Organic Process Research & Development **2008,** *12,* 989–994

Continuous Reaction/Crystallization Process for Production of a Hazardous Intermediate

John G. Van Alsten,*[,†] Lisa M. Reeder,[‡] Corey L. Stanchina,[§] and Donald J. Knoechel[⊥]

Chemical R&D, Pfizer Global Research and Development, Kalamazoo Laboratories, Kalamazoo, Michigan, U.S.A.

Abstract:

Perchloric acid appears unique in its ability to catalyze stereoselective trans-acetalizations of steroids. However, the requisite recipes result in an intermediate phase enriched in perchlorate and organic material with the potential for catastrophic decomposition. We present here a discussion of the relevant chemistry and the engineering of a continuous reactor/crystallizer/quench for the safe production of a candidate for asthma and irritable bowel syndrome.

Introduction

Corticoid acetals are useful compounds for indications such as asthma and irritable bowel syndrome. They are usually formed by the acid-catalyzed reaction of a diol or acetonide with an aldehyde:

Two epimers of the product result, but the final API must often be highly enriched in the *R* form. A typical minimum API specification is ~97% of the *R* isomer, and ~1% each of the *S* isomer and the starting material. Obtaining high stereochemical purity with high conversion is thus the major chemical challenge. As recrystallizations leads to high product losses,[1] it is clearly advantageous to chemically generate material in the correct isomer as highly enriched as possible. For efficient upgrading, we found that the chemical reaction should result in levels of about 3% for each of these impurities.

The seeming simplicity of this reaction belies some complex and intriguing chemistry. While many acids catalyze this reaction, most are stereochemically inefficient, providing *R*/*S* epimer ratios on the order of 3:6.[2] This relatively low degree of stereoselectivity requires extensive purification for upgrading and consequent yield losses. However, 70% perchloric acid appears unique in that, depending on the specific system and the perchloric concentration, it can produce material extraordinarily enriched in the favored *R* epimer.

Furthermore, it is the physical nature of the reaction medium that is key to obtaining high stereoselectivity. When initiated using either isooctane or methylene chloride the system quickly becomes two liquid phases, with a heavy perchloric acid-rich phase extracting the reactants from the organic and leaving this phase virtually devoid of starting material. Kinetic measurements show that the conversion of starting material to product is roughly linear with time, suggesting that the reaction is limited by mass transfer of steroid and aldehyde into the heavy perchloric phase. Thus, the sole purpose of the organic "solvent" is to facilitate transport of reactants into the perchloric acid phase. The reaction reaches a conversion of ~98% within 10 min at room temperature. The steroid−perchloric phase is first observed as heavy oil swirling about in clear solvent and tends to "plate out" on hydrophilic surfaces such as the walls of the reaction vessel. After a period of time the oil crystallizes to a gummy semisolid. What is particularly interesting is that the stereochemical purity is (a) strongly dependent on the quantity of perchloric acid used and (b) contingent on crystallization of the steroid−perchlorate intermediate. Figure 1 shows that during the "oil" stage the epimer ratio of the product is quite low (<10) but on solidification undergoes a dramatic increase. Hence, this process has the unusual feature where the stereochemistry is actually driven by the physical process of crystallization in a manner similar to that of dynamic resolution. The stereochemical purity of the slurry continues to improve under prolonged agitation, albeit sluggishly.

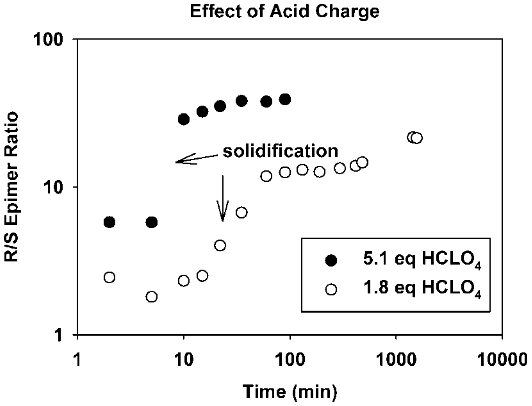

Figure 1. **Evolution of stereochemistry during the reaction with perchloric acid. System: Dihydrofluocinolone acetonide/butyraldehyde. The initially formed oil phase is characterized by low selectivity to the *R* epimer, but on crystallization is transformed to a state substantially enriched with the desired product.**

To summarize, obtaining high selectivity requires perchloric acid, more acid gives higher selectivity, and this selectivity is determined by crystallization of a perchlorate−steroid intermediate. Once the reaction is complete, a large excess of water is added to break the steroid−perchlorate phase and leave an organic phase rich in product and an aqueous phase rich in acid.

