Efficient conversion of D-mannitol into 1,2:5,6-diacetonide with Aquivion-H as a recyclable catalyst

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Abstract

Heterogeneous solid catalysis by the commercially available perfluorosulfonic ionomer Aquivion-H allowed 1,2:5,6-diacetonide of D-mannitol (**1**), immediate precursor of important unichiral C3-synthons, to be efficiently obtained from D-mannitol and 2,2-dimethoxypropane in DMF at room temperature. The 1,2-monoacetonide, whose intermediate formation is the rate-limiting step, could be almost completely converted into **1** with limited concurrent transformation of **1** into triacetonides. In line with recent literature reports, these results indicate that heterogeneous catalysis by Aquivion-H surpasses the performances of homogeneous acidic catalysis assuring, presumably for its peculiar morphology, a higher product selectivity. Easy recovery at the end of the reaction and recyclability are additional advantages of this solid acid catalyst.

Keywords: D-mannitol, Aquivion-H, 1,2:5,6-di-*O*-isopropylidene-D-mannitol, 2,2-dimethoxypropane, acetonides

Introduction

Conversion into cyclic acetals and ketals is one of the most common methods to protect 1,2-diols and, among these, one of the most studied and applied procedure is the acetonation of the two terminal diols of the natural hexa-alcohol D-mannitol to 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**1**). Thanks to the identical *S* configuration of C(2) and C(5), oxidative cleavage of unprotected central diol of **1** affords, with 100% atom economy, two molecules of (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**2**) [1] and, upon reduction, of (*S*)-1,2-*O*-isopropylideneglycerol (**3**) [2,3], two of the most important C3-synthons within the chiral pool (Figure 1). Apart from their predictable wide use in the synthesis of the numerous molecules including the mono-, di- or trisubstituted glycerol framework, **2** and **3** are useful blocks to build other chiral linear molecules [4] and chiral cyclic systems. Examples of the latter are hexahydroindenes [5] benzomorpholines [6], benzodioxanes [7-11], dihydropyrroles [12], dihydrooxazines [12], dioxanes [13,14], pyridodioxanes [15,16], 2-oxazolidinones [17], spirobisdioxanes [18], and spirobisoxathianes [18].

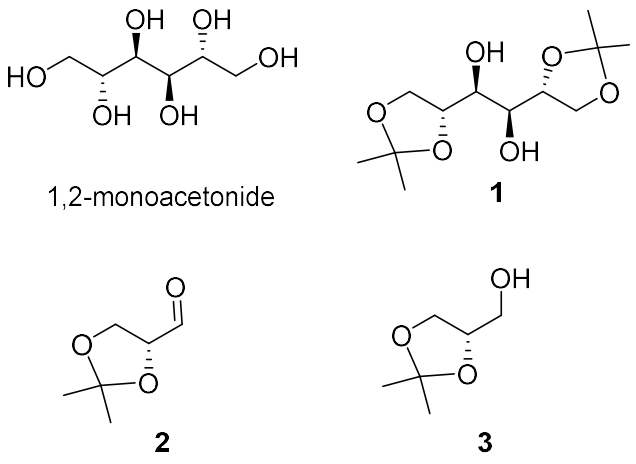


Figure 1

The first satisfactory method of acetonation of mannitol to the diacetonide **1** was developed in the decade between the thirties and the forties by Baer by using acetone and more than stoichiometric zinc chloride at room temperature [19]. The procedure, which involves a laborious removal of the

large amount of zinc chloride, affords the desired 1,2:5,6 diacetonide, after crystallization from dibutyl ether, in 42% yield. In more recent years, a significant improvement of the method yield (82%) was reported by avoiding any heating treatment during the reaction work up and the product purification [20,21].

