

**Synthesis of Acetylenic Alcohols by Base Catalyzed  $\beta$ -Elimination of 3-Chloro-4,5-Dihydrofuran or 5-Chloro-3,4-Dihydro-2H-Pyran and their Alkyl Derivatives as Well as Alkylation of  $\omega$ -Hydroxy-Alk-1-Ynes.**

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**Summary:** Acetylenic alcohols were synthesised from 3-chloro-4,5-dihydrofuran and its 2-alkyl derivatives, or 5-chloro-3,4-dihydro-2H-pyran and its 6-alkyl derivatives via base catalyzed  $\beta$ -elimination using sodium metal in THF. Also alkylation followed by hydrolysis of the dilithium salt of  $\omega$ -hydroxy-alk-1-yne in THF/HMPT leads to the corresponding acetylenic alcohols.

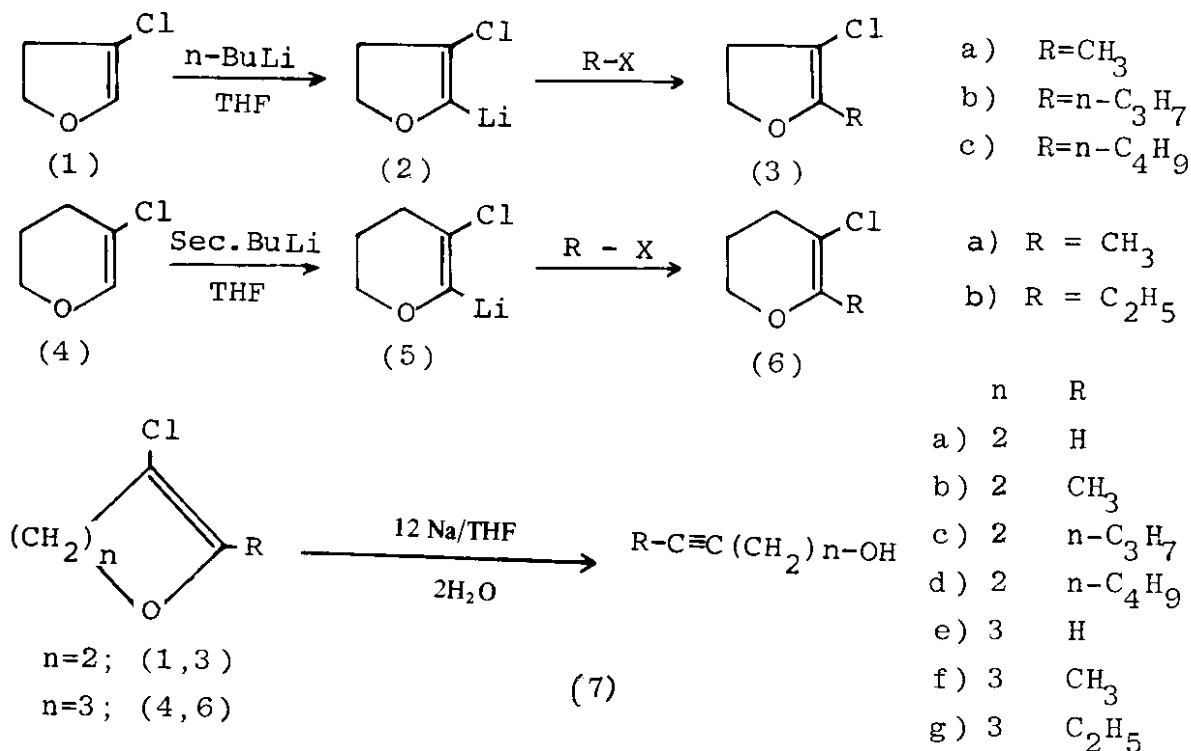
### Introduction

Treatment of 3-chloro-4,5-dihydrofuran (1) with n-butyllithium in THF at  $-78^\circ\text{C}$  gives quantitatively 3-chloro-4,5-dihydro-2-furyllithium (2)<sup>1</sup>, which is quenched by alkyl halides to give 2-alkyl-3-chloro-4,5-dihydrofuran (3a-c). In an analogous step, the treatment of 5-chloro-3,4-dihydro-2H-pyran (4) with sec. butyllithium under the same conditions gives 5-chloro-3,4-dihydro-2H-pyran-6-ylithium (5), which is quenched by alkyl halides to give 6-alkyl-5-chloro-3,4-dihydro-2H-pyran (6a and b).

