ORGANIC PROCESS RESEARCH & DEVELOPMENT
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Intensification of Nitrobenzaldehydes Synthesis from Benzyl Alcohol in a Microreactor

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ABSTRACT: A one-step process to produce 2- and 3-nitrobenzaldehyde isomers starting from benzyl alcohol in aqueous mixed nitric and sulfuric acid was developed as an inherently safe continuous flow process in a microreactor. The previously published kinetic model was validated in a microreactor and used to optimize operating conditions *in silico* to attain the desired product distribution. The molar fractions of nitric and sulfuric acids were increased up to 0.35, 0.45, and temperature to 68 °C, which was impossible to do under batch conditions. Experiments under continuous flow conditions have shown that yields of about 42% and 96% for the ortho- and the meta- isomers, respectively, can be achieved.

INTRODUCTION

Nitrobenzaldehydes are important intermediates involved in the synthesis of a wide range of bulk and fine chemicals.[1,2] The most recent literature shows an increasing interest in the synthesis of new high value molecules involving ortho-[3−8] and meta-nitrobenzaldehyde isomers,[9−12] that have applications as anti-inflammatory, antibacterial, and antitumor agents, as well as therapeutic candidates for cardiovascular diseases, fluorescence markers and optical materials. 3-Nitrobenzaldehyde is traditionally produced via direct fed-batch nitration of benzaldehyde using mixtures of concentrated nitric and sulfuric acids at 5−10 °C, leading to the formation of 2-nitrobenzaldehyde as a side product with yields up to 20%.[13,14] As a consequence, different processes have been successively developed in order to profitably synthesize the ortho-isomer, such as cinnamic acid nitration, 2-nitrostyrene oxidation, and 2-nitrobenzyl bromide oxidation.[13] However, most of these processes involve highly exothermic reactions, requiring stringent control of operating conditions, evident by the low operating temperatures and the limited tolerance toward changes in the nitrating agent composition. Specifically, during the direct nitration of benzaldehyde the process could easily undergo explosive thermal runaway, due to the exothermic oxidation and nitration reactions occurring in the acid mixture, if the reaction is performed in a conventional refrigerated batch reactor. In this respect, the possibility of performing the direct nitration process safely under various, and preferably more intensive, operating conditions is of great interest. Which is why we turned our attention to compact and microreactors, which reportedly allow safe operation of the highly hazardous processes, such as direct oxidation of hydrogen,[15−17] oxidation of hydrocarbons with molecular oxygen at elevated pressures and temperatures,[18,19] and reactions with HF or hydrazoic acid,[20−22] as some examples.

Continuous flow microreactors have been applied in the syntheses of highly value/low-throughput molecules[23−25] including, specifically, nitrated products.[26−29] The peculiarity of the small-diameter devices with embedded mixing and heat exchange, is the ability to enhance heat and mass transfer, allowing to precisely control temperature and concentration profiles. This allows to safely carry out reactions, adopting conditions under which a traditional batch reactor cannot operate.[30] Especially when involving fast exothermic reactions.[31,32] Several studies pointed out the possibility of successfully suppressing hot spots, leading to improvements in yield, selectivity, product quality, and safety, while enabling to perform hazardous reactions under unusual conditions.[33−35]

Previous investigations also show an interest in increasing the 2-nitrobenzaldehyde yield during the direct nitration of benzaldehyde in order to overcome safety problems associated with some of the alternative proposed processes.[2,36,37] These studies demonstrated that an increase in nitric acid concentration can increase the yield of 2-nitrobenzaldehyde, but warn about a consequent increase in the reactivity and the generated reaction heat. A recent kinetic study under batch conditions was undertaken in order to evaluate the kinetic parameters and predict the behavior of the reacting system at varying operating conditions.[2] Literature findings[14,38,39] and recent kinetic modeling[40] also showed the possibility of selectively converting benzyl alcohol to benzaldehyde in the same nitrating mixtures in order to overcome the drawbacks of the traditional route of toluene oxidation to produce benzaldehyde that requires expensive catalysts as well as temperatures and pressures up to 160 °C and 70 atm, respectively.[14] In the present article a new process to synthesize 2- and 3-nitrobenzaldehyde isomers through benzyl alcohol oxidation/nitration is proposed, adopting a commercial glass microreactor. The advantage of using the microreactor chosen for this study, is that the scaled-up versions with similar

Received: December 16, 2016
Published: February 20, 2017

DOI: 10.1021/acs.oprd.6b00426
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

functionalities are commercially available from Corning, in glass, or Chemtrix, in silicon carbide. In this respect, the first aim of this article is to validate the model prediction by adopting experimental conditions different from those used to develop the model in the previous batch experiments. Furthermore, the kinetic model was used to identify the experimental conditions to maximize the yield of 2- and 3-nitrobenzaldehyde in a continuous process, and the results confirmed the possibility of producing the two isomers with the highest yield published so far.

