Pergamon

Tetrahedron Letters, Vol. 37, No. 21, pp. 3705-3708, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00646-6

Silyl Triflate-Catalyzed Oxonium-Ene Reaction of Lactol Allylic Ethers: A New and Stereocontrolled Route to Substituted Oxygen Heterocycles

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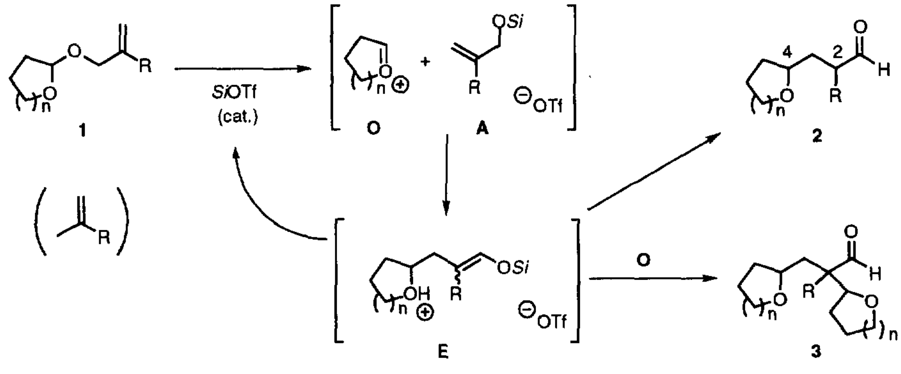
Abstract : An ene-type reaction of lactol-derived allylic ethers is found to be catalyzed by silyl triflates to afford the propionaldehyde-substituted tetrahydrofuranes and -pyrans stereoselectively via the cyclic oxonium ion intermediate and allyloxysilyl moiety derived from the lactol allylic ethers. Copyright © 1996 Elsevier Science Ltd

A substituted oxygen heterocycle with side chain chirality is a characteristic feature of natural products and, hence, methods for assembling these structural units in a stereocontrolled fashion have attracted current attention.[1] During the course of our research project to develop the carbonyl-ene reaction[2,3] as a stereocontrolled method in organic synthesis, we made unanticipated observations: Propionaldehyde unit-substituted tetrahydrofuran was obtained with high diastereoselectivity over the 1,3-relationship between the newly created stereogenic centers in an attempted oxonium-ene reaction[4] of γ-butyrolactol-derived allylic ethers with a simple olefin as an external ene component (Scheme 1). The formation of propionaldehyde-substituted tetrahydrofuran is presumably due to the ene reaction of the allyloxysilyl moiety into the cyclic oxonium ion.[5] The mechanistic and stereochemical features of the silyl triflate-catalyzed oxonium-ene reaction are the subject of this communication.



Scheme 1

Representative results are summarized in Table I. To a dichloromethane solution of lactol-derived allylic ether **1a** (n=1, R=Me) was added a Lewis acid such as methylaluminum dichloride ($MeAlCl_2$)[6] in a stoichiometric amount (100 mol%) at -78 °C[7] to give the tetrahydrofuranyl aldehyde **2a** with some detectable amount of bis-tetrahydrofuran **3a**. The bis-furan **3a** is obtained probably from the reaction of the oxonium ion

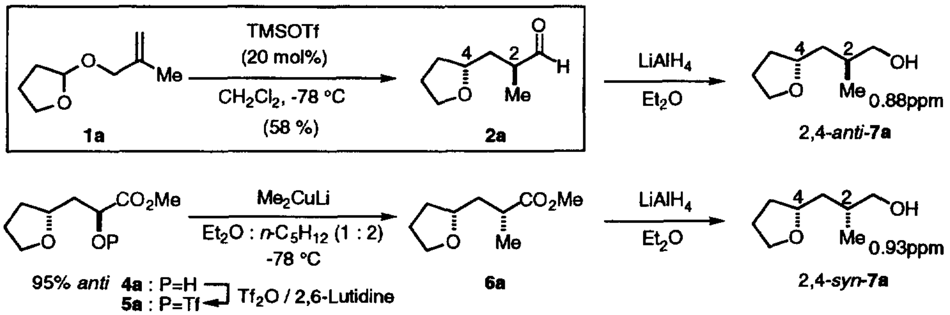
(**O**) with the metal enolate intermediate (**E**) formed through the oxonium-ene reaction with allyloxymetal species (**A**). Lewis acids such as aluminum chloride, boron trifluoride, and tin tetrachloride provide a low yield even by using 100 mol% of the Lewis acid (entries 1, 2, and 3). The use of silyl trifluoromethanesulfonate instead of aluminum chloride as the Lewis acid was then examined in order to trap the enolate intermediate (**E**) as the silyl enol ether.

