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Aminolysis of Epoxides in a Microreactor System: A Continuous Flow Approach to β-Amino Alcohols

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Abstract:

The use of a continuous flow microreactor for β-amino alcohol formation by epoxide aminolysis is evaluated. Comparison to microwave batch reactions reveals that conditions obtainable in the microreactor can match or improve yields in many cases. By increasing the pressure of the system, maximum temperatures can also exceed those accessible using a microwave unit. The use of a microreactor for epoxide aminolysis reactions in the synthesis of two pharmaceutical relevant compounds is described.

Introduction

β-Amino alcohols are an important class of compounds to the synthetic and pharmaceutical communities. Oxycontin, Coreg, and Toprol-XL display this functional group pattern, and other pharmaceutical drugs such as Zyvox and Skelaxin feature oxazolidones that can be formed through β-amino alcohol precursors. A variety of methods to construct β-amino alcohols have been described in the literature, and one of the more frequently used approaches involves ring-opening of epoxides with amine nucleophiles.[1] Significant advances have been made in the promotion of epoxide aminolyses by addition of lanthanide triflates,[2] Lewis acids,[3] solid acid supports,[4] or by using solvents such as water.[5] While these methods are effective for relatively simple substrates, the opening of epoxides with amines at high temperatures remains one of the more general means of amino alcohol formation. Microwave irradiation is often used to rapidly achieve high reaction temperatures; indeed, Lindsay and co-workers recently described microwave-assisted aminolysis of epoxides in an efficient and straightforward manner.[3b,6]

The use of microreactor technology and continuous flow approaches has become an increasingly popular endeavor in both academia and the pharmaceutical industry.[7] This technology can serve as a means to streamline efficiency in the production of biologically active materials.[8] The commercial availability of continuous flow devices as well as detailed descriptions of "homemade" ones has enabled easier access to this expanding field. Microreactors in particular have unique advantages over conventional batch processes. Due to rapid heat and mass transfer, reaction profiles are often improved, and high temperatures and pressures not easily attainable in batch chemistry can now safely be realized while allowing for rapid reaction monitoring.[7b] Many of these same principles can be achieved using microwave chemistry;[9] however, limitations in microwave penetration depth have hampered scale-up to the industrial realm. The advent of continuous flow microwave processes has quickly become one of the answers to the scale-up issues.[10] However, conditions attainable in microreactors can often rival those obtained in traditional microwave processes.[11] Continuous flow microreactors also eliminate the need to scale up hazardous batch reactions, can easily be "scaled out" by linking them in parallel, and have the further benefit of not requiring microwave generators.[12]

Our efforts have focused on adapting pharmaceutically prevalent batch reactions, such as β-amino alcohol formation through epoxide aminolysis, to a continuous flow microreactor process. To the best of our knowledge, this constitutes the first

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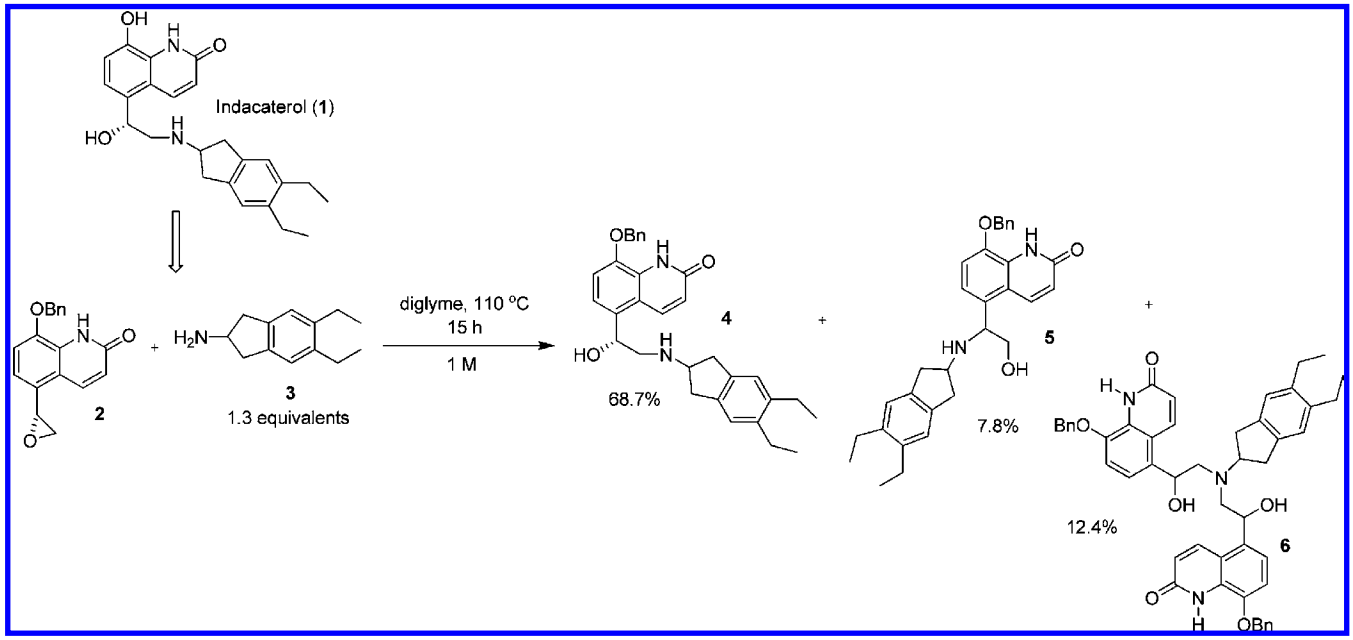
Scheme 1. **Aminolysis reaction conducted in the synthesis of the COPD drug indacaterol (1)**



study of epoxide aminolysis completed in a microreactor.[13] Further interest in this area was piqued by reports of the β-amino alcohol indacaterol **1** (Scheme 1), a novel β-adrenoceptor agonist developed by Novartis.[14] This drug candidate, currently in phase III clinical trials, is used in the treatment of chronic obstruction pulmonary disease (COPD) and has shown promise as a one-dose daily bronchodilator.[15]

