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Investigation of the Moffatt−Swern Oxidation in a Continuous Flow Microreactor System

Jacobus J. M. van der Linden, Peter W. Hilberink, Claudia M. P. Kronenburg, and Gerardus J. Kemperman*

N.V. Organon, Department of Process Chemistry, P.O. Box 20, 5340 BH Oss, The Netherlands

Abstract:

The Moffatt−Swern oxidation of different alcohols is performed in a continuous flow microreactor system. The microreactor process offers significant advantages over the batch process. First, because of the small reactor volume, accumulation of the labile trifluoroacetoxydimethylsulfonium salt (3) and alkoxydimethylsulfonium salt (5) is minimized. Second, because of the short residence times, which can be applied in the microreactor, the exothermic Pummerer rearrangement of the unstable intermediate 3 is limited. Because of this, the process can be operated at remarkably high temperatures in comparison with a batch reaction, viz. 0−20 °C instead of −70 °C. In the present study, a continuous flow microreactor system was optimized using reactors of different volumes allowing modulation of the residence times of labile intermediates. The efficiency of mixing was studied using different mixing devices. It has been shown that the continuous flow microreactor is an ideal tool for rapid optimization of reaction parameters. Furthermore, the scaleability and reliability of the microreactor was tested by running the system for several hours. For testosterone, the system was in process for 1.5 h without any problems, resulting in an 4-androstene-3,17-dione production rate of 64 g·h^{-1}.

Introduction

In the pharmaceutical industry reactions are traditionally performed in multipurpose batch reactors.[1] However, for extremely exothermic reactions or reactions that proceed through highly reactive and unstable intermediates, the use of batch reactors has major disadvantages that are related to temperature control and safety problems.[2,3] This is mainly attributed to a diminishing cooling capacity and diminishing heat- and mass transport through a batch reactor due to a limited stirring capacity upon scale-up.[4] In addition, in a batch reactor there is the possibility of accumulation of reactive intermediates that impose a risk for a runaway reaction.

Continuous flow microreactors could, in principle, provide a solution to the above-mentioned problems. In a microreactor, mixing and chemical reactions take place on a scale with characteristic dimensions in the submillimeter range and with reaction volumes in the nanoliter-to-milliliter range.[5] As a result, mixing and heat transfer in the microreactor are extremely fast. These features are quite advantageous for conducting fast and highly exothermic reactions. Additionally, the volume of a microreactor is very small compared to that of a batch reactor, which ensures that only small amounts of reactive, and potentially dangerous, intermediates can accumulate. This contributes to an increased safety.

In order to assess the advantages of microreactors for highly exothermic reactions, the Moffat−Swern oxidation was investigated in a microreactor system from the company Ehrfeld Mikrotechnik BTS (GmbH).[6]

The Moffatt−Swern oxidation is a multistep process by which a number of side products can be formed (Scheme 1) according to the mechanism as postulated by Omura et al.[7,8] The Moffatt−Swern oxidation is a versatile metal-free oxidation method that finds application in the transformation of primary and secondary alcohols into aldehydes and ketones, respectively. However, application of Moffatt−Swern oxidation in process chemistry is hampered by the low temperature requirement, viz. −70 °C, and the highly exothermic behavior, which makes temperature control very difficult. In addition, the reaction proceeds through labile reactive intermediates, viz. trifluoroacetoxydimethylsulfonium salt (**3**) and alkoxydimethylsulfonium salt (**5**), which imposes the risk of a runaway when a certain temperature is exceeded. The exotherm causing the runaway can be attributed to the Pummerer rearrangement of intermediates **3** and **5** which takes place above −30 °C and leads to the formation of trifluoroacetoxymethyl methyl sulfide (**7**) and methylthiomethyl ether (**8**), respectively. The trifluoroacetoxymethyl methyl sulfide (**7**) can subsequently react with benzyl alcohol to benzyltrifluoroacetate (**9**) under the basic conditions after the quench. Obviously the uncontrolled decomposition of intermediates **3** and **5** is also detrimental to the yield of the process.

A continuous flow process would be an ideal setup to consume the trifluoroacetoxydimethylsulfonium salt (**3**) and

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* Corresponding author. E-mail: Gerjan.kemperman@organon.com. Telephone: +31 412 669375. Fax: +31 412 663513.

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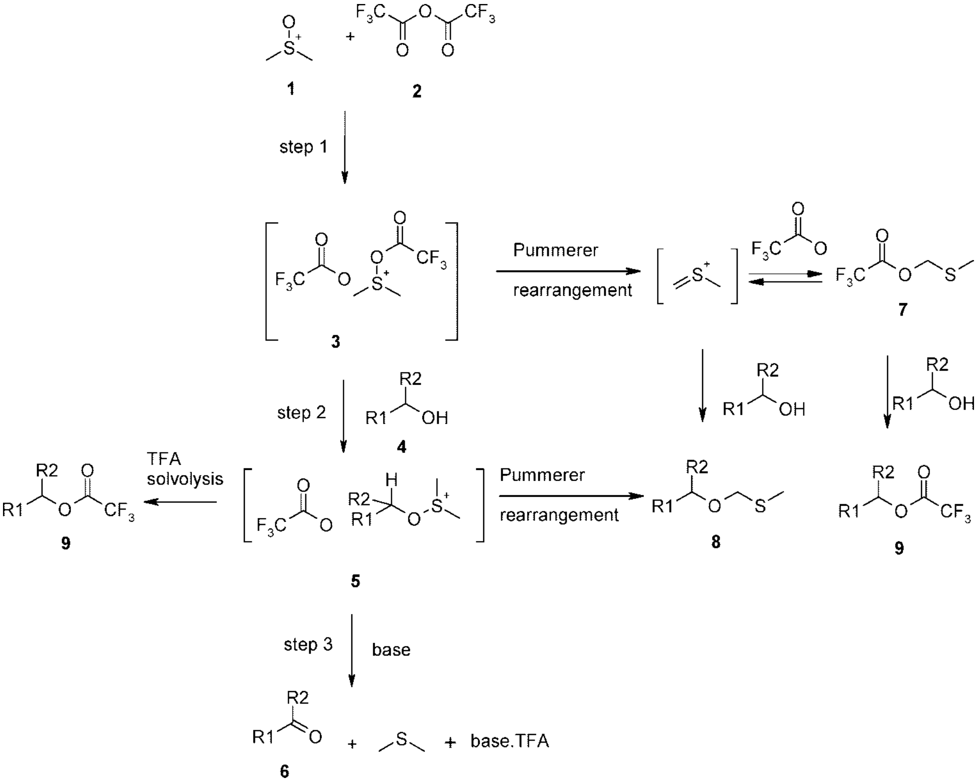
Scheme 1. **Moffatt−Swern oxidation**



alkoxydimethylsulfonium salt (**5**) directly after their formation, such that no accumulation takes place. Furthermore, the highly efficient heat transfer in the microreactor should solve the problem of limited cooling capacity experienced in a batch reactor.

