MgI_2 Etherate-Catalyzed Three-Component Allylation: A Facile and Efficient Synthesis of Homoallylic Amines

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Abstract: MgI_2 etherate-catalyzed three-component condensation of aldehydes, amines and allyltributylstannane under mild and neutral reaction conditions was developed and efficiently afforded the corresponding homoallylic amine derivatives in good to excellent yields.

Keywords: Aldehydes, allyltributylstannane, homoallylic amines, MgI_2 etherate.

INTRODUCTION

Lewis acid-catalyzed carbon-carbon bond forming reactions are of great importance in organic synthesis due to their high reactivity and selectivity under mild reaction conditions [1-3]. Among them, Lewis acid promoted nucleophilic addition of allylic organometallics to aldimines is one of the most important carbon-carbon bond forming reactions, which provides a useful method for the preparation of homoallylic amines [4]. Recently, a straightforward synthesis of homoallylic amines involves the nucleophilic addition of allyltin reagents to imines, which are generated *in situ* from aldehydes and amines in the presence of a Lewis acid catalyst such as $TiCl_4$, $BF_3{\bullet}OEt_2$, $PdCl_2(PPh_3)_2$, $PtCl_2(PPh_3)_2$, bis-π-allylpalladiumcomplex, lanthanide triflates, $SnCl_2$, $LiClO_4$ and montmorillonite KSF clay [5]. However, many of these methods have some drawbacks, which involve use of strong Lewis acids, expensive metal triflate or precious metal catalysts, prolonged reaction time, vigorous reaction conditions, and was difficult to handle especially on a large scale. Therefore, the development of a facile and efficient one-pot synthesis of homoallylic amines is an active ongoing research area and there is scope for further improvement towards milder reaction conditions. From the viewpoints above, the development of less expensive, environmentally benign, and easily handled promoters for one-pot operation of allylation to form homoallylic amines is still highly desirable.

In continuation of our interest on the catalytic applications of MgI_2 etherate for various organic transformations [6], we will wish to describe a simple and efficient protocol for one-pot synthesis of homoallylic amines catalyzed by MgI_2 etherate under mild and neutral reaction conditions (Scheme **1**).

RESULTS AND DISCUSSION

We initiated our studies by carrying out the allylation of an equimolar amount of benzaldehyde and aniline with allyltributylstannane using 20 mol % of freshly prepared MgI_2 etherate [7] in CH_2Cl_2 at room temperature. After stirring for 2.0 h, the desired homoallylic amine was afforded in 92% yield. Encouraged by this result, we investigated one-pot allylation of a variety of aldehydes, such as aromatic, heteroaromatic, aliphatic and α,β-unsaturated aldehydes, with aniline, *p*- methoxyaniline, *p*-toluidine, *p*-nitroaniline, *o*-aminophenol and benzylamine. The results were summarized in Table **1**. The good to excellent yields strongly suggest that $MgI_2{\bullet}(OEt_2)_n$ is an efficient Lewis acid catalyst for the three-component allylation of aldehydes, amines and allyltributylstannane. The reaction proved to be general and could be utilized into a wide range of aldehydes. Specifically, there is no need to exclude moisture and oxygen from the reaction system. Moreover, the aromatic aldehydes bearing electron-donating and electron-withdrawing groups in the aromatic ring were reacted smoothly to afford the desired homoallylic amines in good to excellent yields (Table **1**, entries 1-8). Vinyl aldehydes such as cinnamaldehyde reacted with *p*-methoxyaniline to afford the homoallylic amine derivatives in good yields under the present reaction conditions (Table **1**, entry 9). Heteroaromatic aldehydes such as furfuraldehyde and 2-thenaldehyde were good substrates as well (Table **1**, entries 10-12). 3-phenylpropanal also led to the product **1m** with good yield (Table **1**, entry 13). In general, both aromatic, heteroaromatic, aliphatic and α,β-unsaturated aldehydes underwent the conversion smoothly in a short period whereas ketones did not yield any product even prolonging the reaction time in the presence of MgI_2 etherate (Table **1**, entries 14-16). This is due to the lower reactivity of ketimines, compared to aldimines, towards allylstannanes [8]. Moreover, the aromatic amines bearing electron-donating and electron-withdrawing groups in the aromatic ring were carried out smoothly to afford the desired homoallylic amines in good to excellent yields. The use of *o*-aminophenol as the imine component was also examined and the allylation products **1f-1h** were obtained in good yields (Table **1**, entries 6-8). The use of aniline as the imine component gave the better results than the use of benzylamine (Table **1**, entries 11 and 12).

