Organic Process Research & Development

Communication

pubs.acs.org/OPRD

Application of Continuous Flow Micromixing Reactor Technology for Synthesis of Benzimidazole Drugs§

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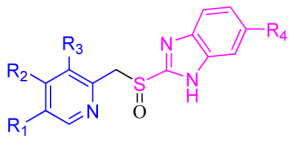
ABSTRACT: Synthesis of pharmaceutically active compounds by employing continuous flow micromixing reactor technology is an interesting research area. In this article we describe the synthesis of benzimidazole core drugs, such as lansoprazole (**1a**), pantaprazole (**1b**), and rabeprazole (**1c**) by using a continuous flow micromixing reactor technology. A key feature of the sulfoxidation includes the decreasing the reaction time from 3 h to ∼1 s to minimize the formation of sulfone impurities and improve the yields.

INTRODUCTION

Development of efficient and cost-effective synthetic processes for active pharmaceutical ingredients (APIs) is a challenging task for the pharmaceutical industry. The technologies employed in the development of APIs are primarily long-established batch processes.[1−5] Even though the traditional technologies have achieved an impressive progress in the synthesis of various APIs, there is scope to further integrate with the emerging continuous technologies,[6−8] such as micromixing reactor, microreactor, plug flow reactor, spinning disk reactor and loop reactor, static mixers, etc. These technologies, compared to those commonly used today, are expected to bring dramatic improvements in manufacturing and processing, substantially decreasing the equipment size, production capacity ratio, energy consumption, and ultimately resulting in less expensive, sustainable technologies.[9−11] One of the advantages obtainable through the application of emerging engineering technologies is cost-effective process intensification in terms of heat and mass transfer.[12] Moreover, over the past few years the pharmaceutical and fine chemicals industries have shown an increasing interest in considering process intensified technology as a viable alternative to the traditional stirred tank reactors.[13−15] Drivers for this are considerably reduced capital investment cost, reliable scale-up, and increased inherent safety due to a relatively small reacting inventory.[16,17] Although continuous processing technologies such as static mixers have been successfully used in the oil industry for a significant length of time, literature about their application to the manufacture of APIs, drug intermediates, or fine chemicals is limited.[18]

To evaluate the performance of continuous processing technologies we investigated the application of continuous flow micromixing reactor technology for synthesis of benzimidazole drugs, which are a group of drugs that elicit pronounced and long-lasting pharmacological effect by reducing the gastric acid production. These drugs are among the most widely marketed drugs in the world due to their outstanding efficacy and safety.[19] As shown in Figure 1, lansoprazole **1a**, pantaprazole **1b** and rabeprazole **1c** are members of benzimidazole drugs that act as proton pump inhibitor (PPIs) and therefore used to prevent ulcers.[20]

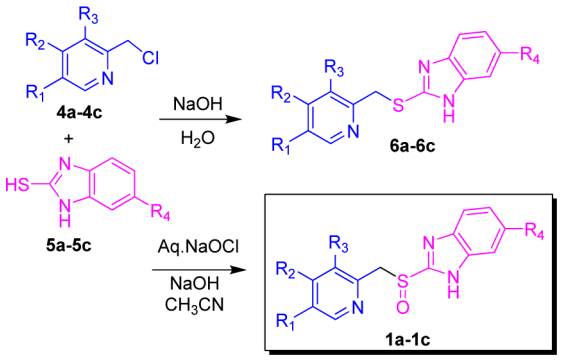


	Drug name	R1	R2	R3	R4
1a	Lansoprazole	-H	F_3CCH_2O-	Me	-H
1b	Pantaprazole	-H	MeO	MeO	F_2CHO-
1c	Rabeprazole	Me	MeO $(CH_2)_3O$	Me	-H

Figure 1. Benzimidazole core drugs.

