4
Liquid- and Liquid–Liquid-phase Reactions – Aromatic Substitution Reactions

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4.1
Electrophilic Aromatic Substitution

Electrophilic aromatic substitution reactions are a very important class of chemical reactions that allow the introduction of substituents on to arenes by replacing a hydrogen atom covalently bonded to the aromatic ring structure by an electrophile. The most common reactions of this type are aromatic nitrations, halogenations, Friedel–Crafts alkylations and acylations, formylations, sulfonations, azo couplings and carboxylations – to name just a few.

Most of these substitution reactions have already been investigated in microstructured reactors, some of them more intensively than others. Researchers were in particular interested in finding routes to process optimization and process intensification compared with macroscopic processes by making use of the improved heat and mass transfer characteristic of microstructured reactors. In this context, microreactors turned out to be efficient tools for systematic and fast parameter screenings under conditions of continuous processing, consuming only small amounts of chemicals.

When handling strong exothermic processes or hazardous substances, safety issues also became a major driver for the use of microreactors. Finally, several academic studies can be found in the literature focusing on the analysis of mass transport and flow characteristics within microfluidic channels by using electrophilic aromatic substitutions as model reactions.

4.1.1
Friedel–Crafts Reactions

The acid-catalyzed syntheses of alkylated and acylated aromatic compounds, first discovered by Charles Friedel and James Mason Crafts in 1877, are well-known electrophilic substitution reactions finding broad application in the chemical industry.

In Friedel–Crafts alkylations, aromatic hydrogen is substituted by an alkyl group. A variety of alkylating agents (for example, olefins, alkyl halides and alcohols) can be

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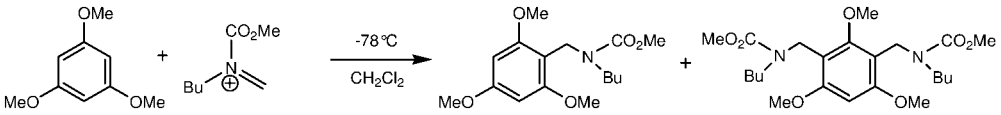
applied. In principle, all aromatic substrates (including heteroaromatic compounds) accessible to electrophilic substitution can be used. Friedel–Crafts alkylations are usually fast and exothermic reactions, in most cases carried out in the liquid phase. A common problem with Friedel–Crafts alkylations is the enhanced reactivity of the first alkylation product compared with the aromatic starting material due to the electron-donating properties of the introduced alkyl group. As a consequence, subsequent alkylation steps proceeds more readily than the first alkylation step. To overcome the problem of unavoidable dialkylations or polyalkylations, Friedel–Crafts alkylation processes are often run with a huge excess amount of the aromatic starting material (for example, by utilizing the starting material as solvent) which obviously has a negative impact on the overall process economics.

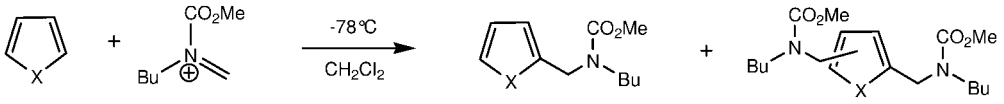
Therefore, one of the major drivers for running Friedel–Crafts alkylations in microstructured reactors is to improve the selectivity of monoalkylation products under reasonable stoichiometric conditions, in particular by achieving significantly accelerated and intensified mixing and mass transport than achievable in macroscopic processes. Moreover, it is also expected that the exothermic alkylation reactions additionally benefit from the improved heat transfer characteristics of microreactors.

Yoshida and coworkers have impressively demonstrated the benefits of using micromixers for different Friedel–Crafts alkylations [1, 2]. They described the (amino)alkylation of 1,3,5-trimethoxybenzene with *N*-acyliminium ions (a highly reactive alkylation agent generated by the so-called "cation pool" method [3]) conducted in a multilamination micromixer by mixing both reagents 1 : 1 at −78 °C (Scheme 4.1). The product solution leaving the micromixer was immediately quenched with triethylamine to avoid any subsequent reactions. The monoalkylation product was obtained with a very high selectivity whereas the amount of the dialkylation product was very low (mono:di = 96 : 4; total yield 96%). The same reaction was also conducted in a conventional batch process and in a T-shaped tube mixer of 500 µm diameter. In both cases, only poor selectivities were achieved by obtaining the monoalkylation and dialkylation products in nearly similar amounts. These comparison experiments clearly underlined the importance of very rapid and efficient micromixing to avoid any gradients of reactant concentrations. However, in the case of less reactive aromatics such as 1,3,5-trimethylbenzene, a fairly selective formation of the monoalkylation product (69%) is already obtained in batch experiments. Here, the second alkylation step is slower than the first, since protonation of the monoalkylation product decreases its reactivity [2].

Yoshida and coworkers could also show that flow rate and thus mixing efficiency and also reaction temperature have a considerable influence on the process selectivity [1, 2]. As expected, with increasing temperature the yield of the monoalkylation



Scheme 4.1 Friedel–Crafts alkylation of 1,3,5-trimethoxybenzene.

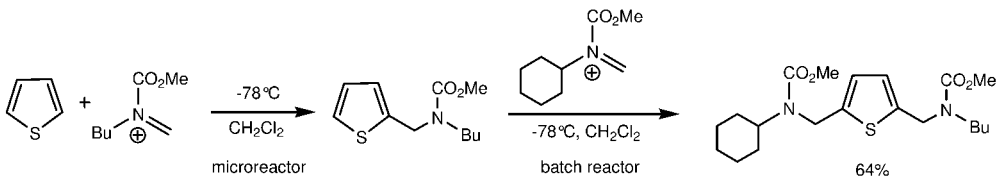


Scheme 4.2 Friedel–Crafts alkylation of thiophene (X=S), furan (X=O) and *N*-methylpyrrole (X=N−Me).

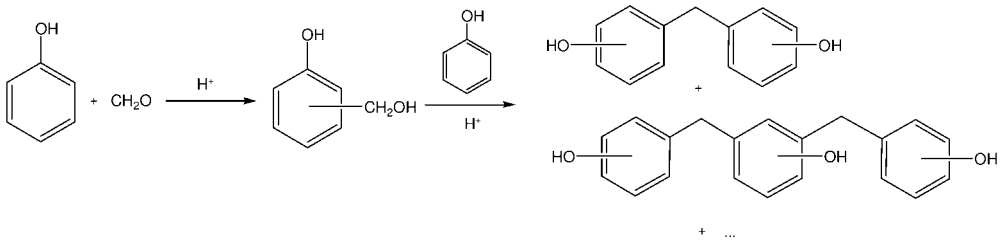
product dropped drastically whereas the yield of the dialkylation product increased. Hence precise temperature control, as can be provided by microstructured reactors, is essential for the entire process.

In further (amino)alkylation experiments employing different *N*-acyliminium ions as alkylation agents, the same group confirmed the huge potential of microstructured reactors for overcoming the problems of di- and polyalkylation in Friedel–Crafts reactions. For example, heteroaromatic compounds such as thiophene, furan and *N*-methylpyrrole could be converted with high selectivity to the corresponding monoalkylation products (Scheme 4.2). Moreover, even sequential alkylation reactions allowing subsequent introduction of two different alkyl groups into one aromatic ring structure were successfully demonstrated. A monoalkylation product of thiophene, which was obtained in a microreaction process with high selectivity, was directly alkylated with a different *N*-acyliminium ion within a batch reactor to obtain the disubstituted thiophene derivative (Scheme 4.3) [1].

