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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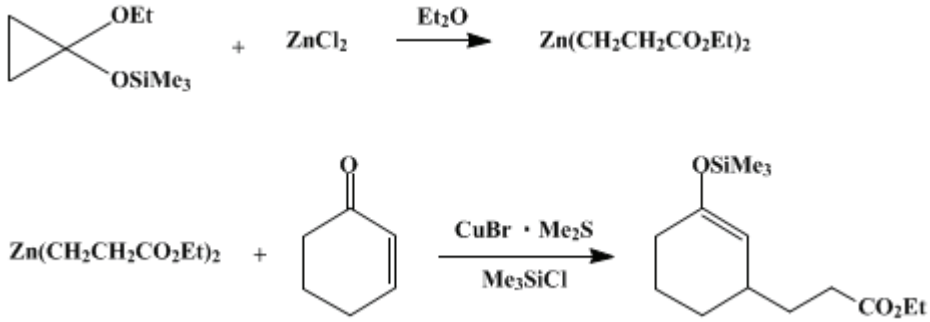
Organic Syntheses, Coll. Vol. 8, p.277 (1993); Vol. 66, p.43 (1988).

COPPER-CATALYZED CONJUGATE ADDITION OF A ZINC HOMOENOLATE: ETHYL 3-[3-(TRIMETHYLSILYLOXY) CYCLOHEX-2-ENYL]PROPIONATE

[2-Cyclohexene-1-propanoic acid, 3-[(trimethylsilyl)oxy]-, ethyl ester]



Submitted by Eiichi Nakamura and Isao Kuwajima[1].
Checked by Tina M. Kravetz, Daniel Cheney, and Leo A. Paquette.

1. Procedure

In a tared 1-L, three-necked flask, two necks of which are covered with rubber septa and the other connected to a nitrogen-vacuum source, is placed 17.2 g of zinc chloride (Note 1). The flask is evacuated to approximately 2 mm and heated with a burner with swirling until practically all of the salt melts. The flask is cooled and filled with nitrogen. The dried salt weighs 16.4–17 g (ca. 0.12 mol) (Note 2). An efficient magnetic stirring bar and a Dimroth condenser in place of a rubber septum are set in position, and the flask is again flushed with nitrogen. Ether (300 mL) (Note 3) is introduced via the septum, and stirring is initiated and maintained throughout the reaction. The mixture is refluxed gently for 1 hr to aid dissolution of the solid state (Note 4). The flask is cooled, and 1-trimethylsilyloxy-1-ethoxycyclopropane (41.80 g, 0.24 mol) (Note 5) is introduced with the aid of a hypodermic syringe during 5 min. The cloudy mixture is stirred at room temperature for 1 hr; the more dense lower layer may have mostly disappeared at this point. The mixture is refluxed for 30 min to complete homoenolate formation. The clear, colorless solution of the zinc homoenolate and chlorotrimethylsilane is cooled in an ice bath, and cuprous bromide/dimethyl sulfide complex (0.4 g, 2 mmol) (Note 6) is added by removing the septum while nitrogen adequate to exclude air is introduced through the inlet. 2-Cyclohexen-1-one (9.62 g, 0.1 mmol) (Note 7) is introduced via the septum during 1 min, and then hexamethylphosphoric triamide (HMPA) (34.8 mL, 0.2 mol) (Note 8) and (Note 9) is added during 5 min. A slightly exothermic reaction occurs initially and the bath is removed after 20 min. After 3 hr at room temperature, 40 g of silica gel (Note 10) and 300 mL of dry hexane (Note 11) are added while the mixture is stirred vigorously for 3 min. The supernatant liquid is decanted, and the residue is suspended in 60 mL of dry ether. Dry hexane (60 mL) is added and the supernatant liquid is decanted. This extractive procedure is repeated once and the combined organic phase is filtered through Celite (Note 12). After concentration with a rotary evaporator, the oily product is distilled under reduced pressure (ca. 2 mm). 1-Trimethylsilyloxy-1-ethoxycyclopropane (8–10 g) is recovered as the first fraction (bp 26°C at 2.3 mm). The majority of the HMPA remaining after workup distils at 80–120°C/2.3 mm. Finally, the desired product (18.9–20.5 g, 70–76%) is obtained as a fraction boiling at 130–132°C/2.3 mm (Note 13).

