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Continuous Processing to Control a Potentially Hazardous Process: Conversion of Aryl 1,1-Dimethylpropargyl Ethers to 2,2-Dimethylchromenes (2,2-Dimethyl-2*H*-1-Benzopyrans)

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Abstract:

The thermal Claisen rearrangement of 4-cyanophenyl 1,1-dimethylpropargyl ether (4) to 6-cyano-2,2-dimethylchromene (5), (6-cyano-2,2-dimethyl-2*H*-1-benzopyran), which is used in the synthesis of a potassium channel activator drug candidate, BMS-180448, created a significant process development issue. The resulting large heat release in this conversion posed not only a safety risk but could also cause product degradation if done in a batch-wise manner. The solution was to exploit the high surface-to-volume ratio of a plug-flow reactor that would maximize the heat transfer, thereby permitting tight and responsive temperature with better reaction control. In the course of successfully testing the plug-flow concept on "micro"-flow scale (gram quantity) and "kilo"-flow scale (∼10 kg), a generalized mathematical model capable of predicting the reaction performance based on the physical properties of any given plug-flow reactor was generated. The model provides requisite information to design and operate a plug-flow reactor of any size for this reaction. This model would optimize reaction conditions for an acquired reactor system capable of producing ∼7 kg/h of the dimethylchromene. Application of plug-flow reactor technology enabled production of high quality 2,2-dimethylchromenes in good yield (>98 mol %) without the use of solvents and with virtually no waste streams.

Introduction

The variety and relatively small annual production of many compounds produced in the pharmaceutical and fine chemical industries lead to a flexible production capability based on batch or semibatch processing. However, some chemical processes or reactions would be hazardous or unnecessarily risky if performed in this manner. The preparation of 2,2-dimethylchromene (2,2-dimethyl-2*H*-1-benzopyran) derivatives **3** necessitated consideration of an alternative processing approach due to a high heat of reaction that could lead to an uncontrollable temperature rise from batch-wise preparation.

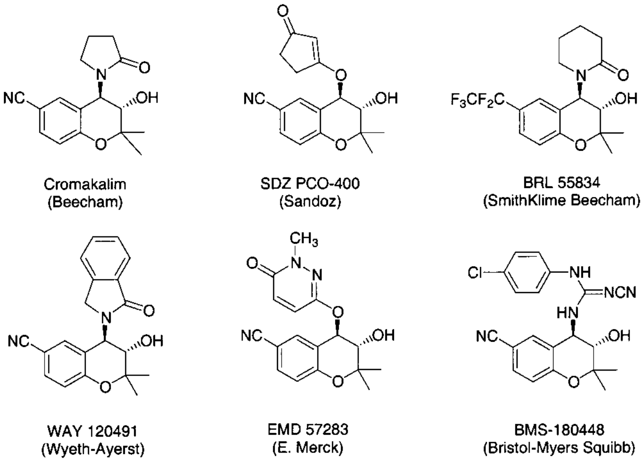
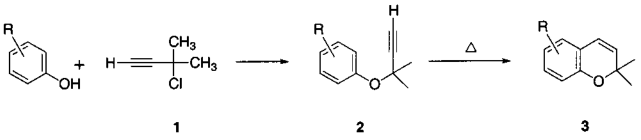


Figure 1. **Benzopyran-based potassium channel activators.**

Scheme 1



The impetus for designing processes for large-scale production of these compounds stems from the large number of naturally occurring 2,2-dimethylchromene (2,2-dimethyl-2*H*-1-benzopyran) derivatives **3** and the considerable interest in them due to their biological activity in plants and animals.[1] A series of benzopyran-based potassium channel activators[2] (Figure 1) has generated intense interest in the synthesis of 2,2-dimethylchromenes, particularly those bearing an electron-withdrawing group.

The O-alkylation of phenols with 3-chloro-3-methylbutyne (**1**) followed by thermal rearrangement of the resulting aryl

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[†] Lafayette College.

(1) Chromenes, Chromanones, and Chromones. In *The Chemistry of Heterocyclic Compounds*; Ellis, G. P., Ed.; John Wiley and Sons: New York, 1977; Chapter 2.

(2) Ashwood, V. A.; Buckingham, R. E.; Cassidy, F.; Evans, J. M.; Faruk, E. A.; Hamilton, T. C.; Nash, D. J.; Stemp, G.; Willcocks, K. *J. Med. Chem.* **1986**, *29*, 2194−2201; Fozard, J. R.; Menninger, K.; Cook, N. S.; Blarer, S.; Quast, U. *Br. J. Pharmacol.* **1990**, *99*, 6P; Buckle, D. R.; Eggleston, D. S.; Pinto, I. L.; Smityh, D. G.; Tedder, J. M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1161−1164; Bergmann, R.; Eiermann, V.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 2759−2767; Atwal, K. S.; Grover, G. J.; Ahmed, S. Z.; Ferrara, F. N.; Harper, T. W.; Kim, K. S.; Sleph, P. G.; Dzwonczyk, S.; Russell, A. D.; Moreland, S.; McCullough, J. R.; Normandin, D. E. *J. Med. Chem.* **1993**, *36*, 3971−3974.

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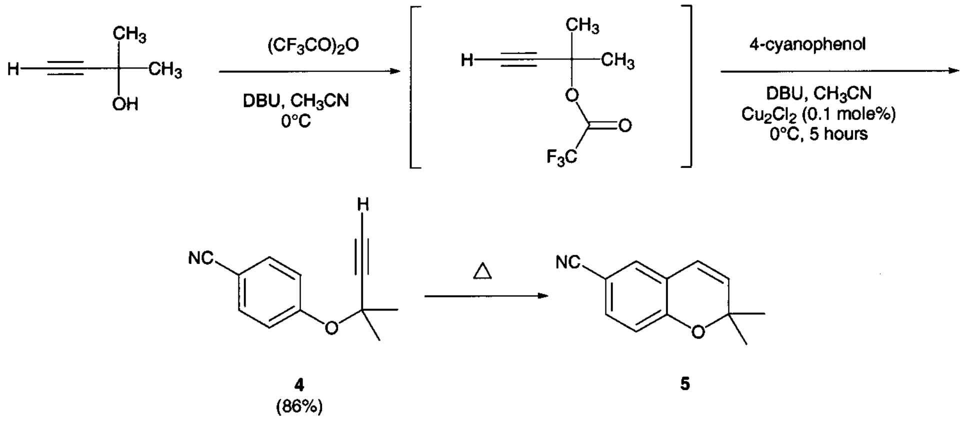
Scheme 2



1,1-dimethylpropargyl ether, **2**, remains a convenient method for the preparation of 2,2-dimethylchromenes **3** (Scheme 1).[3] This method is based on the work of Iwai and Ide[4] who demonstrated that thermal rearrangement of simple aryl propargyl ethers yielded chromenes. Subsequent work at Bristol-Myers Squibb demonstrated that the conversion of **1** to **2** is catalyzed by copper I and II salts and that the trifluroacetate corresponding to **1** (generated in situ*)* is an effective alkylating agent in the presence of copper (Scheme 2).[5]

