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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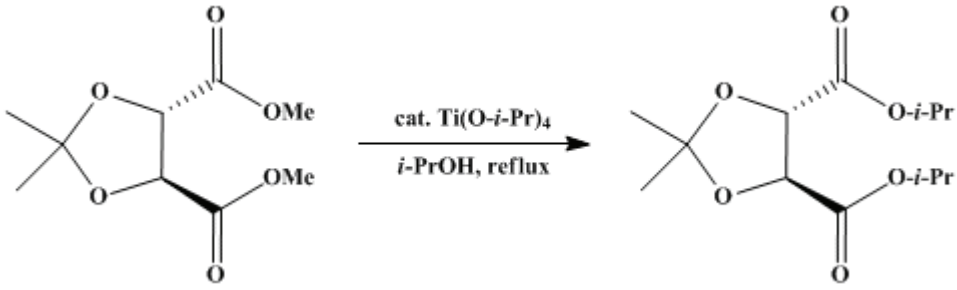
DIISOPROPYL (2*S*,3*S*)-2,3-*O*-ISOPROPYLIDENETARTRATE

[1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl-, bis(1-methylethyl)ester, (4*R*-*trans*)-]



Submitted by René Imwinkelried, Martin Schiess, and Dieter Seebach[1].
Checked by Isao Kurimoto and Ryoji Noyori.

1. Procedure

A dry, 500-mL, two-necked flask equipped with a magnetic stirrer and a reflux condenser is flushed with nitrogen and charged with 8.4 mL (45.8 mmol) of dimethyl (2*S*,3*S*)-2,3-*O*-isopropylidenetartrate (Note 1) and 250 mL of absolute 2-propanol (Note 2). To the resulting solution is added with a plastic syringe and hypodermic needle 1.35 mL (4.6 mmol) of tetraisopropyl titanate (Note 1). The mixture is refluxed with stirring for 2 hr. To remove the methanol formed, the flask is transferred to a rotary evaporator, and the contents are concentrated to 10–12 mL. The oily residue is once more dissolved in 250 mL of absolute 2-propanol (Note 2) and refluxed for 2 hr. The solvent is removed again in a rotary evaporator, and the resulting yellow oil is dissolved in 100 mL of diethyl ether. After addition of 5 mL of water (Note 3) the pale mixture is vigorously stirred for 10 min and then dried over anhydrous magnesium sulfate. The flaky suspension is filtered and the filter cake washed with three 25-mL portions of ether. The ether solution is concentrated in a rotary evaporator. The residue, 12.5–13.1 g of a slightly yellow oil, solidifies on standing. This solid is freed from small amounts of solvent by an oil-pump vacuum (ca. 0.01 mm) at room temperature for 2 hr. Further purification by short-path distillation at 91–93°C/0.05 mm furnishes 11.5–12.0 g (91–95%) of a slightly yellow solid, which turns colorless on crushing, mp 41.5–42.5°C, $[\alpha]_D^{RT}$ +42 ± 0.3° ($CHCl_3$, c 4).

2. Notes

1. Commercial (Fluka purum) (−)-or (+)-dimethyl 2,3-*O*-isopropylidenetartrate and tetraisopropyl titanate can be used without further purification.
2. 2-Propanol was heated at reflux over $CaSO_4$, distilled, and redistilled with addition of tetraisopropyl titanate (ca. 10 g/L).
3. This is done to hydrolyze titanium alkoxides. Part of the titanium alkoxides is removed during evaporation of the solvents in the rotatory evaporator [$Ti(OCHMe_2)_4$, bp 78°C/12 mm].

3. Discussion

Normally, transesterifications are acid- or base-catalyzed (e.g., sulfuric acid, *p*-toluenesulfonic acid, and potassium or sodium alkoxides in the appropriate alcohols).[2] These methods fail with molecules containing acid- or base-labile functional groups. The titanate-mediated esterifications, deacylations, and transesterifications of rather simple, monofunctional substrates are described in the patent literature; see the references in a recent article.[3] Recently, Seebach et al.[3,4,5] have demonstrated that this method is applicable also to substrates with additional functional groups that would not survive acid- or base-catalyzed transesterification conditions, such as C≡C and C≡N bonds, acetals, β-hydroxy and β-acyloxy esters, β-lactams, *tert*-butyldimethylsilyloxy groups, BOC,[6] and other carbamate protecting groups. The

possible applications of this transesterification are illustrated in Scheme 1, and some characteristic examples are given in Table I. Of course, the method can only establish equilibrium conditions. Therefore, depending on the particular case, components of the equilibria have to be removed (see procedure above) or used in large excess to drive the conversion to the desired products.

