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Advantages of Synthesizing *trans*-1,2-Cyclohexanediol in a Continuous Flow Microreactor over a Standard Glass Apparatus

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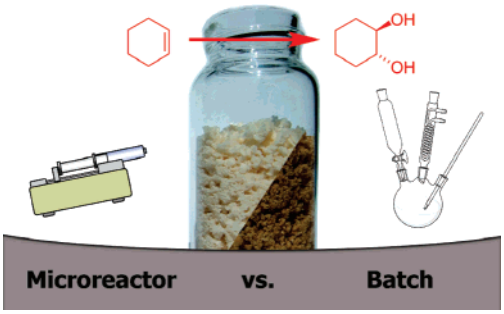
Received August 10, 2007



Comparison is made between the preparation of *trans*-1,2-cyclohexanediol in standard glassware (conventional batch production) and in a microreactor (continuous flow production). The reaction sequence involved two exothermic steps where the standard procedure demands slow reagent addition and careful temperature control. In the microreactor, the reaction could be carried out safely with up to 3 times higher reagent concentration. Synthetic benefits were a faster reaction rate and a higher purity product free of colored impurities (a feature of the batch procedure).

Increased attention is currently paid at the R&D level to performing synthetic reactions in microreactors, especially by chemical suppliers and pharmaceutical companies.[1−5] A microreactor is a miniaturized flow reactor with channel diameters between 10 μm and 1 mm. Under these conditions, fluid flow is laminar while mass transfer is dominated by molecular diffusion. Despite the success of custom-made microfluidic devices, they have the disadvantage of being generally based on silicone rubber, a polymer incompatible with most organic solvents and reagents. For this reason, microreactors for chemical synthesis are preferably made from glass, silicon, or steel substrates which require specialist equipment for fabrication. Not surprisingly, the top-of-the-range commercial microreactors preferred in industry can be quite expensive. All this has prevented a more widespread use of microreactors in the synthetic organic laboratory despite their numerous advantages. McQuade and co-workers have shown that a much simpler version of a microreactor—consisting of PVC tubing into which reactants are delivered by syringe pumps—can provide a relatively cheap and viable alternative.[1,6] Even combination of two or more reactant streams is easily achieved through micromixers, such as those used in standard low-pressure liquid chromatography systems.

A number of organic reactions have already been adapted successfully to microreactors.[1−5] Reactions that are exothermic and/or involve unstable reagents (recent examples include Swern oxidations[7] or the generation of benzyne-free *o*-bromophenyllithium)[8] benefit most from being run in a microreactor. Improved mass transfer and the use of higher temperatures and/or concentrations ensure that chemical reactions proceed at faster rates in microreactors when compared with a batch system. Small (≤1 mm) channel diameters guarantee a high surface-to-volume ratio that facilitates effective heat transfer. This has the advantage that even highly exothermic reactions can be carried out more safely in a microreactor, allowing otherwise hazardous conditions to be circumvented. Improved temperature control leads to better reproducibility compared to reactions in conventional flasks or in batch reactors where fluctuations in temperature and hot spots are often responsible for poor selectivity and the formation of byproducts. Scale-up, on the other hand, is generally accomplished by running a microreactor continuously or by operating ("numbering up") several microreactors in parallel.

Here, we report an adaption of a 2-step synthesis of *trans*-1,2-cyclohexanediol (**5**) to a simple continuous flow microreactor. To illustrate the scope of this approach, we have scaled up the synthesis to a laboratory scale typical for starting materials in a synthetic sequence.[9] The results in a microreactor were subsequently compared with those obtained in a round-bottom glass flask (batch reaction) based on an *Organikum* and *Organic Synthesis* protocol.[10]

Scheme 1 shows the synthetic sequence. We anticipated that a switch of this 2-step synthesis from batch to continuous microreactor operation would have the following advantages:

(1) Both steps 1 and 2 are exothermic. Whereas the *Organikum* suggested a reaction temperature of 70 °C for step 1, *Organic Synthesis* recommended that the temperature is maintained at 40 °C by adjusting the rate of addition of cyclohexene