■ EXPERIMENTAL SECTION

Materials. All reagents (acetonitrile ≥99.9%; methanol ≥99.9%; phosphoric acid 85 wt% in H_2O; benzyl alcohol anhydrous 99.8%; benzaldehyde ≥99%; 2-nitrobenzaldehyde 98%; 3-nitrobenzaldehyde 99%; 4-nitrobenzaldehyde 98%; benzoic acid ≥99.5%; 2-nitrobenzoic acid 95%; 3-nitrobenzoic acid 99%; 4-nitrobenzoic acid 98%; nitric acid fuming ≥99%; sulfuric acid 99.999%; ethylene glycol technical with corrosion inhibitor; urea 99%) were purchased from Sigma-Aldrich and used as received. Water for experiments was obtained by means of a Maxima (USF) Milli-Q system.

Procedures. The experiments were carried out in both batch and continuous modes. The adopted batch reactor is a magnetically stirred jacketed glass reactor (3.0×10^{-2} L) refrigerated using a circulator (Thermo-Scientific DC30 K20; cooling fluid: ethylene glycol). A scheme of the reactor can be found elsewhere.[40] Nitric acid, sulfuric acid, and water in appropriate amounts were previously mixed and equilibrated at the operating temperature. Benzyl alcohol was then added and samples (10^{-4} L) were collected at different reaction times and rapidly quenched by diluting (1:100) with a solution of urea in acetonitrile (6.66×10^{-2} M), and analyzed by HPLC.

The continuous flow experimental runs were carried out in a commercial glass microreactor with embedded static mixer, heat exchange, and three sampling ports along the reactor length (Little Things Factory XXL-ST-04). A scheme of the reactor is shown in Figure 1.

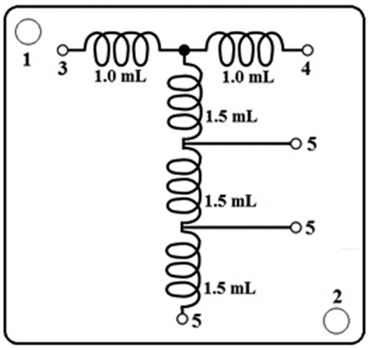


Figure 1. Scheme of the microreactor. (1) Coolant inlet. (2) Coolant outlet. (3) Mixed acid inlet. (4) Benzyl alcohol inlet. (5) Sampling points.

Mixed acids and benzyl alcohol were separately fed by means of a peristaltic pump (V-3 pump, Vapor tec Ltd.) and a syringe pump (PhD Ultra Harward Apparatus), and preheated to the operating temperature. Temperature was kept constant in the reactor during each experimental run by using the thermostated circulator connected to the embedded heat exchanger. Samples were collected at three different outlets at different residence times. The residence time in the reactor was changed varying both the flow rate and the volume in the ranges 0.45−9.99 mL·min^{-1} and 1.5−4.5 mL, respectively. The collected samples were rapidly diluted and analyzed.

HPLC analysis was performed using a Shimadzu Prominence HPLC, a UV DAD detector, and a Phenomenex Synergi 4 μm polar RP/80A column, thermostated at 303 K. The mobile phase (1.0 mL·min^{-1}) was constituted of eluant (A) (buffer solution: CH_3OH 5% v/v; H_3PO_4 0.4% v/v; H_2O 94.6% v/v) and eluant (B) (acetonitrile). The gradient was as follows: 15% B for 8 min, increased to 25% B in 10 min, and successively decreased to 15% B in 5 min. The signals were acquired at wavelength of 230, 250, and 265 nm.

■ RESULTS AND DISCUSSION

Reaction Mechanisms. Based on the previously published kinetics,[2,40] the following simplified reaction scheme can be proposed for the ortho- and meta-nitrobenzaldehyde syntheses starting from benzyl alcohol, Scheme 1.

Benzyl alcohol (**1**) is completely converted to benzaldehyde through the formation of protonated benzyl nitrite (**2**) as a key-intermediate. Moreover, benzaldehyde can be either directly nitrated on the aromatic ring to give 3-nitrobenzaldehyde (**3**) or can coordinate a nitronium ion (**4**) on the aldehyde group[2,36] (**6**) and internally rearrange to form the ortho-isomer (**5**). The internal rearrangement occurs when the coordinated species (**6**) is attacked by another nitronium ion.[2,36] Nitronium ion concentration is affected by nitric acid concentration in mixed acid due to the following equilibrium:

