The Preparation of Ethyl Levulinate Facilitated by Flow Processing: The Catalyzed and Uncatalyzed Esterification of Levulinic Acid

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The catalyzed and uncatalyzed preparation of ethyl levulinate from levulinic acid and ethanol is presented. In the case of acid-catalyzed reactions, conditions were optimized in batch using microwave heating and then scaled-up using continuous-flow processing. Both *p*-toluenesulfonic acid and sulfuric acid were used as catalysts, the latter proving most amenable. For the uncatalyzed reactions, all reactions were performed under continuous-flow conditions, using apparatus capable of operating at high temperature and pressure. Optimal conditions for the uncatalyzed process required heating a 3.6-M solution of levulinic acid in ethanol at 270 °C with a residence time of 30 min.

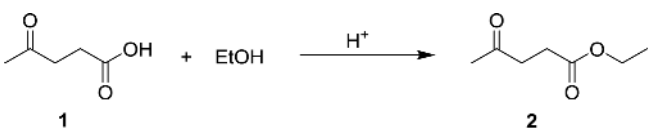
Keywords: esterification, high pressure, biomass

1. Introduction

Levulinic acid (**1**) can be obtained from biomass and converted into a wide range of value-added chemicals [1]. One of these, ethyl levulinate (**2**), is employed in the flavor and fragrance industry [2] and can also be used as a diesel-miscible biofuel at up to 5 wt.% [3]. The esterification of **1** with ethanol proves to be a useful approach to ethyl levulinate (Scheme 1). The esterification reaction has been performed using both homogeneous and heterogeneous acid catalysts [4]. In some cases, **2** can be prepared directly from biomass, albeit in variable yield and purity [5, 6]. Given the interest in **2** and the volume that is generated on an annual basis and the use of flow chemistry for valorization of biomass previously [1, 7], our interest turned to the development of a continuous-flow approach to the esterification of **1**. Our attention focused first on a homogeneous acid-catalyzed esterification approach and then moved to performing the reaction catalyst free. To optimize reaction conditions, we used microwave heating as our method of choice. There is a parallel between microwave irradiation and conventionally heated continuous-flow processing. Both offer the ability to heat reaction mixtures rapidly, safely, and (in most cases) easily. It therefore comes as no surprise that synthetic methods developed on small scale in batch using microwave heating can be scaled-up using conventionally heated flow reactors [8]. When using flow reactors, the rapid heat transfer that is possible means that comparable heating rates can often be obtained regardless of whether the thermal energy comes from a conventional or microwave source. We report our results here.

Using sulfuric acid or *p*-toluenesulfonic acid (PTSA) as the catalyst and employing batch microwave heating, we screened a range of reaction conditions for the conversion of a mixture of levulinic acid and ethanol to ethyl levulinate (Table 1). Working with a **1**-to-ethanol ratio of 1:5 and using 10 mol% PTSA as the catalyst, a conversion of 80% was obtained after heating at 120 °C for 30 min (Table 1, entry 1). Reducing the reaction time to 5 min did not affect the outcome of the reaction (entry 2) and neither did a subsequent halving of the catalyst loading to 5 mol% (entry 3). Lowering the reaction temperature to 100 °C or reducing the catalyst loading to 2.5 mol%, both had a deleterious effect on the conversion to product (entries 4 and 5). However, performing the reaction using a **1**-to-ethanol ratio of 1:10, and at a catalyst loading of 2.5 mol%, complete conversion was attained after heating at 120 °C for 5 min (entry 6). Identical results were obtained when using these optimized conditions but replacing PTSA by sulfuric acid as the catalyst (entry 7).

Scheme 1. Preparation of ethyl levulinate (**2**) from levulinic acid (**1**)



1 **2**

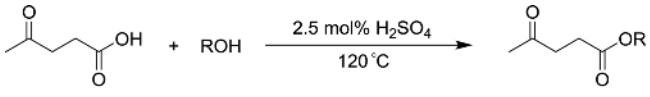
Table 1. Optimization of reaction conditions for the acid-catalyzed esterification of levulinic acid with ethanol[a]

Entry	1:Ethanol ratio	Catalyst	Catalyst loading (mol%)	Temp. (°C)	Time (min)	Conversion (%)
1	1:5	PTSA	10	120	30	80
2	1:5	PTSA	10	120	5	80
3	1:5	PTSA	5	120	5	83
4	1:5	PTSA	5	100	5	60
5	1:5	PTSA	2.5	120	5	60
6	1:10	PTSA	2.5	120	5	100
7	1:10	H_2SO_4	2.5	120	5	100

[a] Reactions were performed in a 10-mL capacity sealed tube with microwave heating on the 8.6 mmol scale (levulinic acid).

