

Dr Charlotte Wiles

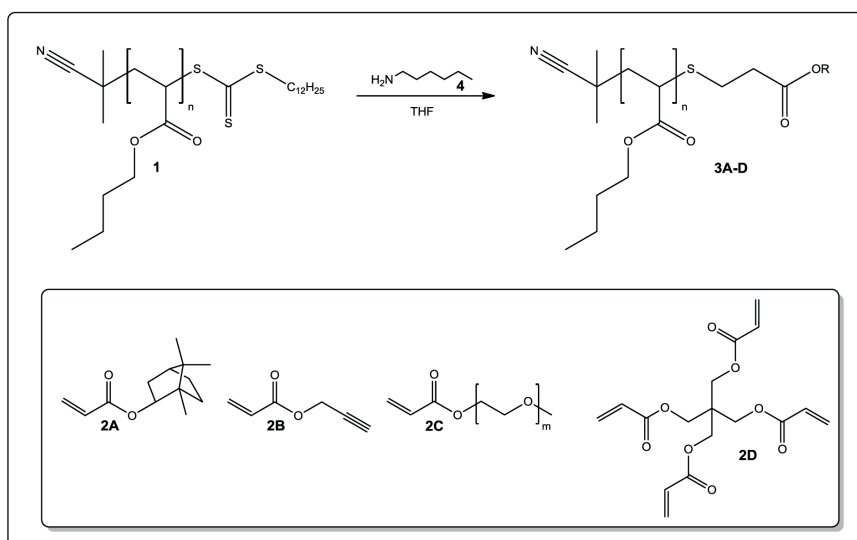
Chemtrix BV

'Thiol-ene Functionalisation of RAFT-derived Poly(*n*-butyl acrylate) Polymers in a Labtrix® Micro Reactor'

J. Vandenberg and T. Junkers



Polymer Reaction Design Group, Institute for Materials Research (IMO), Universiteit Hasselt, Diepenbeek, Belgium



Introduction: Owing to the significant challenges associated with scaling controlled polymerisations whereby laborious synthetic processes suffer losses in reaction efficiency at scales beyond the microgram level, Junkers *et al.* [1] at the Universiteit Hasselt (Belgium), Hornung *et al.* [2,3] at CSIRO (Australia) and Seeberger *et al.* [4] at Freie Universitat Berlin (Germany) have assessed the performance and derivitisation of RAFT-polymers using the emerging technique of continuous flow. With numerous operational advantages [5,6] illustrated for conventional organic synthetic reactions, such as increased reaction selectivity, reduced reaction times and access to novel processing windows [7], it has been proposed that this methodology could provide access to a high degree of reproducibility and process control for polymerisations and their associated reactions; facilitating scaling of their preparation.

It must be considered however that the use of micro reactors for the manipulation of pre-polymers & polymer products can be more challenging than executing conventional organic synthetic transformations owing to the significant changes in viscosity observed when transitioning from a monomeric solution to the final polymeric product. That said, Yoshida and co-workers [8] have demonstrated many such processes obtaining decreased polydispersity and increased molecular weight control under such flow conditions – care must however be taken to select the correct reactor type.

Focussing on end group modification, Junkers and Vandenberg [1] assessed the preparation of several functional materials *via a* continuous *in-situ* aminolysis and thiol-ene 'click-type' reaction of a RAFT-derived poly(*n*-butyl acrylate). Taking advantage of the ease with which reaction time and temperature can be varied and optimised within such systems.

Materials: *n*-Butyl acrylate (99 %, Acros Organics), isobornyl acrylate **2A** (99 %, Acros Organics), propargyl acrylate **2B** (98 %, Sigma Aldrich), poly(ethylene glycol methyl ether acrylate **2C** (98 %, Sigma Aldrich), pentaerythritol tetraacrylate **2D** (10-40 % tri-ester, Sigma Aldrich), 1,1'-azobis(isobutyronitrile) (AIBN) (98 %, Sigma Aldrich), hexylamine **4** (97 %, Sigma Aldrich), 2-cyano-2-propyldodecyltrithiocarbonate (97 %, Sigma Aldrich) and tetrahydrofuran (THF) were used as received unless otherwise stated.

