₂O). C₁₂H₁₀OClF₃ requires M-H₂O, 262.0372].

3-(Chloromethyl)-4-hydroxy-4-phenyl-2-butanone (1d).

Colorless oil: 85 mg (80%); a; IR(KBr) ν 1720 cm⁻¹ (C=O); ¹H-NMR (CDCl₃, 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⁺). C₁₁H₁₃O₂Cl requires M, 212.0604].

3-(Chloromethyl)-4-hydroxy-4-(4′-ethylphenyl)-2-butanone (1e).

Colorless solid: 87 mg (72%); mp 69-71 °C; IR(KBr) ν 1720 cm⁻¹ (C=O); ¹H-NMR (CDCl₃, 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⁺). C₁₃H₁₇O₂Cl requires M, 240.0917].

3-(Chloromethyl)-4-hydroxy-4-(4′-chlorophenyl)-2-butanone (1f).

Colorless oil: 86 mg (70%); a; IR(KBr) ν 1720 cm⁻¹ (C=O); ¹H-NMR (CDCl₃, 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⁺). C₁₁H₁₂O₂Cl₂ requires M, 246.0214].

3-(Chloromethyl)-4-hydroxy-4-butyl-2-butanone (1g).

Colorless oil: 43 mg (45%); a; IR(KBr) ν 1720 cm⁻¹ (C=O); ¹H-NMR (CDCl₃, 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⁺). C₉H₁₇O₂Cl requires M, 192.0917].

Preparation of 2-(chloromethyl)-3-hydroxy-3-(4′-nitrophenyl)-propionitrile (1h).

Colorless oil: 45 mg (37%); IR(KBr) ν 1720 cm⁻¹ (C=O); ¹H NMR (CDCl₃, 300 MHz) δ 2.50 (1H, s, OH), 3.28 (1H, q, J 6.1 Hz), 3.70 (1H, dd, J 11.3, 4.5 Hz), 3.96 (1H, dd, J 11.3, 5.8 Hz), 7.67 (2H, d, J 8.3 Hz), 8.28 (2H, d, J 8.3 Hz); MS (EI) m/e 240 (M⁺, 38.75), 205 (M⁺-35, 30), 152 (M⁺-149, 100); [HRMS (EI) m/z 240.0310 (M⁺). C₁₀H₉ClN₂O₃ requires M, 240.0302].
3-[(4'-nitrophenyl)hydroxymethyl]-3-buten-2-one (2a).

A known compound [9]. Its physical data was comparable to that reported in literature: mp 66-68°C; 1H-NMR (CDCl3, 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).

Typical Procedure for the Preparation of 3-(Chloromethyl)-4-(4'-nitrophenyl)-3-buten-2-one (3a).

To a solution of triethylamine (10.1 mg, 0.1 mmol, 14.0 µL) in CH2Cl2 (1.3 mL) was added 1.0 N titanium tetrachloride (0.7 mL, 0.7 mmol) in CH2Cl2 at room temperature (20 °C). After stirring for 5 min, a solution of p-nitrobenzaldehyde (76 mg, 0.5 mmol) in CH2Cl2 (1.0 mL) and methyl vinyl ketone (105 mg, 1.5 mmol, 123 µL) were added into the reaction solution at room temperature. The reaction mixture was kept for 24 h at room temperature. The reaction was quenched by addition of saturated aqueous NaHCO3 solution (1.0 mL). After filtration, the filtrate was extracted with CH2Cl2 (5.0 mL x 2) and dried over anhydrous MgSO4. The solvent was removed under reduced pressure and the residue was purified by flash silica gel chromatography to give compound 3a (110 mg, 92%) as a colorless solid (eluent: ethyl acetate/petroleum ether=1/8): mp 134-136 °C; IR(KBr) ν 1640 cm-1 (C=O); 1H-NMR (CDCl3, 300 Hz) δ 2.55 (3H, s, Me), 4.38 (2H, s, CH2), 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% C11H10ClNO3 requires C, 55.13; H, 4.21; N, 5.84%].

3-(Chloromethyl)-4-(2'-nitrophenyl)-3-buten-2-one (3b).

A colorless solid: 103 mg (86%); mp 120-122 °C; IR(KBr) ν 1640 cm-1 (C=O); 1H-NMR (CDCl3, 300 MHz) δ 2.52 (3H, s, Me), 4.23 (2H, s, CH2), 7.64 (1H, td, J 6.4, 1.5 Hz, Ar), 7.72 (1H, d, J 6.7 Hz, Ar), 7.80 (1H, t, J 7.5 Hz, Ar), 8.02 (1H, s), 8.27 (1H, d, 7.5 Hz, 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+). C11H10ClNO3 requires M, 239.0349].

3-(Chloromethyl)-4-(4'-trifluoromethylphenyl)-3-buten-2-one (3c).

