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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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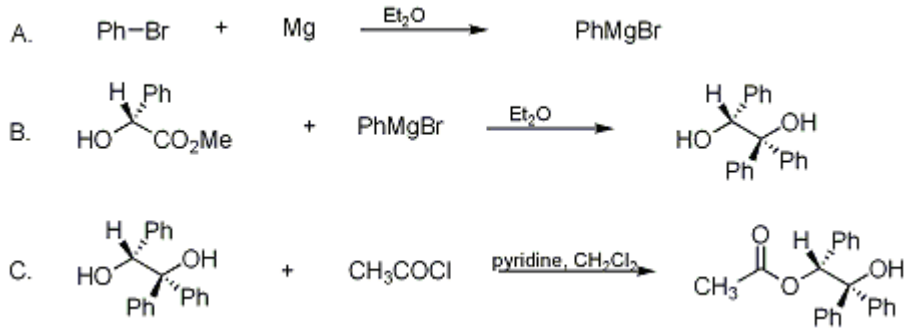
(R)-(+)-2-HYDROXY-1,2,2-TRIPHENYLETHYL ACETATE

[1,2-Ethanediol, 1,1,2-triphenyl-, 2-acetate, (R)-]



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1. Procedure

A. *Phenylmagnesium bromide* (Note 1). Ether (100 mL) is added to magnesium (Mg) turnings (74.6 g, 3.07 mol) in a dry, 5-L flask equipped with an overhead stirrer, reflux condenser, and addition funnel. Iodine (several crystals) is added and the mixture is stirred for several minutes (the color dissipates). Bromobenzene (9.23 mL, 13.76 g, 87.64 mmol) is added and the mixture is heated with a heat gun to initiate the reaction. A solution of bromobenzene (322.8 mL, 481 g, 3.06 mol) in ether (600 mL) is added dropwise over 2.75 hr, maintaining a gentle reflux. The dark brown mixture is stirred an additional 3 hr at ambient temperature under nitrogen and then cooled in an ice/methanol bath to 0°C.

B. *(R)-(+)-1,1,2-Triphenylethanediol*. A solution of methyl (R)-(−)-mandelate (92.3 g, 0.556 mol) (Note 2) in ether (500 mL) (Note 3) is added dropwise to the cold solution of phenylmagnesium bromide prepared in Step A at a rate such that the temperature does not rise above 10°C (1.25 hr required). The mixture is then allowed to stir an additional 2 hr with cooling (final temp 6°C) before heating to reflux. After 3 hr at reflux the solution is allowed to stand overnight at ambient temperature under nitrogen. The solution (*CAUTION: Contains benzene*) is poured onto 1 kg of ice contained in a 5-L, round-bottomed flask placed in an ice bath and equipped with an overhead stirrer and reflux condenser. A solid mass results that is broken up with a spatula so that it is partly stirrable. Hydrochloric acid (6 N, 516 mL) is added dropwise, while monitoring the pH, to a pH of 3.9. The two-phase, liquid mixture is stirred for 1 hr at ambient temperature. The layers are separated and the aqueous layer is extracted with methylene chloride (CH_2Cl_2) (3 × 250 mL). The combined organic layers are dried ($MgSO_4$), filtered, and concentrated to a thick caramel-like oil (179 g). Methanol (300 mL) is added causing crystallization and the mixture is heated to reflux to give a clear yellow solution. The solution is allowed to cool to room temperature over several hours. It is then cooled in an ice bath to 0° C and aged for 1 hr. The product is collected on a filter and washed with cold (−10°C) methanol (200 mL). The solid is dried under reduced pressure at 50°C (106.6 g, 66%), mp 123–127°C, $[\alpha]_D^{20}$ +220° (95% ethanol, *c* 1). Liquid chromatographic (LC) analysis shows 96.6% purity with 3.2% benzoin contamination (area %, uncorrected for relative response).

C. *(R)-(+)-2-Hydroxy-1,2,2-triphenylethyl acetate [(R)-HYTRA]*. Acetyl chloride (32.6 mL, 0.458 mol) in CH_2Cl_2 (85 mL) is added dropwise to R-(+)-triphenylethanediol (103.04 g, 0.355 mol) and pyridine (46.4 mL, 0.574 mol) in CH_2Cl_2 (860 mL) at 0°C (ice/methanol bath). The rate is controlled so that the temperature does not exceed 5°C. After the addition is complete, the mixture is allowed to warm to ambient temperature and aged for 4 hr. LC assay shows 1% unreacted diol. Water (430 mL) is added and the mixture is stirred vigorously for 30 min (pH was 3.5). The mixture is concentrated on a rotary evaporator until second phase CH_2Cl_2 is no longer observed in the distillate or in the reaction mixture. Water (100 mL) is used to aid transfer of the solids to a filter, the filter cake is washed with water (600

