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Synthesis of Alkyl Levulinates from α-Angelica Lactone Using Methanesulfonic Acid as a Catalyst: A Sustainable and Solvent-Free Route

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Abstract: In the present study, a green and readily effective route is presented, using for the first time, methanesulfonic acid (MSA) as a catalyst to produce alkyl levulinates (ALs) via the addition of alcohols to α-angelica lactone (α-AL). A smooth procedure was developed that resulted in the production of high-purity ALs, with complete conversions and high yields (99.1–99.8%), within 20 to 60 min of reaction in the presence of 0.5 mol% MSA. The reactions were carried out solvent-free, at room temperature, and in atmospheric air. Reaction conditions were optimized, and equimolar amounts of alcohol reagent were used. This work presents the main advantages of the use of a catalyst (MSA) that is low cost, easily biodegradable, and does not release toxic gases into the environment, but has an acidic strength comparable to that of other mineral acids. Therefore, this study proves the remarkable efficiency of MSA as a catalyst in the synthesis of ALs through an economically and environmentally favorable route.

Keywords: alkyl levulinates; α-angelica lactone; solvent-free synthesis; sustainable synthesis

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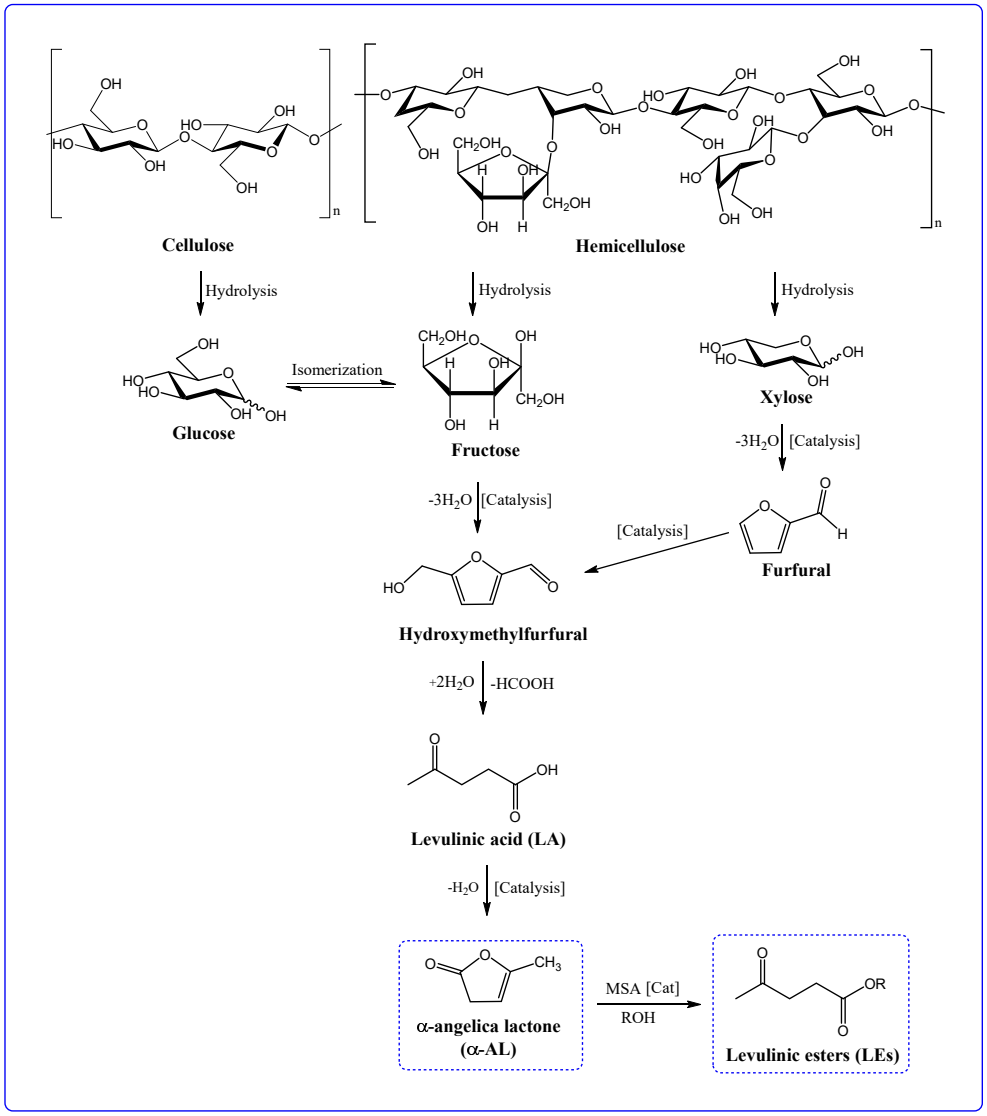
1. Introduction

The global consumption of materials and energy from fossil fuels has increased over the years [1]. Renewable and sustainably sourced materials have been seen as a favorable alternative for slowing environmental degradation [2]. Currently, with the emergence of new environmental regulations that favorably move towards the concept of circular economy, whose scope prioritizes the reduction in waste production and low energy consumption, it has been challenging for both industry and science to form a widespread consensus on the importance of a sustainable economy [3]. Therefore, investigations have focused on converting materials into products with high added value and in doing so, provide the possibility of eliminating waste [4], including lignocellulosic residues, such as forest residues [5].

