Tetrahedron Letters 49 (2008) 6245–6249

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Regioselective and stereoselective synthesis of tetrahydrofurans from a functionalized allylic silane and an aldehyde via formal [3+2]-cycloaddition reaction

Steven R. Angle *, Inchang Choi

Department of Chemistry, Wright State University, Dayton, OH 45435, United States
Department of Chemistry, University of California-Riverside, Riverside, CA 92521, United States

ARTICLE INFO

Article history:
Received 23 May 2008
Revised 8 August 2008
Accepted 11 August 2008
Available online 15 August 2008

ABSTRACT

Allylsilanes are known as useful reagents for the stereoselective formation of ring systems. Previous studies have shown that tetrahydrofurans can be constructed via formal [3+2]-cycloadditions of aldehydes and allylsilanes. A new challenge is to understand the intermediate, after a nucleophile attacks a carbonyl activated by the Lewis acid, in which two silyl-protected alkoxy groups with chemical equivalency could undergo formal cycloaddition reaction to afford a disubstituted and/or a trisubstituted tetrahydrofuran. Preparation of the protected α-hydroxy aldehyde and a functionalized allylic silane is discussed, as well as their formal cycloaddition reaction to form tetrahydrofurans.

1. Introduction

Allylic silanes are important reagents that undergo highly stereoselective reactions with a variety of electrophiles including carbonyl groups, iminium ions, and enones.[1–4] They have also played a key role in the synthesis of natural products exhibiting a variety of biological activities such as superstolide A,[5] (−)-allo-muscarine,[6] (+)-epimuscarine,[6] (9*S*)-dihydroerythronolide A,[7] and (±)-peduncularine.[8]

Previous studies from our research group[6,9,10] and others[7,8,11–14] show that allylsilanes are potent nucleophiles that can be used to prepare tetrahydrofurans (THFs) and tetrahydropyrans (THPs). The mechanistic details of the addition of allylic silanes and allylic stannanes to aldehydes have been controversial. As part of an effort to understand the transition state of this formal [3+2]-cycloaddition, we prepared a functionalized allylic silane and studied its Lewis acid-mediated reaction with α-triethylsiloxy aldehydes. The result may shed some light on the orientation of the Lewis acid-activated aldehyde relative to the allylsilane in the transition state.

2. THF synthesis

The formal [3+2]-cycloaddition reaction might produce a mixture of six different compounds via pathways a–f (Scheme 1). Based on results from previous studies,[15] a triethylsilyl-protected hydroxy group is a better nucleophile than a Lewis acid-complexed alkoxide ion. Thus, pathways c and d are unlikely. In addition, in a study of a similar formal [3+2]-cycloaddition reaction, only THF was obtained; no tetrahydropyran was observed.[6] Accordingly, pathways a and f are also unlikely. This leaves two likely pathways for the proposed cycloaddition reaction: pathways b and e. These two pathways would generate constitutional isomers **5** and **8**, respectively (Scheme 1). The reaction of the allylic silane with the aldehyde should afford intermediate **3**, with two chemically similar triethyl siloxy groups. Either siloxy group could undergo reaction with the silyl-stabilized cation (pathway b or e) to form trisubstituted THF **5** or disubstituted THF **8**.

An attempt to prepare (*E*)-alkene **14** via a trialkylaluminate intermediate resulted in a difficult to separate mixture of primary alcohols in low yield. Accordingly, an alternative method for the synthesis of **14** was explored (Scheme 2). Terminal alkyne **10** was treated with DIBAl-H to generate (*E*)-alane complex **11**, which yielded (*E*)-vinyl iodide **12** upon reaction with I_2.[16] Metal–halogen exchange, followed by addition of ethylene oxide, afforded β-hydroxy allylic silane **13** in 30% yield from **11**. Protection of **13** as the triethylsilyl ether gave **14**. The known α-triethylsilyloxyaldehyde **1** was prepared by DIBAl-H reduction of the corresponding ester.[10]

