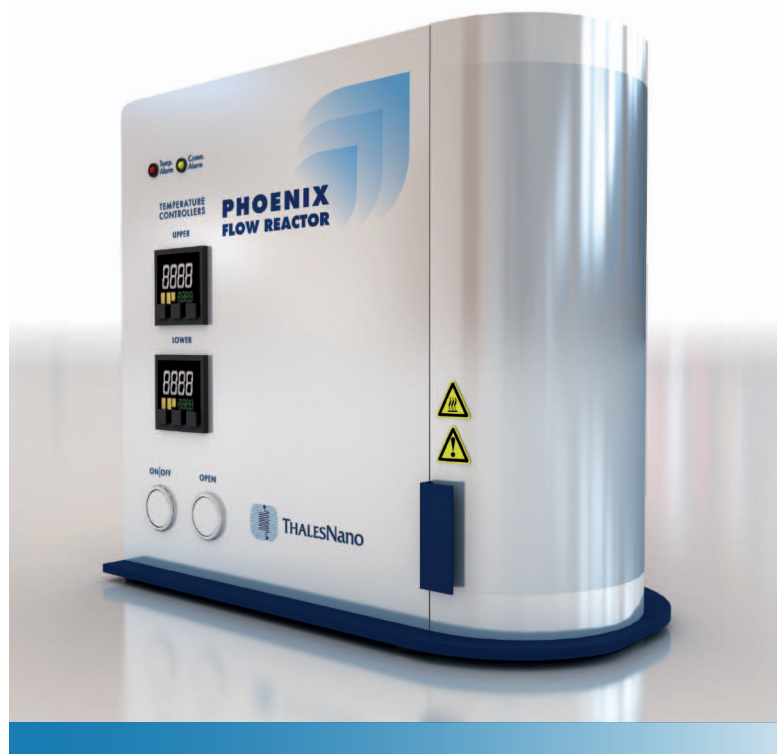




# A High Temperature Green Method for Direct *N*-Alkylation with the Phoenix Flow Reactor

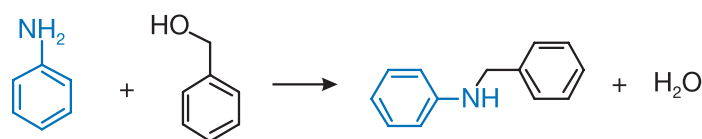
## INTRODUCTION

*N*-alkylation reaction is frequently used in various industrial, pharmaceutical, and agrochemical processes, such as the production of Piribedil; a drug used in the treatment of Parkinson's disease. The most common way of performing *N*-alkylation to produce secondary amines is the reaction between a primary amine and an alkyl halide. However, this methodology often results in byproducts (overalkylation) and the produced halide acid needs to be removed from the product mixture. The use of halide derivatives should be avoided due to their toxic nature, therefore other environmentally friendly processes have been sought. *N*-alkylation reactions, where alkyl alcohols are used instead, may provide possible green procedures. Such reactions are based on hydrogen-borrowing processes, where usually a Ru- or Ir containing homogeneous catalyst complex is required. In 2010, Lin He et al. published a paper about one-pot selective *N*-alkylation, screening many heterogeneous catalysts, and found that gold on titanium catalysts showed high activity and resulted in high yields of different *N*-alkylated products [1.]. Based on these results Mimi Hii and her group performed *N*-alkylation in flow, also using Au/TiO<sub>2</sub> catalyst. Several amines and alcohols were reacted and showed high conversion and selectivity. Notably these results were achieved under aerobic conditions with a commercially available Au catalyst compared to the previous method, where a gold nanoparticle catalyst was used under a N<sub>2</sub> atmosphere [2.]. Precise temperature control also had a major influence on the outcome of the reaction (150-180°C).



## INSTRUMENTATION

The Phoenix Flow Reactor coupled with the H-Cube Pro™ system is a novel, high temperature, high pressure flow reactor. The system works by using an HPLC pump to generate a continuous-flow of reaction mixture into an exchangeable reaction coil or cartridge at flow rates of up to 3 mL/min. The reaction coil or cartridge can be heated and pressurized up to 450 °C and 100 bar respectively. The reaction mixture is then cooled through a heat exchanger before eluting into a collection vessel. Reaction coils and cartridges for solid supported materials are available in various sizes.