In this context, the valorization of biomass, mainly lignocellulosic biomass from wood residues [6] and its derivatives [7], has become an alternative to the use of fossil resources since they can be used for the production of energy and materials with high added value; therefore, they meet one of the principles of green chemistry, which is the production of raw materials from renewable sources [8].

Levulinic esters (levulinates, LEs) are chemical products with high added value, and since they are derived from biomass, they can be considered of sustainable origin [9]. LEs have a high potential that allows them to be transformed into various other materials. For example, they can be used in the organic synthesis of pharmaceutical products, in the production of fragrances, and as flavoring agents [10].

Alkyl levulinates (ALs) (Scheme 1) are derived from lignocellulosic biomass, which have been frequently used as precursors in the production of biofuels and additives for existing fuels in agroindustry, as well as in the production of resins, plasticizers, and solvents [11,12].



Scheme 1. Proposed synthetic pathways to produce ALs from lignocellulosic biomass derivatives.

ALs are a class of LEs that can be obtained through catalytic levulinic acid (LA) esterification with alkyl alcohols [10]. Still, these reactions have the drawback of being dependent on thermodynamic equilibrium [13], requiring a high excess of alcohol so that there is a significant change in the equilibrium, which can efficiently drive towards forming esters from LA. On the other hand, the main consequence of excess alcohol in the LA esterification reactions is the decrease in the yield of the ALs [14].

Lignocellulosic biomass can be used for direct conversion into ALs via catalysis with ionic liquids [15], via alcoholysis using acid catalysts [16], or via acid hydrolysis [17]. However, these routes have limitations such as a low yield of products and low economy throughout the process. In addition, the presence of lignin can affect the conversion of lignocellulosic materials into ALs [18]. A pretreatment of the biomass is often needed [19]. Thus, the production of LEs from lignocellulosic biomass depends on approaches involving several reaction steps.

As an alternative to using raw biomass, ALs can be produced directly from sugars, such as from fructose [20,21] and xylose [22] via the conversion of furfural to hydroxymethylfurfural [23] and glucose [20,24]. However, this route also has the drawback of requiring reactions containing several steps to reach the final product, such as dehydration, alcoholysis, and esterification reactions [20]. Thus, the use of this pathway for the formation of ALs depends on the high consumption of reagents and solvents, making the production process unfeasible.

Finally, ALs can be readily obtained from α-angelica lactone (5-methyl-2(3H)-furanone, α-AL) by catalytic processes via homogeneous [25,26] and heterogeneous acid catalysis [27,28], via enzymatic catalysis [29], or through acid catalysis with ionic liquids [26].

The α-AL can be readily produced from levulinic acid (LA) by an intramolecular condensation reaction followed by dehydration [30]. Moreover, α-AL is a biologically based molecule arising from forming C-C bonds between intermediates resulting from the depolymerization of biomass [31].

Currently, there are few studies on the production of ALs from reactions involving the addition of alcohols to α-AL. However, according to the literature, the use of α-AL can be seen as a promising alternative to the use of other raw materials, such as LA [13], sugars derived from biomass [20,22,24] (fructose, xylose or glucose), or crude biomass [16]. Additionally, the formation of ALs via α-AL can overcome the equilibrium problems caused by the direct esterification of LA.

Generally, the synthesis of ALs involves the use of catalysts that contain materials that are toxic to the environment, such as metals [26] or halogenated acids [27], which are necessary to transform them into heterogeneous and recyclable catalysts. However, preparing these heterogeneous catalysts may involve reactions in several stages and the costly use of reagents and solvents [26,28,32], making the process economically and environmentally unfeasible. In this sense, the need to develop studies on using homogeneous, non-toxic, and environmentally friendly catalysts becomes relevant.

Methanesulfonic acid (MSA) has been frequently used in organic synthesis, mainly because it is considered a green acid since it is readily biodegradable [32–35], it does not release toxic gases and its degradation forms sulfate and CO_2 [35]. Furthermore, it is commercially available and has a low cost relative to other mineral acids.

MSA is a strong Brönsted acid (pKa: −1.9) and non-volatile. Therefore, it is highly reactive, ionizes in aqueous solutions of 0.1 M, and appears as a liquid at room temperature [36,37]. Thus, MSA is an acid that has comparable acid strength to strong mineral acids, such as sulfuric acid (H_2SO_4), hydrochloric acid (HCl), and nitric acid (HNO_3), but has the advantage of being much less toxic and corrosive than these acids [38,39].

In this sense, the present study presents, for the first time, the development of an investigation of the catalytic activity of MSA for the production of ALs from the addition of alcohols to α-AL. In this study, methyl levulinate (ML), ethyl levulinate (EL), propyl levulinate (PrL), and butyl levulinate (BL) were produced with a high degree of purity and excellent yields (>99%).

2. Materials and Methods

2.1. Materials

All reagents and solvents used (α-angelica lactone, alcohols, methanesulfonic acid, dichloromethane, or hexane) are analytical grade, with a minimum purity of 99.0%, and were purchased from Sigma-Aldrich, Alfa Aesar, and Acros. All chemicals were used without further purification. After product purification, a BUCHI V-850 rotary evaporator was used to concentrate the solutions.