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* Corresponding author. E-mail: john.g.vanalsten@pfizer.com.

[†] Present address: Engineering Technologies Laboratory, Pfizer Global R&D, Eastern Point Rd., Groton, CT 06340, U.S.A.

[‡] Present Address: Bristol Meyers Squibb & Co., Princeton, NJ 08540, U.S.A.

[§] Present address: Research API, Pfizer Global R&D, Eastern Point Rd., Groton, CT 06340, U.S.A.

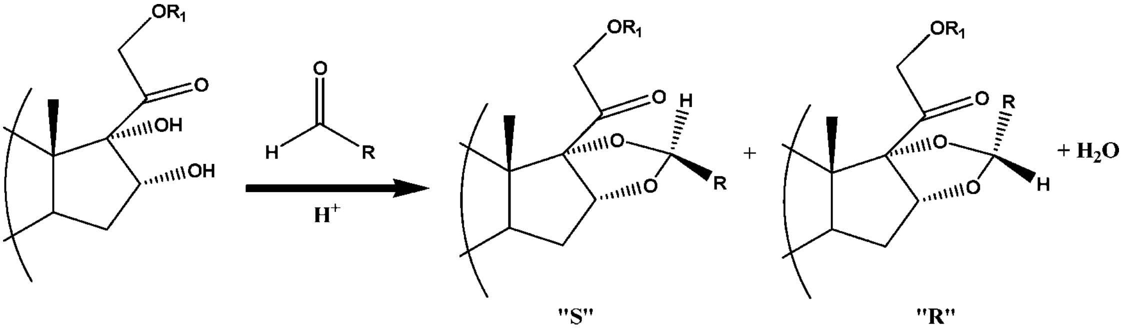
[⊥] Present Address: Global API Technology, Pfizer Global Manufacturing, 7000 Portage Rd., Kalamazoo, MI 49001, U.S.A.

(1) Pierluigi, R.; MacDonald, P. L. WO 2007/056181 A2, 2007.

