Synthesis of *N*-methyl amino acids in a flow tube-in-tube reactor with a gas-liquid/liquid-liquid semi-permeable membrane

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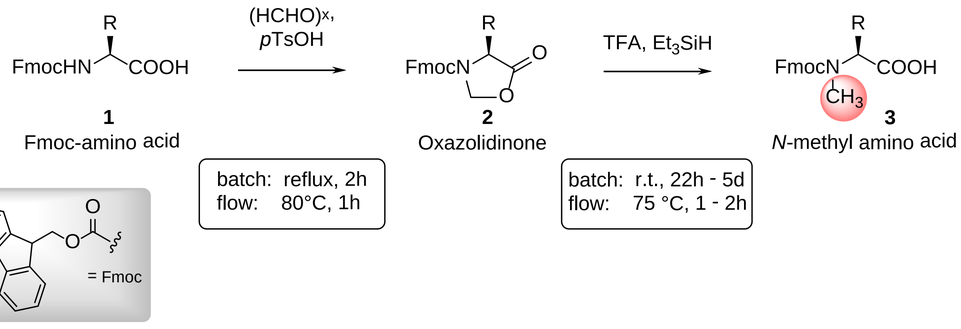
Introduction

Liquid-liquid transfer for Teflon® AF 2400 membrane in a tube-in-tube reactor is demonstrated. This concept was proven by application to flow-through synthesis of *N*-methyl amino acids in two steps via oxazolidinones according to Freidinger et al.[1] Both steps for *N*-methylation of Fmoc amino acids were carried out in a micro-structured tube-in-tube reactor with a semipermeable Teflon® AF 2400 membrane as applied in gas/liquid syntheses by Ley et al.[2] In the first step, gaseous formaldehyde passed the inner membrane providing the conversion of Fmoc amino acids **1** to the corresponding oxazolidinones **2**. In the second step, liquid-liquid transfer of trifluoroacetic acid was used for the first time in such a reactor.[3] Here, trifluoroacetic acid selectively permeated the membrane into solution at r.t. providing the reductive ring opening of oxazolidinones **2** to give Fmoc *N*-methyl-amino acids **3**.

Synthesis of *N*-Methyl amino acids



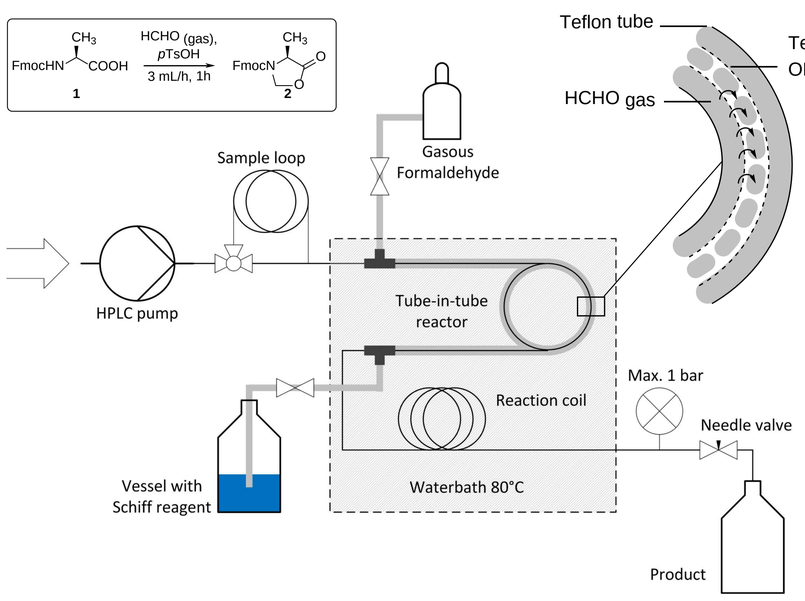
Freidinger's synthesis[1]:

- selective access to *N*-methyl amino acids
- mild reaction conditions
- no racemization

Improvment by flow-through application:

