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5-Exocyclic Products, 2,3,5-Trisubstituted Tetrahydrofurans via Prins-Type Cyclization†

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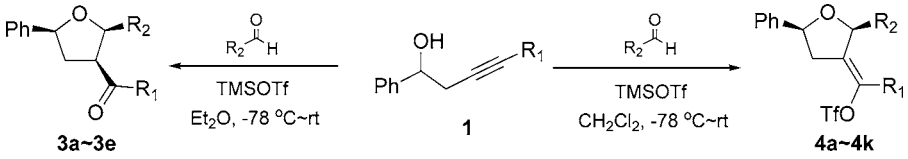
ABSTRACT



5-Exocyclic products, 2,3,5-trisubstituted tetrahydrofurans, were synthesized from homopropargylic alcohols with terminally substituted alkynes and various aldehydes via Prins-type cyclization. It is of interest that the exocyclic vinyl cation generated as a result of Prins-type cyclization could be trapped as a vinyl triflate when CH_2Cl_2 was used as a solvent, whereas in ethereal solution the vinyl cation underwent hydrolysis to give the corresponding ketone product.

Prins-type cyclization from homoallylic alcohols and aldehydes is a powerful method of preparing *cis*-2,6-disubstituted tetrahydropyrans,[1] which has been applied to the syntheses of many natural products.[2] Prins-type cyclization of homoallylic alcohols prefers 6-endocyclic products (tetrahydropyrans) to 5-exocyclic products (tetrahydrofurans).[3] Tetrahydrofurans are also ubiquitous in nature, occurring in a wide range of biologically active substances. Therefore, there has been much interest in the development of methods for the stereoselective synthesis of these subunits.[4,5] Rarely has pure Prins-type cyclization been used for the synthesis of tetrahydrofurans, though Prins-type cylcization followed by pinacol rearrangement gives tetrahydrofurans.[6]

There are two examples of synthesizing substituted tetrahydrofurans via Prins-type cyclization from a homoallylic or homopropargylic alcohol and aldehydes which utilize a functional group such as a trimethylsilyl group to stabilize the generated carbocation, resulting in driving 5-exo cyclization to tetrahydrofurans instead of 6-endo cyclization to tetrahydropyrans.[7] Previous investigations in our laboratory have shown that Lewis acid catalyzed Prins-type cyclization

† This paper is dedicated to Dr. Moon Ho Chang (KIST) on the occasion of his 61st birthday.

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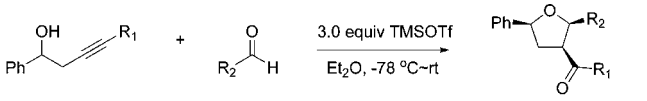
of a homopropargylic alcohol with a trimethylsilylmethyl group and aldehydes induces 5-exo cyclization to give *cis*-2,5-disubstituted 3-allenyltetrahydrofurans.[7a] To expand the scope of this useful Prins-type cyclization, we set out to devise a novel cyclization substrate which can introduce a substitutent at the 3-position. In this paper, we report Prins-type cyclization and the stereochemistry of homopropargylic alcohols with terminally substituted alkynes.

Prins-type cyclization of a homopropargylic alcohol **1a** with 4-nitrobenzaldehyde **2a** (1.0 equiv, −78 °C, Et_2O) in the presence of TMSOTf (3.0 equiv) for 8 h gave all *cis*-configured product **3a** in 35% yield (Scheme 1). In general,

Scheme 1. Synthesis of 2,3,5-Trisubstituted Tetrahydrofurans



1a R_1 = phenyl
1b R_1 = CH_3

2a R_2 = 4-nitrophenyl
2b R_2 = phenyl
2c R_2 = methyl
2d R_2 = isopropyl

3a R_1 = phenyl, R_2 = 4-nitrophenyl (35%)
3b R_1 = methyl, R_2 = 4-nitrophenyl (41%)
3c R_1 = methyl, R_2 = phenyl (38%)
3d R_1 = methyl, R_2 = methyl (30%)
3e R_1 = methyl, R_2 = isopropyl (18%)

a homoallylic alcohol with an alkyl substituent at the terminal carbon of the alkene undergoes the reaction in a 6-endocyclic manner to give a tetrahydropyran.[3f] However, this Prins-type cyclization provided 5-exocyclic products. The reaction was highly stereoselective to give a single stereoisomer of which relative stereochemistry was confirmed to be *all-cis* by single-crystal X-ray crystallography.[8] As with other Prins-type cyclization,[2,3] the complete *cis* stereoselectivity between the C2 and C5 positions must be the result of a cyclic transition state, and the stereochemistry at the C3 center results from the protonation from the α-face during the hydrolysis. Thus, a series of aliphatic or aromatic aldehydes **2a**−**d** with a methyl-substituted homopropargylic alcohol **1b** were tested under the Prins-type cyclization conditions to give the corresponding tetrahydrofuran analogues **3b**−**e** (Scheme 1).

