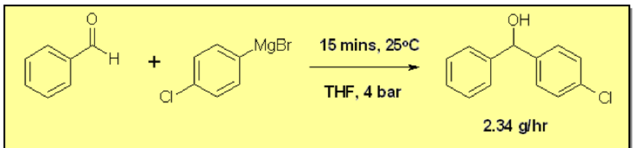
Application Note 35:

E-Series – Reaction of Grignard Reagents under Continuous Flow Conditions.

Produced by Vapourtec

Abstract

This application note illustrates the use of the Vapourtec E-Series system to run reactions such as Grignard reactions under continuous flow conditions for extended periods with no pump issues.



Scheme 1

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Background

Continuous flow chemistry offers easy access to scaling reactions from milligrams to kilograms, and many successful examples have been well documented. The Vapourtec E-Series system is a new flow chemistry system that offers simplicity and robustness to the range of available flow chemistry apparatus. The unique pumping system allows reliable and smooth pumping across a wide range of flow rates and is capable of pumping strong acids, light suspensions and organometallic reagents as we will demonstrate. The pumping system also allows consecutive immiscible solvents to be pumped offering a distinct advantage to commonly used methods. The self-priming mechanism allows this system to be up and running in a matter of minutes.

The Grignard reaction was discovered over a hundred years ago and continues to be an important reaction in the synthetic chemist's tool kit. The Grignard reaction is traditionally described as the reaction between an alkyl- or aryl-magnesium halide adding to the carbonyl group in an aldehyde or ketone. Grignard reagents however show excellent reactivity to a wide range of electrophiles such as thiols, imines and nitriles making them extremely versatile in C-C bond formation.

In reactions involving Grignard reagents the exclusion of water and air is important as the reagent is rapidly destroyed by protonolysis or oxidation. Although Grignard reagents are produced in industry for use in situ a wide range are commercially available. We demonstrate in this application the reaction of a commercially available Grignard reagent. This offers use the advantage of allowing us to aspirate and pump directly from a sealed bottle limiting exposure to the user and exposure of the reagent to moisture.

Grignard reactions are exothermic, and this exothermic nature must be considered when a reaction is scaled-up from laboratory to production plant. The use of coil tube reactors allows the control of such exotherms by the greater heat dispersion (due to the high surface area to volume ratio of the tube) and makes scaling reaction of this nature safer and easier.

This application note demonstrates the pumping capability of the E-Series in optimizing and delivering a scalable method for the addition of Grignard reagents to aldehydes.

Method (Optimization)

As stated above, the aim of this work was to demonstrate the continuous pumping of a Grignard reagent and its reaction with an aldehyde, while avoiding any detrimental solid formation from hydrolysis.

Setup

The flow reactor was set up using the **E-Series** pump module as shown in Fig 1.

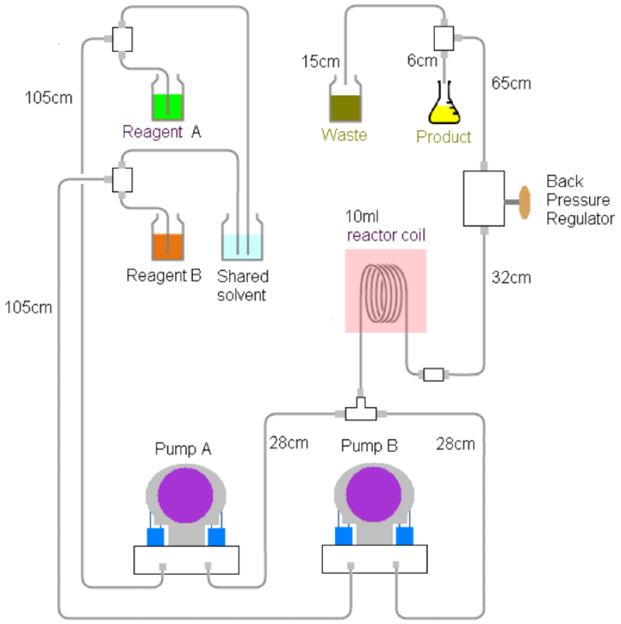

Fig 1: E-Series Setup

A 10 mL PFA reactor was installed with a connecting tube in series with a manually adjustable back pressure regulator. The elution outflow was collected via the waste/collection switching valve.

Pump Tubing

It is to be noted that the V-3 pump used by the E-Series is based on the peristaltic principle, and so features a high performance fluoropolymer tube at its core. More than one pump tube type is available to ensure compatibility with the broadest possible range of solvents, so selection of the correct tube for a given application is critical.

A table showing recommended tube type compatibility with a wide selection of solvents, acids and bases is available both within the E-Series user manual and also built into the User Interface software.

In this case

- blue tube was used for the Benzaldehyde / THF
- blue tube was used for the Chlorophenylmagnesium bromide / diethyl ether

Drying the System

It is also important for a flow system to be as dry as possible to carry out these reactions, to prevent unwanted salts forming (though this is or reaction purity, rather than any issue with pumps). Therefore all reagent and solvent bottles were kept under a nitrogen atmosphere using the 4 way low pressure regulated inert gas manifold that is built into the E-Series system.