In a recent study, the Friedel–Crafts reaction of phenol and formaldehyde was reported to improve the selectivity of the final bisphenol product [4, 5]. In the first alkylation step of this process, hydroxybenzyl alcohol (HBA) is formed, which immediately proceeds to react with phenol, forming bisphenol F, an important material for the production of special epoxy resins (Scheme 4.4). Unfortunately, higher order condensates (trisphenols etc.) are also typically formed due to unwanted consecutive reactions of HBA with bisphenol, leading to worse material properties of the final product such as higher viscosities [5]. As a consequence, in commercial processes the molar ratio of phenol to formaldehyde is fixed at very high values of 30–40 to avoid over-reaction. However, in the microreactor study conducted, reactions were carried out in special micromixers to suppress the consecutive over-reaction to trisphenols and other undesired products by providing fast and efficient mixing performance. Highest bisphenol selectivities of up to 90% were obtained using a so-called K–M micromixer [6], developed for instantaneous mixing on basis of a center-collision design. In comparison with the commercial process, high bisphenol selectivities were achieved even at low phenol:formaldehyde ratios. Hence, the phenol:HBA ratio could be significantly reduced, by 50% [4, 5].



Scheme 4.3 Sequential alkylation of thiophene.



Scheme 4.4 Scheme of bis- and trisphenol synthesis via initial Friedel–Crafts reaction.

For the sake of completeness, it should be mentioned that the use of microreactors and miniaturized flow reactors for the Friedel–Crafts alkylation of aromatic compounds has also been documented by other authors. For example, the Friedel–Crafts alkylation of benzene with cyclohexene using H_2SO_4 as a catalyst has been described [7]. The reaction was conducted in a static micromixer giving 58% cyclohexylbenzene. Poliakoff and coworkers have carried out the Friedel–Crafts alkylation of anisole with *n*-propanol in supercritical CO_2, testing five different Brønsted solid acid catalysts under systematic variation of process conditions such as temperature and pressure [8].

The methylation of anonymized substituted aromatics using tertiary methylamine was described by Woerz [9]. The methylation was conducted in a microreactor at 0 °C and was completed within 6 s, providing a yield of 95%. A similar yield was also obtained in a semi-batch process. However, in the macroscopic process the reaction time is significantly longer (15 min) and the temperature has to be kept at −70 °C.

Finally, Friedel–Crafts acylation reactions are also mentioned in the literature. For example, the acid catalyzed acylation of anisole with benzofuran conducted in a static micromixer has been briefly described [10].

4.1.2 Nitrations

Nitration reactions are among the basic reactions used in chemical synthesis, and have remained indispensable for the synthesis of pharmaceuticals, agricultural chemicals, pigments, explosives and precursors for polymers.

The majority of nitrations give off considerable amounts of heat. The highly exothermic nature of these reactions – sometimes with explosive potential – along with the acidic corrosivity of the nitrating agent, makes nitration processes potentially very hazardous. Marked warming can also cause large numbers of secondary, consecutive and decomposition reactions to accompany nitration processes. The occasional result is the formation of unwanted by-products such as higher nitrated compounds or oxidation products. As a consequence, exothermic nitrations exhibit restrictions with respect to yield and purity of target products.

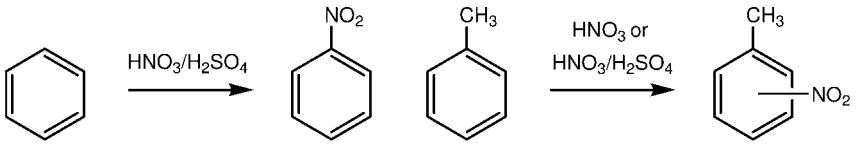
Nitrations of aromatic compounds are usually electrophilic substitution reactions which require the acid-catalyzed formation of nitronium ions (NO_2^+) as reactive species, typically realized by employing a mixture of sulfuric acid and nitric acid [11]. The purpose of using sulfuric acid is not only to donate protons to the nitric acid, thus forming nitronium ions, but also to bind water that is formed during the reaction.

Another effective dehydrating agent is anhydrous acetic acid. In addition to an electrophilic attack of the aromatic ring structure, radical mechanisms are also well known, involving a single electron-transfer reaction. A popular example is the nitration of phenol using nitric acid [11].

The use of microreactors for performing aromatic nitration reactions has been described by several authors [12–24]. The main drivers in most cases were to find routes to overcome restrictions in heat and mass transfer resulting in improved process performance and safety.

For example, the nitration of benzene and other aromatic compounds is often strongly limited by the mass transfer performance within the reactor that is used. In particular in the case of biphasic nitration reactions, a good mass transfer performance is essential to suppress the formation of unwanted by-products such as higher nitrated compounds (e.g. dinitro and trinitro compounds) or oxidation products. Therefore, the use of microreactors offers a good possibility to overcome common restrictions in mass transport and thus achieve higher yields and selectivities in nitration reactions.

Burns and Ramshaw [12] were among the first to describe the use of microreactors for the isothermal nitration of aromatic compounds (Scheme 4.5). They chose the nitration of benzene as a first test reaction to study the concept of enhancing diffusion in a capillary slug flow microreactor applied for the reaction of two immiscible liquid phases [in this case benzene and aqueous nitrating acid (H_2SO_4 + HNO_3)]. A high sulfuric acid concentration was used to ensure fast nitration kinetics and promote a mass transfer-limited regime. The reaction was performed in stainless-steel capillaries of different width (127 and 254 μm) at temperatures between 60 and 90 °C (in later studies, PTFE capillary microreactors were used to avoid corrosion problems within the setup). Relative high conversion rates achieving up to 50% nitrobenzene were obtained for residence times of only a few seconds; 94% conversion was obtained in 24 s while maintaining low by-product levels. As expected, the narrower capillary reactor yielded significantly higher conversion than the broader reactor due to smaller diffusion lengths [12–14]. An enhancement of reaction rate was also observed when higher flow rates were applied, leading to increased mixing [14]. In general, similar results were obtained for the biphasic nitration of toluene in PTFE capillaries with variation of temperature and acid strength. Results for both benzene and toluene nitration indicated reaction rates in the range 1–8 min^{-1} that can be provided from a capillary slug-flow reactor depending on the process conditions applied. Consequently, residence times for complete conversion were estimated to be in the range 10–60 s [14].

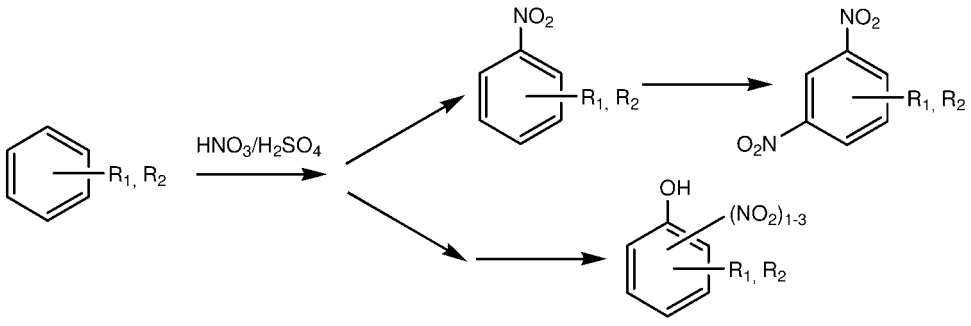


Scheme 4.5 Mononitration of benzene and toluene [12–14, 16–18].

The capillary microreactor concept was also chosen by Dummann *et al.* to investigate the liquid–liquid nitration of an anonymized disubstituted single ring aromatic compound [15]. Within a PTFE capillary, a well–defined pattern of alternating plugs of the two phases (mixed acid and aromatic compound) was formed, giving a constant and uniform specific surface area for mass transfer between the two phases. Mass transfer experiments were conducted at different flow rates but identical residence times. The influence of mass transfer on the formation of the mononitrated main product, dinitrated by-products from sequential reactions and phenolic by-products from parallel reactions was investigated (Scheme 4.6). The authors observed an increase in conversion with increasing flow rate, which clearly indicated that the reaction is strongly mass transfer limited. The amount of phenolic by-products also increased with increasing flow rate whereas the amount of dinitrated products decreased. Simulations using a mathematical model describing interphase mass transfer and homogeneous chemical reactions showed increasing mass transfer coefficients at higher flow rates, suggesting that the mass transfer between the two phases is enhanced by the flow rate, providing higher conversion and larger amounts of parallel by-products [15]. Additional CFD calculations indicated that the enhancement of mass transfer is a result of an internal circulation flow within the plugs (Figure 4.1). As a consequence, mixing inside the plug is also enhanced, yielding decreasing amounts of sequential by-products [15].

