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Technical Notes

A Practical and Scaleable Preparation of 1,4-Anhydroerythritol

Karla G. Childers,* Spencer D. Dreher, Jaemoon Lee, and J. Michael Williams

Department of Process Research, Merck & Co., Inc. P.O. Box 2000, Rahway, New Jersey 07065, U.S.A.

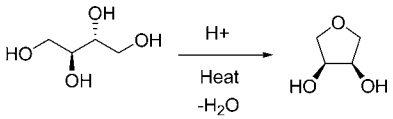
Abstract:

A practical and efficient kilogram-scale preparation of 1,4-anhydroerythritol from *meso*-erythritol is described. A novel silica gel and sodium bicarbonate slurry/filtration protocol is utilized to purify the product, giving commercial-grade material in 60−65% yield.

Introduction

Functionalized tetrahydrofurans can be found in numerous natural products and pharmaceutically useful compounds possessing a wide range of biological activity.[1] The ability to construct useful synthetic tetrahydrofuran intermediates for further elaboration is essential for practical implementation on large scale. In connection with an ongoing program, we required an efficient and scaleable method for the preparation of kilogram quantities of 1,4-anhydroerythritol, **2**. This simple tetrahydrofuran diol has been utilized in the synthesis of natural products,[2] potential antiviral targets,[3] polymers,[4] sugar silicates,[5] metal complexes,[6] and oligonucleotides.[7] Additionally, this versatile compound has found a place in commercial experimentation, including solvent preparation,[8] fuel additive synthesis,[9] and as a component in health and beauty products.[10] While 1,4-anhydroerythritol (**2**) is commercially available in small quantities (25 g), availability in bulk is limited, presumably due to currently available methods for its preparation. In this note, we disclose a practical, highly efficient, kilogram-scale preparation of 1,4-anhydroerythritol (**2**).

Scheme 1. **Acid-catalyzed cyclodehydration**



Literature methods of preparation of **2** involve the dehydration of *meso*-erythritol (**1**) with catalytic amounts of strong acids including ion-exchange resins,[11] mineral acids[12] or organic acids (sulfonic acids[13] and pyridinium chloride[14]) at >120 °C (Scheme 1). Molecular sieves have also been used to effect the cyclization.[15] Since oligomerization byproducts are a major problem in all of these protocols, concomitant high-vacuum distillation of **2** is typically employed to remove the crude product from the reaction medium. In addition, the crude distilled product, which typically contains oligomeric byproducts as well as unreacted **1**, often requires additional purification (redistillation[11,13] or chromatography[14,15]) to obtain **2** in sufficiently high purity. A low-yielding Soxhlet-style extraction utilizing chloroform has also been reported.[16]

Initial Reaction Optimization

Our initial efforts began by examining known procedures.[11,13,14] Attempted dehydration of **1** under the prescribed literature conditions with concomitant high-vacuum distillation on scales >20 g proved inefficient and difficult to engineer for large-scale preparation. Additionally, in our hands, multigram experiments employing various solvents and acid catalysts gave only moderate conversions (<50%)

* To whom correspondence should be addressed. E-mail: karla_childers@merck.com.

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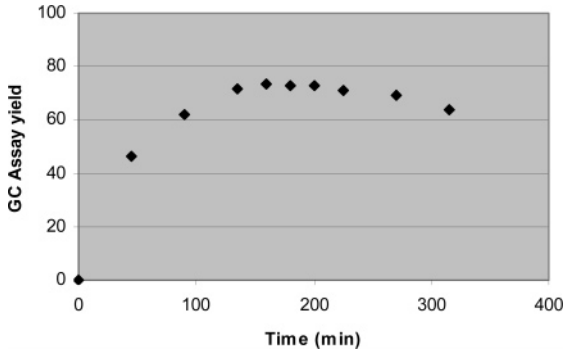

Figure 1. **Cyclodehydration with 5 mol % *p*-toluenesulfonic acid monohydrate at 125 °C.**