2. Notes

1. Zinc chloride was purchased from Koso Chemical Company and used as such (cf. *Org. Synth., Coll. Vol. VI*, **1988**, 692). Alfa's ultra pure-grade reagent resisted complete dissolution and appeared less suitable. The checkers used "Baker Analyzed" reagent zinc chloride with prior drying at 0.3 mm.

2. The amount of zinc chloride may be in slight excess of the theoretical amount (i.e., 0.5 equiv of the cyclopropane).
3. Ether was distilled from sodium benzophenone ketyl immediately before use.
4. A two-layer mixture results.
5. This cyclopropane was prepared according to an Organic Syntheses procedure (*Org. Synth., Coll. Vol. VII*, **1990**, 131).
6. Cuprous bromide/dimethyl sulfide complex was purchased from Aldrich Chemical Company, Inc. and used as such.
7. Cyclohexenone was purchased from Tokyo Kasei Chemical Company or Aldrich Chemical Company, Inc. and used after simple distillation at reduced pressure.
8. Hexamethylphosphoric triamide (HMPA) was purchased from Tokyo Kasei Chemical Company and used after distillation from calcium hydride under reduced pressure.
9. This step was also checked, substituting *N,N′*-dimethylpropyleneurea (DMPU),[2] supplied by Aldrich Chemical Company, Inc. or Fluka, for HMPA. The yield of final product dropped somewhat to 16.36–17.36 g (60–64%), but otherwise the reaction proceeded as described.
10. Ordinary silica gel (Wakogel C-300, Wako Chemical Company) was used.
11. Hexane was distilled from calcium hydride and stored over a potassium mirror. The checkers stored the redistilled hexane over molecular sieves.
12. Since the product has only moderate hydrolytic stability, the extractive procedure should be carried out rapidly under a flow of nitrogen. Operation in a nitrogen-filled plastic bag may eliminate the possibility of hydrolysis.
13. When the workup is performed as described (Note 11), the product may contain small amounts of residual HMPA and up to 5% (GLC estimation) of the keto ester resulting from hydrolysis of the enol silyl ether. Retardation factor values of the keto ester and the silyl ether or thin-layer analysis (Merck silica gel plates coated with a 0.25-mm layer of Kieselgel 60 F_{254}, developed with 30% ethyl acetate in hexane) were 0.4 and 0.8, respectively; gas-chromatographic (GLC) analysis (OV-101, capillary glass column of 0.25 mm × 20 m, 120°C) showed retention times of 2.56 and 4.96 min for these two compounds, respectively. GLC analysis also indicated the ratio of the regioisomers of the enol silyl ether as >99 : 1 (4.96 and 6.13 min, respectively). On a smaller scale where the product can readily be handled on silica gel chromatography, a yield over 85% may be attained. Correct elemental analysis has been obtained for a sample purified by chromatography and distillation. Spectral properties of the product are as follows: ^{1}H NMR (300 MHz, CCl_4) δ: 0.04 (s, 9 H), 1.10 (t, 3 H, J = 7.1), 1.3–2.2 (m, 11 H), 3.93 (q, 2 H, J = 7.1), 4.55 (br s, 1 H); IR (neat film) cm^{-1} 1730 (s), 1655 (s), 1445 (m), 1365 (s), 1245 (s), 1180 (vs), 840 (vs), 745 (s).

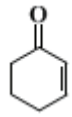
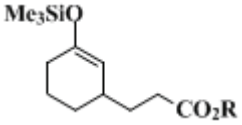
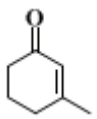
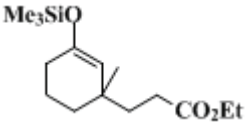
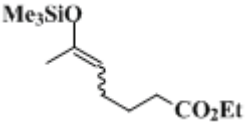
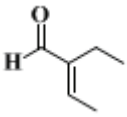
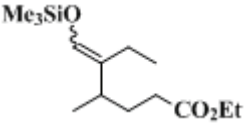
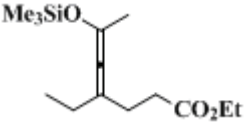
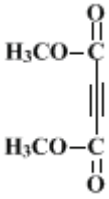
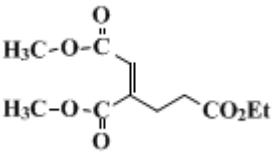
3. Discussion