An alternative type of processing the biphasic nitration of benzene was described by Haswell and coworkers, employing a borosilicate glass microreactor [16]. Benzene was introduced and mobilized as a microemulsion by electroosmotic flow (EOF) while the nitrating agent (mixed acid) underwent electrophoretic-induced mobility. Sodium dodecyl sulfate was used as surfactant and butan-1-ol as co-surfactant to generate oil-in-water microemulsions. The benzene microemulsion was run as the main reagent stream treated by segmented injections of mixed acid, followed by a 60 s stopped-flow reaction time. The products formed (mono-, di- and trinitrobenzene) were found to be dependent on the applied electric field, injection time and frequency. For mononitrobenzene a maximum yield of 65% was achieved.

Antes *et al.* have shown that the nitration of toluene can be also conducted in microreactors in the absence of sulfuric acid by using fuming nitric acid only [17].



Scheme 4.6 Formation of dinitrated by-products from sequential reactions and phenolic by-products from parallel reactions.

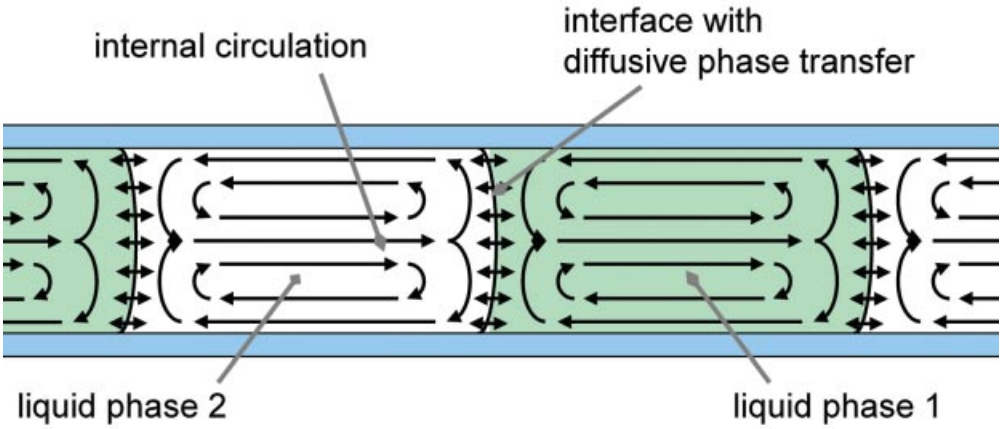
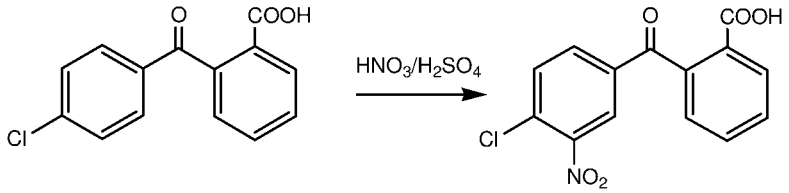


Figure 4.1 Scheme of internal circulation generated within immiscible slug (or plug) flow.

Since the purification and regeneration of waste nitrating acid are nowadays one of the major expense factors in industrial nitration processes, new routes towards cost-saving nitration processes were sought. To enhance heat and mass transfer, a so-called "split-and-recombine" microreactor made of silicon was used, providing high mixing efficiencies. The highest yield for mononitrotoluenes (89–92%) were obtained during an isoperibolic processing at $-10\,^{\circ}C$, a molar ratio of 2.56 (HNO_3:toluene) and a residence time of 3 s. Moreover, in the microreaction process the selectivity of *para*-substituted mononitrotoluene could be significantly increased up to 43.5% [17].

Recently, further studies on the nitration of toluene using concentrated nitric acid have been reported by Halder *et al.* [18]. They used a T-mixer coupled to a subsequent tube microreactor, packed with ZSM-5 catalyst and glass beads. In macroscopic nitration processes ZSM-5 is used as a solid acid catalyst to increase the selectivity of *p*-nitrotoluene. However, they found that the isomeric distribution using solid acids packed in microreactors was very similar to what is obtained in mixed-acid nitrations. A very rapid reaction of toluene with concentrated nitric acid was already observed at room temperature in the absence of sulfuric acid or solid acid catalysts due to self-protonation of the nitric acid forming nitronium ions. In contrast to the results described by Antes *et al.* [17], no changes in the isomeric distribution of mononitrotoluenes were observed, which might be explained by the less intensive mixing achievable in the tube microreactor used by Halder *et al.* [18] in comparison with the "split-and-recombine" microreactor used by Antes *et al.* [17] providing superior mass transfer characteristics.

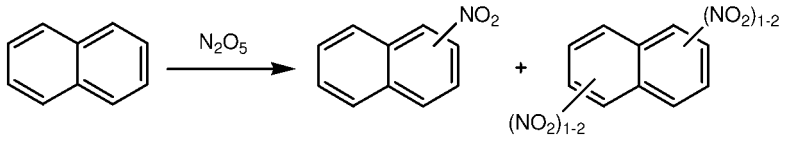
Slight changes in the internal geometries of microreactors can have an impact on the conversion and product spectrum of mixing-sensitive nitrations, as was shown for the regioselective mononitration of 2-(4-chlorobenzoyl)benzoic acid to 2-(4-chloro-3-nitrobenzoyl)benzoic acid, a precursor for the synthesis of a pharmaceutical agent (Scheme 4.7) [19]. The single-phase reaction, which is hardly described in literature, is conducted by dosing HNO_3 to a solution of 2-(4-chlorobenzoyl)benzoic acid in concentrated sulfuric acid.



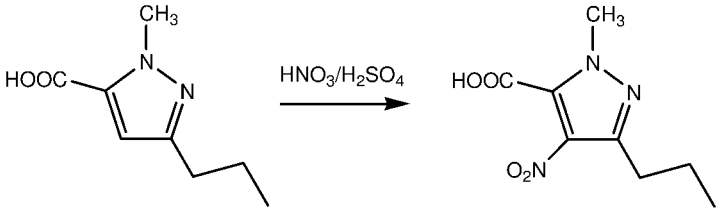
Scheme 4.7 Regioselective mono-nitration of 2-(4-chlorobenzoyl)benzoic acid.

The potential of microreaction processes to influence isomeric product distributions was demonstrated by Loebbecke *et al.* [20]. They reported on the nitration of naphthalene at moderate temperatures in different types of microreactors to ensure isothermal processing and precise control of residence time (Scheme 4.8). A deliberate synthesis of either mono- or dinitro-substituted naphthalene with high selectivities was achieved, in contrast to a broad product spectrum obtained under macroscopic batch conditions. In particular, isomeric ratios of 1- to 2-mononitronaphthalene and also 1,5- to 1,8-dinitronaphthalene could be significantly increased compared with batch processes.

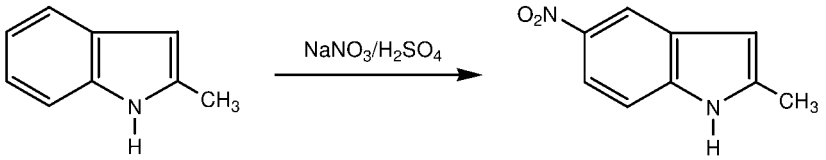
In macroscopic nitrations, safety issues often require deceleration of the exothermic processes, for instance by working at reduced temperatures, low concentrations or slow dosing rates. Microreactors have been used to overcome these limitations by shifting the process parameters towards more intensified conditions or so-called "new process windows". For example, Taghavi-Moghadam and coworkers reported on the microreactor-based nitration of a five-membered aromatic ring structure, namely pyrazole-5-carboxylic acid (Scheme 4.9), a key intermediate in the synthesis of the life-style drug Sildenafil [21]. The mononitration with mixed acid is a strongly exothermic process releasing $\sim$250 kJ mol^{-1}. To avoid decarboxylation of the nitropyrazole product, the process temperature has to be kept below 100 °C. In batch processes, safe operation is only possible when the nitrating agent is added slowly at 50 °C in small portions, resulting in process times of $\sim$10 h. Nitropyrazole is then



Scheme 4.8 Nitration of naphthalene.



