CHAPTER-III

Synthesis of allyl chlorides from Baylis-Hillman adducts
3.1. INTRODUCTION TO BAYLIS-HILLMAN REACTION

The carbon–carbon bond formation and the functional group interconversions are the most fundamental reactions for the design of a molecular framework and are highly important in synthetic organic chemistry.\(^1\)\(^-\)\(^4\) Carbon-carbon bond forming reactions and their applications in organic chemistry have been well documented in literature.\(^5\)\(^-\)\(^14\)

In recent years, the Baylis-Hillman reaction\(^15\)\(^-\)\(^18\) attracted synthetic chemists as an excellent functional group generator and its atom economy\(^19\) made its addition to the list of other useful and efficient carbon-carbon bond-forming reactions.

3.1.1. Discovery and Development

Baylis-Hillman reaction\(^15\) is a two component coupling reaction discovered by two German scientists A. B. Baylis and M. E. D. Hillman in 1972. It involves the coupling of \(\alpha\)-position of activated alkenes with carbon electrophiles under the catalytic influence of a tertiary amine providing a simple process for synthesis of densely functionalized molecules.\(^15\)\(^-\)\(^18\) The reaction attracted the attention of synthetic chemists as a novel and versatile C–C bond forming protocol. Publication of a large number of research papers including three major reviews,\(^16\)\(^-\)\(^18\) proved the potential of Baylis-Hillman chemistry.
3.1.2. Mechanism of Baylis-Hillman Reaction

Mechanism involves the Michael-initiated addition-elimination sequence. The most plausible mechanism\textsuperscript{16-18} of the amine (DABCO) catalyzed reaction between acrylate ester (as an activated olefin) and an aldehyde (as an electrophile) as a model case is depicted below (Scheme 3.1).

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\begin{tikzpicture}
\node[align=center] (X) at (0,0) {X};
\node[align=center] (R) at (X.north east) {R};
\node[align=center] (R1) at (R.north east) {R\textsuperscript{1}};
\end{tikzpicture}};
\node (E) at (X.north) {EWG};
\node (W) at (R1.north) {EWG};
\node (Y) at (R1.east) {Baylis-Hillman adduct};
\node[align=center] (A) at (Y) {\begin{tikzpicture}
\node[align=center] (X) at (0,0) {X};
\node[align=center] (R) at (X.north east) {R};
\node[align=center] (R1) at (R.north east) {R\textsuperscript{1}};
\end{tikzpicture}};
\node (B) at (Y.east) {tertiary amine};
\node[align=center] (T) at (B) {\begin{tikzpicture}
\node[align=center] (X) at (0,0) {R};
\node[align=center] (R1) at (X.north east) {R\textsuperscript{1}};
\end{tikzpicture}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 3.1}

\begin{itemize}
\item R = alkyl, aryl, heteroaryl; R\textsuperscript{1} = H, COOR, Alkyl;
\item X = O, NCOOR, NTS, NSO\textsubscript{2}Ph;
\item EWG = COR, CHO, CN, COOR, PO(OEt)\textsubscript{2}, SO\textsubscript{2}Ph, SO\textsubscript{3}Ph, SOPh.
\end{itemize}

In the first step, the Michael-type nucleophilic addition of the tertiary amine to the activated alkene (acrylate ester) occurs to produce a zwitter ionic enolate A. This zwitter ionic enolate A generates zwitter ion B by nucleophilic attack onto the aldehyde in an aldol fashion (Scheme 3.2).
Subsequent proton migration and catalyst release provide the desired multifunctional molecules which are commonly known as Baylis-Hillman adducts.

### 3.1.3. Components of Baylis-Hillman Reaction

The Baylis-Hillman reaction requires three essential components, i) activated alkene, ii) electrophile and iii) catalyst.

#### 3.1.3.1. Activated Alkenes

The most commonly used activated alkenes in Baylis-Hillman reaction are alkyl vinyl ketones, alkyl (aryl) acrylates, acrylonitrile, acrylamides, vinyl sulfonates and vinyl phosphonates (Scheme 3.3).

