

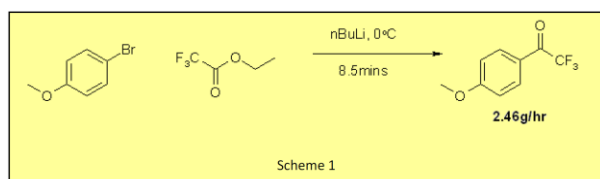
Application Note 34: Reaction of Organolithium Reagents using Vapourtec E-Series system

Produced by Vapourtec



Abstract

This application note illustrates the use of the Vapourtec E-Series system to run organometallic reagents such as n-Butyl lithium under continuous flow conditions.



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Background

Continuous flow chemistry offers easy access to scaling reactions from mg to kg, 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 this study demonstrates. 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.

Organolithium reagents are generally prepared by the metal-halogen exchange between an organic halide compound (usually an iodide or bromide) and an organolithium species. This method is often used to prepare vinyl- aryl- and primary alkyl lithium reagents. They are highly reactive nucleophiles and react with almost all types of electrophiles. They are comparable to Grignard reagents, but are much more reactive. Due to this reactivity they are incompatible with water and oxygen and must be handled under an inert atmosphere such as nitrogen.

Organolithium reagents are commercially available in a range of concentrations. In this application the reaction of a commercially available

n-Butyl lithium solution is demonstrated. This offers the advantage of allowing aspiration and pumping directly from a sealed bottle (as supplied) limiting exposure to the user and exposure of the reagent to moisture.

As mentioned organolithium reagents react violently with water and reactions involving them are exothermic, and this exothermic nature must be considered when a reaction is scaled-up from laboratory to production plant. The use of small bore 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 a reaction of this nature safer and easier.

This application demonstrates the pumping capability of the E-Series in optimizing and delivering a scalable method for the formation of aryl lithium intermediates by bromo-lithium exchange and their reaction with methanol and ethyl trifluoroacetate.

Optimisation of the Bromo-Lithium Exchange.

As stated above, the aim of this work was to demonstrate the continuous pumping of a butyl lithium solution in a continuous flow reaction while minimising any detrimental solid formation from hydrolysis.

The first series of experiments focused on the optimisation on the bromo-lithium exchange to find the condition that gave full conversion to the des-bromo compound (anisole) from the lithiated intermediate. To this effect the system was set up with a methanol quench.

Setup

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

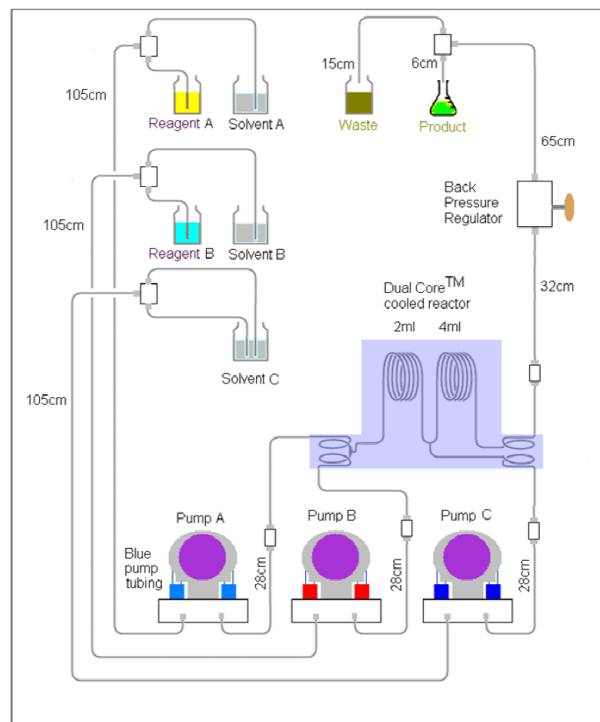


Fig 1. easy-Scholar™ plumbing for the experiment.

A cooled reactor was configured with a “Dual Core” 2 ml / 4 ml reaction coil allowing extended residence time for the quenching of the reaction with the desired electrophile. This was housed in the standard low temperature reactor manifold. The reactor was connected 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 Bromoanisole / THF
- red tube was used for the BuLi / hexane
- blue tube was used for the methanol.

