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Microwave-Assisted Homogeneous Acid Catalysis and Chemoenzymatic Synthesis of Dialkyl Succinate in a Flow Reactor

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Received: 12 February 2019; Accepted: 8 March 2019; Published: 16 March 2019

Abstract: Two new continuous flow systems for the production of dialkyl succinates were developed via the esterification of succinic acid, and via the trans-esterification of dimethyl succinate. The first microwave-assisted continuous esterification of succinic acid with H_2SO_4 as a chemical homogeneous catalyst was successfully achieved via a single pass (ca 320 s) at 65–115 °C using a MiniFlow 200ss Sairem Technology. The first continuous trans-esterification of dimethyl succinate with lipase Cal B as an enzymatic catalyst was developed using a Syrris Asia Technology, with an optimal reaction condition of 14 min at 40 °C. Dialkyl succinates were produced with the two technologies, but higher productivity was observed for the microwave-assisted continuous esterification using chemical catalysts. The continuous flow trans-esterification demonstrated a number of advantages, but it resulted in lower yield of the target esters.

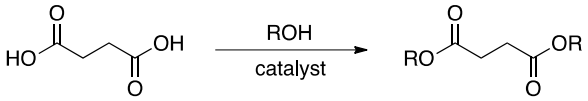
Keywords: continuous flow; dialkyl succinates; homogeneous catalysis; lipase Cal B; succinate

1. Introduction

With the depletion of oil-based resources, wood-based biomass and especially plant waste rich in lignocellulosic feedstocks appear to be the main alternatives for the production of platform molecules. Among them, succinic acid (SA) as a linear C-4 dicarboxylic acid is considered as one of the top 12 prospective building blocks derived from sugars by the US Department of Energy. SA is mainly produced via a chemical catalytic route starting from maleic acid and maleic anhydride. The use of furan-derived SA at laboratory-scale using chemical process, as well as via biotechnological process (i.e., by fermentation) have also been studied [1]. SA can be used as a precursor to produce different chemical intermediates [2], such as tetrahydrofuran [3], γ-butyrolactone [4], and 1,4-butanediol [5]. Particularly, SA ester products can be used in the chemical industry as a green solvent, or plastic and fuel additive, as well as in the pharmaceutical and cosmetic industries [6]. Different processes using chemical homogeneous catalysis [7–10], heterogeneous catalysis [11–21], and chemo-enzymatic reaction [22] have been reported in batch process, but few reports have described continuous flow dialkyl succinate synthesis [21,23]. Among the dialkyl succinates with value-added properties, dimethyl-, diethyl-, di-isobutyl-, and dioctyl succinates can be used as green solvents; dibutyl-, didecyl-, diamyl-, and diisoamyl succinates can be used as plastic and fuel additives; tocopherol, estriol, chloramphenicol, and hydrocortisone succinates as pharmaceutical ingredients; and dipropyl, diethoxyethyl, or diethylhexyl succinates in cosmetic application [1]. Processes for the production of dialkyl succinates in a batch

reactor were developed in 2010 (Table 1). Among them, the use of sulfonic acid was the most described [8–11,14–17], followed by carboxylic acid [18] and phosphoric acid [19]. It is difficult to compare each result since the processes were conducted in different conditions by different groups. Nevertheless, the use of alcohol as both solvent and reagent was often in excess at temperature in the range of 25–160 °C for 25 h. Dialkyl succinates were produced in yields higher than 66%. Al_2O_3 was described as a heterogeneous catalyst at 25 °C for 48 h for the synthesis of dimethyl ester **2b** in 70% yield [20]. Among the recent reports, Zhang et al. described the continuous flow synthesis of diesters **2a**, **2b**, and **2d** in the presence of "man-made" heterogeneous catalyst in quantitative yield [21]. Moreover, Fabian et al. described the use of batch microwave radiation as alternative tool for the esterification of SA [14]. To the best of our knowledge, the chemoenzymatic production of diesters **2a–i** using both pure SA (**1**) and pure dimethylester **2b** as reactants has never been reported. Nevertheless, Delhomme et al. used crude fermentation broths produced from recombinant *Escherichia coli* for the synthesis of **2h** in the presence of lipase Cal B [22].