Scheme 4.9 Mononitration of pyrazole-5-carboxylic acid.



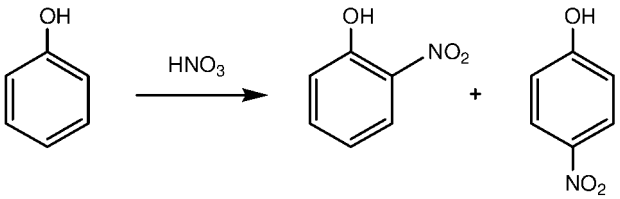
Scheme 4.10 Mononitration of 2-methylindole.

obtained with an overall yield of 75%. The synthesis was transferred to a commercial microreaction system providing a residence time of 35 min. The reaction temperature was deliberately increased in comparison with the batch process and kept at 90 °C. Nitropyrazole was obtained in 73% yield without any further optimization. Although the optimized batch process nowadays provides 96% yield, a significant acceleration of the process under safe process conditions could be achieved in the microreaction process.

Taghavi-Moghadam and coworkers also reported on the exothermic mononitration of 2-methylindole (Scheme 4.10) [21]. Under batch conditions, a solution of $NaNO_3$ in H_2SO_4 has to be added slowly to the starting material in order to keep the temperature at 0 °C (yield 80%). The reaction was carried out in a commercial microreaction system under isothermal conditions at 3 °C and a reduced residence time of only 0.8 min. The product was obtained with an overall yield of 70% without any further optimization. Again, a drastic process acceleration was achieved, indicating a high reaction rate.

The far better heat transfer characteristics of microreactors, which allow safe operation under strongly exothermic process conditions, was also a major driver for the investigation of the autocatalytic nitration of phenol by HNO_3 (Scheme 4.11), as reported by Ducry and Roberge [22]. In contrast to the batch process, the reaction was performed under nearly solvent-free conditions, except for 10% water used to liquefy phenol and the water present in the nitric acid. The autocatalysis started spontaneously in the mixing zone of the glass microreactor under safe control of the reaction progress. Compared with the batch experiments, the amount of unwanted polymeric by-products was drastically reduced by a factor of 10 while the yield of *o*- and *p*-nitrophenol increased correspondingly up to 77% (obtained with 1.4 equiv. of nitric acid at 20 °C).

Microreactors have also been used to investigate aromatic nitrations under less common process conditions such as adiabatic conditions [23] or by applying alternative nitrating agents such as dissolved dinitrogen pentoxide (N_2O_5) [17, 20]



Scheme 4.11 Autocatalytic mononitration of phenol.

or acetyl nitrate [21, 24]. In contrast to mixed acid, N_2O_5 permits the nitration of acid-sensitive substances and thus offers access to higher levels of reactivity and selectivity. Acetyl nitrate is generated *in situ* from neat nitric acid and acetic anhydride. As a potentially explosive material, it finds no broad application in the chemical industry. However, the use of microreactors allows the safe handling of acetyl nitrate due to the small hold-ups and low *in situ* concentrations in the process. Exemplary results have been reported [21] for the mononitration of toluene, obtaining slight differences in the isomer distribution compared with conventional toluene nitration processes applying mixed acids. The synthesis of 3-methyl-4-amino-5-nitrobenzoic acid by using mixtures of acetic anhydride and fuming nitric acid has been also described [24]. In this way, the formation of the unwanted 6-nitro isomer could be successfully reduced to below 1% – in contrast to other nitrating agents. As a consequence, no further product purification was required, leading to significant economic savings.

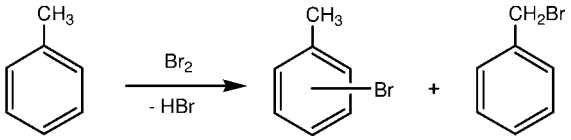
4.1.3 Brominations and Iodinations

Halogenations of aromatic compounds have been investigated using different types of microstructured reactors. A good overview comprising the gas–liquid processes of fluorinations and chlorinations and also liquid-phase brominations has been presented [26]. However, in this section only liquid-phase brominations and iodinations of aromatic compounds are considered.

In macroscopic chemistry, the experimental procedures for the bromination of aromatic compounds depend greatly on the nature and reactivity of the starting material. Activated aromatics such as phenol and aniline can be brominated to the tri- and tetrabrominated derivatives by using dilute aqueous solutions of bromine, whereas a controlled monobromination is very challenging and often requires cryogenic conditions. On the other hand, thermally controlled brominations of less activated aromatics such as toluene are rather sluggish reactions. They often require photoinitiation and the use of Lewis acids as catalysts.

To overcome current limitations and restrictions in the monobromination of aromatic compounds, microstructured reactors were tested by Loeb and coworkers [26–28] under intensified process conditions. Due to the improved safety features of microreactors, parameter screenings were extended to elevated temperatures and pressures. Moreover, undiluted elemental bromine was used as bromination agent, discarding the use of catalysts and radiation. In particular, the competitions between (a) single versus multiple substitutions and (b) core versus side-chain substitutions were investigated.

Bromination of toluene was investigated in a standard micromixer–tube setup using either a triangular interdigital micromixer made of glass or a caterpillar micromixer made of steel. The molar ratio of bromine to toluene was set to 1.0. The competing formation of benzyl bromide and the three monobromotoluene isomers (Scheme 4.12) was analyzed in a wide temperature range from 0 to 120 °C. As expected for less activated aromatics, conversion increased with temperature,

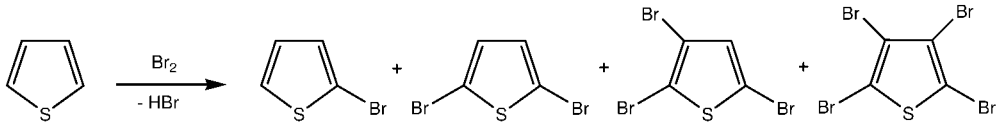


Scheme 4.12 Bromination of toluene: competition between core and side-chain substitution.

reaching full conversion at 80–100 °C depending on the flow rate and residence time conditions. Only low selectivities of benzyl bromide were obtained, which further decreased with increase in temperature. At 80 °C, only core substituted monobromotoluene was obtained and no multiple bromination products were detected at any time. Although the reaction was started as a liquid-phase process, the phase behavior in the microreactor is expected to become complex due to the release of gaseous HBr as reaction product and gaseous Br_2 when the temperature is above the boiling point of bromine. Depending on the phase conditions, residence times were estimated to be in the range from 3 s (gas/liquid) up to 4 min (liquid phase). However, it was clearly shown that the use of microstructured reactors provides access to a fast and selectivity-controlled monobromination of toluene under safe and solvent-free conditions [26–28].

In contrast to toluene, the bromination of heteroaromatic compounds such as thiophene (Scheme 4.13) is very fast even at low temperatures of 0 °C or below. Loeb and coworkers investigated the bromination of thiophene with regard to the control of multiple bromination employing a similar setup to that used for the bromination of toluene [26–28]. At a fixed bromine:thiophene molar ratio of 1.0 the temperature was varied between 0 and 60 °C, showing nearly no changes in the 1 : 1 ratio between one- and two-fold brominated products. The amount of three-fold substituted thiophene increased only slowly at elevated temperatures. At a fixed temperature of 50 °C, the authors varied systematically the molar ratio of bromine to thiophene from 1.0 to 5.0. The resultant product distribution obtained under conditions of complete thiophene conversion is shown in Figure 4.2. For 2,5-dibromothiophene (a relevant compound for the synthesis of OLED materials), a selectivity of up to 80% could be achieved at a bromine:thiophene molar ratio of 2.0.

