Preparation of Novel Dideuterioallyl Mercaptan

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Mass spectrometry is known to be the most accurate method for the quantitative analysis of flavor ingredients in food. For successful analysis with the method called 'stable isotope dilution assay', the isotopically labeled compound of each component is necessary.\(^1\) A difference in mass units of two or more gives the best results in the quantitative determination of each ingredient.

In order to analyze the allyl mercaptan present in the odor of bulgogi (a popular Korean dish) we needed to have allyl mercaptan-1,1- d_2 or allyl mercaptan-2,3- d_2 . Neithr compound has been reported in the literature. One of the logical schemes for the synthesis is to preparing corresponding allyl alcohol (2) and converting it to the corresponding mercaptan. Allyl alcohol- d_5 (CD₂=CDCD₂OH) is commercially available, but the -1,1- d_2 or -2,3- d_2 alcohol is not. Allyl alcohol-1,1- d_2 has been reported to be prepared by reduction of acryloyl chloride with LiAlD₄.²

There are numerous citations of the use of LiAlH₄ for the reduction of α , β -unsaturated carboxylic acids to alkenols. For example, a reference book states that lithium aluminum hydride reduces *exclusively* the carbonyl group, even in an unsaturated acid with α , β -conjugated double bonds.³ The reference that was cited for the statement reported the reduction of acetylenedicarboxylic acid to 2-butene-1,4-diol (84% yield with 98% purity), fumaric acid to 2-butene-1,4-diol (78% yield), acrylic acid (1) to allyl alcohol (2, 68% yield), and propiolic acid (5) to allyl alcohol (2, 85% yield).⁴

Allyl alcohol (2) was not reduced to *n*-propyl alcohol (3) under the conditions, but such reduction was accomplished in 26% yield by heating the mixture in dibutyl ether at 100 °C for 3 h.⁵ It should be pointed out that 0.75 mole of LiAlH₄ is required for reduction of 1 mole of RCOOH to RCH₂OH and H₂. But 0.283 mole of 1 and 0.35 mole of LiAlH₄ in ether was reacted at room temperature for 16 h for the reduction of 1 to 2.⁴

Therefore, we attempted the reduction of acrylic acid (1) with LiAlH₄ to establish the suitable reaction conditions which would be adapted for the reduction with LiAlD₄.

To our surprise the reaction was not as simple as described in the literature.^{3,4} When we slowly added acrylic acid (1) in ether to a mixture of LiAlH₄ in ether at 0 °C, refluxed for 18 h, and followed the typical work-up procedure (H₂O and NaOH) involving extraction with diethyl ether, the reaction mixture was quite complex. Its NMR spectrum clearly showed the presence of allyl alcohol (2) and *n*-propyl

alcohol (3) in a ratio of *ca.* 1 : 8 (Table 1, Entry 1). There were also some unidentified compounds which could have formed from dimer (1') and trimer (1") of 1.

$$CH_{2}=CH \xrightarrow{\square}OH \xrightarrow{LiAlH_{4}} CH_{2}=CHCH_{2}OH + CH_{3}CH_{2}CH_{2}OH$$

$$1 \qquad 2 \qquad 3$$

$$+ CH_{3}CH_{2} = OH + unidentified compounds$$

$$4 \qquad cH_{2}=CH \xrightarrow{\square}OH = CH_{2}CH_{2} \xrightarrow{\square}OH$$

$$1' \qquad CH_{2}=CH \xrightarrow{\square}OH + CH_{2}CH_{2} \xrightarrow{\square}OH$$

$$1 \qquad CH_{2}=CH \xrightarrow{\square}OCH_{2}CH_{2} \xrightarrow{\square}OCH_{2}CH_{2} \xrightarrow{\square}OH$$

On the other hand, when the aqueous layer was acidified with aq. HCl and then extracted with diethyl ether, the starting acid (1) was recovered in about 5% yield along with propionic acid (4) in about 45% yield. The relative ratio of the products varied depending on the reaction conditions, but the recovery of the acids 1 and 4 was more than 50% in our attempts. Compound 3 was the major component in the ethereal extract as shown in Table 1. It seems apparent that the reduction of 1 cannot be the method of choice because not only was the yield of 2 low but the separation of 2 from the mixture was difficult.