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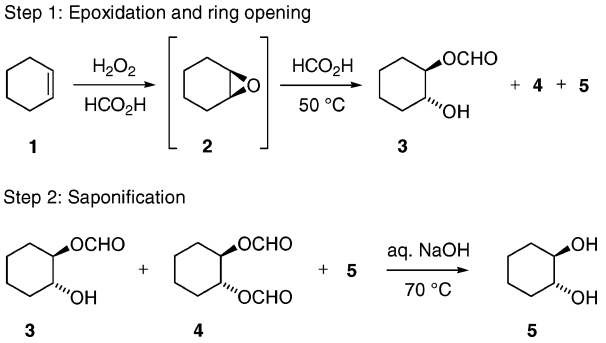
(8) Usutani, H.; Tomida, Y.; Nagaki, A.; Okamoto, H.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 3046−3047.
(9) Diol **5** is used as the starting material for the synthesis of artemisinin model compounds.
(10) (a) Roebuck, A.; Adkins, H. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, pp 217−219. (b) Autorenkollektiv. *Organikum*: *Organisch-chemisches Grundpraktikum*, 19th ed.; Deutscher Verlag der Wissenschaften: Leipzig, 1993; p 273.

10.1021/jo701758p CCC: $37.00
Published on Web 11/15/2007

SCHEME 1. Synthesis of *trans*-1,2-Cyclohexanediol (5)



to the oxidant through a dropping funnel and, if necessary, by cooling in an ice−water bath.

(2) Although the overall sequence is relatively free of side reactions, diol **5** made by the batch procedure tended to be discolored and therefore had to be purified further. We believed that this is due to the extended reaction times used under batch conditions (step 1: 2 h; step 2: 45 min)[10b] and that a much shorter contact time (i.e., the time that reactants would be exposed to elevated temperatures) in a microreactor would provide a higher purity crude product, thus eliminating the need for an extra recrystallization or distillation step.

The batch reaction was carried out following the *Organikum* procedure[10b] on a scale designed to give an overall yield of ca. 10−14 g of crude diol **5**. Two main problems became immediately apparent with the reported batch procedure when standard glassware was used. First, step 1 was highly exothermic as evident from a sharp rise in temperature from 20 °C to above 90 °C when cyclohexene (12 mL) was added to a 1 M solution of H_2O_2 in formic acid (100 mL). Second, the large amount of solvent (formic acid) was essential to dilute all reactants in the batch system in order to keep the reaction under control. A further increase in the concentration of H_2O_2, in order to make the reaction faster, would therefore be inadvisable for the batch reaction. Both issues had to be addressed when the reaction was switched to a microreactor. While the microreactor would cope well with the exothermicity of the reaction, we were also keen to increase the concentration of the reactants. Not only would this reduce the amount of waste solvent generated but it would also ensure a higher reaction rate and guarantee a sufficient throughput when the reaction was to be carried out on a 40−50 mL scale.

Our microreactor setup for step 1 made use of two syringe pumps, one dispensing cyclohexene and the other a mixture of formic acid and hydrogen peroxide, into poly(tetrafluoroethylene) (PTFE) tubings with an inner diameter of 1 mm (Figure 1). The two reactant streams were adjusted so that they combined to generate the requisite 1:1 stoichiometry in a static T mixer. A mixing unit was essential to facilitate rapid dissolution of cyclohexene in formic acid.[11] After leaving the T mixer, the reactant stream was delivered at a constant rate

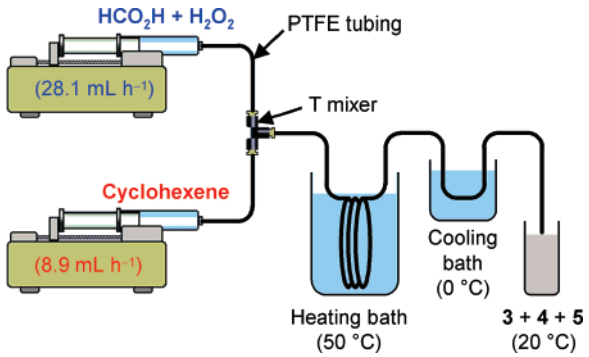


FIGURE 1. Schematic diagram of the microreactor setup for step 1 (flow rates and temperatures are given in parentheses). The flow rates were adjusted to achieve a stoichiometric ratio of the reactants.

TABLE 1. Conditions for Epoxidation/Ring-Opening: Step 1

conditions	batch reaction[10b]	microreactor
reaction temp, °C	70	50
H_2O_2 concn, mol L^{-1}	1.0	2.9
contact time, min	120	1
reaction time, min	120	82

through a 0.80 m long coil of PTFE tubing immersed in a heated poly(ethylene glycol) bath. The reaction mixture then passed through a short piece of tubing cooled in an ice−water bath before finally being collected in a flask.