In the meantime, namely in the eighties and in the nineties, the 1,2:5,6 diacetonation of D-mannitol was deeply investigated [22-24]. With the analytical support of gas chromatography and of ^{13}C NMR spectroscopy, the monitoring of the Baer's method and of some newly developed procedures highlighted the major concern of any preparation of **1**. This is to limit the formation of triacedonides and competing diacetonides, primarily 1,2:4,6- and secondarily 1,2:3,6-di-*O*-isopropylidene-D-mannitol, while maximizing consumption of D-mannitol and of the 1,2-monoacetal, whose initial formation is the rate-determining step because of the very poor solubility of D-mannitol in non-aqueous solvents [22,23] (Figure 2). Such studies, based on GC analyses of the reaction mixtures at different times, converged on identifying the acetone/zinc chloride procedure by Baer [19,25,26] and the transacetonation with 2,2-dimetoxypropane (2.4 equiv) and catalytic tin(II) chloride in 1,2-dimethoxyethane successively developed by Chittenden [27-29] as the two methods capable of achieving, respectively, the maximal 60 and 55% conversion of D-mannitol into **1**. After 16-24 hours at room temperature, the former procedure yields minimal quantities of triacetonides and other diacetonides but leaving behind almost 30% residual mannitol and 1,2-diacetonide. In 2-3 hours at reflux, the latter achieves a similar yield converting almost all mannitol and 1,2-diacetonide but producing more than 30% of triacetonides and other undesired diacetonides. Furthermore, the same studies showed that a third procedure, based on the treatment of D-mannitol with two equivalents of 2-methoxypropene and catalytic *p*-toluenesulfonic acid in DMF at 0 °C, affords **1** with 36% yield and not with 90% yield as previously claimed [30]. However, it is to be noted that this latter procedure interestingly differs from the two previous ones: the products mixture is richer in diacetals (72%), represented by **1**, 1,2:4,6- and 1,2:3,6-di-*O*-isopropylidene-D-mannitol in 3:2:1 ratio, while triacetals are practically absent and the quantities of monoacetonides and unreacted mannitol are modest. The

use of catalytic *p*-toluenesulfonic acid was proposed also in conjunction with 2,2-dimethoxypropane (2.5 equiv) or acetone (4.9 equiv) in DMSO claiming a 62% and 77% yield of **1** respectively [31,32].

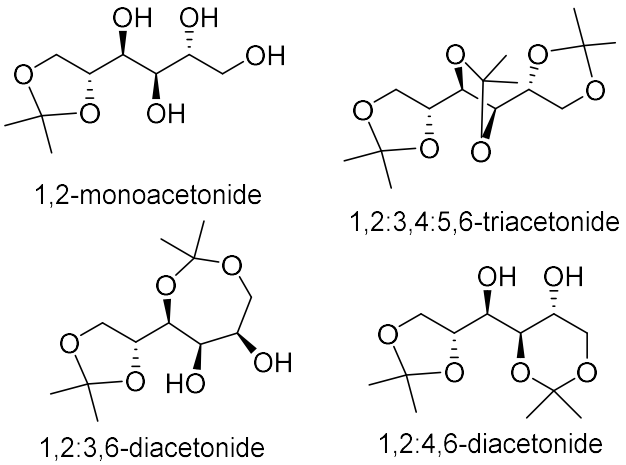
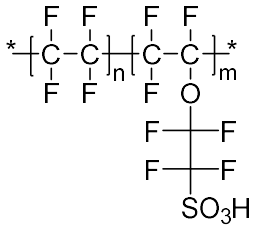


