Synthesis of (all-*rac*)-α-Tocopherol Using Fluorinated NH-Acidic Catalysts

Werner Bonrath,[a,*] Alois Haas,[b] Eike Hoppmann[b], Thomas Netscher,[a] Horst Pauling,[a] Frank Schager,[a] Angela Wildermann[a]

[a] Research and Development, Roche Vitamins Ltd, 4070 Basel, Switzerland
Fax: (+41)-61-687-2117, e-mail: werner.bonrath@roche.com
[b] Ruhr-Universität Bochum, Fakultät für Chemie, FNO 034/036, 44780 Bochum, Germany

Received October 15, 2001; Accepted November 11, 2001

Abstract: The synthesis of (all-*rac*)-α-tocopherol starting from trimethylhydroquinone and isophytol using fluorinated NH-acidic catalysts is described. Scope and limitations of this type of catalysts are discussed. Advantages of this new procedure are high yield and selectivity, no waste problem and mild reaction conditions. Best results in the synthesis of (all-*rac*)-α-tocopherol (94% yield) using NH-acidic compounds are obtained in polar solvents. The used catalyst could be recovered.

Keywords: (all-*rac*)-α-tocopherol; biphasic catalysis; catalysis; fluorinated NH-acidic catalysts; Friedel–Crafts alkylation.

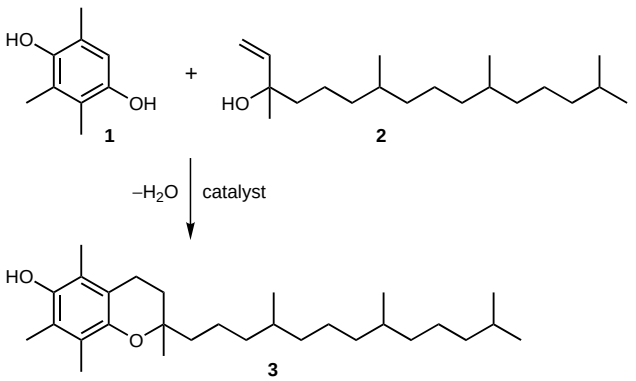
Vitamin E is the most important fat-soluble antioxidant in biological systems.[1] The economically most valuable form of vitamin E is synthetic (all-*rac*)-α-tocopherol (**3**), an equimolar mixture of all eight stereoisomers, mainly applied as its acetate derivative.[1,2] The world market of vitamin E is about 25000 tons per year and is constantly increasing.[3]

All industrial syntheses of (all-*rac*)-α-tocopherol (**3**) are based on the reaction of trimethylhydroquinone (**1**) with isophytol (**2**) or phytyl halides (Scheme 1).[1,2] Lewis acids and Brønsted acids, e.g., zinc chloride and a mineral acid, serve as catalysts in this reaction.[2] BF_3, $AlCl_3$, Fe/HCl, or the combination of boric acid and carboxylic acids are good catalysts.[2] The reaction can be carried out in various solvents, e.g., esters or hydrocarbons. From an industrial view-point, most of these methods suffer from two major disadvantages: corrosion problems and/or a potential contamination of waste water.

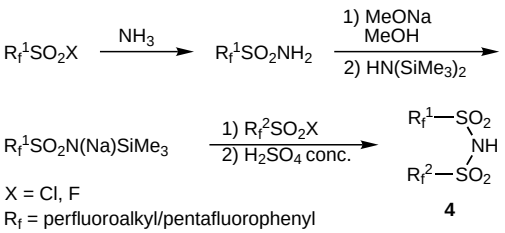
To overcome these disadvantages of the known syntheses of (all-*rac*)-α-tocopherol (**3**) several approaches were followed. The use of supercritical fluids as solvents in the reaction of **1** and **2** as well as in the purification of **3** has been published.[4–6] Furthermore, we have used a heterogeneous acid based on Nafion as replacement for mineral acids. These Nafion catalysts possess beneficial environmental effects of heterogeneous catalysis, e.g., recycling of catalyst.[7,8] The application of 'microencapsulated' catalysts (MC), e.g., microencapsulated scandium tris-triflate [MC-Sc(OTf)$_3$], a new type of catalyst for the reaction of isophytol (**2**) and trimethylhydroquinone (**1**), was described in ref.[9] Furthermore, it was reported that imides, e.g., $(CF_3SO_2)_2NH$, catalyze the synthesis of (all-*rac*)-α-tocopherol.[10]

In this paper we report our results on the systematic development of fluorinated (fluorinated in this context means that the sulfonyl group bears perfluoroalkyl and/or pentafluorophenyl substituents) NH-acidic catalysts of type **4** for the efficient synthesis of **3.** The imides **4** have been prepared starting from commercially available sulfonyl halides originating from electrochemical fluorination. As outlined in Scheme 2, they have been obtained *via* the sulfonamides and silyl derivatives as highly air-sensitive solids, according to literature procedures[11–13] under slightly modified conditions.

