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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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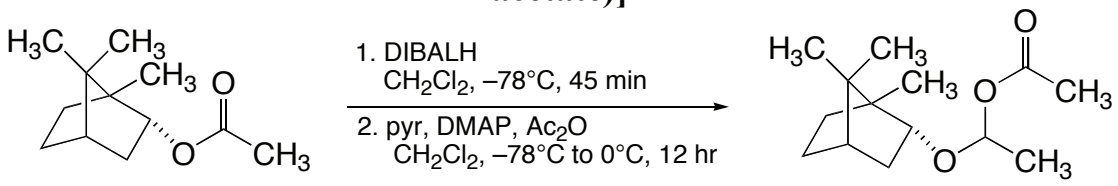
PREPARATION OF α-ACETOXY ETHERS BY THE REDUCTIVE ACETYLATION OF ESTERS: *endo*-1-BORNYLOXYETHYL ACETATE

[(Ethanol, 1-[[(1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy]-, acetate)]



Submitted by David J. Kopecky and Scott D. Rychnovsky.[1]
Checked by Guillaume L. N. Péron, Cédric R. N. Fischmeister, and Andrew B. Holmes.
Discussion Addendum: *Org. Synth.*, **2012**, *89*, 143.

1. Procedure

A flame-dried, 2-L, three-necked, round-bottomed flask, equipped with a large Teflon magnetic stirring bar and three rubber septa, is charged with 5.5 g (28.1 mmol) of (−)-bornyl acetate (Note 1) in 162 mL of dichloromethane (Note 2) under an argon atmosphere. A thermocouple (Note 3) is immersed in the solution through one of the rubber septa. The flask is placed in a dry ice/acetone bath and cooled to an internal solution temperature of −78°C. Stirring is begun and diisobutylaluminum hydride, 54.4 mL of a 1.0M solution in hexanes (54.4 mmol, 2 eq), is added as a slow stream via a glass syringe over a period of 13 min; during this addition, the internal solution temperature does not exceed −72°C (Notes 1,4). The clear solution is stirred for an additional 45 min at −78°C, then 6.6 mL of pyridine (6.5 g, 81.6 mmol, 3.0 eq) is added dropwise via a glass syringe, maintaining the internal temperature below −76°C. Immediately following, a solution of 6.5 g of 4-dimethylaminopyridine (DMAP) (54.5 mmol, 2.0 eq) in 80 mL of dichloromethane (Note 2) is added slowly via an 18-gauge stainless steel cannula (Note 5). The internal temperature is not allowed to rise above −72°C during this addition. Acetic anhydride (15.4 mL, 16.6 g, 163.2 mmol, 6.0 eq) is then added dropwise via a glass syringe over 5.5 min at a rate to maintain the internal temperature below −72°C.

The resultant light yellow solution is stirred at −78°C for 12 hr (Note 6). During this time, the color of the solution intensifies considerably. The bright yellow solution is warmed to 0°C in an ice water bath and stirred for 35 min, during which time the color of the solution becomes bright yellow-orange. The reaction is then quenched by the sequential addition of 270 mL of saturated aqueous ammonium chloride and 200 mL of saturated aqueous sodium potassium tartrate. The emulsion is removed from the ice water bath and stirred vigorously for 50 min, by which time adequate phase separation is observed (Note 7). The biphasic mixture is transferred to a 2-L separatory funnel and is extracted with four 175-mL portions of dichloromethane. The combined extracts are washed sequentially with two 500-mL portions of an ice-cooled 1M aqueous solution of sodium bisulfate, three 500-mL portions of saturated aqueous sodium bicarbonate and 500 mL of saturated aqueous sodium chloride. The solution is dried over anhydrous sodium sulfate, filtered, and is concentrated under reduced pressure to afford 8.5 g of a yellow oil.

The residue is purified using flash chromatography with 145 g of triethylamine-deactivated Merck 9385 silica gel 60 (230-400) (Note 8) eluting with 5% ethyl ether in hexanes (Note 9). Fractions of 50-mL are collected, and product-containing fractions are identified by TLC analysis (Note 10). The product (6.4 g, 95%) is obtained as a clear oil (Notes 11,12). ^{1}H NMR and ^{13}C NMR spectra indicate that the product is a 2.8:1 mixture of diastereomers. Short path vacuum distillation of a portion of the product afforded material of comparable purity, bp 73.5−75°C (2 mm).

