Article

Methanetrisulfonic Acid: A Highly Efficient Strongly Acidic Catalyst for Wagner-Meerwein Rearrangement, Friedel-Crafts Alkylation and Acylation Reactions. Examples from Vitamin E Synthesis

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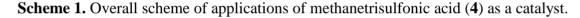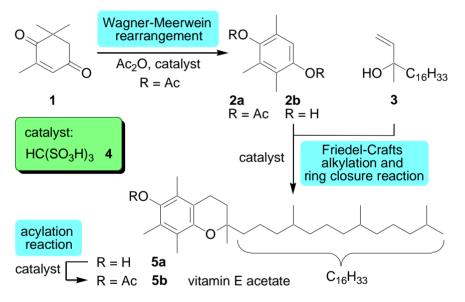
Abstract: Methanetrisulfonic acid had been prepared for the first time over 140 years ago, but it was used only scarcely in chemical transformations. In the course of our activities dealing with key-steps of industrial syntheses of vitamins, e.g. economically important vitamin E (acetate), we found that methanetrisulfonic acid is an extremely effective catalyst in a variety of reactions. Examples of its applications are Wagner-Meerwein rearrangements, Friedel-Crafts alkylations and ring closures, as well as acylation reactions. Use of this catalyst in truly catalytic amounts (0.04-1.0 mol%) resulted in highly selective transformations and yields over 95%. (Remark by the authors: We are describing only one example each for the various types of reactions. Therefore, it would be more appropriate to write (here and in the Introduction and in the Conclusion sections): "Wagner-Meerwein rearrangement, Friedel-Crafts alkylation and ring closure, as well as acylation reactions")

1. Introduction

The development of catalytic processes is a fundamental issue in the field of vitamins and fine chemicals industry [1]. Many acid catalyzed key-steps of industrial syntheses of vitamins, e.g. economically important vitamin E (acetate) **5a,b** [2,3], are usually mediated by conventional Lewis or Brønsted acids like BF_3, $AlCl_3$, $ZnCl_2$, HCl, or H_2SO_4. The use of those acids, however, often causes severe problems, due to corrosion and formation of waste material. In the course of our search for efficient and environmentally benign production processes we found that methanetrisulfonic acid (**4**) is an extremely effective catalyst in a variety of reactions. We like to point out that we did not observe corrosion in any of the applications when using **4** as catalyst. Methanetrisulfonic acid (**4**) had been prepared for the first time over 140 years ago [4], but it was used only scarcely in chemical transformations. In this communication, we would like to report our results when using this overlooked and easily available strongly acidic compound **4** as a catalyst in a variety of transformations. Examples (Scheme 1) are Wagner-Meerwein rearrangements (**1** $\rightarrow$ **2a** [5]), Friedel-Crafts alkylations and ring closures (**2b** + **3** $\rightarrow$ **5a** [6]), as well as acylation reactions (**5a** $\rightarrow$ **5b** [7]).

Scheme 1. Overall scheme of applications of methanetrisulfonic acid (**4**) as a catalyst.

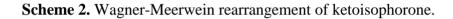## 2. Results and Discussion

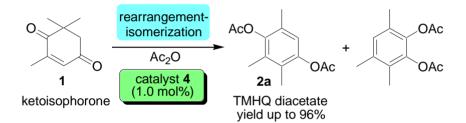### 2.1. Preparation of methanetrisulfonic acid (**4**)

Alkanepolysulfonic acids are a group of very acidic compounds [8]. No direct pK measurement for acid **4** is known, to the best of our knowledge. From reference [8] the pK_{a1} value can be assumed to be below -3. The preparation of tri-potassium methanetrisulfonate and its corresponding free acid **4** had already been reported by Theilkuhl in 1868. After several reports on this chemistry [9-16], an improved procedure developed by Sartori and Jüschke made the tri-potassium salt easily available on a laboratory (deca-gram) scale from cheap acetone and oleum (H_2SO_4/SO_3) [17]. Purification via the barium salt and subsequent acidification by sulfuric acid is based on the work of Bagnall and further optimization

