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Synthesis of vitamin E succinate catalyzed by nano-SiO₂ immobilized DMAP derivative in mixed solvent system

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Abstract: Catalytic efficiency in synthesis of vitamin E succinate was dramatically increased via the preparation of robust catalyst and the improvement of reaction system. 4-dimethylaminopyridine (DMAP) was covalently immobilized on nano-SiO₂ to avoid the catalyst contamination of the product and permit the easy recycling of DMAP. Then, a hexane-acetone mixed solvent system was firstly introduced to replace the traditional single-solvent system, which was employed to improve the activity of immobilized DMAP derivative and the substrate solubility of the reaction system. The highest vitamin E succinate yield of 94% was achieved. In addition, the recyclability and stability of the immobilized DMAP derivative was excellent, the yield of vitamin E succinate had no obvious loss and remained 90% after recycling 20 times. The excellent results make this technology be a promising candidate for the industrial production of vitamin E succinate.

Keywords: vitamin E succinate; nano-SiO₂; 4-dimethylaminopyridine (DMAP); immobilization; mixed solvent system

1 Introduction

Vitamin E as antioxidant has many applications in the treatment of cardiovascular disease, microvascular and hypercholesterolemia [1-3]. However, vitamin E is unstable and its antioxidant value is easily reduced

by light, air, oxidizing agent and heat [4,5]. Therefore, many researchers have devoted to increase its stability and developed many relevant derivatives. In all kinds of vitamin E, α -tocopherol is the most representative isoform, which shows the highest vitamin E activity [6,7]. To increase its stability, many relevant α -tocopherol derivatives have been developed [8]. As reported, α -tocopherol succinate was the most biologically and chemically active, in which the original hydroxyl of α -tocopherol was converted to the succinic anhydride ring-opened carboxyl group. The obtained α -tocopherol succinate showed the great stability and the excellent performance as the antioxidant. In addition, the pharmacological effects of α -tocopherol succinate have been also confirmed in animal experiments and clinical researches with the treatments of cancer and cataract [9-14].

Generally, α -tocopherol succinate was prepared by enzymatic or chemical synthesis. For example, it has reported that α -tocopherol succinate was obtained over modified Novozym-435 lipase-catalyzed reaction [15]. However, the unsatisfactory stability and high cost of enzyme were the serious problems of biocatalytic approaches. Recently, ionic liquids were employed for the synthesis of α -tocopherol succinate [16]. A serious drawback of the system was the complicated process of separation of the product. And the expensive price of ionic liquids was another limiting factor for future industrial production. So far, a variety of organic catalysts were widely used for the synthesis of α -tocopherol derivatives, which was involved in DMAP, tertiary amine and pyridine [17,18]. Among these catalysts, DMAP was deemed as the best candidate due to its high catalytic activity and great reaction selectivity. However, the application of DMAP for industrial production was easily limited by the problem of difficulty in separating from the solvent. In addition, it has reported that the toxicity of DMAP made it inappropriate for production of food and medicine [19]. With regard to α -tocopherol derivatives as medicine for human being, the DMAP contamination of the product should be avoided.

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In the present work, DMAP was covalently immobilized on the surface of nano-SiO₂ to prepare a robust catalyst for the synthesis of α -tocopherol succinate. The obtained immobilized DMAP derivative permitted the easy separation of catalyst from the product, avoiding DMAP contamination and raising the safety of the product. Moreover, the immobilization also provided a promising way for the easy recycling of DMAP, which can reduce the production cost significantly. It is worth noting that nano-SiO₂ was a kind of inexpensive nanoparticles (NPs) with unique properties including large area, suitable density and great mechanical properties [20,21]. Thus, the use of nano-SiO₂ was adequate for the properties of carrier.

The reaction solvent is another crucial factor affecting the catalytic performance of the reaction system. It has reported that a high-polar solvent presumably promoted the protonation of DMAP by intermediate by-product acid, which would result in the deactivation of DMAP. [22,23]. However, the solubility of succinic anhydride increased with increasing the polarity of solvent. Therefore, it was very hard to obtain a balance between catalyst activity and substrates solubility just through the single solvent. Herein, α -tocopherol succinate was efficiently synthesized in the mixed solvent system using immobilized DMAP derivative. The mixed solvent consisted of hexane and acetone, the less-polar hexane was used to improve the activity of catalyst and the high-polar acetone was to increase the solubility of succinic anhydride. Moreover, hexane and acetone belonging to class 3 residual solvents were promising candidates toward environmentally friendly solvents due to their no health-based exposure limit and low toxicity [24]. In addition, the phase resistance was also avoided due to the miscible property of two solvents. Comparing with other reported approaches, we developed a promising way for the industrial production of α -tocopherol succinate, which completely avoided the catalyst contamination and significantly enhanced the safety of product.

