Organic Process Research & Development **2008,** *12,* 995–1000

Continuous Flow Nitration of Salicylic Acid

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Abstract:

Continuous flow nitration of salicylic acid using HNO_3/AcOH was studied in the SS316 tubular microreactor. At specific reaction conditions, complete conversion of the reactant was achieved in less than 7 min. It yielded only mononitro derivatives with a higher selectivity of 5-nitrosalicylic acid. Presence of the lower amount of acetic acid in the reaction mixture was seen to be detrimental, leading to precipitation of the desired product (5-nitrosalicylic acid). Reaction at higher temperatures yielded byproducts. The continuous mode operation using the system comprising the microdevices was demonstrated for 2 h with consistent composition at the outlet.

Introduction

Continuous flow synthesis using microreactors is an upcoming approach in the synthesis of key pharmaceutical intermediates and fine chemicals where either the reactions are highly exothermic or there are situations where the selectivity of the product is an issue.[1−8] It allows high throughput screening of catalysts and also of reactions. The subject of microreaction technology has achieved significant attention in the laboratory-scale research and development for the design of new devices towards specific applications, viz. for carrying out specific reactions, heat removal, attaining narrow residence time distribution, continuous synthesis of nanoparticles, and also in checking their feasibility for multistep processes.[9] In the past few years, there have been reported in the literature, several reactions that have better yield when carried out in microreactors than when carried out in the conventional batch mode operation.[10] Typical classes of reactions which are studied using microreactors include fluorination, oxidation, hydrogenation, nitration, chlorination, biphasic Heck reaction, Wittig reaction, Kumada−Suzuki coupling, etc. The high heat transfer area helps to achieve a better control on the temperature variation in the microreactor. This further helps to maintain the rates of reaction in specific ranges and thus avoids byproduct formation. Also, the small length scales help to achieve faster mixing, thereby reducing the possibility of byproduct formation in fast reactions. These advantages of microreactors are now known, and as a result, they have been used for the continuous flow synthesis.[1−8,10] A detailed discussion on the advantages of continuous flow synthesis and a list of different classes of reactions that can be carried out in continuous flow mode can be seen in a recent review by Wiles and Watts.[11] Also, since the concept of continuous flow synthesis is feasible in the devices having dimensions that do not offer any transport limitations, it is not always necessary to carry out the flow synthesis using the microdevices, and dimensions slightly greater than a millimeter may also be feasible.

Nitration of aromatic compounds is usually exothermic and fast, and in the presence of excess nitrating agent or at higher temperatures, it can undergo polynitration.[12,13] In many aromatic nitrations to avoid the effect of high temperatures that may be generated in the presence of excess nitrating agent, conventionally, the nitrating agent is slowly added to the aromatic substrate (which can be in the form of solid or liquid). To overcome this situation due to poor heat transfer in the system, in the past few years, the advantage of high heat transfer area and better mixing in microreactors is exploited to check the feasibility of nitration of aromatic compounds. Some of the important initial studies include the following: (i) Burns and Ramshaw[14] have reported the nitration of benzene and toluene using mixed acids in a microreactor. In their experiments, the two-phase slugs were generated using a "T", and the reaction was studied in SS tubes (127, 178, and 254 μm i.d., 1/16 in. o.d.) and PTFE tubes (127−300 μm i.d., 1/16 in. o.d.). For all the experiments, acid to organic flow ratio was maintained at 10.5, while the benzene to nitric acid mole ratio was in the range of 0.8−1.8. With similar experiments of toluene nitration in a 150 μm PTFE tube, these authors have shown that higher concentration of H_2SO_4 pushes the reaction in mass transfer limited regime and smaller diameter tubes yield better initial nitration rates. Also, higher

