Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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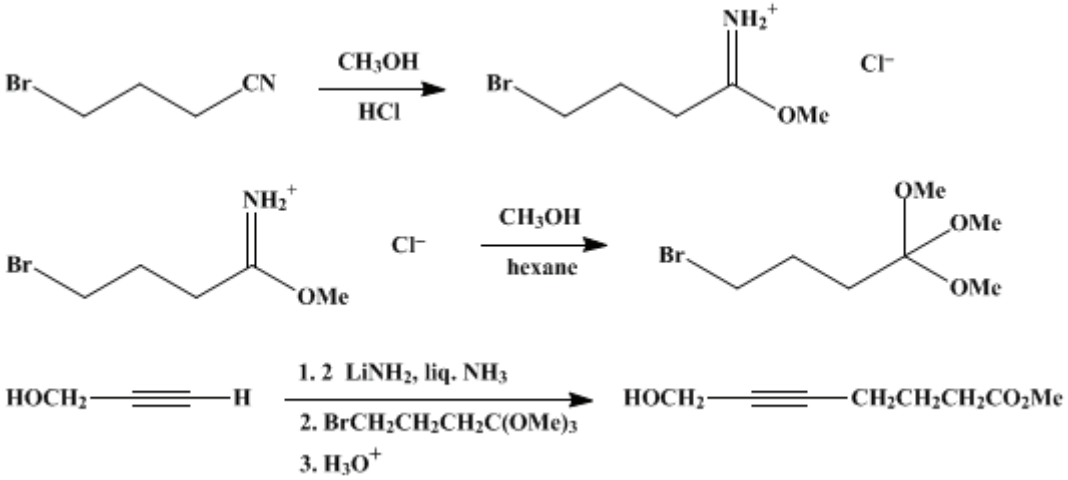
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.067.0193

Organic Syntheses, Coll. Vol. 8, p.415 (1993); Vol. 67, p.193 (1989).

METHYL 7-HYDROXYHEPT-5-YNOATE

[5-Heptynoic acid, 7-hydroxy-, methyl ester]

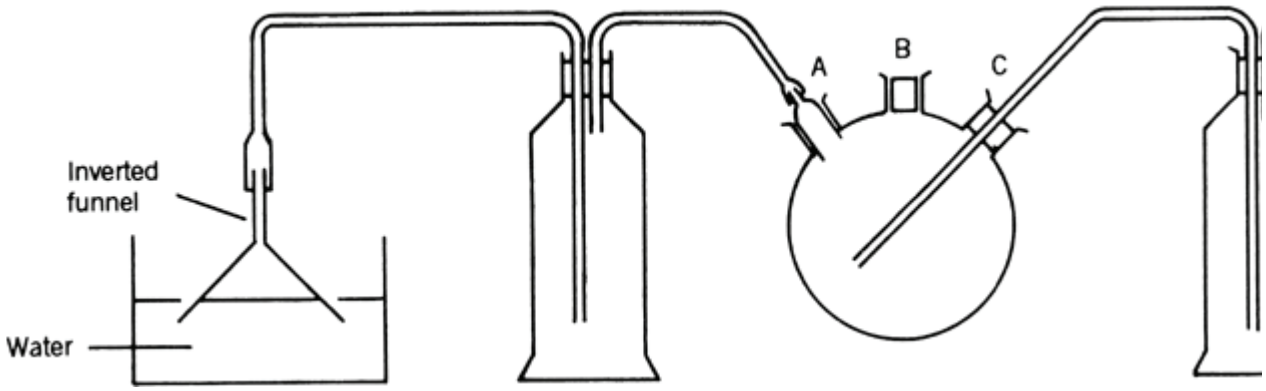


Submitted by Guy Casy[1], John W. Patterson[2], and Richard J. K. Taylor[1].
Checked by Friedhelm Balkenhohl and E. Winterfeldt.