Table 1. Selected catalysts reported for the conversion of succinic acid (**1**) to dialkylsuccinates **2.**



1

2a (R = CH_2CH_3)
2b (R = CH_3)
2c ($CH_2CH_2CH_3$)
2d ($CH_2CH_2CH_2CH_3$)
2f ($CH_2(CH_2)_4CH_3$)
2g ($CH_2CH(CH_2CH_3)_2CH_2(CH_2)_2CH_3$)
2h ($CH_2(CH_2)_6CH_3$)
2i ($CH(CH_3)_2$)

Entry	Reactor	Catalyst	Reaction Conditions [a]	2	Yield of 2 (%)	Ref
1	batch	H_2SO_4	nd:2:110:18	**2g**	69	[8]
2	batch	H_2SO_4	nd:2.3:110:18	**2f**	78	[9]
3	batch	H_2SO_4	nd:2.3:110:18	**2h**	70	[9]
4	batch	OPP-SO_3H-1	10:50:70:6	**2b**	88	[15]
5	batch	SS-0.010	10:2:100:6.5	**2a**	94	[16]
6	batch	Glu-TsOH	100:80:80:4	**2a**	100	[17]
7	batch [b]	$CH_3SO_3H@Al_2O_3$	332,000:2:80:8	**2b**	97	[14]
8	batch [b]	$CH_3SO_3H@Al_2O_3$	332,000:2:80:8	**2a**	97	[14]
9	batch [b]	$CH_3SO_3H@Al_2O_3$	332,000:2:80:8	**2c**	97	[14]
10	batch [b]	$CH_3SO_3H@Al_2O_3$	332,000:2:80:8	**2i**	97	[14]
11	batch	$C_2(Mim)_2HSO_4$	2:3:60:3	**2b**	76	[10]
12	batch	$C_3(Mim)_2HSO_4$	2:3:60:3.5	**2a**	68	[10]
13	batch	$C_4(Mim)_2HSO_4$	2:4:60:4	**2c**	74	[10]
14	batch	*N*-Butyl-2,4-dinitro-anilinium *p*-toluenesulfonate	1:2:99:25	**2h**	93	[7]
15	batch	nano-SO_4 2-/TiO_2	5:3:160:2	**2g**	97	[11]
16	batch	TSA_3/MCM-41	0.1:3:80:14	**2a**	66	[18]
17	batch	TSA_3/MCM-41	0.1:3:80:14	**2d**	90	[18]
18	batch	TPA_2/MCM-41	100:3:80:8	**2d**	68	[19]
19	batch	TPA_2/MCM-41	100:3:80:8	**2f**	68	[19]
20	batch	TPA_2/MCM-41	100:3:80:8	**2h**	73	[19]
21	batch	Al_2O_3	50:1.6:25:48	**2b**	70	[20]
22	flow	PIL-A	5:1.2:85:5	**2b**	100	[21]
23	flow	PIL-A	5:1.2:87:4	**2a**	100	[21]
24	flow	PIL-A	5:1.2:100:3.5	**2d**	100	[21]

[a] Reaction conditions: amount of catalysts (% *w*/*w*, in some cases unit is mg):mole ratio of alcohol/succinic acid:reaction temperature (°C):reaction time (h). [b] Microwave-assisted esterification. OPP-SO_3H-1: organic knitted porous polyaromatics with pyrene; SS-0.001: silica-supported sulfate with sulfate loading 0.001 mol; TSA_3/MCM-41: 12-tungstosilicic acid (30 wt%) anchored to MCM-41; TPA_2/MCM-41: terephthalic acid (20%) anchored to MCM-41; PIL-A: acidic poly(ionic liquid).

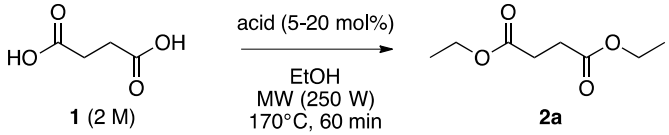
Recently, the use of homogeneous and heterogeneous flow systems in organic chemistry have been widely studied because of their highly efficient heat transfer compared with batch methodologies,

good temperature monitoring, and enhanced mass transfer [24–33]. This innovative approach also permits the time required to progress from research to pilot scale and production to be reduced. Due to our interest in the topic of green chemistry and alternative technologies, two continuous-flow systems for the production of dialkyl succinate were envisaged to develop an intensified process. Herein, we report an efficient extension of this work in order to establish a comparison between the homogeneous acid and the enzymatic continuous flow system for the production of selected dialkyl succinates.