Unlike their enolate counterparts, homoenolates have been underrated because of a prior lack of synthetic accessibility.[3] Many of the previously known homoenolates cyclize readily to the cyclopropanolate tautomer and behave chemically as the latter. 1-Alkoxy-1-silyloxycyclopropanes[4] have provided, for the first time, examples of reactive yet characterizable homoenolates (of alkyl propionates). A titanium homoenolate undergoes 1,2-addition to carbonyl compounds, providing an efficient synthetic route to γ-lactones.[4] The present procedure represents an unique and highly efficient method for the preparation of the zinc homoenolate of an alkyl propionate and illustrates its copper-catalyzed conjugate addition.[5] The reaction consists of two stages; the first part of the present procedure generates a mixture of the zinc homoenolate and chlorotrimethylsilane, from which the homoenolate can be isolated by removal of the volatile material under reduced pressure, and the second part involves the chlorotrimethylsilane-assisted conjugate addition of the transient copper homoenolate. Only one of the propionate moieties on the zinc metal is available for the conjugate addition. The reaction mechanism has already been discussed briefly.[6]

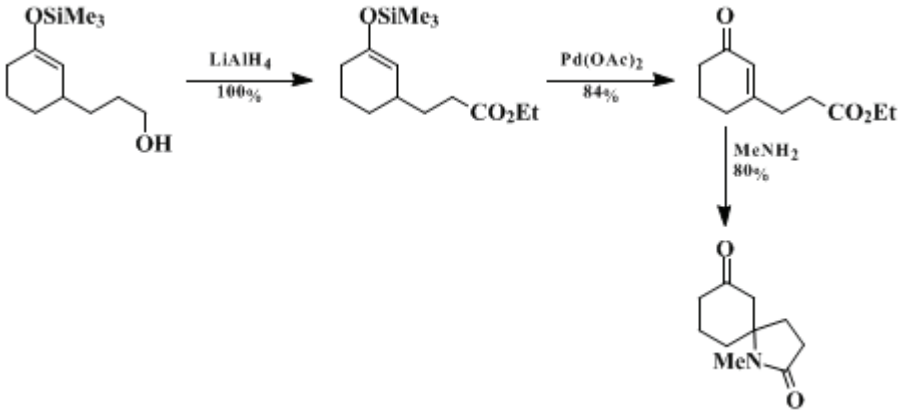
The reaction is applicable to a variety of enones, enals, and acetylenic carbonyl compounds (Table I). No 1,2-addition is seen under copper-catalyzed conditions since the zinc homoenolate does not generally undergo a 1,2-addition reaction to carbonyl compounds. The conjugate adduct is useful for organic synthesis as indicated by the scheme below. The enol silyl ether moiety acts either to protect or activate the ketone functionality. The ready hydrolytic generation of the keto ester from the conjugate adduct provides an efficient entry to 6-keto esters. Replacement of the enone with an acyl halide leads

to 4-keto esters in high yield,[5] and the palladium-catalyzed reaction with aryl and vinyl halides gives 3-aryl- and 3-vinyl propionates.[7] The purified homoenolate undergoes 1,2-addition to aldehydes in the presence of chlorotrimethylsilane.[8]

TABLE I
CONJUGATE ADDITION OF HOMOENOLATE OF ESTERS

Acceptor	Product	%Yield		
		R= i-Pr 93	R = Et 76	R = Me 91
				92
				80
		75		
		73		
		63		

No other synthetic method is known that achieves the equivalent transformation. Rather elaborate procedures using an allylic anion type of the homoenolate "equivalents"[6] or homoenolate radicals[9] have been reported, but their tolerance to the structure of the enone acceptor is much narrower.



This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 274
- Org. Syn. Coll. Vol. 10, 411

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

silica gel

sodium benzophenone ketyl

dimethyl sulfide complex

ethyl acetate (141-78-6)

ether (60-29-7)

nitrogen (7727-37-9)

cuprous bromide (7787-70-4)

zinc chloride (7646-85-7)

cyclopropane (75-19-4)

dimethyl sulfide (75-18-3)

hexane (110-54-3)

calcium hydride (7789-78-8)

2-cyclohexen-1-one,
cyclohexenone (930-68-7)

hexamethylphosphoric triamide (680-31-9)

CHLOROTRIMETHYLSILANE (75-77-4)

silyl ether (13597-73-4)

N,N'-dimethylpropyleneurea (7226-23-5)

1-trimethylsilyloxy-1-ethoxycyclopropane (27374-25-0)

ETHYL 3-[3-(TRIMETHYLSILYLOXY)CYCLOHEX-2-ENYL]PROPIONATE,
2-Cyclohexene-1-propanoic acid, 3-[(trimethylsilyl)oxy]-, ethyl ester (90147-64-1)