At the start of our study a paper from Yoshida et al.[9] appeared, in which the Moffatt−Swern oxidation was carried out at higher temperatures in a microreactor. However, whereas Yoshida used syringe pumps to feed reagents into the microreactor, in our system HPLC pumps were employed, allowing for a real continuous process.

The Moffatt−Swern oxidation was investigated in different setups for the microreactor and by using a series of aromatic alcohols as the substrate. We also report on our efforts to perform reaction parameter screening in the microreactor. The effects of mixing efficiency and residence time were investigated in order to reveal the root cause for the beneficial effects of a continuous flow microreactor on the Moffat−Swern oxidation. Finally, the scaleability and consistency of the Moffatt−Swern oxidation were tested using several more functionalized alcohols such as a steroid and carbohydrates.

Results and Discussion

Microreactor Setup. A schematic drawing of the microreactor setup used is shown in Figure 1. The microreactor consists of three stainless-steel LH2 stand-alone micromixers (**M1**, **M2**, and **M3**).[6] This type of micromixer is based on the principle of multilamination, i.e. successive splitting and rearrangement. For that purpose each micromixer contains a mixing plate with 2 × 10 slides and a slit diameter of 50/50 μm and an aperture plate with a slide diameter of 50 μm and a length of 2 mm. The mixers were connected with stainless-steel tube reactors (**R1**, **R2**, and **R3**) of different lengths and diameters in order to vary the residence times (see Experimental Section). The micromixers were placed in a homemade double jacketed stainless-steel vessel. The Teflon lid contains two holes for cooling, four inlet holes for the reagents, one outlet hole and one hole for a Pt-100 thermometer. The vessel is cooled or heated by a Julabo LH85. The reagents were fed into the system using Knauer K501 HPLC pumps (**P1**, **P2**, **P3**, and **P4**).

The reactor volumes of **R1**, **R2**, and **R3**, in the different setups (I−IV) as referred to in the paper are detailed in the Experimental Section. The reactor volumes of **R1**−**R3** are in the range of 2–253 μL. The volumes of the mixers are negligible in comparison with those of the reactors. This implies that the reactions predominantly take place in the reactors and not in the mixers.

Mechanistic Considerations and Development of an Appropriate Analytical Method. All HPLC analyses were performed off-line. Due to the short reaction times, it was possible to collect a large number of samples from the microreactor in a relatively short time (up to 20 samples in 1 h). Therefore, it was important that the collected samples were stable before injection. The effluent of the microreactor contains, besides dichloromethane, alcohol, the corresponding ketone or aldehyde, DMSO, several side products such as the trifluoroacetate ester **9**, methylthiomethyl ether **8**, and the base. As discussed in the Introduction, on the basis of the proposed mechanism of the Moffat−Swern oxidation, the trifluoroacetate ester **9** can be formed by reaction of Pummerer rearrangement product **7** with the alcohol. In order to investigate whether reactions between various species could take place in the sample, alcohol was exposed to freshly prepared Pummerer rearrangement product **7** under acidic conditions (TFA, 10 min and 1 h) and under basic conditions (triethylamine, 10 min and 1 h). This revealed that under acidic conditions, compound **7** can react with the alcohol to give methylthiomethyl ether **8**, but under basic conditions, this reaction is not observed. As the alcohol is only exposed to compound **7** in an acidic medium during the short residence time in reactor **R2**, it can be concluded that the pathway from compound **7** to methylthiomethyl ether **8** can be ignored in the microreactor setup. This implies that the amount of methylthiomethyl ester **8** in the sample is predominantly formed by Pummerer rearrangement of intermediate **5**. It was also found that under basic conditions, the Pummerer rearrangement product **7** reacts with the alcohol to give the trifluoroacetate ester **9** as is indicated in Scheme 1. This reaction appears to be nearly completed in 10 min, while the quenched samples taken from the flow coming out of **R3** are stored for up to 16 h. According to the mechanism shown in Scheme 1, trifluoroacetate ester **9** can also be formed by solvolysis of intermediate **5**. However, as this solvolysis can only take place during the short residence time in **R2**, it is conceivable that most of the trifluoroacetate ester **9** is formed after quench and sample storage. The trifluoroacetate **9** can thus be considered as "protected" alcohol formed by reaction of alcohol with Pummerer rearrangement product **7** under the basic conditions after quench. As such, there is a correlation between the amount of Pummerer rearrangement taking place in **R1** and the amount of trifluoroacetate **9** that is formed. The more Pummerer rearrangement takes place in **R1**, the more trifluoroacetate **9** is formed upon quench. A sample stability study disclosed that, when a sample of effluent was diluted (1:200) with THF, which was the preferred injection solvent for the HPLC system used, unfortunately the trifluoroacetate ester **9** in the samples is instantaneously hydrolyzed to alcohol. Hence, the amount of unreacted alcohol cannot be distinguished from the amount of trifluoroacetate ester **9** formed by reaction of alcohol with Pummerer rearrangement product **7**. Also the Pummerer rearrangement product **7** is hydrolyzed in the sample matrix, resulting in small volatile molecules; thus, a direct measure of the amount of Pummerer rearrangement taking place in **R1** was not possible. Considering the extremely fast rate of the reaction between the alcohol and intermediate **3**, it can be safely assumed that any unreacted alcohol in the reaction mixture results from an insufficient amount of intermediate **3** being fed into reactor **R2** due to partial conversion of intermediate **3** into compound **7** via Pummerer rearrangement. Therefore, the amount of alcohol in the sample is the most reliable indirect measure for the amount of Pummerer rearrangement to compound **7** taking place in **R1**. It was demonstrated that by using this quench the methylthiomethyl ethers **8** were stable, and thus, a direct measurement of the amount of Pummerer rearrangement taking place in **R2** was possible. In the graphs and tables throughout this paper, the conversion of benzyl alcohol to aldehyde (or ketone) and to the corresponding methyl thiomethyl ether **8** is provided. The amount of alcohol in the reaction mixture can be deduced from these numbers and is therefore not explicitly presented.

Optimization of Reaction Parameters. First a systematic variation of process parameters such as temperature, residence time, and equivalents of reagents was studied. Benzyl alcohol (**4a**) was used as a test substrate in these experiments. As discussed in the previous section, the amount of unconverted benzylalcohol is related to the amount of Pummerer rearrangement in reaction **R1**. The amount of methyl thiomethylether is a direct measure for the amount of Pummerer rearrangement in reactor **R2**.

The optimization of the microreactor was investigated with three different types of setups as shown in Table 1. The error in the measured conversions has been established to be approximately 2%.[10]

Comparison of the Batch Reaction with the Continuous Flow Reaction in Setups I, II, and III. Comparison of the temperature profiles obtained from the different microreactor setups (Table 1) with the temperature profile of the batch reactions (Table 2) shows that the conversion to benzaldehyde (**6a**) in the microreactor at the same temperature is higher than in the batch reactor. It is notable that even at temperatures above -20 °C, the conversion is still reasonable, while at these temperatures there was no conversion at all in the batch reactions.