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 solids 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 30mins.

Reagents

All reagents and solvents were used as purchased from Aldrich;

Reagent A

0.75 M 4-Bromoanisole in THF (Aldrich, CAS 696-62-8)

Reagent B

1.6 M n-Butyl lithium in Hexanes (Aldrich 186171, CAS 109-72-8)

Reagent C

Anhydrous Methanol (Aldrich 322415, CAS 67-56-1)

System Parameters

System solvent :	Pump A	Anhydrous Tetrahydrofuran (THF)
System solvent :	Pump B	Anhydrous Hexane
System solvent :	Pump C	Anhydrous Methanol:
Reagent A:	0.75 M 4-Bromoanisole in THF	
Reagent B:	1.6 M n-Butyl lithium in Hexanes	
Reagent C:	Anhydrous Methanol:	
Flow rate A:	variable	
Flow rate B:	variable	
Flow rate C:	variable	
Stoichiometry A:B	variable (1.0 – 6.0 eq B)	
Reactor volume:	modified cooled reactor (2 ml reaction + 4 ml quench coil).	
Reactor temperature:	variable -10 – 20 °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 system solvent: Both selection valves were set to 'Solvent' and the pumps were `primed with the required system solvent. Pump A was primed with anhydrous THF, Pump B was primed with anhydrous Hexanes and Pump C was primed with anhydrous Methanol. This is done by selecting 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 with hexane used as the 'solvent'.
- 3) Reaction optimisation: A selective range of conditions were run using the Easy-Scholar™ manual control software. Residence times of 1.0, 1.5, 2.0, 3.0 and 5 minutes were run at with a variable stoichiometry (1.0 - 6.0 eq n-BuLi) in a modified cooled reactor (2 ml + 4 ml) at variable temperatures (-10 – 0 °C). A 4 ml aliquot of solution A (3.0 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.

Results

4-Bromo - anisole	n-BuLi eq	Reaction Residence Time (mins)	Quench Residence Time (mins)	Reaction Temp. °C	4-Bromo - anisole	Wurtz Coupling	Anisole
1	1	3	3	0	38.6	12.7	35.1
1	1.2	3	3	0	31.1	12.8	47.1
1	1.4	3	3	0	3.7	15.8	72.1
1	1.6	3	3	0	2.1	13.2	76
1	1.8	3	3	0	1.9	9.7	79.7
1	2	3	3	0	1.4	8.1	82.2
1	2	5	3	0	1.5	9	82
1	2	5	3	-10	1.3	7.8	82.4
1	1.5	5	3	-10	1.4	10.7	78.4
1	1.5	5	3	-20	1.7	7.6	81.2
1	2.5	3	3	0	1.5	6	84.4
1	2.5	2	3	0	1.3	4.1	86.4
1	3	3	3	0	1.4	4.7	87.8
1	3	2	3	0	1.7	4.3	88
1	3	1	3	0	11.2	3.5	73.7
1	3	1.5	3	0	10.8	3.2	75.6

Table 1: Results of optimization experiments

From the series of optimization experiments it was shown that using molar equivalents less than 1.6 of n- BuLi showed a significant amount of the homo-coupled product (Wurtz coupling) by HPLC. When 1.0 -1.2 eq n-BuLi was used with a 3 min residence time for the intermediate formation at 0 °C the reaction was incomplete with the starting substrate (4-bromoanisole) observed. Increasing the residence time for the intermediate formation to 5 mins showed no improvement in conversion. Similarly decreasing the reaction temperature from 0 °C to -10 and -20 °C showed no change in the reaction profile.

Increasing the equivalents of n-BuLi and decreasing the residence time was tried next. It was found that 3.0 eq of n-BuLi at 0 °C showed the best result with a 2 minute residence time for the intermediate formation. Decreasing the residence time below 2 mins showed a decrease in conversion. With 3.0 eq of n- BuLi the Wurtz coupling product remained constant at 4% (by HPLC) over all experiments. The reaction was quenched with anhydrous MeOH at 0 °C with the flow rate varied to maintain an arbitrary residence time of 3 mins. The reaction was quenched immediately after collection in a saturated ammonium chloride solution.