2. Results and Discussion

Initial batch diesterification was performed using SA (**1**, 2 M) and ethanol (10 mL) in the presence of H_2SO_4 (10 mol %) at 170 °C under microwave irradiation for the production of the corresponding diester **2a** (Table 2). In the presented work, the reaction time was determined by HPLC monitoring either until no more conversion of the starting diacid **1** was observed, or within the maximum time of one hour with magnetic stirring (600 rpm). The optimization of the reaction conditions for the esterification of SA (**1**) with both acid catalysts and enzymes was first realized with a single-variable strategy, by varying one variable at a time while keeping the others constant. For the present work, error bars represent the standard deviation of five replicates. Different Bronsted acids, including H_2SO_4, H_3PO_3, *p*-touluenesulfonic acid (PTSA) and 10-camphorsulfonic acid (CSA), were tested with a concentration of 10 mol % (Table 2, entries 1–4). CSA and H_2SO_4 gave identical yields, and for economic reasons, H_2SO_4 was selected for the following study. It should be pointed out that the use of PTSA and H_3PO_4 as acid catalysts resulted in a lower yield (77% and 50%) for the same reaction time (Table 2, entries 1 and 3). The experimental results with variation of H_2SO_4 (5–20 mol %) demonstrates that the maximum yield was obtained in the presence of 20 mol % of the acid (Table 2, entry 5). Using these conditions without catalyst, compound **2a** was obtained in a low yield (9%). The acidity of the catalysts used were different (PTSA pKa −6.5; H_2SO_4 pKa −3.0, 1.9; CSA pKa 1.2 and H_3PO_4 pKa 2.1, 7.0 and 12.0). The lack of reactivity of H_3PO_4 can be related to its low acidity compared with H_2SO_4 while PTSA with a strong acidity may favor the saponification of the ester **2a**.

Table 2. Batch microwave-assisted diethyl succinate (**2a**) synthesis by varying the nature and the amount of acid at 250 W.



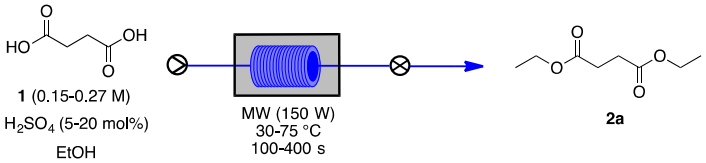
Entry	Acid	[Acid] (mol %)	Yield of 2a (%) [a]	Error Bar
1	PTSA	10	77	1.48
2	CSA	10	84	1.09
3	H_3PO_4	10	50	1.52
4	H_2SO_4	10	84	0.55
5	H_2SO_4	20	87	0.84
6	H_2SO_4	30	82	1.14
7	H_2SO_4	5	70	3.36

[a] The diethyl succinate yield was calculated from gas chromatography analysis with a calibration curve. CSA: 10-camphorsulfonic acid; PTSA: *p*-touluenesulfonic acid.

Based on these previous results obtained in a batch reactor, the initial reaction using the microwave continuous flow was conducted with SA (**1**, 0.15–0.27 M) in the presence of H_2SO_4 (5–20 mol %) in ethanol. The molar concentration was more diluted in the flow device compared with the batch reactor due to viscosity. Starting from SA (**1**, 0.22 M) and H_2SO_4 (20 mol %), the temperature was fixed close to the boiling point of ethanol (75 °C) with a power input of 150 W, and the residence time was fixed at 100 s for this mixture. Conversion of SA (**1**) and the yield of diethyl succinate (**2a**) were 45% and

32%, respectively. In order to improve the process, residence times were increased from 100 to 400 s. The optimal residence time was obtained at 320 s with a quantitative conversion of SA (**1**) and yield of diethyl succinate (**2a**). Using a lower amount of H_2SO_4 (5 and 10 mol %) and variation of the amount of SA (**1**, 0.15 and 0.27 M) resulted in lower yields of diethyl succinate (Table 3, entries 5–8). The use of lower temperature (30 °C and 50 °C) did not lead to improvement in conversion and yield (Table 3, entries 9 and 10).

Table 3. Continuous flow microwave-assisted diethyl succinate (**2a**) synthesis by varying the amount of SA (**1**), H_2SO_4, the residence time, and the temperature at 150 W.