Results and Discussion

An ongoing project required the preparation of a substantial amount of 6-cyano-2,2-dimethyl-[2*H*]-chromene (**5**).[5] With the previously described improvements to the preparation of the propargyl ether **4**, efforts shifted to the conversion of **4** to **5**. In the past, the thermal Claisen rearrangement−cyclization of **4** had been performed by heating in *o*-dichlorobenzene,[5] *N*,*N*-diethylaniline,[6] or peanut oil.[7] On a small scale, the reaction proceeded well, but with further laboratory scale-up, an uncontrolled temperature excursion occurred when the substrate and solvent were mixed at room temperature and then heated, due to the rapid and highly exothermic reaction. A semibatch approach, by portion-wise addition of **4** into hot (~180 °C) *N*,*N*-diethylamine, provided yields of 80−85% after crystallization. However, diethylamine removal required dilution with toluene and extraction with aqueous acid. Handling the toxic amine solvent (the OSHA exposure limit is a time weighed average of 5 ppm over 8 h) on a large scale and the relatively lengthy cleanup procedures discouraged consideration of this approach for further scale-up efforts. Varying success in incorporating other "high" boiling solvents (dodecane, ethylene glycol, 1,3-dimethyl-2-imidazolidone, 2-benzylpyridine, or 2,4,6-collidine) for the conversion prompted a small (2−5 g), laboratory-scale assessment of the thermal rearrangement−cyclization reaction on neat **4**. Although showing promise, these experiments demonstrated the difficulties of controlling the extremely energetic reaction.

Hazard Lab Evaluation. A hazards evaluation utilizing differential scanning calorimetry (DSC), accelerating rate calorimetry (ARC), and the reactive system screening tool (RSST) provided information to guide further experimentation, resulting in the development of a strategy to enable safe and consistent operations on pilot and (potential) commercial scale.

DSC testing (Figure 2) showed two broad exotherms with onset temperatures of 105 and 240 °C, respectively. The adiabatic ARC test (Figure 3) showed the temperature and pressure history of the thermal conversion of **4** under adiabatic mode from which the heat of reaction and the reaction kinetics were quantified. On the basis of the ARC data, no thermal reaction would be expected to occur below the onset temperature of ~105 °C. However, in the absence of sufficient temperature control, the heat generated in the desired thermal reaction could propel the system temperature above the onset of a secondary decomposition reaction. The intramolecular nature of the reaction suggested first-order kinetics. The data treatment of the calorimetric data empirically confirmed this observation. The heat rate versus temperature plot (Figure 4) allowed calculation of the first-order rate constant according to the kinetic expression:

$$\frac{\mathrm{d}C(4)}{\mathrm{d}t} = kC(\mathbf{4}) = -4.6 \times 10^{14} \exp\left(\frac{-32000/}{RT}\right) C(\mathbf{4})$$

in which:

$C(\mathbf{4})$ = the concentration of reactant **4** (mol/mL)

t = time (min)

k = rate constant (min^{-1})

R = gas constant, 1.987 (cal/mol K)

T = reaction temperature (K).

Assuming a specific heat for the ether derivative **4** of 0.61 cal/g °C, the heat of reaction was calculated to be 41.2 kcal/mol. This value translates to an adiabatic temperature rise of ~375 °C during the course of the reaction. RSST

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(3) Hlubucek, J.; Ritchie, E.; Taylor, W. C. *Tetrahedron Lett.* **1969**, 1369−1370; Hlubucek, J.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1971**, *24*, 2347−2354.

(4) Iwai, I.; Ide, J. *Chem. Pharm. Bull.* **1963**, *11*, 1042−1049.

(5) Godfrey, J. D., Jr.; Mueller, R. H.; Sedergran, T. C.; Soundararajan, N.; Colandrea, V. C. 208th ACS National Meeting; American Chemical Society: Washington, DC, August 21−25, 1994.

(6) Harfenist, M.; Thom, E. *J. Org. Chem.* **1972**, *37*, 841−848.

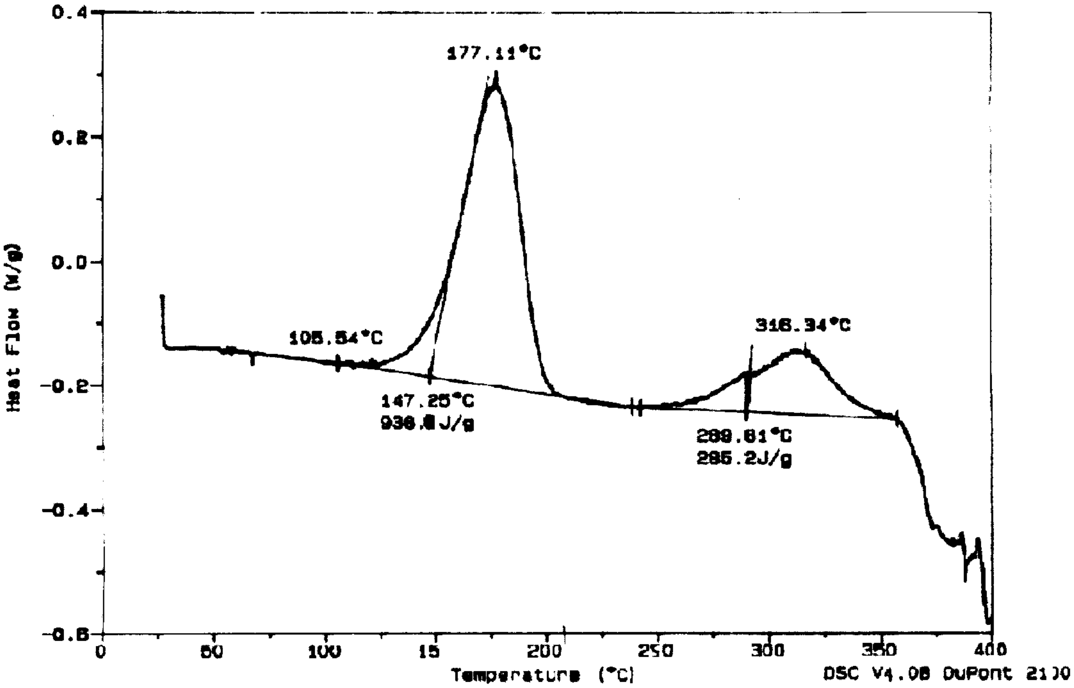


Figure 2. **DSC thermograph of compound 4 (1 °C/min, 4.5 mg in aluminum crucible).**

