Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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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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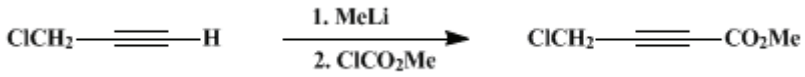
ALKOXYCARBONYLATION OF PROPARGYL CHLORIDE: METHYL 4-CHLORO-2-BUTYNOATE

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



Submitted by M. Olomucki and J. Y. Le Gall[1].
Checked by H. T. M. Le and M. F. Semmelhack.

1. Procedure

Caution! Propargyl chloride, methyl chloroformate, and methyl 4-chloro-2-butynoate are vesicants and lachrymators. This preparation should be conducted in a ventilated hood and protective gloves should be worn.

A 250-mL, round-bottomed flask is equipped with stirring bar (Note 1), thermometer, and pressure-equalizing dropping funnel (dried in an oven at 80°C, assembled while still hot), and the system is placed under argon (Note 2). Via syringe, 7.45 g (7.16 mL, 0.1 mol) of propargyl chloride (Note 3) and 35 mL of anhydrous diethyl ether (Note 4) are added. The solution is stirred and cooled to −50 to −60°C (Note 5) with an alcohol–dry ice bath (Note 6). Under gentle argon pressure, 72.4 mL of a 1.41 *M* solution of methyllithium in diethyl ether (Note 7) is added dropwise over ca. 20 min (Note 8). Stirring is continued for 15 min and 18.9 g (0.2 mol) (Note 9) of methyl chloroformate (Note 10) is added through the dropping funnel over ca. 10 min. The reaction mixture is allowed to warm slowly (3–4 hr) to 0 to −5°C, during which time a fine precipitate appears. Water (40 mL) is added dropwise with efficient stirring; the ether layer is separated and the aqueous layer is extracted 2 times with ether. The combined ether solutions are dried over anhydrous magnesium sulfate, and the ether is removed under reduced pressure with a rotary evaporator. The residual liquid is distilled in a simple distillation assembly under reduced pressure, affording 10.7–11.1 g (81–83%) of methyl 4-chloro-2-butynoate as a colorless liquid, bp 41°C (0.25 mm), n_D^{22} 1.4728 (Note 11).

2. Notes

1. The submitters specify a mechanical stirrer; the checkers find magnetic stirring to be more convenient and equally effective.
2. The system was alternately evacuated with an oil pump and then filled with argon 3 or more times, and a positive pressure was maintained throughout the reaction period. The submitters used nitrogen in place of argon.
3. Propargyl chloride (98% purity), obtained from Fluka AG, was used without further purification.
4. Ether was dried over sodium wire.
5. Although cooling to −20 to −30°C is sufficient, the addition of methyllithium is more convenient at lower temperatures.
6. The checkers used a constant temperature refrigerated bath (Cryocool).
7. Methyllithium in the form of solutions in diethyl ether is supplied by Aldrich Chemical Company, Inc. in rubber septum stoppered bottles, which should be stored in a refrigerator.
8. The solution of methyllithium was conveniently handled using techniques for the manipulation of air-sensitive reagents.[2]
9. Lower yields were obtained when less methyl chloroformate was used. Thus, the yield was about 55% when the reaction was performed with 1 equiv of methyl chloroformate, and 70–72% with 1.5 mol of the latter per mole of propargyl chloride.
10. Methyl chloroformate was used as supplied by Fluka AG (98% purity).
11. The product gives satisfactory elemental analysis and shows the following IR spectrum (film) cm^{-1}:

2267, 1725, 720.

3. Discussion

Methyl 4-chloro-2-butynoate has been prepared[3] in 54% yield by treatment of 4-chloro-2-butynoic acid with 10% sulfuric acid in methanol. 4-Chloro-2-butynoic (chlorotetrolic) acid has been prepared[3] in 40% yield by chromic acid oxidation of 4-chloro-2-butyn-1-ol (the latter obtained[4] in 45% yield by the reaction of 2-butyne-1,4-diol with thionyl chloride) or in 85% yield by treatment of the lithium derivative of propargyl chloride with carbon dioxide.[5]

The present synthesis illustrates a convenient preparation of chlorotetrolic esters that can be performed in one step starting from commercially available and inexpensive products; it is faster and gives better yields as compared with the overall yields of the multistep preparations described earlier. Since chlorotetrolic acid is not an intermediate in this synthesis, the necessity of distilling this explosive product is eliminated. In contrast to the acid, explosions were never observed during distillations of the lower-boiling chlorotetrolic esters.

Other 4-chloro-2-butynoic esters can be obtained by varying the alkyl chloroformates. Thus, ethyl 4-chloro-2-butynoate was prepared[6] in the same way in 60% yield, and *tert*-butyl 4-chloro-2-butynoate in 73% yield; the procedure could probably be further generalized. When butyllithium is used in these syntheses instead of methyllithium, much lower (ca. 30%) yields are obtained.

Chlorotetrolic esters are small, highly functionalized, reactive molecules; of particular interest is the possibility of using them as reagents for chemical modification of biological macromolecules. Different protein nucleophiles react under mild conditions with methyl 4-chloro-2-butynoate by addition across the triple bond and/or substitution of chlorine[7] while the triple bond and the ester group are involved in the reaction of chlorotetrolic esters with nucleic acid bases.[8]

References and Notes

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

4-Chloro-2-butynoic (chlorotetrolic) acid

lithium derivative of propargyl chloride

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

thionyl chloride (7719-09-7)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

chlorine (7782-50-5)

sodium wire (13966-32-0)

chromic acid (7738-94-5)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

methyl chloroformate (79-22-1)

Methyllithium (917-54-4)

argon (7440-37-1)

PROPARGYL CHLORIDE (624-65-7)

Methyl 4-chloro-2-butynoate,
2-Butynoic acid, 4-chloro-, methyl ester (41658-12-2)

4-chloro-2-butynoic acid,
chlorotetrolic acid

4-chloro-2-butyn-1-ol

2-butyne-1,4-diol (110-65-6)

ethyl 4-chloro-2-butynoate

tert-butyl 4-chloro-2-butynoate