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Continuous Flow Nitration of Benzaldehyde

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Abstract:

The nitration of benzaldehyde can be carried out in a safe manner in continuous mode using a microreactor system. Choice of a micromixer was seen to affect the performance of this two-phase reaction significantly. The reaction time could be brought down to 2 min by increasing the reaction temperature and thereby taking advantage of higher heat transfer area. The simple T-micromixer is seen to be inefficient for two-phase reactions. Further scope of process intensification is also discussed.

Introduction

Microreactors are being used for several fast and exothermic reactions, and a vast amount of information on the feasibility of many homonegeous and heterogeneous reactions in miniaturized devices is reported in the literature.[1−4] A few of the important advantages of microreactors are: (i) very high heat transfer area, which helps carry out exothermic reactions, (ii) smaller residence time, which helps carry out fast reactions at true kinetic rates, (iii) better control of the overall reaction rates, which helps achieve the desired selectivity by providing the possibility of introducing the reactant(s) at different spatial locations, (iv) the need for very much smaller amounts of chemicals to obtain the necessary kinetic information, (v) safe operation, (vi) the ability to withstand extreme conditions because of smaller reaction volumes, etc. Nitration of aromatic substrates is one such class of reactions, where the above-mentioned advantages are useful for achieving better yield and selectivity when the reactions are done in microreactors. Since the channel dimensions are small, the diffusion time scales are much smaller than in conventional batch operations. This results in rapid mixing, which subsequently reduces the possibility of byproduct formation in fast reactions, and it also yields higher mass transfer rates in case of two-phase flows. A detailed discussion of 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.[5] In reality, the concept of continuous flow synthesis is feasible in devices where the characteristic flow dimensions offer significantly fewer transport limitations. This indicates that it is not always necessary to carry out the flow synthesis in devices with very small channel sizes (<100 μm), and channel sizes slightly greater than a millimeter may also be feasible. Here we illustrate one such example of aromatic nitration, where the process intensification can be achieved using a micromixer followed by reaction channel size slightly greater than 1 mm.

The nitro derivatives of aromatic compounds[6] find applications in a variety of fields and are synthesized in quantities ranging from bulk chemicals to fine chemicals to drug intermediates. The nitro derivatives of benzaldehyde find applications in dyes, pesticides, pharmaceutical drugs, and nonlinear optical materials. Nitrobenzaldehyde also serves as a raw material for the preparation of benzodiazepines and other cardiovascular drugs of the dihyropyridine group. Specifically, *o*-nitro derivative has explicit applications and is usually desired in good yield and high purity. However, in most of the conventional synthesis routes of direct nitration of benzaldehyde, the meta isomer is obtained in large quantities, and the usual mole ratio of the products is o:m = 1:4. This ratio can be varied by changing the w/w amount of the nitrating mixture with respect to the substrate (benzaldehyde) or even by varying the internal composition of the nitrating mixture (HNO_3:H_2SO_4, mol/mol). The condensation of 2-nitrotoluene followed by hypochlorite oxidation yields only a trace amount of nitrobenzaldehyde.[8] For a brief review of the other methods used for direct synthesis of the ortho derivative, the reader may refer to Sainz-Diaz.[7] In the typical batch reaction of direct nitration of benzaldehyde, the mixing of the nitrating mixture and the substrate is done very slowly by adding either the substrate to the nitrating agent or vice versa. The reaction is usually carried out in the temperature range of −5 to 15 °C, and depending upon the composition of the nitrating agent and the mole ratio of reacting species, the reaction time reported in the literature falls in the range of 2.3−6 h. These issues stress adoption of new synthesis methods that help to achieve a better control on the product composition, safe handling of hazardous materials, and reduced release of the toxic materials in the environment.

In the case of direct nitration of benzaldehyde, as per the reaction mechanism itself, the nitration in the ortho position is very unlikely due to steric hindrance and low nucleophilic character of this position. This is mainly due to the solvation of the aldehyde group in the strongly protic system of the nitrating mixture containing higher proportions of H_2SO_4.

