PHOENIX

Direct Alkylation of *N*-Heterocycle Under Heterogeneous Catalytic Conditions in Flow

INTRODUCTION

Flow reactors are now being applied to conduct high temperature and high pressure chemistry towards extending the accessible chemical space to access new applications.[1] Also, the ability to precisely control the residence time and other reaction parameters results in higher yields and tunable selectivity values for existing transformations. In addition, the utilization of extreme temperature and pressure environment eliminates the need for high boiling point solvents making the workup process faster, greener and economically more friendly.[2]

In this application note, we demonstrate the versatility of our Phoenix Flow Reactor™ by presenting results from the direct alkylation of *N*-heterocycle, which is described as an alternative route to the standard C-C cross coupling methods (one of the most frequently used synthetic reaction types in medicinal chemistry).

INSTRUMENTATION

The Phoenix Flow Reactor™ is a versatile high temperature and pressure flow reactor capable of handling both reaction loops and packed columns to perform homogeneous or heterogeneous catalytic reactions respectively up to 450 °C and 200 bar.

It is most frequently used as a modular flow unit coupled with an HPLC pump and a pressure regulator to facilitate reactions up to 200 bar. Alternatively, it can be linked to an H-Cube Pro™ system to provide the necessary back pressure (100 bar). In the following example, we have used the latter setup. Besides the actual reactor space, another essential part of the Phoenix Flow Reactor™ is the Heat Exchanger. It efficiently transfers heat from the product mixture into the reactant line while cooling down the former one to minimize the dead volume of the system and ensure maximum efficiency for product collection at nearly room temperature.

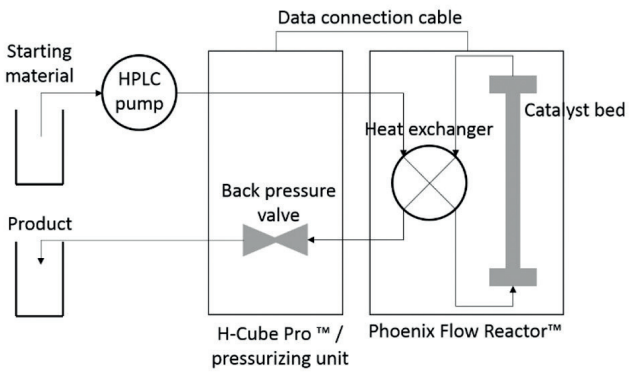

Figure 1. Schematic diagram of the system

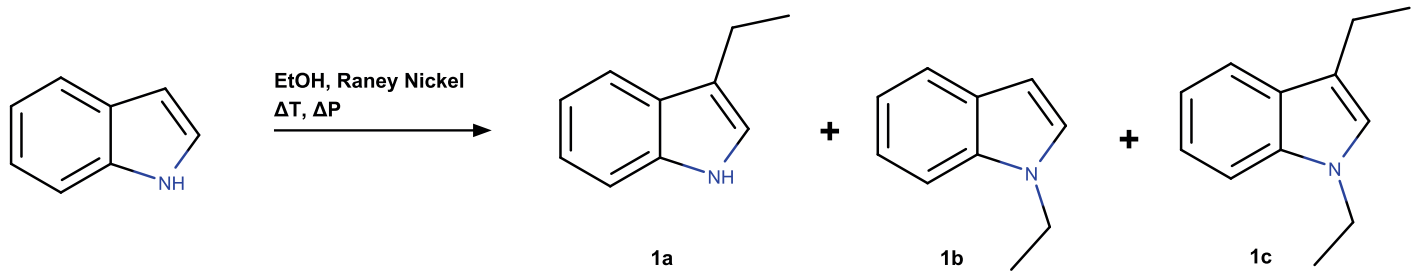

Figure 2. High temperature C-H activation of indoles towards direct alkylation

CHEMISTRY GOAL

We have chosen the region-selective alkylation of indole (in the 3. position) as a model reaction for C-H activation of heteroaromatic rings in continuous-flow. As our results show, using the Phoenix Flow Reactor™ under conditions of high temperature and high pressure provides a feasible alternative for direct C-C bond formation that is potentially a "greener" solution (less waste produced, non-precious metal catalyst) than the typical multistep reactions used by industry.[3]

EXPERIMENT

The catalyst bed, filled with Raney® Nickel, was washed with distilled water. The pressure (100 bar) and the temperature (200–300 °C) were set with water before changing the inlet to ethanol, which was also used as the direct alkylation agent. Indole was then dissolved in ethanol (0.1 M), and pumped through the reactor (0.5–1.5 mL/min). Fractions were collected after the calculated half-time of the dead volume. After all of the starting solution was used, the system was washed with pure alcohol until no reagent was observed by TLC (TLC plate with F254 silica at 254 nm UV). Conversion and selectivity values were determined by GC/MS and after purifying and isolating the products, NMR was used for further characterization. Additional specifics can be found in our recently published paper.[4]

"Optimized the reaction so fast I did not even have time to get used to the smell of the indole!", said Tamas.

CONCLUSION

Through a selected example of indole ethylation we have shown a considerably efficient replacement of common coupling reactions towards alkylated heterocycles. The direct transformation performed in our Phoenix Flow Reactor™ does not only involve short reaction time and high atom economy, but runs on a cost effective catalyst load as opposed to organometallics and other noble metals. Longevity measurements of 24 hrs resulted in an observed minimum decay in conversion (93%), which further grounds the applied flow process.

Temperature °C	Flow rate (mL/min)	Conversion (%)	Selectivity (%)			
			1a	1b	1c	other
250	0.5	>99	58	5	22	15

Figure 3. Chosen parameters & observed results for indole ethylation

REFERENCE

1) Razzaq, T.; Kappe, C.O.; *Chem. Asian J.*; **2010**; 5; 1274–1289
2) Newman, S.G.; Jensen, K.; *Green Chem.*; **2013**; 15; 1456–1472
3) Daugulis, O.; Do, H.Q.; Shabashov, D.; *Acc. Chem. Res.*; **2009**; 42; 1074–1086
4) Sipocz, T.; Lengyel, L.; Sipos, G.; Kocsis, L.; Dorman, Gy.; Jones, R.V. and Darvas, F.; *J. Flow. Chem.* **2015**; 6; 117–122

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