

Use of a continuous-flow microreactor for thiol–ene functionalization of RAFT-derived poly(butyl acrylate)[†]

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This study describes the synthesis of functionalized RAFT-derived poly(*n*-butyl acrylate) polymers *via* the use of a continuous-flow microreactor, in which aminolysis as well as thiol–ene reactions are executed in reaction times of just 20 minutes. Poly(*n*-butyl acrylate) ($M_n = 3800 \text{ g mol}^{-1}$, PDI = 1.10) with a trithiocarbonate end group was prepared *via* a conventional RAFT process. The polymer was then functionalized *via* aminolysis/thiol–ene reactions in the micro-flow reactor with isobornyl acrylate, propargyl acrylate, poly(ethylene glycol) methyl ether acrylate and pentaerythritol tetraacrylate. To optimize the reaction time and reaction temperature of the micro-flow reactor, freshly collected samples were studied with soft ionization mass spectrometry. With this technique, efficient and very fast aminolysis and subsequent thiol–ene reactions take place on the RAFT-precursor polymer, yielding quantitative end group conversion within 20 min and functionalized polymers of $3700\text{--}4000 \text{ g mol}^{-1}$, depending on the type of acrylate coupled. The use of a continuous-flow microreactor opens the pathway towards upsizing lab scale methods into larger processes without suffering from problems associated with reproducibility and tedious optimization issues.

An often less valued key aspect of contemporary polymer synthesis, be it in the realm of controlled polymerization, *click*-like modifications or polymer analogous reactions, is the ability to upscale existing synthesis protocols. The adaption of procedures from microgram scale to significant production of materials on gram scale or larger is often tedious and accompanied with a loss in reaction efficiency or unreasonable reaction volumes. A convenient solution to this problem is the employment of microreactor technology.¹ Miniaturized flow reactors offer the ability to optimize reaction conditions on a small scale while concomitantly allowing for simple upscale of reactions by going from small reactors to massive parallelization in reactor arrays or simply longer runtimes of the individual reactors. Also accelerations of the reactions can often be achieved by the rapid mixing of the components due to short diffusion lengths inside the

microreactor,² as well as employing unconventional temperature regimes making microreactors in that respect comparable to the use of microwave reactors. The improved heat transfer of microreactors is a distinct advantage of these devices making their use especially interesting for highly exothermic reactions.³ While a wide array of commercial microreactors already exists, only a few studies have been reported so far on applications from the polymer field. Recently, Bally *et al.* described the synthesis of branched polymers from atom transfer radical polymerization (ATRP),⁴ in a tubular microreactor.⁵ Also, polymerizations following the reversible addition fragmentation transfer (RAFT)⁶ protocol have been described lately^{7,8} as well as end group modifications.⁹ Some earlier work on polymerizations in flow microreactors is summarized in a recent review.¹⁰ When discussing these studies, it must be noted that the majority of approaches employed to date make use of tubular (coil) reactors^{11,12} rather than true microfluidic lab-on-a-chip reactor devices. Tubular reactors are efficient, allow on the other side however only for little flexibility. More reaction conditions can be targeted with chip reactors since they allow for better miniaturization, more complex reactor designs and faster exchange of the reactor itself in devices.

Besides the ability for facile upscaling, working with polymer materials in microreactors has several additional advantages. One is the high reproducibility of reaction conditions and very stable operation over extended periods of time, which has not only beneficial influence on the kinetics of the reaction but also on the product structures where the polymer product is determined by the kinetics of the individual chain reactions. Another advantage is the inherent simplicity of the approach, making the flow reaction not more complicated than a classical batch reaction on the lab scale. Additionally, microreactor technology can be seen as an intrinsically green technology since it displays far superior thermal transfer than batch systems. Therefore excess heating/cooling of vessels can be avoided, leading to a more energy-saving setup. Microreactors are thus – in addition to the inherent advantage of simple scale-up and the general flexibility of application – very interesting for industrial application, at least for production of materials on a kilogram scale.