Propiolic acid (5) has also been known to give allyl alcohol (2).⁴ Reduction with LiAlD₄ may give trideuterated allyl alcohol, which should be acceptable for preparation of a deuterated allyl mercarptan and eventually for the analysis of the odor component. However, our attempt to reduce 5 with LiAlH₄ was also troublesome because not only 2 but 3 and propargyl alcohol (6) were also present in the reaction mixture (Table 1, Entries 3, 4).

$$H = \frac{O}{\parallel}OH = \frac{\text{LiAlH}_4}{\text{OH}} + \frac{1}{2} + \frac{1}{3} + \text{unidentified compounds}$$

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Table 1. Reduction of Acrylic Acid (1). Propiolic Acid (5), and Propargyl Alcohol (6) with LiAlH₄ in Diethyl Ether

Exp.	Subs."	LAH	Conditions	Products (%) ^h
1	1, 32	44	1 to LAH at 0° reflux 18 h	2 (5), 3 (42), 1 (5)°, 4 (45)
2	1. 87	66	1 to LAH at 0° reflux 8 h	2 (8), 3 (34), 1 (15)°, 4 (35)
3	5. 49	98	5 to LAH at 0° 0° 2 h, reflux 8 h	2 (44), 3 (50), 6 (6)
4	5 , 49	98	5 to LAH at 0° reflux 2 h	2 (40), 3 (51)
5	6, 52	39	5 to LAH at 0° RT 20 h, reflux 6 h	2 (35). 6 (60)
6	6. 34	34	5 to LAH at 0° reflux 48 h	2 (70). 6 (5)
7	6, 68	34	5 to LAH at 0° RT 20 h, reflux 6 h	2 (40). 6 (50)

[&]quot;Mmole, "Relative percentage, "Recovery percent,

The apparent failure to obtain **2** from **1** or **5** led us to investigate an alternative method, which is the reduction of **6** to **2**. There are a few reports⁶⁻⁸ related to similar reaction with alkynols of HOCR¹R²C=C-R³ to allyl alcohols HOCR¹R²CH=CH-R³, but reduction of **6** (R¹=R²=H) to **2** has not been reported. Since we have to have a dideuterated allyl alcohol, any procedure by which D₂ component should add to a C-C triple bond should be useful, and naturally, we became interested in the mechanism of the conversion of **6** to **2**.

When a mixture of $\bf 6$ and LiAlH₄ (1:1 mole ratio) in diethyl ether was heated at reflux for $\bf 48$ h and then quenched

with aqueous NaOH, **2** was the sole product in 70% yield (Table 1, Entry 6). On the other hand, quenching with NaOD in D_2O gave 3-deuterioallyl alcohols, 7 and **8** in a ratio of 10:1. Similar reaction of **6** with LiAlD₄ and subsequent quenching with aqueous NaOH gave 2-deuterioallyl alcohol **9**. Alternatively, quenching with NaOD in D_2O gave a mixture of 2,3-dideuterioallyl alcohols **10** and **11** in a ratio of 9:1.

6 LiAlH₄ [Int]
$$H_{\gamma c}$$
 $H_{\gamma c}$ H_{β} $H_{\gamma c}$ $H_{\gamma c}$

The structures of the reduction products were readily confirmed by NMR spectroscopy as shown in Figure 1. The signal of H_{β} appears in the most downfield region (δ 5.97) as an overlapping *ddt* with coupling constants of 17.2 ($J_{\beta,n}$),

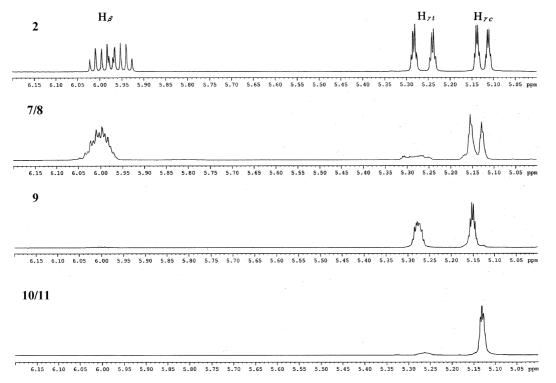


Figure 1. NMR spectra of the vinyl portion of allyl and deuterated allyl alcohols.

10.5 $(J_{\beta,\kappa})$ and 5.1 $(J_{\beta,\alpha})$ Hz. The signals of H_{γ} and H_{γ} appear at δ 5.26 and 5.13, respectively. The disappearance of the signals in Figure 1 clearly shows the position of deuterium atom in the allyl alcohols 7-11.