2. Notes

1. (−)-Bornyl acetate, purchased from Aldrich Chemical Company, Inc., was of 97% purity and was used as received. Diisobutylaluminum hydride (DIBALH) (1.0M solution in hexanes) and 4-dimethylaminopyridine were purchased from Aldrich Chemical Company, Inc. and used as received. Pyridine was purchased from Aldrich Chemical Company, Inc. and was distilled from calcium hydride at atmospheric pressure prior to use. Acetic anhydride was purchased from Fisher Scientific, Inc. and was distilled at atmospheric pressure prior to use.

2. The checkers obtained dry dichloromethane by distillation from calcium hydride. The submitters dried dichloromethane through an alumina filtration system.[2]

3. A Digi-Sense digital thermometer was used. The internal temperature needs to be monitored, and the additions should be slow enough to avoid significant exotherms. The checkers found that temperature control is the major factor influencing the outcome of the reaction. The initial procedure was submitted as double scale [i.e. 11 g (56.2 mmol) (−)-bornyl acetate]. However, the checkers found temperature control on full scale to be difficult, resulting in incomplete reaction and/or over-reduction of the bornyl acetate. The checkers found that the procedure is reliably reproducible on half scale (5.5 g (−)-bornyl acetate).

4. The checkers found that reproducible results were obtained when a freshly opened bottle of diisobutylaluminium hydride was used.

5. The cannula transfer was accomplished by briefly evacuating the reaction flask using a vacuum line connected to a vacuum pump, and then pressurizing the flask containing the DMAP solution with just over 1 atmosphere of argon.

6. A bath temperature of −78°C was maintained during the 12 hr period by packing the bath with dry ice and covering the bath and reaction flask with aluminum foil.

7. Although the two phases separated, the aqueous phase remained cloudy.

8. The submitters used ICN 230-400 mesh silica gel. The silica gel was deactivated by mixing it with 325 mL of 2% (v/v) triethylamine in hexanes. The resultant slurry was poured onto the column, packed, and then flushed with 200 mL of 5% ethyl ether in hexanes to remove residual triethylamine before product loading.

9. The head pressure of the flash column during chromatography was 2.5 psi.

10. The α-acetoxy ether elutes with an R_f of 0.32 on Merck silica gel F_{254} in 5% (v/v) ethyl ether in hexanes (product stains yellow-green in an acidic solution of *p*-anisaldehyde).

11. The submitters obtained the equivalent of 6.4 g (95%). Physical and spectroscopic properties are as follows: IR (mixture of isomers, neat) cm^{-1}: 2952, 2879, 1737, 1452, 1372, 1247, 1175, 1141, 1072, 1033, 1009,

929, 833; ^{1}H NMR (500 MHz, $CDCl_3$, mixture of isomers) δ: 0.81-0.85 (m, 9 H), 0.99 (dd, 1 H, *J* = 13.1, 3.4, minor isomer), 1.10 (dd, 1 H, *J* = 13.3, 3.4, major isomer), 1.16-1.28 (m, 2 H), 1.38 (d, 3 H, *J* = 5.4, minor), 1.40 (d, 3 H, *J* = 5.3, major), 1.59 (t, 1 H, *J* = 4.5, major). 1.64 (t, 1 H, *J* = 4.5, minor), 1.63-1.74 (m, 1 H), 1.90-2.01 (m, 1 H), 2.04 (s, 3 H, major), 2.05 (s, 3 H, minor), 2.07-2.19 (m, 1 H), 3.81 (ddd, 1 H, *J* = 9.9, 3.2, 2.0), 5.93 (q, 1 H, *J* = 5.2, minor), 5.94 (q, 1 H, *J* = 5.2, major); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of isomers) δ: 13.4 (minor isomer), 13.6 (major isomer), 18.8 (major), 18.8 (minor), 19.7 (major), 19.7 (minor), 20.9 (major), 21.2 (minor), 21.4 (minor), 21.6 (major), 26.4 (minor), 26.6 (major), 28.1 (major), 28.2 (minor), 36.1 (minor), 37.0 (major), 44.9 (minor), 45.0 (major), 47.2 (major), 47.6 (minor), 48.8 (minor), 49.3 (major), 82.6 (minor), 85.9 (major), 95.3 (minor), 97.7 (major), 170.6 (major), 170.9 (minor). Anal. Calcd for $C_{14}H_{24}O_3$: C, 70.0; H, 10.1. Found: C, 70.0; H, 10.0. The submitters obtained C, 70.0; H, 10.0.

12. The product contained a 3% impurity of (−)-bornyl acetate as indicated by the presence of the following diagnostic peaks in the ^{1}H NMR spectrum: 0.87 (s, 3 H), 0.90 (s, 3 H), 0.96 (buried dd, 1 H), 2.06 (s, 3 H). This impurity originates from incomplete reduction and/or over-reduction.

