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Two-step continuous flow synthesis of α-terpineol

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ABSTRACT

α-Terpineol is a naturally occurring monoterpene present in essential oils, of high value on the market as it is widely used as flavoring in the cosmetics and food industry. This study aims to produce α-terpineol by two different synthetic strategies, using both batch and continuous flow systems, focusing on the optimization of the process, improving the reaction conversion and selectivity. The first strategy adopted was a one-stage hydration reaction of (+)-α-pinene by an aqueous solution of chloroacetic acid (molar ratio 1:1 between pinene and the acid) in continuous flow conditions. This reaction was carried out at 80 °C with a residence time of 15 min, obtaining good conversion (72%) and selectivity (76%), and productivity of 0.53 kg.day^{-1}. The second strategy accomplished was a two-step cascade reaction with (+)-limonene as starting material, where the first step is a chemospecific double bond addition using trifluoroacetic acid, and the second step is the basic hydrolysis of the ester promoted by a solution of sodium hydroxide (2.25 M) in methanol (1:1). This reaction was adapted to a continuous flow condition, where all steps involved a residence time of 40 min, at 25 °C, with no quenching between steps required, with 97% conversion, 81% selectivity and up to 0.14 kg.day^{-1}.

Introduction

Over the decades, flavors and fragrances sector have been growing in all its applications and nowadays they represent a multi-billionaire global market. The growing global industrialization has led to the massive production of processed food, beverages, personal care products, detergents, cleaning products and soaps, which show the industry's necessity to produce scented or flavored products. Thereby, such a high demand for natural products in this particular area could be seen as a disadvantage because of the fluctuating prices of raw materials. To outline the problem and continue expanding the market, scientific innovations are needed to deliver synthetic fragrances and flavors [1–3].

α-Terpineol is a high-value naturally occurring monoterpene present in essential oils widely used as a flavoring aromatic substance. Likewise, it is also used as an anti-fungal agent, as a disinfectant in cleaning commodities [4], as a fine chemical building block [5], and has antibacterial [6] and antitumoral activities [7,8]. Consequently, there is an intense search for more effective synthetic ways to obtain α-terpineol [4,9]. The use of the terpene as a chemical platform has been already investigated, and many new catalytic processes were reported affording the target compound *via* chemical [8] or biochemical [9] catalytic conversion. Thus, different methods to produce α-terpineol have been described in the literature, using both monoterpenes (+)-limonene and (+)-α-pinene and oxygenated terpenes as starting materials under acidic conditions (Scheme1) [4,9–13]. However, a comparative and systematic study of different catalysts under mild reaction conditions for the production α-terpineol has not been reported in literature.

In this context, the development of chemoselective synthesis of α-terpineol has, as main challenge, to avoid degradation and isomerization products which current leads to low yield and selectivities [14].

The adoption of continuous flow technology for the synthesis of natural product on safer and more efficient conditions has become popular. Providing better control on reaction parameters such as mixing, mass and heat transfer and on-line purification, downstream processing help minimize solvent usage, waste and manual handling [15–17]. In this context, our research group [16,18–21] have been involved in the development of flow chemistry methodologies for organic synthesis and biocatalysis [15,16] and herein we report the evaluation of continuous flow technology for the synthesis of α-terpineol starting from readily available (+)-limonene and (+)-α-pinene [10,22,23].

Results and discussion

We began our work evaluating batch reactions already described in literature for α-terpineol synthesis starting from read-

