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Aqueous Kolbe−Schmitt Synthesis Using Resorcinol in a Microreactor Laboratory Rig under High-p,T Conditions

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Abstract:

The aqueous Kolbe−Schmitt synthesis using resorcinol to yield 2,4-dihydroxy benzoic acid was performed in a microreactor rig. This small-scale plant was equipped initially with one capillary reactor and one microstructured cooler only. Later, two upgraded versions were constructed, having in addition a microstructured cooler and a microstructured mixer, respectively. The chemical protocol was significantly varied as compared to standard laboratory operation as described in the literature. Higher temperatures (up to 220 °C) and pressures (up to 74 bar) were employed in a facile manner, termed high-p,T processing. In this way, the reaction time could be shortened by orders of magnitude, from about 2 hours to less than one minute, in some cases to some seconds. This resulted in a remarkable increase of the space-time yield by a factor of 440 at best. Productivity was in the L/h range and yielded at best 111 g/h product, corresponding to 4 t/a. Scale-out solutions are indicated. Drawbacks of the microreactor operation were also identified such as high sensitivity to fouling and delicate regulation of the system pressure, leading to partly unstable plant operation. Possibly even a considerable part of the product was rearranged to 2,6-dihydroxybenzoic acid and then thermally decomposed under the harsh reaction conditions. Solutions to overcome or at least diminish these restrictions are envisaged, and in the hope that this may be achieved, a process innovation and business perspective for the high-p,T microreactor processing is depicted.

1. Need for Adapted Chemical Protocols for Chemical Micro Process Engineering: Enabling instead of Subduing Chemistry

Microstructured reactors are these days typically employed for niche processes where conventional equipment fails or the performance is much too low.[1−15] Typically, in a first run the batch experimental protocols are mimicked. Often, the batch protocols are adapted slightly thereafter, the main difference probably being the notable shortening of the reaction time. The use of higher temperatures has been reported in a few cases. However, this typically does not exceed a few 10 °C. Bearing in mind that most of the protocols take into account the relatively slow mass- and heat-transfer characteristics of batch reactors (even concerning small laboratory ones), it stands to reason that a purposefully drastic tailored change in the operating conditions is once required to exploit the full potential of microreactor technology.

Reactions in batch processes actually often have features of "domesticated" processing[14] (see also ref 15), e.g. as given by the typical addition of reactants drop-per-drop to exert control over heat releases of highly exothermic reactions or the replacement of very harsh reactants by slowly reacting ones. Actually, batch processing has been established for centuries,[16,17] and the chemistry is made "around the reactor",[17] i.e., adapted; when needed, it is "domesticated"[14] rather than customising the reactor for a chemical process. Now that expertise on chemical micro process engineering is growing, it is time to change the chemistry in microstructured reactors. A list of specific measures has been prepared to explain what exactly this implies. Among such issues are:[14]

- operation at unusually high temperatures and pressure
- solvent-free or reactant-rich solution processing
- operation in the explosive regimes
- use of unusually harsh reactants or unstable intermediates
- combining multiple reactions in a row

In the following, one of the first applications of the first item is reported, i.e., to change a chemical protocol by operating at much higher temperatures to reduce reaction times and, in turn, to increase productivity. Since this includes setting the pressure much higher to maintain a single-phase liquid processing, such an approach is termed high-p,T processing in the following. The Kolbe−Schmitt synthesis reported in this paper is actually one of the two

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(1) Hessel, V.; Hardt, S.; Löwe, H. *Chemical Micro Process Engineering: Fundamentals, Modelling and Reactions*; Wiley-VCH: Weinheim, 2004.
(2) Hessel, V.; Kolb, G.; Müller, A.; Löwe, H. *Chemical Micro Process Engineering: Processing and Plants*; Wiley-VCH: Weinheim, 2005.
(3) Pennemann, H.; Watts, P.; Haswell, S.; Hessel, V.; Löwe, H. *Org. Process Res. Dev.* **2004**, *8*, 422.
(4) Pennemann, P.; Hessel, V.; Löwe, H. *Chem. Eng. Sci.* **2004**, *59*, 4789.
(5) Kolb, G.; Hessel, V. *Chem. Eng. J.* **2004**, *98*, 1−38.
(6) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406.
(7) Hessel, V.; Löwe, H. *Chem. Eng. Technol.* **2003**, *26*, 13.
(8) Gavriilidis, A.; Angeli, P.; Cao, E.; Yeong, K. K.; Wan, Y. S. S. *Trans. Inst. Chem. Eng. A* **2002**, *80*, 3.
(9) Jensen, K. F. *Chem. Eng. Sci.* **2001**, *56*, 293.
(10) Jensen, K. F. *AIChE J.* **1999**, *45*, 2051.
(11) Jensen, K. F. *Nature* **1998**, *393*, 735.
(12) Haswell, S. T.; Watts, P. *Green Chem.* **2003**, *5*, 240.
(13) Fletcher, P. D. I.; Haswell, S. J.; Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Zhang, X. *Tetrahedron* **2002**, *58*, 4735.
(14) Hessel, V.; Löb, P.; Löwe, H. *Curr. Org. Chem.* **2005**, *9*, 765.
(15) Hessel, V.; Löb, P.; Löwe, H. *Chem. Eng. Technol.* **2005**, *28*, 267.
(16) Acricola, G. *De Re Metallica*; Froben, Episopius: Basel; Vol. XII, p 1556.
(17) Stankiewicz, A. I.; Moulijn, J. A. *Chem. Eng. Prog.* **2000**, *1*, 22.

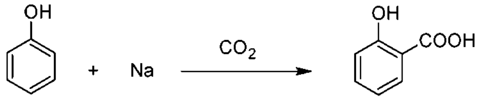
10.1021/op050045q CCC: $30.25

first two reaction examples carried out at IMM to validate the implementation of the novel concept. The other reaction was the thermal side-chain monobromination of *m*-nitrotoluene which was also presented recently.[18]

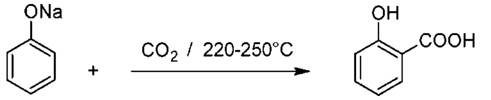
2. Conventional Kolbe–Schmitt Synthesis and Its Variants

The Kolbe–Schmitt synthesis is a standard route to introduce carboxylic moieties into a phenolic core, usually in ortho position to the hydroxyl group (see a review in ref 19). This reaction route was applied within the well-known industrial process for the manufacture of the drug Aspirin of the Bayer Company, used in headache tablets. The aqueous Kolbe–Schmitt synthesis, which is reported in this paper, is these days still applied for the synthesis of β- and γ-rescorcylic acids for uses in dyestuff additives, pharmaceuticals, reprographic chemicals, cosmetic preparations, chelators for resins, and fine organic chemicals.

Many variants of the Kolbe–Schmitt synthesis have been reported over a period of time, and some of the important ones shall be briefly given here. The initial work was performed already about one and a half centuries ago by Kolbe.[20] Salicylic acid was obtained by heating a mixture of phenol and sodium in the presence of carbon dioxide at atmospheric pressure.

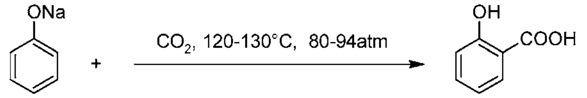


This synthesis was not easily scaled out, as there was a larger request for salicylic acid. Also, the yields on a laboratory level changed remarkably under seemingly similar reaction conditions. This was a result of volatilization of the reactant phenol and the consumption of sodium by reactions to species other than the salicylic acid anion, e.g., sodium phenoxide and sodium carbonate. For these reasons the solid hygroscopic sodium phenoxide, prepared from evaporated solutions of phenol and sodium hydroxide, was later used directly as a starting reagent by Kolbe.[21]

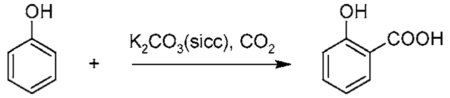


The dried sodium phenoxide was heated in an iron retort to 180 °C and carbon dioxide passed slowly over the hot salt. About half of the phenol distilled under these conditions so that the yield was never larger than 50%.

