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Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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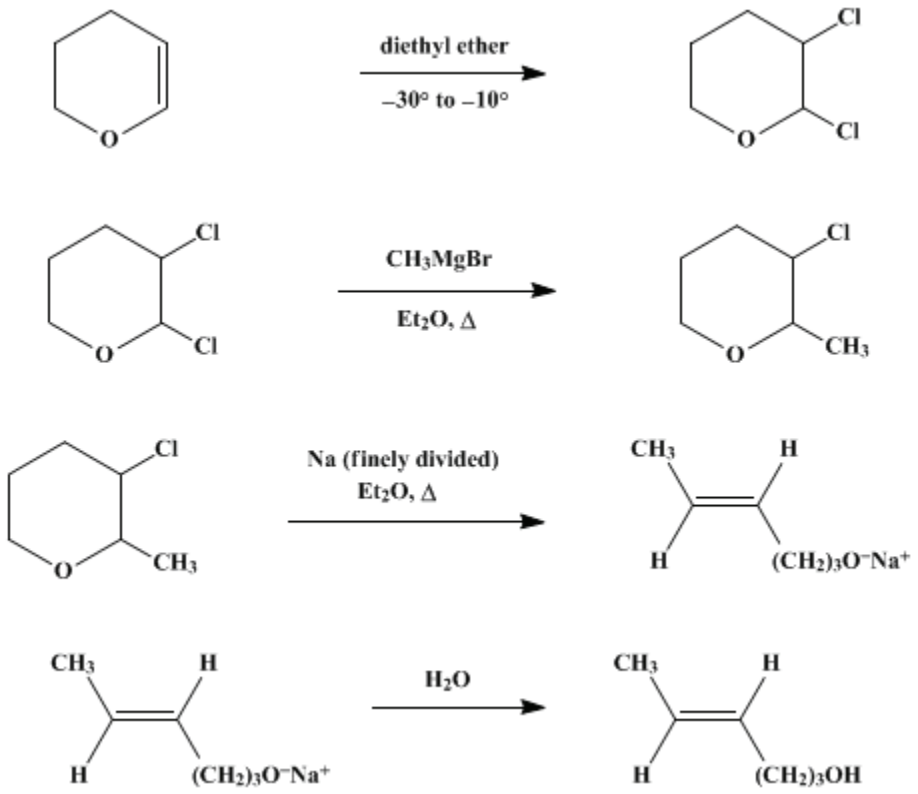
(*E*)-4-HEXEN-1-OL



Submitted by Raymond Paul, Olivier Riobé, and Michel Maumy[1].
Checked by Edward J. Zaiko and Herbert O. House.

1. Procedure

Caution! All operations described in this procedure should be performed in an efficient hood, because toxic chlorine and methyl bromide are used in Steps A and B, respectively, and hydrogen is evolved in Step C.

A. 2,3-*Dichlorotetrahydropyran*. A 1-l., three-necked, round-bottomed flask fitted with a glass-inlet tube extending nearly to the bottom of the flask, a low-temperature thermometer, an exit tube attached to a calcium chloride drying tube, and a Teflon®-coated magnetic stirring bar is charged with a solution of 118 g. (1.40 moles) of dihydropyran (Note 1) in 400 ml. of anhydrous diethyl ether. While the solution is stirred continuously it is cooled to −30° with an acetone–dry ice bath. Anhydrous chlorine (Note 2) is passed through the solution and introduced at such a rate that the temperature of the reaction solution does not rise above −10° (Note 3). Completion of the addition process (*ca.* 1 hour) is indicated by a rapid development of a yellow color (excess chlorine) in the reaction solution and a distinct decrease in the temperature of the reaction mixture. When the addition is complete, several drops of dihydropyran are added to discharge the yellow color, and the colorless solution is stored at −30° (Note 4) until it is used in the next step.

B. 3-*Chloro*-2-*methyltetrahydropyran*. A dry, 4-l., three-necked, round-bottomed flask fitted with a powerful mechanical stirrer, a reflux condenser protected by a calcium chloride drying tube, and a gas-inlet tube extending nearly to the bottom of the flask is charged with 51 g. (2.11 g.-atoms) of magnesium turnings and 1.2 l. of anhydrous ether. Methyl bromide (200 g., 2.15 moles) is allowed to distill (Note 5) into the continuously stirred reaction mixture at such a rate as to maintain gentle