The reported current synthesis of **1** centers on the aminolysis of epoxide **2** with amine **3** to afford precursor **4** under a protracted reaction time.[16] In addition, the regioisomer **5** and a product of double alkylation **6** are also formed in significant quantities. Our initial efforts focused toward decreasing reaction time in order to enable the use of a microscale flow system. Attempts to catalyze the aminolysis with solid acid supports such as PMA-alumina,[4d] Amberlyst-15,[4b] and $ZnClO_4$-alumina[4c] led to little or no product formation even after extended periods of time. Catalysis with lanthanide triflates such as $Er(OTf)_3$[2b] and $Yb(OTf)_3$[2a] ultimately led to shorter reaction times (approximately 5 h) but yielded large amounts of undesired byproduct.

In contrast, we found that simple heating of the reaction in ethanol at 150 °C under microwave irradiation or in an oil bath resulted in complete conversion within 35 min with moderate (~60%) product formation. Given the demonstrated effectiveness of microreactors in achieving high temperatures and pressures in a continuous flow manner, we pursued a study of epoxide aminolysis reactions using this technology. These results as well as the application of this technique toward the synthesis of pharmaceutically relevant compounds indacaterol and metoprolol are presented herein.

Results and Discussion

Microfluidic System. A 120 μL silicon microreactor system was used, providing a chemically and physically robust environment capable of rapid thermal equilibration (Figure 1). The silicon channels were coated with silicon nitride to provide chemical resistance, enabling the reactor to withstand slightly basic conditions at high temperatures. Although the use of silicon nitride is a slight departure from typical glass systems, the significantly higher resistance of nitride to caustic corrosion, as compared to that of oxide, is a major advantage, expanding the utility of the microreactor to a wider range of chemical systems. Additionally, as the microfabrication process of nitride deposition is no more difficult than that of silicon oxide growth, there is no inherent drawback to its usage over that of oxide.

Combined with Kalrez (a fluoroelastomer) O-rings, the reactor system is capable of withstanding a wide range of solvents and chemical conditions. The elasticity of the O-rings and rigidity of silicon easily allows for the 500 psi pressure applied in this study to access the desired temperatures; similar reactor configurations have been applied to synthesis at supercritical fluid conditions.[17]

Interfacial forces are dominant at the microfluidic scale. Combined with the smoothness of the channel walls, these forces result in solvent superheating to above boiling temperatures, which has been confirmed experimentally. Using the Antoine equation, the boiling points for ethanol and acetonitrile were calculated at 250 psi to be at 174 and 208 °C, respectively, and at 500 psi, 206 and 259 °C, respectively. However, within the microreactor, pure ethanol was not observed to boil at 250 psi until 217 °C was attained, with freshly incoming material ceasing to boil when the reactor was cooled to 206 °C. At 500

(13) We are aware of one report of epoxide aminolysis in a continuous flow manner: Tachibana, S.; Yoshiyama, R., Oishi, T.; Sakurai, M.; Ishida, K.; Tsujiuchi, T.; Hidehisa, M.; Araki, R.; Saito K. WO/2007/JP65354, 2007;*Chem. Abstr.* **2007**, *149*, 56033.

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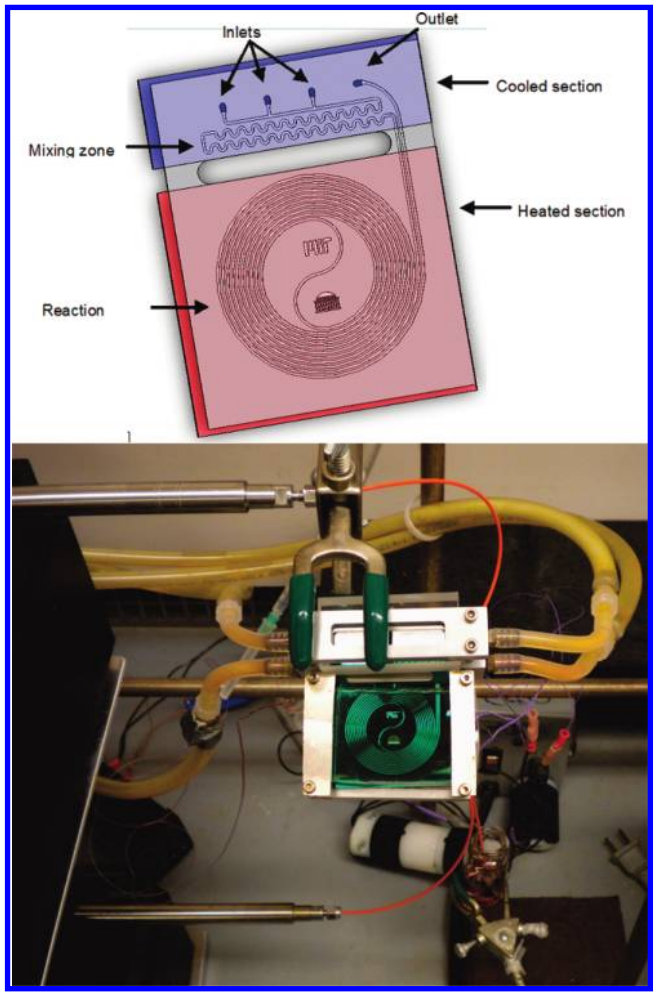


Figure 1. **Microreactor layout diagram and setup for epoxide aminolysis.**

psi, ethanol did not boil until 250 °C, with flashing ceasing when cooled to 246 °C. A similar effect was observed with acetonitrile, which, at 250 psi, only boiled at 246 °C, ceasing at 239 °C. At 500 psi, boiling was not achieved even when heated to 300 °C. Thus, the dominance of interfacial forces on the microscale further extends the range of operating temperatures beyond even those afforded by the pressurization.

