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Digest paper

Importance of Baylis-Hillman adducts in modern drug discovery

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ABSTRACT

The Baylis-Hillman (BH) reaction plays a fascinating role in the field of synthetic and medicinal chemistry. BH adducts and their derivatives have been used as crucial synthons for the synthesis of various pharmaceutically useful natural products and compounds with carbocyclic or heterocyclic frameworks. This digest letter aims to discuss some key ideas for the synthesis of biologically active scaffolds using BH reaction and raise the awareness of this emerging research domain in modern drug discovery. In this review, we will present and discuss recent reports of various biologically active scaffolds derived from BH reaction, and their reported biological activities.

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Contents

Introduction

The construction of a carbon-carbon bond and the functional group interconversions are the most fundamental approaches to access diverse molecular frameworks [1]. In fact, the generation of carbon-carbon bond has become one of the most valuable and powerful tools in modern organic chemistry. Among the fascinating work in the field of carbon-carbon bond formation, Morita-Baylis-Hillman (MBH) or Baylis-Hillman (BH) reaction has become one of the most elegant and rapidly developing carbon-carbon bond forming reactions in the scientific community [2]. The BH reaction is a three-component reaction between the α-position of activated alkenes (such as ethyl or methyl acrylate, acrylonitrile and methyl vinyl ketone) and electrophilic sp^2 carbon (aldehyde or imines) in the presence of an appropriate catalyst, generally a tertiary amine or phosphine, leading to the formation of highly functionalized molecular frameworks in an atom-economical manner, which are generally referred as BH adducts (Scheme 1). Generally, in a chemical point of view, BH adducts possessing various reactive functionalities i.e. alkene, hydroxyl, and an electron withdrawing

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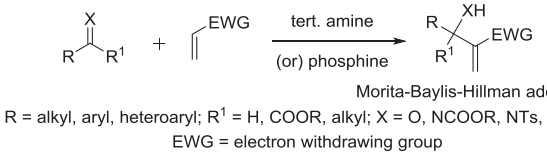


Scheme 1. The Morita-Baylis-Hillman reaction.

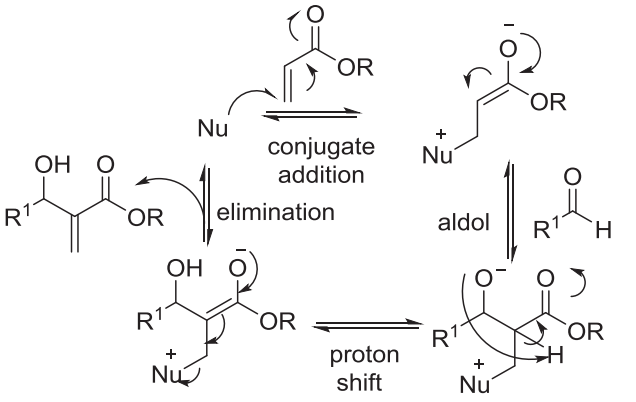
functional group in close proximity, which are crucial structural motifs for a diverse array of new organic reactions and chemical transformations [3].

The BH reaction plays a prominent role in synthetic and medicinal chemistry due to its inherent credentials, such as eco-friendly, high atom economy, solvent-free reaction conditions, organocatalysis, and wide functional group tolerance. Furthermore, BH adducts and their acetate, carbonate or bromide derivatives have also been used as crucial synthons and valuable precursors for the synthesis of useful natural products, unnatural products, compounds with carbocyclic or heterocyclic frameworks, and pharmaceutically relevant functional molecules in achiral and chiral fashion [4,5]. In this context, various promising scaffolds of BH reaction displayed prominent pharmacological activities [5].

The aim of this digest letter is to discuss some key ideas and diverse reactivities of BH reaction for the synthesis of biologically active scaffolds and raise the awareness of this emerging field in modern drug discovery. In this review, we present and discuss recent reports of various biologically active scaffolds derived from BH reaction and is outlined as follows: (i) Synthesis of biologically active molecular frameworks and (ii) Synthesis of biologically active molecular frameworks with their bio-evaluation. We understand that this report will trigger and promote further developments in this emerging research domain.