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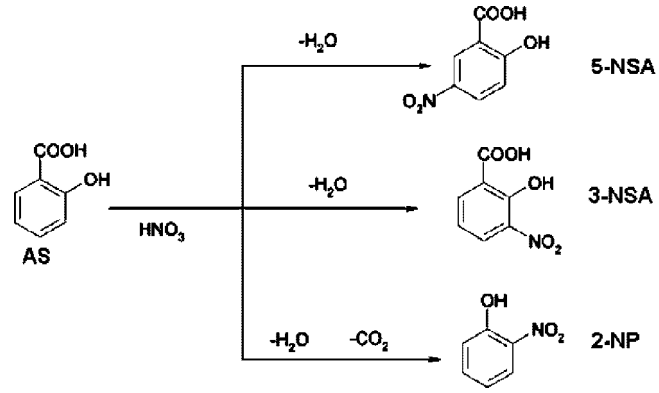
10.1021/op800112u CCC: $40.75
Published on Web 08/23/2008

acid to organic ratio yielded lower rates while higher percentages of H_2SO_4 yielded higher initial rates of nitration independent of flow velocities and hence higher amounts of DNT. (ii) Ducry et al.[15] have reported the nitration of phenol in a glass microreactor with a channel width <0.5 mm and 2.0 mL internal volume. They have shown that the nitration reaction in a microreactor yields a better fraction of the mononitrated products and a reduction in the amounts of polymerized products. (iii) Nitration of single-ring aromatic compounds in a system comprising a Y-mixer followed by a PTFE capillary (0.5−1 mm i.d. and 1−10 m length) immersed in a thermostat are reported by Dummann et al.[16] (iv) Panke et al.[17] have used the CYTOS microreaction system for the nitration of pyridine-*N*-oxide (T = 120 °C, yield of 78% vs 72% in the flask experiment) and 4-nitropyridine-*N*-oxide. (iv) Antes and co-workers[18−20] have developed and analyzed continuous processes for the nitration of aromatics. For the case of strongly exothermic nitration of naphthalene using N_2O_5, these authors have reported that, while the nitration in conventional batch operation requires temperatures from −50 to −20 °C, the continuous flow process in microreactors can be carried out at 30 °C with a flow rate of 1 mL/min at a residence time of 3 s with large yields of mononitro derivatives with small amounts of the dinitro compounds. They have also carried out the nitration of urea derivatives in microreactors. The authors have reported a new two-step route to the dinitrated products using thiourea derivatives as the starting compounds was carried out in the batch process and also in a microreactor. The nitration of corresponding thioureas in a two-step procedure yielded the mononitro urea derivative with nearly 100% selectivity. Thus, although a few reports on the nitration in microreactors are available in the literature, one of the reasons that might have prohibited carrying out several exothermic nitration reactions using microreactors is the possibility of precipitation of one of the products. Since many of the pharmaceutical intermediates are in the particulate form, and the reactions are exothermic and also have issues of selectivity, it is necessary to identify the avenues to exploit the advantages of microreactors for such cases.

With the above discussion in background, in the present work, we have demonstrated the nitration of salicylic acid to selectively yield mononitro salicylic acid (5-nitro salicylic acid, 5NSA, and 3-nitro salicylic acid, 3NSA) (Scheme 1). Among the synthesized mononitro products, isomer 5NSA is the desired

Scheme 1[a]



[a] AS, salicylic acid; 5NSA, 5-nitrosalicylic acid; 2-NP, 2-nitrophenol; 3NSA, 3-nitrosalicylic acid.

one,[21] which upon its further reduction yields 5-amino salicylic acid (also known as mesalazine[22]). 5-ASA finds applications in the treatment of ulcerative colitis. As of 2001 for the pharmaceutical industry itself, the worldwide requirement of 5-ASA is about 300 tons/year. Thus, if proven efficient, a technology for the synthesis of 5NSA based on continuous flow chemistry using microreactors can be extended for further continuous reduction to yield the desired 5-ASA. In this work, we deal with the first step only, and we bring out several of our observations that would be useful for the researchers who would like to work on analogous systems. The second step of continuous reduction of 5NSA will be discussed elsewhere. The literature findings for the nitration of salicylic acid are based on batch experiments[23−25] and also one patent on continuous nitration[26] in the glass microreactor. In the rest of the manuscript, we bring out the new findings from our studies and also compare them with the relevant literature.

