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An approach for continuous-flow processing of reactions that involve the in situ formation of organic products

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ABSTRACT

A simple adaptation allows batch protocols developed using microwave heating that involve formation of solid organic products to be scaled up using conventionally-heated flow chemistry with minimal or no re-optimization or modification. The product stream is intercepted with a flow of a suitable organic solvent upon exiting the heated zone, this solubilizing the product and allowing it to pass through the back-pressure regulator without aggregation of particulate material.

Continuous-flow processing on micro- and meso-scale is currently a technology of considerable interest.[1,2] It is possible to perform reactions effectively both at high and low temperatures by means of heating or cooling blocks around which the reactants pass in tubing of various diameters. While many synthetic transformations are amenable to flow processing, homogeneity of the reaction mixture must be considered. When working at elevated temperatures, use of a back-pressure regulator allows for solvents and reaction mixture to be heated well above their boiling points. However, if the product precipitates out of solution upon cooling, blockage of the back pressure or the exit tube can be a potential problem. While specialized equipment is available for processing slurries, when using most commercially available apparatus issues of heterogeneity can be a hurdle that needs to be overcome when moving from batch to continuous-flow. Many reactions are designed in batch such that the product precipitates out of solution, facilitating the isolation step. When transitioning to flow, one option is to change the solvent so as to ensure that both starting materials and product are soluble throughout. This can require re-optimization of reaction parameters such as residence time or temperature. Recently, ultrasound has been used for dispersing aggregates of manganese oxide formed in the permanganate oxidation of alcohols and aldehydes.[3] In our laboratory we have recently used another approach to overcome the problem; namely mixing organic solvent with the product stream prior to entering the back-pressure regulator. We report our method here and take methodologies developed using microwave-heating and directly translate them to a flow approach, keeping parameters such as time and temperature unchanged.

The work was performed using a commercially available continuous-flow unit.[4] The reaction mixture was pumped through a 14 mL capacity PTFE coil reactor which fitted snugly around an aluminum heating block. A T-piece mixer was placed at the exit of the coil reactor, and this linked to a second input line allowing introduction of organic solvent. A short length of PTFE tubing was placed between the T-piece and a 100 psi rated back-pressure regulator. Another small length of PTFE tubing was attached to the exit of the back-pressure regulator, this being used to take the product mixture to a collection vessel. The configuration is shown in Figure 1.

Much of our recent research effort has been directed around the use of microwave heating as a tool for synthesis both on small and larger scales.[5] We have become interested in translating a number of our protocols from processing in batch using microwave heating to conventionally-heated flow (Scheme 1). The synthesis of 3-acetylcoumarin from salicylaldehyde and ethylacetoacetate was one such transformation of interest. In our microwave heating approach, we perform the reaction at 130 °C for 8 min using either ethyl acetate or ethanol as solvent and piperidine as a catalyst.[5] The coumarin product precipitates from the mixture upon cooling at the end of the reaction. Our initial attempts to transition to flow were unsuccessful due to build up of the product over time both in the back-pressure regulator and also the exit line. We knew that the coumarin was very soluble in acetone and thought that if we

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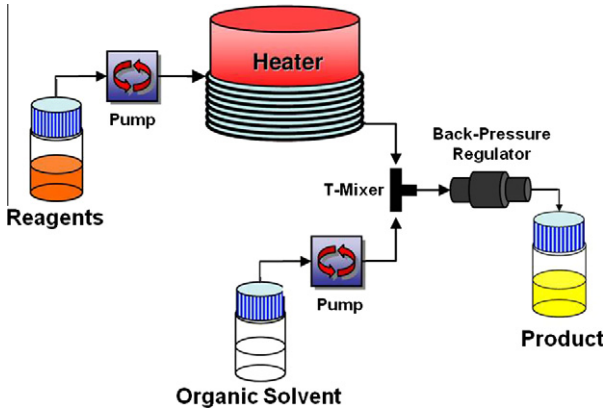
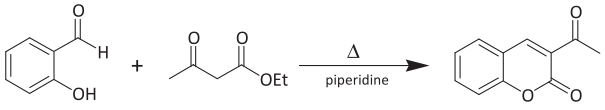


Figure 1. Configuration for processing reaction mixtures where the product precipitates from solution.