2 Materials and methods

2.1 Materials

Succinic anhydride, α -tocopherol, nano-SiO₂, 30 nm diameter, γ -chloropropyltrimethoxysilane (CPTMS) and 4-methylaminopyridine (MAP) were obtained from Aladdin Chemistry Co., Ltd (Shanghai, China), all other reagents and salts were standard laboratory grade.

2.2 Preparation of γ -chloropropyl-functionalized nano-SiO₂ particles (NS-Cl)

The γ -chloropropyltrimethoxysilane (CPTMS) was covalently bonded on the surface of nano-SiO₂ particles. Five grams of nano-SiO₂ was added in 70 mL absolute ethanol/water (4:1 volume ratio). Then, 5 mL γ -chloropropyltrimethoxysilane (CPTMS) was added, and the reaction mixture was stirred for 24 h at room temperature. The resulting γ -chloropropyl-functionalized nano-SiO₂ was separated by centrifugation and washed with 40 mL deionized water for 4 times. Finally, the pure γ -chloropropyl-functionalized nano-SiO₂ was dried at 60°C for 12 h under vacuum.

2.3 Preparation of nano-SiO₂ immobilized DMAP derivative (NS-DMAP)

Nano-SiO₂ immobilized DMAP derivative catalyst was prepared as follows: 0.90 mmol 4-methylaminopyridine (MAP) was dissolved in 25 mL *o*-xylene. Then, 0.40 g nano-SiO₂, 1.35 mmol K₂CO₃ and 0.90 mmol KI were added, and the reaction mixture was stirred at 120°C for 12 h under nitrogen. The reaction was monitored by HPLC. The loading capacity of DMAP was calculated by the content of free MAP before and after reaction. The resulting catalyst was separated by centrifugation and washed with *o*-xylene (3 $\times$ 15 mL), absolute ethanol (2 $\times$ 15 mL), deionized water (2 $\times$ 15 mL). Finally, the pure immobilized DMAP derivative was dried at 60°C for 12 h under vacuum.

2.4 Synthesis of vitamin E succinate

Vitamin E succinate was synthesized in mixed solvent using immobilized DMAP derivative. The details were as follows: 0.15 mmol α -tocopherol was dissolved in 5 mL mixed solvent (hexane/acetone). Then, 0.45 mmol succinic anhydride, 0.1 mmol NS-DMAP (the molar amount of DMAP that covalently bonded on nano-SiO₂) was added, and the reaction mixture was stirred at the setting temperature for 24 h under N₂ atmosphere. After reaction, the reaction mixture was cooled and filtered to regenerate nano-SiO₂ immobilized DMAP derivative. Small amount of filtrate was analyzed by HPLC to determine the yield of α -tocopherol succinate. The other filtrate was concentrated under vacuum and then diethyl ether was added to remove unreacted succinic anhydride

under low temperature, the crude product was purified by hexane to obtain the pure α -tocopherol succinate.

2.5 HPLC analysis

Analysis of reaction solution was performed on a Shimadzu LC-20A HPLC system (Shimadzu, Japan). The detector was SPDFSPD-20A Ultraviolet-Visible Detection Device. HPLC analysis of supernatant of catalytic reaction was carried out under UV wavelength of 254 nm. The column was a BDS Hypersil C18 stainless steel column (250 × 4.6 mm), and the column temperature was 40°C. Mobile phase was chromatographic grade methanol/water/phosphoric acid (60:39.75:0.25 volume ratio) with a flow rate of 1.0 mL/min. HPLC analysis of filtrate of acylation reaction was carried out under UV wavelength of 284 nm. The column was a Discovery C18 column (250 × 4.6 mm), and the column temperature was 40°C. Mobile phase was chromatographic grade methanol/glacial acetic acid (500:3.2 volume ratio) with a flow rate of 1.2 mL/min.

