Tetrahedron 72 (2016) 3687–3700

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

N-Boc-aminals as easily accessible precursors for less accessible *N*-Boc-imines: facile synthesis of optically active propargylamine derivatives using Mannich-type reactions

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ARTICLE INFO

Article history:
Received 2 February 2016
Received in revised form 14 March 2016
Accepted 22 March 2016
Available online 26 March 2016

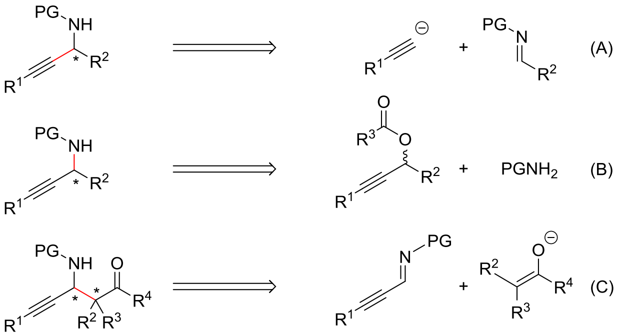
Keywords:
Aminal
Imine
Mannich reaction
Enantioselective catalysis

ABSTRACT

We developed a facile and practical synthesis of *N*-Boc-aminals, which can be used as precursors for less accessible *N*-Boc-imines. Aminals were obtained via simple dehydration condensation reactions of *t*-butyl carbamate (BocNH$_2$) and various aldehydes in acetic anhydride, followed by filtration and washing with hexane. The obtained *N*-Boc-alkynylaminals could be successfully applied in enantioselective Mannich-type reactions, catalyzed by chiral phosphoric acids, to afford optically active propargylamine derivatives.

1. Introduction

As optically active propargylamines are attractive building blocks for the construction of highly functionalized amines,[1,2] efficient synthetic pathways to such propargylamines have been pursued for several decades. So far, the most prevalent synthetic route is the enantioselective addition of nucleophilic terminal alkynes to imines or in situ-generated iminium intermediates (Scheme 1A). In this context, chiral transition metal catalysts, based on Cu(I), Ag(I), and Zn(II), which can form the corresponding metal acetylides, have also been intensively investigated.[3–6] Enantioselective propargylic aminations represent a powerful alternative approach, since stable and easily attainable racemic propargyl esters can be used as substrates (Scheme 1B).[7] In these methods, asymmetry is introduced only at the propargylic position. In contrast, the enantioselective nucleophilic addition to alkynylimines allows the simultaneous generation of two adjacent stereocenters with several prochiral nucleophiles (Scheme 1C).[8,9] These imines contain both amino and alkynyl groups, and structurally diverse propargylamines can be easily prepared by using various nucleophiles. A few examples have been reported to use isolable *N*-aryl-protected alkynylimines in such reactions.[8,9] *N*-Boc-imines are especially appealing substrates due to their high reactivity and ease of deprotection. However, despite their synthetic utility, simple routes to *N*-Boc-alkynylimines still remain unprecedented.[1]



Scheme 1. Retrosynthetic approach to optically active propargylamines: (A) enantioselective addition of terminal alkynes to imines, (B) propargylic amination of racemic propargyl esters, and (C) enantioselective addition of a nucleophile to alkynylimines.

N-Boc-alkynylimines are most effective when they are generated in situ and consumed rapidly. Efficient and easily accessible precursors for such imines are accordingly attractive research targets. Unfortunately, amidosulfones,[10] which are widely used imine precursors, are not suitable for this purpose, as those containing alkynyl groups are nontrivial to synthesize. Hence, we focused on *N*-Boc-protected aminals as potential precursors for such imines;[11] *N*-Boc-aminals exhibit an N–C–N substructure, which can be converted into highly reactive iminium cations under acidic

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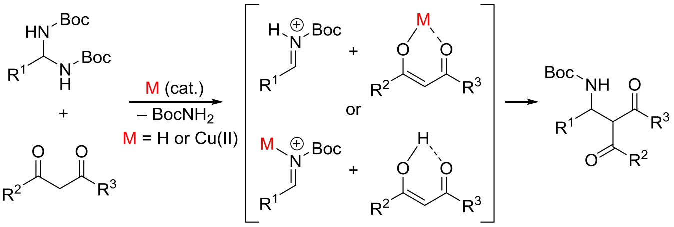
http://dx.doi.org/10.1016/j.tet.2016.03.076

conditions by releasing one of the two carbamoyl groups on the central carbon atom. Recently, we successfully demonstrated that *N*-Boc-imines can be generated in situ from *N*-Boc-aminals, and that a subsequent acid-catalyzed Mannich-type reaction generates *N*-Boc-amines (Scheme 2).[12,13] Herein, we summarize the chemical properties of these *N*-Boc-aminals and describe their synthetic utility, especially with respect to the enantioselective synthesis of *N*-Boc-propargylamines. For the reactions involved, we also propose reaction mechanisms.



