

# Dibal-H Reduction of Methyl Butyrate into Butyraldehyde using Microreactors

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## Abstract:

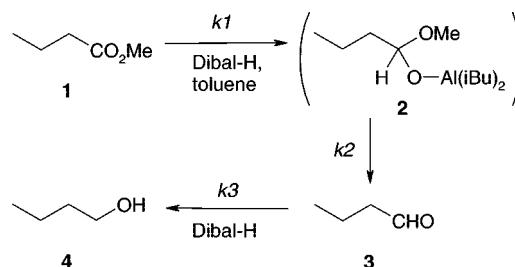
The reduction of methyl butyrate into butyraldehyde with Dibal-H in microreactors is described. Running the reaction continuously in a microreactor afforded results similar to those of batch experiments, but very low temperatures are not necessary and the reaction may be scaled-up without selectivity decrease. Different microreactors were used, and their mixing performances were compared. Increasing the reaction concentration and thus the throughput showed that even when working with microreactors, heat management should not be underestimated. Multi-injection was tested as a way to better control the temperature at the mixing point(s).

## Introduction

The availability of simple methods to synthesize aldehydes is of considerable interest to process chemists. Although Lonza produces kilo- up to ton-scale quantities of various aldehydes via ozonolysis of olefins, we decided to further broaden our technology platform by improving our control over the reduction of carboxylic esters into aldehydes. With most reducing agents, the reduction of carboxylic esters gives the primary alcohol and not the corresponding aldehyde. Complete reduction up to the alcohol followed by reoxidation to the aldehyde, for example, via Swern oxidation, is thus often carried out, for example, in total synthesis. As alternative to this lengthy procedure, the partial reduction of carboxylic esters with Dibal-H, has been reported for some time.<sup>1</sup> In this case, the intermediate formed by addition of the metal hydride to the ester may be sufficiently stable so that no significant amount of aldehyde is released before the aqueous workup. Under conditions where the rate constant  $k_1$  is larger than  $k_2$ , little aldehyde is present during the reaction. Thus, little or no alcohol can be formed even if  $k_3$  is larger than  $k_1$ , which is generally the case since the carbonyl group of aldehydes is more reactive than that of esters.

Although some additives were reported to give improved results,<sup>2</sup> hardly any simple and general procedure applicable to all esters is available as yet. A further limitation is the very low temperatures required to stabilize the organo-aluminium intermediate (**2**) and to obtain the desired partial reduction. This is well exemplified by the Dibal-H reduction of methyl butyrate (**1**), which we studied as a model reaction (Scheme 1). Whereas

**Scheme 1.** Mechanism of the Dibal-H-mediated reduction of methyl butyrate (**1**)



**Table 1.** Batchwise reduction of methyl butyrate (**1**) with Dibal-H

entry	$T$ [°C]	butyraldehyde ( <b>3</b> ) [area %]	methyl butyrate ( <b>1</b> ) [area %]	<i>n</i> -butanol ( <b>4</b> ) [area %]
1	−65	83	<1	17
2	−55	63	10	27
3	−35	30	28	42
4	−15	21	40	39
5	5	16	49	35
6	20	2	53	45

at −65 and −55 °C, butyraldehyde (**3**) is formed as the major product, at higher temperatures a mixture consisting mainly of starting material **1** and alcohol **4** was obtained (Table 1).

Not to mention the extra cost associated with low temperature, the industrial application of this approach is limited by the exothermicity of the reaction. In the methyl butyrate (**1**) reduction, ca. 240 kJ/mol is released according to RC1 measurements in a Mettler Toledo calorimeter. Thus, for isothermal operation, the Dibal-H addition time increases with the scale of the reaction. As a consequence of the limited half-life of the intermediate **2** (even at −78 °C) and of the extended dosage times associated with the scale-up, this reaction can hardly be used batchwise on an industrial scale. Indeed, even with precooling of the Dibal-H solution, the addition time becomes long enough in 630 L vessels that a considerable quantity of aldehyde is released before the end of the reaction. This results not only in alcohol formation but also in Dibal-H consumption. For the reduction of another ester, ca. 95 area % of the corresponding aldehyde was achieved on laboratory scale at −78 °C, whereas on pilot scale only ca. 80 area % purity was obtained at the same temperature. Running such a reaction in a continuous fashion could be an interesting alternative to circumvent this problem, but the reaction exothermicity (vide supra), combined with its rapid rate, requires good mixing properties and high heat transfer performance. Recently, microreactor technology has emerged as an attractive synthetic tool to handle such