Based on these results the model reaction of aniline *N*-alkylation by benzyl-alcohol was further investigated by applying high temperature (up to 450 °C). Catalyst screening reactions showed that the much cheaper RaNi catalyst resulted in the highest activity for *N*-alkylation [3.]. Finally 6 different *N*-alkylated products were synthesized using high temperature between 200-300 °C (Table 1.).

## GENERAL PROCEDURES

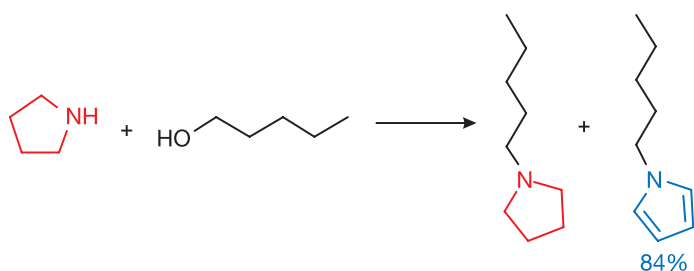
**Method A:** 1.0 M solution of the substrate (amine) in the corresponding alcohol was pumped through the Phoenix Flow Reactor twice under the following conditions: 200 °C, 80 bar, 0.5 mL/min, 70 mm long CatCart filled with Raney Nickel 4200. The mixture was analyzed with GC-MS. HCl in dioxane was added to the solution and it was stirred for an hour.

When crystallization occurred, the crystals were filtered and washed with ether. In other cases the solvent was evaporated and the residue was extracted with water and ether. 0.1 M NaOH was added to the aqueous layer (pH was set to neutral). Afterwards dichloromethane was used for extraction. The organic layer was dried over magnesium-sulfate and the solvent was evaporated.

**Method B:** A 0.5 M solution (50 mL) of piperidine in *n*-propanol was pumped through a 70 mm CatCart® filled with RaNi 4200 in the prototype of the Phoenix Flow Reactor with a 1.5 mL/min flow rate at 300 °C, 130 bar. The product was purified with distillation by applying a Vigreuxx -type fractionating column.

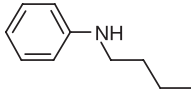
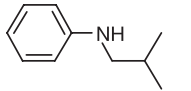
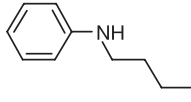
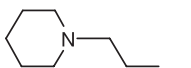
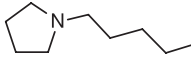
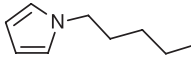
### INTERESTING RESULT

During the *N*-alkylation of pyrrolidine with pentanol at 350 °C unexpectedly *N*-alkyl-pyrrole was observed in 84% yield. In a control reaction, where pyrrole was reacted directly under analogous conditions it failed to produce the desired *N*-alkyl-pyrrole.



### SUMMARY OF THE RESULTS

Direct *N*-alkylations of amines with alcohols were carried out in fair yields in less than half an hour with a cheap Raney Ni catalyst instead of the earlier reported gold catalyst. In our study the alcohol component served also as a solvent, so the amine component could have been applied in relatively high concentration (1 M). Elevating the temperature in certain cases (pyrrolidine vs. pyrrole) meant aromatization followed the *N*-alkylation leading to aromatic *N*-alkyl species that can not be obtained by direct alkylation of the aromatic ring.

Entry	Amine	Alcohol	Main product	Conditions	Isolated Yield / %
1	aniline	<i>n</i> -butanol		Method A	51 %
2	aniline	<i>i</i> -pentanol		Method A	60 %
3	aniline	<i>n</i> -pentanol		Method A	54 %
4	piperidin	<i>n</i> -propanol		Method B	55 %
5	pyrrolidine	<i>n</i> -pentanol		Method C	64 %
6	pyrrolidine	<i>n</i> -pentanol		Method D	47 %

**Table 1.:** Results of *N*-alkylation reactions

**Method C:** Same as Method B, but pumping the starting material twice into the system at 200 °C, 80 bar, 1.0 mL/min

**Method D:** Same as Method B, but pumping the starting material twice into the system at 80 bar, 1.0 mL/min

### REFERENCES

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- 3.) Sipos, G.; Gyollai, V.; Sipocz, T.; Dorman, Gy.; Kocsis, L.; Jones, R. V.; Darvas, F.; Important industrial procedures revisited in flow: Very efficient oxidation and *N*-alkylation reactions with high atom-economy; *J. Flow Chem.*; Accepted publication; 10.1556/JFC-D-12-00025

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