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Article

Tandem Transesterification-Esterification Reactions Using a Hydrophilic Sulfonated Silica Catalyst for the Synthesis of Wintergreen Oil from Acetylsalicylic Acid Promoted by Microwave Irradiation

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Abstract: SiO_2-SO_3H, with a surface area of 115 m^2/g, pore volume of 0.38 cm^3g^{-1} and 1.32 mmol H^+/g, was used as a 20% w/w catalyst for the preparation of methyl salicylate (Wintergreen oil or MS) from acetylsalicylic acid (ASA). A 94% conversion was achieved in a microwave reactor during 40.0 minutes at 120 ºC in MeOH. The resulting crude product was purified by flash chromatography. The catalyst could be re-used three times.

Keywords: Sulfonated silica catalyst (SiO_2-SO_3H); methyl salicylate; green chemistry; methylating agent; deacetylation (acyl nucleophilic substitution); solid acid catalyst

1. Introduction

Wintergreen (*Gaultheria procumbens* L.), also known as checkerberry or teaberry, is a small ericaceous plant found growing in the undergrowth of dense forests in the U.S. Wintergreen is cultivated for use in the landscape industry, and it is the source of the essential oil of wintergreen (WO) [1,2]. The essential oil of wintergreen is prepared commercially by steam distillation; however, the most commonly used form of WO is synthetic. Wintergreen is now commonly used as a flavoring agent, but its leaves were historically used by North American natives for the treatment of aches and pains because of their "aspirin-like" quality. In fact, WO, the most common salicylate in commercial wintergreen preparations, is routinely used in topical ointments for the treatment of inflammation [2].

WO is a clear liquid with a peppermint and minty scent, and it most likely serves as a defense from herbivores. For example, when a plant is infected with herbivorous insects, the production of WO attracts other insects that kill these herbivorous insects [3]. WO can also be used by plants as a pheromone to warn other plants of pathogens such as the tobacco mosaic virus [4], and it is used as a clearing agent for preparing slides of Aedes mosquito larvae for microscopic examination [5]. It is also extensively used in the synthesis of solvents, perfumes, cosmetics, food preservatives, chiral auxiliaries, plasticizers, drugs and pharmaceuticals [6,7]. Ribnicky et al. (2003) determined the presence of salicylates other than methyl salicylate that could act as alternatives for aspirin [8]. Recently,

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the authenticity of methyl salicylate (MS) in the essential oils from *Gaultheria procumbens L.* and *Betula lenta L.* was determined using isotope ratio mass spectrometry [9].

Among the methods found in the literature for the synthesis from salicylic acid (SA), the preparation of methyl salicylate (MS) using diazotization chemistry is emphasized [10]. In that experiment, the use of diazonium salts for the replacement of an aromatic amine group by a phenolic hydroxyl was demonstrated. Many reports have been published on the synthesis of WO by esterification of SA with dimethyl carbonate (DMC), such as, "Green synthesis of WO using novel sulfated iron oxide-zirconia catalyst" [11]. Sreekumar et al. reported the reaction of SA with DMC using zeolite, wherein monomethylation was observed [12]. Kirumakki et al. obtained a 90% conversion of salicylic acid and 95% selectivity in the reaction of SA with DMC over zeolites when treated for 4 h at 135 °C [13]. Zheng et al. reported 98% conversion and 96% selectivity with DMC over the AlSBA15-SO_3H catalyst when treated for 8 h at 200 °C [14]. Su et al. obtained 99% conversion of SA and 77% selectivity for the reaction of SA with DMC over mesoporous aluminosilicate [15], and Zhang et al. reported 93% conversion and 99% selectivity with methanol using Ce^{4+}-modified cation-exchange resins when treated for 12 h at 95 °C [16]. In all these studies, equilibrium in the esterification reaction is overcome by using dimethyl carbonate instead of methanol as the methylation agent.

Some studies have reported the formation of MS from the esterification reaction of SA with MeOH as a methylation agent using different solid catalysts. Hua Shi et al. reported that a variety of Brönsted acidic ionic liquids were screened as catalysts for the esterification of salicylic acid in a microwave-accelerated process [17].

Esterification or transesterification using microwave irradiation, in addition to being environmentally friendly, is also marked by a considerable reduction in reaction time in comparison with conventional esterification [18,19]. Furthermore, to the best of our knowledge, tandem esterification-transesterification of ASA in hydrophilic sulfonated silica catalyst has not yet been achieved. As a part of an ongoing research on the use of the SiO_2-SO_3H catalyst for clean synthesis [20], this catalyst was used in the highly selective, one-pot, tandem, transesterification-esterification reactions of ASA with MeOH in the microwave-accelerated synthesis of MS. A high catalytic activity in a very short period of time was observed. The stability and reuse of SiO_2-SO_3H were also examined.