Scheme 1. Titanate-mediated transesterifications. X = functional group (see accompanying text); (a) transesterification in alcoholic solvents, with removal of acyl protecting groups and exchange of the alcohol component of ester groups in the substrate; (b) transesterification in ester solvents, with acylation of hydroxy groups and exchange of the alcohol or of the acid component of ester groups in the substrate.

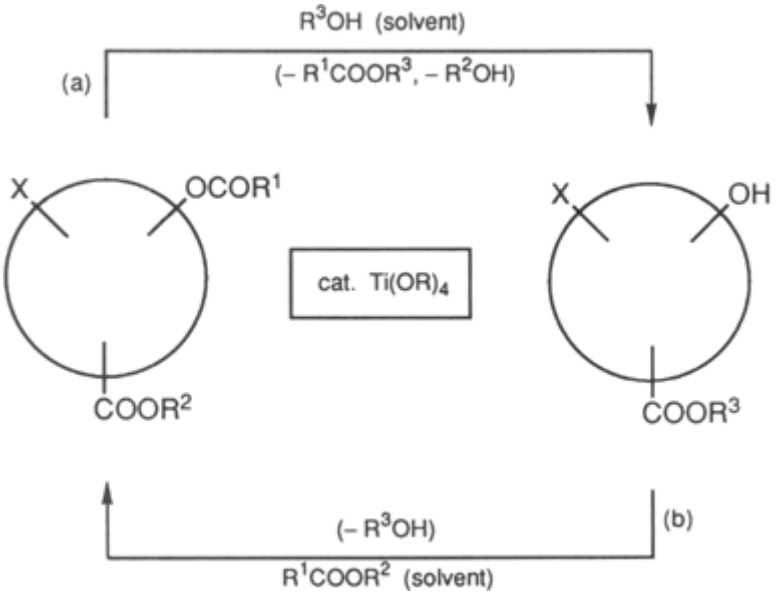
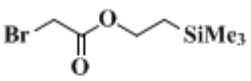
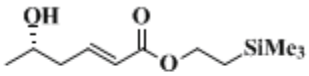


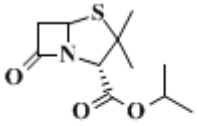
TABLE I
PRODUCTS OF TRANSESTERIFICATION WITH TITANATE CATALYSIS[3,4,5,6]



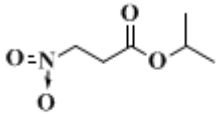
71% from ethyl ester and 2-trimethylsilylethanol



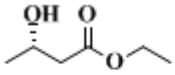
74% from methyl ester and 2-trimethylsilylethanol



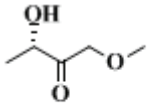
91% from methyl ester and 2-propanol



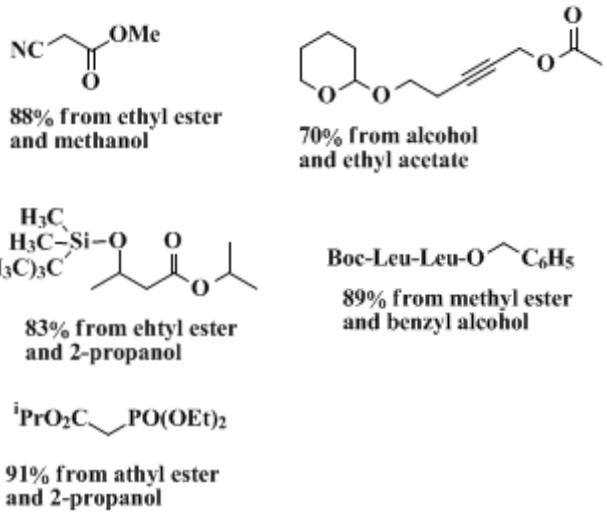
50% from methyl ester and 2-propanol



90% from 0-3,5-dinitrobenzoate and ethanol



60% from O-propanoyl derivative and ethanol



This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 495

References and Notes

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

(−)-or (+)-dimethyl 2,3-O-isopropylidenetartrate

$CaSO_4$

$Ti(OCHMe_2)_4$

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

2-propanol (67-63-0)

magnesium sulfate (7487-88-9)

p-toluenesulfonic acid (104-15-4)

BOC

tetraisopropyl titanate

Diisopropyl (2S,3S)-2,3-O-isopropylidenetartrate (81327-47-1)

1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl-, bis(1-methylethyl)ester, (4R-trans)-

dimethyl (2S,3S)-2,3-O-isopropylidenetartrate (37031-30-4)