Experimental Section

The experiments were carried out in batch mode as well as in continuous mode. The initial experiments in batch mode (20 °C) were mainly aimed to confirm our approach and the analysis method based on the literature.[23−25] In all the experiments, the mixture of acetic acid and nitric acid was used as the nitrating agent for the nitration of salicylic acid (all the chemicals were of synthesis grade and procured from Merck). For the batch experiments, the initial reactant composition was mole ratio SA: HNO_3 = 1:5 and SA:AcOH = 1:3. The reaction was carried out in a 100 mL glass reactor (heat transfer area per unit volume $\approx$ 106.6 m^2/m^3) with a jacket for circulating cooling water. Nitric acid was slowly added to the mixture of salicylic acid and acetic acid with constant stirring. The nitric acid was

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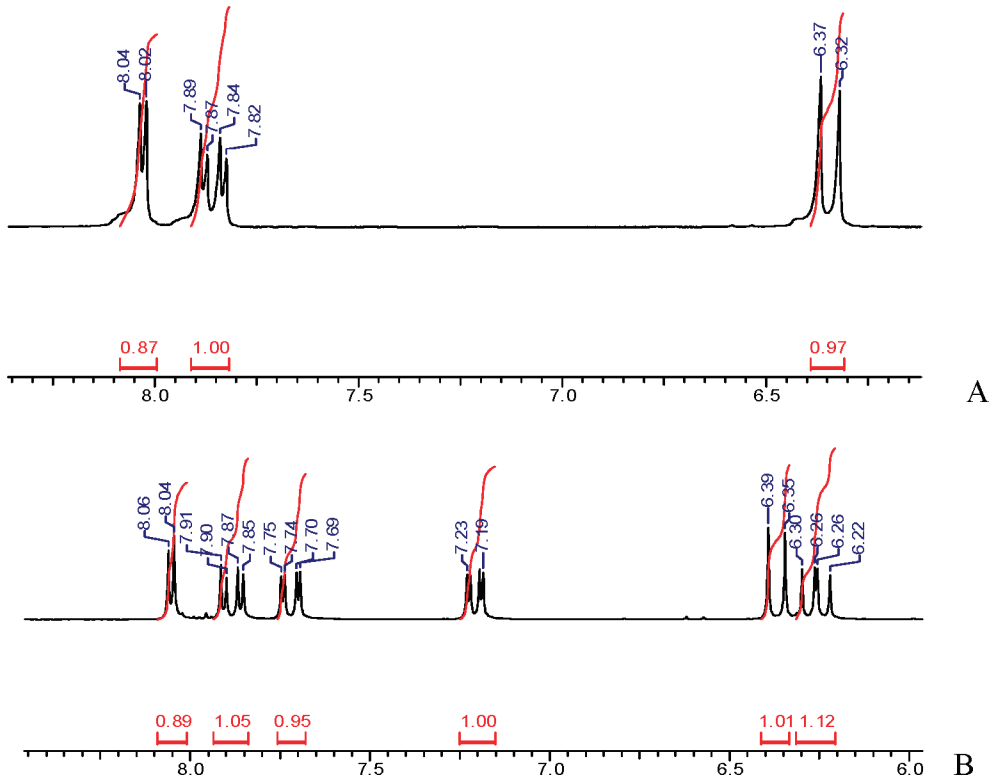

Figure 1. **Proton spectra for (A) 5NSA and (B) a mixture of 3NSA and 5NSA.**

completely added within 6 min after starting the agitation. The samples were withdrawn at different time intervals and analyzed using HPLC (Agilent model 1100 II, equipped with a UV−vis detector and a Phenomenex Synergi 4 μ polar RP/80A column). To the withdrawn samples, a solution of urea in methanol was added for denitrification.[27] The mobile phase used for analysis consisted of 80% buffer (vol %: CH_3OH 5%, H_3PO_4 0.4%, H_2O 94.6%) and 20% of acetonitrile. For all analyses HPLC grade reagents were used. The HPLC analysis was carried out at three different wavelengths, viz. 240, 280, 350 nm; the column temperature was maintained at 25 °C; and the flow rate was set at 1 mL/min. As a part of the analysis procedure, mononitro derivatives were obtained (A solution of 2.5 g of salicylic acid in 40 mL of acetic acid was heated at 50 °C. Eleven milliliters of concentrated HNO_3 was slowly added to the above solution and stirred for 10 min. The reaction was quenched by pouring the reaction mixture on 50 g of crushed ice.) and used for calibration of the HPLC response. Upon quenching of the reaction on ice, a yellow solid was obtained. This solid was filtered and washed with cold water. The mother liquor was kept at 0−5 °C for over 12 h, and the second crop was isolated after further filtration. The solid products isolated in these two steps were analyzed using NMR (NMR spectra were recorded in D_2O/NaOD. The ^1H measurements were carried out on a Bruker AV 400 NMR spectrometer). The proton spectrum (shown in Figure 1) confirmed the first crop to be 5NSA (also confirmed by measuring its melting point ~230−232 °C),and the second crop of nitrated product was found to be a mixture of 3- and 5-mononitro salicylic acid (1:1). The samples from these two crops were used for the calibration needed for HPLC analysis. On confirming the entire procedure and the analysis method, we extended it for the continuous flow experiments.