Experimental Conditions: Prior to use, 1,1'-azobis(isobutyronitrile) (AIBN) was recrystallised twice from ethanol and all acrylate derivatives were de-inhibited by passing over a column of activated basic alumina. The RAFT-polymer, poly(*n*-butyl acrylate) **1**, was prepared using a standard batch technique which involved treatment of *n*-butyl acrylate (80 eq.) with AIBN (0.1 eq.) and 2-cyano-2-propyldodecyltrithiocarbonate RAFT agent (1 eq.) in a sealed Schlenk tube. After 3 freeze-pump-thaw cycles, the mixture was polymerised in a glove box at 60 °C for 1.75 h and subsequently quenched using a solution of methanolic hydroquinone. The residual monomer was separated to afford the poly(*n*-butyl acrylate) **1** and analysis confirmed the polymer **1** to have an average molecular weight (M_n) of 3800 g mol⁻¹ and a poly dispersity index (PDI) of 1.1. Prior to use, the polymer **1** and acrylate derivatives were prepared as solutions in THF and, unless otherwise stated, de-gassed in preparation for use within the Labtrix® Start micro reactor.

Flow reactions were performed using a standard PEEK Labtrix® Start system (Figure 1), fitted with a glass micro reactor (Reaction type = 3227; Reactor volume = 19.5 µl) containing an SOR static micro mixer. Reactant solutions were introduced into the micro reactor using 1 ml glass, gas-tight syringes (x3) and pressure maintained within the device using an ultra-low dead volume back pressure regulator set to 20 bar at 25 µl min⁻¹. Employing a thermal controller, the system can be operated at temperatures ranging from -20 to 195 °C utilising Peltier technology which circumvents the need for a thermal fluid.



Figure 1. Photograph illustrating a user with Labtrix® Start, the turn-key flow chemistry equipment from Chemtrix BV.

Analytical Methodology: The polymeric products prepared were analysed using a series of standard techniques including GPC for molecular weight distribution (MWD) determination, ESI-MS and UV-Vis spectroscopy.

GPC: Using a Tosoh EcoSEC system equipped with a PLgel 5.0 µm guard column (50 x 8 mm) and three PLgel 5.0 µm Mixed-C columns (300 x 8 mm) and a differential refractive index detector, THF was used as the eluent at 1 ml min⁻¹ and 40 °C. The system was calibrated using linear polystyrene standards and toluene as a flow marker.

ESI-MS: Using a Thermo Fisher Scientific LCQ Fleet mass spectrometer fitted with an atmospheric pressure ionisation source, operating in the nebuliser assisted electrospray mode. A constant spray voltage of 5 kV was employed, along with a capillary voltage of 25 V, an offset voltage of 120 V, a capillary temperature of 275 °C and N₂ used as an auxiliary gas. The instrument was calibrated using a caffeine standard and 250 µl aliquots of sample injected at a concentration of 20 µg ml⁻¹, with THF/MeOH (3:2) used as solvent.

UV-Vis Spectroscopy: Using a Varian CARY 50 UV-Vis-NIR spectrophotometer with a scan rate of 600 nm min⁻¹ samples were analysed as solutions in THF/MeOH (3:2).

RAFT-Polymerisation under Flow Conditions: Initially employing isobornyl acrylate **2A** as the derivatising agent, thiol-ene functionalisation of poly(*n*-butyl acrylate) **1** was assessed, using hexylamine **4** as an organic base, under continuous flow conditions. Utilising a 19.5 µl glass micro reactor (Labtrix® Start; Device = 3227), a pre-mixed solution of poly(*n*-butyl acrylate) **1** (100 mg ml⁻¹; 0.027 M) and isobornyl acrylate **2A** (0.27 M, 10 eq) in THF was employed as feed solution 1, hexylamine **4** in THF as feed solution 2 (0.27 M, 10 eq.) and THF as the diluents, introduced via the quench inlet. Using a static micro mixer the reactants were efficiently mixed within the glass device and the effect of reaction time on the degree of derivatisation assessed using offline techniques which included UV-Vis spectrometry, ESI-MS and GPC.

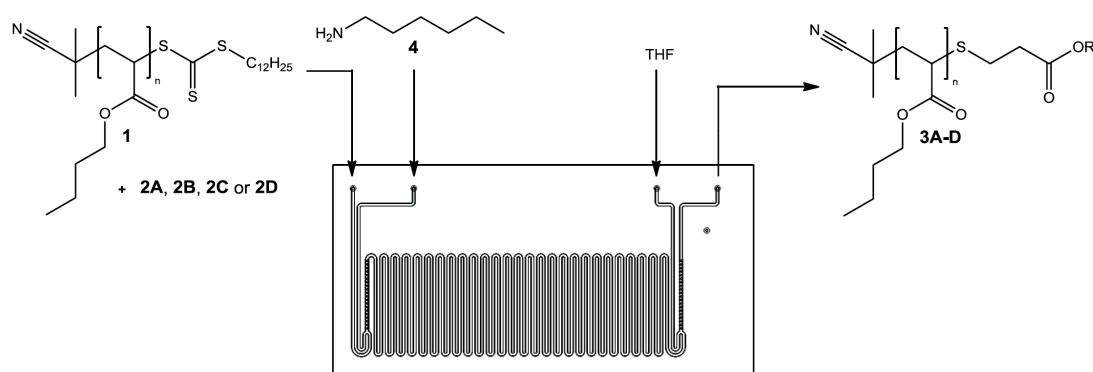


Figure 2. Illustration of the reaction manifold used to assess the thiol-ene functionalisation of RAFT-derived poly(*n*-butyl acrylate) **1**.