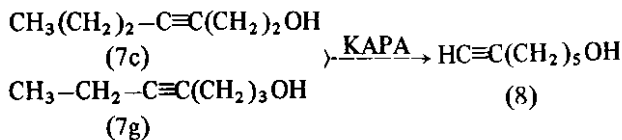
As is well known<sup>1,2</sup> potassium-sodium alloy in THF

is used as a base for ring opening with  $\beta$ -elimination of 3-chloro-2-methyl-4,5-dihydrofuran to give with subsequent isomerization pent-3-yn-1-ol and pent-4-yn-1-ol.

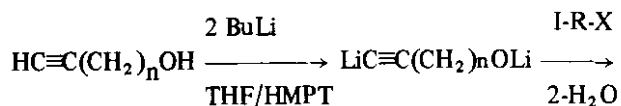
We now wish to report a highly convenient and simple method for synthesis of acetylenic alcohols without any isomerization. Sodium metal in THF is used as mild base at  $25^\circ\text{C}$  for ring opening with  $\beta$ -elimination of 3-chloro-4,5-dihydrofuran (1) or its 2-alkyl derivatives (3) and 5-chloro-3,4-dihydro-2H-pyran (4) or its 6-alkyl derivatives (6) to give after hydrolysis with water the corresponding acetylenic alcohols (7) in good yield.



Recently, it was reported that potassium-3-amino-propylamide (KAPA) causes rapid, and quantitative multipositional isomerization of the internal triple bond to the chain terminus<sup>3,4</sup>. Treatment of hept-3-yn-1-ol (7c) or hept-4-yn-1-ol (7g) with KAPA in 3-aminopropylamine as solvent at 0°C gives hept-6-yn-1-ol (8) in quantitative yield.



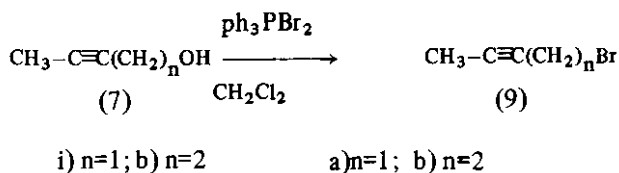
On the other hand, many methods have been published for the synthesis of acetylenic alcohols from  $\omega$ -hydroxy-alk-1-yne<sup>5-7</sup>. In this original work, acetylenic alcohols (7) are prepared by alkylation of the dilithium salt of  $\omega$ -hydroxy-alk-1-yne in THF/HMPT mixture in good yields.



R-C≡C(CH <sub>2</sub> ) <sub>n</sub> OH		
(7)	n	R
b)	2	CH <sub>3</sub>
c)	2	n-C <sub>3</sub> H <sub>7</sub>
d)	2	n-C <sub>4</sub> H <sub>9</sub>
f)	3	CH <sub>3</sub>
g)	3	C <sub>2</sub> H <sub>5</sub>
h)	1	CH <sub>3</sub>
i)	5	n-C <sub>3</sub> H <sub>7</sub>
j)	5	n-C <sub>5</sub> H <sub>11</sub>

We made many attempts under different conditions to prepare the acetylenic alcohols (7) by alkylation of the disodium salt of  $\omega$ -hydroxy-alk-1-yne but it afforded in  $\omega$ -alkoxy-alk-1-yne as the main product.

Treatment of but-2-yn-1-ol (7i) or pent-3-yn-1-ol (7b) with triphenylphosphine dibromide in dichloromethane gave 1-bromo-but-2-yne (9a) or 1-bromo-pent-3-yne (9b) respectively.



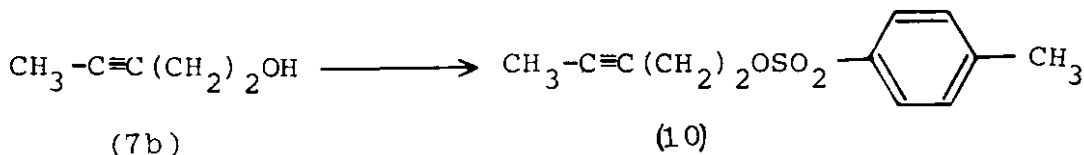
Treatment of pent-3-yn-1-ol (7b) with toluene-*p*-sulphonyl chloride in pyridine was found to afford pent-3-ynyl-toluene-*p* sulphonate (10).

