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An Efficient One-Stage Deprotection/Reduction of 1,2-*O*-Isopropylidene Furanoses to the Corresponding Tetrahydrofurans

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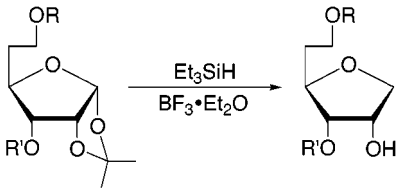
ABSTRACT



Treatment of 1,2-*O*-isopropylidenefuranose derivatives with triethylsilane/boron trifluoride etherate results in generation of the corresponding tetrahydrofurans. This one-stage process removes the 1,2-*O*-isopropylidene group with accompanying deoxygenation at the anomeric position and is compatible with several hydroxyl protecting groups.

Highly functionalized tetrahydrofurans occur frequently in natural products and have been incorporated into numerous synthetic biologically active compounds.[1,2] A number of approaches have been developed for their preparation, including several that use monosaccharides as precursors. Unfortunately, various procedures that utilize carbohydrates employ harsh conditions or involve multiple steps.[1,2] We now report an efficient one-step procedure for the reductive deoxygenation of 1,2-*O*-isopropylidenefuranose derivatives into the corresponding tetrahydrofurans.

Gray had used triethylsilane and boron trifluoride etherate (or trimethylsilyl triflate) to convert methyl furanosides or pyranosides into 1,4- or 1,5-anhydroalditols, respectively.[3] This was extended to the generation of *C*-glycosides[4] from ulose hemiacetals, but attempted application of the method for reductive deprotection of 1,2-*O*-isopropylidenefuranoses was less successful. Only moderate product yields with the formation of troublesome byproducts were observed.[5] Our requirement for several 1,4-anhydroalditol derivatives[6] led us to reexamine this method with isopropylidenefuranoses.

Treatment of 1,2-*O*-isopropylidenefuranose derivatives **1** with $Et_3SiH/BF_3{\cdot}Et_2O$ produced the tetrahydrofurans **2** in high yields (Table 1). However, it is noteworthy that the replacement of $BF_3{\cdot}Et_2O$ by TMS triflate resulted in the formation of 2-*O*-isopropyl ethers[5] (10−20%) in addition to

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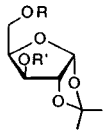
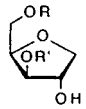
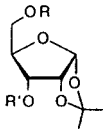
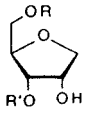
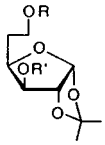
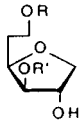
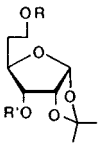
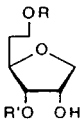
Table 1. Deprotection/Reduction of 1,2-*O*-Isopropylidenefuranoses to the Corresponding Tetrahydrofurans[a−c]

entry	substrate 1	product 2	yield (%)[d]
			
1	**1a** R = TBDPS, R' = H	**2a**	72
2	**1b** R = R' = Bn	**2b**	88
3	**1c** R = Bz, R' = Me	**2c**	90
			
4	**1d** R = Bn, R' = allyl	**2d**	87
			
5	**1e** R = Bz, R' = Me	**2e**	87
6[e]	**1f** R = R' = Bz	**2f**	81
			
7	**1g** R = Bz, R' = Me	**2g**	95
8	**1h** R = Bz, R' = allyl	**2h**	90
9	**1i** R = R' = allyl	**2i**	85

[a]Reactions were performed as described in the general procedure[8] unless otherwise noted. [b]Substrates and products displayed satisfactory ^1H and ^{13}C NMR spectra and HRMS. [c]No migration of protecting groups was observed with reactions listed in Table 1. [d]Isolated yields. [e]TFA (6 equiv) was required for complete reaction.

the desired products. These boron and silicon Lewis acid promoters might have different affinities for O1 versus O2. Although ~10 equiv each of Et_3SiH and $BF_3{\cdot}Et_2O$ was used in our standard conditions, comparable yields were obtained in recent experiments with 3−5 equiv of each reagent. No reaction was observed after 1 h at 0 °C, but conversions were complete (TLC) in 1.5 h at ambient temperature. The protecting groups on all compounds in Table 1 were stable under these conditions. However, the known equilibration of acetyl or benzoyl groups between O3 and (newly deprotected) O2 in ribofuranose derivatives and benzoyl migration (O5 to O3) in the reaction with 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose did occur (data not shown). Of particular concern is the mixture of 3- and 2-*O*-benzyl ethers (~2:1) that was obtained by standard treatment of the 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose substrate (not shown).

The only furanose derivative that did not react rapidly with $Et_3SiH/BF_3{\cdot}Et_2O$ was **1f**. Reaction was sluggish and did not proceed to completion within 3 days in the absence of trifluoroacetic acid (TFA). Possible interactions between the 3-*O*-benzoyl group and the cationic anomeric center might be unfavorable.

The utility of this methodology is readily apparent by comparison with a route used to prepare **2d** from **1d**. That five-step sequence[2d] (55% overall) is much less convenient and efficient than the present one-stage process (87%).

In summary, treatment of 1,2-*O*-isopropylidenefuranose derivatives with triethylsilane and boron trifluoride etherate provides convenient and efficient one-stage access to the correspondingly substituted tetrahydrofurans. This is an appealing route to various 1,4-anhydroalditol derivatives, because many 1,2-*O*-isopropylidenefuranose precursors with different hydroxyl protecting groups can be used. These furanose derivatives are readily accessible in a few steps from inexpensive, commercially available carbohydrates. The 1,4-anhydroalditol products can be modified by standard carbohydrate transformations to provide a variety of functionalized tetrahydrofurans and other derivatives.[7]

Acknowledgment. We thank the Brigham Young University development fund for support.

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(8) **General Procedure for Deprotection/Reduction of 1,2-*O*-Isopropylidene Furanoses.** To a solution of **1g** (3.6 g, 11.2 mmol) in CH_2Cl_2 (45 mL) at 0 °C were added Et_3SiH (16.7 mL, 12.1 g, 104 mmol) and $BF_3{\cdot}Et_2O$ (13.3 mL, 14.9 g, 105 mmol), and the reaction was stirred at ambient temperature for 2 h. The reaction was quenched by *careful* addition to saturated $NaHCO_3/H_2O$ (50 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted (CH_2Cl_2, 3 × 50 mL), and the combined organic phase was washed (brine) and dried ($MgSO_4$). Purification by flash chromatography (2.5 → 3% MeOH/CH_2Cl_2, silica gel) gave **2g** (2.83 g, 10.6 mmol, 95%) as an oil.