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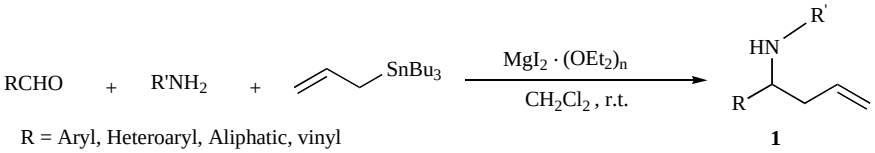
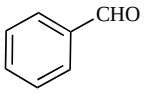
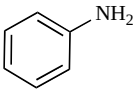
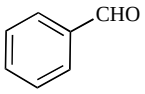
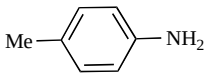
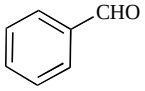
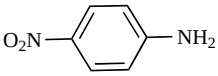
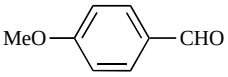
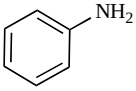
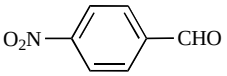
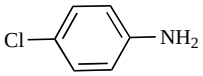
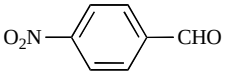
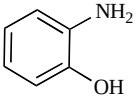
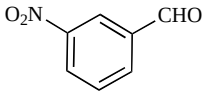
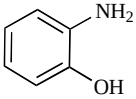
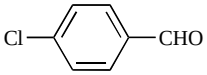
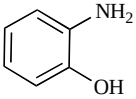
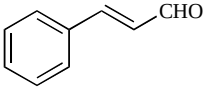
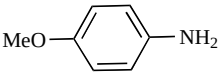
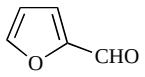
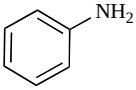
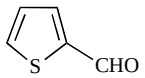
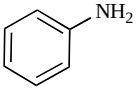
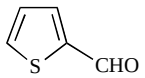
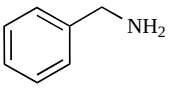
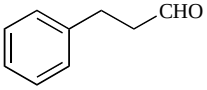
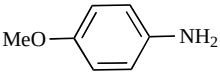
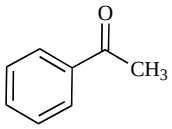
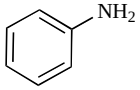
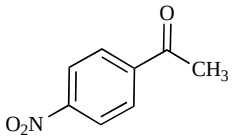
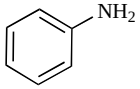
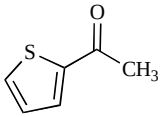
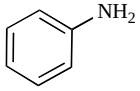


Scheme 1. MgI_2 etherate-catalyzed three-component allylation.

Table 1. Three-Component Synthesis of Homoallylic Amines Catalyzed by MgI_2•$(OEt_2)_n$[a]

Entry	Aldehyde/Ketone	Amine	Time (h)	Product [b]	Yield (%) [c]	Refs.
1			2	1a	92	[10]
2			1	1b	97	[10]
3			3	1c	88	[11]
4			1	1d	92	[12]
5			1	1e	93	[13]
6			1	1f	91	[14]
7			1	1g	92	[14]
8			1	1h	90	[14]
9			2	1i	95	[10]
10			1	1j	96	[15]
11			2	1k	95	[16]
12			2	1l	86	[17]
13			2	1m	84	[18]

(Table 1). Contd…..

Entry	Aldehyde/Ketone	Amine	Time (h)	Product [b]	Yield (%) [c]	Refs.
14			10	NA [d]	NR [e]	
15			10	NA	NR	
16			10	NA	NR	

[a]Reactions were run in a mixture of aldehyde (0.5 mmol), amine (0.5 mmol), allyltributylstannane (0.6 mmol) and 20 mol % of MgI_2 etherate in CH_2Cl_2 at room temperature.
[b]All products were identified by their ^1H NMR spectra.
[c]Yields of products isolated by column chromatography.
[d]NA = Not available.
[e]NR = No reaction.

To examine the halide anion effect, halogen analogs of MgI_2 etherate, $MgCl_2$ etherate, $MgBr_2$ etherate and $Mg(ClO_4)_2$ were compared under parallel reaction conditions (20 mol % of catalyst) in one-pot allylation reaction of benzaldehyde and aniline with allyltributylstannane. $MgCl_2$ etherate and $MgBr_2$ etherate are almost inactive. $Mg(ClO_4)_2$ is less effective in terms of substrate conversion and yield. Apparently, the unique reactivity of MgI_2 etherate is attributed to the dissociative character of iodide counterion and a more Lewis acidic cationic $[MgI]^+$ species as a result of Lewis base activation of Lewis acid [9].

