A New Synthesis of Trimethylsilyl-Substituted Enyne and (Z)-Enediyne Compounds

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Trimethylsilyl (TMS)-substituted enynes 9—11, 13—17 and (Z)-enediynes 18 were prepared by dehydration of the TMS-substituted propargyl alcohols 1—8 with polyphosphoric acid trimethylsilyl ester.

Key words: enyne; (Z)-enediyne; polyphosphoric acid trimethylsilyl ester; trimethylsilylenyne

Recently, the anticancer and antibiotic activities shown by conjugate enediyl compounds has attracted the attention of organic chemists and pharmaceutical scientists.1) General synthetic methods involve the Pdcatalyzed cross-coupling reactions of sp and sp2 carbons.2) We have already reported a convenient synthesis of Z-enediyls and Z-enediynes by the dehydrogenation reaction of propargyl alcohols using polyphosphoric acid trimethylsilyl ester (PPSE).3) This dehydrogenation reaction has been found to be strongly affected by the substituent on the acetylenic carbon of the propargyl alcohols. A reaction of sulfur-substituted propargyl alcohols and PPSE gave the alkenoate thioesters via the Meier–Schuster rearrangement in good yields.4) We were interested in the substituent effects on the acetylenic carbon and examined the dehydrogenation of silyl-substituted propargyl alcohols using PPSE. The acid-catalyzed dehydrogenation of silyl-substituted propargyl alcohols has been reported to give theynes via the Meier–Schuster rearrangement.5) However, it is difficult to obtain the enyne silanes by the dehydrogenation of silyl-substituted propargyl alcohols, as concomitant desilylation reactions occur. However, silyl acetylenes are good tools for the synthesis of terminal alkynes,6) yrones7) and the acetylenic sulfones.8) If this method is applicable to the synthesis of the silyl-substituted enynes and (Z)-enediynes, it would provide convenient intermediates for the synthesis of enediyl analogs.

Trimethylsilyl (TMS)-substituted propargyl alcohols are prepared from the reactions of 1-(trimethylsilyl)acetylene/EtMgBr and aldehydes or ketones. First, we performed the reaction of cyclodecanol 1 and PPSE at 83°C to give 1-(trimethylsilylthynyl)-1-cyclododecene (9) in 91% yield. Structural assignment of 9 was performed based on its IR, 1H- and 13C-NMR spectroscopies. The IR spectrum showed the disappearance of the hydroxy group and the 1H-NMR spectrum showed the olefinic H at δ 5.36 (t, J = 8 Hz). The cyclohexanol derivative 2 also gave the enyne silane 10 in good yield. The bulky alkynyl alcohol 3 afforded the enyne silane 11 accompanied by the ether 12 in 40% yield. The reaction of 3 and PPSE under diluted conditions gave the ether 12 in low yield and the enyne 11 was obtained in 63% yield. Methyl-substituted propargyl alcohols 4 and 6 gave the enynes 13 and 16, respectively, accompanied by the exo-methylene derivatives 14 (41%) and 17 (17%). The stereochemistry of the products 13 and 16 was determined by means of difference Nuclear Overhauser effect (DNOE) experiments. Irradiation of the methyl protons substituted at the olefinic carbon of 13 and 16 increased the intensities of the olefinic proton signals. 3H,4H-Dihydropaphthalene 15 was obtained in good yield. The synthesis of a Z-enediyne compound also produced 18 Z-selectively; however, the propargyl alcohol 8 gave a complex mixture.

