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Transition-Metal-Free Nucleophilic Allylic Substitutions of Morita-Baylis-Hillman Bromides with Aliphatic and Aromatic Amines

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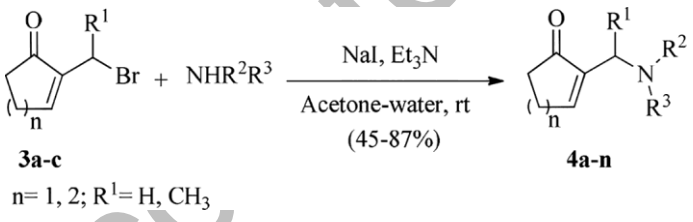
Abstract

Under mild, **transition-metal-free** conditions, a simple protocol for the preparation of functionalized allylic amines from the reaction of Morita-Baylis–Hillman (MBH) bromides with amines, is described herein. The treatment of the MBH bromides with various amines in the presence of NaI and Et_3N in aqueous acetone solution and at room temperature, affords the corresponding functionalized allyl amines in moderate to good yields (45-87%). The reaction is rapid and carried out at room temperature.

Graphical Abstract



KEYWORDS: Morita Baylis-Hillman Bromide; Allylic substitution; Allylic amines

INTRODUCTION

In recent years, nucleophilic substitution reactions of allyl compounds have been developed very well [1]. Among them, the allylic amination has attracted considerable

attention [1,2] as it provides an efficient synthetic approach for biologically active compounds with an allylamino moiety that represents an important structural motif frequently found in natural products, pharmaceuticals, as well as versatile building blocks for the synthesis of molecules of higher complexity [3]. These reports revealed that the direct nucleophilic displacements on allyl substrates could be performed under metal-free catalytic conditions as well as under catalytic conditions in order to expand the scope of the allylic substitutions.

The literature reported a large number of synthetic methods, allowing access to allyl amines. Over the last decades, their preparation using the MBH adducts through nucleophilic substitution reactions, has become a method of choice, generally simple and efficient [4]. In 2002, Rajesh and co-workers [5] reported a palladium-catalyzed allylic amination of the MBH acetates, with moderate regioselectivity. Moreover, in 2007, Nemeto and co-workers [6] studied the asymmetric allylic amination reactions of the MBH adducts, in which they described a highly enantioselective allylic amination of MBH carbonates using Pd catalyst systems. Recently, Wang and co-workers [7] reported a palladium-catalyzed α-regioselective allylic amination of MBH acetates with aromatic amines.

The α-(*N*,*N*-dialkylaminomethyl)cyclic enones are of great interest in organic synthesis [8]. Tamura and co-workers have reported a successful method for their preparation by denitro-amination and desulfonyl-amination of the corresponding allylic derivatives [9]. Moreover, Liu and co-workers [10] have described a highly α-regioselective $In(OTf)_3$-

catalyzed *N*-nucleophilic substitution of cyclic MBH adducts with aromatic amines, providing an efficient route to aromatic allylic amines bearing cyclic unsaturated ketone unit.

The syntheses of allyl amines, under mild conditions, still an important industrial and synthetic goal. The development of efficient and highly selective methods for their preparation merits a thorough investigation [11]. To the best of our knowledge, the *N*-allylation of amines with cyclic MBH bromides **3a-c** has not been extensively studied under Pd-free conditions. Hence, we wish to report in this paper an efficient method for the synthesis of various functionalized allyl amines, in aqueous acetone and at room temperature, from the cyclic MBH bromides.

RESULTS AND DISCUSSION

Allylic alcohols **2a-c** were first prepared through the MBH reaction involving the cyclic enones **1a-b** [12,13,14], followed by their direct conversion into the corresponding allylic bromides **3a-c** using aqueous 48% hydrobromic acid (Scheme 1) [15].

It is noted that these allyl bromides **3a-c** are of limited stability, particularly when neat. Therefore, they were prepared from the MBH alcohols **2a-c** and then directly used without further purification.

With the desired allylic bromides **3a-c** in hand, our first challenge was the development of a general and efficient route for a range of allyl amines. In our preliminary attempts,

the reaction of morpholine and the MBH bromide **3a** in THF was carried out for 1 hour, at room temperature, without any additive. In this case, we have observed that the allyl amine **4a** was obtained but with a low 30% yield. Therefore, we thought that a more efficient route would work in a homogeneous and basic medium, so we investigated the behavior of the allyl bromide **3a** with morpholine in the presence of Et_3N in THF as solvent. Under these conditions, we have actually noticed an increase in the yield of the reaction from 30 % to 50 %. In order to more improve this modest yield, morpholine was reacted, this time, with the allylic bromide **3a**, but in the presence of sodium iodide and Et_3N as additives in an acetone-water (1:1 v/v) mixture, as solvents mixture. The allyl amine **4a** was selectively obtained and the yield was significantly improved from 50 to 80 % (Entry 1, Table 1). Encouraged by these results, we attempted to extend this simple synthetic methodology to a series of amines (Scheme 2).