$$HNO_3{\cdot}H_2O + H_2SO_4 \leftrightarrow NO_2^+ + HSO_4^- + 2H_2O$$

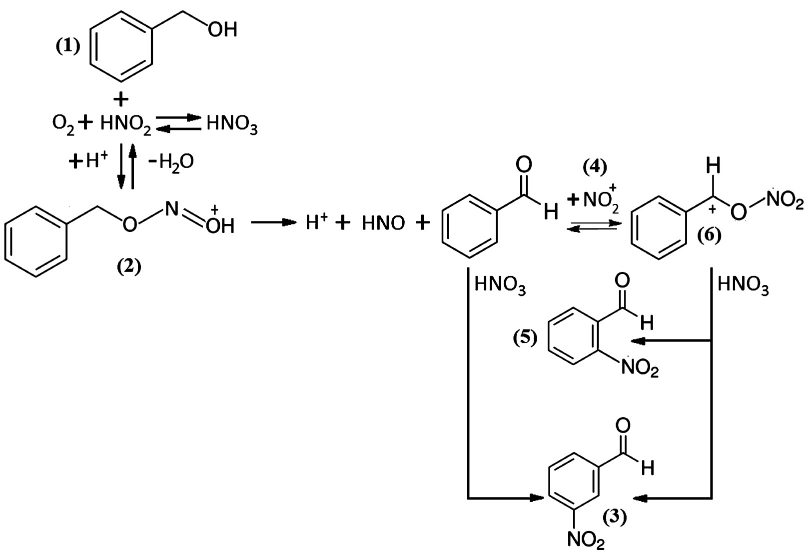
Russo et al.,[2] pointed out that direct nitration of the aromatic ring to form 2-nitrobenzaldehyde is negligible compared to the latter mechanism of internal rearrangement. It is worth pointing out, that according to the published kinetic model[2] the internal rearrangement is only possible in ortho-position because of its spatial closeness to the aldehydic group, whereas the meta-isomer (**3**) is formed by the aromatic ring direct nitration of both benzaldehyde and species (**6**); the latter can lose the coordinated $-NO_2$ on the aldehydic group after direct nitration in meta-position.[2] In the previous investigations[1,2] there was no significant evidence of 4-nitrobenzaldehyde and dinitrated products formation.

For the sake of clarity, the oxidation pattern leading to the formation of benzoic acid, 2- and 3-nitrobenzoic acid has been discarded in Scheme 1. However, under most of the adopted conditions these secondary products were not detected, or were measured at trace levels.

Batch Reactions and Evaluation of Reaction Hazard. Some preliminary batch experimental runs were carried out in a homogeneous phase to confirm the possibility of producing 2 and 3-nitrobenzaldehydes from benzyl alcohol. Figure 2 shows results of an experimental run carried out by adding benzyl alcohol (C_0 = 45 mM) into the standard mixed acid (HNO_3 = 20% w/w; H_2SO_4 = 60% w/w; H_2O = 20% w/w).

The results clearly show that it is possible to obtain 2- and 3-nitrobenzaldehydes starting from benzyl alcohol. Moreover, under the adopted conditions, the rate of benzyl alcohol oxidation to benzaldehyde is much faster than that of nitration so that no traces of benzyl alcohol are detected even for the sample collected immediately after addition of the alcohol. Benzaldehyde was instantaneously formed and slowly nitrated.

Scheme 1. Simplified Scheme of Nitrobenzaldehydes Synthesis from Benzyl Alcohol in Mixed Acids



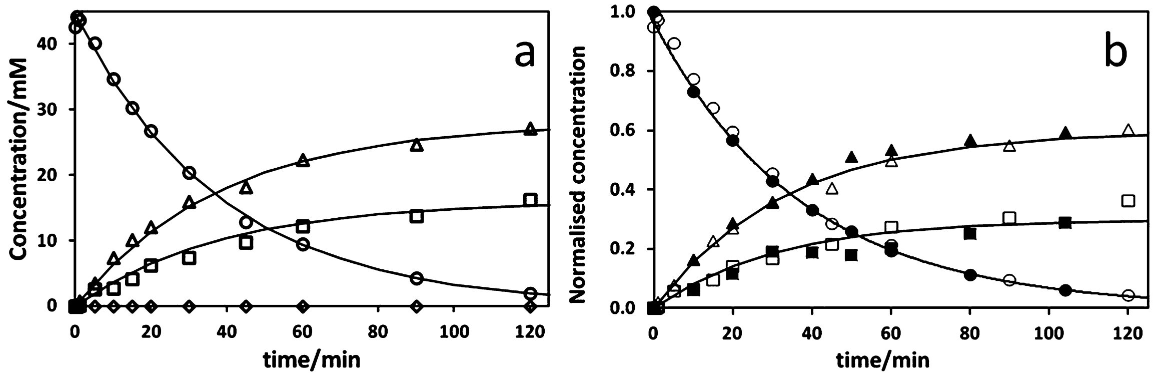


Figure 2. Oxidation/Nitration of benzyl alcohol. (a) Reaction performed by adding benzyl alcohol to acid. (b) A comparison of two runs starting from benzaldehyde (full symbols) or benzyl alcohol (empty symbols). Figure legend: (●,○) Benzaldehyde; (■,□) 2-nitrobenzaldehyde; (▲,△) 3-nitrobenzaldehyde; (◇) benzyl alcohol; T = 20 °C; (lines are for convenience of the eye).

