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Fluorinations, chlorinations and brominations of organic compounds in micro reactors

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Abstract

This paper gives an overview of the application of micro reactors for fluorination and chlorination of organic compounds supplemented by reporting about first investigations by the authors on the topic of bromination reactions in a micro reactor system. After a brief introduction illuminating the status of micro-chemical processing in general and covering the basic advantages of microstructured reactors, the different micro reactors used so far for halogenation reactions will be described with respect to fabrication, range of operation and performance. Thereafter, investigated reaction systems will be described and discussed.

All the reactions have in common that halogenation is achieved by using elemental halogens. Beside one gas phase chlorination, the described fluorinations and chlorinations are gas/liquid processes investigated in specialised gas/liquid micro reactors. In contrast, bromination reactions were performed in a micro mixer/tube set-up not specially adopted e.g. to gas/liquid conditions. Phase conditions here are quite complex through evaporated bromine and gaseous hydrogen bromide formed during the reaction.

The range of reactions comprises aromatic electrophilic substitutions and free radical substitutions of alkanes and in the side chain of aromatic compounds. The experimental results underpin the benefits of micro reactors for halogenation reactions as improved process control, process safety, improved selectivity and yields, shortening of syntheses and higher space-time yields. Furthermore, another aspect is the potential for an accelerated process development.

Keywords: Micro reactor; Direct fluorination; Chlorination; Bromination

1. Introduction

The benefits of microstructured reactors for chemical processing have been proved for a broad range of applications at laboratory scale and moreover the number of examples where microstructured reactors are integrated to pilot plants or even production plants is rising [1,2]. Beneficial use of microstructured reactors in the field of organic synthesis can especially be anticipated for fast reactions hindered by mass and/or heat transport [1–9]. In the past, processes were often so developed that they had to fit to existing equipment, mostly stirred vessels, which are ideal for operating slow reactions or in the case of fast reactions if one reactant is added very slowly due to immediate heat release. Protocols and aggressive reactants that could further speed up the reactions were not considered because of lacking suited equipment or safety considerations.

The direct fluorination of aromatics with elemental fluorine is a good example for this consideration. Albeit the high reaction speed of fluorine itself as fluorination agent was known since the 1930s, the insufficient selectivities and, quite frequently, the hazardous nature of the processing, including severe explosions, hindered a wide-spread synthetic usage. Instead complex syntheses play an important role. The direct routes demand for absolute precise temperature control because overheating of the reaction media increases radical formation [10–15] The number of radicals formed determines which reaction path dominates, the radical or electrophilic one. Another issue refers to increasing mass transfer. To really utilise the potential of the extremely fast fluorination reaction, fluorine has to cross over the interface from the gas to the liquid

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phase. Since fluorine is hardly soluble in any organic solvent, the largeness of the interface becomes of special importance. In turn, control over this quantity with regard to time and space, besides heat setting, allows handling the delicate direct fluorination reaction. This is accompanied by a demand for precise residence time setting as the fluorination reaction is extremely fast and any too long exposure to the aggressive fluorine results in secondary reactions as multi-fluorinations, C–C bond breakage by additions, and polymerisations.

From the beginning of the 1960s or so, several experimental works deal with slowing down the fluorine conversion rate by extreme dilution of fluorine and the substrates and by decreasing the temperature down to a cryogenic level [16–22]. Indeed, by these measures control over product spectra and defined reaction paths were achieved. Now, for selected substrates direct fluorination is possible also at a preparative level. However, alternative routes to fluorinated products, e.g. using Lewis acid-type fluorides, have become of major importance [23–28].

The forthcomings of microfabrication technology, microfluidics and its application in the field of chemical engineering, allow now another approach: rather adaption of the processing equipment to reaction than vice versa. The drivers for performing direct fluorinations in micro-channel environment directly refer to the elemental advantages of micro reactors. Their large internal surfaces and interfaces facilitate mass and heat transport by building up large concentration and temperature gradients. Residence times can be controlled much more precisely than, e.g., in a stirred-tank reactor. Finally, the small hold-up volumes make the process safe, even if very high fluorine concentrations and so large conversion rates are employed [13].

All the following presented reactions deal with similar requirements as described above. Moreover, also other aspects as efficient photoreaction will be of importance.

2. Micro reactor systems for halogenation reactions

This section describes functional principle and basic features of micro reactors used for the presented halogenation reactions. The falling film micro reactor, the micro bubble column, the dual-micro-channel chip reactor and the single/tri-channel thin-film micro reactor are specially designed for gas/liquid processes. The micro heat transfer module is used for gas phase processes. The micro mixer/tube set-up is while not specially adapted to gas/liquid processes applicable for a broad range of operation conditions.

2.1. Falling film micro reactor

The falling film principle utilises the wetting of a surface by a liquid stream, governed by gravity force, which thus spreads to form an expanded thin film. The falling film micro reactor (Fig. 1) transfers this renowned macro-scale concept to yield films of a few tens of micrometer thickness [10,29,30]. For this reason, the streams are guided through micro-channels. To obtain reasonable throughput, many micro-channels are operated in parallel.

Fig. 1. Photograph of a falling film micro reactor [29].

The liquid enters the micro-channel device via a large boring that is connected to a micro-channel plate via a slit (Fig. 2). The slit acts as flow restrictor and serves for equipartition of the many parallel streams [10,29,31]. The liquid streams are recollected via another slit at the end of the microstructured plate and leave the device by a boring. The gas enters a large gas chamber, positioned above the micro-channel section, via a boring and a diffuser and leaves via the same type of conduit. Both a co-flow and counter-flow operation mode is possible; however, regarding to the low gas velocities usually employed this makes no practical difference [32].

Internal heat exchange is realised by heat conduction from the microstructured reaction zone to a mini channel heat exchanger, positioned in the rear of the reaction zone [10,29,31]. The reactor can be equipped, additionally, with an inspection window allowing—depending on the selected material—visual observation of the falling film, temperature measurement via IR-camera (material: silicon) [31,32] and performing photochemical reactions (material: quartz glass) [33]. Dimensions of the microstructured components and further information about the reactor are given in Table 1.

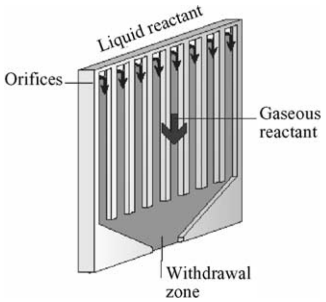


Fig. 2. Principle of contacting liquid and gaseous reactants in a falling film micro reactor [1].

Table 1
Reactor specifications of the falling film micro reactor

Falling film micro reactor	
Material in contact to reaction fluids apart from sealings	Steel
Outer dimension without connectors	120 mm × 76 mm × 40 mm
Pressure stability	10 bar (20 bar without inspection window)
Temperature stability	Up to 180 °C
Micro-fabrication methods used	μEDM, etching, micro milling
Micro-channels of reaction plate (standard version): number; width; depth	64; 300 μm; 100 μm
Performance data (exemplarily)	
Residence time	17 s (at 25 ml/h)
Interfacial area	20000 m^2/m^3 (at 25 ml/h)
Active inner volume	100 mm^3 (per plate)
Total inner surface	1690 mm^2 (per plate)

2.2. Micro bubble column

The micro bubble column uses dispersion of gas in a liquid stream (Fig. 3) (and to a minor extent dispersion of liquid in a gas, as e.g. given for spray flow) [10,30,34]. Different flow pattern can be observed. The *slug flow* pattern, comprising bubbles of a diameter approaching that of the micro-channel (Taylor bubbles) and segmented by liquid slugs, has a large range of stability; the flow pattern *bubbly flow*, which is on the macro-scale a dominating flow pattern, is also found on the microscale, but with limited stability [34,35]. In addition, other flow patterns known from the macro scale such as *annular* or *spray-flow* patterns were identified in the micro bubble column too [34,35]. The *annular-flow* pattern has the largest internal surface, as one uniform thin liquid film is formed. This is notably different from *slug flow* having a coexistence of thin liquid wall-wetting films and thick liquid bubble segmenting slugs.

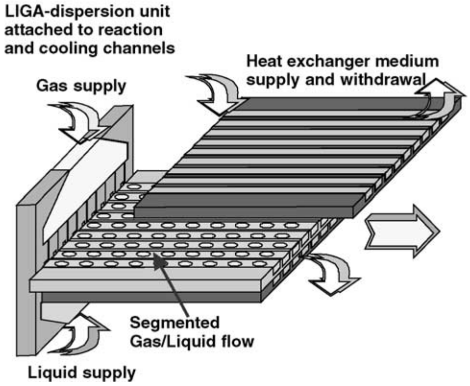


Fig. 3. Schematic illustration of contacting liquid and gaseous reactants in a micro bubble column [1].

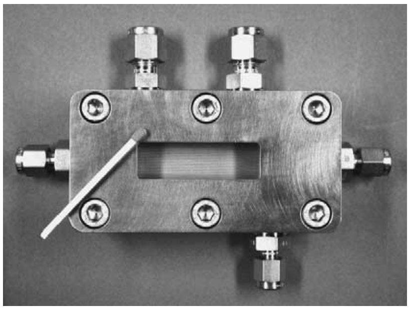


Fig. 4. Micro bubble column (redesigned version) [1].

The central parts of the micro bubble column (Fig. 4) are the micro mixing unit and the micro-channel plate [10,34,35]. In order to achieve equipartition the mixing unit comprises an interdigital feed structure with very different hydraulic diameters for gas and liquid feed. Each of the micro-channels on the micro-channel plate is thereby fed by a separate gas and liquid stream. The flow pattern observed is then determined by the process parameters, in particular the gas and liquid velocities. The gas and liquid streams merge to be removed from the micro-channel section.

