

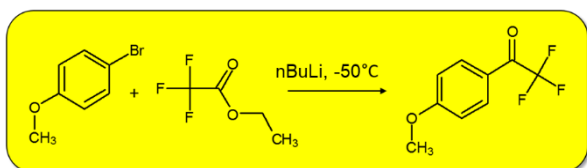
Application Note 34: Butyl Lithium In Flow

Produced by Vapourtec



Abstract

This application note illustrates the use of the Vapourtec E-Series system to run organometallic reagents such as n-Butyllithium 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 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 and other publications demonstrate [1].

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 they 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. They are often highly exothermic in nature which must be recognised in any scale up process. The use of small bore tube reactors allow 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.

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

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

Setup

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

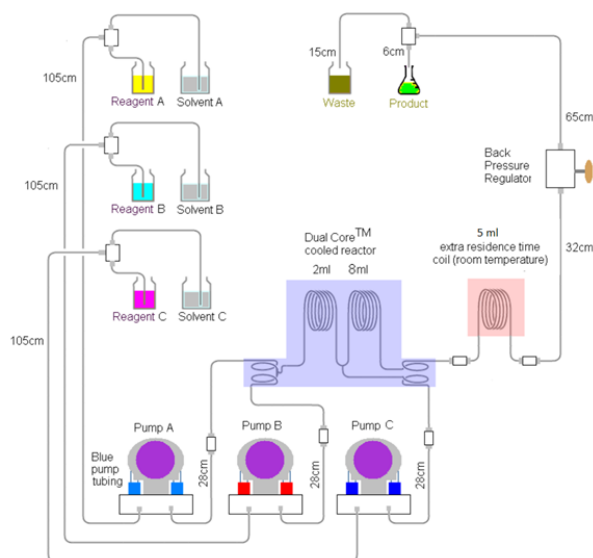


Figure 1 - easy-Scholar™ setup for the experiment

A cooled reactor was configured with a “Dual Core” 2 ml / 8 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 (BPR). The elution outflow was collected via the waste/collection switching valve.

Pump Tubing

It is to be noted that the V-3 pump used in the E-Series is a high-pressure precision peristaltic pump and features a high performance fluoropolymer tube at its core. Four tubes are available to ensure compatibility with the broadest possible range of solvents, so selection of the correct tube for a given application is critical.

Vapourtec has prepared a Pump tube compatibility guide which shows recommended tube with a wide selection of solvents, acids and bases. This guide is built into the User Interface software as well as available online. In this case the following tube COLOURS were used:

In this case

- BLUE tube was used for 4-bromoanisole / THF
- RED tube was used for n-Butyllithium / hexane
- BLUE tube was used for methanol and for ethyl trifluoroacetate

Drying the System

It is critical for a flow system to be as dry as possible when using organometallic reactions, to prevent quenching it with residual water. All reagent and solvent bottles were kept under a nitrogen atmosphere using the inert gas manifold that is built into the E-Series system.

After drying the pumps and reactors (following the Pumping organometallic reagents' protocol) both solvent and reagent lines were primed.

Reagents

All reagents and solvents were used as purchased from Aldrich;

Reagent A

0.4 M 4-Bromoanisole in tetrahydrofuran (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, CAS 67-56-1) for the optimization of the bromo-lithium exchange
- 0.4 M Ethyl trifluoroacetate in anhydrous THF (Aldrich, CAS 383-63-1)

System Parameters

System solvent : Pump A Anhydrous Tetrahydrofuran (THF)

System solvent : Pump B Anhydrous Hexane

System solvent : Pump C Tetrahydrofuran (THF)

Reagent A: 0.75 M 4-Bromoanisole in THF

Flow rate A: variable

Flow rate B: variable

Flow rate C: variable

Stoichiometry 1.1 eq

A:B

Stoichiometry 1.2 eq

A:C

Residence time: 5 minutes in 8 ml reactor

Reactor volume: modified cooled reactor (2 ml reaction + 8 ml quench coil).

Reactor

temperature: Step 1: -50 °C, Step 2: 25 °C

Back pressure 4 bar set with an adjustable

regulator: BPR

Optimisation of the Bromo-Lithium Exchange

As stated above, the aim of this work was to demonstrate the continuous pumping of a n-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 conditions 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.

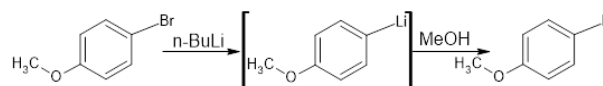


Figure 2 - Reaction schematic of the intermediate formation and quench with methanol

The optimization of this step screened stoichiometry and residence across a range of temperatures using only the cooled tube reactor between -70 °C and 0 °C. The crude product was washed with deionized water and the organic phase was evaporated and the crude product was analysed by ¹H-NMR.

The optimum reaction conditions were:

- Residence time** 75 seconds for the Bromo-Lithium exchange, 5 minutes for the quench step
- Temperature** -50 °C
- Equivalents of n-Butyllithium** 1.1 eq of n-Butyllithium

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 0.4 M ethyl trifluoroacetate and a series of experiments were carried out to optimize the best conditions to facilitate the continuous formation of our desired compound.

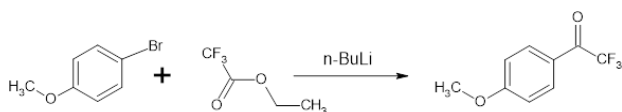


Figure 3 - Reaction schematic of the synthesis of 4-(trifluoroacetyl)anisole

The quench of the lithiated species took place in the second reactor (8 ml) of the Dual-Core. At -50 °C, after 5 minutes of residence the reaction with ethyl trifluoroacetate did not yield full conversion and the lithiated species was quenched in the collection pot.

For that reason, a 5 ml standard tubular set at room temperature was added after the cooled reactor. This provided an additional 3 minutes reaction time at 25 °C, yielding 4-(trifluoroacetyl)anisole in high purity.

Conclusion

The work described in this report demonstrates the Vapourtec E-Series capabilities to carry out organometallic reactions with n-Butyllithium 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 working day with no detrimental effect on performance nor reaction yield.

The use of the cooled tube reactor provided excellent temperature control between room conditions down to -70 °C, which allowed a rapid screening of different sub-zero reaction conditions for the reaction between n-butyllithium and 4-Bromoanisole. The fast Bromo-Lithium exchange was optimized with just 1.1 equivalents of n-butyllithium at -50 °C. These conditions were then transferred to the synthesis of 4-(trifluoroacetyl)anisole.

References

[1] P. R. D. Murray, D. L. Browne, J. C. Pastre, C. Butters, D. Guthrie, and S. V Ley, "Continuous Flow-Processing of Organometallic Reagents Using an Advanced Peristaltic Pumping System and the Telescoped Flow Synthesis of (E/Z)-Tamoxifen," *Org Process Res Dev*, vol. 17, no. 9, pp. 1192–1208, Sep. 2013, doi: 10.1021/op4001548.

Supporting information

NMR Analysis of crude product