With conditions in hand, we moved to flow processing (Scheme 2). Esterification reactions using flow chemistry have been the subject of previous reports in the literature with a range of apparatus and processing techniques being used [9]. In our case, we employed a unit comprising of two pumps capable of operating at flow rates ranging from 0.1 to 10 mL/min. A variety of reactors can

Scheme 2. Preparation of levulinate esters from levulinic acid (**1**) using flow processing



R	Flow rate (mL/min)	Conversion (%)
Me	1	94
Et	1	100
Pr	1	96
Bu	0.85	95

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be used with the system, the most commonly used being 10-mL perfluoroalkoxy alkane (PFA) coils capable of operation up to 150 °C. The system can operate up to a pressure of 42 bar across the whole flow rate range. Levulinic acid has a melting point of 33–35 °C, making it somewhat challenging to handle if not kept at or above this temperature. Rather than pumping streams of the individual reagents and mixing them as they reach the reactor coil, we instead prepared a mixture of **1**, ethanol, and sulfuric acid (molar ratio 1:10:0.025) and used that as our input stream. To mimic the reaction time of 5 min at 120 °C used in the microwave heating trials, we passed our stream of reagents through a 10-mL coil heated to 120 °C at a flow rate of 2 mL/min. After one pass through the reactor, a conversion to **2** of 78% was obtained. Passing the mixture through the coil a second time led to complete conversion. By reducing the flow rate to 1 mL/min, we were able to obtain complete conversion in one pass. There was no visible formation of humins (polymerized products), usually evidenced by discoloration of the reaction mixture or precipitation of solids. We also extended the scope of the reaction to the preparation of other levulinic esters, preparing methyl, propyl, and butyl levulinate. While when using methanol and propanol as reagents, it was possible to operate under identical reaction conditions as in the case of ethanol, to obtain optimal conversion with butanol, it was necessary to reduce the flow rate slightly to 0.85 mL/min.

Our next objective was to leverage some of the advantages of flow chemistry for the development of a catalyst-free approach to the esterification of **1**, namely, the ability to operate safely, easily, and efficiently at high temperature and pressure. Catalyst-free reactions have garnered significant interest in the broader remit of cleaner, greener chemistry [10], and flow processing has been used as a tool [11]. The catalyst-free esterification of other alcohols in batch mode has been the subject of a number of recent publications [12], as have transesterification reactions [13]. In general, this class of reactions is performed in sealed reactors at temperatures above 200 °C either under autogenic pressure or with prepressurization. The catalyst-free esterification of benzoic acid to ethyl benzoate has been performed under continuous-flow conditions [14], as has the preparation of ethyl oleate from oleic acid [15]. In the case of the former, the reaction was performed at 300 °C, and the reaction mixture passed three times through the 4-mL heated steel coil at a flow rate of 1 mL/min. Working on the 1-mmol scale with a 0.33-M solution of benzoic acid in ethanol, an 87% yield of ethyl benzoate was obtained. In the latter, optimal conditions were found to be heating at 325 °C with a residence time of 40 min.

In order to reach the temperature and pressure ranges required, we moved from using a 10-mL PFA coil to an assembly where all fluid tubing and the pump manifold itself are made of stainless steel (Figure 1). The system has a maximum pressure limit of

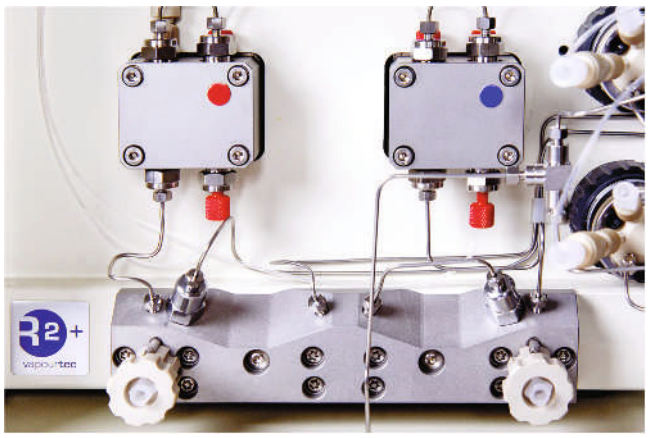

Figure 1. The pump assembly of the flow unit used for the uncatalyzed esterification of **1**