The acid-catalyzed overall reaction in the formation of α-tocopherol (**3**) from **1** and **2** consists of a Friedel–Crafts alkylation reaction followed by a ring-closure reaction (Scheme 1). This is based on the fact that alcohols and preferably tertiary allylic alcohols like **2**, easily lose water in the presence of acids[14] to form highly reactive carbocations. Therefore, formation of considerable amounts of dehydration products, so-called phytadienes, is a general problem of such procedures. Contrary to our expectation, however, we found only small amounts of phytadienes (generally less than 4%, and



Scheme 1. Synthesis of (all-*rac*)-α-tocopherol (**3**).



Scheme 2. Preparation of catalysts **4.**

  1615-4150/02/34401-037–039 $ 17.50+.50/0

less than 1.5% with the best catalysts) when **2** was reacted with **1** in the presence of catalytic amounts of imides **4** under the conditions specified in the experimental section. Under those conditions, the conversion of **2** is around 99% and the yield of (all-*rac*)-α-tocopherol (**3**) is in the range of 94%. Results obtained from experiments with NH-acidic catalysts are presented in Table 1.

Table 1. Reaction of **1** and **2** in various solvents using NH-acidic compounds of the type $(R_f^1SO_2)(R_f^2SO_2)NH$ (**4**).

4	R_f^1	R_f^2	solvent[a]	yield **3** (%)[b]
a	CF_3	CF_3	toluene (50)	89.5
a	CF_3	CF_3	EC (40)/hept. (50)	91.0
b	CF_3	C_4F_9	toluene (50)	89.6
b	CF_3	C_4F_9	EC (40)/hept. (50)	94.0
c	C_2F_5	C_4F_9	toluene (50)	90.2
d	CF_3	C_6F_5	diethyl ketone (50)	83.8
d	CF_3	C_6F_5	γ-but.lac (40)/hept. (50)	87.4
d	CF_3	C_6F_5	PC (40)/hept. (50)	92.6
e	C_2F_5	C_2F_5	EC (40)/hept. (50)	93.6
f	C_3F_7[c]	C_3F_7[c]	EC (40)/hept. (50)	94.5
g	C_6F_5	C_6F_5	EC (40)/hept. (50)	87.2
g	C_6F_5	C_6F_5	PC (40)/hept. (50)	84.9
h	$CF_2CF_2CF_2$		EC (40)/hept. (50)	94.5
i	C_4F_9	C_4F_9	PC (40)/hept. (50)	94.0
k	C_4F_9	C_6F_5	PC (40)/hept. (50)	93.3
m	CF_3	C_8F_{17}	PC (40)/hept. (50)	86.4
n	C_8F_{17}	C_8F_{17}	PC (40)/hept. (50)	85.6
o	C_4F_9	C_8F_{17}	PC (40)/hept. (50)	91.1

[a] In mL, γ-but.lac = γ-butyrolactone, hept. = heptane, EC = ethylene carbonate, PC = propylene carbonate.
[b] Yields are based on **2**, determined by GC analysis of the crude product.
[c] Mixture of *n/iso*.

The key findings are:

- Maximum yields of (all-*rac*)-α-tocopherol are obtained in polar aprotic solvents.
- Best yields are obtained in two-phase solvent systems.
- The optimal number of C-atoms for alkyl-substituted imides **4** is between two and four.
- The cycloaliphatic imide **4h** is among the best catalysts.
- In **4**, the optimal perfluoroaliphatic substituents are more efficient than pentafluorophenyl substituents.
- Mixed alkyl-/aryl-substituted catalysts **4** are better than aryl-/aryl-substituted ones.