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Table 1. **Observations from the batch experiments (BA: benzaldehyde); for experiment no. 1–5, samples were withdrawn only after 120 min**

Sr. No.	HNO_3:BA (mol/mol)	HNO_3/H_2SO_4 (mol/mol)	time (min)	temperature (°C)	conversion (%)	isomer mole ratio (o:m)
1	1.88	0.121	120	0	91	1:5.51
2	2.35	0.189	120	0	100	1:6.15
3	2.35	only HNO_3	120	0	0	NA
4	1.18	0.189	120	0	86	1:1.38
5	1.65	0.264	120	0	100	1:3.88
6	1.65	0.264	15	0	100	1:4.12
7	1.18	0.554	15	0	100	1:4.29
8	1.18	0.554	4	0	60	1:3.76

However the ortho substitution can be achieved by using a high concentration of HNO_3 yielding a relatively higher o:m ratio. In all, the nitration of meta position is always favored thermodynamically; however, the kinetically higher concentration of nitric acid slightly favors the nitration of the ortho position. In view of this, here we demonstrate the direct nitration of benzaldehyde using a nitrating mixture ($HNO_3 + H_2SO_4$) in a continuous mode miniaturized system and analogous experiments in conventional batch mode.

Experimental Section

In the batch mode, the nitrating mixture was prepared by stirring concentrated sulfuric acid with nitric acid (70%, sp. gr. 1.42), with sufficient cooling by an ice bath. The reaction was carried out in a glass jacketed reactor (50 mL), and the temperature of the reaction mixture was maintained by circulating water from a thermostat (Julabo, Germany). Benzaldehyde was added with good stirring in 5 min, and stirring was continued for 30 min. Continuous stirring was done vigorously to keep the reactants dispersed. Experiments were carried out in the temperature range of 0−25 °C. Samples of the reaction mixture (from the dispersion of two phases) were withdrawn regularly, and the organic phase was extracted in diethyl ether before it was subjected to analysis. The samples were analyzed using gas chromatography (Agilent 6890) with an HP5 capillary column and an FID detector. The injector temperature was maintained at 280 °C.

For the continuous flow experiments, the experimental setup consisted of two syringe pumps (Boading Longer, China) loaded with 20 mL glass syringes connected to SS316 tubes (1/16 in. o.d.) through an in-house developed and fabricated glass-to-metal connector made in PTFE. The two metallic tubes were subsequently connected to a micromixer followed by a residence time tube (1/16 in. o.d., 1.38 mm i.d. and 6 m long) made of Hastelloy (Vindum Engineering, U.S.A.). A heating-chilling thermostat (Julabo, Germany) was also used (see Figure 1). Both the syringes were filled with the nitrating mixture and benzaldehyde, respectively. The SS316 tubes carrying the reactants, the micromixer as well as the Hastelloy tube, were immersed in the thermostat. It needs to be noted that the flow of nitrating mixture and benzaldehyde is a two-phase flow and in a Hastelloy tube, the nitrating mixture (aqueous phase) is continuous, while benzaldehyde is present in the form of discontinuous slugs. Two different types of micromixers were used to bring the reactants in contact with each other. The details are discussed later under the section of Results and Discussions. As mentioned previously, from the samples collected at the outlet, the organic phase was extracted in diethyl ether and the samples were subjected to analysis. The reaction composition was varied by changing the flow ratio at the inlet and the composition of the nitrating mixture, while the temperature was changed by changing the bulk temperature in the thermostat.

Results and Discussion

The observations for different conditions from the batch experiments performed are given in Table 1. The observations clearly indicate that, when the internal composition of nitrating mixture contains a relatively low amount of sulfuric acid and also with lesser amount of nitrating agent, it is possible to achieve 100% conversion of benzaldehyde yielding an o:m ratio close to 1:4 but in a time much shorter than in the data from the literature. In fact at identical reaction temperatures, the reaction time with this composition of reacting mixture was seen to decrease by 8 times. These experiments were done mainly to get an estimate of the time scales involved in this reaction to achieve complete conversion. It is necessary to mention that the usage of nitrating mixture comprising of HNO_3 and acetic acid was seen to be less efficient for this case (no noticeable conversion even after many hours) and hence was not used further.