With the requisite allylic silane **14** and aldehyde **1** in hand, we were poised to examine the formal [3+2]-cycloaddition reaction. A series of reaction conditions were studied in an attempt to optimize formation of THF products (Table 1). Under most conditions trisubstituted THF **15** was formed along with desilylated THF **16**. The diastereomer ratio of **15** and **16** varied from 3.0:1 to 3.3:1 (^{1}H NMR analysis). It is important to note that another potential constitutional isomer, disubstituted THF **8** (Scheme 1), could have been formed in this formal cycloaddition reaction; THF **8** was not

* Corresponding author. Tel.: +1 937 775 3035; fax: +1 937 775 2421.
E-mail address: steven.angle@wright.edu (S. R. Angle).

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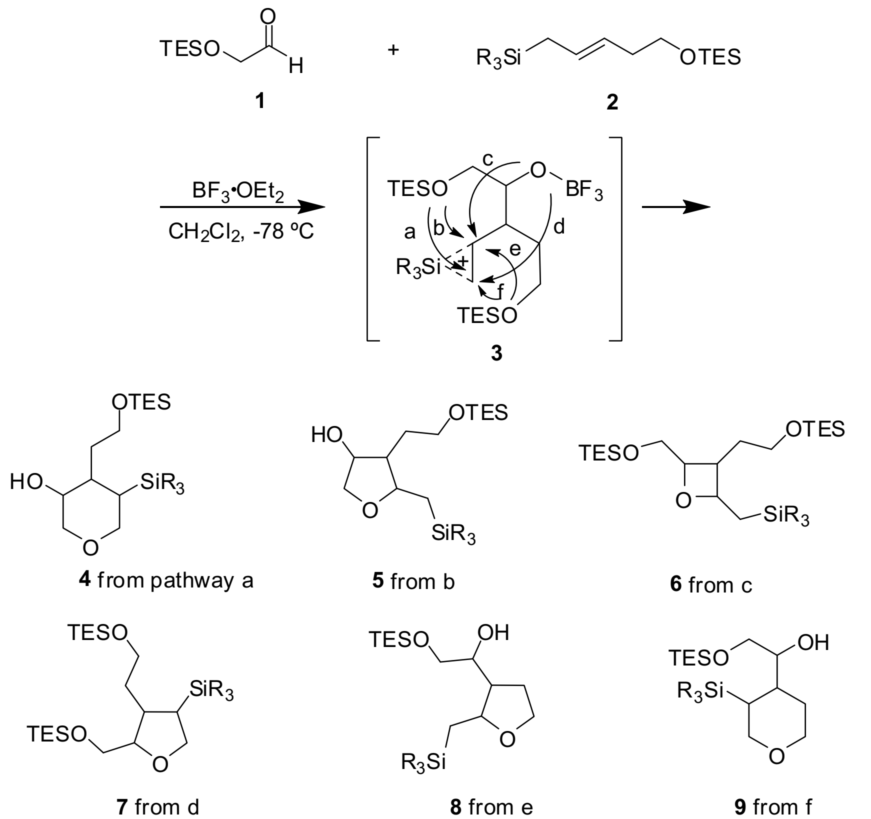
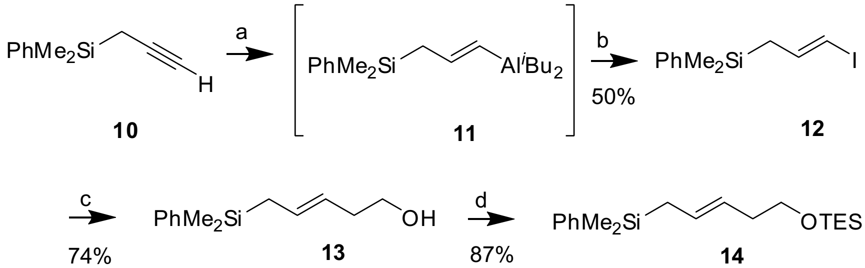
doi:10.1016/j.tetlet.2008.08.046



Scheme 1. Possible products from formal [3+2]-cycloaddition reaction.



