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RESEARCH NOTE

Synthesis of D,L-α-Tocopherol Using Strong Solid Acids as Catalysts

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The synthesis of D,L-α-tocopherol starting from trimethylhydroquinone and isophytol using a heterogeneous solid acid catalyst, e.g., Nafion NR 50, is described. Advantages of this new procedure are high yield and selectivity, facile recovery of the catalyst, no waste problems, and mild reaction conditions. © 1999 Academic Press

Key Words: D,L-α-**tocopherol; Friedel–Crafts reaction; solid acids.**

Industrial syntheses of D,L-α-tocopherol are based on the condensation of trimethylhydroquinone (**1**) with isophytol (**2**) or phytol halides (1). Lewis acids and Brønsted acids, e.g., zinc chloride and a mineral acid, serve as catalysts for this reaction (2). BF_3, $AlCl_3$, Fe/HCl, or the combination boric acid and carboxylic acids are good catalysts (1). The reaction can be carried out in various solvents, e.g., ethyl acetate or hydrocarbons. Disadvantages of all the known methods are corrosion problems and/or a potential contamination of waste water with zinc ions.

To overcome the disadvantages of the known syntheses of D,L-α-tocopherol we used for mineral acids the strongly acidic sulfonic acid Nafion NR 50 as replacement. The acidity of this acid perfluorosulfonic acid resin, which is a copolymer of tetrafluoroethene and a perfluorsulfonylether, has been suggested to be similar to concentrated sulfuric acid (3). A considerable number of reactions catalyzed by Nafion have already been described (4–6). Olah and co-workers demonstrated that alcohols are efficiently dehydrated in the presence of Nafion. The ease of dehydration is in the order tertiary > secondary > primary alcohol. At higher temperature the alcohols are dehydrated nearly quantitative yield (7). We also used Amberlyst 15, a strongly acidic cation exchange resin with a SO_3H functional structure.

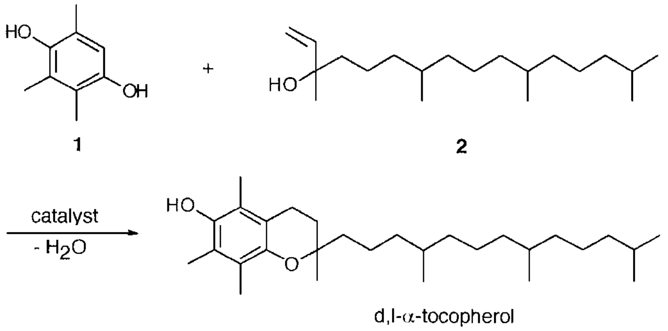
In this paper, we show that the condensation of **1** and **2** can be carried out using strong solid acids in various solvents. Contrary to our expectations and to the literature (7), the tertiary alcohol **2** was not dehydrated under these conditions. As outlined in Scheme 1, the acid-catalyzed condensation consists of a Friedel–Crafts reaction followed by a condensation reaction. The aim of our work was to find a good solvent system, to study the reproducibility catalysts used, and to test the property of the recycled catalyst.

The reactions were carried out in batch reactors under argon atmosphere. The catalyst, reactants, and solvents were used without purification. Yields and purity were determined by GLC analysis.

The reactions were carried out on a 200 mmol scale, 1 h heating at 100–140°C, and ambient pressure. The reaction solution consists of 33 wt% solvent, 21 wt% **1**, 40 wt% **2**, and 5 wt% catalyst. The conversions are around 95% and the yields of tocopherol are in the range of 75–92%. In Table 1 the results of the condensation reaction between **1** and **2** are summarized.

A first remarkable observation is that the D,L-α-tocopherol yields are maximized in polar aprotic solvents. A second observation is, surprisingly, that Nafion NR 50 is the most efficient catalyst for this reaction (8). Other heterogeneous polysulfonic acid catalysts, e.g., Dowex 50WX8 (20%) or Amberlite 200 (60%), are less active.

