Synthetic Methods

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Controlled Autocatalytic Nitration of Phenol in a Microreactor

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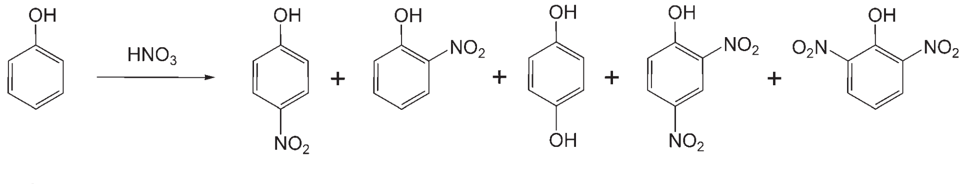
Nitration reactions can often show extremely exothermic behavior, and this, combined with the decomposition or explosion potential of many nitro compounds, places them amongst the most hazardous industrial processes.[1] In this context, continuous processes are attractive for safety reasons because of the much smaller reaction volumes used.[2] Continuous production is of commercial importance for very fast nitrations, such as that of phenol (Scheme 1).[3] Moreover, microreactors[4] should allow better control of the reaction thanks to their efficient mixing and heat transfer, as already described for nitration reactions.[5] The nitration of phenol (**1**) was chosen as a model reaction to investigate the potential of microreactors from both a chemical and a safety point of view.



Scheme 1. Nitration of phenol (**1**) affords the mononitro isomers **2** and **3** as main products. Some hydroquinone (**4**), dinitrophenols (**5** and **6**), and polymeric side-products are also formed. *para*-Nitrophenol (**2**) is the most valuable regioisomer commercially.

The general mechanism for the acid-catalyzed nitration of aromatic compounds is electrophilic and involves the nitronium ion (NO_2^+) as the reactive species.[6] The nitration of phenol (**1**) and other aromatic substrates activated toward electrophilic substitution is, however, essentially different in that it is catalyzed by nitrous acid.[7] The rate of phenol nitration by nitric acid in water was first reported by Martinsen, who showed that the reaction is autocatalyzed by the nitrous acid it produces.[8] The importance of the presence of HNO_2 could suggest that the nitrosonium ion (NO^+) acts as the reactive species. Catalysis by nitrous acid can not, however, involve a nitrosation followed by an oxidation by HNO_3, since nitrosation is *para*-selective whereas nitration affords a mixture of *ortho*- and *para*-nitrophenols.[9] Evidence has since been gained that phenol nitration mainly occurs by a radical mechanism involving a single electron-transfer reaction.[10]

The autocatalytic nature of phenol nitration was first verified by carrying out the reaction in a Mettler RC1 calorimeter (Table 1, entries 1 and 2). The addition of 65% HNO_3 to a 23% phenol solution in CH_3CO_2H (6%, used to increase the phenol solubility) and water (71%) was carried out in two portions (Figure 1). Essentially no reaction took place during the addition of the first HNO_3 portion (corresponding to 0.67 equiv). The small heat signal observed during this addition corresponds to the slightly exothermic dilution of the acid. A first exothermic reaction (35 kJ mol^{-1}) was observed shortly after the first addition. Once this reaction was over, the HNO_3 addition was resumed; again, the reaction did not start immediately. It was only towards the end of the second addition (2.0 equiv HNO_3 added in total) that the strongly exothermic reaction took place (170 kJ mol^{-1}; 115 °C total adiabatic temperature rise). It is important to note that despite the relatively small reaction volume (< 1 L) and the efficient cooling system of the calorimeter, a significant temperature rise occurred (55 °C). Scaling-up such a semibatch reaction would almost certainly be impracticable for safety reasons. Analysis of the final organic phase by differential scanning calorimetry (DSC) showed a small exotherm starting at 104 °C (30 J g^{-1}) followed

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Table 1: Phenol nitration in semibatch or in continuous mode (microreactor, MR).[a]