2.6 NS-DMAP characterizations

Thermogravimetric analysis (TG) was performed with a Thermogravimetric analyzer (STA449F3, Netzsch, Germany). The measurement was carried out under N₂ atmosphere at a uniform heating rate of 10°C/min from room temperature to 750°C. The Fourier Transform Infrared (FT-IR) spectroscopy was recorded on a Fourier transform infrared spectrometer (Frontier, PerkinElmer, America) in the range from 400 to 4000 cm⁻¹.

3 Results and discussion

3.1 Catalyst preparation

The rationale of immobilizing DMAP derivative on nano-SiO₂ was a two-step process described in Figure 1. First, the

Figure 1: Preparation of heterogeneous catalyst (NS-DMAP).

γ -chloropropyltrimethoxysilane (CPTMS) was covalently coupled on the surface of nano-SiO₂ particles for the preparation of γ -chloropropyl-functionalized nano-SiO₂; next, 4-methylaminopyridine (MAP) reacted with the coupled chloropropyl and was covalently bonded on the modified nano-SiO₂ over N-alkylation reaction, which was promoted by KI and K₂CO₃.

To investigate the optimal loading capacity of DMAP, the effects of reaction temperature, KI and K₂CO₃ concentration and reaction time were investigated systematically. As shown in Figure 2, the reaction temperature of 120°C, a molar ratio of KI to MAP of 1:1, a molar ratio of K₂CO₃ to MAP of 1.5:1 and reaction time of 12 h were found to be the optimal conditions for the N-alkylation reaction. The maximum loading capacity of DMAP reached 0.68 mmol/g under the optimal conditions.

3.2 Catalyst characterizations

Next, the obtained immobilized DMAP derivative was characterized in details. As shown in Figure 3, the weight loss of nanoparticles between 30°C and 750°C was observed by TG and DTG curves. For nano-SiO₂ (NS), γ -chloropropyl-functionalized nano-SiO₂ particles (NS-Cl) and nano-SiO₂ immobilized DMAP derivative (NS-DMAP), the weight loss from 30 to 200°C was attributed to the desorption of physically absorbed water [25], which could be confirmed by the peak of DTG at 30 to 200°C. And another main weight loss was observed at 400°C to 600°C, which was ascribed to the decomposition of coupled CPTMS. Besides, DTG showed that the peak at 400 to 600°C only can be observed by NS-Cl and NS-DMAP, the result demonstrated that the CPTMS was successfully coupled on external surface of nano-SiO₂. The last weight loss between 200 and 400°C was attributed to the decomposition of DMAP, and the characteristic peak of DTG only can be observed by NS-DMAP [26]. The results indicated that nano-SiO₂ immobilized DMAP derivative has been successfully prepared.

To prove the structure of the catalyst, the FT-IR spectra of NS, NS-Cl and NS-DMAP was taken and shown in Figure 4. In all curves, the peaks at 1072 cm⁻¹ and 796 cm⁻¹ were assigned to the Si-O-Si asymmetric and symmetric stretching, respectively [27]. After γ -chloropropyl-functionalization of nano-SiO₂, the peak corresponding to C-Cl stretching bond appeared at 653 cm⁻¹, and the stretching peaks of alkyl C-H was clearly observed at 2981 cm⁻¹ and 2891 cm⁻¹ [28].

Figure 2: The optimal conditions of N-alkylation reaction.

For the curve of NS-DMAP, the new characteristic peak at 1658 cm^{-1} was assigned to stretching bond of aromatic ring [26]. From the analysis of FT-IR, it can be ascertained that we have successfully prepared the catalyst.

3.3 Comparison of the catalytic effect of different carriers immobilized DMAP derivative

In order to investigate the role of carriers in the immobilization, DMAP was immobilized on several different carriers including nano-SiO₂ (NS), silica gel (SG) and mesoporous crystalline material (MCM-41). The maximum loading capacity of NS-DMAP, SG-DMAP and MCM-DMAP reached 0.68 mmol/g , 0.89 mmol/g and 1.35 mmol/g , respectively. Then, the performances of three kinds of catalysts were systematically assessed in the synthesis of α -tocopherol succinate. Although the

higher loading capacity was observed in preparation of SG-DMAP and MCM-DMAP, the highest catalytic activity was observed during the use of NS-DMAP. SG and MCM-41 with the porous structure had higher specific surface area. Thus, they showed higher DMAP loading capacity than NS. However, their small porous structure also accompanied by the serious internal resistance and reduced reaction rate. As shown in Figure 5, the initial reaction rate of NS-DMAP reached $1.5\text{ mmol}\cdot\text{mol}_{\text{DMAP}}^{-1}\cdot\text{min}^{-1}$, which was more than twice the activity of other two catalysts. DMAP immobilized on the external surface of nonporous NS, which can completely eliminate the internal diffusion problem. More importantly, according to the Stokes-Einstein and collision theory, NS with a very smaller size can enhance the collision between catalysts and reaction substrates, which was the main resistance for substrates availability between the bulk solution and material surface particularly in a biphasic system [29,30]. After reaction, the leakage of DMAP was

