ABSTRACT

Construction of carbon-carbon bond is one of the most fundamental reactions in organic chemistry and hence the development of new methodologies and strategies for formation of carbon-carbon bonds has been and continues to be one of the most challenging and fascinating endeavors in organic chemistry. Recent developments in organic chemistry demand the concepts of atom economy, selectivity and generation of chemospecific functional groups, for developing any efficient synthetic reaction, particularly C-C bond forming reaction. The Baylis-Hillman carbon-carbon bond forming reaction is one such reaction, well equipped with the concepts of atom economy and generation of densely functionalized molecules. The Baylis-Hillman reaction is basically a three-component reaction involving an activated alkene, an electrophile and a catalyst (usually a tertiary amine) leading to the coupling of α-position of activated alkene with an electrophile providing an interesting class of highly, synthetically useful multifunctional molecules.

This thesis deals with the studies in the applications of Baylis–Hillman chemistry and consists of three chapters, that is, 1. Introduction 2. Objectives, Results & Discussion and 3. Experimental. The first chapter, that is, Introduction presents a brief literature
survey on recent developments in the Baylis–Hillman reaction and applications of the Baylis–Hillman adducts in the organic synthesis.

The second chapter deals with the objectives, results and discussion. With a view to study the applications of Baylis-Hillman chemistry in organic synthesis, we have undertaken a research program with the following objectives.

1). To employ alkyl 2-(bromomethyl)prop-2-enoates, derived from Baylis-Hillman adducts, as valuable electrophiles in the Baylis-Hillman coupling reaction with various activated alkenes with a view to develop a one-pot convenient methodology for synthesis of 2,4-functionalized 1,4-pentadienes.

2). To employ the Baylis-Hillman adducts as valuable substrates for tandem construction of C-O and C-C bonds involving Prins type and Friedel-Crafts type reactions with an aim of developing one-pot facile methodology for synthesis of 2-benzoxepine derivatives.

3). To develop highly diastereoselective methodology for transformation of alkyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates, obtained from the Baylis-Hillman adducts, derived from chiral acrylates and aldehydes into propargylic and phenolic ethers of Baylis-Hillman adducts.
4). To describe the first organobase mediated Cannizzaro reaction of reactive aldehydes.

**Applications of alkyl 2-(bromomethyl)prop-2-enoates as valuable electrophiles in the Baylis-Hillman reaction: a one-pot facile synthesis of 2,4-functionalized 1,4-pentadienes**

We have successfully employed alkyl 2-(bromomethyl)prop-2-enoates (101a-c) as useful electrophiles for Baylis-Hillman coupling with various activated alkenes such as acyclic & cyclic enones, acrylonitrile and alkyl acrylates, in the presence of tertiary amines such as DABCO (or DBU), thus leading to the development of a one-pot convenient methodology for synthesis of 2,4-functionalized 1,4-pentadienes (102-114) in 77-85% isolated yields (eqs 22-28 and Table 1).

**Tandem construction of C-O and C-C bonds: a one-pot facile transformation of the Baylis-Hillman adducts into 2-benzoxepine derivatives**

2-Benzoxepine moiety is an important structural unit present in many natural products and biologically important molecules which are found to be antiinflammatory, spasmylytic, analgesic, antipyretic, neuroleptic, antinaphylactic, hypotensive, antiulcer agents and are also found useful for treatment of depression and schizophrenia. Hence, development of simple and convenient methodologies for the synthesis of 2-
benzoxepine derivatives represents an attractive and interesting area of research in synthetic organic chemistry and medicinal chemistry. We have successfully developed one-pot facile methodology for synthesis of 2-benzoxepine derivatives (133a-e, 134a,b) via the tandem construction of C-O and C-C bonds involving the Prins type and Friedel-Crafts type reactions of Baylis-Hillman adducts (131a-e, 132a,b) (derived form various aromatic aldehydes and alkyl acrylates) with HCHO in the presence of conc. H$_2$SO$_4$ in 44-61% isolated yields (eqs 30, 32 & Table 2). We have also successfully transformed the rearranged alcohol (135a) into the desired 2-benzoxepine derivative (133a) in 59% isolated yield (eq 34).

Chiral auxiliary mediated diastereoselective synthesis of propargylic and phenol ethers of Baylis-Hillman adducts from the alkyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates

With a view to examine the chiral auxiliary mediated diastereoselective $S_N2'$ addition of oxygen nucleophiles on to the allyl bromides derived from Baylis-Hillman adducts, which in turn would be obtained from chiral acrylates (14 & 18) and aldehydes, we have selected two auxiliaries (-)-menthol (151) and (1S,2R,4R)-1-(diisopropyl-aminosulfonyl)methyl-7,7-dimethylbicyclo(2.2.1)heptan-2-ol (162). We have prepared representative allyl bromides (154a,b, 155 & 169-174) according to the Schemes 76 & 82. Then we have examined nucleophilic (SN2') addition of propargyl alcohol and
phenol on to the bromides (154a,b 155) in the presence of triethylamine at room temperature, which provided the required (−)-menthyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates (156a,b 157) and (−)-menthyl 3-aryl-2-methylene-3-phenoxypropanoates (158a,b 159) in 4-23% and 26-35% diastereoselectivities respectively (Schemes 77-80 and Table 5). Similar SN2’ addition of propargyl alcohol and phenol on to the allyl bromides (169-174) provided the desired (1'S,2'R,4'R)-1’-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates (175-180) and (1'S,2'R,4'R)-1’-(diisopropylaminosulfonyl)methyl-7',7'-dimethylbicyclo(2.2.1)hept-2'-yl 3-aryl-2-methylene-3-phenoxypropanoates (181-186) in 51-88% and 54-82% diastereoselectivities respectively (Scheme 83, eqs 38,40,41 and Tables 7 and 9).

**First example of organo base induced Cannizzaro reaction**

During our attempts to perform the Baylis-Hillman reaction between phenyl vinyl sulfoxide (188) and pyridine-4-carboxaldehyde (130j) under the influence of TMG (1,1,3,3-tetramethylguanidine) (187) in aqueous/dioxane medium, we have observed that there was no Baylis-Hillman reaction and in fact, we have isolated 4-pyridinemethanol (189) as a major product, which was produced due to the Cannizzaro reaction (Scheme 86). We have confirmed this TMG-induced Cannizzaro reaction by treating pyridine-4-carboxaldehyde (130j) with TMG in H2O, which provided 4-
pyridinemethanol in 42% isolated yield (eq 44). However, our attempts to isolate pyridine-4-carboxylic acid in pure form were not successful. We have then successfully employed TMG for promoting Cannizzaro reaction of reactive aromatic aldehydes (130k-n) (eq 45-47 and Table 10) (however, our attempts to isolate corresponding acids in case of pyridine-3-carboxaldehyde (130k) and pyridine-2-carboxaldehyde (130l) met with failure). In case of 4-nitrobenzaldehyde (130m) and 3-nitrobenzaldehyde (130n), we have also successfully isolated acids (194 and 196) (oxidized product) respectively. We have also performed TMG-promoted cross-Cannizzaro reaction of these aldehydes (130j-n), with HCHO to provide the corresponding alcohols (189,191-193,195) in good yields (eq 48, Scheme 88 and Table 12). Thus we have for the first time described the TMG (organobase) mediated Cannizzaro reaction of reactive aromatic aldehydes.

The third chapter deals with the detailed experimental procedures, IR, $^1$H NMR, $^{13}$C NMR, mass spectral data, microanalyses, physical constants (bp, mp) and optical rotations.