Finally, Loeb and coworkers investigated the bromination of *m*-nitrotoluene at elevated temperatures (170–230 °C) and pressures (up to 15 bar) to synthesize the corresponding benzyl bromide via side-chain bromination [26–28] (which, of course, is not electrophilic aromatic substitution in the true sense, as predominantly regarded in this chapter). In comparison with the macroscopic process, the reaction could be drastically accelerated in microreactors, thus enhancing the space–time yield by a factor of 18. A further process intensification was achieved by running the



Scheme 4.13 Bromination of thiophene: competition between single and multiple substitution.

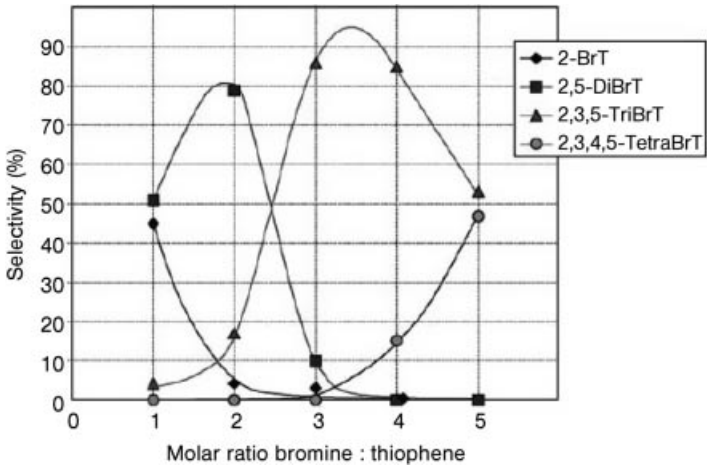


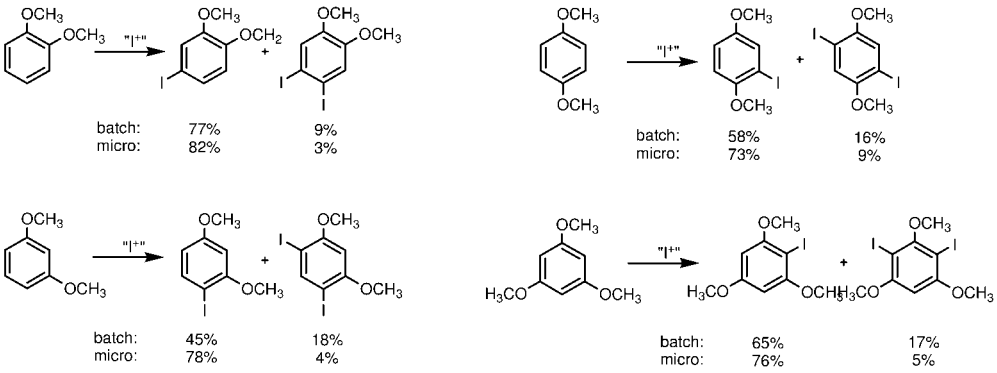
Figure 4.2 Bromination of thiophene: product distribution at 50 °C. Taken from [26].

bromination at an elevated pressure of 15 bar. The authors reported an increased turnover of nitrotoluene from ~40% to 95% [28].

In summary, it can be said that the use of microstructured reactors allow significantly acceleration and intensification of aromatic bromination reactions.

For the sake of completeness, it should be mentioned that a further microreactor-based bromination reaction has also been briefly described [29]. The reaction of 1,3,5-trimethylbenzene with elemental bromine gave the monobrominated product in 73% yield.

Apart from brominations, iodinations of aromatic compounds have also been investigated in micromixers to overcome the problem of monoiodination/diiodination selectivity [30]. Yoshida and coworkers [30] described the selective monoiodination of di- and trimethoxybenzene (Scheme 4.14) using electrochemically generated "I^+" as an iodination agent. "I^+" was obtained via electrochemical oxidation of elemental iodine in acetonitrile giving $CH_3CN–I^+$ or $(CH_3CN)_2–I^+$ species [31]



Scheme 4.14 Iodination of di- and trimethoxybenzenes: competition between mono- and disubstitution.

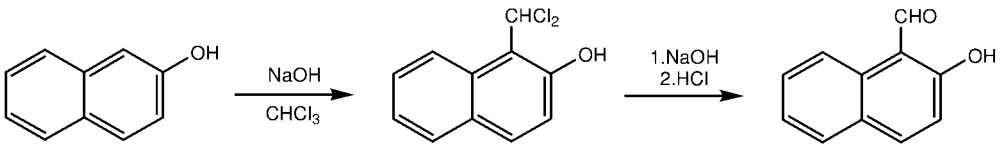
that were used in the subsequent iodination reaction. In a batch experiment, 1,3-dimethoxybenzene was iodinated with "I^+" at 0 °C, obtaining the monoiodo compound in 45% yield and the diiodo product in 18% yield. Although the monoiodo compound is less reactive than the starting material due to the electron-withdrawing properties of its iodo substituent, the diiodo product is formed in batch processes as a result of inhomogeneous mixing and concentration gradients. Running the reaction in a multilamination micromixer, the monoiodo product was obtained in 78% yield, whereas the diiodo product was obtained in only 4% yield. Similar results were obtained for the iodination of 1,2- and 1,4-dimethoxybenzene and also for the iodination of 1,3,5-trimethoxybenzene. In all cases fast and efficient mixing in micromixers gave rise to increased selectivities of the monoiodo product [30].

4.1.4
Other Electrophilic Aromatic Substitutions

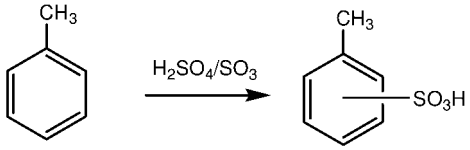
Several other classes of electrophilic aromatic substitution reactions have occasionally been investigated in microreactors. Some exemplary studies are summarized in this section.

Iles *et al.* described the *Reimer–Tiemann formylation* of β-naphthol (Scheme 4.15) [32]. Reimer–Tiemann reactions are strongly exothermic reactions utilized for the formylation of activated aromatic ring structures such as phenols and pyrroles (other formylation reactions conducted in microreactors such as the Vilsmeier reaction are more generally described in the patent literature [33]). Since the Reimer–Tiemann reaction requires a very precise temperature control during the entire course of reaction, the authors developed a special type of glass microreactor comprising additional microchannels near the reaction channels, which were filled with temperature-sensitive thermochromic liquid crystals (TLCs). Internal thermal conditions were monitored in real time using reflectance spectra of the TLCs. Thin-film resistive elements were incorporated into the microreactor as a means of heating the microfluidic channels. Although the bulk yields of 10–20% could not be improved in the microfluidic process, the temperature dependence of yield between 50 and 75 °C could be analyzed in detail.

Sulfonations are a further important type of electrophilic substitution reaction. However, only very few examples can be found in the literature describing the use of microstructured reactors for the strongly exothermic liquid-phase sulfonation of aromatics (sulfonation of toluene with gaseous SO_3 was described by Jaehnisch *et al.* [34]). Burns and Ramshaw [25, 35] claimed that their concept of performing liquid/liquid nitration reactions in a slug-flow capillary-microreactor can be also



Scheme 4.15 Reimer–Tiemann formylation of β-naphthol.



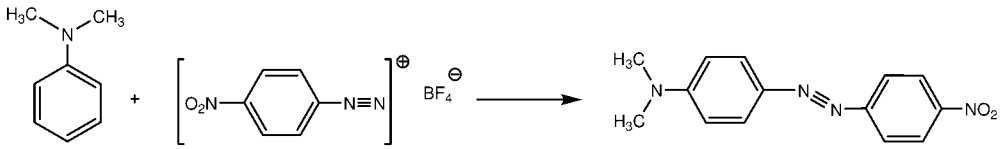
Scheme 4.16 Sulfonation of toluene.

applied to the sulfonation of an aromatic compound using sulfuric acid as the sulfonating agent. The aromatic compound is slowly consumed in the reaction yielding a single aqueous phase. Loebbecke *et al.* described briefly the continuous sulfonation of toluene (Scheme 4.16) with oleum carried out in a modular microreaction system at 80 °C to achieve high *para* selectivities under thermodynamic control [36]. A 100% conversion of toluene and 93% selectivity for *p*-toluenesulfonic acid were achieved after instantaneous quenching of the reaction mixture to 20 °C in a subsequent micromixer. In comparison with laboratory batch experiments, an increase in *para* selectivity of ~15% was achieved.