Figure 2

Although the efficiency of the *p*-toluenesulfonic acid catalyzed conversion of D-mannitol into **1** with 2-methoxypropene or 2,2-dimethoxypropane in polar aprotic solvents is questionable in some respects, we were interested in developing a procedure for the preparation of **1** preferring the catalytic use of an acid, in particular of a sulfonic acid, to stoichiometric zinc chloride. In terms of sustainability, the catalytic approach is superior and, in the present case, an additional attractive feature could be a heterogeneous catalysis with the recyclable solid catalyst we intended to use. This was Aquivion-H (Figure 3), a commercially available perfluorosulfonic ionomer (Aquivion PW87S), possessing superacid character, used to prepare polymer electrolyte membranes [33], whose iron-salt we have recently reported as an efficient recyclable catalyst of one-pot reductive aminations [34,35]. Furthermore, in the reported polyols acetonidations utilizing DMF and *p*-TsOH, such as the one mentioned above of D-mannitol with 2-methoxypropene [22,30], or in those of pentoses with 2,2-dimethoxypropane [36], the reaction seems more directable to mono-, di- or three-acetonidation by adjusting reaction parameters, such as temperature, time, and quantity of the acetalating agent, anyway without leaving starting material unreacted. The same is not feasible when working with

solvents, such as acetone or dimethoxyethane, in which, unlike in DMF, mannitol is insoluble at all [37,38]. In these solvents, complete consumption of mannitol necessarily results in high percentages of triacedonides.

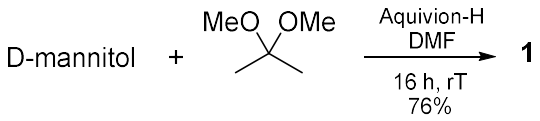


Aquivion-H

Figure 3

Results and discussion

Given the above considerations, we developed the here reported procedure of conversion of D-mannitol into **1** by treatment with 2,2-dimethoxypropane in DMF in the presence of catalytic Aquivion-H at room temperature for 16 hours (Scheme 1). The catalyst was used in 2.8% mol of H^+ relative to mannitol, namely 133 mg per gram of substrate, since stabilized powdered Aquivion-H PW87S has, insofar as sulfonic acid (R-SO_3H), a nominal equivalent weight of 870 g/eq. The acetalating agent, 2,2-dimethoxypropane, was used in 4:1 molar ratio to mannitol, namely 2.7 ml per gram of substrate, while the solvent DMF in 5:1 v/w to mannitol, namely 5 ml per gram of substrate.



Scheme 1

The reactions were initially performed on one gram of mannitol. After 16 hours vigorous stirring, the reaction mixture was filtered to remove the catalyst. The filtrate was concentrated under vacuum at 40 °C. The resultant solid was triturated in cyclohexane (15 ml) and recovered by filtration to give **1** in 76% yield. At the end of the first catalytic cycle, Aquivion-H was washed with acetonitrile and then dried under vacuum. Aquivion-H was then recycled for five times without appreciable variation in its catalytic performances (Figure 4).

The reactions were successively performed on ten grams of mannitol by the same protocol without difficulties and yield decrease.

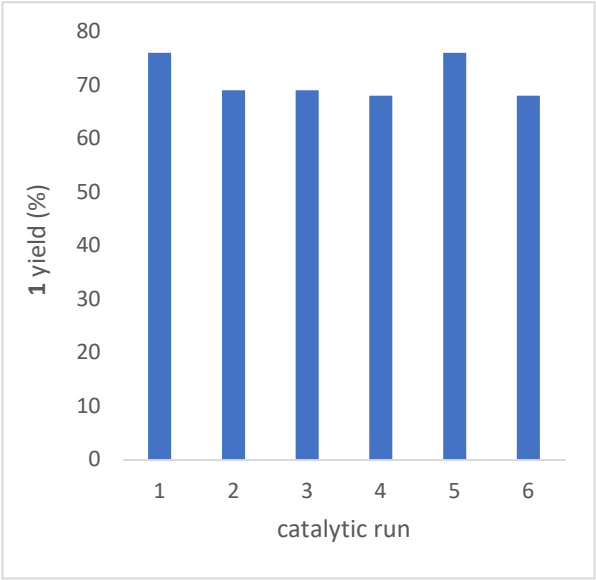


Figure 4

Based on the previously mentioned literature investigations, pointing out how complex mixtures of mono- and poly-acetonides can form from mannitol, we carefully analyzed both the crude resulting from DMF removal and final **1** obtained by trituration in cyclohexane. Besides routinary melting point and ^{1}H NMR determinations, we relied on ^{13}C NMR and on GC analyses of the acetylated derivatives. The spectroscopic analysis clearly distinguishes among dioxolane, 1,3-dioxane and 1,3-dioxepane substructures thanks to the different shifts of the dimethylated acetal carbon thus revealing the undesired 4,6-acetonidation (1,3-dioxane) and 3,6-acetonidation (1,3-dioxepane) [23]. The GC analysis elutes, in the order, the triacetonides, the diacetyl derivatives of the diacetonides, the

