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Sn-mediated one-pot four-component allylation of aldimines

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A convenient and facile method for the synthesis of homoallylic amines was disclosed. The one-pot reaction of aldehydes, aromatic amines and allylic bromide with tin powder at room temperature could afford the homoallylic amines in good to excellent yield without any promoter or additive. The method is highly efficient and environmentally benign with low cost and concise manipulation. Copyright © 2014 John Wiley & Sons, Ltd.

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Keywords: tin powder; one-pot; allylation; homoallylic amines

Introduction

Nucleophilic addition of allylic organometallics to carbonyl compounds or their derivatives constitutes a representative method for preparing homoallylic compounds,[1–4] which are versatile building blocks and synthons in the synthesis of many biologically active molecules and natural products.[5–16] Among the existing methods to construct these biologically active molecules and natural products, the Barbier[17–19] or Barbier-type reaction[20–25] is one of the easiest and most convenient strategies. In the past few decades, several kinds of allylic organometallics such as allyl Si,[26,27] Sn,[28–31] Sm,[32,33] Mg,[34,35] Zn,[36–38] B[37,39] and In[40–43] have been intensively investigated in allylation reaction.[44–47] Among these, allyltributyltin is an effective and commonly used reagent for allylation of aldehydes or imines to give homoallylic alcohols or amines.[8] Although it has several advantages such as easy availability, air and moisture stability and compatibility with a variety of functional groups,[48] its application is still limited because of the toxicity of organotin compounds and the formation of an unwanted byproduct containing the $SnBu_3$ group during the reaction.[49–52] Furthermore, only the allyl group in allyltributyltin is delivered into the product molecule and the $SnBu_3$ group is usually discarded as waste after the reaction. Thus, this transformation is not an efficient method from the viewpoint of atom economy. Moreover, Lewis acids or Brønsted acids are often needed in the allylation of imines with allyltributyltin to activate the substrates,[52–61] generally because of the lower reactivity of imine compared with the corresponding aldehyde.[44,46,62–64] In this context, there is ongoing interest in developing an environmentally benign and bench-friendly process for allylation of imines with non-toxic tin reagents. As we know, tin powder is much less toxic than the organostannes. If the organostannes can be replaced by tin powder in organic reactions, the process would be more environmentally benign. To our knowledge, there are few reports on four-component allylation in the presence of tin powder.[65] Herein, we report a one-pot four-component procedure for preparation of homoallylic amines, involving *in situ* generation[66–68] of imines and allyltin without any additive.

Results and Discussion

Initially, the one-pot allylation was performed in 1,4-dioxane using benzaldehyde(1 equiv.), aniline (1 equiv.), allylic bromide (1 equiv.) and tin powder (1 equiv.) at room temperature. The corresponding homoallylic product was readily formed, but the yield was only 12% (Table 1, entry 1). In order to optimize the product yield, the different mole ratios of the substrates and solvents were checked. As summarized in Table 1, the best product yield was obtained by carrying out the reaction at room temperature in 1,4-dioxane with a mole ratio of benzaldehyde/aniline/allylbromide/tin of 1.0/1.5/1.5/2.0. Under these conditions **4a** was obtained in 87% yield in 12 h (Table 1, entry 6).

In order to study the scope of this new protocol, reactions of various aromatic amines with benzaldehyde were investigated first (Table 2, entries 1–12). Anilines bearing electron-withdrawing groups such as Cl and Br in the *para* position underwent allylation smoothly to furnish the desired adducts **4** in good yields (Table 2, entries 2 and 3). However, *para*-NO_2-substituted aniline could not give the desired product (Table 2, entry 4). Anilines with electron-donating groups in both the *ortho* and *para* position could also provide the corresponding homoallylic amines with slightly low yields (Table 2, entries 5–8). This is possibly due to the lower stability of the formed imines compared with the electron-withdrawing ones. Interestingly, when bulky anilines **2i** and **2j** were exposed under the optimal condition, the desired products **4i** and **4j** were obtained in good yield (Table 2, entries 9 and 10). 2-Naphthyl amine gave the product **4k** in moderate yield. Unfortunately, aliphatic amine could not behave well in this transformation. The reason for this may be that

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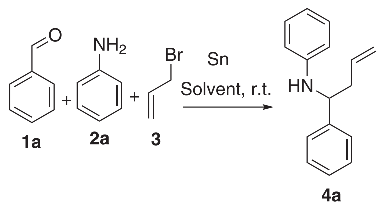
imines formed from the aliphatic amines are labile and amenable to side reactions. (Table 2, entry 12).

