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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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.063.0147

Organic Syntheses, Coll. Vol. 7, p.131 (1990); Vol. 63, p.147 (1985).

CYCLOPROPANONE ETHYL HEMIACETAL FROM ETHYL 3-CHLOROPROPANOATE

[Cyclopropanol, 1-ethoxy-]

Submitted by J. Salaün and J. Marguerite[1].
Checked by Steven D. Young, Syun-ichi Kiyooka, and Clayton H. Heathcock.

1. Procedure

A. *1-Ethoxy-1-(trimethylsilyloxy) cyclopropane*. A 1-L, three-necked, round-bottomed flask is fitted with an efficient mechanical stirrer (Note 1), a reflux condenser provided with a calcium chloride tube, and a 500-mL pressure-equalizing dropping funnel equipped with a nitrogen inlet at the top. The flask is flushed with dry nitrogen, and 500 mL of anhydrous toluene (Note 2) and 52.9 g (2.3 g-atom) of sodium cut in small pieces (Note 3) are introduced. The mixture is brought to reflux by means of a heating mantle and the sodium is finely pulverized by vigorous stirring. Heating and stirring are stopped (Note 4), and the mixture is allowed to cool to room temperature. Toluene is removed under nitrogen pressure by means of a double-ended needle and replaced by 500 mL of anhydrous diethyl ether (Note 5) and (Note 6). At this point, 108.5 g (1 mol) of chlorotrimethylsilane (Note 7) is added to the flask. To the mixture, 136.58 g (1 mol) of ethyl 3-chloropropanoate is added dropwise with stirring at a rate sufficient to maintain a gentle reflux over a 3-hr period (Note 8). When about 0.3 mol of chloro ester has been added, a deep-blue precipitate appears (Note 9). When the addition is over, the reaction mixture is heated at reflux for 30 min. The contents of the flask are cooled and filtered through a sintered-glass funnel under a stream of dry nitrogen (Note 10). The precipitate is washed twice with 100 mL of anhydrous diethyl ether.

The colorless filtrate is transferred to a distilling flask and the solvent is distilled through a 25-cm vacuum-jacketed Vigreux column, and the residue is distilled under reduced pressure. After a small forerun (1–2 g), 1-ethoxy-1-(trimethylsilyloxy) cyclopropane is obtained at 43–45°C (12 mm) as a colorless liquid, 106 g (61%) (Note 11).

B. *Cyclopropanone ethyl hemiacetal*. Into a 500-mL Erlenmeyer flask fitted with a magnetic stirring bar is placed 250 mL of reagent-grade methanol. Freshly distilled 1-ethoxy-1-(trimethylsilyloxy) cyclopropane (100 g, 0.56 mol) is added all at once to the methanol and the solution is stirred overnight (12 hr) at room temperature (Note 12). An aliquot (50 mL) of the solution is concentrated by slow evaporation of methanol with a rotary evaporator at room temperature (Note 13) and formation of the methanolysis product is checked by NMR examination of the residue (Note 14). When the reaction is complete (Note 15), the solution is concentrated by removal of the methanol (Note 16). Distillation of the residue through a 20-cm helix-packed, vacuum-insulated column under reduced pressure gives 52 g (89%) of 1-ethoxycyclopropanol, bp 60°C (20 mm) (Note 14) and (Note 17), which contains trace amounts of 1-methoxycyclopropanol (Note 18) and (Note 19).

2. Notes

1. An efficient stirrer is used at a spinning rate sufficient to disperse the molten sodium into small beads of a diameter of approximately 0.1 mm. The checkers found it necessary to use a mechanical stirrer equipped with a nichrome wire "beater" rather than a Teflon paddle. If the sodium sand particles are too large, the final product will be contaminated with starting chloro ester, from which it is very difficult to separate.
2. Toluene is freshly distilled from phosphorus pentoxide into the reaction flask.