After priming with fresh anhydrous solvents the system was dried by running the dry solvent through the pumps and reactor at a low flow rate for 30 mins.

Reagents

All reagents and solvents were used as purchased from Aldrich;

Reagent A

0.5 M Benzaldehyde in THF (Aldrich B1334, CAS 100-52-7)

Reagent B

4-Chlorophenylmagnesium bromide solution, 1.0 M in diethyl ether (Aldrich 262188, CAS 873-77-8).

System Parameters

System solvent:	Anhydrous Tetrahydrofuran (THF)
Reagent A:	0.5 M Benzaldehyde in THF
Reagent B:	4-Chlorophenylmagnesium bromide, 1.0 M in diethyl ether
Flow rate A:	variable (167 – 3333 μL/min)
Flow rate B:	variable (167 – 2500 μL/min
Stiochiometry A:B	variable (1.0 – 2.0 eq B)
Reactor volume:	10 mL PFA reactor.
Reactor temperature:	room temperature 25 °C
Back pressure regulator:	4 bar set with the variable BPR

Then the optimization reactions followed the sequence of event listed below;

1) *Priming the pumps with tetrahydrofuran (THF):* Both selection valves were set to 'Solvent' and the pumps were `primed with THF. This is done by electing the prime function from the touchpad control and is fully automated.
2) *Priming the pumps with reagents:* The selection valve for line 1 was set to 'Reagent', the prime function selected and the line connecting the valves to stock bottle 1 was filled with Solution A. The selection valve was set back to 'Solvent' and THF pumped through the lines using the 'prime' function. The same process was repeated with line 2, Solution B to fill the second reagent line.

3) *Reaction optimisation:* A selective range of conditions were run using the easy-Scholar™ software . Residence times of 2, 5, 7.5, 10, 15 and 30 minutes were run at with a variable stoichiometry (1.0 - 2.0 eq Grignard reagent) in a 10 ml reactor at room temperature (25 °C). A 4 ml aliquot of solution A (2.0 mM substrate 1) was used in each experiment.
4) *Work-Up and Analysis*: The collection stream was directed into a flask containing a saturated ammonium chloride solution. The resulting partition was extracted with DCM, the combined organic extracts washed with brine, dried (Magnesium sulfate) and the filtrate concentrated in-vacuo.

The initial reaction conditions of 25 °C, with a 30 minute residence time and 2.0 eq of Grignard reagent showed (after work-up) an excellent conversion to the desired product (4-chlorobenzhydrol) 91% by HPLC. The aim of the optimization process was to find conditions that would give the highest throughput and use the lowest amount of reagent. With this in mind subsequent reactions looked at reducing both the residence time and the molar equivalents of the Grignard reagent. It was observed that a rapid drop in the relative conversion to the product by HPLC occurred at residence times below 10 mins. At a 2 min residence time with 2.0 eq Grignard reagent the formation of the product was still observed at low conversion 16%. At a 15 minutes residence time with stoichiometric amount of 2.0 eq we observed identical conversion to that at 30 mins. Reducing the amount of Grignard reagent to 1.5 eq continued to show an excellent conversion of 90% at 15 mins. Reducing the stoichiometric excess further showed a rapid drop in conversion.

Reactor 1
Actual Temperature 25 °C
Set Point 25 °C
Power 0 W

Reactor 2
Actual Temperature 1 --- °C
Set Point 20 °C
Power 0 W

Pressure 4.1 bar
Limit 10 bar

Pump A
Actual Flow Rate 0.38 ml/min
Set Point 381 µl/min
Pressure 4.1 bar
S←R Reagent

Pump B
Actual Flow Rate 0.29 ml/min
Set Point 286 µl/min
Pressure 4.1 bar
S←R Reagent

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

Fig 2: E-Series Manual Control screen for this reaction.

Method (Scale Up Conditions)

With the conditions optimized for the formation of our target compound the intention was then to demonstrate that the E-Series was able to run Grignard reactions under continuous conditions over an increased amount of time.

The optimum reaction condition where found to be;

Temperature 25 °C, 15 mins residence time with 1.5 eq 4-chlorophenylmagnesium bromide solution.

Applying these optimised reaction conditions a 60ml aliquot of the benzaldehyde solution (30 mM) was processed over 150 minutes (2.5 hrs). The reaction was monitored at 15 minute intervals by HPLC and showed repeat chromatography over the course of the experiment.

Setup

The equipment was exactly as used in the optimization.

Reagent A

0.5 M Benzaldehyde in THF (Aldrich B1334, CAS 100-52-7)

Reagent B

4-Chlorophenylmagnesium bromide solution, 1.0 M in diethyl ether (Aldrich 262188, CAS 873-77-8).

