

CONTINUOUS FLOW SYNTHESIS OF HYDROXAMIC ACIDS

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Introduction

Recently, **flow technologies** have received a great deal of attention and a fair number of scientific publications have demonstrated their potential for improving productivity in organic synthesis.¹

Established advantages of micro-flow processes are:

- precise mixing
- immediate heat transfer
- rapid optimization of reaction conditions
- reproducibility
- easy scale-up
- *in-situ* generation and use of hazardous intermediates
- solvent superheating

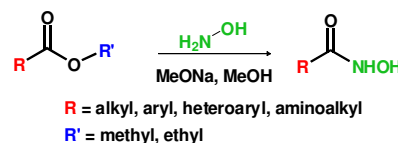
This technology was applied to the synthesis of **hydroxamic acids**, well known inhibitors of important biological targets as metalloproteinases and histone deacetylases,² representing a challenge for organic chemists because of their low solubility and stability.

Scope of the project

• Set-up of optimal reaction conditions for the transformation of carboxylic esters into the corresponding hydroxamic acids using a continuous flow reactor.

• Preparation of a small collection of hydroxamic acids having a range of functional groups.

• Process scale-up.

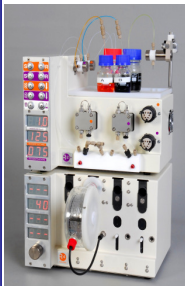


Tools

All experiments were performed using **Vapourtec R Series Flow Chemistry System**.³

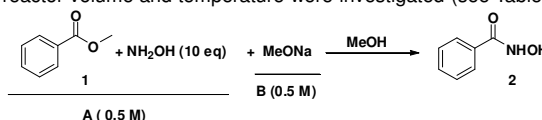
Instrument configuration:

- The inlet selection valves were separately connected to the bottles containing the reagents.
- The reactor channels were combined at a T-piece mixer, connected to a Dual-Core™ tubing reactor (5 - 15 mL) and heated to the desired temperature (up to 150 °C).
- A 150 psi backpressure regulator was connected in-line between the tubing reactor and the connection valve.



Set-up of optimal reaction conditions

The reaction set-up was firstly performed using methyl benzoate (**1**) with hydroxylamine in the presence of MeONa in MeOH. The effects of flow rate, reactor volume and temperature were investigated (see Table).



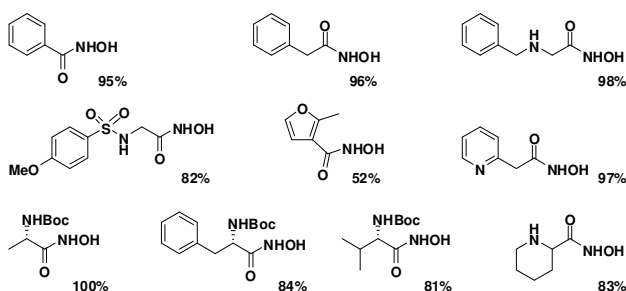
Entry	Flow (ml/min)	Reactor Volume (ml)	Residence Time (min)	T (°C)	Conversion (%) [*]	
					1	2
1	1	5	5	50	48	52
2	1	5	5	70	35	65
3	1	5	5	80	32 [§]	58
4	0.5	10	20	60	24	76
5	0.5	10	20	70	26	74
6	0.5	15	30	70	20	80

^{*}LC/MS at 215 nm, [§] presence of carboxylic acid as byproduct

- Higher conversion of the desired product (**2**) increasing the temperature.
- Formation of a byproduct at temperatures higher than 80 °C.
- Increased Residence Time using lower flow rate and longer tubing reactor.
- Best conditions in Entry 6: 82% yield of isolated product (theoretical output: 1.7 g/h).
- 58% Conversion (LC/MS) obtained after 30 minutes using traditional equipment (round-bottom flask) at the same temperature and concentration.

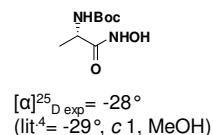
Preparation of a set of hydroxamic acids

The optimized reaction conditions (concentration, retention time and temperature) were successfully applied for the preparation of a collection of hydroxamic acids. Good yields of isolated products, purity (>95%) and high reproducibility were achieved.



Stereochemical consideration

The method was successfully applied to enantiomerically pure esters without loss of stereochemical integrity, as for *N*-Boc-alanine.



Scale-up

In one experiment 4.3 g of *N*-hydroxy-2-phenylacetamide were straightforwardly produced after 1.5 hour (output 2.9 g/h). Yield and purity were similar to the smaller scale assay. We then demonstrated that this flow process can be readily scaled up to provide a relevant amount of material.

Conclusion

A fast optimization of reaction conditions was performed for the conversion of methyl or ethyl esters into hydroxamic acids. The best results were obtained at 70 °C and with a residence time of 30 minutes. This protocol demonstrates high reproducibility with good purity and yields of final products. Aryl, alkylaryl, amino esters (both *N*-protected and unprotected), heterocyclic and sulfonamido esters were suitable substrates. Stereochemical integrity in the conversion of α -aminoacids and reproducible scale-up were assessed.

1 Mason, B.P.; Price, K.E.; Steinbacher, J.L.; Bodgan, A.R.; McQuade, D.T. *Chem. Rev.* **2007**, *107*, 2300.

2 Bolden, J.E.; Peart, M.J.; Johnstone, R.W. *Nature Rev. Drug Discovery* **2006**, *5*, 769.

3 www.vapourtec.com

4 Mordini, A.; Reginato, G.; Russo, F.; Taddei, M. *Synthesis* **2007**, *20*, 3201-3204.



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