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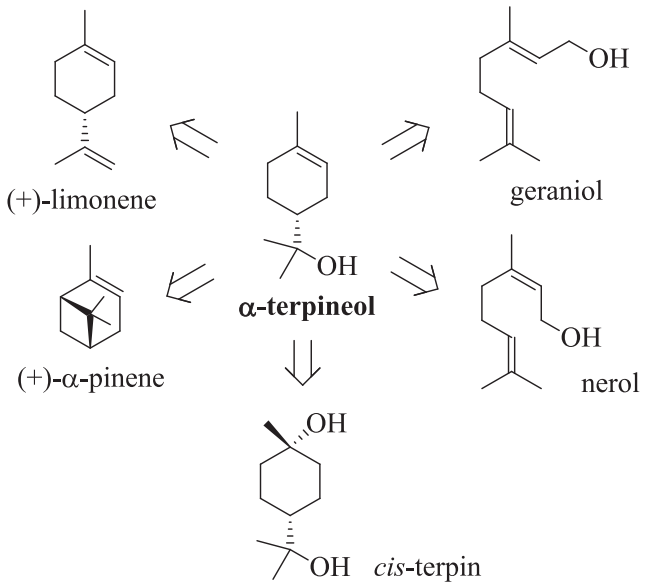


Scheme 1. Different starting materials for α-terpineol synthesis.

ily available monoterpenes (+)-α-pinene and (+)-limonene. The reaction studied for α-terpineol synthesis starting from (+)-α-pinene was reproduced according to Román-Aguirre *et al* [4] (23 M chloroacetic acid aqueous solution, 73 mmol substrate, 4 h at 70 °C) leading to the desired product with 58% of selectivity. Further optimization of reaction parameters (reaction time, temperature, catalyst concentration) leaded us to a slight reduction on reaction time (3 h) with an increase on selectivity (67%) without yield reduction, at 70 °C using a 27 mol. L^{-1} chloroacetic acid stock solution (supporting information, Table S1).

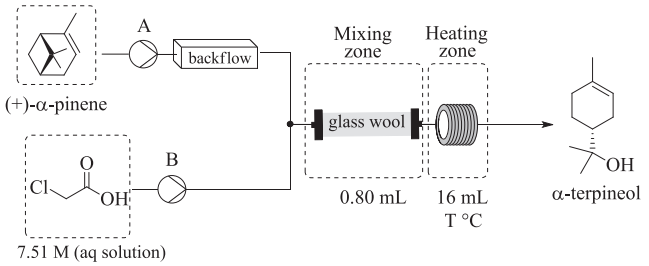
The best condition was found, using (+)-α-pinene (10 mmol), chloroacetic acid in water (7.51 mol/L) at 70 °C for 3 h, with a conversion value of 84% and selectivity of 67% (supporting information, entry 1, Table S1). From the batch reaction studies we learned that: the reaction showed sensibility to temperature, we could reduce in one hour the reaction time described by Román-Aguirre *et al* [4], and the best molar ratio between the substrate and the acid was 1:1. The best batch conditions were adapted to continuous flow systems.

After this initial assessment we decided to translated batch protocol to continuous flow conditions connecting two syringe pumps (A: α-pinene and B: 7.51 M chloroacetic acid aqueous solution) through a *T*-mixer into a mixing zone (PBR filled with glass wool) and a reaction zone at temperatures between 70 and 90 °C. It is important to highlight that it was necessary an implementation of a homemade static mixer, before tubular reactor mixer, as mixing intensification strategies, increasing the homogeneity of the reaction medium and avoiding the presence of hotspots. Flow rates were adjusted in order to have a 1:1 mixture of reagents, according to the desired residence time. Results are found on Table 1, and all conversion values were analyzed by a GC/MS considering the substrate, (+)-α-pinene, consumption.

Under the conditions outlined in Table 1, first experiments at 70 °C have shown that long residence time (60 min) led to lower selectivity towards the desired product (entries 1 and 3, Table 1). At this point, 30 min (entry 2, Table 1) residence time already gave us moderate conversion (60%) with high selectivity (81%) and increasing reaction temperature to 80 and 90 °C, keeping residence time on 15 min, allowed a slight increase on reaction conversion with similar selectivity (entries 5 and 7, respectively, Table 1). Under the best conditions found for α-terpineol synthesis (entry 5, Table 1) a space–time-yield of 0.53 Kg. day^{-1} can be obtained (based on conversion values, selectivity and pinene flow). The results highlight that the replacement of conventional batch to flow reactor allowed decreasing both reaction time.