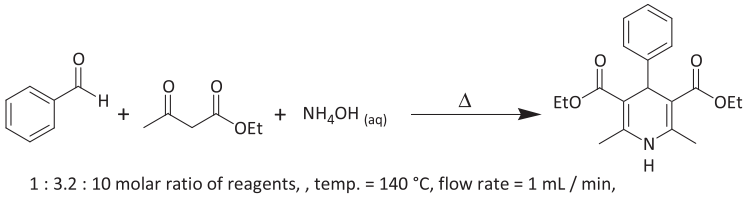
mixed the product stream with a flow of acetone as it left the heated zone, but prior to passing through the back pressure regulator, we could solubilize the coumarin and collect it with ease. To achieve this, we placed a T-mixer at the exit of the heater column and introduced the acetone at this point (Fig. 1). Performing the reaction at the 1 M concentration in ethyl acetate as solvent and flowing at 1.5 mL/min we mixed the product stream with acetone also flowing at 1.5 mL/min. Using this approach, we could easily process our desired quantity of 50 mmol of material, obtaining 3-acetylcoumarin in 74% yield.[6] This is comparable with the yields obtained using microwave heating in batch on both small and larger scales (72–78%). A question that could arise is why not perform the reaction using acetone, given that the product and starting materials are soluble in this solvent. As a control we ran the reaction in acetone, working on the 5 mmol scale using batch microwave heating. After 8 min at 130 °C, we obtained only a 10% yield of the product.[7]

Having found the approach worked well for the preparation of 3-acetylcoumarin, we turned our attention to the Hantzch synthesis of a 1,4-dihydropyridine. Again we had developed a batch approach to this reaction using microwave heating and again the product was insoluble in the solvent mixture used.[8] The batch methodology was performed at 110 °C for 15 min using a 1:1 mixture of water and ethanol as solvent system. Transitioning to flow and using benzaldehyde, ethyl acetoacetate and ammonium hydroxide as reagents (1:3.4:10 stoichiometric ratio, respectively), we performed the reaction at the same temperature at a flow rate of 1 mL/min. We intercepted the product stream with ethyl acetate (1 mL/min) as it exited the heated zone. Performing the protocol on the 50 mmol scale, we collected the product stream in a separatory funnel, removed the aqueous layer, washed the organics with a portion of 50% aqueous calcium chloride to extract as much of the ethanol as possible from the ethyl acetate solution prior to removing the organic solvent and isolating the product. A 53% yield of the desired 1,4-dihydropyridine was obtained, this comparing well to methodologies using microwave heating.[9,10]

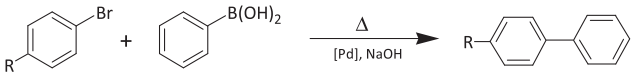
Next we moved to the Suzuki coupling reaction. We have developed a number of approaches to this reaction, most involving the use of low loadings of simple palladium salts as catalysts.[11] The biaryl products are generally insoluble in the water/ethanol reaction mixtures used and thus make for good candidates for our flow approach. We first focused attention on the coupling of 4-bromoanisole and phenylboronic acid, performing the reaction on the 100 mmol scale using a 1:1 water/ethanol solvent mixture, sodium hydroxide as base and a catalyst loading of 0.008 mol % palladium(II)chloride. At a concentration of 0.5 M, we flowed the reagents through the heated zone (150 °C) at a rate of 2 mL/min (residence time of 7 min) and intercepted the product stream with ethyl acetate (2 mL/min). The outlet stream was collected, the aqueous layer was discarded and the organic solvent was removed. A quantitative conversion to the desired biaryl was obtained.[12] We then moved to using 4-bromoacetophenone as the aryl halide substrate. Our motivation for this was 2-fold. Firstly, the 4-bromoacetophenone is a solid at room temperature unlike 4-bromoanisole which is a liquid. Secondly, 4-acetylbiphenyl has a melting point of 116–118 °C as compared to for 4-methoxybiphenyl. As a result, processing 4-bromoacetophenone would be more difficult both in terms of dissolving the starting material in our solvent system and also because the product would be more prone to crystallization upon exiting the heated zone. We found that it was necessary to reduce the reagent concentration to 0.2 M in order to dissolve all the 4-bromoacetophenone starting material. We were pleased to find, using the same protocol as with 4-bromoanisole, no aggregation