Schmitt modified the Kolbe procedure by applying pressure which resulted in greatly improved yields.[22] Dry sodium phenoxide is heated with carbon dioxide at 120–130 °C for several hours at a pressure of about 80 to 94 bar. No phenol is lost, and almost a quantitative yield of salicylic acid is obtained. This now so-called Kolbe–Schmitt method is still the standard method for the preparation of a wide variety of aromatic hydroxyl acids.



A further variant, introduced by Marasse, made the procedure even simpler, while maintaining the performance.[23] A mixture of the free phenol and excess anhydrous potassium carbonate is carbonated under pressure and at elevated temperatures.



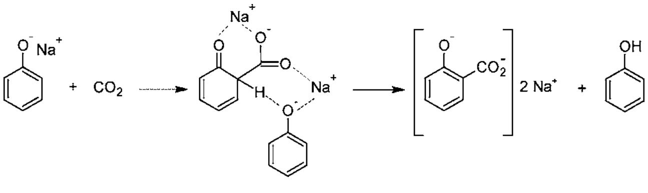
For an industrial application, however, the Marasse variant is quite expensive due to the costs of the carbonates used.

Carbonations were also made in the presence of solvents. For the more reactive di- and trihydric phenols such as resorcinol, pyrogallol, and phloroglucinol monocarbonation is achieved simply in alkaline aqueous solutions at atmospheric pressure, avoiding the harsh reaction conditions reported above.[24] Resorcinol, for example, is reacted at ambient pressure in water under reflux conditions with the weak base $KHCO_3$ to give 2,4-dihydroxybenzoic acid.[25,26] Then, a reaction time of approximately 2 h is needed.

The use of organic solvents such as toluene was also reported for carbonations of phenol at ambient pressure.[27] Suspensions formed out of the mixture of reactants and solvent. This prodcedure is recommended where pressure equipment is not available.

The conversion of potassium-2-naphthoxide to 2-naphthol was performed at an industrial scale in the framework of the Wacker process.[28]

The mechanism of the Kolbe–Schmitt synthesis was investigated and an intermediate proposed which predicts that two sodium phenoxide molecules act as chelating agents for the carbon dioxide.[29,30] In this way, the ortho orientation is fixed. Recent investigations give more detailed information. Three intermediates and three transitions are revealed by applying density functional theory (DFT) modelling.[31]



Recent works on the Kolbe–Schmitt synthesis are concerned with the effects of alkali and alkaline earth metals

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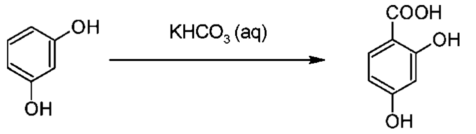
[18] Löb, P.; Löwe, H.; Hessel, V. *J. Fluorine Chem.* **2004**, *125*, 1677.
[19] Lindsey, A. S.; Jeskey, H. *Chem. Rev.* **1957**, *57*, 583.
[20] Kolbe, H.; Lautemann, E. *Ann.* **1860**, *113*, 125.
[21] Kolbe, H. *J. Prakt. Chem.* **1874**, *10*, 89.
[22] Schmitt, R. *J. Prakt. Chem.* **1885**, *31*, 397.
[23] Marasse, S. German Patent 73,259, 1893; Frdl. 3, 821.
[24] Thiele, J.; Jaeger, K. *Ber.* **1901**, *34*, 2840.
[25] Hale, D. K.; Hawdon, A. R.; Jones, J. I.; Packham, D. I. *J. Chem. Soc.* **1952**, 3503.
[26] Becker, H. G. O. et al. *Organikum*; Deutscher Verlag der Wissenschaften: Berlin, 1986; pp 334–336.
[27] Oddo, G.; Mameli, L. *Gazz. Chim.* Ital. **1901**, *31*, 244.

on the Kolbe−Schmitt synthesis[32] and with achieving regioselective carboxylation.[33]

3. Aqueous Kolbe−Schmitt Synthesis Using Resorcinol in the Microreactor Rig

In this paper, the reaction of resorcinol to 2,4-dihydroxybenzoic acid in aqueous solution at high temperatures and high pressure using a microreactor rig is reported[34] (compare refs 24−26). This process was taken as a model reaction to explore the possibility to significantly reduce the reaction times and, respectively, to increase the space-time yields by operation in a microreactor rig at temperatures much above the normal level. This is seen in the context of providing specially adapted chemical protocols for novel microreactor chemistry as outlined above.



The Kolbe−Schmitt synthesis was selected for the following reasons:

Unlike many organic syntheses neither gas nor solid is introduced or evolved. The reaction is only temperature-driven, i.e., premixing of the reactants in an external conventional flask can be done which renders the processing simpler by avoiding an integrated mixing step in the first run. Finally, the use of water as solvent stands for safe processing with an inexpensive and harmless solvent under the quite extreme conditions. This is particularly relevant for a later scale-up towards throughputs in the 100 or 1000 L/h range. The reactants resorcinol and potassium bicarbonate are cheap and available in large quantities. Actually, purum-grade (and not puriss -grade) qualities were used for all experiments to be a bit closer to real-word technical applications.

4. High p,T-Processing in Microreactor Rigs

4.1. Increasing the Temperature Processing Window for Liquid Single-Phase Operation. Most of the laboratory organic syntheses are performed under reflux operation at ambient pressure in multiple-necked stirred glass flasks and thus have an upper limit for setting the reaction temperature given by the boiling point of the liquid. However, chemical processing can extend to temperatures of about 80−90 °C for many solvents (including water) higher than the boiling point simply by applying overpressures of only 10 bar (see Figure 1).[35] This is especially facile for microreactor rigs with their small internal volumes, few numbers of seals, and low safety precautions needed.

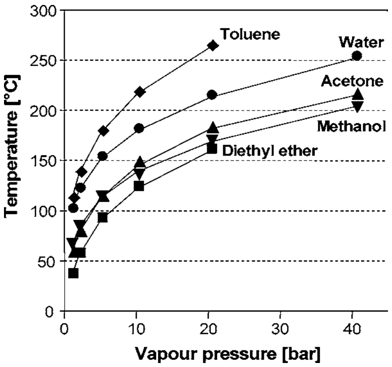


Figure 1. **Enhancement of boiling temperatures of typical solvents for organic reactions by rising pressure. Thus, by having overpressure, a single liquid-phase operation can be achieved much above the boiling point.**

5. Experimental Section

5.1. Construction of the Microreactor Rig. For initial experiments for process development, a simple first-hour process flow sheet was applied consisting only of a capillary reactor and a micro heat exchanger for cooling the reaction mixture which was operated with premixed reactant solutions (see Figure 2). In later experiments for process optimisation with premixed solutions, an advanced microreactor rig was installed consisting of a micro preheater, used when operating at high flow rates. Still later, another version of the microreactor rig was equipped with a microstructured mixer (and alternatively a T-junction) in addition so that two separate reactant solutions could be fed.

Concerning the heating-up of reactant solutions, both calculations and temperature measurements revealed that solely a certain entrance section of the capillary reactor is sufficient at low flow rates up to 500 mL/h. At higher flow rates, a second micro heat exchanger was used, since otherwise a notable portion of the capillary reactor would have to be used and most of the reaction would have been conducted under ramping and unknown temperature conditions.