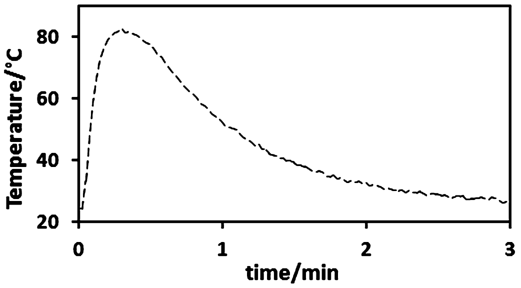


Figure 3. Temperature profile of the reacting mixture. Organic/nitrating reagents ratio = 0.4 w/w. Standard mixed acids. T_0 = 23 °C.

In Figure 2b the normalized concentrations measured in two different runs carried out under the same conditions but starting either from benzyl alcohol or from benzaldehyde, are reported. The concentrations profiles are coincident, suggesting that the nitration process is not affected by the starting material, since oxidation rate of benzyl alcohol is much higher than nitration rate of benzaldehyde.

Tandem oxidation-nitration process starting from benzyl alcohol seems an attractive option, but it presents a serious safety concern due to both the very fast rate of the highly exothermic oxidation step and the consequent nitration. The results shown in Figure 2 were obtained at low concentrations of the reactants and long reaction times, to allow for heat transfer, thus operating at isothermal conditions. An increase in concentrations of either the acids or the reactants will significantly increase the demand for heat removal. Figure 3 shows temperature profile of the reacting mixtures resulting from the addition of benzyl alcohol to the standard mixture of acids using an organic/nitrating mixture ratio 0.4 w/w at T = 23 °C. The results clearly show that temperature can very rapidly increase up to 83 °C.

These results suggest that the process could not be safely carried out adopting a standard batch reactor in which the prevention of the thermal runaway explosion cannot be guaranteed.

Moreover, assuming a heat of reaction of about ΔH_{ox} = 1100 $J\cdot g^{-1}$ and ΔH_n = 1185 $J\cdot g^{-1}$ (estimated by group contribution method[41]) for the oxidation and the nitration reactions respectively, and a mean specific heat c_p of 2 $J\cdot g^{-1}\cdot K^{-1}$[42] it is possible to estimate the adiabatic temperature rise for complete oxidation/nitration of the organic substrate as follows (eq 1):

$$\Delta T_{ad} = \frac{\Delta H_{ox} + \Delta H_n}{c_p} \cdot \frac{m_{Ar}}{m_{Ar} + m_{mix}} \quad (1)$$

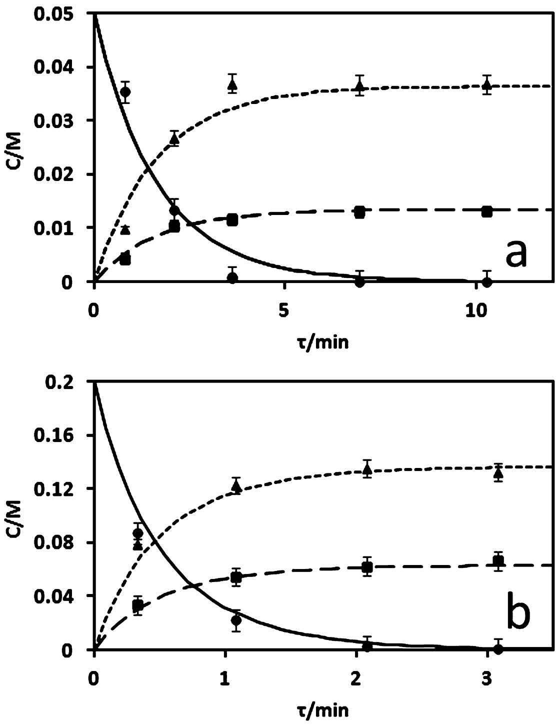


Figure 4. Concentration vs residence time. Calculated (lines) and experimental data (symbols). (●) Benzaldehyde; (■) 2-nitrobenzaldehyde; (▲) 3-nitrobenzaldehyde. (a) x_n (nitric acid molar fraction) = 0.197; x_s (sulfuric acid molar fraction) = 0.347; T = 6 °C; C_0 = 0.05 M. (b) x_n = 0.199; x_s = 0.348; T = 25 °C; C_0 = 0.2 M.

where m_{Ar} and m_{mix} are the masses of the aromatic substrate and mixed acid, respectively. Assuming a ratio m_{Ar}/m_{mix} of 0.5 (a common choice in industrial applications)[43] the adiabatic temperature rise is estimated to be $\Delta T_{ad} \approx 380\ K$. Under adiabatic condition, even adopting lower m_{Ar}/m_{mix} ratios, the increase in temperature can trigger side reactions (dinitration, trinitration, side oxidations) leading to the formation of unstable intermediates with release of gaseous species and vessels pressurizations and/or explosion.[43]

Microreactor Performance. To safely carry out the process under harsher conditions, namely higher temperature and stronger acidic media, the glass microreactor with embedded heat transfer and static mixer was adopted.

