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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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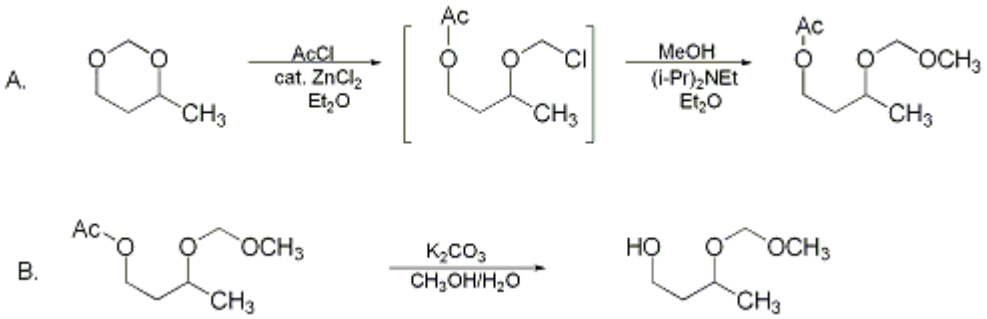
SELECTIVE PROTECTION OF 1,3-DIOLS AT THE MORE HINDERED HYDROXY GROUP: 3-(METHOXYMETHOXY)-1-BUTANOL

[1-Butanol, 3-(methoxymethoxy)-]



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Checked by Thierry Happaerts and Leon Ghosez.

1. Procedure

Caution! All operations should be conducted in an efficient fume hood. The chloromethyl ether acetate intermediate is potentially toxic.

A. 1-Acetoxy-3-(methoxymethoxy)butane . A 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, condenser fitted with a nitrogen inlet, 50-mL pressure equalizing addition funnel, and a rubber septum is flame-dried and allowed to cool to room temperature under nitrogen. The flask is charged with 30.0 g (0.294 mol) of 4-methyl-1,3-dioxane (Note 1), 200 mL of anhydrous diethyl ether (Note 2), and 0.5 mL of a 1.0 M solution of zinc chloride in anhydrous diethyl ether (Note 3). The solution is stirred under a positive pressure of nitrogen and 25.0 mL (0.352 mol) of acetyl chloride (Note 4) is added dropwise over a 10-min period, resulting in a slightly exothermic reaction; the resulting solution is stirred for 3 hr at room temperature. A separate 500-mL, three-necked, round-bottomed flask, equipped with a mechanical stirrer, 500-mL addition funnel fitted with a rubber septum, and a condenser fitted with a nitrogen inlet, is charged with 61.0 mL (0.350 mol) of N,N-diisopropylethylamine (Note 5), 45.0 mL (1.11 mol) of anhydrous methanol (Note 6), and 60 mL of anhydrous diethyl ether (Note 2), and the flask is cooled in an ice-bath. The chloromethyl ether acetate solution is rapidly transferred to the addition funnel via a double-tipped needle under a positive pressure of nitrogen and the solution is added dropwise over a 15-min period to the mechanically stirred, ice-cold solution of alcohol and amine. Copious quantities of ammonium salt form during the addition. After the addition is completed, the cooling bath is removed and the reaction mixture is stirred for 1 hr at room temperature. The entire two-phase reaction mixture is then transferred to a 500-mL, round-bottomed flask and volatile components are removed by rotary evaporation at water aspirator pressure. Pentane (ca. 20 mL) is added to the residue and the flask is cooled in an ice-bath for 1 hr to induce crystallization of the ammonium salt. The entire two-phase mixture is then filtered with suction through 50 g of neutral alumina (Note 7) contained in a 4.3-cm × 15-cm medium porosity, sintered-glass funnel and the salt is washed well with pentane (ca. 500 mL). Concentration of the combined filtrate and washings by rotary evaporation at water aspirator pressure affords 40.0-47.2 g (77-91%) of essentially pure 1-acetoxy-3-(methoxymethoxy)butane (Note 8). This material is used in the next step without further purification.