Recently we reported an efficient, scalable synthesis of antiulcer drugs (**1a−1c**), by employing aqueous sodium hypochlorite (cost: ∼$0.1/kg) in place of expensive *m*-CPBA (cost: ∼$44/kg) for oxidation of thioether **6a−6c** (Scheme 1).[21] The NaOCl oxidation significantly improved the yield and quality of the sulfoxides, generating only NaCl and H_2O as by products. The first step of our synthesis commences with

Scheme 1. Synthetic path of lansoprazole (1a), pantaprazole (1b) and rabeprazole (1c)

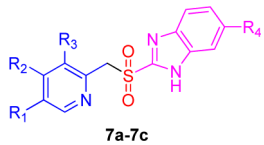


Special Issue: Engineering Contributions to Chemical Process Development

Received: November 9, 2012

   dx.doi.org/10.1021/op300325f | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

condensation of pyridine compounds **4a**, **4b**, and **4c** and thio compounds **5a**, **5b**, and **5c** in the presence of sodium hydroxide using water as a solvent to afford thioether compounds **6a−6c**, respectively. Subsequently the **6a−6c** compounds were oxidized with sodium hypochlorite in a mixture of water and acetonitrile solvent system to yield **1a**, **1b**, and **1c** compounds (Scheme 1). Although our earlier approach[21] efficiently provided the desired sulfoxides **1a−1c**, controlling the formation of sulfone byproducts **7a−7c** (Figure 2) required strict process controls such as mole equivalence of oxidant and reaction stirring time and temperature.



7a-7c

Figure 2. Structure of sulfone impurities (**7a−7c**).

In order to intensify the above process, we investigated the alkylation of sulfides and subsequent sulfoxidation in micromixing reactor technology, and the same has been described in this article.

RESULTS AND DISCUSSION

In our investigation the above optimized protocol[21] of **1a−1c** was directly taken (with minor process modification) and tested in the continuous flow micromixing reactor (see Experimental Section).

Description of Equipment. A schematic drawing of the micromixer reactor setup is shown in Figure 3. The

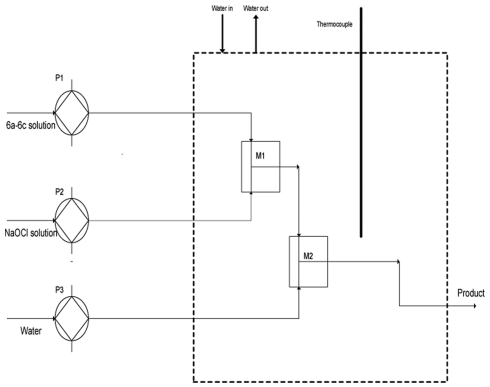


Figure 3. Schematic diagram of continuous flow micromixing reactor.

micromixing reactor made up of SS-316 consists of two inlets and one outlet. This type of micromixer reactor is based on the principle of high-shear axial collision. For that purpose each micromixing reactor contains two slit angles at 180° with diameters varying from 0.35−1.5 mm and an aperture at 90° above both slits with diameter varying from 0.35−1.5 mm and having a mixing volume of 0.2−1 mL. The micromixer reactors were connected with stainless-steel tube tubing through pumps P1and P2 for feeding the reagents, and the product was collected from the outlet of reactor. To vary the residence time, flow rates were changed. The micromixer reactors were placed in a locally fabricated double jacketed stainless-steel water bath equipped with Julaboo heating and cooling circulator with external temperature sensor. To increase the residence time or offer multiple collisions, a series of micromixers was connected for maximum conversion. For reactions with one step, quenching can be done by using another micromixing reactor with inlet 1 from M1 and inlet 2 connected through pump P3 with a quenching agent. An external coil can also be connected to the outlet of a micromixer for the reactions which are moderately slow. P1, P2, and P3 are pumps from Knauer with 0−1000 L/min. Different pump heads for regulating the flow rates of the M1 and M2 micromixer reactors were fabricated from local vendors (SS-316 and Hastelloy 22).