The micro bubble column comprises an internal cooling via heat conduction from the reaction zone to a mini channel heat exchanger [3,9,10]. Either two such heat exchange plates can encompass the reaction plate or only one. In the latter case, the free position is occupied by an inspection window which allows direct observation of the quality of the flow patterns. Dimensions of the microstructured components and further information about the reactor are given in Table 2.

2.3. Dual-micro-channel chip reactor

This reactor is based on two parallel micro-channels that are separated by a wall. In front of the micro-channel section, one hole is placed for liquid feed, followed by two holes for gas feed [11,12]. The liquid feed enters in line with the wall long axis, while the gas feeds have the position of the two channels. Consequently, the liquid flow has to split. A silicon chip covered by bonded Pyrex® bears these central functionalities. For corrosion reason the silicon was thermally oxidised and covered with a thin nickel film The silicon chip was compressed between a transparent top plate and a base plate with all fluid connections [11,12]. Generally, heat removal is facilitated by the special reactor arrangement acting as heat sink. Different flow pattern were observed (a detailed flow-pattern map for nitrogen/acetonitrile is given in [11]). Beside bubbly, slug, churn and annular flows, additionally wavy annular and wavy annular-dry flows were detected with less extended stability region. Generally, the annular-flow processing was favoured due to the high specific interface and the simple conception relying on an inner gas core and surrounding liquid only.

Table 2
Reactor specifications of the micro bubble column

Micro bubble column	
Material in contact to reaction fluids apart from sealings	Steel, nickel
Outer dimension without connectors	95 mm × 50 mm × 36 mm
Pressure stability	30 bar
Temperature stability	Up to 180 °C
Micro-fabrication methods used	Etching, micro milling, μEDM, UV-lithography/ electroforming
Reaction plate	
Micro-channels of reaction plate: number; width; depth; length, micro-channel width; depth; length	32; 200 μm; 70 μm; 60.5 mm
Micro mixer unit	
Feeding micro-channels: number; width; depth	2 × 16; 7 μm (gas), 20 μm (liquid); 20 μm
Performance data (exemplarily)	
Residence time	0.56 s (at 10 ml/h liquid flow; 600 ml/h gas flow)
Interfacial area of liquid films	20000 m^2/m^3 (at 25 ml/h)
Active inner volume	15.3 mm^3 (per plate)
Total inner surface	860 mm^2 (per plate)
Interfacial area of liquid films	100 mm^3 (per platelet)

Dimensions of the microstructured components and further information about the reactor are given in Table 3.

2.4. Single/tri-channel thin-film micro reactor

This micro reactor (Fig. 5) has a three-plate structure [13,36]. The first plate is a thin frame for screw mounting and provides an opening for visual inspection of the single micro-channel section. The second plate serves as top plate shielding the micro-channel section and comprising the fluid connections. This plate has also seal function and is transparent to allow viewing of the flow patterns in the single micro-channel. The bottom plate is a metal block bearing the micro-channel. The metal plate is highly polished to ensure gas tightness [36].

Table 3
Reactor specifications of the dual-channel micro reactor

Dual-micro-channel chip reactor	
Material in contact to reaction fluids apart from sealings	Silicon thermally oxidised and covered with a thin nickel layer, Pyrex
Micro-fabrication methods used	Photolithography, silicon etching, nickel evaporation, anodic bonding
Volume of the reactor	2.7 μl
Micro-channel: width; depth; length	435 μm; 305 μm; 20 mm (triangular cross-section)
Performance data (exemplarily)	
Surface-to-volume ratio of micro-channels	18000 m^2/m^3

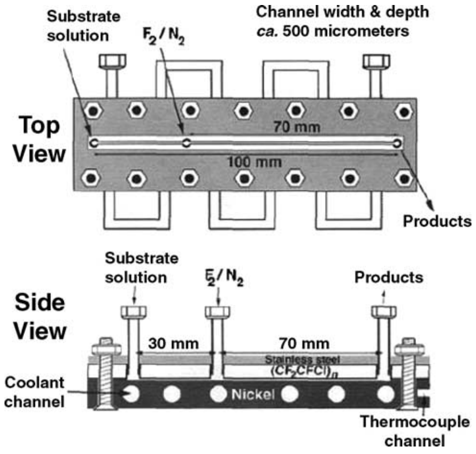


Fig. 5. Schematic illustration of the single-channel micro reactor [13].

The liquid is fed at one end of the micro-channel and runs through the single micro-channel for a certain passage to adapt temperature. Then the gas stream is introduced in the flowing liquid via a second port in rectangular flow guidance [13,36]. Thereby, the gas/liquid flow pattern is derived and the reaction initiated. After a reaction flow passage, the product mixture leaves the micro reactor via a third port. Before carrying out the fluorination reactions, passivity of the micro reactor has to be ensured by exposure of the micro-channel to increasing concentration of fluorine in nitrogen [13]. A coolant channel is guided through the metal block in a serpentine fashion [36]. The micro reactor was initially made as single-micro-channel version [36] and later as numbered-up (scale-out) three-micro-channel-version [13]. Dimensions of the microstructured components and further information about the two reactors are given in Table 4.

2.5. Micro heat transfer module

The micro heat transfer module (Fig. 6) can be used to heat up gas fast e.g. to reaction temperature [1,37].

Table 4
Reactor specifications of the three-channel thin-film micro reactor

Three-channel thin-film micro reactor	
Material in contact to reaction fluids apart from sealings	Nickel, polytrifluorochloroehylene
Outer dimension without connectors	96 mm × 52 mm × 12 mm
Micro-fabrication methods used	Cutting
Micro-channel (reaction part): width; depth; length	500 μm; 500 μm; 60 mm (500 μm; 500 μm; 70 mm)[a]
Distance liquid/gas entries	13 mm (30 mm)[a]

[a] Values for the single-channel version.

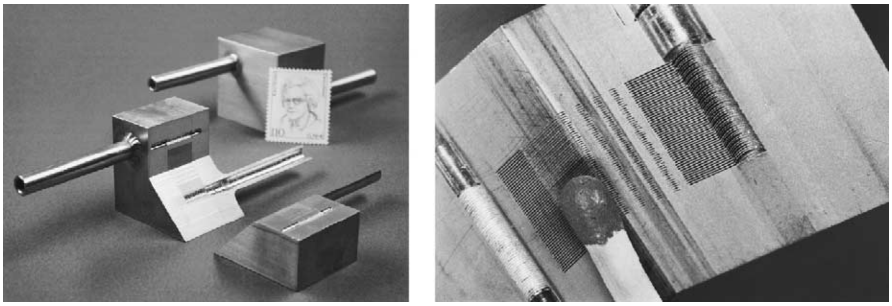


Fig. 6. Micro heat transfer module [37].

It comprises a stack of microstructured platelets which are irreversibly bonded. The module is heated by external sources, e.g. by placing it in an oven or by resistance heating. The single parallel flows are all guided in the same direction on the different levels provided by the platelets. Before and after, distribution and collection zones are found, connected to inlet and outlet connectors. The precise specifications are given in Table 5.

2.6. Micro mixer/tube set-up

The authors used for their bromination experiments combinations of different micro mixers and a connected tube section of variable length. Both were embedded in thermostated baths. Depending on reaction requirements, additional thermostated tube sections before the micro mixer were employed for pre-heating of the reactants. Furthermore, it was possible to apply pressure to the system via a modified valve at the outlet of the tube section. Two different micro mixers were applied depending on reaction conditions: the so-called triangular interdigital micro mixer (TIMM; Fig. 7a, top) [1] and one so-called caterpillar micro mixer with the denomination CPMM-R600/12 made of PVDF (Fig. 7b, top) fabricated by IMM especially for these investigations. The mixing principle of both mixers aimed at achieving fine lamellae of the two fluids contacted in an alternating way. Therefore, in the triangular interdigital micro mixer the two fluids are split into several fine substreams via an interdigital microstructured feeding system and then contacted in alternating way in the mixing chamber (see Fig. 7a, bottom). The width of the mixing chamber decreases in flow direction, thereby decreasing the width of the lamellae and improving mixing quality. The caterpillar micro mixer uses a mixing principle called "split-and-recombine": several repetitions of the sequence dividing the streams, folding/guiding over each other and recombining them. This ideally ends up also in an alternating arrangement of fine lamellae of the two fluids (see Fig. 7b, bottom). The difference to the first mixing principle is that the fluids are already in contact before they are split into fine lamellae. More details are given in Table 6.

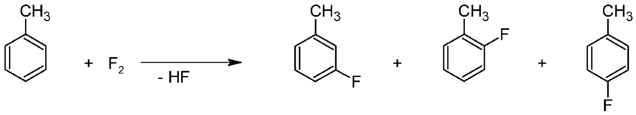
Table 5
Reactor specifications for the micro heat transfer module

Micro heat transfer module	
Material	Stainless steel
Outer dimension without connectors	32 mm × 32 mm × 26 mm
Pressure stability	Up to 50 bar
Temperature stability	Up to 700 °C
Micro-fabrication methods used	Etching, laser welding
Micro-channel width; depth; length	500 μm; 100 μm; 8 mm
Number of platelets	50
Number of channels on one platelet	13
Device inner volume	2.6×10^{-7} m^3
Total micro-channel surface area	6.24×10^{-3} m^2

3. Fluorination reactions in micro reactors

3.1. Aromatic electrophilic substitution reactions

3.1.1. Direct fluorination of toluene using elemental fluorine



Jähnisch et al. [15] investigated the direct fluorination of toluene in the falling film micro reactor and the micro bubble column and also compared the results with those obtained in experiments in a conventional laboratory bubble column. Thereby pure and diluted toluene at medium and high concentration of fluorine, being 10 or 50% in nitrogen, was used. Besides proving the feasibility of the direct fluorination in micro reactors, the investigations aimed at determining the influence of fluorine-to-toluene ratio, volume flow rate, temperature, solvent and micro-channel dimensions on conversion, selectivity and yield. An overview of the reaction conditions and results is given below, followed by a more detailed view on the results.

