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Continuous Production of the Diazomethane Precursor *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide: Batch Optimization and Transfer into a Microreactor Setup

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Abstract:

The goal of this study was to develop a continuous multistep synthesis for the preparation of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (3, MNTS, Diazald) starting from *p*-toluenesulfonyl chloride (1), making use of microreaction technology (MRT). MNTS is an important precursor for diazomethane, a highly reactive and selective reagent for the production of pharmaceuticals and fine chemicals. Due to the properties of the successive reaction steps (exothermic reactions, use of toxic and highly reactive reagents), it was envisaged that MRT could provide advantages when compared to its batch-wise preparation. The research strategy included preliminary batch investigations, in which the effects of the solvent system, feed concentration, relative molar ratio, temperature, and residence time were established. Starting from these results, the reactions were translated into the MRT setup. As a result, the amidation of 1 to *N*-methyl-*p*-toluenesulfonamide (2) as the first reaction step is performed continuously in >90% yield and maximum space-time yields of up to 75 kg L^{-1} h^{-1}. By making use of salting-out effects, the product separates nearly quantitatively in high concentrations in organic solution from the saline-waste stream. It is continuously converted to 3 by addition of $NaNO_2$ with quantitative conversions: yields of >90% and maximum space-time yields of up to 9 kg L^{-1} h^{-1}. The method presented allows for the connection of the diazomethane precursor preparation to its continuous liberation by addition of a base, and conversion with a substrate, as previously demonstrated using MRT (Struempel, M.; Ondruschka, B.; Daute, R.; Stark, A. *Green Chem.* 2008, *10*, 41).

Introduction

Diazomethane (**4**, CH_2N_2) is valued for its reactivity and selectivity under mild conditions in a plethora of reactions[1,2] important for the production of pharmaceuticals and fine chemicals. However, due to its rather unpleasant properties (reactivity, toxicity, explosiveness, gaseous state), it is commercially not available as such, but in 'deactivated' precursor forms such as *N*-methyl-*N*-nitrosourea and, more importantly, *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS),[3] from which it is liberated by addition of a base and reacted *in situ*. Most applications are thus restricted to small scale in specialized apparatus,[4] e.g. derivatizations for analytical purposes. For industrial applications, it has been demonstrated that the liberation of diazomethane from a precursor and its successive conversion is feasible,[5,6] but requires elaborate safety equipment.[7]

The most important precursor is MNTS (**3**), which in addition to being a methylating agent can also be used for nitrosations under mild conditions.[8,9] This compound is less hazardous, albeit still carcinogenic[10,11] and sensitizing.[12] Being a solid, it is more facile to store and to handle in a process than is gaseous diazomethane.

Although **3** is commercially available, its on-demand production for the direct liberation of diazomethane and its conversion with the desired substrate would make the industrial production independent from delivery specifications and fluctuations in demand, in particular for small- and medium-sized businesses (SMBs) producing fine chemicals and specialties. A further advantage is the reduced cost for the provision of **3**, since the starting materials **1**, methylamine, $NaNO_2$, and HCl are relatively inexpensive basic chemicals.

Especially with regard to handling dangerous compounds, microreaction technology (MRT) has shown great potential: the high surface/volume ratio allows for efficient heat exchange, even for highly exothermal reactions.[13−16] The system is

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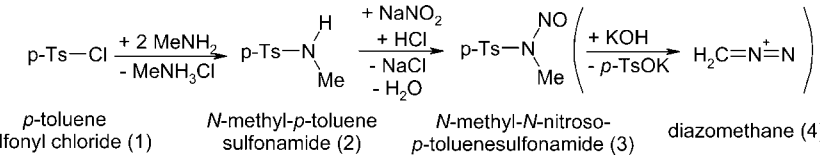
Scheme 1. **Multistep synthesis of the diazomethane precursor MNTS (3) and the *in situ* liberation of diazomethane, starting from *p*-toluenesulfonyl chloride (1)**



equipped with several temperature and pressure sensors, and automatically shuts down if certain threshold values are overshot. Additionally, due to low spacio-temporal concentrations in such enclosed, continuously operating setups, the risk of exposure for operating personnel and environment is dramatically reduced.

With regard to research and development expenditure, numbering-up instead of scaling-up may prove a valuable tool to reduce development time. Furthermore, the modular setup of MRT-based production lines allows for the flexible manufacture of chemicals in the same setup with short changeover times.

The continuous liberation of diazomethane from its precursors and its conversion in a microreaction setup have been demonstrated previously on the model compound benzoic acid.[17,18] Hence, it is the goal of this contribution to provide an efficient multistep synthesis for the diazomethane precursor MNTS (**3**) making use of a continuous microreactor setup.