A colorless solid: 114 mg (87%); mp 43-45 °C; IR (KBr) ν 1640 cm-1 (C=O); 1H-NMR (CDCl3, 300 MHz) δ 2.54 (3H, s, Me), 4.39 (2H, s, CH2), 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+). C12H10ClF3O requires M, 262.0372].

Preparation of 3-(chloromethyl)-4-(4'-chlorophenyl)-3-buten-2-one (3d).

A colorless solid: 86 mg (75%); mp 87-89 °C; IR (KBr) ν 1640 cm-1 (C=O); 1H-NMR (CDCl3, 300 MHz) δ 2.51 (3H, s, Me), 4.42 (2H, s, CH2), 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_{2}O requires M, 228.0109].

**Preparation of 3-(chloromethyl)-4-(3′-fluorophenyl)-3-buten-2-one (3e).**

This compound was prepared in the same manner as that described above: 87 mg (82%); a colorless solid; mp 63-64 °C; IR (KBr) ν 1640 cm⁻¹ (C=O); ¹H-NMR (CDCl₃, 300 MHz) δ 2.51 (3H, s, Me), 4.42 (2H, s, CH₂), 7.10-7.50 (4H, m, Ar), 7.69 (1H, s); MS (EI) m/e 212 (M+, 15), 177 (M+-35, 40), 99 (M+-113, 40), 43 (M+-169, 100); [HRMS (EI) m/z 212.0411 (M+). C_{11}H_{10}ClFO requires M, 212.0404].

**Preparation of 3-(chloromethyl)-4-(4′-ethylphenyl)-3-buten-2-one (3f).**

This compound was prepared in the same manner as that described above: 67 mg (60%); a colorless oil; IR (KBr) ν 1640 cm⁻¹ (C=O); ¹H-NMR (CDCl₃, 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, CH₂), 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 (3g).**

This compound was prepared in the same manner as that described above: 75 mg (77%); a colorless oil; IR (KBr) ν 1640 cm⁻¹ (C=O); ¹H-NMR (CDCl₃, 300 MHz) δ 2.52 (3H, t, J 7.1 Hz, 2.51 (3H, s, Me), 2.67 (2H, q, J 7.1 Hz), 4.48 (2H, s, CH₂), 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-nonyl-3-buten-2-one (3h).**

This compound was prepared in the same manner as that described above: 62 mg (50%); a colorless oil; IR (KBr) ν 1640 cm⁻¹ (C=O); ¹H-NMR (CDCl₃, 300 MHz) δ 0.83 (3H, t, J 7.1 Hz, 1.10-1.40 (12H, m, CH₂), 1.40-1.60 (2H, m, CH₂), 2.36 (3H, s, Me), 2.34 (2H, td, J 7.6, 7.6 Hz), 4.32 (2H, s, CH₂), 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].

**X-Ray Crystallography**

Suitable single crystals of compounds 1a and 3a were mounted on the tip of a glass capillary. Data were collected on a Rigaku AFC7R diffractometer with graphite-monochromated Mo-K(α) radiation λ = 0.71069 (Å) using the ω-2θ technique at 20°C. The data were corrected for Lorentz polarization effects. The structure was solved by direct methods and expanded using Fourier techniques [16]. The non-hydrogen atoms were refined anisotropically by full-matrix least squares. All hydrogen atoms were
included in the calculated positions. All calculations were performed using the TEXSAN crystallographic software package. The resulting crystal structures have been deposited at the Cambridge Crystallographic Data Center and have been allocated deposition numbers CCDC 144817 for \textit{1a} and CCDC 142973 for \textit{3a}, respectively.

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14. The X-ray crystal data for compound \textit{1a}: Empirical formula: C\textsubscript{11}H\textsubscript{12}ClNO\textsubscript{4}; Formula Weight: 257.67; Crystal Color, Habit: colorless, column; Crystal dimensions: 0.28 x 0.30 x 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\textsuperscript{3}; Space group: P2\textsubscript{1}2\textsubscript{1}2\textsubscript{1} (#19); Zvalue = 4; D\textsubscript{calc} = 1.441 g/cm\textsuperscript{3}; F\textsubscript{000} = 536.00; \(\mu\)(MoK\textsubscript{a}) = 3.23 cm\textsuperscript{-1}; Residuals: R; Rw = 0.065; 0.052.

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P2₁/n (#14); Z value = 4; D$_{calc}$ = 1.429 g/cm$^3$; F$_{000}$ = 992.00; u(MoKα) = 3.33 cm$^{-1}$; R = 0.066, R$_w$ = 0.061. TEXSAN, Crystal Structure Analysis Package, Molecular Structure Corporation, Houston, TX, 1985 and 1992.

Sample Availability: Samples are available from the authors.