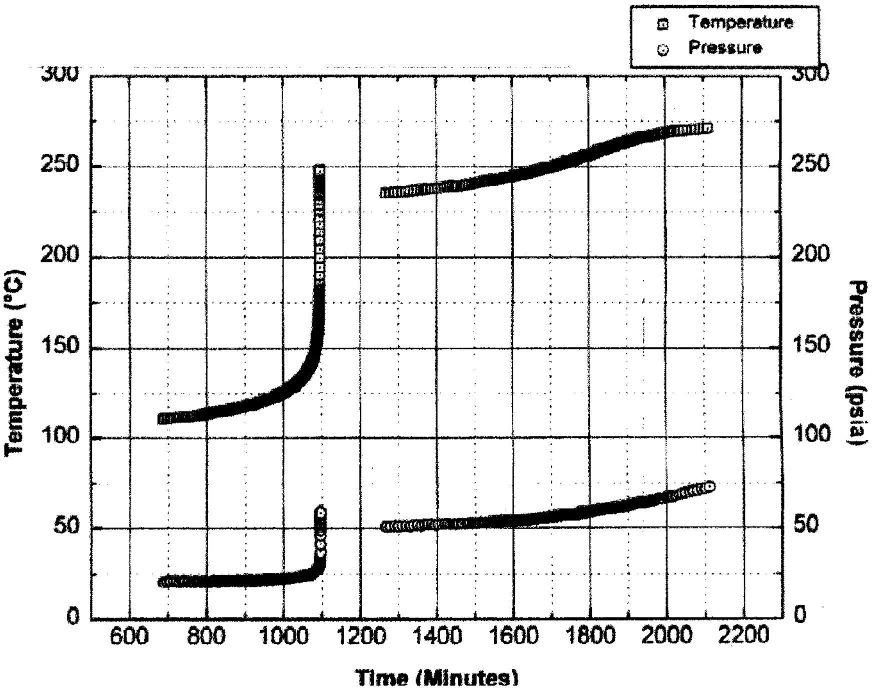


Figure 3. **ARC temperature and pressure vs time plot.**

evaluation of neat material showed thermal stability behavior with a self-heat rate of less than 2 °C/min for temperatures below 145 °C, consistent with adiabatic studies in the ARC which showed similar self-heating rates (<1−1.5 °C/min) at 150 °C. For these low self-heating rates, an adequately jacketed batch reactor should control the reaction up to ∼140−150 °C. However, at >150 °C the rapid acceleration of the reaction rate and hence the accelerating self-heating creates the potential for an uncontrolled reaction. In one test, the temperature of the reaction rose from 180 to 445 °C within 33 seconds.

Scale-Up Studies. On the basis of these data, safety and operating concerns had to be addressed prior to further experimentation and scale-up. The concerns centered around maintaining control of the reaction temperature while driving the reaction to completion. Although temperature control increases with lower operating temperatures, lower operating temperatures prolong the time to reach reaction completion (∼27 h at 140 °C vs ∼10 h at 150 °C). This encourages using an operating temperature that is as high as can be safely controlled while, at the same time, controlling the risk of the accelerating heat generation at the higher temperatures.

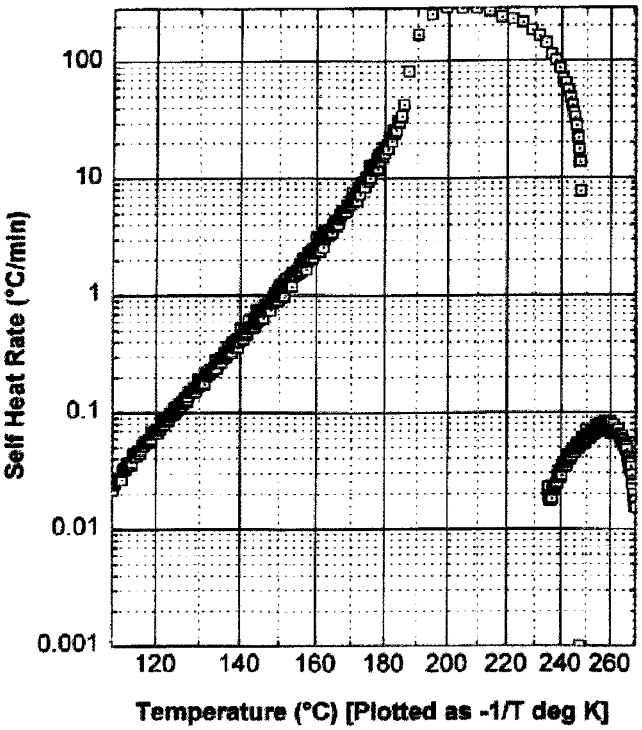


Figure 4. **ARC self-heat rate data (ϕ factor = 2.15, Ti bomb).**

For a batch system, selection of the operating temperature requires that sufficient spare heat-exchange capability be designed in the reactor to control potential thermal excursions and avoid a "runaway" reaction. Typically, batch operations use a solvent system to maintain a fixed boiling point of the mixture at the desired reaction control point and to remove the heat of reaction in the condenser system. Keeping the overall boiling point within the desired temperature control range using solvents typically available in pharmaceutical/fine chemical manufacturing (boiling point typically below 120 °C) requires careful maintenance of the solvent/substrate ratio. The operating temperature range would have to be optimized in conjunction with the heat-transfer capabilities of the reactor and the condenser to prevent loss of solvent. Loss of solvent (through insufficient condensing capacity, loss of coolant, excessive reflux) would accelerate the reaction (due to increased boiling point of the batch), leading to further solvent loss. Should the rate of heat generation exceed control limitations, a rapid and excessive pressure buildup in the reactor (from solvent evaporation and possible product decomposition) could cause the material to entrain from the reactor in a potentially violent manner. The thermal potential for compound **4** with various solvents was tested with the reactive system screening tool (RSST). Figure 5 shows the runaway potential with only 5% of **4** in diethylaniline. In the absence of controls, this reaction mixture could begin to accelerate at ~140−150 °C and reach a maximum temperature of ~215 °C.

Increasing the operating scale of the batch reaction exacerbates the control problem. Since most of the heat transfer is through the wall of the reactor, the available surface (S) for the volume (V) of reaction decreases inversely as the diameter of the reaction vessel increases:

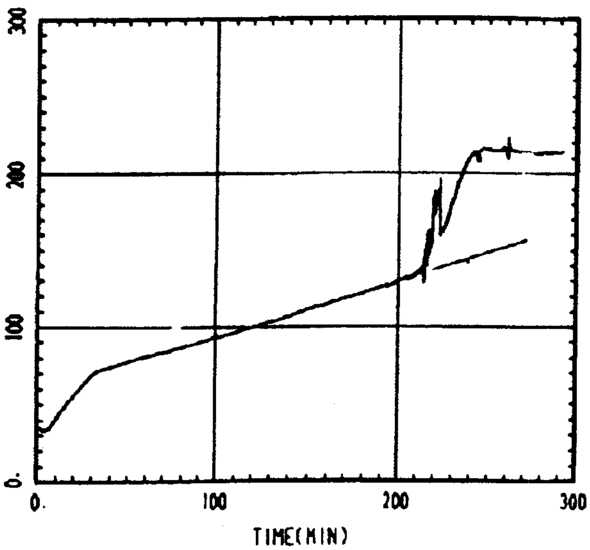


Figure 5. **RSST temperature vs time plot (5% compound 4 in diethylaniline, heat rate = 0.25 °C/min).**

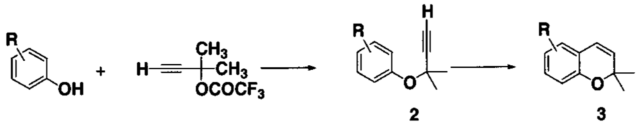
$$S/V = \frac{\Pi DL}{\Pi (D/2)^2 L} = 4/D$$

thus, further hindering the ability to control the reaction.