As a second strategy we decided to evaluate the approach of starting from (+)-limonene for α-terpineol synthesis, which requires a two-step methodology consisted in an oxidation reaction mediated by trifluoroacetic acid leading to trifluoroacetyl-α-terpineol, an unstable intermediate, which proceeded to the next step with the crude mass, followed by hydrolysis of this intermediate ester. We have used the work of Mattos *et al* [24] as a starting point where the reaction was performed at room temperature for 1 h in cyclohexane. It was performed a previous optimization in batch conditions evaluating the conversion and selectivity values in function of reaction time (supporting information, Table S2). These results showed that after 30 min of reaction time no further enhancement on conversion and selectivity values were observed. Moreover, other experiments evaluating molar ratio condition of

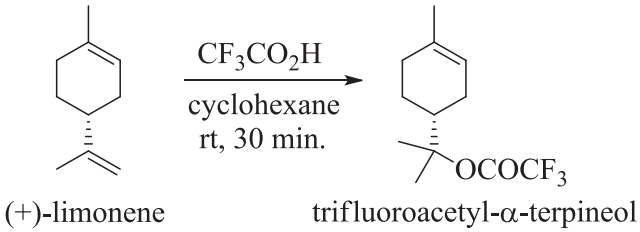
Table 1
Results on continuous flow protocol using (+)-α-pinene as substrate.



Entry	T (°C)	Res. time (min)	Conv. (%) ± SD*	Select. (%) ± SD*
1	70	60	48 ± 1.63	65 ± 0.94
2	70	30	60 ± 0.94	81 ± 5.91
3	80	60	68 ± 10.96	57 ± 2.45
4	80	30	73 ± 5.79	71 ± 0.82
5	80	15	72 ± 2.45	76 ± 1.25
6	90	30	84 ± 1.63	75 ± 2.16
7	90	15	72 ± 4.19	76 ± 1.70

Reaction using α-pinene 98%, chloroacetic acid aqueous solution (7.51 M). *All conversion and selectivity values were determined by GC/MS considering the substrate, (+)-α-pinene, consumption. Values were measured in triplicate; the medium value is reported, as well as the standard deviation (SD).

Table 2
(+)-Limonene in the synthesis of trifluoroacetyl-α-terpineol.



Entry	Molar ratio ((+)-limonene:acid)	Conv. (%)*	Select. (%)*
1	1:1	88	87
2	1:1.2	90	90
3	1:2	81	75
4	1:1 (no solvent)	93	80

Reaction using (+)-limonene (10 mmol) and CF_3CO_2H 10 mmol (1:1), at room temperature, for 30 min. *All conversion and selectivity values were determined by a GC/MS considering the substrate, (+)-limonene, consumption.

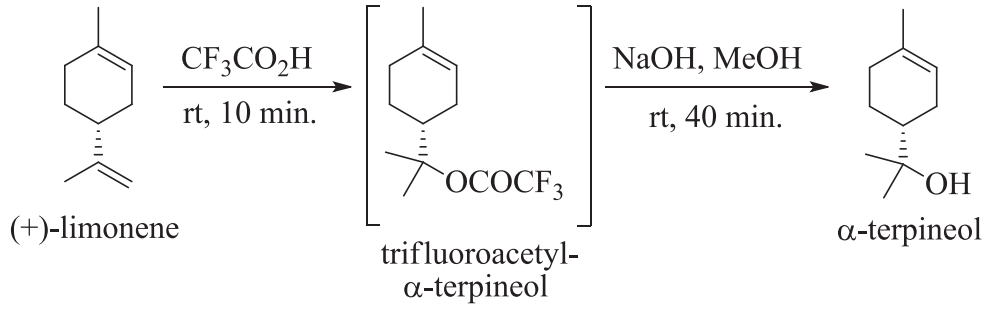
(+)-limonene and trifluoroacetic acid were also tested on batch condition (Table 2).