tetraacetyl derivatives of the monoacetonides and, finally, the peracetylated mannitol and furthermore it can separate the different isomers within each group. GC analyses of the crudes from three consecutive reactions revealed that triacetonides made up less than 10 % of the crude solid resultant from removal of the catalyst and DMF, while the 1,2-monocetonide was present in traces and mannitol was absent. The remainder consisted of a largely preponderant product, namely the desired diacetonide **1**. Consistently, ^{1}H NMR spectrum of the crudes appeared like that of a unitary product (See the ^{1}H NMR spectrum of crude **1** and that of pure **1** reported in Supplementary Information). Indeed, the revealing signals, namely those for the hydroxylated methines and for the geminal methyls, were relatively clean. ^{13}C NMR spectrum showed only one signal for the dimethylated acetal carbons, positioned at 109.4 ppm and imputable to the desired acetonidation of vicinal diols to dioxolane rings. Furthermore, it is noteworthy that the main impurity of the crudes was represented by less polar triacetonides and not by the highly polar 1,2-monoacetonide. This fact allowed us to avoid the purification of **1** by the usual crystallization from di-*n*-butyl or diisopropyl ether. Simple trituration of the crudes in more acceptable solvents, such as cyclohexane or cyclohexane and 'green ether' (CPME, TAME, MeTHF), recently employed by us in the esterification of amino acids [39,40], was enough to remove the minority by-products, namely the triacetonides, which were dissolved leaving **1** as a white solid with >98% GC purity. Indeed, when we halved the catalyst amount, the main impurity became the 1,2-monoacetonide and, as expectable, trituration of the crude in cyclohexane did not remove it but enriched **1** in it. Therefore, it was necessary to wash an ethyl acetate solution of the crude with water first and only then to triturate the solid resultant from ethyl acetate removal in cyclohexane.

These results indicate that, in a polar aprotic solvent and under the selected conditions, the heterogeneous catalysis by Aquivion-H can efficiently promote diacetonidation of mannitol with almost complete consumption of the starting material and of the intermediate monoacetonide and minimal formation of triacetonides. Such an output is in line with those of the reported homogeneous catalysis by *p*-TsOH in DMF or in DMSO, but here, the preferential formation of diacetonides over

the other acetals is more pronounced and what is more with a much larger prevalence of the desired diacetonide **1**.

We think that a key role in determining the efficiency (high conversion into diacetonides) and the selectivity (high yield of the diacetonide **1**) of the procedure is the combination of a polar aprotic solvent with a heterogeneous solid catalyst such as Aquivion-H. In less polar aprotic solvents, such as acetonitrile, glyme, ethyl acetate or acetone, the Aquivion-H catalyzed acetonidation led to triacetals as the main products, as indicated by the almost exclusive presence of singlets imputable to the geminal methyls of the 1,2:3,4:5,6 triacetonide in the most upfield region of the ^{1}H NMR spectra of the crudes and by the concomitant absence, at lower field, of the diagnostic signals for **1**, namely those of the two hydroxylated methines. DMF, in which the solubility of mannitol at room temperature is low but not null as in the above less polar solvents, can ensure a supply of dissolved substrate proportioned to the turnover frequency of the catalysts, which is, as desirable, lower than that of soluble acids such as *p*-TsOH or H_2SO_4. In this heterogeneous catalysis, other key aspects able of modulating the reactivity of the species involved are the more difficult accessibility to the catalytic sites by the reactants, reasonably varying with their acetonidation extent, and the amphiphilic nature of the polimer Aquivion-H favoring the reactivity of a highly hydrophilic substrate, such as mannitol, in a non-aqueous environment. The synergy of these factors allows a fine control of the reaction and tunes the reaction selectivity. Evaluation of the individual weigh of such factors would imply further ad hoc investigations. However, our statements are supported by the negative or less positive results obtained replacing Aquivion-H with soluble acids or DMF with solvents unable to dissolve mannitol.