measured to investigate the stability of the immobilized DMAP derivative by HPLC [31]. The result indicated that the obtained immobilized DMAP derivative possessed

the greater stability and completely avoided the DMAP contamination of product, raising the product safety.

Figure 3: TG, DTG curves of (1) NS, (2) NS-Cl, (3) NS-DMAP.

Figure 4: FT-IR spectra of (a) NS, (b) NS-Cl, (c) NS-DMAP.

3.4 Effect of organic solvents on yield of vitamin E succinate

The reaction solvent was a crucial factor affecting the catalytic performance [22]. Table 1 showed the effect of organic solvents on the yield of α -tocopherol succinate in the single solvent system. It was found that the yield of α -tocopherol succinate was higher in a less-polar solvent. The phenomenon was attributed to the significantly reduced amount of DMAP protonation in the less-polar solvent [22,23]. However, the lowest yield was observed in the lowest-polar petroleum ether. The main reason was that the solubility of succinic anhydride decreased with decreasing the polarity of solvent. Therefore, a small amount of succinic anhydride was dissolved in petroleum ether, which limited ring-opened reaction of

Figure 5: Effect of different carriers. Conditions of reaction: 0.15 mmol α -tocopherol, 0.45 mmol succinic anhydride, hexane/acetone (4 mL/1 mL), DMAP equivalent to 0.10 mmol (the same below).

Table 1: Effect of different organic solvents.

organic solvents	solvent polarity	Yield
petroleum ether	0.01	5.56%
hexane	0.06	55.45%
toluene	2.40	30.91%
trichloromethane	4.40	25.87%
acetone	5.40	14.65%
dimethyl sulfoxide	7.2	10.91%

Conditions of reaction: 0.15 mmol α -tocopherol, 0.45 mmol succinic anhydride, 0.10 mmol NS-DMAP, 5 mL organic solvent described above, 55°C, nitrogen, 24 h.

Figure 6: Proposed mechanism for the synthesis of α -tocopherol succinate using NS-DMAP in hexane and acetone.

succinic anhydride in the first step of mechanism reaction described in Figure 6, affecting the effectivity of the whole reaction [32,33].

Herein, a mixed solvent system was introduced for the synthesis of α -tocopherol succinate, which consisted of the less-polar organic solvent hexane and the high-polar organic solvent acetone. The less-polar hexane was used to mitigate DMAP protonation, preventing the deactivation of catalyst, and the high-polar acetone was to increase the solubility of succinic anhydride. Hexane and acetone were environmentally friendly solvents with the properties of no health-based exposure limit and low toxicity [24]. Besides, the phase resistance was also avoided due to the miscible property of two solvents. The mixed solvent system enhanced the activity of the whole system and the safety of product. As shown in Figure 7a, it was found that the yield of α -tocopherol succinate was

higher in the mixed solvent system than single solvent system. The optimal volume ratio of hexane to acetone was confirmed as 4:1. Then, the reaction was carried out in four different systems, which was showed in Figure 7b. The result indicated that hexane-acetone mixed solvent system showed higher yields of α -tocopherol succinate and reaction rates comparing with hexane single solvent system in all cases no matter which form of DMAP was employed. Although free DMAP showed the highest catalytic activity in the mixed solvent among four reaction systems, the problem of separation limited its industrial applications. With regard to α -tocopherol succinate as medicine for human being, the DMAP contamination of the product should be avoided. Therefore, a highly efficient and environmentally friendly technology process for the synthesis of α -tocopherol succinate was employing nano-SiO₂ immobilized DMAP derivative as catalyst and

hexane-acetone mixed solvent as the reaction solvent. The initial reaction rate of $1.5 \text{ mmol} \cdot \text{mol}_{\text{DMAP}}^{-1} \cdot \text{min}^{-1}$ of NS-DMAP in mixed solvent was obviously higher than the highest initial reaction rate of $1.1 \text{ mmol} \cdot \text{mol}_{\text{DMAP}}^{-1} \cdot \text{min}^{-1}$ in single solvent. Besides, the contamination of DMAP can be completely avoided and this may be the first description of the remarkably high improvement of the efficiency of the production of α -tocopherol succinate.