#### 3.1.3.2. Electrophiles

Various aliphatic, aromatic and hetero-aromatic aldehydes have been used as a primary source of electrophiles (Scheme 3.4) along with \(\alpha\)-keto esters, non enolizable 1,2-diketones, aldimine derivatives and activated alkenes.
3.1.4. Catalysts

The most commonly used catalyst is DABCO (1). The other tertiary amine catalysts such as quinuclidine (2), 3-HQD (3), 3-quinuclidone (4) and indolizine (5) were also used to perform the Baylis-Hillman reaction.\textsuperscript{18}
3.1.5. Parameters: Solvents and Temperature

Usually, the Baylis-Hillman reaction is a slow reaction requiring a few days to a few weeks. In order to improve both reaction rate and yield, various conditions were employed depending upon the reactivities of both the activated alkene and electrophile.

Although, the dilution slowed down the Baylis-Hillman reaction, numerous solvents were used for this reaction. The solvents are mainly used to solubilize non-homogeneous reaction mixtures and to promote the zwitterionic species. For this reason, polar and/or protic solvents are the most appropriate ones (acetonitrile, DMSO, DMF and water).\textsuperscript{32}

Most of the reactions were carried out at room temperature. Sometimes, heating allows the acceleration of the reaction but can promote side reactions like polymerization of olefin. Thus, application of reactive activated alkenes and electrophiles,\textsuperscript{16,18,33,34} microwave irradiation,\textsuperscript{22} use of excess catalyst,\textsuperscript{16,18,33,34} the concept of hydrogen bonding (having a hydroxyl group either in the catalyst or in the substrate),\textsuperscript{35} aqueous medium\textsuperscript{36} and high pressure\textsuperscript{37,38} have been examined and considerable success has been achieved.
3.2. PRESENT WORK

A Simple and Efficient Protocol for Chlorination of Baylis–Hillman Adducts Using PPh₃/CCl₄

During the work carried out in our laboratory on the Baylis–Hillman adducts¹⁵,¹⁸ 17 (3-hydroxy-2-methylene alkanoates) and 18 (3-hydroxy-2-methylene alkanenitriles), we employed PPh₃/CCl₄ reagent for chlorination of these adducts. The combination of 17 or 18 and PPh₃/CCl₄ was refluxed for 2–3 h to produce the corresponding allyl chloride 19 or 20 in stereoselective manner (Scheme 3.5).

Scheme 3.5

The allyl halides prepared from Baylis–Hillman adducts are utilized for the preparation of various natural bioactive molecules and their analogues such as α-methylene-γ-butyrolactone 21 and flavonoids 22 etc.⁴³-⁴⁵ Generally, a metal halide or a strong acid was used for the conversion of a Baylis–Hillman adduct into the corresponding allyl halide.²²,⁴³,⁴⁶-⁴⁹ However, we conveniently utilized PPh₃/CCl₄ system for the preparation of allyl chlorides 19 and 20 from the adducts 17 and 18 respectively in high yields (83–98 %).
As the reaction is a nucleophilic substitution associated with allylic rearrangement, the solvent plays a key role. Usually a solvent which doesn’t trap the nucleophile (Cl⁻ ion) is preferred. The solvent used in the present reaction not only satisfies the preference but also acts as a nucleophilic source (Cl⁻ ion) which makes the reaction more facile.

A series of compounds have been prepared from different Baylis–Hillman adducts having both ester and nitrile moieties (Table 3.1). Several functionalities such as halogen, nitro, ether, and ester remained unchanged. The adducts with electron-donating as well as electron-withdrawing groups underwent the conversion smoothly. CCl₄ served both as a reagent and as solvent. When the reaction was carried out at room temperature, the products were formed in poor yields even after 24 h.

Table 3.1. Synthesis of (Z)- and (E)-allyl chlorides using PPh₃/CCl₄

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product (19 or 20)</th>
<th>Time/h</th>
<th>Yieldb/%</th>
<th>Z:E</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td></td>
<td>2</td>
<td>98</td>
<td>100:0</td>
</tr>
<tr>
<td>b</td>
<td></td>
<td>2</td>
<td>98</td>
<td>100:0</td>
</tr>
</tbody>
</table>

Table 3.1. Synthesis of (Z)- and (E)-allyl chlorides using PPh₃/CCl₄
The structures of the products were settled from their spectral (IR, $^1$H NMR, and MS) data.

