

A RING OPENING REACTION OF OXETANES WITH LITHIUM
ACETYLIDES PROMOTED BY BORON TRIFLUORIDE ETHERATE¹

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(Received in Japan 8 August 1984)

Abstract - Several substituted oxetanes were treated with lithium acetylides in the presence of boron trifluoride etherate to give β -hydroxyacetylenes. The reaction conditions were varied and several synthetic features of the present reaction were revealed.

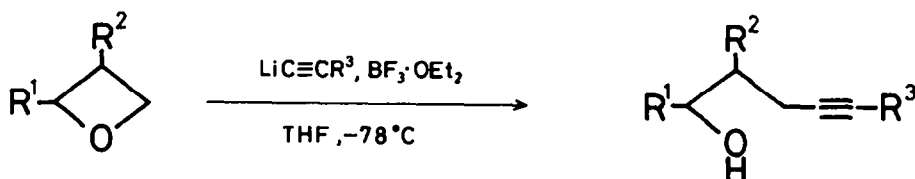
The ring opening reaction of oxiranes with a variety of C-nucleophiles to give carbon homologated alcohols is a well known synthetic method in organic chemistry.² The strain in the three-membered ring facilitates the ether cleavage. Oxetanes, a higher homologue of oxiranes, also would be a good substrate for three carbon homologation by the ring opening, considering the strain of the four-membered ring. Only a few reports,^{3,5} however, appeared concerning this carbon-carbon bond formation reaction. One of the reasons for this deficiency would be low reactivity of the oxetanes toward cleavage. It was also mentioned in a literature,⁴ that the oxygen atoms of oxetanes were more basic than that of oxiranes. Thus, oxetanes were suggested to be more reactive in the presence of the Lewis acid.⁵

The alkylation of oxetanes with metal acetylides to give β -hydroxyacetylenes is generally unsatisfactory. Thus, the use of magnesium acetylides often leads to halohydrin formation by the ring opening with halide anions.⁶ And, in the case of lithium acetylide, no β -hydroxyacetylene was detectable by the reaction with oxetane in THF at r.t.

In this report, we wish show that in the presence of a Lewis acid, oxetanes are effectively activated to react with lithium acetylides, and β -hydroxyacetylenes are obtained in high yield. The reaction conditions were examined in detail and some discussion of the reactive species is presented.


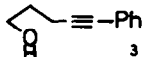
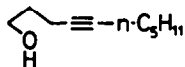
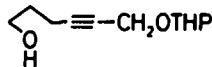
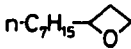
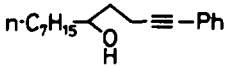
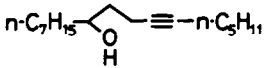
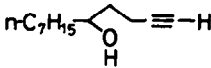

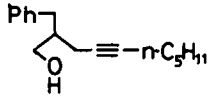
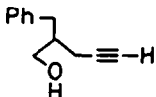
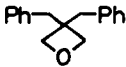
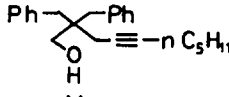
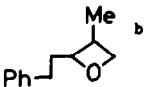
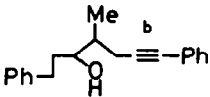
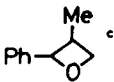
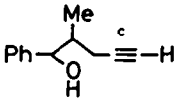
RESULTS AND DISCUSSIONS

The results of the reaction shown in Scheme 1 are summarized in Table I. The reaction was



Scheme 1

Table I. Synthesis of β -Hydroxyacetylenes.^a

entry	oxetane	acetylene	product	%, yield
1		HC≡CPh		84 (82) ^d
2		HC≡Cn-C ₅ H ₁₁		quant.
3		HC≡CCH ₂ OTHP		92
4		HC≡CPh		67
5		HC≡Cn-C ₅ H ₁₁		84
6		HC≡CH		93
7		HC≡Cn-C ₅ H ₁₁		67
8		HC≡CH		91
9		HC≡Cn-C ₅ H ₁₁		79
10		HC≡CPh		87
11		HC≡CH		62

^a The reaction was carried out as depicted in the General Procedure. And isolated yields are shown.

^b A 1:1 mixture of stereoisomers.

^c A 1:1.5 mixture of stereoisomers.