Mechanism, origin and growth aspects

The initial adequate mechanism for the BH reaction was investigated by Hoffmann and Rabe in 1983. Subsequently, Hill and Isaacs described mechanistic aspects based on kinetic studies. Later, extensive mechanistic studies of this versatile reaction are described by various research groups in the published reviews [4b,6]. Generally, mechanism of the BH reaction associated with three main successive steps through Michael type nucleophilic addition (between tertiary amine and acrylate), aldol approach (formation of carbon-carbon bond between aldehyde and acrylate), and subsequent elimination process (detachment of tertiary amine) in one-pot (Scheme 2).



Scheme 2. Mechanism of Baylis-Hillman reaction.

This fascinating reaction was first introduced by Morita [7] (tertiary phosphine-catalyzed) in 1968 and by Baylis and Hillman [8] (tertiary amine-catalyzed) in 1972, unfortunately, it was ignored for a long time by organic chemists. Later, Drewes, Perlmutter, Hoffmann, Basavaiah, and Kim started tremendous improvements on this elegant reaction. As of now, various research efforts have also been devoted to BH based chemistry. Over the past years, several groups have reviewed the scope and development of this BH reaction, and its applications have been well documented in reviews or books [3–6,9]. Recently, our group has also principally investigated the development of attractive methodologies based on the BH chemistry and its application towards the synthesis of new heterocyclic frameworks [10]. Our promising heterocyclic molecular constructs also displayed a plethora of biological activities.

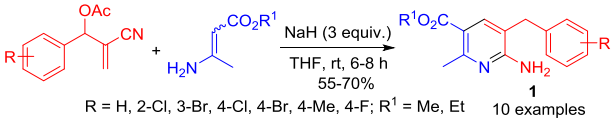
Synthesis of biologically active molecular frameworks using Baylis-Hillman reaction

From Baylis-Hillman acetates

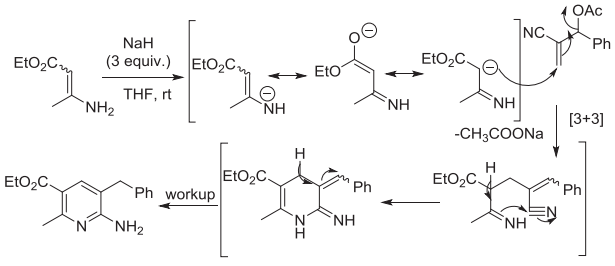
Jayathirtha Rao and co-workers [10a] developed base-mediated [3+3] annulation protocol for the synthesis of new aminonicotinates from BH acetates of acrylonitrile with enamines under metal-free conditions (Scheme 3a). This reaction provided a facile and highly efficient access to functionalized pyridine frameworks (**1**) in moderate to good yields, which are useful intermediates for further chemical manipulation. This fast reaction proceeds through three consecutive steps involving addition, cyclisation, and subsequent isomerization in one pot (Scheme 3b).

Recently, the electrophilic reactivity of BH acetates of electron deficient alkenes has been greatly investigated for the synthesis of various heterocycles and carbocycles. Namboothiri and co-workers [11] reported an efficient and regioselective one-pot method for the construction of biologically active imidazo[1,2-a] pyridine frameworks (**2**) via inter- and intramolecular double aza-Michael addition of BH acetates of nitroalkenes as 1,2-bielectrophiles with 2-aminopyridines as binucleophiles in MeOH at room temperature under metal-free conditions (Scheme 4). It could be noted that this elegant method could be successfully employed for the synthesis of anxiolytic drug Alpidem and hypnotic drug Zolpidem.

Furans are an important class of heterocycles, which are present in many natural products and biologically active scaffolds. In 2013,



Scheme 3a. Synthesis of aminonicotinates.



Scheme 3b. A plausible mechanism for aminonicotinate derivatives.

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