AN INTRODUCTION TO FLOW CHEMISTRY:

A Practical Laboratory Course

vapourtec

IN ASSOCIATION
WITH:

Dr Nicholas E. Leadbeater &
the New Synthetic Methods Group
University of Connecticut , USA

PREFACE

By using continuous-flow processing, chemists are finding that they can do new and exciting chemistry in a clean, safe and easy way. As such, flow chemistry equipment is becoming an integral tool for running reactions both in industrial settings as well as research labs in colleges and universities. But this new technology should not be relegated to graduates, it should be used by the very people that will be the chemists of tomorrow – undergraduates. The aim of this manual is to bring flow chemistry into the undergraduate teaching lab. In developing the ten experiments gathered here, we have focused on reactions that are used widely by preparative chemists and that also bring some of the key transformations learned in organic chemistry lecture courses. There are a number of reactions that simply could not be done traditionally in a typical laboratory period, thereby exposing students to chemistry they otherwise would not have had the opportunity to run. There is some considerable emphasis on cleaner, greener chemistry, as particularly illustrated by an oxidation reaction performed using household bleach as the oxidant. Metal-catalysed reactions also feature highly. Indeed we feature two Nobel Prize winning reactions – a palladium-catalysed cross-coupling and a ruthenium-catalysed alkene metathesis. We also include the synthesis of heterocycles, a rearrangement reaction and a sweet-smelling esterification, amongst others.

The manual was developed using the Vapourtec E-series flow unit. This easy-to-use, robust system is ideally suited for the undergraduate teaching laboratory but also is a great addition to the research laboratory. A discussion of how to use the E-series is found in the "Using the Equipment" chapter. Each experiment comes with a brief introduction and then step-by-step instructions for performing the reaction. It is assumed that the instructor has set up the equipment with the appropriate tubing and reactors so that students can get straight to work, following the steps outlined in the protocol.

The experiments were designed, developed, tested and re-tested by two talented graduate students, Christopher Kelly and Michael Mercadante. We are also grateful to other students in the laboratory, especially the undergraduate interns, that tested some of the reactions. We thank in particular, Rebecca Wiles, Meghan Negus, Robin Cywar and Brittany Mantha.

Two additional people that deserve a special mention are Amanda Heggland (ajh design) for designing the cover of this manual and David Griffin of Vapourtec for his input in the initial plan for the manual.

We hope that you enjoy the experiments and, as well as learning new techniques in the lab, discover some of the excitement that is building around flow chemistry.

Nicholas Leadbeater and the New Synthetic Methods Group
Connecticut, USA
September 2013

CONTENTS

Preface

Flow Chemistry: The Basics

Flow Chemistry: Using the Equipment

An Introductory Experiment using Flow Chemistry

Diels-Alder [4+2] Cycloaddition: Preparation of a Bicyclic Lactone

Preparation of a Heterocycle: A Paal-Knorr Pyrrole Synthesis

Preparation of a Bromarene: Electrophilic Aromatic Substitution

Preparation of a Carbamate: The Hoffmann Rearrangement

Preparation of an Ester: Oxidation of an Aldehyde to a Methyl Ester

Preparation of a Coumarin: A Knoevenagel Condensation

Preparation of a Cyclopentene: A Ring-Closing Metathesis Reaction of a Diene

A Nucleophilic Acyl Substitution Reaction: Preparation of an Ester

Preparation of a Biaryl: A Suzuki Coupling Reaction

FLOW CHEMISTRY: THE BASICS

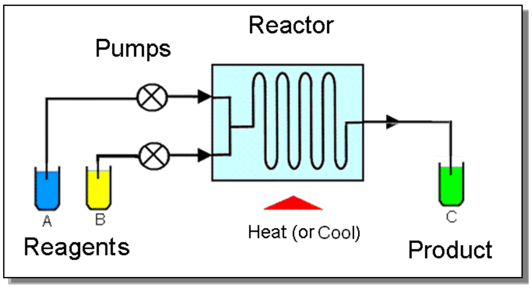
LEARNING GOALS

- *To understand the key concepts of flow chemistry*
- *To learn the key factors involved in performing a flow chemistry experiment*
- *To appreciate when reactions are or are not amenable to flow chemistry*

INTRODUCTION

There are two ways to perform a chemical reaction. The first is in a test tube, a beaker or a flask. The reagents and solvent are put into the container and the reaction mixture stirred, heated, or cooled depending on what conditions are required. This is called *batch processing*. A reaction can be performed on a small scale in, for example, a small round-bottom flask. When doing it on a larger scale, a larger flask can be used. But as the scale continues to increase, so the size of the flask becomes increasingly larger too – to a level where it can become impractical. Also, while it is quite easy to stir, heat or cool a reaction in a small flask, these functions become increasingly more difficult when it is scaled up. For example, 100 ml of water can be heated quickly to a boil but 100 litres of water takes a lot longer to heat. Another issue is that if the reagents are hazardous, performing the reaction on a large scale can be dangerous. When working in a small flask, only a small amount of the reagents are used but on a large scale, significant amounts of the reagents are in the reaction vessel at one time. This means that if something goes wrong, it can have serious consequences.

To overcome these problems, chemists are increasingly turning to *continuous-flow processing*, also just called “flow chemistry”. Rather than running the reaction in a flask, it is performed in a tube and the reagents are pumped through it. The reaction takes place inside the tube, which can be heated or cooled. Because of the high surface area to volume ratio the contents can be heated or cooled quickly. This eliminates temperature gradients often seen in batch reactors. The high surface area also allows for rapid heat dissipation which is a benefit in highly exothermic reactions. Finally, since only a small amount of the reaction mixture is in the tube at any one time, if something goes wrong it is not as bad as if there had been a problem with a large batch reaction.



