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Fast multigram scale microwave-assisted synthesis of vitamin E and C_{10}-, C_{15}- analogues under vacuum

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A novel protocol for the microwave-assisted synthesis of (all-*rac*)-α-tocopherol, including its C_{10}- and C_{15}- analogues, is reported. A rotating microwave reactor working under vacuum favoured the rapid evaporation of condensation water and solvent at the end of the process. The main advantages of this fast procedure are its high yield, selectivity, easy workup and-scalability.

Introduction

Vitamin E is the most important lipid-soluble antioxidant in biological systems[1] because of its well documented radical scavenger effects.[2] It can be found in edible oils sunflower seeds, corn and palm fruits.[3] Vitamin E is actually a class of compounds that are derived from the 6-chromanol moiety and divided into the main group of tocotrienols (containing a 3',7',11' unsaturated C_{16} side chain) and tocopherols (with a saturated C_{16} aliphatic side chain), of which α–tocopherol shows the highest biological activity. In fact, the commercially available (all-*rac*)-α-tocopherol (an equimolar mixture of all eight stereoisomers), is the most important lipid soluble antioxidant.[4] It has found important markets in animal nutrition, pharmaceuticals, cosmetics and food formulations, which are all in steady growth.[5]

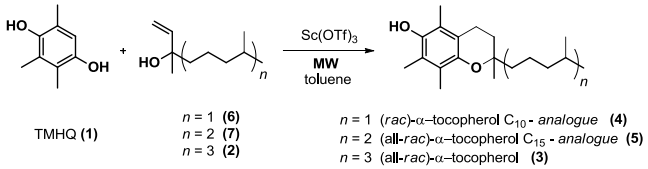
The acid catalyzed Friedel-Crafts alkylation of trimethylhydroquinone (TMHQ) (**1**) with (all-*rac*)-isophytol (IP) (**2** or a C_{20} equivalent thereof, e.g. phytol or a phytyl halide), and the subsequent ring closure reaction (Scheme 1), are the final steps in the total synthesis of (all-*rac*)-α-tocopherol (**3**). Early investigations into vitamin E synthesis from TMHQ were published by Karrer *et al.*,[6] Bergel *et al.*[7] and Smith *et al*.[8] in 1938. The pioneering work of Karrer and Isler[9] led to the first production of vitamin E at Roche in Basel in the early 1950s and a large number of publications on the final step of (all-*rac*)-α-tocopherol synthesis have been reported in the literature since then.[10] The Friedel-Craft reaction between **1** and **2** is traditionally catalyzed by Lewis and Brønsted acids, or combinations thereof, such as $ZnCl_2$/HCl, BF_3 and $AlCl_3$ in various organic solvents. From an industrial point of view, however, these procedures have suffered from numerous drawbacks; by-product formation, issues with corrosion and wastewater contamination (zinc and halide ions).[11] Several alternatives that aim to circumvent these hurdles have been reported in the literature and several will be mentioned here. Environmentally friendly procedures have been performed in supercritical fluids giving catalyst recycling and easy product recovery.[12] Multiple-phase-solvent systems (e.g. ethylene or propylene carbonate and hydrocarbons) have been used as alternative reaction media.[13-15] A great deal of effort has been invested in heterogeneous catalysis using acidic zeolites,[16] silica- or alumina-based systems,[17] ion exchange resins,[18] Nafion®[19] or micro-encapsulated catalysts.[20] Other reports have described the combined use of boric and oxalic (tartaric, citric) acids,[21] and the application of new types of efficient Friedel–Crafts mediators in truly catalytic amounts. Striking examples of catalysis can be found in the use of rare earth metal triflates, e.g. $Sc(OTf)_3$,[22] heteropolytungstic acids,[14] polyfluorinated compounds,[23] and *tris*(oxalato)phosphorus acid derivatives. [24] The remarkable feature of these systems is not only the high chemical yield that they provide, but particularly the extremely high selectivity of the overall condensation reaction between TMHQ and (all-*rac*) IP. The formation of isomeric products, e.g. benzofuran compounds, is considerably reduced, thus facilitating the purification of the final product.

Only a small number of publications have dealt with the synthesis and application of α-tocopherol analogues with a modified isoprenoid side chain (such as chromanols (**4)** and (**5)**, termed tocopherol C_{10}- (C_{15}-) analogues).[25,26] More highly hydrophilic vitamin E parent compounds with shorter isoprenoid side chains present higher antioxidant capacity as documented by Pentland *et al.* in their study on cellular arachidonic acid metabolism.[27] Moreover, it has been suggested by Kagan *et al*.[28] that vitamin E analogues may play a critical role in the prevention of human LDL oxidation.[29]

The rise of so-called “enabling technologies”, in particular microwave (MW) and ultrasound (US) technologies,[30] could play a pivotal role in the industrial-level synthesis of vitamin E derivatives as dielectric heating and cavitational effects strongly affect kinetics and reaction rates.[31] Despite MW irradiation being commonly used in organic synthesis, only a few publications have investigated vitamin preparation using this method.[32] The aim of this work is the optimization of the final synthesis step of vitamin E and its C_{10}- and C_{15}- analogues under MW irradiation and its potential scaling to multigram scale.