2.2. General Procedure for the Synthesis of Alkyl Levulinates (ALs)

A round bottom flask (50 mL) was charged with α-angelica lactone (55.6 mmol), alcohol (55.6 mmol; methanol, ethanol, 1-propanol, or 1-butanol), and the catalyst methanesulfonic acid (0.28 mmol, 0.5 mol%). The reaction mixture was stirred at 300 rpm under

magnetic stirring at room temperature. After completion of the reaction, the post-reaction mixture was extracted in dichloromethane–water (1: 1; 3 × 2 mL), the organic phase was dried over anhydrous $MgSO_4$, the solvent was evaporated in a rotary evaporator (40 °C), and alkyl levulinates were obtained with purity > 99% and yields > 99.1%.

2.3. Characterization of Alkyl Levulinates (ALs)

Alkyl levulinates were characterized by nuclear magnetic resonance (NMR) and Fourier transformed infrared (FTIR-ATR) (Supplementary Materials). ^{1}H NMR (400.13 MHz) and ^{13}C NMR APT (100.62 MHz) spectra were recorded using a Bruker Avance 400 MHz NMR spectrometer at 25 °C. Samples of pure ALs (30 mg) were dissolved in 0.6 mL of deuterated chloroform. FTIR-ATR analysis was performed on a Spectrum Two-Perkin Elmer spectrometer. The spectra were captured from 600 to 4000 cm^{-1} and analyzed using Perkin Elmer–Spectrum IR software (version 10.3).

Methyl Levulinate (ML). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 3.48 (s, 3H), 2.59 (t, *J* = 6.5 Hz, 2H), 2.39 (t, *J* = 6.5 Hz, 2H), and 2.01 (s, 3H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ (ppm): 206.42, 172.91, 51.41, 37.60, 29.47, and 27.44. FTIR (ATR, cm^{-1}): 2955, 2910, 1714, 1359, and 1156.

Ethyl Levulinate (EL). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 3.96 (q, *J* = 7.1 Hz, 2H), 2.60 (t, *J* = 6.5 Hz, 2H), 2.39 (t, *J* = 6.5 Hz, 2H), 2.03 (s, 3H), and 1.09 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ (ppm): 206.49, 172.52, 60.35, 37.71, 29.62, 27.82, and 13.96. FTIR (ATR, cm^{-1}): 2983, 2908, 1718, 1362, and 1155.

Propyl levulinate (PrL). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.92 (t, *J* = 6.7 Hz, 2H), 2.65 (t, *J* = 6.5 Hz, 2H), 2.47 (t, *J* = 6.6 Hz, 2H), 2.09 (s, 3H), 1.54 (qt, *J* = 7.1 Hz, *J* = 6.7 Hz, 2H), and 0.83 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ (ppm): 206.59, 172.70, 66.10, 37.84, 29.72, 27.89, 21.85, and 10.24. FTIR (ATR, cm^{-1}): 2971, 2873, 1716, 1355, and 1154.

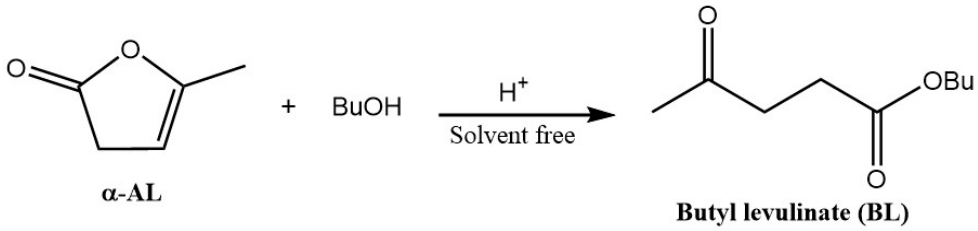
Butyl levulinate (BL). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 4.01 (t, *J* = 6.7 Hz, 2H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.51 (t, *J* = 6.6 Hz, 2H), 2.13 (s, 3H), 1.54 (dt, *J* = 6.8 Hz, *J* = 7.5 Hz, 2H), 1.31 (qt, *J* = 7.4 Hz, *J* = 7.5 Hz, 2H), and 0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ (ppm): 206.71, 172.83, 64.52, 37.96, 30.62, 29.85, 28.01, 19.10, and 13.69. FTIR (ATR, cm^{-1}): 2961, 2872, 1717, 1357, and 1157.

3. Results

In the present study, we present a green route for the synthesis of alkyl levulinates (ALs) from α-AL as raw material in the presence of MSA as an acid catalyst, using the following alcohols as substrates (molar ratio: 1:1): methanol (MeOH), ethanol (EtOH), butanol (BuOH), or propanol (PrOH), at room temperature and in solvent-free reactions (Table 1). We report in this study the catalytic performance of MSA, used for the first time as a homogeneous catalyst for the conversion of α-AL into ALs, which were obtained with high purity and quantitative yields (99.1–99.8%). The structure and high purity of the ALs were confirmed by an analysis with NMR spectroscopy (^{1}H and ^{13}C) and Fourier transformed infrared (FTIR-ATR).

For the initial experiments, the reaction conditions involving the catalyst loading (MSA) necessary for the conversion of α-AL into ALs were tested. Secondly, after analyzing the MSA loading optimization results, the reaction times were optimized according to the yield obtained for the isolated products (ALs).