Schematic of a flow chemistry set-up

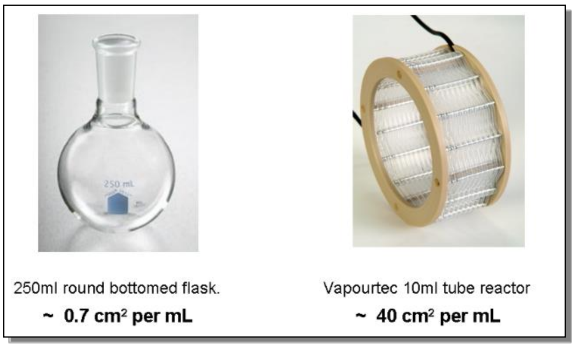
FLOW RATE AND RESIDENCE TIME

When using flow chemistry, two inter-related variables are of key importance. They are the flow rate and the residence time (the time spent by any given molecule in the reactor). If a batch reaction takes 10 minutes at 50 °C in a flask, to convert that to an identical flow process it would need to spend 10 minutes passing through the tube at 50 °C. That means it needs to have a *residence time* of 10 min. If the tube has a total volume of 10 mL then the reaction mixture would need to pass through at 1 mL per minute to be in there for 10 min. That means it needs to have a *flow rate* of 1 mL / min. If, instead, the tube had a volume of 100 mL then the flow rate would have to be 10 mL / min to give the same residence time of 10 min.

While a batch reaction can be run in flow with similar conditions (the same temperature, and a residence time similar to the original batch reaction time), the same chemistry can often be performed *more quickly* in flow by operating a higher temperature. That same reaction which took 10 minutes at 50 °C may be complete in 5 minutes at 60 °C, or 2.5 minutes when run at 70 °C. While the difference between 10 minutes and 5 minutes may not seem that great, it means that the reaction can be run at twice the flow rate and so twice as much product can be made each minute for a given reactor size.

HEAT TRANSFER

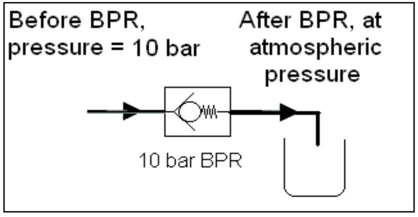
The surface-area-to-volume-ratio of a 1-mm diameter tube reactor is approximately *fifty times higher* than that of a 250-mL round-bottom flask. This means that reagents passing through the flow reactor can be very effectively (and quickly) heated or cooled. Some reactions are very temperature sensitive. They can generate product very fast but then that product can decompose or form by-products over time at the high temperatures used. In a large flask, because it takes a long time to heat the reaction mixture up and cool it down, by-product formation can be a real issue. Using flow chemistry this is not the case; the mixture is in the reactor for a short time and then the product comes out and goes back to room temperature. For highly exothermic reactions, taking heat *out* of the reaction is often important. In batch processing, removing heat can be a major challenge meaning that some reactions are deemed too hazardous to perform. These same reactions can be performed safely and easily in flow because the heat can be removed much more effectively. An example is the nitration of organic molecules.



Difference in surface-area-to-volume-ratio of a 250-mL round-bottom flask and a 1 mm diameter tube reactor

USING ELEVATED PRESSURES

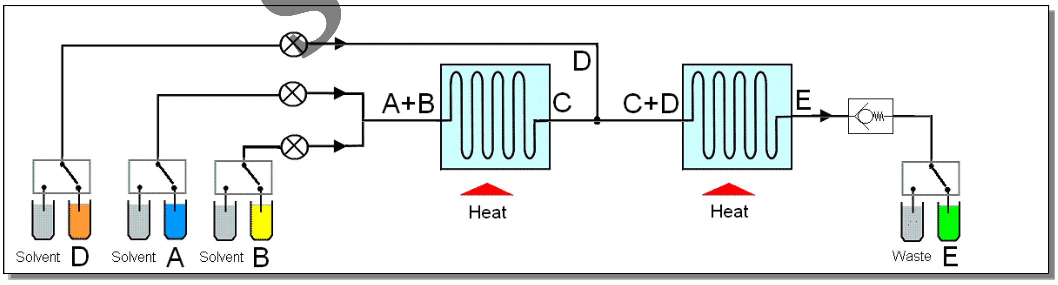
Reactions can be performed at elevated temperatures and also elevated *pressures*. While water boils at 100 °C at atmospheric pressure, the boiling point is increased to approximately 175 °C at a pressure of 10 bar. So, if a reaction is to be performed in water at 170 °C it is necessary to have the tube under a pressure of at least 10 bar to keep the water in the liquid phase. To do this, a device called a *back-pressure regulator* (BPR) is placed at the end of the tube, after the reactor. There are two types of BPR. One acts as a valve with a spring holding it closed. The pump has to push the valve open to get the reaction mixture out of the tube. Another BPR design works by restricting flow through a small inert tube. Using a screw-like clamp, the pressure can be varied.



Flow through a BPR

A CHEMICAL FACTORY

When using flow chemistry, scale is essentially unlimited. It is like leaving a tap on. Product will keep coming out until the tap is turned off. The tap can be left on for a minute to make a small quantity of product or for a day to make a large amount. Also, multiple reactions can be performed in sequence. Reagents **A** and **B** can be combined in a tube and they react to make compound **C**. Then, reagent D could be introduced and **C** and **D** passed through another tube to make **E**, and so on. Therefore, in principle, a whole series of reactions can be run and the final product will come out at the end. It is like a modern car factory, molecules passing along the conveyer belt with reactions taking place along the way until the final product is made.



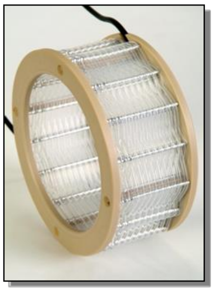
Multi-step flow chemistry

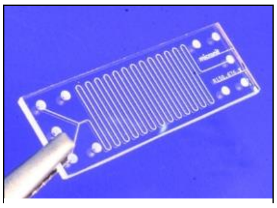
CONTROLLING A FLOW REACTION

With all these parameters playing a role in the reaction, it is important that they can be monitored. As well as being able to change the flow rate easily, modern flow chemistry equipment comes with sensors for temperature and pressure measurement. They can serve as safety mechanisms too. If the pressure sensor measures an unexpected change, it can shut the system down safely. So, if the back-pressure regulator becomes blocked by a solid product or by-product (pressure rise) or if a tube leaks (pressure drop) then the flow system can be quickly shut down automatically.

REACTORS

The simplest type of flow reactor is a length of tubing, generally coiled to save space and help with temperature control. The internal diameter of tube reactors can range from less than 0.5 mm in small-scale flow units to many centimetres in larger scale industrial equipment. At the smaller end, microreactors, featuring small passageways in a metal, ceramic, glass or plastic base are used. These may feature specific internal forms designed to promote mixing of reactants, and the passageways may be as small as 0.1 mm in diameter.


