ORGANIC LETTERS

2006
Vol. 8, No. 16
3617−3619

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

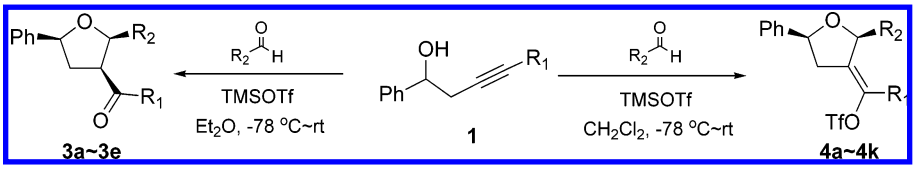
Satish N. Chavre, Hyunah Choo, Joo Hwan Cha, Ae Nim Pae, Kyung Il Choi, and Yong Seo Cho*

Biochemicals Research Center, Korea Institute of Science and Technology, P.O. Box 131, Cheongryang, Seoul 130-650, Korea

ys4049@kist.re.kr

Received June 22, 2006

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.

(1) (a) Hanschke, E. *Chem Ber.* **1955**, *88*, 1053. (b) Stapp, P. R. *J. Org. Chem.* **1969**, *34*, 479.

(2) (a) Gremyachinskiy, D. E.; Samoshin, V. V.; Gross, P. H. *Tetrahedron Lett.* **2003**, *44*, 6587. (a) Muramoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919. (b) Welch, S. C.; Chou, C.; Grubber, J. M.; Assercq, J. M. *J. Org. Chem.* **1985**, *50*, 2668.

(3) (a) Lee, C.-H. A.; Loh, T.-P. *Tetrahedron Lett.* **2006**, *47*, 1641. (b) Chan, K.-P.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 4491. (c) Miranda, L. S. M.; Vasconcellos, M. L. A. A. *Synthesis* **2004**, 1767. (d) Miranda, L. S. M.; Marinho, B. G.; Leitao, S. G.; Matheus, M. E.; Fernandes, P. D.; Vasconcellos, M. L. A. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1573. (e) Cho, Y. S.; Kim, H. Y.; Cha, J. H.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Chang, M. H. *Org. Lett.* **2002**, *4*, 2025. (f) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679.

(4) (a) Heitzman, C. L.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. *Org. Lett.* **2005**, *7*, 2405. (b) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2003**, *5*, 4281. (c) Cassidy, J. H.; Marsden, S. P.; Stemp, G. *Synlett* **1997**, 1411. (d) Taber, D. F.; Song, Y. *J. Org. Chem.* **1996**, *61*, 6706.

(5) For brief review, see: (a) Overman L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (b) Overman L. E. *Aldrichim. Acta* **1995**, *28*, 107. (c) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

(6) (a) Cohen, F.; MacMillan, D. W. C.; Overman, L. E.; Romero, A. *Org. Lett.* **2001**, *3*, 1225. (b) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354. (c) Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748.

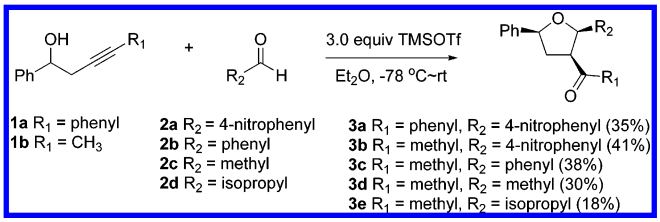
(7) (a) Shin, C.; Chavre, S. N.; Pae, A. N.; Cha, J. H.; Koh, H. Y.; Chang, M. H.; Choi, J. H.; Cho, Y. S. *Org. Lett.* **2005**, *7*, 3283. (b) Mohr, P. *Tetrahedron Lett.* **1993**, *34*, 6251.

10.1021/ol061528x CCC: $33.50
Published on Web 07/04/2006

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



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).

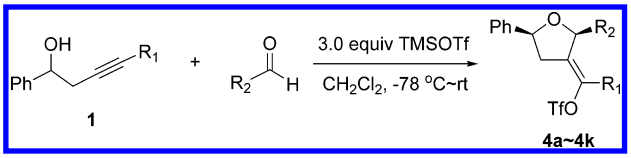
To optimize the reaction conditions, the solvent was changed from Et_2O to CH_2Cl_2 resulting in significant improvement in yield up to 77% (Table 1). However, to our surprise, the obtained tetrahydrofuran analogues were proven to have an exocyclic vinyl triflate moiety instead of the desired 3-acetyl 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

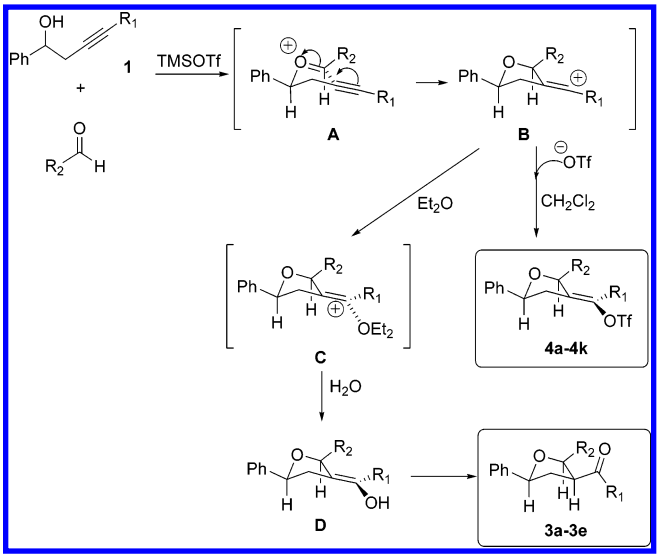


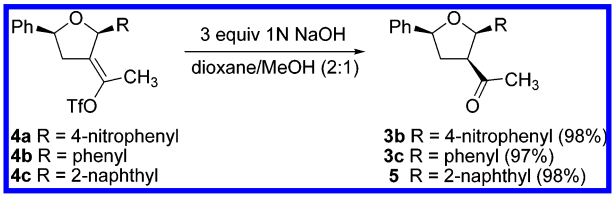
Figure 1. Proposed mechanism for the two different solvent systems.

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

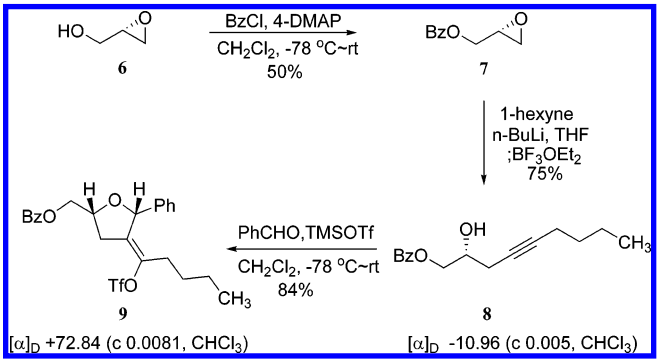


To expand our synthetic method, the Prins-type cyclization was applied to a chiral nonracemic starting material, (*S*)-glycidol **6** (Scheme 3). (*S*)-Glycidol **6** was treated with benzoyl chloride and 4-DMAP in CH_2Cl_2 to give benzoylated glycidol **7** in 50% yield, which was converted under the 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]

(9) Yamaguchi, M.; Hirao, I, *Tetrahedron lett.* **1983**, *24*, 391.

(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



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.

Acknowledgment. This work was supported by the Korea Institute of Science and Technology (2E18800, 2E18970).

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.

OL061528X