The previously obtained kinetic parameters[2,40] were used to adapt the mathematical model to a continuous flow reactor based on the assumption of a plug flow reactor (PFR). For each species the mass balance has been described as (2)

$$\frac{dc_i}{d\tau} = \sum_j r_j \tag{2}$$

where c_i is the concentration of the i-th species, τ is the mean residence time in the reactor (ratio between the volume and the flow rate), and r_j is the j-th reaction rate of formation (positive) or consume (negative) of the i-th species. Details of experimental conditions for all the microreactor runs reported in Figures 4–8 are summarized in Table 1. The model was validated by comparing its prediction to the experimental results for the different experimental conditions showing a good predictive capability of the kinetic model, Figure 4.

Once validated, the model was used to define the best conditions to maximize the yield of the two isomers. Figure 5 shows the effect of temperature and mixed acid composition on the yield of 2-nitrobenzaldehyde in the neighborhood of the local optimum. An upper limit temperature was fixed at 70 °C to avoid a significant decomposition of nitric acid in mixed acids at higher temperatures (bold vertical line).

An optimal temperature, which maximizes the yield of ortho-nitrobenzaldehyde can be found at a fixed mixed acid composition. An increase in acid concentration shifts the maximum point to higher temperatures and is reflected in an increase of the yield. The effect of nitric acid, Figure 5a, and sulfuric acid, Figure 5b, are qualitatively similar to each other. However, according to the model prediction, the effect of an

Table 1. Detailed Experimental Conditions Adopted for Microreactor Runs[a]

run	x_n	x_s	T (°C)	C_0 (M)	Q^{mix} (mL·min^{-1})	Q^{org} (μL·min^{-1})	V (mL)	reported in
1	0.197	0.347	6	0.05	0.45	2.317	1.5, 3.0, 4.5	Figure 4a
2	0.197	0.347	6	0.05	1.50	7.724	1.5, 3.0	Figure 4a
3	0.199	0.348	25	0.2	5.00	103.0	1.5	Figure 4b
4	0.199	0.348	25	0.2	1.50	30.90	1.5, 3.0, 4.5	Figure 4b
5	0.250	0.450	50, 60, 68	0.05	9.99	51.44	1.5	Figure 5a
6	0.450	0.450	68	0.05	9.99	51.44	1.5	Figure 5a
7	0.250	0.350	50, 60, 68	0.05	9.99	51.44	1.5	Figure 5b
8	0.350	0.350	57, 65	0.05	9.99	51.44	1.5	Figure 5b
9	0.350	0.450	68	0.05, 0.5	9.99	51.44, 514.4	1.5, 3.0	Figure 5a-b, Figure 6
10	0.300	0.400	52	0.05	9.99	51.44	1.5, 3.0	not shown
11	0.134	0.350	59	0.05	3.00	15.45	1.5, 3.0, 4.5	Figure 7a
12	0.134	0.350	59	0.05	7.50	38.62	3.0	Figure 7a
13	0.130	0.318	68	0.05	5.63	28.97	3.0, 4.5	Figure 7b
14	0.130	0.318	68	0.05	9.99	51.44	1.5	Figure 7b
15	0.130	0.450	45, 60	0.05	3.00, 7.5	15.45, 38.62	3.0	Figure 8a
16	0.130	0.270	68	0.05	1.67	8.599	3.0	Figure 8a
17	0.130	0.320	45, 55	0.05	0.20, 0.75	1.029, 3.862	4.5	Figure 8a
18	0.200	0.320	45, 55, 68	0.05	1.50, 3.00, 9.99	7.724, 15.45, 51.44	3.0	Figure 8b
19	0.080	0.320	55, 68	0.05	0.28, 1.23	1.448, 6.333	4.5	Figure 8b

[a] x_n = nitric acid molar fraction; x_s = sulfuric acid molar fraction; C_0 = benzyl alcohol initial concentration; Q^{mix} = nitrating mixture flow rate; Q^{org} = benzyl alcohol flow rate; V = microreactor volume.