Application of a Plug-Flow Reactor. The nature of this reaction makes it an ideal candidate for further scale-up in a plug-flow reactor (PFR). The "plug flow" nature of the reactor stems from the "flat" (constant) cross-sectional velocity profile due to the turbulent nature of the flow or induced by the use of static mixers. A PFR improves the efficiency of heat transfer by maintaining a high surface-to-volume ratio as the operation increases in scale. Scale-up could mean simply using multiple identical tubular reactors as were used in a pilot campaign within a large heat exchanger. Although the material is processed continuously, only a relatively small portion of the overall material is committed to the reaction at a given time, limiting the extent of problems, should difficulties arise with the reaction. Should the process-monitoring equipment indicate a loss of control of the desired steady-state operating conditions, adjustments can be made to the flow rate of the reactant and the flow rate and temperature of the heat-transfer fluid to reestablish control or to quickly bring the operation to a safe halt by allowing the residual material in the reactor to expend its energy in a controlled fashion.

Lab Results-Experimental. The feasibility of the continuous plug-flow approach was tested at bench scale using a 0.0625 in. i.d. × 10 ft stainless steel coil immersed in an oil bath at 220 °C. Neat **4** was pumped through the coil using a syringe pump at a rate such that the liquid residence time (reactor volume/volumetric flow rate) varied from 3.5 to 17.7 min over the various trials. In all of these trials, compound **4** underwent almost quantitative conversion to **5** of good quality (HPLC purity >96%). The outlet temperature from the steel coil was close to the heating bath temperature (220

Table 1. Conversion of 2 to 3 at Bench-Scale Plug-Flow Reactor



2, R =	temp (°C)	residence time (min)	product(s) 3, R =	3, R =	yield (%)[a]	ref
4-CN	220	3.5	6-CN		98	5
4-OCH_3	240	11.7	6-OCH_3		78	8
4-$COCH_3$	240	5.5	6-$COCH_3$		80	9
4-NO_2	240	5.5	6-NO_2		96	9
4-I	220	5.5	6-I		78	10
3-CF_3	260	17.7	7-CF_3	5-CF_3	86[b]	11
3-NO_2	230	5.5	7-NO_2	5-NO_2	82[b]	8
2-CHO	240	5.5	8-CHO		74[c]	none

[a] Yields refer to purified (crystallization or column chromatography) product. [b] Refers to the combined yields of the regio-isomers (the ratio of **5** to **7** isomer is ca. 5 to 3). The components were separated by column chromatography. [c] Besides the main component (oil) an unknown species (oil) with a molecular weight of 414 was isolated.

Table 2: Conversion of 4 to 5 in a Laboratory Plug-Flow Reactor

batch no.	wt. input **4** (kg)	wt. output **5** (kg)	yield (m%)	HPLC purity (%)
001	13.20	12.02	91.0	95.92
002	10.70	10.48	97.9	96.70
003	10.90	10.30	94.7	97.93
004	10.67	10.43	97.7	97.86
005	6.82	6.52	95.6	97.79

°C). Since the steel coil was long enough and immersed in a hot oil bath, the heat generated from the reaction was well dissipated to the bath by the time the product exited the reactor. The limited extent of each trial provided sufficient qualitative information on the extent of the reaction and yield to encourage further development efforts. The generality and usefulness of this method was further demonstrated by applying this technique for the conversion of other aryl 1,1-dimethylpropargyl ethers[5] **2** to the corresponding 2,2-dimethylchromenes **3**[5,8−10] (Table 1).

Kilo Lab Results-Experimental. To provide quantities of material for subsequent process development, **4** was converted to **5** in a stainless steel PFR, which was a 0.125 in. i.d. × 25 ft tubing coil immersed in a constant-temperature bath maintained at 195−200 °C. A flow of 20 mL/min afforded the reaction mixture a residence time of ~4 min. Conversion reached completion in each of the five batches. Although yields varied; the losses can be attributed to residual material in the reactor and physical handling losses (Table 2).

Mathematical Modeling

The PFR demonstrated its utility for handling this highly exothermic reaction on small scale. However, any further scale-up would require changes in PFR capacity (diameter, length, flow rates) to handle the increased volume of material to be processed. In turn, this necessitates a means to predict the performance of the reactor system to (1) ensure safe operating conditions, (2) set conditions for optimal performance within the constraints of the heat-transfer capabilities of a given PFR, and (3) avoid operating conditions that could compromise product quality. The hazard analysis confirmed the first-order nature of the reaction through data treatment that gave an excellent fit to the first-order expression allowing derivation of the rate constant and its temperature dependence. The resulting kinetic rate expression enabled the generation of a mathematical model reaction system capable of predicting the extent of conversion and the temperature profile throughout a given PFR. Substitution of the appropriate physical and operating parameters for a given PFR into the model allows prediction of conversion and extent of the temperature rise within the reactor.

Development of the Model. For a PFR, the material balance equation becomes:

$$u\frac{\mathrm{d}C(\mathbf{4})}{\mathrm{d}z} = -kC(\mathbf{4}) = -4.6 \times 10^{14}\exp\left(\frac{-32.08}{RT}\right)C(\mathbf{4})$$

where time (t) is replaced by z/u such that

z = distance along the axial length of the PFR (cm)

u = fluid velocity (cm/min)

Because heat generation may exceed the heat-ttransfer capabilities of the reactor, the reaction must be modeled as a nonisothermal system. Hence, to predict the conversion of **4** through the reactor, the model has to take into account the effect of the change in temperature throughout the reactor due to the extent of conversion and the degree of heat transfer along the reactor length. With the assumption of constant reaction mixture density and heat capacity, the energy balance that provides this information is given by:

$$\rho u C_\mathrm{p}\frac{\mathrm{d}T}{\mathrm{d}z} = -\Delta H k C(\mathbf{4}) - Ua(T - T_\mathrm{c})$$

In this expression,

ρ = density (1.01 g/mL)

C_p = heat capacity, (0.6 cal/(g °C)

$-\Delta H$ = heat of reaction (41 200 cal/g mol)

U = heat-transfer coefficient (cal/(cm^2 min °C)

a = specific area (S/V) = $4/D$

This model requires a simultaneous solution of the two first-order, ordinary differential equations. Because the equations are coupled by the dependent variables (the temperature variable appears in the material balance expression, and the concentration variable appears in the energy

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(7) Mark, C. P.; Reber, J.-L.; Peham, M.; Schultz, R.; Berthold, R.; Collect, A.; Malthete, J. 9th International Conference on Organic Synthesis, University of Montreal: Montreal, Quebec, Canada, June 28−July 2, 1992.