Entry	1 (mol L^{-1})	H_2SO_4 (mol %)	Temperature (°C)	Residence Time (s)	Conversion (%) [a]	Yield of 2a (%) [a]	Error Bar
1	0.22	20	75	100	45	32	0.71
2	0.22	20	75	180	60	48	1.30
3	0.22	20	75	320	100	99	0.45
4	0.22	20	75	400	100	99	0.55
5	0.22	10	75	320	85	82	0.89
6	0.22	5	75	320	75	68	0.89
7	0.27	20	75	320	95	90	2.17
8	0.15	20	75	320	82	78	1.52
9	0.22	20	50	320	73	68	1.52
10	0.22	20	30	320	35	16	2.41

[a] The diethyl succinate yield was calculated from gas chromatography analysis with a calibration curve.

Various primary and secondary alcohols having linear and branched carbon chains were subjected to the continuous esterification under our optimized conditions (Figure 1). Due to viscosity, butan-1-ol and alcohols with higher molecular weight were used at 0.18 M. Yields decreased proportionally with the increase in the number of carbons in the chain. Using primary alcohols, the conversion of SA (**1**) and yields of the selected dialkyl succinates (**2a**–**e**) were higher than 95% and 88%, respectively (Table 4, entries 1–5). For those primary alcohols with more than six carbon atoms, productivity decreased with yields between 65% and 80% (Table 4, entries 6–8). In contrast, the use of secondary alcohols gave similar conversion (98%) and lower yields (36% for **2i** and 89% for **2j**) (Table 4, entries 9 and 10). To the best of our knowledge, this is the first investigation which reports dialkyl succinates produced in a continuous flow. More parameters can be explored, but the present yields were similar to those obtained in the literature with batch process.

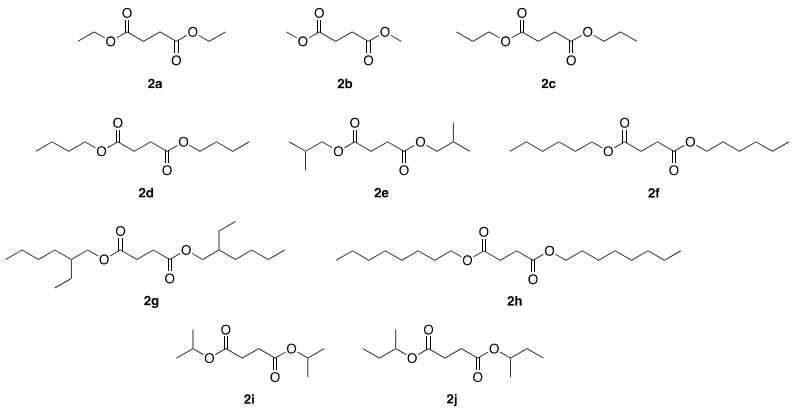
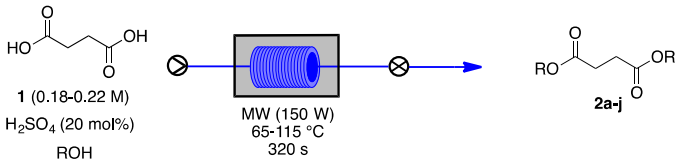


Figure 1. Selected dialkyl succinates **2a**–**j**.

Table 4. Scope of the microwave-assisted continuous flow dialkyl succinate **2a–j** synthesis at 75 °C.



Entry	1 (mol L^{-1})	Temperature (°C)	Conversion (%) [a]	Diesters 2	Yield of 2a–j (%) [a]	Error Bar
1	0.22	65	100	**2b**	100	0.89
2	0.22	75	100	**2a**	99	0.55
3	0.22	95	95	**2c**	92	0.89
4	0.18	115	98	**2d**	89	0.55
5	0.18	115	98	**2e**	88	1.30
6	0.18	115	97	**2f**	78	1.30
7	0.18	115	98	**2g**	80	4.55
8	0.18	115	96	**2h**	65	0.84
9	0.22	80	98	**2i**	89	1.64
10	0.18	96	98	**2j**	36	1.95

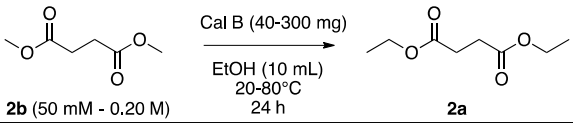
[a] The dialkyl succinate yield was calculated from gas chromatography analysis with a calibration curve.