B. 3-(Methoxymethoxy)-1-butanol . A solution of 17.6 g (0.10 mol) of 1-acetoxy-3-(methoxymethoxy)butane in 100 mL of methanol is added to a solution of 35.0 g (0.253 mol) of

potassium carbonate (Note 9) in 50 mL of water contained in an open 250-mL, round-bottomed flask equipped with a magnetic stirring bar. The resulting two-phase mixture is stirred vigorously at room temperature for 2 hr. The flask is then connected to a rotary evaporator and methanol is removed at 20-30°C (18 mm). The two-phase residue is extracted with four 20-mL portions of diethyl ether and the combined ethereal extracts are dried over anhydrous potassium carbonate . Solvent is removed by rotary evaporation at water aspirator pressure and the resulting oil is distilled at reduced pressure, bp 94-96°C at 18 mm (Note 10), to give 11.9-12.4 g (89-92%) of pure product (Note 11) as a colorless oil.

2. Notes

1. 4-Methyl-1,3-dioxane, available from the Aldrich Chemical Company, Inc. , is used as received. Alternatively, the formal may be prepared from 1,3-butanediol and aqueous formaldehyde as previously described.[2]
2. Anhydrous diethyl ether was purchased from J. T. Baker Inc. and used as received.
3. A 1.0 M solution of zinc chloride in diethyl ether is available from the Aldrich Chemical Company, Inc. Alternatively, a few crystals of anhydrous zinc chloride may be added to the reaction solution to catalyze the acylation reaction.
4. Reagent grade acetyl chloride is freshly distilled immediately prior to use.
5. N,N-Diisopropylethylamine was purchased from the Aldrich Chemical Company, Inc. , and distilled from potassium hydroxide immediately prior to use.
6. Anhydrous methanol was purchased from J. T. Baker Inc. and used as received.
7. Neutral, activity 1 alumina (50-200 μm particle size) purchased from ICN, Inc. was used to fill the sintered-glass funnel.
8. This material is sufficiently pure for most purposes. Distillation of the methoxymethyl ether acetate through a 5-in Vigreux column affords 42.4-43.7 g (82-84%) of pure product: bp 120-122°C (50 mm) [lit.[3] bp 95-98°C (20 mm)]. The product has the following spectroscopic properties: ^{1}H NMR ($CDCl_3$) δ: 1.18 (d, 3 H, J = 6.20), 1.75-1.79 (m, 2 H), 2.02 (s, 3 H), 3.33 (s, 3 H), 3.79 (apparent sextet, 1 H, J = 6.20), 4.14 (t, 2 H, J = 6.56), 4.57 and 4.67 (AB-pattern, 2 H, J_{AB} = 6.92) ; ^{13}C NMR ($CDCl_3$) δ: 19.9, 20.2, 35.5, 54.6, 60.7, 69.4, 94.4, 170.7 .
9. Reagent grade, anhydrous potassium carbonate purchased from J. T. Baker Inc. was used.
10. The literature bp is 67-69°C at 5 mm.[4]
11. 3-(Methoxymethoxy)-1-butanol has the following spectroscopic properties: ^{1}H NMR ($CDCl_3$) δ: 1.18 (d, 3 H, J = 6.21), 1.68-1.79 (m, 2 H), 2.45 (br s, 1 H), 3.36 (s, 3 H), 3.66-3.79 (m, 2 H), 3.90 (apparent sextet, 1 H, J = 6.23), 4.59 and 4.69 (AB-pattern, 2 H, J_{AB} = 6.80) ; ^{13}C NMR ($CDCl_3$) δ: 20.2, 39.2, 55.3, 59.8, 71.8, 95.2 .

