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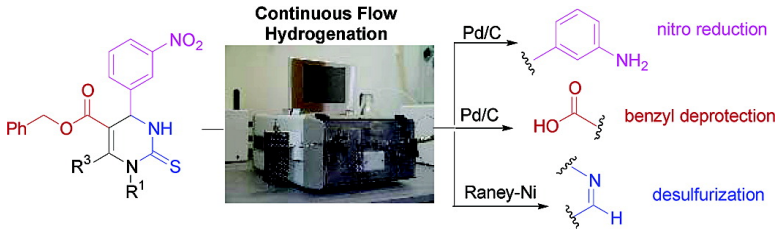

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Heterogeneous Hydrogenation Reactions Using a Continuous Flow High Pressure Device

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The hydrogenation of organic compounds through addition and/or hydrogenolysis, typically carried out in the presence of a suitable heterogeneous metal catalyst, is of great significance not only in research laboratories but also in the chemical and pharmaceutical industries. Functional group reductions (e.g., alkene, alkyne, nitro) and deprotections (e.g., benzyl) are very common in catalytic hydrogenations.[1] Small-scale batch hydrogenations pose an operational hazard in the use of hydrogen gas, requiring dedicated high-pressure resistant reactors or autoclave conditions. Alternative hydrogenation methodologies that are efficient, viable, avoiding the hazards of using exogenic hydrogen gas under high-pressure conditions, and with the feasibility to scale-up key hydrogenation steps are sought after persistently.

In recent years, the concept of carrying out laboratory-scale organic chemical transformations under continuous flow conditions has received increased attention. Flow-through processes using cartridge-based reactors containing immobilized reagents or catalysts have the potential to deliver compounds in high intrinsic purities by automated, workup-free, solution-phase methods often without the need for subsequent chromatographic purification. As a consequence, flow-through reactors are increasingly being viewed attractive for implementing smaller laboratory-scale processes.[2] In addition, microreactor technology based on microfluidic flow has found considerable current interest in organic and high-throughput synthesis.[3]

In this context, Kobayashi and co-workers[4] recently described a microfluidic device for conducting hydrogenation reactions under continuous flow conditions. In these microreactor-type devices substrate solutions and external hydrogen gas are pumped through a palladium-immobilized microchannel (ca. 100−200 μm in width and depth) at ambient temperature and atmospheric hydrogen pressure. This technology promises high compatibility with multiphase catalytic hydrogenations and an efficient interaction between hydrogen, substrates, and a palladium catalyst to afford a smooth reaction.[4a] Alternatively, catalytic transfer hydrogenations in continuous flow format have been described by Kunz and co-workers, employing nanopalladium clusters in monolithic polymer/carrier materials.[4b]

Nonetheless, the development of laboratory-scale continuous flow hydrogenation systems utilizing substrate flow rates exceeding 0.1 mL/h and allowing for high-pressure and temperature conditions is still in its infancy. Here we wish to report on efficient continuous flow hydrogenation reactions using either Pd/C or Raney-Ni as heterogeneous catalysts in a compact, continuous flow (mesofluidic) device, suitable for high-pressure heterogeneous hydrogenations and feasible for high-throughput processing. The device (H-cube)[5] is a compact, high-pressure heterogeneous hydrogenator with an HPLC-like platform for substrate delivery, enabling heterogeneous hydrogenations at temperatures up to 100 °C and 100 bar of hydrogen pressure in a continuous flow mode (Figure 1). The electrolytic decomposition of water generates in-situ hydrogen of up to 100 bar. A pre-packed, replaceable cartridge of the heterogeneous catalyst (30 × 4 mm i.d., ca. 100−200 mg of catalyst/cartridge) contained in the system, allows a uniform substrate flow (mixed with hydrogen) without catalyst leaching, circumventing the need to filter the catalyst from the substrate after the desired hydrogenation. The instrument allows a continuous monitoring of the reaction progress and modification of the reaction parameters (temperature and hydrogen pressure) during an experiment for rapid optimization.[5]