For the continuous flow experiments, typically the experimental setup involved two HPLC pumps (Laboratory Alliance, U.S.A.) followed by a micromixer, which was then connected to a 12 m long stainless steel (SS316) tube (1/16 in. o.d. and 1.38 mm i.d.). The SS tube was immersed in a thermostat (Julabo - ME12, Germany), and the samples were collected at the outlet of the tube. The residence time was varied by changing the flow rates. Experiments were carried out at different conditions as shown in Table 1. The samples were collected in glass vials immersed in an ice bath (to quench the temperature of the reacting mixture and thereby avoid any further reaction), and after getting volume sufficient for analysis, the unreacted nitric acid was removed by adding urea in methanol solution. The supernatant was subjected to analysis after further dilution. It is necessary to note that the results from the HPLC analysis were based on calibration of the column response for different concentrations of the reactants and the products. A schematic of the continuous flow setup is shown in Figure 2.

Results and Discussions

As mentioned previously, in the case of continuous experiments, the outlets from the two pumps were connected to a micromixer. Initially the experiments were carried out using HPIMM interdigital micromixer at 20 °C. It is worth mentioning that, because of the lower solubility of 5NSA in the aqueous medium, upon mixing and subsequent reaction the product precipitated. This resulted in the blocking of the HPIMM micromixer and also a very high pressure drop. In order to avoid such a situation, we used a simple T-mixer (800 μm i.d.) for

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Table 1. **Experimental conditions**

parameters	authors		
	this work	Andreozzi et al.[25]	ref 26
mode of operation	batch and continuous	batch	batch and continuous
system	batch: 40 mL volume in a glass reactor continuous: tubular reactor in SS316 (1.58 mm o.d., 1.38 mm i.d. and length = 12 m)	batch: 20 mL glass reactor	batch: 100 mL glass reactor continuous: Corning Glass microreactor (Corning Inc.)
temperature (°C)	20, 30, 40, 50	15, 20, 25	45, 75
SA:AcOH	1:5−1:16	1:2.43	1:5−1:20
SA:HNO_3	1:1−1:10	1:5	1: 1.1−1:2
batch time or residence time	6−25 min	15−40 min	10−20 s

mixing of the fluids. It was observed that, although replacing the HPIMM micromixer with the T-mixer helped in eliminating the blockage in the mixer itself, for the SA:AcOH mole ratio in the range of 1:3 to 1:9, the product clogged the tube completely, and practically nothing came out of the tube. This was also observed for different orientations of the coiled tube (vertical, horizontal, etc.) and also for the tube of larger diameter (3.175 mm o.d. and 2.77 mm i.d.) even in a serpentine configuration oriented horizontally. On removing the clogged compound, it was confirmed to be 5NSA. In order to avoid such situations, the mole ratio of SA:AcOH was taken as 1:16, and the experiments were carried out without any blockage problems in the entire setup. In all these experiments, the mole ratio of SA:HNO_3 was maintained at 1:5. The observed outlet yields at 20 °C at different residence times (for continuous mode) or sampling times (for batch mode) are shown in Figure 3. The results from the batch experiments (mainly carried out to verify the analysis approach quantitatively) were compared with the reported data in Andreozzi et al.[25] at identical conditions and were seen to agree well. It can be seen that the percent yield of 5NSA observed in the continuous experiments in the tube of 1.38 mm i.d. was better than that of the batch experiments. It needs to be noted that, although in the batch as well as the continuous experiments the SA:HNO_3 mole ratio was maintained the same, the continuous flow experiments contained very high amounts of AcOH, resulting in lowering the overall concentration of the reactants. Importantly, the continuous flow experiments yielded only the mono-NSA as products, while in the batch experiment we observed 3,5-dinitrosalicylic acid as a byproduct along with the mono-NSA. It needs to be mentioned that the measured area available for heat transfer per unit volume of fluid was 3318.63 m^2/m^3, which was sufficiently high to maintain the constant temperature in the entire reaction tube. Further, the selectivity of 5NSA, which was the desired compound was close to 60%. Details of a few of the continuous flow experiments are given in Table 2. The residence time in the tubular reactor as well as the value of the ratio of the outlet mole fraction of the nitrated isomers corresponds to 100% conversion of the salicylic acid for the conditions mentioned in Table 2. The literature[25] data on the

