Microwave-assisted synthesis of all-rac-α-tocopherol catalyzed by ionic liquids

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Abstract: Several kinds of pyridinium ionic liquids were synthesized and applied to the synthesis of all-rac-α-tocopherol. The study found that the more substituents on the pyridine ring, the better the catalytic synthesis of all-rac-α-tocopherol. With the molar ratio of ZnCl₂ in the 3-methyl-N-butylpyridinium bromide and zinc chloride ([MBPy]Br/ZnCl₂) to Trimethylhydroquinone (TMHQ), the temperature and reaction time increasing, the purity and yield of product both first increase and then decrease. When the molar ratio of ZnCl₂ to TMHQ is 1:1, react 30 minutes at 60 degrees Celsius, the reaction rate can reach 74.61% and the purity can reach 78.24%.

1. Introduction

Vitamin E plays an extremely important role in biological systems because of its unique effects of scavenging free radicals [1], prolonging the life of red cells, anti-oxidation [2], anti-aging, anti-tumor, cardiovascular disease prevention and other characteristics [3]. It can also work in coordination with vitamin C to protect the liver and reduce chemical liver injury which has been confirmed by Chinese scholar Shezong Sun [4]. Natural vitamin E is actually a mixture of four tocopherols (α, β, γ, δ) and four tocotrienols (α, β, γ, δ), most of which is found in oily seeds, fruits, vegetables, nuts, lean meat, milk, eggs and pressed vegetable oil instead synthetic vitamin E refers to α-tocopherol, showing the highest biological activity [5] and usually is applied when it becomes α-tocopherol acetate [6].

Industrial synthetic all-rac-α-tocopherol based on the condensation of trimethylhydroquinone (TMHQ) with isophytol (IP) contains eight types of optical isomers, each with an equal proportion of 12.5% [7], forming a racemic tocopherol. The most classic and traditional catalysts are Lewis acid, BrØnsted acid or the combination of the acids, e.g. ZnCl₂, ZnCl₂/HCl, BF₃, AlCl₃, FeCl₂/Fe/HCl [8]. These catalysts are mild and inexpensive, but large-scale production can lead to corrosion and water wastage, especially Zn²⁺ ions and Cl⁻ ions. Moreover, in order to achieve higher yield and faster reaction, larger amount of catalyst and excess isophytol (IP) is used, which results in wastage of raw materials, low rate of recovery and utilization of catalyst, more by-products, low selectivity and low yield. Aimed at overcoming the shortcomings of traditional catalysts, researchers have made some improvements to the traditional catalysts.
In 2000, researchers in Korea SK Co. Ltd. produced α-tocopherol of a high purity and high yield using alumina-silica coated with zinc ions as the catalyst. Juraj Gomory applied supported solid catalyst which means ZnCl\(_2\) impregnated with montmorillonite (KSF) and aluminosilicate clay (Rudex) to the Friedel-Crafts alkylation condensation, realized the fewer quantities and reuse of catalyst, meanwhile got as much product as reactions before [9]. In 2011, they improved research on this basis, the recovery rate of ZnCl\(_2\) reached 98% and the yield was above 90% [10]. S. M. Coman et al synthesized AlF\(_3\) nanoparticles partially hydroxylated after fluorination in sol-gel as an alternative to catalyze the reaction, turned out that the selectivity of all-rac-α-tocopherol was 99.99% [11].

Because of the excellent performance of sulfonic acid catalysts in the formation of C-C bonds, Makoto et al produced all-rac-α-tocopherol with high purity and yield by metal triflates particularly Scandium(III) trifluoromethanesulfonate [12]. In 2007, W. Bonrath developed a new catalyst rare metal trifluoromethanesulfonate, such as Bi(OTf)\(_3\), Ga(OTf)\(_3\), Tm(OTf)\(_3\), Hf(OTf)\(_3\), found that this type of catalyst could achieve high yield and selectivity (94%), further exploration would work fast on the purification of the product [13].