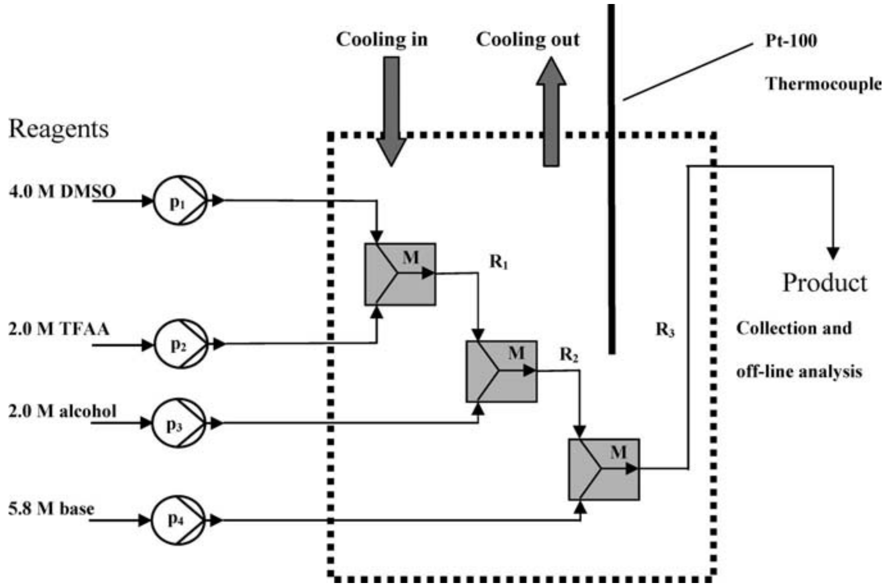


Figure 1. **Microreactor setup.**

Table 1. **Conversion[a] to benzaldehyde (6a) and methylthiomethyl ether (8a) in reactor setups I, II, and III**

	conversion[b] (mol/mol %)					
	benzaldehyde (**6a**)			methylthiomethyl ether (**8a**)		
temp (°C)	setup I	setup II	setup III	setup I	setup II	setup III
−20	81	81	77	3.9	3.8	4.2
−10	82	81	76	3.3	3.9	3.9
0	40	79	75	2.1	3.8	4.1
10	3.8	54	54	0.2	2.8	4.2
20	1.5	10	25	0.0	0.5	1.7

[a] Conditions: DMSO (4.0 M); TFAA (2.1 M); benzyl alcohol (2.0 M), TEA (5.8 M). Flow rates of all the pumps were 5.0 mL/min^{-1}. [b] Conversion determined by HPLC. The residence times (ms) of the different reactors at a flow rate of 5.0 $\text{mL}\cdot\text{min}^{-1}$ setup I: **R1** = 760; **R2** = 507; setup II: **R1** = 12; **R2** = 507; setup III: **R1** = 12; **R2** = 20.

Table 2. **Temperature profile of the Moffatt−Swern oxidation performed in a conventional batch reactor**

	conversion (mol/mol %)[a]	
temp (°C)	benzaldehyde (**6a**)	methylthiomethyl ether (**8a**)
−70	88	1.6
−45	58	1.5
−30	28	1.2
−10	2.1	1.4
10[b]	0.0	0.0
20[b]	0.0	0.0

[a] Conversion determined by HPLC. [b] Isolation of only benzyl alcohol (**4a**).

The maximum conversion of ~81 mol/mol % obtained at −20 °C in the microreactor is for every setup the same and is comparable with the maximum conversion obtained in the batch reactor at much lower temperature (−70 °C). At higher temperature the conversion in the microreactor also decreases. In setup I, the conversion starts to decrease at −10 °C; for setups II and III, the conversion is still good at −10 °C and starts to decrease at 0 °C. This higher conversion in setups II and III is related to the low thermal stability of trifluoroacetoxydimethylsulfonium salt (**3**) and its shorter residence time in setups II and III compared to that in setup I. By going from setup I to II and III the residence time of **3** in **R1** decreases from 760 ms to 12 ms. As a result of this shorter residence time, the Pummerer rearrangement of **3** to **7** is suppressed, since **3** reacts almost instantaneously with benzyl alcohol (**4a**). The difference between the results in setup I and those in setups II and III is even more pronounced at temperatures above 0 °C.

At temperatures above 0 °C the conversion in setup II and III also decreases in spite of the short residence time in **R1**, indicating that at these temperatures the Pummerer rearrangement occurs even faster. Going from setup II to setup III the residence time in **R2** changed from 507 ms to 20 ms, and the temperature profile gave a similar result, with a slightly higher conversion for setup III at higher temperatures. In order to increase the conversion even further, the temperature of the cryovessel was lowered to −30 °C. However, at this temperature the microstructures in the mixers were blocked due to the precipitation of trifluoroacetoxydimethylsulfonium salt (**3**). This finding is in accordance with literature data,[11,12] indicating that **3** can crystallize at −30 °C. These initial microreactor results were very promising for further studies and showed indeed that the Moffatt−Swern oxidation is an almost instantaneous reaction, taking place in the time frame of milliseconds.

It is notable that in the batch reactor at higher temperatures no increased amounts of methylthiomethyl ether are observed. This indicates that the Pummerer rearrangement of intermediate **5** does not play a major role, which is in contrast to conclusions in prior literature.[7]

Investigation of the Stoichiometry of the Reaction. The optimization of process parameters was continued by investigating the stoichiometry of the reaction. To increase the obtained conversion to benzaldehyde of ~78 mol/mol % the effect of the amount of trifluoroacetoxydimethylsulfonium salt (**3**) relative to benzylalcohol (**4a**) was studied using setup III at −20 °C. This was done by changing the flow rate of the reagents in two different types of experiments. It was ensured that in all cases DMSO was present in excess to TFAA such that a competition between TFAA and trifluoroacetoxydimethylsulfonium salt (**3**) is avoided. In the first experiment the flow rates of DMSO and TFAA were varied between 1.0 and 10.0 $\text{mL}\cdot\text{min}^{-1}$, and the flow rates of benzyl alcohol (**4a**) and TEA were maintained constant at 5.0 $\text{mL}\cdot\text{min}^{-1}$. By doing this, the residence times in **R1**, **R2**, and **R3** were variable. In the second experiment only the flow rate of benzyl alcohol (**4a**) was varied between 1.0 and 8.0 $\text{mL}\cdot\text{min}^{-1}$, and the flow rates of DMSO, TFAA, and TEA were maintained constant at 5.0 $\text{mL}\cdot\text{min}^{-1}$. As a consequence, the residence time in **R1** was constant, and the residence times in **R2** and **R3** were variable. According to the results shown in Figure 2, the maximum conversion to benzaldehyde is still around ~80 mol/mol %.