Table 1. The optimization of reaction conditions [1] for the synthesis of BL from adding BuOH to α-AL, using MSA as a catalyst.



α-AL Butyl levulinate (BL)

Entry	MSA Loading (mol%)	Time (min)	Yield (%)
1	0.1	30	58.5
2	0.1	60	65.3
3	0.1	90	74.5
4	0.1	120	85.2
5	0.1	150	91.5
6	0.1	180	99.1
7	0.2	30	65.5
8	0.2	60	70.1
9	0.2	90	81.5
10	0.2	120	92.5
11	0.2	150	99.3
12	0.3	20	67.3
13	0.3	30	69.5
14	0.3	60	78.4
15	0.3	90	85.3
16	0.3	120	99.5
17	0.4	10	60.3
18	0.4	20	72.5
19	0.4	30	75.5
20	0.4	60	82.5
21	0.4	90	99.6
22	0.5	10	66.5
23	0.5	20	79.6
24	0.5	30	83.4
25	0.5	40	89.5
26	0.5	60	99.8

[1] Conditions: α-AL (55.6 mmol); BuOH (55.6 mmol); solvent free; rotation at 300 rpm; room temperature.

3.1. Influence of MSA Catalytic Activity

Initially, several experiments were carried out in the presence of different amounts of MSA catalyst (0.1–0.5 mol%) to observe the influence exerted by MSA on the conversion of α-AL into ALs and the yield of ALs after their isolation. For the first test, butanol (BuOH) was chosen, which was used in equimolar amounts (1:1) concerning α-AL. These first reactions led to obtaining butyl levulinate (BL) with high yields (Table 1).

When 0.5 mol% MSA was used, the yield of BL after its isolation was 99.8% in only 60 min of reaction (Table 1, entry 26). However, when 0.1 mol% MSA was used, it took 180 min to reach a 99.1% yield for the BL (Table 1, entry 6). Therefore, it is observed that it was possible to obtain a yield above 99% for BL, both for the maximum loading (0.5 mol%) of the catalyst (MSA) as well as for the minimum loading of MSA (0.1 mol%) (Table 1).

Table 1 shows that for the use of 0.4 mol% MSA (Table 1, entry 21), it took 90 min to obtain BL with a yield of 99.6%. However, when 0.3 mol% MSA was used, it took 120 min to produce BL with a 99.5% yield (Table 1, entry 16). However, using MSA at 0.2 mol% promoted the formation of BL with a quantitative yield of 99.3% (Table 1, entry 11) after 150 min of reaction.

Through some experiments carried out with low loadings of MSA (Table 1, entries 2, 8, and 14), it was possible to verify that even lower loadings of MSA (0.1, 0.2, and 0.3 mol%)

efficiently catalyzed the additions of BuOH to α-AL, leading to the formation of BL with good yields above 65.3% (Table 1, entry 2).

Reasonable yields continued to be observed when optimizing BL synthesis. In the tests in Table 1 (entries 1, 7, 13, 19, and 24), all reactions conducted for 30 min showed yields above 58% for BL, with an emphasis on the test referred to in entry 24 (Table 1), which presented a good yield of 83.4% when 0.5 mol% MSA was used.

Regarding the conversion of α-AL into BL, some assays showed 100% conversion in just 30 min of reaction (Table 1, entries 19 and 24), using 0.4 and 0.5 mol% MSA. However, 0.3 mol% MSA (Table 1, entry 16) promoted the complete conversion of α-AL to BL after 60 min of reaction. However, for tests performed with a loading of 0.1 mol% MSA (Table 1, entry 6), it took only 180 min to reach 100% α-AL conversion.

The results obtained in the present work, which are related to the conversions of α-AL into BL, can be compared with previous studies reported in the literature. For example, it was reported that using acid catalysts Amberlyst 36 [25] promoted complete conversions of α-AL to BL after 240 min of reaction, yielding up to 94.0% under heating conditions (75 °C). However, compared to using these two catalysts, we proved in the present study that MSA has the advantage of promoting complete α-AL conversions into BL in reactions conducted at room temperature. These results show that MSA has superior catalytic capacity than Amberlyst 36, presenting higher yields.

The use of MSA as a catalyst in the BL formation reactions revealed that this catalyst has high catalytic activity since the complete conversion of α-AL was observed after a short reaction time (Table 1). Additionally, these conversions were confirmed by NMR analysis (^{1}H and ^{13}C).

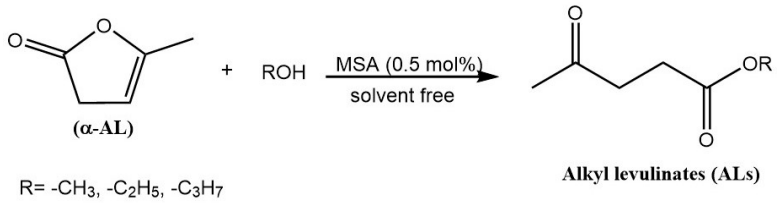
It has been reported in studies involving the formation of BL via the addition reaction of BuOH to α-AL that in the first step of the reaction, a *pseudo*-butyl levulinate (*pseudo*-BL) can be formed, which subsequently undergoes a transesterification to form BL [25]. The transition from *pseudo*-BL to BL has been considered the limiting step of the reaction [26] and, therefore, requires sufficient acidic strength to overcome the transesterification barrier. Thus, catalysts with strong acidic sites have an additional advantage, as there seems to be a dependence between the reactivity and the acid strength of the catalytic system in forming ALs by adding alcohols to α-AL [13]. In this sense, MSA is favorable for promoting complete conversions faster; since it is a strong and highly reactive Brönsted acid [36,37], it has enough acidic strength to overcome the transesterification stage, promoting complete conversions more efficiently.