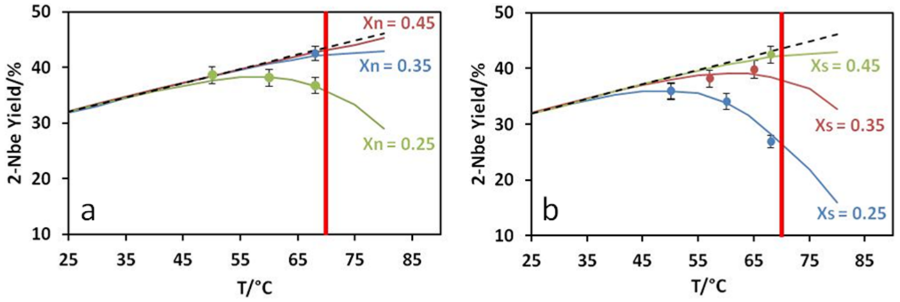


Figure 5. Percentage yield of 2-nitrobenzaldehyde. (a) The effect of nitric acid at fixed x_s (sulfuric acid molar fraction) = 0.450; (b) the effect of sulfuric acid at fixed x_n (nitric acid molar fraction) = 0.350. Model prediction (continuous lines); experimental data (symbols); theoretical limit by model predictions (dashed lines).

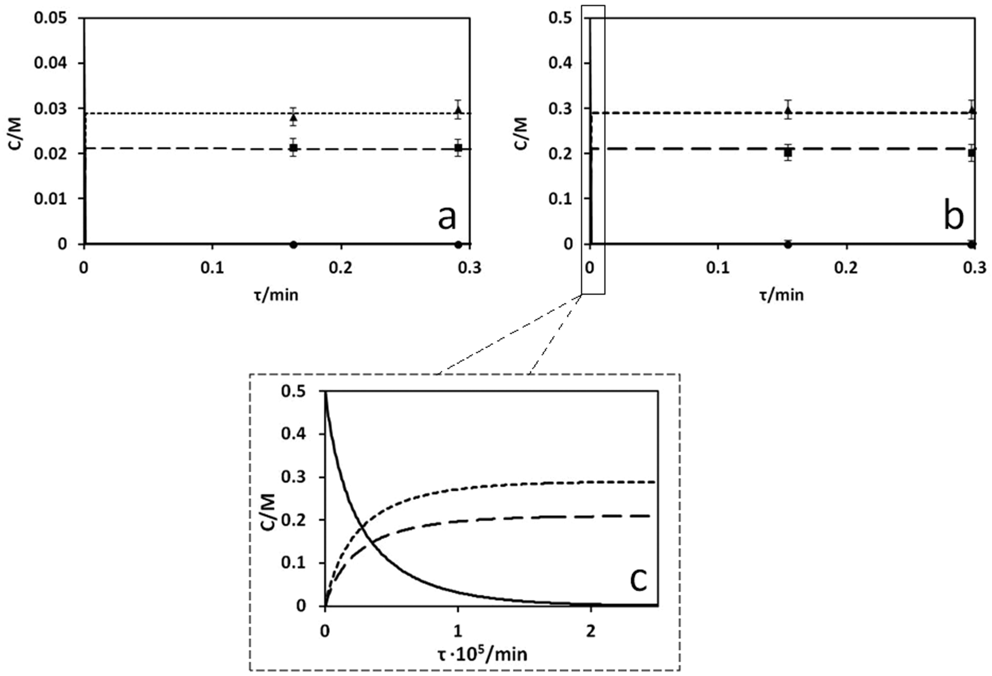


Figure 6. Concentration vs residence time in the neighborhood of the optimum point. x_n (nitric acid molar fraction) = 0.350; x_s (sulfuric acid molar fraction) = 0.450; T = 68 °C; calculated (lines) and experimental data (symbols). (●) Benzaldehyde; (■) 2-nitrobenzaldehyde; (▲) 3-nitrobenzaldehyde. (a) C_0 = 0.05 M. (b) C_0 = 0.5 M. (c) zoom in, C_0 = 0.5 M.

increase in acids concentration in the reported ranges does not seem to significantly affect the yield at temperatures below 45 °C and for molar fractions higher than 0.350 and 0.450 for nitric acid (x_n) and sulfuric acid (x_s), respectively (limit dashed line). For this reason, the experimental runs were carried out under these conditions: x_n = 0.350; x_s = 0.450; T = 68 °C.

The experimental results and the comparison with the model prediction are reported in Figure 6. It is worth noting that the reaction is very fast and a complete conversion is achieved in less than 2 ms according to the model simulation shown in Figure 6c. However, the lowest residence time attainable in the microreactor was about 9 s. Under these conditions, the side reactions of oxidation were too slow to affect the yield and no differences were measured in the samples collected with residence times up to about 18 s (Figure 6a,b). No significant variations in the yield were recorded increasing the initial concentration of the organic substrate from 0.05 to 0.5 M, Figure 6a,b. However, for the highest concentration a significant volume of the gas phase formed was evident through the reactor glass. Even though bubbles were efficiently carried by the liquid stream, the presence of the gas phase will necessarily affect the residence time distribution. In this specific case this did not affect the yield. In fact, as shown in Figures 6a,b, the yields of the two isomers are constant at different residence times. The average experimental 2-nitrobenzaldehyde percentage yield was 41.6% while the space-time yields were 0.33 and 3.29 $g \cdot L^{-1} \cdot s^{-1}$ for the runs reported in Figure 6a,b, respectively.

