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Fast multigram scale microwave-assisted synthesis of vitamin E and C₁₀⁻, C₁₅⁻ analogues under vacuum

L. Rotolo,* E. Calcio Gaudino, D. Carnaroglio,* A. Barge,* S. Tagliapietra,* G. Cravotto**

A novel protocol for the microwave-assisted synthesis of (all- rac)-α-tocopherol, including its C₁₀⁻ and C₁₅⁻ 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 because of its well documented radical scavenger effects. It can be found in edible oils sunflower seeds, corn and palm fruits. 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 C₁₆ side chain) and tocopherols (with a saturated C₁₆ 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. It has found important markets in animal nutrition, pharmaceuticals, cosmetics and food formulations, which are all in steady growth.

The acid catalyzed Friedel–Crafts alkylation of trimethylhydroquinone (TMHQ) (1) with (all- rac)-isophytol (IP) (2 or a C₂₀ 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., Bergel et al. and Smith et al. in 1938. The pioneering work of Karrer and Isler 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. The Friedel-Crafts reaction between 1 and 2 is traditionally catalyzed by Lewis and Brønsted acids, or combinations thereof, such as ZnCl₂/HCl, BF₃ and AlCl₃ 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). 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. Multiple-phase-solvent systems (e.g. ethylene or propylene carbonate and hydrocarbons) have been used as alternative reaction media. A great deal of effort has been invested in heterogeneous catalysis using acidic zeolites, silica- or alumina-based systems, ion exchange resins, Nafion or micro-encapsulated catalysts. Other reports have described the combined use of boric and oxalic (tartaric, citric) acids, 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, heteropolytungstic acids, polyfluorinated compounds, and tris(oxalato)phosphorus acid derivatives. 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 C₃₀⁻ (C₁₅⁻) analogues). 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. Moreover, it has been suggested by Kagan et al. that vitamin E analogues may play a critical role in the prevention of human LDL oxidation.

The rise of so-called “enabling technologies”, in particular microwave (MW) and ultrasound (US) technologies, could play a pivotal role in the industrial-level synthesis of vitamin E derivatives as dielectric heating and cavitation effects strongly affect kinetics and reaction rates. Despite MW irradiation being commonly used in organic synthesis, only a few publications have investigated vitamin preparation using this method. The aim of this work is the optimization of the final synthesis step of vitamin E and its C₁₀⁻ and C₁₅⁻ 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 C₂₀ 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).
The Friedel-Craft alkylation 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. 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 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).

As previously reported in the literature a small amount of condensation benzo furans 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.

The synthesis was extended to a number of other isoprenoid allyl alcohols (scheme 1) in an attempt to confirm the versatility of the protocol. C20 and C24 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

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**Table 1.** Synthesis of α-tocopherol and its C15– and C20– analogues under conventional conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isoprenoid chain</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Benzo furans (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C20(2)</td>
<td>0.5</td>
<td>80.30</td>
<td>3.62</td>
</tr>
<tr>
<td>1b</td>
<td>C20(2)</td>
<td>0.5</td>
<td>77.31</td>
<td>4.16</td>
</tr>
<tr>
<td>1c</td>
<td>C20(2a)</td>
<td>0.5</td>
<td>73.48</td>
<td>10.58</td>
</tr>
<tr>
<td>2</td>
<td>C20(6)</td>
<td>0.5</td>
<td>69.14</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>C15(7)</td>
<td>0.5</td>
<td>75.68</td>
<td>--</td>
</tr>
</tbody>
</table>

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

table 2) (scheme 2).

\[ \text{Scheme 1} \quad \text{MW-assisted synthesis of (all-rac)-α-tocopherol and its C}_{15}^{−} \text{ and C}_{20}^{−} \text{ analogues under vacuum.} \]

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 C20 - (2), C10 - (6), C15 - (7).

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

**Table 2.** MW-assisted synthesis of α-tocopherol and its C15– and C20– analogues.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isoprenoid chain</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<td>--</td>
</tr>
<tr>
<td>3</td>
<td>C15(7)</td>
<td>0.5</td>
<td>75.68</td>
<td>--</td>
</tr>
</tbody>
</table>

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).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isoprenoid chain</th>
<th>Method</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C20 (2)</td>
<td>Conv.</td>
<td>180</td>
<td>70.24</td>
</tr>
<tr>
<td>2</td>
<td>C20 (6)</td>
<td>MW</td>
<td>30</td>
<td>78.30</td>
</tr>
<tr>
<td>3</td>
<td>C2 (7)</td>
<td>MW</td>
<td>180</td>
<td>59.67</td>
</tr>
<tr>
<td>4</td>
<td>C15 (7)</td>
<td>Conv.</td>
<td>30</td>
<td>65.26</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Conv.</td>
<td>180</td>
<td>65.67</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>MW</td>
<td>30</td>
<td>70.45</td>
</tr>
</tbody>
</table>

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-Si5ILMS) 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 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 -C10 and -C15 analogues (6, 7) were dropped via syringe pump over 30 min. 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) 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 C10- and C15- 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

**Acknowledgements**

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**Notes and references**