In our experiments a small decrease on selectivity was detected when 1:2 M ratio (limonene: trifluoroacetic acid) was used (entry 3, Table 2). It is important to highlight that with the aim of finding a better condition to continuous flow process, we decided to evaluate a solvent free reaction, giving excellent conversions and good selectivity's (entry 4, Table 2). Considering these preliminary results, this reactional condition has become a very interesting protocol for process intensification. Therefore, a study monitoring the reaction time on solvent-free condition allowed us to observe that after only 5 min 93% of conversion was already achieved with very good selectivity, 89% (supporting information, Table S3).

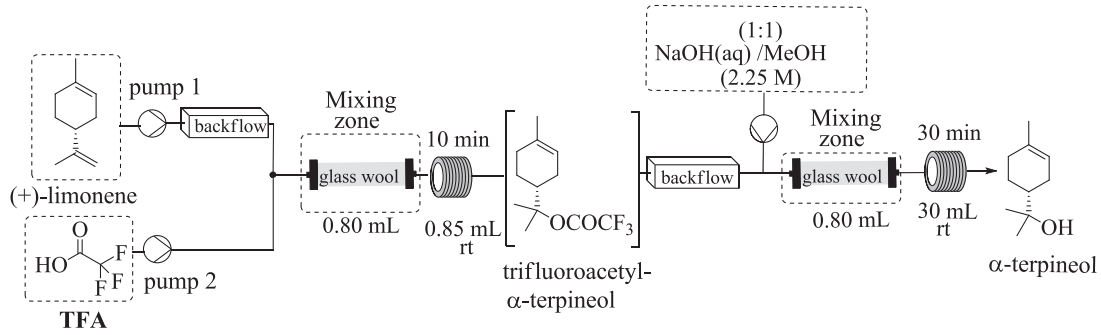
As mentioned before, in order to access at the desired product, we need to run a two-step reaction. Since the ester intermediate is very unstable in acidic media, a cascade batch process is needed to fully understand the potential of this solvent-free approach (Scheme 2). Therefore, the methanolic sodium hydroxide solution was added directly to the reaction media after the first step reaction time and samples were taken to follow product formation. After 40 min of total reaction time, the conversion was maximum (97%) and with excellent selectivity (93%).

It is well-established that this methodology for the conversion of (+)-limonene into α-terpineol occurs with retention of the absolute configuration without loss of optical activity [24]. As the main goal of this work is the evaluation of flow system for the synthesis of α-terpineol, so we did not evaluated the optical purity of the α-terpineol obtained.

From these results, we decided to move forward in order to translate batch protocol to a continuous flow cascade process. Firstly, the reaction first step was study in flow conditions (supporting information, Table S4) and later on, the second step was assembled. The complete continuous flow setup is shown on Scheme 3 and it is composed of three syringe pumps, two mixing



Scheme 2. Two-step cascade batch reaction of the α-terpineol synthesis.



Scheme 3. Cascade continuous flow setup for the synthesis of α-terpineol.

zones and two reaction zones, both at room temperature. Residence time was also adjusted in order to fit equipment requirements. The conversion and selectivity values were determined by GC/MS considering the substrate (+)-limonene consumption. Those values were measured in triplicate so we could obtain standard deviation values.

The continuous flow cascade system starting from (+)-limonene could reproduce similar conversions to the batch system (97%, SD = 0.47%) with a slight decrease on selectivity (80%, SD = 1.25), where changes on residence time could not allow better results. Residence time on the first step had a small change compared to the optimization protocol in order to have a flow rate where we could meet the second step requirements of residence time. For the second reaction, mixing is a crucial step, so we decided to have an extended residence time in order to accomplish the hydrolysis reaction. Space time yield obtained for this cascade process is 0.14 kg.day^{-1} (based on conversion values, selectivity and limonene flow), lower than the one obtained for the continuous flow strategy starting from (+)-α-pinene. The final compound can be easily purified by distillation from reaction crude mixture.