3. Sodium pieces are washed in dry pentane or toluene to remove oil.
4. It is essential that stirring be discontinued before cooling is begun to prevent the molten sodium from coalescing into one gigantic lump.
5. Diethyl ether is dried by molecular sieves and distilled from lithium aluminum hydride.
6. To remove the toluene completely, the finely divided sodium is washed under nitrogen with anhydrous diethyl ether (3 × 50 mL).
7. Chlorotrimethylsilane, obtained from Aldrich Chemical Co. or Prolabo (France), is distilled from quinoline or calcium hydride.
8. For the acyloin condensation of diesters it has been recommended that the diester and chlorotrimethylsilane be added together to the sodium dispersion;[2] no difference has been noted with our procedure.
9. The deep-blue color seems to be indicative of a satisfactory reduction. When the color is yellow–green, the yield is usually poor.
10. *Caution! Because of the pyrophoric nature of finely divided alkali metal residues or production of free acid (HCl) from the chlorosilane, the products are sensitive to moisture. Unreacted sodium is destroyed by careful addition of ethanol to the residual solid.*
11. The yield varies from 60 to 85%, bp 50–52°C (18 mm); 60–62°C (35 mm); 66–68°C (40 mm); the proton magnetic resonance (PMR) spectrum (CCl_4 solution, $HCCl_3$ external reference) shows absorption at δ: 0.08 (s, 9 H), 0.70 (m, 4 H), 1.05 (t, 3 H, J = 7.11) and 3.55 (q, 2 H, J = 7.11); the IR spectrum (CCl_4) exhibits absorption at 3090 and 3010 (cyclopropane), 1250, 845, and 758 cm^{-1} ($-Si[CH_3]_3$).
12. After the solution is stirred for 5–10 min, the clear solution becomes slightly turbid for a few minutes and then turns clear again. When these changes are not observed, methanolysis has not occurred.
13. If some 1-ethoxy-1-(trimethylsilyloxy) cyclopropane is still present, it will be lost by too rapid evaporation of methanol.
14. The product has the following spectral properties: IR (CCl_4): 3600 and 3400 (hydroxyl), 3010 and 3090 cm^{-1} (cyclopropyl); ^1H NMR (CCl_4) δ: 0.84 (s, 4 H), 1.18 (t, 3 H, J = 7.11), 3.73 (q, 2 H, J = 7.11) and 4.75 (m, 1 H).
15. Lack of NMR absorption around δ 0.08 shows that the trimethylsilyloxy group has been completely removed.
16. If the reaction is not complete, as shown by the presence of a singlet around δ 0.08, a spatula tip full of pyridinium *p*-toluenesulfonate[3] is added and the mixture is stirred for 4 hr. Methanol is then removed, and the residue is dissolved in 200 mL of diethyl ether. The solution is washed with saturated sodium chloride until neutral, dried over anhydrous sodium sulfate, and concentrated. Addition of a drop of HCl or of chlorotrimethylsilane is also effective to complete the reaction. Then, the hydrochloric acid is removed with methanol. (Thus, it is not necessary to wash with saturated sodium chloride until neutral.)
17. The yield varies from 78 to 95%, bp 51°C (12 mm), 64°C (25 mm), 75°C (46 mm).
18. On standing with methanol at 25°C for 1 week, 65% of 1-ethoxycyclopropanol is converted into 1-methoxycyclopropanol; conversion appears to be complete after 15 days.[4] The spectral properties of the 1-methoxycyclopropanol are: IR (CCl_4): 3600 and 3400 (hydroxyl), 3010 and 3090 cm^{-1} (cyclopropyl); ^1H NMR (CCl_4) δ: 0.85 (s, 4 H) and 3.40 (s, 3 H).
19. Cyclopropanone hemiacetal can be kept unaltered for several months at 0°C in the refrigerator. On heating above 100°C or on standing in acidic solvents, it undergoes ring opening to give ethyl propionate.

3. Discussion

Cyclopropanone ethyl hemiacetal was first synthesized by the reaction of ketene and diazomethane in ether at −78°C in the presence of ethanol.[4] The yield is low (43%) and the reaction is hazardous, especially when a large-scale reaction is required. The method described in this procedure for the preparation of cyclopropanone ethyl hemiacetal from ethyl 3-chloropropanoate is an adaptation of that described previously;[5] the procedure described for the synthesis of 1-ethoxy-1-(trimethylsilyloxy) cyclopropane is patterned after the method reported by Rühlmann.[6]

Cyclopropanone ethyl hemiacetal is a molecule of considerable interest since its reactions appear to involve the formation of the labile cyclopropanone.[7] It readily undergoes nucleophilic addition of Grignard reagents,[4,5] azides,[4] and amines[8] to provide 1-substituted cyclopropanols in high yields. It has

been reported that upon treatment with an equimolar amount of methylmagnesium iodide, the cyclopropanone ethyl hemiacetal is converted into iodomagnesium 1-ethoxycyclopropylate,[9] which can react with hydrides, organometallic reagents, cyanide carbanion, and phosphorus ylides[10] to provide useful synthons. The preparation of some challenging 2,3-disubstituted cyclopentanones including a total synthesis of the 11-deoxyprostaglandin has been reported from the cyclopropanone hemiacetal.[11] The ready availability of this compound should lead to other synthetic applications. For a recent review dealing with the chemistry of the cyclopropanone hemiacetals, see [12].