The first-hour microreactor rig comprised a syringe pump (1000D; Teledyne ISCO Inc., Lincoln, NE/USA). As capillary reactor, commercial bent-steel tubing was used. As mixing tools, the IMM split-and-recombine micromixers CPMM-R600 and CPMM-R1200 of the caterpillar series[17] and a T-junction with minute internal tubing (Ø: 2.3 mm) were applied. A simple electrically heated tube device (abbreviated Tube HTMD)[33] was selected for heating the cold premixed solution to reaction temperature and a cross-flow fluidically driven micro heat exchanger (CRMH)[33] to quench the hot reacted solution down to ambient temperature.

The pressure increase in the microreactor rig to overpressures up to about 75 bar was achieved by a fine-metering

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(28) Wacker, A. Br. Patent 384,619, 1932; *Chem. Abstr.* **1932**, *27*, 1895.

(29) Hales, J. L.; Jones, J. I.; Lindsey, A. S. *J. Chem. Soc.* **1954**, 3145.

(30) Hunt, S. E.; Jones, J. I.; Lindsey, A. S.; Killoh, D. C.; Turner, H. S. *J. Chem. Soc.* **1958**, 3152.

(31) Markovic, Z.; Engelbrecht, J. P.; Markovic, S. *Z. Naturforsch., A: Phys. Sci.* **2002**, *57*, 812.

(32) Rahim, A. R.; Matsui, Y.; Kosugi, Y. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 619.

(33) Rahim, A. R.; Matsui, Y.; Matsuyama, T.; Kosugi, Y. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2191.

(34) Hessel, V.; Hofmann, C.; Löb, P.; Löhndorf, J.; Löwe, H. *Chem. Eng. Trans.* **2005**, *6*, 49.

(35) Lide, D. R. *Handbook of Chemistry and Physics*; CRC Press LLC: Boca Raton, 1998.

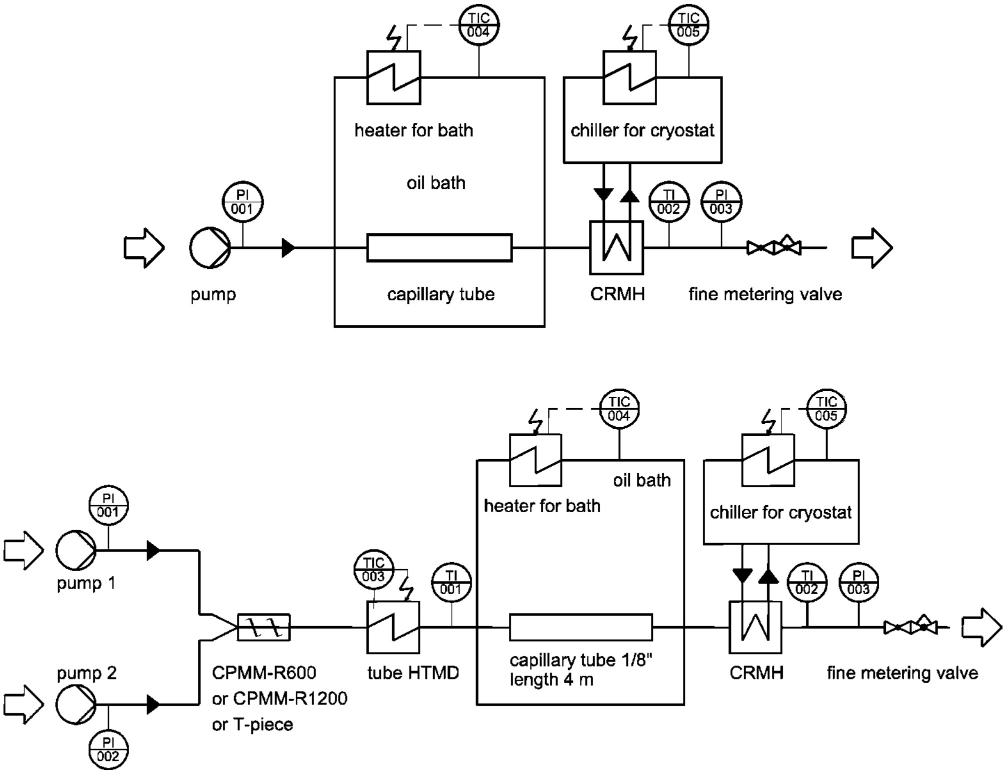

Figure 2. **Process flow sheets of two of three laboratory rigs used for performing process development for the aqueous Kolbe−Schmitt synthesis using resorcinol. (Top) Initial rig for process development fed by premixed reaction solution and without microstructured heater. (Bottom) Advanced rig for process optimization using two separate reactant solutions and having an additional heat-exchange function for preheating.**

valve which was adjusted manually by the operator. A manual pressure adjustment was favoured over an automatic, control-looped setting, owing to a reduced sensitivity of the valve flow path to fouling and blocking. This allowed the Kolbe−Schmitt synthesis to be performed under single liquid-phase conditions even at temperatures as high as 220 °C and above (see Figure 1) instead of having two-phase gas−liquid processing. The latter would negatively impact conversion by decreasing residence time through the gas consuming much of the capillary reactor and thereby pushing the liquid segments towards higher flow velocity. Accordingly, the chosen high-pressure equipment allows long reaction times under high p,T-operation.

5.2. Microreactor Devices Used. *5.2.1. Liquid Split-and-Recombine Micromixer CPMM-Series.* This micromixer has a ramp-like internal microstructure (see Figure 3) within one channel which is alternately directed up and down[1] (see ref 36 for the second-generation device). This induces at low Reynolds numbers a split-and-recombine action which is a sequential multiplication of the number of fluid lamellae, while halving their width[36] (see also ref 37). At high Reynolds numbers, circulatory flow gives eddies which lead to interfacial stretching. Thus, diffusion is the major mixing mechanism at low Reynolds numbers, while convection (followed by diffusion) is effective at high Reynolds numbers. Two versions of the CPMM mixer were used in the experiments. One with a small channel of 600 μm, CPMM R600, supposed to exhibit faster mixing, and one with a large channel of 1200 μm, CPMM R1200. The CPMM devices were manufactured by 3-D micromilling.

mixer type	CPMM: up−down ramped, split-and-recombine micromixer, caterpillar- type
mixer material	stainless steel SS 316 Ti
number of SAR steps	8
number of microstructured plates	2
channel width	1.2 mm
channel depth	1.2 mm
channel length (all 8 steps)	19.2 mm
mixer type	R1200
ramp width	0.6 mm
ramp length	1.2 mm
channel width	0.6 mm
channel depth	0.6 mm
channel length (all 8 steps)	9.6 mm
mixer type	R600
ramp width	0.3 mm
ramp length	1.2 mm
O-seal material	washer FPM
outer device dimensions	2 mm × 4 mm × 96 mm
total volume flow	up to 70 L/h
operational temp	up to 200 °C
system pressure	up to 30 bar/435 psig
liquid mixing time	20−100 ms

5.2.2. Electrical Preheater Tube HTMD. This electrically operated preheater (see Figure 3) comprises an open tube in which a microstructured body carrying parallel straight

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(36) Schönfeld, F.; Hessel, V.; Hofmann, C. *Lab Chip* **2004**, *4*, 65.
(37) Hessel, V.; Löwe, H.; Schönfeld, F. *Chem. Eng. Sci.* **2005**, *60*, 2479.