The Moffatt−Swern oxidation is a very fast reaction, and consequently, it takes a short time to reach steady state in the microreactor. This feature offered the advantage that many different settings could be tested in a short period of time (more than 20 experiments in 1 h). This illustrates that the microreactor is an ideal tool for continuous flow high throughput experimentation. The standard deviation (typical in the order of <2% of the average) calculated over three consecutive samples showed that, when the system is in steady-state, the conversion is very reproducible. Identical settings were repeated also at different days, resulting in similar amounts of **6a** and **8a**. This consistency is, of course, a vital prerequisite for successful development and scale-up of a microreactor process.

Investigation of the Residence Times at Different Temperatures. Subsequently, the residence time was investigated as a reaction parameter (Figure 3). This was done by increasing the flow rate of the four pumps from 2.0 $\text{mL}\cdot\text{min}^{-1}$ up to 10 $\text{mL}\cdot\text{min}^{-1}$ (the maximum flow of the pumps), while maintaining the ratio of the flow rates, and thus the reagents, constant.

Decreasing the residence time appeared to have no effect on the conversion at low temperature (−20 °C). At higher temperature (10 °C) it is evident that at short residence times a higher conversion to benzaldehyde (**6a**) is achieved. This effect is again explained by the low thermal stability of the trifluo-

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(10) A table with all data points from which the errors can be calculated is included in the Supporting Information.

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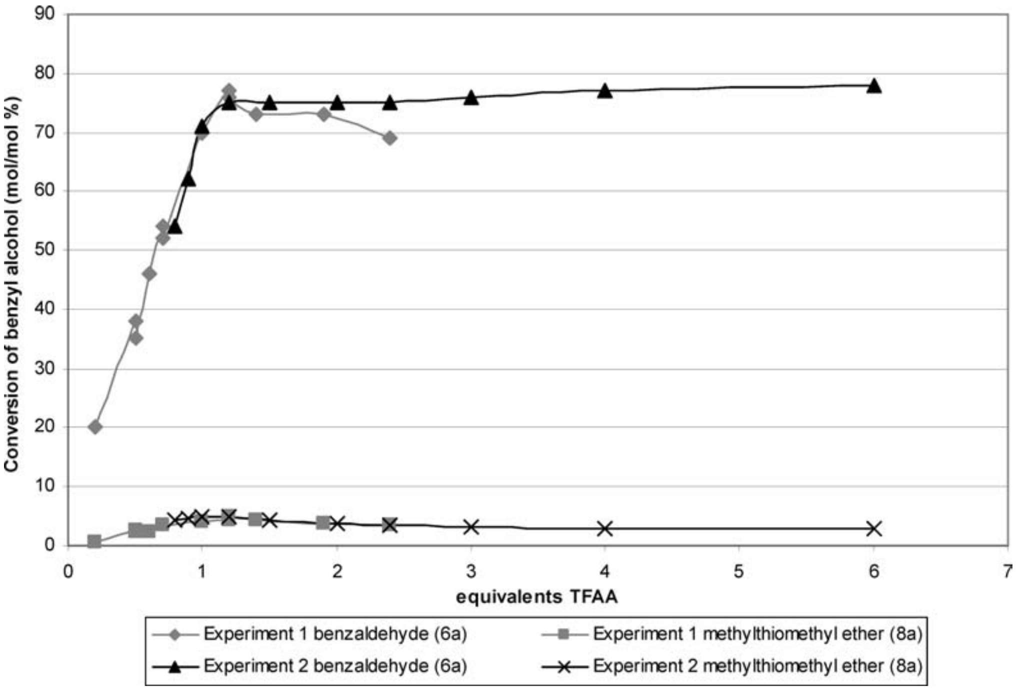

Figure 2. **Conversion of benzyl alcohol into benzaldehyde (6a) and methylthiomethyl ether (8a) as function of the equivalents TFAA at –20 °C in microreactor setup III. Conditions: DMSO (4.0 M); TFAA (2.1 M); benzyl alcohol (2.0 M), TEA (5.8 M). Flow rates of DMSO, TFAA, and benzyl alcohol were variable; flow rate of TEA was 5.0 mL/min^{-1}. Conversion determined by HPLC.**

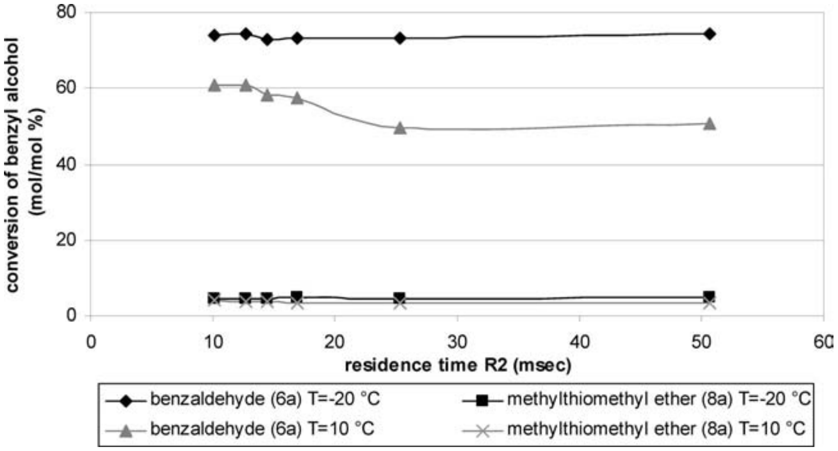

Figure 3. **Conversion of benzyl alcohol into benzaldehyde (6a) and methylthiomethyl ether (8a) as a function of the residence time in microreactor setup III at two different temperatures. Conditions: DMSO (4.0 M); TFAA (2.1 M); benzyl alcohol (2.0 M), TEA (5.8 M); flow rates 2.0 mL·min^{-1} up to 10 mL·min^{-1}; conversion determined by HPLC.**

roacetoxydimethylsulfonium salt (**3**) and alkoxydimethylsulfonium salt (**5**). At higher temperature the decomposition of these intermediates by the Pummerer rearrangement is faster which can be counterbalanced by shorter residence times.

Figure 4 shows the temperature dependence of the Moffatt–Swern oxidation when in **M1** DMSO and benzylalcohol (**4a**) were premixed followed by the addition of TFAA in **M2** and TEA in **M3**. In this microreactor setup (named setup IV) the reaction volumes (**R1**–**R3**) are identical to those of setup III.

The study of the temperature dependence in setups III and IV shows that at 20 °C the conversion in setup IV is 70%, whereas in setup III the conversion is only 25%. This influence on the maximum temperature at which the process can be operated, can be explained as follows: In microreactor setup IV, upon addition of TFAA in **2**, the trifluoroacetoxydimethylsulfonium salt (**3**) is formed in the presence of benzyl alcohol. Thereby, **3** is immediately intercepted by benzyl alcohol leaving virtually no time relative to the rate of the Pummerer rearrangement even at a temperature of 20 °C. In setup III, intermediate **3** is first transported from **M1** to **M2** where it is mixed with benzyl alcohol, resulting in longer residence time during which the Pummerer rearrangement can take place.