Further experiments were carried out in continuous mode. A simple T-mixer (1 mm i.d.) was seen to be inefficient in mixing the two phases (nitrating mixture and benzaldehyde), yielding only the slug flow conditional to the flow rates and hence was not used for further experiments. Hence, we used a spilt and recombine type caterpillar micromixer (IMM, Germany), which was then connected to the Hastelloy tube. Experiments were carried out to identify the optimum composition of the reacting mixture as well as the nitrating agent. The effect of variation in the mole ratio of nitric acid to benzaldehyde (with fixed HNO_3:H_2SO_4 composition) is shown in Figure 2. All the experiments were carried out at 5 °C. For all the inlet mole fraction of benzaldehyde, the amount of meta isomer was seen to increase continuously with time. However, the rate of change in the isomer mole ratio was higher for higher amounts of nitric acid in the system. On complete conversion, the maximum mole fraction of the meta isomer was observed when the HNO_3:BA mole ratio was 3.5. In order to check the effect of the composition of nitrating mixture, experiments were carried out with the HNO_3:BA mole ratio of 3.5:1 (Figure 3). At the completion of the reaction, the amount of meta isomer was seen to decrease with an increase in the amount of nitric acid in the nitrating mixture. With these key observations,

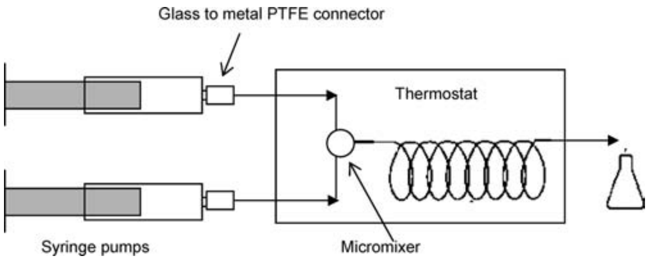

Figure 1. **Schematic of the experimental setup.**

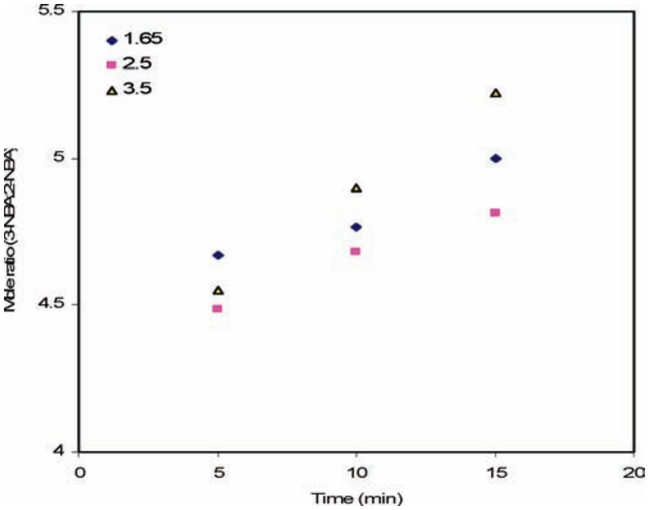

Figure 2. **Effect of nitric acid on the benzaldehyde (HNO_3: BA) mole ratio at the inlet of the continuous flow system on the product composition. All the experiments are performed at 5 °C. Legends indicate the mole ratio of nitric acid to benzaldehyde.**

further experiments were carried out to realize the effect of temperature on the reaction and outlet composition.

The experiments were carried out at three different temperatures, 5, 15, and 25 °C. The observations are shown in Figure 4. As expected, with an increase in the reaction temperature, the time required for completion of the nitration reaction decreased significantly. Although at lower conversions the m:o ratio was relatively lower, it was more important to note that increase in temperature has a positive effect on the amount of ortho isomer formed in the reaction. However, on finding the quantitative relation between the *m:o* mole ratio and temperature from the three data sets, it was clear that within the boiling point of the aqueous phase, it is difficult to bring this ratio to less than 2.8. This means that, although higher temperature would yield a relatively higher amount of ortho isomer, the formation of the meta isomer is always favored.

In order to check the product composition from a batch reaction at identical conditions, a separate experiment was carried out in the glass reactor (batch) at 25 °C. Samples were withdrawn regularly. It was observed that in the batch mode, almost 30 min was needed to complete the reaction and the mole ratio of *m:o* isomers was seen to increase continuously until the reaction was complete. One of the main reasons is the relatively poor mixing of the two immiscible phases, in addition to inefficient interfacial mass transfer and heat transfer in the batch reactor.