A tube reactor


A microreactor

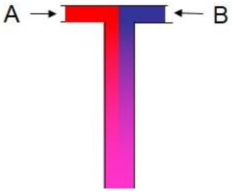
Many reactions require catalysts to make them go. The catalyst could be dissolved in the reaction mixture (called homogeneous catalysis) or alternatively placed onto a solid support (heterogeneous catalysis). In the case of the latter, flow chemistry can be very useful. The reagents can be passed through a bed of the catalyst in a tube. Since the reagents are surrounded by the supported catalyst, the local catalyst concentration is very high and that means that the reaction can be very fast. The catalyst is held in place while the reagent mixture travels on to collection or to another reaction stage. The tube filled with solid catalyst is known as a packed bed or column reactor.


A column reactor

There are also membrane reactors, in which a gas and a liquid stream are separated by a semi-permeable membrane. The gas can cross the membrane and enter the stream of liquid reagents. Using this approach, reactions such as hydrogenations can be performed safely and effectively.

MIXING

When using batch processing, stirring the reaction mixture is important. It helps mix the reagents. Mixing is also important when using flow chemistry, especially if the reaction mixture is viscous or contains components that are not soluble in each other – like oil and water. The simplest way to mix reagents in flow is to bring two (or more) streams together using a T-piece. Once they then go into the tube and start to react, diffusion is often enough to provide adequate mixing in a small flow cross section.



Mixing reagents A and B using a T-piece

Sometimes reactions can be controlled by limiting the mixing. For example, in a very fast exothermic reaction it may be counterproductive to mix too quickly since heat may be generated faster than it can be removed. Instead of mixing the reagents together at once it may be better to add portions of the reagent to the reaction at multiple positions along the reactor length. This way the heat of the reaction can be removed in a controllable way.

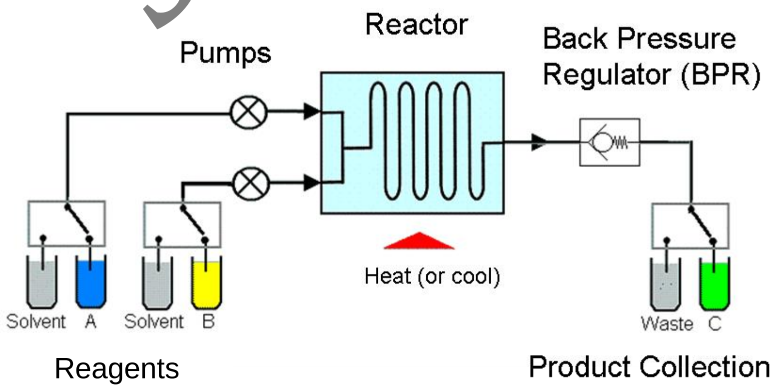
PERFORMING A REACTION IN FLOW

In a typical experiment there is a sequence of steps that are followed. First, the reactor is put in place and plumbed in to the lines that will introduce the reagents, and a back pressure device is fitted (after the reactor) which will determine the pressure at which the reaction takes place. Before reagents are sent through the reactor, correct reaction conditions must be established. First some solvent is pumped through the reactor (slowly to minimise solvent usage, but at sufficient rate to ensure the reactor is pressurised before heating begins if the reaction is to be run at elevated temperature). Then the reactor is heated (or cooled) to the desired reaction temperature.

Once the reactor is at temperature, the flow rate is changed to the target value and the liquid stream is changed from solvent to reagents. The reaction mixture now starts flowing into the reactor, while at the other end, the solvent that was inside the reactor will still be passing out through the back-pressure regulator. This is collected in a waste container.

When the product starts to come out of the reactor it is important to direct that into a different place. So, when the product mixture just starts to emerge from the reactor, the exit stream is diverted from waste to a collection vessel. Once all the reagents have been loaded into the reactor, the liquid stream is changed back to solvent but the target flow rate and the reactor temperature are maintained to ensure every last bit of the reagent mixture experiences the correct reaction conditions.

The exit stream is finally diverted back to waste once all the product has emerged from the reactor. The heating (or cooling) ceases, the pumps are turned off and the experiment is complete. Depending on the equipment used, this sequence of events may be manually controlled or fully automated.



Schematic for a typical flow reaction

LIMITATIONS TO FLOW CHEMISTRY

Flow chemistry is a very versatile and useful approach to performing a chemical reaction but there are some drawbacks to consider. It relies on the reagents being mobile – moving along the length of the reactor. If either a reagent or a product is a solid, this can pose a problem. Solids often do not move well along tube reactors and they can also block the tube, especially as they build up at the back-pressure regulator.

To avoid the build-up of solids, a number of approaches can be taken. Ideally, a solvent can be chosen in which all the reagents and products are known to be soluble. In the case of a reaction where a solid is formed as the reaction mixture cools down, the entire length of the tube, right up to the exit, can be held at a temperature above the melting point of the solid.

In some reactions, while the starting materials may be soluble in the solvent used, the product may not be. Therefore if the product stream is intercepted as soon as it leaves the reactor with a stream of a solvent in which it is totally soluble, blockages can often be avoided.

