Continuous Flow Optimisation of the Pudovik Reaction and Phospha-Brook Rearrangement Using DBN

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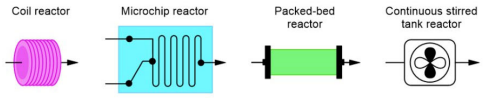
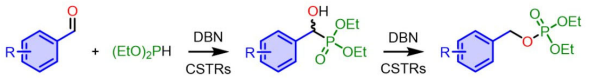
Introduction

Over the past two decades, flow chemistry has become highly versatile, offering benefits in efficiency, scalability, and sustainability.[1] Continuous flow methods enable faster, safer reactions and can handle more challenging processes.[2] While devices like coil, microchip, and packed-bed reactors are common, continuous stirred tank reactors (CSTRs) offer advantages such as uniform mixing, steady-state conditions, and improved temperature control. CSTRs also simplify multi-step synthesis, reduce reaction times, and facilitate easier scalability compared to coil reactors.[3,4]



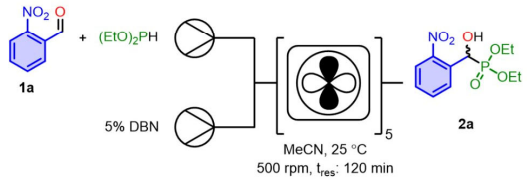
Aims and objectives

This study explores the use of continuous stirred tank reactors (CSTRs) to optimise the synthesis of α-hydroxyphosphonates via the Pudovik reaction, followed by phosphate formation through the phospha-Brook reaction by adjusting the amount of DBN used. The research also demonstrates that a one-pot tandem Pudovik and phospha-Brook rearrangement can be achieved, significantly reducing reaction times compared to batch processes while maintaining similar yields.



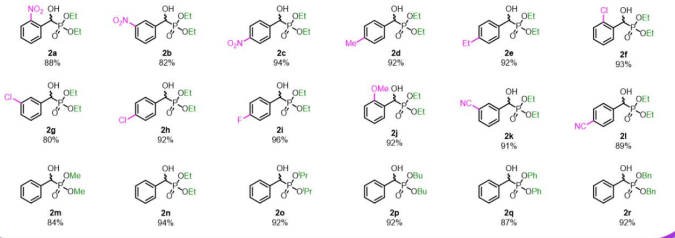
Pudovik reaction

To study the phospha-Brook rearrangement, α-hydroxyphosphonates were first synthesised via the Pudovik reaction, building on Kabachnik's work using DBN and microwave irradiation for high yields.[5,6] The reaction between 2-nitrobenzaldehyde and diethyl phosphite was optimised.



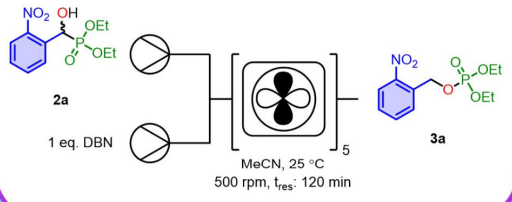
α-Hydroxyphosphonates

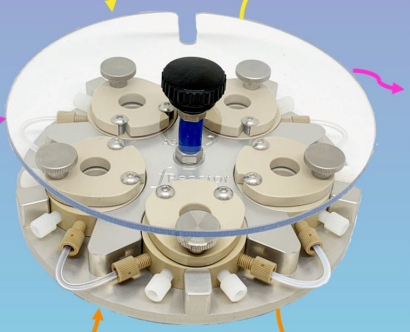
A range of α-hydroxyphosphonates were synthesised using the optimised conditions for the Pudovik reaction



Phospha-Brook rearrangement

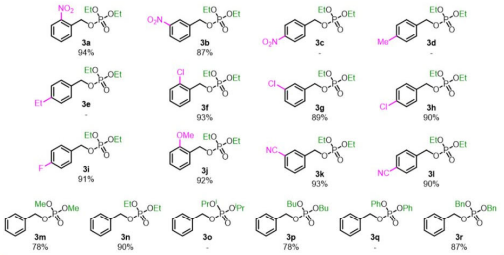
The phospha-Brook rearrangement, previously optimised with DBN in MeCN over 16 hours in batch,[7] was studied in CSTRs to reduce reaction time by improving mixing efficiency. The 2-nitro derivative **2a** was used as a model substrate for optimisation.





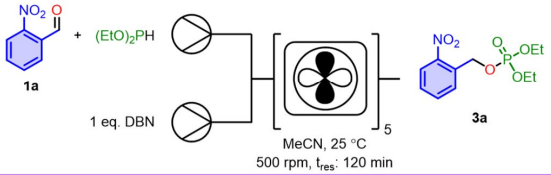
Aryl phosphates

A range of substituted aryl phosphates were synthesised using the optimised conditions for the phospha-Brook rearrangement.



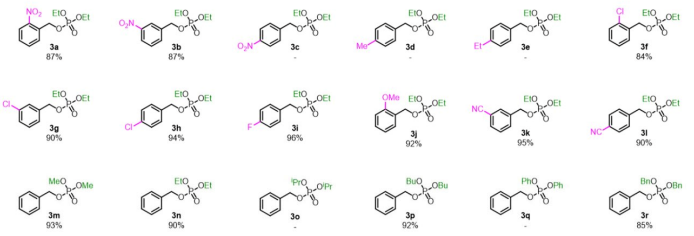
One-Pot Pudovik-phospha-Brook rearrangement

Previous catalysts for the one-pot Pudovik-phospha-Brook rearrangement include BuLi, DBU, and $Cu(OTf)_2$.[8-11] Optimisation for the one pot synthesis involved varying the amount of DBN, stirring rate, temperature, and residence time with 2-nitrobenzaldehyde **1a** and diethyl phosphite.



Substituted aryl phosphates

A range of substituted aryl phosphates were synthesised using the optimised conditions for the phospha-Brook rearrangement.



Conclusion & Future Work

A time-efficient method has been developed for synthesising both α-hydroxyphosphonates and phosphates at room temperature under continuous flow conditions, depending on the amount of DBN used. Reaction times have been reduced to two hours compared to traditional batch processes. This methodology was successfully applied to a wide range of substrates, yielding α-hydroxyphosphonates and phosphate diesters in excellent yields, demonstrating its broad applicability.

References

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