The main by-products in this reaction are phytadienes and the furan derivative **4** (Scheme 2), which has already been found by Yamamoto and co-workers in the



SCHEME 1

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TABLE 1

Condensation of 1 and 2 in Different Solvents Using Strong Solid Acids

Catalyst	Solvent[a]	Yield (%)[b]
Nafion[c]	Toluene	75
Nafion	Diethyl ketone	84
Nafion	Isobutylmethyl ketone	83
Nafion	Propylene carbonate[d]	92
Nafion	γ-Butyrolactone	80
Amberlyst[e]	Toluene	83
Amberlyst	Diethyl ketone	82
Amberlyst	Isobutylmethyl ketone	79
Amberlyst	Propylene carbonate[d]	90
Amberlyst	γ-Butyrolactone	77

[a] 50 ml solvent.

[b] Yield is based on **2**, determined by GLC analysis of the crude reaction products; in some cases all products were isolated and the yields compare well with that optained by GC analysis.

[c] Nafion, Nafion NR 50 (H^+-Form, 7–9 mesh).

[d] Two-phase system with heptane (one to one mixture).

[e] Amberlyst, Amberlyst 15 (H^+-Form, 20–50 mesh).

TABLE 2

Reproducible Synthesis of D,L-α-Tocopherol Using Nafion NR 50 in Propylene Carbonate

Run	Yield (%)[a]
1	92.3
2	91.3
3	90.5
4	91.4
5	91.0

[a] Yield is based on **2**, determined by GLC analysis of the crude reaction products.

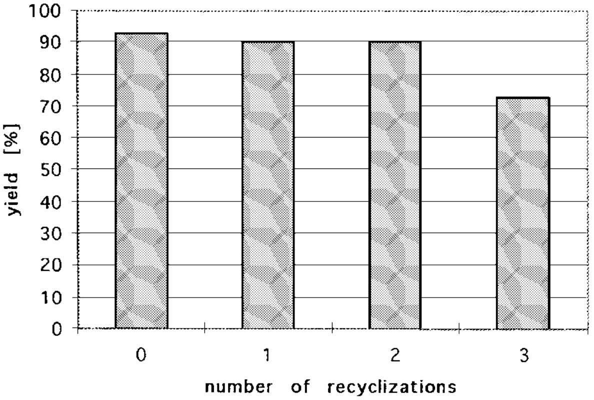
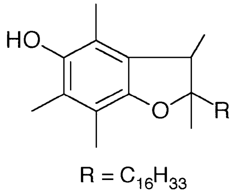


FIG. 1. Synthesis of D,L-α-tocopherol with reused Nafion NR 50 in propylene carbonate.



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SCHEME 2

scandium(III) trifluoromethanesulfonate catalyzed condensation of **1** and **2** (9).

In further experiments, the reproducibility of the Nafion NR 50 results was examined. The results are summarized in Table 2. The reactions are carried out under the aforementioned conditions with Nafion NR 50 as catalyst in propylene carbonate as solvent.

The conversions are around 95%. The yield is in the range of 90.5–92.5%. The reproducibility of these experiments is remarkably good (Table 2): the average yield is higher than 91%.

Figure 1 represents the results we obtained by reusing the catalyst under the aforementioned conditions with Nafion NR 50 in propylene carbonate as solvent.

We found that the yield of D,L-α-tocopherol decreases after a few experiments. This is explained by deactivation of the catalyst, because unchanged starting material and a higher amount of phytadienes are detected. However, the catalyst can be reactivated (10). The yields for reusing Amberlyst 15 are in the range of 50–60%.

In comparison with 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 catalyst D,L-α-tocopherol yields of approximately 80% could be achieved (11). In contrast to our results, Amberlyst 15 in combination with the metal ions Sn(IV), Sn(II), or Zn(II) decreases the yield of D,L-α-tocopherol (12). Another advantage of the new procedure is the low amount of catalyst.

The described procedure has advantages over the known processes for the synthesis of D,L-α-tocopherol, i.e., high yield conversion and selectivity. Therefore, it can be emphasized that the strong solid acid catalyst Nafion NR 50 shows a better catalytic performance. It has to be pointed out that the heterogenously catalyzed synthesis of D,L-α-tocopherol is improved by using a polar aprotic solvent, such as propylene carbonate.

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