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 reductive acetylation of esters and lactones can be accomplished by treatment of the ester with a two-fold excess of DIBALH at −78°C followed by trapping of the resulting aluminum hemiacetal intermediate with acetic anhydride in the presence of pyridine and DMAP at low temperature.3 This transformation has been successfully applied to a wide range of esters and lactones, including sterically-hindered acyclic esters, β-alkoxy esters, benzyl esters and macrolactones. A compilation of representative examples is presented in Table I.[3a] Upon exposure to mild acid, the α-acetoxy ether

products undergo facile conversion to the corresponding oxacarbenium ions, which can be trapped by a wide variety of carbon- or heteroatom-based nucleophiles.[3b] For example, (*endo*)-1-bornyloxyethyl acetate can be efficiently allylated by treatment with boron trifluoride etherate and allyltrimethylsilane (82% yield; d.r. = 3.7:1), or ethylated with trimethylsilyl triflate and diethylzinc (87% yield; d.r. = 1.9:1).[4] α-Acetoxy ethers have also been utilized as Prins cyclization precursors in our studies toward the diastereoselective synthesis of polyfunctionalized tetrahydropyran ring systems.[5]

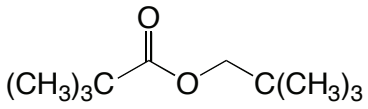
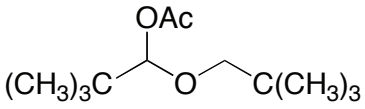
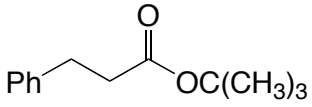
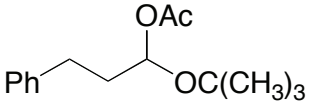
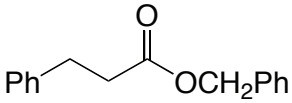
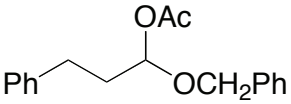
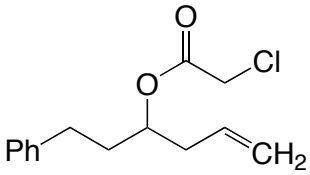
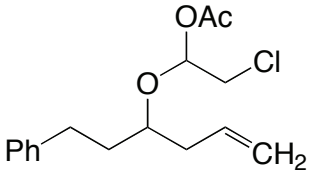
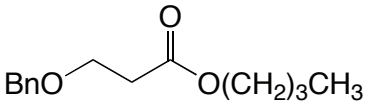
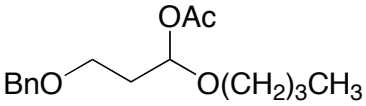
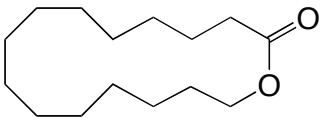
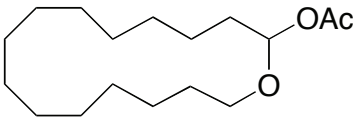
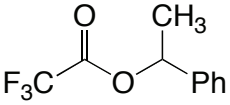
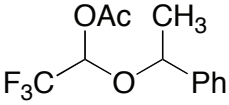
References and Notes

1. Department of Chemistry, University of California, Irvine, CA 92697-2025.
2. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
3. (a) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191; (b) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317.
4. Both reactions were performed in dichloromethane at −78°C.
5. (a) Rychnovsky, S. D.; Hu, Y. ; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271 (b) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217 (c) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679.

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

endo-1-Bornoxyethyl acetate:
Ethanol, 1-[[(1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]-hept- 2-yl]oxy]-, acetate (9); (284036-61-9)
(−)-Bornyl acetate: Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, acetate, (1*S*,2*R*,4*S*)- (9); (5655-61-8)
Diisobutylaluminium hydride: Aluminum, hydrobis(2-methylpropyl)- (9); (1191-15-7)
Pyridine (8, 9); (110-86-1)

TABLE 1[3a]
DIBALH REDUCTIVE ACETYLATION OF VARIOUS ESTERS

Entry	Substrate	Product	Yield(%)
1			87
2			90
3			78
4			92 (d.r. = 1.1:1)
5			81
6			84
7			93 (d.r. = 2.2:1)

4-(Dimethylamino)pyridine: 4-Pyridinamine, *N,N*-dimethyl- (9); (1122-58-3)

Acetic anhydride: Acetic acid, anhydride (9); (108-24-7)