Most of the experiments used fluorine with a content of 10% in nitrogen. The falling film micro reactor experiments were performed for temperatures from −15 to −42 °C. The molar ratio of fluorine-to-toluene spans the range from 0.20 to 0.93. The concentration of toluene in the solvent was (and in the experiments with the other reactors) 1.1 mol/l and liquid

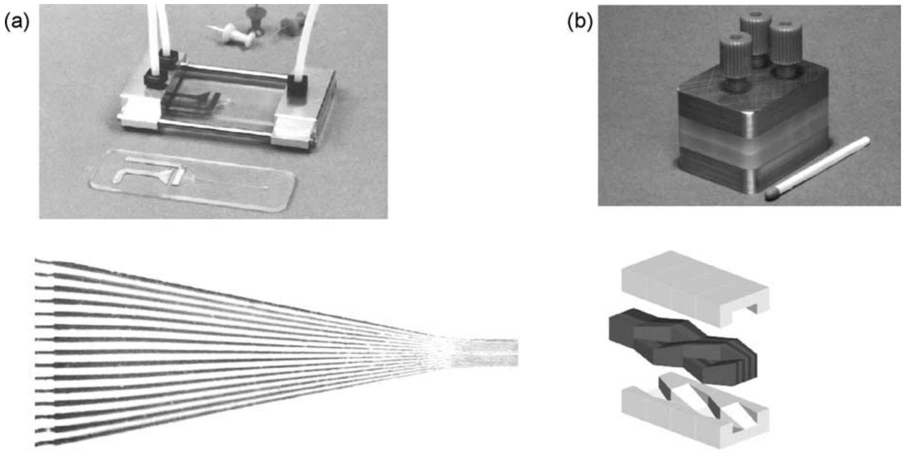


Fig. 7. (a) Triangular interdigital micro mixer (TIMM; top) and experimentally visualised flow pattern in the mixing chamber (bottom) illustrating the mixing principle; (b) caterpillar micro mixer CPMM-R840 PVDF (top) and idealised flow pattern (two mixing steps; bottom) also illustrating the mixing principle. Source: IMM.

volume flows 11.1, 11.6 or 19.6 ml/h were applied. Using acetonitrile as solvent, the conversions ranged from 14 to 50% at selectivities of 33–57%, corresponding to yields of 5–20%. Using methanol, the conversions ranged from 12 to 42% at selectivities of 9–58%, corresponding to yields of 3–14%.

Table 6
Reactor specifications of the micro mixer/tube set-up combination

Micro mixer/tube set-up	
Micro mixer: triangular interdigital micro mixer (TIMM)	
Outer dimension with housing	106 mm × 56 mm × 25 mm
Pressure stability	Up to 2 bar
Temperature stability	Up to about 200 °C (because of the Teflon tubing)
Micro-fabrication methods used	Photostructuring of glass, diffusion bonding
Material in contact to reaction fluids	Glass, Teflon
Mixer feed channels: number; width; depth / Width of separating walls	2 × 15; 60 μm; 150 μm/50 μm
Mixing chamber: length; initial width; height	8 mm; 3.25 mm; 150 μm
Mixing channel: length; width; height	19.4 mm; 500 μm; 150 μm
Micro mixer: caterpillar micro mixer CPMM-R600/12 PVDF	
Outer dimension with housing	27 mm × 30 mm × 40 mm
Pressure stability	Up to 10 bar
Temperature stability	−30 to 150 °C
Micro-fabrication methods used	Milling
Material in contact to reaction fluids	PVDF
Mixing channel: cross-section; length; number of mixing steps	600 μm × 600 μm; 14.4 mm; 12
Tube section	
Material	PFA
Inner diameter; outer diameter; length of the tube	1.59 mm; 3.18 mm; 2.5 m

The micro bubble column experiments were performed at −15 °C with molar ratios of fluorine-to-toluene from 0.20 to 0.83. Acetonitrile was taken as solvent. A liquid volume flow of 13 ml/h was applied. The gas volume flow was varied from 12.1 to 50.0 ml/min. Two different reaction plates were used: 50 μm × 50 μm reaction channels, 300 μm × 100 μm reaction channels. Using 50 μm × 50 μm reaction channels, the conversions ranged from 4 to 28% at selectivities of 21–75%, corresponding to yields of 3–11%. Using 300 μm × 100 μm reaction channels, the conversions ranged from 9 to 41% at selectivities of 22–28%, corresponding to yields of 2–11%.

The experiments with the laboratory bubble column were performed at −17 °C. Molar ratios of fluorine-to-toluene from 0.40 to 1.00 were applied. Liquid batch volume was always 20 ml. Acetonitrile was taken as solvent. The gas volume flow was either 20 or 50 ml/min. The conversion ranged from 6 to 34% at selectivities of 17–50%, corresponding to yields of 2–8%.

Experiments with higher fluorine contents (greater than 10%) were only performed in the falling film micro reactor. The temperature was set at −16 °C, acetonitrile was used as solvent and the molar ratio of fluorine-to-toluene ranges from 0.40 to 2.0. The liquid volume flow was always set to 19.6 ml/h. The conversions ranged from 7 to 76% at selectivities of 31–43%, corresponding to yields of 3–28%.

Conversion and yield refers here always to toluene and not generally to the non-stoichiometric component. Yield and selectivity are given for the sum of the three ring monofluorinated toluene isomers.

The determined substitution pattern for the falling film micro reactor using fluorine of 10% in nitrogen is 5:1:3, with respect to the *ortho*, *meta* and *para* product, which is in accordance with an electrophilic substitution mechanism [15]. Increase of the fluorine content to 50% leads to preferred formation of the *para* product (ratio of *ortho* to *para* 1:4).

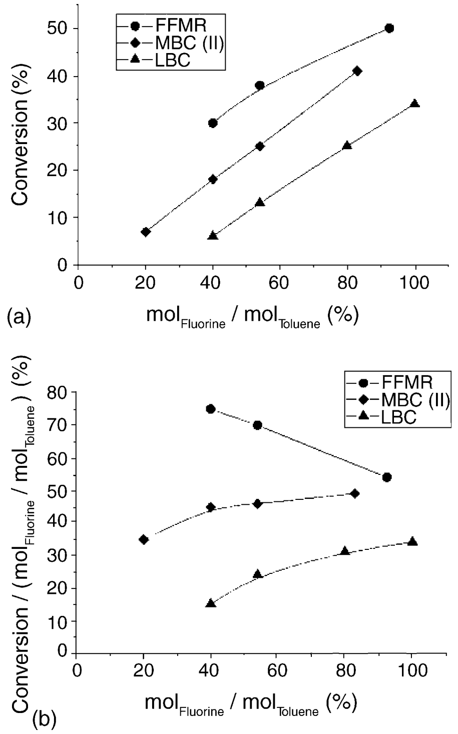


Fig. 8. Conversion of the direct fluorination of toluene in different reactor types as a function of the molar ratio of fluorine-to-toluene (a) and efficiency of these reactors, defined as conversion normalised by the molar ratio of fluorine-to-toluene, as a function of the molar ratio of fluorine-to-toluene (b). Falling film micro reactor (FFMR); micro bubble column with 50 μm × 50 μm reaction channels (MBC II); laboratory bubble column (LBC) [15].

Beside one exception the yields obtained in the falling film micro reactor exceed those of the laboratory bubble column. The best yield of 28% thereby is more than three times larger than for the laboratory bubble column. The yields in the micro bubble column also exceed those of the benchmark but only to a minor extent. The selectivities in the micro reactors ranging from 30 to 50% seem to be unattractive on a first look, but they are comparable to the best results of experiments in conventional equipment described in literature [15]. Furthermore, only in the case of the micro reactors high toluene concentrations, high fluorine contents in the inert gas and elevated reaction temperatures were applied. Thereby, the results indicate that an efficient temperature control and mass transfer was achieved in the micro reactors.

In Fig. 8 [15], toluene conversion is given as a function of the fluorine-to-toluene ratio, achieved by variation of fluorine (10% in nitrogen) volume flow at a fixed liquid flow rate. For all investigated reactors conversion increases with the fluorine-to-toluene ratio. This basically means that transport resistance would most likely not prohibit using still higher fluorine contents for increasing productivity of the reactor. The efficiency of fluorine conversion in the micro reactors is for all operating conditions investigated better than in the laboratory bubble column, mostly because of the huge differences in interfacial areas (see Fig. 8 [15]).

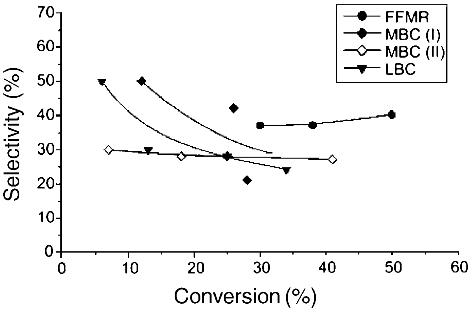


Fig. 9. Comparison of performance of a typical laboratory column (LBC) with several micro reactor devices. Falling film micro reactor (FFMR); micro bubble column with 300 μm × 100 μm reaction channels (MBC I) and 50 μm × 50 μm reaction channels (MBC II) [15].

As to be expected, conversion for the direct fluorination rises with increasing temperature. For the falling film micro reactor (10% fluorine in nitrogen, fluorine-to-toluene ratio 0.40) conversion is increased from 15 to 30% when going from −40 to −15 °C. The selectivity varies largely between 30 and 50% without a clear and understood tendency.