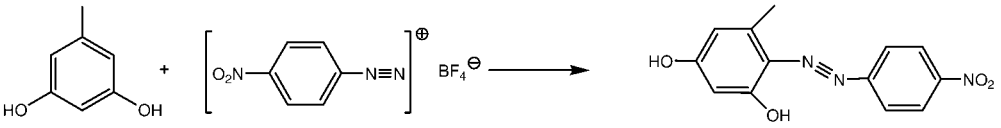
Azo couplings are the most widely used industrial reactions in the production of dyes and pigments. Aromatic diazonium ions act as electrophiles in coupling reactions with activated aromatics such as anilines and phenols. Usually, the substitution occurs at the *para* position; if this position is already occupied, the *ortho* position is favored.

A particular challenge in azo couplings is the hazardous potential of diazonium salts, which tend to undergo abrupt decomposition or even explosion when exposed to light, heat or mechanical impact. Therefore, a major driver for using microreactors is to ensure safe processing of potentially hazardous azo couplings.

In 1997, Harrison and coworkers reported on the synthesis of an azobenzene compound in microfluidic channels [37] for the purpose of combinatorial synthesis. The azo coupling of *N*,*N*-dimethylaniline and 4-nitrobenzene diazonium tetrafluoroborate (Scheme 4.17) was carried out in a Pyrex microreactor driven by electroosmotic flow. A few years later, Hisamoto *et al.* described a phase transfer diazo coupling reaction carried out in a microfluidic chip [38]. By providing a huge liquid–liquid interface between a solution of 5-methylresorcinol dissolved in ethyl acetate and an aqueous solution of 4-nitrobenzenediazonium tetrafluoroborate (Scheme 4.18), 100% conversion within a 2.3 s residence time was achieved. In contrast to macroscale experiments, the reaction could be accelerated and the formation of unwanted precipitates and bisazo side products was successfully suppressed.



Scheme 4.17 Azo coupling of *N*,*N*-dimethylaniline and 4-nitrobenzenediazonium tetrafluoroborate.



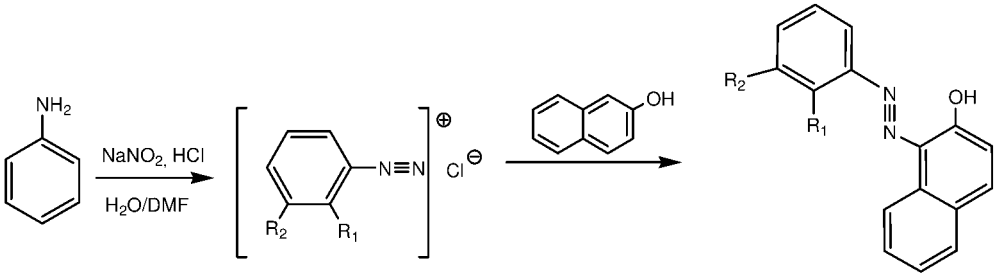
Scheme 4.18 Azo coupling of 5-methylresorcinol and 4-nitrobenzenediazonium tetrafluoroborate.

Later, de Mello and coworkers described the two-step syntheses of three different azo dyes in a pressure-driven microreactor made of glass [39]. They integrated both reaction steps (generation of the diazonium salt and its subsequent *in situ* reaction to the azo dyes) into one microfluidic reactor design. The diazonium salt was synthesized by the reaction of an arylamine with sodium nitrite in aqueous DMF. After passing a residence time microchannel to allow complete conversion, the dissolved diazonium salt was mixed with a basic solution of β-naphthol to form the corresponding azo dye with yields up to 52% (Scheme 4.19).

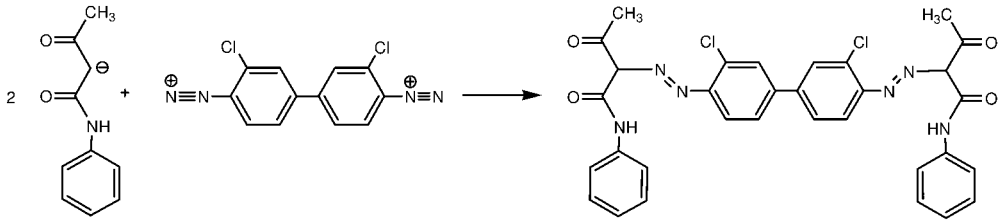
The application of microreaction technology for the industrial production of red and yellow azo pigments in the pilot-scale range was demonstrated by the company Clariant [40, 41]. The azo pigments produced exhibited improved color properties compared with the corresponding batch process. Although the details of the diazotization chemistry were kept undisclosed, the importance of mixing efficiency in the process was clearly demonstrated, leading to the concept of numbering-up of microfluidic structures instead of scale-up to achieve greater throughput of $30\,L\,h^{-1}$ while maintaining dye qualities.

Improved properties of the azo pigment Yellow 12 were also achieved in a micromixer-based azo coupling process (Scheme 4.20), providing a smaller pigment size distribution [42]. Compared with the corresponding commercially available standard, the glossiness of Yellow 12 was increased by 73% and the transparency by 66% while maintaining the tinctorial power.

Recently, Koehler and coworkers reported on various azo couplings of 2-naphthol and cresol novolaks (to form polymeric azo dyes) carried out in a microfluidic segmented flow system [43]. The generation and transport of the fluid segments were supported by the addition of a surfactant. Since fluid segments represent isolated reaction volumes of 0.05–1.00 μL, the segmented flow technique allows systematic



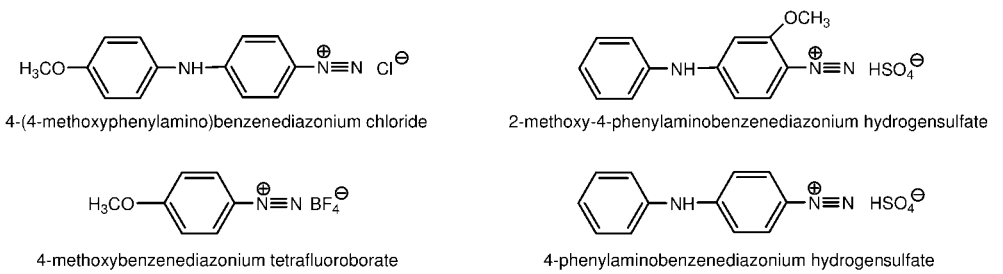
Scheme 4.19 Synthesis of the azo dyes 1-(phenylazo)-2-naphthol (R_1=H, R_2=H), 1-(2-methylphenylazo)-2-naphthol (R_1=CH_3, R_2=H) and 1-(3-methylphenylazo)-2-naphthol (R_1=H, R_2=CH_3).



Scheme 4.20 Synthesis of the azo dye Yellow 12.

variation of reagents to generate substance libraries of azo dyes. A double-injector microreactor was used to inject directly solutions of four different diazonium salts (Scheme 4.21) into moving fluid segments containing the corresponding coupling compounds. The azo couplings were conducted at room temperature without active cooling, since reaction in the small fluid segments is faster than the decomposition of the dissolved diazonium salts. The azo dye formation was monitored with a microscope video system and each reaction compartment was spectroscopically characterized on-line.