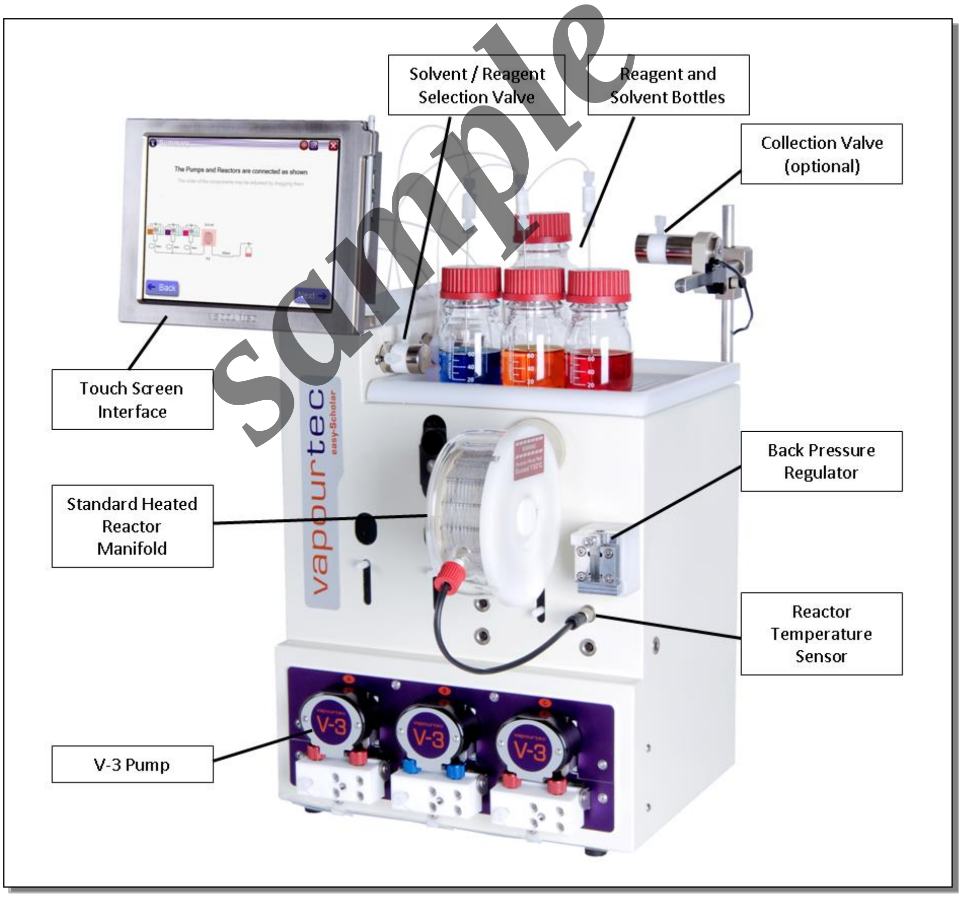
While many reactions are amenable to being performed at elevated temperatures for short times, some are not. This means that some reactions simply take a long time to reach completion. These are not suitable to flow chemistry. The general rule is that if a residence time of more than one hour is required, flow chemistry may not be the best approach to use.

FLOW CHEMISTRY: USING THE EQUIPMENT

LEARNING GOALS

- *To become familiar with the Vapourtec E-series and its capabilities*
- *To understand how to set up the equipment*
- *To use the equipment correctly for performing experiments*

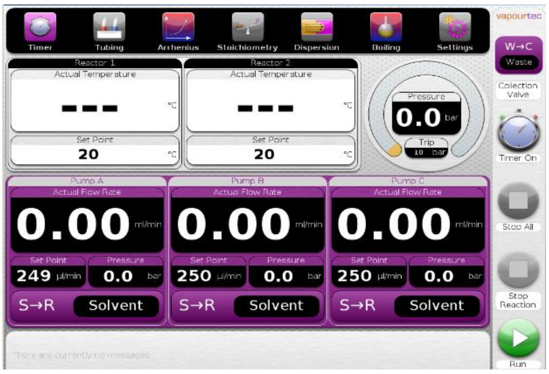
OVERVIEW



Vapourtec E-Series flow reactor (shown with 3 pumps and a collection valve fitted)

USING THE TOUCHSCREEN USER INTERFACE

The Vapourtec E-Series flow reactor has a touchscreen interface used for all control functions. The main areas of the screen are shown below.



Reactor 1 Actual Temperature --- °C Set Point 20 °C

Reactor 2 Actual Temperature --- °C Set Point 20 °C

Pressure 0.0 bar Trip 10 bar

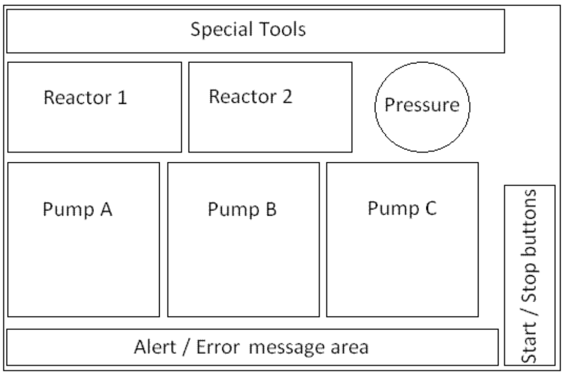
Pump A Actual Flow Rate 0.00 ml/min Set Point 249 µl/min Pressure 0.0 bar

Pump B Actual Flow Rate 0.00 ml/min Set Point 250 µl/min Pressure 0.0 bar

Pump C Actual Flow Rate 0.00 ml/min Set Point 250 µl/min Pressure 0.0 bar

There are currently no messages

Typical Screenshot



Areas of the screen

PUMPS

The E-Series flow reactor system uses advanced peristaltic pumps, labelled A, B (and C if the system has three pumps). Each pump uses a short length of pump tubing, of which there are two types; known simply as **blue** and **red**. Each tube type is compatible with a wide range of solvents, but *neither is compatible with every solvent*. Pumping a solvent with which the selected tube is incompatible can cause serious damage to the system in a matter of minutes. It is very important to ensure the correct tube colour is selected before turning on the pumps. If it is necessary to change pump tubing, the user manual for the flow reactor should be referred to.

In the experimental procedures,

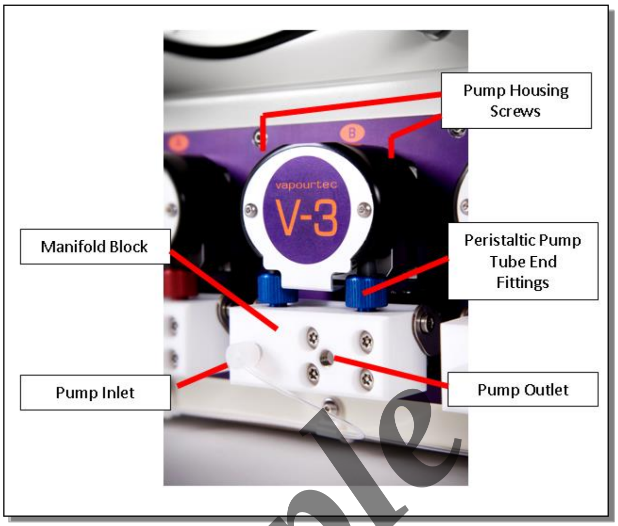
- the term **blue pump** is used to denote a tube with a blue tube fitted
- the term **red pump** is used to denote a tube with a red tube fitted

Pump with blue tubing (**blue pump**)

Pump with red tubing (**red pump**)

CONNECTING THE PUMPS

Each pump has two connections, the inlet (which is permanently connected) and the outlet which may need connecting at the start of the experiment. Tubing needs to be firmly screwed in to each port

