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A microfluidic flow chemistry platform for organic synthesis: the Hofmann rearrangement

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ABSTRACT

We report on the use of commercially available chemical microreactors to effect the Hofmann rearrangement of aromatic amides to the corresponding carbamates.

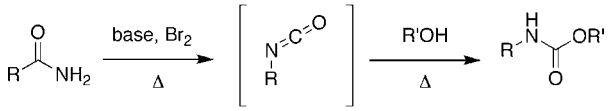
There is considerable current interest in microfluidic systems and in other continuous flow processes for conducting organic synthesis programmes.[1] The many advantages and efficiency gains, such as reduced reaction times, that can be achieved by the use of these systems the ability to conduct superheated and/or pressurized reactions, together with containment of hazardous, noxious or unstable intermediates particularly attractive.[2] Moreover, the enhanced safety, reduced solvent usage and lower waste generation, combined with the potential for automation and 24 h working schedules, adds considerable value to the concept. Our group is interested in developing improved tools,[3] techniques[4] and materials for use in flow-based operations[5] including multistep processes and complex molecule assembly.[6,7] As part of this programme, we have evaluated micro- and meso-fluidic equipment for affecting challenging chemical processes, especially those that have strategic value. Herein, we report the use of a commercially available microfluidic flow chemistry platform that was primarily designed for positron emission tomography (PET) applications, but one, which we felt, could be readily expanded to include other important chemical transformations. The Hofmann rearrangement is a special example in that it uniquely converts amides to the corresponding carbamates via C–C to C–N bond rearrangement, thereby affording a new product range that is not easily accessible by other routes[8] (Scheme 1). Recently, the Hofmann rearrangement was reported to be a key step in an alternative total synthesis of (−)-Oseltamivir (Tamiflu)[9] as well as of other biologically active natural products.[10] However, the potential toxicity of bromine (or bromine equivalent) and high reaction temperatures used in these reactions can be problematic using conventional laboratory methods.

We decided, therefore, that this reaction would be a good testbed for the new equipment. The integrated microfluidic synthesis platform used in this work is the Advion NanoTek LF™ device,[11] which consists of a base module comprising up to three computer-controlled microsyringe pumps and an array of four microfluidic fused silica tubular reactors (Fig. 1).

The total internal volume of each individual reactor ranges from 7.9 to 35.4 μL. The reactors can be heated up to 200 °C, over flow rates ranging between 5 and 5000 μL/min, and can be configured for multi-step or parallel syntheses. The system employs PEEK polymer reagent loops (200–400 μL) and flow tubes. Exiting products can be collected using a concentrator module that enables in-line concentration or evaporation of solvents. Final product purification may also be achieved in-line by solid-phase extraction (SPE) or by direct injection of flow products into an attached HPLC system.

A series of preliminary experiments were carried out on the flow equipment to profile the reaction in terms of optimum reaction temperature, concentration, residence time, solvent and stoichiometry. Following rapid screening of conditions, we fixed upon a set of reacting parameters for conducting the Hofmann rearrangement (Scheme 2). Two separate reagent streams were used in the reaction, which were then combined in a T-mixing piece prior to entering a single microreactor coil.

The first flow stream contained the amide, base and appropriate alcohol, and the second stream comprised brominating agent and alcohol. The most suitable conditions involved *N*-bromosuccinimide (NBS) as the brominating agent, together with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base in either methanol or



Scheme 1.

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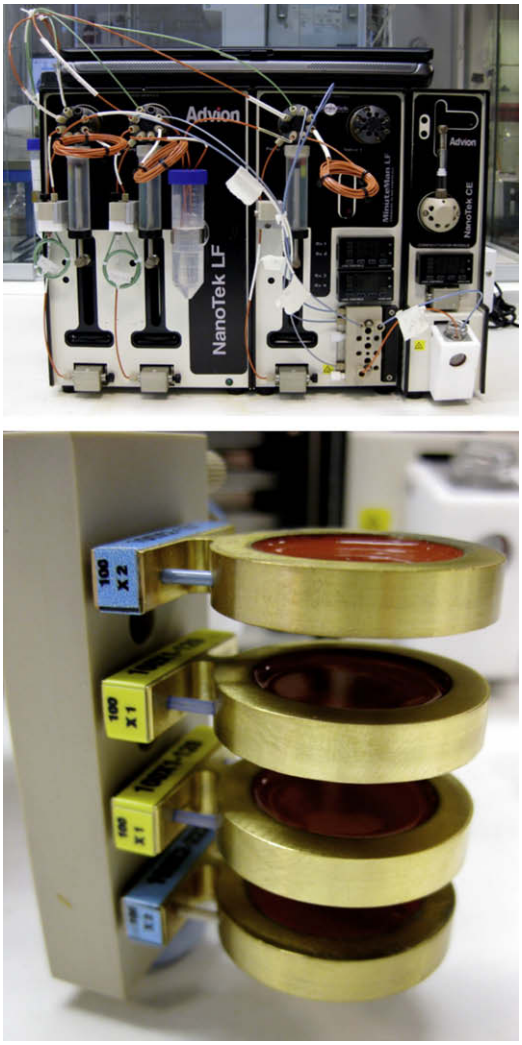
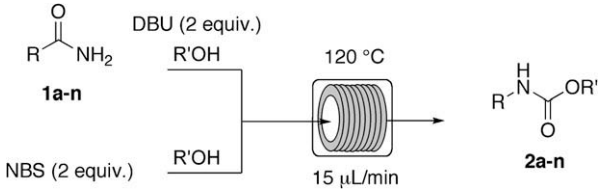


Figure 1. Advion NanoTek LF™ microreactor platform. The microreactor array is shown at the bottom.