We have, thus, found that silyl triflates can be used as the Lewis acid catalyst (20 ~ 30 mol%)[8] for this type of oxonium-ene reaction to give a higher chemical yield of the furanyl aldehyde **2a**, although, not in the silyl enol ether form (entries 4, 5, and 8). An enhanced level of diastereoselectivity (84%) was obtained at lower temperature (-94 °C) over the newly created stereogenic centers, C-2 and C-4 (entry 6). In the reaction of the sterically demanding substrate **1b** (n=1, R=*iso*-Pr), no bis-furan formation was observed (entries 11 and 12). In toluene or acetonitrile, a slightly lower level of diastereoselectivity was observed. Pyranyl aldehyde **2a'** (n=2, R=Me) was also obtained in a similar level of chemical yield and diastereoselectivity after prolonged reaction time (entry 13).

Table I. Silyl Triflate-Catalyzed Oxonium-Ene Reaction of Lactol Allylic Ethers. [a]

Entry	R (n)	Lewis acid	Mol%	Solvent	Temp (°C)	Time (h)	Aldehyde **2** % Yield [b]	*Anti* : *Syn*
1	Me (1)	$MeAlCl_2$	100	CH_2Cl_2	-78	6	12	77 : 23
2	Me (1)	$SnCl_4$	100	CH_2Cl_2	-78	2	30	77 : 23
3	Me (1)	$BF_3.Et_2O$	100	CH_2Cl_2	-78	3	10	78 : 22
4	Me (1)	TMSOTf	100	CH_2Cl_2	-78	1	40 (9)	80 : 20
5	Me (1)	TMSOTf	20	CH_2Cl_2	-78	1	58 (9)	78 : 22
6	Me (1)	TMSOTf	20	CH_2Cl_2	-94	1	44 (9)	84 : 16
7	Me (1)	TMSOTf	20	CH_3CN	-20	0.3	22	53 : 47
8	Me (1)	TBDMSOTf	20	CH_2Cl_2	-78	3	50 (8)	82 : 18
9	Me (1)	TfOH	20	CH_2Cl_2	-78	1	33	78 : 22
10	Me (1)	TfOH	20	CH_2Cl_2	0	0.3	42	55 : 45
11	iso-Pr (1)	TMSOTf	20	CH_2Cl_2	-78	0.3	39 [c]	85 : 15
12	iso-Pr (1)	TMSOTf	20	toluene	-78	2	32 [c]	67 : 33
13	Me (2)	TMSOTf	20	CH_2Cl_2	-78	1.5	40	76 : 24