^d The reaction was carried out with 5 mmol of oxetane.

relatively insensitive to the substituents on the oxetane ring, and 2,3- or 3,3-disubstituted oxetanes as well as 2- or 3-monosubstituted ones reacted smoothly at the less hindered site (entries 4, 5, 6, 10, 11). In case of 2,3-disubstituted oxetanes, the diastereomer ratio

of the starting materials is preserved in the ring opening reaction (entries 10, 11). Thus, cis- and trans-2,3-disubstituted oxetanes are both reactive under these conditions. When oxetanes were treated with mono-lithiated acetylene, generated from acetylene and n-

butyllithium at -78°C , monoalkylated products, 1-alkyn-5-ols were obtained in high yield, and no dialkylated product was detected (entries 6, 8, 11).

In order to reveal synthetic features of the reaction, we examined the reaction conditions in detail using the reaction of trimethylene oxide (1) and lithium phenylacetylide (2) (entry 1, Table I). At first, the molar ratio of the reagents was changed. A 3-fold excess of 2 was required to obtain 5-phenyl-4-pentyn-1-ol (3) in high yield (84%); with only 1.0 equiv. of the nucleophile, 59% yield was still realized (Table II).

Table II. The Effect of the Molar Ratio of 1, 2, and $\text{BF}_3 \cdot \text{OEt}_2$ on the yield of 3.

molar ratio (mmol)			<u>3</u> , yield (%)
<u>1</u>	<u>2</u>	$\text{BF}_3 \cdot \text{OEt}_2$	
1.0	1.0	1.0	59
1.0	1.5	1.5	69
1.0	2.0	2.0	71
1.0	3.0	3.0	84

^a The reaction was carried out in THF at -78°C .

Variation of the amount of the Lewis acid gave some information concerning the reaction intermediate. As shown in Figure I, the molar ratio of 1 : 2 : $\text{BF}_3 \cdot \text{OEt}_2$ = 1 : 3 : 3 gave a

high yield of the product 3, and the decrease in the amount of $\text{BF}_3 \cdot \text{OEt}_2$ diminished the yield of the alcohol 3. Without $\text{BF}_3 \cdot \text{OEt}_2$, no alcohol 3 was detected even reacting at r.t. It should be noted that the use of the molar ratio of 1 : 2 : $\text{BF}_3 \cdot \text{OEt}_2$ = 1 : 3 : 0.1 (mmol) gave 3 in 34% (0.34 mmol) yield, which indicates that the Lewis acid can function as a catalyst. As for the reactive species, trivalent alkynyl boranes 4, which we initially assumed⁷ to be involved, are not responsible for these reactions, because they require a stoichiometric amount of $\text{BF}_3 \cdot \text{OEt}_2$ to give high yields of 3. The reactive intermediate is assumed to be lithium acetylide, which attacks oxetane activated with the Lewis acid. At present, we can not rule out tetravalent alkynyl borate 5 as a reactive species.⁸ Lithium acetylide (2), however, seems more probable, as the use of other Lewis acids such as TiCl_4 or SnCl_4 also leads to ring opening product (in low yield, 31% and 14% respectively, under similar reaction conditions).⁹



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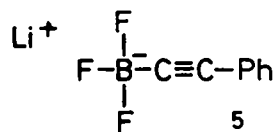
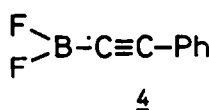
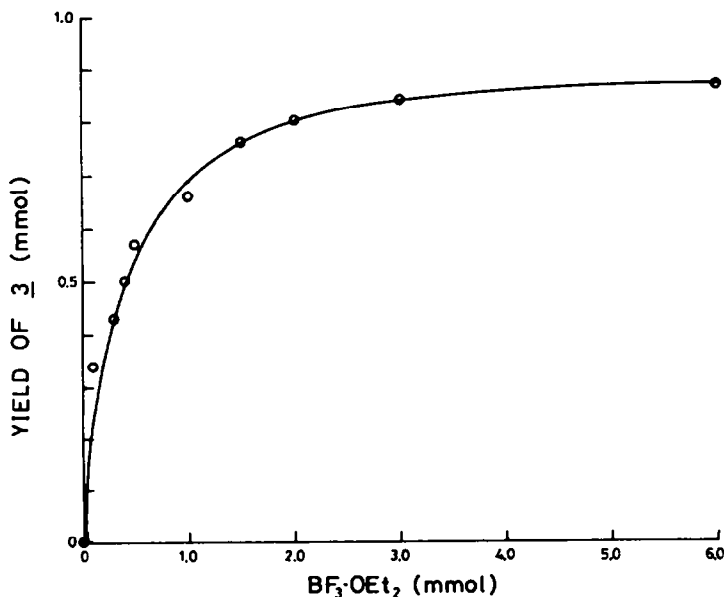


Figure I. The Yield of 3 by the Reaction of 1 (1.0 mmol) and 2 (3.0 mmol) in the Presence of $\text{BF}_3 \cdot \text{OEt}_2$ (0-6.0 mmol) in THF at -78°C .