Scheme 2. Acid-catalyzed Mannich-type reaction of *N*-Boc-iminium intermediates, generated in situ from *N*-Boc-aminals.

2. Results and discussion

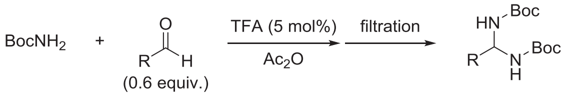
2.1. Preparation of *N*-Boc-aminals as imine precursors

Initially, we investigated a general and highly effective synthetic protocol for the preparation of *N*-Boc-aminals from readily available aldehydes. We expected to obtain the desired *N*-Boc-aminals from a simple dehydration condensation using *t*-butyl carbamate ($BocNH_2$) and aldehydes, and we speculated that acetic anhydride (Ac_2O) should be an effective solvent for this reaction. When phenylpropargyl aldehyde was stirred with $BocNH_2$ (1.67 equiv) in the presence of a catalytic amount of trifluoroacetic acid (TFA) in Ac_2O for 30 min at room temperature, the desired dehydration proceeded smoothly. Fortunately, the resulting aminal precipitated from the reaction mixture, and filtration, followed by washing with hexane afforded the pure aminal as an air-, moisture- and light-stable white powder. A wide variety of aldehydes containing alkynyl, alkenyl, alkyl, and aryl groups were also applicable to this synthetic method, furnishing the corresponding aminals in high yield (Table 1). In contrast, ketones such as benzophenone were inert under otherwise identical conditions (Scheme 3). All *N*-Boc-aminals were isolated as white powders, which were stable under ambient conditions, while the corresponding *N*-Boc-imines are sensitive towards atmospheric moisture.

2.2. Reactivity of *N*-Boc-aminals under acidic conditions

With a wide variety of the *N*-Boc-aminals in hand, we then evaluated their potential as the corresponding imine precursors under acidic conditions. For the Lewis acid-catalyzed Mannich-type reaction of these aminals, diethyl malonate was used as nucleophile of choice. In the presence of 10 mol % $Cu(OTf)_2$, the desired nucleophilic addition to the in situ-generated *N*-Boc-imines from the corresponding aminals proceeded smoothly to afford the β-amino acid derivatives (Table 2). Most notably, this is the first practical example for the synthesis of *N*-Boc-propargylamines via a Mannich-type reaction of in situ-generated *N*-Boc-alkynylimines. Conversely, Brønsted acid catalysts, such as e.g., TFA, were found to be inefficient for the present transformation (Scheme 4).

Table 1
Preparation of *N*-Boc-aminals from a dehydration condensation of $BocNH_2$ and aldehydes[a]



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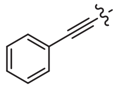
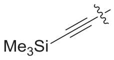
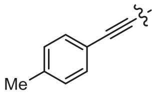
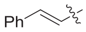
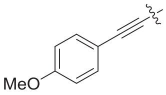
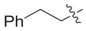
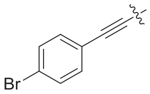
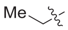
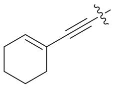
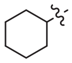
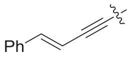
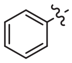
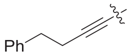
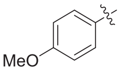
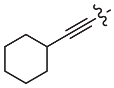
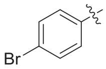
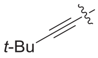
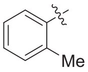
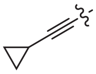
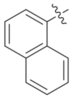
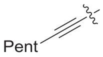
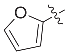
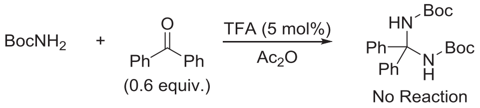
1		92	12		90
2		80	13		54
3		89	14		71
4		81	15		91
5		69	16		85
6		42	17		77
7		50	18		64
8		84	19		66
9		70	20		62
10		61	21		81
11		73	22		57

[a] Reaction conditions: aldehyde (3.3 mmol), $BocNH_2$ (5.5 mmol), Ac_2O (750 μL), and TFA (0.028 mmol, 5 mol % with respect to $BocNH_2$). The precipitated aminal was isolated by filtration and washed with hexane.

[b] Isolated yield.



Scheme 3. Attempted formation of the corresponding *N*-Boc-aminal from benzophenone.

Other *C*-nucleophiles than malonate, e.g., a β-ketoester and a silyl enol ether, also afforded the target adducts. Using these *C*-nucleophiles, we investigated Lewis acid-catalyzed reactions with *N*-Boc-aminals, bearing phenyl, phenylethynyl, (*E*)-phenylethenyl, and phenylethyl groups (Tables 3 and 4). It should be noted that, depending on their substituents, the aminals exhibited different reactivity. While Mannich-type reactions with the β-ketoester converted *N*-Boc-aminals carrying phenyl and phenylethynyl groups effectively into the corresponding adducts, those carrying