3.5 Effect of molar ratio of substrates on yield of α -tocopherol succinate

The reaction equilibrium was easy to affect by substrates concentration. Therefore, an excess of succinic anhydride would be essential to shift the reaction equilibrium towards to the formation of α -tocopherol succinate [34]. The effect of molar ratio of succinic anhydride to α -tocopherol was showed in Figure 8. The obtained result suggested that the increase in molar ratio of succinic

anhydride to α -tocopherol significantly improved the yield of α -tocopherol succinate from 64% to 94%. However, there was no obvious increase in the yield of α -tocopherol succinate when the molar ratio of succinic anhydride to α -tocopherol was higher than 3:1. Therefore, the optimal molar ratio of succinic anhydride to α -tocopherol was confirmed as 3:1.

3.6 Effect of temperature on yield of α -tocopherol succinate

Temperature was another crucial factor affecting the activity of the whole reaction system [35]. As shown in Figure 9, it can be clearly observed that the yield of α -tocopherol succinate increased with increasing the

Figure 7: (a) Effect of mixed solvent system; (b) Effect of different catalytic reaction system. Conditions of reaction: 0.15 mmol α -tocopherol, 0.45 mmol succinic anhydride, 0.10 mmol catalyst, hexane/acetone (4 mL/1 mL), 55°C, nitrogen, 16 h.

Figure 8: Effect of molar ratio of substrates. Conditions of reaction: 0.15 mmol α -tocopherol, 0.15 to 0.75 mmol succinic anhydride, 0.10 mmol NS-DMAP, hexane/acetone (4 mL/1 mL), 55°C, nitrogen, 16 h.

Figure 9: Effect of different temperature. Conditions of reaction: 0.15 mmol α -tocopherol, 0.45 mmol succinic anhydride, hexane/acetone (4 mL/1 mL), 0.10 mmol NS-DMAP, nitrogen, 16 h.

Figure 10: Catalytic recycle times. Conditions of reaction: 0.15 mmol α-tocopherol, 0.45 mmol succinic anhydride, hexane/acetone (4 mL/1 mL), 0.10 mmol NS-DMAP, nitrogen, 16 h.

temperature from 35 to 55°C. The result suggested that an increase in reaction temperature had a significant effect on the catalytic reaction. However, further increase in the temperature, the yield of α-tocopherol succinate showed no considerable increase. Besides, the structure of α-tocopherol and the color of product were easily affected in a high temperature. The result indicated that the optimal temperature was 55°C.

3.7 Stability of catalyst

The longevity and reusability of heterogeneous catalysts were crucial factors from economy and environmental points of view. Therefore, the recyclability of nano-SiO₂ immobilized DMAP derivative was investigated under optimal conditions for the synthesis of α-tocopherol succinate. And the reaction was conducted by the decrease in amount of reaction substrates with catalyst amount loss. As showed in Figure 10, the catalyst showed no significant loss of catalytic activity even after reusing for 20 times. Furthermore, comparing the FT-IR spectrum of the reused catalyst with the fresh catalyst, Figure 11 showed that they had no significant changes. It clearly demonstrated that nano-SiO₂ immobilized DMAP derivative showed the excellent stability during the catalytic cycles.

4 Conclusion

Vitamin E succinate was successfully synthesized with a satisfactory yield in an effective reaction system. Nano-SiO₂ immobilized 4-dimethylaminopyridine derivative

Figure 11: Comparison of FT-IR for fresh catalyst with reused catalyst.

(NS-DMAP) was employed to synthesize α-tocopherol succinate, which avoided the catalyst contamination of the product and permitted the easy recycling of DMAP. Besides, a hexane-acetone mixed solvent was aimed to improve the activity of immobilized DMAP derivative and the substrate solubility. The maximum yield of α-tocopherol succinate reached 94% under the optimal conditions. To the best of our knowledge, it is the first example that vitamin E succinate was synthesized in a hexane-acetone mixed solvent system using nano-SiO₂ immobilized DMAP derivative. And it will be a potential application for the industrial production of vitamin E succinate.