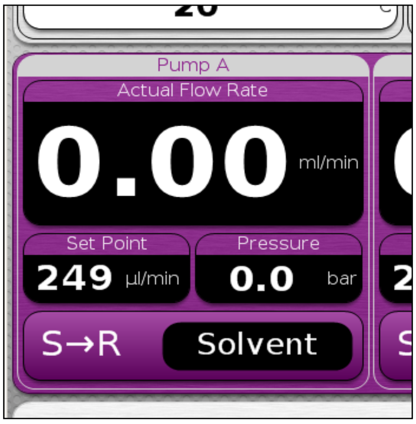


The V-3 pump

CONTROLLING THE PUMPS

The area on the screen dedicated to each pump can alternate between two modes, "display" and "set". In "set" mode it is possible to:

- Prime the pump
- Turn the pump "on" or "off"
- Switch between solvent and reagent
- Set a target flow rate
- See the set and actual flow rate
- See the pressure at the pump outlet

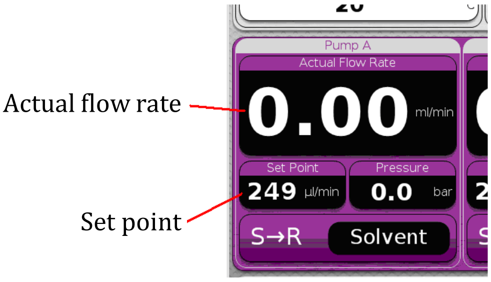


Pump A
Actual Flow Rate 0.00 ml/min
Set Point 249 µl/min
Pressure 0.0 bar

Pump area in "display" mode

SEEING THE FLOW RATE

The flow rate can be seen and changed on the screen whether or not the pump is running. Any changes only take effect when the pump is set to "On" and the system is set to "Run". The displayed value will match the set point if the pump is running or will be zero if it is not.



Pump area in "display" mode

SWITCHING BETWEEN SOLVENT AND REAGENT RATE

At the base of the area is a rectangular button for controlling whether the pump is pumping from the solvent bottle or the reagent bottle. Pressing this button toggles between the two.

Selecting solvent or reagent

PUMP DELIVERY PRESSURE

The pressure at the outlet of each pump is displayed. Note that the main pressure display (top right of the screen) displays the highest of the two (or three) pump delivery pressures.

Real-time pump pressure display

SETTING THE FLOW RATE

Touching the pump interface area of the screen (other than the solvent/reagent button) switches it "set" mode. There is an on/off button which toggles the pump on and off. The "up" and "down" arrows change the set point value. If the pump is running then, as the value is changed, the flow rate also changes in real time. The pumps can operate at flow rates of between 0.1 and 10mL min^{-1}.

Pump area in "set" mode

PRIMING A PUMP

Priming means passing some fluid through a pump to prepare it for use. The "prime" button is visible in "set" mode. Pressing it once starts the priming process. Pressing it a second time while the priming is in progress cancels it. To prime a pump fully, it is necessary to perform four steps:

- Select "reagent" on the pump interface area of the screen
- Press "prime", and wait for the operation to complete
- Select "solvent" on the pump interface area of the screen
- Press "prime" a second time, and wait for it to complete

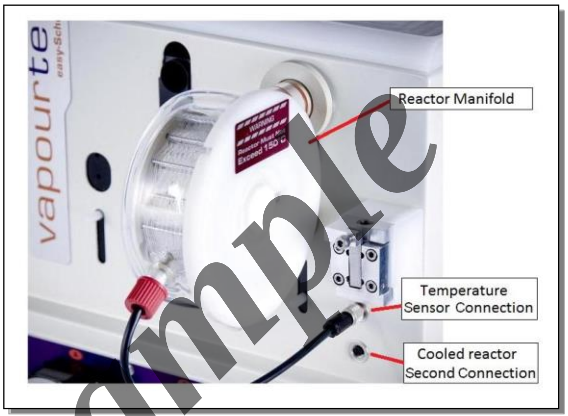
The "Prime" button

Prime in progress

REACTORS

Each reactor is housed inside a glass outer shell. There are different shell types for different reactors. The most common reactor is a coiled tube which sits in a cylindrical shell with a white face (as shown to the right). The tubing is made of a plastic called PFA, similar in nature to poly(tetrafluoroethene) – also known as PTFE or Teflon.

There are two reactor positions on the E-Series system. Each reactor is attached to the flow unit and held in place with magnets and connects to the heater system airflow at the top and bottom. The reactor also has a temperature sensor connection, which enables the flow unit to detect that a reactor is present, and to give feedback of the exact reactor temperature. If the reactor temperature sensor is not correctly attached there will no display of temperature for that reactor position.

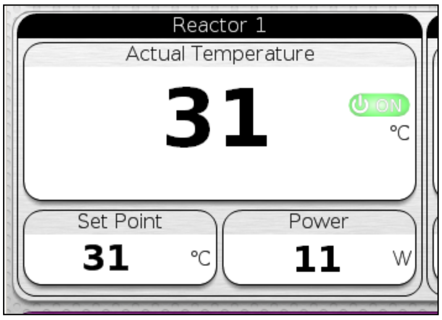


A tube reactor manifold fitted into the right-hand position on the E-Series

SETTING THE REACTOR TEMPERATURE

Like the pumps, the reactors have a dedicated area of the screen which can be in “display” or “set” mode. In display mode, it is possible to see:

- The desired set-point temperature
- The actual temperature
- How much power is being used to keep the reactor at the set temperature



Reactor 1

Actual Temperature 31 °C

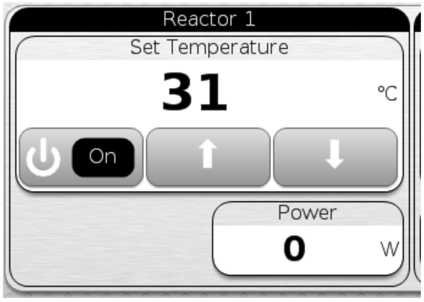
Set Point 31 °C

Power 11 W

Reactor screen in “display” mode

Pressing anywhere in this area of the screen will switch it into "set" mode, from which it is possible to:

- turn the reactor on or off
- change the temperature set-point – it is important to remember that standard coiled tube reactor (made of PFA tubing) must not be heated to a temperature greater than 150 °C



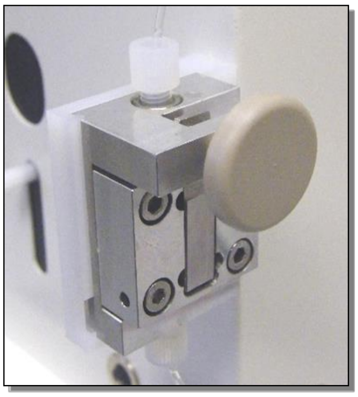
Reactor screen in "set" mode

As with the pumps, any changes only take effect when the reactor is set to "On" and the system is set to "Run".