(8) Naidu, V.; Rao, K. *Ind. J. Chem.* **1979**, *17B*, 73−75. Also see, Ahulwalia, V. K.; Mekherjee, I.; Mukherjee, K. *Ind. J. Chem.* **1984**, *23B*, 1124−1125.

(9) North, J. T.; Kronental, D. R.; Pullockaran, A. J.; Real, S. D.; Chen, H. Y. *J. Org. Chem.* **1995**, *60*, 3397−3400.

(10) Ding, C. Z.; Rovnyak, G. C.; Misra, R. N.; Grover, G. J.; Miller, A. V.; Ahmed, S. Z.; Kelly, Y.; Normadin, D. E.; Sleph, P. G.; Atwal, K. S. *J. Med. Chem.* **1999**, *42* (*18*), 3711−3717.

balance) a simple analytical solution cannot be provided. An approximation, such as the Runge−Kutta method,[12] can solve systems of such equations by an iterative, numerical technique. An adaptive step fifth-order Runge−Kutta algorithm,[13] part of the *Mathcad 8* Professional software,[14] was used to solve the equations defining the model.

To simplify and generalize the analysis, dimensionless variables convert the differential equations to the following:

$$\frac{\mathrm{d}X}{\mathrm{d}\bar{z}} = -\bar{k}X \exp\left[-\epsilon\left(\frac{1-\bar{t}}{\bar{t}}\right)\right]$$

$$\frac{\mathrm{d}\bar{t}}{\mathrm{d}\bar{z}} = \beta X \exp\left[-\epsilon\left(\frac{1-\bar{t}}{\bar{t}}\right)\right] - \bar{U}(\bar{t} - t_c)$$

where

X = unreacted fraction of **4** [$C(\mathbf{4})/C_0(\mathbf{4})$]

$C_0(\mathbf{4})$ = the initial concentration of **4**

$\bar{z} = z/L$ = ratio of the distance (z) in the reactor to the reactor length (L)

$\bar{k} = k_0L/u$ = dimensionless reaction constant

$$k_0 = A_0 \exp(-\epsilon)$$

$\bar{t} = T/T_0$ = ratio of the reaction temperature to the inlet temperature

$$\epsilon = E/RT_0$$

$$\beta = -\Delta H k_0 C_0 L/\rho C_p T_0 u$$

$\bar{U} = ULa/\rho C_p u$ = dimensionless heat-transfer coefficient

$t_c = T/T_c$ = ratio of the reaction temperature to the jacket temperature

subjected to the initial conditions:

$$\bar{z} = 0, X = 1, \bar{t} = 1$$

Discussion of Modeled Reactor Performance

Application of the model to the reaction system implies turbulent flow or more specifically a flat velocity profile across the reactor diameter. Turbulent flow indicates good mixing and hence a constant temperature profile. For the nature of this reaction system, laminar flow should be avoided for this very reason. Static mixers incorporated in the reactor improve the cross-sectional mixing and enhance the heat transfer. This discussion demonstrates the use of the model as a guide for selecting appropriate reaction conditions (temperature, reactor length, reactor diameter, and flow rate) to ensure adequate control of a thermally sensitive reaction.

The variables that can be manipulated to control the system response include the diameter and length of the PFR, the volumetric flow rate of the reactant, and the temperature of the heat-transfer medium. [For simplicity in this analysis, a constant temperature of the heat-transfer medium will be assumed. Depending on the system, (the flow rate and heat capacity of the heat-transfer fluid), this temperature may vary along the length of the reactor in co-current or counter-current operation. An energy balance on the heat-transfer fluid can be included in the model and solved simultaneously with the continuity equations for the reaction.]. A critical parameter, the overall heat-transfer coefficient, cannot be independently set as a control variable. The fluid properties of the reaction mixture and the heat-transfer fluid, the thickness and conductivity of the wall separating the two fluids, and the incorporation of baffles and fins used to improve mixing and heat-transfer influence this parameter. The overall heat-transfer coefficient must be determined for a given reactor system.

An early consideration of running this reaction in a batch-recycle manner highlights the risk of insufficient completion of this reaction in the PFR. The reactant within a batch reactor (storage vessel) achieves partial conversion passing through a heated reactor. Prior to the return to the storage vessel, the material passes through a heat exchanger thereby, returning to the safe holding temperature. During the operation, a potential exists of introducing heated material into the hold vessel in the event of loss of cooling to the heat exchanger or circumstances that might upset the heat balance in the system. Until sufficient material is converted, a risk remains that the reaction could proceed in an uncontrolled manner in the recycle vessel. Therefore, if the operation strategy for a given PFR dictates incomplete conversion, the reactor should be operated to convert the majority of material in a single pass. This conversion should ensure that any conversion of the material in the hold tank would limit the temperature rise well below the boiling point of the mixture and the onset of decomposition. As a precaution, additional heat removal capabilities should be designed for the hold vessel.

Figures 6 and 7 provide temperature profiles and conversions along a PFR for three different regimes of operation. The most desirable situation would be the isothermal case wherein the operating conditions are set so that heat is removed as fast as it is generated, and the reaction mixture is maintained at the temperature of the heating fluid. As shown in Figure 7, for a properly designed reactor, the reaction reaches completion at the end of the reactor. As long as the temperature of the reaction mixture does not reach the regime where thermal decomposition begins, a less desirable, but operable, case occurs where the heat generated exceeds the capability for heat removal. With careful consideration of reactor performance and good temperature control, this can be a means to improve reactor throughput. As the corresponding conversion curve in Figure 7 shows, this particular reactor is over-designed as the reaction reaches completion within the first 25% of the length of the reactor. Capacity can be increased by increasing the flow rate, or a

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(11) Evans, J. M.; Stemp, G.; Tedder, J. M. PCT Int. Appl. 1991.

(12) Carnahan, B.; Luther, H. A.; Wilkes, J. O. *Applied Numerical Methods*, John Wiley and Sons: New York, 1969.

(13) Press, H. E.; Flannery, S. A.; Teukolsky, B P.; Vetterling, W. T. *Numerical Recipes in C*; Cambridge University Press, New York, 1992.

(14) *Mathcad 8 Professional*; MathSoft, Inc.: Cambridge, MA, 1998.