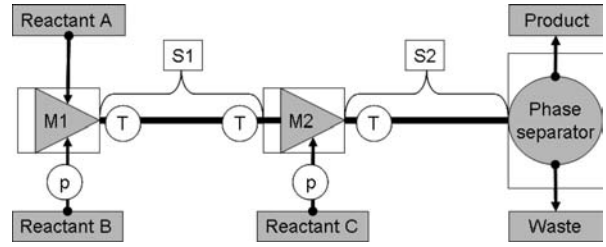
A literature search was conducted to determine the most efficient synthetic strategy starting from readily available starting materials, leading to the design of a two-step synthesis. Starting from *p*-toluenesulfonyl chloride (**1**), *N*-methyl-*p*-toluenesulfonamide (**2**) is produced by amidation with methylamine, followed by nitrosation to *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (**3**, MNTS) using $NaNO_2$ under acidic conditions (Scheme 1).

In order to avoid precipitation and thus clogging in the microreactor, preliminary data had to be obtained in batch experiments, with emphasis on solvent choice, concentrations, and relative ratios of reactants. In addition, the times required to complete the reaction and heat development observed in batch experiments were used as an indication for the initial setup (e.g., with regard to residence time and cooling unit, respectively). These conditions were transferred to the microreactor setup, where further improvements were achieved by alteration of residence times and flow rates. Finally, the combination of the single reaction steps to a stable continuous pilot plant was accomplished.

Experimental Section

Chemicals. Chemicals and solvents were obtained from Sigma-Aldrich (*p*-toluenesulfonyl chloride (**1**, 97%), *N*-methyl-*p*-toluenesulfonamide (**2**, 98%), *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (**3**, MNTS, 99%), sodium hydrogencarbonate (99.5%), sodium nitrite (40% aq), methylamine (40% aq),

Scheme 2. **Continuous microreactor setup used for the amidation or nitrosation (P = pressure sensor, T = temperature sensor, M = mixer device 1 or 2, S = residence section 1 or 2)**



toluene (98%), ethanol (98%), carbitol (98%)) or Merck Chemicals (hydrochloric acid (25 and 32% aq), THF (98%), acetonitrile (99%), dioxane (98%), diethyl ether (98%), ethyl acetate (98%)), and were used as received.

All experiments were carried out in a fume-hood. Batch experiments were carried out on 10 mM scale.

Continuous Setup. The working mechanism of the continuous microreactor setup is shown in Scheme 2.

As mixing devices, either a commercially available Y-shaped micromixer (mixer A, Little Things Factory GmbH, Ilmenau, Germany, type ST MI018, 0.12 mL internal volume, channel dimensions 1.4 × 1.8 × 125 mm disregarding static mixing elements) was used. For comparison, a PTFE-capillary (Upchurch Scientific, Oak Harbor, USA, inner diameter 1.55 mm, no mixing elements) connected to simple T-pieces (mixer B, PTFE) was used. The fluid streams were generated by a microdosing syringe pump MDSP3f, i-14 (Micro Mechatronic Technologies GmbH, MMT, Siegen, Germany). The setup was centrally controlled with a computer, for which a control and automation program was developed with the visual programming software Agilent Vee Pro 8.5. Additionally, the setup was equipped with temperature sensors (0−150 °C, Typ K, Ni-CrNi, Conatex GmbH, St.Wendel, Germany) and pressure sensors (0−10 bar, Typ 26PC, Sensortechnics) programmed for shutdown if the internal pressure reaches 5 bar.

Amidation. *Discontinuous Amidation.* **1** was dissolved in the respective solvent (acetonitrile, THF, dioxane, toluene, diethyl ether, carbitol, ethanol) in the required concentration (0.5−7.0 M) and treated with methylamine (40% aq, 1−9 mol equiv relative to **1**). The temperature rise of the exothermic reaction was monitored. The reaction was quenched by addition of an excess aqueous HCl (32% aq, 1.1 equiv relative to the theoretically remaining methylamine). Quantities of 10 μL were taken as samples, diluted with acetonitrile and water to 0.02 mol L^{-1}, and filtered (0.2 μm) where necessary. Analysis was carried out by HPLC (*vide infra*).

Continuous Amidation. Solutions of **1** in acetonitrile or THF (2−3 M) and methylamine (40% aq, 2.7−5.4 mol equiv relative to **1**) were dosed *via* PTFE capillaries into the mixing device 1

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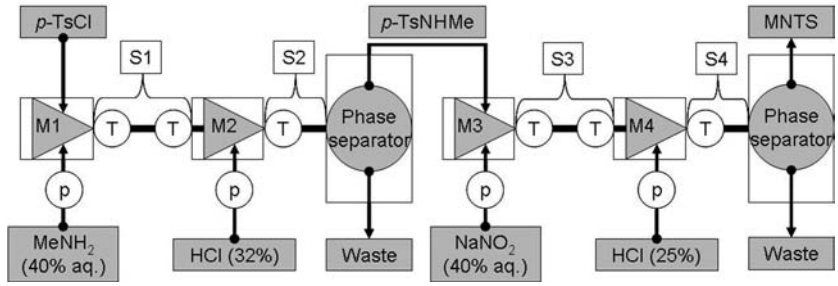
Scheme 3. **Combination of the microreactor setups of the amidation and consecutive nitrosation for the continuous production of 3 starting from 1 (P = pressure sensor, T = temperature sensor, M = mixer device, S = residence section)**



