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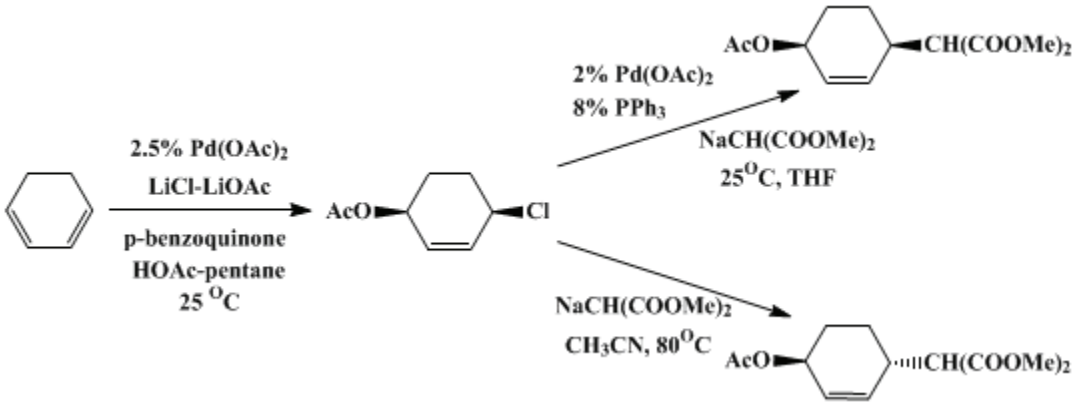
STEREOSELECTIVE 1,4-FUNCTIONALIZATIONS OF CONJUGATED DIENES: *cis*- AND *trans*-1-ACETOXY-4-(DICARBOMETHOXYMETHYL)-2-CYCLOHEXENE

[Propanedioic acid, [4-(Acetyloxy)-2-cyclohexen-1-yl]-, dimethyl ester, *cis*- and *trans*-]



Submitted by Jan-E. Bäckvall and Jan O. Vågberg[1].
Checked by Michael R. Sestrick and Albert I. Meyers.

1. Procedure

A. *cis-1-Acetoxy-4-chloro-2-cyclohexene.* A 1-L, one-necked, round-bottomed flask equipped with a magnetic stirring bar is charged with 200 mL of acetic acid, 5.1 g (0.12 mol) of lithium chloride, 12.2 g (0.12 mol) of lithium acetate dihydrate, 0.67 g (3 mmol) of palladium acetate, and 12.9 g (0.12 mol) of *p*-benzoquinone. The contents of the flask are stirred at room temperature until all components are dissolved, and 300 mL of pentane is added. To the pentane phase of the biphasic system formed is added 4.82 g (60 mmol) of 1,3-cyclohexadiene (Note 1). The reaction mixture is stirred at a moderate rate (Note 2) at room temperature and after 4 hr, 2.87 g (33 mmol) of manganese dioxide (Note 3) is added. After the flask is stirred for another 4 hr at room temperature, the organic phase is separated and saved, and 2.87 g (33 mmol) of manganese dioxide and 20 mL of acetic acid are added to the remaining acetic acid, which is vigorously stirred for 30 min. To the mixture are added 2.6 g (60 mmol) of lithium chloride and 300 mL of pentane. A new portion of 4.82 g (60 mmol) of 1,3-cyclohexadiene is added and the reaction mixture is stirred at a moderate rate (Note 1) at room temperature overnight (12–15 hr). To the reaction mixture is added 70 mL of saturated sodium chloride solution and the organic phase is separated and saved. The aqueous phase is filtered and extracted with pentane (2 × 300 mL). The combined organic phases are washed with water (2 × 120 mL), 120 mL of saturated aqueous sodium carbonate, 120 mL of 2 *M* sodium hydroxide, 120 mL of water, and 120 mL of saturated sodium chloride solution. The organic phase is dried over magnesium sulfate and the solvent is removed by rotary evaporation at reduced pressure, giving 16.5–17.5 g (79–84%) of a yellow oil. Kugelrohr distillation (95–105°C, 1 mm) of the crude product affords 14.6–15.6 g (71–75%) of pure *cis*-1-acetoxy-4-chloro-2-cyclohexene (>98% *cis*). Analysis by HPLC and GLC [high-performance (pressure) liquid and gas chromatograph] shows about 1% contamination of diacetate as the only impurity. No dichloride can be detected (<0.5%).

B. *cis-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene.* A 2-L, two-necked, round-bottomed flask equipped with a magnetic stirrer, a nitrogen-vacuum inlet, and a rubber septum is charged with 17.5 g (0.1 mol) of *cis*-1-acetoxy-4-chloro-2-cyclohexene, 0.49 g (2.2 mol) of palladium acetate and 2.4 g (9.0 mmol) of triphenylphosphine (Note 4). The flask is flushed with nitrogen (Note 5). To the flask is added 550 mL of a 0.2 *M* solution (0.11 mol) of sodium dimethyl malonate in tetrahydrofuran (THF) by

syringe (Note 6). The flask is again flushed with nitrogen and the reaction mixture, which now has turned yellow, is stirred at room temperature for 2 hr (Note 7). The flask is opened and 200 mL of saturated aqueous sodium bicarbonate is added. The stirring is continued for 20 min, and then 100 mL of water and 200 mL of ether are added. The contents of the flask are transferred into a 2-L separatory funnel and the organic phase is separated. The remaining aqueous phase is extracted with ether (3 × 300 mL). The combined organic phases are washed with 200 mL of saturated brine, dried over anhydrous magnesium sulfate, concentrated on a rotary evaporator to approximately 400 mL, and then filtered through a short silica gel column (Note 8). Removal of the rest of the solvent by rotary evaporation at reduced pressure gives 30.4–31.3 g of a light-brown oil. Excess dimethyl malonate is removed by Kugelrohr distillation at 100°C (1 mm). Kugelrohr distillation (140°C, 0.2 mm) of the remaining crude product affords 25.9–26.7 g (91%) of *cis*-1-acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene as a light-brown oil. Analysis by GLC indicates a chemical purity of 95–98%.