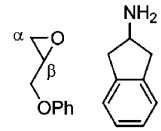
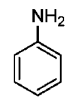
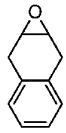
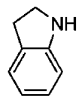
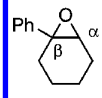
Boiling was easily observed visually, as the top side of the microreactor consists of transparent borosilicate glass, allowing an unfettered view into the reaction channel and further demonstrating the utility of the applied reactor design. When it occurred, boiling was observed at the transition between the cooled mixing zone and the heated reaction zone, where the reaction stream flashed, or was rapidly transformed primarily into gas phase with only small volumes of liquid phase remaining. When temperature was sufficiently decreased, flashing was seen to cease, with the reaction stream remaining homogeneous (liquid-phase) throughout the reaction zone.

The high thermal conductivity of silicon (148 W/m/K compared to stainless steel ~40 W/m/K) greatly aids in spreading heat and significantly reduces the occurrence of hot spots. The use of aluminum for the heating chuck and of graphite as the liner between the chuck and the reactor further helped distribute the heat while providing high heat transfer. Based on heat transfer calculations and finite element modeling, the temperature at any point within the silicon reaction zone was expected to be within 2 °C of that measured by the thermocouple, inserted into the heating chuck 0.5 mm below the chuck surface. Additionally, the spiral channel layout ensured that any inhomogeneity in temperature would have little effect on the reaction. The etched-out area of the reactor establishes thermal separation between the inlet/outlet area (including the mixing zone) and the reaction area of the reactor. This allows the area in contact with polymer O-rings and fittings to remain at room temperature when the compression chuck is water-cooled, while the reaction zone is at temperatures of up to 300 °C. In addition to enabling simple fluidic packaging, the small volumes within the microreactor ensure that the reaction mixture is rapidly brought to room temperature upon leaving the reaction zone, providing highly efficient quenching and accurate residence time evaluation.

General Aminolysis of Epoxides. In order to test the limitations and effectiveness of microreactors in the aminolysis of epoxides, a variety of substrates were investigated. Of particular interest was the direct comparison of results obtained under standard batch microwave protocols and those obtained using the microreactor under similar conditions. We selected this comparison for many reasons. For one, microwave reactors allow for superheating of organic solvents in a medium-to-high throughput fashion (using an autosampler). More importantly, the heating profile in microfluidic reactors appears to be more akin to that in microwave reactors than that observed in typical batch heating, particularly the time to reach desired reaction temperature. However, it should be noted that the *cooling* profile in microfluidic reactors is far superior to that generally observed in batch microwave reactors, and moreover, it is important to consider that the microreactor setup is capable of operating at higher temperatures than those ultimately obtained in the microwave due to higher pressure tolerances. Ethanol was chosen as the initial solvent due to its good solvating properties, high dielectric constant, and low toxicity. The results of these reactions are summarized in Table 1.

The ring-opening of phenyl glycidyl ether **7** with 2-aminoindan **8** was first investigated. Under microwave irradiation in a sealed vial, complete conversion was obtained in 30 min at 150 °C (Table 1, entry 1). The pressures attained in a 5 mL vial with 1 mL of solution ranged anywhere from 100 to 130 psi during the course of the reaction. The major product obtained resulted from nucleophilic attack at the α-terminal end of the epoxide, and only minor isolated amounts (~1−2%, not quantified by HPLC analysis) of the regioisomer were observed. Formation of the bis-alkylated product, derived from the subsequent reaction of the product with an additional equivalent of the epoxide, was also prevalent in this example and overall mass balances were excellent. Using a 250 psi backpressure regulator and a flow rate of 4 μL/min (30 min residence time) at 150 °C, complete conversion was obtained in the microreactor, and product distributions mirrored those of the microwave experiment (Table 1, entry 2). With an epoxide concentration of 1 M and 250 psi of backpressure, ethanol was easily superheated to 195 °C without boiling being observed in the microreactor, and near complete conversion was realized at this temperature in 2 min (Table 1, entry 2).

Table 1. **General aminolysis reactions performed in a continuous-flow microreactor**