Perfluorinated sulfonic acid is an ion exchange polymer and it is considered to be very strong solid Bronsted acid. Frank Schager and Werner Bonrath in 1999 discovered strong solid acid, such as NR50, Dowex 50WX8 and Amberlite 200, could produce all-rac-α-tocopherol with high yield only in polar aprotic solvent and NR50 was more efficient than the others. In the subsequent validation experiment, they took NR50 as catalyst and propylene carbonate as solvent to conduct reactions, the results showed the conversion rate was about 95%, the yield was 90.5%-92.5%, but the catalyst could only be reused 3 times, moreover, the yield decreased and the by-product increased obviously in the last experiment [14]. M. Schneider made a further exploration of a series of Nafion catalysts, found that Nafion/SiO\(_2\) was more stable than NR50, the reaction was faster because of the better dispersion of Nafion in Nafion/SiO\(_2\), but the reusability still needed more exploration [15]. In 2005, M. C. Lauffer used nanocomposite consisting of perfluorinated sulfonic acid resin and silica as catalyst, found that when the content of perflurosulfonic acid was 40%, the catalytic effect was best and when the usage was wt% = 0.6%, the yield was highest. However, after third reactivation, the catalyst efficiency can only achieve 30%, which made the application of this nano material be greatly limited [16].

Recently, due to the further study of ionic liquids, many researchers have applied ionic liquid catalysts to the synthesis of vitamin E. Huabing Xing etc. explored the efficiency of the reaction catalyzed by functionalized sulfonic acid ionic liquids, proved that the catalytic efficiency was determined by their anion and that [PSPy][BF\(_4\)] had the highest efficiency in the mixed solvent of propylene carbonate and heptane [17]. Luo Man also used [(C\(_2\)H\(_5\))\(_2\)NH][ZnCl\(_2\)] as catalyst, found that when the mole fraction of ZnCl\(_2\) in ionic liquid was 0.66, yield of vitamin E could reach 87.4% and the ionic liquid could be reused 5 times without significant decrease in catalytic performance [18].

L. Rotolo et al placed the TMHQ and IP in a rotating microwave irradiation vacuum reactor reacting for half an hour at 110 degrees Celsius, 82% yield of all-rac-α-tocopherol was obtained[19].

Based on the above three documents, in this work, a series of ionic liquids were designed, synthesized as catalysts and applied to the microwave-assisted synthesis of all-rac-α-tocopherol from TMHQ and IP.

2. Experimental section

2.1. Materials and equipment

Trimethylhydroquinone (TMHQ, purity: 97%), isophytol (IP, purity: 96%) and 4-chloropyridine hydrochloride were purchased from Aladdin Industrial Corporation. Vitamin E acetate (purity: 97%) was obtained from Alfa Aesar (China) Chemicals Co., Ltd. N-ethylpyridinium bromide ([EPy]Br), N-butylpyridinium bromide ([BPy]Br), 3-methyl-N-butylpyridinium bromide ([MBPy]Br), Tetraethylammonium tetrafluoroborate ([TEAm] BF\(_4\)) and 1-butyl-3-methylimidazolium chloride ([BMIm]Cl) were from Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences. Pyridine hydrochloride was purchased from Yanfeng Technology (Beijing) Co., Ltd. Zinc chloride...
was obtained from Sinopharm Chemical Reagent Co., Ltd. Zinc bromide was from Shanghai Macklin Biochemical Co., Ltd. N-heptane and ethyl acetate were bought from Beijing Tongguang Fine Chemicals Company. Other chemicals were supplied from the market without treatment.

All condensation reactions were performed in a MAS II microwave synthesis / extraction reaction station provided by Sineo Microwave Chemistry Technology Co., Ltd. All-rac-α-tocopherol was detected by UPLC on an apparatus from Waters equipped with an HPLC Column Venusil XBP C18(T) (length: 150mm, diameter: 4.6mm, particle size: 5μm) purchased from Agela Technologies.

2.2. Methods

2.2.1. Preparation of Ionic liquids. Put some \(\text{ZnCl}_2\) and \([\text{EPy}]\text{Br}\) (replaced with following chemicals in Figure 1 in other similar reactions), whose molar ratio is 2:1 in a 250ml three-necked round-bottomed flask provided with a mechanical stirrer. Added heptane 20ml and reacted for four hours refluxing at temperature of 90 degrees Celsius in the oil bath while nitrogen passed through. Then raised the temperature to a certain temperature until the product was transparent, distilled heptane to liquid receiver, continued heating and stirring for about 12 hours, removed the transparent viscous liquid and placed it in a vacuum dryer. Similarly, other ionic liquids were prepared, as shown in Figure 2.