Acid strength is also related to BL yield. In a study carried out by Yi et al. [13] in which choline-exchanged heteropoly acid catalysts were used to produce BL from α-AL, the Brönsted acid strength of these catalysts was measured, and it was reported that the heteropoly acids that had higher levels of acid strength led to the production of BL with higher yields.

By analyzing the results obtained in the present study, we found an increase in the BL yield as a function of the increase in the loading of the MSA catalyst (Table 1). Therefore, these results align with previous studies reported in the literature since the increase in the acid strength of the reaction medium through the acidic strength of the catalyst can also lead to an increase in the BL yield [13,25].

After confirming the efficiency of the synthetic route that we developed for the production of BL from α-AL using MSA as a catalyst and after optimization regarding the catalyst loading, it was verified that the MSA loading at 0.5 mol% promoted the best conversion (100%) of α-AL and the best yield (99.8%, Table 1, entry 26) for BL after isolation. In this context, the following steps consisted of applying the method developed in addition to reactions to α-AL catalyzed by MSA (0.5 mol%), using methanol (MeOH), ethanol (EtOH), and propanol (PrOH) as reactants; the results obtained, and the respective yields of the isolated compounds, are shown in Table 2.

Table 2. Synthesis of ALs via the addition of alcohols to α-AL in the presence of the MSA catalyst (0.5 mol%) [1].



(α-AL)

R= -CH_3, -C_2H_5, -C_3H_7

Alkyl levulinates (ALs)

Entry	Alcohol	Time (min)	Yield (%)
1	MeOH	5	62.3
2	MeOH	10 [2]	76.5 [2]
3	MeOH	15	85.4
4	MeOH	20	99.1
5	EtOH	5	63.5
6	EtOH	10 [2]	78.2 [2]
7	EtOH	20	86.5
8	EtOH	30	99.3
9	PrOH	10	66.1
10	PrOH	20 [2]	75.3 [2]
11	PrOH	30	84.5
12	PrOH	40	99.7

[1] General conditions: α-AL (55.6 mmol); MeOH (55.6 mmol); EtOH (55.6 mmol); PrOH (55.6 mmol); solvent free; rotation at 300 rpm; room temperature. [2] Complete conversion of α-AL.

The experiments carried out with different alcohols (MeOH, EtOH, and PrOH) showed that in all reaction times, it was possible to obtain ALs (Table 2). In this sense, the most relevant results were observed in the production reactions of methyl levulinate (ML) (Table 2, entry 2) and ethyl levulinate (EL) (Table 2, entry 6), where the complete conversion of α-AL occurred in just 10 min of reaction at room temperature. Regarding the production of propyl levulinate (PrL) (Table 2, entry 10), the complete conversion of α-AL was observed in only 20 min of reaction.

Excellent yields were observed using the MeOH, EtOH, and PrOH alcohols in the presence of 0.5 mol% MSA (Table 2). ML was obtained after 20 min of reaction with an isolated product yield of 99.1% (Table 2, entry 4). EL was produced with a 99.3% yield (Table 2, entry 8) after 30 min of reaction. PrL, on the other hand, was obtained with a yield of 99.7% (Table 2, entry 12) after 40 min of reaction.

Referring to the reactions with α-AL that presented lower yields due to the shorter reaction times (Tables 1 and 2), it was observed that the use of the optimized MSA loading (0.5 mol%) promoted a yield of 66.5% for BL (Table 1, entry 22) and 66.1% for PrL (Table 2, entry 9) after 10 min of reaction. However, for ML and EL (Table 2, inputs 1 and 5), the yield was 62.3% and 63.5%, respectively, after 5 min of reaction. Therefore, it can be suggested that with the use of lower MSA loadings (Tables 1 and 2), more reaction time may be needed to overcome the *pseudo*-AL transesterification step, mainly because this has been considered as the limiting step in the addition reactions of alcohols to α-AL [25]. Blank experiments were carried out with all alcohols used, and it was verified that there were no reactions between α-AL and alcohol in the absence of the catalyst.

A behavior similar to BL synthesis was observed in the ML, EL, and PrL syntheses since the MSA catalyst presented a high reactivity potential in the presence of the different alcohols (Table 2). After the addition of alcohols and just after the first minutes of the reactions, the total conversion of α-AL and the formation of the desired products (ALs) was observed, which was confirmed by NMR analysis (^{1}H and ^{13}C).

In this sense, the results obtained through the experiments related to adding different alcohols to α-AL (Table 2) revealed a tendency in the behavior of the alkyl chains. Thus, concerning reactivity, it was possible to observe a trend involving chain linearity according

to the following order: methanol > ethanol > propanol > butanol. Therefore, it was observed that there is a correlation between the conversion time of α-AL into ALs and the structures of the alkyl chains of the alcohols used as substrate in the addition reactions.