Epoxide	Amine	Entry	Conditions[a] (psi)	Amine equiv	Temp (°C)	Flow rate[b] (μL/min)	Time	Product[c] (α-Opened) (%)	Isomer (β-Opened) (%)	Bis-alkyl[d] (%)	conv. (%)
 **7**	**8**	1	Batch (μw)[e]	1.2	150	-	30 min	72	-[f]	26	> 99
		2	μreactor (250)	1.2	150	4	30 min	73	-	26	>99
		3	μreactor (250)	1.2	195	60	2 min	72	-	24	98
		4	μreactor (250)	1.2	195	120	1 min	71	-	21	93
 **7**	 **9**	5	Batch (μw)[e]	1.2	150	-	30 min	75	-	24	> 99
		6	Batch (μw)[g]	1.2	150	-	30 min	82	-	17	> 99
		7	μreactor (250)	1.2	150	4	30 min	82	-	16	> 99
		8	μreactor (250)	1.2	195	40	3 min	82	-	13	98
		9	μreactor (250)	2.0	195	120	1 min	84	-	6	92
 **10**	 **9**	10	Batch (μw)[e]	1.2	150	-	30 min	57	7	21	90
		11	Batch (μw)[g]	1.2	150	-	30 min	62	10	19	97
		12	μreactor (250)	1.2	150	4	30 min	62	7	16	94
		13	μreactor (250)	1.2	195	24	5 min	60	8	14	91
		14	μreactor (250)	2.0	195	24	5 min	66	9	8	91
 **7**	 **11**	15	Batch (μw)[e]	1.2	150	-	30 min	72	-	25	> 99
		16	μreactor (250)	1.2	195	24	5 min	63	-	18	82
		17	μreactor (250)	2.0	195	24	5 min	81	-	13	95
 **13**	 **12**	18	Batch (μw)[e]	1.2	150	-	30 min	54	-	-	58
		19	μreactor (250)	1.2	150	4	30 min	39	-	-	40
		20	μreactor (250)	1.2	195	4	30 min	66	-	-	72
		21	μreactor (500)	1.2	245	4	30 min	71	-	-	93
 **15**	 **14**	22	Batch (μw)[e]	5.0	150	-	30 min	19	3	-	22
		23	μreactor (250)	5.0	150	4	30 min	15	2	-	17
		24	μreactor (500)	5.0	240	4	30 min	68	6	-	78

[a] All reactions were run in ethanol at 1 M concentration in epoxide. [b] Combined flow rate of both reagents. [c] All yields are calculated by HPLC analysis with an internal standard with the exception of Trials 10−14 which were analyzed by GC. [d] Bis-alkylation arises from product reaction with starting material to give the tertiary amine. [e] 1 mL volume in a 5 mL vial. [f] ∼1−2% of regioisomer was isolated but not quantified. [g] 2 mL volume in a 5 mL vial.

The role of volatile amines in epoxide aminolysis was critical to understanding the benefits of microreactors over typical batch conditions. *tert*-Butylamine **9** was utilized for this study due to its relatively low boiling point (46 °C) and because it enabled the examination of a rather hindered substrate. Opening of phenyl glycidyl ether at the terminal position of the epoxide was complete after microwave irradiation for 30 min. However, the product distributions were found to be dictated by the reaction volumes (Table 1, entries 5 and 6). Notable increases in the amount of bis-alkylation product were observed when 1 mL of solution was heated in a 5 mL sealed vial, whereas 2 mL of the reaction mixture gave improved results. This variance

is likely due to the reduction in available headspace and concomitant decrease in the amount of amine in the vapor phase. Since the amine is more volatile than the solvent, its vaporization decreases its concentration in solution, reducing the reaction efficiency. In contrast, the absence of headspace in the continuous-flow microreactor led to consistent product distributions, independent of reaction volumes (Table 1, entry 7). When this volatile amine was used, reaction temperatures could also be maintained at 195 °C to afford almost complete conversion with residence times of 3 min (Table 1, entries 8 and 9). Product distribution as a function of vial headspace was also observed in the opening of styrene oxide **10** with *tert*-butylamine (Table 1, entries 10−12).

Internal and trisubstituted epoxides were also examined under microreactor conditions. Using the hindered secondary amine, indoline **12**, and 1,4-dihydronaphthalene oxide **13**, aminolysis was conducted both in the microwave and microreactor at 150 °C (Table 1, entries 18 and 19). Unfortunately, only moderate substrate conversion was obtained in each case. The higher conversions observed in the microwave process compared to the microreactor can be attributed to two factors. First, the overall concentration in a microwave vial is somewhat higher due to the headspace available to volatilize the solvent. Second, microwave reaction times are slightly extended due to periods of warming and cooling during the pre- and post-reaction phases. Since microreactors take advantage of large surface-to-volume ratios, high reaction temperatures are achieved rapidly and passage through the "cooling zone" allows for a similar prompt lowering of the overall temperature after the reaction. Replacement of the 250 psi backpressure regulator in the initial microreactor setup with a 500 psi regulator allowed for superheating of ethanol to 245 °C before boiling was observed. At this reaction temperature, nearly complete conversion was observed in 30 min; however, the appearance of a new unidentified byproduct was observed by HPLC analysis. It is probable that degradation of the product occurs at such high temperatures. It is notable that temperatures approaching 245 °C for ethanol in a microwave vial were ultimately not attainable in batch reactions due to the pressure limitations of the microwave system.[18]

Ring-opening of trisubstituted epoxides has also been a challenge in microwave-assisted aminolysis of epoxides.[3b] As expected, the microreactor gave similar results and poor conversions, even when a large excess of propylamine **14** was used to open 1-phenylcyclohexene oxide **15** (Table 1, entries 22 and 23). Gratifyingly, the use of the 500 psi backpressure regulator enabled a reaction temperature of 240 °C to be reached, affording moderate conversions after 30 min residence times (Table 1, entry 24). The use of 5 equiv of amine represents flowing almost a neat amine solution in one syringe; however, high reaction temperatures could still be maintained in the microreactor without flashing.