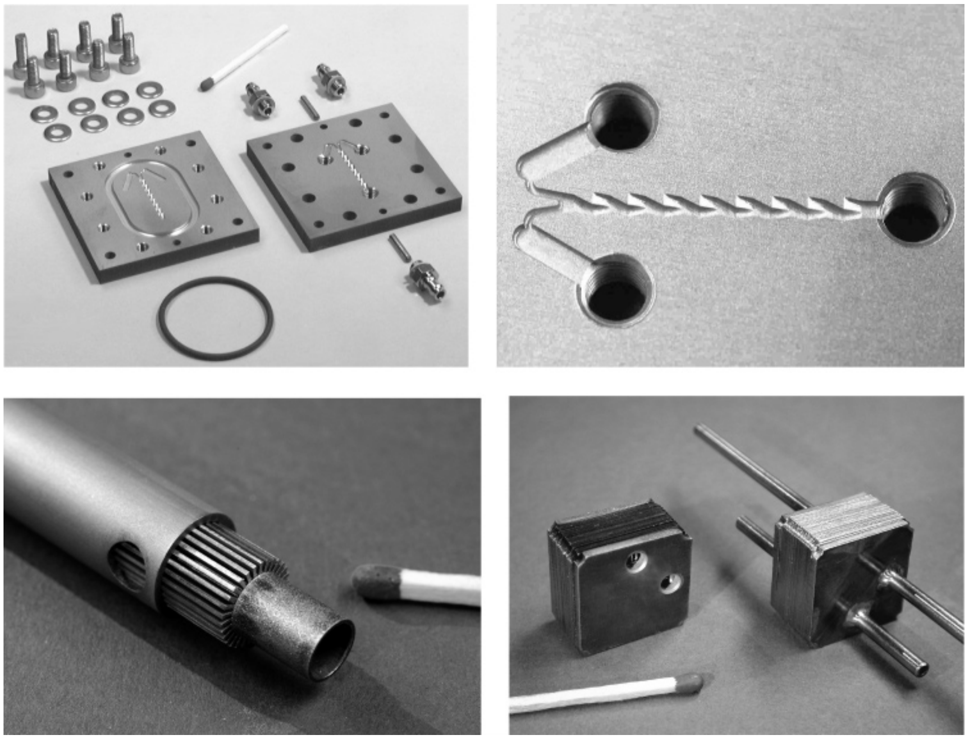

Figure 3. **Microstructured devices used. (Top left) Disassembled caterpillar micromixer CPMM-R1200, mainly showing the two microstructured housing plates. (Top right) Up−down curved ramp-type microstructured channel in the CPMM mixer. (Bottom left) Electrically stirred liquid microstructured preheater "Tube HTMD". (Bottom right): fluidically driven liquid microstructured cooler "CRMH".**

channels is inserted.[38] It has a simple overall architecture with minimal bends, i.e., having two-inlet feed and only straight channels in the interior. The device was manufactured by micromilling.

heat exchanger type	HTMD: electrically heated micro heat exchanger tube
mixer material	stainless steel SS 316Ti
number of microchannels per tube	32
channel width	0.5 mm
channel depth	1.5 mm
total length	60 mm
device diameter	12 mm
device length	80 mm
inlet diameter	$^1/_4$ in.
outlet diameters	$^1/_8$ in.
$\text{power}_{\text{electrical}}$	200 W

5.2.3. Capillary reactor. Two commercial capillaries (Harry Rieck GmbH, Hilden/Germany) were used as reactor and delay loop.

reactor type	bend capillary
mixer material	stainless steel SS 316Ti
tube inner diameter	1.3 mm
tube outer diameter (1st capillary)	$^1/_8$ in.
tube inner diameter	1.76 mm
tube outer diameter (2nd capillary)	$^1/_8$ in.
length (1st capillary)	4.4 m
length (2nd capillary)	3.9 m

5.2.4. Liquid Cross-Flow Cooler CRMH. This preheater (see Figure 3) is fluidically driven and uses a cross-flow guidance of the reaction and cooling fluids in a complex multiple-stack architecture.[33] The plates have multiple breakthroughs which are sealed by other plates, thereby creating microchannels. The plates are turned by 90° each, thus giving the cross-flow architecture. The plates were manufactured by punching and joined by diffusion bonding (the latter done by the Heatric Company, Poole/U.K.).

heat exchanger type	CRMH: cross-flow micro heat exchanger
mixer material	stainless steel SS 304
number of microchannels per plate	9
number of microstructured plates	52
channel width	0.7 mm
channel depth	0.2 mm
channel total length (mm)	12.0 mm
sealing	diffusion bonding
outer device dimensions	22 mm × 22 mm × 14 mm
total volume flow	up to 130 L/h
operational temperature	up to 300 °C
system pressure	up to 50 bar
heat transfer coefficient	4000 W/(m^2·K) for water at 30 L/h
specific heat transfer area	12800 m^2/m^3
active inner volume	15 mm^3
pressure drop	1 bar at 72 L/h watery fluid

5.3. Chemical Protocol. To focus on establishing the novel means of microreactor p,T-processing, the number of microstructured devices was reduced to those absolutely needed in the first experimental runs. The $KHCO_3$ concentration (253 g/L) had to be set close to the solubility limit (which is 333 g/L), and the resorcinol concentration was similarly high. Initial experiments revealed that precipitation

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(38) IMM, unpublished.

of such a concentrated solution may occur when exposed to high temperature. Thus, the use of a micromixer was omitted in the initial experiments, as this component is known to be liable to clogging. Consequently, premixed solutions with both reactants dissolved were used. This is justified, since it was known that the reaction hardly proceeds at room temperature.

The type of reactants and their concentrations were oriented on a standard protocol of the German student textbook for chemical practical courses in organic synthesis.[26]

- resorcinol: 73.5 g (0.782 mol)
- $KHCO_3$: 202.0 g (2.02 mol)
- water: 669.0 g

The result is an 800-mL aqueous stock solution with a 0.98 mol/L concentration of resorcinol. The textbook's recommendation, a 4−5-fold excess of $KHCO_3$ to resorcinol, was not used; instead was used only a 2.5-fold excess to avoid particle precipitation and clogging of the microreactor rig. Temperatures (100−220 °C), overpressures (1−74 bar), and reaction times (4−390 s) were set as given below.

For the later experiments using the caterpillar micromixer, two solutions of the following composition were fed.

- solution 1: 147 g of resorcinol (1.564 mol) in 105 g of water
- solution 2: 404 g of $KHCO_3$ (4.04 mol) in 1233 g of water

Most of the solvent water was given to solution 2 (owing to the low solubility of $KHCO_3$), resulting in an asymmetric ratio of about 10 for the two individual flow rates. While the function of many micromixers may be reduced at such flow ratios, the mixing efficiency of the caterpillar micromixer is not altered.

5.4. Materials. 2,4-Dihydroxybenzoic acid ($C_7H_6O_4$, 154.12 g/mol, Fluka, ≥98%), resorcinol ($C_6H_6O_2$, 110.11 g/mol, Aldrich, 99%), and potassium hydrogen carbonate ($KHCO_3$, 100.12 g/mol, Fluka, ≥98%) were used. The water was deionised by double distillation. The aqueous solutions were degassed by exposure to ultrasound and subsequently bubbled with nitrogen to remove the oxygen contents before use, because dissolved oxygen could lead to undesired oxidation reactions at the high temperatures envisaged.

5.5. HPLC Product Analysis. The contents of the reaction mixture were determined by HPLC (Shimadzu *VP* series with UV−vis detector) with acetonitrile (Aldrich) as eluent and the following chromatographic conditions: isocratic flow 0.6 mL/min, (50/50) CH_3CN/0.5 mol/L KH_2PO_4 in 1% H_3PO_4, 250 mm × 4.0 mm Nucleosil 120 C18, 5 μm column (Macherey Nagel, Düren/Germany purchased via MZ-Analysentechnik, Mainz/Germany), and UV detection at 220 and 260 nm.