Reaction conditions such as temperature and contact time were optimized initially on a small scale (corresponding to 0.4 mL of cyclohexene). On a 30-fold larger laboratory scale equivalent to 12 mL of cyclohexene, essentially the same conditions were maintained, only the reactor had to be run for a longer period. A temperature of 50 °C was deemed most appropriate as it was slightly higher than that recommended in the original *Organic Syntheses* procedure[10a] but still well below the boiling points of cyclohexene and formic acid.[11] A contact time of only 1 min was sufficient to achieve full conversion in the microreactor. By carrying out step 1 inside thin PTFE tubing we were able to increase the H_2O_2 concentration in formic acid to 2.9 M, almost 3-fold compared to the original literature procedure.[10b] The conditions for batch and optimized microreactor operation are summarized in Table 1.

GC analysis showed that three compounds had formed, and cyclohexene (**1**) or epoxide **2** had reacted completely. After destruction of excess H_2O_2 with sodium hydrogensulfite and concentration in vacuum, an oil was isolated that was analyzed by ^1H and ^{13}C NMR spectroscopy. The crude product from step 1 was found to consist of a mixture of monoester **3**, diester **4**, and diol **5**. The only byproducts present were traces of adipic acid resulting from over-oxidation.[12] The ratio of **3**:**4**:**5** after 1 min in a microreactor was 1:0.1:0.4, quite different from that (1:1.3:0.1) obtained at prolonged contact times of up to 2 h in the batch reaction. The increase in the ratio of diester **4** to diol **5** indicated that both monoester **3** and diol **5** underwent esterification with time under the reaction conditions.

The batch reaction for step 2 revealed again two concerns. A colored impurity formed within 10−15 min under the reaction

(11) Even in a microreactor, insufficient mixing can result in overheating of the reaction mixture, albeit only on a small scale since the volume exposed to higher temperature was less than 0.8 mL per meter of PTFE tubing. Overheating was observed when a simple T coupler was used instead of a static T mixer and the reaction temperature was raised to 70 °C. Under these conditions, cyclohexene droplets several millimeters in length formed inside the PTFE tubing and their subsequent reaction with H_2O_2 generated so much heat that the formic acid mixture exhibited "bumping". Surprisingly, the overall yield of diol **5** was still virtually the same (88%) as that obtained with the optimized procedure.

(12) Hydrogen peroxide is able to oxidize diol **5** to adipic acid under acidic conditions, although a promoter such as sodium tungstate is needed to make this conversion synthetically useful: Venturello, C.; Ricci, M. *J. Org. Chem.* **1986**, *51*, 1599−1602.

TABLE 2. Conditions for Saponification: Step 2

conditions	batch reaction[10b]	microreactor
reaction temp, °C	90	70
equiv of NaOH	2.5	1.2
contact time, min	45	0.5
reaction time, min	45	35
yield of crude diol **5**, %	86	88
mp of crude diol **5**, °C	100.2	102.0
appearance of crude product	brown	colorless

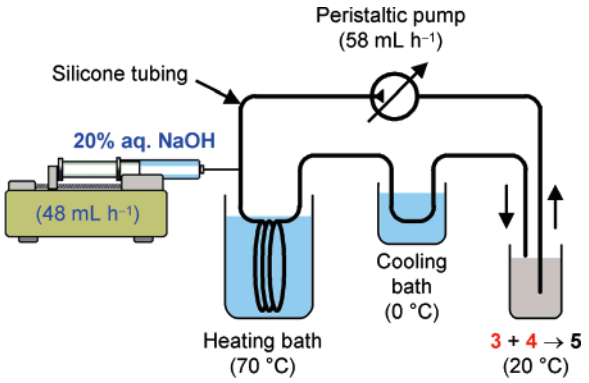


FIGURE 2. Schematic diagram of a continuous flow recycle reactor consisting of a syringe pump and a peristaltic pump for step 2 (flow rates and temperatures are given in parentheses).

conditions,[13] leading us to infer that short contact times would be advisable. Although the literature procedure suggested the use of 2.5 equiv of sodium hydroxide, a large excess of inorganic salts was likely to interfere with the extraction of diol **5** upon workup. In adapting the saponification of the ester mixture to a microreactor, we opted for a cyclic flow system. A continuous flow recycle reactor is not usually considered in microreactor technology for reasons of reduced space−time yield. It does, however, have a role to play in special cases, for example, in feeding microwave reactors where the closed loop arrangement allows a short residence time from a single pass to be extended until the conversion has reached satisfactory levels.[14] In our case, it allowed us to monitor the extent of saponification by thin-layer chromatography and keep, at the same time, the excess of NaOH to a minimum. This was more easily achieved in a cyclic flow system since the required stoichiometry could vary depending on the amount and ratio of esters **3** and **4** (as well as residual formic acid) present. Conditions for batch and microreactor reaction are summarized in Table 2.