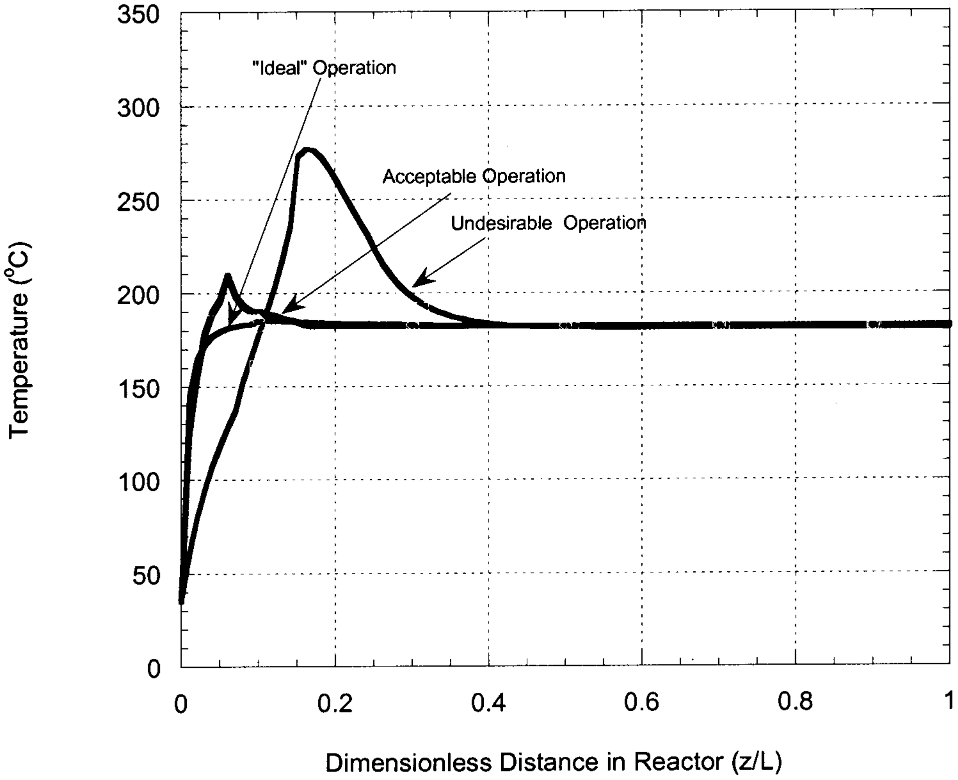

Figure 6. **Temperature profile throughout reactor for different modes of operation.**

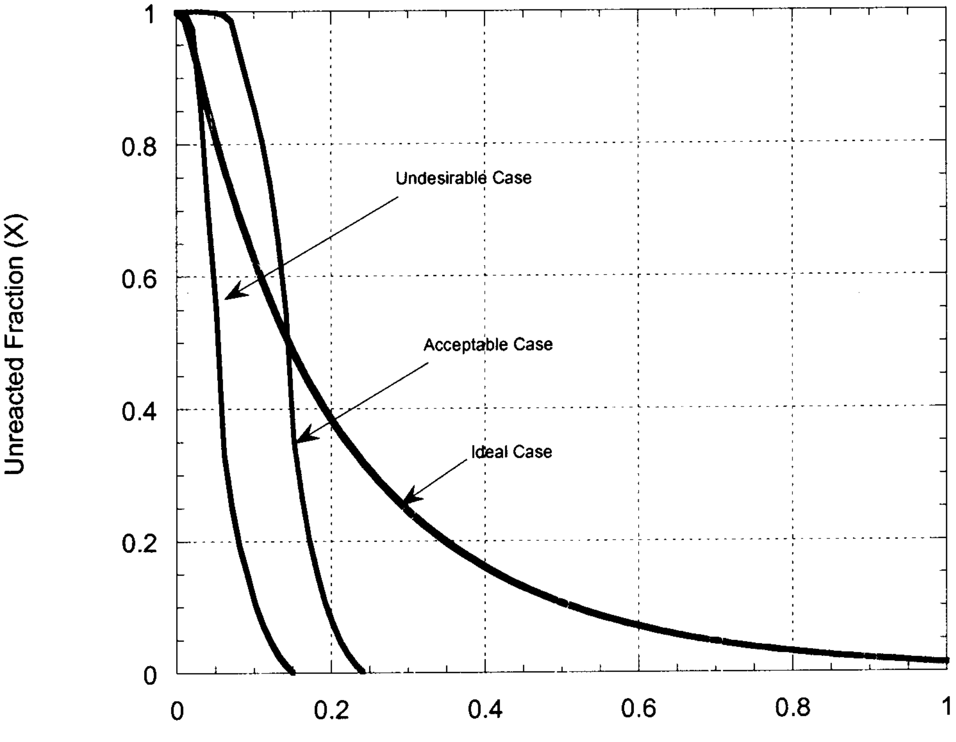

Figure 7. **Conversion profile across reactor for various operating conditions.**

much shorter reactor can be used to achieve the same performance.

The undesirable case occurs if the reaction mixture temperature exceeds the threshold of thermal decomposition. In this case, the operating temperature may be too high or the volumetric flow rate may be too low (or the combination of both) for the specific reactor configuration. For this case, Figure 7 shows that conversion is complete within the initial part of the reactor. Milder operating conditions can be employed to avoid the high-temperature excursion and to

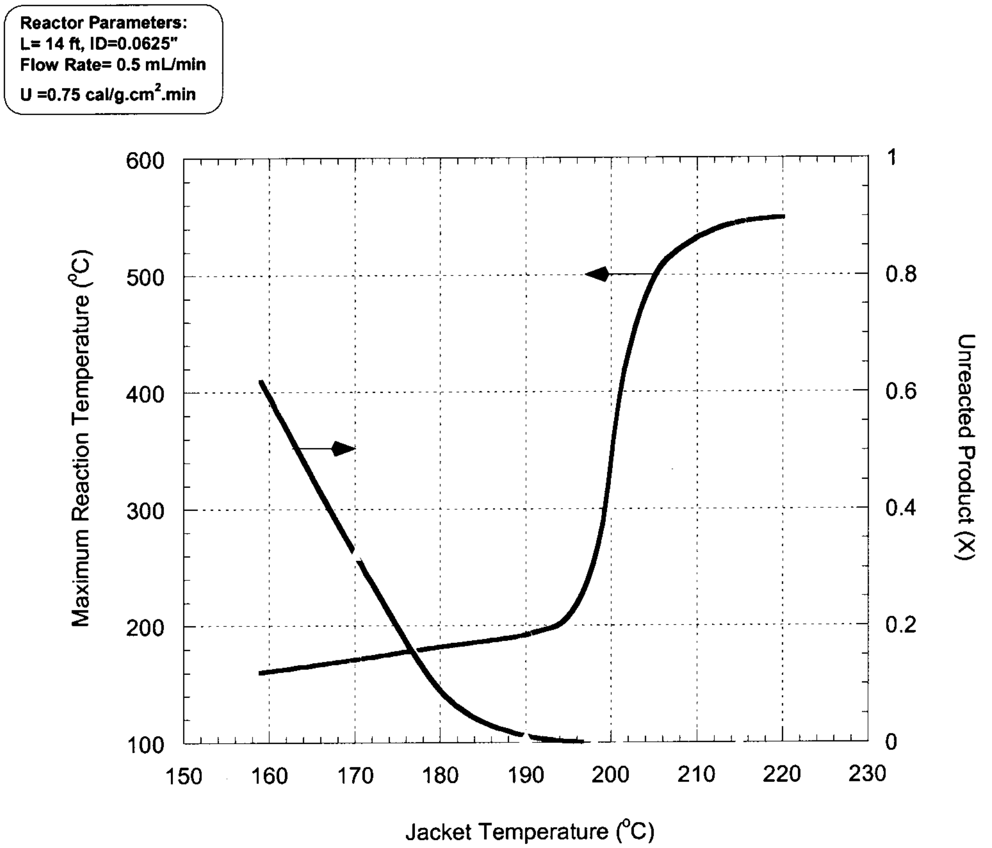

Figure 8. **Effect of jacket temperature on maximum temperature in reactor.**

make better use of the overall capacity of the reactor. Ideally, the reactor should be sized or the operating parameters set to complete the thermal conversion by the time the material exits the PFR. In cases where a PFR not specifically designed for this application is used, total conversion might not be possible on a single pass. As stated above, the first pass should convert a majority of the material to ensure that the partially converted material can be safely cooled and held prior to final pass to complete the reaction.