Upon increasing the flow rate at 10 °C, the conversion increased in setup III. The opposite effect was found for setup IV (Figure 5); where at higher flow rates the conversion decreased slightly from 73% to 68%. This indicates that at these very short residence times, the residence time approaches the required reaction time for the formation of alkoxysulfonium salts (**3** and **5**). This appears to be the first instance in which

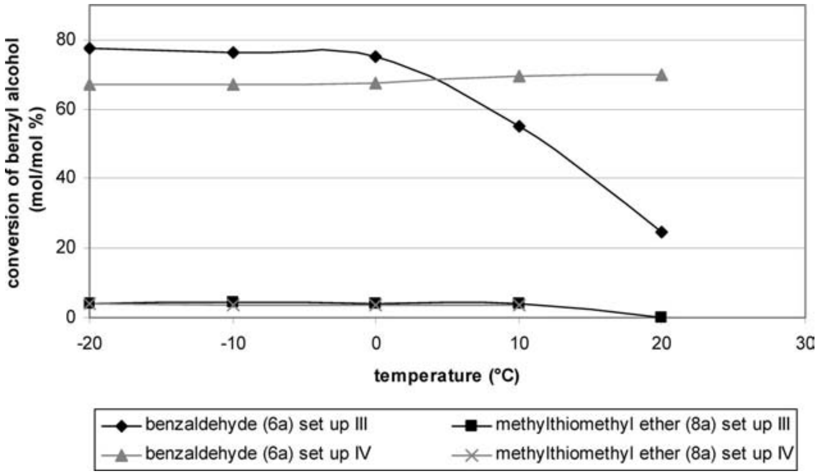

Figure 4. **Conversion of benzyl alcohol into benzaldehyde (6a) and methylthiomethyl ether (8a) as a function of the temperature for setups III and IV. Conditions: DMSO (4.0 M); TFAA (2.1 M); benzyl alcohol (2.0 M), TEA (5.8 M); flow rates of all pumps were 5.0 mL·min^{-1}; conversion determined by HPLC.**

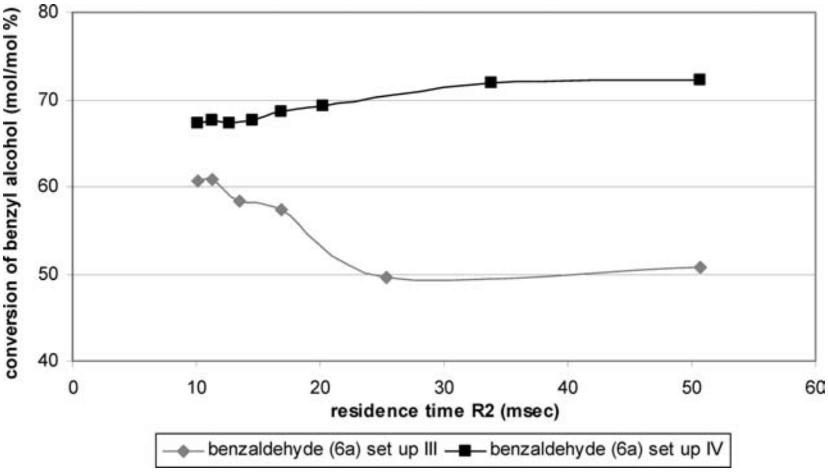

Figure 5. **Residence-time dependence, in microreactor setups III and IV. Conditions: DMSO (4.0 M); TFAA (2.1 M); benzyl alcohol (2.0 M), TEA (5.8 M); reaction temperature 10 °C; flow rates 2.0 mL·min^{-1} up to 10 mL·min^{-1}; conversion determined by HPLC.**

Table 3. **Effect of amine bases on the Moffatt−Swern oxidation[a] of benzyl alcohol (4a) at different temperatures in microreactor setup III**

	TEA (5.8 M)	DIPEA (5.8 M)
temp (°C)	benzaldehyde (**6a**) (mol/mol%)	benzaldehyde (**6a**) (mol/mol%)
−20	77	88
−10	76	87
0	75	87
10	54	86
20	25	84

[a] Conditions: DMSO (4.0 M); TFAA (2.1 M); benzyl alcohol (2.0 M), base (5.8 M). Flow rates of all the pumps were 5.0 mL/min^{-1}. Conversion to benzaldehyde determined by HPLC.

the reaction rates of steps 1 and 2 in scheme 1 become a limiting factor in this microreactor.

It is known from literature that, besides triethylamine (TEA), other tertiary amines could also be used.[8] When diisopropylethylamine (DIPEA) was used in the oxidation of benzyl alcohol (**4a**), higher conversions were obtained, and also the amount of methylthiomethyl ether (**8a**) decreased (Table 3). The difference between triethylamine and diisopropylethylamine is not well understood mechanistically but has been noted by others as well.[8]

Effects of Micromixing. The effect of micromixing was investigated by measuring the temperature dependence in two different types of mixers in setup III. The results are presented in Figure 6 showing that there is not an evident difference in the conversion to benzaldehyde (**6a**). These experiments clearly show that for fast exothermic Moffatt−Swern oxidations, it is not necessary to mix the reagents on microscale. Simple T-shaped joints, in which mixing took place on milliscale, worked well and gave, in some cases, even better results. This outcome is in contrast with the findings of Yoshida et al.,[9] who concluded that the high selectivity at elevated temperatures can be attributed to both the short residence times and the extremely fast and efficient mixing. The above results indicate that the high selectivity is merely an effect of the short residence times, and is not influenced by the use of a micromixer.

Scope and Limitations. This section describes the results of the Moffat−Swern oxidation of a variety of alcohols carried (Figure 7) out in a conventional batch reactor and in the microreactor with setups III and IV. With both setups, the

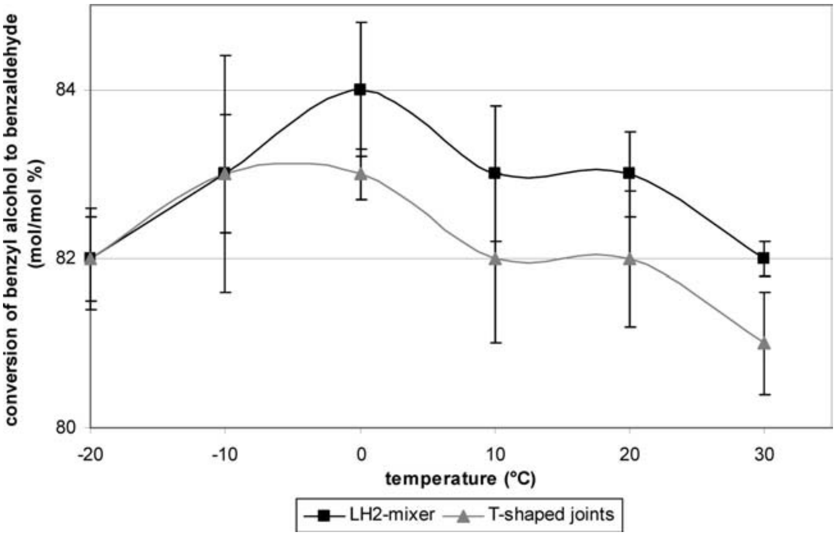

Figure 6. **Effect of a micromixer in comparison with a T-shaped joint, measured in setup III. Data plotted as an average ($n = 3$) and 2× the standard deviation. Conditions: DMSO (4.4 M); TFAA (2.4 M); benzyl alcohol (2.0 M), DIPEA (5.8 M). Flow rates of all the pumps were 5.0 mL/min^{-1}. Conversion determined by HPLC.**