2. Experimental

2.1. Raw materials and chemicals

All the reagents (analytical grade), including ASA, were supplied by Vetec, São Paulo, Brazil and were used without further purification.

2.2. Instrumentation

MS content and yield were determined with a GC/MS-QP 2010/AOC 5000 AUTO INJECTOR/Shimadzu Gas Chromatograph/Mass Spectrometer equipped with a 30 m Agilent J&W GC DB-5 MS column. Direct insertion spectra were measured at 70 eV. Quantitative analyses were performed on a Shimadzu GC-2010 gas chromatograph equipped with a flame ionization detector [20]. ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker *Avance* 400 Spectrometers [20]. All the reactions were monitored by TLC using Silica Gel 60 F 254 on aluminum. The chromatograms were visualized by UV light or by using the ethanolic vanillin developing agent [20]. The purification of the products was achieved by flash column chromatography using a mixture of hexane/ethyl acetate in a 9/1 proportion as the eluent [20]. The MW reactions were performed in 10 mL G-10 vials of an Anton Paar single-mode MW Monowave 300 synthesis reactor, powered by an 850 W magnetron, and equipped with temperature sensor and magnetic stirring [21].

2.3. Preparation of the silica gel and sulfonated silica (SiO_2-SO_3H)

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The preparation of silica gel and the sulfonated silica SiO_2-SO_3H catalyst have been reported previously [20].

2.4. Typical procedures

2.4.1. Tandem esterification and transesterification of ASA using SiO_2-SO_3H as the catalyst in MeOH.

To a 10 mL microwave reactor vial, 180.0 mg (1.00 mmol) of ASA (purified by column chromatography), 1.0 mL of MeOH and 0.0360 g of SiO_2-SO_3H (20% w/w in relation to ASA) were added. The vial was heated in the microwave reactor at 120 °C for 40 min. The mixture was cooled to room temperature, and 10.0 mL of CH_2Cl_2 was added. The organic solution obtained after filtration of the solid catalyst was transferred to an extraction funnel and partitioned between 10 mL of CH_2Cl_2 and 20 mL saturated $NaHCO_3$, dried with magnesium sulfate, filtered and evaporated under reduced pressure. The resulting residue was subjected to a GC/MS analysis, which demonstrated the absence of unreacted SA. The residue was then purified by flash column chromatography on silica using hexane:ethyl acetate (9:1) as the mobile phase to yield MS as a colorless oil.

3. Results and Discussion

One of the first syntheses of MS from ASA (contained in commercial aspirin tablets) was related by Aaron M. Hartel and James M. Hanna Jr as a short, single-pot preparation that can be performed via a tandem transesterification-Fischer esterification. The crushed aspirin tablets are mixed with MeOH to dissolve the aspirin, and insoluble material is removed by filtering through a cotton plug. Concentrated H_2SO_4 was added to the aspirin solution, and it was either refluxed for 90 minutes or heated in a scientific microwave system at 120 °C for 5 minutes. The MS was obtained in yields approaching 70% [22].

Esterification reactions are reported with various homogeneous acid catalysts such as HCl, H_2SO_4, HF and H_3PO_4. However, these methods have drawbacks such as the generation of undesired inorganic salts, hazardous conditions, difficulty in catalyst recovery and reuse [23,24].

The SiO_2-SO_3H catalyst has been used by us as a replacement for conventional mineral acid catalysts (H_2SO_4) in various studies involving the esterification of different carboxylic acids [20]. However, the use of this catalyst in transesterification reactions has only been tested with triglycerides [25]. In the present case, the reaction proceeds via a tandem transesterification-esterification.

In this work, we studied the rapid synthesis of MS in a single reaction vessel, where the SiO_2-SO_3H catalyzed the acyl substitution on the carboxylic group of ASA with MeOH as the nucleophilic reagent (the methylating agent) to give an ester. Simultaneously, the transesterification of the acetyl group with the nucleophilic MeOH yielded methyl acetate as a by-product and MS (principal product, Fig. 1).