In addition, we found that the yield is strongly dependent on the solvent polarity, corroborating results from earlier work.[7] The main by-products in this reaction are phytadienes and furan derivatives, which have already been characterized by Yamamoto and coworkers in the scandium(III) trifluoromethanesulfonate-catalyzed condensation of **1** and **2.**[15]

Compared to the results of zinc chloride/Brønsted acid- or BF_3-catalyzed reactions, we found good yields and selectivities. Using $ZnCl_2$/HCl or BF_3 as catalysts, (all-*rac*)-α-tocopherol (**3**) could be obtained in yields of approximately 80% at best.[16] Another advantage of the new procedure is the low amount of catalyst (as low as 0.1 mol %) needed.

It must be pointed out that an additional advantage of this type of imide catalysts is documented by an extremely high selectivity of the overall reaction. Compared to other syntheses of **3**,[9] it was found that the ratio of benzopyran to -furan was higher than 200, and the amount of phytadienes was in the range of a few percent only.

In further experiments the recovery of the NH-acidic catalysts was investigated. In polar aprotic solvents within a temperature range from 50 to 100 °C, the catalyst could be recovered ten times without detectable loss of activity and selectivity.

With regard to the synthesis of **3** we recommend the use of perfluorinated NH-acidic imides **4** as excellent catalysts. Their principal advantage when applied in biphasic solvent systems is based on the combination of activity and selectivity of homogeneous catalysts with heterogeneous solvent systems.

Experimental Section

General

Trimethylhydroquinone (**1**), toluene, heptane, propylene carbonate, ethylene carbonate, and $(CF_3SO_2)_2NH$ (**4a**) were purchased from Fluka and $(C_2F_5SO_2)_2NH$ (**4e**) and [4*H*]1,3,2-dithiazine-4,4,5,5,6,6-hexafluorodihydro-1,1,3,3-tetroxide (**4h**) from K. F. Meyer (Fussgönheim). Isophytol was obtained from Teranol AG and $(C_4F_9SO_2)_2NH$ (**4i**) from Bayer AG (Leverkusen). All the compounds listed above were used without further purification. All solvents and liquid reagents were degassed by three freeze-thaw cycles before use.

The catalytic reactions were carried out in a batch reactor under an argon atmosphere using Schlenk techniques. Gas chromatographic analyses (GC) were carried out on a HP 5890 apparatus equipped with an autosampler and a capillary column Macherey-Nagel type Optima 5 (30 m × 0.32 μm). The compounds elute at detected retention times of 10.5 min (**1**), 13.1 min (**2**), and 23.7 min (**3**). The crude product was analyzed by GC with an internal standard.

Preparation of Imides 4

For the synthesis of imides **4** not being commercially available, literature procedures[11,12] were followed and slightly adapted to the individual compounds (*cf.* Scheme 2). The products were obtained after high-vacuum sublimation or short-path distillation from conc. H_2SO_4. Their air-sensitivity requires strict handling under an argon atmosphere. Aryl derivative **4g** was isolated from the water-insoluble ammonium salt after use of cation exchange resin (Amberlite IR-A 120). All compounds were fully characterized by $^1H/^{19}F$ NMR, IR, MS, microanalysis, and mp.

Typical Procedure for the Catalytic Preparation of 3

To a mixture of **1** (7.69 g, 50.0 mmol) and the catalyst (0.1 mol %, based on **2**) in 40 mL ethylene carbonate and 50 mL heptane (Table 1), **2** (10.0 g, 11.9 mL, 33.0 mmol) was added at 100 °C during 20 min. The reaction mixture was stirred for an additional 30 min at reflux temperature monitored by thin layer chromatography. After total conversion, (all-*rac*)-α-tocopherol (**3**) was isolated from the reaction mixture by cooling to 60–80 °C, separation of the catalyst by decanting (phase separation) and distilling off the non-polar solvent. Excess **1** (contained in the ethylene carbonate phase) may be re-used. Unambiguous identification of products was made by comparison of GC retention times and spectroscopic measurements (NMR) with authentic samples. In the case of **4b** (in EC/heptane) crude **3** was transformed (pyridine, Ac_2O) to the more stable acetate derivative. After distillation (250 °C/10^{-1} mbar) (all-*rac*)-α-tocopheryl acetate was obtained as pale yellow oil; yield: 93.2% (based on **2**).