Under the above optimized reaction conditions, we have observed that the six-membered allylic bromide **3a** rapidly reacted with relatively hard secondary amines (Entries 1-4, Table 1) as well as the relatively soft aniline derivatives (Entries 5-8, Table 1), affording, within 5 min, in 60-87% yields, the allyl amines **4a-d** and **4e-h**, respectively. This allylation reaction of amines also worked with the six-membered bromide **2b** but the latter is less reactive than its homologous compound **2a**, presumably as it is slightly hindered at the □-allyl bromide carbon atom bearing a methyl group. The corresponding amines **4i-k** were obtained within 60 min and in 45-55% moderate yields (Entries 9-11, Table 1).

Next, we have explored the effect of the substrate ring size **3** on the steric course of the amination reaction. For this purpose, we have selected the five-membered allylic bromide **3c**. Successfully, the corresponding allyl amines **4l-n** were obtained within 5 min and in 70-85% high yields (Entries 12-14, Table 1).

We note that the spectroscopic data of allyl amines **4a-n** are in agreement with those of literature [4,9].

Furthermore, the acceleration of the amination reaction can be explained by the *in situ* formation of the iodinated intermediate **I** that subsequently undergoes a relatively rapid S_N2-type reaction in the presence of amines, affording the allyl amines **4a-n** (Scheme 3). Indeed, the iodine is more polarizable than bromine and the iodide ion is a better leaving group than the bromide ion in a S_N2-type reaction. We note that the role of triethylamine in this reaction is to trap the hydrogen bromide formed in the reaction medium.

We believe that, in the present study, the various amines, first react in a 1,4-addition-elimination of the iodide ion, to give the S_N2' intermediate **I2** (i and ii), which then undergo a second β'-1,4-addition-elimination of the amine, affording the S_N2' products **4** (Scheme 4).

EXPERIMENTAL SECTION

***Typical Procedure For The Preparation Of Allyl Bromides (*3a-C)**

An aqueous 48% hydrobromic acid (4 mL, 4 mmol) was added to the corresponding MBH alcohols **2a-c** (4 mmol) and the reaction mixture was stirred at room temperature until TLC indicated complete consumption of the starting material. It is noted that the reaction was carried out for 1 hour in the case of the MBH alcohols **2a** and **2c** and it took 3h in the case of the alcohol **2b**. Then the reaction was quenched with water (4 mL) and the aqueous phase was extracted with methylene chloride (3×10 mL). The organic phase was washed with a saturateted solution of $NaHCO_3$, with brine, dried over $MgSO_4$ and concentrated *in vacuo.* The resulting residue was then used without further purification.

Typical Procedure For The Preparation Of Allyl Amine (4a)

To a solution of the allyl bromides **3a** (4 mmol) in 5 mL of acetone-water (1:1 v/v) mixture, was added Et_3N (6 mmol) and NaI (6 mmol). The reaction mixture was stirred for 10 min then the hard-soft amine was added (6 mmol).

The mixture was stirred at room temperature until TLC indicated complete consumption of the starting material. The reaction was then quenched with water and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in *vacuo*. The resulting residue was purified by a column chromatography on silica gel (ether/petroleum ether).

CONCLUSION

In summary, a concise and practical approach for the synthesis of a series of functionalized allyl amines **4a-n** has been disclosed using the allyl bromides **3a-c**,

directly obtained from the corresponding MBH alcohols **2a-c**. This strategy is considered attractive as it involves commonly available inexpensive reagents and does not require any elaborate reaction conditions.

SUPPORTING INFORMATION

Supporting Information: Full experimental detail, IR,^{1}H and ^{13}C NMR spectra and GC-MS /HRMS. This material can be found via the "Supplementary Content" section of this article's webpage.