6. Results and Discussion

6.1. Process Development. A time of 2 h is reported for completion of the reaction when operating in a laboratory-scale flask.[25,26] However, this setting has to be questioned, as most of the organic protocols do not refer to intrinsic kinetics and thus are set (by far) too long. For this reason, a kinetic study for the batch operation was performed to get a more exact estimation of the actual reaction time. Samples were taken from a stirred 1000-mL laboratory flask at defined intervals and analysed. In this way, it was, for example, found that a 40%-yield at a selectivity of about 90% was obtained after 120 min of reaction time (see Figure 4). In the literature, a maximum yield of 50% is reported after 2 h of operation so that in this case the protocol operation time was set quite accurately. This also means that it is not likely that a microreactor operation will give better results when keeping the same temperature and reaction time settings. On the contrary, other protocol settings have to be found for the microreactor to yield process intensification. In addition, the selectivity was determined using the batch data. A selectivity of about 90% to the product was found when the reaction was completed.

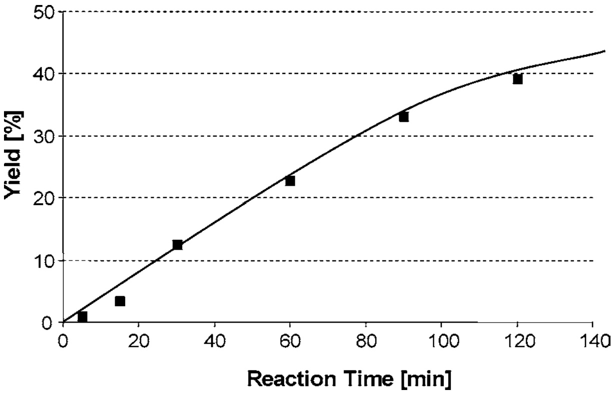


Figure 4. **Batch operation of the aqueous Kolbe−Schmitt synthesis using resorcinol in a typical laboratory stirred vessel under reflux conditions. Samples were taken at defined time intervals.**

Table 1. **Impact of overpressure on yield of the aqueous Kolbe−Schmitt synthesis using resorcinol, validating the high-p,T processing microreactor concept and sketching the threshold pressure value for stable single-liquid phase operation**

temp [°C]	flow rate [mL/h]	reaction time [s]	overpressure [bar]	yield [%]
120	84	390	0.3	23
120	84	390	8	46
120	84	390	16	45
120	84	390	32	47

The first-hour microreactor experiments were made at a reaction time of 390 s (equalling a total flow rate of 84 mL/h), respectively 6.5 min, and a temperature of 120 °C, varying the overpressure from 0.3 to 32 bar. On the basis of this information and the fact that approximately a doubling of the reaction time may be expected for each 10 °C temperature rise (i.e., 16-fold at 140 °C, when 100 °C is the reference temperature), the very first microreactor experiments were made at a reaction time of 706 s (equalling a total flow rate of 50 mL/h), respectively nearly 12 min, and a temperature of 140 °C. Actually, much longer reaction times are hardly feasible and useful, as this implies usage of still longer reaction capillaries, respectively higher pressure drops, and reduced space-time yields.

It was found that an overpressure of about 8 bar or more is required for stable and efficient operation. The following

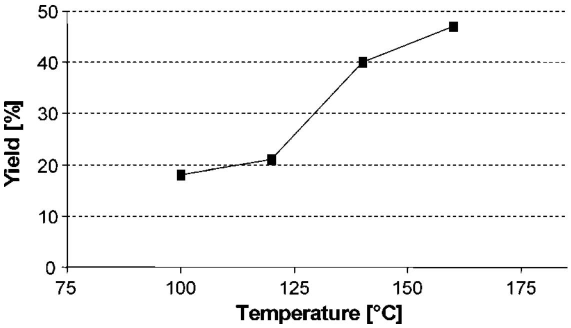


Figure 5. **Yields for the aqueous Kolbe−Schmitt synthesis using resorcinol in the microreactor rig: variation of reaction temperature at low flow rates, respectively long residence times, and moderate overpressures.**

experiments being conducted at 8 bar show that the yield increases with reaction temperature (see Figure 5). At 140 °C, the continuous-flow microreactor performance (yield: 48%) approaches that of the batch, albeit at much reduced reaction times. However, fouling and clogging (most likely by resorcinol- and $KHCO_3$ precipitation) were significant at these low flow rates. This was a result of unstable plant operations during part of the time and also because of less accurate and reliable analytical data concerning the product formation. The determination of the resorcinol conversion differed under seemingly the same conditions, and thus the analysis was only based on determining the product yield. In consequence, higher flow rates at still higher temperatures and overpressure were chosen for the next experiments. For these reasons, the plant rig was changed as well to a more robust version, less prone to fouling; the choice of the Tube HTMD micro heat exchanger especially constituted a major improvement.

6.2. Process Optimization. *6.2.1. In-depth Investigation of Residence Time and Temperature Effects.* In the second part of experiments, a more systematic variation of process parameters such as residence time and temperature was undertaken for a large parameter range from 6 to 560 s and 100 to 220 °C (see Table 2).

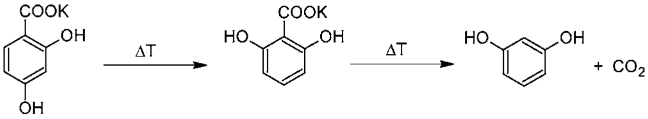
The yields approached and even exceeded 40% (e.g., 160 °C, 40 bar, 500 mL/h, 65 s or 200 °C, 40 bar, 2000 mL/h, 16 s; see Table 3). Thus, the performance of the batch operation (yield: 59%) was nearly reached.[26] The two microreactor operations mentioned above, accordingly, amount to a 110- or 450-fold reduction in reaction time as compared to standard batch-operation (see Table 3 and Figure 5).

In some sources other than ref 26, higher yields up to 60% are reported,[25] especially in the presence of carbon dioxide gas in addition to the carbonating $KHCO_3$. It is also cited basically for all variants of the Kolbe−Schmitt synthesis that both β−(2,4-di-hydroxy)- and γ−(2,6-di-hydroxy)-resorcylic acids are formed.[25] The exact share of both isomers is mainly determined by the reaction time and temperature. Generally, long reaction times (some 10 h) and high temperatures (>150 °C) favour the formation of the γ-resorcylic acid, the content of which then can amount up to 50%.[25] It is usually assumed that the γ-resorcylic acid is formed by follow-up rearrangement of the β-resorcylic acid initially generated. At high temperatures the γ-resorcylic acid readily decomposes to resorcinol and carbon dioxide.[25]

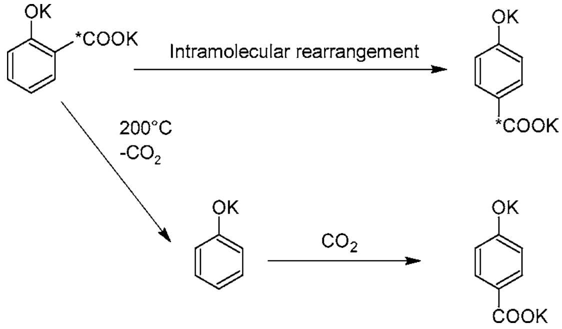
Table 2. **Optimised protocol settings for the aqueous Kolbe−Schmitt synthesis using resorcinol in the microreactor rig: reaction temperatures being further increased, flow rates being set higher, respectively shorter residence times, and overpressures are increased to about 40 bar[a]**

temp [°C]	flow rate [mL/h]	reaction time [s]	overpressure [bar]	yield [%]
120	500	65	40	12
140	84	390	40	47
140	250	130	40	35
140	500	65	40	28
140	1000	32	40	12
140	2000	16	40	4
140	3000	11	40	1
160	250	130	40	38
160	500	65	40	37
160	1000	32	40	15
160	2000	16	40	5
160	3000	11	40	1
180	500	65	40	43
200	250	130	40	34
200	500	65	40	35
200	1000	32	40	34
200	2000	16	40	38
200	3000	11	40	17
200	4000	8	40	10
200	5000	6	40	8
220	500	65	40	31

[a] The respective yields are indicated.