The opening of styrene oxide with aniline represents a unique aminolysis example as selectivity for the terminal over the benzylic position can be poor.[19] Indeed, a batch microwave reaction in methanol led to aminolysis favoring the attack on

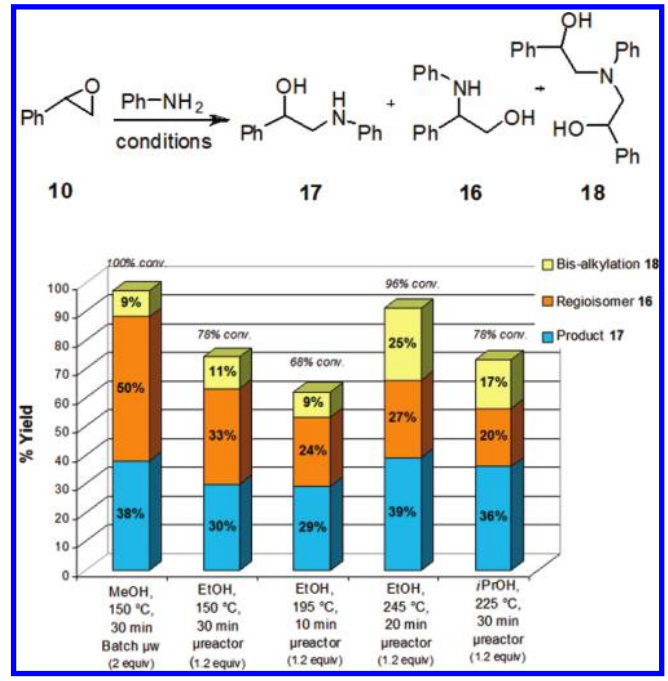


Figure 2. **Altering regioselectivity in the aminolysis of styrene oxide with aniline.**

the benzylic position (giving **16**) over the terminal position (leading to **17**) (Figure 2). Switching to bulkier solvents, such as ethanol and isopropanol, eventually led to attack favoring the terminal end of the epoxide. Interestingly, increasing the temperature in the microreactor from 150 to 245 °C also gave a reversal in selectivity, with attack favored at the terminal end of the epoxide.

Application to Metoprolol. Following our initial success with epoxide aminolysis reactions using a continuous flow microreactor, we intended to highlight this approach through the formation of pharmaceutically relevant β-amino alcohols. We first chose metoprolol **19**, a selective β_1-adrenoreceptor blocking agent, due to its rather simple structure, (Table 2) to illustrate the efficiency of epoxide aminolysis using the newly developed method.

Metoprolol is used in the treatment of hypertension[20] and is licensed under a variety of different names.[21] Currently, a shortage of metoprolol exists and a new efficient means of production could prove useful. The synthesis centers around the aminolysis of the readily available epoxide **20** with isopropyl amine. The epoxide aminolysis is typically performed using multiple equivalents of isopropyl amine at reflux in a polar protic solvent, with reaction times ranging from 2 to 5 h.[22] In examining batch microwave conditions, we again noted that the amount of **19** and bis-alkylation side product **21** were dependent on reactor headspace due to the low boiling point of isopropyl amine (Table 2, entries 1 and 2). Under microre-

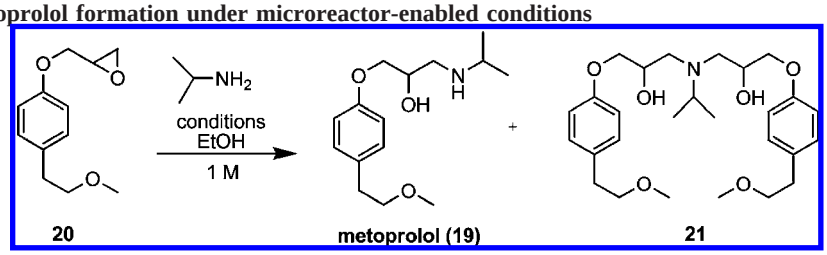
(18) The Biotage Initiator used for the batch reactions has a pressure limitation of 20 bar.

(19) For examples of poor selectivity in the aminolysis of styrene oxide see ref 5.

(20) Waagstein, F.; Bristow, M. R.; Swedberg, K.; Camerini, F.; Fowler, M. B.; Silver, M. A.; Gilbert, E. M.; Johnson, M. R.; Gross, F. G.; Hjalmarson, A. *Lancet* **1993**, *342*, 8885.

(21) Metoprolol is isolated as the succinate or tartrate salt and is sold under a variety of names including: Lopressor (Novartis), Toprol-XL (AstraZeneca, Novartis), Metrol (Arrow Pharmaceuticals), Betaloc (AstraZeneca), Neobloc (Trima Pharmaceuticals), and Corvitol (Berlin-Chemie AG) among others.

Table 2. **Results of metoprolol formation under microreactor-enabled conditions**



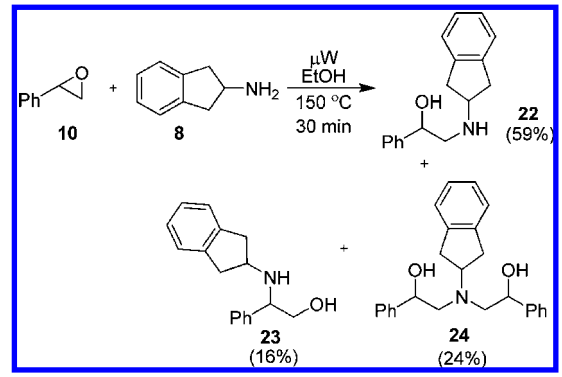
entry	conditions (psi)	amine (equiv)	temp (°C)	flow rate[a] (μL/min)	time	yield **19**[b,c] (%)	yield **21** (%)	conversion (%)
1	batch μw[d] (~100)	1.2	150	–	30 min	65	31	100
2	batch μw[e] (~100)	1.2	150	–	30 min	69	28	100
3	μreactor (500)[f]	1.2	240	480	15 s	61	14	76
4	μreactor (500)[f]	1.2	240	240	30 s	69	21	92
5	μreactor (500)[f]	1.2	240	120	1 min	72	24	99
6	μreactor (500)[f]	2.0	240	480	15 s	80	8	89
7	μreactor (500)[f]	2.0	240	240	30 s	86	12	99
8	μreactor (500)[f]	4.0	240	480	15 s	91	6	98