The positions of deuterium atoms in 7-11 strongly suggest a mechanism in which a hydride transfer from aluminum hydride to β -C of 6 like II as shown in Scheme 1. Once an sp^2 -hybridized carbanion forms, it may form a complex **IV**. Apparently, the complex IV is not reactive enough to form a bis-allyl complex such as V. Instead it survives until being quenched by aqueous NaOH. We tested the possibility by measuring the hydrogen gas evolved. During the stage of addition of 6 (68 mmol) to LiAlH₄ (34 mmol) in diethyl ether, 1 equiv. (34 mmol) of hydrogen gas was evolved, but further generation of the gas was not observed during the reflux. Upon quenching about 2 equiv. (68 mmol) of the gas was evolved. The quenched mixture was extracted with diethyl ether to give a mixture of 2 in 40% yield and 6 which together accounted for about 50% of the starting material. The result may be explained by two sets of stoichiometric equations as follows:

$$[(CH=CH-CH2O)2Al] Li + 4H2O$$

$$\rightarrow 2H2C=CH-CH2OH + Al(OH)3 + LiOH (2)$$

 $HC=C-CH_2OH + LiAIH_4$

$$\rightarrow [(CH=CH-CH_2O)AlH_2] Li + H_2$$
 (1')

[(CH=CH-CH₂O)AlH₂]Li + 4H₂O

$$\rightarrow$$
 H₂C=CH-CH₂OH + Al(OH)₃ + LiOH + 2 H₂ (2')

If the reduction is to take place by Eqns. (1) and (2), quantitative amount of H_2 gas should be formed during the stage of addition and reflux. On the other hand, Eqns. (1') and (2') indicate that one equiv. of H_2 should be formed at first and then two equiv. of the gas should be evolved during the quenching stage. Our observation is consistent with the latter.

It is known that alkynes which are not activated by an adjacent hydroxyl group react much more slowly with LiAlH₄. Our observation that the H atom of the terminal

alkyne does not exchange with D atom when LiAlD₄ was used as reducing agent and a solution of NaOD in D₂O was used for quenching clearly indicates that the hydride transfer from LiAlH₄ to C-C triple bond is intramolecular as for **II** and not intermolecular. If it is intermolecular, the hydride should attack γ -C preferably on the grounds of stereoelectronic effect. Therefore, H-D exchange is likely to take place.

Finally, conversion of 10 to 2,3-dideuterioallyl mercaptan (12) was achieved by reacting with thiourea in aqueous HCl solution at 80 °C for 24 h and subsequently quenching with aqueous NaOH solution. The final product was purified by distillation to give 46% yield.

CHD=CD-CH₂OH + S=C(NH₂)₂
$$\xrightarrow{\text{HCl}}$$

10

[CHD=CD-CH₂-S-C(NH₂)=NH₂*Cl] $\xrightarrow{\text{NaOH}}$ CHD=CD-CH₂SH

Experimental Section

General. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX-400 FT NMR spectrometer in the Central Lab of Kangwon National University at 400 MHz for ¹H and 100 MHz for ¹³C and were referenced to tetramethylsilane. Infrared spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer. Mass spectra were obtained using Micromass Autospec M363.

Materials. Acrylic acid (1), propiolic acid (5), propargyl alcohol (6), LiAlH₄, LiAlD₄ and NaOD in D₂O were used as received as the commercial products. Diethyl ether was distilled from over sodium metal prior to use.

Reduction of Acrylic Acid (1): A Representative Procedure. A mixture of LiAlH₄ (2.5 g. 66 mmol) and diethyl ether (120 mL) was cooled to 0 °C. Acrylic acid (96.0 mL, 87 mmol) was added in drops while the generated H₂ gas was collected in a graduated cylinder. The mixture was heated at reflux for 8 h and then cooled in an ice-water bath. Water (2.5 mL), 15%-NaOH (2.5 mL), and then water (7.5 mL)were added in sequence, and the resulting mixture

was extracted with ether ($3 \times 50 \text{ mL}$). The pooled ethereal extract was dried over MgSO₄. Then the ether was removed by fractional distillation using a Vigreux column. The residual liquid was analyzed by NMR spectroscopy showing that it was a mixture of allyl alcohol (2) and 1-propanol (3) in a ratio of 1:8, and unidentified compounds. The aqueous layer was acidified with 2M-HCl to pH 4 and then extracted with ether to give the starting acid and propionic acid (4) in a ratio of 1:9.

