SUMMARY

In Table 2, the experimental results of the reactions carried out on the X-Cube Flash™ and the corresponding literature results from batch experiments are shown. In general, reactions can be performed faster in the X-Cube Flash™ reactor when compared to the data obtained from the corresponding literature references. In most cases, complete conversions and high selectivities for the desired products were achieved. To scale up the processes, the reaction mixture can be simply left to run under the optimized conditions until the desired amount of compound is obtained.

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[5] Loupy, A.; Maurel, F.; Sabatié-Gogová, A.; *Tetrahedron*; **2004**; 60; 1683-1691

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Chemistry at High Temperature and Pressure – Using the X-Cube Flash™ Continuous-Flow Reactor

The X-Cube Flash™ is a continuous-flow system that can heat and pressurize solutions up to 350°C and 200 bar respectively. The high temperature and pressure significantly decrease reaction times and allows solvents to be reacted under supercritical conditions. This application note demonstrates the results of important chemical reactions carried out in the X-Cube Flash™ reactor with comparison to literature results based on conventional batch or microwave-assisted reactions.

INTRODUCTION

The ability to perform reactions at high temperature and pressure is limited by the equipment utilized in standard laboratories. Microwave (MW) reactors have extended the boundaries as to how chemistry is performed in the synthetic lab by increasing the chemists' capabilities to carry out reactions at high temperatures. This increases the reaction rates significantly and reactions typically progress well in minutes. However, microwave reactions are typically performed in batch, and their application is limited to small scale. Scale up of microwave reactions must be performed in conventional thermally heated batch reactors. The choice of the solvent is also limited to those having a sufficient dipole moment.
The X-Cube Flash™ is a state of the art flow reactor capable of performing reactions at 350ºC and 200 bar, which allows the user to perform reactions with solvents above their boiling points and therefore extends the boundaries of conventional lab synthesis.

Table 1. shows the critical temperatures of the most common solvents, which clearly indicates that such solvents can be reacted under supercritical conditions on the X-Cube Flash™ system.

Solvent	T_{crit} (°C)	p_{crit} (bar)
Ethanol	240.9	61.4
Methanol	239.4	80.8
Ethyl acetate	250	38
Acetonitrile	272.3	48.3
Water	374	221

Table 1.: The temperatures and pressures of common solvents needed to achieve supercritical conditions

This application note will describe some specific chemistry examples of reactions performed on the X-Cube Flash™ at high temperatures and pressures. Wherever possible, comparisons with chemistry performed by using microwave or conventional batch technology will be provided.

X-Cube Flash™ Application Note

FUNCTIONAL GROUP TRANSFORMATION

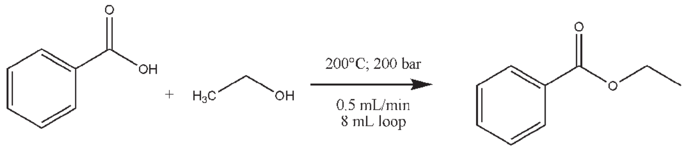
General Experimental Procedure

The X-Cube Flash™ system is very easy to operate. The paragraph below is a brief description of how to run a reaction on the X-Cube Flash™.

Select the desired loop length and place it into the X-Cube Flash™. Pump pure solvent through the X-Cube Flash™ system at the desired flow rate. The solvents should be the same as those used to dissolve the reactants and reagents in the reaction mixture flask. Set the required temperature and pressure of the system using the touch screen. After the system has equilibrated at the desired temperature and pressure, swap over to the reaction mixture flask and pass the solution through the X-Cube Flash™. When the reaction mixture flask is almost empty, add pure solvent to flush the system.

The following reactions were performed using the above method.

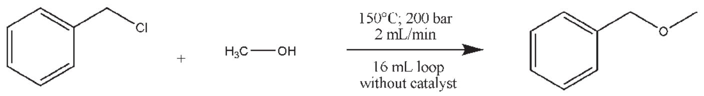
1. Esterification



Results of Esterification

Performing the reaction in ethanol at 200°C and 200 bar gave a 100% conversion and 94% purity for the desired product at 0.5 mL/min flow rate of the reactant solution in the presence of few drops of cc. H_2SO_4 by GC-MS analysis. During the experiment an 8 mL loop was applied, so the residence time of the reactants in the system was 16 minutes. In batch mode a recent publication [1] reported a 99% yield, but in the presence of CCl_4 and using UV irradiation with a 72 h reaction time.

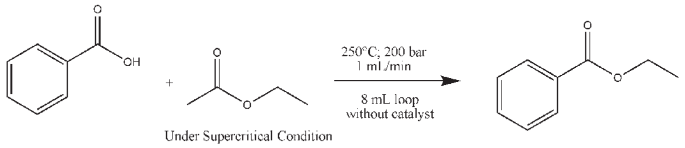
2. Alkylation



Results of Alkylation

From the GC-MS results, 100% conversion and 95% purity were obtained for the desired product when 150°C reaction temperature and 200 bar pressure were applied to the system. The flow rate of the reactant in methanol was 2 mL/min, and a 16 mL loop was used. These results and the calculated 8 min residence time is superior to the reported batch procedure [2] where phosphorane was used to promote the reaction achieving a 67% yield and a 24 h reaction time.