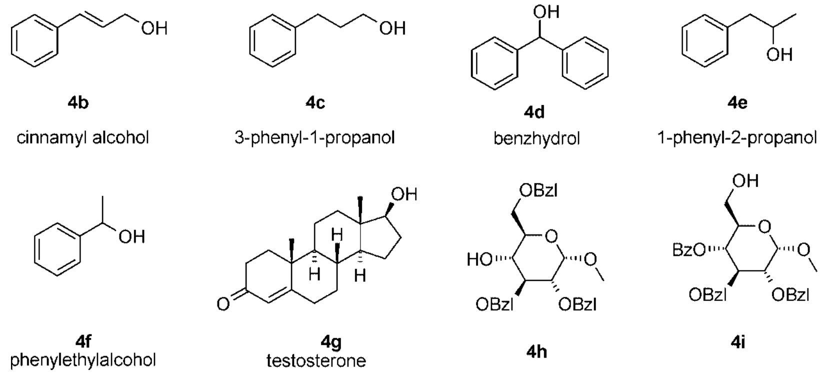

Figure 7. **Different types of alcohols used in the Moffatt−Swern oxidation, either in batch or the microreactor.**

temperature was varied between −20 and 30 °C at a constant flow rate of 5 mL·min^{-1}.

Comparison of the temperature profiles of the Moffat−Swern oxidation of alcohols **4b**−**4f** in batch reactions with those in the microreactor with setups III and IV (Table 4) reveals the same general trends as observed for benzyl alcohol (**4a**). In the batch reactor, the conversion of the aldehydes or ketones sharply decreases above −45 °C, while in the microreactor the conversions remain the same for alcohols **4b**, **4c**, **4e**, **4f**, **4g**, **4h**, and **4i** at temperatures up to 10 °C. Setup IV allows for even higher reaction temperatures than setup III. However, in setup III the conversion at temperatures below 10 °C is for all alcohols higher than for setup IV. By using the in situ generation (setup IV) of trifluoroacetoxydimethylsulfonium salt (**3**), conversions up 93 mol/mol % can be obtained evan at 30 °C, viz. 1-phenyl-2-propanol (**4e**), phenylethylalcohol (**4f**), and testosterone (**4 h**).

The remarkably high conversions obtained for the nonbenzylic alcohols (**4e**−**4i**) in contrast to the benzylic alcohols (**4a**, **4b**, **4d**), can be explained in terms of the lower susceptibility of the alkoxysulfonium salts (**5**) to solvolytic attack by TFA.[7,8] Oxidation of the alcohols **4g**, **4 h**, and **4i** in batch experiments showed that addition of DIPEA at 20 °C results in a similar conversion when DIPEA was added at −70 °C, indicating that the alkoxysulfonium salts (**5g**−**5i**) were stable at 20 °C. For

Table 4. **Aldehyde/ketone conversion of the Moffatt−Swern oxidation of different aromatic alcohols in the microreactor using setups III and IV and a batch reactor**

		conversion to aldehyde or ketone (mol/mol %)							
	temp (°C)	6b[a,b]	6c[a,b]	6d[a,b]	6e[a,b]	6f[a,b]	6g[b,c]	6h[c,d]	6i[c,d]
setup III	−20	83	62	54	96	97	97	99	91
	−10	82	61	53	96	97	97	98	92
	0	82	60	47	94	97	96	98	92
	10	80	61	36	94	97	94	98	79
	20	76	61	20	89	93	86	18	1.7
	30	62	50	10	74	77	71	6.4	n.d.
setup IV	−20	65	59	46	93	94	94	n.d	n.d
	−10	67	58	51	93	95	94	n.d	n.d
	0	68	57	49	93	95	93	n.d	n.d
	10	67	56	40	94	95	92	n.d	n.d
	20	67	55	26	94	95	91	n.d	n.d
	30	64	55	12	93	94	91	n.d	n.d
batch	−70	88	86	98	95	98	98	99	95
	−45	87	78	24	89	95	90	n.d.	92
	−30	20	41	0.5	32	43	45	60	32
	−10	0	4.1	0.4	4.0	3.3	2.8	n.d.	3.3
	10	0	0	0.4	0	0.8	0.5	n.d.	n.d.
	20	0	0	0.1	0	0	0.2	0	0

[a] Conditions: DMSO (4.0 M); TFAA (2.1 M); alcohol (2.0 M), DIPEA (5.8 M); flow rates of all the pumps were 5.0 mL·min^{-1}. [b] Conversion determined by HPLC. [c] Conditions: DMSO (4.4 M); TFAA (2.2 M); alcohol (0.5 M), DIPEA (5.8 M); flow rates of alcohol pump was 8.0 mL·min^{-1}, flow rates of the other pumps were 5.0 mL/min^{-1}. [d] Conversion determined by ^{1}H NMR.

Table 5. **Scaleability of the continuous flow Moffatt−Swern oxidation for testosterone at 0 °C using setup III**[a]

	conversion[b] (mol/mol %)		
time (min)	testosterone (**4g**)	4-androstene-3, 17-dione (**6g**)	methylthiomethyl ether (**8g**)
2	1.9	98	0.4
6	2.1	98	0.4
15	1.9	98	0.4
30	0.5	99	0.6
50	3.3	96	0.3
60	0.5	99	0.6
75	2.1	97	0.5
90	1.2	98	0.9
average	1.7	98	0.5
stdev	0.9	0.8	0.2
after workup	0.9	99	0.5

[a] Conditions: DMSO (1.1 M); TFAA (0.6 M); testosterone (0.5 M), DIPEA (1.45 M); flow rate of all the pumps was 7.5 mL/min^{-1}; reaction temperature −20 °C. [b] Conversion determined by HPLC.

both setups benzhydrol (**4d**) showed the most significant decrease of product with increasing temperatures probably by solvolysis of the corresponding alkoxydimethylsulfonium salt (**5d**) for which this bis-benzylic species is more susceptible than the other alcohols.

Scalability and Consistency. Scale-up of a continuous flow microreactor process involves running the process for a longer period of time. The scaleability and consistency of the microreactor over a longer period of time has been demonstrated using the more functionalized alcohols **4g**, **4 h**, and **4i**.