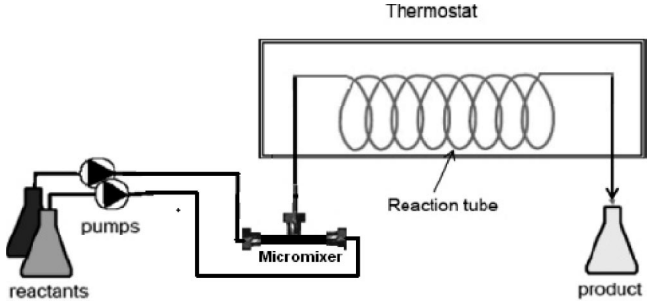

Figure 2. **Schematic of the experimental setup.**

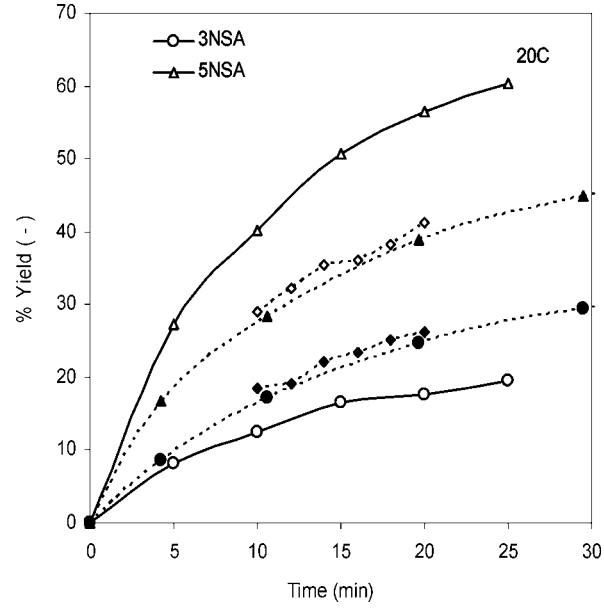

Figure 3. **Comparison of the experimental % yields of 5NSA and 3NSA obtained from the batch and continuous experiments at 20 °C and with the data reported by Andreozzi et al.[25] The experimental conditions are identical, except that for the continuous experiments the acetic acid was taken in excess to avoid the precipitation of 5NSA in the tube and its subsequent blocking. Δ - 5NSA continuous, ◇- 5NSA batch, ○ - 3NSA continuous, ♦ - 5NSA batch, ▲- 5NSA batch,[25] ● - NSA batch.[25]**

Table 2. **Inlet composition, experimental conditions, and results for continuous flow experiments**

	inlet mole ratio				outlet mole ratio
sr. no.	SA: AcOH	SA: HNO_3	T (°C)	residence time (min)	5NSA: 3NSA
1	1:16	1:5	20	44	1.66
2	1:16	1:3	20	44	1.62
2	1:16	1:3	30	21	1.65
3	1:16	1:3	40	7	1.70
5	1:16	1:3	50	6	1.78
6	1:16	1:5	50	4	1.77
7	1:10	1:3	50	7	1.85