For fair comparison, compounds **2f–h** were obtained by Stuart et al. [8,9] starting with a molar ratio of alcohol:SA (2:1) in the presence of H_2SO_4 as a catalyst at 110 °C for 18 h in a batch reactor. The yields of compounds **2f–h** were 78%, 69%, and 70%, respectively. In our optimized microwave-assisted flow synthesis, alcohols were used in large excess at similar temperature range (115 °C) for a residence time of 320 s. In this study, the yields of diesters **2f–h** were similar. It is obvious that the decrease in residence time (18 h vs. 320 s) led to significant improvement in the synthesis of biobased chemicals via esterification.

In order to explore high selectivity and smooth reaction conditions, continuous flow and bioconversion with Novozymes® 435, the lipase B from *Candida antarctica* immobilized on acrylic resin (Cal B) were studied in batch and flow reactors. The optimization of the reaction conditions for the trans-esterification of dimethylester **2b** with enzymes was realized as reported above with the acid catalysts. To probe the scope of the methodology, the influence of thermal heating, the amount of starting material **2b**, and the amount of Cal B were examined (Table 5). Dimethyl ester **2b** (50 mM) and Cal B (270 g) in ethanol were mixed in a batch reactor for 24 h by varying the temperature. Whatever the temperature used, the yield of diethyl succinate **2a** was 60% except for temperature above 60 °C due to the instability of the enzyme at high temperature (Table 5, entries 1–4). For these reasons, temperature of 20 °C was chosen and variation of the amount of enzyme was studied. For a quantity of 200 mg and 270 mg, the yields of the diesters **2a** were similar while for smaller quantities the yield of diethyl succinate **2a** were too low (Table 5, entries 5–7). The use of concentrated solution of dimethylester **2b** were tested at 20 °C in the presence of Cal B (200 mg), but the yield of diethyl succinate **2a** decreased (Table 5, entries 8 and 9).

For the transfer of the enzymatic trans-esterification from batch to continuous flow, dimethyl ester **2b** (50 mM) and Cal B (200 mg) were tested at 20 °C with different residence times (7, 2.3, and 1.2 min). The longer the time, the better the yield, regardless of the amount of the diester **2b**, enzyme dosage, and temperature (Table 6). Only dimethyl ester **2b** in the presence of a minimum amount of enzyme (200 mg) at 40 °C with a time of 7 min allowed the production of diethyl ester **2a** with a yield higher than 20% (Table 6, entries 4 and 13). It should be noted that for a doubling time of 14 min, the diester **2a** yield was 48% (Table 6, entry 23). In these optimized conditions, the use of Cal B (100 mg) resulted in only 34% (Table 6, entry 24).

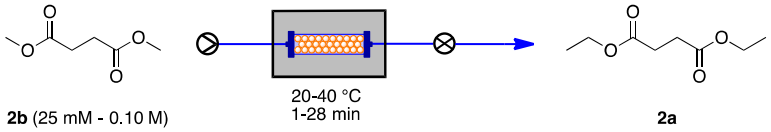
Table 5. Batch chemoenzymatic synthesis of diethyl succinate (**2a**) by varying the concentration and temperature.



Entry	2b (M)	Cal B (mg)	Temperature (°C)	Yield of 2a (%) [a]	Error Bar
1	0.050	270	20	60	0.89
2	0.050	270	40	60	1.22
3	0.050	270	60	60	0.55
4	0.050	270	80	20	2.51
5	0.050	40	20	30	1.30
6	0.050	130	20	55	1.73
7	0.050	200	20	60	1.09
8	0.10	200	20	50	1.30
9	0.20	200	20	45	1.30

[a] The yield of diethyl succinate was calculated from gas chromatography analysis with a calibration curve.

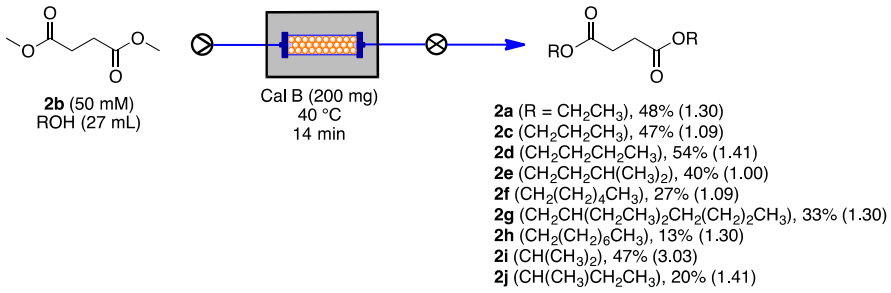
Table 6. Flow chemoenzymatic synthesis of diethyl succinate (**2a**) by varying the concentration, temperature, and residence time.