Table 5 shows that the microreactor can be operated for over 1.5 h, with a high conversion and consistent product selectivity. The isolated yield of 4-androstene-3,17-dione (**6g**) was 95 mol/mol %, with a production rate of 60 g·h^{-1} and a throughput of 23.6 g·L^{-1}·h^{-1}.

It was attempted to increase the throughput by increasing the reagent concentrations and keeping the testosterone concentration constant. In order to use the same equivalents of reagents, the flow rate of testosterone was increased to 8.0 mL·min^{-1} and that of the reagents was decreased to 2.0 mL·min^{-1}. By doing this, the total amount of effluent is decreased. However, at a lower flow rate the residence time of the intermediates is longer. As a consequence, with these settings the optimum temperature for the process was −20 °C instead of 0 °C.

Using these optimized conditions the reaction was run for 40 min again with a highly consistent product quality. The isolated yield of 4-androstene-3,17-dione (**6g**) was 93 mol/mol %, with a production rate of 64 g·h^{-1} and a throughput of 117 g·L^{-1}·h^{-1}, an improvement with a factor of 5, compared to the previous experiment.

The generality of the process developed for testosterone, was also tested in the scaleability experiments for the two carbohydrates (Tables 6, and 7). The isolated yield of ketone **6 h** after 20 min was 81 mol/mol %, with a production rate of 91.2 g·h^{-1} and a throughput of 350 g·L^{-1}·h^{-1}; for aldehyde **6i** after running the reaction for 25 min these figures were respectively 72 mol/mol %; 79.7 g·h^{-1} and 257 g·L^{-1}·h^{-1}. The above presented result shows that with these two substrates the process can be operated for more than 20 min without any problems.

Conclusions

It has been demonstrated that the Moffatt−Swern oxidation can be performed in the Ehrfeld microreactor system. The microreactor process offers significant advantages over the batch process. First, because of the small reactor volume, the accumulation of the labile trifluoroacetoxydimethylsulfonium salt (**3**) and alkoxydimethylsulfonium salt (**5**) is avoided, which increases the safety of the Mofatt−Swern oxidation drastically. Second, because of the short residence times (millisecond), which can be applied in the continuous flow microreactor, the exothermic Pummerer rearrangement of these unstable intermediates is avoided. As a result, the process can be operated at remarkably higher temperatures, thus avoiding the need for cryogenic temperatures.

The present study has also shown that optimization of a microreactor process can be executed in a very efficient manner by sequential variation of the process parameters followed by sampling when a steady state has been reached. Clearly, parameter screening can be performed much faster in continuous mode than in batch mode. Therefore, the microreactor could serve as an ideal tool for high throughput experimentation. However, in order to speed up the process optimization, fast online analysis tools must be implemented in the microreactor system.

For this fast exothermic Moffatt−Swern oxidation, the use of a micromixer instead of T-shaped joints does not enhance the conversion of benzylalcohol to benzaldehyde. Neither do the micromixers influence the temperature at which the continuous flow Moffat-Swern reaction can be performed. The use of T-shaped joints give the same results as obtained with the micromixers.

The microreactor could also serve as a tool for quick scale-up of Moffatt−Swern oxidations. This was demonstrated during the scaleability experiments. Throughput rates for testosterone at consistent product quality up to 117 g·L^{-1}·h^{-1} have been achieved for periods up to 1.5 h.

Experimental Section

General Information. NMR spectra were recorded on a Bruker advance DPX 400. Chemical shifts are reported in parts per million (ppm). ^{1}H NMR chemical shifts are referenced to TMS as internal standard (abbreviation s singlet; d doublet; dd double doublet; dt double triplet; m multiplet). For the carbohydrates, the conversion was determined by measuring the integrals of the methoxy group of the starting material and the products. The conversion of the other reaction mixtures were determined by HPLC (Gilson system consists of a 305 and a 306 pump, an 811C gradient mixer, an 805 manometeric module, and a 155 UV/vis dual wave detector) with acetonitrile and water as eluent. The HPLC system consists of the following chromatographic conditions: chromolith Performance RP18e column with 100 mm × 4.6 mm dimensions, flow rate 2.0 mL·min^{-1}; water/acetonitrile: initial (5/95); 2.0 min (5/95); 7.5 min (95/5); 9.7 min (95/5); 9.8 min (5/95); 15 min (5/95). Analysis channels 210 and 240 nm. Integration was done on the 210 nm channel, except that for the steroids the 240 nm channel was used.

All commercially available chemicals were used as received. Testosterone and the two carbohydrates were obtained from the

Table 6. **Scalability of the continuous flow Moffatt−Swern oxidation for carbohydrates (4h and 4i) using setup III**

time (min)	**4h**, conversion (mol/mol %)[a]	**6h**, conversion (mol/mol %)[a]	time (min)	**4i**, conversion (mol/mol %)[a]	**6i**, conversion (mol/mol %)[a]
2	8.8	91	2.0	1.5	98
10	6.8	93	14.0	1.5	98
20	7.5	92	25.0	1.7	98
average	7.7	92	average	1.6	98
stdev	1.0	1.0	stdev	0.1	0.1
after workup	7.5	92	after workup	1.6	98

[a] Conditions: DMSO (4.4 M); TFAA (2.4 M); carbohydrates (0.5 M), DIPEA (5.8 M); flow-rate for DMSO, TFAA, DIPEA was 2.0 mL·min^{-1}; carbohydrates, 8.0 mL·min^{-1}; reaction temperature primary alcohol (**4h**) and secondary alcohol (**4i**) respectively 0 and 10 °C. [b] Conversion determined via ^{1}H NMR.

Table 7. **Different microreactor setups used**

setup I	length (cm)	internal diameter (mm)	volume (μL)	residence time[a] (ms)
R1	10	1.27	127	760
R2	10	1.27	127	507
R3	20	1.27	253	760
		setup II		
R1	4	0.254	2	12
R2	10	1.27	127	507
R3	20	1.27	253	760
		setup III		
R1	4	0.254	2	12
R2	10	0.24	5.1	20
R3	20	1.27	253	760
		setup IV		
R1	4	0.254	2	12
R2	10	0.24	5.1	20
R3	20	1.27	253	760

[a] The residence time in the different reactors, calculated with a flow rate of all the pumps fixed to 5.0 mL·min^{-1}.

in-house stock supply and used without purification. The reagent solutions were made accurately by weighing the reagent into preweighed volumetric flasks. After dilution with dichloromethane, the flasks were again weighed, so that the density of the stock solution was known. The density is used for the conversion of the flow rates from gr·min^{-1} measured by the balances to mL·min^{-1}.