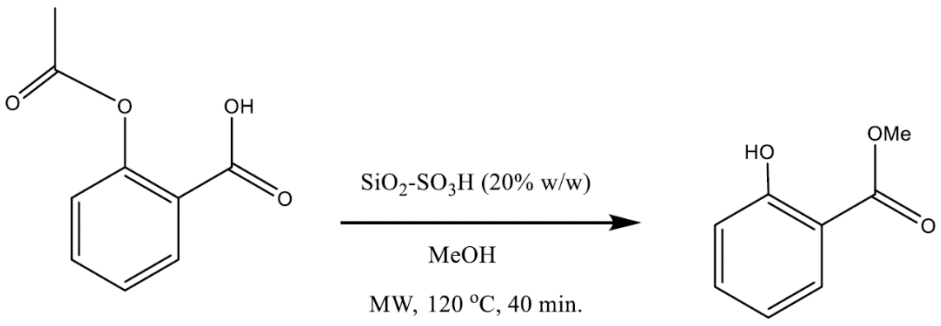

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Figure 1. Reactions of the conversion of ASA into MS. The synthesis proceeds via a tandem transesterification-esterification catalyzed by SiO_2-SO_3H.

The ASA easily absorbs humidity, and intramolecular catalysis leads to the formation of acetic acid and salicylic acid (ASA + H_2O → SA + CH_3COOH) [24]. Therefore, the ASA was purified by recrystallization using aqueous ethanol prior to use. The NMR spectrum demonstrating the purity of the ASA used for the synthesis is shown in Figure 2 [27].

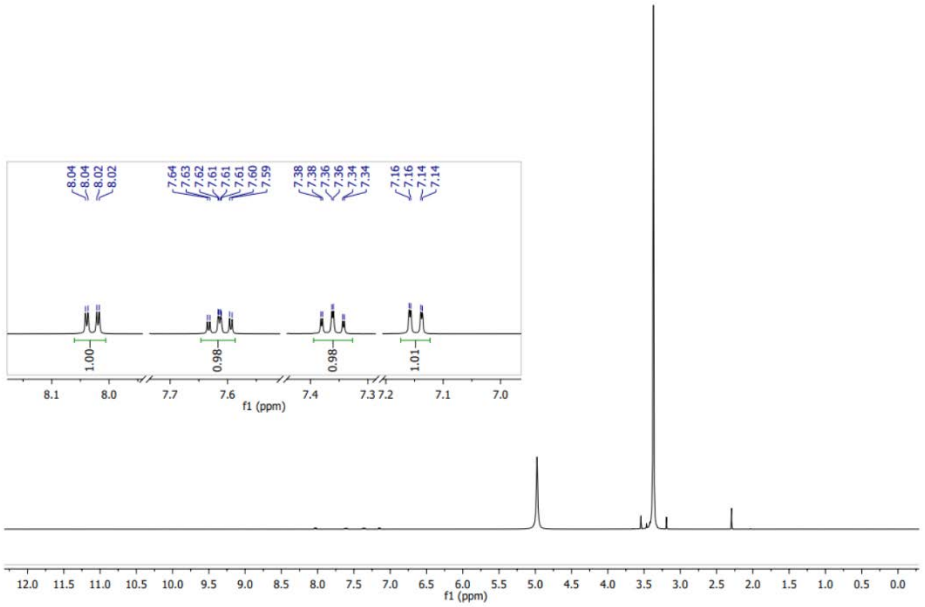

Figure 2. ^1H NMR spectrum (in MeOH) of the purified ASA utilized for the study of the transesterification-esterification reaction catalyzed by SiO_2-SO_3H.

The tandem transesterification-esterification reaction was tested under different conditions using a microwave reactor as a heating source. Triplicate results (entries 8, 8 'and 8'') were obtained to evaluate reproducibility using the best reaction condition obtained (Table 1).

Table 1. The experimental results obtained for the transesterification-esterification of ASA.

Entry[(a)]	MeOH (mL)	SiO_2-SO_3H catalyst (%)	Time (min.)	Temperature (°C)	Yield (%)
1	1.0	10	10	120	60
2	1.0	10	20	120	56
3	1.0	20	5	120	23
4	0.5	20	10	120	52
5	1.0	20	10	120	62
6	1.0	20	20	120	54
7	2.0	20	20	120	37
8	1.0	20	40	120	94
8’	1.0	20	40	120	93
8’’	1.0	20	40	120	93

(a) MW: Anton-Parr Monowave 300 microwave reaction, non-inert conditions, 850W power.

In a reaction medium containing SiO_2-SO_3H, the acetate ester group of ASA is initially transesterified to form methyl acetate and SA (methanolysis). Under the same conditions, the carboxylic acid group of the resulting salicylic acid undergoes Fischer type esterification to form MS. The procedure gives MS in good yield (94%) in 40 min in a microwave-irradiated process (850 W) at atmospheric pressure and 120 °C in high purity, as determined by ^1H NMR (Figure 3).

