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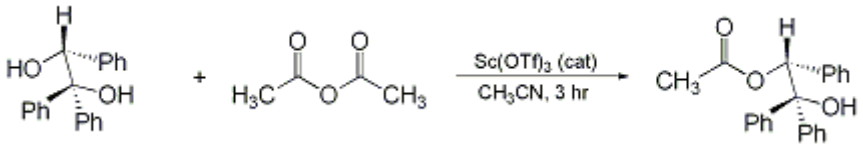
(R)-(+)-2-HYDROXY-1,2,2-TRIPHENYLETHYL ACETATE

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



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1. Procedure

(R)-(+)-2-Hydroxy-1,2,2-triphenylethyl acetate [(R)-HYTRA]. To a mechanically stirred solution of (R)-(+)-1,1,2-triphenyl-1,2-ethanediol (35.0 g, 0.121 mol, (Note 1)) and acetic anhydride (17.1 mL, 0.181 mol, 1.5 eq, (Note 2)) in anhydrous acetonitrile (500 mL, (Note 3)) at room temperature under nitrogen is added a solution of scandium(III) trifluoromethanesulfonate (1.23 g, 2.5 mmol, 2 mol%, (Note 4)) in anhydrous acetonitrile (125 mL) over approximately 35 min (Note 5). After about 8 min a white precipitate begins to appear, and the resulting mixture is stirred at room temperature under nitrogen for a total of 3 hr. The solid is filtered, washed with acetonitrile (2 × 25 mL), and dried under vacuum at 40°C overnight to afford (R)-(+)-2-hydroxy-1,2,2-triphenylethyl acetate (35.42 g, 0.107 mol, 88%) as a white solid (Note 6).

2. Notes

1. Commercially available 1,1,2-triphenyl-1,2-ethanediol in either antipode can be used. The checkers used (R)-(+)-1,1,2-triphenyl-1,2-ethanediol from Aldrich Chemical Company, Inc. , ($[\alpha]_D^{20}$ +210° (C_2H_5OH, *c* 1). Alternatively, 1,1,2-triphenyl-1,2-ethanediol can be prepared via the procedure in *Organic Syntheses*.[2]
2. Acetic anhydride was purchased from Aldrich Chemical Company, Inc., (99+% purity) , and used without additional purification. A 50% excess of acetic anhydride is needed for the reaction to be complete in a reasonably short period of time. Greater than a 50% excess of acetic anhydride does not appreciably improve the reaction time to completion.
3. Acetonitrile was purchased from Aldrich Chemical Company, Inc., (anhydrous, 99.8% purity in SureSeal™ bottles) and used without additional purification.
4. Scandium(III) trifluoromethanesulfonate [$Sc(OTf)_3$] was purchased from Aldrich Chemical Company, Inc., (99% purity) and used without additional purification.
5. The order of addition of the reagents has a significant effect on the yield of the reaction. The optimal order of addition of reagents is described above (i.e., addition of Sc[III]$(OTf)_3$ slowly, last). Continual addition of the scandium(III) triflate during the course of the reaction maintained the pace of the process. Bolus addition of the catalyst resulted in a reaction that slowed down or stopped part way, resulting in lower yields. Premixing the Sc[III]$(OTf)_3$ with the diol and adding the acetic anhydride last led to reproducibly lower yields of (R)-HYTRA and a longer time to precipitation of (R)-HYTRA. Absolutely seminal to the reaction was the choice of solvent since all starting materials were soluble in acetonitrile, whereas the product acetate was not, thus allowing purification by simple filtration.
6. Spectral data are as follows: mp 198-200°C (crude product); $[\alpha]_D^{22}$ +196° (pyridine , crude product, *c* 1); mp 213-221°C (benzene);[3 4 5 2] $[\alpha]_D^{22}$ +201° (pyridine, *c* 1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.97 (s, 3 H), 2.80 (s, 1 H), 6.66 (s, 1 H), 7.01-7.16 (m, 10 H), 7.24-7.38 (m, 3 H), 7.52-7.56 (m, 2 H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 21.1, 78.5, 80.3, 126.2, 126.3, 127.0, 127.3, 127.5, 127.8, 127.9, 128.4, 128.5, 135.9, 142.7, 144.8, 169.7 ; IR ($CHCl_3$) cm^{-1}: 3064, 3024, 1737, 1495, 1372, 1239, 1168, 779 ; HRMS calcd for $C_{22}H_{19}O_2$ ($[MH^+]$-H_2O), m/z 315.1385, found 315.1386 .

