ABSTRACT

The Baylis-Hillman reaction which originated from a patent has now become one of the most popular C-C bond forming reaction as evidenced by large number of publications and several major and minor reviews. Baylis-Hillman reaction is an atom economy reaction which involves three components \textit{i.e.} activated alkenes, electrophiles and catalyst or catalyst system and provides diverse classes of multifunctional molecules. These multifunctional molecules have been used for various organic transformations and also for synthesis of several hetero & carbocyclic frameworks including natural products as well as biologically active compounds. Our research group is working on this fascinating reaction from last 29 years and contributed significantly for the development of this reaction.

This thesis deals with the applications of the Baylis-Hillman adducts in synthesis of spiro-oxindole frameworks and densely functionalized epoxides and is divided into three chapters 1) Introduction 2) Objectives, Results \& Discussion and 3) Experimental. The first chapter, \textit{i.e.} Introduction describes a brief account of literature on the development of the reaction and also presents a briefly on the applications of the Baylis-Hillman adducts in various aspects of organic synthesis. The second chapter describes the objectives, work plan and discussion of the experimental results. The thesis has the following objectives.

1) To utilize the Baylis-Hillman bromides as a source of 1,3-dipoles with a view to understand the reactivity profile of three sterically different allyl bromides (46-48) [derived from i) Baylis-Hillman alcohol, obtained from HCHO and methyl
acrylate ii) Baylis-Hillman alcohols, obtained from aryl aldehydes and methyl acrylate iii) Baylis-Hillman alcohols, obtained from aromatic aldehydes and acrylonitrile] in dipolar addition reactions with isatin derivatives 59.

2) To utilize the dipoles generated from Baylis-Hillman bromides 47, 48 for cycloaddition reactions with ethyl glyoxalate and diethyl ketomalonate with a view to understand their reactivity profiles.

3) To utilize carbonates of Baylis-Hillman alcohols (derived from cyclohexenones and isatin derivatives) for synthesis of nitrone-spirooxindole-frameworks 79 in one pot operation.

The Baylis-Hillman Bromides as a Source of 1,3-Dipoles : Steric Factors Directed Synthesis of Oxindole Fused Spiro Oxirane and Dihydrofuran Frameworks

Spiro-oxindole moiety is one of the important structural frameworks frequently found in many natural products. Therefore development of simple synthetic strategies for obtaining spiro-oxindole derivatives has been and continues to be an attractive area in synthetic and medicinal chemistry.

It has been well documented in the literature that Baylis Hillman adducts (or their derivatives) containing ester group (prepared from alkyl acrylates) and nitrile group (prepared from acrylonitrile) showed remarkable opposite stereochemical directions in various chemical transformations. These stereochemical reversals have been mostly attributed to the steric differences between nitrile (smaller group) and ester functionality (larger group). To the best of our knowledge, there is no systematic study
in understanding the stereochemical directions in cycloaddition reactions of the Baylis-Hillman adducts (or their derivatives) containing ester group and nitrile group. Therefore, it occurred to us that the dipoles generated from Baylis-Hillman bromides containing ester and nitrile groups, should in principle show different reactivities in cycloaddition reactions with isatin derivatives. We have selected three sterically different Baylis-Hillman bromides 46-48 and various isatin derivatives (59) as reaction partners for our study.

In this direction we have carried out the cyclo-addition reaction of these sterically different allyl bromides 46-48 with isatin derivatives under the influence of Me2S in the presence of Cs2CO3 in DMF at 15-20 °C for 8 hr. It was interesting to note that the allyl bromide 46 on cycloaddition with isatin derivatives 59 provided five membered spiro-dihydrofuran-oxindole derivatives 61a-g (Table 2), whereas the allyl bromide 47 provided three member spiro-epoxyoxindoles (63a-j & 64a-j) as a separable mixture of diasteromers (Table 7). The allyl bromide 48 on cycloaddition reaction with isatin derivatives 59 under same conditions provided spiro-dihydrofuran-oxindole derivatives (67a-f) in diastereomerically pure form (Eq. 21, Table 10).

From these studies it is quite clear that steric factors direct cyclo-addition reactions between the dipoles generated from Baylis-Hillman bromides 46-48 and isatins 59 as dipolarophiles, thus providing an interesting methodologies for synthesis of spiro-epoxy-oxindoles (63 & 64) and spiro-dihydrofuran-oxindoles (61 & 67).
The Baylis-Hillman Bromides: Synthesis of Densely Functionalized Epoxides via Cyclo-addition strategy

After successfully examining the steric influences in cyclo-addition reactions of the isatin derivatives with three sterically different Baylis-Hillman bromides (46-48) we undertook to investigate cycloaddition reaction of allyl bromides (47 & 48) with reactive carbonyl compounds *i.e.* ethyl glyoxalate and diethyl ketomalonate with a view to understand the reactivity profile of these allyl bromides in these reactions.

In this direction we have employed the allyl bromide 47 for cycloaddition reaction with ethyl glyoxalate or diethyl ketomalonate under the influence of Me$_2$S/K$_2$CO$_3$ in CH$_3$CN/H$_2$O solvent system. In these reactions three membered ring *i.e.* densely functionalized epoxide derivatives 70a-f were obtained (Eq. 23, Table 14). Similarly cycloaddition reactions using the allyl bromide 48 with ethyl glyoxalate or diethyl ketomalonate also resulted in the formation of three member ring *i.e.* epoxide derivatives 71a-g (Eq. 24, Table 17). In these reactions we did not notice the formation of any dihydrofuran derivatives.

Facile One-pot Synthesis of Nitrone-spiro-oxindoles Frameworks using Carbonates of Baylis-Hillman alcohols

In recent years there has been increasing interest in understanding the free radical mediated oxidative damage to cells because it is considered to be one of the major factors responsible for many diseases such as neuro-degeneration, stroke, cancers *etc.* After the initial studies on the applications of PBN (α-phenyl-tert-butyl-nitro) and its derivatives for trapping free radical in chemical systems, research work from various
leading laboratories has been directed toward examining the utility of nitrones as spin
traps in biological systems and many significant results were achieved in this
direction. In fact the present day synthetic and medicinal chemistry demand the
design, synthesis of appropriate nitrone framework for addressing the problems of
oxidative damage to tissues.

As mentioned above, spirooxindole skeleton is another unique structural framework
that is present in several natural products and biologically active molecules. It
occurred to us that molecules containing both nitrone skeleton and spirooxindole
structural unit might show interesting biological activities.

Accordingly we have developed a facile protocol for synthesis of nitrone-spiro-
oxindoles frameworks (79) via the alkylation of nitromethane with the carbonates (77)
of Baylis-Hillman alcohol (76) followed by reductive cyclization with Fe/HCl in EtOH
according to the Scheme 63 (Table 22).

The third chapter provides detailed experimental procedures, physical constants like
melting point, IR, $^1$H & $^{13}$C NMR, HRMS spectral data.