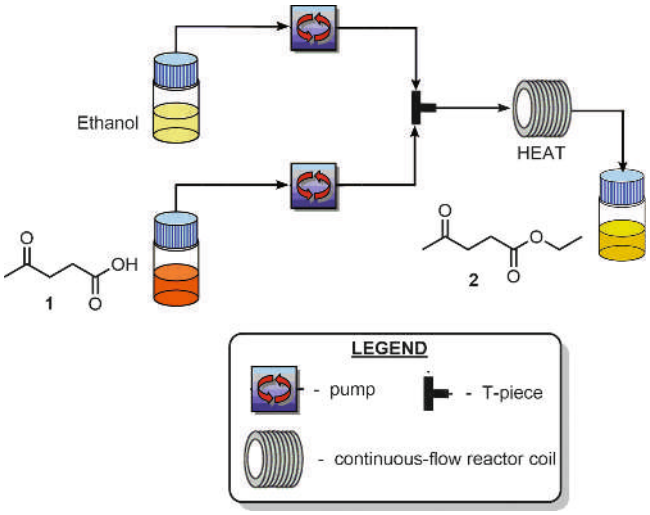

Figure 2. The flow configuration used for the uncatalyzed esterification of **1**

200 bar and can operate from room temperature to 250 °C. Using a 1:2 stoichiometric mixture of **1** and ethanol and passing it at 1 mL/min though, the coil heated at 250 °C resulted in a conversion to **2** of 60% (Figure 2) (Table 2, entry 1). Changing the reagent stoichiometry to make it richer in ethanol did not have a noticeable effect (entries 2 and 3). Using a 1:3 stoichiometric mixture of **1** and ethanol, we probed the effect of residence time. Decreasing the flow rate to 0.5 mL/min (residence time of 20 min) did improve the outcome, a product conversion of 73% being obtained (entry 4). This could be increased to 78% by reducing the flow rate further to 0.33 mL/min (entry 5). Using the same flow equipment, we used a modified reactor module capable of operating at 270 °C to allow us to increase the reaction temperature. Using a 1:3 stoichiometric mixture of **1** and ethanol, we first performed the reaction at a flow rate of 1 mL/min and obtained a 68% conversion to **2** (entry 6). Reducing the flow rate to 0.33 mL/min improved the product conversion to 85% (entry 7). Operating under these optimized conditions equated to processing a 3.6-M solution of **2** and a throughput of 8.3 g of levulinic acid per hour. As with the acid catalyzed studies, we did not observe humin formation during the course of the reaction.

In summary, we present both the catalyzed and uncatalyzed preparation of ethyl levulinate, a valuable commodity chemical, from levulinic acid and ethanol. In the case of acid-catalyzed reactions, conditions were optimized in batch using microwave heating and then scaled-up using continuous-flow processing. For the uncatalyzed reactions, optimization was performed under continuous-flow conditions, using a reactor capable of operating at high temperature and pressure. We were also able to prepare other esters of levulinic acid in a rapid and easy manner using the acid-catalyzed route. Having proven the process on a laboratory scale, attention now is turning to increasing the scale.

Table 2. Optimization of reaction conditions for the uncatalyzed esterification of levulinic acid with ethanol

Entry	1:Ethanol ratio	Temp. (°C)	Flow rate (mL/min)	Conversion (%)
1	1:2	250	1.00	60
2	1:3	250	1.00	61
3	1:5	250	1.00	60
4	1:3	250	0.50	73
5	1:5	250	0.33	78
6	1:3	270	1.00	63
7	1:3	270	0.33	85