Acknowledgements

The authors are grateful to Dr. G. Schiefer and Mr. H. Kleissner for support in analytics, Mrs. E. Vazquez and Mr. F. Aquino for technical assistance, and Drs. C. Dittel and Th. Pabst for helpful suggestions during preparation of the manuscript. A sample of imide ***4i*** *was kindly provided by Mr. H. B. Alteweier (Bayer AG).*

References and Notes

[1] O. Isler, G. Brubacher, S. Ghisla, B. Kräutler, in *Vitamine II*, Thieme, Stuttgart, **1988**, pp. 126 – 151.
[2] K.-U. Baldenius, L. von dem Bussche-Hünnefeld, E. Hilgemann, P. Hoppe, R. Stürmer, in *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. A27, VCH, Weinheim, **1996**, pp. 478 – 488.
[3] *Chemical Market Reporter*, November 10, **1997**, p. 5.
[4] G. Brunner, T. Malchow, K. Stuerken, T. Gottschau, *J. Supercrit. Fluids* **1991**, *4*, 72 – 80.
[5] R. Lowack, J. Meyer, M. Eggersdorfer, P. Grafen (BASF), *EP Application* 603695 A1, **1994**; *Chem. Abstr*. **1994**, *121*, 179408.
[6] S. Wang, W. Bonrath, H. Pauling, F. Kienzle, *J. Supercrit. Fluids* **2000**, *17*, 135 – 143; W. Bonrath, S. Wang (F. Hoffmann-La Roche), *EP Application* 1000940 A1, **2000**; *Chem. Abstr*. **2000**, *132*, 334646.
[7] F. Schager, W. Bonrath, *J. Catal*. **1999**, *182*, 282 – 284.
[8] F. Aquino, M. Schneider, K. Zimmermann, W. Bonrath, *Appl. Catal. A: General* **2001**, *220*, 51 – 58.
[9] F. Schager, W. Bonrath, *Appl. Catal. A: General* **2000**, *202*, 117 – 120.
[10] M. Baak, W. Bonrath, H. Pauling (F. Hoffmann-La Roche), *WO Patent Application* 9821197, **1998**; *Chem. Abstr*. **1998**, *129*, 28106; K. Ishihara, M. Kubota, H. Yamamoto, *Synlett* **1996**, 1045 – 1046.
[11] J. N. Meussdoerfer, H. Niederprüm, *Chem. Ztg.* **1972**, *96*, 582 – 583; H. Niederprüm, J. N. Meussdoerfer (Bayer AG), *Deutsche Offenlegungsschrift* 2239817, **1974**; *Chem. Abstr*. **1974**, *80*, 120260.
[12] J. Foropoulos Jr., D. D. Desmarteau, *Inorg. Chem.* **1984**, *23*, 3720 – 3723; D. D. Desmarteau, M. Witz, *J. Fluorine Chem.* **1991**, *52*, 7 – 12.
[13] Alternative preparation via ammonium or metal salts: K. Pohmer, R. Weber, C. Dörzbach-Lange, K. Stachulla, H.-H. Moretto, M. Wienand (Bayer AG), *DE Offenlegungsschrift* 4217366 A1, **1993**; *Chem. Abstr*. **1994**, *120*, 301651; H. Sakaguchi, K. Fujii, S. Sakai, Y. Kobayashi, Y. Kita (Central Glass Co.), *DE Offenlegungsschrift* 19533711 A1, **1996**; *Chem. Abstr*. **1996**, *124*, 342658.
[14] J. March, *Advanced Organic Chemistry*, 4th Ed., John Wiley & Sons, New York, 1992, p. 1011.
[15] M. Matsui, N. Karibe, K. Hayashi, H. Yamamoto, *Bull. Chem. Soc. Jpn*. **1995**, *68*, 3569 – 3571.
[16] P. Karrer, O. Isler (Hoffmann-La Roche), *US Patent* 2411967, **1938**; *Chem. Abstr*. **1941**, *41*, 8100; S. B. Greenbaum, W. Hacke, H. Horn (Diamond Shamrock Corp.), *US Patent* 3708505, **1972**; *Chem. Abstr*. **1972**, *77*, 164485; J. L. Finnan (BASF), *EP Application* 100471 A1, **1984**; *Chem. Abstr*. **1984**, *101*, 23778; B. Schulz, E. Renauer (BASF), *DE Patent Application* 3203487 A1, **1983**; *Chem. Abstr*. **1983**, *99*, 176106; D. R. Nelan (Eastman Kodak), *US Patent* 3444213, **1969**; *Chem. Abstr*. **1969**, *71*, 13238.