Investigation of Alkylation of Sulfides. Our investigation started with condensation of pyridine compound **4a** and thio compound **5a** in the presence of sodium hydroxide and water. In this study the **4a** solution was first injected into a T-shaped micromixer by using a Knauer preparative pump (P1). At the same time, a mixture of **5a** (1 equiv of **5a**, 2.1 equiv of NaOH solution) was also injected into the micromixture by using another pump (P2). At this point, identical flow rates were maintained for pumps P1 and P2. Afterwards, the reaction mixture was admitted through a stainless steel tube, and conversion of **6a** was observed within ∼1 s. Afterwards, the product stream was diluted with water and **6a** was isolated by filtration in 97.1% yield with 99.6% HPLC purity. Thereafter the same protocol was performed for condensation of **4b** and **4c** and **5b** and **5c** and corresponding intermediates, **6b** and **6c**, with 97.2% and 96.9% yields and 99.3% and 99.5% HPLC purity, respectively. With this investigation the alkylated sulfides (**6a−6c**) were prepared with comparable yields of the batch processes and also the reaction times decreased from 5 h to ∼1 s (Table 1).

Investigation of Sulfoxidation Step. Sulfoxidation is the crucial step in the synthesis of prazole drugs because the formation of overoxidation sulfone impurity is the common problem for all benzimidazole drugs (Figure 2). In this sulfoxidation, first a solution of **6a** in acetonitrile (200 mL/min) was injected into a T-shaped micromixer by using a

Table 1. Process comparison of batch and microreactor synthesis of 6a−6c

					HPLC purity (%)		
entry	condensation of **4** and **5**	method of synthesis	residence time	yield (%)	**6a−6c**		SMI
1	**4a** and **5a**	batch process	3.0 h	97.5	**6a**	99.5	0.07
2	**4b** and **5b**		5.0 h	97.2	**6b**	99.4	0.05
3	**4c** and **5c**		4.0 h	98.0	**6c**	99.8	0.08
4	**4a** and **5a**	CFMMR*	∼1 s	97.1	**6a**	99.6	0.05
5	**4b** and **5b**		∼1 s	97.2	**6b**	99.3	0.09
6	**4c** and **5c**		∼1 s	96.9	**6c**	99.5	0.08

*CFMMR: continuous flow micromixing reactor.

dx.doi.org/10.1021/op300325f | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Knauer preparative pump (P1). At the same time, a solution of aq NaOCl with aq NaOH was also injected into a micromixter by another Knauer preparative pump (P2). The flow rates of pumps P1 and P2 were adjusted to maintain the mole ratio of reagents. In this high-shear axial collision, the sulfoxidation reaction was completed within ~1 s. The selectivity of **1a** was observed at 97.94%, and sulfone **7a** was 0.02% in the reaction mass HPLC analysis. Afterwards, the product **1a** stream was diluted with water (P3 pump) and the pH adjusted to 9.0−9.5; **1a** was isolated as a solid with 90% yield and 98.5% purity and sulfone **7a** at 0.02%. Here, the flow rate of reagents appears to be crucial in achieving the best selectivity of sulfoxide **1a**. By decreasing the flow rate of reagents to 100 mL/min, the selectivity of **1a** was decreased to 95.72% with 0.30% of **7a**. When the flow rate was increased to 250 mL/min, the selectivity of **1a** achieved 97.94%, and that of **7a** was 0.08% (Table 2 and Figure 4). The reason for this may be a short

Table 2. Effect of flow rate on the conversion of 1a

		reaction mass HPLC purity (%)		
entry	flow rate (mL/min)	**6a**	**1a**	**7a**
1	100	0.95	95.72	0.30
2	150	0.75	96.92	0.04
3	**200**	**0.30**	**97.94**	**0.02**
4	250	0.70	97.70	0.08

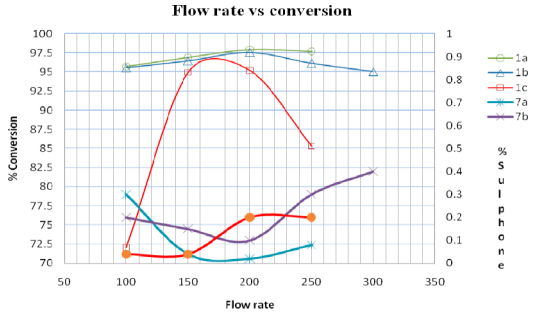


Figure 4. Effect of flow rates on conversion of **1a**−**1c**.

residence time (200 mL/min) so that the formed **1a** product may not be available for the oxidant, thus minimizing the formation of the **7a** impurity, whereas in delayed residence time (100 mL/min) the formed product **1a** may be contacting the oxidant and thus lead to the formation of **7a** (Table 2). Hence, the shorter residence time (flow rate 200 mL/min) was chosen as an optimal condition for further examination of process parameters.