refluxing. The formation of an ethereal solution of methylmagnesium bromide requires approximately 2 hours. The gas-inlet tube is then replaced with a dry, 1-l. dropping funnel, protected with a calcium chloride drying tube. The reaction mixture is cooled with stirring in an ice–salt bath. The cold, ethereal 2,3-dichlorotetrahydropyran solution is placed in the dropping funnel and added dropwise, with continuous stirring and cooling, to the solution of methylmagnesium bromide at such a rate that the reaction solution does not reflux too vigorously. When this addition is complete, the resulting slurry is refluxed with stirring for 3 hours, then cooled in an ice bath. To the resulting cold (0°), vigorously stirred suspension is slowly added 900 ml. of cold 15% hydrochloric acid. The organic layer is separated, and the aqueous phase is extracted with two 200-ml. portions of ether. The combined ethereal solution is dried over anhydrous potassium carbonate, then concentrated by distillation at atmospheric pressure. The residual liquid is distilled under reduced pressure through a 12-cm. Vigreux column, separating 122–136 g. (65–72%) of a mixture of *cis*- and *trans*-3-chloro-2-methyltetrahydropyran as a colorless liquid, boiling over the range 48–95° (17–18 mm.) (Note 6), sufficiently pure for use in the next step (Note 7).

C. (E)-4-*Hexen*-1-*ol.* A dry, 3-l., three-necked, round-bottomed flask fitted with a powerful mechanical stirrer, a 500-ml. dropping funnel, and a reflux condenser protected by a calcium chloride drying tube is charged with 53 g. (2.3 g.-atoms) of finely divided sodium (Note 8) and 1.2 l. of anhydrous ether. 3-Chloro-2-methyltetrahydropyran (136 g., 1.01 moles) is added dropwise to the rapidly stirred, ethereal suspension of sodium. When the reaction commences (Note 9), the reaction mixture turns blue. After the reaction has started, the remaining chloro-ether is added, dropwise and with stirring over approximately 90 minutes, at such a rate that a brisk reflux is maintained. The resulting mixture, which remains dark blue throughout the addition of the chloro-ether, is refluxed with stirring for an additional hour (Note 10), then cooled in an ice–salt bath. The cold reaction mixture is stirred vigorously as 30 ml. of absolute ethanol is added dropwise and with caution to the reaction mixture, after which, 700 ml. of water is added dropwise, with stirring and cooling. After the organic layer has been separated, the aqueous phase is extracted with two 200-ml. portions of ether, and the combined ether extracts are dried over anhydrous potassium carbonate and concentrated by distillation at atmospheric pressure. The residual liquid is distilled under reduced pressure through a 12-cm. Vigreux column, separating 89–94 g. (88–93%) of (*E*)-4-hexen-1-ol as a colorless liquid, b.p. 70–74° (19 mm.), n_D^{25} 1.4389 (Note 11).

2. Notes

1. Dihydropyran (purchased from Eastman Organic Chemicals) was distilled before use; b.p. 84–86°.
2. The chlorine, obtained from a compressed gas cylinder, was passed through a wash bottle containing concentrated sulfuric acid before being passed into the reaction solution.
3. This addition of chlorine has been carried out at −5−0°, but the yield is slightly decreased and the time required for the addition is greatly extended.
4. 2,3-Dichlorotetrahydropyran may be stored for a few hours at 0°, but the yield in the subsequent step is decreased and partial decomposition may have occurred.
5. The checkers employed a sealed ampoule of methyl bromide (b.p. 5°, obtained from Eastman Organic Chemicals), which was cooled to 0° and opened. After a boiling chip had been added to the ampoule, it was connected to the gas-inlet tube of the reaction apparatus with rubber tubing and warmed in a water bath to distill the methyl bromide into the reaction vessel.
6. The submitters report that the boiling point of this mixture is 50–70° (18 mm.) or 60–80° (45 mm.), $n_D^{19.5}$ 1.4596. However, the checkers found that the product obtained from the initial distillation should be collected over a wider range [45–90° (17–18 mm.)], because the boiling point of the final portion of the product is raised by the higher molecular weight residue that remains in the stillpot. The isomers have been isolated by fractional distillation through a 90-cm. Crismer column.[2] The physical constants for the lower boiling *trans*-isomer: b.p. 56° (23 mm.), n_D^{21} 1.4543; for the higher-boiling *cis*-isomer: b.p. 72° (23 mm.), n_D^{21} 1.4646.
7. The checkers found that a fraction, b.p. 45–71° (18 mm.), had the following spectral properties; IR (CCl_4): no absorption in the 3300–1600 cm.$^{-1}$ region attributable to OH, C=O, or C=C vibrations; ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.0–2.5 (m, 7H, C*H*$_3$ and 2C*H*$_2$), 3.1–4.2 (m, 4H, C*H*Cl and C*H*$_2$OC*H*). TLC analysis of this fraction on silica gel plates using chloroform as eluent indicated the presence of a major component (the *cis*- and *trans*-isomers), R_f = 0.60, and a minor