1. Procedure

A. *Methyl 4-bromo-l-butanimidate hydrochloride.* A 500-mL, three-necked, round-bottomed flask is connected via neck A to a hydrogen chloride water trap using the arrangement shown in Figure 1. A stream of nitrogen (Note 1) is introduced via neck C; the flask is flame-dried and allowed to cool. The stopper is removed from neck B and the flask is charged with 29.6 g (0.20 mol) of 4-bromobutanenitrile (Note 2), 200 mL of dry ether (Note 3) and 7.7 g (0.24 mol; 1.2 equiv based on 1.0 equiv of 4-bromobutanenitrile) of dry methanol (Note 3). The stopper is replaced, and the weight of the flask and its contents are recorded. The flask and its contents are cooled to −5°C by immersion in an ice–salt bath, the nitrogen source is removed, and the gas inlet tube is connected to the cylinder of hydrogen chloride. The cylinder tap is cautiously opened, and hydrogen chloride is allowed to bubble through the reaction mixture at a steady but controlled rate until 18.2 g (0.50 mol; 2.5 equiv based on 1.0 equiv of 4-bromobutanenitrile) has been absorbed (Note 4). A stopper is placed in each neck of the flask and a strip of Parafilm is bound around the edge of each ground-glass connection to ensure an airtight seal.

Figure 1



The flask is stored at 5°C (refrigerator) for between 48 hr and 5 days (Note 5), after which time a copious precipitate of the title compound is obtained. The mixture is filtered with suction through a dry

100-mm sintered-glass funnel. After all of the product is collected, a large inverted funnel connected to a nitrogen source is positioned about 15 cm above the sintered funnel to provide a blanket of dry, inert gas (Note 6). The product is washed thoroughly with several portions of dry ether, totaling 500 mL, and then dried to constant weight over solid potassium hydroxide in a desiccator evacuated at 12–20 mm (water aspirator). There is obtained 39.0 g (90%) (Note 7) of methyl 4-bromo-1-butanimidate hydrochloride as fine white crystals, mp 95–97°C (Note 8).

B. *Trimethyl ortho-4-bromobutanoate.* A 1-L, two-necked, round-bottomed flask containing an efficient magnetic stirring bar is purged with nitrogen (Note 1) introduced via a pressure-equalizing glass bubbler (Note 9). The flask is charged with 38.9 g (0.18 mol) of methyl 4-bromo-1-butanimidate hydrochloride, 450 mL of dry hexane (Note 3), and 17.3 g (0.54 mol) of dry methanol (Note 3). A stopper is placed in one neck of the flask; the glass bubbler is removed from the other neck and immediately replaced with a gas outlet adapter to which is attached a balloon filled with nitrogen (Note 10). Finally, a strip of Parafilm is bound around the edge of each ground-glass connection to ensure an airtight seal. The reaction mixture is stirred at room temperature for 48 hr, then filtered with suction to remove the precipitated ammonium chloride. The filter cake is washed with two 30-mL portions of dry hexane, and the filtrate and washings are concentrated under reduced pressure (water aspirator) at 30–40°C by rotary evaporation to leave a slightly turbid, colorless liquid, to which is added 0.25 g of anhydrous potassium carbonate. This material is distilled under reduced pressure to afford 36.4–36.7 g (89–90%) (Note 11) of trimethyl *ortho*-4-bromobutanoate as a colorless oil, bp 65°C (0.5 mm) (Note 12).