We then examined the sulfoxidation of **6b** and **6c** with different flow rates of reagents by increasing the flow rate to 300 mL/min. The obtained selectivity of **1b** was only 95% purity, with 1.36% of **6b** and 0.40% of **7b** observed, whereas decreasing the flow rate to 100 mL/min provided **1b** with 95.56% purity and 0.76% of **6b**. Hence, the optimal 200 mL/min flow rate was chosen for further examination of process parameters (Table 3).

In the case of **1c** synthesis, first the **6c** solution and aq NaOCl solution was injected into T-shaped micromixture with a flow rate 150 mL/min. In this condition only 33.3% of conversion (**1c**) was seen (Table 4). In order to improve the conversion, the micromixture (M1) outlet was connected to another two micromixers (M2 and M3) to perform multiple collisions, but the conversion was increased to only 52.8%.

Table 3. Effect of flow rate on the conversion of 1b

		reaction mass HPLC purity (%)		
entry	flow rate (mL/min)	**6b**	**1b**	**7b**
1	100	0.76	95.56	0.06
2	150	0.75	96.45	0.10
3	**200**	**0.13**	**97.54**	**0.10**
4	250	0.80	96.14	0.30
5	300	1.36	95.00	0.40

Table 4. Influence of the number of mixtures on conversion of 1c[22,23]

			reaction mass HPLC purity (%)		
entry	micromixings	flow rate (mL/min)	**6c**	**1c**	**7c**
1	1	150	58.1	33.3	0.02
2	3	150	45.2	52.8	0.03
3	**5**	**150**	**1.98**	**95.2**	**0.04**

Hence, the number of micromixers was further increased from three to five (M4, M5), and the conversion was improved to 95.2%. Certainly, the extended micromixing collisions allowed the substrate **6c** and oxidant NaOCl to react efficiently and afford the maximum conversion of **1c**. Hence, the five micromixers were employed in further flow rate optimization studies (Table 4 and Figure 5).

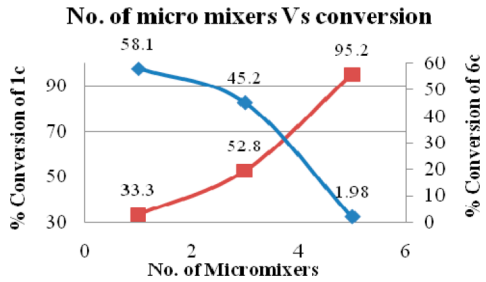


Figure 5. Influence of number of mixtures on conversion of **1c**.

Afterward the flow rate of **6c** was examined; in this experiment, incomplete conversions and formation of higher levels of sulfone **7c** impurity were observed when the flow rates were increased to 200 and 250 mL/min. On other hand, maximum conversion was achieved with the flow rate of 150 mL/min (Table 5).

Table 5. Effect of flow rate on conversion of 1c

		reaction mass HPLC purity (%)		
entry	flow rate (mL/min)	**6c**	**1c**	**7c**
1	100	25	72.0	0.04
2	**150**	**1.9**	**95.5**	**0.04**
3	200	2.4	95.2	0.20
4	250	13	85.3	0.20

Next, we investigated the sulfoxidation of **6a**, **6b**, and **6c** with different mole ratios of aq NaOCl. As shown in Figure 6, the oxidation of **6a** with 1.05 equiv of sodium hypochlorite gave the best results, and the desired sulfoxide **1a** was obtained in 98.9%, **7a** in 0.03%, and a little higher level of **7a** was observed for 1.1 and 1.2 equiv of NaOCl. In the case of **6b** and **6c** the maximum oxidation was achieved with a stoichiometric amount of sodium