The best conditions were found to be 3.0 eq n-BuLi with a 2 minute residence time at 0 °C. This gave the relative conversion to anisole as 88% by HPLC.

	2ml reaction coil	4ml (quench) coil
4-Bromoanisole flow (ml/min)	0.417 (1 eq)	0.417
BuLi flow (ml/min)	0.583 (3 eq)	0.583
Methanol (quench) flow (ml/min)		0.333
Total flow (ml/min)	1	1.33
Residence time	2 mins	3 mins

Table 2 : Flow rate and residence time for 2 stages

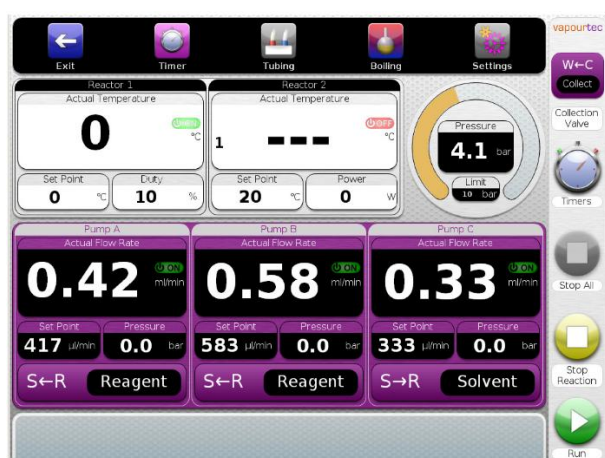


Fig 2 Easy-Scholar™ manual Control interface setup

Optimization of the 4-(Trifluoroacetyl)anisole Formation.

With the conditions optimized for the formation of the lithiated intermediate attention turned to the formation of 4-(trifluoroacetyl)anisole. Methanol was substituted with ethyl trifluoroacetate and a series of experiments were carried out to optimize the best conditions to facilitate the continuous formation of our desired compound.

Setup

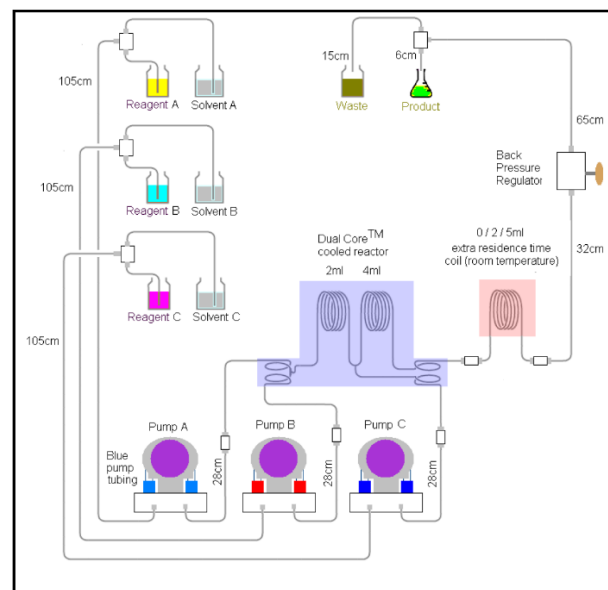


Fig 3 – Plumbing for 4-(Trifluoroacetyl)anisole Formation

All reagents and solvents were used as purchased from Aldrich;

Reagent A

0.75 M 4-Bromoanisole in THF (Aldrich , CAS 696-62-8)

Reagent B

1.6 M n-Butyl lithium in Hexanes (Aldrich 186171, CAS 109-72-8)

Reagent C

1.5 M Ethyl trifluoroacetate in THF (Aldrich E50000, CAS 383-63-1).

System Parameters

- System solvent** Anhydrous Tetrahydrofuran (THF)
- :Pump A**
- System solvent** Anhydrous Hexane
- :Pump B**
- Reagent A:** 0.75 M 4-Bromoanisole in THF
- Reagent B:** 1.6 M n-Butyl lithium in Hexanes