[a] Combined flow rate of both reagents. [b] All yields and conversions are calculated on the basis of HPLC analysis with an internal standard. [c] ~1% of the regioisomer can be isolated but was not quantified. [d] 1 mL in a 5 mL vial. [e] 2 mL in a 5 mL vial. [f] Backpressure regulator.

actor conditions, loss of the volatile amine at high temperatures was not a concern; accordingly we focused on maximizing conversion and throughput. At 500 psi, temperatures up to 240 °C were achieved before flashing of ethanol was observed in the microreactor. Increasing the amount of isopropyl amine at this temperature led to decreases in both bis-alkylation and the reaction time, with complete reaction occurring in as short as 15 s (Table 2, entry 8). Under these conditions, a single 120 μL microreactor working under continuous flow operation is capable of delivering 7.0 g/h (61 kg/year) of metoprolol. Operating 17 microreactors in parallel could ultimately produce over 1 t of this important drug per year.

Application to Indacaterol. The adaptation of the indacaterol aminolysis to a microreactor system presented several unique challenges. First, the reported reaction time in diglyme at elevated temperatures was approximately 15 h (Scheme 1).[16] Such lengthy residence times are not possible in a microreactor system due to difficulties in delivering the fluid in a stable (nonpulsating) manner at such low flow rates. As described above, attempts to catalyze this reaction with a variety of known aminolysis promoters ultimately did not lead to reaction times that were amenable to microreactors. Fortuitously, heating at elevated temperatures in polar protic solvents such as ethanol resulted in reaction times that could be considered in microreactors (approximately 30 min). In order to better understand the effect of solvent on the aminolysis of a complicated example such as indacaterol, we decided to take a deeper look into a similar model system. We reasoned that the aminolysis of styrene oxide with 2-aminoindan **8** should provide a similar electronic and steric environment as the reaction between **2** and **3**. Heating of this reaction mixture in the microwave at 150 °C for 30 min led to complete conversion, giving 59% of the desired product **22,** as well as significant amounts of the regioisomer **23** and bis-alkylation **24** side products (Scheme 2). While this represented a significant decrease in reaction time, the overall selectivity for terminal over benzylic attack of the epoxide was decreased relative to the indacaterol reaction in diglyme.

Scheme 2. **Microwave aminolysis of styrene oxide with 2-aminoindan for 30 min at 150 °C**



As mentioned previously, regioselectivity was an issue in ethanol. However, it has been reported that polar aprotic solvents can improve selectivity in aminolysis reactions at the expense of overall reaction rate.[3b,23] With this in mind, we were able to take advantage of two unique aspects of microreactor technology. First, by altering temperature and flow rate, reaction conditions can be scanned quickly to find optimum conversion and product yield. Second, due to the absence of headspace, mixtures of polar protic and polar aprotic solvents can easily be employed without concern for the relative boiling point of each component. In this manner, we could consider a polar protic solvent as a potential promoter for the reaction. Using ethanol as a baseline, the microreactor aminolysis was nearly complete in 5 min at 195 °C to afford 59% of **22** along with 14% of the regioisomer **23**. Switching to acetonitrile as the solvent and operating with a 250 psi backpressure regulator, temperatures up to 240 °C were easily obtained before flashing of the solution was observed in the microreactor. Even at this increased temperature, product yields were markedly lower

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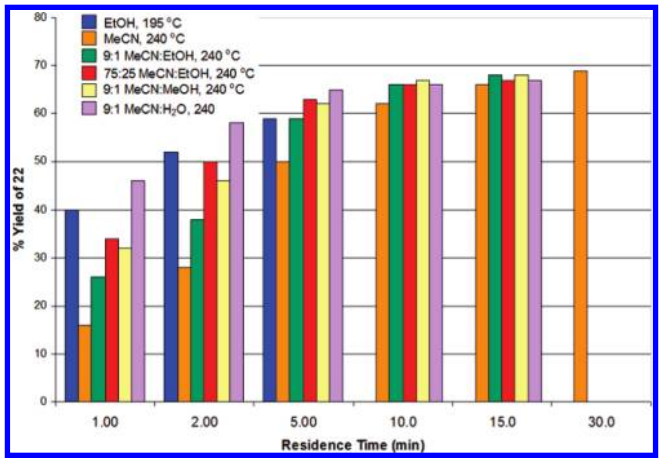

Figure 3. **Study of polar protic cosolvents as promoters in the formation of 22.**

when compared to those in ethanol at similar residence times (Figure 3). However, a 30 min residence time resulted in completion of the aminolysis and up to 69% of **22** was obtained, as quantified by HPLC analysis. The increase in overall product yield was derived mainly from the improved regioselectivity of the reaction, as attack at the terminal position of the epoxide over the benzylic position is favored. Incorporation of a 9:1 mixture of acetonitrile to ethanol in the microreactor efficiently accelerated the reaction to where conversions of 99% were achieved in only 15 min. Yields of **22** were maintained at a high level (68%). Changing the solvent system to either 75:25 acetonitrile/ethanol or 9:1 acetonitrile/methanol also gave improved conversions at comparable residence times. Finally, using a ratio of 9:1 acetonitrile/water, conversions at similar time intervals surpassed those obtained in pure ethanol at 195 °C and nearly complete aminolysis was observed at a 10 min residence time with 66% yield of **22**.