This trend relative to the conversion of α-AL as a function of the alkyl chains of the alcohols used in the addition reactions (Table 2) is favorably comparable with studies reported in the literature. For example, the use of Amberlyst 36 [25] promoted an increase in the conversion of α-AL depending on the nature of the alkyl chain of alcohols, following the following order: ethanol > butanol > octanol. Choline-exchanged heteropoly acids [13] were used as catalysts in alcohol addition reactions to α-AL, and it was reported that there was a decrease in the reaction rate according to the following order: methanol > ethanol > butanol. When ionic liquids containing trifloaluminate anions [26] were used as catalysts in the synthesis of ALs from α-AL, it was reported that there was a trend in reactivity depending on the alkyl chain of the alcohols used as substrates in the addition reactions, in the following order: ethanol > 2-methyl-1-propanol > 2-ethyl-1-hexanol. Therefore, this observed trend shows that the steric hindrance of the alkyl chain may be a relevant factor concerning the reactivity of alcohols in addition to reactions involving α-AL as a raw material and may even interfere with the speed of reactions.

Interestingly, for the BL (Table 1) and all the ALs obtained and described in Table 2 (ML, EL, and PrL), a clear trend towards an increase in yield as a function of reaction time was observed. In this sense, tests were carried out with longer reaction times for all alcohols (MeOH, EtOH, PrOH, and BuOH) used as substrates in the addition reactions to α-AL in the presence of 0.5 mol% MSA (Figure 1). The results of these tests showed that the yield increased up to a time limit and, after that time limit, it remained unchanged. This suggests that the addition reactions are moving towards an equilibrium point. Thus, in the formation of ML, the reactional equilibrium was observed after 20 min of reaction (Figure 1a), for EL, after 30 min (Figure 1b), for PrL, after 40 min (Figure 1c) and, for BL, the equilibrium was observed after 60 min of reaction (Figure 1d).

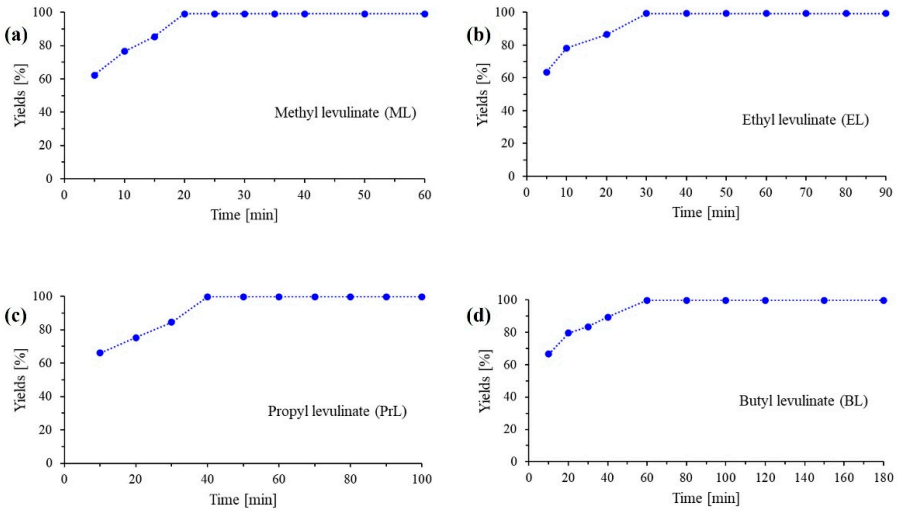


Figure 1. Synthesis of ALs from α-AL using different alcohols as substrates in addition reactions. (**a**) Methyl levulinate; (**b**) Ethyl levulinate; (**c**) Propyl levulinate; (**d**) Butyl levulinate. General conditions: α-AL (55.6 mmol); MeOH (55.6 mmol); EtOH (55.6 mmol); PrOH (55.6 mmol); BuOH (55.6 mmol); MSA (0.5 mol%); solvent free; rotation at 300 rpm; room temperature.

When comparing the results obtained in the present work with data from the existing literature, it becomes evident that the synthesis route that we proposed for the production of Als in the presence of MSA as the catalyst is more effective, economical, and presents better yields, compared to the use of other catalysts reported in the literature.

Over the last 20 years, few studies have been reported on the use of alcohol addition reactions to α-AL to produce ALs. Concerning catalytic activity, it has been reported that

acid catalysts are more effective than bases [40,41]. In this sense, Manzer et al. [41] reported in their study that the use of the Amberlyst 15 ion exchange resin promoted the formation of BL with a yield of 98% after 60 min of reaction, using excess alcohol (ratio: 1:3), under high temperatures (100 °C), and under a nitrogen atmosphere. On the other hand, in another study by Manzer et al. [40], it was reported that the use of Dabco as a base catalyst led to the formation of BL with only a yield of 58%.