The final example of electrophilic aromatic substitutions discussed in this chapter is the *Kolbe–Schmitt reaction*, which was intensively investigated by Hessel and coworkers [44, 45]. In general, Kolbe–Schmitt reactions are base-promoted carboxylation reactions of phenols, introducing a carboxylic group in *ortho* position to the hydroxyl group. Kolbe–Schmitt reactions are typically applied for the synthesis of aromatic hydroxy acids, the most popular example being the synthesis of salicylic acid and its derivatives. Microreactors were used to intensify Kolbe–Schmitt processes by deliberately shifting the process conditions towards high-temperature/pressure regimes. The combination of isothermal processing, precise control of residence time and steep heating/cooling gradients allow reactions to be run in microreactors far above the temperature limits known from macroscopic batch conditions. Hessel *et al.* [44] reported on the aqueous Kolbe–Schmitt conversion of resorcinol (1,3-dihydroxybenzene) to 2,4-dihydroxybenzoic acid in a microreactor rig at high temperatures up to 220 °C and high pressures up to 74 bar (Scheme 4.22). $KHCO_3$ was used as carboxylation agent. In comparison with the macroscopic laboratory process, the reaction time was reduced from ~2 h to less than 1 min, thus increasing the space–time yield by a maximum factor of 440. The maximum yield was roughly 45%



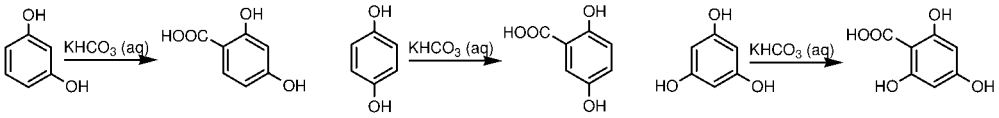
4-(4-methoxyphenylamino)benzenediazonium chloride

2-methoxy-4-phenylaminobenzenediazonium hydrogensulfate

4-methoxybenzenediazonium tetrafluoroborate

4-phenylaminobenzenediazonium hydrogensulfate

Scheme 4.21 Diazonium salts used for azo couplings of 2-naphthol and cresol novolaks [43].



Scheme 4.22 Kolbe–Schmitt reactions of di- and trihydroxybenzenes.

and thus similar to values obtained in macroscopic processes. Later, the authors extended their studies to the aqueous Kolbe–Schmitt conversion of hydroquinone (1,4-dihydroxybenzene) and phloroglucinol (1,3,5-trihydroxybenzene) [45] (Scheme 4.22). Whereas the synthesis of 2,5-dihydroxybenzoic acid from hydroquinone gave only poor yields, a relatively high yield of 50% was obtained for the synthesis of 2,4,6-trihydroxybenzoic acid from phloroglucinol, which is about 20% higher than in laboratory batch synthesis. Moreover, the reaction time could be drastically reduced again in the microreaction process, from 2 h to less than 1 min. Since the acid product tends to undergo thermally induced decarboxylation (forming phloroglucinol again), the maximum process temperature was limited to 130 °C.

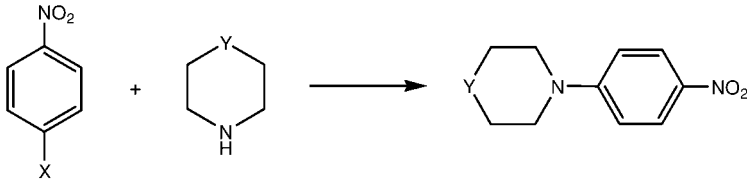
4.2
Nucleophilic Aromatic Substitution

In nucleophilic aromatic substitutions a nucleophile replaces a good leaving group such as a halide (F, Cl, Br or I) covalently bonded to an aromatic ring. Usually, an additional electron-withdrawing substituent such as a nitro group is required in an *ortho* or *para* position to the leaving group to allow the nucleophilic attack on a carbon of the aromatic ring (S_NAr addition–elimination mechanism). The reaction proceeds more easily according to the number of electron-withdrawing substituents bonded to the aromatic compound.

In addition to the S_NAr mechanism, several other mechanisms are known for nucleophilic aromatic substitutions. For example, an S_N1 mechanism is relevant for nucleophilic substitution reactions which encounter aromatic diazonium salts. Radical–nucleophilic aromatic substitutions ($S_{RN}1$) are known in reactions where no electron-withdrawing group is available, whereas a mechanism via a benzyne intermediate is of relevance for substitutions employing NH_2^- as a nucleophile.

However, in comparison with the variety of electrophilic aromatic substitutions, the number of nucleophilic aromatic substitutions is relatively small; many applications can be found in the preparation of biologically active compounds. In the following, an overview of exemplary nucleophilic aromatic substitutions investigated in microstructured reactors is given.

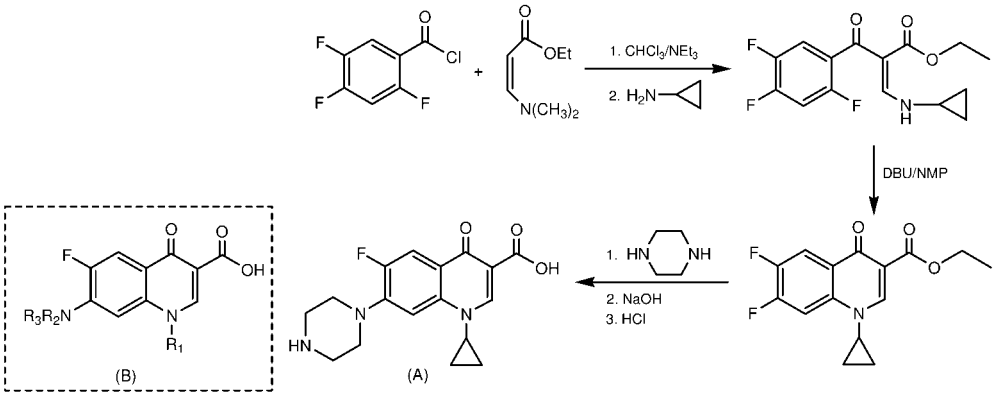
A series of nucleophilic aromatic substitutions was systematically investigated by Verboom and coworkers in a high-pressure capillary microreactor [46]. *p*-Halonitrobenzenes (with X=F, Cl, Br) were reacted with a 10-fold excess of three different amines (pyrrolidine, piperidine and morpholine) at pressures up to 600 bar to give the corresponding *p*-*N*,*N*-dialkylaminonitrobenzenes (Scheme 4.23). The pressure dependences of the reaction rates were quantitatively analyzed with on-line



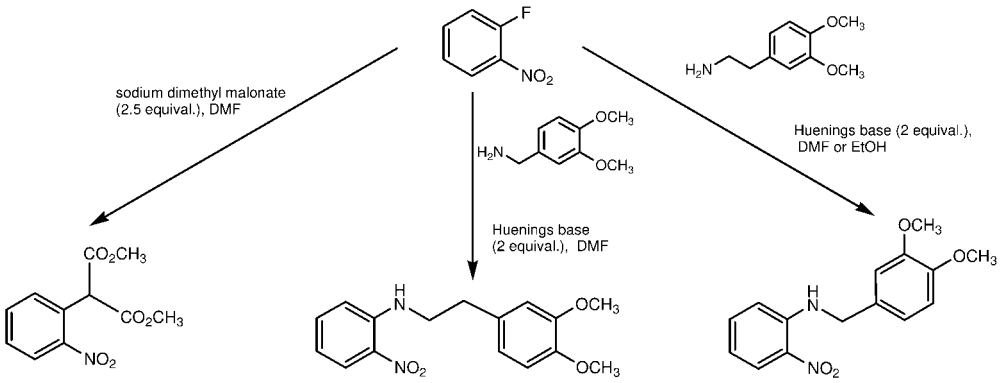
Scheme 4.23 Nucleophilic substitution reactions of *p*-halonitrobenzenes (X=F, Cl, Br) with pyrrolidine (Y=–), piperidine (Y=CH_2) and morpholine (Y=O).

UV–visible spectroscopy by monitoring the product concentration at a wavelength of 391 nm. The kinetic data obtained show the order of reactivity for the leaving groups to be F > Cl > Br, and the reactivity of the three different amines was in the order pyrrolidine > piperidine > morpholine. Activation volumes were calculated from the measured pressure dependences of the rate constants showing most negative activation volumes for the fastest reaction, e.g. that of *p*-fluoronitrobenzene with pyrrolidine. Finally, substitution reactions were investigated at different amine concentrations, showing that the reactions are base catalyzed with the amine being the catalyst.