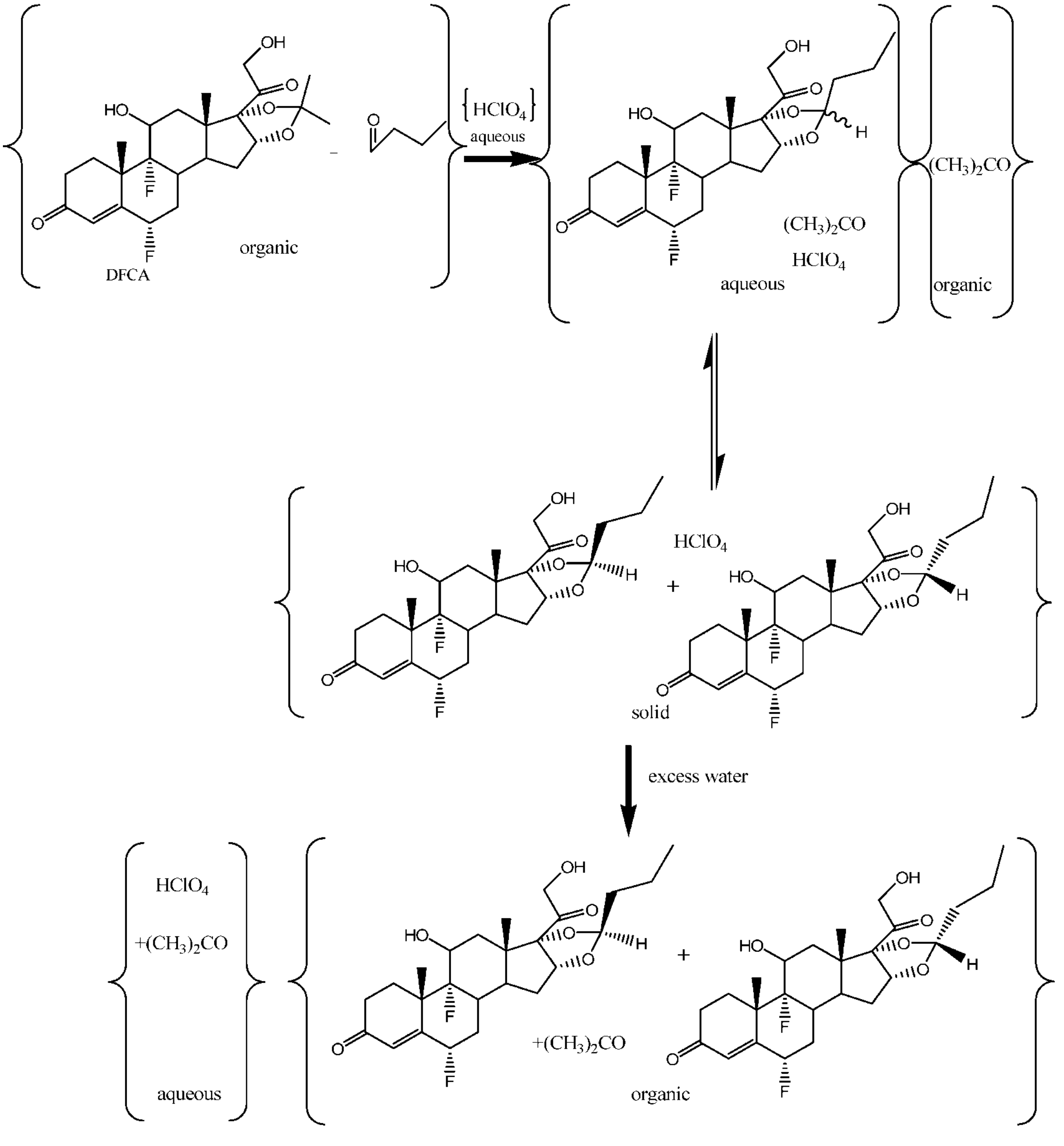
(2) (a) Gutterer, B. DE 100 55 820 C 1, 2002. (b) Amschler, H.; Flockerzi, D.; Riedel, R.; Postius, S.; Stoeck, M.; Beume, R.; Zech, K. WO 94/22899, 1994. (c) Jakupovic, E.; Sourander, R. T.; Stenhede, J. U.; Svensson, R. P. EP 0 262 108 A1, 1987.

10.1021/op800128g CCC: $40.75

Scheme 1. **Acetalization of a corticosteroid**



Scheme 2. **Schematic representation of the acetalization of dihydrofluocinolone acetonide with butyraldehyde**



The complete chemical step for the system we present here is represented in Scheme 2, with the brackets connoting separate phases.

Experimental Section

Batch experiments were performed at small scale using disposable 20-mL reactors at room temperature (21−23 °C) agitated by magnetic stir bars. DFCA (0.5 g, 1.10 mmol, 1 equiv) and 0.12 g of butyraldehyde (1.6 mmol, 1.5 equiv) were dissolved in 8 mL of methylene chloride. $HClO_4$ (0.86 g of 70%, 5.4 equiv) was subsequently charged in a single rapid shot by pipet. Samples of the reaction media were acquired over time via pipet and immediately quenched into 50/50 acetonitrile/water spiked with 0.5% triethylamine. HPLC analysis was performed on these samples to determine both conversion and composition.

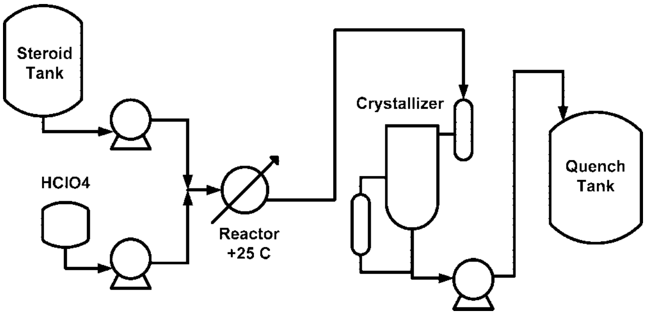


Figure 2. **Continuous reaction/crystallization/quench system for production of steroidal acetals at ~100 g/h.**

Development of the flow system will be described in the body of the paper. The flow process was performed in a modified facility utilized for scale-up studies. A schematic of the system is presented as Figure 2. One kilogram (2.20 mol, 1 equiv) of DFCA and 0.486 kg of butyraldehyde (6.75 mol, 3 equiv) were dissolved in 15.8 L of methylene chloride in a 20-L tank, and a line to the feed pump (Micropump 187-000) was fitted to the bottom valve. The flow rate for this stream was 50 mL/min. Perchloric acid (70%) was fed from a bottle mounted on a scale via a diaphragm pump (Prominent gammaL) at 3 mL/min. Calibrations of the pumps were performed on the streams independently and the feeds recycled to the respective tanks.