The observations from the above experiment indicate that the continuous flow nitration of benzaldehyde can be practically carried out in a kinetically controlled manner, and no effect of interfacial mass transfer is visible. Also, for a given composition of nitrating mixture and the mole ratio of nitric acid to substrate, the selectivity was seen to be a function of the temperature. Thus, either the steric hindrance or the nucleophilic character of ortho position is affected by the temperature. The observations also indicate that if the preheated reactants are mixed at the relatively higher temperature using a micromixer, the reaction can be made instantaneous, leading to the complete conversion of the reactants (provided sufficient interfacial area and surface renewal rate is available for the rapid mass transfer).

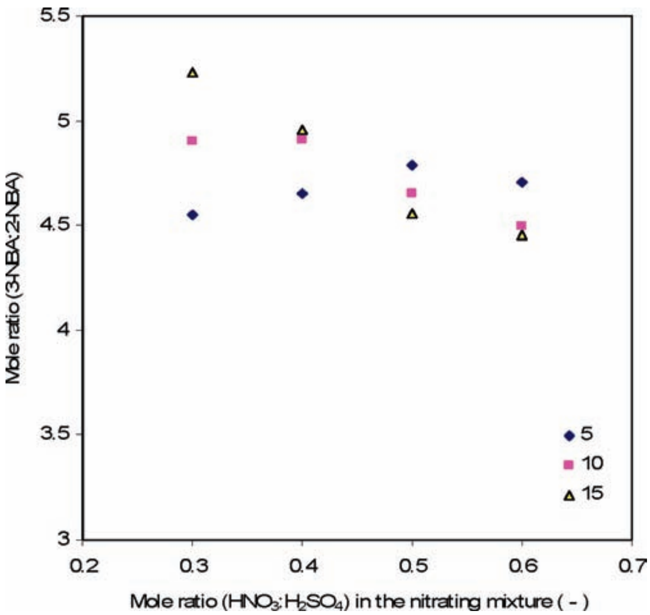

Figure 3. **Effect of composition of the nitrating mixture (nitric acid to sulfuric acid, mol/mol) at the inlet of continuous flow system on the product composition. All the experiments are performed at 5 °C and with a fixed mole ratio of nitric acid to benzaldehyde (3.5:1). The legends show the residence time maintained in the system in minutes.**

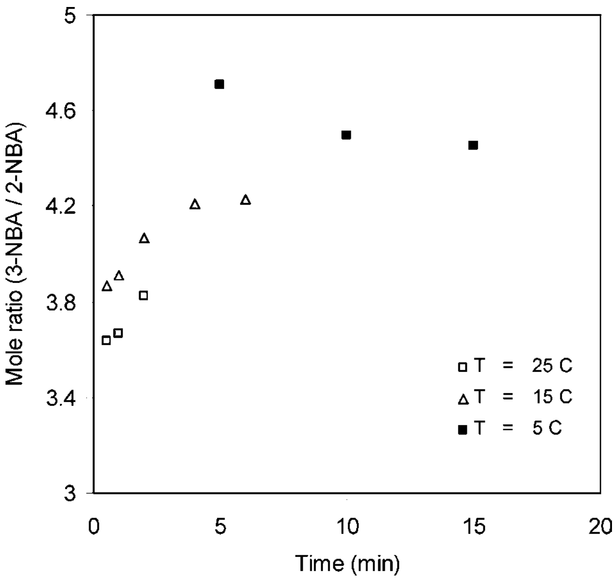

Figure 4. **Effect of temperature on the outlet product composition. The inlet composition is fixed at nitric acid to sulfuric acid, mol/mol ratio 0.6:1 and nitric acid to benzaldehyde mole ratio 3.5:1.**

Thus, having a suitable micromixer would help to eliminate the residence time tube, thereby opening several options for scaling up the miniaturized system for this reaction. It will also be useful to design an inline separator (L-L extractor) for the separation of the two isomers.

Thus, this work demonstrates that the nitration of benzaldehyde can be carried out in a safe manner in continuous mode using the microreactor system. The mixing is critical, specifically at higher temperatures where the reaction is very fast. The choice of a micromixer affects the performance significantly. While the important issues (viz. inline separation of product isomers, checking the economic feasibility of this continuous nitration, etc.) need separate attention, the above observations would help to intensify this step of nitration in the entire process.

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