It is important to report that a relatively high percentage yield of 38.9% was measured under milder conditions (i.e., T = 52 °C; x_n = 0.300; x_s = 0.400) (data not shown).

Furthermore, the MATLAB *fmincon* optimization routine was used to maximize the yield of 3-nitrobenzaldehyde yield. In Figure 7 are reported the results and the prediction for the best measured percentage yield of 93% and 96%, corresponding to space-time yields of 0.078 and 0.12 $g \cdot L^{-1} \cdot s^{-1}$, respectively.

A similar study of the influence of nitric acid, sulfuric acid, and temperature on the yield of 3-nitrobenzaldehyde was carried out. In Figure 8 the maximum predicted obtainable yields of the meta-isomer are plotted at varying nitric acid sulfuric acid molar fractions and different temperatures. At the lowest temperatures and acid concentrations the significant

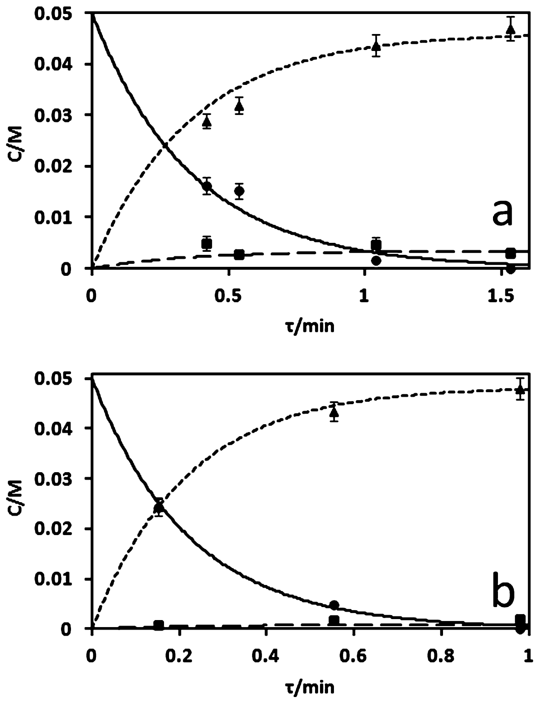


Figure 7. Concentration vs residence time. Calculated (lines) and experimental data (symbols). (●) Benzaldehyde; (■) 2-nitrobenzaldehyde; (▲) 3-nitrobenzaldehyde. (a) x_n = 0.134; x_s = 0.350; T = 59 °C; C_0 = 0.05 M. (b) x_n = 0.130; x_s = 0.318; T = 68 °C; C_0 = 0.05 M.

occurrence of the oxidation of 3-nitrobenzaldehyde to 3-nitrobenzoic acid reduces the yield. As a result, the dependences at low temperatures are significantly different from the case of 2-nitrobenzaldehyde, Figure 5, and no limit linearity can be observed. Moreover, unlike the ortho-isomer, an increase in the acid concentration does not always result in an increase in the yield, and an optimum nitric acid molar fraction exists at fixed temperature and sulfuric acid molar fraction, Figure 8c. This is in accord with the previous investigations[36,37] that pointed out an increase in 2-nitrobenzaldehyde yield (and, hence, a decrease in 3-nitrobenzaldehyde yield) for the nitric acid molar fractions above 0.14, Figures 8b,c. The effect of an increase in either nitric or sulfuric acid molar fraction in the neighborhood of the optimum point are qualitatively similar (but quantitatively different) as shown by the comparison in Figure 8a,b. It is important to stress that the decrease in temperature and acid concentration results in the increase in the residence time necessary to achieve the maximum yield by 2 orders of magnitude. In fact, a decrease in the yield is often associated with an increase in the residence time to achieve it.

Further experiments carried under the same experimental conditions adopted for the runs of Figure 7b, but with higher concentrations of 3-nitrobenzaldehyde (up to 0.5 M) resulted in formation of liquid−liquid heterogeneous flow. In fact, even though the nitrated products are still soluble in the acidic aqueous homogeneous phase, the formed benzaldehyde is poorly soluble under less acidic conditions such that the amount of converted benzaldehyde is limited by the solubility of the organic in the aqueous phase, in which the reaction takes place. As a result, a significant amount of unconverted benzaldehyde was collected at the outlet of the reactor at residence times longer than 1 min. The same experiments were run again starting from benzaldehyde instead of benzyl alcohol to rule out the possibility that this could be entirely ascribed to the significant gas formation during the instantaneous oxidation reaction of benzyl alcohol (data not shown). However, for these experimental runs the average measured percentage selectivity for 3-nitrobenzaldehyde was 96.3%, in agreement with the one reported for the homogeneous phase experiments (selectivity = yield for a complete conversion). The measured selectivities are reported in Table 2.