Conclusions

Based on the results presented, it was possible to develop two processes for the synthesis of α-terpineol under continuous flow. Synthesis of α-terpineol in continuous flow was performed using (+)-α-pinene as starting material and chloroacetic acid in molar ratio 1:1, at 80 °C with a total residence time of 15 min, obtaining good conversion values (72% ± 2.45) and selectivity (76% ± 1.25). These results proved to be much more interesting than those obtained in batch, where the reactions were carried out at 70 °C for 4 h resulting in 88% conversion and 67% selectivity. Although the conversion value was higher for the batch reaction, in the continuous flow system the reaction time was reduced in 94%, providing a huge increase in the efficiency of the reaction, resulting in a productivity of 0.53 kg.day^{-1} under the best conditions found.

For the two-step cascade reaction to the obtainment of α-terpineol starting from (+)-limonene, excellent conversion (97% ± 0.47) and selectivity (80% ± 1.25) results were presented. The advantages of this reaction system were: the first step was carried out without solvent, the second was carried in aqueous solution, and the hole processes could be done at room temperature, and the total residence time of 40 min. As described, in batch, the total reaction time was of 2.5 h and resulted in 56% conversion and 81% selectivity. The productivity of this flow system was 0.14 kg.day^{-1}.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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All experimental information is in the supporting information.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153318.