Regarding the production of BL from α-AL, using MSA (0.5 mol%) as a catalyst promoted its obtention with a 99.8% yield after 60 min of reaction without a solvent at room temperature and under atmospheric air. Amberlyst 36 was used by Al-Shaal et al. [25] in addition to the reactions of BuOH to α-AL; it took 240 min at 75 °C and an inert gas atmosphere to reach a yield of 94.0% for BL. Yi et al. [13] used a catalytic system containing choline-exchanged heteropoly acids to produce BL from α-AL, but the maximum BL yield was 79.4% after 60 min of reaction at 75 °C and in an open system. In the study by Onkarappa et al., [27] a catalytic system composed of perchloric acid supported on silica ($HClO_4$-SiO_2) promoted the formation of BL with yields of 94% after 120 min. However, although the product (BL) was obtained through a solvent-free reaction, an excess of alcohol was used in the reactions. Szelwicka et al. [29] reported the use of enzyme catalysis containing lipase B from *Candida antarctica* to produce BL with 97% yield after 120 min at 20 °C, but the reactions were also conducted using an excess of alcohol (molar ratio: 1:2 α-AL/BuOH).

When ionic liquid catalysts containing trifloaluminate anions (0.1 mol%) [26] were used as catalysts, BL was produced with over a 99% yield after 60 min. However, the BL formation reactions were conducted under heating conditions of 60 °C. In addition, the preparation of ionic liquids with trifloaluminate anions requires the use of procedures with an increased consumption of reagents and solvents, as well as the use of equipment whose maintenance has a high cost, such as the use of a glovebox. Therefore, using ionic liquids composed of trifloaluminate anions is neither environmentally nor industrially viable.

Ciptonugroho et al. [28] recently reported using catalysts with different tungsten loadings (WO_x/ZrO_2) to produce BL from α-AL. However, 5% of the catalyst loading (WO_3/ZrO_2, 15 wt.%) to the BL yield was only 48% after 360 min of reaction at 75 °C. In this sense, it is observed that the reactions of the addition of alcohols to α-AL conducted in the presence of catalysts containing metallic oxides (WO_x/ZrO_2) require a longer duration and higher temperatures to reach higher yields since said catalysts containing tungsten do not have acid sites with sufficient strength to overcome the transesterification step of the *pseudo*-BL, which has been reported as an intermediate of the BL formation reaction.

Concerning the results presented here, which are related to ML, EL, and PrL, their yields can be compared with studies previously reported in the literature. In the present work, the use of MSA (0.5 mol%) as a catalyst in alcohol addition reactions to α-AL promoted the formation of ALs with quantitative yields, namely 99.1% for ML (Table 2, entry 4) after 20 min of reaction, 99.3% for EL (Table 2, entry 8) after 30 min, and 99.7% for PrL (Table 2, entry 12) after 40 min, with reactions at room temperature and under air atmospheric. However, when the Amberlyst 36 catalyst was used by Al-Shaal et al. [25], the yield for EL was 91.3% after 180 min at 75 °C. Now, using catalysts containing choline-exchanged heteropolyacids [13], in reactions conducted at 75 °C for 60 min, resulted in the formation of ALs with a yield of 90.2% for ML and 87.9% for EL.

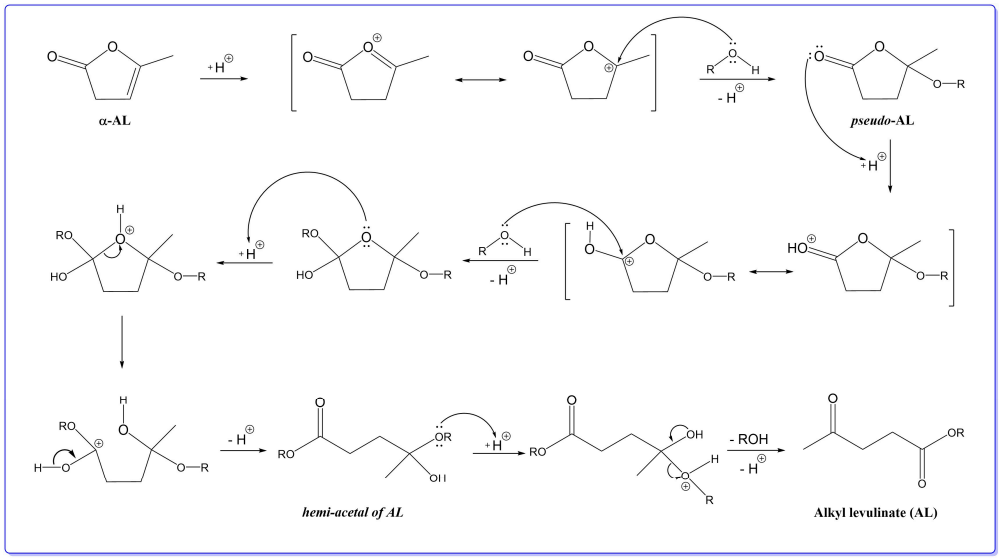
When perchloric acid supported on silica ($HClO_4$-SiO_2) [27] was used to produce ALs from α-AL, the yield shown for ML and EL was 91%, and for PrL, it was 92% after 120 min of reaction at 90 °C. However, using ionic liquids containing trifloaluminate anions (0.1 mol%) [26] promoted the formation of EL with a yield above 99% after 15 min, but the reactions were conducted at 60 °C. Finally, the enzymatic catalytic system involving the use of lipase B from *Candida antarctica* [29] led to the formation of EL with a yield of 85% and of PrL with a yield of 96%, after 120 min at 20 °C, but with the use of excess alcohol.