A mixture of **3**, **4**, and **5** in aqueous methanol was placed in a beaker from which it was continuously circulated through a silicone tubing (inner diameter 1 mm) with use of a peristaltic pump. A syringe pump dispensed aqueous NaOH through a needle piercing the tubing wall just before the ester mixture was heated to 70 °C. The starting material/product mixture was finally fed back to the beaker that contained the original ester mixture, allowing a continuous loop process (Figure 2). Complete saponification required a contact time of only 0.5 min. Controlled addition of NaOH to the ester mixture made it furthermore possible to minimize the excess NaOH needed.

(13) Although the identity of the colored impurity remains unclear, possible sources for such an impurity are trace residues of stabilizer present or oxidation byproducts formed over time in commercial cyclohexene.

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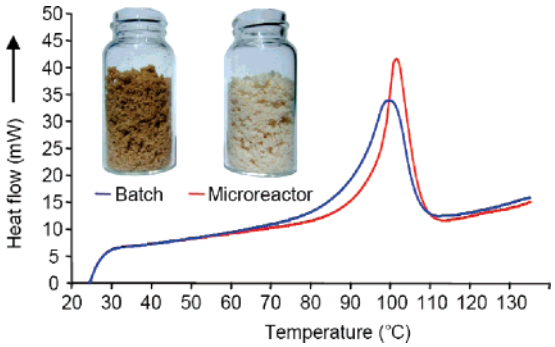

FIGURE 3. Differential scanning calorimetry traces (heating rate 10 deg min^{-1}, arrow indicates direction of endothermic transitions) of diol **5** prepared by a batch reaction versus reaction in a microreactor. The photographs of the two samples show the discoloration (impurity) of the product obtained in the batch reaction.

We were thus able to reduce the amount of waste salts (NaCl and sodium formate) that were obtained after neutralization with hydrochloric acid and from which product **5** was to be extracted.

Diol **5** was isolated by extracting the concentrated residue from step 2 with chloroform. The overall yield of the crude **5** obtained by the 2-step batch reaction (86%) differed little from the yield in the microreactor (88%). However, the product from the batch reaction was noticeably discolored (Figure 3). When the reaction sequence was conducted in a microreactor, a *colorless crude* diol **5** was obtained instead. Differential scanning calorimetry of crude samples produced in the batch and microreactor reaction showed a melting temperature of 100.2 vs 102.0 °C (Figure 3). The higher melting temperature (comparable to recrystallized batch product), elemental analysis, and sharper melting peak indicated a higher purity for the product produced in the microreactor.

In summary, both the highly exothermic epoxidation/ring-opening step 1 and the saponification step 2 benefitted from being run in a continuous flow microreactor system. Our microreactor was assembled simply from syringes, ordinary laboratory tubing, a mixing unit, and either two syringe pumps or one syringe pump and a peristaltic pump. Apart from improved temperature control, reactions inside the thin tubing could be carried out safely at much higher reagent concentrations, thus increasing the reaction rate considerably while also reducing the amount of solvent waste. Full conversion was achieved with contact times of 1 (step 1) and 0.5 min (step 2). Advantages of the microreactor reaction from an organic chemist's point of view were a noticeable improvement in purity of diol **5** (circumventing the extra distillation or recrystallization step required in the batch procedure), reproducible yields, and slightly shorter overall reaction times. Moreover, since the conditions remained identical whether the reaction was carried out on a small or a larger scale, the microreactor facilitated the scaling up of this 2-step synthesis of a typical starting material just by running the reaction for a longer period. These benefits were achieved with a simple and relatively inexpensive microreactor setup (using common plastic syringes, laboratory tubing, HPLC mixing unit and fittings, and syringe/peristaltic pumps) and should be applicable to many other exothermic reactions that similarly demand careful temperature control and slow reagent addition.