Next, the reaction was conducted in various solvent systems (Table III), and THF was found to be most effective. Notably, the reaction was not completely suppressed by the addition of excess hexamethylphosphoryl amide (HMPA), a strongly coordinating co-solvent. In the presence of tetramethylethylenediamine (TMEDA), however, no detectable acetylenic alcohol **3** was formed.

Table III. The Effect of the Solvents on the Reaction of **1** and **2**.^a

solvent	3 , yield (%)
THF	84
THF-HMPA (5:1)	55
THF-TMEDA (5:1)	0
DME	72
Et ₂ O	50
toluene	50
CH ₂ Cl ₂	22
hexane	trace

^a The reaction was carried out at -78°C using **1** (1.0 mmol), **2** (3.0 mmol), and BF₃·OEt₂ (3.0 mmol).

Variations in the procedure were examined by employing three methods: (A) BF₃·OEt₂ was added to a THF solution of oxetane **1** and acetylide **2**; (B) oxetane **1** was added to a THF solution of **2** and BF₃·OEt₂; (C) acetylide **2** was added to a THF solution of **1** and BF₃·OEt₂. These variations did not affect the yield of **3**, if the reaction was carried out at -78°C. Thus, **3** was obtained in about 80% yield according to the procedure A, B, or C (Table IV), showing that the reagents were stable at this temperature. A difference was observed at higher temperatures. The yield of **3** gradually decreased as the reaction temperature was raised using procedure A, although 35% yield was realized even at 0°C. Employing procedure B, however, the yield dramatically changed as the temperature was raised, from an 80% yield at -65°C to 18% at -55°C (Table IV). The results may be explained as follows. At the lower temperature, lithium acetylide **2** and BF₃·OEt₂ do not react to form inactive trivalent alkynyl borane **4**. At higher temperatures, **4** is formed rapidly, and the yield of **3** falls especially in procedure B, where BF₃·OEt₂ and **2** are mixed prior

to the addition of oxetane. These results also support the conclusion concerning the reactive species.

Table IV. The Effect of Temperature and Order of Addition of Reagents on the Reaction of **1** and **2**.^a

temperature (°C)	3 , yield (%)		
	procedure ^b	A	B C
0		35	0
-40		69	
-50			0
-55			18
-60			61
-65			80
-78		84	81 79

^a The reaction was carried out using **1** (1.0 mmol), **2** (3.0 mmol), and BF₃·OEt₂ (3.0 mmol).

^b Procedure A: BF₃·OEt₂ was added to a THF solution of **1** and **2**. B: Oxetane (**1**) was added to a THF solution of **2** and BF₃·OEt₂. C: Acetylide **2** was added to a THF solution of **1** and BF₃·OEt₂.

In summary, lithium acetylides, in the presence of BF₃·OEt₂, act as an exceedingly useful nucleophile for the ring opening of oxetanes to give δ -hydroxyacetylenes. The Lewis acid is required for successful application, and it is thought to function by activation of the oxetanes.

EXPERIMENTAL

¹H-NMR and ¹³C-NMR spectra were obtained on a JEOL JNM-FX-60. Chemical shift values, all in CDCl₃, are given in ppm relative to internal Me₄Si. IR spectra were recorded on a Shimadzu IR-408. High resolution mass spectra were taken with a JEOL JMS-DX-300. All distillations were performed by kugel-rohr using a Shibata Glass Tube Oven GTO-250, and bath temperatures were recorded. Chromatographies (silica gel) were conducted on Wako gel B5F or C-200 (Wako Pure Chemical Industries LTD.).

Oxetane (**1**) was purchased from Tokyo Kasei Kogyo, Co., LTD. Other substituted oxetanes were prepared from the corresponding 1,3-diols according by a literature method.¹⁰

2-Heptyloxetane. bp 100°C (15 mm); ¹H-NMR δ 0.7-1.0 (3H,m), 1.0-1.8 (12H,m), 2.0-2.9 (2H,m), 4.3-5.0 (3H,m). IR (neat) 2910, 975 cm⁻¹. MS m/e 127 (M⁺-29).

3-Benzyloxetane. ¹H-NMR δ 2.8-3.7 (3H,m), 4.43 (2H,t,J=6Hz), 4.76 (2H,t,J=6Hz), 6.9-7.4 (5H,m). IR (neat) 2850, 975, 720, 700 cm⁻¹.