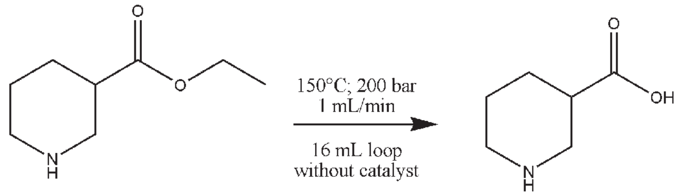
3. Transesterification



Results of Transesterification

To reach 100% conversion and 100% purity for ethyl benzoate, 250°C and 200 bar temperature and pressure were applied respectively with a residence time of 8 minutes. Performing the reaction in ethyl acetate the above conditions clearly indicate that the solvent was supercritical during the reaction. The literature example [3] gave an 80% yield and a 2 h reaction time.

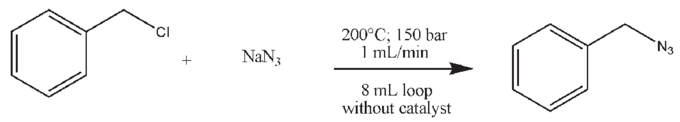
4. Hydrolysis



Results of Hydrolysis

From GC-MS results, 100% conversion and 100% selectivity were obtained for the desired product when 150°C reaction temperature and 200 bar pressure were applied to the system. The flow rate of the reactant in water was 1 mL/min, and a 16 mL loop was used.

5. Azide formation



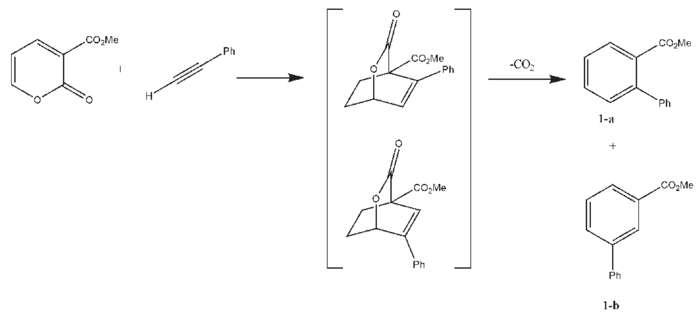
Results of Azide formation

To reach 100% conversion and 90% selectivity, 200°C and 150 bar temperature and pressure were applied. The flow rate of reaction mixture in methanol was 1 mL/min and an 8 mL loop was used. Literature data [4] gave 69% yield and a 1.5 h reaction time in the presence of a catalyst.

DIELS-ALDER REACTION

General Experimental Procedure

Acetonitrile as solvent was passed through the X-Cube Flash™ with 1 mL/min flow rate using an 8 mL loop. The pressure of the system was set to 80 bar and the temperature to 350°C. After the system equilibrated, 1.54 g (0.01 mol) of methyl-2-oxo-2*H*-pyran-3-carboxylate and 2.04 g (0.02 mol) phenylacetylene in 100 mL of acetonitrile was pumped through the X-Cube Flash™. After 5 minutes an analytical sample was taken, and analyzed by GC-MS.



Results of Diels-Alder reaction

The optimized reaction parameters gave 98% conversion and 100% selectivity for product **1-a**, methyl-2-phenyl benzoate, compared to the literature example [5] which reported a 60% yield and 65% selectivity with a 24 h reaction time in toluene using extended heating. Under microwave conditions without solvent, the desired **1-a** product was synthetized with a 100% selectivity and a 64% yield after 3 hours. The residence time of the reactants in the X-Cube Flash™ was only 8 minutes. The reaction at this temperature and pressure was performed under supercritical conditions.

A summary of all the results are given below:

Reaction	Results with X-Cube Flash™	Literature results using batch synthesis
Esterification	100% conversion, 100% purity, 4 min residence time	Yield: 99% Reaction time: 72 h [1]
Alkylation	100% conversion, 100% purity, 8 min residence time	Yield: 67% Reaction time: 24 h [2]
Transesterification	100% conversion, 100% purity, 8 min residence time	Yield: 80% Reaction time: 2 h [3]
Hydrolysis	100% conversion, 100% selectivity, 16 min residence time	-
Azide Formation	100% conversion, 90% yield, 8 min residence time	Yield: 69% Reaction time: 1.5 h [4]
Diels-Alder Reaction	98% conversion, 100% selectivity, 8 min residence time	Yield: 60%, selectivity: 65% Reaction time: 24 h [5]

Table 2: Comparison of results of the X-Cube Flash™ experiments and literature results