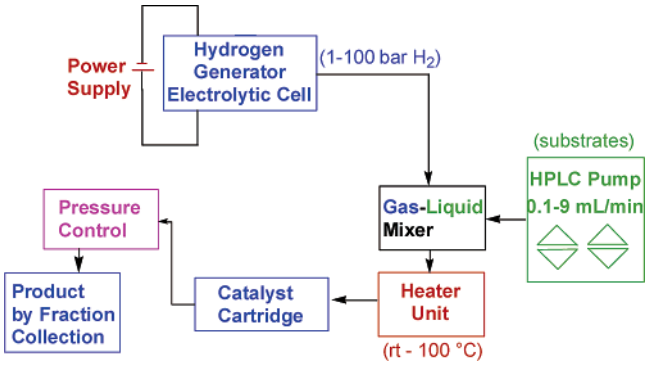

Figure 1. Laboratory-scale hydrogenation device H-cube (schematic).[5]

As suitable model reactions for investigating the scope of this hydrogenation technology we have explored various deprotection and reduction pathways on a multifunctionalized heterocyclic dihydropyrimidine (DHPM) core.[6] Several interesting pharmacological properties have been associated with these "privileged" DHPM scaffold,[7] and our laboratory has previously reported on a number of different high-throughput methods for the synthesis and scaffold decoration of this type of heterocycle.[8]

In the context of our earlier scaffold decoration work,[8] it became apparent that carboxylic acid functionality at the C5 position of the multifunctionalized DHPM core would serve as an excellent platform to introduce greater diversity into the scaffold at this position. While the preparation of the desired acids by simple acid or base-catalyzed hydrolysis of the corresponding alkyl esters (readily prepared by three-component Biginelli condensation) is troublesome,[9] the synthesis of the acids can be readily achieved by hydrogenolysis of the corresponding benzyl esters.[10] Previous reports in the literature demonstrate the feasibility of obtaining DHPM acids of type **2** in moderate to high yields by

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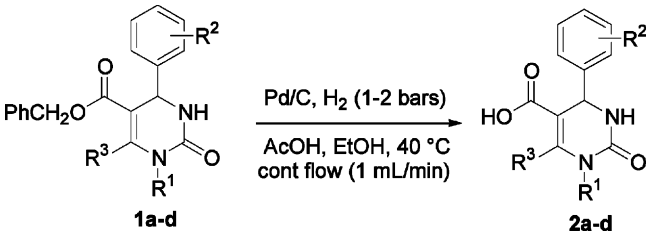
Table 1. Hydrogenation of DHPM C5 Benzyl Esters **1a**−**d** Under Continuous Flow Conditions[a]



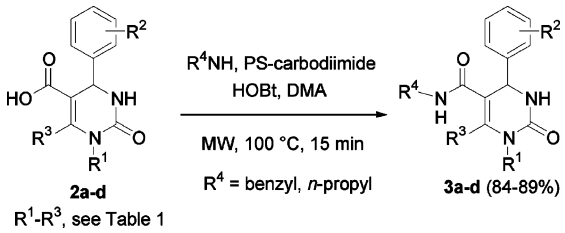
entry	R^1	R^2	R^3	yield (%)[b]
1a	H	H	Me	96
1b	H	H	Ph	81
1c	Me	H	Me	83
1d	H	4-Me	Me	87

[a] Reaction conditions: Continuous flow hydrogenations (1.0 mL/min flow rate), 0.01−0.025 M stock solutions of **1a**−**d** in an ethanol/acetic acid 7:3 (v/v) solvent mixture (25 mL). See Supporting Information for further details. [b] Yields refer to isolated yields of pure products (>98% by ^{1}H NMR and HPLC).

standard batch hydrogenolysis (20 °C, 8−24 h) of DHPM benzyl esters **1** using hydrogen gas (3 bar), a 5−10% Pd/C catalyst, and methanol solutions of the corresponding substrates.[10] Arguably, such batch hydrogenations with the hazards of using external hydrogen gas have few prospects to be adapted to a high-throughput library synthesis format. We therefore set out to examine the continuous flow heterogeneous catalytic hydrogenation of several DHPM C5 benzyl esters **1a**−**d** as model substrates using the hydrogenation reactor. Our results (Table 1) clearly demonstrate the superiority of the continuous flow approach over the standard batch process in terms of product yield, workup, and ease of reaction optimization.