3,3-Dibenzoyloxetane. bp 170°C (0.6 mm); ¹H-NMR δ 2.90 (4H,s), 4.54 (4H,s), 6.8-7.3 (10H,m). IR (neat) 2850, 980, 745, 700 cm⁻¹. Exact mass calcd for C₁₇H₁₈O: 238.1356. Found: 283.1346.

3-Methyl-2-phenethyloxetane. bp 90°C (1 mm); ¹H-NMR δ 1.14 (1.5H,d,J=7Hz), 1.18 (1.5H,d,J=7Hz), 1.8-2.2 (2H,m), 2.4-3.1 (3H,m), 4.0-5.0 (3H,m), 7.22 (5H,s). ¹³C-NMR δ 13.4 and 17.8, 30.4 and 31.0, 31.9 and 33.6, 35.8 and 38.7, 75.0 and 75.6,

84.0 and 89.0, 125.8, 128.3, 141.5 and 141.7. IR (neat) 2900, 1600, 1490, 1450, 750, 700 cm^{-1} . Exact mass calcd for $\text{C}_{12}\text{H}_{16}\text{O}$: 176.1200. Found: 176.1196. This compound was a 1:1 mixture of stereoisomers.

3-Methyl-2-phenyloxetane. ^{12}C $^1\text{H-NMR}$ δ 0.78 (1.8H,d,J=7Hz), 1.30 (1.2H,d,J=7Hz), 2.7-3.6 (1H,m), 4.0-5.0 (2H,m), 5.33 (0.4H,d,J=7Hz), 5.91 (0.6H,d,J=8Hz), 7.1-7.5 (5H,m). This compound was a 1.5:1 mixture of stereoisomers.

General Procedure for the Synthesis of β -Hydroxyacetylenes from Mono-substituted Acetylenes and Oxetanes. Under a nitrogen atmosphere, a n-hexane solution of n-butyllithium (2.0 ml, 3.0 equiv.) was added to a THF (4 ml) solution of 1-alkyne (3.0 equiv.) at -78°C and the mixture was stirred for 10 min. The oxetane (0.5-1.0 mmol) in THF (2 ml), and boron trifluoride etherate (3.0 equiv.), were added successively. After stirring 30-60 min at -78°C , the reaction was quenched by adding aqueous ammonium chloride and organic materials were extracted by ethyl acetate. The organic phase was washed with water and brine, dried, and evaporated. The residue was purified by thin layer or column chromatography on silica gel with ether: hexane (1:3) as the eluent.

5-Phenyl-4-pentyn-1-ol (3). ^{13}C Yield 84%. bp 160°C (3 mm); $^1\text{H-NMR}$ δ 1.6-2.1 (2H,m), 2.17 (1H,s), 2.52 (2H,t,J=7Hz), 3.79 (2H,t,J=6Hz), 7.1-7.5 (5H,m). IR (neat) 3300, 2240, 750, 690 cm^{-1} . Exact mass calcd for $\text{C}_{11}\text{H}_{12}\text{O}$: 160.0888. Found: 160.0964. The reaction was also carried out with 5 mmol of oxetane (1), giving 81% of 3.

4-Decyn-1-ol. ^{14}C Quantitative yield; bp 140°C (3 mm); $^1\text{H-NMR}$ δ 0.7-1.1 (3H,m), 1.1-1.9 (9H,m), 1.9-2.4 (4H,m), 3.6-4.0 (2H,m). IR (neat) 3350, 2220 cm^{-1} .

6-(2H-tetrahydropyran-2-yloxy)-4-hexyn-1-ol. Yield 92%. bp 170°C (3 mm); $^1\text{H-NMR}$ δ 1.3-2.0 (9H,m), 2.1-2.5 (2H,m), 3.4-4.0 (4H,m), 4.22 (2H,t,J=2Hz), 4.80 (1H,s). IR (neat) 3350, 2220 cm^{-1} . Exact mass calcd for $\text{C}_{11}\text{H}_{18}\text{O}_3$: 198.1256. Found: 198.1234.

1-Phenyl-1-undecyn-5-ol. Yield 67%. bp 180°C (3 mm); $^1\text{H-NMR}$ δ 0.7-1.0 (3H,m), 1.1-1.6 (12H,m), 1.6-1.9 (3H,m), 2.55 (2H,t,J=7Hz), 3.5-4.0 (1H,m), 7.1-7.5 (5H,m). IR (neat) 3300, 2230, 755, 690 cm^{-1} . Exact mass calcd for $\text{C}_{16}\text{H}_{20}\text{O}$: 258.1983. Found: 258.1978.