Considering the effect of solvents, it can be stated that generally, the performance when using acetonitrile was much better; for instance, yields ranging from 20 to 28% were gained in the falling film micro reactor. For methanol, the best yield was only 14%. This is somehow in contrast to literature findings showing an increase in product yield with increasing solvent polarity (see citations in [15]). So far, no explanation for the differing micro-channel performance was given. When using pure toluene, only a very low yield at high selectivity was found [15].

Variation of the fluorine content in the gas phase of the falling film micro reactor between 10, 25 and 50%, leads to a nearly linear increase in conversion at constant selectivity.

The selectivity–conversion diagram (Fig. 9) derived from the experiments using a mixture of 10% fluorine in nitrogen shows that the falling film micro reactor has the best selectivity–conversion performance [10,15]. The behaviour of the falling film micro reactor and the micro bubble column with narrow channels is characterised by a nearly constant selectivity with increasing conversion, while the bubble column with wide channels shows notably decreasing selectivity with conversion (similar to the laboratory bubble column). The micro bubble column using narrow channels exceeds the selectivities of the laboratory bubble column only at high conversion.

Considering space–time yields values higher by order of magnitude were found for the falling film micro reactor and the micro bubble column as compared to the laboratory bubble column (Fig. 10a [15]). The space–time yields for the micro reactors ranged from about 20,000 to 110,000 mol monofluorinated product/(m^3 h) referring to the reaction volume (micro-channels' volume solely). The ratio with

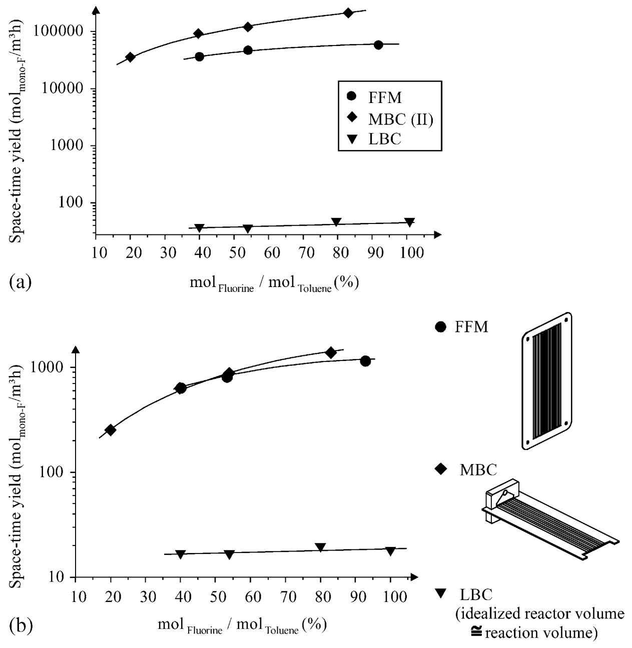


Fig. 10. Comparison of space–time yields of direct fluorination of toluene for the falling film micro reactor (FFMR). Micro bubble column (MBC) and laboratory bubble column (LBC) referred to the reaction volume (a), referred to an idealised reactor geometry (b) [15].

regard to this quantity between the falling film micro reactor and the micro bubble column was about 2. The performance of the laboratory bubble column was in the order of 40–60 mol monofluorinated product/(m^3 h). Even taking into account the construction material of the reactors, the performance of the micro reactors is more than one order of magnitude better (Fig. 10b) [15]. The space–time yields for the micro reactors defined in this way ranged from about 200 to 1100 mol monofluorinated product/(m^3 h).

The investigations of Jähnisch et al. demonstrated the feasibility of performing direct fluorination using elemental fluorine in the selected micro reactors. Also explosive mixtures can be handled safely. The micro reactor performance is superior compared to the laboratory bubble column with regard to yield, efficiency of fluorine conversion, selectivity–conversion behaviour and space–time yield. The yields are comparable to the technically performed multi-step Schiemann process, whereby it has to be kept in mind that the latter delivers only one isomer while the direct route delivers a mixture of three isomers.

The fluorination of toluene was also investigated by Jensen and coworkers [11] using the dual-micro-channel chip reactor. Therefore a 0.1 M (and 1.0 M in one case) toluene solution was fluorinated in various solvents such as acetonitrile, methanol, and octafluorotoluene using 25% fluorine in nitrogen. Reactions were carried out at room temperature in the *annular-dry flow* regime (gas superficial velocity: 1.4 m/s; liquid superficial velocity: 5.6×10^{-3} m/s). The molar ratio of fluorine-to-toluene was varied; gas and liquid flow velocity were kept constant to maintain the same flow pattern for all experiments. The nickel-coated silicon micro reactor was operated for several hours for the reaction conditions given. The nickel films lose to a certain extent their adhesion to the reaction channel with ongoing processing [12].

Selectivities of up to 36% at 33% conversion were achieved using acetonitrile as solvent (molar ratio fluorine-to-toluene: 1.0) [11]. When including multi-fluorinated toluenes and chain-fluorinated toluenes, besides the mono-fluorinated toluenes, in the selectivity balance, the value increases to 49%. The remainder is lost in other side reactions such as additions or polymerisations.

Conversions from 17 to 95% were achieved using methanol as solvent (molar ratio fluorine-to-toluene: 1.0–10.0; 0.1 M toluene; 10 ml/min gas flow; 100 μl/min methanol) [14]. The respective selectivities ranged from 37 to 10%. Taking into account the difluorotoluenes and trifluorotoluenes as well gives a selectivity of about 45%. The yields passed over a maximum at 18%. Conversions of 35 and 52% were achieved at higher toluene concentration and with lower molar ratio fluorine-to-toluene (0.5–1.0 fluorine-to-toluene equivalents; 1.0 M toluene; 10 ml/min gas flow; 100 μl/min methanol) [12]. The respective selectivities were 20 and 17%. The yields amounted to 7 and 9%. The lower performance of the high-concentration processing compared to the more diluted 0.1 M processing is explained by a larger temperature rise leading to more pronounced radical formation causing side reactions. This is in line with calculations on heat transport for the micro reactor.

Regarding the substitution pattern, a ratio of *ortho*, *meta* and *para*-isomers for monofluorinated toluene amounting in average to 3.5:1:2 using acetonitrile as solvent [11]. *Ortho* and *para* products were the main products of the reaction mixture, unless the fluorine equivalents lower than 5 were used. Compared to the result of Jähnisch et al. [15] cited above, the *meta*-isomer content was slightly higher, maybe a consequence of using a higher reaction temperature. Using methanol as solvent, the ratio is in average 5.5:1:2.4. Hence more products referring to an electrophilic substitution were formed [11]. An increase in toluene concentration, from 0.1 to 1.0 M, did not affect the substitution pattern when using acetonitrile as solvent [11].

Conversion shows a linear dependency on molar ratio fluorine-to-toluene in the investigated range from 1.0 to 5.0 (Fig. 11). Conversion increases from 33% for a ration of 1.0–96% for a ratio of 5.0, while selectivity drops from 36% at 11% (0.1 M toluene, acetonitrile). Yield passes over a maximum.

Considering the effect of different solvents, the highest yield (14%; 58% conversion; 24% selectivity) were found using acetonitrile as solvent [13]. Slightly lower yields were obtained for methanol. The selectivities were as high as for acetonitrile, the conversion being lower. Still lower yields (7%) were achieved in octafluorotoluene; selectivity decreasing notably.

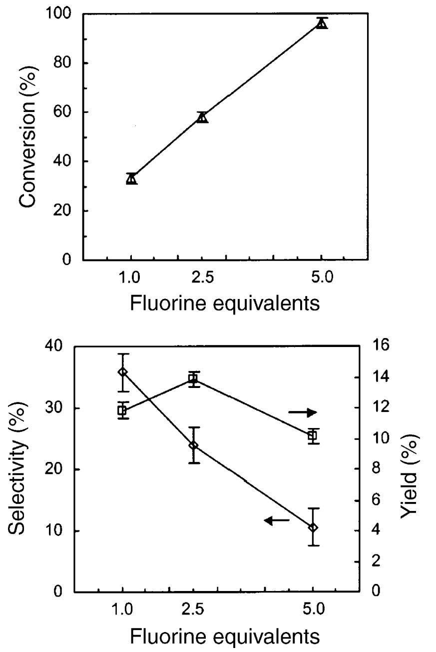
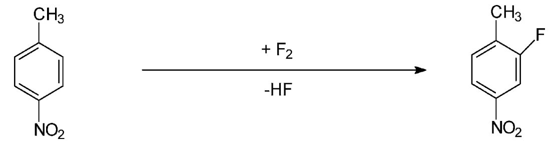


Fig. 11. Influence of the molar ratio fluorine-to-toluene (0.1 M toluene in acetonitrile) on conversion, selectivity, and yield [11].

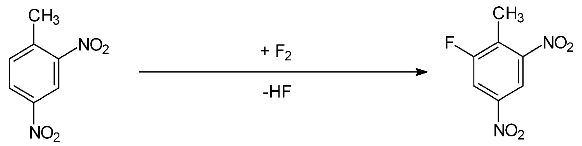
3.1.2. Direct fluorination of para-nitrotoluene using elemental fluorine



Chambers et al. performed safely and successfully the direct fluorination of *para*-nitrotoluene with elemental fluorine in the tri-channel thin-film micro reactor [13]. The flow rates were so set that an *annular-flow* regime results. This flow regime was chosen for its large specific gas/liquid interfaces and the good temperature control achievable by the thin films. The reaction was carried out at temperature of 0 and 5 °C, and room temperature. A gaseous mixture of 10% fluorine in nitrogen at 10 ml/min was used. Formic acid/acetonitrile mixtures of 1:1 and 2:3 were used as well as pure acetonitrile at single-channel flow rates of 1.0 and 2.0 ml/h. Corresponding rate of single-channel substrate addition was in the range of 0.9–1.5 mmol/h. Applying pure formic acid as solvent of choice for selective electrophilic fluorination of aromatic compounds lead to blockage of the micro-channels because of the pure solubility of the substrate. The molar ration fluorine to substrate ranged between 1.7 and 3.0.