USING THE BACK-PRESSURE REGULATOR (BPR)

The BPR is used to regulate the pressure for the reaction and it sits at the end of the flow sequence, after the last reactor. Unlike all the other pipe fittings on the flow reactor system, the pipe fittings in and out of the BPR should **not** be screwed in tightly. They need only be just tight enough to make a seal. Over-tightening will stop the BPR functioning correctly.

The screw knob on the BPR is used to increase or decrease the overall pressure of the flow reactor, as shown on the pressure read-out. When setting the pressure for a reaction it is important that the screw knob is not tightened until all the air has been pumped out of the system and liquid is passing in an uninterrupted flow through the BPR.



The back-pressure regulator (BPR)

The pressure read-out

When adjusting pressure, it is important to:

- always adjust the screw knob slowly and wait for the reported pressure on the screen to change and stabilise
- only make adjustments when liquid is flowing

In the event of a blockage (if the stream of liquid should stop), the screw knob should be gradually released until flow resumes.

RUNNING THE SYSTEM

The flow unit can be set to “Run” or “Stop”. When it is stopped, no reactors are heated or cooled, and no pumps operate. In addition, each reactor position and pump can be set to “On” or “Off”. A pump will only run when the pump is “On” and the system is set to “Run”. Similarly, a reactor will only be heated when the reactor is “On” and the system is set to “Run”. This means that the user can choose which pumps and reactors to employ for a particular experiment and turn them “On” in readiness, but nothing will actual happen until the overall system is set to “Run”. The system “Run” and “Stop” modes are controlled from the buttons on the touch-screen.

Pressing “Stop All” will stop all pumps and stop all temperature controlling of reactors.

Pressing “Stop Reaction” will switch all channels to pumping solvent, but will maintain pumping at the same speed and will maintain temperature control of all reactions.

Pressing “Run” will start all pumps which are “On”, and start temperature controlling all reactors which are “On”.

THE COLLECTION VALVE

The collection valve is an optional accessory and so will not be present on every system. It allows the user to direct the product flow into either a waste vessel or a product vessel as required, without having to manually move the output stream tube while liquid is coming out of it.

The collection valve is the last thing that the product stream goes through. As this is after the back pressure regulator, the liquid is back at atmospheric pressure. The liquid stream enters at the rear of the valve and emerges either at the top (waste) or the bottom (product). There is an onscreen button which toggles between sending the output stream to waste or to the product collection vessel.

The collection valve and gantry

Switching the collection valve

PREPARATION OF AN ESTER:
OXIDATION OF AN ALDEHYDE TO A METHYL ESTER

LEARNING GOALS

- *To perform a flow reaction using two pumps*
- *To perform an oxidation reaction*
- *To prepare an ester*

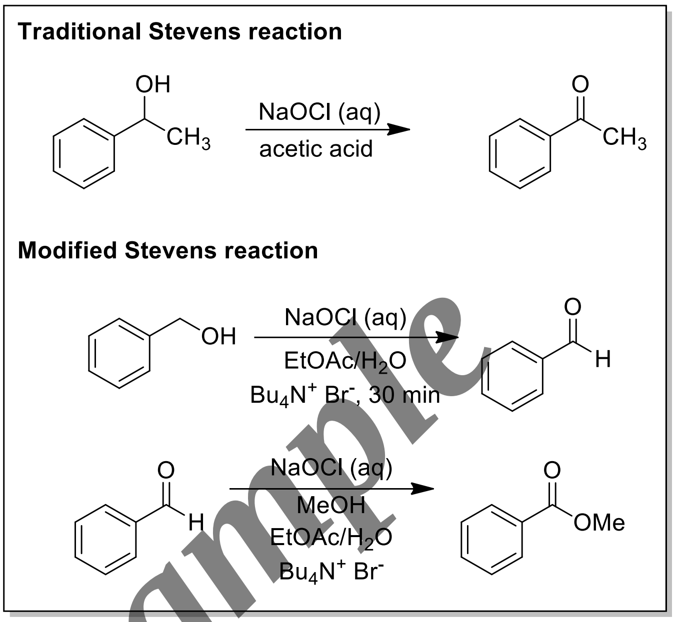
OVERVIEW

In general chemistry courses we are taught that oxidation involves the loss of electrons, often from metals, to form cations. In organic chemistry, oxidation is explained in terms of covalent bonds formed or lost rather than changes in charge. For a working terminology, when dealing with organic compounds we can classify oxidation as:

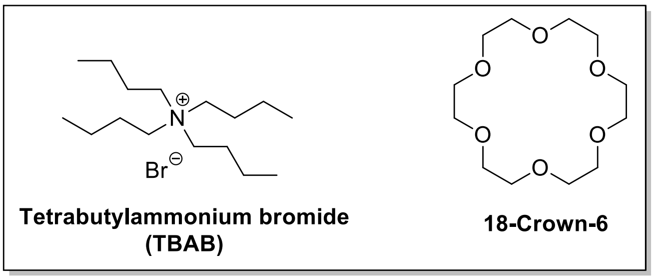
- The addition of more oxygen bonds to carbon
- The addition of more electronegative atoms bonded to carbon
- The loss of hydrogen atoms bonded to carbon.

Oxidation is an extraordinarily valuable tool to the synthetic organic chemist. Among the various functional groups that can be oxidized, arguably the most common are alcohols. Primary alcohols can be oxidized to aldehydes and further oxidized to carboxylic acids. Secondary alcohols are oxidized to ketones while the majority of tertiary alcohols are unable to undergo oxidation. There are many metal-containing oxidizing agents, including chromium and manganese reagents. These metals are relatively inexpensive but often require a stoichiometric amount of the heavy metal, which generates a substantial amount of waste.