![Figure 1. Raw chemicals for producing ionic liquids.](image)

![Figure 2. Synthesis of ionic liquids.](image)

2.2.2. Synthesis of all-rac-α-tocopherol. The reaction was conducted in a three-necked flask equipped with a reflux condenser and a constant pressure funnel in nitrogen atmosphere in a microwave synthesis / extraction reaction station. TMHQ (0.0164mol), ionic liquid catalyst, ethyl acetate (25ml) and concentrated hydrochloric acid (240μl) were put into the flask before the whole device was built up. The molar ratio of \(\text{ZnCl}_2\) in ionic liquid or other catalysts to reactant TMHQ is 1:1. Then IP was evenly dropped into the mixture which was stirred at 400r/min within 10 minutes through the constant pressure funnel. Continuously reacted at a certain temperature for a certain period of time, bronze liquid was obtained. Condensation reaction equation is as Figure 3.

![Figure 3. Synthesis of all-rac-α-tocopherol from TMHQ and IP.](image)
After the reaction, the bronze liquid in the flask was divided into two layers and both contained the product. Mixed up the bronze liquid in the separating funnel with 30ml distilled water, 10ml methanol and 10ml petroleum ether, then shook the funnel. All-rac-α-tocopherol was mostly dissolved in the supernatant. Separated two layers and repeatedly cycling extracted the lower liquid with the mixture of ethyl acetate and petroleum until the color of lower liquid was close to the transparent. Liquid mixture of supernatant and extract was washed several times by distilled water until the PH of elution closed to 7 and were dried with anhydrous MgSO4. Crude all-rac-α-tocopherol was obtained after distilling extra ethyl acetate and petroleum ether by rotary evaporation.

2.2.3. Synthesis of all-rac-α-tocopheryl acetate. Added NaBH4 0.36g and anhydrous sodium acetate 0.025g by analytical balance into the crude all-rac-α-tocopherol in a 50ml round bottomed flask, then dropped acetic anhydride 6.6 ml into the flask. In the presence of nitrogen, reacted 10 minutes at 90 degrees Celsius and 3 hours at 130 degrees Celsius under refluxing. The equation for esterification is as Figure 4. The product was washed by distilled water 30 ml 3 times until the PH of elution closed to 7 and dried with anhydrous MgSO4 after reaction. All-rac-α-tocopheryl acetate was obtained after vacuum evaporation.

![Figure 4. Synthesis of all-rac-α-tocopheryl acetate](image)

3. Results and discussion

3.1. Effects of different Lewis acidic ionic liquids on the purity and yield of product

Five kinds of precursors were chosen to produce different kinds of acidic ionic liquids to catalyze the synthesis reaction. Different cations had a great influence on their catalytic performance and reaction results when the anions were similar. The experimental results were shown in Table 1.

| Entry | Ionic liquids | Temperature (degrees Celsius) | Time (minutes) | Purity (%) | Yield (%) |
|-------|--------------|------------------------------|----------------|------------|-----------|
| 1     | [BSO3HMIm]Cl  | ZnCl2 1:2                    | 60             | 14.48      | 13.94     |
| 2     | [EPy]Br       | ZnCl2 1:2                    | 60             | 68.31      | 72.09     |
| 3     | [MBPy]Br      | ZnCl2 1:2                    | 60             | 78.24      | 74.61     |
| 4     | C3H5N·HCl     | ZnCl2 1:2                    | 60             | 72.09      | 71.36     |
| 5     | [BPy]Br       | ZnCl2 1:2                    | 60             | 74.64      | 73.98     |
| 6     | [TEAm]BF4     |                             | 85             | 9.15       | 8.87      |

Purity and Yield of all-rac-α-tocopheryl acetate.