Use of the mathematical simulation for (1) understanding the behavior of the reaction, (2) helping design a reactor for scaled-up processing, and (3) establishing an operation strategy to maximize productivity while providing the desired product in a safe, controlled, and consistent manner are demonstrated in the following sections.

Simulation of a Small-Scale Reactor. The simulated results in Figure 8 show the significant improvement in conversion that is achieved with small (5−10 °C) increments in the jacket temperature. Although Figure 8 is based on a relatively small reactor (inside diameter = 0.0625 in., with a volumetric flow rate of 0.5 mL/min), a similar performance could be expected with larger reactors. The figure demonstrates that in a region of “lower” jacket temperature, temperature control will not become an issue, although the reaction may not proceed to completion for a fixed length of reactor. Increasing the jacket temperature increases the degree of conversion, but at some point concerns develop about the possibility of a “hot-spot” in the reactor. When the rate of reaction reaches a point that the heat generation exceeds the ability to transfer the heat to the heat-transfer fluid, the temperature rises and reaches a maximum at some point in the reactor. Once the majority of the reaction is complete, the heat-transfer process will bring the temperature of the flowing reactant back toward the control temperature downstream of the maximum point. Figure 8 indicates that a temperature maximum of 550 °C was reached in the reactor when 220 °C was used as the jacket temperature. Figure 8 clearly shows that operation above 200 °C gives a significant liability for exceeding the thermal decomposition limit. The real significance of Figure 8, however, lies in the extreme sensitivity for a thermal excursion at a threshold of ~195 °C. This threshold temperature will vary with reactor systems, based on the diameter of the reactor, the overall heat-transfer coefficient, and the volumetric flow rate. Beyond that temperature, relatively small increases in the reaction temperature can accelerate the reaction and heat generation well beyond the temperature where thermal degradation of the product sets in.

Mathematical Model for Large-Scale Unit. The heat-transfer coefficient plays a determining role in the setting of operating parameters. The model simulation provides insight into the performance of a larger-diameter reactor (length = 35 ft, i.d. = 0.375 in., flow rate = 45 mL/min) operating with a jacket temperature of 172 °C while varying the heat-transfer coefficient from 0.1 to 2.0 cal/(cm^2 min K): values that can be considered a reasonable range for a tubular heat exchanger. For the given reactor and operating conditions, Figure 9 shows the extent of conversion and the

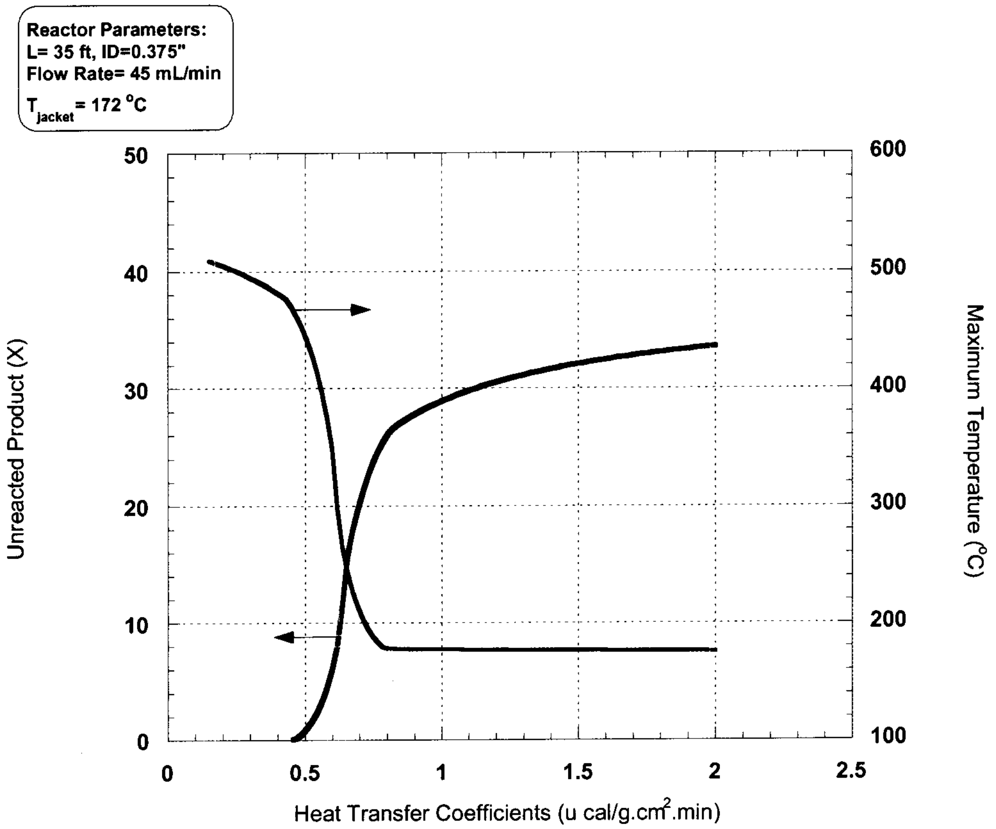

Figure 9. **Maximum conversion and temperature for different heat-transfer coefficients.**

maximum temperature liability. The sensitivity of the operation should the overall heat transfer coefficient be <0.8 cal/(cm^2 min K) is evident. The system shows fairly isothermal behavior for heat-transfer coefficients >0.8 cal/(cm^2 min K), although significant material remains unreacted. Either a longer reactor would be needed, or the material would require an additional pass through the reactor. Clearly, should the heat-transfer coefficient be <0.7 cal/(cm^{2}min K), temperature control can become problematic, especially if heat-transfer performance diminishes (e.g., by fouling on either side of the reactor). For this reactor configuration, a lower operating temperature and higher flow rates, with possibly two cycles through the reactor, would be necessary to avoid the predicted elevated reaction temperature. A potential mode for running this reaction with the low heat-transfer coefficient would be to run the material in two passes while maximizing the flow rate at a jacket temperature of ~172 °C to achieve at least a 50% conversion. Since the majority of the heat of reaction would be dissipated and the converted material would help serve as a heat sink, the second pass can be run at a higher temperature to ensure complete conversion.

