CONTINUOUS FLOW SYNTHESIS OF HYDROXAMIC ACIDS

S. Gagliardi, M. Martinelli, C. Mazzoni, D. Passarella,§ A. Rencurosi, E. Riva,§ D. Vigo

NiKem Research S.r.l., via Zambeletti 25, 20021 Baranzate, Milano, Italy
§Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano,Via Venezian 21, 20133 Milano
www.nikemresearch.com *elena.riva@unimi.it*

Introduction

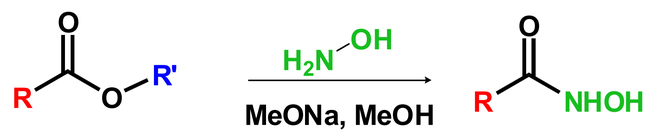
Recently, **flow technologies** have received a great deal of attention and a fair number of scientific publications have demonstrated their potential for improving productivity in organic synthesis.[1]
Established advantages of micro-flow processes are:

- 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.

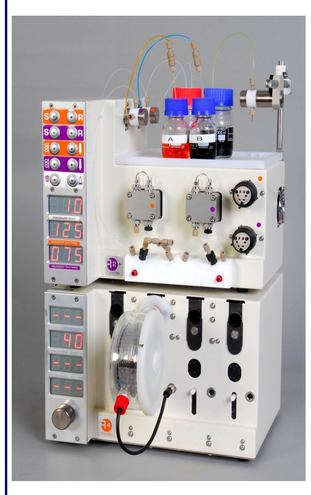
Scope of the project

- 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.



R = alkyl, aryl, heteroaryl, aminoalkyl
R' = methyl, ethyl

Tools



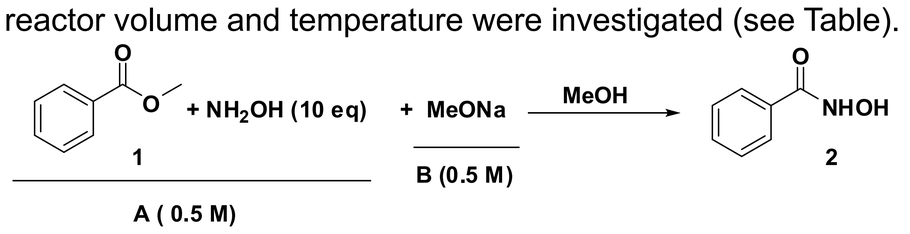
All experiments were performed using **Vapourtec R Series Flow Chemistry System**.[3]

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).



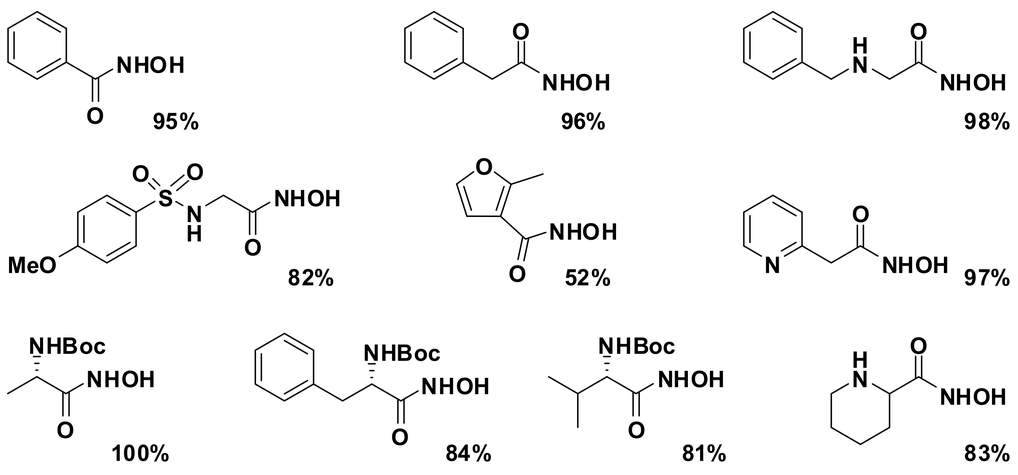
Entry	Flow (ml/min)	Reactor Volume (ml)	Residence Time (min)	T (°C)	Conversion (%)*	
					1	2
1	1	5	5	50	48	52
2	1	5	5	70	35	65
3	1	5	5	80	32§	58
4	0.5	10	20	60	24	76
5	0.5	10	20	70	26	74
6	**0.5**	**15**	**30**	**70**	**20**	**80**

*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.

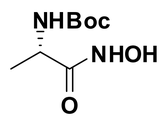
Preparation of a set of hydroxamic acids

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.



$[\alpha]^{25}_{D\ exp}$ = -28°
(lit.[4] = -29°, *c* 1, MeOH)

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.