Microreactor. A schematic drawing of the microreactor setup was given in Figure 1. The reagents were fed into the microreactor with K 501 HPLC pumps purchased from Knauer. The pump chambers (10 mL) were made of ceramics; all the seals used were made of FFKM or Teflon. In order for the pumps to work accurately, back-pressure modules (obtained form Alltech) of 33 bar were placed behind the pump outlets. It was not possible to measure the pressure within the microreactor system. The pressure measured over the total microreactor setup was achieved with the pressure sensors that were integrated in the pumps. Normally the pressure was 35−38 bar. This corresponds to a pressure inside the microreactor system of 2−5 bar. The pumps were also equipped with one-way valves (obtained from Swagelok) to ensure that no reaction products could get back into the pump chambers. The pump of TFAA was equipped with a cooled pump head (obtained from Knauer) because of the low boiling point of the TFAA solution (32 °C). The pump head was cooled with a Huber polystat CC3 at 5 °C. In order to protect the pump against clogging, the reagents were filtered trough 10 μm HPLC stainless steel filters (obtained from Alltech). The flow rate (0.1−10 mL·min^{-1}) of every pump was checked by a balance (obtained from Satorius BP 1200) using the density of the stock solutions. No feedback loop was used to control and adjust the flow rates. The cryovessel is a homemade design and was made in-house. It consists of double-jacketed vessel and a Teflon lid with two holes for cooling, four inlet holes for the reagents, one outlet hole, and one hole for the Pt-thermometer. The cryo-vessel is cooled or heated by a Julabo LH85. The cryovessel contains the three stand-alone LH-2 mixers (Ehrfeld mikrotechnik BTS (GmbH[6]). These mixers are based on the principle of multilamination, successive splitting, and rearrangement. Streams of two different fluids are fanned out in a large number of small streams which are arranged alternately in an interdigital configuration. The LH-2 mixer consists of a mixing plate with 2 × 10 slides and a slide diameter of 50/50 μm and an aperture plate with a slide diameter of 50 μm and a length of 2 mm.

All reagents were precooled in a tube with a volume of 1 mL prior to feeding into the microreactor.

Batch Reactions. To a cooled solution of DMSO (4.0 M) in dichloromethane (2.0 mL) was added slowly a solution of TFAA (2.4 M) in dichloromethane (2.0 mL) under magnetic stirring. After the addition was completed, the resulting mixture was stirred for 10 min at −70, −45, −30, −10, 10, or 20 °C. Then a solution of alcohol (2.0 M) in dichloromethane (2.0 mL) was added. After the addition was completed, the mixture was stirred at the same temperature for 10 min, and TEA or DIPEA (5.8 M) in dichloromethane (2.0 mL) was added. After stirring for 10 min, the temperature was allowed to warm to room temperature. Analyses: 100 μL of the reaction mixture was quenched in a mixture of THF/TEA (1 mL) and analyzed by HPLC. For the carbohydrates the analyses were done via ^{1}H NMR after concentration of the reaction mixtures in vacuum.

Continuous Flow Microreactor. After the temperature of the cooling bath had reached its set-point, the pumps were switched on, and after a steady state was reached (typically this takes ~20 mL of effluent), three 10-mL samples of each effluent were taken, of which 100 μL was quenched in a mixture of THF/TEA (1 mL) and analyzed off-line by HPLC. For the carbohydrates the analyses were performed using ^{1}H NMR after concentration of 10 mL effluent in vacuum.

Scalability and Consistency Experiments. After the temperature of the cooling bath had reached its set-point, the pumps were switched on. At regular time intervals a sample was analyzed. Workup procedure: testosterone (**4g**): In total the reaction was run for 90 min. The effluent (~2600 mL) was washed with water (2 × 2 L) and dichloromethane. The organic phase was removed in vacuo. Toluene was added (2 L), and the reaction mixture was washed with 1 M HCl (2 × 2 L) and water (2 × 2 L). The water phases were extracted with toluene (150 mL). The combined toluene phases were dried on $MgSO_4$ and concentrated in vacuum to yield 92.1 g of 4-androstene-3,17-dione (**6g**) as a white solid.

^{1}H NMR data ($CDCl_3$): δ (ppm): 0.94 (s, 3H, 18-CH_3), 1.00 (dt, 1H, 9α), 1,13 (m. 1H, 7α), 1,22 (s, 3H, 19-CH_3), 1,30 (m, 2H, 12α, 14 α), 1,48 (m, 1H, H11), 1,58 (m, 1H, 15β), 1,70 (m, 3H, 1α, 8β, H11), 1.90 (m, 1H, 12β), 2,00 (m, 3H, 1β, 7β, 15α), 2,11 (t, 1H, H16), 2,35 (m, 1H, 6α), 2,38 (m, 1H, 2α), 2,45 (m, 2H, 2β, 6β), 2,49 (1H, d, H16), 5,75 (s, 1H, H4).

In total 675 mL of the testosterone solution was pumped into the microreactor, and on this basis, the isolated yield was 95 mol/mol %, with a HPLC purity of 99 mol/mol %.

Workup procedure: carbohydrate (**4h**): In total the reaction was run for 25 min. The collected effluent (~310 mL) was concentrated under vacuum. To the obtained oil were added THF (300 mL), MeOH (100 mL), and 0.1 M NaOH (100 mL); these mixtures were stirred for 30 min at room temperature. The pH was set to ~7 with 1 M HCl, solution and the volatiles were removed in vacuo. The aqueous layer was extracted with dichloromethane (2 × 150 mL). The dichloromethane layer was washed with sat. NaCl (2 × 100 mL) and dried on $MgSO_4$. The solvent was removed under vacuum to yield 33.2 g (72 mol/mol %) of **6 h** as a yellowish oil.

^{1}H NMR data ($CDCl_3$): δ (ppm): 3.48 (s, 3H, OMe); 3.68 (1H, dd, H6); 3.80 (1H, dd, 2Hβ), 3.92 (1H, dd, H6′), 4.29 (1H, q, 5Hα), 4.43 (1H, d, 3Hα), 4.59 (2H, q, benzyl CH_2), 4.70 to 4.92 (4H, m, 2× benzyl CH_2), 4.80 (1H, d, 1Hβ), 7.12 to 7.45 (12H, m, benzyl).

Workup procedure: carbohydrate (**4i**): In total the reaction was run for 20 min. The collected effluent (~260 mL) was worked up identically as was described for carbohydrate (**4 h**). This gave **6i** in a yield of 30.4 g (81 mol/mol %) as colorless oil.

^{1}H NMR data (measured at 399.87 MHZ in $CDCl_3$ relative to TMS): δ (ppm): 3.38 (s, 3H, OMe); 3.50 (1H, dd, 2Hβ), 3.58 (1H, dd, 4Hβ), 4.09 (1H, t, 3Hα), 4.18 (1H, d, 5Hα), 4.61(1H, m,1Hβ), 4.63 (2H, d, benzyl CH_2), 4.78 to 5.0 (4H, m, 2× benzyl CH_2), 7.31 to 7.65 (12H, m. benzyl), 9.67 (s, 1H, CHO).

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Note Added after ASAP: The paragraph which states that Supporting Information is available was missing from the version published April 30, 2008. This paragraph is present in the printed version as well as the Internet version published September 19, 2008.

Supporting Information Available

A table with all data points from which the conversion errors can be calculated for optimization of the microreactor. This material is available free of charge via the Internet at http://pubs.acs.org.

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