System Parameters

System solvent:	Anhydrous Tetrahydrofuran (THF)
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Reactor volume:	10 mL PFA reactor.
Reactor temperature:	room temperature 25 °C
Back pressure regulator:	4 bar set with the variable BPR

Then the optimization reactions followed the sequence of event listed below;

1) *Priming the pumps with tetrahydrofuran (THF)*: Both selection valves were set to 'Solvent' and the pumps were `primed with THF. This is done by selecting the prime function from the touchpad control.
2) *Priming the pumps with reagents*: The selection valve for line 1 was set to 'Reagent', the prime function selected and the line connecting the valves to stock bottle 1 was filled with **Solution A**. The selection valve was set back to 'Solvent' and THF pumped through the lines using the 'prime' function. The same process was repeated with line 2, **Solution B** to fill the second reagent line.
3) *Continuous running*: The chosen conditions were run using the Manual Control interface. A residence time 15 minutes was run with stoichiometry (1.5 eq Grignard reagent) in a 10 ml reactor at room temperature (25 °C). A 60 ml aliquot of solutation A (30 mM substrate 1) was processed over a 160 min period. 2 ml was discarded from the beginning and end of the reaction to take into account the dispersion of the reaction segment.
4) *Work-Up and Analysis*: The collection stream was directed into a flask containing a saturated ammonium chloride solution. The resulting partition was extracted with DCM, the combined organic extracts washed with brine, dried (Magnesium sulfate) and the filtrate concentrated in-vacuo. The crude reaction mixture was further purified by column chromatography (SiO2: 20%EtOAc/Hexane: UV detection) to give the desired compound.

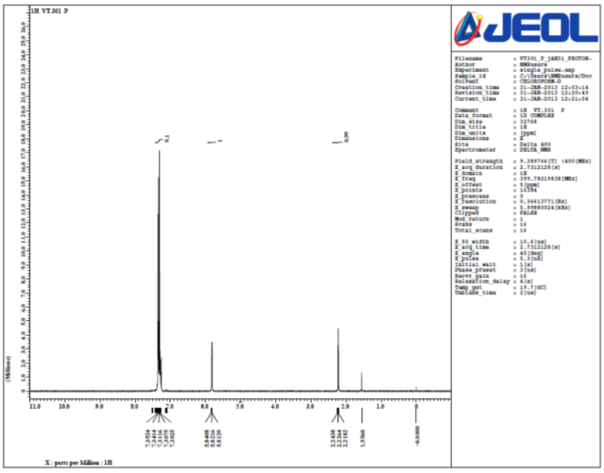
Results (Scale Up Experiment)

60 ml (3.184 g) of **reagent A** (30 mmol) was processed and collected over ~150 mins as shown above. After work-up a colourless solid was isolated. Yield = 6.56 g, 89% (isolated yield based on HPLC).

This demonstrates a throughput of 2.34 g/hr. Extrapolating this experiment, indicates a potential yield of 56 g/ 24hrs under continuous reaction conditions.

NMR Analysis

VT301-P Scale-Up Experiment



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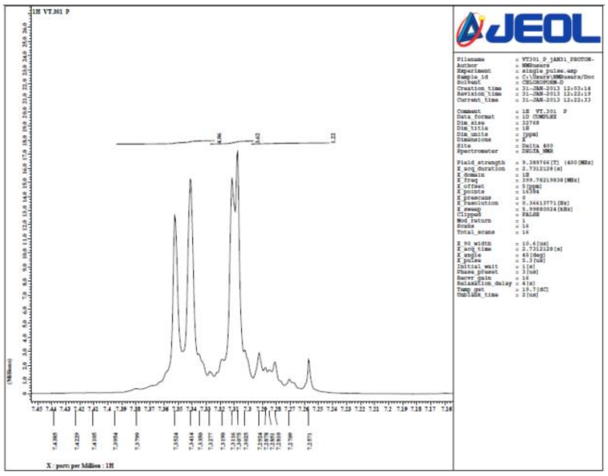

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X_angle            = 45[deg]
X_pulse            = 5.3[us]
Initial_wait       = 1[s]
Phase_preset       = 3[us]
Recvr_gain         = 16
Relaxation_delay   = 4[s]
Temp_get           = 19.7[dC]
Unblank_time       = 2[us]
```

HPLC Analysis:

Rt: 5.25 min, 100% (SM Rt = 3.51)

Conclusion

The work described in this report demonstrates that the Vapourtec E-Series is able to carry out organometallic reactions such as the Grignard reaction in a safe, efficient and continuous manner. The V-3 pumps are shown to be capable of the continued pumping of moisture sensitive reagents over a 2.5 hour time period with no detrimental effect on performance or reaction yield. The mild conditions remove the more general cryogenic temperatures employed with these reactions and the short reaction times and ease of scalability offer advantages for the production of larger quantities of material.

Acknowledgements

Vapourtec would like to thank Andrew Mansfield of Flow Chemistry Solutions Ltd for his assistance in developing this application note

www.flowchemistrysolutions.co.uk