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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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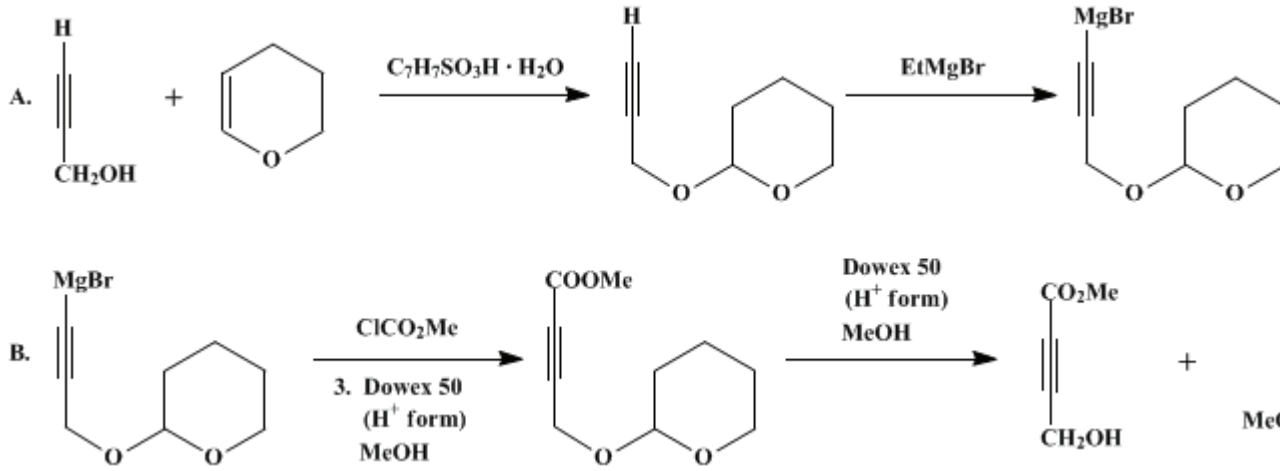
METHYL 4-HYDROXY-2-BUTYNOATE

[2-Butynoic acid, 4-hydroxy-, methyl ester]



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1. Procedure

Caution! Acetylenic compounds are potentially explosive and methyl 4-hydroxy-2-butynoate is a potent vesicant (Note 1).

A. *Tetrahydropyranyl derivative of propargyl alcohol* [*tetrahydro*-2-(2-*propynyloxy*)-2H-*pyran*]. Two crystals (ca. 10 mg) of *p*-toluenesulfonic acid monohydrate are added to 268 g (291.3 mL, 3.2 mol) of warm (60°C) dihydropyran (Note 2) in a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a thermometer, a dropping funnel containing 168 g (174.5 mL, 3.0 mol) of propargyl alcohol (Note 2) and a reflux condenser fitted with a drying tube. Stirring is started, and the propargyl alcohol is added (Note 3) as a thin stream during a period of ca. 30 min. The reaction is mildly exothermic, and the temperature is maintained at 60–65°C by controlling the rate of addition of the propargyl alcohol and by occasional external cooling with an ice bath. After the addition is completed, the temperature is monitored for another 30 min; slight cooling is sometimes necessary to keep the temperature in the range of 60–65°C. The reaction mixture is stirred for a total of 1.5 hr after the addition is completed, and then 0.5 g of powdered sodium bicarbonate is added and the mixture stirred for another hour. The mixture is then gravity-filtered into a 1-L, round-bottomed flask. The reaction mixture is distilled through a 45-cm Vigreux column under reduced pressure (Note 15). A small forerun (ca. 40 mL) with a bp of 45°C (15–20 mm) is followed by the product, bp 47–50°C (3.5–5 mm), 330–355 g (78–92%) (Note 15); n_D^{22} 1.4559 (Note 16); ^{1}H NMR (90 MHz, neat) δ: 1.18–1.93 (br m, 6, $H_{2',2''}$, $H_{3',3''}$, $H_{4',4''}$); 2.47 (t, 1, J = 2, C≡C-*H*), 3.17–3.84 (m, 2, $H_{5',5''}$), 4.03 (d, 2, J = 2, C≡C-CH_2O), 4.63 (s, 1, H_1); IR (neat) cm^{-1}: 3300 (C≡C-*H*), 2117 (C≡C stretch).