An inherent obstacle of such reactors is however their sensitivity to viscosity changes and – more severe – clogging of the reaction channels. Strictly homogeneous reaction conditions are a prerequisite and polymerizations within such reactors are a challenge, even though not impossible. Regardless, in here, we targeted end group modifications of polymers to avoid viscosity effects. End group modifications of polymers are an important step in the synthesis of

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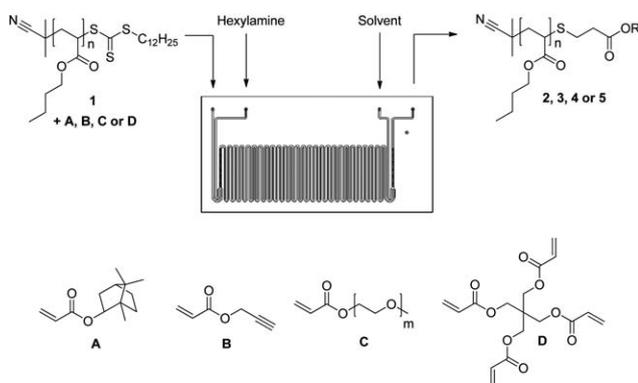
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functional materials, with respect to the creation of linkages and introduction of certain functional groups or (bio)conjugation with other macromolecules.

We present a protocol appropriate for flow microreactors to perform *in situ* aminolysis of polymers obtained from the reversible addition fragmentation transfer (RAFT) process¹³ followed by base-catalysed thiol–ene end group modification, a reaction that is sometimes referred to as belonging to the *click*-type reactions.^{14–17} This reaction cascade was reported before for batch processes and when reaction conditions are chosen adequately it can be performed *one-pot*, thus making this reaction an optimal candidate to transcribe its synthesis procedure to microreactors. For the sake of analysis, we synthesized a short-length polyacrylate (3800 g mol⁻¹, PDI = 1.10) bearing trithiocarbonate functions to allow for mass spectrometric analysis of end groups to monitor the success of reaction and the conversion of the starting material as well as the intermediate thiol-terminated aminolysis product. Functionalizations were carried out with various acrylates as given in Scheme 1.

Various protocols exist for the base catalysed thiol–ene reaction. Generally, a problem that needs to be considered is the formation of disulphide bridges which complicate the product spectrum.¹⁸ Thus, either reducing agents such as triethylphosphite can be added to the reaction to suppress coupling or alternatively, excesses of acrylate are employed to increase the rate of thiol–ene reaction and thereby limit the amount of side products.^{19,20} In the latter case alkyl amines act as suitable agents for the aminolysis as well as the thiol–ene reaction. In all literature procedures, reaction solutions were freed from oxygen, and relatively fast reaction on the order of few hours were reported. To obtain reference spectra, the 4 acrylates as given in the scheme were reacted with the RAFT polymer following the procedure of Boyer *et al.*²¹ with subsequent full characterization of the products. Disappearance of the RAFT-characteristic UV absorption is in all cases observed and a clear shift of the product peaks observed in ESI-MS analysis²² with unambiguous assignment of all product peaks (for details see ESI†).

In order to transfer the reaction protocol from the batch reaction to flow conditions, several factors need to be considered. Due to the relatively small reactor volumes only limited reaction times can be chosen, given by the flow rate of the injected solutions. In what follows, a reactor with an internal volume of 19.5 μL was employed,



Scheme 1 Aminolysis and thiol–ene reaction on RAFT derived *p*(*n*-BuA) in a continuous-flow microreactor. The lower part of the scheme shows the different acrylates that were used for functionalization of chains.

which is the largest reactor available for the microreactor setup. A schematic of the reactor is depicted in Scheme 1. *Via* two reactant inlets solutions can be individually injected into the reactor. Fast mixing of the components is ensured *via* a diamond-shaped mixer. At the end of the reaction channel an additional inlet is foreseen to dose in a quenching agent to stop the reaction after a well-defined reaction time. In the present case an organic acid such as trifluoroacetic acid or toluenesulfonic acid can be used to stop the thiol–ene reaction, in most cases, however, this channel was only used to dilute the reaction mixture since the presence of such acids complicates ESI-MS analysis significantly. The collected product was subjected to characterization without delay to avoid a situation where further reaction may occur after exit from the reactor. It is thereby noteworthy that tests using a quenching agent were performed where the product was examined with UV-Vis spectroscopy, indicating success and completion of the full reaction within the given reaction time.