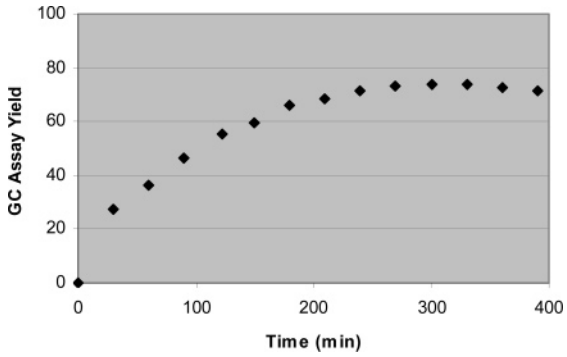

Figure 2. **Cyclodehydration with 2 mol % *p*-toluenesulfonic acid monohydrate at 125 °C.**

to **2**. Of the available literature conditions noted above for the preparation of **2**, we opted to focus on the neat, high-temperature dehydration of **1**, employing *p*-toluenesulfonic acid monohydrate (TsOH) as the acid catalyst. While methane sulfonic acid was also examined and found to give similar yield and conversion, TsOH was chosen for ease of handling on scale.

Optimization experiments were designed which (1) focused on temperature, acid charge, and reaction time in order to identify conditions that minimized formation of oligomeric byproducts and (2) allowed for maximum conversion of starting material to product. Initial optimization experiments were conducted at 400 mm/Hg with concomitant removal of water from the reaction mixture. After careful examination of the reaction parameters, it was discovered that addition of 5 mol % of TsOH to neat, completely molten **1** at 125−135 °C resulted in smooth conversion of **1** to **2** with ∼78% conversion (based on ^{1}H NMR and GC analysis) and 70−75% GC assay yield in just over 2 h (Figure 1). There was a steady decrease in reaction yield upon heating for >5 h.[17] While the reaction proceeded with 2 mol % TsOH, these reactions required prolonged heating at 125 °C for >5 h in order to achieve 75% conversion to **2** (Figure 2). Increasing the temperature accelerated not only the rate but also the amount of decomposition to oligomeric products. When the reaction was conducted at 150 °C employing as little as 1 mol % TsOH, a rapid drop in yield was noted after only 1.5 h (Figure 3). In order to minimize the reaction time and oligomeric decomposition, optimal conditions employed 5 mol % TsOH at 125−135 °C for 2.5 h, which routinely gave assay yields >70−75% (by ^{1}H NMR and GC).

(17) In order to obtain an accurate reaction profile, the dehydration reactions were run by adding TsOH once *meso*-erythritol (**1**) had reached the reaction temperature.

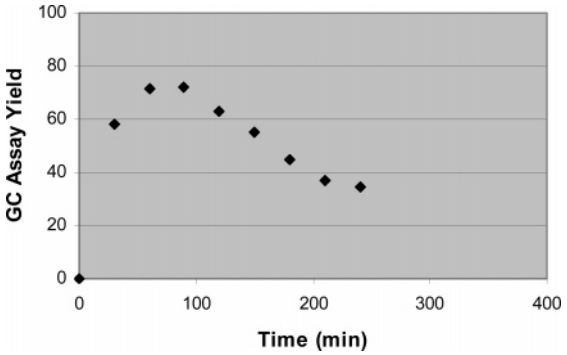

Figure 3. **Cyclodehydration with 1 mol % *p*-toluenesulfonic acid monohydrate at 150 °C.**

Purification Optimization

With a balance struck between conversion and yield, our attention turned to the isolation of **2** from the crude reaction mixture. Efforts focused on eliminating distillation under reduced pressure or the need to perform careful column chromatography on a multikilogram scale. Furthermore, we required that the isolated product be ≥95% purity by both GC and ^{1}H NMR analysis and free of any trace amounts of acid (TsOH). It was found that both *meso*-erythritol (**1**) and the oligomeric byproducts had a higher affinity for silica gel than 1,4-anhydroerythritol (**2**) and could be effectively removed by slurrying the crude reaction in ethyl acetate (EtOAc) containing silica gel, followed by filtration. However, the resulting stream still contained unacceptable amounts of TsOH. The solution to this problem was found in the addition of solid $NaHCO_3$ to the crude silica gel slurry, which effectively removed any trace amounts of acid (TsOH). The optimized purification process involved cooling the crude reaction mixture to 90 °C and transferring the free-flowing liquid[18] into a slurry of EtOAc (3 L/kg) containing 125 wt % silica gel and 10 mol % solid $NaHCO_3$ (all charges based on **1**). After stirring for 1 h at ambient temperature, the slurry was filtered, and the resulting solids were washed with an additional portion of EtOAc (15 L/kg total) to provide **2** in 60−65% assay yield and >95 wt % purity.[19] If the elution was pushed to maximum recovery, oligomeric products and unreacted **1** were leached from the silica gel, resulting in diminished purity of the product (<95 wt %). Using the procedure described above, the solution of **2** could be used in subsequent transformations without the need for further purification.