by Backer [12,14]. Hygroscopic colourless crystals of a hydrate of acid **4** obtained by these procedures (cf. Experimental Section) were used in the reactions described below. Although this catalyst synthesis does not fulfill the criteria of green chemistry, and a more efficient and environmentally benign procedure has still to be developed, we think that the examples for the use of **4** given here represent considerable improvements for the transformations selected.
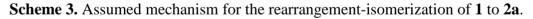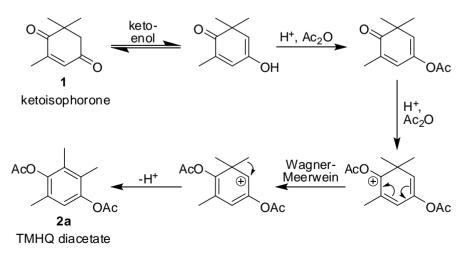
2.2. Wagner-Meerwein rearrangement

Ketoisophorone (**1**), derived from acetone via α- and β-isophorone, followed by oxidation, serves as a cheap key intermediate for the carotenoid astaxanthin, as well as a valuable starting material for an alternative access to trimethylhydroquinone (TMHQ) diacetate (**2a**, Scheme 2) [1,3]. Diacetate **2a** can be further processed to α-tocopherol (**5a**) via conventional saponification to TMHQ (**2b**), or to α-tocopheryl acetate (**5b**) via highly selective monosaponification [18].

Scheme 2. Wagner-Meerwein rearrangement of ketoisophorone.

When ketoisophorone (**1**) was treated with acetic anhydride in the presence of 1.0 mol% of catalyst **4**, the Wagner-Meerwein rearrangement, followed by an isomerization (aromatization) reaction took place in a highly selective manner. Excellent yields of up to 96% of diacetate **2a** were obtained. Formation of the unwanted regioisomer, catechol diacetate, could thus be efficiently diminished [5]. An assumed mechanism for the transformation of **1** into **2a** is depicted in Scheme 3.

Scheme 3. Assumed mechanism for the rearrangement-isomerization of **1** to **2a**.
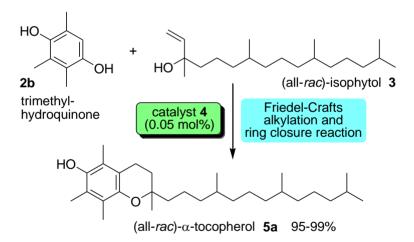
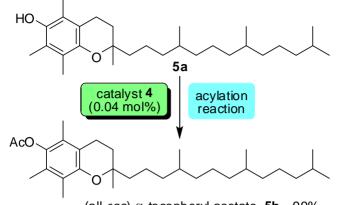## 2.3. Friedel-Crafts alkylation and ring closure reaction

The Friedel-Crafts type condensation reaction of trimethylhydroquinone (**2b**) with isophytol (**3**) (Scheme 4) is the key step in all industrial syntheses of (all-*rac*)-α-tocopherol (**5a**), produced on a scale of > 30,000 tons per annum. Therefore, major efforts have been directed towards the development of efficient, environmentally benign catalytic processes for this transformation [1,2,19]. We were delighted to find that methanetrisulfonic acid (**4**) is able to catalyse this important reaction in a surprisingly clean and effective manner, although tertiary allylic alcohols like **3** tend to dehydrate when treated under acidic reaction conditions. In contrast to most systems known, the use of **4** in amounts as low as 0.05 mol% delivers tocopherol **5a** in extremely high yields (up to 99%) [6]. Furthermore, the application of the pure Brønsted acid **4** avoids product contamination and even waste streams containing metal or halide ions, as well as corrosion problems. While this argument is also valid for other conventional Brønsted acids, it must be pointed out that the advantage of **4** is not only the reduced amount of catalyst needed, but in particular the increased yield and selectivity. For example the application of 0.13 mol% sulfuric acid as the catalyst under similar conditions results in 93% yield [20]. Therefore, acid **4** is one of the most efficient catalysts ever found for this transformation.