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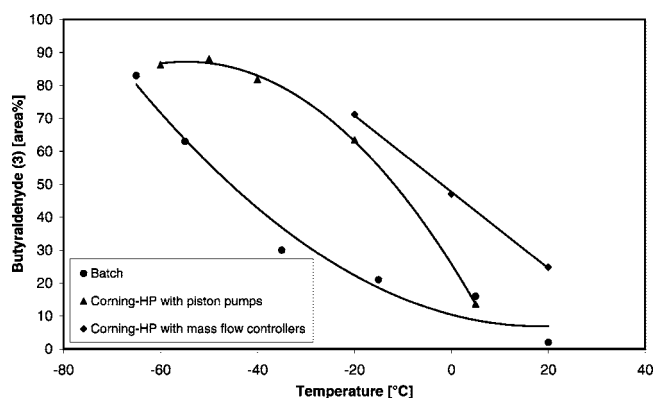
**Table 2.** Dibal-H reduction of methyl butyrate (1) in the Corning-HP microreactor using piston pumps

entry	T [°C]	butyraldehyde (3) [area %]	methyl butyrate (1) [area %]	n-butanol (4) [area %]
1	-60	86	1	13
2	-50	88	1	11
3	-40	82	1	17
4	-20	63	17	20
5	5	14	51	35

continuous reactions.<sup>3</sup> Thereafter, we report our results obtained in the Dibal-H-mediated reduction of ester 1 using different microreactors.

## Results and Discussion

Initially, a 2.3% methyl butyrate (1) solution in toluene (feed 1) and a commercially available 20% Dibal-H solution in toluene (feed 2) were pre-cooled and continuously pumped through the Corning-HP microreactor using piston pumps. A total flow rate of 11–12 g/min with a 6/1 split (corresponding to ca. 1.0 equiv of reducing agent) was used. As in the batch systems, the temperature was found to play a key role, with the decrease in selectivity occurring at higher temperatures. Over 80% butyraldehyde (3) was obtained at temperatures up to -40 °C (Table 2). The aldehyde 3 was still the major product at -20 °C, whereas in batch a temperature as low as -55 °C was necessary to obtain a similar result (Figure 1). The ability to selectively perform the partial reduction of esters at higher temperatures presents a clear economical advantage.



**Figure 1.** Selectivity as a function of temperature for batch experiments (Table 1, entries 1–6) versus experiments with the Corning-HP microreactor (Table 2, entries 1–5 and Table 3, entries 12–14).

As a result of their tiny dimensions, most microreactors have laminar flow regimes with low Reynolds numbers, depending on the microreactor size and flow rate. Good mixing properties are actually one of the main advantages of microreactors,<sup>4</sup>

although significant differences among microreactors exist. At -20 °C and above, the Dibal-H reduction of 1 is very fast (half-life below 1 s, type A reaction),<sup>5</sup> and is predominantly controlled by the mixing process.<sup>6</sup> This reaction can thus be used to compare the performance of various microreactors. Surprisingly, early experiments afforded very similar results, regardless of the microreactor type or the flow rate. This observation made us realize that the pulsation of the piston pumps was limiting the mixing quality. Our initial laboratory system was assembled with Ismatec valveless piston pumps having pulsation frequencies in the range of 200–1800 rpm. This pulsation proved to be the dominant quality factor, masking the different mixing properties of the various microreactors tested (Figure 1). It is worth mentioning that a number of commercially available microreactor systems still use this type of dosage pump. At -20 °C, the Corning-HP microreactor afforded 63 area % of butyraldehyde (3) with piston pumps (Table 2, entry 4) and 71 area % with mass flow controllers (Table 3, entry 12). For passive-mixing microreactors, it is thus critical to use a pump system without pulsation. The reactions described thereafter were all carried out with thermal mass flow controllers from Brooks, allowing pulsation-free operation of the microreactors.