### Experimental

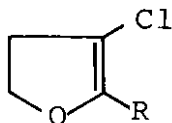
Tetrahydrofuran was distilled over KOH followed by distillation over sodium metal in the presence of benzophenone and stored under nitrogen. *n*-, and *sec*. butyllithium (Metallgesellschaft AG, Frankfurt a. M.) were standardized by the method of Weston and Eastham<sup>8</sup>. The infrared spectra were obtained by Beckman IR-20A Spectrophotometer using CCl<sub>4</sub> as a solvent. The nuclear magnetic resonance were recorded by Bruker WP-80-CW spectrophotometer using CDCl<sub>3</sub> as a solvent and TMS as an internal standard. The mass spectra were measured by Hewlett-Packard 5980A Spectro-photometer using direct introduction technique at 70eV. A Hewlett-Packard 5750 gas chromatography was used for quantitative analysis using C-20 M\*, 8%, 3 m and OV-17, 10%, 3m as stationary phases and decane was used as an internal standard.

#### 2-Alkyl-3-chloro-4,5-dihydrofuran (3a-c)

To a solution of 3-chloro-4,5-dihydrofuran<sup>1</sup> (52.0 g., 0.5 mol) in absolute THF (300 ml), *n*-butyllithium in hexane (333.3 ml, 0.5 mol., 1.5 M solution) was added dropwise during 1 hr. at -78°C under nitrogen. 3-Chloro-4,5-dihydrofuryllithium was precipitated during the addition. The solution was kept at -78°C for 2 hr. after complete addition with stirring. It was warmed up gradually to -20°C and then methyl, *n*-propyl, or *n*-butyl iodide (0.55 mol.) was added dropwise. The solution was kept for 2 hr. at -20°C with stirring and then warmed up to room temperature. Water (500 ml) was added, and the aqueous solution was extracted with ether (3 x 100 ml) dried over CaSO<sub>4</sub> and the solvent



was distilled using Widmer column. The product was distilled under vacuum to give 2-alkyl-3-chloro-4,5-dihydrofuran (3a-c) (see Table 1).



(3)

Table 1

Compd.	R	b.p./mm	Yield %
a	CH <sub>3</sub>	47–49°/45	79
b	n-C <sub>3</sub> H <sub>7</sub>	53–55°/12	81
c	n-C <sub>4</sub> H <sub>9</sub>	64–66°/12	85

NMR: (1)  $\delta$  6.37 (t, 1H, olefinic C<sub>2</sub>-H), 4.36 (t, 2H, C<sub>5</sub>-H<sub>2</sub>) & 2.77 ppm (txd, 2H, allylic C<sub>4</sub>-H<sub>2</sub>).  
 (3a)  $\delta$  4.35 (t, 2H, C<sub>5</sub>-H<sub>2</sub>), 2.97 (txd, 2H, allylic C<sub>4</sub>-H<sub>2</sub>) & 1.80 ppm (t, 3H, C<sub>2</sub>-CH<sub>3</sub>).  
 (3b)  $\delta$  4.31 (t, 2H, C<sub>5</sub>-H<sub>2</sub>), 2.87 (txd, 2H, allylic C<sub>4</sub>-H<sub>2</sub>), 2.48 (m, 2H, exocyclic allylic C<sub>2</sub>-CH<sub>2</sub>), 1.49 (m, 2H, exocyclic -CH<sub>2</sub>) & 1.03 ppm (m, 3H, CH<sub>3</sub>).  
 (3c)  $\delta$  4.29 (t, 2H, C<sub>5</sub>-H<sub>2</sub>), 2.83 (txd, 2H, allylic C<sub>4</sub>-H<sub>2</sub>), 2.25 (m, 2H, exocyclic allylic C<sub>2</sub>-CH<sub>2</sub>), 1.46 (m, CH<sub>2</sub>-CH<sub>2</sub>) & 0.96 ppm (m, 3H, CH<sub>3</sub>).