The second obstacle to performing the indacaterol aminolysis in the microreactor was low solubility of the starting epoxide **2** in commonly used solvents. The quinolinone structure provided a highly crystalline material that had a limited solubility (<0.1 M) in most organic solvents, including ethanol and acetonitrile. Formation of solids in the microreactor ultimately would clog the inlets and prevent flow. To solve this problem, a solvent screen was conducted. *N*-Methylpyrrolidone (NMP) emerged as a likely reaction solvent, as **2** exhibited moderate solubility (~0.5 M), and the dielectric constant of NMP is similar to that of acetonitrile. Operationally, we would also be able to keep the concentration of the reaction high by premixing the amine and epoxide in order to flow the mixture from one syringe. This technique avoids further dilution of the reaction when the two components are introduced separately, and thus enables higher overall conversion.

The last issue to address in the formation of **4** was the thermal stability of the product as a free base; it has been reported that **4** is unstable in organic solvents.[16] In our own studies we observed significant decomposition when the indacaterol precursor was heated to temperatures above 200 °C. Considering these issues, a solution of **2** and **3** was prepared in NMP, and 10% water was added as a promoter for the aminolysis reaction. Initially, a 0.4 M solution was pumped through the microreactor at 185 °C and varying flow rates in order to establish reaction parameters. Excellent conversion (97%) was obtained at 185 °C in only 15 min with 68% of the desired indacaterol precursor **4** produced (Table 3, entry 4). Yields and selectivities observed under microreactor conditions mirrored those obtained by heating in diglyme for a period 60 times longer.[16] Small amounts of **2** were found to have crystallized out in the syringe after 12 h but did not lead to crystallization and clogging in the microreactor.[24] At a slightly decreased concentration of the starting solution (0.38 M), **2** was completely soluble, and performing the aminolysis reaction in quadruplicate under the same conditions led to only minor variation in the yield of **4 (**minimum of 68, maximum of 70%) (Table 3, entries 5 and 6). Decreasing the temperature to 165 °C reduced the degree of thermal decomposition of **4** and slightly increased yields were obtained at the expense of longer reaction times (Table 3, Trial 7). Similarly, increasing the temperature to 200 °C led to better conversion at shorter times at the expense of overall product yield (Table 3, entry 8). Under the best observed conditions (Table 3, entry 5), 1.5 g/d (0.5 kg/year) of the indacaterol precursor **4** could be obtained from a single 120 μL microreactor.

Conclusion

In summary, the aminolysis of epoxides using a continuous flow microreactor proved to be a highly efficient process. Excellent yields and conversions with simple terminal epoxides can be obtained at residence times under 5 min in ethanol under high temperature and pressure. The aminolysis of more sterically hindered epoxides also proved successful, although longer reaction times were necessary. The continuous flow microreactor is capable of reaching temperatures that are not attainable in microwave batch processes, and due to the elimination of headspace, volatile amines can be used in the reaction without affecting overall product distributions. The use of a small amount of a polar protic solvent to accelerate the aminolysis reaction can also be applied without concern for the volatility of the solvent components. Application of epoxide aminolysis in a continuous flow microreactor towards the production of metoprolol led to product outputs of 7.0 g/h. In a more challenging example, the penultimate intermediate in the synthesis of indacaterol was also produced by this method at a residence time that was 1/60th of that reported in the literature with similar yield.

Experimental Section

Materials and Methods. The indacaterol substrates **2**[14,16,25] and **3**[26] were prepared according to literature procedures. The epoxide **20** for metoprolol was synthesized from the corresponding phenol and epichlorohydrin according to published reports.[22a]

All aminolysis reactions were initially performed as 1 M solutions in ethanol using a Biotage Initiator single

(24) Approximately 3% conversion to **4** was obtained in the syringe after 12 h at rt.

(25) (a) Beeley, J. L.; Dean, D. K. WO 1995/25104, 1995. *Chem. Abstr.* **1995**, *124*, 117293. (b) Lohse, O.; Vogel, C.; Abel, S. WO 2005/123684, 2005. *Chem. Abstr.* **2005**, *144*, 88180. (c) Mammen, M.; Trevor, M. WO/2006/023457, 2006. *Chem. Abstr.* **2006**, *144*, 274145.

(26) Prashad, M.; Hu, B.; Har, D.; Repič, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2006**, *10*, 135.

Table 3. **Results of indacaterol precursor formation under microreactor-enabled conditions**

entry	conditions (psi)[a]	solvent	concn[b] (M)	**2** (equiv)	temp (°C)	flow rate (μL/min)	time	yield **4**[c] (%)	yield **5** (%)	yield **6** (%)	conv. (%)
1	Novartis (batch)	diglyme	1	1.2	110	–	15 h	68.7	7.8	12.4	–
2	oil bath (batch)	diglyme	1	1.2	110	–	15 h	68.4	6.4	10.4	95.4
3	batch (μW)	9:1 NMP/H_2O	0.5	1.2	185	8	15 min	68.1	6.3	7.7	95.4
4	μreactor (250)	9:1 NMP/H_2O	0.4	1.2	185	8	15 min	67.8	8.6	9	97
5	μreactor (250)	9:1 NMP/H_2O	0.38	1.2	185	8	15 min	70	8	7.1	92.8
6	μreactor (250)	9:1 NMP/H_2O	0.38	1.2	185	8	15 min	68.3	8.2	7.5	95.1
7	μreactor (250)	9:1 NMP/H_2O	0.38	1.2	165	4	30 min	72.1	8.6	7.9	92.4
8	μreactor (250)	11:1 NMP/H_2O	0.37	1.2	200	12	10 min	60.7	6.8	6.4	92.3