The outlet of the tubular reactor fed a continuous crystallizer with a total volume of 2 L and a working volume of 0.5 L. As this vessel contained the highest quantity of intermediate, it was also equipped with a feed line of water for rapid quenching in the event of an undesirable processing excursion. Product was taken off by insertion of an inverted standpipe at the desired level and was driven by a continuously running peristaltic pump (Masterflex I/P 73). This stream was discharged into a stirred 30-L quench vessel.

Startup commenced by initiating a small-batch reaction in the continuous crystallizer. Fourteen grams of DFCA and 7 g of butyraldehyde were dissolved in 230 mL of methylene chloride, and then 24 g of 70% perchloric acid was charged. After ~15 min, the crystallizer was seeded with ~0.1 g of previously reserved intermediate and stirred for ~30 min more to fully crystallize the contents. The feed and slurry discharge pumps were then turned on, and the material was processed and collected in the quench vessel precharged with 4 L of water, 6 L of methylene chloride, and 1 L of isooctane. Once processing was complete, agitation in the quench tank was turned off, and the phases were allowed to settle. The lower product-containing phase was transferred in two portions to the cleaned 20-L tank precharged with 0.03 kg (0.15 equiv) of sodium bicarbonate dissolved in 8.5 L of water, and washed. The lower organic portions were combined. During this time, the pH of the remaining aqueous perchloric acid solution was adjusted to 7−9 with aqueous NaOH and sodium bicarbonate and disposed of, and the 30-L tank was cleaned with water and acetone rinses. The product solution was transferred to the 30-L tank and 3.7 L of isooctane added, and the solution atmospherically concentrated to a pot temperature of 50 °C. The system temperature was lowered to ~−5 °C, and the slurry was filtered and washed with 1 L of isooctane. Product was dried overnight in a vacuum oven at 50 °C. The crude product yield was ~95%.

Process Safety Studies. Combinations of organic materials with perchloric acid are well-known to be potentially hazardous.[3] In our case, the reaction to the correct epimer is driven by the formation and crystallization of a steroid−butyraldehyde−perchloric acid intermediate containing over 5 equiv of perchloric acid. One aspect that makes this interesting from a process safety perspective is that, while neither the starting materials nor the final products of the reaction are particularly hazardous, the unisolated intermediate formed during the reaction is potentially catastrophic. For safety evaluation small samples of the perchloric acid−steroid semisolid intermediate were carefully isolated, then subjected to thermal analysis in the process safety laboratory. DSC (Figure 3) shows that the intermediate contains a thermal energy of ~3400 J/g, or approximately 75% that of trinitrotoluene, with a DSC onset temperature of ~80 °C. Accelerated rate calorimetry (ARC) determined a self-heating onset temperature of 55 °C. These temperatures are sufficiently low to be of concern. To further accentuate this hazard, both the ARC and glass DSC experiments concluded with explosive decomposition of the material, necessitating repair of the instruments.

It was thus apparent that batch-wise manufacture of more than ~100 g of product would include the accumulation of a significant quantity of material with an unacceptable blast potential. Each kilogram of starting material charged to the reactor would produce 2.7 kg of intermediate, with a potential decomposition energy equivalent to ~2 kg of TNT. It is therefore clear that a safe process to manufacture this material would need to reduce the quantity of perchlorate intermediate present in the system. If the reaction could be run in a semicontinuous fashion, this quantity could be minimized to a level at which safe operation could be assured. The design and operation of such a system is described next.

Reaction Engineering. The conversion of DFCA to its butyral derivative occurs in two stages:

(1) Conversion of DFCA to a low selectivity oil.

(2) Crystallization of low selectivity oil to high selectivity solid.

Both features need to be incorporated into the process. Once crystallization has been achieved, the final slurry needs to be quenched with water to separate the organic fuel from the inorganic oxidant.