1 : 1 molar ratio of reagents, ethyl acetate as solvent, temp. = 140 °C, flow rate = 1.5 mL / min, residence time = 7 min, intercept with acetone at 1.5 ml / min; 74 % yield



1 : 3.2 : 10 molar ratio of reagents, , temp. = 140 °C, flow rate = 1 mL / min, residence time = 15 min, intercept with ethyl acetate at 1 ml / min; 53 % yield



R = OMe, COMe, 1 : 1.2 molar ratio of reagents, 1 : 1 ethanol / water as solvent, temp. = 150 °C, flow rate = 2 mL / min, residence time = 7 min, intercept with ethyl acetate at 2 ml / min; quantitative conversion

Scheme 1. Reactions screened in this study.

of biaryl occurred when intercepting the product stream with ethyl acetate (2 mL/min). Again, a quantitative conversion was obtained and, upon isolation, a 97% yield recorded.[13]

In summary, we have shown that a very simple adaptation allows batch protocols developed using microwave heating that involve formation of solid organic products to be scaled up using conventionally-heated flow chemistry without need for re-optimization or modification of the reaction conditions. Upon exiting the heated zone, the product stream is intercepted with a flow of organic solvent solubilizing the product and allowing it to pass to the collection vessel without aggregation of particulate material.