Further nucleophilic substitution reactions of aryl fluorides and amines carried out in microreactors were described by Schwalbe *et al.* [47]. They reported on the use of a commercial microreaction system in combinatorial chemistry by performing sequential library syntheses of structural analogues of ciprofloxacin, a synthetic bactericidal antibiotic which is commercially available under the brand names Cipro, Ciproxin and Ciprobay. The five-step synthesis of ciprofloxacin (A) comprises two substitutions of fluorine moieties at the aromatic ring by two different amines (Scheme 4.24). In the combinatorial approach described [47], various amines were used in the substitution reactions which gave rise to a number of viprofloxacin analogues (B) synthesized in good overall yields and purities. Therefore, the use of continuous microreaction technology turned out to be a promising concept for the



Scheme 4.24 Synthesis of ciprofloxacin (**A**) and general structure of ciprofloxacin analogues (**B**).



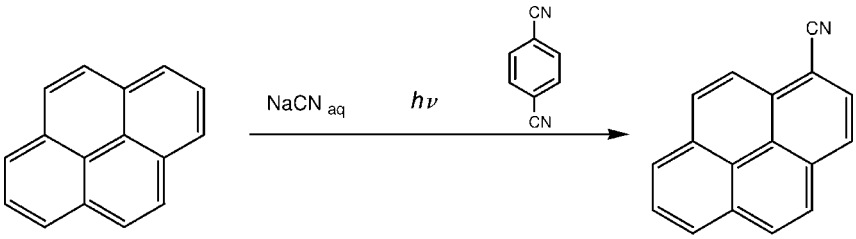
Scheme 4.25 Nucleophilic substitution reactions of *m*-fluoronitrobenzene [48].

synthesis of small- or medium-sized libraries in any quantity required by pumping sequences of reactants and spacer pulses through the microreactor.

Three nucleophilic substitution reactions of *m*-fluoronitrobenzene with two different amines and sodium diemethylmalonate (Scheme 4.25) carried out in a microcapillary flow reactor were reported by Comer and Organ [48]. The setup consists of a stainless-steel mixing chamber with three inlet ports that merge into one outlet port which is connected to a simple glass reaction capillary. To increase reaction rates, microwave irradiation is applied by assembling the straight reaction capillary into the chamber of a microwave synthesizer. In all three reactions considered, good to excellent conversions of 66–100% were achieved within reaction times of ~3–6 min (at flow rates of 25–40 μL min^{-1}). In most cases, the microwave irradiation power was set to 170 W. In contrast to larger scale microwave-assisted processes, no precipitation and therefore no clogging problems occurred in the microcapillary experiments, which was explained as being a result of shorter irradiation times and the use of short and straight capillaries. Finally, in some of the experiments using amines as substituents, a thin Pd film on the inner surface of the glass capillaries was utilized as an immobilized catalyst. In comparison with the Pd-free reactions, a significant increase in conversion of 12% and more could be observed.

A different kind of nucleophilic aromatic substitution reaction, namely cyanation reactions, was described by Kitamura and coworkers [49]. They investigated the photocyanation of pyrene by mixing an aqueous solution of NaCN and a propylene carbonate solution of pyrene and 1,4-dicyanobenzene in Y-shaped microfluidic chips made of polymers (Scheme 4.26). Since the reaction takes place at the oil–water interface, an increase in interfacial area was a major driver for employing microreactors.

Photocyanation reactions are based on photoinduced electron transfer processes. Upon irradiation, pyrene is transferred to its cation radical, which is substituted at the oil–water interface by nucleophilic attack of the cyanide anion. Running the reaction at room temperature and with a 210 s contact time between the two phases resulted in a 28% yield of 1-cyanopyrene. A further drastic increase in conversion was achieved by increasing the number of fluid layers inside the microchip from two (water–oil) to



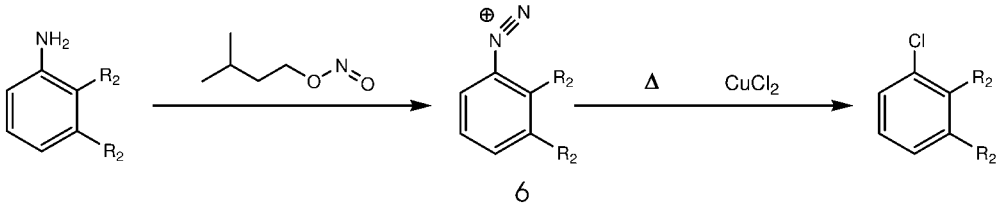
Scheme 4.26 Photocyanation of pyrene to 1-cyanopyrene.

three (water–oil–water) by using a microchip with a third inlet channel. Due to the significant extension of the specific interfacial area (ratio of the oil–water interfacial area to the oil volume), the conversion could be increased to 73%. Consequently, when the composition of the three-layer flow is changed from water–oil–water to oil–water–oil, conversion is decreased again by ~50% due to a twofold larger volume of the oil phase [49].

In a subsequent study, the authors investigated the electrochemical cyanation of pyrene in polymer microfluidic chips with integrated electrodes [50]. As in the photocyanation experiments [49], the reaction was carried out in an oil–water system. 1-Cyanopyrene was obtained as the sole product in quantities depending on flow rate and on the position of the electrodes inside the microfluidic chips. Moreover, the electrochemical cyanation of pyrene was also carried out by employing an acetonitrile solution of pyrene containing tetrabutylammonium perchlorate and an aqueous solution of NaCN. 1-Cyanopyrene was obtained in 61% yield and the amount of 1,3-dicyanopyrene could be successfully reduced from 14% obtained in macroscopic processes to 4% obtained in the microfluidic setup.

A final example of nucleophilic aromatic substitution reactions conducted in microstructured reactors is the Sandmeyer reaction, investigated by de Mello and coworkers [51]. In Sandmeyer reactions, aryl halides are synthesized from aryldiazonium salts that are formed by the reaction of aromatic amines with nitrites. In the presence of copper halides, the aryl diazonium salts decompose, forming the corresponding aryl halides. The authors described a continuous microfluidic process comprising both reaction steps within one device: formation of the aryldiazonium salt and its conversion to aryl chlorides [51]. Aniline and *o*- and *m*-toluidine were diazotized with amyl nitrite under anhydrous conditions to form the corresponding diazonium compound, which was subsequently chlorinated with $CuCl_2$ (Scheme 4.27). Since alkyl nitrites and diazonium salts are known as potentially hazardous compounds that exhibit high sensitivity to heat, light, shock and other stimuli, enhanced safety was a major driver for employing a microstructured reactor. Moreover, instead of preparing diazonium salts in an aqueous medium, as is traditionally done in macroscopic processes due to the stabilizing effect of water, the authors described the synthesis of the aryldiazonium compounds under dry conditions.

Chlorobenzene and *o*- and *m*-chlorotoluene could be obtained with a 15–20% increased yield compared with macroscopic processes due to the enhanced heat and



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Scheme 4.27 Sandmeyer reaction of aniline (R_1=H, R_2=H), *o*-toluidine (R_1=CH_3, R_2=H) and *m*-toluidine (R_1=H, R_2=CH_3).

mass transfer attainable in the microfluidic setup. Total yields were in the range from 55% (*m*-chlorotoluene) to 70% (chlorobenzene).

4.3 Conclusion

In the past decade, a wide variety of aromatic substitution reactions has been intensively investigated by applying microreaction technology in conjunction with appropiate process settings to identify routes towards optimized process performance. Enhanced heat and mass transport characteristics achievable in microstructured reactors have been deliberately used to obtain higer product yields, selectivities and purities. Moreover, microreactors have been suceessfuly used to identity synthesis routes towards new products and process conditions which are not attainable in macroscopic bacth processes.

Although microreactors have been mostly used so far as a lab tool for the screening and in-depth analysis of aromatic substitution reactions, first examples have already demonstrated that microreaction technology is becoming increasingly considered ever for industrial production purposes.

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