#### 5-Chloro-3,4-dihydro-2H-Pyran (4)

A stream of dry chlorine gas was passed into a solution of 3,4-dihydro-2H-pyran (84.0 g, 1.0 mol.) in dry CCl<sub>4</sub> (600 ml) at -30°C. After the solution became yellow in colour it was warmed up to room temperature and then a stream of nitrogen was passed till the solution became colourless. The solution was added dropwise to tributylamine (222.5 g, 1.2 mol.) in a three-necked flask (500 ml) at 150°C under 150-160 mm. Hg pressure during 3 hr. The CCl<sub>4</sub> was removed by distillation and then further distillation using Widmer column at 43–45°C/18 mm.Hg gave 5-chloro-3,4-dihydro-2H-pyran (4, 72.0 g., 61% yield).

NMR:  $\delta$  6.7 (t, 1H, olefinic C<sub>6</sub>-H), 3.95 (t, 2H, allylic C<sub>4</sub>-H<sub>2</sub>), 2.48 (t, 2H, C<sub>2</sub>-H<sub>2</sub>) & 2.12 ppm (dxt, 2H', C<sub>3</sub>-H<sub>2</sub>)

#### 6-Alkyl-5-chloro-3,4-dihydro-2H-pyran (6a and b)

In a 250 ml three-necked flask containing 5-chloro-3,4-dihydro-2H-pyran (4) (11.8 g, 100 mol) in THF (50 ml) at -78°C, secondary butyllithium (142.8 ml, 100 m mol, 0.7 M solution) was added dropwise during 1 hr. under a nitrogen atmosphere and the solution was stirred for 2 hr. at -78°C after complete addition. Methyl ethereal iodide (120m mol) was added and then the solution was kept at -78°C with stirring. The solution was gradually warmed to room temperature with stirring for 30 min., and then water (30 ml) was added. The solution was extracted with ether (3x50 ml). ethereal extracts were dried by CaSO<sub>4</sub>. The solvent was distilled off and the product was distilled: 6a at 58–60°C/18 mm. Hg (69% yield) 6b at 63–65°C/18 mm.Hg (78% yield).

NMR: (6a):  $\delta$  4.27 (t, 2H, C<sub>2</sub>-H<sub>2</sub>), 2.43 (dxt, 2H, allylic C<sub>2</sub>-H<sub>2</sub>), 2.02 (q, 2H, C<sub>3</sub>-H<sub>2</sub>) & 1.77 ppm (t, 3H, C<sub>6</sub>-CH<sub>3</sub>). (6b):  $\delta$  4.23 (t, 2H', C<sub>2</sub>-H<sub>2</sub>), 2.32 (dxt, 4H, allylic C<sub>4</sub>-H<sub>2</sub> and C<sub>6</sub>-CH<sub>2</sub>), 1.92 (q, 2H, C<sub>3</sub>-H<sub>2</sub>) & 1.05 ppm (t, 3H, CH<sub>3</sub>).

#### Synthesis of acetylenic alcohols (7a-g)

##### Method (A)

A mixture of 3-chloro-4,5-dihydrofuran (1) and its 2-alkyl derivatives (3) or 5-chloro-3,4-dihydro-2H-pyran (4) and its 6-alkyl derivatives (6) (50 mmol.), were dissolved in THF (50 ml) and sodium metal powder (3.6 g, 150 mmol.) was added with stirring at 25°C for 48 hr. The dark blue suspension was poured into ice (50 g.) and the solution was extracted with ether (3x50 ml) and dried with CaSO<sub>4</sub>. The solvent was removed by distillation and then the product was distilled under vacuum (Table 2)

The NMR signals of alcohols (7) range are:—  
 $\delta$  1.7–2.1 (t, 1H, HC≡), 1.5–1.8 (m, 3H, ≡C-CH<sub>3</sub>), 1.8–2.5 (m, 2H, ≡C-CH<sub>2</sub>), 3.3–3.9 ppm (t, 2H, CH<sub>2</sub>-CH<sub>2</sub>-OH) and unfixed position for 1H of OH group.

The IR spectra of alcohols (7) showed bands ranges at 2100–2130cm<sup>-1</sup> (HC≡), 2930–2959cm<sup>-1</sup> (-C≡C-) and 3300–3320cm<sup>-1</sup> (OH).