Plausible mechanisms are shown in Chart 2. The oxygen atom of the alcohol 19 attacks the phosphorus atom of PPSE to give the intermediate 21A. The intermediate 21A formed from the secondary alcohol (R1 = H) does not undergo dehydration of the alcohol 19 (R1 = H) because of the γ-substituent effect of the propargyl alcohols. γ-Silyl-substituted propargyl alcohols have been found to be very slow to undergo dehydration of the alcohols compared to γ-sulfur-substituted alcohols.4) 1-(Phenylthioethyl)ycycloalkanols readily underwent dehydration by PPSE at room temperature to give the enyne sulfides and the alkenethioates; however, the dehydration of the silyl-substituted propargyl alcohol 2 at room temperature did not proceed and the alcohol was recovered. These results show that electron-donating substituents at the acetylenic carbon strongly affected the dehydration reactions of the alcohols. In other words, the carbon–oxygen bond of the γ-silyl-substituted intermediate 21A would be more difficult to cleave than that of the γ-sulfur-substituted alcohols and the alkyl silyl ketones 24 could not be obtained via the Meier–Schuster rearrangement. On the contrary, the phosphorus pentavalent intermediate 21A (R1 ≠ H), formed from the tertiary alcohol, is cleaved more readily than intermediate 21A (R1 = H) and gives the products in good yields. The dehydration of the alcohol would proceed via the 6-membered transition state 25A and 25B, which gives the (Z)- and (E)-enyne silanes, respectively. The (Z)-stereoselectivity of the products can be explained as follows: the dehydration of 21A, in which the alkynyl groups of the alcohol lie on the side opposite to the bulky phosphorus moiety 25A, would proceed and

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Chart 1
Table 1. Reaction of Alkynyl Alcohols with PPSE

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkynyl alcohol</th>
<th>Products (% yields)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Alkynyl alcohol 1" /></td>
<td><img src="image2" alt="Product 1" /> 9 (91)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Alkynyl alcohol 2" /></td>
<td><img src="image4" alt="Product 2" /> 10 (60)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Alkynyl alcohol 3" /></td>
<td><img src="image6" alt="Product 3" /> 11 (55)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Alkynyl alcohol 4" /></td>
<td><img src="image8" alt="Product 4" /> 11 (63)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Alkynyl alcohol 5" /></td>
<td><img src="image10" alt="Product 5" /> 13 (47)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Alkynyl alcohol 6" /></td>
<td><img src="image12" alt="Product 6" /> 12 (18)</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Alkynyl alcohol 7" /></td>
<td><img src="image14" alt="Product 7" /> 14 (41)</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="Alkynyl alcohol 8" /></td>
<td><img src="image16" alt="Product 8" /> 15 (92)</td>
</tr>
<tr>
<td>9</td>
<td><img src="image17" alt="Alkynyl alcohol 9" /></td>
<td><img src="image18" alt="Product 9" /> 16 (48)</td>
</tr>
<tr>
<td>10</td>
<td><img src="image19" alt="Alkynyl alcohol 10" /></td>
<td><img src="image20" alt="Product 10" /> 17 (17)</td>
</tr>
<tr>
<td>11</td>
<td><img src="image21" alt="Alkynyl alcohol 11" /></td>
<td><img src="image22" alt="Product 11" /> 18 (51)*</td>
</tr>
</tbody>
</table>

*a) E:Z = 1:4.*
(Z)-selectively give the enediene. The dehydration of the bulky cyclohexyl derivative (21A: R2, R3 = (CH3)3) is difficult and the nucleophilic attack of another alcohol 19 gives the ether 28. We are now examining the dehydration reactions of γ-alkoxy-substituted propargyl alcohols. These results will be reported elsewhere.

**Experimental**

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra of solids (KBr) and liquids (film) were recorded on a JASCO IRA-100 spectrophotometer. 1H NMR spectra were obtained for solutions in CDC13 on JEOL GX-270 and Varian-Semini-2000 spectrometers at the instrument center of Gifu University with tetramethylsilane as an internal standard, unless otherwise indicated. The 13C spectra were run on JEOL GX-270 and Varian Gemini-2000 spectrometers. Mass spectra were recorded on a JEOL JMS-D300 spectrometer with a direct-insertion probe at 70 eV.

Exact mass determination was done with a JMA 2000 on-line system.

1-(Trimethylsilyl)ethyldodecane-1-ol (1). Typical Procedure for Syntheses of Propargyl Alcohols: An Et2O (5 ml) solution of 1-(trimethylsilyl)acetylene (1.96 g, 20 mmol) was added to an Et3NBr solution (prepared from Mg (0.32 g, 13.0 mmol) and EtBr (1.42 g, 13.0 mmol) in 15 ml of Et2O) at room temperature. The reaction mixture was refluxed for 0.5 h. An Et2O (20 ml) solution of cyclohexancene (1.82 g, 10.0 mmol) was added dropwise to the mixture at 0°C. The whole was added to water (100 ml) and extracted with ether. The extracts were concentrated, dried over MgSO4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica-gel with AcOEt:n-hexane (1:10). 1 (mp 114-116°C (2.38 g, 85%) was obtained as white needles.