[a] Pressure of backpressure regulator. [b] Concentration of epoxide in reaction vessel or in one syringe premixed with the amine. [c] All yields and conversions are based on HPLC analysis with an internal standard.

cavity microwave reactor under normal absorption and in 0.5−2 mL sealed vials (5 mL total volume). The products were then separated either with preparative TLC on precoated silica gel 60 F254 glass sheets or by chromatography on Silicycle silica gel (230−400 mesh), eluting with hexane/ethyl acetate or dichloromethane/methanol. All components were analyzed by ^{1}H and ^{13}C NMR spectroscopy using a Bruker-Avance 400 MHz spectrometer and compared to known literature compounds when available (see Supporting Information). HPLC quantitative analysis was performed on an Agilent 1200 Series LC/MS using either an Eclipse XDB-C18 or a Zorbax Eclipse Plus C18 reverse phase column, a methanol/water mobile phase, and a 254 or 210 nm wavelength detector. Yields were calculated on the basis of normalization of response factors using naphthalene as an internal standard. GC quantitative analysis was performed on an Agilent 7890A GC system. Yields were calculated on the basis of normalization of response factors using dodecane as an internal standard.

Microreactor Fabrication and Set Up. The microreactor was fabricated using standard silicon micromachining techniques.[27] Channel layout was defined by photolithography and realized by deep reactive ion etching (DRIE) of a silicon wafer (15 cm diameter; 0.65 mm thickness) to a depth of 0.40 mm. A silicon nitride layer (500 nm) was grown on the silicon surface, and the entire device was capped and sealed by anodically bonding a Pyrex wafer (1.0 mm thickness).

The inlet and outlet sections of the reactor were compressed in a custom microfluidic chuck machined out of aluminum. Kalrez O-rings (Z1028 FFKM, size 005, Marco Rubber) were used to seal the fluidic connections. The chuck was machined with 10−32 ports, and polyetheretherketone (PEEK) fittings were used (Upchurch Nanotight headless fittings, F-333N), connecting to 1/16" OD, 0.020" ID PEEK tubing. The third inlet, which remained unused, was capped with a PEEK plug (Upchurch P-550). Inlet tubing was connected to 8-mL high-pressure stainless steel syringes (702267, Harvard Apparatus), which were independently driven by two syringe pumps (PHD 2200, Harvard Apparatus). The outlet tubing was connected to a backpressure regulator, either 250 psi (U-608, Upchurch) or 500 psi (U-609, Upchurch).

The fluidic compression chuck was cooled by house cooling water via two channels 3/16" in diameter drilled through the chuck. The reaction zone of the reactor was compressed between a 3/8" thick piece of borosilicate glass and a 1/16" thick piece of graphite, which was in direct contact with a custom-machined aluminum heating chuck. The heating chuck was drilled with two holes for insertion of 1/8"-diameter cartridge heaters (35 W, 120 V, CSS-01235/120 V, Omega) and a 1-mm-diameter hole for a wire thermocouple (K-type, SC-GG-K-30-36, Omega), placed 0.5 mm beneath the chuck surface. The thermocouple provided data to a PID controller (CN742, Omega), which controlled the cartridge heaters via a solid-state relay (SSRL240DC10, Omega).

General Batch Microwave Protocol. The desired epoxide (1.0 mmol), amine (1.2 mmol), and internal standard (10−20 mol %) were combined in a 0.5−2 mL (5 mL total volume) microwave vial and diluted to 1 mL with ethanol. The vial was then sealed, placed in the microwave cavity, and irradiated at normal absorption for 30 min at 150 °C. Samples for quantitative analysis were then taken before the reaction mixture was concentrated, and the crude products were purified by chromatography on silica gel or preparative TLC. The desired products were analyzed by ^{1}H and ^{13}C NMR spectroscopy as well as HRMS and were compared to known literature compounds when available (see Supporting Information).

Microreactor Protocols for General and Metoprolol Epoxide Aminolysis. A solution of the desired epoxides (10 mmol) and napthlalene (internal standard, 10−20 mol %) was diluted to 5 mL with ethanol and placed in an 8 mL high-pressure stainless steel syringe. A solution of the amine (12 mmol for 1.2 equiv) was diluted to 5 mL with ethanol and placed in a separate 8 mL syringe before being connected to the microreactor. The reagent streams were pumped through the microreactor (250 or 500 psi backpressure regulators were used) at identical flow rates, and reaction times and temperatures were varied. In general, five microreactor volumes (5 × 120 μL) were allowed to pass through the outlet after each change in conditions in order to achieve steady state before samples were taken for quantitative analysis.

Microreactor Protocol for Formation of Indacaterol Precursor 4. The epoxide **2** (234.2 mg, 0.79 mmol) and naphthalene (internal standard, 15.7 mg, 0.120 mmol) were dissolved in NMP (1.8 mL), and the suspension was heated gently to affect dissolution of the solid. After cooling, H_2O (200 μL) and amine **3** (181.7 mg, 0.96 mmol) were

(27) Jensen, K. F. *Mater. Res. Soc. Bull.* **2006**, *31*, 101.

added to the mixture and stirred before being placed in an 8 mL high-pressure stainless steel syringe and connected to the microreactor. The reaction mixture was pumped through the microreactor (250 psi backpressure regulator) at desired flow rates and temperatures. In general, five microreactor volumes (5 $\times$ 120 μL) were allowed to pass through the outlet before 5 μL samples were taken for quantitative analysis.

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Supporting Information Available

Quantitative analysis procedures and spectral data for aminolysis reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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