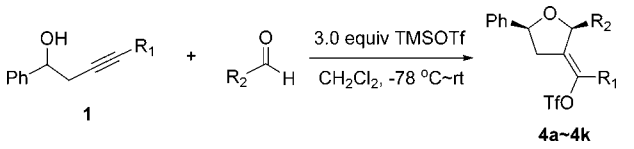
To optimize the reaction conditions, the solvent was changed from Et_2O to CH_2Cl_2 resulting in significant improvement in yield up to 77% (Table 1). However, to our surprise, the obtained tetrahydrofuran analogues were proven to have an exocyclic vinyl triflate moiety instead of the desired 3-acetyl moiety by single-crystal X-ray crystallography.[8] A series of aromatic and aliphatic aldehydes were employed in this cyclization to give the corresponding exocyclic vinyl triflate analogues (**4a**−**k**). Aromatic aldehydes gave the cyclization products in higher yields than aliphatic aldehydes except *o*-nitrobenzenaldehyde (entry 5).

Electron-withdrawing substituents in the aromatic aldehydes also gave higher yields (entry 1 and 4). Two diastereomers (*cis*/*trans*) were obtained in a ratio of 8:1 (entry 4) to 5:1 (entries 7 and 10).

It is of interest that the same conditions except for the solvent (Et_2O or CH_2Cl_2) afforded two different products. It

(8) See the ORTEP drawings in the Supporting Information.

Table 1. Synthesis of 3-Furanylidene Derivatives



entry	R_1	R_2	no.	yield[a] (%)
1	methyl	4-nitrophenyl	**4a**	77
2	methyl	phenyl	**4b**	68
3	methyl	2-naphthyl	**4c**	68
4	methyl	4-chlorophenyl	**4d**	76[b]
5	methyl	2-nitrophenyl	**4e**	35
6	methyl	methyl	**4f**	68
7	methyl	ethyl	**4g**	69[c]
8	methyl	isopropyl	**4h**	60
9	methyl	*n*-pentyl	**4i**	65
10	methyl	2-phenylethyl	**4j**	61[c]
11	phenyl	4-nitrophenyl	**4k**	64

[a] Isolated yields. Two stereoisomers (cis/trans) were obtained in ratios of 8:1[b] and 5:1,[c] respectively, which were determined by ^1H NMR spectroscopy.

is obvious that the propargylic alcohols **1** and an aldehyde make an adduct, an oxocarbenium ion **A** to avoid steric hindrance between the phenyl group of **1** and R group of the aldehyde, resulting in the preferred *cis*-configuration of the two groups (Figure 1). After Prins-type cyclization, the

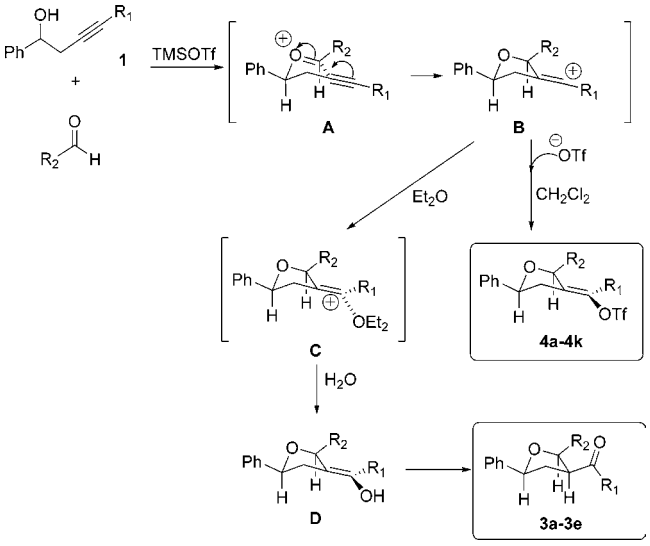


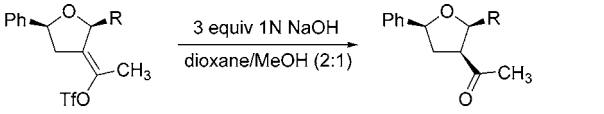
Figure 1. Proposed mechanism for the two different solvent systems.