Scale-Up Conditions

While initial experiments were conducted at 400 mm/Hg with concomitant removal of water from the reaction mixture,

(18) If allowed to cool to room temperature, the crude reaction mixture became a highly viscous liquid that was difficult to manipulate; hence, the inverse addition at 90 °C.

(19) Assay yields and purity were determined by stripping solvent from an aliquot of the final solution and analyzing by ^{1}H NMR using mesitylene as an internal standard and also by GC analysis. After purification, the neat, pale-yellow oil was routinely >95 wt % by ^{1}H NMR and >95% GCAP with a purity profile similar to that of commercial grade 1,4-anhydroerythritol.

subsequent experiments indicated that water removal had no significant effect on the reaction rate, yield, or purity of the isolated product. On the basis of these results, reduced pressure was not used in the scale-up reactions. It was found, however, that the performance of the dehydration on large scale was highly dependent on heating the batch uniformly. Heat distribution using a well-stirred silicon oil bath was much better than when a standard heating mantle was employed. The use of a heating mantle resulted in excessively high temperatures (>250 °C) on the flask's exterior at the point of contact, with temperatures below the melting point of *meso*-erythritol (**1**) above the edge of the mantle.[20] Optimal conditions utilizing the silicon oil bath allowed the level of the material in the reaction vessel to be well-submerged in the oil bath to minimize freezing of the *meso*-erythritol (**1)** on the walls of the flask. While addition of TsOH resulted in a slight (2−3 °C) reduction of the internal temperature, the batch temperature remained stable (±2 °C) with no apparent exothermic behavior during the course of the reaction.

Conclusion

In summary, we have described an efficient, practical solution for the large-scale preparation of 1,4-anhydroerythritol (**2**). The process utilizes inexpensive *meso*-erythritol (**1**), avoids the use of high-vacuum distillation and rigorous column chromatography, and is amenable to large scale. The isolated 1,4-anhydroerythritol is obtained in 60−65% isolated yield and >95 wt % purity and can be used in subsequent transformations without the need for further purification.

Experimental Section

General Methods. All solvents and reagents were used as received from commercial sources.

Gas Chromatography. Gas chromatography was carried out using an Agilent gas chromatograph equipped with an FID detector and Restek RTx-200 column (30 m × 0.32 mm × 1.0 μm). Samples were dissolved in 85:15 acetonitrile/water (5 mg/mL) and analyzed according to the following temperature gradient: 145 °C for 1.5 min, ramp at 4 °C/min to 170 °C (no hold) then 40 °C/min to 275 °C (hold for 1 min) for a total of 11 min. A standard solution of **2** (retention time: 2.0 min) was used to generate a calibration curve and calculate yields. **1** (retention time: 3.8 min) gave a large fronting peak and a nonlinear calibration curve at concentrations greater than ∼2 mg/mL.

Preparation of 1,4-anhydroerythritol (2). To a four-neck, 3-L round-bottom flask equipped with a mechanical stirrer, thermocouple, water-cooled condenser, and 250-mL bump trap was added 1.50 kg (12.3 mol) of **1**. The flask was then lowered into a silicon oil bath equilibrated at 135 °C, and the solid was heated until the internal temperature reached 132 °C and the solid was completely molten. To the resulting melt was added in one portion 120 g (0.63 mol) of *p*-toluenesulfonic acid monohydrate. The resulting mixture was aged for 2.5 h, maintaining temperature between 125 and 135 °C, allowed to cool to 90 °C over 15 min, and inversely quenched into a 25-L, four-neck round-bottom flask containing a slurry of 15 L of ethyl acetate, 1.9 kg of silica gel, and 100 g of $NaHCO_3$ at 25 °C. The resulting slurry was stirred under nitrogen at 25 °C for 1 h. The solids were filtered and washed with ethyl acetate (3 × 7.5 L). A small aliquot of the filtrate was concentrated to dryness under reduced pressure, and the residual oil was assayed by ^{1}H NMR using mesitylene as an internal standard (60% assay yield). The ethyl acetate solution was used in the subsequent step without additional purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.62 (br s, 2 H), 3.98 (t, J = 1.8, 2H), 3.73 (m, 2H), 3.44 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 72.13, 70.89.

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(20) *meso*-Erythritol (**1**) was found to be stable when heated at 135 °C for 24 h in the absence of catalyst.