> **Scheme 4.** Friedel-Crafts alkylation and ring closure reaction in the synthesis of (all-*rac*)-α-tocopherol (**5a**).

2.4. Acylation reaction

Although acylation of a phenolic hydroxyl group is commonly rated as a trivial reaction in organic chemistry, there is a need for potent catalysts and procedures applicable to ecologically acceptable large-scale operations.

Scheme 5. Acylation reaction of (all-*rac*)-α-tocopherol (**5a**).

(all-*rac*)-α-tocopheryl acetate **5b** 99%

The acetylation of (all-*rac*)-α-tocopherol (**5a**) to the corresponding acetate **5b**, the major sales form of vitamin E, is another example for the successful application of methanetrisulfonic acid (**4**) as an acidic catalyst (Scheme 5). When using 0.04 mol% **4** and acetic anhydride as an acylation reagent, (all-*rac*)-α-tocopheryl acetate (**5b**) was obtained in 99% yield [7].

3. Experimental Section

3.1. Preparation of tri-potassium methanetrisulfonate monohydrate [17]

Dry acetone (17.5 mL, 238 mmol) was very slowly added dropwise to oleum (fuming sulfuric acid, 65% free SO_3, 100 mL) at 0 °C while stirring (temperature of the mixture maintained below 5 °C). After completion of the addition, the reaction mixture was heated to 85 °C for 3 h (until evolution of CO_2 was complete). The suspension was poured onto ice/water (500 mL) and neutralized (pH 7) by careful addition of KOH (ca. 210 g). Water (1 L) was added, and the mixture cooled to < 25 °C. The precipitate was separated by suction filtration, washed several times with small portions of distilled water, and recrystallized from water to separate any remaining potassium sulfate. The colourless solid was dried at 20 °C/10^{-3} torr for 18 h; yield of $K_3[HC(SO_3)_3] \times H_2O$: 117.1 g (301 mmol, 79%) .

3.2. Preparation of $Ba_3[HC(SO_3)_3] \times 9\ H_2O$ [14]

A saturated solution of $BaCl_2 \times 2\ H_2O$ (42.99 g, 175.9 mmol) was added dropwise to a boiling solution of $K_3[HC(SO_3)_3] \times H_2O$ (45.58 g, 117.3 mmol) while stirring. A colourless precipitate started to form already after the addition of a few drops. The precipitate was separated by suction filtration and dried at 20 °C/10^{-3} torr for 18 h; yield of $Ba_3[HC(SO_3)_3] \times 9\ H_2O$ as colourless solid: 53.16 g (49.2 mmol, 84%) .

3.3. Preparation of $HC(SO_3H)_3 \times n\ H_2O$ (**4**) [12]

Sulfuric acid (96%, 9.81 g, 96.0 mmol) was added dropwise to a stirred warm suspension of $Ba_3[HC(SO_3)_3] \times 9\ H_2O$ (34.59 g, 32.0 mmol). After completion of the addition, the reaction mixture

was stirred at 80 ℃ for 3 h. The precipitate of $BaSO_4$ formed was separated by careful decantation after settling for several hours (suction filtration of the very fine powder was not possible), and the remaining $BaSO_4$ was washed ($\times$ 3) with small amounts of distilled water. The combined aqueous solutions were evaporated *in vacuo*, until a highly viscous clear residue had formed. This syrup was dried over concentrated H_2SO_4 in a vacuum dessicator, and crystals of acid **4** begun to form. After several days (the H_2SO_4 was replaced daily by fresh material), the deliquescent crystals (only a part of the product crystallized out) were further dried over H_2SO_4 on a porous plate; yield of colourless crystals of $HC(SO_3H)_3 \times 3(?) H_2O$: 5.33 g (17.2 mmol, 27%).