Reagent C:	1.5 M Ethyl trifluoroacetate in THF
Flow rate A:	variable
Flow rate B:	variable
Flow rate C:	variable
Stoichiometry A:B	variable (1.0 – 6.0 eq B)
Stoichiometry A:C	variable (1.0 – 5.0 eq B)
Reactor volume:	Dual Core™ cooled reactor (2 ml reaction + 4 ml quench coil) + extra residence coil (up to 5 ml PFA reactor)
Reactor temperature:	Step 1 – 0 °C, step 2 – part 0 °C, part room temperature (25 °C)
Back pressure regulator:	4 bar set with the variable BPR

The optimization reactions followed the sequence of event listed below;

- 1) Priming the pumps with system solvent: Both selection valves were set to 'Solvent' and the pumps were primed with the required system solvent. Pump A and Pump C were primed with anhydrous THF, Pump B was primed with anhydrous Hexanes. This is done by selecting 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 with Solution B and line 3 with Solution C.

Note: Hexane used as the solvent for line 2.

- 3) Reaction optimisation: A selective range of conditions were run using the Easy-Scholar™ software. Condition were kept constant for step 1 (bromo-lithium exchange) - residence times of 2.0 minutes, 3.0 eq n-BuLi at 0 °C. Step 2 (electrophilic quench) were varied. A 4 ml aliquot of solution A (3.0 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 optimization of this step involved extra complexity with the stoichiometry, residence time and temperature of the electrophilic quench needing to be included. The apparatus set-up from the optimization of the intermediate formation was used with the ethyl trifluoroacetate solution added after the bromo-lithium exchange in the cooled reactor. The second stage of the reaction was passed through the quench coil (4ml) at the same reaction temperature.

Initial experiments using 2.0 eq of solution C at 0 °C showed a modest conversion to the desired product (~68% by HPLC) with a residence time of ~3 mins in the 4 ml 2nd reactor coil.

In order that reaction conditions for the first step were maintained (2 mins residence time, 3.0 eq n-BuLi, 0 °C) through the first stage of the cooled coil (2 ml), it was therefore necessary to vary the 2nd stage reactor size to experiment with both 2nd stage residence times and stoichiometry. Therefore

an extra residence coil was added (standard 2, 5 and 10 ml coils were available for the investigation) The extra residence coil also helped to contain any exotherm generated in the quenching of the aryllithium intermediate, and enabled an increase in the reaction temperature after the initial low temperature quench of the aryllithium intermediate.

Experiments increasing both the stoichiometry of solution C and residence time of the second step were carried out but the reaction did not progress further than ~75% conversion. Increasing the stoichiometry of the n-BuLi was investigated and resulted in a significant improvement on the conversion to the desired compound.

Increasing the molar equivalents from 3.0 to 5.0 showed an incremental increase in conversion by HPLC from 75% to 84%. Increasing the equivalents of n-BuLi further showed no significant improvement. The concentration of butyllithium in commercially available solutions tends to decrease over time as the BuLi reacts with air. The use of a freshly prepared butyllithium solution by titration of known concentration may reduce this effect.

From this optimization series the best conditions were found to be;

- 5.0 eq n-BuLi,
- 2.0 eq ethyl trifluoroacetate
- with a combined residence time of ~ 9 mins (2 min – step 1, ~ 7 min step 2).

Table 3: Flow rate and residence time for 2 stages (3 reactor zones)

	2ml reaction coil	4ml (cooled) coil	5ml (room temperature) coil
4-Bromoanisole flow (ml/min)	0.299 (1 eq)	0.299	0.299
BuLi flow (ml/min)	0.701 (5 eq)	0.701	0.701
ethyl trifluoroacetate flow (ml/min)		0.299 (2 eq)	0.299
Total flow (ml/min)	1	1.299	1.299
Residence time	2 mins	3.1 mins	3.85 mins



Fig 4 – E-Series parameters for optimized conditions

The conversion of 84% from our best conditions closely matched that of the best conversion to anisole from our reaction quenching with MeOH.