Table 2.

 Synthesis of acetylenic alcohols (7)  
 $R-C\equiv C(CH_2)_nOH$ 

Compd.	n	R	b.p./mm	Yield %	Analysis % Found/Calcd.	
					C	H
7a	2	H	126°/760	77	68.45 68.51	8.67 8.63
7b	2	CH <sub>3</sub>	57°/13	78	71.32 71.39	9.58 9.59
7c	2	n-C <sub>3</sub> H <sub>7</sub>	150°/19	81	75.78 75.89	10.68 10.71
7d	2	n-C <sub>4</sub> H <sub>9</sub>	89°/7	84	76.07 76.13	11.08 11.19
7e	3	H	143°/760	69	71.59 71.39	9.62 9.59
7f	3	CH <sub>3</sub>	74°/8	73	73.38 73.47	10.13 10.20
7g	3	C <sub>2</sub> H <sub>5</sub>	91°/18	73	74.94 74.94	10.73 10.79

MS: (7b) m/e 40 (100%), 84 (4%).  
 (7e) m/e 40 (100%), 84 (14%).  
 (7g) m/e 80 (100%), 112 (3%).

1.9 (t, 1H, HC≡), 1.55 (m, 6H, 3 CH<sub>2</sub>) and 1.6 ppm (s, 1H, OH).

IR: 2130 (HC≡), 2950 (C≡C) and 3310 cm<sup>-1</sup> (OH).  
 MS: m/e 80 (100%), 112 (3%).

#### Hept-6-yn-1-ol (8)

To a solution of KAPA (80 mmol) [prepared by adding 1,3-diaminopropane (50 ml) to potassium hydride (3.2 g, 80 mmol.) under argon at 25°C till no hydrogen evolved, with the formation of clear yellow solution], hept-2-yn-1-ol (7c) or hept-4-yn-1-ol (7g) (2.24 g., 20 mmol.) was injected rapidly at 0°C with vigorous stirring for 2 hr and the mixture kept at 25°C for 2 hr. The reaction mixture was quenched by water (50 ml). The solution was extracted with ether (3x100 ml) and washed by HCl (4M solution). The ethereal solution was dried by CaSO<sub>4</sub>/K<sub>2</sub>CO<sub>3</sub>. The solvent was removed by distillation and the product was then distilled at 83–5°/10 mm.Hg to give hept-6-yn-1-ol (2.1 g, 94% yield).

C<sub>7</sub>H<sub>12</sub>O (112.1) Found: C, 74.91; H, 10.90

Calcd: C, 74.94; H, 10.79

NMR: δ 3.6 (t, 2H, -CH<sub>2</sub>O), 2.2 (dxt, 2H, ≡C-CH<sub>2</sub>-),

#### Synthesis of acetylenic alcohols (7b-d & f-j).

##### Method B

To a solution of ω-hydroxy-alk-1-yne (20 mmol) in THF (30 ml), n-butyllithium (40 mmol) was added dropwise at 0°C and the solution was stirred for 1 hr. and then alkyl halide (20 mmol) in HMPT (60 ml) was added at 0°C for 1 hr and the solution allowed to stand at 25°C for 2 hr. The solution was poured into ice (100 g) and extracted with ether (3x50 ml). The ethereal solution was washed by water (3x50 ml.) and dried over CaSO<sub>4</sub>. The solvent was distilled off and the product was then distilled under vacuum (Yield 68–75%) (Table 2).

C<sub>4</sub>H<sub>6</sub>O (7h): Found: C, 68.37; H, 8.72.

Calcd: C, 68.55; H, 8.63.

NMR:  $\delta$  4.2 (t, 2H, CH<sub>2</sub>-O), 3.5 (s, 1H, OH) and 1.8 ppm (t, 3H, CH<sub>3</sub>).

IR: 2920 (C≡C) and 3350 cm<sup>-1</sup> (OH).

MS: m/e 70 (100%), 40 (84%).