unidentified component, R_f = 0.14.
8. The finely divided sodium was prepared under boiling toluene or boiling xylene by agitation of the molten sodium with a Vibromixer. After the dispersion had cooled and the sodium had settled, the toluene or xylene was decanted, and the finely divided sodium was washed with two portions of anhydrous ether.
9. The reaction generally commences with the addition of approximately 5% of the chloro-ether; if not, the mixture should be heated to boiling to initiate the reaction. If a much larger proportion of the chloro-ether has been added before the reaction commences, initiation of the reaction may be too violent to control. The *cis*-isomer was found to be more reactive toward sodium than the *trans*-isomer.
10. The submitters reported that the blue color of the mixture fades during the reflux period, leaving a cream-white colored reaction mixture. In the checkers' runs (performed under a nitrogen atmosphere) the blue color was not discharged until ethanol was added to the reaction mixture.
11. The product exhibits the following spectral properties; IR (CCl_4) cm.$^{-1}$: 3620 (OH), 3330 broad (associated OH) 970 [(*E*) CH=CH]; ^{1}H NMR ($CDCl_3$) δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.3–2.4 (m, 4H, 2CH_2), 1.64 (d of d, *J* = 1 and *J* = 5, 3H, CH_3), 3.05 (broad, 1H, O*H*), 3.62 (t, *J* = 6.5, 2H, CH_2O), 5.1–5.9 (m, 2H, C*H*=C*H*); mass spectrum *m/e* (relative intensity): 100 (M, 3), 82 (38), 67 (100), 55 (47), 54 (22), 41 (95), 39 (36), and 31 (28). The submitters report that their product exhibited a single GC peak on several columns. GC analysis of the sample obtained by the checkers using a 6-m. column packed with 1,2,3-tris(β-cyanoethoxy)propane on Chromosorb P revealed one major peak having a retention time of 20.2 minutes and a second minor peak (6% of the total peak area) having a retention time of 22.6 minutes. The mass spectrum of this minor peak exhibited the following abundant peaks: *m/e* (relative intensity), 100 (M, 3) 82 (38), 67 (100), 55 (42), 54 (25), 41 (97), 40 (100), 39 (35), and 31 (30). Hence, this minor component appears to be an isomer of the major product, (*E*)-4-hexen-1-ol.

3. Discussion

This procedure illustrates a general method for the stereoselective synthesis of (*E*)-disubstituted alkenyl alcohols. The reductive elimination of cyclic β-halo-ethers with metals was first introduced by Paul,[3] and one example, the conversion of tetrahydrofurfuryl chloride to 4-penten-1-ol, is described in an earlier volume of this series.[4] In 1947 Paul and Riobé[5] prepared 4-nonen-1-ol by this method; subsequently, the general method has been used to obtain alkenyl alcohols with other substitution patterns.[2,6,7,8] (*E*)-4-Hexen-1-ol has been prepared by this method[9] and in lower yield by an analogous reaction with 3-bromo-2-methyltetrahydropyran.[10]

The coupling reaction of 2,3-dichlorotetrahydropyran and Grignard reagents, RMgBr, has been effected with a number of reagents including those where R = CH_3,[2] C_2H_5,[2] $CH_3CH_2CH_2$,[2] $CH_3(CH_2)_2CH_2$,[11] C_6H_5,[11] $CH_3(CH_2)_4CH_2$,[12] β-cyclohexenylethyl,[6] β-phenylethyl,[7,13,14] vinyl,[15] and ethynyl.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 586

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether,
diethyl ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

chlorine (7782-50-5)

toluene (108-88-3)

sodium (13966-32-0)

methyl bromide (74-83-9)

xylene (106-42-3)

methylmagnesium bromide (75-16-1)

dihydropyran

4-Penten-1-ol (821-09-0)

Tetrahydrofurfuryl chloride (3003-84-7)

vinyl (2669-89-8)

2,3-Dichlorotetrahydropyran (5631-95-8)

3-Chloro-2-methyltetrahydropyran (53107-05-4)

4-nonen-1-ol

3-bromo-2-methyltetrahydropyran (156051-16-0)

β-cyclohexenylethyl

β-phenylethyl

(E)-4-Hexen-1-ol (6126-50-7)

trans-3-chloro-2-methyltetrahydropyran

cis-3-chloro-2-methyltetrahydropyran (53107-04-3)