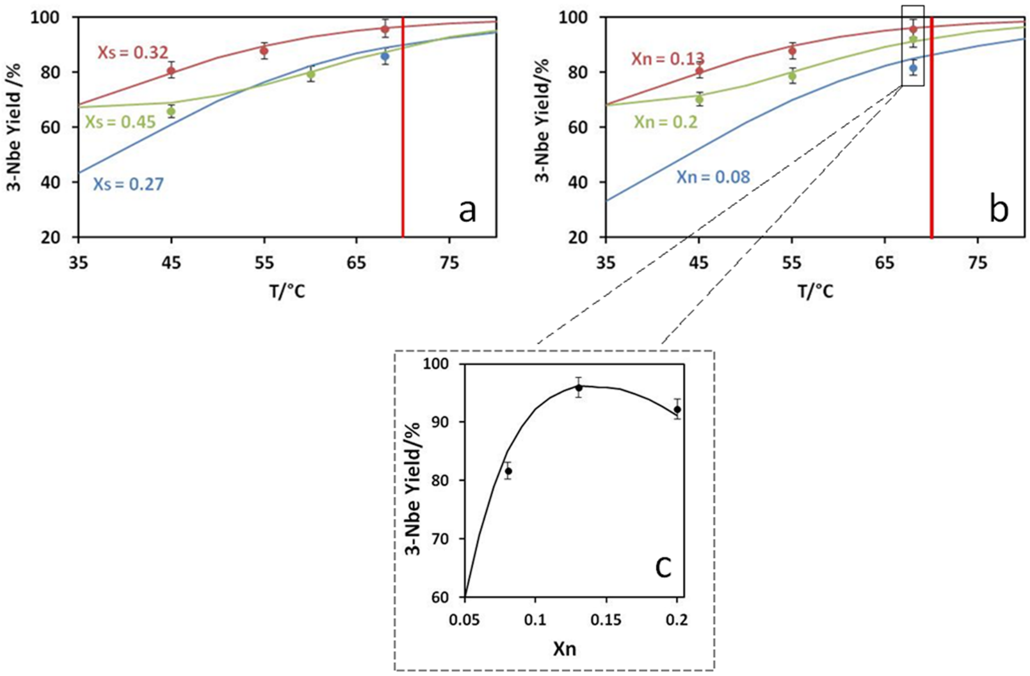


Figure 8. Percentage yield of 3-nitrobenzaldehyde in the neighborhood of the optimum point. (a) The effect of sulfuric acid at fixed x_n = 0.130. (b) The effect of nitric acid at fixed x_s = 0.320. (c) The effect of nitric acid at fixed x_s = 0.320 and T = 68 °C.

Table 2. Measured 3-Nitrobenzaldehyde Selectivities under Heterogeneous Conditions[a]

run	1	2	3	4	5	6	7	8	9	10	average
selectivity (%)	95.5	92.4	95.1	97.9	94.5	97.4	97.2	97.8	97.2	97.7	96.3

[a] $x_n = 0.130$; $x_s = 0.318$; $T = 68$ °C; C_0: 0.3−0.5 M.

CONCLUSIONS

In this article the production of 2- and 3-nitrobenzaldehydes from benzyl alcohol by means of mixed acid was studied under homogeneous conditions. The adoption of a commercial microreactor enabled us to carry out the process under unusual conditions of high temperatures and strongly acidic media, identifying the conditions to maximize the yield of the two isomers. The latter are significantly higher than the currently accessible through the direct nitration of benzaldehyde in traditional refrigerated batch reactors. The adoption of more acidic media and higher temperature is also convenient to increase the solubility of the organics in the mixtures. However, a significant increase in the organic substrate concentration can easily lead to the formation of a biphasic system, affecting the residence time necessary to achieve complete conversion. When adopting less acidic mixtures this could affect the yields because of the significant occurrence of the undesired oxidation product, mainly 2- and 3-nitrobenzoic acids. Further study of the solubilities of the organics, namely benzaldehyde, nitrobenzaldehydes, and nitrobenzoic acid isomers, in the nitrating mixtures is in progress. Despite the promising results, more effort must be made in the future to investigate the possibility of safely carrying out the process under heterogeneous conditions and to integrate the current kinetic results in a comprehensive model taking into account the occurrence of demixing.

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Notes

The authors declare no competing financial interest.

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