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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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\textsuperscript{TM} 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.

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.

\begin{align*}
\text{Conversion (\%)*} & \quad \text{Entry} & \quad \text{Flow (ml/min)} & \quad \text{Reactor Volume (ml)} & \quad \text{Residence Time (min)} & \quad \text{T (°C)} & \quad \text{Conversion (\%)*} \\
\text{1} & \text{2} & \text{1} & \text{1} & \text{5} & \text{5} & \text{50} & \text{48} & \text{52} \\
\text{2} & \text{1} & \text{1} & \text{5} & \text{5} & \text{70} & \text{35} & \text{65} \\
\text{3} & \text{1} & \text{1} & \text{5} & \text{5} & \text{80} & \text{32} & \text{58} \\
\text{4} & \text{0.5} & \text{10} & \text{20} & \text{60} & \text{60} & \text{74} \\
\text{5} & \text{0.5} & \text{10} & \text{20} & \text{70} & \text{26} & \text{74} \\
\text{6} & \text{0.5} & \text{15} & \text{30} & \text{70} & \text{20} & \text{80} \\
\end{align*}

\*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.

Stereochemical consideration

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

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 \(\alpha\)-aminoacids and reproducible scale-up were assessed.