Two key advantages of microreactor technology are that residence times can be easily adjusted by flow rates as well as the possibility to use a wide temperature range. Since the reactors are pressurized (in the present case to 20 bar), temperatures well above the boiling point may be explored, thus significantly speeding up reactions. In the case of thiol–ene this is, however, associated with severe problems. For once, RAFT polymers often still contain residual radical initiators that may (in the case of acrylates) not easily be removed. Hence, when operating the reactor at significant temperatures, radicals are created that may interfere with the RAFT end group.²³ We thus purified a small sample of the polymer *via* preparative GPC. Nevertheless, when testing for the reactivity of the RAFT polymer alone at elevated temperatures, thermal cleavage of the RAFT end group – as described several years ago already by Postma *et al.* – occurred,²⁴ obscuring any effort to carry out thiol–ene reaction at higher temperatures. While the RAFT polymer itself is stable up to at least 80 °C, we carried out all further experiments at 25 °C to stay on the side of caution. Under such conditions also the initiator AIBN poses no problem and does not need to be removed prior to the experiments. Fig. 1 depicts the success of the reaction with isobornyl acrylate **A** as the conjugated acrylate after different reaction times (realized *via* adjusting the individual flow rates). For this particular reaction, 100 mg mL⁻¹ polymer in THF solution was mixed with 10 eq. of acrylate. The reaction was started *via* mixing in the reactor with the second component, a THF solution of 10 eq. hexylamine. THF was chosen as solvent in order to be able to directly study the produced polymer samples in ESI-MS, without having to purify each sample prior to analysis. Before the reaction, the mass spectrum shows a clean spectrum of the desired RAFT polymer bearing the trithiocarbonate end group. Due to the peak molecular weight being outside the measurable *m/z* range, single, double and triple charged species are seen. A significant change occurs in the spectrum after the reaction at a flow rate of 2 $\mu\text{L min}^{-1}$, representing a residence time of practically 5 min. Already after such a short time more reaction product is observed (indicated by dark red markers) compared to the starting material (yellow markers) (for a detailed peak assignment of all single or multi-charged species see ESI†). At the same time, however, also the intermediate thiol-capped polymer (green) is observed in significant concentrations. After 10 minutes (flow rate of syringes = 1 $\mu\text{L min}^{-1}$) the desired conjugated product is the most abundant species and almost all starting material has reacted (close inspection of the spectra reveals a small amount of the initial RAFT polymer to be still present; the peak is, however, overlapped with