Therefore, considering the production of ML, EL, PrL, and BL, the method we developed for their production using MSA is readily more effective than other methods reported

in the literature [25,27], and those that use other acid catalysts, including homogeneous catalysts such as ionic liquids containing trifloaluminate anions [25]. Mainly because in the protocol that we present, the reaction uses a solvent-free reaction and an inexpensive, biodegradable, non-toxic, and environmentally benign catalyst [42], allowing the synthesis of ALs to be reproducible on a large scale and even industrially.

3.2. Mechanistic Considerations

Since the first investigations on the production of ALs from α-AL via acid catalysis [25,43], the formation of a *pseudo*-AL (Scheme 2) has been reported as a reaction intermediate, and its subsequent rearrangement may finally lead to the formation of ALs as a final product. In this sense, the presence of *pseudo*-AL as an intermediate was initially reported by Langlois et al. [44] when using hydrochloric acid (HCl) as a catalyst to form ALs using α-AL as a raw material. Thus, according to the literature reported [25,26], chemical transformations are irreversible except for transition states.



Scheme 2. Proposed mechanism for the synthesis of ALs from α-AL in the presence of MSA as the catalyst.

In the study by Al-Shaal et al. [25], in which Amberlyst 36 was used as a catalyst to produce ALs, the formation of *pseudo*-AL was reported as a reaction intermediate, but also the presence of other byproducts, such as the traces of levulinic acid (LA) and small amounts of water even in inert atmosphere conditions. It was also reported that in some cases, the isomerization of α-AL into β-AL, which upon suffering the opening of its ring, can induce the formation of penta-2,4-dienoic acid, which in turn, in the presence of an alcohol as substrate, can undergo esterification with the subsequent formation of water [25].

When choline-exchanged heteropoly acids were used by Yi et al. [13] to produce BL from α-AL, the presence of considerable amounts of *pseudo*-BL was also reported, especially in reactions conducted in the presence of heteropoly acids with low proton content. These data suggest that catalyst acid strength may strongly influence the conversion of *pseudo*-AL to ALs.

In the AL formation reactions, the conversion of α-AL into *pseudo*-AL has been described as a fast step, but its transesterification with the subsequent formation of ALs has been considered as the rate-limiting step in the reaction [25,26,44]. In this sense, studies indicate that the transesterification step may be strongly related to the strength of the acid of the catalyst and the nucleophilicity of the alkoxide group of alcohol [13,25,28], respectively.

In this context, based on the previous studies, we propose a reaction mechanism for the formation of ALs from the addition of alcohols to α-AL in the presence of MSA as a catalyst. As shown in Scheme 2, α-AL initially undergoes protonation by the MSA acid

catalyst, leading to a stabilized carbocation, which subsequently undergoes nucleophilic alcohol addition to form a *pseudo*-AL. This, in turn, undergoes a protonation in the ester moiety, allowing, once again, another nucleophilic addition of the alcohol and the subsequent opening of its ring, forming a hemiacetal of the alkyl levulinate [25,26]. Finally, the elimination of the hemiacetal alcohol occurs to form alkyl levulinate.

4. Conclusions

In summary, a green and efficient route was developed in this work for the production of alkyl levulinates (ALs) from α-angelica lactone (α-AL) in the presence of methanesulfonic acid (MSA) (0.5 mol%) as the catalyst, using alcohols as substrates in equimolar amounts via solvent-free reactions and at room temperature.

This study reported the catalytic activity of MSA for the production of a set of ALs, namely methyl levulinate (ML), ethyl levulinate (EL), propyl levulinate (PrL), and butyl levulinate (BL), which were produced with yields between 99.1% to 99.8%. In this sense, reaction conditions such as catalyst loading (MSA) and reaction time effects were optimized.

The developed protocol has the advantages of high yield (>99%) and a high purity of the produced ALs. The ecological aspect of the route we developed is demonstrated by carrying out the reactions with an environmentally friendly catalyst in relatively short reaction times, as well as using economical procedures both in the preparation and purification of the ALs without the need for a chromatographic column; thus, this generates economical savings throughout the AL production process, as other purification methods tend to be expensive.

Therefore, the protocol we present may be easily scalable to industrial levels due to the conditions used in addition to the low cost of the raw materials used. Thus, these characteristics make the route we have developed an alternative to the existing ones to produce ALs. Moreover, using MSA has shown to be highly promising for converting α-AL into ALs with complete conversions and quantitative yields through an environmentally friendly protocol.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemengineering8050103/s1. Figure S1: ^{1}H NMR spectrum of methyl levulinate in $CDCl_3$; Figure S2: ^{13}C NMR spectrum of methyl levulinate in $CDCl_3$; Figure S3: FTIR-ATR spectrum of methyl levulinate; Figure S4: ^{1}H NMR spectrum of ethyl levulinate in $CDCl_3$; Figure S5: ^{13}C NMR spectrum of ethyl levulinate in $CDCl_3$; Figure S6: FTIR-ATR spectrum of ethyl levulinate; Figure S7: ^{1}H NMR spectrum of propyl levulinate in $CDCl_3$; Figure S8: ^{13}C NMR spectrum of propyl levulinate in $CDCl_3$; Figure S9: FTIR-ATR spectrum of propyl levulinate; Figure S10: ^{1}H NMR spectrum of butyl levulinate in $CDCl_3$; Figure S11: ^{13}C NMR spectrum of butyl levulinate in $CDCl_3$; and Figure S12: FTIR-ATR spectrum of butyl levulinate.

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