Reduction of Propiolic Acid (5): The procedure is essentially similar to the reduction of 1. The acid 5 (3 mL, 49 mmol) was added to a mixture of LiAlH₄ (3.72 g, 98 mmol) in ether (130 mL) at 0 °C, and the resulting mixture was heated at reflux for 12 h. Quenching with aqueous NaOH and extraction with ether gave a mixture of 6 (6%). 2 (40%), and 3 (51%).

Reduction of Propargyl Alcohol (6): A Representative Procedure. The alcohol 6 (2 mL. 34 mmol) was added to LiAlH₄ (2.20 g. 52 mmol) in ether (100 mL) at 0 °C and the resulting mixture was heated at reflux for 12 h. Quenching with aqueous NaOH and subsequent extraction with ether gave a mixture of 2 (75%) and 6 (20% recovery).

Preparation of β-deuterioallyl alcohol (9). The alcohol 9 was prepared by following the procedure for the reduction of 6 above except the quenching with NaOD-D₂O in 50% yield.

Preparation of *trans-β,*γ-dideuterioallyl alcohol (10). The alcohol 10 was prepared by following the procedure for the reduction of 6 above using LiAlD₄ in same scale and subsequent quenching with NaOD-D₂O. The isolated product (44%) was a mixture of 10 and 11 in a ratio of 9: 1 by NMR. Repeated column chromatography with silica gel with hexane-EtOAc (9:1) gave essentially pure form of 10.

Preparation of β , γ dideuterioally l mercaptan (12). Conc. HCl (2.2 mL) was added to a solution of thiourea (1.81 g. 24 mmol) in water (2 mL). β , γ -Dideuterioally l alcohol (10, 1.4 g. 23 mmol) was slowly added to the

solution. The resulting solution was heated at 80 °C for 24 h. After cooling to room temperature, a solution of NaOH (1.50 g) in water (2 mL) was added slowly. The solution was fractionally distilled to give 12 as a colorless liquid in 46% yield. IR (neat): 3079 (w, =C-H). 2923 (ms. CH₂). 2558 (w. S-H). 1617 (ms. C=C), 1410 (ms, CH₂), 1220 (m. C-S), 919 (s, C=C-H); 1 H-NMR (CDCl₃) δ 1.43 (t, 1 H, S-H. J = 7.7 Hz). 3.17 (d. 2H, CH₂, J = 7.6 Hz), 5.01 (brs. 1H. C=C-H); 13 C-NMR (CDCl₃) ppm 27.45 (CH₂). 115.16 (t. CHD, J = 23.4 Hz). 136.90 (t. CD. J = 24.0 Hz): Mass. m/z (%) 152 (100, dimeric M⁺). 108 (84. dimeric M⁺ - CH₂S). 75 (74, CHD=CD-CH₂S⁻).

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References

- Werkhoff, P.; Brennecke, S.; Bretschneider, W.; Bertram, H.-P. In Flavor, Fragrance, and Odor Analysis: Marsili, R., Ed.; Marcel Dekker: New York, 2002; pp 179-194.
- Casey, C. P.; Vosejpka, P. C.; Underiner, T. L.; Slough, G. A.; Gavney, Jr., J. A. J. Am. Chem. Soc. 1993, 115, 6680.
- Hudlicky, M. Reductions in Organic Chemistry. Halsted Press: 1984; p 138.
- 4. Benedict, G.; Russell, R. R. J. Am. Chem. Soc. 1961, 73, 5444.
- Hochstein, F. A.; Brown, W. G. J. Am. Chem. Soc. 1948, 70, 3484
- Bates, E. B.; Jones, E. R. H.; Whiting, M. C. J. Chem. Soc. 1954. 1854.
- 7. Magoon, E. F.; Slaugh, L. H. Tetrahedron 1967, 23, 4509.
- Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. J. Am. Chem. Soc. 1967, 79, 4245.
- Hochins, R. O.; Hutchins, M. G. K. Reduction of Triple-bonded Groups in The Chemistry of Triple-bonded Functional Groups, Part 1. Supplement C; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: 1983; p 578.