We next examined the substrate scope of aldehydes. As shown in Table 3, a variety of aromatic aldehydes with both electron-withdrawing groups and electron-donating groups could react with aniline under the optimized reaction conditions to produce homoallylic amines in good yield. Nevertheless, the former gave better yields than the latter (Table 3, entries 1–3 versus 4). 2-Furaldehyde and 2-thenaldehyde also afforded appropriate products in fair yield (Table 3, entries 5 and 6). As reported in the literature, for aliphatic aldehydes having α-protons, the allylation reaction usually takes place with many side reactions to dramatically decrease the product yield.[62,63] Keeping this in view, pivaldehyde without α-protons was used in our reaction, and the product **4s** was obtained in 73% yield (Table 3, entry 7).

As indicated above, the use of an electron-deficient aldehyde and amine is beneficial to this allylation reaction. To further confirm this fact, electron-rich *para*-anisaldehyde and electron-poor *ortho*-fluorobenzaldehyde were selected as substrates to react anilines with different electronic properties. As expected, the reactions of electron-rich *para*-anisaldehyde with electron-poor anilines could furnish the desired products in higher yield than the reaction with electron-rich anilines (Table 4, entries 1–4). These results are in agreement with those obtained from the reaction of electron-poor *ortho*-fluorobenzaldehyde with various anilines (Table 4, entries 5–8). Based on the above investigation, it is further confirmed that the use of electron-poor aromatic aldehydes and/or anilines is more suitable in the present four-component allylation protocol.

A plausible mechanism for this tin-mediated allylation process is proposed in Scheme 1 on the basis of experimental results and previous reports.[29,69,70] As illustrated by Chan and co-workers,[29] allyltin bromide **5** and diallyltin dibromide **6** are generated as organometallic intermediates in this process. According to the optimized condition, the ratio of allylic bromide and tin powder is 1:1.3. Thus we believe that the intermediate **5** is the favored intermediate. Moreover, neither Brønsted acid nor Lewis acid is required for the reaction, which indicates that the nucleophilicity of organometallic intermediate **5** is enough to react with

Table 1. Optimization of reaction conditions for one-pot four-component allylation[a]

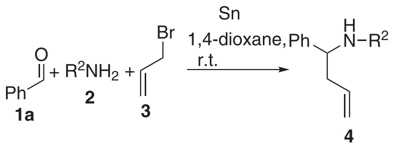


Entry	Mole ratio of **1a**/**2a**/**3**/Sn	Solvent	Time (h)	Yield (%)[b]
1	1.0/1.0/1.0/1.0	1,4-Dioxane	24	12
2	1.0/1.0/1.0/1.5	1,4-Dioxane	24	24
3	1.0/1.0/1.5/2.0	1,4-Dioxane	24	63
4	1.0/1.0/2.0/2.0	1,4-Dioxane	12	83
5	1.0/1.0/2.0/2.5	1,4-Dioxane	12	85
6	1.0/1.5/1.5/2.0	1,4-Dioxane	12	87
7	1.0/2.0/2.0/2.0	1,4-Dioxane	12	86
8	1.0/2.0/2.0/2.5	1,4-Dioxane	12	87
9	1.0/1.5/1.5/2.0	THF	24	78
10	1.0/1.5/1.5/2.0	Ether	24	72
11	1.0/1.5/1.5/2.0	Toluene	24	47
12	1.0/1.5/1.5/2.0	DCM	24	60
13	1.0/1.5/1.5/2.0	EtOH	24	66

[a] Reaction conditions: benzaldehyde (**1a**, 1.0 mmol), aniline (**2a**, 1.0–2.0 mmol), allylic bromide (**3**, 1.0–2.0 mmol), tin (1.0–2.0 mmol), solvent (3.0 mL).

[b] Isolated yield.