The conversion in pure acetonitrile was with 15% low. The raw product contained after removal of solvent 71% product. Higher conversion rates (44–77%) were obtained using formic acid/acetonitrile mixtures. The crude product contained 60–78% of the product.

3.1.3. Direct fluorination of 1-methyl-2,4-dinitrobenzene using elemental fluorine

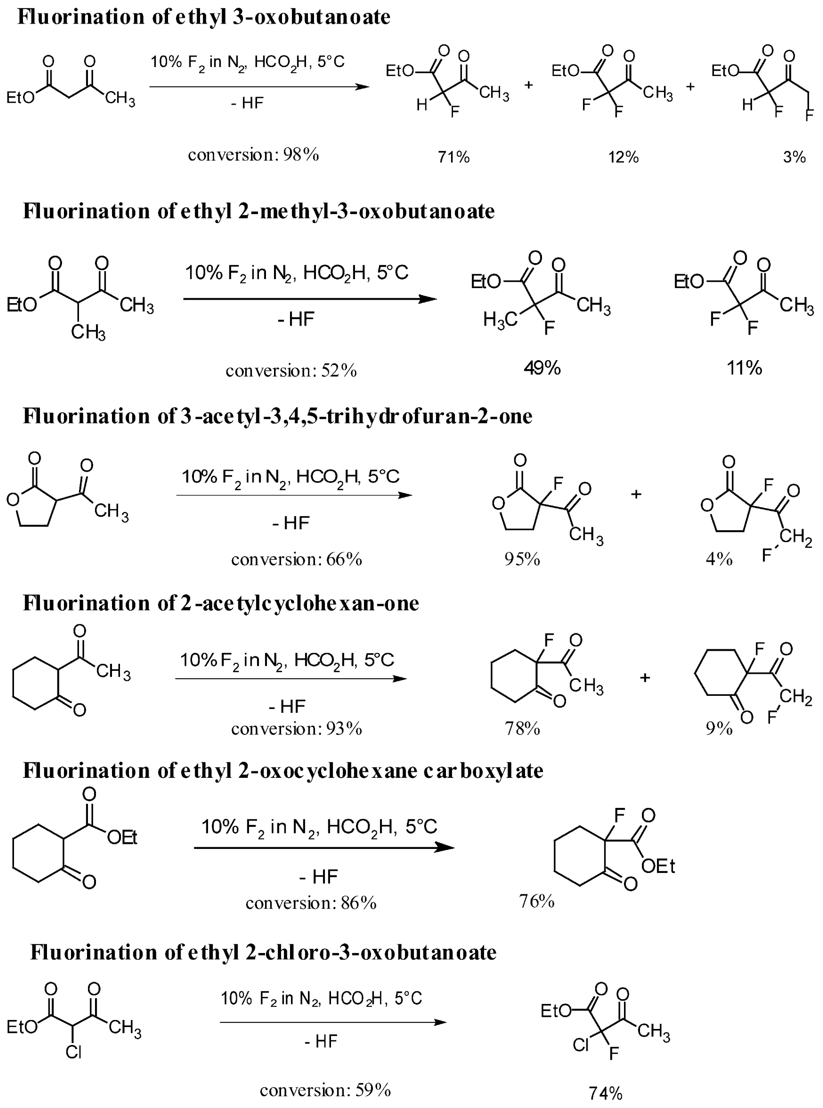


Chambers et al. performed additionally to the fluorination of *para*-nitrotoluene the fluorination of 1-methyl-2,4-dinitrobenzene with elemental fluorine in the tri-channel thin-film micro reactor [13]. The reaction was carried out at 0 °C. A gaseous mixture of 10% fluorine in nitrogen at 10 ml/min per channel and a formic acid/acetonitrile mixtures of 2:3 at a single-channel flow rate of 2.0 ml/h (corresponding rate of single-channel substrate addition: 0.88 mmol/h) was used. The conversion was 40%. The raw product contained after removal of solvent 70% product.

3.2. Free radical substitution reactions—fluorination of aliphatics and other species

Beside the fluorination of nitrotoluene derivatives as examples for aromatic electrophilic substitution, Chambers et al. investigated also fluorination reactions belonging to the group of free radical substitution reactions in the single and/or tri-channel thin-film micro reactor using elemental fluorine: fluorination of a range of β-dicarbonyl compounds [13,36], synthesis of organic sulfur pentafluorides [13,36] and perfluorinations [36]. The experiments were performed again with flow rates leading to the *annular-flow* regime with large specific gas/liquid interfaces and good temperature control.

Scheme 1 gives an overview of the investigated fluorinations of β-dicarbonyl compounds with selected reaction conditions and results. The fluorinations of the β-dicarbonyl compounds in the single-channel thin-film micro reactor were performed at 5 °C with a gaseous mixture of 10% fluorine in nitrogen at 10 ml/min. Formic acid as reaction media was used and the liquid flow rate set to 0.5 ml/h, corresponding to 2.2 mmol substrate/h. The obtained conversions and yields for all of the reactions carried out were at least as high as for fluorination reactions in conventional equipment [13]. The conversions obtained ranged from 52 to 98% for the different substrates. The amount of the monofluorinated species in the crude product after solvent removal was between 49 and 95%. For the fluorination of ethyl 2-chloro-3-oxobutanoate much higher yields were found compared to conventional batch processing which has low conversion only. The observed higher yield was attributed to the catalytic effect of the fluorinated metal surface of the micro-channel on enol formation. The rate of the fluorination of α-keto esters is usually correlated to the enol concentration or the rate of enol formation as this species actually is fluorinated [13,36].

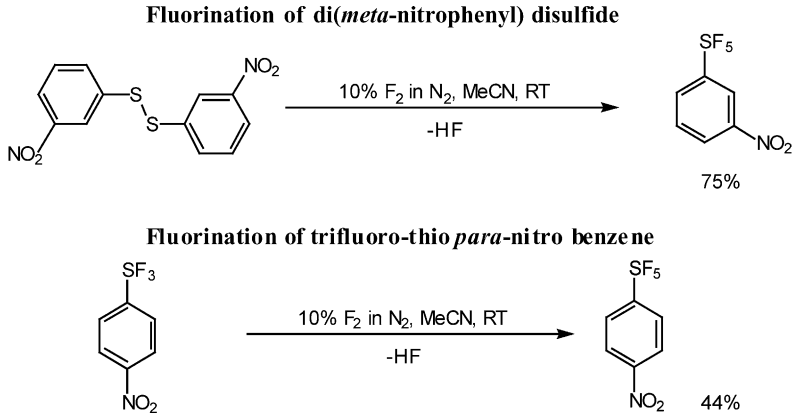


Scheme 1. Fluorinations of β-dicarbonyl compounds investigated by Chambers et al. [13]. Selected reaction conditions and results are given. The last reaction was carried out in the tri-channel thin-film micro reactor, the others in the single-channel reactor version. The percentages below the products indicate their content in the raw product after solvent removal.

A selection of these reactions (and an additional one) was also carried out in the three-channel reactor version for demonstrating an increased throughput by numbering-up [13]. The feeding of the three channels is not described in detail. Temperature, fluid composition and flow rate per channel was kept constant. Conversion (apart from one case) and product composition seems to be roughly similar compared to the results of the single-channel reactor experiments. There is no explanation given for the great deviation on conversion in one case. Nevertheless, Chambers et al. pointed out by these experiments the principal feasibility of numbering-up for these fluorination reactions.

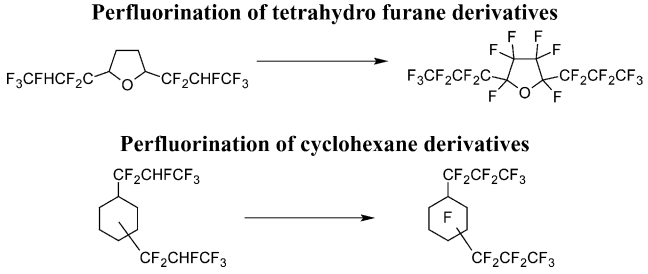
The syntheses of the organic sulfur pentafluorides was studied in the case of *meta* [13,36] and *para*-nitrophenylsulfur pentafluoride [36] (see Scheme 2). The *para*-derivative was synthesised starting with *para*-nitrophenylsulfur trifluoride obtained from batch fluorination of di(*para*-nitrophenyl) disulfide in the single-channel thin-film micro reactor [36]. The *meta*-derivative was synthesised directly from di(*meta*-nitrophenyl) disulfide in one step in the (single-channel) micro reactor [36] and also in a two-step procedure as for the *para*-derivative with reaction finalisation in the (three-channel) micro reactor [13]. The two-step procedure started her with batch fluorination of di(*meta*-nitrophenyl) disulfide in acetonitrile as solvent. The conversion was 62%. The reaction mixture containing the sulfur trifluoride was then pumped with a flow rate of 7.3 ml/h (0.51 mmol/h) per channel through the micro reactor (kept at 20 °C) and contacted with a fluorine stream. The obtained raw product contained 56% of the pentafluoride.

The investigated perfluorination reactions (see Scheme 3) were investigated in the single-channel thin-film micro



Scheme 2. Synthesis of organic sulfur pentafluorides studied by Chambers et al. in the single-channel thin-film reactor [36].