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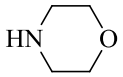
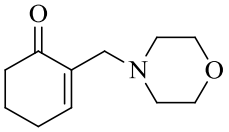
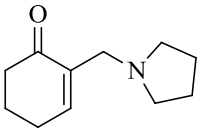
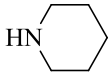
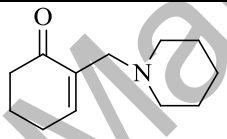
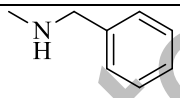
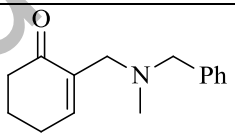
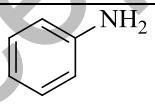
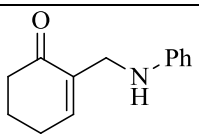
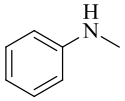
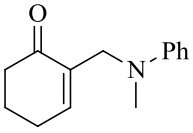
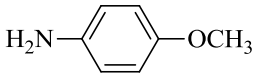
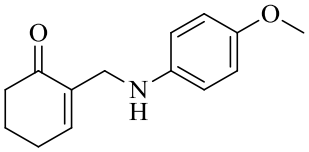
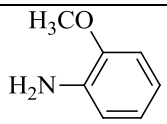
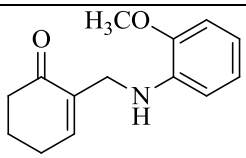
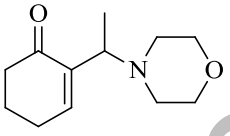
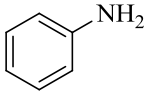
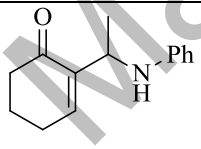
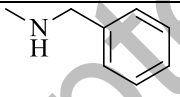
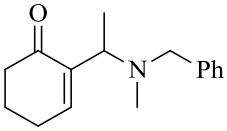
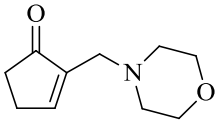
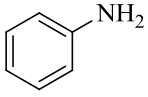
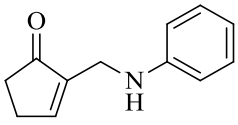
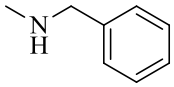
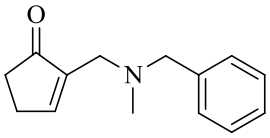
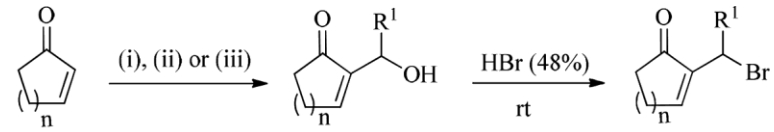
Table 1. Synthesis of allyl amines **4a-n** from the MBH bromides **3a-c**

Entry	R	Hard-soft amine	Allyl amine **4**	Reaction time/min	Yield **4** (%)
1	H (**3a**)		 **4a**	5	80
2	H (**3a**)		 **4b**	5	60
3	H (**3a**)		 **4c**	5	85
4	H (**3a**)		 **4d**	5	75
5	H (**3a**)		 **4e**	5	87
6	H (**3a**)		 **4f**	5	70

7	H (**3a**)		 **4g**	5	75
8	H (**3a**)		 **4h**	5	65
9	CH_3 (**3b**)		 **4i**	60	45
10	CH_3 (**3b**)		 **4j**	60	55
11	CH_3 (**3b**)		 **4k**	60	45
12	H (**3c**)		 **4l**	5	70
13	H (**3c**)			5	85

			4m		
14	H (**3c**)		 **4n**	5	84

Scheme 1. Synthesis of the MBH bromides **3a-c**



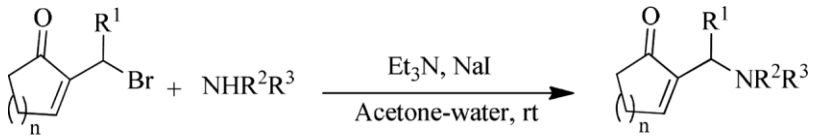
n = 2 **1a**
n = 1 **1b**

2a n = 2, R^1 = H
2b n = 2, R^1 = CH_3
2c n = 1, R^1 = H

3a n = 2, R^1 = H
3b n = 2, R^1 = CH_3
3c n = 1, R^1 = H

Reagents and conditions: (i) **2a** :HCHO, DMAP, THF-H_2O (60%)
(ii) **2b:** CH_3CHO, imidazole THF-H_2O (40%)
(iii)**2c:** HCHO, imidazole THF-H_2O (30 %)

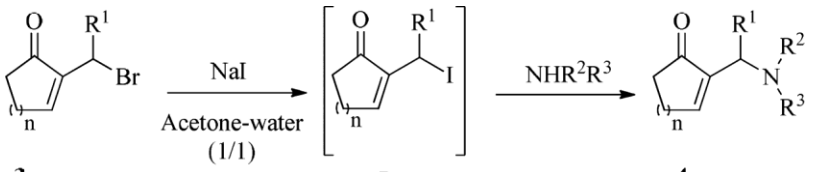
Scheme 2. Synthesis of allyl amines **4a-n** from the MBH bromides **3a-c**



3a-c **3a** : n = 2, R^1 = H
3b : n = 2, R^1 = CH_3
3c : n = 1, R^1 = H

4a-n

Scheme 3. Formation of allyl amines **4a-n** in a two-step sequence



3 a-c **I** **4a-n**

n = 1, 2 ; R^1= H, CH_3

Scheme 4. Proposed mechanism for the synthesis of allyl amines **4a-n** from the intermediate I