exocyclic vinyl cation **B** would be transiently formed. It is plausible that the production of exocyclic vinyl triflates **4a**−**k** was the result of trapping the exocyclic vinyl cation **B** by the triflate anion, which attacks the vinyl cation **B** from the front rather than from the back because of steric hindrance

with R group of the aldehyde. On the other hand, tetrahydrofuran products (**3a**−**e**) in Et_2O suggest that the exocyclic vinyl cation **B** would be stabilized by ether solvent itself (refer **C**) and hydrolyzed by H_2O to give the enol **D** which is tautormerized to the corresponding tetrahydrofurans (**3a**−**e**). During the tautomerization, the proton could attack the enol from the less hindered side, that is, α-face to give *all-cis* trisubstituted tetrahydrofurans (**3a**−**e**).

Additionally, the exocyclic vinyl triflates **4a**−**c** could be readily converted to the 3-acetyltetrahydrofurans (**3b**, **3c**, and **5**), respectively, by treatment with aqueous NaOH in a 2:1 mixture of 1,4-dioxane and methanol at room temperature with 97−98% yields (Scheme 2).

Scheme 2. Hydrolysis of 3-Furanylidene Derivatives



4a R = 4-nitrophenyl
4b R = phenyl
4c R = 2-naphthyl

3b R = 4-nitrophenyl (98%)
3c R = phenyl (97%)
5 R = 2-naphthyl (98%)

To expand our synthetic method, the Prins-type cyclization was applied to a chiral nonracemic starting material, (*S*)-glycidol **6** (Scheme 3). (*S*)-Glycidol **6** was treated with benzoyl chloride and 4-DMAP in CH_2Cl_2 to give benzoylated glycidol **7** in 50% yield, which was converted under the known conditions to compound **8**.[9] Compound **8** underwent Prins cyclization to give a furanylidene derivative **9** in 84% yield with a $[\alpha]_D$ value of +72.84. The diasteromeric ratio of compound **9** was over 99:1, which was detected by HPLC.[10]

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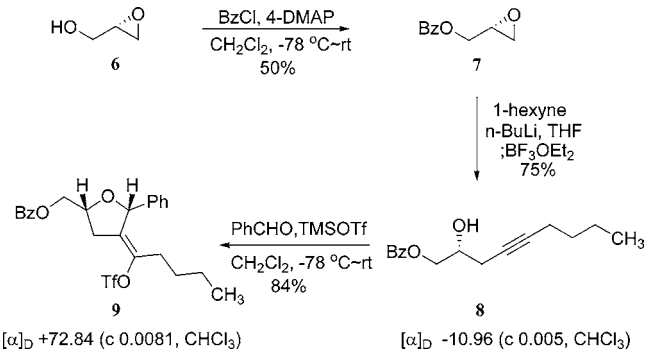
(10) Retention time: 3.63 min, HPLC conditions: column type. CHIRALPAK AD (Daicel Chemical Industries, LTD, Japan); column size, 4.6 mm i.d. × 250 mm; column temperature, rt; flow rate 1.0 mL min^{-1}; detection, 256 nm; eluent, 5% 2-propanol in hexane.

Scheme 3. Application to Chiral Synthesis



$[\alpha]_D$ +72.84 (c 0.0081, $CHCl_3$)

$[\alpha]_D$ -10.96 (c 0.005, $CHCl_3$)

In summary, the key features of this new tetrahydrofuran synthesis are that all *cis*-configured 2,3,5-trisubstituted tetrahydrofurans were synthesized via Prins-type cyclization and that the exocyclic vinyl triflates were obtained, which can be applied for the preparation of various synthetically useful intermediates as a new scaffold. It is also of great interest to note that the exocyclic vinyl cation generated as a result of Prins-type cyclization could be trapped as a vinyl triflate when CH_2Cl_2 was used as a solvent, whereas in ethereal solution the same intermediate underwent hydrolysis to give the corresponding ketone product. Further manipulation of the vinyl triflates such as Suzuki cross-coupling would give more various trisubstituted tetrahydrofurans, which could be good intermediates to synthesize natural products.

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Supporting Information Available: Experimental procedures and spectral data of all new compounds including ORTEP drawings of compounds **3a** and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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