Experimental Section

Microreactor Reaction of Cyclohexene with Hydrogen Peroxide in Formic Acid. The epoxidation/ring-opening step 1 was carried out in a microreactor assembled from two syringe pumps, PTFE tubing (1 mm inner diameter, 1/16 in. outer diameter), and a static T mixer as shown in Figure 1. Luer fittings were used to connect PTFE tubing with syringes and mixing tee. A 50 mL glass syringe was filled with aqueous hydrogen peroxide (47%, 8.69 g, 0.12 mol) in formic acid (98%, 33 mL) and mounted on a syringe pump. A 20 mL polypropylene syringe was filled with cyclohexene (9.86 g, 12.2 mL, 0.12 mol) and mounted on a second syringe pump. Flow rates were adjusted so that the two reagent streams were combined in an equimolar ratio in a static mixing tee (flow rates: 29 mL h^{-1} for aqueous H_2O_2, 9 mL h^{-1} for cyclohexene). Upon leaving the mixer, the resulting solution was allowed to pass through 0.80 m of PTFE tubing immersed in a heating bath (50 °C) followed by a 0.10 m section of tubing cooled in an ice−water bath. The resulting product solution was collected in a round-bottomed flask. After removing the solvent in a vacuum, a clear oil (17.7 g) was obtained and identified as a mixture of *trans*-1,2-cyclohexanediol diformate (**3**), *trans*-1,2-cyclohexanediol monoformate (**4**), and *trans*-1,2-cyclohexanediol (**5**). **3**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18−1.47 (m, 4H), 1.64−1.78 (m, 2H), 1.98−2.12 (m, 2H), 3.55 (∼td, J = 9.7, 4.6 Hz, 1H), 4.62 (td, J = 9.1, 5.0 Hz, 1H), 5.44 (br s, 1H, O*H*), 8.10 (s, 1H, OC*H*O); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.6 (CH_2), 23.7 (CH_2), 29.9 (CH_2), 30.0 (CH_2), 72.2 (CH), 78.0 (CH), 161.3 (CH); R_f (ethyl acetate) 0.50. **4**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18−1.47 (m, 4H), 1.64−1.78 (m, 2H), 1.98−2.12 (m, 2H), 4.85−5.00 (m, 2H), 8.02 (s, 2H, OC*H*O); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.2 (CH_2), 32.8 (CH_2), 73.2 (CH), 160.4 (CH); R_f (ethyl acetate) 0.64.

Microreactor Saponification Step. The oily mixture of **3**, **4**, and **5** from step 1 was dissolved in a water−methanol mixture (5 mL:1 mL) and placed in a beaker. The solution was circulated through a 2.20 m long silicone tube (inner diameter 1 mm) by using a peristaltic pump set at a flow rate of 58.8 mL h^{-1}. A polypropylene syringe was filled with an aqueous solution of NaOH (20%, 24 mL, 0.12 mol) and mounted on a syringe pump. The NaOH solution was dispensed into the reaction stream, through a 27-gauge blunt-edged needle inserted halfway into the silicone tubing, at a flow rate of 48.0 mL h^{-1}. A 0.80 m section of the tubing was immersed in a heating bath kept at 70 °C, while 0.10 m of tubing nearer the outlet was cooled in an ice−water bath. At the outlet, the reaction solution was allowed to flow back into the beaker containing the starting material, as shown schematically in Figure 2. The reaction was stopped once the NaOH solution had been completely dispensed and **3** or **4** could be detected no longer by thin-layer chromatography. The mixture was neutralized with concentrated HCl and the solvent was removed in a vacuum. The residue was extracted with chloroform (5 × 30 mL) and the organic layers were combined. After removing the solvent in a vacuum, a colorless solid was isolated and dried. Yield 12.3 g (88%); DSC 102.0 °C (99.3 J g^{-1}, lit.[10a] mp 101.5−103 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18−1.47 (m, 4H), 1.64−1.78 (m, 2H), 1.98−2.12 (m, 2H), 3.26−3.27 (m, 2H, C*H*OH), 3.55 (br s, 2H, O*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.2 (CH_2), 32.8 (CH_2), 75.7 (CH); R_f (ethyl acetate) 0.32. Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found (after drying): C, 61.19; H, 10.29. Found (after sublimation): C, 62.09; H, 10.59.

Acknowledgment. We thank the Royal Society, the School of Engineering & Physical Sciences at Heriot-Watt University, and ScotCHEM for support.

Supporting Information Available: Detailed experimental procedures, NMR and GC analyses, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701758P