Scheme 2. Alternate route for formation of (e)-pentenyl silyl ether **14**. Reagents and conditions: (a) DIBAL-H, hexanes, −78 °C to 40 °C; (b) I2, THF, −78 °C to rt; (c) (i) *t*-BuLi, ether, −78 °C, (ii) ethylene oxide; (d) TESCl, Et3N, CH2Cl2, 0 °C to rt.

observed. The formation of constitutional isomer **15** (but not **8**) was also confirmed by NMR studies, including COSY, of compounds **15** and **16**,[17] and the X-ray crystal structure of **19a**.

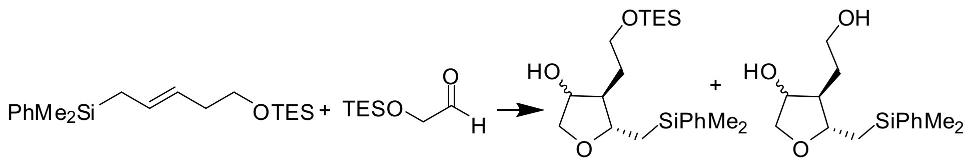
The stereochemistry of the major diastereomer of trisubstituted THF **15** was determined as described below (Scheme 3). Oxidation of **15** (3:1 mixture of diastereomers) afforded ketone **17** as a single diastereomer. This oxidation reaction confirmed that the carbon with the secondary alcohol was the diastereomeric center. Subsequent reduction of ketone **17** with $NaBH_4$ gave **15** as 5.5:1 mixture of diastereomers in 80% yield.

The two diastereomers of **15a/b** were separated by HPLC. The major diastereomer **15a** was desilylated to afford diol **16a** (99% yield) and the desilylation of THF **15b** gave diol **16b** in 91% yield. The 3.3:1 mixture of diastereomers **16a/b** was reacted with *p*-nitrobenzoyl chloride to give a mixture of diesters **18a/b** in 71% yield (Scheme 4). After separation, **18a** was recrystallized to afford X-ray quality crystals. X-ray analysis showed **17a** (and thus **15a**) to have a trans–trans relative stereochemistry of substituents about the THF ring (Fig. 1).

The regioselective outcome of the formal [3+2]-cycloaddition reaction shows that in intermediate **3**, the triethyl siloxy group on the aldehyde backbone attacks the β-silylcation/siliranium ion (pathway b in Scheme 1), whereas its counterpart triethyl siloxy group on the allylic silane does not (pathway e in Scheme 1). In an effort to see if the triethyl siloxy group on the allylic silane could act as a nucleophile toward the β-silylcation/siliranium intermediate, an aldehyde lacking an α-triethyl siloxy group (benzaldehyde) was used in the formal cycloaddition reaction under same reaction conditions (Scheme 5). We did not observe (^{1}H NMR analysis) any cyclized product **20** in this reaction. The only isolable product of the reaction was a compound tentatively assigned as terminal alkene **21** (by ^{1}H NMR, ^{13}C NMR).

This result might be explained by proposed intermediate **19** in Scheme 5. After nucleophilic addition of allylic silane **2** to benzaldehyde, backside approach of the silyloxy group to the β-silyl cation via the *si*-face was blocked by the bridging β-silylcation/siliranium ion, and *re*-face approach was also hindered by a bulky phenyl group. Such difficulty in accessing the silyloxy group may

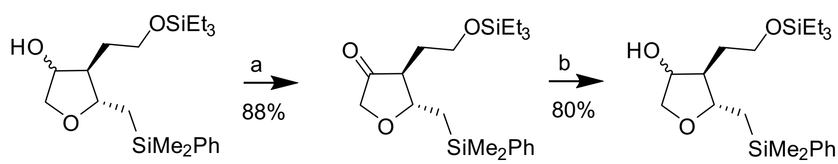
Table 1
Formal [3+2]-cycloaddition reaction