Results & Discussion: Whilst the RAFT-polymer **1** has been shown to be stable up to temperatures of 80 °C, the assessment of thermal effects on the flow reaction was outside of the scope for this initial proof of concept investigation – enabling the RAFT-polymer **1** to be used without removal of the thermal initiator, AIBN. Employing a reaction time of 5 min at 25 °C, the authors determined by ESI-MS the presence of unreacted poly(*n*-butyl acrylate) **1**, a thiol intermediate **5** and a small proportion of target thiol-ene derived poly(*n*-butyl acrylate) **3A**. Increasing the reaction time to 10 min led to complete consumption of the precursor **1**, a reduction in thiol intermediate **5** and an increase in the target product **3A**. A final increase to 20 min, achieved by reducing the reactant flow rates to ~ 1 µl min⁻¹, was met with quantitative conversion of the RAFT-polymer **1** to the desired conjugated product **3A** demonstrating a nine-fold reduction in reaction time compared to batch (20 min *cf.* 3 h). Furthermore, unlike analogous batch protocols, where peroxide formation of the terminal groups can occur in THF, it was not found to be necessary to de-gas the reactant solutions in order to remove O₂.

Comparison of the ESI-MS spectra obtained from the product generated in flow with a sample prepared under conventional batch conditions, the authors comment that no changes in the product quality was obtained – despite employing a low temperature and a reduction in reaction time. Consequently, equivalent results were obtained within the micro reactor using a simple, robust and transferrable method when compared to the aminolysis and thiol-ene click reaction performed using conventional batch techniques which employ laborious Schlenk protocols.

Scope of the Derivatisation Method: In an extension to the investigation, a series of acrylate monomers (**2B-D**) were assessed under the aforementioned conditions. As Table 1 illustrates, propargyl acrylate **2B**, PEG-acrylate **2C** and pentaerythritol tetraacrylate **2D** were substituted for isobornyl acrylate **2A** affording excellent levels of thiol-ene derivatisation for products **3A**, **3B** and **3C**; whilst **3D** was found to contain a small proportion of a higher molecular weight polymer attributed to the formation of a double coupling product – disulphide bridge architecture – leading to a slight increase in polydispersity.

Table 2 illustrates the masses of products identified by ESI-MS within the derivatised polymer samples; the m/z values of single charged species are highlighted in blue.

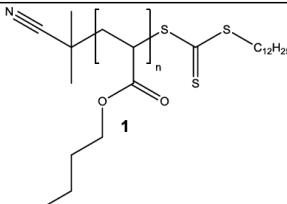
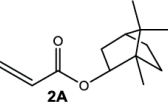
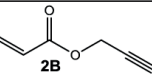
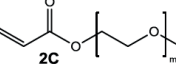
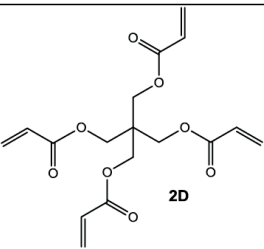
Acrylate Derivative	Polymer	M_n (g mol ⁻¹)	PDI
 1	1	3800	1.10
 2A	3A	4000	1.12
 2B	3B	3700	1.12
 2C	3C	4300	1.11
 2D	3D	3900	1.2

Table 1. Summary of the results obtained for the derivatisation of poly(*n*-butyl acrylate) with a series of acrylate (**2A-D**) monomers achieved within Labtrix® Start.