The present procedure of mannitol diacetonidation catalyzed by Aquivion-H places itself beside the recently reported Aquivion catalyzed acetalizations of sugars with fatty alcohols to give amphiphilic alkyl glycosides [41-43], surfactants of great interest for many desirable intrinsic properties. There, acetalization reaction was between hydrophilic carbonyl compounds (glucose, cellulose) and a hydrophobic alcohol (*n*-dodecanol). Here, on the contrary, a highly hydrophilic

alcohol (mannitol) reacts with a hydrophobic acetalating agent (2,2-dimethoxypropane). In both cases, due to its amphiphilic nature, Aquivion-H proves to be able to efficiently catalyze the reaction between substrates of very different polarity while showing, because of its structured catalytic sites, good selectivity for a single product inside a large series of candidate products. Among a dozen of mono-, di- and triacetonides, Aquivion-H selectively catalyzes the formation of the desired 1,2:5,6 diacetonide although in the presence of exceeding acetalating agent for moderately long time at room temperature, maintaining such a performance unaltered through several recycles.

Experimental

D-Mannitol (1 g, 5.49 mmol), Aquivion-H (133 mg, 0.153 mmol), 2,2 dimethoxypropane (2.7 ml, 22.0 mmol) and 5 mL of dimethylformamide were introduced into a round bottom flask under inert atmosphere. The reaction mixture was vigorously stirred for 16 hours at room temperature. Afterward the suspension was filtered to remove the catalyst and the filtrate was concentrated under vacuum to obtain a white solid crude that was triturated in cyclohexane (15 ml). **1** was recovered by filtration as a white solid in 76% yield (1.09 g): mp = 120.3-121.6 °C; $[\alpha]_D^{25}$ = +2.6 (*c* 1, EtOH). ^{1}H-NMR ($CDCl_3$) δ 4.19 (q, *J* =6.2 Hz, 2H), 4.12 (dd, *J*=8.4 Hz and 6.4 Hz, 2H), 3.97 (dd, *J*=8.4 Hz and 5.6 Hz, 2H), 3.75 (t, *J*=6.6 Hz, 2H), 2.59 (d, *J*=6.6 Hz, 2H), 1.42 (s, 6H), 1.36 (s, 6H). ^{13}C-NMR ($CDCl_3$) δ 109.4, 76.3, 71.2, 66.7, 26.7, 25.2. GC analysis of the diacetylated derivative showed >98% purity. The catalyst removed from the reaction mixture was rinsed with acetonitrile, dried under vacuum, and recycled for five times.

GC analyses were conducted on samples acetylated by treatment with pyridine and acetic anhydride overnight at room temperature with a Thermo Fisher Trace gas chromatograph using a fused silica capillary column DB-5MS UI (30 m × 0.25 mm) (Agilent); temperature, 5 °C/min from 180 to 280 °C; carrier gas, helium 1.0 ml/min; detector: FID. Under these conditions, the R_t of 1,2:3,4:5,6-triacetal, diacetylated **1**, tetraacetylated 1,2-diacetal and peracetylated mannitol were

3.80, 5.80, 7.49 and 9.55 min, respectively. Their peaks were identified by peak-matching with authentic samples obtained by acetylation of mannitol and of the acetals, in turn isolated from reaction crudes by chromatography on silica gel and identified by comparison of their ^{1}H NMR spectra with those reported in the literature.

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Supplementary data

Supplementary data to this article can be found online at https.//doi.org/

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