Two types of microstructured reactors with contrasting mixing principles were compared. The Ehrfeld cryo reactor is a stainless steel microreactor with multi lamination mixing.<sup>7</sup> Its theoretical mixing time ( $t$ ) depends on the width of the laminar sheets ( $d$ ) and the diffusion coefficient ( $D$ ) according to eq 1. The fluid lamellae are generated from the width ( $d$ ) of the laminar sheet. Two different sheets were used, one with 25  $\mu\text{m}$  opening (ER-25), and one with 50  $\mu\text{m}$  openings (ER-50).

$$t = \frac{d^2}{D} \quad (1)$$

The Corning microreactors, made of glass, have a mixing principle based on a chaotic flow regime in the mixing zone.<sup>8</sup> Two such microreactors were used, namely, the Corning-LP and the Corning-HP, the later having the same geometry but smaller channels (larger internal structures) resulting in a higher pressure drop (HP) in the mixing zone.

The Ehrfeld microreactor has an integrated cooling system designed for carrying out reactions at low temperatures. The ER-25 afforded close to 90% selectivity in favor of the target aldehyde 3 at -55 °C (Table 3, entry 1). As expected, the selectivity decreased with increasing temperatures, but at significantly higher temperatures than batchwise or with the Corning-HP used under pulsating conditions. The ER-50 and the Corning-HP followed the

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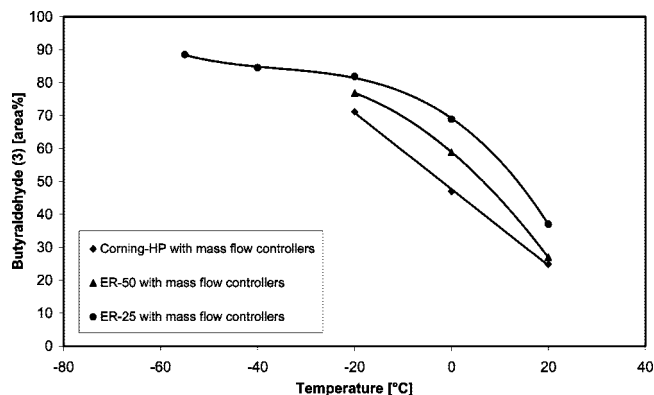
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**Table 3.** Dibal-H reduction of methyl butyrate (**1**) in various microreactors using mass flow controllers

entry	microreactor	$T$ [°C]	flow rate [g/min]	feed 1 concn [%]	pressure drop [mbar]	butyraldehyde ( <b>3</b> ) [area %]	methyl butyrate ( <b>1</b> ) [area %]	<i>n</i> -butanol ( <b>4</b> ) [area %]
1	ER-25	-55	12	2.3	1160	89	<1	11
2	ER-25	-40	12	2.3	830	85	<1	15
3	ER-25	-20	12	2.3	635	82	<1	18
4	ER-25	0	12	2.3	520	69	9	22
5	ER-25	20	12	2.3	510	37	32	31
6	ER-50	-20	12	2.3	640	77	2	21
7	ER-50	0	12	2.3	550	59	15	26
8	ER-50	20	12	1.2	500	36	28	36
9	ER-50	20	12	2.3	480	27	35	38
10	ER-50	20	10	3.5	420	19	42	39
11	ER-50	20	10	5.0	400	13	45	42
12	Corning-HP	-20	12	2.3	500	71	1	28
13	Corning-HP	0	12	2.3	380	47	21	31
14	Corning-HP	20	12	2.3	300	25	37	38
15	Corning-HP	20	20	2.3	690	34	28	37
16	Corning-LP	20	12	2.3	45	8	60	33
17	Corning-LP	20	20	2.3	110	19	53	29

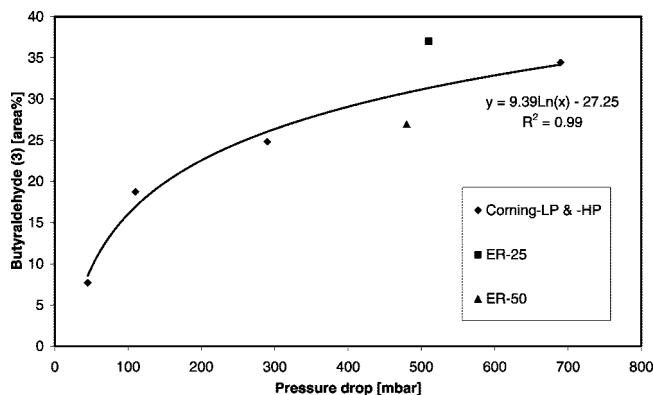
same trend as the ER-25 but with lower yields at comparable temperatures (Figure 2).