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The tandem transesterification-esterification reaction was confirmed by monitoring the reaction process by gas chromatography from the first minutes of the reaction. We detected the total conversion of ASA into SA (89.10% yield). The attack of MeOH on the acetyl group to yield free SA (ASA + MeOH → SA + AcOMe) is normally catalyzed intramolecularly by the ortho-carboxylate group [26]. However, under the conditions utilized in this study, 25.75% conversion of ASA to SA in the absence of the solid catalyst was observed, but no MS was formed with microwave irradiation at 120 °C during one minute. The transesterification reaction is totally favored by the catalysis by SiO_2-SO_3H, and it is complete within one minute.

The esterification reaction (SA + MeOH → MS) catalyzed by the SiO_2-SO_3H also initiates within one minute, and MS (10.90% yield) is formed. After five minutes of reaction, the reaction medium consisted of SA (80.00% yield) and MS (20.00% yield). At the end of 40 minutes of reaction, the reaction medium contained SA (6.33% yield) and MS (93.67% yield). At this point, the reaction was terminated.

Kirumakki et al. [13] reported that the conventional esterification reaction using acid and alcohol results in the formation of water as a co-product and leads to leaching of active sites in many liquid phase reactions, which decreases the activity of the catalyst. As can be seen from the yield (94%) obtained in the MS synthesis, these drawbacks were minimized when SiO_2-SO_3H was used as the catalyst.

The MS product was analyzed by ^{13}C or ^{1}H NMR spectroscopy, and the spectra were in accordance with the structure.

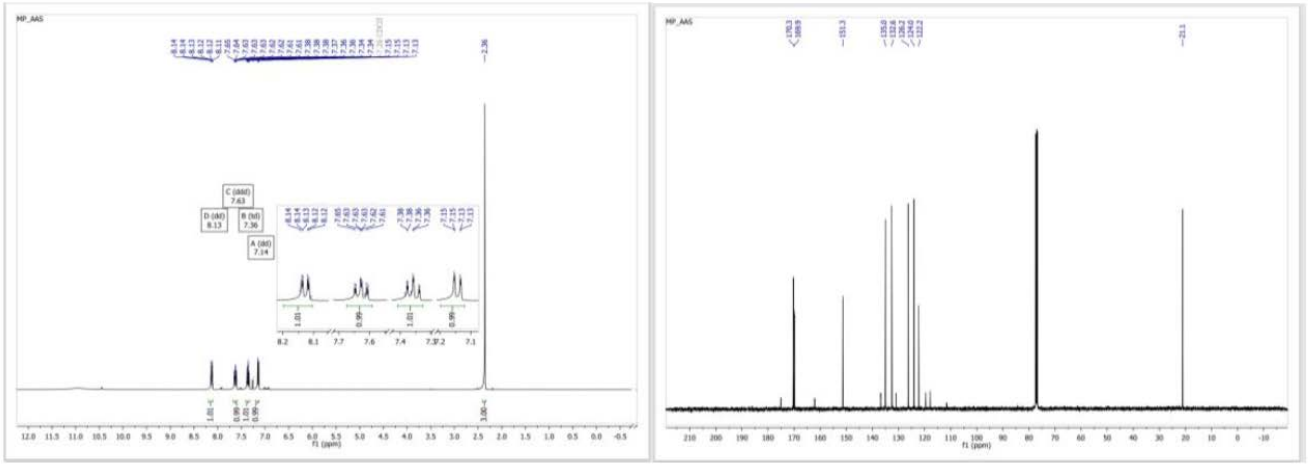

Figure 3. ^{13}C and ^{1}H NMR spectra of a sample of MS obtained from the SiO_2-SO_3H-catalyzed transesterification-esterification of ASA.

Green and efficiency are two principal issues in this tandem process. These issues can be characterized in terms of atom economy, Green Chemistry Principle 2 [28]. In this work, the two reactions with no byproducts are desirable, and clean and reliable reactions must be employed when planning the synthesis of MS. Step economy is another fundamental aspect to consider when minimizing the number of reaction steps to MS. Reducing the number of steps reduces the length, cost, development time, execution time, effort, number of separation methods, and environmental impact of MS synthesis. Step economy was clearly influenced by selecting the right reaction method and sequence to allow for an optimal increase in target-relevant complexity. In this process, two reactions were performed in the same microwave oven reactor for 40 minutes. When two reactions are conducted in a single reactor, without isolating or purifying the intermediates (SA), for greenness and practicability in synthesizing MS.

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4. Conclusions

The use of microwave irradiation decreased the time required for the production of MS by transesterification-esterification of ASA with MeOH at 120 °C by a factor of four in the presence of the SiO_2-SO_3H catalyst, and a 94% conversion and 100% selectivity were observed. The product MS is extensively used in the food and pharmacy industries because of its antiinflammatory activity.

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