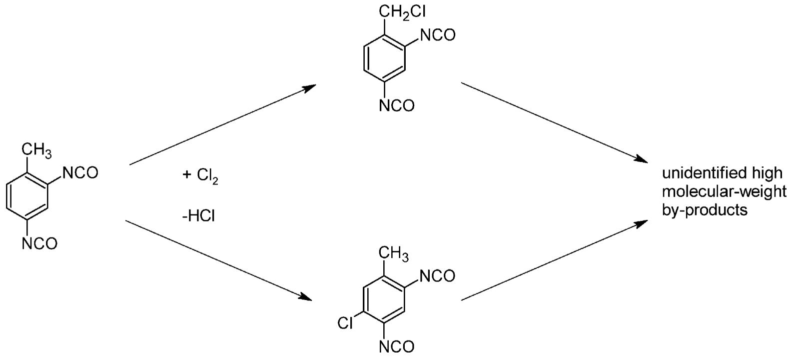
reactor with an additional heating stage connected to the outlet for completion of the reaction [36]. For some of the examples described here significantly lower temperature can be used to achieve as high yield of the perfluorinated product as when employing traditional reactors. Furthermore the use of cobalt trifluoride employed as catalyst in traditional reactors is not necessary [36]. Another important aspect of the experiments is that these hazardous perfluorination processes can be carried safely out in micro reactors with high yield [36].



Scheme 3. Perfluorinations of organic compounds studied by Chambers et al. [15]. Reagents and conditions: (i) 0.5 ml/h, 50% F_2 in N_2 (15 ml/min), room temperature; (ii) 0.5 ml/h, 50% F_2 in N_2 (15 ml/min), room temperature, then 280 °C; (iii) 0.5 ml/h, 20% F_2 in N_2 (20 ml/min), room temperature; (iv) 0.5 ml/h, 50% F_2 in N_2 (10 ml/min), room temperature, then 50 °C; (v) 0.5 ml/h, 50% F_2 in N_2 (15 ml/min), room temperature, then 280 °C.

4. Chlorination reactions in micro reactors

4.1. Photochlorination of toluene-2,4-diisocyanates



Jähnisch investigated the photochlorination of toluene-2,4-diisocyanates [33]. Side-chain photochlorination of toluene isocyanates yield important industrial intermediates for polyurethane synthesis, one of the most important classes of polymers [33]. This gas/liquid reaction proceeds via chlorine radicals formed by photoinduced chlorine molecule cleavage. Performed at higher temperatures the chlorination of the side chain of the alkyl aromat is quite selective, yielding 1-chloromethyl-2,4-diisocyanatobenzene [38]. The electrophilic ring substitution, instead, is favoured using Lewis catalysts in polar solvents at low temperature. As a ring-substituted side product, toluene-5-chloro-2,4-diisocyanate is formed in minor quantities.

The motivation for micro-channel processing stems mainly from enhancing the performance of the photo-process. Illuminated thin liquid layers should have much higher photon efficiency (quantum yield) than given for conventional processing. Therefore, the most relevant micro reactor property in this context is the capability to provide thin liquid films. This is given for the selected falling film

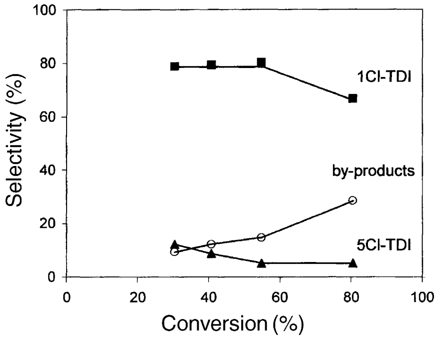


Fig. 12. Selectivities of main and side product as a function of toluene-2,4-diisocyanate conversion when using a nickel-plate equipped micro reactor (reactant ratio 1:1; 130 °C) [33].

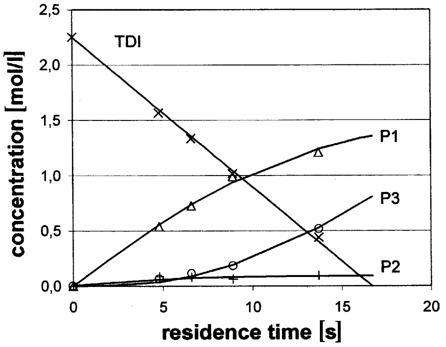


Fig. 13. Comparison of reaction product concentrations (symbols) and model (solid line) as a function of residence time given in [33]. Toluene-2,4-diisocyanate; 1-chloromethyl-2,4-diisocyanatobenzene (P1); toluene-5-chloro-2,4-diisocyanate (P2); high molecular consecutive products (P3) [33].

micro reactor. Besides increased photon efficiency, the mass transfer across the gas/liquid interface is also facilitated [38]. Both may lead to the use of low-intensity light sources and considerably decrease the energy consumption for a photolytic process [33,39]. Furthermore, the planar layer structure of the chosen falling film micro reactor yields a uniform illumination, which can be kept when increasing throughput by numbering-up [33]. Here, the individual reaction units could be assembled in parallel again on a plane, only a larger one. As another result, the residence time may be notably reduced, thereby decreasing side and follow-up reactions. Overheating as a consequence of using high-intensity light sources at low efficiency can be avoided, thus reducing thermally induced side reactions. The use of low-intensity light sources may change the technical expenditure needed for photoreactions and result in a complete different cost-investment scenario when building a new plant.

The reaction was investigated in a falling film micro reactor with reaction plates with channel dimension of 600 μm × 300 μm made of pure nickel and iron. The micro device was equipped with a quartz window transparent for the wavelength desired. A 1000 W xenon lamp was located in front of the window. The spectrum provided ranges from 190 to 2500 nm; the maximum intensity of the lamp is given at about 800 nm. For the range of flows applied (0.12, 0.23, 0.38 and 0.57 ml/min), the average film thickness was calculated to be 21–36 μm. The corresponding residence times and specific interfacial areas amount to 4.8–13.7 s and 28,000–48,000 m^2/m^3. The gas flow was in the range of 14–56 ml/min. This provides a equimolar ratio of toluene-2,4-diisocyanate and chlorine. A solution of 0.1 mol toluene-2,4-diisocyanate (14.4 ml) in 30 ml tetrachloroethane was used (concentration: 3.3 mol/l). The reaction temperature was 130 °C.

Conversions from 30 to 81% at selectivities from 79 to 67%, respectively, yields from 24 to 54%, were found. A selectivity–conversion plot for the product, the ring-substituted by-product, and other, so far unidentified by-products is shown in Fig. 12. While the content of the ring-substituted product decreased with increasing conversion (12–5%), the other by-products were formed in much larger amount (8–29%). This also indicates that the other by-products are formed by consecutive reactions at longer residence times. Control experiments in a batch reactor (30 ml reaction volume) at 30 min reaction time resulted in a conversion of 65% at 45% selectivity. Interestingly, the selectivity of the ring-substituted by-product is 54%, different from the more dominant resin-formation in the micro reactor (see Fig. 12). The superior performance of the micro reactor is explained by the better photon yield stemming from the use of very thin liquid films. The low penetration of light in the conventional batch reactor generates largely reaction conditions which are not photoinduced, hence favouring ring-chlorination.

The effect of flow rate was also investigated. When using lower flow rates, conversion is increased as a consequence of both increasing residence time and decreasing film thickness [33]. Reducing flow rate from 0.57 to 0.12 ml/min leads to an increase in conversion from 30 to 81%. Selectivity is nearly unaffected, with the exception of the smallest flow rate. Considered from the residence time side, conversion increases as a function of residence time linearly from 30 to 81% at selectivities from 79 to 67% [33]. The associated yield increase is non-linear and seems to approach a plateau (Fig. 13). Hence residence times much larger than 14 s are not suited anymore to increase reactor performance.

The impact of Lewis-acid formation on the reaction course was tested by using an iron plate (instead of a non-active nickel plate), the impact of Lewis-acid formation on the reaction course could be tested [33]. As a result, the selectivity to the target product drops drastically, e.g. at a conversion of 80–50% (from 67% using a nickel plate). Interestingly, the content of ring-substituted isomer is not enhanced (actually it is reduced), but probably resin-type condensation products are formed instead yielding the product (Fig. 14).

Space–time yields up to 401 mol/(l h) in the case of usage of a nickel reaction plate and 346 mol/(l h) in the case of the usage of an iron reaction plate were achieved in the falling film micro reactor [33]. The control experiments in a batch

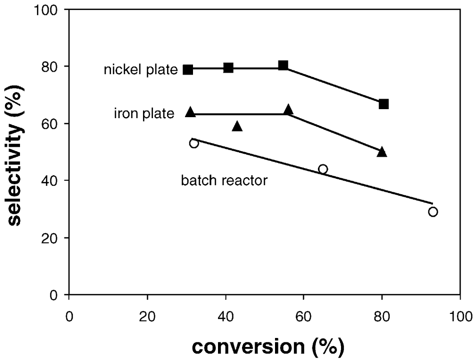


Fig. 14. Influence of different reactor materials on selectivity for 1-chloromethyl-2,4-diisocyanatobenzene and toluene-2,4-diisocyanate conversion [33].

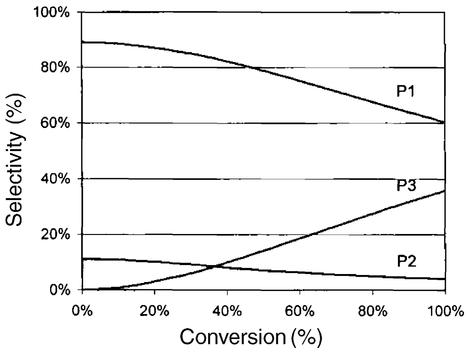
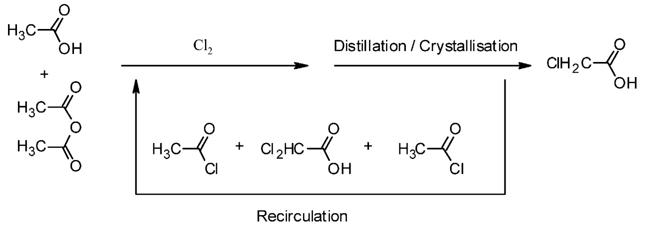


Fig. 15. Simulated selectivity vs. conversion of toluene-2,4-diisocyanate. P1 is the target product 1-chloromethyl-2,4-diisocyanatobenzene; P2 is the side-product 5-toluene-5-chloro-2,4-diisicyanate; P3 represents high molecular consecutive products [33].

reactor resulted in a space–time yield of only 1.3 mol/(l h), hence are by orders of magnitude smaller.