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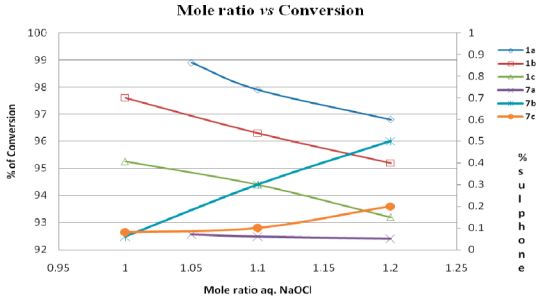

Figure 6. Effect of aq NaOCl mole ratio on the conversion of **1a**, **1b**, and **1c**.

hypochlorite, and with increasing the oxidant to 1.1 or 1.2 equiv, the formation of relatively higher levels of **7b** and **7c** were observed (Figure 6).

Rapid mixing using the micromixer enabled us to oxidize sulfides (**6a**–**6c**) in a shorter reaction time, and regulation of the relative amount of sodium hypochlorite to that of the sulfides by using pumps prevented formation of the over-oxidation impurity (**7a**).[24]

We compared the results obtained from continuous flow micromixing reactor synthesis with the batch process synthesis (Table 6). The results clearly reveal that the application of platform micromixing reactor technology not only reduced reaction time from hours to seconds but also improved the overall yield and throughput of benzimidazole drugs.

CONCLUSION

In conclusion, we successfully investigated and established platform micromixing reactor technology for the synthesis of benzimidazole core drugs such as lansoprazole **1a**, pantaprazole **1b**, and rabeprazole **1c**. A key feature of the sulfoxidation includes decreasing the reaction time from 3 h to ∼1 s to minimize the formation of sulfone impurities and improve the yields.

EXPERIMENTAL SECTION

Materials. All commercially available materials and solvents were used as received without any further purification.

Common Process for Condensation of 4a–4c with 5a–5c. A solution of 2-mercaptobenzimidazole **5a** (96.4 g, 0.446 mol) in sodium hydroxide (37.5 g, 0.937 mol, in 1000 mL) solution and pyridine analogue **4a** (100 g, 0.446 mol) solution in water (500 mL) were fed into a T-shaped micromixer M1 at a total outlet flow rate of 150 mL/min using P1 (volume/flow rate: 1100 mL/100 mL/min) and P2 (volume/flow rate: 550 mL/50 mL/min) pumps. Product was collected from the outlet, and the compound **6a** was isolated from water with yield of 97.1% and HPLC purity of 99.6%. **6b**: yield 97.2%, HPLC purity 99.3%. **6c**: yield 96.9%, HPLC purity 99.5%.

Synthesis of Lansoprazole 1a. 2-[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methylthio-1*H*-benzimidazole **6a** (20 kg, 56.29 mmol) solution was prepared by dissolving the **6a** into a solution of acetonitrile (60 L) and NaOH (2.72 kg, 68 mmol in 8 L of water). This **6a** solution along with a mixture of aq NaOCl (46 kg, 67.91 mmol) and NaOH solution (1.36 kg, 34 mmol in 4 L water) was fed into a T-shaped micromixer M1 by using pump P1 (volume/flow rate: 80.0 L mL/553.85 L/min) and P2 (volume/flow rate: 50 L/346.15 L/min) at a total flow rate of 900 mL/min, respectively. The outlet was connected to another micromixer, M2, which was fed with water (60 L) by using pump P3 (flow rate: 415.38 L/min) to quench the reaction mass. After that the reaction mixture from M3 was collected into the reactor, and pH was adjusted to 9.0–9.5 by using 10% acetic acid at 0–10 °C. To this suspension was added the water (140 L), and the mixture was stirred for 4 h. The isolated solid was filtered and dried to give the crude **1a** in 89% yield (18.5 kg) with 94.5% HPLC purity. After that the crude **1a** was recrystallized from the THF and water (1:2, 16 vol) and **1a** was obtained as a slurry from ethyl acetate (3 vol), and **1a** was obtained pure in 79.4% yield with 99.9% HPLC purity.