(mixer A or B, total flow rate 100−1080 mL h^{-1}), which was connected to the first residence section S1 (7 cm for mixer A (0.07 mL), 5−90 cm capillary for mixer B (0.09−1.7 mL)). The neutralization (32% aq HCl, 1.0−4.0 mol equiv relative to **1**) took place in the mixing device 2 equipped with a residence section S2 (5.5 cm for mixer A (0.05 mL) plus 75 cm capillary within mixer A (1.42 mL), 75 cm capillary for mixer B (1.42 mL)) and entered a phase separator (separating funnel) after total residence times of approximately 5−60 s. Temperature sensors were placed in front of S1 and S2, and behind S1. Pressure sensors were placed in the feed inlets of methylamine and HCl. When required, cooling was achieved by placing S1 and S2 in a stirred water bath or thermostat. The volumes of the phases obtained were determined and 10 μL samples taken for analysis.

Nitrosation. *Discontinuous Nitrosation.* **2** was dissolved in the respective solvent (acetonitrile, THF) at concentrations between 1 and 4 M, and treated with $NaNO_2$ (40% aq, 1.3−3.1 mol equiv relative to **2**). Acid (HCl, 25% aq, 2.0−3.0 mol equiv, or acetic acid, 1.3−10.0 equiv relative to **2**) was added dropwise. In all addition steps, the temperature was monitored. Cooling was not applied to quantify heat development. Quantities of 50 μL were taken as samples and neutralized by addition of 500 μL of a saturated $NaHCO_3$ solution. The sample was diluted to 3 mL with acetonitrile, filtered (0.2 μm), and analyzed by HPLC (*vide infra*).

In cases where a solution of **2** was used directly from the amidation, the addition of slightly overstoichiometric amounts of HCl relative to the theoretically remaining methylamine was sufficient prior to the nitrosation.

Continuous Nitrosation. The same setup as for the continuous amidation was used. In the mixing device 1 equipped with residence section S1 (7 cm for mixer A (0.07 mL), 5 cm capillary for mixer B (0.09 mL), a solution of **2** (0.5−3.0 M in THF or acetonitrile) was mixed with $NaNO_2$ (40% aq, 3 mol equiv relative to **2**). HCl (25% aq, 2.6 mol equiv relative to **2**) was added in the mixing device 2 before the residence section S2 (5.5 cm within mixer A (0.05 mL) plus either 200 or 260 cm capillary (3.80 or 4.91 mL) after mixer A, and 200 or 260 cm capillary for mixer B (3.80 or 4.91 mL)). The total flow rate of this reaction was between 90−540 mL h^{-1}, translating into a residence time of 33−200 s. Sample preparation was performed as in the discontinuous experiments.

In cases where the solution of **2** from the amidation was used directly (i.e., the organic phase), a second setup (Scheme 3) was connected to the phase separator, and M1, M2, S1, and S2 are hence extended by M3, M4, S3, and S4.

Analytics. Yields were determined using calibrations from commercial standards on a Jasco HPLC equipped with a Prontosil NC-04 (250 mm × 4 mm), 120-5-C18H 5 μm column from Bischoff Chromatography, using isocratic 50% water: 50% acetonitrile as eluent. Detection was achieved with an UV-diode array detector at 236 nm.

In cases where biphasic solutions resulted, the quantitative phase separation was often hampered because of the relatively small scale, and cross-contamination of the respective other phase occurred; the analytical error was thus estimated to be 10%.

Results and Discussion

Amidation. In the literature, various reports describe the discontinuous synthesis of **2**[19−21] with yields >70% on laboratory scale. Due to the exothermal behavior of the reaction, cooling is applied and the amine added slowly. An excess of amine is required to scavenge HCl formed during the reaction.

However, these batch procedures are not easily transferred to MRT, since oftentimes liquid−solid heterogeneous reaction mixtures are used or precipitation of the product occurs. Therefore, a simple procedure had to be developed for the amidation of **1** in a completely liquid environment under mild conditions. It should be mentioned here that the chosen method is clearly not applicable for large-scale batch synthesis, due to the fast reaction in conjunction with high heat development.

In the investigation presented herein, a commercially available aqueous solution of methylamine (40%) was used throughout for the amidation. Hence, finding a second solvent to homogenize and avoid solid precipitation was required, since **2** is a solid and insoluble in water.

The excess of amine was the second aspect: On the one hand, a 2-fold excess is theoretically required to drive the reaction to completion and avoid the formation of *N*-methyl-*N*,*N*-di(*p*-toluenesulfonyl)amide as a side product.[22,23] On the other hand, excessive amounts of amine are disadvantageous from an environmental and economic point of view.

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Table 1. **Solvent screening in the batch-wise conducted amidation of 1 to 2 using methylamine: phase behavior**

solvent	max concentration of **1** [mol L^{-1}][a]	no. of liquid phases[b]	ppt
carbitol	2.5	1	permanent after addition of HCl
dioxane	3.0	2	no
acetonitrile	3.0	2	no
THF	3.0	2	no
diethyl ether	0.5	2	temporary
toluene	1.0	2	temporary; permanent after addition of HCl
EtOH	1.0	1	no

[a] For other conditions and yields, see Table 2, entries 1−7. [b] Number of liquid phases formed during amidation; no change after acidification with HCl, if not otherwise indicated.

Table 2. **Selected results of the batch-wise amidation (including acidification with HCl) of 1**

entry	solvent	**1** in org. solvent [mol L^{-1}]	mol equiv of $MeNH_2$ rel. to **1**	total yield [%]
1	carbitol[a]	2.5	3.0	96.4
2	dioxane[a,b]	3.0	3.0	86.4
3	acetonitrile[a]	3.0	3.0	97.4
4	THF[a]	3.0	3.0	90.8
5	diethyl ether[a]	0.5	3.0	93.7
6	toluene[a]	1.0	3.0	98.2
7	EtOH[a]	1.0	3.0	91.7
8	diethyl ether	0.5	1.5	44.9
9	diethyl ether	0.5	2.2	65.3
10	diethyl ether	0.5	3.7	98.5
11	toluene	0.5	1.3	61.7
12	toluene	0.5	2.2	95.2
13	toluene	0.5	3.4	99.5
14	acetonitrile[c]	0.5	0.7	27.5
15	acetonitrile[c]	0.5	1.5	57.6
16	acetonitrile[c]	0.5	2.2	82.4
17	acetonitrile[c]	0.5	3−9	90−100

[a] Results of experiments displayed in Table 1, T = autothermal, t = 10−15 min. [b] Experiments refer to experiments shown in Figure 1. [c] Experiments refer to experiments shown in Figure 2, yields quoted are for the organic phase only; yield of entry 17 for molar equivalents of methylamine between 3−9.

Discontinuous Amidation. A solvent screening was conducted to determine solvents which allow for high reactant concentrations while avoiding the formation of temporary or permanent precipitates during the amidation and the successive acidification. Table 1 shows selected results of these investigations. Up to 3 M solutions of **1** can be processed without the occurrence of precipitates in dioxane, acetonitrile, and THF, while lower concentrations were achieved with carbitol and ethanol. Temporary precipitation occurred in toluene and diethyl ether (≤1.0 M in toluene, ≤ 0.5 M in diethyl ether), while permanent precipitations were observed at higher concentrations. In the case of carbitol and toluene, solids formed after the acidification with HCl. Except for carbitol and ethanol, a biphasic liquid−liquid system was obtained. In all instances, boiling of the solvent occurred at concentrations of **1** > 2.5 mol L^{-1} due to the exothermic nature of the reaction.

Table 2 (entries 1−7) shows that high yields (90−98%) of **2** result in this fully selective reaction in all cases with the exception of dioxane, in which a somewhat lower yield of 86% was obtained. Overall, the reaction outcome appears to be independent of the solvent used.

The influence of the ratio of methyl amine relative to **1** was tested (Table 2). In any of the solvents used, the yield increased with increasing ratio, with quantitative yields obtained if an excess of 2.5−3 mol equiv is used. For stoichiometric compositions (2 mol equiv of methylamine) conversions are quantitative, but the yield of **2** is <100%. This phenomenon is not fully understood, but may have its origin in the formation of *N*-methyl-*N*, *N*-di(*p*-toluenesulfonyl)amide, which has been described to occur at substoichiometric compositions[22,23] but was not detected with the HPLC method currently employed.

The time dependence was next investigated. It was found that the amidation reaction takes place immediately and is completed already after a few seconds, as can be seen from the first exotherm occurring (Figure 1). The second exothermal event observed relates to the heat development during the acidification with HCl. The sensitivity of the thermosensor detects very precisely the progress of the reaction. This is reflected in the constant temperature rise (to about 70 °C for 1 M solutions of **1** in carbitol, and to about 90 °C for 3 M solutions of **1** in dioxane) during the amidation step, irrespective of the molar equivalents of methylamine used, while the heat development of the neutralization is proportional to the excess methylamine. These findings allow for two conclusions for the transferal of the reaction to the continuous MRT setup. First, due to the high reaction rates, very short residence times are required. Second, the efficient heat exchange properties known for microreactors[13−16] will be beneficial to control these fast and highly exothermic reactions.

As pointed out above (Table 1), some solvents which are in principle water-miscible, such as acetonitrile and THF, showed liquid−liquid phase separation at certain ratios of methylamine/**1**, which was further enhanced by the addition of HCl in the quench. This salting out effect can be beneficially used in the process to separate the product-rich organic phase from the saline waste phase and introduce it directly into the next step, the nitrosation. Several investigations relating to the phase behavior in dependence of the concentration of **1**, methylamine and the solvent gave a complex picture. For example, the mitigation in yields for acetonitrile, shown in Figure 2 for >4 mol equiv of methylamine is due to this phenomenon; the remaining product traces are found in the aqueous phase.

Other water-soluble solvents, such as ethanol and carbitol, did not result in biphasic systems. Although these also gave **2** in high yields, they were not further investigated as the maximum initial concentrations of **1** are rather low (see Table 1). Furthermore, an additional separation step would be required in these instances to reduce the saline load.

From these investigations, optimal conditions were derived: high feed concentrations are achieved in acetonitrile or THF (<3 M **1**), and at molar excesses of 2.5−3 equiv of amine relative to **1**, quantitative yields result. In this instance, the total volume was reduced by 35−40% aqueous solution, whereas >90% of **2** remained in the organic phase. Further analysis of this phase revealed a water content <5% (automated Karl-Fischer titration), and the concentration of **1** was below the detection limit of the HPLC analysis (<0.03 mol L^{-1}) in the

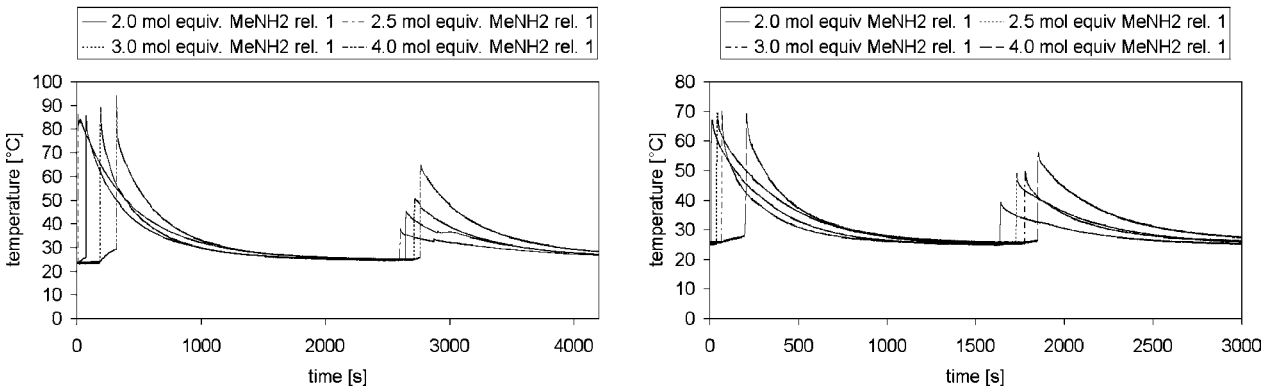

Figure 1. **Temperature profile of the amidation of 1 with methylamine (40% aq) followed by neutralization with HCl (32% aq). Left: 1 M 1 in carbitol; right: 3 M 1 in dioxane.**

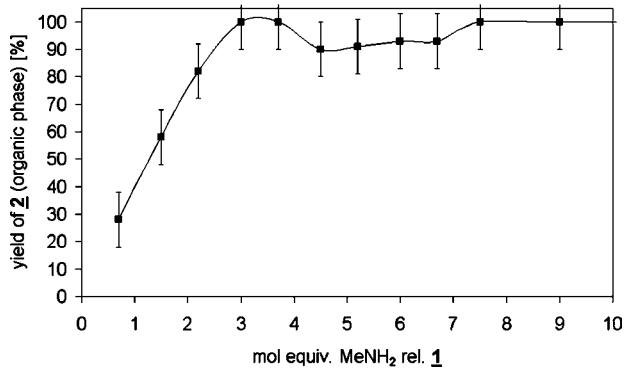

Figure 2. **Effect of the amount of methylamine on the yield of 2 in the organic phase (0.5 M 1 in acetonitrile, autothermal, 10 min).**

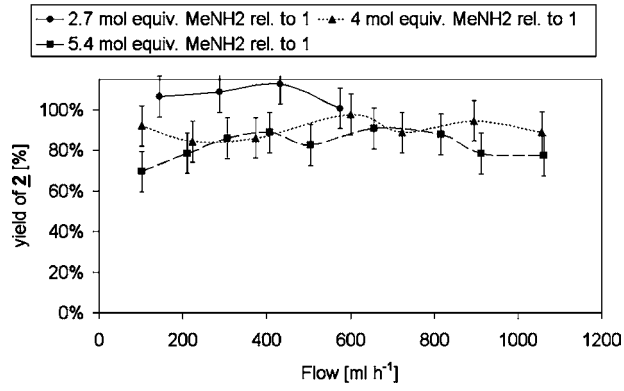

Figure 3. **Dependence of the yield of 2 obtained in the continuous amidation of 1 with methylamine on the theoretical flow rate at various excesses of methylamine (2.5 M 1 in acetonitrile).**

samples taken. The chloride content was determined to be 3.0% of the total chloride derived from **1**, i.e. before acidification (automated chloride titration against $AgNO_3$).

Continuous Amidation. During the transfer of the optimized conditions obtained in batch mode, it occurred that with 3.0 M solutions of **1** in acetonitrile and THF, slightly turbid solutions resulted at the outlet of the microreactor, which were, however, processable without clogging. Hence, the amount of methylamine was varied between 2.7−5.4 mol equiv with respect to **1** under continuous reaction conditions, and the effect of the adjusted (theoretical) flow rate (100−1080 mL h^{-1}, Figure 3) was investigated. Within the analytical error, no effects on the yield (90−100%) were observed in an autothermal setup, allowing for extremely low calculated residence times (5−60 s). However, considerable fluctuations resulted due to the boiling of the solvent (formation of gas bubbles). THF gave results similar to those of acetonitrile in all cases.

Table 3. **Five-hour run of the continuous amidation of 1 in THF with methylamine (2.7 equiv rel. to 1)**

operation time [h][a]	>5
S1, S2	90 cm (1.7 mL) and 75 cm (1.4 mL) PTFE-capillaries
mixer amidation	mixer A
mixer acidification	mixer B
c(**1**) [mol L^{-1}]	3.0
flow rate [mL h^{-1}]	60
c($MeNH_2$) [mol L^{-1}]	11.6
flow rate [mL h^{-1}]	42
c(HCl) [mol L^{-1}]	12.0
flow rate [mL h^{-1}]	24
averaged total yield [%]	104 ± 10
average experimental flow rate [mL h^{-1}]	107 ± 8
Δp [bar]	0.2 ± 0.1
ΔT [°C][b]	0.5 ± 0.2
STY [kg L^{-1} h^{-1}]	11.2 ± 1.0
capacity [kg h^{-1}]	0.04 ± 0.003

[a] Values averaged over 17 samples, each drawn after 20 min of continuous operation. [b] Setup temperature controlled with thermostat at 23 °C, temperatures measured directly after M1 and after residence section 1, outside thermostat fluid.

The reaction was found to be independent of the mixer type (Y-shaped micromixer, T-piece). However, with mixer B (T-piece), the variation of the residence sequence S1 is more flexible, as the length of the PTFE-capillary is easily varied. In order to reduce the fluctuations of the flow rate (due to boiling of the solvent), S1 of the capillary was extended to 90 cm (1.7 mL) and cooled using a water bath. It was found that the temperature decreases to about 20 °C at the end of S1, with the flow being steadier. As for the residence section S2, a capillary length of 75 cm (1.4 mL) was maintained to allow for the control of the exothermic HCl quench. At the highest flow rate tested (1080 mL h^{-1}, Figure 3), a space-time yield (STY) of approximately 75 kg L^{-1} h^{-1} is obtained, which translates into a capacity of 0.23 kg h^{-1} of this setup with a reaction volume of 3.1 mL.

The stability of this process step was tested in a 5-h continuous run in a temperature-controlled setup (Table 3) at a total flow rate of 126 mL h^{-1}. From the temperature profile

obtained, a start-up time of 20 min was estimated before the steady-state of the system would be achieved. It should be noted that the standard deviation results from the fact that a biphasic mixture results, which is difficult to quantitatively separate on a relatively small scale. An averaged experimental flow rate of 107 mL h^{-1} was determined by measuring the volume output every 20 min. It deviates from its theoretical flow rate due to nonideal mixing behavior of the solutions. The average yield obtained during this experiment is quantitative.

In summary, the transfer of the optimum amidation reaction conditions into the continuous microreactor setup was accomplished without problems. Either acetonitrile or THF can be used as solvents, with 2.5−3.0 M concentrations of **1**, 2.7 mol equiv of methylamine, and 1 mol equiv of HCl relative to **1**. As in the discontinuous experiments, a biphasic system resulted, in which >90% yield (at 100% conversion) is isolated with the organic phase (containing, beside the product, <5% water and 3% chloride). Both mixer types gave comparable results. Although the reaction is extremely fast and does not require long residence times, the addition of a water-cooled residence section S1 (90 cm) and S2 (75 cm) to allow for efficient cooling and, hence, reduced fluent fluctuation is advisible. With an optimum flow rate (1080 mL h^{-1}) and a calculated residence time of 13 s, a maximum STY of up to 75 kg L^{-1} h^{-1} is achieved. A 5-h continuously conducted experiment showed that the system is sufficiently stable for small-scale production.

Nitrosation. For the nitrosation of **2** to **3**, a method was adapted from literature[19,24,25] using aqueous acidic $NaNO_2$. Conventionally, the acidic environment for $NaNO_2$ is provided by addition of acetic acid, and in only a few cases has HCl[26] been reported.

Discontinuous Nitrosation. In batch experiments, the nitrosation of **2** was optimized with respect to the type of acid, the reaction time, the type of solvent, the ratio of acid and $NaNO_2$ with respect to **2**, and the concentration of the reactants in solution.

According to literature,[27] the nitrosation is carried out at 0 °C. However, in order to obtain information about the heat development during the reaction, experiments were carried out autothermally while recording the solution temperature. In all instances, the temperature rise was uncritical with <30 °C.

In the optimization experiments, acetonitrile and THF were used as these were the most efficient solvents in the preceding reaction step (*vide supra*).

In general, an excess $NaNO_2$ is needed for complete nitrosation, due to partial decomposition to nitrous gases such as NO and NO_2. Investigations in the range of 1.3 to 3.1 mol equiv of $NaNO_2$ relative to **2** (1 M **2** in acetonitrile, 7-fold excess of acetic acid relative to **2**, 4 h) showed that a 2.5−3.0-fold excess $NaNO_2$ to **2** gives quantitative conversions. Similar considerations affect the ratio of acid to **2**, because $NaNO_2$ requires acidic conditions to release the active species NO^+.

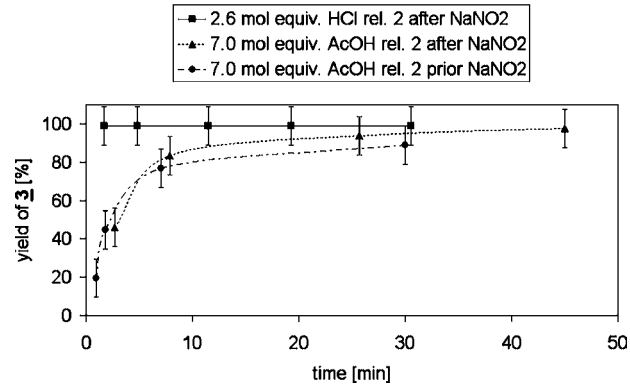

Figure 4. **Nitrosation of 2 to 3 with $NaNO_2$: Dependence of the total yield on the reaction time for different protocols (3 M 2 in THF, 7 mol equiv of acetic acid or 2.6 mol equiv of HCl, and 3 mol equiv of $NaNO_2$ relative to 2).**

With acetic acid, which is mainly used in literature,[24,25] a 7-fold excess is required to obtain best performance, whereas with HCl, only a 2.6-fold excess is needed (1 M **2** in acetonitrile, 3-fold excess $NaNO_2$ relative to **2**, 4 h). Economic considerations as well as the atom efficiency[28,29] (NaCl-waste vs CH_3CO_2Na-waste) favor HCl. Additionally, with acetic acid, a single liquid phase and frequent precipitations also restrict the transfer into MRT. HCl instead is a driver for liquid−liquid phase separation, especially in water-miscible solvents. Only HCl as 25% aqueous solution (or lower) gives precipitation-free reactions, because otherwise $NaNO_2$ becomes insoluble.

An investigation of the dependency of the reaction time (3 M **2** in THF, 7 mol equiv of acetic acid or 2.6 mol equiv of HCl, and 3 mol equiv of $NaNO_2$ relative to **2**) showed, that with HCl the product is formed immediately (<1 min), whereas with acetic acid, the product is formed quantitatively only within 15 min, despite the higher acid concentration (Figure 4). Only after very long reaction times (several days), does decomposition of the product **3** occur, thus allowing for the production of the diazomethane precursor somewhat in advance to its usage.

As in the amidation, the reaction mixture separates into a biphasic liquid−liquid system in both solvent systems. The slightly yellow organic phase contains the product **3** (about 90% of the total yield).

In order to run the process at the highest possible substrate concentrations of **2** in THF or acetonitrile, concentration studies were carried out, which showed that up to 4 M of **2** can be converted, but at >1 M, the solution becomes turbid, and **3** precipitates slowly at >3 M. Hence, the highly concentrated product solution from the amidation can be used without having to change solvents. This was tested in batch experiments (one-pot synthesis); although nitrous gases developed and led to foaming, consistent yields were obtained. The reaction outcome is independent of the sequence of adding acid and $NaNO_2$ to **2**. However, mixing $NaNO_2$ with acid before addition of **2** is disadvantageous, as $NaNO_2$ decomposes unselectively prior to reacting with **2**. This is evidenced by the formation of larger amounts of gases (bubbles and brown fumes).

In conclusion, optimal batch conditions for the transfer into MRT, considering economic and ecological aspects, were

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Table 4. **Five-hour run of the continuous nitrosation of 2 in THF with $NaNO_2$**

operation time [h][a]	>5
S1	14.5 cm (0.3 mL)
S2	12.5 cm (0.12 mL) within mixer A and 200 cm (3.8 mL) PTFE-capillaries
mixer for **2** with $NaNO_2$	mixer B
mixer for addition of HCl	mixer A
c(**2**) [mol L^{-1}]	3.0
flow rate [mL h^{-1}]	30
c(HCl) [mol L^{-1}]	7.5
flow rate [mL h^{-1}]	30
c($NaNO_2$) [mol L^{-1}]	7.5
flow rate [mL h^{-1}]	30
average total yield [%]	101 ± 8.5%
theoretical flow rate [mL h^{-1}]	90
Δp [bar]	1.5 ± 0.5
ΔT [°C][b]	8.0 ± 0.5
STY [kg L^{-1} h^{-1}]	4.6 ± 1.0
capacity [kg h^{-1}]	0.02 ± 0.005

[a] Values averaged over 12 samples, each drawn after 20 min of continuous operation. [b] Setup not cooled, temperatures measured directly after M1, M2 and after residence section 2.

determined to be 3 M solutions of **2** in THF or acetonitrile, 2.6 mol equiv of HCl and 2.5−3 mol equiv of $NaNO_2$ relative to **2**, at a reaction time <10 min. These conditions lead to quantitative conversion of **2** and highest yields (>90%) of **3** in the organic phase.

Continuous Nitrosation. The optimized conditions of the batch experiments (2.5 mol equiv of HCl, 2.5 mol equiv of $NaNO_2$ relative to **2**) were adapted to the continuous mode. All reactions were carried out autothermically.

Experiments were conducted to investigate the effect of the residence time (by variation of the flow rate between 90 and 540 mL h^{-1}). It was found that the total yield increased from 70% to 100% for residence times between 30 and 100 s and remained constant thereafter (up to 210 s tested). For a given preadjusted flow rate of 180 mL h^{-1}, the required length of the residence section S2 is hence theoretically >260 cm. Under these conditions, STYs of up to 9 kg L^{-1} h^{-1} (capacity: 0.04 kg h^{-1}) were achieved. Experimental flow rates and residence times could not be determined, as the formed gases highly accelerated the flow and led to fluctuation and pressure rise.

Table 4 shows the conditions and results obtained during a 5-h continuous production of **3** at a theoretical flow rate of 90 mL h^{-1}, demonstrating the good stability of the system, even if fluctuations of the flow occur due to the formation of nitrous gases. Quantitative yields are obtained.

Using a microreactor adds the advantage that liberation of hazardous gases can be controlled, and with the closed system, no cooling is required to reduce the amount of nitrous gases to a minimum.

In conclusion, the transfer of the optimized batch conditions to MRT leads to a high-performance continuous process with good STYs of 9 kg L^{-1} h^{-1} and a capacity of 0.04 kg h^{-1} at a optimum flow rate of 180 mL h^{-1} with the presently used setup. Furthermore, these conditions also match the resulting product phase of the preceding amidation. The combination to a closed process unit is thus the logical consequence.

Combination of Amidation and Nitrosation. The two continuous synthetic steps were connected to a single process step, advantageously exploiting the phase separation occurring after the amidation to reduce the overall saline load. All residence sections were cooled in a water bath (20 °C). **1** is mixed with methylamine and reacted in residence section S1, HCl is added to quench the amidation (S2). The reaction mixture separates in a separation funnel. The organic top phase containing most of the product **2** (2.7−3 M solution) is continuously fed into M3, where it is mixed with the aqueous $NaNO_2$ solution, followed by the introduction of HCl into M4 (Scheme 3). Using this methodology, an overall yield of **3** starting from **1** of 70−80% has been achieved. The experimental setups described in Tables 3 and 4 were used for this investigation.

A calculation of the chemical costs at kg-scale, taking into account net prices of fine chemical catalogues, indicated a price of approximately 40 Euros/mol MNTS, disregarding personnel costs and apparatus expenditure.

Combination of Nitrosation with Diazomethane Liberation and Conversion. Previous work has focused on the liberation of diazomethane from its precursor MNTS by addition of an alcoholic KOH solution, and successive conversion of a model compound in a continuously operated micoreactor.[17] It has been demonstrated that yields of 75% and a production rate of 2.5 mol product (the model compound methyl benzoate) per day are achievable using a single efficient micromixer, with flow rates between 100 and 800 mL h^{-1}. In that study, the diazomethane liberation and conversion was best achieved in carbitol, since in THF, precipitation occurred. Precipitation was also a problem in carbitol solution, however, at maximum MNTS concentrations of <0.4 mol L^{-1}, a homogeneous reaction mixture was maintained.

Hence, to prove the concept, the concentrated organic feed from the nitrosation (2.5 mol L^{-1}) was washed with a saturated $NaHCO_3$ solution and diluted with carbitol to 0.4 mol L^{-1}. This solution was then used in the methylation of the model compound benzoic acid, under the conditions described previously.[17] Without further optimization, quantitative conversions of MNTS and yield of 50−60% of the desired methyl benzoate were obtained, demonstrating the connectivity of these reaction steps.

Therefore, future research can focus on the fine-tuning of the successive reaction steps in conjunction with the transfer to industrially relevant reactions of diazomethane.

Conclusions

In conclusion, an efficient two-step synthesis for the diazomethane precursor MNTS has been developed, making use of a continuous microreactor setup. Starting from readily available starting materials, *p*-toluenesulfonyl chloride is converted by amidation to *N*-methyl-*p*-toluenesulfonamide, followed by nitrosation to *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide using $NaNO_2$ under acidic conditions. Deliberate solvent choice allows for the conversion of highly concentrated solutions at yields >90% in both single steps, with the added advantage of liquid−liquid phase separation due to salting out effects. This phenomenon reduces the saline load, and hence the risk of

precipitation to a minimum. Batch-wise extraction of the aqueous phases may be used to recover the remaining traces of products from each resulting aqueous phase. The methodology presented allows for the connection of the diazomethane precursor preparation to its liberation by addition of a base, and conversion with a substrate, as previously demonstrated using MRT.[17]

Both the amidation and nitrosation are exothermic reactions, which are advantageously carried out using MRT and its excellent heat dissipation properties. This aspect, due to the inherently low spacio-temporal concentrations, renders the manufacture of the diazomethane precursor operationally safe.

In the light of the recent shortage of acetonitrile on the world market, flexible solvent choice has become more important with respect to economic MNTS production. Hence, the similar performance of both acetonitrile and THF with regard to yields, maximum concentrations of feeds, and phase separation is beneficial.

Overall, this methodology now allows for the production and conversion of the diazomethane precursor MNTS **3** on site and on demand. This possibility reduces the risk of chemical storage considerably and achieves independence from the delivery times for MNTS, especially for SMBs.

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