As shown in table 1, untreated [TEAm]BF4 was the worst catalyst. When the cation was [BSO3HMIm]+, the yield of all-rac-α-tocopheryl acetate was much lower than it is pyridine or its derivatives. The catalytic efficiency of C3H5N·HCl was worse than [EPy]Br, [BPy]Br and [MBPy]Br which had substituents on pyridine N, probably because more substituents led to larger the volume of ionic liquid and more uniform charge distribution, so the Coulombic force and the viscosity of ionic liquid was decreased. The smaller the viscosity of ionic liquid was, the more favorable contact
between the ionic liquid catalyst and the reactant was, the higher yield of all-rac-α-tocopherol would be obtained. \([\text{MBPy}]\text{Br/ZnCl}_2\) was the best one among all the ionic liquids and was chosen to do the next experiment.

3.2. Effect of the amount of \([\text{MBPy}]\text{Br/ZnCl}_2\) on the purity and yield of product
Effect of the amount of \([\text{MBPy}]\text{Br/ZnCl}_2\) on the yield of product were investigated in this part. As could be seen from Figure 5, the amount of \([\text{MBPy}]\text{Br/ZnCl}_2\) had a great influence on the yield of all-rac-α-tocopherol. When the amount of \([\text{MBPy}]\text{Br/ZnCl}_2\) was less than 0.6:1, the catalytic activity was very low, the yield was only 37.03%. With the increase of the amount of \([\text{MBPy}]\text{Br/ZnCl}_2\), the catalytic efficiency first increased and then decreased, and reached the highest 74.61% at 1:1. Reason was the higher the amount of \([\text{MBPy}]\text{Br/ZnCl}_2\), the stronger the activity of ionic liquid and the higher the catalytic activity would be. However, the yield decreased when the amount of \([\text{MBPy}]\text{Br/ZnCl}_2\) was 1.2:1, because the active site was too much, resulting in more by-products. In summary, when the amount of \([\text{MBPy}]\text{Br/ZnCl}_2\) is 1:1, it was used to continue to explore follow-up reactions.

![Figure 5. Effect of \([\text{MBPy}]\text{Br/ZnCl}_2\) composition on the purity and yield of product.](image)

![Figure 6. Effect of temperature on the purity and yield of product.](image)

3.3. Effect of temperature on the purity and yield of product
As could be seen from the Figure 6, the reaction temperature had a relatively high effect on the purity and yield of the product. With the reaction temperature changed from 50 degrees Celsius to 60 degrees Celsius, the yield was increased a lot. This was due to the increased reaction temperature could not only greatly reduce the viscosity of the ionic liquid catalyst and construct the catalytic active center distribution more uniform, but also accelerate the reaction of molecular motion and increase the molecular effective collision number, thus greatly improving the product yield. When the reaction temperature was increased to 60 degrees Celsius, the yield reached the optimum. As the temperature continued to rise, the yield of product decreased slightly and repeatedly, the reason was with increasing reaction temperature, reaction speed of main reaction and side reaction in the synthesis of vitamin E both accelerated, but the side reaction rate accelerated more, resulting in a slight decrease in yield at 70 and 80 degrees Celsius. Thus, selected the optimum temperature 60 degrees Celsius.

3.4. Effect of reaction time on the purity and yield of product
The result was shown in Figure 7, the yield was increased with the reaction time. When the reaction time was 10 minutes, the yield of the product was only 47.35%. When reaction time was prolonged to 30 minutes, the yield reached 74.61%, gained an increase of nearly 30%. However, when the temperature rose again, the yield began to decrease greatly. Considered the more reaction time, the greater the energy consumption, the reaction time 30 minutes was superior and compared with the traditional process, the reaction time substantially reduce 150 minutes under microwave condition.
Figure 7. Effect of reaction time on the purity and yield of product

4. Conclusion
Pyridine Ionic Liquid can be used to catalyze the synthesis of all-rac-α-tocopherol, and the more substituents on the pyridine ring, the better the catalytic effect. When the molar ratio of ZnCl$_2$ to [MBPy]Br is 2:1, the amount of ZnCl$_2$ in the [MBPy]Br/ZnCl$_2$ to TMHQ was 1:1, react 30 minutes at 60 degrees Celsius, the reaction rate can reach 74.61% and the purity can reach 78.24%. The subsequent exploration should focus on the post treatment of the reaction so that the reuse rate of the catalysts can be improved. Only in this way can we achieve greener appeals.

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