The total yields of the products ($Z + E$ isomers) after purification.

The present conversion underwent with high stereoselectivity where the allyl chlorides with ($Z$)- stereochemistry (19) were formed as the sole products when an ester group was present in the adducts
(17). However, if –CN group was present in the adducts (18) the allyl chlorides with (E)- stereochemistry (20) were formed as the major products. The structures and stereochemistries of 19 and 20 were settled from their spectral (1H NMR and MS) data. In the 1H NMR spectrum the β-vinyllic proton cis and trans to the ester group is known to resonate at ca. δ 7.5 and 6.5 respectively while the same proton cis and trans to the nitrile group resonates at ca. δ 7.5 and 7.0 respectively.49-53

In the 1H NMR spectrum (Fig. 3.1) of 19h (4-ClC₆H₄), the down field chemical shift value at δ 7.78 with sharp singlet for single proton indicated the presence of olefinic proton and the sharp singlet at δ 4.36 for two protons indicated the presence of –CH₂Cl, which in turn confirmed the formation of allyl chloride. Further, the structure of the compound 19h was confirmed by molecular ion peak at m/z 244 in its EIMS (Fig. 3.2).

We then considered adducts having nitrile moiety. For example, in the 1H NMR spectrum (Fig. 3.3) of 20k (4-ClC₆H₄), the down field chemical shift value at δ 7.18 with sharp singlet for single proton indicated the presence of olefinic proton and the sharp singlet at δ 4.28 for two protons indicated the presence of –CH₂Cl, which in turn confirmed the formation of allyl chloride. Further, the structure of the compound 20k was confirmed by molecular ion peak at m/z 211 in its EIMS (Fig. 3.4).

In the present conversion, PPh₃ reacts with CCl₄ to form the intermediate A which then reacts with an adduct to produce the
alkylyphosphonium salt B. The subsequent attack of chloride ion to this salt furnishes the allyl chloride and \( \text{Ph}_3\text{PO} \) (Scheme 3.6).

![Scheme 3.6]

The stereochemistry of the present conversion is explained by considering the transition state models I, II, and III (Fig. 3.5) where Model I is more favored than II when EWG is an ester and (Z)-products are predominantly formed. However, model III is more favored than I when EWG is –CN which is attributed to its linear alignment.

![Fig. 3.5]

Fig. 3.5 Conformational transition-state analysis for the rationalization of the observed stereoselectivity.

The steric effect in III due to the proximity of Ar and –CN is less when compared to that in I resulting from the proximity of Ar and –CH\(_2\)Cl groups thus providing (E)- compounds as the major products.
Thus, we have successfully employed PPh$_3$/CCl$_4$ as a simple and inexpensive reagent system, for stereoselective synthesis of (Z)- and (E)-allyl chlorides from the Baylis–Hillman adducts under metal and acid-free conditions. The method is highly stereoselective and the reaction conditions are compatible with several functional groups. The operational simplicity, requirement of no additional catalyst and excellent yields are the advantages of the present protocol.

“*A method gains importance when it finds synthetic applications.*”

Augmenting this sentence, we successfully extended the present method for the preparation of allyl chlorides from Baylis–Hillman adducts and synthesized semiplenamide C and semiplenamide E thereafter which will be discussed in chapter IV.
3.3. EXPERIMENTAL

3.3.1. Preparation of Baylis-Hillman adducts:

*General Procedure:* The adducts were prepared normally following the reported procedure in the literature.\(^\text{32}\)

A solution of aldehyde (30 mM) and methyl acrylate (8.04 mL, 90 mM) in 75 ml of 1:1 dioxane-water (v/v) was stirred at room temperature in the presence of 100 mol% DABCO (3.36 g, 30 mM). Upon completion (as monitored from TLC), the reaction mixture was partitioned between tert-butylmethyl ether (750 mL) and water (200 mL). The organic phase was washed with brine (2 x 120 mL), dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexane-ethyl acetate, 4:1 to 1:1) to give adduct as colorless oil.