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References

- [1] Vardi M., Levy N.S., Levy A.P., Vitamin E in the prevention of cardiovascular disease: the importance of proper patient selection. *J. Lipid Res.*, 2013, 54, 2307-2314.
- [2] Lonn E., Yusuf S., Hoogwerf B., Pogue J., Zinman B., Bosch J., et al., Effects of vitamin E on cardiovascular and microvascular outcomes in high-risk patients with diabetes: results of the HOPE study and MICRO-HOPE study. *Diabetes Care*, 2002, 25, 1919-1927.

- [3] Bium S., Vardi M., Nina S., The effect of vitamin E supplementation on cardiovascular risk in diabetic individuals with different haptoglobin phenotypes. *Atherosclerosis*, 2010, 211, 25-27.
- [4] Duhem N., Danhier U., Preat V., Vitamin E-based nanomedicines for anti-cancer drug delivery. *J. Control. Release*, 2014, 182, 33-34.
- [5] Drotleff A.M., Busing A., Willenberg I., Empl M.T., Steinber P., Ternes W., HPLC separation of vitamin E and its oxidation products and effects of oxidized tocotrienols on the viability of MCF-7 breast cancer cells in vitro. *J. Agric. Food Chem.*, 2015, 63, 8930-8939.
- [6] Ghanem E.N.B., Clark S., Du X., Wu D., Camilli A., Leong J.M., et al. The α -tocopherol form of vitamin E reverses age-associated susceptibility to *Streptococcus pneumoniae* lung infection by modulating pulmonary neutrophil recruitment. *J. Immunol.*, 2015, 194, 1090-1099.
- [7] Hu X.X., Fu L., Li Y., Lin Z.B., Liu X., Wang J.F., et al., The cardioprotective effect of vitamin E (α -tocopherol) is strongly related to age and gender in mice. *PLoS One.*, 2015, 10, 1-12.
- [8] Torres P., Duarte R.D., Cortes L.N., Ferrer M., Ballesteros A., Plou F.J., Acetylation of vitamin E by *Candida antarctica* lipase B immobilized on different carriers. *Process Biochem.*, 2008, 43, 145-153.
- [9] Yang P., Zhao J., Hou L.Y., Yang L., Wu K., Zhang L., Vitamin E succinate induces apoptosis via the PI3K/AKT signaling pathways in EC109 esophageal cancer cells. *Mol. Med. Rep.*, 2016, 14, 1531-1537.
- [10] Hou L., Zhang H., Xu P., Zhang L., Zhang X., Sun Y., et al., Effect of vitamin E succinate on the expression of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor in gastric cancer cells and CD4+ T cells. *Mol. Biosyst.*, 2015, 11, 3119-3128.
- [11] Truksa J., Dong L.F., Rohlena J., Stursa J., Vondrusova M., Goodwin J., et al., Mitochondrially targeted vitamin E succinate modulates expression of mitochondrial DNA transcripts and mitochondrial biogenesis. *Antioxid. Redox Signal.*, 2015, 22, 883-900.
- [12] Song Y., Cai H., Yin T., Huo M., Ma P., Zhou J., et al. Paclitaxel-loaded redox-sensitive nanoparticles based on hyaluronic acid-vitamin E succinate conjugates for improved lung cancer treatment. *Int. J. Nanomed.*, 2018, 13, 1585-1600.
- [13] Savitskaya M.A., Onischenko G.E., α -Tocopheryl succinate affects malignant cell viability, proliferation, and differentiation. *Biochemistry-Moscow*, 2016, 81(8), 806-818.
- [14] Xu Z., Comparison of extraction methods for quantifying vitamin E from animal tissues. *Bioresource Technol.*, 2008, 99, 8705-8709.
- [15] Yin C.H., Zhang C., Gao M., Enzyme-catalyzed synthesis of vitamin E succinate using a chemically modified Novozym-435. *Chin. J. Chem. Eng.*, 2011, 19, 135-139.
- [16] Tao Y.F., Dong R.J., Pavlids I.V., Chen B., Tan T., Using imidazolium-based ionic liquids as dual solvent-catalysts for sustainable synthesis of vitamin esters: inspiration from bio- and organo- catalysis. *Green Chem.*, 2016, 18, 1240-1248.
- [17] Trombino S., Cassano R., Ferrarelli T., Cilea A., Muzzalupo R., Cione E., et al., Synthesis and antioxidant activity evaluation of novel broom and cotton fibers derivatives. *J. Appl. Polym. Sci.*, 2009, 114, 3177-3188.
- [18] Bonrath W., Netscher T., Catalytic processes in vitamins synthesis and production. *Appl. Catal. A-Gen.*, 2005, 280, 55-73.
- [19] Lu N., Chang W.H., Wei R.J., Fang Y.C., Han T.W., Wang G.Q., et al., *Pyridinium saccharinate* salts as efficient recyclable acylation catalyst: a new bridge between heterogeneous and homogeneous catalysis. *Tetrahedron*, 2016, 72, 3468-3476.
- [20] Talebian N., Elham Z.E., Structure and antibacterial property of nano-SiO₂ supported oxide ceramic. *Ceram. Int.*, 2014, 40, 281-287.
- [21] Yu W.Q., Fu J.F., Dong X., Chen L., Jia H., Shi L., Highly populated and nearly monodispersed nanosilica particles in an organic medium and their epoxy nanocomposites. *ACS Appl. Mater. Inter.*, 2013, 5, 8897-8906.
- [22] Tanaka S., Iwata T., Iji M., Solvent effects on heterogeneous synthesis of cardanol-bonded cellulose thermoplastics. *Polymer*, 2016, 99, 307-314.
- [23] Sakakura A., Kawajiri K., Ohkubo T., Kosugi Y., Ishihara K., Widely useful DMAP-catalyzed esterification under auxiliary base- and solvent-free conditions. *J. Am. Chem. Soc.*, 2007, 129, 14775-14779.
- [24] Directorate E.I.E., European pharmacopoeia Germany. *Acid-Free Paper*, Germany, 2013.
- [25] Tavassoli M., Isfahani A.M., Moghadam M., Tangestanibejad S., Mirkhani V., Baltork I.M., Copper dithiol, complex supported on silica nanoparticles: a sustainable, efficient, and eco-friendly catalyst for multicomponent click reaction. *ACS Sustain. Chem. Eng.*, 2016, 4, 1454-1462.
- [26] Li B., Chen D., Zhang X.L., Dong W., Zhao B., A convenient method to immobilize 4-dimethylaminopyridine on silica gel as a heterogeneous nucleophilic catalyst for acylation. *Chem. Pap.*, 2018, 72, 1339-1345.
- [27] Ahangaran F., Hassanzadan A., Nouri S., Surface modification of Fe₃O₄@SiO₂ microsphere by silane coupling agent. *Int. Nano Lett.*, 2013, 3, 3-7.
- [28] Girija D., Naik H.S.B., Kumar B.V., Sudhamani C.N., Synthesis of functionalized iron oxide nanoparticle with amino pyridine moiety and studies on their catalytic behavior. *Am. Chem. Sci. J.*, 2011, 1, 97-108.
- [29] Jia H., Zhu G., Wang P., Catalytic behaviors of enzymes attached to nanoparticles: the effect of particle mobility. *Biotechnol. Bioeng.*, 2003, 84, 406-414.