References

[1] Flavors and Fragrances Market Size to Reach USD 38.56 Billion by 2026, Rise in Demand for Scented and Flavored Cosmetics will Help Attract High Revenue, Foresees Fortune Business Insights™, 2020. Available at: https://www.globenewswire.com/news-release/2020/03/02/1993151/0/en/Flavors-and-Fragrances-Market-Size-to-Reach-USD-38-56-Billion-by-2026-Rise-in-Demand-for-Scented-and-Flavored-Cosmetics-will-Help-Attract-High-Revenue-Foresees-Fortune-Business-Ins.html (accessed: 2nd May 2020).
[2] A. Sales, L.D.O. Felipe, J.L. Bicas, Production, Properties, and Applications of α-Terpineol, Food Bioprocess Technol. 13 (2020) 1261–1279.
[3] M.G. Speziali, De aromas e perfumes, o mercado da indústria do“ cheiro”, Química nova. 35 (2012) 861–864.
[4] M. Román-Aguirre, L. De La Torre-Sáenz, W.A. Flores, A. Robau-Sánchez, A.A. Elguézabal, Synthesis of terpineol from α-pinene by homogeneous acid catalysis, Catal. Today 107–108 (2005) 310–314.
[5] W. Zhu, X. Liu, Y. Wang, Y. Tong, Y. Hu, Discovery of a novel series of α-terpineol derivatives as promising anti-asthmatic agents: Their design, synthesis, and biological evaluation, Eur. J. Med. Chem. 143 (2018) 419–425.
[6] A.C. Guimarães, L.M. Meireles, M.F. Lemos, M.C.C. Guimarães, D.C. Endringer, M. Fronza, R. Scherer, Antibacterial Activity of Terpenes and Terpenoids Present in Essential Oils, Molecules 24 (2019) 1–12.
[7] F.A. Batista, S.B.C. Fontele, L.K.B. Santos, L.A. Filgueiras, S.Q. Nascimento, J.M.D. C.E. Sousa, J.C.R. Gonçalves, A.N. Mendes, Synthesis, Characterization of a-terpineol-loaded PMMA nanoparticles as proposed of therapy for melanoma, Mater. Today Commun. 58 (2020).
[8] M.V. Sobral, A.L. Xavier, T.C. Lima, D.P. De Sousa, Antitumor Activity of Monoterpenes Found in Essential Oils, Sci. World J. ID (2014) 953451.
[9] T. Prakoso, J. Hanley, M.N. Soebianta, T.H. Soerawidjaja, A. Indarto, Synthesis of Terpineol from α-Pinene Using Low-Price Acid Catalyst, Catal. Letters 148 (2018) 725–731.
[10] V.T. Murakami, I.O. Marques, R. Cella, Ultrasound-Assisted Conversion of Biomass Turpentine into α -Terpineol, Chem. Sel. 4 (2019) 8800–8806.
[11] L.H.B. Baptistella, P.M. Imamura, L.V. de Melo, C. Castello, Preparação do (+)-α-terpineol a partir do (+)-limoneno.pdf, Quim. Nova 32 (2009) 1069–1071.
[12] L.M.T. Frija, C.A.M. Afonso, Amberlyst ® -15: A reusable heterogeneous catalyst for the dehydration of tertiary alcohols, Tetrahedron 68 (2012) 7414–7421.
[13] J. An, L. Bagnell, T. Cablewski, C.R. Strauss, R.W. Trainor, Applications of High-Temperature Aqueous Media for Synthetic Organic Reactions, J. Org. Chem. 62 (1997) 2505–2511.
[14] J. Xie, Q. Han, J. Wang, L. Bai, J. Lu, Z. Liu, Kinetics, Catalysis, and Reaction Engineering Enhanced -terpineol yield from a-pinene hydration via synergistic catalysis using carbonaceous solid acid catalyst, Ind. Eng. Chem. Res. 58 (2019) 22202–22211.
[15] A.M.G. Russell, T.F. Jamison, Seven-Step Continuous Flow Synthesis of Linezolid Without Intermediate Purification, Angew. Chemie - Int. Ed. 58 (2019) 7678–7681.
[16] C.A.A. Adarme, R.A.C. Leão, S.P. de Souza, I. Itabaiana, R.O.M.A. de Souza, C.M. Rezende, Continuous-Flow Chemo and Enzymatic Synthesis of Monoterpenic Esters with Integrated Purification, Mol. Catal. 453 (2018) 39–46.
[17] J. Wegner, S. Ceylan, A. Kirschning, Flow Chemistry – A Key Enabling Technology for (Multistep) Organic Synthesis, Adv. Synth. Catal. 354 (2012) 17–57.
[18] A.R. Aguillón, M.N. Avelar, L.E. Gotardo, S.P. de Souza, R.A.C. Leão, I. Itabaiana, L. S.M. Miranda, R.O.M.A. de Souza, Immobilized lipase screening towards continuous- flow kinetic resolution of (±)-1,2-propanediol, Mol. Catal. 467 (2019) 128–134.
[19] R.O.M.A. De Souza, R. Aguiar, R.A.C. Leão, L.S.M. Miranda, C.O. Kappe, D. Cantillo, A. Mata, Continuous-Flow Protocol for the Synthesis of Enantiomerically Pure Intermediates of anti Epilepsy and anti Tuberculosis Active Pharmaceutical Ingredients, Org. Biomol. Chem. 17 (2019) 1552–1557.
[20] A.D.S. França, R.A.C. Leão, R.O.M.A. de Souza, Two step continuous-flow synthesis of benzocaine, J. Flow Chem. 10 (2020) 563–569.
[21] M.T. Lima, F.G. Finelli, A.V.B. de Oliveira, V. Kartnaller, J.F. Cajaiba, R.A.C. Leão, R.O.M.A. de Souza, Continuous-flow synthesis of dimethyl fumarate: A powerful small molecule for the treatment of psoriasis and multiple sclerosis, RSC Adv. 10 (2020) 2490–2494.
[22] M.A. Martín-Luengo, M. Yates, M.J. Martínez Domingo, B. Casal, M. Iglesias, M. Esteban, E. Ruiz-Hitzky, Synthesis of p-cymene from limonene, a renewable feedstock, Appl. Catal. B Environ. 81 (2008) 218–224.
[23] B.E. Sawe, Top Orange producing countries in the world, 2017. Available at: https://www.worldatlas.com/articles/top-orange-producing-countries-in-the-world.html (accessed: 6th December 2019).
[24] M.C.S. De Mattos, R.B. Coelho, A.M. Sanseverino, Chemospecific Preparation of Both Enantiomers of α-Terpinyl Trifluoroacetate, Synth. Commun. 34 (2004) 541–545.