For the salicylic acid synthesis, a mechanistic analysis was made to determine how such arrangements of the hydroxyl group may occur.[33] It is expected that this proceeds in a similar way for the β-resorcylic acid.



It is also known that γ-resorcylic acid decomposes to resorcinol and carbon dioxide.[25] Other mechanistic investigations revealed how such thermal decomposition occurs for the potassium and other salts of salicylic acid.[30]

In view of this information, it is likely that at the high temperatures used some of the product β-resorcylic acid actually converted to γ-resorcylic acid and finally was decomposed to resorcinol. As a net effect, the yield may

Table 3. **Optimised protocol settings for the aqueous Kolbe−Schmitt synthesis using resorcinol in the microreactor rig: reaction temperatures being further increased, flow rates being set higher, respectively shorter residence**

type of processing	assumed processed flow rates [mL/h]	concentration [g/L]	productivity [g/h][a]	space-time yield [kg/h·m^3]	normalized space-time yield [−]
microreactor processing: single capillary (9 mL inner volume)	2000	88	111	12,330	440
batch processing (1 L flask)	500 (= 1000 mL/2 h)	88	28	28	1
microreactor processing: 5 parallel capillaries (9 mL inner volume)	2000	88	555	12,330	440

[a] Assuming 45% yield.

Table 4. **Protocol settings and yields for the aqueous Kolbe−Schmitt synthesis using resorcinol in the microreactor rig using three mixing tools, the caterpillar micromixers CPMM 600 and CPMM 1200 and a commercial T-junction**

mixing tool	temp [°C]	total flow rate [mL/h]	individual flow rates $KHCO_3$/resorcinol [mL/h]	reaction time [s]	overpressure [bar]	yield [%]
CPMM-R600	160	100	86/14	325	40	48
CPMM-R600	160	200	172/28	162	40	38
CPMM-R600	160	500	430/70	65	40	44
CPMM-R600	160	1000	861/139	32	40	37
CPMM-R600	160	2000	1721/279	16	40	28
CPMM-R1200	160	500	430/70	65	40	46
CPMM-R1200	160	1000	861/139	32	40	41
CPMM-R1200	160	2000	1721/279	16	40	27
T-junction	160	500	430/70	65	40	43
T-junction	160	1000	861/139	32	40	43

have been decreased and this is why not much more than about 45% yield was reached at maximum; all the γ-resorcylic acid contents which were generated may have been vanished in situ. A simple control experiment would be the guidance of commercially purchased β-resorcylic acid and γ-resorcylic acid under the high p,T-conditions through the microreactor rig and comparison of initial and final concentrations.

6.2.2. Productivity and Space-Time Yield. From the yield and other data given in the last chapter, an increase in the space-time yield by microreactor operation can be confirmed (see Table 4). A 440-fold increase as compared to the batch performance (1-L-flask; based on data from ref 8) can be stated, assuming a flow rate of 2000 mL/h for the microreactor and a yield of 45%. This is, to a considerable extent, owing to the small inner volume of the microreactor capillary (9 mL), whereas the outer footprint of the microreactor plant is certainly not much below that of the stirred 1-L batch reactor. Thus, the productivity in terms of material produced per time is probably the more relevant figure of merit. Such microreactor productivity, using the current settings, amounts to 111 g/h, which is 4 times that of the batch. Table 3 also gives an outline for productivity to be reached with five capillary reactors operated in parallel, which is feasible according to in-house experience. Then, a productivity of about 0.55 kg/h is achieved, respectively 13.2 kg per day and 4.4 t per year (assuming 24-h daily operation and 8000 h per year, excluding maintenance).

6.2.3. Variation of Flow Rate and Residence Time. In Figure 6, the dependency of the yield on the flow rate and the residence time is given for three selected temperatures of 140, 160, and 200 °C.

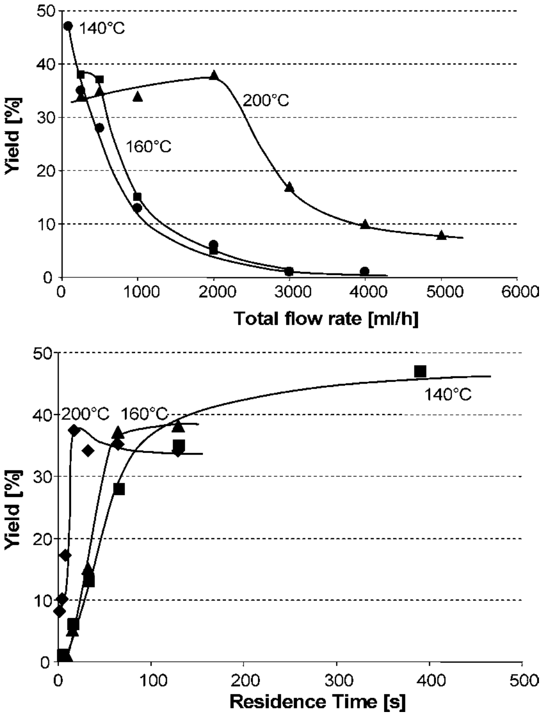


Figure 6. **Impact of setting the residence time via modifying the total flow rate on the yield of the aqueous Kolbe−Schmitt synthesis using resorcinol in the microreactor rig.**

The highest productivity is given at a temperature of 200 °C and a flow rate of 2000 mL/h with a yield of 30% where the interplay between throughput and conversion is maximal

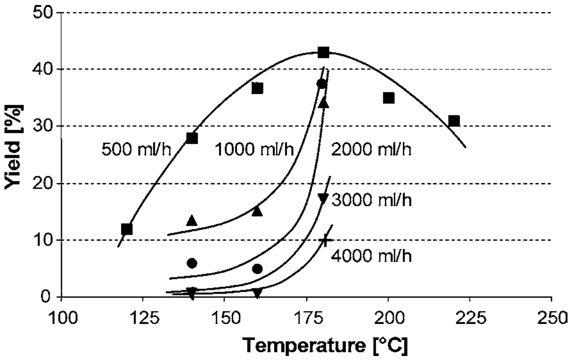


Figure 7. **Impact of setting the residence time via modifying the total flow rate on the yield of the aqueous Kolbe−Schmitt synthesis using resorcinol in the microreactor rig.**

(see Figure 5). At total flow rates above 2000 mL/h, the reaction time provided is not sufficient anymore, resulting in incomplete conversion. Below 2000 mL/h at a too-long residence time, the yield decrease may refer to selectivity losses, i.e., by increasing the content of side and consecutive reactions.

6.2.4. Variation of Temperature. In Figure 7, the dependency of the yield on the reaction temperature is plotted for various flow rates against residence times. It is evident that the yield increases largely with temperature up to about 180 °C for all data sets.

For one data set (500 mL/h) operation at still higher temperatures was performed as well. The performance decreased for the reasons given above. The possible relationship for the other four curves (1000 to 4000 mL/h) is less clear, when considering the few data points gathered. These curves seem to have a different dependency, as they have a much larger gradient of the yield increase; however, caution must be taken concerning too far-fetched conclusions, because of the small number of data points and the problems encountered with stable operations without any precipitation.

6.3. Processing with Online Mixing by Micromixers. *6.3.1. In-depth Investigation of Residence Time and Temperature Effects.* The use of premixed solutions poses limits. Most important, offline mixing creates safety constraints the larger these volumes become. Therefore, such operation is certainly not acceptable at a production level. Second, one cannot completely exclude pre-reactions such as with oxygen. Moreover, a simple screening of the concentrations of the reactants is not possibl; rather, manifold stock solutions would have to be prepared. Finally, a transfer of the high-p,T processing developed here towards other organic reactions, which have mixing sensitivity, would not be easily possible.