C. *Methyl 7-hydroxyhept-5-ynoate.* A 2-L, three-necked, round-bottomed flask equipped with a dry-ice condenser and a mechanical stirring rod is charged with 750 mL of anhydrous ammonia, via a gas inlet tube, at −33°C (Note 13) under nitrogen (Note 1) and (Note 14). The gas inlet tube is removed, and about 0.1 g of lithium wire (Note 2) is added in small portions until a permanent blue color is obtained. Ferric nitrate (0.1 g) is added to discharge the blue color, and after the solution is stirred for 5 min, 4.24 g (0.611 mol; 2.5 equiv based on 1.0 equiv of propargyl alcohol) of lithium wire is added in small portions. After the addition is complete, the flask is fitted with a 100-mL pressure-equalizing, serum-capped dropping funnel. Stirring is continued for 20 min to obtain a gray suspension of lithium amide, to which is added slowly and dropwise a solution of 13.7 g (0.245 mol; 1.5 equiv based on 1.0 equiv of trimethyl *ortho*-4-bromobutanoate) of redistilled propargyl alcohol (Note 2) in 15 mL of dry ether (Note 3). After the solution is stirred for 20 min, a solution of 36.4 g (0.160 mol) of trimethyl *ortho*-4-bromobutanoate in 40 mL of dry ether is added dropwise. Stirring is continued for 3 hr, the reaction vessel is opened to the atmosphere, and its contents are allowed to warm to room temperature over 16–18 hr. The mixture is heated at 50°C on a water bath under a stream of nitrogen to remove any remaining ammonia. This furnishes a gray solid, which is cooled to 0°C, and 5% sulfuric acid is added in 100-mL portions until a pH of 1 is obtained (Note 15). The resulting suspension is stirred at room temperature for 30 min, and extracted with three 200-mL portions of ether. The combined organic extracts are washed with 200 mL of saturated sodium bicarbonate, dried over magnesium sulfate, and filtered. The filtrate is concentrated under reduced pressure (water aspirator) at 30–40°C by rotary evaporation, to leave 19.1 g (77%) of an essentially pure amber oil (Note 16). This material can be distilled under reduced pressure to afford 16.8 g (67%) (Note 17) of methyl 7-hydroxyhept-5-ynoate as a colorless oil, bp 100°C (0.05 mm) (Note 18) and (Note 19).

2. Notes

1. Oxygen-free nitrogen, dried by passage through activated molecular sieves, was used.
2. 4-Bromobutanenitrile was obtained from Lancaster Synthesis Ltd. Alternatively it can be prepared from 1,3-dibromopropane and potassium cyanide using the procedure of Derrick and Henry.[3] Lithium wire (3.2-mm diameter, containing ca. 0.01% sodium) and propargyl alcohol were obtained from the Aldrich Chemical Company, Inc. The latter was dried with potassium carbonate and then distilled prior to use.
3. Diethyl ether and hexane were freshly distilled from blue solutions obtained with sodium and benzophenone. Methanol was distilled from magnesium and iodine. The use of high-purity solvents (e.g., Mallinckrodt AR anhydrous ether, Nanograde hexane, and AR methanol) as received gave only small reductions in yield.