Entry	Equipment	T [°C]	HNO_3 [equiv]	CH_3CO_2H [%]	H_2O [%]	Yield [%]	Ratio **2**/**3**	Purity [wt%]	**1** [wt%]	**4** [area%]	**5** [area%]	**6** [area%]	Polymers [area%]
1	RC1	25	1.5	6	71	54	1.2	56.5	0.1	0.6	0.5	0.0	32.3
2	RC1	25	2.0	6	71	55	1.2	57.8	0.0	0.0	0.0	1.9	32.2
3	MR	35	1.5	6	71	70	1.1	71.1	0.1	0.8	0.0	0.0	18.0
4	MR	45	1.1	6	71	65	1.2	65.8	4.6	0.8	0.0	0.0	18.8
5	MR	45	1.2	6	71	68	1.2	67.4	0.6	1.6	0.0	0.0	20.4
6	MR	45	1.5	6	71	73	1.1	74.8	0.0	1.4	0.6	0.0	13.2
7	MR	45	1.8	6	71	75	1.1	79.4	0.0	1.6	0.0	0.6	9.0
8	MR	60	1.6	6	71	76	1.0	78.2	0.0	2.4	0.8	0.0	8.6
9	batch	0	2.0	0	78	30	1.2	25.3	0.0	0.0	0.0	0.0	64.7
10	batch	10	2.0	0	78	32	0.7	17.9	0.0	0.0	0.0	0.0	72.1
11	batch	20	2.0	0	78	21	0.6	12.8	0.0	0.0	0.0	0.0	77.2
12	MR	20	1.4	0	10	77	1.0	74.6	0.3	3.8	4.2	1.9	7.1
13	MR	20	2.0	0	10	69	1.0	73.9	0.4	2.3	6.8	2.7	6.6
14	MR	20	2.3	0	10	65	0.9	72.4	0.4	2.0	7.8	3.0	7.4
15	MR	5	1.7	0	10	74	0.9	77.4	0.0	2.9	3.2	0.0	6.5
16	MR	15	1.7	0	10	70	0.9	75.7	0.3	2.9	4.2	1.3	6.9
17	MR	25	1.7	0	10	70	0.9	74.5	0.3	3.1	5.5	1.9	6.6
18	MR	35	1.7	0	10	69	0.9	73.1	0.3	3.2	6.6	2.3	6.8
29	MR	45	1.7	0	10	65	0.9	70.7	0.4	2.8	7.4	2.4	8.7
20	MR	55	1.7	0	10	65	0.9	69.3	0.4	3.1	8.7	2.8	8.5

[a] The nitrated solution was analyzed by GC (quantitative results for **1**, **2** and **3**, area% for the side-products). The yield (calcd) and purity correspond to the total amount of mononitro products **2** and **3**. The water concentration does not take into account the water contained in nitric acid.

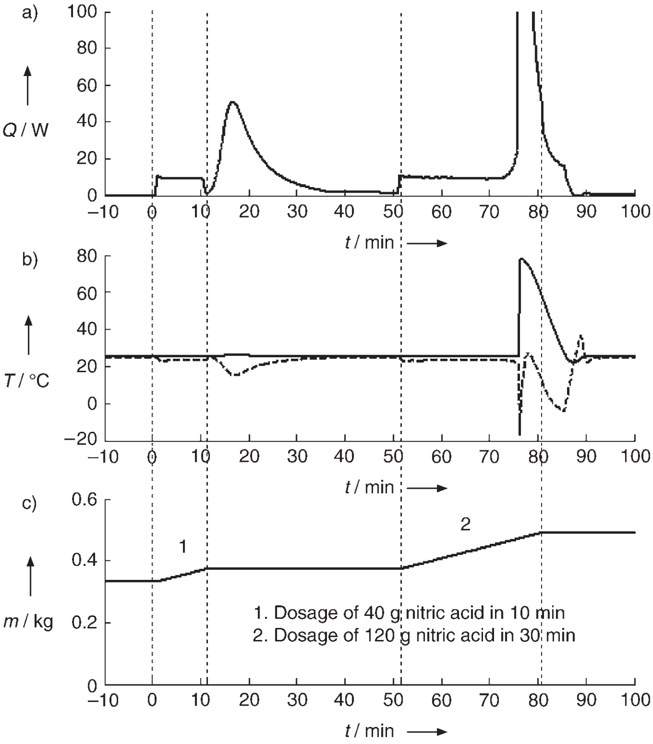

Figure 1. Semibatch nitration of phenol at 25 °C with acetic acid (Table 1, entry 2): a) heat signal (Q, positive values denote exothermic reactions); b) reaction temperature (T, ——) and temperature of the cooling system (T, -----); c) addition rate (m) versus reaction time (t).

by a large one at 185 °C (1500 J g^{-1}), which actually corresponds to a thermal runaway scenario.