3.3.2. Synthesis of \([2Z]-2-(\text{chloromethyl})\) alk-2-enoates and \([2E]-2-(\text{chloromethyl})\) alk-2-enenitriles:

*General Procedure for the preparation of allyl chlorides:*

To a solution of Baylis–Hillman adduct (2 mmol) in CCl\(_4\) (10 mL) PPh\(_3\) (3 mmol) was added. The mixture was stirred under reflux conditions and the progress of the reaction was monitored by TLC. After completion the solvent was concentrated under reduced pressure. The product was extracted with EtOAc (2 x 10 mL), washed with water (2 x 10 mL) and brine (1 x 10 mL), dried over anhydrous
Na$_2$SO$_4$, concentrated and chromatographed over silica gel to obtain the corresponding allyl chloride.

**(Z)-ethyl 2-(chloromethyl)-3-(4-chlorophenyl)acrylate 19c:**

![Structure of 19c](image)

$^1$H NMR (200 MHz, CDCl$_3$) (Fig. 3.6): $\delta$ 8.32 (2H, d, $J=8.0$ Hz), 7.89 (1H, s), 7.70 (2H, d, $J=8.0$ Hz), 4.35 (2H, s), 4.32 (2H, q, $J=7.0$ Hz), 1.37 (3H, t, $J=8.0$ Hz); FABMS (Fig. 3.7): $m/z$ 281, 283, 285 [M + Na]$^+$; Anal. Calcd. for C$_{12}$H$_{12}$Cl$_2$O$_2$: C, 55.81; H, 4.65%. Found: C, 55.76; H, 4.61%.

**(Z)-methyl 2-(chloromethyl)-3-(4-methoxyphenyl)acrylate 19g:**

![Structure of 19g](image)

$^1$H NMR (200 MHz, CDCl$_3$) (Fig. 3.8): $\delta$ 7.82 (1H, s), 7.55 (2H, d, $J=8.0$ Hz), 6.98 (2H, d, $J=8.0$ Hz), 4.51 (2H, s), 3.86 (6H, s); FABMS (Fig. 3.9): $m/z$ 263, 265 [M + Na]$^+$; Anal. Calcd. for C$_{12}$H$_{13}$ClO$_3$: C, 59.98; H, 5.41%. Found: C, 59.94; H, 5.38%.

**(Z)-methyl 2-(chloromethyl)-3-(4-chlorophenyl)acrylate 19h:**

![Structure of 19h](image)

$^1$H NMR (CDCl$_3$, 200 MHz) (Fig. 3.2): $\delta$ 7.78 (1H, s), 7.48 (2H, d, $J=8.0$ Hz), 7.35 (2H, d, $J=8.0$ Hz), 4.36 (2H, s), 3.84 (3H, s); FABMS (Fig. 3.3): $m/z$ 245, 247, 249 [M$^+$+H]; Anal. Calcd. for C$_{11}$H$_{10}$Cl$_2$O$_2$: C, 54.10; H, 4.10%. Found: C, 54.03; H, 4.07%.
(E)-2-(chloromethyl)-3-(4-chlorophenyl)acrylonitrile 20k:

\[
\text{Cl} \quad \text{C} \quad \text{CN} \quad \text{Cl}
\]

\(^1\)H NMR (200 MHz, CDCl\(_3\)) (Fig. 3.4): \(\delta\) 7.79 (2H, d, \(J = 8.0\) Hz), 7.44 (2H, d, \(J = 8.0\) Hz), 7.28 (1H, s), 4.28 (2H, s); FABMS (Fig. 3.5): \(m/z\) 234, 236, 238 [M + Na]\(^+\); Anal. Calcd. for C\(_{10}\)H\(_7\)Cl\(_2\)N: C, 56.87; H, 3.32; N, 6.63%. Found: C, 56.92; H, 3.29; N, 6.59%.
3.4. REFERENCES


Selected $^1$H NMR, and Mass Spectra of Compounds Pertaining to Chapter-III
Fig. 3.2: $^1$H NMR spectrum of compound 19h

Fig. 3.3: Mass spectrum of compound 19h
Fig. 3.4: $^1$H NMR spectrum of compound 20k

Fig. 3.5: Mass spectrum of compound 20k
Fig. 3.6: $^1$H NMR spectrum of compound 19c

Fig. 3.7: Mass spectrum of compound 19c
Fig. 3.8: $^1$H NMR spectrum of compound 19g

Fig. 3.9: Mass spectrum of compound 19g