Results and discussion

The synthesis of (all-*rac*)-α-tocopherol moieties (**3**) involves the acid-catalyzed Friedel–Crafts alkylation of TMHQ (**1**) with IP (**2**), (or with a C_{20} equivalent), followed by a ring closure reaction (scheme 1). The first attempt was optimized under conventional condition using $Sc(OTf)_3$ as the catalyst in toluene under reflux (Yamamoto *et al.* 1995).[22]



Scheme 1. MW-assisted synthesis of (all-*rac*)-α-tocopherol and its C_{10}-, C_{15}-analogues under vacuum.

Under conventional conditions, tocopherol derivatives (**3**), (**3a**), (**4**) and (**5**) were obtained in good yields after 3 hours (table 1, scheme 1 and scheme 2) from all considered allyl alcohols C_{20} - (**2**), C_{10} - (**6**), C_{15} - (**7**).

Furthermore, MW-assisted condensation gave shorter reaction times and higher purity in all α-tocopherol analogues (table 2).

Table 1. Synthesis of α-tocopherol and its C_{15}- and C_{10}- analogues under conventional conditions.[a]

Entry	Isoprenoid chain	Yield (%)	Benzofurans (%)
1	C_{20}(**2**)	76.24	8.89
1b	C_{20}(**2**)	73.48	12.89
1c	C_{20}(**2a**)	71.32	8.63
2	C_{10}(**6**)	65.67	--
3	C_{15}(**7**)	67.67	--

a) Reaction time: 3 h (toluene under reflux), TMHQ purity degree 96%.. b) TMHQ purity degree <96%. c) Natural phytol (**2a**) used as isoprenoid allyl alcohol

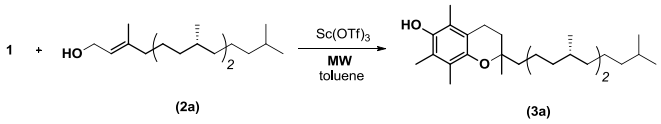
The Friedel-Craft alkylations of **1** with **2** were carried out in a dedicated multimode MW reactor equipped with an internal sloping system (45° inclined) connected to an external vacuum pump.[33] A α-tocopherol yield of 80.30% was achieved under MW irradiation and vacuum (200 mbar) in only 30 min at 110 °C (table 2) by halving the use of organic solvents required for conventional heating. Also catalyst pre-activation step was avoided in for MW reactions tanks to MW efficient energy transfer effects. The influence of the vacuum on the reaction rate is truly remarkable if we consider the poor conversion (55.6%) that was observed when the same reactions were performed in a closed MW system in 1 h (table 2, entry 1d). The efficient removal of condensation water efficiently brings the reaction to completion and avoids the inactivation of the catalyst. It is worth noting that the purity of the final products is strongly dependent on TMHQ purity degree (entry 1b, table 1 and entry 1c, table 2).

Table 2. MW-assisted synthesis of α-tocopherol and its C_{10}- and C_{15}- analogues.[a]

Entry	Isoprenoid chain	Time (h)	Yield (%)	Benzofurans (%)
1		0.5	80.30	3.62
1b	C_{20} (**2**)	0.5	77.31	4.16
1c		0.5	73.48	10.58
1d	C_{20} (**2a**)	1	55.6	6.22
2	C_{10} (**6**)	0.5	69.14	--
3	C_{15} (**7**)	0.5	75.68	--

a) Reaction conditions (110 °C, 400 W, under vacuum). TMHQ purity degree 96%.
b) Natural pythol (**2a**) used as phytol chain (*E*: 96.2%; *Z*: 1.2%).
c) TMHQ purity degree <96%. d)Reaction conditions (110 °C, 400 W, closed MW system).

As previously reported in the literature[22,34] a small amount of condensation benzofurans are always detected besides the expected α-tocopherol product (**3**), both under MW and conventional heating (table 1 and table 2). Luckily, the MW-assisted α-tocopherol synthesis was efficient and faster, paving the way for promising vitamin E industrial synthesis protocols.



Scheme 2 MW-assisted synthesis of optically pure α-tocopherol under vacuum using natural pythol (**2a**) (*E*: 96.2%; *Z*: 1.2%).

The MW-assisted synthesis of α-tocopherol was repeated using natural phytol (**2a)** (*E*: 96.2%; *Z*: 1.2%). The previous good results were confirmed (77.3%) after 30 min irradiation and the optical purity degree of the 2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-ol product (**3a**) was not affected (entry 1b, table 2) (scheme 2).

The synthesis was extended to a number of other isoprenoid allyl alcohols (scheme 1) in an attempt to confirm the versatility of the protocol. C_{10} and C_{15} α-tocopherol analogues (**4** and **5**) were synthesized in good yields in only 30 min (table 2, entry 2 and 3). As expected, yields of products with shorter isoprenoid chains were slightly lower (<10-15%) than those obtained from the reference alcohol (IP). Possible explanations for this result could be either the lower solubility of the shorter-chain alcohols or the different polarities of the transition states in the applied solvent system. The advantages of working in a rotating MW reactor under vacuum are faster reaction and workup times as well as the elimination of condensation water and finally toluene.

