Scale-up of Microwave Heated Reactions without Re-optimization Including Automatic Solid Handling

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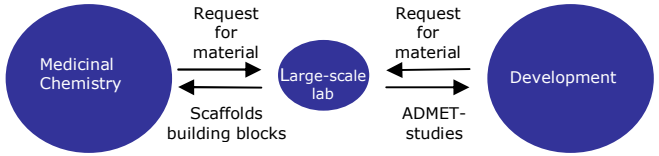
Introduction

The trend within pharma industry is clearly to speed up the process from lead identification to selection of candidate drug. One of the major limitations is the availability of larger amounts, typically hundreds of grams, of the potentially active substance to be further investigated.



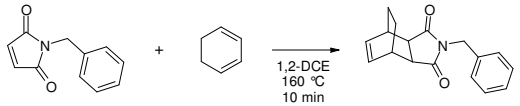
Microwave assisted organic synthesis (MAOS) is now a commonly accepted technique, used to rapidly heat up chemical reactions and thus accelerate the reaction rates.
Biotage has recently introduced Advancer Kilobatch, an instrument for scaling up mw-heated reactions with an automated solid handling carousel incorporated (see picture below) and a syringe pump for adding liquids. We have also presented data that shows cycle-to-cycle and batch-to-batch reproducibility using the same reaction parameters for the small scale instrument, Initiator, and Advancer Kilobatch.[1] Here, we present the results from four additional studies.

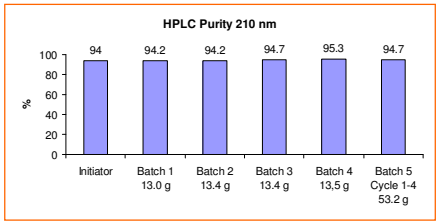
General Experimental Procedure

Batches 1-4: These four batches were run and collected individually after flash cooling according to the procedure described, in order to compare them to the outcome from the run on the Initiator, but also to examine the batch-to-batch reproducibility. The reaction mixtures from these batches were not worked up.
Batch 5 (Batch 1), Cycle 1-4: This batch consists of four sequential cycles which were run and collected unattended as a single batch after flash cooling according to both the procedure and the work-up described below.

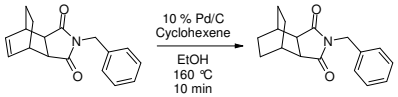
Results

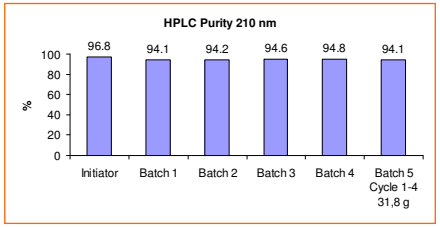
Diels-Alder Reaction (Batches 1-4 and Batch 5, Cycle 1-4)
With the syringe pump, 125 mL of 0.4 M *N*-benzylmaleimide in 1,2-DCE (9.35 g, 50.0 mmol) and 125 mL of 0.6 M 1,3-cyclohexadiene in 1,2-DCE (7.15 g, 75.0 mmol, 1.5 equiv) were mixed and heated to 160 °C for 10 minutes. After evaporation the remaining solid was dried under vacuum.



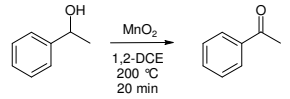


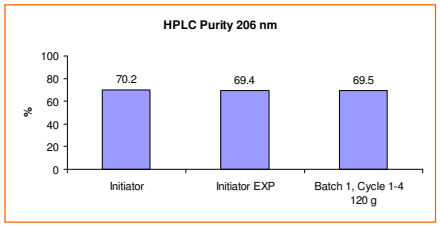
Catalytic Transfer Hydrogenation (Batches 1-4)
To each of the small compartments of the solid adding carousel was added 958 mg (0.90 mmol, 0.03 equiv) 10 % Pd/C, and to each of the large compartments was added 8.02 g (30.0 mmol) starting material. With the syringe pump, 125 mL (0.18 M, 45.0 mmol, 1.5 equiv) of cyclohexene in ethanol was added. The resulting slurry was heated to 160 °C for 10 minutes.
Batch 5, Cycle 1-4: After filtration through Celite and evaporation, the residue was dried under vacuum yielding 31.8 g (98 %) of the product (purity: 94.2 % by HPLC-MS and 92 % by ^{1}H NMR).



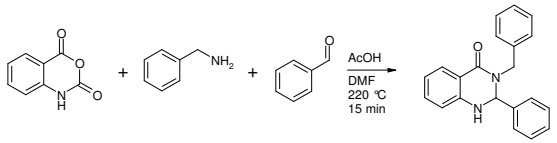


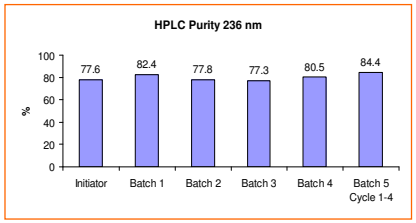
Oxidation of alcohol with MnO_2 (Batch 1, Cycle 1-4)
To each of the large compartments of the solid adding carousel was added 26.1 g (300 mmol, 1.20 equiv) MnO_2. With the syringe pump, 250 mL (1.0 M, 250.0 mmol) of 1-phenylethanol in 1,2-DCE was added. The resulting slurry was heated to 200 °C for 20 minutes. After filtration through Celite and evaporation, the residue was dried under vacuum yielding 120.2 g (100 % mass recovery, 69.5 % product and 30.5 % starting material by HPLC-MS).





3-Components Reaction (Batches 1-4 and Batch 5, Cycle 1-4)
To each of the large compartments of the solid adding carousel was added 5.78 g (35.4 mmol) isatoic anhydride. With the syringe pump, 125 mL (0.283 M, 35.4 mmol) of benzaldehyde and acetic acid in DMF, and 125 mL (0.283 M, 35.4 mmol) of benzylamine in DMF was added. The resulting slurry was heated to 220 °C for 15 minutes. The residue was analyzed by HPLC-MS and ^{1}H NMR.





References:
1. Panagiotis Ioannidis and Ronny Lundin
17th International Conference & Exhibition
Organic Process Research and Development
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