11-Heptadecyn-8-ol. Yield 84%. bp 170°C (3 mm); $^1\text{H-NMR}$ δ 0.6-1.1 (6H,m), 1.1-1.8 (21H,m), 1.9-2.5 (4H,m), 3.5-3.9 (1H,m). IR (neat) 3300 cm^{-1} . Exact mass calcd for $\text{C}_{17}\text{H}_{32}\text{O}$: 252.2452. Found: 252.2431.

2-Benzyl-4-decyn-1-ol. Yield 67%. bp 195°C (3 mm); $^1\text{H-NMR}$ δ 0.7-1.1 (3H,m), 1.1-1.7 (7H,m), 1.96 (1H,s), 2.0-2.3 (4H,m), 2.68 (2H,d,J=7Hz), 3.64 (2H,d,J=5Hz), 7.22 (5H,s). IR (neat) 3300, 740, 700 cm^{-1} . Exact mass calcd for $\text{C}_{14}\text{H}_{18}\text{O}$: 244.1828. Found: 244.1842.

2,2-Dibenzyl-4-decyn-1-ol. Yield 79%. bp 200°C (1 mm); $^1\text{H-NMR}$ δ 0.7-1.1 (3H,m), 1.1-1.7 (7H,m), 1.87 (2H,t,J=2Hz), 2.1-2.4 (2H,m), 2.82 (4H,s), 3.23 (2H,s), 7.28 (10H,s). IR (neat) 3400, 750, 725, 700 cm^{-1} . Exact mass calcd for $\text{C}_{24}\text{H}_{30}\text{O}$: 334.2295. Found: 334.2273.

1,7-Diphenyl-4-methyl-6-heptyn-3-ol. Yield 87%. bp 210°C (3 mm); $^1\text{H-NMR}$ δ 1.02 (1.5H,d,J=6Hz), 1.06 (1.5H,d,J=6Hz), 1.6-2.0 (4H,m), 2.3-3.0 (4H,m), 3.4-4.0 (1H,m), 7.0-7.5 (10H,m). IR (neat) 3350, 2220, 760, 690 cm^{-1} . Exact mass calcd for $\text{C}_{20}\text{H}_{22}\text{O}$: 278.1669. Found:

278.1655. A 1:1 mixture of diastereoisomers estimated by $^1\text{H-NMR}$.

General Procedure for the Synthesis of β -Hydroxyacetylenes from Acetylene and Oxetanes. The reactions were carried out as described above except that the lithium acetylide was generated by introducing acetylene to a THF-hexane solution of n-butyllithium (4-5 equiv.) at -78°C for 20-30 min.

1-Dodecyn-5-ol. Yield 84%. bp 150°C (3 mm); $^1\text{H-NMR}$ δ 0.7-1.0 (3H,m), 1.0-1.8 (14H,m), 1.95 (1H,t,J=2Hz), 2.1-2.6 (3H,m), 3.5-3.9 (1H,m). IR (neat) 3350, 3280, 2120 cm^{-1} . Exact mass calcd for $\text{C}_{12}\text{H}_{20}\text{O}$: 183.1750. Found: 183.1740 ($\text{M}^+ + \text{H}$).

2-Benzyl-4-pentyn-1-ol. Yield 91%. bp 170°C (0.8 mm); $^1\text{H-NMR}$ δ 2.00 (1H,t,J=2Hz), 2.1-2.3 (3H,m), 2.67 (2H,d,J=6Hz), 2.68 (1H,s), 3.60 (2H,d,J=2Hz), 7.20 (5H,s). IR (neat) 3400, 2130, 740, 700 cm^{-1} . Exact mass calcd for $\text{C}_{12}\text{H}_{14}\text{O}$: 174.1045. Found: 174.1065.

2-Methyl-1-phenyl-4-pentyn-1-ol. Yield 62%. bp 140°C (4 mm); $^1\text{H-NMR}$ δ 0.83 (1.2H,d,J=7Hz), 1.00 (1.8H,d,J=7Hz), 1.7-2.1 (3H,m), 2.1-2.5 (2H,m), 4.47 (0.4H,d,J=7Hz), 4.67 (0.6H,d,J=5Hz), 7.27 (5H,s). IR (neat) 3400, 3370, 2130, 760, 700 cm^{-1} . Exact mass calcd for $\text{C}_{11}\text{H}_{12}\text{O}$: 175.1122. Found: 175.1120 ($\text{M}^+ + \text{H}$). A 1.5:1 mixture of stereoisomers estimated by $^1\text{H-NMR}$.

This work was partially supported by a Grant-in-Aid for Encouragement of Young Scientists No. 58750675 from the Ministry of Education, Science and Culture.

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