In conclusion, we have demonstrated that the unique catalytic reactivity of MgI_2 etherate in the three-component allylation of various aldehydes including aromatic aldehydes, heteroaromatic aldehydes, vinyl aldehydes, aliphatic aldehydes and amines with allyltributylstannane. This magnesium-catalyzed allylation addition is mild, efficient, operationally simple and highly chemoselective. Further investigation on the catalytic reactivity of MgI_2 etherate in other C–C bond constructing reactions is underway.

GENERAL EXPERIMENTAL PROCEDURE

General

For product purification by flash column chromatography, silica gel (200~300 mesh) and light petroleum ether (PE, b.p. 60~90 ^oC) are used. All solvents were commercially available. ^1H NMR spectra were taken on a Bruker AM-500 spectrometer with TMS as an internal standard and $CDCl_3$ as solvent.

The General Procedure for the Synthesis of Homoallylic Aimine

To a stirred solution of benzaldehyde (0.5 mmol) and aniline (0.5 mmol) in CH_2Cl_2 (5 mL) was added a stock solution of MgI_2 in 1:2 Et_2O/benzene (0.5 M, 0.2 mL) at room temperature. After stirring for 10 min, a solution of allyltributylstannane (0.6 mmol) in CH_2Cl_2 (2 mL) was added dropwise *via* a syringe. The resulting homogeneous reaction mixture was stirred at room temperature for 2.0 h and quenched with 1.0 N HCl aqueous solution. Extractive workup with ethyl acetate and chromatographic purification of the crude product on silica gel gave the desired homoallylic amine **1a** (102 mg) in 92% yield.

Spectroscopic Data for Products 1a-1m (Table 1)

Compound (**1a**): ^1H NMR ($CDCl_3$) δ 2.60-2.65 (m, 1H), 2.71-2.75 (m, 1H), 4.29 (br s, 1H), 4.50-4.53 (m, 1H), 5.26-5.33 (m, 2H), 5.85-5.92 (m, 1H), 6.63 (d, 2H, *J* = 7.5 Hz), 6.78 (t, 1H, *J* = 7.5 Hz), 7.19-7.22 (m, 2H), 7.35-7.37 (m, 1H), 7.42-7.50 (m, 4H) ppm.

Compound (**1b**): ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.56-2.60 (m, 1H), 2.67-2.71 (m, 1H), 4.14 (br s, 1H), 4.43-4.46 (m, 1H), 5.22-5.29 (m, 2H), 5.82-5.90 (m, 1H), 6.52 (d, 2H, *J* = 8.5 Hz), 6.99 (d, 2H, *J* = 8.0 Hz), 7.30-7.33 (m, 1H), 7.39-7.42 (m, 2H), 7.42-7.47 (m, 2H) ppm.

Compound (**1c**): ^1H NMR ($CDC1_3$) δ 2.55-2.60 (m, 1H), 2.65-2.69 (m, 1H), 4.50-4.54 (m, 1H), 4.91 (d, 1H, *J* = 4.5 Hz), 5.20-5.26 (m, 2H), 5.71-5.77 (m, 1H), 6.45 (d, 2H, *J* = 9.0 Hz), 7.26-7.30 (m, 3H), 7.34-7.37 (m, 2H), 7.99 (d, 2H, *J* = 9.5 Hz) ppm.

Compound (**1d**): ^1H NMR ($CDC1_3$) δ 2.48-2.52 (m, 1H), 2.58-2.61 (m, 1H), 3.78 (s, 3H,), 4.12 (br s, 1H), 4.33 (dd, 1H, *J* = 5.0, 8.0 Hz), 5.12-5.19 (m, 2H), 5.71-5.80 (m, 1H), 6.48-6.50 (m, 2H), 6.62-6.65 (m, 1H), 6.86 (ddd, 2H, *J* = 2.5, 5.0, 10.0 Hz), 7.05-7.09 (m, 2H), 7.27 (ddd, 2H, *J* = 2.0, 5.0, 10.0 Hz) ppm.

Compound (**1e**): ^1H NMR ($CDC1_3$) δ 2.45-2.52 (m, 1H), 2.59-2.64 (m, 1H), 4.26 (br s, 1H), 4.42-4.45 (m, 1H), 5.18-5.22 (m, 2H), 5.67-5.74 (m, 1H), 6.34 (d, 2H, *J* = 10.0 Hz), 7.01 (d, 2H, *J* = 10.0 Hz), 7.51 (d, 2H, *J* = 10.0 Hz), 8.17 (d, 2H, *J* = 10.0 Hz) ppm.