B. *Methyl 4-hydroxy-2-butynoate*. One mole of ethylmagnesium bromide (Note 4) in diethyl ether is poured into a dry (Note 5) 2-L, three-necked, round-bottomed flask fitted with a mechanical stirrer and a glass stirrer bearing (Note 6), a dropping funnel fitted with a nitrogen-inlet tube, and an efficient condenser fitted with a drying tube. Stirring is started, and a solution of 140 g (1.0 mol, 141 mL) of the tetrahydropyranyl derivative of propargyl alcohol in 1-L of dry (Note 7) tetrahydrofuran is added during ca. 30 min (Note 8). Stirring is continued for an additional 1.5 hr, during which time a dry 3-L, three-necked flask is fitted with a mechanical stirrer, immersion thermometer, and dropping funnel. The 3-L flask is charged with a solution of 104 g (1.10 mol, 85.4 mL) of methyl chloroformate (Note 2) in 250 mL of tetrahydrofuran and the contents stirred and cooled to −20°C with a dry ice-acetone bath. Under

gentle nitrogen pressure the acetylenic Grignard reagent is transferred portionwise through a ¼-in. polypropylene tube to the dropping funnel attached to the 3-L, three-necked flask (Note 9). The acetylenic Grignard reagent is then added dropwise during 1.5 hr to the well-stirred solution of methyl chloroformate in tetrahydrofuran while the temperature is maintained at −15 to −20°C by external cooling. After the addition is completed, the light-brown reaction mixture is stirred another 30 min at −15°C, followed by another 1.5 hr at ice temperature. The reaction mixture is then stored without stirring for 12 hr at +3°C, during which time the remaining magnesium salts separate from solution. The salts are removed by filtration (Note 10) and washed with three 150-mL portions of cold (0°C), dry toluene. The supernatant and washings are combined and concentrated (Note 11) to ca. 500-mL volume. The dark-brown solution is then washed five times with 100-mL portions of saturated brine followed by drying over anhydrous sodium sulfate. The solution is concentrated to remove the toluene and then dissolved (Note 12) in 1 L of anhydrous methanol; 25 mL of Dowex 50-X4 cation resin (H^+ form, prewashed with anhydrous methanol) is then added and the mixture stirred for 1.5 hr at 25°C. The ion-exchange resin is removed by filtration through a sintered-glass filter and is then washed with two 50-mL portions of anhydrous methanol. Solvent and 2-methoxytetrahydropyran are removed by concentration using a water aspirator and then an oil pump at 0.5-mm pressure. The residue from the concentration is then treated a second time (Note 13) with 1 L of anhydrous methanol and 25 mL of Dowex 50, followed by concentration as before. The residue is then distilled through a Claisen head to give methyl 4-hydroxy-2-butynoate (Note 14), 69–74 g (60–65%), by 66–69°C/0.2 mm, n_D^{22} 1.4684 (Note 17); ^{1}H NMR [$(CD_3)_2SO$] δ: 3.79 (s, 3, OCH_3), 4.31 (d, 2, CH_2, J = 6), 5.57 (t, 1, OH); IR (neat) cm^{-1}: 3410 (OH), 2240 (-C≡C-), 1715 (ester).

2. Notes

1. Acetylenic compounds are potentially explosive, and all concentrations and distillations should be carried out behind a safety shield. Methyl 4-hydroxy-2-butynoate is a potent vesicant that causes painful burns on contact with skin. All operations should be carried out in an efficient fume hood and gloves should be worn at all times.
2. As supplied by Aldrich Chemical Company, Inc. (97% purity).
3. The general method of Robertson,[3] whereby toluenesulfonic acid monohydrate is added to a mixture of an alcohol and dihydropyran, is not recommended for this preparation since the reaction is rather exothermic. Reaction temperatures below 60°C are to be avoided for the same reason since unreacted reagents accumulate and the reaction may suddenly get out of hand with resulting boiling and colorization of the reaction mixture.
4. Ethylmagnesium bromide was obtained from Aldrich Chemical Company, Inc. in the form of a 3 *M* solution in diethyl ether containing 133.3 g of ethylmagnesium bromide. Alternately, the ethylmagnesium bromide could be prepared by a standard procedure.[4]
5. Glassware was dried in an oven at 110°C, assembled while still hot, and flushed with dry nitrogen as the assembly cooled to room temperature. All reactions involving the Grignard reagents were carried out under an atmosphere of dry nitrogen and in a fume hood.
6. The bearing was lubricated with mineral oil.
7. Anhydrous tetrahydrofuran from MCB, Inc. was used for the reactions. Freshly opened bottles gave no effervescence when mixed with powdered calcium hydride. If smaller amounts of tetrahydrofuran are used, the acetylenic Grignard reagent often crystallizes out of the reaction mixture.
8. Vigorous gas evolution (highly flammable ethane gas) and boiling take place during the addition.
9. This type of transfer technique[5] is preferred to open-air transfer to minimize losses due to hydrolysis by atmospheric moisture.
10. Filtration and subsequent washing of the hygroscopic salts are best carried out by replacing the dropping funnel in the reaction vessel with a sintered-glass filter stick. The reaction mixture is kept under a slightly positive nitrogen pressure while the supernatant is led from the filter stick through a polypropylene tube to a suction flask that is kept under a slightly negative pressure with the help of an aspirator.
11. Concentrations were carried out using a rotary evaporator and at a pressure of 12–15 mm and a temperature not exceeding 35°C unless otherwise noted.
12. The crude product at this stage shows the following ^{1}H NMR ($CDCl_3$) δ: 1.22–1.97 (m, 6 H, $H_{2',2''}$, $H_{3',3''}$, $H_{4',4''}$), 3.26–4.08 (m, 2, $H_{5',5''}$), 3.76 (s, 3, OCH_3), 4.36 (s, 2, C≡C-CH_2), 4.81 (bs, 1, H_1).