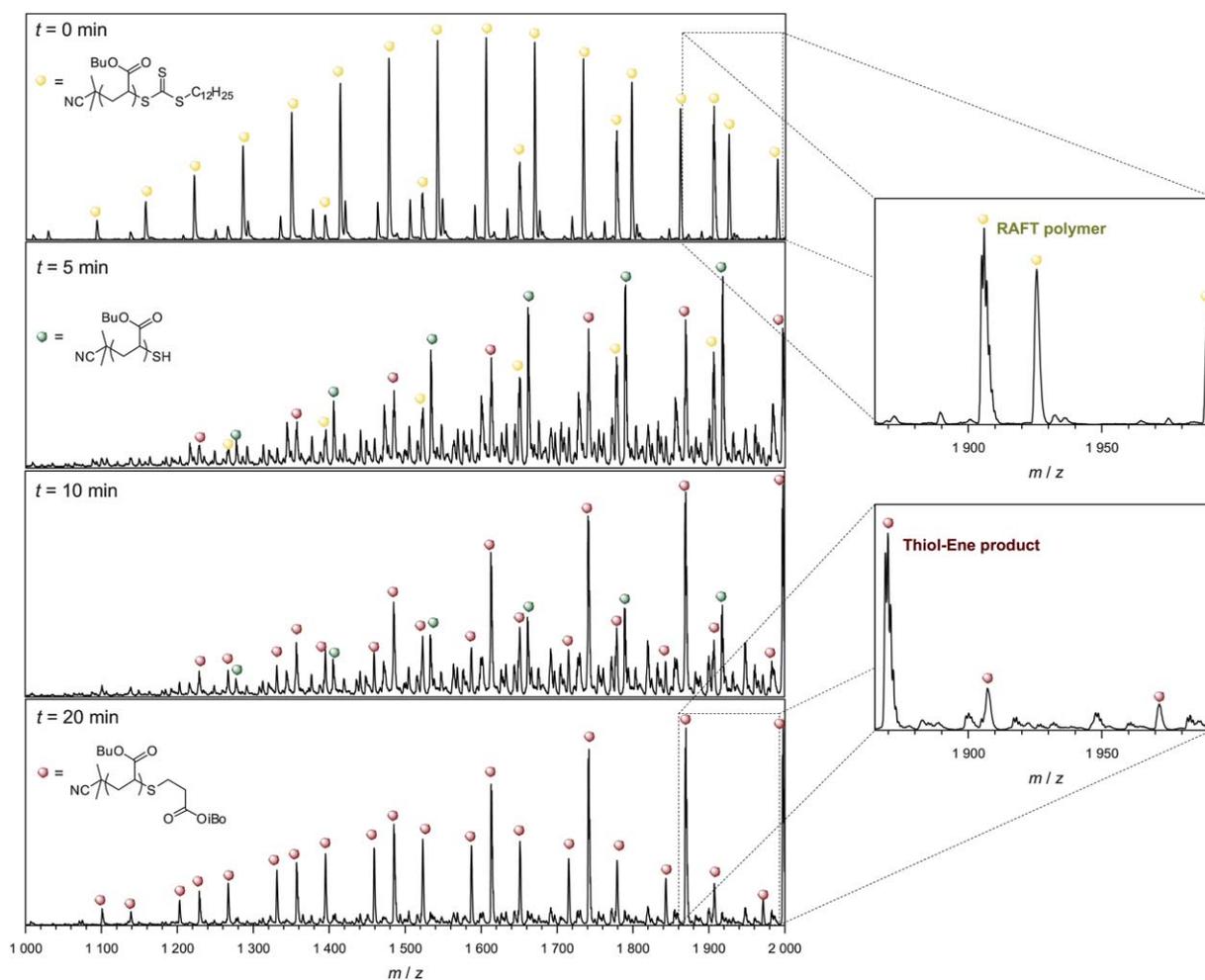


Fig. 1 ESI-MS spectra of the reaction mixture after different reaction times for the reaction at 25 °C.

the double-charged product). Still, small but significant amounts of thiol intermediate are visible and the spectrum is overall noisy, also indicating that the reaction is not yet completed. However, after only 20 minutes (flow rate of $0.5 \mu\text{L min}^{-1}$) a practically clean product spectrum is observed that does not virtually differ from the spectrum obtained from a batch process (for comparison, see ESI†). Thus, despite the low temperature, fast end group modification was achieved in a short reaction time, thus allowing for reasonable flow rates and thereby production of end-product in a significant rate. In this particular test, the reaction was even performed without degassing of the reactant solutions. The small double charged peak at m/z of 1900 Da most likely arises from the presence of oxygen since it disappears when both reactant solutions are degassed prior to attachment to the microreactor. In such case, however, other unassignable peaks are identified, but also with an abundance lower than 5%. Since, THF was used as a solvent in the presence of oxygen, we also checked for the presence of polymer chains with peroxide end groups. However, those species were not observed, indicating that within the time frame of 20 min, oxidation of the polymer end group is not yet an issue. Generally we can conclude that no crucial changes in the product spectra were observed, thus showing that the interference of oxygen with the reaction or promotion of disulphide formation with the intermediate is as good as negligible under these reaction conditions.