Within one cycle of hydrogenation in the continuous flow reactor using a fresh heterogeneous catalyst cartridge (10% Pd/C) each of the DHPM benzyl esters **1a**−**d** readily afforded the corresponding DHPMs acids **2a**−**d** in 81−96% isolated yield (Table 1). In a typical flow experiment a 0.01−0.025 M stock solution of the corresponding benzyl ester **1a**−**d** in an acetic acid/ethanol solvent mixture was passed through the hydrogenation device at 40 °C using a 1−2 bar hydrogen pressure setting and a 1 mL/min flow rate. The degree of conversion was readily established by monitoring the composition of the reaction mixture after being exposed to the hydrogenation conditions by HPLC analysis. Adjusting the proper settings on the instrument (H_2 pressure, temperature, flow rate) "on the fly" allowed the optimization of the reaction conditions in these and related transformations (see below). Using the 1 mL/min flow rate described above, typically 100−150 mg of product could be produced within 30 min. In these experiments the catalyst activity is retained for several cycles with no difference in isolated product yields. Importantly, once the conditions for a specific transformation have been optimized, a number of related substrates (here different DHPM C5 benzyl esters) can be subjected to the same reaction conditions by simply switching the HPLC injection setup to the next stock solution reservoir. This method is ideal for carrying out library synthesis on a large number of compounds; each compound is injected into the system at timed intervals, hydrogenated, and then collected as fractions at the end of the reaction.[5] For the reported set of four DHPM acids a total processing time of 2−3 h was required to prepare a >100 mg quantity of each compound (including washing/rinsing the catalyst bed with reaction solvent after completion of each run). Another advantage of the flow-through concept concerns the handling of the catalyst. In standard batch reactions, the filtration of the substrate from a hydrogen-saturated pyrophoric catalyst generates a serious safety issue. In the current system, the catalyst remains in the cartridge throughout the entire experiment. In case of the DHPM C5 acids **2a**−**d** the only workup that was required was the evaporation of solvent, producing the desired products in >98% purity (^{1}H NMR and HPLC) and high yields.

Scheme 1. Microwave-Assisted Synthesis of DHPM C5 Amides

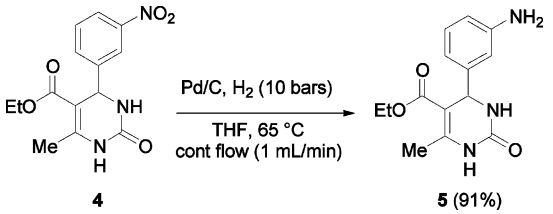


The resulting DHPM C5 carboxylic acids **2** can serve as useful templates for the generation of structurally diverse compound libraries (e.g., transforming the acid functionality into esters or amides). To highlight the possible integration of the above-mentioned hydrogenation device with existing high-throughput synthetic methods, we have performed subsequent amide coupling reactions with acids **2a**−**d**. For this purpose, the recently reported highly efficient microwave-assisted amidation protocol by Sauer et al.[11] was adapted to DHPM acids **2a**−**d**. This high-speed analoging method utilizes a resin-bound carbodiimide reagent and an efficient solid-phase extraction (SPE) procedure for post-reaction purification.[11] We have carried out the synthesis of a set of DHPM C5 amides **3a**−**d** using DHPM C5 acids **2a**−**d** and two selected amines (benzylamine and propylamine) as starting materials. Within 15 min of controlled microwave heating[12] at 100 °C, the corresponding amides were quickly obtained in high isolated yields (Scheme 1, for further details see the Supporting Information). The purification of the reaction mixture by simple filtration through a Si-carbonate SPE cartridge and the isolation of the corresponding DHPM amides **3a**−**d** by evaporation of the filtrate highlights the high-throughput character of this synthetic protocol.[13]

In a related chemistry example involving the hydrogenation device, the reduction of the aromatic nitro group in DHPM **4** was investigated (Scheme 2).