The experiments were supplemented by reaction modelling assuming *plug-flow* behaviour and taking into account consecutive elemental reactions. Therewith the dynamic development of the species' concentrations was predicted [33]. The modelling fits well to experimental data when a reaction order of 0.1 is used (compare Fig. 15 with Fig. 12).

4.2. Chlorination of acetic acid under gas/liquid conditions



The motivation of an industrial development performed by Clariant/Frankfurt was to increase selectivity for mono-chlorination of acetic acid to give chloro acetic acid [39]. This product is amenable under reaction conditions by further chlorination to give dichloro acetic acid by consecutive reaction. The removal of this impurity is not simply possible, but rather demands for laborious and costly separation. The consecutive reaction will be triggered by too long exposure of already chlorinated product in an environment with high density of chlorine radicals. Accordingly, controls over residence time, concentration profiles and efficient heat transfer have the potential to cope with such problem.

This process is carried out on an industrial scale in bubble columns [39]. Acetic acid and acetic anhydride are fed together with a recycle solution composed of acetic acid, acetyl chloride, mono-chloro acetic acid, dichloro acetic acid, and hydrogen chloride. Under these conditions, acetic anhydride and hydrogen chloride give spontaneously acetyl chloride. This mixture is fed into bubble columns and contacted to chlorine gas at 3.5 bar and 115–145 °C. A typical reaction mixture has a composition of 38.5% acetic acid, 11.5% acetic anhydride, and 50% chlorine gas. The crude product is first purified by distillation. Thereafter, either crystallisation or hydrogen reduction at Pd catalyst is conducted to separate the mono-chlorinated from the di-chlorinated product.

The employed micro reactor is a modified falling film micro reactor (also termed micro capillary reactor in [39]). The exact design is not disclosed. Micro-channels of 1500 μm width and 300 μm depth, separated by fins of 150 μm width, were employed. Experiments were performed using acetic acid and 10, 15, or 20% acetyl chloride. The mass-flow rate was set at 45 g/min and a temperature of 180 or 190 °C were applied. Chlorine gas was fed at 5 or 6 bar in co-flow mode that a residual content of only 0.1% results after reaction.

By micro flow processing a yield of 85% was obtained similar to large-scale bubble column processing [39]. Selectivity was much better since only less than 0.05% dichloro acetic acid was formed, while conventional processing typically gives 3.5%. Increasing both temperature and pressure slightly, increases the yield from 85 to 90%.

4.3. Chlorination of alkanes in the gas phase

$$R_mC_nH_{2n+2-m}\xrightarrow{Cl_2}R_mC_nH_{2n+2-m-o}Cl_o$$

An industrial investigation carried out by Siemens-Axiva/Frankfurt on pilot-scale studied the radical chlorination of alkanes in the gas phase using a micro heat exchangers [37,40]. It was known from prior studies in a reactor consisting of two conventional tubes, one for pre-heating and one for heating, placed in an oven each that too slow approaching reaction temperature and overheating are detrimental for reactor performance, i.e. decreasing conversion and space–time yield. Accordingly, a micro reactor with fast thermal ramping and without overshoots for the process fluids is requested. This way, the radicals formed can be most efficiently utilised for reaction, without losses, e.g. by recombination.

Therefore a micro heat exchanger was employed which substituted the conventional pre-heater. In terms of plant construction, the implementation of two such micro devices in a pilot-scale industrial chlorination plant is a good example for multi-scale processing, as only the pre-heating tube was replaced by a micro heat exchanger, while the conventional tube, encompassed by a large oven, still was used for reaction. The externally heated micro heat transfer modules used for pre-heating are several times smaller than the former used combination of a long tube reactor and a surrounding oven.

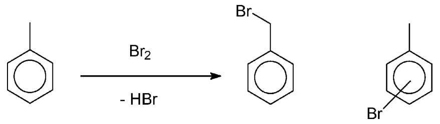
With this hybrid-plant configuration, using two micro heat transfer modules in series and a conventional tube reactor attached, a significant increase in conversion by about 25% was achieved (500 °C; 0.3–2.3 s; 500 l(STP)/h; 0.4 bar). Selectivity increases with decreasing residence time, both for the conventional two-tube reactor and the micro module-tube reactor configurations. The equal performance of micro and macro processing is explained by running the process at the thermodynamic equilibrium. The micro heat transfer modules exhibited a steep increase in temperature of the processing fluid. A 10 times faster heating up of the reactants is achieved as compared to the conventional pre-heating tube. This way, the operating temperature is reached without thermal overshoots. The residence time in the micro heat transfer modules amounts to 10 ms; it is 3 ms when referred to the micro-channels only. The residence time in the conventional tube reactor is 400 ms. When using a conventional pre-heating tube, instead of the micro module, its residence time equals that of the reactor tube, i.e. by micro-flow heating the time could be reduced by a factor of 40. With a hybrid-plant configuration, using two micro heat transfer modules and a conventional tube reactor attached, a significant increase of space–time yield of about 240–430 g h^{-1} l^{-1} was achieved (Fig. 16) (500 °C; 0.3–2.3 s; 500 l(STP)/h; 0.4 bar).

The hybrid-plant configuration could be run for 24 h without shutdown. Thereafter, starting corrosion of the micro device was observed. However, this did not lead to immediate shutdown [37,40].

5. Bromination reactions in micro reactors

The authors investigated bromination of a range of organic compounds using elemental bromine without using any solvents in a micro mixer/tube combination. Different to the reactions described so far the halogenation media is fed as a liquid and not as a gas into the reactor. The phase behaviour in the micro reactor can be quite complex and is strongly dependent on the selected reaction conditions. Mixing in the micro mixer is—at least for temperatures below the boiling point of bromine—initially a liquid/liquid process, but on-set of the reaction and thereby formation of gaseous hydrogen bromide already in the mixer led to a gas/liquid system. Considering the tube section, the phase behaviour could additionally change at higher temperatures through evaporated bromine in the gas phase. Some experiments with pressure (2–3 bar) applied to the system were also performed with a direct impact on the gas/liquid phase behaviour. Although, the aim of applying pressure was mainly to reduce the necessary reactor volume, it has to kept in mind that this may also influence the reaction pathway, e.g. by a change in solvent polarity through a higher content of dissolved gas in the liquid phase. The great range of phase conditions makes comparison of experimental results obtained under different reaction conditions often difficult. The precise description of phase behaviour was not the focus of the investigations. Rather, it was aimed to get a broad overview about the potential of micro reactors in a range of reactions covering different syntheses tasks. Micro reactor processing thereby addresses the following aspects: transformation of batch in continuous-processing, avoidance of solvents, safe processing, increase of space–time yields, influence of process conditions on selectivity and yield and fast experimentation.

5.1. Bromination of toluene



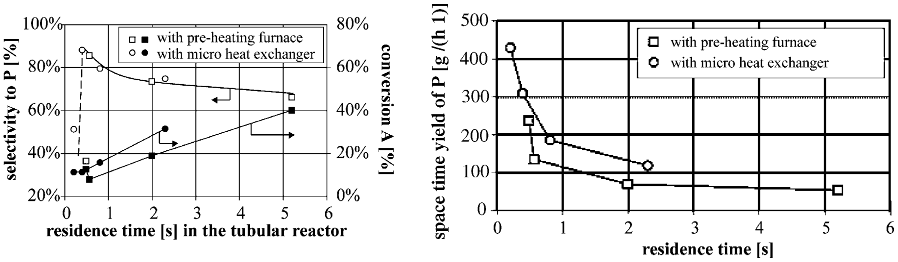


Fig. 16. Selectivities and space–time yields for the hybrid-plant configuration, using two micro heat transfer modules and a conventional tube reactor attached, and for the conventional tube-reactor plant [37].

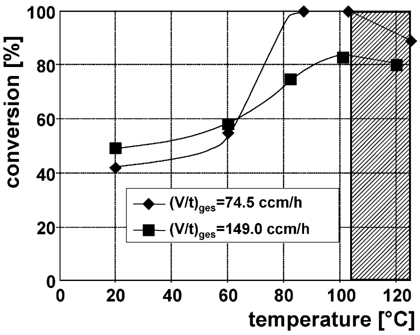


Fig. 17. Conversion of toluene as a function of temperature for two different total flow rates.

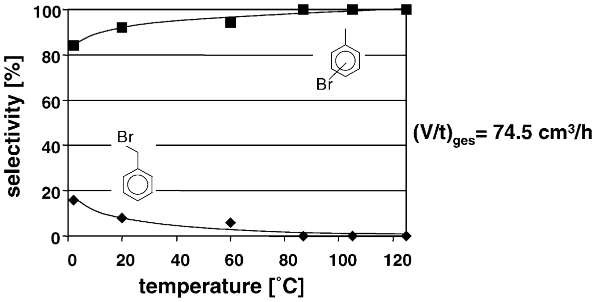


Fig. 18. Selectivity in the bromination of toluene as a function of temperature for a total flow rate of 74.5 cm^3/h.