In the following we applied this flow-reactor protocol to various acrylates to test if similar efficiencies can be reached with different substrates. Therefore, isobornyl acrylate **A** from the above model study was replaced by propargyl acrylate **B**, PEG-acrylate **C** ($M_n \approx 480 \text{ g mol}^{-1}$) or pentaerythritol tetraacrylate **D**, resulting in the modified polymers **2**, **3**, **4** or **5**, respectively. ESI-MS showed likewise a good match between the spectra from the flow reactor and the batch process and the desired product peaks can be clearly assigned. Polymers **2** and **3** allow for unambiguous assignment of all peaks. In the case of the PEG acrylate **C** (polymer **4**) a complex (block) copolymer spectrum is obtained effectively with – as is typical for PEG adducts – high charge states, prohibiting a more detailed analysis. Product **5** also features complete disappearance of the starting material and the intermediate thiol product, but also additional peaks. Clear assignment of all peaks is not possible, but indication is given that these peaks stem from impurities in the starting materials (in fact, the commercially available tetraacrylate **D** contains up to 40% triester, for its characterization, see ESI†) since identical product patterns and SEC elugrams are observed in the products from the batch reactions.

Table 1 lists the characterization results of the initial RAFT polymer and the different products from size exclusion chromatography. Products **2–4** feature unchanged polydispersity and small shifts in the molecular weight as can be expected from the mass of the

Table 1 SEC characterization of the modified polymers. For identifiers of products see Scheme 1 ($K = 12 \times 10^{-3} \text{ mL g}^{-1}$, $\alpha = 0.7$)²⁵

	1	2 (1 + A)	3 (1 + B)	4 (1 + C)	5 (1 + D)
$M_n/\text{g mol}^{-1}$	3800	4000	3700	4300	3900
PDI	1.10	1.12	1.12	1.11	1.20

cleaved RAFT group and the addition of the acrylate. Only the distribution of product **5** indicates a side reaction. A slight increase in polydispersity caused by a high molecular weight tail of the distribution is observed after the reaction. With ESI-MS, no disulfide formation was observed. Therefore, even though the acrylate was employed in excess, a small percentage of chains may have coupled twice to the multifunctional compound, thus creating also a distinct proportion of chains with doubled molecular weight. This is an interesting observation, since with the same excess of a similar tetrathiol compound no double coupling with acrylates was observed in radical thiol-ene reactions.¹⁶ The amount of this side product is, however, small and can be safely considered to be negligible, especially concerning the impurity of the starting material.

Overall, the application of the microreactor allows for qualitatively very good results that are comparable to a batch process under similar reaction conditions. A fast reaction with completion within 20 minutes is achieved and a diverse range of acrylates can be coupled with ease to the initial RAFT polymer. Since the reactions were performed at ambient temperature further optimization of the reaction appears to be possible when the temperature is increased to levels just below the temperature where thermal cleavage of the RAFT group occurs. With polyacrylates the residual initiator poses a problem in that respect, but with polymers such as polystyrene or polymethacrylates that can be purified in a facile procedure by precipitation (and that feature more stable RAFT end groups) such acceleration should be feasible and reaction times in the range of a few minutes may be achievable. As is known already from batch reactions, the chain length of the polymers plays no larger role and the results discussed above can safely be assumed to be representative for any RAFT polyacrylate with good end group fidelity, irrespective of its size.

Conclusively, the results presented herein not only demonstrate the adjustment of thiol-ene end group modifications for a commercial flow-microreactor system, but also demonstrate how easily polymer reactions can be adapted for such reactor type in general. This signifies a substantial step since microreactors allow for simple scale up of the reactions and at the same time continuous production of functional polymers. In the present case only milligram-scale reactions were carried out, thus comparable in the amount of product formed with the according batch process. However, extending the runtime of the reactor as well as using longer reactor channels and parallelization of identical reactors (allowing for higher throughput of material by increase of the flow rate while maintaining the residence time) will allow for a quick upscale to gram scale and beyond without the necessity of further optimization. Using commercially available parallelized reactors, production of several hundred grams to kilograms per day is directly possible by employing the same reaction

conditions. It should thereby not be forgotten how simple the approach is. With only two simple solutions, one containing RAFT-derived polymer and the acrylate and the other containing the base, the product is obtained virtually without further effort under strictly reproducible and very well controlled conditions even when solutions are not degassed.

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