For a somewhat longer reactor (length = 100 ft), the simulation results in Figure 10 demonstrate how flow rate can be adjusted to establish a tradeoff between conversion and thermal liability, thereby using this variable as part of the operating strategy. For the operating (jacket) temperature of 182 °C, Figure 10 demonstrates the interrelationship of conversion with maximum reaction temperature as the flow rate changes over a ±~20% flow range from 1500 to 2200 mL/min. As might be anticipated for high throughput operation, temperature excursions are of little concern, but residence time does not allow sufficient conversion. The flow rate for this particular reactor configuration must slow to less than 1700 mL/min before conversion increases significantly, but temperature liability rapidly becomes problematic with small decreases in flow rate. Confronted with this configuration, the alternatives are: (1) higher jacket temperature with a higher flow rate for maximum productivity or (2) or lower jacket temperatures with lower flow rates for greater limitation on temperature liability. In either case, multiple reactor passes will need to be incorporated to achieve full conversion.

Commentary

Theoretically, the conversion from the starting aryl propargyl ether **4** via a Claisen condensation/ring closure seemed simple: application of sufficient heat to initiate the reaction with the potential for complete reaction in quantitative yields. The reality of inducing the reaction at a high temperature accompanied by the rapid onset of heat generation provided a challenge in developing a scheme to safely scale up the process in a predictable, controllable, and consistent manner. The application of known continuous processing concepts not only reduced safety and quality risks but provided a means for producing large volumes of material with a minimal commitment of reactor volume. The positive results demonstrated by the PFR performance at the "micro"- and "kilo"-scales and the mathematical model capable of

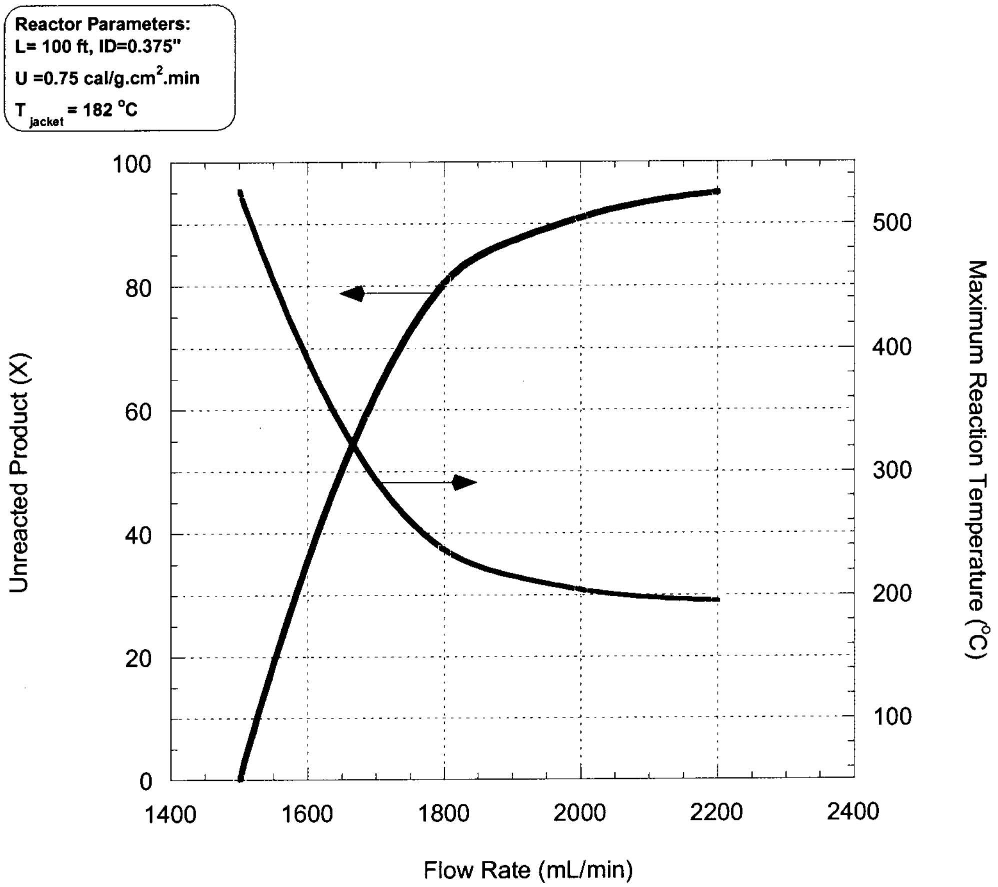

Figure 10. **Effect of flow rate on conversion and maximum temperature.**

guiding further development efforts led to acquisition of a large-scale (3/8 in. × 10 ft) jacketed reactor capable of producing ~7 kg/h of the dimethylchromene **5**.

A wide range of parameters can be employed to improve the control and safety of the operation. The PFR discussion is specific to the reaction in a solvent-free manner: a worst-case scenario from the extent of the potential thermal excursion. However, from a production standpoint, safety and efficiency might dictate operating the system diluted with solvent, presumably directly from the process that prepared the aryl propargyl ether. Solvent removal from the aryl propargyl ether exposes the material to elevated temperatures which (under an upset condition) might initiate the thermal reaction in an uncontrolled manner. Further, the nature of the aryl propargyl ether increases handling concerns since the solvent-free material solidifies at 40 °C. Should the neat material be stored, it would need to be in a cool area and some means of gentle warming devised for melting the solid for transfer prior to further processing. For safety and practicality, the reaction mixture from the preparation of the aryl propargyl ether can be pumped directly to the PFR and allows the reaction to proceed at the elevated pressures generated by the partial pressure of the solvent. The pressure would not be extreme based on conventional practices in the chemical industry and the dilution of the aryl propargyl ether would provide a heat sink, thereby minimizing the extent of the thermal excursion.

Conclusions

During process development of the conversion of aryl propargyl ethers to chromenes, a strategy to control a potentially hazardous reaction involves (1) maximizing the primary means of controlling the reaction temperature (heat transfer area) and (2) thoroughly understanding the sensitivity of the reaction system to the variables that influence the reaction performance. Use of a continuous PFR minimizes the amount of material exposed to reaction conditions at any given time, further limiting liability in the event of a processing upset. Encouraging results of the preparation of the dimethylchromene at “micro”- and “kilo”-scales enabled and encouraged investment in a large-scale jacketed reactor capable of producing ~7 kg/h.

The mathematical model of the process generated during the course of the development effort not only provides insight into the performance of the reaction in a given PFR but also allows development of the knowledge of reaction sensitivity to operational parameters. Thereby, the model provides a means for safely developing operational strategies and determining effects of process adjustments prior to confirmation by actual operation. The dimensionless nature of the model allows it to be applied to any PFR handling this reaction by substitution of the appropriate physical (length, diameter, and heat-transfer coefficient) and operating (flow rate, inlet temperature, and heating medium temperature) parameters.

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