For all these reasons, it was tested if the implementation of a micromixer into the rig would give as good or even better performance. Because it was recently found that T-junctions with minute diameter may have a mixing performance similar to that of micromixers,[39−41] this option was tested as well. Actually, two micromixers of the caterpillar series were tested with differing internals. It was tested how the choice of a mixer with a larger inner diameter, which is the means to match an increase in productivity demands, may affect the performance of the Kolbe−Schmitt synthesis. Large asymmetric flow ratios were used because of very different solubilities of the reactants (see section 4.3.).

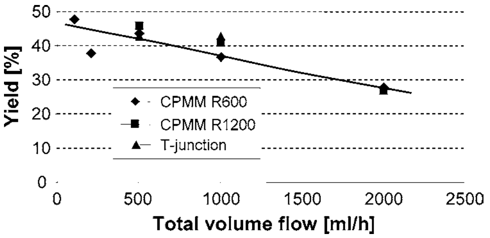


Figure 8. **Yields of the aqueous Kolbe−Schmitt synthesis using resorcinol, when different mixing tools are incorporated into the microreactor rig, placed in front of the capillary reactor. CPMM R600: caterpillar micromixer with 600-μm inner channel; CPMM R1200: caterpillar micromixer with 1200-μm inner channel; commercial T-junction with 2.3-mm inner channel.**

Figure 8 shows the yield as a function of the total volume flow at a temperature of 160 °C, when the different mixing tools are used (see also Table 4).

For all three devices, a decrease in yield can be observed with increasing total volume flow, due to the reduction of residence time. No major difference between the two microstructured mixers and the T-junction is given, at least in the flow range investigated here. This is not surprising as the T-junction is probably operated in the “intertwined” regime where the streamlines of the two solutions to be mixed are effectively entangled.[39−41] Probably the performance of the T-junction would decline for operation at low Reynolds numbers (here, at still lower total volume flow), because then a “stratified” flow is exhibited, similar to a bi-laminated fluid system with large diffusion distances and respectively inefficient mixing.

Bearing in mind that mixing was performed here using largely asymmetric flow ratios of about 10, the results also show that micromixers can be effectively used for performing the aqueous Kolbe−Schmitt synthesis even under these constraints. No loss in efficiency is observed as compared to the option with premixed solutions.

6.3.2. Preparative Product Isolation, Purification, and Identification. The crude product (from one experiment with the CPMM-R600 mixer at 1000 mL/h, 160 °C, 40 bar) was isolated by dropping the reaction solution into concentrated HCl solution.[26] The precipitated crystals were filtrated. Then, the crude product was heated with a small volume of water in a stirred flask with reflux condenser until boiling was achieved. The suspension was fed slowly with water until complete dissolution of the solid is achieved. Heating and stirring were stopped immediately, and the clear solution was slowly cooled without any shaking. Precipitates were formed and filtrated again. The purified product is composed of white crystals (215 °C, decomposition) which turn slightly pink after some days due to oxidation of the electron-rich aromatic core. A yield of about 22% of the purified product (2.59 g)

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(39) Wong, S. H.; Ward, M. C. L.; Wharton, C. W. *Sens. Actuators, B* **2004**, *100*, 359.

(40) Wong, S. H.; Bryant, P.; Ward, M.; Wharton, C. *Sens. Actuators, B* **2003**, *95*, 414.

(41) Engler, M.; Kockmann, N.; Kiefer, T.; Woias, P. *Chem. Eng. J.* **2004**, *101*, 315.

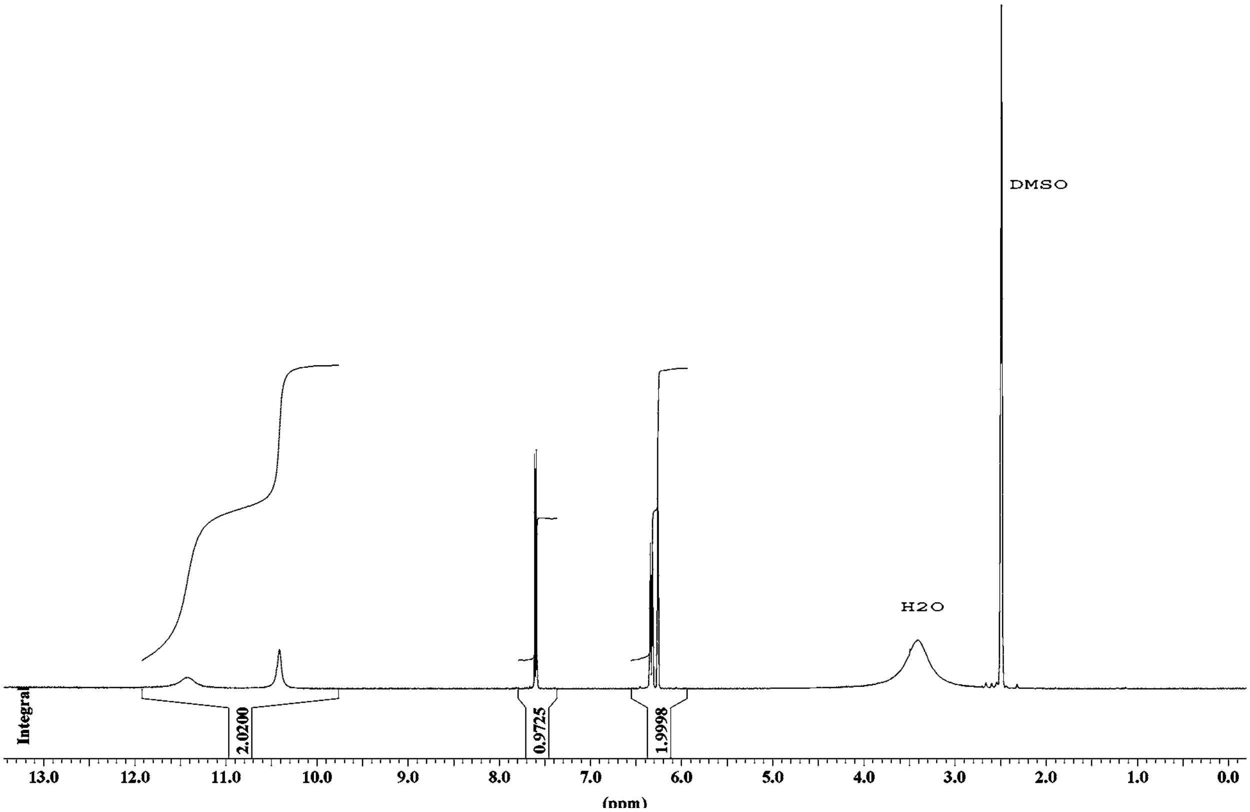

Figure 9. **^{1}H NMR spectra (solvent d_6-DMSO) of the purified product synthesized by the aqueous Kolbe−Schmitt synthesis in the microreactor rig. No side products are detectable.**

was obtained, which is considerably lower than the analytical HPLC yield of 40% and the literature data of 50%. Obviously, some losses of the product β-resorcylic acid occurred during precipitation. Further optimization of the purification step was not an objective within the works reported in this paper. Probably the use of additional extraction steps with diethyl ether will help here.[25]

The chemical nature of the product was confirmed in detail by ^{1}H NMR, ^{13}C NMR, FTIR, GC−MS, and elemental analysis. The NMR spectra show no traces of other organic molecules, in particular demonstrating that the reactant resorcinol was effectively separated (see Figures 9 and 10).

The elemental analysis with regard to C and H, however, differs notably from the calculated data. This is explained by the remainder of $KHCO_3$ in the purified product, which coprecipitates with the β-resorcylic acid. Since the product formation was undoubtedly identified by the other methods, no further attempts to remove the $KHCO_3$ contents were undertaken within the works reported here.