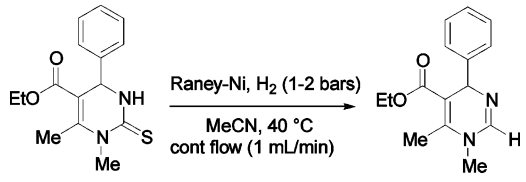
Previous work from our laboratory has demonstrated that this transformation can also be performed by catalytic transfer hydrogenation using ammonium formate as hydrogen source and 5% Pd/C as a heterogeneous catalyst under sealed vessel microwave irradiation conditions.[14] The resulting aniline derivative **5** is the starting material for the preparation of known neuropeptide Y (NPY) inhibitors.[15] Employing the continuous flow hydrogenation device, THF was quickly identified as the most favorable solvent for the reduction

Scheme 2. Reduction of an Aromatic Nitro Group under Continuous Flow Conditions



4 5 (91%)

Scheme 3. Reductive Dethionation of 3,4-Dihydropyrimidin-2-thiones under Flow Conditions



6 7 (95%)

reaction. A stepwise increase in both reaction temperature and hydrogen pressure—while monitoring reaction progress in-situ by HPLC—led to an optimal reaction temperature of 65 °C and a hydrogen pressure of 10 bar. Under those conditions, clean and quantitative conversion of a 0.025 M stock solution (25 mL) of the nitro compound **4** was achieved within one cycle, leading to a 91% isolated product yield.

In another application of the continuous flow hydrogenation method, we attempted the reductive dethionation of 3,4-dihydropyrimidine-2-thione **6** (Scheme 3). Previous work by Khanina et al. has confirmed that 3,4-dihydropyrimidine-2-thiones of type **6** can be subjected to reductive dithionation with Raney-Ni under batch conditions (acetone, reflux temperature, 1 h) to produce basic, amidine-like 1,4-dihydropyrimidines **7**.[16]

In our hands, a 0.012 M acetonitrile solution (25 mL) of 2-thioxo-DHPM **6** was subjected to hydrogenation conditions at 40 °C and a minimum hydrogen pressure (1−2 bar). Using the typical 1 mL/min flow rate complete consumption of the starting material was experienced providing a nearly quantitative product yield after one cycle within 30 min. The known 1,4-dihydropyrimidine **7** was isolated as homogeneous product by simple evaporation of the reaction solvent. In this case, during the run a minimum hydrogen pressure of >1 bar was maintained to ensure complete desulfurization of the substrates and compensate the depletion of active hydrogen retained in the Raney-Ni catalyst cartridge.

In conclusion, a novel continuous flow laboratory-scale hydrogenation device[5] has been evaluated in heterogeneous hydrogenations using Pd/C and Raney-Ni as catalysts. The continuous flow reduction of an aromatic nitro group, benzyl deprotections, and desulfurization reactions of selected dihydropyrimidine analogues have been conducted successfully. While only hetereogeneous hydrogenations have been discussed herein, the technology should subsequently also find scope with homogeneous hydrogenations as well as continuous flow reactions involving other catalysts or immobilized reagents (not involving hydrogen gas). Work along these lines is currently in progress in our laboratories.

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Supporting Information Available. Full experimental details and spectral data (NMR, MS) for all transformations and compounds described. This material is available free of charge via the Internet at http://pub.acs.org.

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