1-(Trimethylsilyl)ethyldodecane-1-ol (1): IR (KBr cm-1): 3460 (OH), 2150 (CO), 1609 (C=O). 1H NMR (270 MHz, CDCl3): δ 0.16 (9H, s, TMS), 1.35 (15H, br s, H), 1.61-1.70 (4H, m, al CH+OH), 2.18-2.38 (4H, m, al H). Anal. Calc. for C16H36O2Si: C 72.79, H 11.50. Found: C 72.76, H 11.48.

4-tert-Butyl-1-(trimethylsilyl)ethyldodecane (8): mp 145-148°C (IR (KBr cm-1): 3420 (OH), 2960, 2710 (acetylene). 1H NMR (270 MHz, CDCl3): δ 0.17 (9H, s, TMS), 0.87 (9H, s, tert-Bu), 1.34-1.53 (6H, m, al H), 1.71-1.77 (2H, m, al H and OH), 1.96-2.01 (2H, m, al H). Anal. Calc. for C16H36OSi: C 71.36, H 11.18. Found: C 71.23, H 11.30.

1-(Phenyl-3-(trimethylsilyl)prop-2-yn-1-yl)-3(4)-phenyldienecyclohexane (II) (11): IR (film cm-1): 2100 (acetylene). 1H NMR (270 MHz, CDCl3): δ 0.22 (18H, s, TMS), 1.76-1.78 (4H, m, al H), 2.37 (2H, br t, J = 6 Hz, al H), 2.81 (2H, br t, J = 6 Hz, al H), 3.73 (5H, sh, al H). 13C NMR (67.5 MHz, CDCl3): δ 0.00 (9H, s, TMS), 0.86-0.87 (9H, s, tert-Bu), 1.09-1.31 (2H, m, al H), 1.73-1.90 (2H, m, al H), 2.04 (1H, br H, al H), 2.08-2.18 (2H, m, al H), 6.18 (1H, brs, olefinic H). MS m/z 234 (M+).

(Z)-Methyl-1-(trimethylsilyl)-3-phenyl-1,3-dioxolan-4-one (15): IR (film cm-1): 3200 (OH, 1710 (CO). 1H NMR (270 MHz, CDCl3): δ 0.16 (9H, s, TMS), 0.72 (3H, J = 7 Hz, Me), 1.30 (16H, brs, H, 1.46 (3H, s, Me), 1.60-1.67 (2H, m, al H). Anal. Calc. for C16H36O2Si: C 77.19, H 12.19. Found: C 77.72, H 12.15.

5-Phenyl-1-(trimethylsilyl)-1-tridecen-3-yl (8): IR (film cm-1): 3400 (OH), 2170 (CO). 1H NMR (270 MHz, CDCl3): δ 0.16 (9H, s, TMS), 0.72 (3H, J = 7 Hz, Me), 1.30 (16H, brs, H, 1.46 (3H, s, Me), 1.60-1.67 (2H, m, al H). Anal. Calc. for C16H36O2Si: C 77.19, H 12.19. Found: C 77.72, H 12.15.

1,2,3,4-Tetrahydropyran-4-yl (5): IR (film cm-1): 3450 (OH), 2170 (CO). 1H NMR (270 MHz, CDCl3): δ 0.17 (9H, s, TMS), 2.15-2.20 (4H, m, al H), 2.32 (1H, brs, OH), 2.80-2.82 (2H, al H), 7.09 (1H, am H), 7.20-7.24 (2H, br H), 7.73-7.77 (1H, br H). Anal. Calc. for C16H36O2Si: C 73.71, H 8.25. Found: C 73.58, H 8.05.