A glass microreactor with a 10 × 0.5-mm channel width and 2.0 mL internal volume was next used for the nitration experiments (entries 3–8). The phenol solution (23 %) in a mixture of CH_3CO_2H (6 %) and water (71 %, feed 1) and the 65 % HNO_3 solution (feed 2) were continuously pumped through the mixer at a total flow rate of approximately 21 g min^{-1} (phenol throughput of 3.7 g min^{-1}). The split between the phenol (**1**) and the nitric acid solutions was varied between 3.9:1 and 2.3:1, which corresponds to 1.1 to 1.8 equivalents of HNO_3. The efficient cooling of the microreactor allowed safe control of the exothermic reaction. With 1.5 equivalents of HNO_3, a one-minute delay was observed at 45 °C before the start of the autocatalysis (Figure 2). The autocatalysis started immediately at a higher temperature with 1.5 equivalents of HNO_3 (entry 8), whereas at lower temperatures the autocatalysis did not start at all, was extinguished, or partially took place outside the microreactor. Similar trends were also observed on variation of the amount of HNO_3: the nitration was completed within the microreactor with 1.8 equivalents of HNO_3 (entry 7), while the reaction proved slower and occurred partially outside the reactor (residence time: 7 s) at a lower stoichiometry. One advantage of a glass microreactor is the possibility to observe the reaction as it takes place. After the start of the autocatalysis, the violent evolution of a colorless gas suggests that gaseous nitrogen dioxide (N_2O_4) is formed in the catalytic cycle. However, the true reactive species for this reaction is presumably the dissociated nitrogen dioxide radical ($NO_2^{\bullet}$) which couples with the radical cation from the phenol in a single electron-transfer mechanism.[10]

Reduced amounts of polymeric side-products, increased purities, and up to 20 % higher yields were obtained when performing the reaction continuously in a microreactor. Only

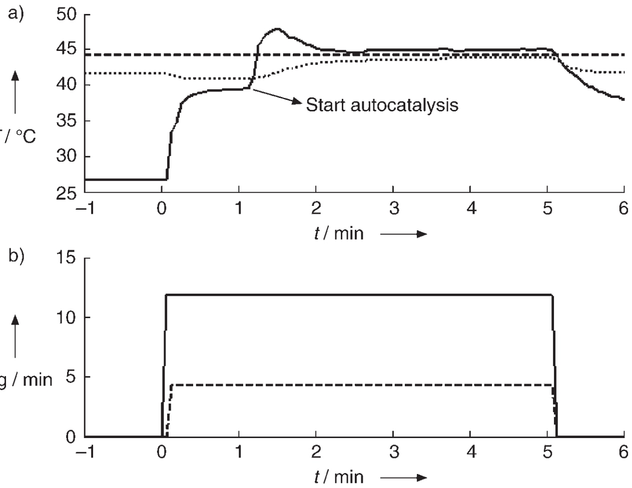

Figure 2. Phenol nitration in a microreactor at 45 °C with acetic acid (Table 1, entry 6): a) temperature of the thermal fluid inlet (*T*, -----), temperature of the thermal fluid outlet (*T*, •••••), and temperature of the reaction mixture outlet (*T*, ——); b) phenol addition rate (*F*, ——) and nitric acid addition rate (*F*, -----) versus time on stream (*t*).

about 9 % of polymers were formed when 1.6 and 1.8 equivalents of HNO_3 were used (entries 7 and 8). Lower HNO_3 stoichiometries resulted in intermediate amounts of polymers, possibly reflecting the part of the nitration which took place outside the microreactor (batch instead of flow reaction). While the *para* isomer **2** was slightly favored in batch reactions, especially at lower temperature, no significant regioselectivity was observed with the microreactor.

In a second set of experiments, phenol nitration was studied without CH_3CO_2H. For comparison purposes, the reaction was again first performed batchwise in a jacketed 100-mL reactor. Continuous addition of 65 % HNO_3 to a 24 % aqueous phenol solution was carried out at various temperatures (Figure 3). These conditions correspond to a liquid–liquid biphasic system where the phenol (**1**) is dispersed as a fine emulsion. The reactions only started after a delay of 15, 18, and 24 minutes at 20, 10, and 0 °C, respectively, as judged by the heat signal. Not surprisingly, the lower the temperature, the longer the time required to start the autocatalysis. In each case, the exotherm was such that a 50 °C temperature rise occurred. These conditions led mainly to polymer formation and only 21–32 % yield of nitrophenols **2** and **3** (entries 9–11).

