Flow Chemistry

DOI: 10.1002/anie.201202795

Continuous Synthesis and Purification by Direct Coupling of a Flow Reactor with Simulated Moving-Bed Chromatography**

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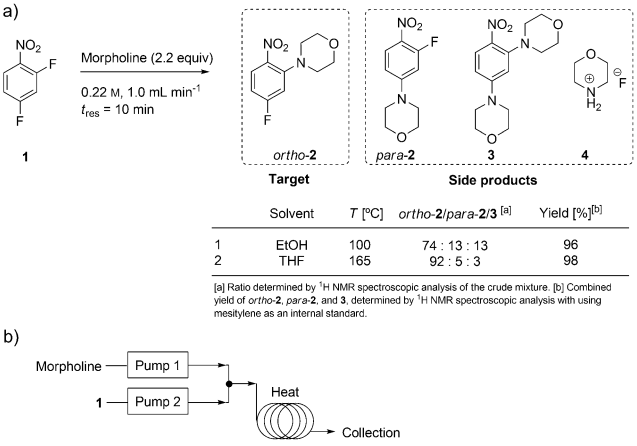
Continuous-flow reactors have increased the scale of reactions that can be carried out in the laboratory, and can ease the transition from the research to production environment.[1] Performing a reaction in flow can be advantageous in cases where heat, mass, or light-transfer influence reactivity, or where hazardous reagents are used at high temperature and pressure.[2] However, purification is often a bottleneck in synthesis and can negate the benefits ascribed to flow reactors, unless side-products can be removed by crystallization or liquid–liquid extraction.[3] In-line solid-supported reagents that scavenge undesired byproducts[4] have finite lifetimes and cannot be operated in a continuous manner without regeneration. Additionally, separating complex mixtures of products often necessitates recourse to batch column chromatography. Simulated moving-bed (SMB) chromatography,[5,6] a form of continuous counter-current chromatography widely used industrially, offers a solution. Based on efforts to integrate both enzymatic and crystallization processes with SMB chromatography[7,8] we envisioned that a flow reactor could be coupled with SMB chromatography to synthesize and purify complex molecules in a single, continuously operated system. Herein, we report the first successful coupling of flow synthesis and SMB chromatography to continuously produce pure product.

The nucleophilic aromatic substitution (S_NAr) reaction of 2,4-difluoronitrobenzene (**1**) with morpholine (Figure 1a) affords a mixture of products and thus was selected to demonstrate the approach. The reaction can be performed in a range of solvents at various temperatures and concentrations.[9,10] From the outset we were mindful of the fact that the ideal solvent, concentration, and flow rates for the synthetic transformation would likely differ from those for purification. In an initial experiment using a commercially available flow reactor (Vapourtec,[11] R2/R4 see the Supporting Information), solutions of **1** and morpholine in ethanol were mixed and heated to 100 °C in a 10 mL stainless steel loop connected to an 8 bar back pressure regulator to give a mixture of *ortho*-**2**, *para*-**2** and disubstituted product **3** (Figure 1a, Conditions 1). In these preliminary experiments, salt byproduct **4** was removed by batch aqueous extraction. Classical four-zone SMB chromatography, a binary separation technique, requires that the target elutes either as the first or last component. The target product, *ortho*-**2** eluted last in reversed-phase chromatography (hydrophobic stationary and hydrophilic mobile phases) and was selected for separation from all the other reaction components.



	Solvent	T [°C]	*ortho*-**2**/*para*-**2**/**3** [a]	Yield [%][b]
1	EtOH	100	74 : 13 : 13	96
2	THF	165	92 : 5 : 3	98

[a] Ratio determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [b] Combined yield of *ortho*-**2**, *para*-**2**, and **3**, determined by ^{1}H NMR spectroscopic analysis with using mesitylene as an internal standard.

Figure 1. a) S_NAr reaction of 2,4-difluoronitrobenzene (**1**) with morpholine under continuous flow conditions. b) Plan of the flow system.