mL), and air dried (with suction) overnight. The resulting wet cake is transferred to a 3-L flask equipped with an overhead stirrer, a distillation head, and an addition funnel. Toluene (2 L) is added and the azeotrope is removed by atmospheric distillation. After 480 mL of distillate is collected (80 mL of second phase water), 300 mL of toluene is added; an additional 460 mL of distillate is collected and fresh toluene (500 mL) is added. After 100 mL of clear distillate is collected, fresh toluene (200 mL) is added a third time and the mixture is finally distilled to a 1.5-L mark on the flask (a total of 1620 mL of distillate, including 90 mL of second phase water, is collected). The mixture is allowed to cool overnight with stirring and then cooled to 0°C and aged for 2 hr. The product is collected on a filter, washed with toluene (room temperature, 400 mL) and dried under reduced pressure at 60°C for 7 hr (Note 4); 108.91 g (92.3%), mp 249–251°C, $[\alpha]_D^{25}$ +213° (pyridine, *c* 1), $[\alpha]_D^{20}$ +218° (pyridine, *c* 1). LC analysis shows 100.0% pure (Note 5) and (Note 6).

2. Notes

1. The preparation of phenylmagnesium bromide follows approximately the procedure of Allen, C. F. H.; Converse, S. *Org. Synth., Coll. Vol. I* **1941**, 226.
2. Commercial methyl (R)-(−)-mandelate can be used. The submitters prepared it from (R)-(−)-mandelic acid (BASF AG, D-Ludwigshafen), $[\alpha]_D^{20}$ −154.9° (water, *c* 2): A 2-L, round-bottomed flask equipped with a condenser with a drying tube and a magnetic stirrer is charged with 100 g (0.66 mol) of (R)-(−)-mandelic acid and 500 mL of dry methanol. One milliliter of sulfuric acid is added and the mixture is heated under reflux for 2 hr. (LC analysis showed a 97:3 ratio of ester to acid which did not change after 2 hr further reflux). The flask is cooled in an ice bath and 50 mL of water and 7 g (83 mmol) of sodium bicarbonate ($NaHCO_3$) are added under stirring, which is continued until the pH rises to 7.6 The mixture is filtered and concentrated on a rotary evaporator at 50°C. On cooling the two-phase liquid mixture a solid mass is obtained that is broken up with a spatula; water (200 mL) is added and the slurry is stirred for 2 hr. The product is collected on a filter, washed with water and dried under reduced pressure to give 93.0 g (85%) of white solid, mp 56–58°C, $[\alpha]_D^{25}$ −133° (95% ethanol, *c* 1) [lit.[2] $[\alpha]_D^{25}$ −128.6° (ethanol, *c* 1)].
3. Molten methyl mandelate dissolves readily in diethyl ether.
4. Careful drying is strongly recommended, since methanol is retained tenaciously by crystalline 1,1,2-triphenyl-1,2-ethanediol. Material containing minor amounts of methanol can be used in the following step provided that the acylation is performed with a 50% excess of acetyl chloride.
5. (R)- and (S)-HYTRA are commercially available from Merck AG, D-Darmstadt.
6. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.96 (s, 3 H, CH_3), 2.78 (s, 1 H, OH), 6.68 (s, 1 H, PhCH), 7.05–7.40 (m, 13 H, ArH), 7.54–7.57 (m, 2 H, ArH).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

(R)-(+)-1,1,2-Triphenyl-1,2-ethanediol is available from methyl[3] and ethyl[4] (R)-(−)-mandelate by treatment with phenylmagnesium bromide. The synthesis of (R)-(+)-2-hydroxy-1,2,2-triphenylethyl acetate [(R)-HYTRA] has been reported previously by the submitters.[5,6] (S)-(−)-2-Hydroxy-1,2,2-triphenylethyl acetate is available according to this procedure starting from the enantiomeric methyl (S)-(+)-mandelate or (S)-(+)-mandelic acid, respectively, both of which are commercially available. Doubly deprotonated HYTRA can be used to introduce an acetate moiety into achiral as well as chiral aldehydes in an enantioselective manner.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 497
- Org. Syn. Coll. Vol. 10, 464

References and Notes

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

(R)-(+)-2-hydroxy-1,2,2-triphenylethyl acetate [(R)-HYTRA]

methyl (R)-(−)-mandelate

(R)-(−)-mandelic acid

(S)-(−)-2-Hydroxy-1,2,2-triphenylethyl acetate

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

acetyl chloride (75-36-5)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

nitrogen (7727-37-9)

iodine (7553-56-2)

pyridine (110-86-1)

Benzoin (119-53-9)

toluene (108-88-3)

bromobenzene (108-86-1)

Phenylmagnesium bromide (100-58-3)

methylene chloride (75-09-2)

(R)-(+)-1,1,2-triphenyl-1,2-ethanediol,
(R)-(+)-1,1,2-Triphenylethanediol (95061-46-4)

1,1,2-triphenyl-1,2-ethanediol

(R)-(+)-2-Hydroxy-1,2,2-triphenylethyl acetate (95061-47-5)

1,2-Ethanediol, 1,1,2-triphenyl-, 2-acetate, (R)- (95061-47-5)

R-(+)-triphenylethanediol

methyl mandelate (4358-87-6)

methyl (S)-(+)-mandelate (771-90-4)

(S)-(+)-mandelic acid (17199-29-0)