14 **1** **15a/b** **16a/b**

Entry	Reaction condition	**15** (%)	**16** (%)	Additive (equiv)
1	24 h at −78 °C	40	Trace	None
2	24 h at −78 °C	49	3	DBMP (1.0)
3	2 h at rt	43	20	DBMP (1.0)
4	1 h at rt	66	9	DBMP (1.0)
5	1 h at rt	None	49	None

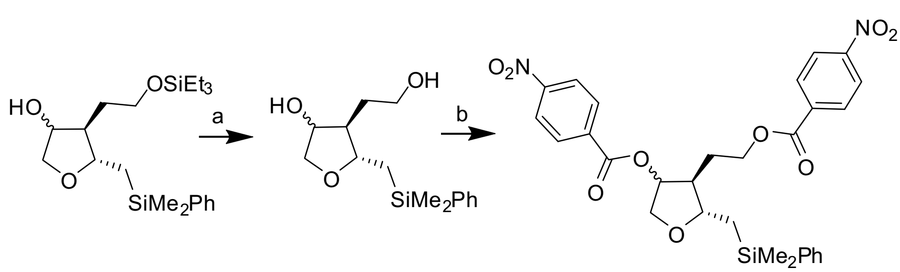
General procedure: to a solution of **1** and **14** (1.5 equiv) in CH_2Cl_2 (1 M) was added $BF_3{\cdot}OEt_2$ (1.5 equiv) at −78 °C. After being stirred for the time shown in the table, the mixture was poured into sat. $NaHCO_3$ with stirring.



15a/b **17** **15a/b**

d.r., **15a**:**15b** = 3.3:1 Single Diastereomer **15a**:**15b** = 5.5:1

Scheme 3. Oxidation of THF. Reagents and conditions: (a) Dess–Martin periodinane, CH2Cl2, 0 °C to rt; and (b) NaBH4, MeOH, 0 °C to rt.



15a **16a** (99%) **18a** (57%) and **18b** (14%)
15b **16b** (91%) from 3.3:1 mixture of **16a/b**

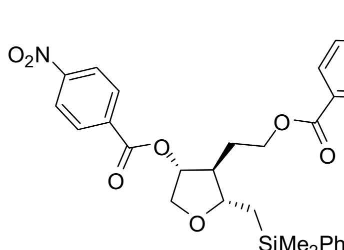
Scheme 4. Preparation of THF derivative. Reagents and conditions: (a) TBAF, THF, 0 °C to rt; and (b) *p*-nitrobenzoyl chloride, pyr., DMAP, CH_2Cl_2, 0 °C to rt.

have led to the failure of cyclization. Moreover, the Lewis acid-complexed alkoxide ion did not participate in a cyclization. The major products were terminal alkene **21** derived from desilylation, and decomposed allylsilane (deprotected β-hydroxy alkene **13**).

Thus, in the formal cycloaddition reaction of functionalized allylic silane **14** with an α-siloxy aldehyde, we might explain why trisubstituted THF **15** was formed as follows: in intermediate **3** (Scheme 1), the triethyl siloxy group originally from aldehyde **1** was more accessible to the β-silylcation/siliranium ion compared to its counterpart on the allylic silane. This led to the formation of the trisubstituted THF only.