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

The (R)- and (S)-HYTRA (2-Hydroxy-1,2,2-Triphenylethyl Acetate) esters have been used in the diastereoselective addition of a chiral acetate to chiral and prochiral electrophiles, usually aldehydes.[6] The generality of this reaction led to the commercialization of these agents and the precursor 1,1,2-triphenyl-1,2-ethanediols. Furthermore, Braun, Gräf, and Herzog had previously detailed a 100-plus-g synthesis.[2] However, the HYTRA esters are costly,[7] and the synthesis previously reported was straightforward until the final step, in which acetyl chloride reacted with the 1,1,2-triphenyl-1,2-ethanediol to produce the HYTRA ester.[2] In this procedure, the HYTRA acetate was prepared in 92% yield (108 g), but the reaction work up was tedious and time consuming. To purify the HYTRA ester in this procedure, the reaction mixture is quenched with water, reaction solvent (CH_2Cl_2) is removed by evaporation under reduced pressure, and the resulting solids are filtered, washed with water, and then transferred to a flask with toluene . Water is removed from the solid by an azeotropic distillation using toluene. The product is finally filtered from toluene to yield the acetate.

Yamamoto and co-workers reported the use of scandium(III) triflate as an esterification catalyst when acetic anhydride was used as the acetate source.[8,9] While they only reported on monoalcohols (1°, 2°, and 3°) on a small scale, the submitters modified the Yamamoto procedure to suit the submitters' reaction with the 1,1,2-triphenyl-1,2-ethanediol. As detailed above, the current procedure provides a yield of the HYTRA acetate that is comparable to the procedure reported by Braun and co-workers,[2] but via simple, direct filtration for the reaction mixture.

References and Notes

1. Astra Zeneca, Three Biotech, One Innovation Drive, Worchester, MA 01605. Present address for J. M.: Bristol-Myers Squibb, Pharmaceutical Research Institute, P. O. Box 4000, Princeton, NJ 08543.
2. 249-251°C (from toluene), Braun, M.; Gräf, S.; Herzog, S. *Org. Synth., Coll. Vol. IX* **1998**, 507.
3. Several different melting points are reported in literature: (a) m.p. 220-221°C (from diethyl ether), Polansky, O.; Schinzel, E.; Wessely, F. *Monatsh. Chem.* **1956**, *87*, 24-46;
4. mp 220-220.5°C (from diethyl ether/CH_2Cl_2), Corey, E. J.; Casanova, J. *J. Am. Chem. Soc.* **1963**, *85*, 165-169;
5. 224.5-225.5°C (from benzene), Ito, N.; Nishino, H.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3527-3528;
6. Braun, M.; Gräf, S. *Org. Synth., Coll. Vol. IX* **1998**, 497, and references cited therein.
7. (R)-HYTRA ester in the 1998-1999 Aldrich Chemical Company catalog (p. 1499, item 37,650-7) is $29.10/g.
8. Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413-4414.
9. Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560-4567.

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

(R)-(+)-2-Hydroxy-1,2,2-triphenylethyl acetate:
[(R)-HYTRA]:
1,2-Ethanediol, 1,1,2-triphenyl-, 2-acetate, (R)- (11); (95061-47-5)

(R)-(+)-1,1,2-Triphenylethanediol:

1,2-Ethanediol, 1,1,2-triphenyl-, (R)- (11); (95061-46-4)

Acetic anhydride (8);
Acetic acid anhydride (9); (108-24-7)

Acetonitrile: TOXIC: (8,9); (75-05-8)

Scandium(III) trifluoromethanesulfonate:
Methanesulfonic acid, trifluoro-, scandium (3+) salt (13); (144026-79-9)