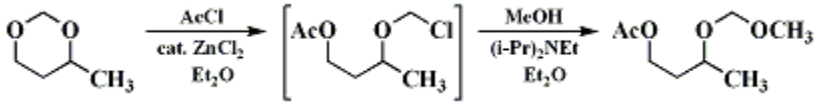
Waste Disposal Information

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

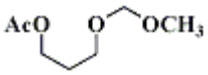
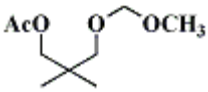
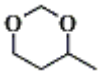
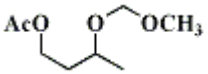
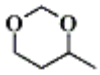
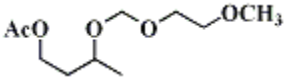
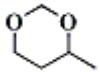
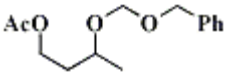
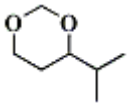
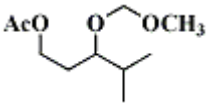
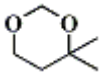
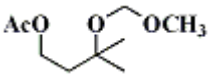
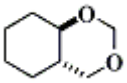
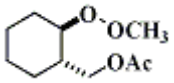
3. Discussion

The procedure described above provides a simple, general method for the selective, differential protection of both symmetrical and unsymmetrically substituted 1,3-diols using readily available, inexpensive reagents.[3] Additional examples are summarized in the Table.[3]

TABLE
SELECTIVE PROTECTION OF 1,3-DIOLS



entry	acetal	R'OH	product	yield, %

1		MeOH		97
2		MeOH		85
3		MeOH		90
4		$MeO(CH_2)_2OH$		88
5		$PhCH_2OH$		75
6		MeOH		95
7		MeOH		89
8		MeOH		90

While a variety of techniques are available for the monoprotection of symmetrical diols, there are few methods that allow for the chemoselective functionalization of the more hindered hydroxyl in an unsymmetrical 1,3-diol.[5] The acid-catalyzed reaction of an unsymmetrically substituted cyclic formal with acetyl chloride described here invariably proceeds via preferential rupture of the less congested C (2)-O bond to give a product having an acetate at the less congested site and a chloromethyl ether moiety at the more hindered hydroxyl (Table). This highly selective acylative cleavage is a consequence of rate-limiting attack by the electrophilic acylating agent that is acutely sensitive to steric effects.[2] Using the procedure outlined above, the reactive OCH_2Cl moiety may be converted to any of a variety of traditional alkoxymethyl ether protecting groups by treatment of the intermediate chloromethyl ether acetate with an appropriate alcohol in the presence of N,N-diisopropylethylamine (Table, entries 3-5). Removal of the acetate from the alkoxymethyl ether acetate affords a diol that is selectively protected as an alkoxymethyl ether at the more sterically encumbered center. This ability to site-selectively protect the more hindered hydroxyl in an unsymmetrical 1,3-diol is a particularly attractive feature of the methodology since it complements the normal chemoselectivity that favors functionalization of the primary site in the reaction of an unsymmetrical 1,3-diol with a derivatizing reagent.[5]

References and Notes

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3. Bailey, W. F.; Zarcone, L. M. J.; Rivera, A. D. *J. Org. Chem.* **1995**, *60*, 2532.
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5. Greene, T. W.; Wuts, P. G. M. In "Protective Groups in Organic Synthesis"; Wiley Interscience: New York, 1991.

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

3-(Methoxymethoxy)-1-butanol:
1-Butanol, 3-(methoxymethoxy)- (9); (60405-27-8)

1-Acetoxy-3-(methoxymethoxy)butane:
1-Butanol, 3-(methoxymethoxy)-, acetate (13); (167563-42-0)

4-Methyl-1,3-dioxane:
m-Dioxane, 4-methyl- (8);
1,3-Dioxane, 4-methyl- (9); (1120-97-4)

Acetyl chloride (8,9); (75-36-5)

N,N-Diisopropylethylamine:
Triethylamine, 1,1'-dimethyl- (8);
2-Propanamine, N-ethyl-N-(1-methylethyl)- (9); (7087-68-5)