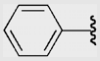
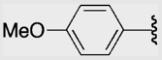
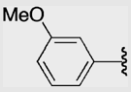
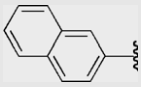
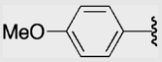
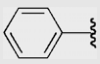
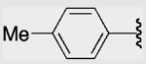
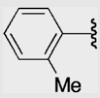
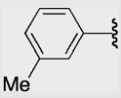
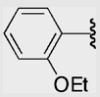
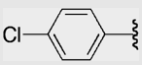
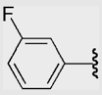
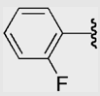
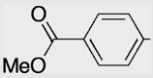


Scheme 2. General scheme for the Hofmann rearrangement of aromatic amides using the Advion NanoTek LF™ Microreactor Platform.

ethanol (R′OH),[12] to trap the intermediate rearranged isocyanate. A total flow rate of 15 μL/min (equating to a residence time of 1 min) and a reaction temperature of 120 °C ensured optimal conversion to the carbamate.

Reactions were carried out on a 50–100 μg scale (75–150 mM of reagents in the appropriate alcohol) in a 15.70 μL coil per experimental pass. Under these conditions, a collection of aromatic amides **1a–n** was transformed into their corresponding carbamates **2a–n** (Table 1). These commercially available substrates were chosen to examine aromatic substituent effects on the rearrangement under flow conditions.[13] The products were obtained after bulk collection and rapid purification through a short plug of silica gel. Typically,

Table 1
Carbamate products **2a–n** from the Hofmann rearrangement of amides **1a–n** under flow conditions using the Advion NanoTek LF™ microreactor platform (via Scheme 2)

Entry	R=	R′=	Product (yield %)
1		Me	**2a** (79)
2		Me	**2b** (80)
3		Me	**2c** (62)
4		Me	**2d** (71)
5		Et	**2e** (46)
6		Et	**2f** (32)
7		Me	**2g** (80)
8		Me	**2h** (78)
9		Me	**2i** (67)
10		Me	**2j** (74)
11		Me	**2k** (77)
12		Me	**2l** (41)
13		Me	**2m** (57)
14		Me	**2n** (55)

Isolated yields are shown.

20–25 reaction runs were performed with very high reproducibility, and samples combined to provide material for full analysis to determine the reaction integrity and efficiency. As shown in Table 1, the microfluidic platform is broadly applicable to achieve the rearrangement of aromatic amides to the corresponding carbamates in good to high yields (typically 70–80% yields), and afforded very clean isolated material (⩾97% by NMR). Notably, both electron-donating and withdrawing substituents were tolerated under the conditions,

and bromination of the benzene ring was not observed for the benzamides with electron-donating substituents. Keillor and co-workers[14] have reported the batch synthesis of methyl carbamates **2a–b**, **g** and **k** via Hofmann rearrangement using NBS/DBU; however, these conditions typically required reaction times of 25 min or more in refluxing methanol. Conversely, the preparation of these compounds using microfluidic conditions has resulted in a 25-fold reduction in reaction time with comparable yields. This demonstrates that under the present conditions, enhanced reaction rates result primarily from the laminar flow interaction of reagents and the superheating of methanol. From these experiments, we can conclude that the reaction profiling process is rapid, and that reliable reaction conditions can be found to deliver a useful chemical transformation, which further extends the use of the NanoTek™ flow platform.

Furthermore, in other experiments, we were able to show that the reaction parameters defined for this equipment can be readily transferred to other flow apparatus. In particular, the use of the Uniqsis FlowSyn™ continuous flow reactor[15] readily scales the Hofmann rearrangement reactions reported herein up to 1 g scale. The fully integrated instrument employs a dual channel flow system, with each channel independently driven by a variable high-pressure pump. The starting materials and reagents are united in a T-mixing piece and then passed into either a coil or column reactor. For our scale-up experiments, the rearrangement conditions established on the NanoTek™ flow platform were replicated. In a general procedure, a mixture of DBU (2 equiv) and the appropriate amide (1 equiv) was loaded into one channel, and NBS (2 equiv) into the second channel. The concentration of reagents in methanol was 75–150 mM. The combined reactant streams were directed into a stainless steel coil reactor (20 mL volume) and a total flow rate of 2.4 mL/min. The reactor temperature was maintained at 120 °C to ensure complete conversion. The resulting flow stream was collected, then purified by passage through a short silica plug. These conditions allowed for the scale-up synthesis of methyl carbamates **2a**, **g** and **l** at 88%, 74% and 37% yields, respectively. The successful gram scale synthesis of these compounds demonstrates the transferability and robustness of the optimized reactions established on the NanoTek™ flow platform, and they are readily scalable when used in other flow equipment, such as the Uniqsis FlowSyn™ system.

It is clear that the incorporation of microfluidic flow chemistry platforms is very effective device for effecting transformations for organic synthesis programmes. Advances in this area of science are developing rapidly, and the use of new, commercially available, modular reactors has an important role to play in their future applications.[16]

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