Continuous Synthesis of 4-(Trifluoroacetyl)anisole

To increase the mass transfer of the reaction a 2.5 M solution of n-BuLi was used for the continuous experiment. The increased concentration showed no detrimental effect on yield or pump performance. To maintain the stoichiometry, the flow rates changed as follows:

Table 4: Flow rate and residence time with 2.5 M BuLi solution

	2ml reaction coil	4ml (quench) coil	5ml (extra residence) coil
4-Bromoanisole flow (ml/min)	0.4 (1 eq)	0.4	0.4
BuLi flow (ml/min)	0.6 (5 eq)	0.6	0.6
ethyl trifluoroacetate flow (ml/min)		0.4(2 eq)	0.4
Total flow (ml/min)	1	1.4	1.4
Residence time	2 mins	2.86	3.56



Fig 5 – E-Series parameters for conditions with 2.5 M BuLi

With these conditions the intention was to demonstrate that the E-Series was able to run organolithium reactions under continuous conditions over an increased amount of time. With this in mind the apparatus was set up to process 60 ml (45 mM) of the 4-bromoanisole solution. The reaction was run over 2.5 hrs. The reaction was monitored at 15 minute intervals by HPLC and showed repeat chromatography over the course of the experiment.

Setup

All reagents and solvents were used as purchased from Aldrich;

Reagent A

0.75 M 4-Bromoanisole in THF (Aldrich , CAS 696-62-8)

Reagent B

2.5 M n-Butyl lithium in Hexanes (Aldrich 230707, CAS 109-72-8)

Reagent C

1.5 M Ethyl trifluoroacetate in THF (Aldrich E50000, CAS 383-63-1).

System Parameters

System solvent :Pump A	Anhydrous Tetrahydrofuran (THF)
System solvent :Pump B	Anhydrous Hexane
Reagent A:	0.75 M 4-Bromoanisole in THF
Reagent B:	2.5 M n-Butyl lithium in Hexanes
Reagent C	1.5 M Ethyl trifluoroacetate in THF
Flow rate A:	400 µL/min
Flow rate B:	600 µL/min
Flow rate C:	400 µL/min
Stoichiometry A:B	5.0 eq
Stoichiometry A:C	2.0 eq
Reactor volume:	modified cooled reactor (2 ml reaction + 4 ml quench coil) + 5ml PFA reactor
Reactor temperature:	Step 1 – 0 °C, step 2 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 system solvent: Both selection valves were set to 'Solvent' and the pumps were primed with the required system solvent. Pump A and Pump C were primed with anhydrous THF, Pump B was primed with anhydrous Hexanes. This is done by selecting 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 with Solution B and line 3 with Solution C. Note: Hexane used as the 'solvent' for line 2.
- 3) Reaction Conditions: 1.0 eq Solution A, 3.0 eq Solution B and 2.0 eq Solution C were flowed through reactor 1 (2 ml + 4 ml PFA) at 0 °C with a residence time of 4.8 mins then reactor 2 (5 ml PFA) at room temperature (25 °C) with a residence time of 3.7 mins. 60ml of solution A was reacted.
- 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 resulting pale yellow oil was further purified by column chromatography (SiO₂: 5% TBME:Hexane, UV detection)

Results (Continuous Experiment)

60 ml (8.416 g) of reagent A (45 mmol) was processed and collected over ~150 mins as shown above. After work-up a colourless oil was isolated. Yield = 6.16 g, 72% (isolated yield based on GCMS).

This demonstrates a throughput of 2.46 g/hr. Extrapolating this experiment indicates a

potential yield of 59 g/ 24 hrs under continuous reaction conditions.

Analysis

NMR

NMR confirms the presence of the desired CF₃ group by ¹⁹F and ¹³C-¹H decoupled experiments.

NMR (CDCl₃): ¹H (400MHz), δ 7.45-7.43 (dd, 2H, J = 8.7Hz), 6.93-6.91 (dt, 2H, J = 9.0Hz), 3.82 (s, 3H).

NMR (CDCl₃): ¹³C – ¹H dec (100MHz), δ 13.1 – 12.2 (q, J = 285Hz, CF₃)

NMR (CDCl₃): ¹⁹F (470.6MHz), δ 80.28 (CF₃)

GCMS

Rt: 5.57 min 89.10%, m/z 205 [M+1] Product

Rt: 5.59 min 10.90%, m/z 195 [M+1] Aliphatic By-Product

HPLC

Rt: 5.59 min, 100% (SM Rt = 4.03)

Conclusion

The work described in this report demonstrates the Vapourtec E-Series capabilities to carry out organometallic reactions with n-butyl lithium 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