C. *trans-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene.* In a 1-L, two-necked flask equipped with a reflux condenser, a nitrogen gas inlet, and a magnetic stirring bar are placed 8.73 g (50 mmol) of *cis*-1-acetoxy-4-chloro-2-cyclohexene and 400 mL of a 0.18 *M* solution (72 mmol) of sodium dimethyl malonate in acetonitrile (Note 9). The flask is flushed with nitrogen and then heated in an oil bath at reflux for 21 hr. The reaction mixture is cooled to room temperature and 5 g of solid sodium hydrogen carbonate is added. The mixture is stirred for 2 hr, poured into 800 mL of ether, and the resulting mixture is filtered. The organic phase is collected and the solvent is removed on a rotary evaporator to afford 16.1 g of the product together with dimethyl malonate. The excess dimethyl malonate is removed by Kugelrohr distillation at 70°C (0.2 mm). The residual crude yellow oil was dissolved in a minimal amount of ethyl acetate and passed through a short silica plug (30–35g, Alfa silica) gel (53 μm) eluting with a small amount of fresh ethyl acetate. Removal of ethyl acetate on a rotary evaporator and further concentration at 0.2 mm overnight yielded 11.6–12.2 g (86–90%) of *trans*-1-acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene as a clear oil, essentially pure (99% by GLC) (Note 10).

2. Notes

1. 1,3-Cyclohexadiene was obtained from Aldrich Chemical Company, Inc. and distilled before use. It can also be synthesized according to *Org. Synth., Coll. Vol. V*, **1973**, 285.
2. A stirring rate 5–10 revolutions per second (rps) was used (only a small vortex was present).
3. Commercial, active manganese dioxide from Merck-Schuchardt was used.
4. Palladium acetate and triphenylphosphine generate the active tri- or tetrakis (triphenylphosphine) palladium(0) catalyst on addition of sodium dimethyl malonate.
5. A manifold system connected to a vacuum line and a nitrogen line was used.
6. Sodium dimethyl malonate was prepared from equimolar amounts of sodium hydride and dimethyl malonate.
7. The reaction is usually over after 30 min. The reaction was checked by GLC or TLC to confirm completion.
8. This filtration was done in order to remove remaining palladium species and phosphine oxide. A column (4 × 8 cm) packed with Alfa silica gel (58 μm) was used.
9. Acetonitrile was stirred overnight with calcium hydride and then distilled onto freshly activated Linde 4A molecular sieves.
10. All GLC analyses were performed on a 2.4-m × 6-mm glass column packed with 5% SE-30 on Chromosorb W or crosslinked 50% phenylmethylsilicone.

3. Discussion

This procedure for stereoselective 1,4-functionalization of 1,3-dienes is based on 1,4-acetoxychlorination[2,3] and allows the preparation of 1,4-disubstituted 2-cyclohexenes with full stereocontrol of the carbon–carbon bond formation in the 4-position. It is also highly regioselective. Other procedures[4,5] for obtaining 4-alkyl-substituted 3-cyclohexenol derivatives use 1,3-cyclohexadiene monoepoxide as starting material. None of the previous methods allow the selective preparation of both stereoisomers as shown here.

The present procedure uses palladium catalysis in the first step and in one of the second steps. These

reactions occur under very mild conditions (room temperature), and the catalyst used is commercial palladium acetate.

Since the title compounds can be stereoselectively functionalized in the 1-position by metal-catalyzed nucleophilic substitutions of the acetoxy group, a great number of 1,4-disubstituted 2-cyclohexenes with defined 1,4-relative stereochemistry are available.

While this process works for a great number of conjugated dienes, a few, such as 1,3-cyclopentadiene and those acyclic dienes that have an oxygen substituent in an allylic position, did not give a chloroacetoxylation product.[2] Control of the 1,4-relative stereochemistry and preparation of compounds analogous to the title compounds also work for acyclic dienes,[2,6] This process was used to obtain remote stereocontrol in acyclic systems and applied to the synthesis of a pheromone.[6]

References and Notes

1. Department of Organic Chemistry, Royal Institute of Technology, 100 44 Stockholm, Sweden. Present address of J. E. B.: Department of Organic Chemistry, University of Uppsala, Box 531, 751 21 Uppsala, Sweden.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Propanedioic acid, [4-(Acetyloxy)-2-cyclohexen-1-yl]-, dimethyl ester, cis- and trans-

saturated brine

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

sodium bicarbonate,
sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

palladium (7440-05-3)

manganese dioxide (1313-13-9)

Pentane (109-66-0)

p-benzoquinone (106-51-4)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

Lithium chloride (7447-41-8)

1,3-cyclopentadiene (542-92-7)

calcium hydride (7789-78-8)

triphenylphosphine (603-35-0)

1,3-Cyclohexadiene (592-57-4)

phosphine oxide

lithium acetate dihydrate (6108-17-4)

sodium dimethyl malonate

1,3-cyclohexadiene monoepoxide

palladium acetate (3375-31-3)

dimethyl malonate (108-59-8)

tetrakis (triphenylphosphine)palladium(0) (14221-01-3)

trans-1-ACETOXY-4-(DICARBOMETHOXYMETHYL)-2-CYCLOHEXENE (82736-53-6)

cis-1-Acetoxy-4-chloro-2-cyclohexene (82736-39-8)

cis-1-acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene

cis- and trans-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene