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Addition of Secondary Amines to α,β-Unsaturated Carbonyl Compounds and Nitriles by Using Microstructured Reactors

H. Löwe,*[†,§] V. Hessel,[‡,§] P. Löb,[§] and S. Hubbard[⊥]

Johannes Gutenberg University Mainz, Institute of Organic Chemistry, Duisbergweg 10-14, 55128 Mainz, Germany, Eindhoven University of Technology, Chemical Engineering and Chemistry, 5600 MB Eindhoven, PO Box 513, STW 1, 35, The Netherlands, IMM Institut für Mikrotechnik Mainz GmbH, Carl Zeiss Strasse 18-20, 55129 Mainz, Germany, and Europa Fachhochschule Fresenius, Department of Chemistry and Biology, Limburger Strasse 2, 65510 Idstein, Germany

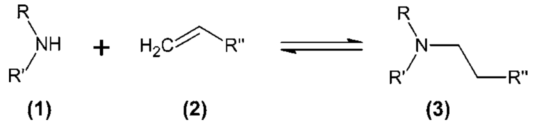
Abstract:

Several additions of amines to α,β-unsaturated carbonyl compounds (Michael additions) were performed in a continuous-flow microstructured reactor rig and compared to the respective batch reaction. Dimethylamine/diethylamine/piperidine and acrylic acid ethyl ester/acrylonitrile were employed as two sets of reactants, giving six reactions. Some of these reactions are highly exothermal. Using the traditional batch procedure the olefin must be added quite slowly to the diluted amine to ensure temperature control and safe operation; especially this is necessary for the addition of dimethylamine (40 mass % aqueous solution) to acrylonitrile. Good yields (>85%) are achieved in this way; however, processing time is very long (17−25 h). To reveal the intrinsic kinetic potential and thus to accelerate these reactions, the reactants were mixed in a continuous-flow microstructured reactor rig which allows rapid mixing and efficient removal of the reaction heat. In this way, reaction time was decreased to a few seconds up to about half an hour, which is a change by 2 orders of magnitude. While the yields achieved with the continuous-flow microstructured reactor rig matched those for the batch procedure, the space-time yields for the microflow processing are much higher, in the best case by a factor of about 650.

1. Introduction

Additions of amines to α,β-unsaturated carbonyl compounds such as acrylic acids, acrylic acid esters, or acrylonitrile have been well investigated and are thus one of the constituting organic synthesis pathways for modern chemistry of today.[1] In this variant of the Michael addition, the C═C bond reacts with nucleophilic compounds, e.g., secondary amines, due to the transfer of electrons from the carbonyl group or from carbonyl analogues such as nitriles. As a result, the nucleophilic amine is added on the C═C double bond. The activity found for the α,β-unsaturated nitriles is generally higher than for the α,β-unsaturated acrylic acid esters.

According to the overall high reactivities, amines **1** easily add to the α,β-unsaturated carbonyl compounds **2** at ambient temperature even without any catalyst.



(1) **(2)** **(3)**

with R, R' = alkyl-
R" = -COOR, -CN

This reaction is reversible at high temperatures above 200 °C. Therefore, the reverse pathway, the thermal cleavage of a secondary amine from **3** is also exploited as common procedure to form α,β-unsaturated carbonyl compounds.

With the use of a batch procedure these reactions give good yields, in some cases more than 85%; however, the protocols recommend long reaction times of up to 24 h. This long reaction time is for most reactions not caused by the intrinsic kinetics but by the high exothermicity that causes selectivity issues. In order to enable safe removal of the heat created by the reaction, it is necessary to add quite slowly the α,β-unsaturated compound to the amine.[2]

These characteristics indicate that the use of a continuous flow rig with microstructured reactors may accelerate the performance of the reaction without losing thermal control as, obviously, rapid mixing of the reactants as well as efficient heat removal have to be ensured. Such capability of this novel approach has been demonstrated many times, even under demanding processing conditions.[3−8]

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* To whom correspondence should be addressed. E-mail: loewe@uni-mainz.de.

[†] Johannes Gutenberg University Mainz.

[‡] Eindhoven University of Technology, Chemical Engineering and Chemistry.

[§] IMM Institut für Mikrotechnik Mainz GmbH.

[⊥] Europa Fachhochschule Fresenius.

(1) Ranu, B. C.; Dey, S. S.; Hajra, A. Solvent-free, catalyst free Michael-type addition of amines to electron-deficient alkenes. *ARKIVOC* **2002**, *2,* 76−81.

(2) Autorenkollektiv, *Organikum*, 15th ed.; VEB Deutscher Verlag für Grundstoffindustrie: Berlin, 1981.

(3) Chang, C.-H.; Liu, S.-H.; Doneanu, A.; Tennico, Y.; Rundel, J. T.; Remcho, V. T.; Blackwell, E.; Tseng, T.; Paul, B. K. *Progress towards high-throughput dendrimer synthesis*; AIChE Spring National Meeting, Atlanta, GA, U.S.A., 10−14 April, 2005.

(4) Liu, S.; Chang, C.-H.; Paul, B. K.; Remcho, V. T. High-rate synthesis of lower generation dendrimers with a continuous flow microreactor. In preparation.

(5) Schwalbe, T.; Autze, V.; Hohmann, M.; Stirner, W. Novel Innovation Systems for a Cellular Approach to Continuous Process Chemistry from Discovery to Market. *Org. Process Res. Dev.* **2004**, *8*, 440−454.

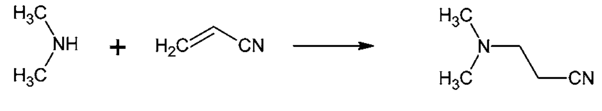
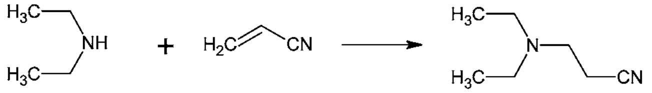
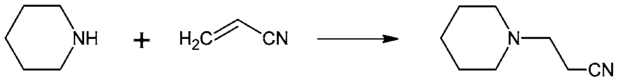
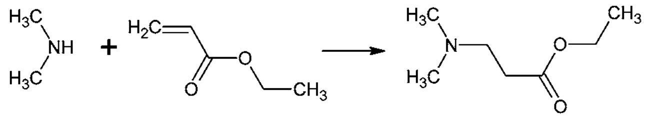
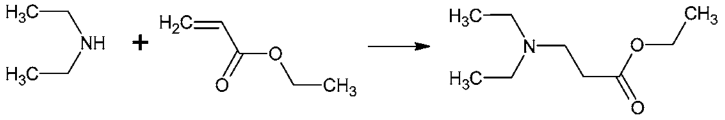
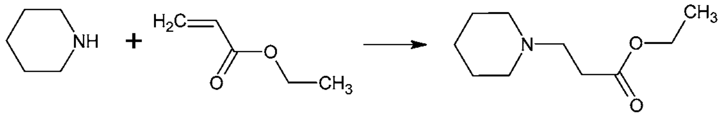
(6) Pennemann, H.; Watts, P.; Haswell, S.; Hessel, V.; Löwe, H. Benchmarking of Microreactor Applications. *Org. Process Res. Dev.* **2004**, *8*, 422−439.

(7) Pennemann, H.; Hessel, V.; Löwe, H.; Forster, S.; Kinkel, J. Improvement of Dye Properties of the Azo Pigment Yellow 12 Using a Micromixer-Based Process. *Org. Process Res. Dev.* **2005**, *9*, 188−192.

(8) Hessel, V.; Hofmann, C.; Löwe, H.; Meudt, A.; Scherer, S.; Schönfeld, F.; Werner, B. Selectivity Gains and Energy Savings for the Industrial Phenyl Boronic Acid Process Using Micromixer/Tubular Reactors. *Org. Process Res. Dev.* **2004**, *8*, 511−523.

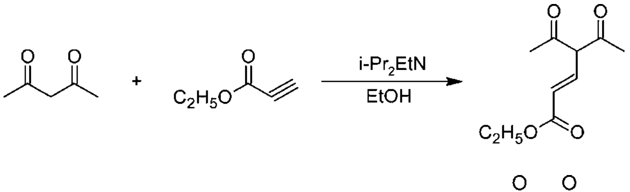
10.1021/op0501949 CCC: $33.50

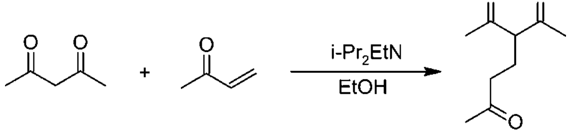
Table 1. **Additions of amines to α,*β*-unsaturated carbonyl compounds**[a]

Synthesis of 3-dimethylamino propionitrile, Reaction (R1)
 **(1a)** **(2a)** **(3a)**
Synthesis of 3-diethylamino propionitrile, Reaction (R2)
 **(1b)** **(2a)** **(3b)**
Synthesis of 3-piperidino propionitrile , Reaction (R3)
 **(1c)** **(2a)** **(3c)**
Synthesis of 3-dimethylamino propionic acid ethyl ester, Reaction (R4)
 **(1a)** **(2b)** **(3d)**
Synthesis of 3-diethylamino propionic acid ethyl ester, Reaction (R5)
 **(1b)** **(2b)** **(3e)**
Synthesis of 3-piperidino propionic acid ethyl ester, Reaction (R6)
 **(1c)** **(2b)** **(3f)**

[a] **1a**: pure substance or dissolved as 40 mass % water solution. **1b**: pure substance or dissolved as 40 mass % ethanol solution. **1c**: pure substance.

In literature, there are several reports on the use of microstructured reactors for Michael additions (using enolates of 1,3-dicarbonyl compounds, instead of the amines used here) to couple to α,*β*-unsaturated alkene or alkyne-based derivatives. Among others, the addition of 2,4-pentanedione enolate to ethyl propiolate and the addition of 2,4-pentanedione enolate to methyl vinyl ketone was investigated.[9]





These Michael additions were made in smart, glass chip-type devices under electroosmotic flow conditions. Thus, flow rates were very low, in the mL/h range, and the investigations were analytically oriented. For the first reaction, a conversion of 56% was achieved (batch synthesis:

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(9) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. 1,4-Addition of enolates to α,*β*-unsaturated ketones within a micro reactor. *Lab Chip* **2002**, *2,* 62−64.

89%).[9] Using stopped-flow technique (2.5 s with field applied; 5.0 s with field turned off) to enhance mixing, a conversion of 95% was determined. In a further study, substrates with diketone moieties of known different reactivities, such as 2,4-pentadione, benzoyl acetone, and diethyl malonate, were processed, each with the same acceptor ethyl propiolate. Also, a reaction with the less alkynic Michael acceptor methyl vinyl ketone was carried out. The conversions observed followed the sequence of reactivity found by carrying out batch experiments in advance. For example, only 15% conversion was found for the less reactive reagent benzoyl acetone in the microreactor experiment, while a 56% conversion was determined when using the more reactive 2,4-pentadione (batch syntheses: 78% and 89%, respectively).[9] Using stopped-flow to enhance mixing, the conversions for both syntheses were increased to 34% and 95%, respectively. Using a further improved stopped-flow technique (5.0 s with field applied; 10.0 s with field turned off), conversion could be further enhanced to 100% for the benzoyl acetone case. For the two other substrates, diethyl malonate and methyl vinyl ketone, similar trends were observed.

In terms of processing time, the microreactor synthesis turned out to be much faster than the batch synthesis. To achieve comparable amounts of conversion, 24 h operation time was needed for batch synthesis, whereas microreactor operation needed only about 20 min.[9]

One application for the type of Michael addition using amines reported here is the synthesis of dendrimers, e.g., built up from polyamidoamine (PAMAM). Ethylene diamine reacts with methyl acrylate to form the first half-generation, and from there, further branching occurs. By using a continuous-flow microstructured reactor rig, the reaction time could be shortened from 96 h (batch) to 13 s (microstructured reactor) at 99% yield without any detectable side products.[3]

2. Experimental Section

2.1. Materials. As secondary amines, dimethylamine (“dissolved”, 40 mass % in water, Aldrich), dimethylamine (“pure”, gas, Air Liquide), diethylamine (purum ≥ 99.0%, Fluka), piperidine (purum ≥ 99.0%, Fluka) were considered in this investigation. As α,β-unsaturated compounds, acrylonitrile (purum ≥ 99.0%, Aldrich) and acrylic acid ethyl ester (purum ≥ 99.0%, Aldrich) were taken.

2.2. Reactions. Table 1.

2.3. Batch Processing. For reasons of comparison, most of the reactions were performed additionally as batch process. A common Michael addition protocol was used,[2] with some minor variations as indicated below. All batch processes were carried out in a 500-mL three-necked flask, equipped with a magnetic stirrer, reflux cooler, thermometer, and a tap funnel. The reactions were performed by slowly dripping the acrylic compound into the dissolved and diluted amines. To ensure thermal control of the reactions the reaction mixture was cooled by an external water bath.

Reactions R1 and R4. An amount of 1.0 mol acrylonitrile **(2a)**/acrylic acid ethyl ester **(2b)** was added drop by drop under vigorous stirring to a 40 mass % solution of 1.1 mol dimethylamine **(1a)** in water. The temperature was kept constant at 30 °C. After 16 h/24 h, respectively, the reaction mixture was analyzed by GC (Table 2).

Table 2. **Comparison of yields for the batch reactions of a stirred 40 mass % aqueous solution of dimethylamine with acrylonitrile (R1) and with acrylic acid ethyl ester (R4)**

	reaction R1	reaction R4
yield (GC)	95.6%	92.5%
literature	96%[20]	87%[21]

Table 3. **Comparison of yields for the batch reactions of a stirred 40 mass % aqueous solution of diethyl amine/piperidine with acrylonitrile (R1/R3) and with acrylic acid ethyl ester (R5/R6)**

	reaction R2	reaction R3	reaction R5	reaction R6
yield (GC)	97.1%	99.7%	99.1%	99.8%
literature	85%[2]	90%[2]	85%[22]	–

Reactions R2, R3, R5, and R6. An amount of 1.0 mol acrylonitrile **(2a)**/acrylic acid ethyl ester **(2b)** was added dropwise under stirring to 1.1 mol amine **(1b–c)** dissolved in 150 mL of ethanol. The process parameter and the analytical procedure were the same as those used for reactions R1 and R4 (see Table 3). Higher yields were found for the performed experiments compared to the literature values, which can be attributed to the fact that conversion was determined by GC directly from the raw reaction mixture without purification steps that lead to loss of yield (Table 3).

2.4. Microstructured Reactors. A slit-type interdigital micromixer (SIMM-V2/Ag40, IMM Institut für Mikrotechnik Mainz GmbH, Germany) was chosen as a microreactor. This device is made of stainless steel and reaches flow rates of about 2 L h^{-1} at a pressure drop of 2.8 bar for water (which is about the limit for the type of pumps used). The mixer is suited for pressures up to 100 bar (using stronger pumps, e.g., HPLC) and temperatures of 200 °C. Inside the mixer, an inlay of 11 mm × 7.5 mm × 3.6 mm size provides interdigitally grouped microstructured channels (width 40 μm and depth 300 μm; material: silver on copper) which ensure the formation of alternate fluid streams. These streams are guided through a tiny confinement of slit shape where they are considerably compressed. In this way, the SIMM-V2/Ag40 mixer thus relies on multilamination and geometric focusing to speed up diffusion between lamellae being only a few 10 μm thick (Figure 1). Segregation indices in the range of about 10^{-3} to 10^{-5} are found, depending on the flow rate.[10–13] By analytical calculations, a mixing time can be derived from this which ranges 0.8–5 ms.

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(10) Hessel, V.; Löwe, H.; Müller, A.; Kolb, G. *Chemical Micro Process Engineering - Processing and Plants;* Wiley-VCH: Weinheim, 2005.

(11) Hessel, V.; Hardt, S.; Löwe, H.; Schönfeld, F. Laminar mixing in different interdigital micromixers - Part I: Experimental characterization. *AIChE J.* **2003**, *49*, 566–577.

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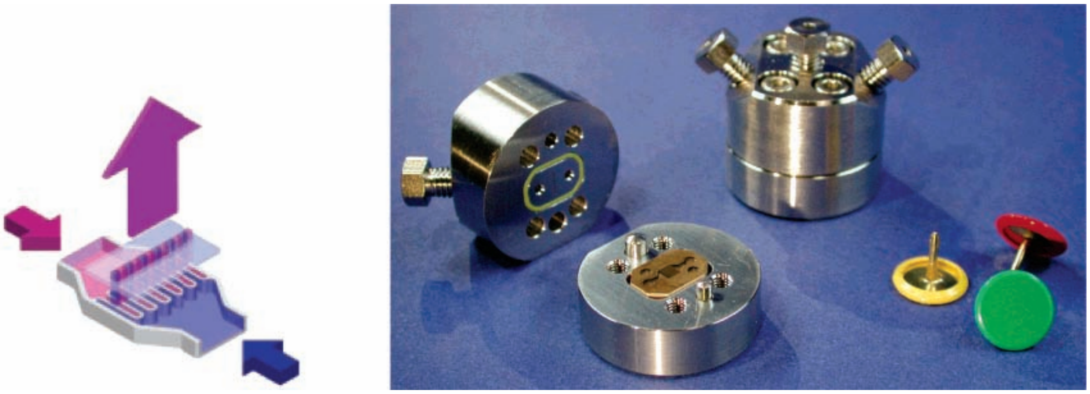

Figure 1. **Mixing principle of slit-interdigital mixer (left) and image of the used device SIMM-V2 (right)**

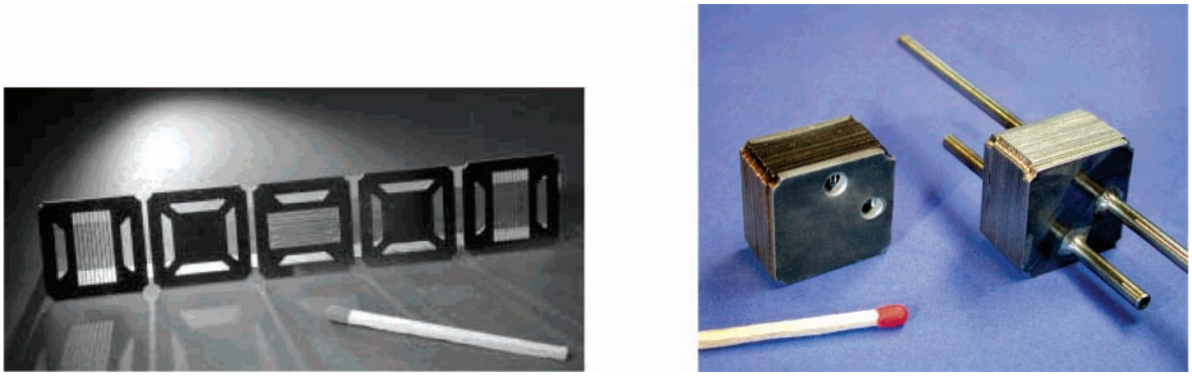

Figure 2. **Microreactor heat exchanger: stainless steel internal platelets (left), diffusion bonded device (right).**

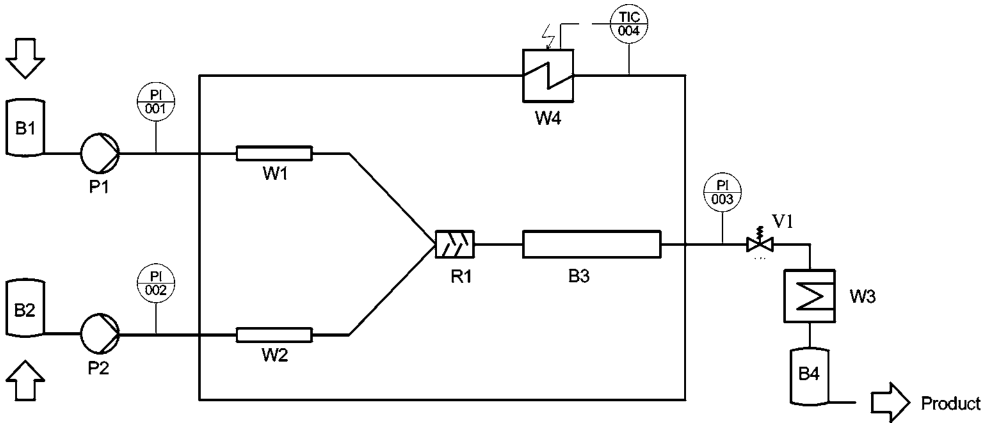

Figure 3. **Flow scheme of the experimental setup for performing a chemical reaction continuously in a microstructured reactor. B1, B2, supply vessels; P1, P2, syringe pumps; W1, W2, preheating capillaries; R1, microstructured reactor/mixer; B3, tubular reactor; W4, water bath; V1, valve; P001, P002, P003, pressure gages; W3, cooler/heat exchanger; B4, storage vessel.[19]**

As a microheat exchanger for quenching the reaction mixture, the device CRMH (IMM Institut für Mikrotechnik Mainz GmbH, Germany) was used. It consists of a stack of stainless steel platelets which guide the coolant and the reaction mixture in cross-flow mode. These platelets have a size of 26 mm × 26 mm × 0.2 mm and consist of nine channels with a length of 12 mm and a width of 700 μm. The internal fluid hold-up of 0.015 mL is very low (Figure 2). With an overall heat exchange surface area of 12,800 m^2 m^{-3} a heat transfer coefficient of 4000 $W(m^2\ K)^{-1}$ for water at a flow rate of 0.5 L min^{-1} was determined.[14−16]

2.5. Experimental Rig. A micromixer/tube reactor rig for continuous flow operation with tailored process flow was constructed, based on off-the-shelf components, as given above. Figure 3 shows the flow-scheme of the experimental setup. Two supply vessels (B1, B2) store the reactants (amines and α,β-unsaturated carbonyl compounds) which are fed by two syringe pumps (P1, P2) (PN 1610 syringe dosing systems, 2.5 mL syringe volume; Postnova Analytics, Landsberg, Germany) in separate capillaries (W1, W2), with a volume of 900 μL, for means of preheating. These hot

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(14) Hessel, V.; Löwe, H. Micro Chemical Engineering: components - plant concepts - user acceptance: Part II. *Chem. Eng. Technol.* **2003**, *26* (4), 391−408.

(15) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. Chemistry in Microstructured Reactors. *Angew. Chem., Int. Ed.* **2004**, *43*, 406−446.

(16) Ehrfeld, W.; Hessel, V.; Löwe, H. *Microreactors;* Wiley-VCH: Weinheim, 2000.

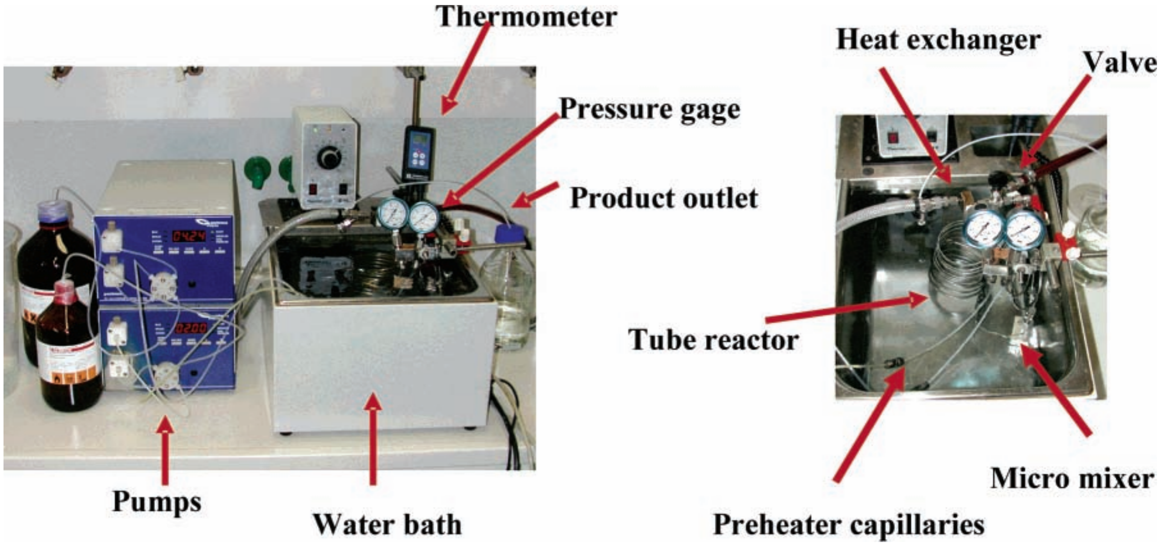

Figure 4. **Photographic image of the microreactor setup.**

flows are then contacted in the mixer/reactor (R1), the SIMM-V2/Ag40 micromixer. For prolongation of residence time, a tube reactor was added as delay loop element. The reaction is thereafter quenched by rapidly cooling the flow via the heat exchanger CRMH (W3) which is connected to an external thermostat. The reaction mixture is then stored in a separate vessel (B4). The preheater capillaries (W1, W2), the reactor (R1), and the tube reactor (B3) are immersed into a thermostat (W4). For heating to higher temperatures, water is replaced by oil. The pressure gauges P001 and P002 in front of the mixer monitor possible blockage of the mixer or of the tube reactor. The gauge P003 controls the pressure of the system which can be manually adjusted by a needle valve (V1).

Two tube reactors of different geometry were used in the experiments, a tube with 1/4″ outer diameter/74.5 mL inner volume and one with 1/8″ outer diameter/9.8 mL inner volume. All experiments were performed under pressure, because the amines (dimethylamine, bp 7 °C, diethylamine, bp 55 °C, and piperidine bp 104−106 °C) would otherwise be or become gaseous under the temperatures employed. For the experiments at not-too-high pressure, all parts of the rig were connected by PTFE tubes. For the experiments using liquefied dimethylamine at 20−30 bar, stainless steel tubes had to be used. The liquified dimethylamine was fed from a pressurized gas cylinder via an HPLC pump. In some experiments the use of a tube section was not necessary; the residence time then only amounts to the time it takes to pass through the micromixer and the subsequent connectors (inner volume approximately about 1 mL). In Figure 4 a photographic image shows the overall experimental setup as well as a detailed view of the mixer/tubular reactor mounted in the thermostat.

2.6. Reaction Analysis. The reaction mixtures were analyzed by a GC (Dani - GC 8610) with a Stabilwax (Crossbound Carbowax-PEG) 30-m column. All samples were injected at a temperature of 250 °C, and the column heating was programmed as a ramp starting from 80 °C to 210 °C with a rate of 10 K min^{-1}. As detector, a FID was used which was operated at 300 °C. Apart from 3-diethyl aminopropionic acid ethyl ester **(3e)**, all reactants and products were commercially available. The commercial samples were used for identification and quantification of the reaction mixtures by using them as calibration substances for the GC.

3-Diethyl aminopropionic acid ethyl ester **(3e)** was synthesized in a batch process, purified by distillation, and then used for GC calibration. Identification was performed by using a GC/MS (GC: 6890 N, MS: 5973 NMSD Quadrupole 69.9 eV, both Agilent Technologies) procedure. A (5%) phenyl methoxysiloxane column was used for separation. The mass spectrum of **(3e)** is given in Figure 5.

3. Results and Discussion

3.1. Development Target. The figure of merit for the experiments using the microreactor was to find process parameters yielding maximal space-time yields. The most governing parameters were assumed to be temperature, residence time (by total flow rate or by volume of the residence time section), and the molar ratio of amine **1** to α,β-unsaturated compound **2** (in the following, described briefly as molar ratio). The goal in the first step was to increase the reaction rate by increasing the temperature with the two other parameters set large; this was expected to promote conversion, since reliable kinetic data were not available. Then, residence time and excess of one of the reactants ought to be reduced as much as conversion is not reduced. Pressure was applied to the system to maintain a single-phase condition, but not with the intention of having an additional parameter for process optimization.

3.2. Reaction Time. Reaction time was decreased by orders of magnitude, from about 16−24 h for the batch processes to, at best, 0.1 min by using microstructured reactors for reaction R1, which adds dimethylamine (40 mass % in water) to acrylonitrile. This process probably is even faster, but this could not be detected with the experiments performed due to limitations in flow rate. Even for the much less reactive diethylamine (40 mass % ethanol), the addition to acrylonitrile was completed within less than 30 min, still

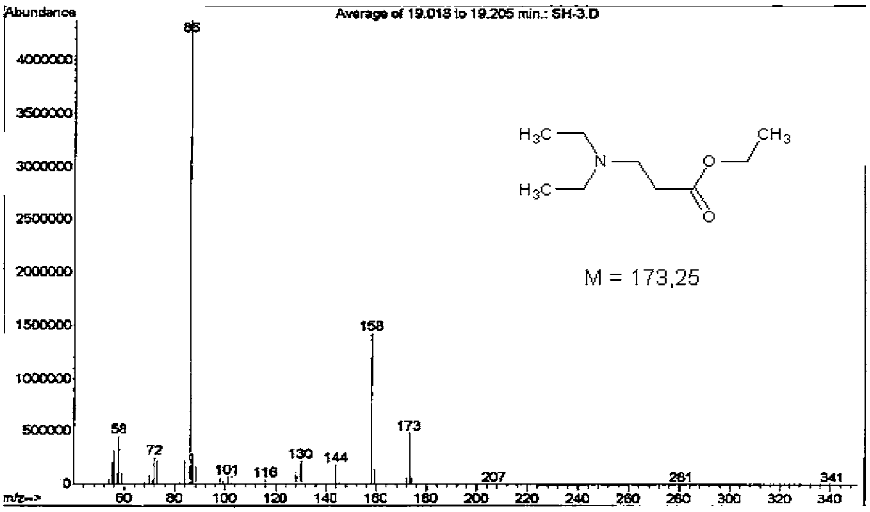

Figure 5. **Mass spectrum of 3-diethyl aminopropionic acid ethyl ester (3e).**

Table 4. **Reactivities of amines (1) and α,β-unsaturated carbonyl compounds (2) under similar conditions**[a]

	conversion acrylonitrile **(2a)** [%]	t_{res} (min)	conversion acrylic acid ethyl ester **(2b)** [%]	t_{res} (min)
dimethyl amine **(1a)** 40 mass % in water	98.7[b]	1.6	96.4	7.2
dimethyl amine **(1a)**	91.5[c]	3.8	–	–
diethyl amine **(1b)** 40 mass % in ethanol	67.3	7.2	61.1	7.4
diethyl amine **(1b)**	40.5	28.8	12.6	14.8
piperidine **(1c)**	97.2	7.7	98.8	7.4

[a] $T = 50$ °C, $P = 3-4$ bar, molar ratio (1) to (2) = 1.1, volume of residence time section: 9.8 mL. Exceptions are indicated. [b] 60 °C. [c] 30 bar.

being sped up by more than 1 order of magnitude compared to the batch process.

3.3. Amine Reactivity. In order to compare reactivities, the yields of the different reactions studied are compiled in Table 4 for similar reaction conditions (molar ratio 1.1; all at 50 °C, with one exception; and at a pressure of 3−4 bar, with the exception of the pure dimethylamine experiment). Since the flow rates were not absolutely equal for reasons of pump pulsation and hysteresis behavior of the pressure regulation valve and even the same residence time section of 9.8-mL volume was applied, differences in the reaction times were given. These, however, are taken into account in the following considerations.

The following sequence of reactivity of the pure amines was found in the reaction with both α,β-unsaturated carbonyl compounds:

dimethylamine > piperidine >> diethylamine

Dimethylamine is much more reactive than its homologue, diethylamine, for both the dissolved and pure compounds. Piperidine is less reactive than dimethylamine, but still exceeds by far the diethylamine. This sequence follows the basicity and steric accessibility of the amines, for example diethylamine being the weakest base ($pK_s = 10.489$),[17] and additionally the nucleophilic attack is sterically hindered by the two ethyl groups. In the case of piperidine ($pK_s = 11.123$),[17] the two alkyl substituents are restricted in their mobility by entrainment into a ring structure. Dimethylamine ($pK_s = 10.732$)[17] is the strongest base and is sterically hindered very little.

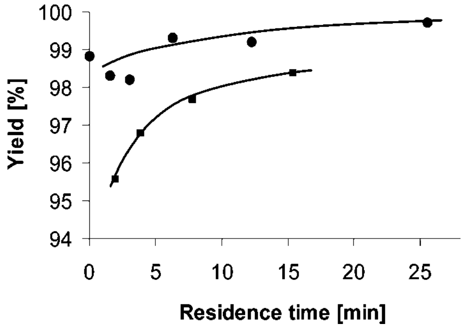

Figure 6. **Yield as a function of residence time for the reaction of dimethylamine (■ pure, 20 °C, molar ratio 1.1, 30 bar; ● 40 mass % aqueous solution, 80 °C, molar ratio 2.0, 3−4 bar) with acrylonitrile in the microreactor.**

Reaction times range from 0.1 min (minimal) for the addition of dimethylamine (40 mass % in water) to acrylonitrile (R1) (50 °C; molar ratio 1.1) for achieving a yield of 99% (Figure 6).

In turn, for pure diethylamine even after the long residence time of 28.8 min, and even despite the high temperature of 90 °C (molar ratio of 1.1), only about half of that yield, 40.5%, was achieved (Figure 7). The reaction of pure piperidine with acrylonitrile (R3) is in between, with 99% yield approached after about 15 min (50 °C; molar ratio 1.1) (Figure 8). By replacing pure diethylamine by diethylamine dissolved in ethanol (40 mass % in ethanol), 30 min reaction

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(17) Lide, D. R. *Handbook of Chemistry and Physics,* 79th ed.; CRC Press LLC: Boca Raton, Fl, 1998.

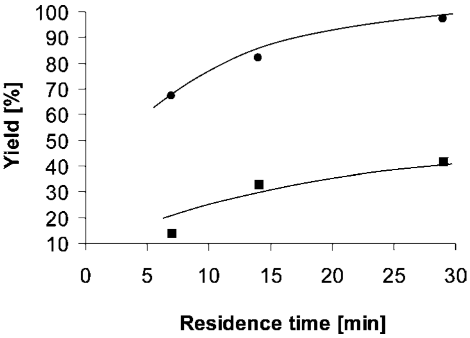

Figure 7. **Yield as a function of residence time for the reaction of diethylamine (■ pure, 90 °C, molar ratio 1.1; ● 40 mass % in ethanol, 50 °C, molar ratio 1.2) with acrylonitrile.**

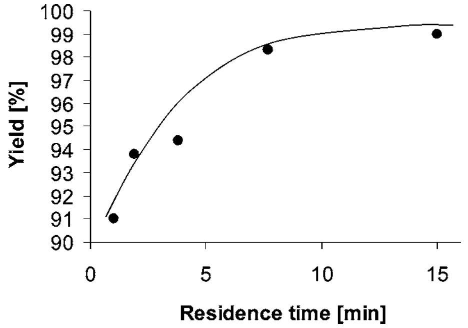

Figure 8. **Reaction of piperidine with acrylonitrile: yield as function of residence time for 50 °C.**

is needed to result in 90% yield (50 °C, molar ratio 1.2), thus effectively doubling the reaction speed.

3.4. α,*β*-Unsaturated Carbonyl Compound Reactivity. The reactivities of the two α,*β*-unsaturated carbonyl compounds investigated, acrylonitrile and acrylic acid ethyl ester, are similar for reactions with dimethylamine or piperidine (Figure 9, right). If diethylamine is applied, however, the reactivity turned out to be different, as follows.

acrylonitrile > acrylic acid ethyl ester

After 25 min reaction, the addition of diethylamine (40 mass % in ethanol) to acrylonitrile is beyond 96% yield (molar ratio 1.2, 50 °C) (Figure 9, left), while it is just about 60% for the ester (molar ratio 1.1, 50 °C). Even if the reaction temperature is increased to 90 °C, a yield of only 90% could be achieved.

3.5. Yields and Selectivity. Near-quantitative yields (~99%) were found for the addition of dimethylamine (40 mass % in water) to acrylonitrile (R1) (50 °C, molar ratio 1.1) (Figure 6) and for the reaction of pure piperidine with acrylonitrile (R3) (50 °C, molar ratio 1.1). Within the time frame of about 30 min,, a yield of only 41% was achieved when using pure diethylamine for (R1) (90 °C, molar ratio of 1.1). The yield with diethylamine (40 mass % in ethanol) was at maximum 90% (50 °C, molar ratio 1.2) (Figure 7).

For all reactions investigated, R1−R6, and under all process conditions, e.g., with either pure amine or dissolved, no traces of side products were found (via GC analysis); thus, it is assumed that conversion equals yield. An exception hereto is reaction R4 showing only traces of a 2-fold addition product **(4)** by GC/MS. This is explained by a very small amount of methyl amine **(1d)** impurities apart from the reactant dimethylamine which can undergo two addition reactions.

3.6. Residence Time. Residence time is expected to increase yield up to a certain value. Indeed, basically all curves show initially a strong increase of yield with residence time which then levels off at longer residence times. The exception hereto is the addition of dimethylamine (40 mass % solution in water) to acrylonitrile (R1) which gives near quantitative yields of 98−99% within the whole residence time interval inspected (Figure 6). It is expected, however, that this addition follows the same dependency as found for the other reactions (R2−R6), but at much lower residence times, which were hardly realizable even with the microreactor setup used. Evidence for this is provided by the less reactive pure dimethylamine showing such trend. The reduction of residence time from about 15.3 to 1.9 min leads here to a certain decrease of yield from 98.4% to 95.6% (Figure 6).

For the still quite reactive piperidine an increase of the yield above 90% with residence time could be demonstrated for addition to acrylonitrile and above 96% for addition to the α,*β*-unsaturated carbonyl ester.

3.7. Molar Ratio. The molar ratio of amine to the unsaturated addition compound was varied from 2-fold excess (2.0) to stochiometric (1.0). Yields were reduced by no more than 10%. Surprisingly, only for the small change from a molar ratio of 1.0 to 1.1 were measurable effects given, and during the increase of the ratio from 1.1 to 2.0, the performance was constant. The largest impact was found for reaction R3 (molar ratio, 1.0: 88% as compared to molar ratio 1.1: 98%; 50 °C; 7.7 min) (Figure 10).

Also for reactions R2 and R6, a notable impact was given. For reaction R2, decreasing the molar ratio to 1.0 decreased yield down to 91.0% (90 °C; 14 min). For reaction R6, yields changed by about only 5% for the same change in molar ratio (1.0: 98.9% as compared to 1.1: 94.8%; 30 °C, 7.4 min). For reactions R1 and R4, the molar ratio had still less impact (molar ratio 1.0, 98.0%; molar ratio 1.1: 97.2%; 30 °C; 3.6 min). For reaction R5 only at high molar ratio, i.e. at large excess of diethylamine, were yields increased (molar ratio 2.0: 97.9%; 90 °C; 27 min).

Thus, the sensitivity of the yield to the molar ratio seems to correlate with the reactivity of the amine. Dimethylamine is so reactive that all molecules are converted under stochiometric conditions; an excess of reactant cannot be helpful here anymore. The lower activities of the two other amines result in sensitivity to excess reactant.

3.8. Solvent-Free with Pure Agents vs Diluted Processing. For reaction R1, the yield is higher when using an aqueous solution of dimethylamine as compared to pure dimethylamine (liquefied at 30 bar) to be added to acrylonitrile (20 °C, molar ratio of 1.1). The same holds for reaction R2 with diethylamine added to acrylonitrile. The latter is noteworthy because in the reaction R5 pure diethylamine reacts very slowly with acrylic acid ethyl ester, as preliminary experiments showed (not given here). An explanation of this behavior can be given by the lack of acidic compounds which

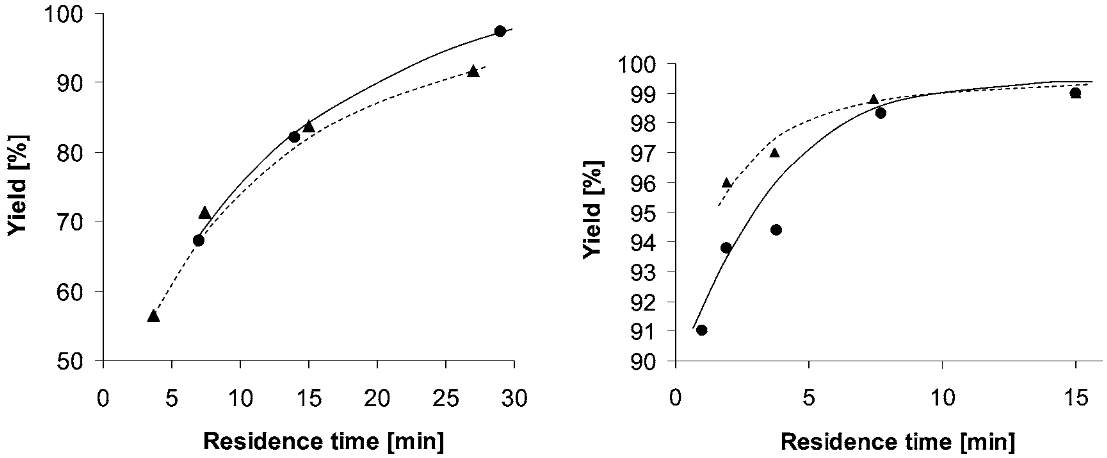

Figure 9. **(Left) Yield as function of residence time for the reaction of diethylamine (40 mass % in ethanol) with acrylonitrile (●, molar ratio 1.2, 50 °C) in comparison with the reaction with acrylic acid ethyl ester (▲; 90 °C, molar ratio 1:1.1) (Right) Yield as function of residence time for the reaction of piperidine with acrylonitrile (●) (molar ratio 1.1, 50 °C) in comparison with the reaction with acrylic acid ethyl ester (▲, 50 °C, molar ratio 1.1).**

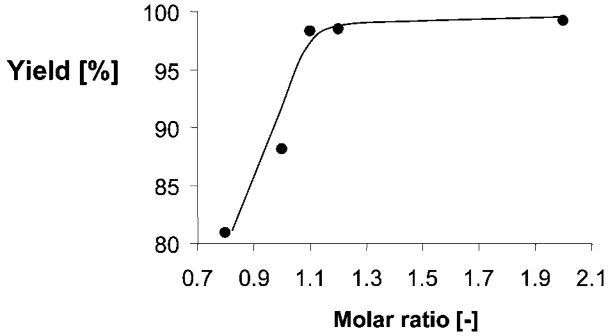

Figure 10. **Reaction of piperidine with acrylonitrile: dependence of yield on molar ratio (temperature 50 °C, residence time 7.7 min, 4 bar).**

can easily protonate the carbonyl compound to enhance reactivity.[18] Therefore, all later microreactor experiments for R5 were carried out with diethylamine dissolved in ethanol (40 mass % solution).

3.9. Temperature. The effects of temperature are twofold, to kinetically increase reaction speed at lower temperatures for the less reactive amines diethylamine and piperidine and to decompose product by thermodynamically reversing the reaction at high temperatures. Reaction R1 is always operated at its kinetic limits, i.e., to full conversion. By a temperature of 50 °C and a pressure of 30 bar, the dimethylamine is kept in liquid phase, and the yield decreases from 97% (20 °C) to 92%, probably due to the fact that the reverse reaction became more noticeable.

For reaction R2, yield rises nearly linearly from 80% to almost 100% as the temperature is increased from 50 to 90 °C for kinetic reasons (Figure 11).

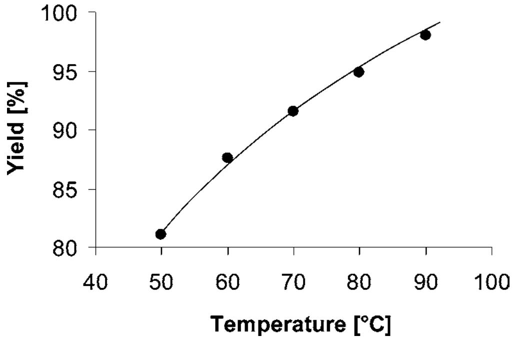

Figure 11. **Reaction of diethylamine (● 40 mass % in ethanol, molar ratio 1.2). Increase of yield as function of reaction temperature.**

Similar trends are found for the other reactions (see Figure 12), albeit with different slopes. Only for the reaction of piperidine with the acrylic acid ester is such dependency not found, as almost full conversion is given for all temperatures considered.

At still higher temperatures, thermodynamics are ruling, and the start of the reverse reaction can be seen, e.g., as for reaction R2. The yields dropped here considerably from 100% at 120 °C to 10.9% and 11.8% for temperatures of 150 °C and 200 °C, respectively (Figure 13).

3.10. Space-Time Yields. The productivity of the batch and continuous processes in the microstructured reactor can be compared on the basis of space-time yields, which normalize the obtained yields (g or mol) with regard to reactor volume (mL) and reaction time (h). In the case of the batch process the sum of the volumes of the two reactants was taken as reactor volume, while in the case of the continuous working microreactor the volume of the residence time section was used (as the micromixer volume can be neglected).

Throughout all reactions and all parameter variations the space-time yield for the chemical processing in the microreactor is much higher than for the corresponding batch process (Table 5), given the fact that even nonoptimal process conditions are included in Table 5. At best, an improvement of space-time yield by a factor of 652 was achieved.

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Table 5. **Comparison of space-time yields for batch processing and continuous-flow processing in microstructured reactors**

	α,*β*-unsaturated carbonyl compound					
	acrylonitrile **(2a)**			acrylic acid ethyl ester **(2b)**		
	space-time yield [g (mL h)$^{-1}$]			space-time yield [g (mL h)$^{-1}$]		
	batch	microreactor	ratio space-time yield microreactor/batch	batch	microreactor	ratio space-time yield microreactor/batch
dimethyl amine **(1a)**	0.03	17.60	652	0.04	0.30	8
40 mass % in water dimethyl amine **(1a)**	–	10.10	–	–	–	–
diethyl amine **(1b)**	0.02	2.24	102	–	2.50	–
40 mass % in ethanol diethyl amine **(1b)**	–	0.6	–	0.02-	0.40	21
piperidine **(1c)**	0.03	6.1	235	0.02	6.80	309

[a] The space-time yields for the microreactor refer to the corresponding conditions given in Table 4.

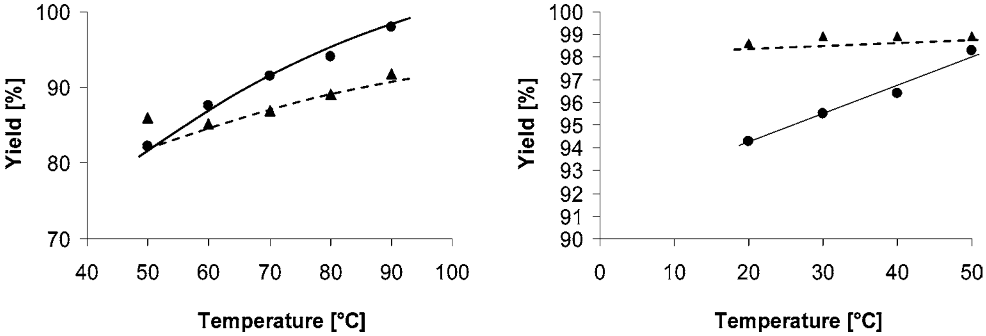

Figure 12. **(Right) Temperature dependence of yield for the reaction of the diethylamine solution with acrylonitrile [(●) molar ratio 1.2, residence time 14 min] and with acrylic acid ethyl ester [(▲) residence time 27 min, molar ratio 1.1]. (Left) Temperature dependence of yield for the reaction of piperidine with acrylonitrile [(●) molar ratio 1.1, residence time 7.7 min] in comparison with the reaction with acrylic acid ethyl ester [(▲) 7.4 min, molar ratio 1.1].**

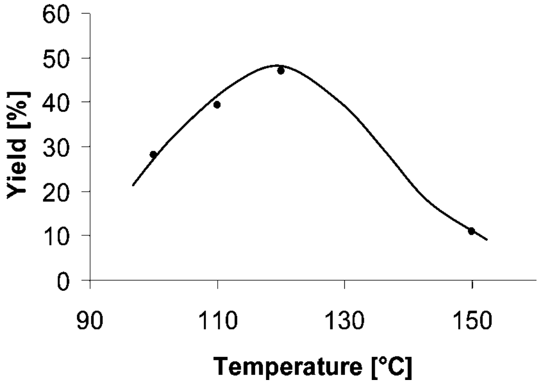

Figure 13. **Decrease of yield for the reaction of diethylamine with acrylonitrile at high temperatures.**

4. Conclusions

For the reaction of secondary amines **1a**–**c** with α,*β*-unsaturated carbonyl compounds and nitriles **2a**–**b** to tertiary amines **3** (a variation of the Michael addition) a continuous microreactor process based on a microstructured mixer/tubular-reactor setup has been established, optimized, and compared to the corresponding batch processes. Using a batch procedure, good yields (>85%) could be achieved; however, the process takes a very long time, up to 17 to 25 h.

The microreactor process accelerated the reaction by orders of magnitude via ensuring fast mixing and efficient, simultaneous removal of reaction heat under improved thermal control. Yields of more than 90% could be achieved in this way which is slightly better than the yields of the batch process. Due to the speed-up of reaction by using microstructured reactors, high production rates are achievable, e.g., space-time yields are increased by a factor of up to 650 compared to those of the batch process.

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