Table 2. Results of the allylation of benzaldehyde with various amines[a]

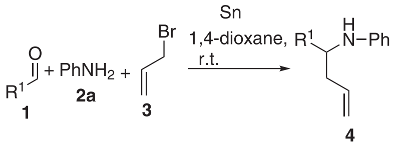


Entry	R^2	Product	Yield (%)[b]
1	Ph	**4a**	87
2	*p*-Cl-C_6H_4	**4b**	78
3	*p*-Br-C_6H_4	**4c**	75
4	*p*-NO_2-C_6H_4	—	NR
5	*p*-CH_3-C_6H_4	**4e**	62
6	*o*-CH_3-C_6H_4	**4f**	69
7	*p*-CH_3O-C_6H_4	**4g**	61
8	*p*-C_2H_5O-C_6H_4	**4h**	64
9	2,6-(*i*-Pr)$_2$-C_6H_3	**4i**	83
10	Mes-	**4j**	81
11	2-Naphthyl	**4k**	63
12	*t*-Bu	—	ND

[a] Reaction conditions: benzaldehyde (1.0 mmol), amines (1.5 mmol), allylic bromide (1.5 mmol), tin (2.0 mmol), 1,4-dioxane (3.0 mL).

[b] Isolated yield.

Table 3. Results of the allylation of aniline with various aldehydes[a]

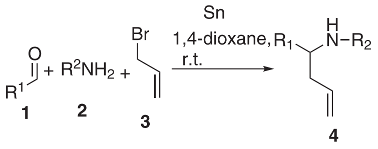


Entry	R^1	Product	Yield (%)[b]
1	*p*-CF_3-C_6H_4	**4m**	83
2	*o*-Cl-C_6H_4	**4n**	82
3	*o*-F-C_6H_4	**4o**	88
4	*p*-CH_3O-C_6H_4	**4p**	72
5	2-Thienyl	**4q**	68
6	2-Furyl	**4r**	74
7	*t*-Bu	**4s**	73

[a] Reaction conditions: aldehydes (1.0 mmol), aniline (1.5 mmol), allylic bromide (1.5 mmol), tin (2.0 mmol), 1,4-dioxane (3.0 mL).

[b] Isolated yield.

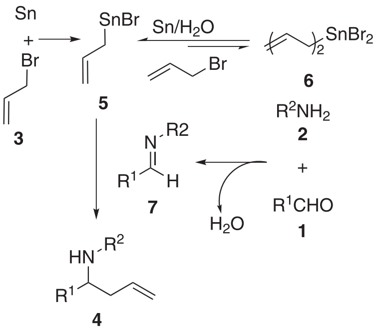
Table 4. Results of the allylation of various aromatic aldehydes with aromatic amines[a]



Entry	R^1	R^2	Product	Yield (%)[b]
1	p-CH_3O-C_6H_4	o-CH_3-C_6H_4	**4t**	68
2	p-CH_3O-C_6H_4	p-CH_3-C_6H_4	**4u**	67
3	p-CH_3O-C_6H_4	p-Cl-C_6H_4	**4v**	89
4	p-CH_3O-C_6H_4	p-Br-C_6H_4	**4w**	90
5	o-F-C_6H_4	o-CH_3-C_6H_4	**4x**	89
6	o-F-C_6H_4	p-CH_3-C_6H_4	**4y**	86
7	o-F-C_6H_4	p-Cl-C_6H_4	**4z**	92
8	o-F-C_6H_4	p-Br-C_6H_4	**4aa**	96

[a] Reaction conditions: aldehydes (1.0 mmol), amines (1.5 mmol), allylic bromide (1.5 mmol), tin (2.0 mmol), 1,4-dioxane (3.0 mL).

[b] Isolated yield.



Scheme 1. A possible mechanism for the one-pot four-component allylation.

the electrophilic aldimine to produce the homoallylic amine. These experimental results are consistent with Chan's observation.

Conclusions

In summary, we have developed a tin-mediated convenient protocol for the preparation of homoallylic amines from *in situ* formed aldimines. The process has the advantages of being additive free, highly efficient, bench friendly and environmentally benign. Specifically, (i) assembling of a C-N and a C-C bond could be achieved in a one-pot procedure without pre-formation of aldimines and pre-formation of allyltin; (ii) allylic tin reagent generated *in situ* from tin powder and allylic bromide was used to replace the toxic allyltributyltin; (iii) Lewis acids and Brønsted acids were not used to activate the imines; (iv) the reaction could be carried out without any additional inert gas atmosphere or anhydrous condition. Further investigations concerning the formation of homopropargyl amines and asymmetric version are now in progress.

Experimental

A solution of R^1CHO (1 mmol), R^2NH_2 (1.5 mmol), allylic bromide (1.5 mmol) and Sn powder (2 mmol) in 1,4-dioxane (3 mL) was stirred at room temperature for 12–24 h (monitored by thin-layer vhromatography), then quenched with saturated NH_4Cl aq., extracted with EtOAc and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, and the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc) to afford the desired product.

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