3. Study of stereochemical outcome

Addition reactions of allylic stannanes and silanes with Lewis acid-activated aldehydes have been studied for decades, and these highly stereoselective reactions have motivated many researchers to attempt to understand mechanistic details, especially the approach of the allylsilane to the aldehyde in the transition state.[2,6,9,18–24] However, a detailed understanding of the transition states for these reactions still remains controversial. Yamamoto et al.[23,24] first proposed that the intermolecular reaction of allylstannanes with aldehydes in the presence of Lewis acid occurs via an open transition state with an antiperiplanar arrangement of the allylstannane and aldehyde being preferred. Along with Yamamoto's proposal, a number of proposals have been advanced to explain the stereochemical outcome of the reaction of allylic stannanes or allylic silanes with aldehydes under Lewis acid-promoted reaction conditions. Denmark et al.[19] demonstrated that in the intramolecular reaction of an allylstannane with an aldehyde in the presence of various Lewis acids, a major diastereomer was derived from the synclinal transition state, not from the antiperiplanar one. Several researchers[11,18,20] have supported a *syn*-synclinal transition state based upon FMO theory. Consistent with the results of others studying Lewis acid-promoted addition of allylstannanes and allylsilanes to aldehydes, our stereochemical results can be rationalized



18a

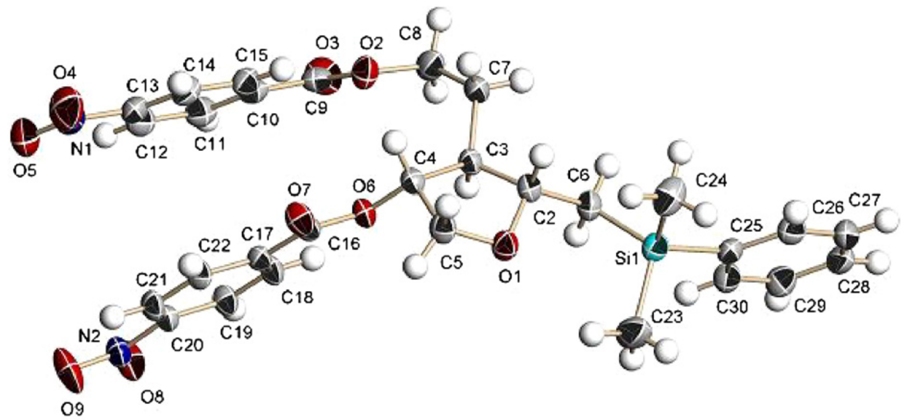
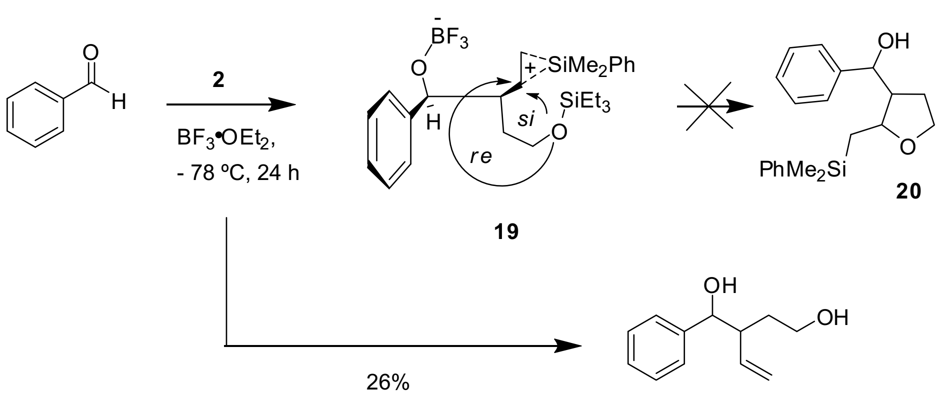


Figure 1. Crystal structure of the major eiester **18a.**



Scheme 5. Allylation of benzaldehyde.

by invoking a syn synclinal transition state. However, it is impossible to make any conclusive statements about the transition state for our reaction.

4. Conclusion

In conclusion, we have completed the formal [3+2]-cycloaddition reaction of the functionalized allylic silane with the α-siloxy aldehyde under BF_3 promoted-reaction condition, which generated the regioselectively as well as stereoselectively enriched THF. This reaction shows that our stereo-outcome more likely follows the *syn*-synclinal transition state over the antiperiplanar even though this topic still remains controversial issue at present time. This methodology development can further be applied toward total synthesis of natural products that contain related stereochemistry on the 5-membered heterocyclic ring system.

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