Although better selectivities are obtained at low temperature, working at 20 °C where the reduction is very fast maximizes the effect of the mixing (mixing controlled conditions) and allows better comparison of the mixing properties of these two types of microreactors. At a flow rate of 12 g/min, better results were obtained with the ER-25 than with the ER-50 and the Corning-HP, which were themselves better than the Corning-LP (Table 3, entries 5, 9, 14, and 16). For the Ehrfeld microreactor, a significant gain in yield is obtained with a very slight increase of pressure drop (Table 3, entries 5 and 9). This is explained by eq 1 where the mixing time is a square function of the width of the laminar sheets ( $d$ ). For multi lamination mixing, small dimensions of 25  $\mu\text{m}$  fluid lamellae allow significant gain in mixing quality with limited increase of pressure drop when compared to 50  $\mu\text{m}$  fluid lamellae. As a consequence of the small channel size, however, the ER-25 and ER-50 reactors were prone to fouling and plugging. This also led to significant result variances when operated for longer period of time, making these reactors impracticable for commercial applications in the context of this reaction. The situation is different for the Corning microreactors, where a higher flow rate

**Figure 2.** Selectivity as a function of temperature for various microreactors (Table 3, entries 1–7, 9, 12–14).

affords faster and better mixing and thus better selectivity but also results in a significant increase in pressure drop (Table 3, entries 14–17). The selectivity was actually found to correlate with the logarithm of the pressure drop (Figure 3). For this microreactor, the mixing is not determined by the lamellae size since, even at low Reynold's number, the flow regime demonstrates chaotic behavior.<sup>9</sup> In fact, the main parameter influencing the micromixing is the amount of energy per volume that is introduced in the mixing zone (watt/liter). This situation is comparable to turbulent flow regimes.<sup>6</sup> Physically, this energy ratio translates into pressure drop, a parameter that is easily measured. The increase in pressure drop can be generated by larger internal structures creating smaller channels (see Corning-HP vs Corning-LP) or by higher flow rates.

These observations are valid as long as the thermal effect remains negligible compared to the mixing effect, that is to say as long as the reaction mixture is highly diluted (2.3% of ester **1** in feed 1, corresponding to an adiabatic temperature rise of ca. 28 °C). Higher feed concentrations afforded poorer selectivities (Table 3, entries 8–11). This is the result of two phenomena working in parallel. At higher concentrations the reaction rate is increased, increasing further the mixing requirements. In

**Figure 3.** Selectivity versus pressure drop at 20 °C (Table 3, entries 5, 9, 14–17).

**Table 4.** Dibal-H reduction of methyl butyrate (1) in the Corning multi-injection microreactor

entry	$T$ [°C]	injection points	flow rate [g/min]	feed 1 concn [%]	butyraldehyde (3) [area %]	methyl butyrate (1) [area %]	<i>n</i> -butanol (4) [area %]
1	20	1	11	2.3	13	62	25
2	20	1	17	2.3	17	59	24
3	20	1	23	2.3	21	56	23
4	0	1	11	2.3	27	52	22
5	0	1	17	2.3	39	44	16
6	0	1	23	2.3	43	42	15
7	0	1	26	10.0	17	56	25
8	0	2	26	10.0	22	53	25
9	0	3	26	10.0	24	52	24
10	0	4	26	10.0	24	52	24
11	0	4	37	10.0	24	52	25
12	0	4	43	10.0	23	53	24

addition, higher local temperature rises (hot spots) are associated with increased concentrations. Even if the influence of the mixing and of the heat management cannot be fully separated, the lower reaction selectivity at high concentration shows that the ER-50 microreactor does not allow sufficient temperature control for this reaction. Despite more efficient heat exchange than in batch reactors, very fast and exothermic reactions carried out in microreactors are not isothermal.