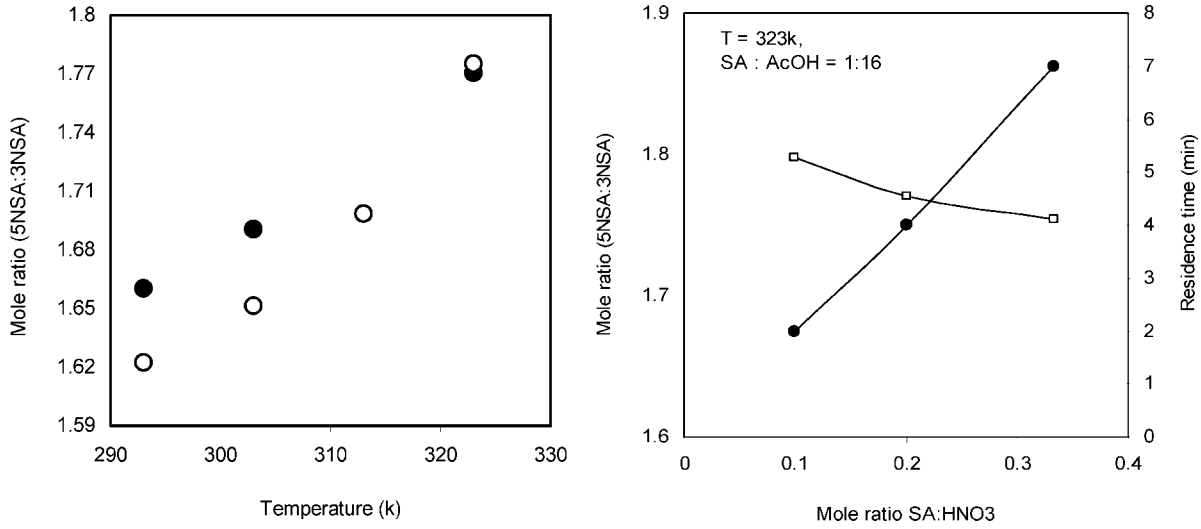

Figure 4. **(A) Effect of temperature on the outlet composition of mononitro salicylic acid in the case of 100% conversion and at ○ SA:HNO_3 = 1:5, □ SA:HNO_3 = 1:3. (B) Effect of mole ratio on the outlet composition and the residence time required for complete conversion at 50C. ● - residence time, □ - outlet composition (mole ratio 5NSA:3NSA). In all these experiments SA:AcOH = 1:16.**

batch experiments show that, irrespective of the different reaction temperatures, at the complete consumption of SA (for example, at temperature of 25 °C the complete conversion takes place in almost 15 min) the maximum selectivity for 5NSA does not exceed 55%. Even the composition of the mixture at the end of a batch reaction has been reported to contain byproducts, viz. 2-NP, 3,5-dinitrosalicylic acid, etc.

Since no byproducts were observed from the continuous experiments at 20 °C, further experiments were carried out at higher temperature (30, 40, and 50 °C) by increasing the flow rates (Table 2). The analysis showed that for the experiments at 50 °C, the complete conversion of salicylic acid was observed in less than 7 min of residence time in the tubular reactor and also with the higher selectivity for the desired product, we repeated the experiments with lower mole ratios of SA:HNO_3 $\approx$ 1:3 and 1:1.1, and the results were seen to be unchanged. In order to further reduce the quantity of AcOH such that the desired product is completely soluble in it, experiments were carried out at SA:AcOH = 1:10. The outlet composition at the completion of reaction showed the complete conversion of salicylic acid with selectivity value of 64.9% for 5NSA with no additional byproduct except 3NSA. At constant temperature and constant mole ratio of SA:AcOH, the selectivity of 5NSA was seen to increase with the concentration of nitric acid. Also, the time required for complete consumption of salicylic acid was seen to decrease with increasing concentration of nitric acid. In all these cases, at the suitable residence time when the salicylic acid is completely consumed, the products were seen to be only the mononitro derivatives of the salicylic acid.

The continuous flow experiments further showed that, at constant mole ratio of salicylic acid to the nitrating agent, the selectivity of 5NSA increased with increasing temperature. Since the data shown in Figure 4A belongs to the complete conversion of salicylic acid, the higher concentration of nitric acid was seen to affect both the residence time required to achieve complete conversion in the reactor tube and also the selectivity of the desired product. This particular observation is depicted in Figure 4B. One of the reasons for having a positive relationship between selectivity of 5NSA and temperatures can be the relatively higher rates of the nitration favoring 5NSA. This is usually found due to higher rate constants for the favored reaction. The data from the literature[21] show that the pre-exponential factor (k_0) for the reaction yielding 5NSA is 1.83 times higher than that of for the 3NSA, while the activation energies of these nitrations are of similar magnitude. As a result with sufficient excess of nitric acid, 5NSA formation is always favored. Further, at any given reaction temperature, the rate constants for the consecutive reactions involving 3NSA are higher than that of the reactions involving 5NSA. As a result, the possibility of extent of reduction in the concentration of 3NSA by successive nitration or decarboxylation is higher than that for the 5NSA. This situation even prevails for the lower SA:AcOH ratio as the 3NSA remains dissolved in the solution while 5NSA gets precipitated as a result of the competitive solubility. This overall situation favors increase in the selectivity of 5NSA with increasing temperature.