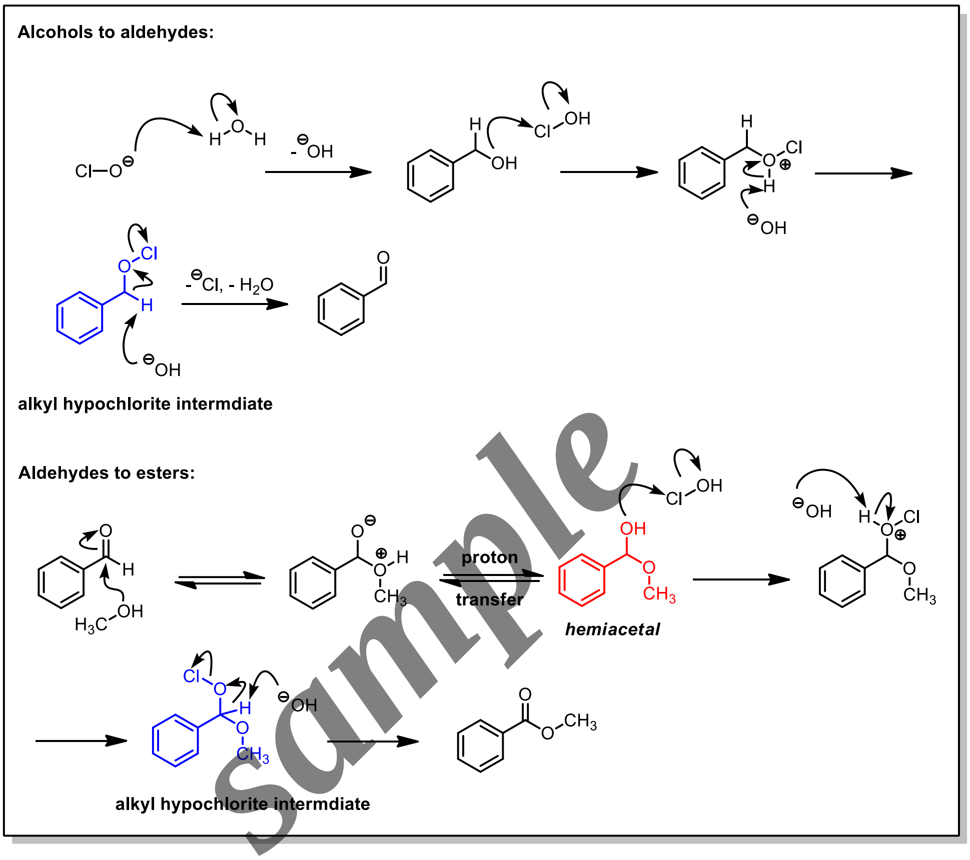
One of the more recently developed oxidations is the Stevens oxidation. It relies on commercially available sodium hypochlorite (bleach) as the stoichiometric oxidant and can readily oxidize secondary alcohols to ketones. Discovered in 1980, many variations have been developed including protocols for oxidizing alcohols to carboxylic acids or for converting aldehydes to esters. The latter is particularly interesting because the esters themselves can be transformed in other reaction to a variety of functional groups from amides to carboxylic acids.



The Stevens oxidation requires the use of biphasic reaction conditions (e.g. water and some organic solvent such as ethyl acetate) and so a phase-transfer catalyst (PTC) is required. Quaternary ammonium salts, such as tetrabutylammonium bromide (TBAB), or cyclic ethers, such as 18-crown-6, at the most common PTCs used to fill this role although others can also be used. PTCs shuttle charged ionic species from the aqueous phase to the organic phase.



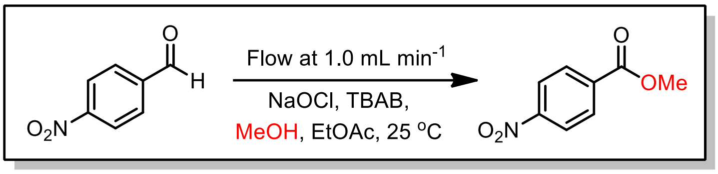
Mechanistically, the Stevens reaction is very interesting. The key intermediate is the alkyl hypochlorite species. This highly unstable compound rapidly decomposes to the corresponding carbonyl. Aldehyde to ester transformations rely on the *in-situ* formation of a hemiacetal followed by alkyl hypochlorite formation.



Today you will be performing the latter transformation; the oxidation of an aldehyde to an ester. You will be using biphasic conditions and therefore you will be employing TBAB as a phase-transfer catalyst.

PROCEDURE

Preparation of methyl 4-nitrobenzoate



Caution: 4-Nitrobenzaldehyde, bleach, tetrabutylammonium bromide (TBAB), methanol, and ethyl acetate are irritants. Bleach is corrosive and methanol is toxic. All the reagents should be dispensed in a fume hood. The use of goggles with side-shields, lab coats and gloves are considered minimum and non-discretionary safety practices in the laboratory.

Table of Reagents and Physical Constants

reagent	equiv.	MW	mmol	mass (g)	density (g/mL)	vol. (mL)	mp/bp °C
4-Nitrobenzaldehyde $C_7H_5NO_3$	1	151.12	5	0.7556	solid	-	m.p. 103-106
6% NaOCl (bleach) NaOCl	-	74.44	-	-	1.080	30	-
Tetrabutylammonium bromide (TBAB) $C_{16}H_{36}BrN$	0.1	322.37	0.5	0.1612	solid	-	m.p. 102-106
Methanol CH_4O	10	32.04	50	1.62	0.790	2	b.p. 65
Ethyl acetate CH_4O	-	-	-	-	-	10	b.p. 77

Prepare the reagent reservoirs:

- ☐ In a 50-mL capacity bottle, combine the tetrabutylammonium bromide (TBAB), 4-nitrobenzaldehyde, methanol and ethyl acetate. Label this bottle “reagent A”
- ☐ Swirl the contents of the flask to ensure adequate mixing of the reagents
- ☐ In another 50-mL capacity bottle place 30 mL of commercial bleach. Label this bottle “reagent B”
- ☐ In a 100-mL capacity bottle place 90 mL of ethyl acetate. Label this bottle “solvent A”