13. Distillation of the residue after the first treatment with Dowex 50 and methanol gives a product containing 7–10% of the tetrahydropyranyl derivative of methyl 4-hydroxy-2-butynoate. Removal of the by-product 2-methoxytetrahydropyran and retreatment with Dowex 50 and methanol gives a product containing only 0.5–1.5% of the undeblocked alcohol.
14. The distillate often turns a light pink or yellow color in the receiver flask.
15. The checkers found that distillation at a pressure of 15–20 mm (submitters) gave a somewhat lower yield (78–84%). A slight yield improvement (78–94%) was obtained by the checkers by using lower pressure in the distillation.
16. The submitters reported n_D^{22} 1.4595.
17. The submitters reported n_D^{22} 1.4720.

3. Discussion

The preparation of the tetrahydropyranyl derivative of propargyl alcohol is a modification of a published[3] general procedure that is simple and useful for large-scale preparations.

Methyl 4-hydroxy-2-butynoate has been prepared[6] in 83% yield by treatment of 4-hydroxy-2-butynoic acid with 2% sulfuric acid in methanol and in 65% yield by carboxylation in an autoclave of the Grignard reagent of 1-(tetrahydropyran-2'-yloxy)prop-2-yne followed by treatment with 10% sulfuric acid in methanol. 4-Hydroxy-2-butynoic acid has been prepared[6] in 65% yield by treating the Grignard reagent of propargyl alcohol with carbon dioxide in an autoclave for 24 hr followed by acidic hydrolysis with aqueous 10% sulfuric acid. 4-Hydroxy-2-butynoic acid has also been prepared[7] in an unspecified yield by bubbling carbon dioxide for 14 days through a suspension of the Grignard derivative of propargyl alcohol in ether.

The first part of the procedure illustrates a method for the preparation of the tetrahydropyranyl derivative of an alcohol which requires no extraction or wash procedures during the workup of the product.

The second part of the preparation illustrates a very efficient, mild method for the preparation of a highly reactive α,β-acetylenic ester via the carbomethoxylation of the Grignard reagent of a terminal acetylenic compound with methyl chloroformate. This preparation of methyl 4-hydroxy-2-butynoate obviates the necessity[6] of carrying out the carboxylation of an acetylenic Grignard reagent in an autoclave. This procedure also eliminates the necessity[6] of carrying out the continuous ether extraction of 4-hydroxy-2-butynoic acid from an aqueous phase.

The use of a mixture of a strongly acidic cation-exchange resin and methanol to remove a tetrahydropyranyl protecting group offers a very mild method of deblocking that does not require the use of a base during the workup.

Methyl 4-hydroxy-2-butynoate has been used[6] as a starting material for the preparation of a δ-hydroxy-α,β-acetylenic ester. It has also been employed[8] as a dipolarophile in a 1,3-dipolar cycloaddition reaction that resulted in the first synthesis of 8-aza-3-deazaguanosine.

References and Notes

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

brine

Tetrahydropyranyl derivative of propargyl alcohol

tetrahydropyranyl derivative of methyl 4-hydroxy-2-butynoate

1-(tetrahydropyran-2'-yloxy)prop-2-yne

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

toluene (108-88-3)

ethylmagnesium bromide (925-90-6)

ethane (74-84-0)

Tetrahydrofuran (109-99-9)

methyl chloroformate (79-22-1)

dihydropyran

calcium hydride (7789-78-8)

toluenesulfonic acid monohydrate

propargyl alcohol (107-19-7)

Methyl 4-hydroxy-2-butynoate,
2-Butynoic acid, 4-hydroxy-, methyl ester (31555-05-2)

2-methoxytetrahydropyran (6581-66-4)

4-hydroxy-2-butynoic acid

p-toluenesulfonic acid monohydrate (6192-52-5)

tetrahydro-2-(2-propynyloxy)-2H-pyran (6089-04-9)