Hardware Sizing and Engineering. The total system volume is fixed by the allowable accumulation of intermediate, which for our development studies we limited to 50 g. This quantity was determined by estimates of a worst-case overpressure of 0.1 bar that defined a distance of closest approach to the unit. In practice, personnel were located roughly 3× this distance during operation. This mass, translated into volumes

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(3) (a) Harris, E. M. *CRC Handbook of Laboratory Safety*, 4th ed.; Section 4.6.2.4, Perchloric Acid ; Furr, A. K., Ed.; CRC Press: Boca Raton, 1995; p 308. (b) Harris, E. M. *Chem. Eng.* **1949**, 116. (c) Graf, F. A. *Chem. Eng. Prog.* **1966**, *62* (10), 109. (d) Elliott, M. A.; Brown, F. W. *Investigations of Explosion Hazards of Perchloric Acid and Mixtures of Perchloric Acid and Organic Materials*; U.S. Bureau of Mines Report of Investigations, 1948.

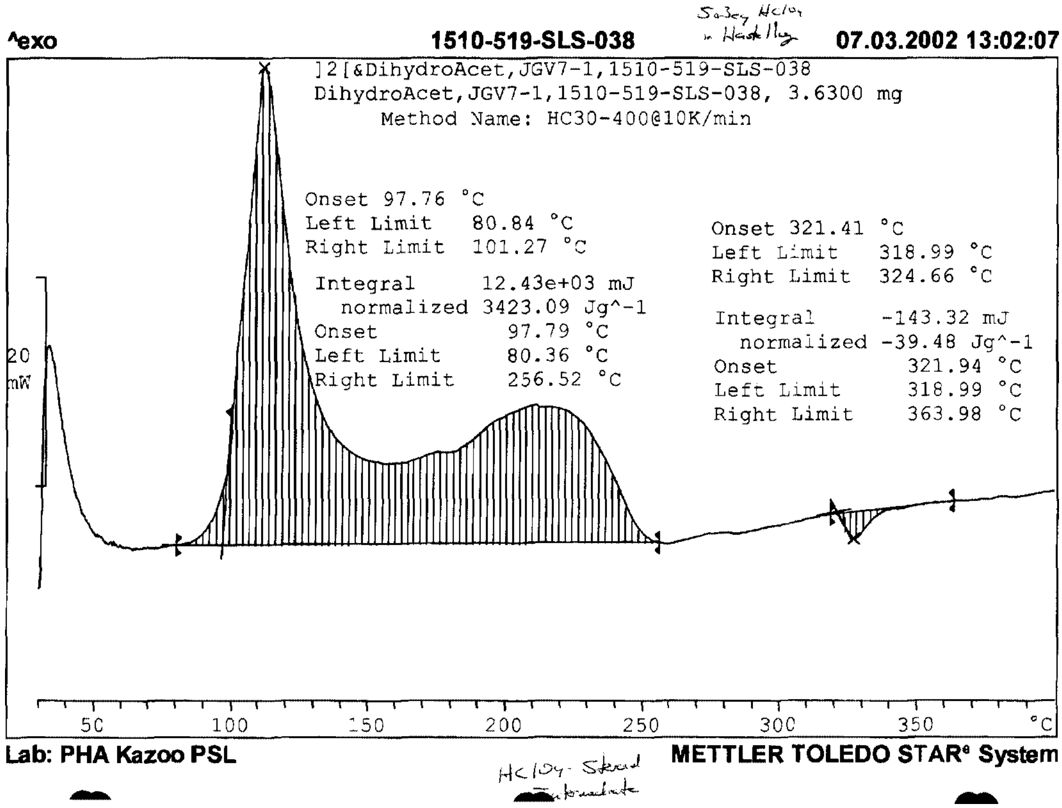

Figure 3. **DSC of the isolated perchlorate−steroid intermediate showing onset temperature of ~80 °C and release of 3400 J/g of energy.**

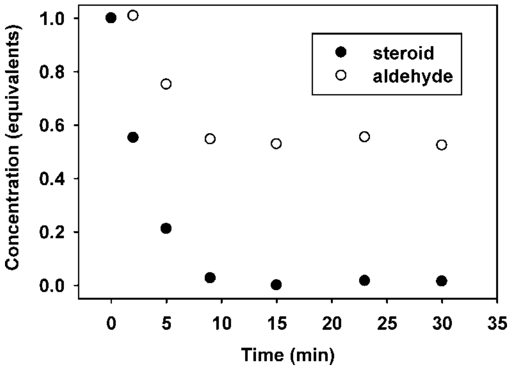

Figure 4. **Batch conversion data of DFCA steroid and butyraldeyhde.**

via the concentration, may then be distributed between the reaction zone and the crystallizer.