On the other hand, silylated cyclopropanols, such as 1-ethoxy 1-(trimethylsilyloxy) cyclopropane, work well as homoenolate anion precursors. They undergo ring opening reactions with a variety of metal halides ($TiCl_4$, $GaCl_3$, $SbCl_5$, $ZnCl_2$, $HgCl_2$ …). Thus, in the presence of suitable catalysts, the zinc homoenolates of alkyl propionates undergo a variety of carbon-carbon bond forming reactions with a very high degree of chemoselectivity.[13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 277
- Org. Syn. Coll. Vol. 8, 556
- Org. Syn. Coll. Vol. 9, 466

References and Notes

1. Laboratoire des Carbocycles, ERA n° 316, Bat. 420, Université de Paris-Sud, 91405 Orsay, France.
2. Bloomfield, J. J.; Owsley, D. C.; Nelke, J. M. *Org. React*. **1976**, *23*, 306; Bloomfield, J. J.; Nelke, J. M. *Org. Synth., Coll. Vol. VI* **1988**, 167.
3. Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem*. **1977**, *42*, 3772.
4. Wasserman, H. H.; Clagett, D. C. *J. Am. Chem. Soc*. **1966**, *88*, 5368; Wasserman, H. H.; Cochoy, R. E.; Baird, M. S. *J. Am. Chem. Soc*. **1969**, *91*, 2375.
5. Salaün, J. *J. Org. Chem*. **1976**, *41*, 1237; **1977**, *42*, 28.
6. Rühlmann, K. *Synthesis* **1971**, 236.
7. Turro, N. J. *Acc. Chem. Res*. **1969**, *2*, 25; Shaafsma, S. E.; Steinberg, H.; de Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 1170.
8. Wasserman, H. H.; Adickes, H. W.; de Ochoa, D. Espejo *J. Am. Chem. Soc*. **1971**, *93*, 5586.
9. Brown, H. C.; Rao, C. G. *J. Org. Chem*. **1978**, *43*, 3602.
10. Salaün, J.; Fadel, A. *Tetrahedron Lett*. **1979**, 4375; Salaün, J.; Bennani, F.; Compain, J. C.; Fadel, A.; Ollivier, J. *J. Org. Chem*. **1980**, *45*, 4129.
11. Salaün, J.; Ollivier, J. *Nouv. J. Chim*. **1981**, *5*, 587.
12. Salaün, J. *Chem. Rev*. **1983**, *83*, 619; Salaün, J. *Top. Curr. Chem*. **1988**, *144*, 1.
13. Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc*. **1987**, *109*, 8056 and references cited therein.

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

chloro ester

1-substituted cyclopropanols

cyanide carbanion

phosphorus ylides

2,3-disubstituted cyclopentanones

11-deoxyprostaglandin

silylated cyclopropanols

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

toluene (108-88-3)

sodium (13966-32-0)

hydroxyl (3352-57-6)

methylmagnesium iodide (917-64-6)

Quinoline (91-22-5)

Pentane (109-66-0)

Ketene (463-51-4)

cyclopropane (75-19-4)

Diazomethane (334-88-3)

ethyl propionate (105-37-3)

lithium aluminum hydride (16853-85-3)

calcium hydride (7789-78-8)

ETHYL 3-CHLOROPROPANOATE (623-71-2)

cyclopropyl (2417-82-5)

CHLOROTRIMETHYLSILANE (75-77-4)

chlorosilane (13465-78-6)

CYCLOPROPANONE (5009-27-8)

Cyclopropanone ethyl hemiacetal,
Cyclopropanol, 1-ethoxy-,
1-ethoxycyclopropanol (13837-45-1)

1-ethoxy-1-(trimethylsilyloxy) cyclopropane,
1-ethoxy 1-(trimethylsilyloxy) cyclopropane (27374-25-0)

1-methoxycyclopropanol

Cyclopropanone hemiacetal

iodomagnesium 1-ethoxycyclopropylate

phosphorus pentoxide (1314-56-3)

pyridinium p-toluenesulfonate