SMB chromatography employs four zones of columns connected end to end in series. A counter-current between the mobile and stationary phases is simulated by periodically shifting the two inlet and outlet ports in the direction of the mobile phase flow after a certain time (the "shift time"). Eluent and the feed mixture to be purified are fed at opposite points in the system while the strongly retained product (extract) and the remaining weakly retained byproducts (raffinate) are collected at the two remaining positions. A separate pump drives each zone: our design assumed that the flow reactor provides the feed input to the system (Figure 2). Criteria for successful operation were not only high yield and purity, but also the continuous and robust operation of the coupled reactor and SMB system.

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[**] We thank the Max-Planck Society and AstraZeneca UK for generous financial support. F.L. is the recipient of a postdoctoral fellowship from Fonds québécois de la recherche sur la nature et les technologies (FQRNT).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201202795.

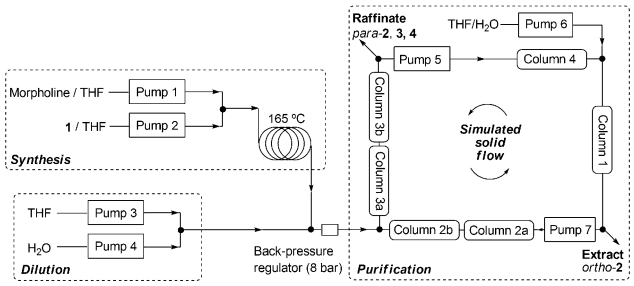

Figure 2. Schematic diagram of the directly coupled system.

HPLC separation of the product mixture using both normal (YMC PAK SIL, 30 μm, *n*-hexane/EtOH, 75:25 v/v) and reversed (LiChrosorb 25–40 μm, H_2O/EtOH, 25:75 v/v) phases highlighted the poor performance of ethanol as a mobile phase for purification. Low solubility of the product mixture in the former case and poor reproducibility in the latter case prompted use of *tert*-butyl methyl ether (MTBE; 2-methoxy-2-methyl propane) and EtOAc as alternatives, although the insoluble salt by-product **4** clogged the reactor in these solvents. Possible accumulation of **4** on the columns under normal-phase conditions prompted further exploration of reverse-phase conditions, which revealed THF/water (40:60 v/v) as an ideal eluent. Upon changing the reaction solvent to THF higher selectivity for *ortho*-**2** was observed. Increased temperature (165 °C),[12] ensured complete consumption of the starting material (Figure 1 a, Conditions 2).[13] A second set of pumps was used to dilute the product stream with THF/water and thereby provide the SMB unit with a feed of appropriate concentration and eluent composition. Thermodynamic and kinetic parameters for SMB design were obtained from preliminary batch chromatography experiments. Operating conditions were estimated using the following constraints: a total feed concentration of 5.5 g L^{-1}, feed flow-rate of 10 mL min^{-1}, and both purity and yield of the target product greater than 99 %. The migration velocity of the solute in the chromatographic column depends on the mobile-phase velocity and the partition ratio. Linear adsorption isotherms were applied. During SMB separations, the stationary-phase movement is simulated by shifting the ports. The shifting time represents the counter-current stationary phase velocity. Each SMB zone has a designated flow-rate ratio (m), that is, the ratio of net liquid-phase flow to simulated solid-phase flow. A specific component moves in the liquid flow direction if the zone flow-rate ratio is larger than the Henry constant of this component. The well-established short-cut triangle method[14] was used to identify the region of possible operating conditions (see the Supporting Information). A detailed evaluation of these conditions was performed by separating the output of the reactor prior to direct connection of the two instruments. The product distribution in the feed leaving the flow reactor as analyzed by off-line HPLC remained constant.[15]

The mixture from the flow reactor was then fed into the SMB system that was arranged in a six column (1-2-2-1) configuration.[16] Fractions of the extract and raffinate were collected after every cycle (six port shifting intervals, 171 s) and the product distribution was determined. The extract contained only *ortho*-**2** (over 99 % purity by HPLC) and the system reached cyclic steady state after three cycles. The raffinate contained the remaining products, accompanied by a small amount of *ortho*-**2** (Figure 3).[17]