The phenol nitration without CH_3CO_2H was next investigated using the microreactor. The phenol concentration was increased to 90 % (feed 1) because of the difficulty to continuously dose a liquid–liquid emulsion. The HNO_3 solution (feed 2) was first diluted with water to obtain the same concentration as in the batch experiments. Based on the good temperature control obtained with the microreactor, the concentration of the nitric acid solution was increased stepwise and commercial 65 % HNO_3 solution was finally used (entries 12–20). Thus, these experiments were performed solvent-free, except for the 10 % water used to liquefy the phenol and the water present in the nitric acid. The flow rate was reduced to about 8 $g\,min^{-1}$ (1.6:1 split, phenol throughput of 2.8 $g\,min^{-1}$). Under these concentrated conditions the autocatalysis always started spontaneously in the mixing zone of the microreactor, thus allowing safe control of the reaction. The amount of polymeric components decreased by a factor of 10 compared to batch experiments, with the yield of the mononitro products **2** and **3** increasing correspondingly. However, the amount of hydroquinone (**4**) and of dinitro compounds **5** and **6** also increased. The best yield (77 %) and purity (74.6 %) of nitrophenols **2** and **3** were obtained with 1.4 equivalents of nitric acid at 20 °C (entry 12). Some unreacted phenol remained at lower stoichiometries, presumably a consequence of HNO_3 consumption in over-nitration and oxidation reactions. In contrast to the series with acetic acid, *ortho* isomer **3** was slightly favored.

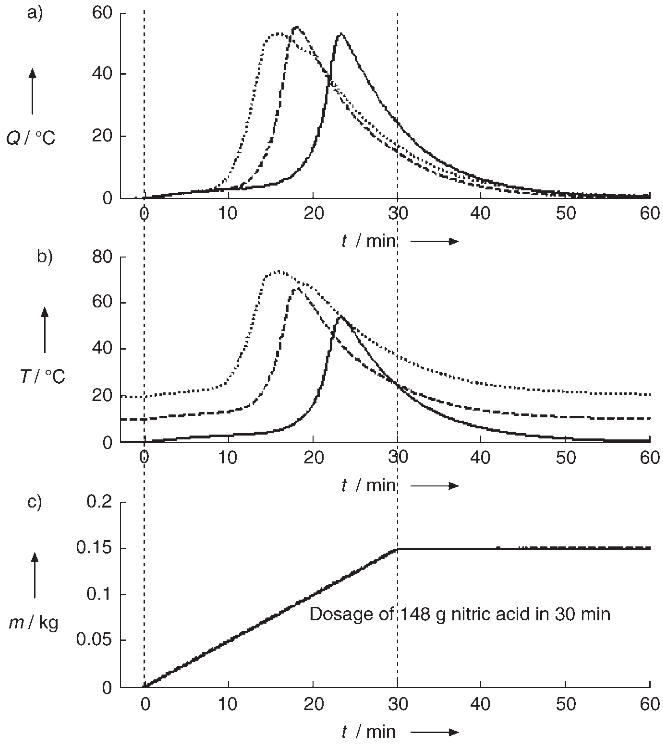

Figure 3. Batchwise phenol nitration at 0 (——), 10 (-----), and 20 °C (•••••) without acetic acid (Table 1, entries 9–11): a) heat signal (*Q*) obtained from the difference of the reactor and jacket temperatures; b) reaction temperatures (*T*); c) mass of nitric acid added (*m*) versus reaction time (*t*).

The results described above indicate that higher yields of nitrophenols are obtained when the nitration of phenol is performed in a microreactor (both with and without CH_3CO_2H). Enhanced heat exchange, good mixing properties, and very rapid radical propagation in a confined volume account for this result. In addition to the small reacting volumes present at any given time, continuous phenol nitration in a microreactor allows for better control of the exothermic reactions. Running the nitration under more concentrated conditions, almost solvent-free and without H_2SO_4 or CH_3CO_2H, is important to ensure that the nitration takes place within the microreactor. Thus, the resulting improved yields and enhanced process safety make microreactor technology attractive to operate autocatalytic reactions such as nitrations on an industrial scale.

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