1-(Trimethylsilyl)-1-tridecyn-3-yl (6): IR (film cm-1): 3400 (OH), 2170 (CO). 1H NMR (270 MHz, CDCl3): δ 0.16 (9H, s, TMS), 0.72 (3H, J = 7 Hz, Me), 1.30 (16H, brs, H, 1.46 (3H, s, Me), 1.60-1.67 (2H, m, al H). Anal. Calc. for C16H36O2Si: C 77.19, H 12.19. Found: C 77.72, H 12.15.

(Diphenyl-1-(trimethylsilyl)-1,5-dienyldiol (7): IR (film cm-1): 3550, 3460 (OH), 2160 (acetylene). 1H NMR (270 MHz, CDCl3): δ 0.22 (9H, s, TMS), 1.67-1.84 (4H, m, al H), 2.53 (2H, J = 8 Hz, al H), 5.07 (1H, J = 17 Hz, 2H), 7.37-7.38 (1H, m, al H), 7.62-7.68 (2H, br H). MS m/z: 286 (small M+).

(Z)-Methyl-1-(trimethylsilyl)-3-tridec-1-en-16 and 2-(Trimethylsilyl)acetylene-1-dodecane (17): IR (film cm-1): 2150 (acetylene). 1H NMR (270 MHz, CDCl3): δ 0.21 (s, 1H, TMS), 0.02 (s, 1H, TMS), 0.88-0.93 (t, J = 7 Hz, 16-17 Me), 1.03 (5H, m, al H), 1.84 (d, J = 2 Hz, 16-Me), 2.13 (br t, J = 17 Hz, CH2), 2.23-2.28 (16-Me, 5H), 5.12 (s, J = 17-H, 15-H), 5.36 (brs, J = 17-olefinic H), 6.78 (J = 17, 16-olefinic H). 13C NMR (67.5 MHz, CDCl3): δ 0.13 (q, 0.00 (q), 13.99 (q), 22.61 (q), 22.66 (q), 27.89 (q), 28.93 (q), 28.99 (q), 29.17 (q), 29.28 (q), 29.36 (q), 29.39 (q), 29.54 (q), 30.55 (q), 31.85 (q), 36.91 (q), 80.16
(s), 93.49 (s), 97.00 (s), 104.83 (s), 105.76 (s), 117.79 (s), 121.51 (t), 131.91 (s), 139.57 (d). MS m/z: 264 (M⁺). The yields of the products 16 and 17 were determined from the intensities of olefinic H in the ¹H-NMR spectrum.

(Z)-3,9-Diphenyl-1-(trimethylsilyl)-3-nonen-1,5-diynie (Z-18): IR (film) cm⁻¹: 2200, 2140 (acetylene). ¹H-NMR (270 MHz, CDCl₃) δ: 0.24 (9H, s, TMS), 1.87—1.96 (2H, m, alkyl H), 2.44—2.50 (2H, dt, J = 2, 7 Hz, alkyl H), 2.81 (2H, t, J = 7 Hz, alkyl H), 6.32 (1H, t, J = 2 Hz, olefinic H), 7.18—7.37 (8H, m, ArH), 7.59—7.62 (2H, m, ArH). ¹³C-NMR (67.5 MHz, CDCl₃) δ: 0.00 (q), 19.40 (t), 30.35 (t), 34.82 (t), 80.18 (s), 99.73 (s), 115.48 (s), 115.52 (s), 115.57 (s), 125.95 (d), 128.35 (d), 128.46 (d), 128.61 (d), 132.00 (s), 136.71 (s), 141.53 (s), 148.90 (s). High-resolution mass Calcd for C₃₅H₃₃Si: 342.1804. Found: 342.1792.

(E)-3,9-Diphenyl-1-(trimethylsilyl)-3-nonen-1,5-diynie (E-18): IR (film) cm⁻¹: 2230 (acetylene). ¹H-NMR (270 MHz, CDCl₃) δ: 0.21 (9H, s, TMS), 2.01—2.16 (2H, m, alkyl H), 2.07—2.75 (4H, m, alkyl H), 7.15—7.34 (9H, m, ArH and olefinic H), 7.70—7.74 (2H, m, ArH). High-resolution mass Calcd for C₃₄H₃₄Si: 342.1803. Found: 342.1813.

References and Notes