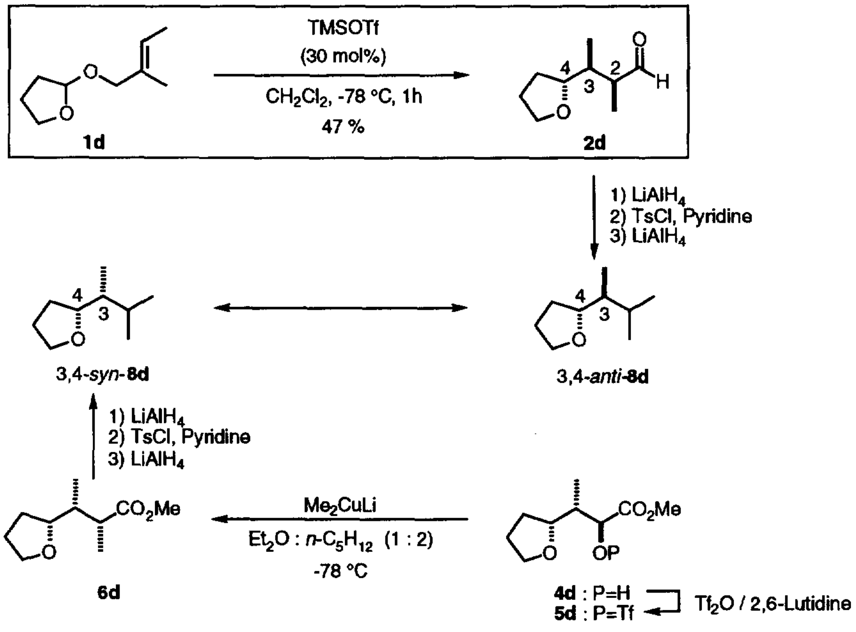
[a] The reaction was carried out as described in the note 8. [b] The values in parenthesis refer to those of bis-furan **3**. [c] No bis-furan formation is observed.



Scheme 2

2,4-*Anti* stereochemistry of the product **2a** is determined through the ^{1}H NMR comparison with the authentic 2,4-*syn*-**7a**, which is obtained through the transformation from the authentic 2,4-*anti*-hydroxy furan **4a**[9] via the inversion process[10] of α-trifluoromethanesulfonyloxy ester **5a** with lithium dimethylcuprate in ether / pentane (Scheme 2).

In the reaction of 2',3'-dimethylallyl ether **1d**, the three contiguous stereogenic centers were generated (Scheme 3). Four possible diastereomers are obtained in a ratio of 7 : 74 : 4 : 15 at -78 ° C. Stereochemistry of the major product **2d** is determined to be 3,4-*anti* after the transformation to the 3,4-*anti*-**8d**, of which the 3,4-*syn*-isomer is obtained from the authentic 3,4-*syn*-**4d**[9].



Scheme 3

2,4-*Anti*-3,4-*anti* stereochemistry of the products **2** has some implications into the oxonium-ene mechanism involving the internal proton shift (Figure 1). There may be an electrostatic association between the oxonium ion and the allyloxysilyl species to hold the *synclinal* six-membered transition states[11] leading to the 3,4-*anti* relationship via the oxonium-ene-type reaction with the allyoxysilyl moiety. Thus, an interior-proton shift would provide the 2,4-*anti* stereochemistry and lead to the re-generation of the silyl triflate catalyst.

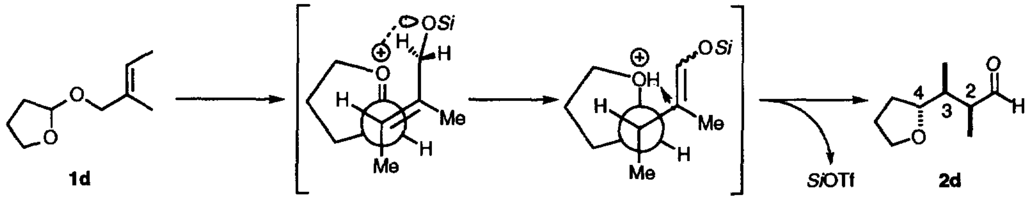


Figure 1

In summary, we have disclosed herein the silyl triflate-catalyzed oxonium-ene reaction of lactol-derived allylic ethers, which provides a new and stereoselective method for the propionaldehyde-substituted tetrahydrofuranes and -pyrans. Further studies along these lines are now underway.

References and Notes

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6 Me_2AlCl provides lower yield of the product **2**.

7 At 0 °C, only low level of diastereoselectivity (1 : 1) was observed.

8 Typical experimental procedure is as follows. To a dichloromethane solution of lactol-derived allylic ether **1a** (n=1, R=Me) was added trimethylsilyl triflate (TMSOTf) in a catalytic amount (20 mol%) at -78 °C. After 1 hour, the usual work-up followed by silica gel chromatography gave the furanyl aldehyde **2a** in 58% yield with 80% diastereoselectivity.

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(*Received in Japan* 18 *December* 1995; *revised* 18 *March* 1996; *accepted* 3 *April* 1996)