Acknowledgements

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5. (a) Schmink, J. R.; Kormos, C. M.; Devine, W. G.; Leadbeater, N. E. *Org. Process Res. Dev.* **2010**, *14*, 205–214; (b) Bowman, M. D.; Schmink, J. R.; McGowan, C. M.; Kormos, C. M.; Leadbeater, N. E. *Org. Process Res. Dev.* **2008**, *12*, 1078–1088.
6. *Preparation of 3-acetylcoumarin*: Salicylaldehyde (5.3 mL, 50 mol), ethyl acetoacetate (6.4 mL, 50 mol) and piperidine (0.4 mL, 8 mol %) and ethyl acetate (50 mL) were combined in a glass bottle equipped with a top that allows tube access. Acetone was placed in another glass bottle. The aluminium block was heated from room temperature to 140 °C, passing ethyl acetate through the coil reactor, from bottom to top, at a rate of 1.5 mL/min. The flow was then changed from solvent to reaction mixture by means of a switch on the control unit. The reaction mixture was then passed through the coil reactor at a rate of 1.5 mL/min. As the mixture neared the end of the coil reactor, an empty, clean collection vessel was put in place and a flow of acetone (1.5 mL/min) started into the T-piece mixer. After all the reaction mixture had entered the coil reactor, the flow was changed back to solvent and this flowed through the reactor at a rate of 1.5 mL/min to push the remaining reaction mixture through and out into the collection vessel. As soon as this was achieved, the flow was stopped. The organic solvent was removed on a rotary evaporator and the product conversion determined by means of NMR spectroscopy. The product was then purified by washing with cold ethanol and dried under vacuum.
7. From a synthetic chemistry perspective, there is the potential for a Knoevenagel condensation between the acetone solvent and the ethyl acetoacetate reagent.
8. Bowman, M. D.; Holcomb, J. L.; Kormos, C. M.; Leadbeater, N. E.; Williams, V. A. *Org. Process Res. Dev.* **2008**, *12*, 41–57.
9. *Hantzch synthesis of a 1,4-dihydropyridine:* Benzaldehyde (5.3 g, 50 mmol), ethyl acetoacetate (21.5 mL, 160 mmol), concentrated ammonium hydroxide (28 mL, 800 mmol), ethanol (50 mL) and water (50 mL) were combined in a glass bottle equipped with a top that allows tube access. Ethyl acetate was placed in another glass bottle. The aluminium block was heated from room temperature to 110 °C, passing ethanol/water (1:1 mixture) through the coil reactor, from bottom to top, at a rate of 1 mL/min. The flow was then changed from solvent to reaction mixture by means of a switch on the control unit. The reaction mixture was then passed through the coil reactor at a rate of 1 mL/min. As the mixture neared the end of the coil reactor, an empty, clean collection vessel was put in place and a flow of ethyl acetate (1 mL/min) started into the T-piece mixer. After all the reaction mixture had entered the coil reactor, the flow was changed back to solvent and this flowed through the reactor at a rate of 1 mL/min to push the remaining reaction mixture through and out into the collection vessel. As soon as this was achieved, the flow was stopped. The contents of the collection vessel were transferred to a separatory funnel, the aqueous layer removed, the organics washed with water, then 50% calcium chloride and finally brine. The organic solvent was removed on a rotary evaporator and the product conversion determined by means of NMR spectroscopy.
10. An approach for Hantzch synthesis of the same 1,4-dihydropyridine has previously been developed using flow chemistry but in a more ethanol-rich solvent mixture, probably keeping the product in solution throughout. A 42% yield was reported: Bagley, M. C.; Fusillo, V.; Lubinu, M. C., Uniqsis Application Note 10 (www.uniqsis.com).
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12. *Preparation of 4-methoxybiphenyl:* 4-Bromoanisole (18.7 g, 100 mmol), phenylboronic acid (14.6 g, 120 mmol), NaOH (8 g, 200 mmol), ethanol (100 mL), water (100 mL) and an aliquot of palladium ICP standard solution (800 μL of a 1000 ppm $PdCl_2$ stock solution) were combined in a glass bottle equipped with a top that allows tube access. Ethyl acetate was placed in another glass bottle. The aluminium block was heated from room temperature to 150 °C, passing ethanol through the coil reactor, from bottom to top, at a rate of 2 mL/min. The flow was then changed from solvent to reaction mixture by means of a switch on the control unit. The reaction mixture was then passed through the coil reactor at a rate of 2 mL/min. As the mixture neared the end of the coil reactor, an empty, clean collection vessel was put in place and a flow of ethyl acetate (2 mL/min) started into the T-piece mixer. After all the reaction mixture had entered the coil reactor, the flow was changed back to solvent and this flowed through the reactor at a rate of 2 mL/min to push the remaining reaction mixture through and out into the collection vessel. As soon as this was achieved, the flow was stopped. The contents of the collection vessel were transferred to a separatory funnel, the aqueous layer removed, the organics washed with water, then 50% calcium chloride and finally brine. The organic solvent was removed on a rotary evaporator and the product conversion determined by means of NMR spectroscopy.
13. *Preparation of 4-acetylbiphenyl:* 4-Bromoacetophenone (5.06 g, 25 mmol), phenylboronic acid (3.65 g, 30 mmol), NaOH (2 g, 50 mmol), ethanol (80 mL), water (60 mL) and an aliquot of palladium ICP standard solution (200 μL of a 1000 ppm $PdCl_2$ stock solution) were combined in a glass bottle equipped with a top that allows tube access. Ethyl acetate was placed in another glass bottle. The aluminium block was heated from room temperature to 150 °C, passing ethanol through the coil reactor, from bottom to top, at a rate of 2 ml/min. The flow was then changed from solvent to reaction mixture by means of a switch on the control unit. The reaction mixture was then passed through the coil reactor at a rate of 2 mL/min. As the mixture neared the end of the coil reactor, an empty, clean collection vessel was put in place and a flow of ethyl acetate (2 mL/min) started into the T-piece mixer. After all the reaction mixture had entered the coil reactor, the flow was changed back to solvent and this flowed through the reactor at a rate of 2 mL/min to push the remaining reaction mixture through and out into the collection vessel. As soon as this was achieved, the flow was stopped. The contents of the collection vessel were transferred to a separatory funnel, the aqueous layer removed, the organics washed with water, then 50% calcium chloride and finally brine. The organic washings were dried over $MgSO_4$, the solvent was removed on a rotary evaporator and the isolated product yield obtained.