As indicated, small-scale batch data showed that the kinetics of conversion were sufficiently fast to make a simple plug flow reactor (PFR) attractive, with >98% conversion of DFCA in less than 10 min (Figure 4). In order to ensure reaction completion, the PFR was sized to a mean residence time of ~15 min. For the 0.159 cm i.d. tubing used in this demonstration system, this fixed the length of the reaction zone tubing at approximately 125 m. This was configured as about 80 wraps around a ~0.5 m diameter spool.

The simplicity of the PFR is critical to its success for this process. When we attempted to incorporate a relatively minor modification by adding static mixing elements we found that the reactors would quickly plug with solidified intermediate. We strongly suspect that this was due to hydrodynamically stagnant points introduced fore and aft of the elements which served as nucleation points for crystal growth. In contrast, the simple tubular PFR never experienced this

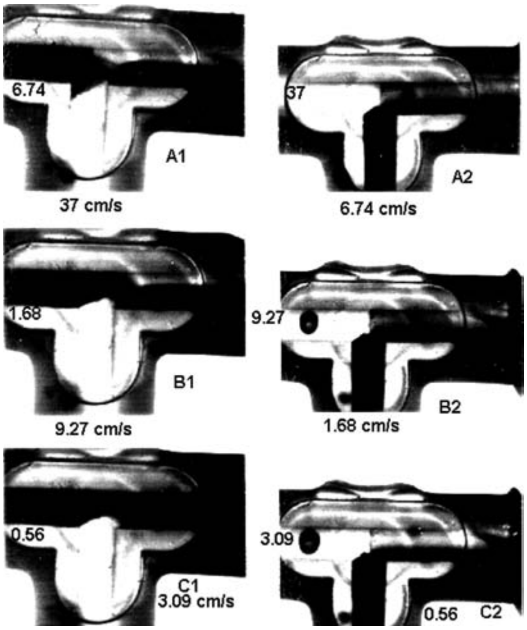

Figure 5. **Segregation in mixed streams of clear and stained water. Micrographs of 0.159 cm i.d. tee mixing experiments using water streams with one stained. Flows enter from left and bottom and exit to the right, with inlet flow rates in cm/s listed. Total Reynold's numbers from top are 720, 180, and 60.**

Table 1. **Representative review of patent literature for the acid-catalyzed acetalization of corticosteroids**[2]

steroid[a]	aldehyde	acid	eq. acid	solvent	*R*/*S*	scale (gm)	yield (%)
16 α-HDP	CCA	$HClO_4$	0.27	CH_3NO_2	60/40	0.5	70
16-HDP	CCA	>$HClO_4$	1.9	>CH_3NO_2	76/24	2	78
16-HDP	CCA	$HClO_4$	3.3	CH_3NO_2	92/8	2	88
16-HDP	CCA	$HClO_4$	3.8	$MeCl_2$	89/11	5	NR
16-HDP	CCA	$HClO_4$	2.2	$MeCl_2$	58/42	300	75
16-HDP	CCA	CH_3SO_3H	4.0	CH_3NO_2	85/15	2	68
16-HDP	CCA	$HClO_4$	2.8	$CH_3CH_2NO_2$	98/2	15	75
16-HDP	CCA	HCl	11.5	dioxane	25/75	2	25
16-HDP	CCA	$HClO_4$	2.8	$CH_3CH_2NO_2$	98/2	15	75
TAA	butanal	$HClO_4$	2.3	isooctane	95/5	2	87
DFCA	butanal	$HClO_4$	4	isooctane	96/4	2	NR
DFCA	butanal	$HClO_4$	5	isooctane	98/2	40	NR

[a] 16-HDP: 16-hydroxyprednisolone. TAA: triamcinolone acetonide. DFCA: dihydrofluocinolone acetonide. CCA: cyclohexanecarbaldehyde. NR: Not Reported.