In an analogous approach of using continuous flow for nitration of aromatic compounds, a recent patent[26] illustrates that the reaction time for nitration of salicylic acid can be reduced to as low as 10−30 s using a glass microreactor at 75 °C with other conditions given in Table 1. In the reported experiments, although the conversion is not complete, the ratio of 5NSA:3NSA was in the range of 1.6−1.7 with many additional byproducts. In comparison to that, we had observed complete conversion of the reactant (SA) and very high yield of 5NSA with practically no byproducts as reported in the literature. One of the main reasons was that the use of a metal tube (which has much higher thermal conductivity thereby achieving better heat transfer) for this reaction helped to maintain almost isothermal conditions in the reactor. The simulations of this system as a plug flow reactor (not shown here) clearly indicated that, with the inlet composition and the inlet temperatures, the extent of variation in the temperature in the tube was less than 0.5% of the temperature of the fluid surrounding the tube. The batch experiments carried out at identified conditions showed the selectivity of 5NSA to be closer

to 55% with complete conversion of the reactant. The LC/MS analysis of the products showed the existence of a byproduct 3,5-DNSA. Moreover, some amount of SA was seen to remain unconverted. This was clearly due to poor mixing and heat transfer that can be achieved in batch mode.

Further to this, we operated the continuous flow microplant for the specific conditions (SA:HNO_3 = 1:3, SA:AcOH = 1:10, T = 50 °C) continuously for 2 h. The residence time in the tube was maintained at 7 min, and samples were taken intermittently to check the composition and analyzed using HPLC. The results were seen to be totally consistent and yielded only the mononitro salicylic acid. These experiments were also repeated with a higher amount of acetic acid (SA:AcOH = 1:16) and were seen to yield identical results. Thus, in order to avoid the possible precipitation of the desired product in the tube and still get better selectivity at complete conversion, it was necessary to work with higher amounts of acetic acid (SA:AcOH = 1:10). Although higher amounts of acetic acid are needed, the separation of acetic acid from the product needs to be dealt with separately as its recycle would be cost-effective. With a suitable recycle mechanism, with a suitable numbering-up strategy (to produce as much as a few kilograms per hour) it would certainly be possible to use this approach for the continuous production of mononitro derivatives of salicylic acid. Further, we would extend the existing experimental system to continuous selective reduction of 5NSA to 5-amino salicylic acid. The intricacies involving continuous removal of HNO_3, selective separation of 3NSA from the mixture, feasibility of reduction in the presence of excess acetic acid, and continuous three-phase reduction under pressure will be dealt with separately.

Thus, the continuous flow nitration of salicylic acid in a SS316 tubular reactor yielded only the mononitro products at the outlet with higher selectivity for 5NSA. The better conductivity of metal, high heat transfer area, and the specific residence time helped to practically bypass the byproduct formation in this process. The experiments at different temperatures showed a positive relationship between the selectivity of 5NSA and temperatures. Also, a higher amount of the nitrating agent was seen to reduce the reaction time and achieve higher selectivity for the desired product. Lower amounts of acetic acid were seen to lead to precipitation of 5NSA in the tubular reactor, causing blockage. A continuous flow experiment at 50 °C with 7 min residence time for 2 h yielded consistent outlet composition. Although the higher amount of acetic acid is needed to keep the desired product in solution, complete recycle of acetic acid would help to reduce the acetic acid inventory. The economics of this continuous process, the optimization of the operating conditions and the design parameters (heat transfer area and heat transfer coefficient) will be discussed elsewhere with the help of systematic modeling and simulations for this system.

Acknowledgment

We acknowledge the financial help from the Consortium on Microreaction Technology (www.ncl-india.org/cmr/). A.A.K. also acknowledges the in-house funding from NCL. The immense help of Dr. R. M. Deshpande and Dr. A. A. Kelkar in HPLC analysis is gratefully acknowledged.

Received for review May 12, 2008.

OP800112U