3.4. Isomerization-aromatization reaction of ketoisophorone [5]

A 50-mL four-necked flat-bottomed flask equipped with a thermometer, a glass-tube ($\varnothing$ 5 mm) for Ar-purge, a reflux condenser and a magnetic stirring bar was charged with methanetrisulfonic acid hydrate (**4**, 171.2 mg, 1.0 mol%) and ketoisophorone (**1**, 10.324 g, 66.0 mmol). Within 2 min, acetic anhydride (200 mmol) was added dropwise under rapid stirring. During addition, the mixture turned from dark yellow to dark brown, finally, and the internal temperature increased. The mixture was cooled to 25 ℃ and maintained at this temperature by means of an oil bath. Samples were taken and submitted to qualitative GC analysis for reaction control. After 22 h reaction time, the reaction mixture was cooled to 20 ℃, and the catalyst deactivated by addition of anhydrous sodium carbonate (3.7 g, 70.0 mmol). After filtration, acetic acid and unreacted acetic anhydride were distilled off at 40 ℃/10 mbar, and the crude product was analyzed by GC using squalane as an internal standard: conversion 100%, yield of TMHQ diacetate (**2a**): 96.6%. This product was further identified by comparison of its NMR data with reference material: ^{1}H-NMR (300 MHz, $CDCl_3$, δ in ppm): 6.65 (s, 1 H, Ar-H), 2.33 (s, 3 H, C(O)CH_3), 2.30 (s, 3 H, C(O)CH_3), 2.11 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3).

3.5. Condensation reaction of trimethylhydroquinone (**2b**) and isophytol (**3**) to (all-rac)-α-tocopherol (**5a**) [6]

A 200-mL four-necked flask equipped with a reflux condenser, a water separator, a mechanical stirrer, and an argon inlet was charged with trimethylhydroquinone (**2b**, 7.55 g, 50.0 mmol, purity 99.7%), ethylene carbonate (40.0 g), and heptane (50 mL). The mixture was heated to reflux (bath temperature 140 ℃), and methanetrisulfonic acid hydrate (**4**) was added as an aqueous solution (4.23 mg catalyst **4**, 0.05 mol% based on the molar amount of isophytol subsequently added). The concentration of catalyst in water (5 % to 50 %) is not critical. Isophytol (**3**, 12.026 mL, 33.0 mmol) was then added at a rate of 0.6 mL/min (i.e. molar ratio **2b**:**3** = 1.5). After completion of the addition (ca. 12 min), the heptane was distilled off, the mixture heated to 125-130 ℃ for 30 min, and then cooled to 80 ℃. Heptane (50 mL) was added to the ethylene carbonate phase, and the reaction mixture was stirred for an additional 10 min at 50 ℃. After phase separation the heptane layer was collected and evaporated *in vacuo* to give (all-*rac*)-α-tocopherol (**5a**) as a viscous oil; yield: 95.3% (determined by GC with squalane as internal standard). Identification of **5a** was done by comparison of its NMR data [21] with reference material.

*3.6. Acylation reaction of (all-*rac*)-α-tocopherol* [7]

A 200-mL four-necked flask equipped with a stirrer, a thermometer, and a reflux condenser with an argon inlet was charged with (all-*rac*)-α-tocopherol (**5a**, 51.09 g, 0.116 mol), acetic anhydride (24.7 g, 0.242 mol), and catalyst **4** (15.6 mg, 0.0503 mmol, 0.0433 mol%). The mixture was stirred at 400 rpm and heated to 100 °C (internal temperature) for 1 h. After cooling and evaporation under reduced pressure (10 mbar, 60 °C), 57.45 g of crude acetate **5b** (yield 98.9% by GC, internal standard; purity 94.4%) were obtained as a brownish oil, identified by comparison of its NMR data [21] with reference material.

4. Conclusions

In summary, the high potential of methanetrisulfonic acid (**4**) in preparatively meaningful and industrially important acid mediated transformations has been shown. This strongly acidic compound, easily accessible from acetone, has been applied as an efficient catalyst used in truly catalytic amounts ranging from 0.04 to 1.0 mol% in Wagner-Meerwein rearrangements, Friedel-Crafts alkylations and ring closures, as well as acylation reactions. The successful use documented by such examples may broaden the scope of applications of this reagent in other areas of organic synthesis.

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