Table 2. **Compositions of the final quenched solutions; analysis by HPLC, assuming constant response factor**

volume processed	conditions	final DFCA	final *R* epimer	final *S* epimer	yield (%)
150 mL	batch reaction	0.6	96.4	3.0	96
1 L	flow with two diaphragm (pulsing) pumps	5.0	90.0	4.0	95
1 L	flow with gear (steroid) + diaphragm (perchloric acid) pumps	0.3	98.2	1.5	95
16 L	flow with gear (steroid) + diaphragm (perchloric acid) pumps	0.4	97.2	2.4	96

difficulty. While in principle a CSTR system is capable of running the chemistry we strongly suspect that it too would be plagued by crystallization and fouling due to the long-lived material inherent in the tail of the reactor residence time distribution.[4] Experimental verification of this was never attempted, however.

The simple PFR still presented significant challenges. In early investigations we found that under low flows the two fluid streams (steroid/aldehyde/solvent and 70% perchloric acid) fluids would quickly segregate into a slug flow regime, where domains of inorganic and organic material would flow though the system with only interfacial mixing between the slugs, leading to incomplete conversion. An investigation was subsequently undertaken to learn how best to defeat this problem.

Even under the best of circumstances mixing relatively small streams presents an insurmountable problem with scaling down flow reactors, namely the irreducibility of fluid momentum required for good mixing. Laminar flow, in which the viscous forces tending to hold the fluid element together dominate the inertial forces tending to disperse the element, is incumbent in most systems involving small tubing dimensions and low flow rates. To more fully investigate this behavior, we tested a mixing tee under the stream inlet flow ratios required (5.5:1) with various inlet configurations and total overall feed rates, using a single liquid (water) as an admittedly imperfect model. Micrographs of these experiments are presented as Figure 5, with the velocities of the inlet streams appended onto the figure. In all cases extensive segregation of the outlet stream occurs, the exact pattern dependent on how the streams are introduced and the overall momentum (Reynold's number) of the system. Two important effects were observed. First, in cases where the inlet velocities are highest, the low flow stream is pushed and stretched to the periphery of the tube, thereby maximizing interfacial contact. Second, the stability of the fluid/fluid interface decreases markedly with increasing Reynolds number, with fluctuations growing to a dimension on the order of the ca. one-half the tube diameter. Although the dynamism of this process is not well-represented in single micrographs, some evidence in the micrographs can be noted by the increasing diffusivity of dye with Reynolds number. It is unfortunate that equipment limitations prevented us from duplicating the true system in these mixing studies.

We thereby concluded that the remedy for slug flow was to operate the system in the turbulent regime. Unfortunately, the large pressure drops incumbent with small dimension tubing prohibited this. Ultimately we were able to operate within the laminar-to-turbulent transition regime, near a Reynold's number of ~2200. This produced cocurrent flow of the two streams with no slug segregation observed within the reaction zone.

Coupling this reaction stage to a seeded continuous crystallizer with level control and a quench tank for the crystallized intermediate completes the system. The volume of the crystallizer is fixed by the desired residence time and the flow rate. For this system a 10-min mean residence time and 50 mL/min flow rate fix the volume at 500 mL.

Results

Table 1 presents the results of three runs using the flow system compared to a small-scale batch reaction. In the final run, ~1 kg of DFCB was produced using the flow system. Note that markedly inferior results were obtained when using the two-diaphragm pump system. This is almost certainly due to the incommensurate pulsating nature inherent in these devices, which allowed the oil/solvent mixture to become segregated even under our near-turbulent conditions. In contrast, substituting a smooth flowing gear pump as the source for the high-flow organic stream moved the mixture through the system

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(4) Levenspiel, O. *Chemical Reaction Engineering*; Wiley: New York, 1972.

smoothly as a uniform dispersion, enabling highly efficient mass transfer and superior results.

Conclusions

This paper is presented as one case study of how continuous processing can be used to perform processes considered unsuitable for batch operation. Roughly 100 g/h of high-quality DFCB crude was produced at this demonstration level. This case demonstrates the continuous reaction, crystallization, and quench of a hazardous intermediate needed to obtain quality material.

Acknowledgment

The careful experimental work of Mr. Gordon Snow and Mr. George Smith is gratefully acknowledged.

Received for review June 3, 2008.

OP800128G