The scale up of MW-assisted Friedel-Craft alkylations was investigated up to a 100 g scale synthesis both for vitamin E and

parent compounds. The good results achieved in 30 min in all cases (table 3, entry 2, 4, and 6) make this protocol potentially suitable for industrial application.

Table 3. Synthesis scale up: MW vs. conventional heating.[a]

Entry	Isoprenoid chain	Method	Time (min)	Yield (%)
1	C_{20} (2)	Conv.	180	70.24
2		MW	30	78.30
3	C_{10} (6)	Conv.	180	59.67
4		MW	30	65.26
5	C_{15} (7)	Conv.	180	65.67
6		MW	30	70.45

a) Reaction conditions (100 g scale, 110 °C, 400 W, under vacuum). TMHQ purity degree 96%.

Experimental section

Commercially available reagents, catalysts and solvents were used without further purification unless otherwise noted (TMHQ: Fluka (96%) and isophytol, natural phytol (*E*: 96.2%; *Z*: 1.2%): Shandong Guangtongbao Pharmaceuticals Co., Ltd.). MW-assisted reactions were carried out in a RotoSYNTH reactor (MLS GmbH, Milestone Srl). GC analyses for reaction control were carried out on a gas chromatograph Agilent 6890A (G1530A) using a capillary column (Restek, BGB Analytik AG) that was 30 m long, while an ID of 0.32 mm and a film thickness of 0.25 mm were used (15°C/min program temperature: from 70°C to 300°C). GC analyses for the quantitative determination of tocopherol and related compound was carried out on a gas chromatograph HP 6890 using a capillary column (Rtx-5SilMS) that was 30 m long, while an ID of 0.28 mm and a film thickness of 0.25 mm were used (5°C/min program temperature: from 150°C to 300°C). Derivatization: squalene (int. standard) in pyridine/BSTFA+1% TMSCl).

General procedure

A suspension of TMHQ **1** (33 mmol; MW 152.19) and $Sc(OTf)_3$ (1.0 mol%; MW 492.16) was heated to reflux in toluene (20 mL) under magnetic stirring (20-30 min, 400 rpm) in a four-necked glass reactor equipped with an internal thermometer, a reflux condenser fitted with Dean-Stark trap (filled with toluene) and an argon inlet. Either neat IP **2**, natural pythol **2a** (33.5 mmol, 1.015 mol equiv., MW 296.54, d=0.841 g/mL) or the C_{10}- and C_{15}- analogues (**6, 7**) were dropped via syringe pump over 30 min. The mixture was heated under reflux (110 °C internal temperature; reaction control by GC). The mixture was cooled to room temperature after 3h and poured into deionized water (20 mL). EtOAc (2x30 mL) was used to completely dissolve all organic material from the flask, while the combined organic extracts were washed twice with deionized water (20 mL), dried over sodium sulphate, filtered, evaporated at 20 mbar/50 °C and finally dried for 2 h at 0.02 mbar/23 °C in order to achieved (**3**), (**3a**), (**4**) and (**5**) products.

General MW procedure

A suspension of TMHQ **1** (33 mmol; MW 152.19), and $Sc(OTf)_3$ (1.0 mol%; MW 492.16) in toluene (10 mL) was poured into a suitable glass vessel (300 mL) for MW irradiation. Either neat IP **2** (33.5 mmol, 1.015 mol equiv., MW 296.54, d=0.841 g/mL) or the -C_{10} and -C_{15} analogues (**6, 7**) were dropped via syringe pump over 5 min inside the MW rotating reaction vessel (200 rpm) and the suspension was heated at 110 °C (400 Watt) for either 1h or 30 min under vacuum (200 mbar). At reaction's end, toluene was evaporated under MW irradiation under more intense vacuum (100 mbar). The mixture was then poured onto deionized water (20 mL) and extracted 3 times with EtOAc (2x30 mL). The combined organic extracts were washed twice with deionized water (20 mL x 2), dried over sodium sulfate, filtered, evaporated at 20 mbar/50°C and finally dried for 2 h at 0.02 mbar/23°C (**3**), (**3a**), (**4**) and (**5**) products.

Conclusion

The study of eco-friendly, cost-effective and highly efficient synthetic methods is still very much a hot research topic for industries, especially in the field of nutritional products. By halving the use of organic solvents herein we report an efficient and rapid synthesis for vitamin E and its C_{10}- and C_{15}- analogues under MW irradiation, using a rotating reactor under vacuum. The excellent versatility and scalability, of up to 100 g scale, are demonstrated, making this a promising enabling technology for potential industrial applications.

Keywords

Microwave-assisted synthesis; α-tocopherol homologues; Friedel-Crafts alkylation; trimethylhydroquinone; isophytol

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