^{1}H NMR (Bruker AMX 400, 400 MHz, d_6-DMSO, δ/ppm): 6.2 (s −C(OH)−C**H**=C(OH)− 1H); 6.4 (d −C**H**=C(OH)−CH=C(OH)− 1H); 7.6 (d −C**H**=C(COOH)− 1H); 10.4 (s −CH=C(COO**H**)− 1H); 10.4 (s =C(COOH)−C(OH)−,1H); (−C(OH)−CH=C(O**H**)−, hidden by broad peak at 3.4 of H_2O traces within the solvent DMSO).

^{13}C NMR (Bruker AMX 400, 100.6 MHz, d_6-DMSO, δ/ppm): 102.3 (−C(OH)−**C**H=C(OH)−), 104.3 (−CH=**C**(COOH)−), 108.0 (=**C**H−CH=C(COOH)−), 131.9 (−**C**-H=C(COO**H**)−), 163.4 (−**C**H=CH−CH=C(COOH)−), 164.1 (=C(COOH)−**C**(OH)−), 172.0 (=C(**C**OOH)−).

FTIR (Nicolet Magna IR 750, KBr, cm^{-1}): ν(ring C−H) 1532, ν(C=O) 1885, ν(CO−OH) 3286, ν(=C−OH) 3640.

GC−MS (Agilent 6890 GC/5973N MSD, EI, *m/z*): 136 ($C_7H_4O_3$); 110 ($C_6H_6O_2$); 81 (C_5H_5O); not found: 154 ($C_7H_6O_4$, product peak), since all product was decarboxylated under the MS conditions.

7. Conclusions and Outlook

The advantages of the new microreactor synthesis for the aqueous Kolbe−Schmitt synthesis compared to a 1-L laboratory flask synthesis[7,8] are as follows.

- reduction of reaction time by orders of magnitude (few tens of seconds instead of minutes)
- increase of space-time yield by orders of magnitude
- increase of throughput by a factor of 2 (with option to one magnitude by numbering-up)
- simple and flexibly upgradeable rig, for laboratory and pilot throughputs

The yield approached data reported in the literature.[8] The process benefits are related to the simple high-p,T operation and the defined setting of short residence times using steep temperature ramps for preheating and cooling. Advantages in terms of mixing and mass transfer are not evident.

The disadvantages of the new microreactor technique are the following:

- partly unstable plant operation due to pronounced sensitivity to fouling
- unreliable resorcinol analysis due to resorcinol deposits and decomposition reactions in the plant

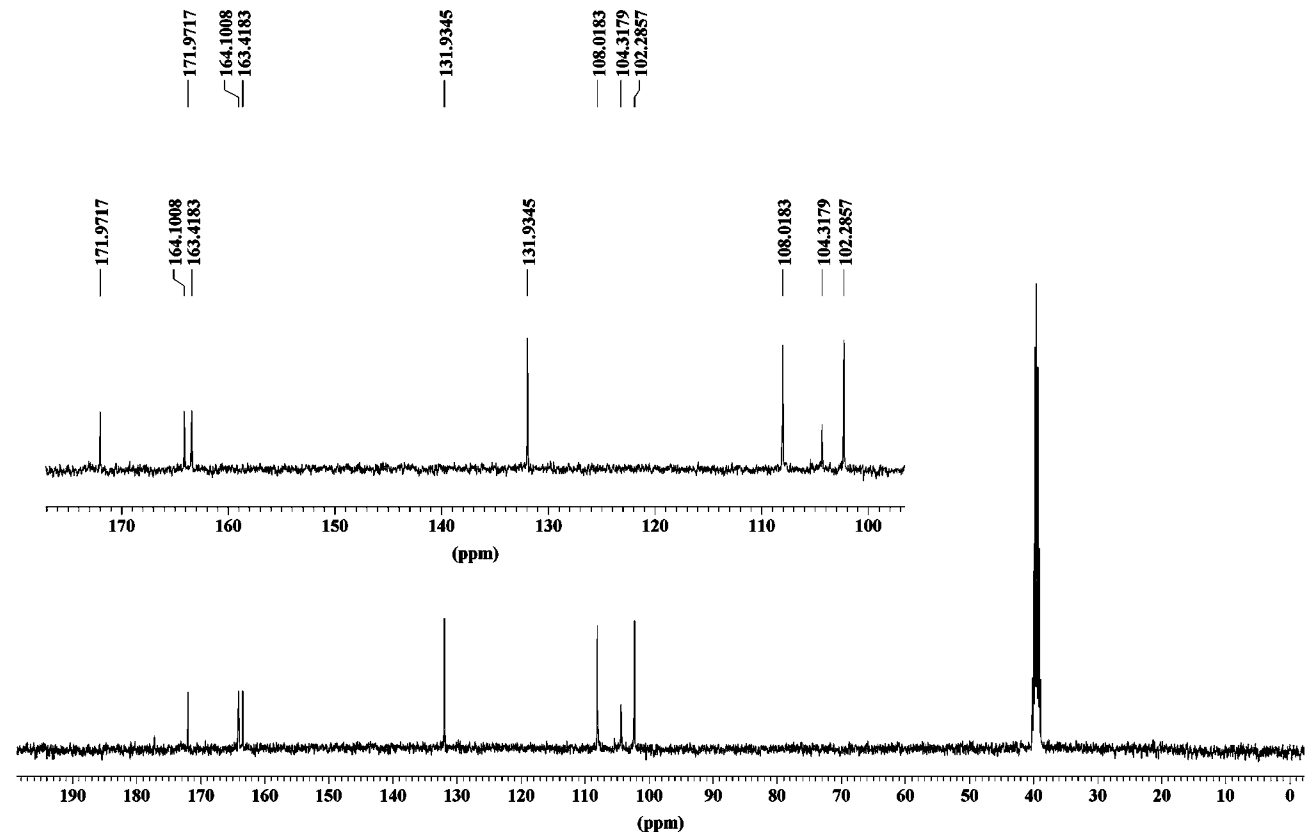

Figure 10. **^{13}C NMR spectra (solvent d_6-DMSO) of the purified product synthesized by the aqueous Kolbe−Schmitt synthesis in the microreactor rig.**

- capital and energy expenditure for high temperature and pressure operation

For optimisation of the microreactor-based aqueous Kolbe−Schmitt synthesis, credit should be given to the following topics, which actually will be investigated in the follow-up R&D.

- finding of additives to the solvent (e.g., cosolvent) for better dissolution of the reactants, in particular concerning the $KHCO_3$
- change to a more soluble carbonating species than $KHCO_3$
- feed of CO_2 as another carbonating agent
- automated pressure build-up and control
- construction of scale-out solutions with several capillaries in parallel

The development of a five-parallel-microreactor capillary plant with one large-throughput microstructured CPMM mixer is actually under way at IMM.

Once these process optimisations have been realised, it may be argued about benefits in terms of whole-plant operation and finally with regard to economic cost calculation—if not of interest for the Kolbe−Schmitt synthesis then certainly for another, similar, high-p,T microreactor process. Generically speaking, the following process innovation links may serve as business arguments for the use of the new technique.

- batch to continuous flow
- variable throughput, production on-demand
- reduction of plant footprint size with the option of mobile transfer for distributed, delocalised production
- modular system with adaptability towards other customized synthesis
- possible reduction in capital costs for equipment since a few inexpensive small-sized parts manage high throughputs

The following business drawbacks concerning microreactor plant operation are seen.

- possibly more dedicated process control loops, in particular to monitor stable flows and fouling
- possibly higher energy costs, in particular for building up high overpressures
- possibly reduction of the concentration and thus a larger share of solvent (which is, however, water only)

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