C<sub>10</sub>H<sub>18</sub>O (7i): Found: 77.16; H, 11.54

Calcd: 77.27; H, 11.67

NMR:  $\delta$  3.9 (t, 2H, CH<sub>2</sub>-O), 2.6 (m, 4H, two ≡C<sub>2</sub>-CH<sub>2</sub>), 1.8 (s, 1H, OH), 1.4 (m, 8H, 4 CH<sub>2</sub>) and 0.98 ppm (t, 3H, CH<sub>3</sub>).

C<sub>12</sub>H<sub>22</sub>O (7j): Found: C, 79.21; H, 12.27

Calcd: C, 79.06; H, 12.16

NMR:  $\delta$  3.58 (t, 2H, CH<sub>2</sub>-O), 2.13 (m, 4H, two ≡C-CH<sub>2</sub>), 2.05 (s, 1H, OH), 1.45 (m, 12H, 6 CH<sub>2</sub>) and 0.88 ppm (t, 3H, CH<sub>3</sub>).

IR: 2940 (C≡C), and 3360 cm<sup>-1</sup> (OH).

MS: m/e 80 (100%), 182 (3%).

#### 1-Bromo-but-2-yne and 1-bromo-pent-3-yne (9a and b)

To a suspension of triphenylphosphine dibromide (120 mmol) in benzene (300 ml), but-2-yne-1-ol (7h) or pent-3-yne-1-ol (7b) (100 mmol) in dichloromethane (45 ml) was added dropwise at 0°C during 1 hr. The solution was stirred at 0°C for 2 hr. after complete addition, and then kept at 25°C for 1 hr. It was filtered to remove triphenylphosphine oxide/HBr adduct and benzene was distilled off. The residue was taken up in hexane (100 ml) and purified by silica gel column chromatography to isolate the residual adduct. The solvent was distilled off and the product was then distilled to give 1-bromo-but-2-yne (b.p. 118–120°C, yield 74%) or 1-bromo-pent-3-yne (b.p. 64–65°C/40 mm.Hg, 84% yield) respectively.

C<sub>4</sub>H<sub>5</sub>Br (9a): Found: C, 36.03; H, 4.23 =

= Calcd: C, 36.13; H, 3.99 =

NMR:  $\delta$  3.85 (t, 2H, CH<sub>2</sub>Br); 1.85 ppm (t, 3H, CH<sub>3</sub>).

IR: 2920 cm<sup>-1</sup> (C≡C).

MS: 80 (100%), 133 (44%).

C<sub>5</sub>H<sub>7</sub>Br (9b): Found: C, 40.91; H, 4.90

Calcd: C, 41.12; H, 4.83.

NMR:  $\delta$  83.28 (t, 2H, CH<sub>2</sub>-Br); 2.55 (m, 2H, ≡C-CH<sub>2</sub>) and 1.75 ppm (t, 3H, CH<sub>3</sub>).

IR: 2940 cm<sup>-1</sup> (C≡C).

MS: 66 (100%), 147 (84%).

#### Pent-3-ynyl-toluene-p-sulphonate (10):

Pent-3-yn-1-ol (4.2 g., 50 mmol.) was added during 45 min at 25°C to stirred slurry of toluene-p-sulphonyl chloride (10.8 g) in pyridine (5 ml). After complete addition, the solution was stirred for 2 hr. and then the mixture was poured into ice (100 g.) and extracted with ether (3x20ml). The ether extract was washed by H<sub>2</sub>SO<sub>4</sub> (2x10 ml, 6N) and then with saturated NaHCO<sub>3</sub> (5 ml), and finally with water (5 ml), dried over K<sub>2</sub>CO<sub>3</sub> and the solvent was distilled off. The solid residue was crystallized from ethanol to give pent-3-ynyl-toluene-p-sulphonate (9.6 g, 81% yield) m.p. 40–41°C.

C<sub>12</sub>H<sub>14</sub>O<sub>3</sub>S (10): Found: C, 60.38; H, 5.98

Calcd: C, 60.48; H, 5.92

NMR:  $\delta$  7.73–7.25 (dxd, 4H, Ar-H), 4.05 (t, 2H, -CH<sub>2</sub>-OSO<sub>2</sub>-), 2.48 (m, 2H, ≡C-CH<sub>3</sub>), 2.42 (s, 3H, Ar-CH<sub>3</sub>), and 1.68 ppm (t, 3H, ≡C-CH<sub>3</sub>).

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