2. Experimental Section

2.1. General Experimental. All reactions were performed without the exclusion of air. All reagents were purchased from Sigma-Aldrich Corporation and used without further purification. For batch optimization reactions, a CEM Discover microwave unit was used. Reactions were performed in 10-mL capacity glass vessels. A Vapourtec R-series flow reactor was used for flow chemistry experiments [16]. For acid-catalyzed reactions, an R2C acid-resistant pumping module was employed. The system was equipped with a 10-mL volume PFA coil (1-mm internal diameter, 12-m length). The "reagent in" port of the reactor coil was connected to the pump with a length of PFA tubing. The "reagent out" port was then directly interfaced with a 250-psi back pressure regulator after which was a length of PFA tubing leading to a collection flask. For uncatalyzed reactions, a high-pressure R2P pump module was used, capable of operating at up to 200 bar. All fluid tubing and the pump manifold were made of stainless steel. A 10-mL volume stainless steel coil (1-mm internal diameter, 12-m length) was employed as the reactor. The standard configuration was capable of operating at temperatures up to 250 °C. For reactions performed at 270 °C, a modified R4 reactor module was used. In each case, the "reagent out" port on the reactor coil was directly interfaced with 2500 psi in back pressure regulators (2×1000 psi+1×500 psi Upchurch Scientific) after which was a length of PFA tubing leading to a collection flask. ^{1}H-NMR spectra were recorded at 298 K using $CDCl_3$ as the solvent. Signals were referenced to residual non-deuterated chloroform (7.26 ppm) in the deuterated solvent.

2.2. General Batch Procedure for Acid-Catalyzed Preparation of Ethyl Levulinate. To a 10-mL capacity microwave tube equipped with a magnetic stir bar, levulinic acid (1.16 g, 10.0 mmol), ethanol (5 mL), and sulfuric acid (0.0235 g, 0.25 mmol) were added. The tube was sealed with a snap-on cap and placed into the microwave cavity. The reaction mixture, being stirred continuously, was heated to the target temperature of 120 °C using a maximum microwave power of 200 W, and then held at this temperature for 5 min. The mixture was then allowed to cool to 60 °C before removing the tube from the microwave unit. The contents of the tube were transferred to a round-bottom flask, and excess ethanol was removed using a rotary evaporator. Analysis of the residue using ^{1}H-NMR spectroscopy showed complete conversion of the levulinic acid to ethyl levulinate. ^{1}H-NMR ($CDCl_3$) δ 4.13 (2H, q), 2.75 (2H, t), 2.57 (2H, t), 2.20 (3H, s), 1.24 (3H, t).

2.3. General Flow Procedure for Acid-Catalyzed Preparation of Levulinic Esters: Ethyl Levulinate. Levulinic acid (16.8 g, 145 mmol), ethanol (85 mL, 1.4 mol), and sulfuric acid (0.2 mL, 3.6 mmol) were combined in a 100-mL capacity glass bottle equipped with a top that allows tube access. The "reagent in" line from the flow unit was placed into this bottle. The "solvent-in" line from the flow unit was placed into a bottle containing ethanol. The flow system was primed using the equipment manufacturer's suggested start-up sequence. The reactor coil was flushed with ethanol for 5 min at a flow rate of 2 mL/min. The flow rate was then decreased to 1 mL/min, and the reactor coil was heated to 120 °C. Once at the target temperature, the flow was then changed from solvent to reaction mixture by means of a switch on the unit. The reaction mixture was then flowed through the heated coil, product collection commencing 10 min after this switch. After the entire contents of the reagent bottle had been loaded into the flow reactor, the flow was changed from reaction mixture back to solvent. Once all the product had exited the heated coil, the flow of ethanol was stopped. The contents of the collection vessel were decanted into a round-bottom flask, and the excess ethanol was removed using rotary evaporation. Product conversion was assayed by ^{1}H-NMR spectroscopy.

2.4. General Flow Procedure for Uncatalyzed Preparation of Ethyl Levulinate. Levulinic acid and ethanol were placed in bottles labeled "Reagent A" and "Reagent B," respectively. A third bottle containing ethanol was labeled "solvent." Two pumps were primed using the equipment manufacturer's suggested start-up sequence. Ethanol was pumped through the stainless steel coil at a flow rate of 1 mL/min as it was heated to 270 °C. The flow was then changed from solvent to reagents by means of switches on the unit. The two reagents were flowed in a 1:3 stoichiometric ratio with an overall reaction mixture flow rate of 0.33 mL/min, switching back to pure ethanol after the requisite amount of reaction mixture had been processed. After ensuring that all the product had exited the reactor coil, the contents of the collection vessel were decanted into a round-bottom flask, and the excess ethanol was removed using rotary evaporation. Product conversion was assayed by ^{1}H-NMR spectroscopy.

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