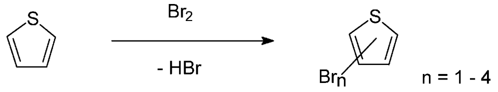
Bromination of toluene was investigated with regard to product distribution as a function of different reaction conditions [41]. Focus thereby laid on competing formation of benzylbromide and the three bromotoluene isomers. Multi bromination was not aim of the reactions carried out. The molar ratio of bromine to toluene was 1:1. A tube section of 2.5 m length corresponding to an inner volume of 4.9 cm^3 was used. Two different total flow rates were applied (74.5 and 149.0 cm^3/h). As rough estimation for residence time in mixer and tube section one can assume single/liquid phase conditions. Therewith, residence time in the mixer is 96 ms (48 ms) and 3.9 min (2.0 min) in the tube section for a total flow rate of 74.5 cm^3/h (149.0 cm^3/h). Taking into account gas formation (hydrogen bromide)—which is more realistic—also on an assumption (conversion of bromine of 50%, hydrogen bromide as ideal gas) residence time in the tube section reduces dramatically to only 3.0 s (1.5 s) for a total flow rate of 74.5 cm^3/h (149.0 cm^3/h).

In a set of experiments temperature was varied between 0 and 120 °C. The triangular interdigital micro mixer was used. The feeding line of toluene, the mixer and the tube section were embedded in the same thermostated bath. Bromine was fed at room temperature. The system was open to atmospheric pressure. For both investigated total flow rates, conversion increases with temperature up to 100 °C, while a decrease was observed going from 100 to 120 °C (Fig. 17). Full conversion is achieved for a total flow rate of 74.5 cm^3/h at 80 and 100 °C, while at the higher flow rate no complete conversion was observed probably because of the reduced residence time. The decrease of conversion for 120 °C can also be attributed to a reduced residence time caused by evaporation of toluene.

The corresponding selectivities are shown in Fig. 18 for a total flow rate of 74.5 cm^3/h. As expected only low selectivities of benzylbromide are obtained, decreasing with an increase in temperature. No significant differences for the two flow rates were observed. The determined ratio 4-bromotoluene to 2-bromotoluene ranges from 1.6 to 1.8. Multiple bromination products were not detected. It was tried to promote side-chain bromination by irradiation of the glass mixer. No significant impact was observed, probably because of the short residence time of the reaction mixture in the mixer.

The same experiments were performed with applying about 1–2 bar of pressure to the system. For these experiments the triangular interdigital micro mixer was substituted by the caterpillar micro mixer CPMM-R600/12 PVDF. A remarkable increase in selectivity of benzylbromide formation was observed. This is not understood by now. It is also not clear if this is (only) an effect of pressure or (also) of the changed mixer.

5.2. Bromination of thiophene



Bromination of thiophene was investigated with regard to multiple bromination [41]. Therefore molar ratios of bromine to thiophene ranging from 1.0 to 5.0 were applied. Again a tube section of 2.5 m length was used. The system was open to atmospheric pressure, the total flow rate was kept constant at 93.5 cm^3/h. The feeding line of thiophene, the mixer and the tube section were embedded in the same thermostated bath. Bromine was fed at room temperature. The triangular interdigital micro mixer was used.

In the investigated temperature range spanning from 0 to 60 °C complete conversion of bromine was observed when applying a molar ratio of bromine to thiophene of 1.0. The corresponding product distribution is given in Fig. 19. The ratio between single and two-fold substituted thiophene is quite constant over the investigated temperature range. Furthermore, an increase of tri-fold substitution product is observed with higher temperatures.

In another set of experiments the molar ratio of bromine to toluene was varied from 1.0 to 5.0 at constant temperature of 50 °C. Fig. 20 shows the found product distribution. For all experiments thiophene conversion is complete; also the conversion of bromine at high molar ratio bromine to thiophene is still high (about 70% for a ratio bromine to thiophene of 5.0).

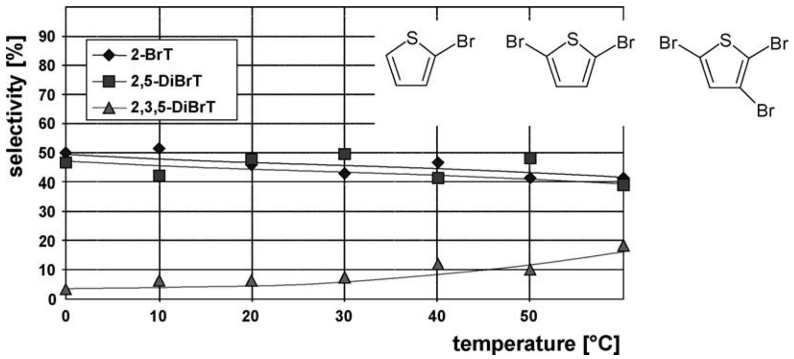


Fig. 19. Product distribution as a function of temperature for the bromination of thiophene using 1 equiv. bromine.

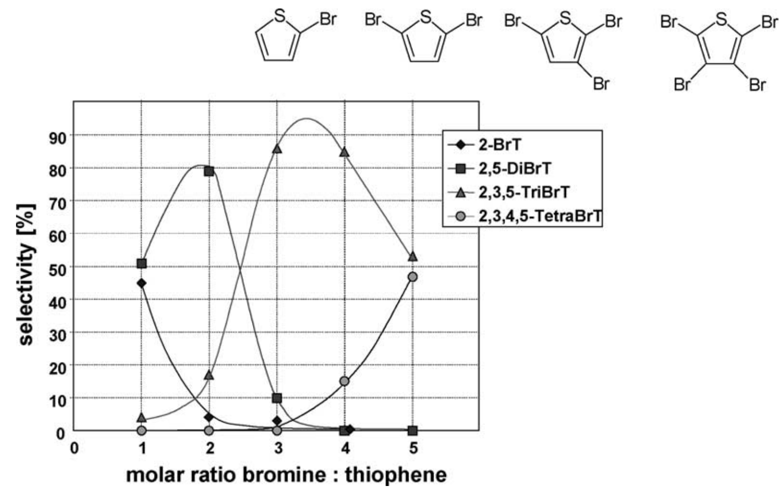
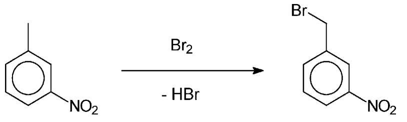


Fig. 20. Product distribution for the bromination of thiophene as a function of molar ratio bromine to thiophene at 50 °C.

5.3. Bromination of meta-nitrotoluene



The bromination of *meta*-nitrotoluene is an example for a high-temperature side-chain bromination. The transformation from batch to continuous processing, the safe operation with bromine at temperatures over 170 °C and the decrease of reaction time/increase of space–time yields were of special interest here. Molar ratios of bromine to *m*-nitrotoluene ranging from 0.25 to 1.00 were applied. A tube section of 1.9 m length with an inner volume of 3.8 cm^3 was used. The system was open to atmospheric pressure, the flow rate of *m*-nitrotoluene was kept constant at 85.7 cm^3/h. Different bromine flow rates were applied (9.0, 19.0 and 37.0 cm^3/h). The reactants are contacted at room temperature in an interdigital micro mixer. Only the tube section was embedded in a thermostated bath. Residence time lies between 1.9 and 2.4 min assuming single phase condition and about 2.5–9.9 s assuming 30% hydrogen bromide formation. Temperature was varied between 170 and 190 °C.

Fig. 21 shows the conversion of bromine as a function of temperature and molar ratio. A complete conversion of bromine was not achieved probably the residence time is too

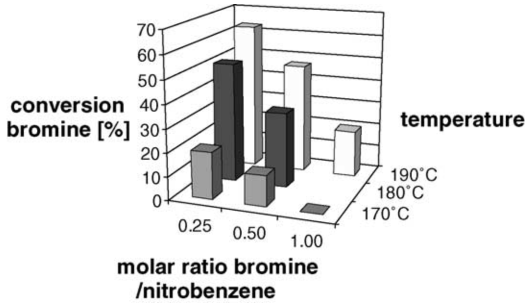


Fig. 21. Conversion of bromine in the bromination of *m*-nitrotoluene as a function of molar ratio bromine to *m*-nitrotoluene for different temperatures.

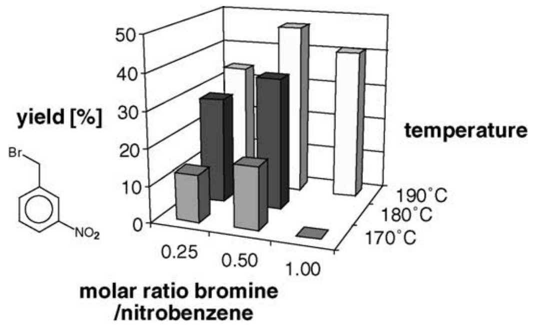


Fig. 22. Yield on benzylbromide derivate in the bromination of *m*-nitrotoluene as a function of molar ratio bromine to *m*-nitrotoluene for different temperatures.

short because of great amounts of bromine in the gas phase at these high temperatures. Conversion of bromine increases with temperature. Since beside the benzylbromide derivate no significant amounts of further products were detected, yield also increases with temperature. The dependency of yield on molar ratio shows an optimum behaviour (Fig. 22). This can be attributed to the short residence time not sufficient for complete conversion. An increase of bromine content over an optimum does not lead to further conversion improvement, since an increase of bromine also means more bromine in the gas phase which reduces residence time.

With the selected continuous set-up, up to 17 experiments a day were performed, underlining the potential for an accelerated process development.

6. Summary and outlook

The principal feasibility of performing halogenations of organic compounds using the elemental halogens in micro reactors has been demonstrated. The range of micro reactors thereby comprises specialised tools for g/l-contacting, gas phase micro heat exchanger and micro mixer/tube combination meeting different requirements for different classes of reactions. Enhancements in selectivity, conversion and space–time yields are given. It is also worth mentioning that partly process improvements could be achieved within months needed for scouting studies, while literature attempts on the same subject with conventional equipment lasted over decades and still seem to give inferior results. Naturally, reactors can and should be further optimised, but the results of the described reaction examples are already justifying a broader use of this technology.

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