4. To monitor uptake of hydrogen chloride, the flask and its contents are periodically weighed. Typically, the process is complete within 5 min.
5. The progress of the reaction can be monitored by tilting the flask slightly to expose clear supernatant liquor. The flask is left in this position overnight, and if no further crystallization is apparent, the product may be isolated.
6. Alternatively, a dry-nitrogen glove box can be employed.
7. In several smaller-scale experiments (0.07–0.14 mol of 4-bromobutanenitrile) yields in the range 83–93% were achieved.
8. The product has the following spectroscopic properties: IR (Nujol) cm^{-1}: 1650, 1405, 1215, 875; ^1H NMR (TFA-d) δ: 2.08–2.64 (m, 2 H), 3.04 (t, 2 H, $J = 7$), 3.48 (t, 2 H, $J = 6$), 4.32 (s, 3 H), 9.52 (br s, 2 H); ^{13}C NMR (TFA-d) δ: 28.53, 30.82, 33.41, 60.77, 183.65.
9. The glassware was dried overnight at 150°C and assembled hot under nitrogen.
10. This arrangement is preferable to a continuous flow of nitrogen; otherwise the quantity of methanol in situ may be critically diminished.
11. In several smaller-scale experiments (0.05–0.12 mol of methyl 4-bromo-1-butanimidate hydrochloride) yields in the range 90–93% were achieved.
12. The product has the following spectroscopic properties: IR (neat) cm^{-1}: 2840, 1740, 1070; ^1H NMR ($CDCl_3$) δ: 1.77–2.03 (m, 4 H), 3.23 (s, 9 H), 3.33–3.60 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ: 26.54, 29.00, 33.87, 49.37, 115.31. This compound is now commercially available from Aldrich Chemical Company, Inc.
13. To minimize evaporation of liquid ammonia, a temperature of −33 ± 5°C was maintained until the workup by means of a Cryocool™–acetone cooling bath. (A dry ice–acetone cooling bath will suffice.) In addition, the dry-ice condenser was continually charged with a saturated dry ice–acetone mixture.
14. The apparatus is maintained under a slight positive nitrogen pressure until the workup. If this precaution is not taken, atmospheric moisture is drawn into the apparatus (see (Note 19).
15. A total volume of 500–600 mL of 5% sulfuric acid is normally required.
16. This material is essentially pure as indicated by TLC and ^1H NMR spectroscopic analyses, and by CH microanalysis. (Anal. calcd. for $C_8H_{12}O_3$: C, 61.5; H, 7.7. Found: C, 61.8; H, 7.9.)
17. On a smaller scale (0.109 mol of trimethyl *ortho*-4-bromobutanoate) in which a magnetic stirring bar was used to agitate the reaction mixture, a distilled yield of 71% (81% before distillation) was achieved.
18. The submitters report bp 120°C (0.06 mm). The product has the following spectroscopic properties: IR (neat) cm^{-1}: 3420, 1735, 1015; ^1H NMR ($CDCl_3$) δ: 1.63–2.63 (m, 6 H), 3.24 (s, 1 H), 3.67 (s, 3 H), 4.12–4.30 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ: 18.02, 23.54, 32.64, 50.73, 51.43, 79.32, 84.31, 173.60.
19. If moisture is drawn into the apparatus, this can diminish the quantity of the dilithio derivative of propargyl alcohol. If any *O*-lithio monoanion is present during the addition of trimethyl *ortho*-4-bromobutanoate, a quantity of the *O*-alkylated derivative, methyl 4-(2-propynyloxy)butanoate will be produced. The latter exhibits the following ^1H NMR ($CDCl_3$) spectrum: δ: 1.61–2.58 (m, 5 H), 3.52 (t, 2 H, $J = 5.5$), 3.65 (s, 3 H), 4.09 (d, 2 H, $J = 2.5$).

3. Discussion

Methyl 7-hydroxyhept-5-ynoate is an important precursor to alkylating agents that are used to introduce the complete prostaglandin α-side chain.[4,5] It is normally prepared from propargyl alcohol using a six-step sequence originally introduced by Corey and Sachdev[6] with subsequent modifications.[7,8,9,10,11] Alternative routes to methyl 7-hydroxyhept-5-ynoate have also been reported[12,13] but appear less efficient than the one described here. The present route arose from the observation that whereas alkylations of propargyl alcohol-derived anions with 4-halobutanoates were unsuccessful,[13,14] the use of trimethyl ortho-4-bromobutanoate gave efficient alkylation.[4] Related reactions using ortho-ester protecting groups have been reported recently[15] and the preparation of such compounds from nitriles using the Pinner reaction, as described herein, is well established.[16] Trimethyl *ortho*-4-bromobutanoate is also the precursor to the useful four-carbon homologating reagent, trimethyl 4-lithioorthobutanoate.[17]

References and Notes

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

Trimethyl ortho-4-bromobutanoate

O-lithio monoanion

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

1,3-dibromopropane (109-64-8)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

iodine (7553-56-2)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

ferric nitrate

4-bromobutanenitrile (5332-06-9)

lithium amide (7782-89-0)

hexane (110-54-3)

propargyl alcohol (107-19-7)

Methyl 7-hydroxyhept-5-ynoate,
5-Heptynoic acid, 7-hydroxy-, methyl ester (50781-91-4)

Methyl 4-bromo-1-butanimidate hydrochloride,
Methyl 4-bromo-l-butanimidate hydrochloride (21367-90-8)

methyl 4-(2-propynyloxy)butanoate

trimethyl 4-lithioorthobutanoate