Synthesis of Pantaprazole 1b. A solution of 5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridinyl)methyl]-thio]-1*H*-benzimidazole **6b** (100 g, 0.272 mol) in acetonitrile (500 mL) and a mixture of aq NaOCl solution (156 g, 0.272 mol, 13% w/w) and NaOH (10.9 g, 0.272 mol in 44 mL of water) was fed into a T-shaped micromixer, M1, at a total flow rate of 202 mL/min using P1 (volume/flow rate: 580 mL/150 mL/min) and P2 (volume/flow rate: 200 mL/52 mL/min) pumps. The outlet from the micromixer is connected to another micromixer, M2, and the reaction mass was quenched using water (2000 mL) fed by the P3 pump (flow rate: 518 mL/min). Then the mixture was filtered and cooled to 0–5 °C; the pH of the reaction mass was adjusted to 6.0–6.5 by using 1 N HCl solution. Thereafter, the isolated solid was filtered and dried to obtain crude **1b** in 94.8% yield (98.9 g) with 97.9% HPLC purity. After that, the dried product **1b** was slurried in ethyl acetate solvent (380 mL), and 89.8% yield (88.8 g) with 99.5% HPLC purity of **1b** was achieved.

Synthesis of Rabeprazole 1c. 2-[[[4-(3-Methoxypropoxy)-3-methyl-2-pyridinyl]methyl]thio]-1*H*-benzimidazole solution was prepared by dissolving **6c** (100 g, 0.292 mol) in acetonitrile (300 mL) and NaOH solution (NaOH 30 g in 120 mL of water) in a container; aq NaOCl solution (156 g, 0.272

Table 6. Process comparison of batch and microreactor synthesis of 1a–1c

				before purification			after purification			
					purity (%)		purity (%)			
entry	oxid'n of **6**	synthesis method	residence time	yield (%)	**1a–1c**	**7a–7c**	**1a–1c**	**7a–7c**	yield (%)	overall yield (%)
1	**6a**	batch process	2.5 h	85.0	97.5	0.13	99.6	0.18	74.0	62.9
2	**6b**		2.5 h	92.9	97.2	0.05	99.7	0.08	86.0	79.8
3	**6c**		2.5 h	85.0	98.2	0.08	99.5	0.05	78.2	66.5
4	**6a**	CFMMR[a]	∼1 s	89.0	96.5	–	99.9	0.06	79.4	71.0
5	**6b**		∼1 s	94.8	97.9	–	99.5	0.07	89.8	85.1
6	**6c**		∼1 s	88.2	98.7	0.10	99.5	0.03	85.1	75.0

[a]CFMMR: continuous flow micromixing reactor.

dx.doi.org/10.1021/op300325f | *Org. Process Res. Dev.* XXXX, XXX, XXX–XXX

mol, 13% w/w) was added to another container. Both solutions were fed into a T-shaped micromixer M1 at a total flow rate of 150 mL/min by using P_1 (volume/flow rate: 480 mL/109 mL/min) and P_2 (volume/flow rate: 180 mL/41 mL/min) pumps, and the outlet M1 was connected to another micromixer M2 which was connected with quenching agent hypochlorite solution (40 g in 200 mL of water) and was fed by using another pump P_3 (flow rate: 50 mL/min). After that the outcome product **1c** was collected and treated with charcoal (20 g). Subsequently, the charcoal was removed by filtration, and the filtrate solution was washed with toluene (100 mL). Afterward the filtrate solution was cooled to 0−5 °C, and the pH was adjusted to 8.0−8.5 by using acetic acid (∼30 mL). Then the isolated solid was filtered and dried to obtain the crude **1c** in 88.2% yield (108.6 g) with 98.7% HPLC purity. After that, crude **1c** was recrystallized from acetone (350 mL) to obtain the pure **1c** in 85.1% yield (92.4 g) with 99.5% HPLC purity.

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Notes

[§]DRL-IPD Communication number: IPDO-IPM-00326.

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the management of Dr. Reddy's Laboratories Ltd. for supporting this research work. Mr. G. Sharathchandra Reddy thanks DRL for allowing him to pursue this work as part of his summer training program.

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