To have a better control of the reaction temperature, a new type of microreactor where one of the feeds is first split and then mixed with the second feed at various injection points was developed by a joint collaboration between Corning and Lonza.<sup>10</sup> This microreactor has very similar mixing design and the same channel sizes as the Corning-HP reactor. It was tested in the context of the methyl butyrate (1) reduction, using 1.0 equiv of Dibal-H solution as previously. In the first experiments, only one injection point was used to test the mixing properties of the multi-injection microreactor and to compare it with the reactors used previously at the same ester concentration of 2.3 wt %. As expected, the multi-injection microreactor gave results similar to those using the Corning-LP microreactor at 20 °C (Table 4, entries 1–3). A better mixing was obtained upon increasing the flow rate (more energy in the mixing zone). The selectivity of the ER-25 and ER-50 reactors was nevertheless not achieved, since the Corning microreactor was designed to operate at higher flow rates in the range of 80 g/min.<sup>10</sup> Logically, higher proportions of the target aldehyde 3 were obtained when lowering the reaction temperature to 0 °C (Table 4, entries 4–6 or Figure 4). Upon increasing the concentration of the methyl butyrate (1) solution from 2.3% to 10.0% (feed 1) and with a 26 g/min flow rate, only 18 area % of butyraldehyde (3) was formed as the consequence of temperature rise at the mixing point (Table 4, entry 7). Splitting the Dibal-H feed and injecting it at several locations afforded better selectivities (Table 4, entries 8–10). The influence is more important when going from

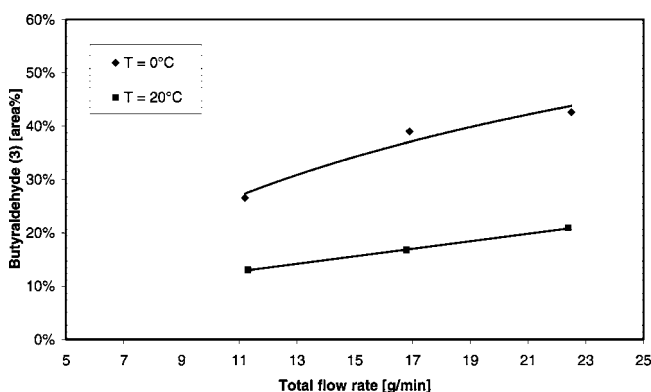
one to two injection points than to three or four. Upon further increasing the flow rate to 37 and 43 g/min., the selectivity did not vary (Table 4, entries 11 and 12). The improved mixing at higher flow rate is presumably compensated by the more severe hot spots.

## Conclusion

The good selectivities obtained batchwise at  $-78$  °C in the Dibal-H reduction of carboxylic esters can be reproduced in microreactors, with the advantage that a continuous microreactor process can be effectively scaled-up without selectivity decrease. The good mixing of microreactors allows good selectivities at temperatures as high as  $-20$  °C. However, better mixing compared to a batch process also means that the exothermicity of the reaction is concentrated in a tiny zone, resulting in a local hot spot. This local thermal effect can be split and thus reduced by using the multi-injection concept. The use of these microreactors should find broad application in the fine chemical and pharmaceutical industry for reaction sensitive to both temperature and mixing.

## Experimental Section

**Reaction Analysis.** The reaction mixtures were analyzed by GC with a HP-1 column. All samples were injected at 200 °C, and the column was heated from 40 to 280 °C



**Figure 4.** Influence of the flow rate on the formation of butyraldehyde (3) in the Corning multi-injection reactor using only one injection point (Table 4, entries 1–6).

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with a rate of 30 K/min. A FID detector was used at 280 °C (oven temperature).

**Batch Reactions.** All experiments were carried out in a 500 mL jacketed vessel equipped with a mechanical stirrer. A 20% Dibal-H solution in toluene (1.0 equiv) was added over 20 min to a 2.3% methyl butyrate solution in toluene at the temperature indicated in Table 1. The reaction mixture was then directly poured into a 2 M aqueous hydrochloric acid solution at 20 °C. The organic phase was analyzed by GC.

**Continuous Reactions.** The reactions were performed with two feeds, namely, the methyl butyrate feed (1.2% to 10.0% solutions in toluene) and the Dibal-H feed (20% solution in toluene). The Dibal-H stoichiometry was kept at 1.0 equiv throughout this work, corresponding to flow rates of 10.3 g/min (ester) and 1.6 g/min (Dibal-H) or a total flow rate of 11.9 g/min, for a 2.3% methyl butyrate feed. The solution at the microreactor outlet was directly

added into a 2 M aqueous hydrochloric acid solution at 20 °C. Parameters such as total flow rate, concentration, temperature, and pump type were varied throughout this work as depicted in Tables 2–4. Corning and Ehrfeld microreactors were used, and their respective characteristics are described in the main text.

#### **Acknowledgment**

We thank our colleagues in the Corning and Lonza microreactor teams.

#### **Supporting Information Available**

Structure of the Ehrfeld and Corning mixers. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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