Compound (**1f**): ^1H NMR ($CDC1_3$) δ 2.55-2.65 (m, 2H), 4.47 (t, 1H, *J* = 6.8 Hz), 5.18-5.24 (m, 2H), 5.71-5.82 (m,

1H), 6.23 (d, 1H, *J* = 8.0 Hz), 6.59 (t, 1H, *J* = 7.6 Hz), 6.67 (t, 1H, *J* = 7.6 Hz), 6.72 (d, 1H, *J* = 4.4 Hz), 7.55 (d, 2H, *J* = 9.2 Hz), 8.18 (d, 2H, *J* = 8.4 Hz) ppm.

Compound (**1g**): ^{1}H NMR ($CDC1_3$) δ 2.57-2.62 (m, 2H), 4.48 (t, 1H, *J* = 6.8 Hz), 5.17-5.23 (m, 2H), 5.73-5.78 (m, 1H), 6.27 (d, 1H, *J* = 7.6 Hz), 6.55-6.59 (m, 1H), 6.64-6.70 (m, 1H), 6.72 (d, 1H, *J* = 7.6 Hz), 7.47 (t, 1H, *J* = 8.0 Hz), 7.72 (d, 1H, *J* = 7.6 Hz), 8.08 (dd, 1H, *J* = 1.6, 8.0 Hz), 8.24 (dd, 1H, *J* = 1.6, 4.0 Hz) ppm.

Compound (**2h**): ^{1}H NMR ($CDC1_3$) δ2.50-2.60 (m, 2H), 4.36 (t, 1H, *J* = 7.6 Hz), 5.13-5.21 (m, 2H), 5.71-5.76 (m, 1H), 6.34 (d, 1H, *J* = 8.0 Hz), 6.60 (t, 1H, *J* = 7.6 Hz), 6.72 (d, 2H, *J* = 8.0 Hz), 7.26-7.31 (m, 4H) ppm.

Compound (**1i**): ^{1}H NMR ($CDC1_3$) δ 2.43-2.50 (m, 2H), 3.73 (s, 3H) 5.14-5.20 (m, 2H), 5.81-5.89 (m, 1H), 6.19 (dd, 1H, *J* = 6.0, 15.5 Hz), 6.57-6.64 (m, 3H), 6.75 (dd, 2H, *J* = 2.5, 6.5 Hz), 7.19-7.36 (m, 5H) ppm.

Compound (**1j**): ^{1}H NMR ($CDC1_3$) δ 2.64 -2.67 (m, 2H), 3.98 (br s, 1H), 4.55 (t, 1H, *J* = 6.5 Hz), 5.12-5.19 (m, 2H), 5.71-5.79 (m, 1H), 6.16 (d, 1H, *J* = 3.5 Hz), 6.28 (dd, 1H, *J* = 1.5, 3.0 Hz), 6.60 (dd, 2H, *J* = 1.0, 8.5 Hz), 6.70 (t, 1H, *J* = 7.5 Hz), 7.14 (dd, 2H, *J* = 7.0, 9.0 Hz), 7.34 (s, 1H) ppm.

Compound (**1k**): ^{1}H NMR ($CDC1_3$) δ 2.64-2.68 (m, 2H), 4.12 (br s, 1H), 4.71 (t, 1H, *J* = 7.5 Hz), 5.15-5.21 (m, 2H), 5.76-5.83 (m, 1H), 6.60 (d, 2H, *J* = 7.5 Hz), 6.68-6.71 (m, 1H), 6.93-6.98 (m, 2H), 7.11-7.17 (m, 3H) ppm.

Compound (**1l**): ^{1}H NMR ($CDC1_3$) δ 2.52-2.55 (m, 2H), 3.62(d, 1H, *J* = 13.0 Hz), 3.81(d, 1H, *J* = 13.5 Hz), 4.02 (t, 1H, *J* = 7.0 Hz), 5.05-5.12 (m, 2H), 5.67-5.76 (m, 1H), 6.97 (t, 1H, *J* = 3.0, 5.0 Hz), 7.24-7.26 (m, 2H), 7.29-7.33 (m, 4H) ppm.

Compound (**1m**): ^{1}H NMR ($CDC1_3$) δ 1.77-1.90 (m, 2H), 2.32 (t, 2H, *J* = 6.5 Hz), 2.70-2.76 (m, 2H), 3.34-3.39 (m, 1H), 3.75 (s, 3H), 5.05-5.10 (m, 2H), 5.76-5.84 (m, 1H), 6.55 (d, 2H, *J* = 8.5 Hz), 6.76 (dd, 2H, *J* = 2.0, 6.5 Hz), 7.16-7.20 (m, 3H), 7.26-7.29 (m, 2H) ppm.

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