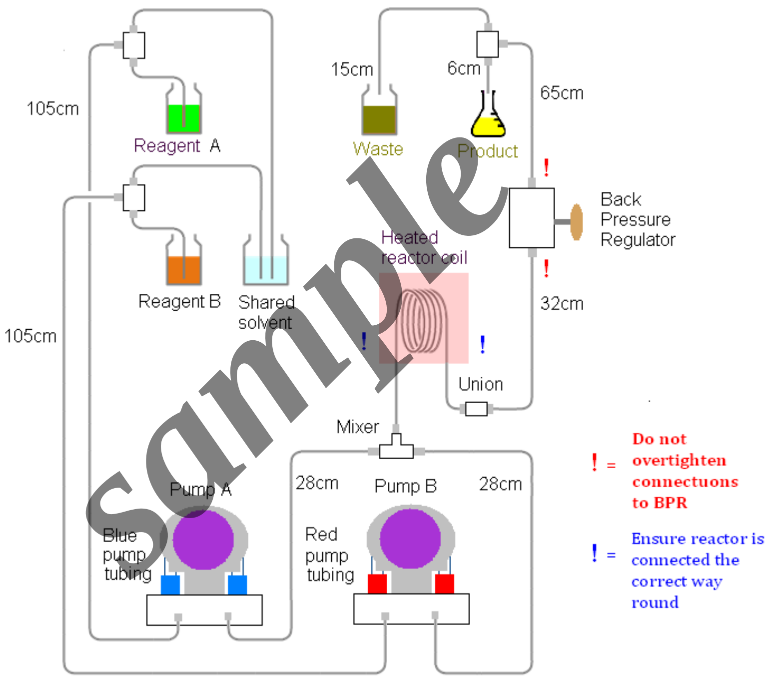
☐ In another 100-mL capacity bottle place 90 mL of deionized water. Label this bottle "solvent B"

Set-up the flow unit:

☐ Equip the flow unit with a 10-mL capacity PFE reactor coil

☐ Select a **blue pump** and a **red pump** for performing the reaction[§]

☐ Ensure tubing is connected as shown below



Connecting the E-Series flow reactor for the experiment

vapourtec

☐ Fully open the back-pressure regulator

☐ Place the exit lines from the "waste" and "collect" ports into individual 50-mL bottles labeled "waste" and "product" respectively

---

[§] It is assumed here that Pump A is set up as the **blue pump** and Pump B is set up as the **red pump**

- ☐ Ensure that the exit stream is set to go to “waste”
- ☐ Place both the “solvent A” and “reagent A” lines for the **blue pump** into the bottle labeled “solvent A”
- ☐ Place both the “solvent B” and “reagent B” lines for the **red pump** into the bottle labeled “solvent B”
- ☐ Turn on the flow unit and prime the solvent and reagent lines for the **blue pump** with ethyl acetate from the “solvent A”
- ☐ Turn on the flow unit and prime the solvent and reagent lines for the **red pump** with deionized water from the “solvent B”
- ☐ Carefully move the reagent line from the bottle labeled “solvent A” to that labeled “reagent A”
- ☐ Carefully move the reagent line from the bottle labeled “solvent B” to that labeled “reagent B”
- ☐ Ensure that both pumps are set back to “solvent” on the screen
- ☐ Pass solvent through the reactor coil at a flow rate of 2.0 mL min^{-1} for each pump until it is filled
- ☐ Once the reactor coil is filled, reduce the flow rate to 0.50 mL min^{-1} for each pump
- ☐ Adjust the back-pressure-regulator carefully to a pressure of 2 bar
- ☐ Set the temperature of the reactor coil to **25 °C**
- ☐ Once the desired temperature is reached and the pressure is stable, the unit is ready to run the reaction

Synthesise the ester:

- ☐ Switch each of the pumps from “solvent” to “reagent”
- ☐ Set the exit stream to go to “collect”
- ☐ When the contents of the “reagent A” bottle are almost all loaded into the reactor, switch both pumps from “reagent” back to “solvent” – It is important to perform this step when there is still a small quantity of liquid remaining in the “reagent A” bottle or else there is the possibility of allowing air into the reactor
- ☐ Continue collecting for another 20 min
- ☐ Once all the reagents have exited the flow unit, press the “Stop All” button

Purify the product:

- ☐ Obtain a 250-mL Erlenmeyer flask and label it “aqueous phase” and a 250-mL Erlenmeyer flask and label it “organic phase”
- ☐ Transfer the contents of the “product” bottle to an 250-mL separatory funnel
- ☐ Rinse the “product” bottle with diethyl ether (5 mL) and add the wash to the separatory funnel
- ☐ Add deionized water (25 mL) diethyl ether (50 mL) to the separatory funnel
- ☐ Carefully stopper the separatory funnel and invert the funnel
- ☐ Immediately vent the funnel by opening the stopcock to release pressure that may have developed
- ☐ Close the stopcock and mix the two layers several times by inverting the funnel repeatedly
- ☐ Vent the funnel
- ☐ Close the stopcock and place the funnel into a ring attached to a retort stand and remove the stopper
- ☐ Allow the layers to separate
- ☐ Remove the bottom aqueous layer through the stopcock into the Erlenmeyer flask labeled “aqueous phase”
- ☐ Extract the aqueous layer twice more with 50 mL of diethyl ether each collecting the organic layer in the Erlenmeyer flask labeled “organic phase”
- ☐ Wash the organic layer twice with 50 mL of deionized water each collecting the aqueous layer in the Erlenmeyer flask labeled “aqueous phase”

☐ Wash the organic layer once with saturated aqueous sodium chloride (50 mL), collecting the aqueous layers in the Erlenmeyer flask labeled “aqueous phase”

☐ Pour the organic phase into the clean Erlenmeyer flask labeled “organic phase”

☐ Dry the organic layer by adding (approximately 5 g) either anhydrous magnesium sulfate ($MgSO_4$) or anhydrous sodium sulfate (Na_2SO_4) to the Erlenmeyer flask containing the organic layer

☐ Decant the diethyl ether solution into a tared 250 mL round bottom flask leaving the drying agent behind

☐ Rinse the Erlenmeyer flask and drying reagent by adding to the flask diethyl ether (10 mL) and swirl the flask

☐ Decant the diethyl ether rinse into the round bottom flask

☐ Remove the organic solvents under reduced pressure until a white solid is obtained and a constant weight is obtained

☐ Weigh the flask containing the product

☐ Calculate the yield and percent yield

Characterise the product:

☐ Obtain ^{1}H-NMR and ^{13}C-NMR spectra in $CDCl_3$ if instructed to do so

☐ Obtain a GC-MS of your compound if instructed to do so