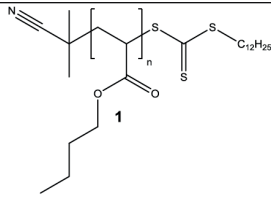
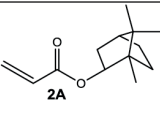
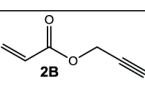
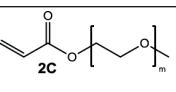
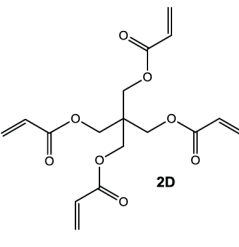
Acrylate Derivative	Polymer	Method	Species	<i>m/z</i> Theoretical (Da)	<i>m/z</i> Experimental (Da)	$\Delta m/z$ (Da)
 1	1	Batch	[Na ⁺]	1520.88	1521.08	0.20
			[2*Na ⁺]	1541.42	1541.50	0.08
			[3*Na ⁺]	1546.93	1548.08	1.15
 2A	3A	Batch	[Na ⁺]	1612.97	1613.92	0.05
			[2*Na ⁺]	1650.50	1651.58	1.05
		Flow	[Na ⁺]	1612.97	1613.00	0.03
			[2*Na ⁺]	1650.50	1651.17	0.67
 2B	3B	Batch	[Na ⁺]	1642.94	1643.17	
			[2*Na ⁺]	1601.45	1602.58	
		Flow	[2*Na ⁺]	1601.45	1602.50	
 2C	3C	Batch	[4*Na ⁺]	-	1510.33	-
		Flow	[4*Na ⁺]	-	1507.50	-
 2D	3D	Batch	[Na ⁺]	1628.86	1628.92	0.06
			[2*Na ⁺]	1594.41	1595.33	0.92
		Flow	X[2*Na ⁺]	1631.44	1632.17	0.73
			[Na ⁺]	1628.86	1629.08	0.22
			[2*Na ⁺]	1594.41	1596.17	1.76
			X[2*Na ⁺]	1631.44	1632.58	1.14
			Y[2*Na ⁺]	-	1646.50	-
			Z[2*Na ⁺]	-	1603.17	-

Table 2. Overview of the product masses identified by ESI-MS for the products generated in Labtrix® Start.

Conclusion: Performing initial condition screening within a Labtrix® micro reactor (Reaction Volume = 19.5 µl), Junkers *et al.* demonstrated the ability to utilise this emerging technology for the highly controlled thiol-ene derivatisation of poly(*n*-butyl acrylate) **1** enabling reaction times to be reduced nine-fold. It is proposed that the methodology developed is applicable generically towards the modification of thiol-ene terminated polymers and could be performed on the g to kg-scale using meso-scale reactor equipment such as KiloFlow® (Chemtrix BV, NL).

This material is taken from 'Use of a Continuous Flow Microreactor for Thiol-ene Functionalization of RAFT-derived Poly(*n*-butyl acrylate)', accepted for publication in the peer-reviewed Royal Society of Chemistry journal *Polymer Chemistry*. Please refer to the original article for a more detailed discussion and illustrations of the materials characterisation [1].

References:

- [1]. J. Vandenberg and T. Junkers, 'Use of a Continuous Flow Microreactor for Thiol-ene Functionalization of RAFT-derived Poly(butyl acrylate)', *Polym. Chem.*, 2012, **3**, 2739-2742.
- [2]. C. H. Hornung, C. Guerrero-Snachez, M. Brasholz, S. Saubern, J. Chiefari, G. Moad, E. Rizzardo and S. H. Thang, 'Controlled RAFT Polymerization in a Continuous Flow Microreactor', *Org. Proc. Res. Dev.*, 2011, **15**, 593-601.
- [3]. C. H. Hornung, A. Postma, S. Saubern and J. Chiefari, 'A Continuous Flow Process for the Radical Induced End Group Removal of RAFT Polymers', *Macromol. React. Eng.*, 2012, **6**, 246-251.
- [4]. C. Diehl, P. Laurino, N. Azzouz and P. H. Seeberger, 'Accelerated Continuous Flow RAFT Polymerization', *Macromol.*, 2012, **43**, 10311-10314.
- [5]. C. Wiles and P. Watts, 'Continuous Flow Reactors: A Perspective', *Green Chem.*, 2012, **14**, 38-54.
- [6]. C. Wiles and P. Watts, 'Microreaction Technology in Organic Synthesis', *CRC Press*, 2011.
- [7]. V. Hessel, B. Cortese and M. H. J. M. de Croon, 'Novel Process Windows – Concept, Proposition and Evaluation Methodology, and Intensified Superheated Processing', *Chem. Eng. Sci.*, 2011, **66**, 1426-1448.
- [8]. A. Nagaki, Y. Takahashi, K. Akahori and J.-I. Yoshida, 'Living Anionic Polymerization of *tert*-Butyl Acrylate in Flow Microreactor System and Its Application to the Synthesis of Block Copolymers', *Macromol. React. Eng.*, 2012, **6**, 467-472.