Entry	2b (M)	Cal B (mg)	Residence Time (min)	Temperature (°C)	Conversion of 2b (%) [a]	Yield of 2a (%) [a]	Error Bar
1	0.050	200	7	20	90	7	1.00
2	0.050	200	2.3	20	79	1	0.55
3	0.050	200	1.2	20	76	1	0.45
4	0.050	200	7	40	99	23	1.30
5	0.050	200	2.3	40	73	3	0.89
6	0.050	200	1.2	40	73	2	0.84
7	0.050	200	7	60	95	18	1.22
8	0.050	200	2.3	60	78	5	1.41
9	0.500	200	1.2	60	73	2	1.00
10	0.050	100	7	40	60	14	1.09
11	0.050	100	2.3	40	68	6	0.89
12	0.050	100	1.2	40	63	traces	0.09
13	0.050	400	7	40	100	24	0.89
14	0.050	400	2.3	40	97	12	1.30
15	0.050	400	1.2	40	91	5	0.89
16	0.025	200	7	40	89	10	1.30
17	0.025	200	2.3	40	72	3	0.89
18	0.025	200	1.2	40	75	1	0.27
19	0.100	200	7	40	94	14	1.41
20	0.100	200	2.3	40	85	5	0.89
21	0.100	200	1.2	40	78	3	0.27
22	0.050	200	28	40	95	18	1.30
23	0.050	200	14	40	96	48	1.52
24	0.050	100	14	40	100	34	1.09

[a] The diethyl succinate yield was calculated from gas chromatography analysis with a calibration curve.

In order to expend the array of substrates, dimethyl ester **2b** was coupled with a variety of primary and secondary alcohols with linear and branched alkyl chains (Scheme 1). In general, the yields were twice as low as those obtained during esterification in the batch reactor. Exceptions were observed for diesters **2f**, **2g**, and **2h**, which were obtained with much lower yields. Nevertheless, the variation in yields according to the alcohol used was similar.



Scheme 1. Scope of the flow chemoenzymatic synthesis of dialkyl succinates **2a** and **2c–j** at 40 °C.

The selectivity of the chemoenzymatic synthesis of dialkyl succinates **2a** and **2c–j** was low using Cal B because the residence time was too low to have the second esterification. With a good conversion of the dimethylester **2b**, the first trans-esterification was obtained to furnish the intermediate and then the second trans-esterification as a limiting step gave the target compounds **2a** and **2c–j** in low-to-moderate 13%–54% yields.

3. Experimental Methods

3.1. Materials

Substrate alcohols (MeOH, EtOH, PrOH, iso-PrOH, BuOH, iso-BuOH, sec-BuOH, HexOH, 2-Et-HexOH, and OctOH) and succinic acid were purchased from Fisher Scientific (Leicestershire, United Kingdom). Diethyl succinate (**2a**) was purchased from TCI Europe (Zwijndrecht, Belgium); dimethyl succinate (**2b**), dipropyl succinate (**2c**), dibutyl succinate (**2d**), and diisopropyl succinate (**2i**) were purchased from Sigma-Aldrich (Saint Louis, MO, USA). Diisobutyl succinate (**2e**) and di-sec-butyl succinate (**2j**) were purchased from AKos Consulting & Solutions GmbH (Steinen, Germany). Dihexyl succinate (**2f**), diethylhexyl succinate (**2g**), and dioctyl succinate (**2h**) were purchased from Hangzhou DayangChem Co. Ltd. (Hangzhou, China), BOC Sciences (Shirley, NY, USA), and Carbosynth Europe (Berkshire, United Kingdom), respectively. All materials were used without purification.