- [30] Charbonneau B., Charbonneau P., Szamel G., A microscopic model of the stokes-einstein relation in arbitrary dimension. *J. Chem. Phys.*, 2018, 148, 1-20.
- [31] Spivery A.C., Charbonneau P., Fekner T., Hochmuth D.H., Maddaford A., Jugroot C.M., et al., Energy barriers to rotation in axially chiral analogues of 4-(Dimethylamino)pyridine. *J. Org. Chem.*, 2001, 66, 7394-7401.
- [32] Singh S., Das G., Singh O.V., Han H., Conformationally restricted 4-dimethylaminopyridine (DMAP) analogs: synthesis and evaluation of catalytic effectiveness. *Tetrahedron Lett.*, 2007, 48, 1983-1986.
- [33] Mao X., Wang S., Shang Y., A DFT study on the mechanism of the organocatalytic synthesis of a benzoxazine-substituted indolizine derivative. *J. Mol. Model.*, 2017, 23, 177-182.
- [34] Reddy C.R., Iyengar P., Nagendrappa G., Prakash B.S.J., Esterification of succinic anhydride to di-(p-cresyl) succinate over Mn⁺-montmorillonite clay catalysts. *J. Mol. Catal. A-Chem.*, 2005, 229, 31-37.
- [35] Avhad M.R., Sanchez M., Bouaid A., Martinez M., Aracil J., Marchetti J.M., Modeling chemical kinetics of avocado oil ethanolysis catalyzed by solid glycerol-enriched calcium oxide. *Energ. Convers. Manage.*, 2016, 126, 1168-1177.