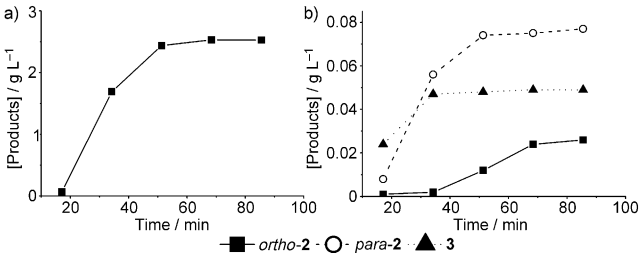

Figure 3. Concentration profiles at the a) extract port in the uncoupled system; b) raffinate port in the uncoupled system.

With effective separation conditions established, we sought to directly couple the instruments, replacing the SMB feed pump with a capillary from the flow reactor and the dilution pumps. During initial attempts, the flow reactor did not tolerate the high pressure generated in the SMB system and the feed flow rate was reduced to 5.0 mL min^{-1} by decreasing the dilution-pump flows. The reduced feed flow rate was compensated for by recalculation of the operating conditions. Feed throughput was maintained by the resulting increase in feed concentration. Aliquots of the feed were analyzed at every cycle. The system took longer to reach steady state under these conditions but continuous operation was achieved (Figure 4 a,b). The extract contained *ortho*-**2** in over 99 % purity, even before steady state was achieved (Figure 4 c,d). Comparison of the input and output concentrations and flow rates allowed calculation of the steady state yield. In the final cycle 89 % of *ortho*-**2** was obtained. Extract

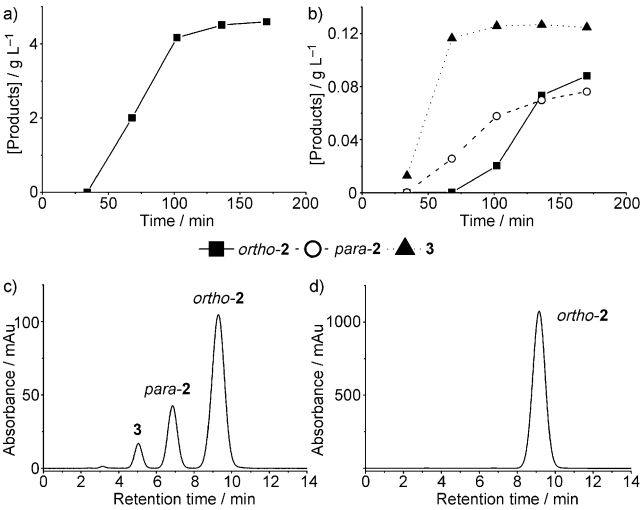

Figure 4. Concentration profiles at the a) extract port in the coupled system; b) raffinate port in the coupled system; c) chromatogram of the feed composition from the flow reactor; d) chromatogram of extract fraction over the final shift in the coupled system.

fractions collected during start-up and washing of the system contained *ortho*-**2** in equivalent purity.

In summary, we have developed a system for the continuous flow synthesis and purification of complex reaction mixtures using SMB chromatography. The system can be operated continuously to provide the target compound in high yield. Based on linear adsorption isotherms the method can be applied to other purification problems in the synthesis of complex organic molecules. This system is one of the very first truly continuous flow-purification systems and should prove of wide applicability for the synthesis of complex molecules and active pharmaceutical intermediates even on large scale.[18] Continuous purification is the key to conducting multi-step reactions in a truly continuous regime.

Received: April 11, 2012
Published online: June 6, 2012

Keywords: continuous synthesis · flow chemistry · nucleophilic aromatic substitution · purification · simulated moving-bed chromatography

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[15] The UV absorptions of compounds **2** and **3** varied. Individual calibration curves were used for quantification.

[16] To enhance separation, two columns were used in each of the two separation zones of the SMB system. The remaining two zones consisted of one column each.

[17] These separation conditions were also successfully applied to the purification of the less-pure product mixture deriving from the reaction in EtOH (Figure 1a, Conditions 1).

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