3.2. Microwave-Assisted Continuous Chemical Esterification

In a typical experiment, a 500-mL Erlenmeyer flask was first filled with succinic acid (**1**, 6.50 g, 55.1 mmol, 1 equiv.) and H_2SO_4 (1.08 g, 11.1 mmol, 0.2 equiv.) in alcohol (250–300 mL). The mixture was stirred at room temperature for 10 min, and it was pumped with a peristatic pump (5 tr·min^{-1}). The solution was passed through a reactor under microwave activation (MiniFlow 200ss, Sairem®) at 65–115 °C (150 W) with a residence time of 320 s. Among the outlet solution, one milliliter of mixture was collected, pH was adjusted to 7 by washing the mixture with 5% NaOH (0.5 mL), followed by water (0.5 mL) and saturated aqueous NaCl solution (0.5 mL). Then, the organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The aqueous phase was analyzed by HPLC in order to determine the remaining succinic acid concentration, and the organic phase was analyzed by gas chromatography to quantify the amount of esters produced.

3.3. Continuous Biochemical Trans-Esterification

In a typical experiment, a solution containing dimethyl succinate (**2b**, 200 mg, 1.37 mmol, 1 equiv.) in alcohol (27 mL) was pumped at 0.05 mL min^{-1} using Syrris Asia equipment (Syrris, England). The solution was passed through a cartridge filled with Cal B (200 mg) at 40 °C, leading to a residence time of 14 min. Among the outlet solution, one milliliter of mixture was collected and saturated aqueous NaCl solution (1 mL) was added. Then, the organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The aqueous phase was analyzed by HPLC in order to determine the remaining succinic acid concentration, and the organic phase was analyzed by gas chromatography to quantify the amount of esters produced.

3.4. Gas Chromatography (GC) Analysis

Gas chromatography analyses of the organic phase were performed by a Perkin-Elmer gas chromatography instrument (Autosystem XL GC) (Perkin-Elmer, Singapore) using an Altech AT HT column with a detector at 300 °C, an injector at 340 °C, and a constant flow of nitrogen of 1 mL min^{-1}. The column was heated at 150 °C for 2 min, and the column temperature was then raised to 350 °C with a temperature gradient of 15 °C min^{-1} before being held at this temperature for 4.67 min. Succinic esters were identified and quantified by comparing GC retention time and peak area with their respective calibration standards.

3.5. High-Performance Liquid Chromatography (HPLC) Analysis

Liquid chromatography analyses of the aqueous phase were performed by a Hewlett-Packard 1090 HPLC using a reversed phase C18 column (Novapak 3.9 mm × 150 mm) held at 40 °C. Water/acetonitrile (ACN) mixture was used as the mobile phase (0.8 mL min^{-1}) in a gradient mode (0% ACN at t = 0 min to 60% ACN at t = 20 min to 90% ACN at t = 25 min to 0% ACN at t = 28 min). The species were identified by UV detection (Hitachi L400H, San Diego, CA, USA) at a wavelength of 210 nm. Succinic acid was identified and quantified by comparing GC retention time and peak area with their respective calibration standard.

4. Conclusions

In this study, two clean, mild, reproducible, and scalable continuous flow process for the production of different dialkyl succinates using H_2SO_4 as the homogeneous catalyst and Cal B as the heterogeneous catalyst were developed. A scope of different linear and branched alcohols was successfully formulated based on the optimized protocols, leading to the target chemicals. The homogeneous protocol furnished excellent yields (≥88%) when alcohols containing less than six carbon atoms were used. One exception was observed with butan-2-ol as the reactant, which is probably due to the hindered or solubility effects. For alcohols with higher molecular weight, productivities decreased with yields between 65% and 80% even if the conversion of SA (**1**) was almost quantitative. In comparison with chemical homogenous catalysis, the chemoenzymatic protocol resulted in lower yields in the order of two at best with longer residence time (14 min vs. 5 min). The lack of reactivity must be due to the lower temperature, which is related to the low thermal stability of the enzyme. To the best of our knowledge, this is the first time that dialkyl succinates have been produced in continuous flow either by chemical catalysis or enzymatic catalysis. The first method gave excellent yields and it is possible on a larger scale. The second method requires optimization through the screening of more effective enzymes.

Author Contributions: C.L. (Carol Sze Ki Lin) and C.L. (Christophe Len) conceived and designed the experiments; L.D. and T.L. performed the experiments; L.D., T.L., C.L. (Carol Sze Ki Lin), and C.L. (Christophe Len) analyzed the data; C.L. (Christophe Len) contributed reagents/materials/analysis tools; C.L. (Carol Sze Ki Lin). and C.L. (Christophe Len) wrote the paper.

Funding: This research received no external funding.

Acknowledgments: Christophe Len is thankful to Audrey Maziere and Sophie Bruniaux for technical support.

Conflicts of Interest: The authors declare no competing financial interest.

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