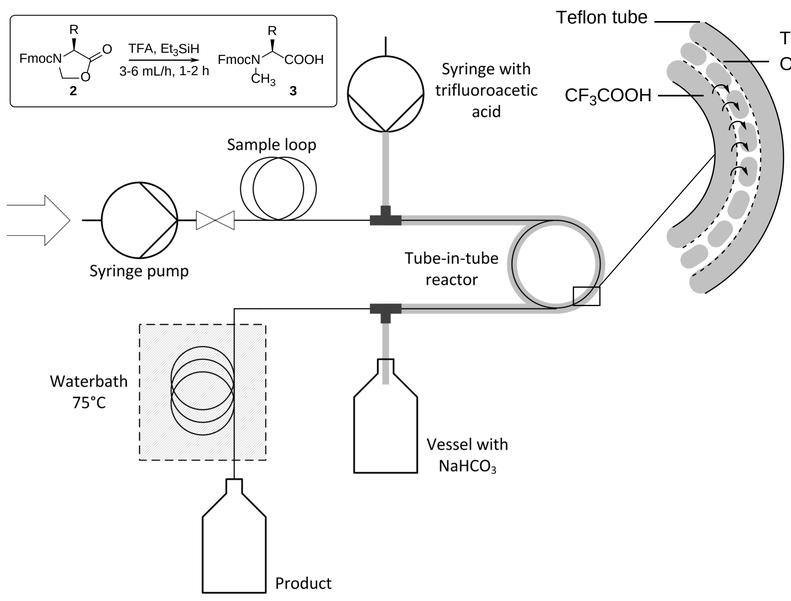
- convenient up-scaling
- shorter reaction times

Tube-in-tube reactor for Oxazolidinones



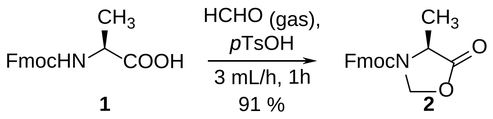
- HPLC pump delivers solvent
- Substrate and acid were injected into the sample loop
- Formaldehyde gas is generated by heating paraformaldehyde
- Membrane lenght 20 cm
- Total volume of the flow reactor 3 mL

Tube-in-tube reactor for *N*-methyl amino acids



- Syringe pump delivers substrate, solvent and Et_3SiH
- Triflouroacetic acid permeates the membrane selectively at r. t. into the solution
- Membrane lenght 60 cm
- Total volume of the flow reactor 6 mL

Results of the 1st step: Oxazolidinones



Acid	Conversion
*p*TsOH	100 %, no by-products
TFA	100 %, many by-products

- Fmoc-L-Alanine was taken as model substrate and yielded in 91 %
- Formaldehyde permeability was tested with Schiff reagent
- Different formaldehyde sources were tested (CuO+MeOH, Paraformaldehyde)
- 1 bar of gas pressure performed best results otherwise outgassing (>1 bar) was observed
- 80 °C watherbath temperature was required to avoid polymerization of formaldehyde → below 75 °C paraformaldehyde percipitates on the membrane
- Investigating TFA as acid catalyst led to several by-products

Results of the 2nd step: *N*-methyl amino acids

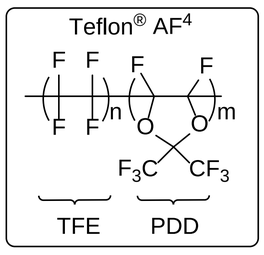
- Less polar solvents provided best results
- Even with flow rates up to 10 mL/h 90 % conversion could be obtained
- Lower temperatures led to decreasing conversions (65°C → 36% conv.)
- Minimum of 2 eq. of Et_3SiH are neccessairy for full conversion

	Flow Yield	Flow Time	Batch[1] Yield	Batch[1] Time
Fmoc-L-Alanine	97 %	6 mL/h, 1 h	98 %	22 h
Fmoc-L-Valine	94 %	3 mL/h, 2 h	100 %	22 h
Fmoc-L-Phenylalanine	90 %	3 mL/h, 2 h	70 %	22 h
Fmoc-L-Methionine	56 %	3 mL/h, 2 h	22 %	5 d
Fmoc-L-Serine(OBn)	95 %	3 mL/h, 2 h	96 %	22 h
Fmoc-L-Glutamic acid	80 %	3 mL/h, 2 h	-	-

- Optimization for each amino acid was performed seperately (Flow-rate and Et_3SiH amount)

Teflon® AF 1600 / 2400

- Teflon® AF is a copolymer of tetrafluoroethylene (TFE) and 2,2-bistrifluoromethyl-4,5-difluoro-1,3-dioxole (PDD)
- Teflon® AF 2400 contains 87 % PDD
- Teflon® AF 1600 contains 65 % PDD
- Chemical resistance to hot acids, hot caustic, chlorine and organic compounds or solvents
- Highly permeable to gases with low molecular weight (e.g. CO_2, N_2, O_2)
- Large fractional free volume (FFV) of 0.327 → free volume elements of 5-7Å



Summary

Teflon® AF 2400 membrane selectively mediated the permeation of not only gases but also trifluoroacetic acid into solution to give Fmoc *N*-methyl amino acids. The liquid-liquid transfer in a tube-in-tube reactor enabled a highly efficient synthesis of various Fmoc protected α-amino acids as interesting components for natural product and drug synthesis. Conduction of both steps, oxazolidinone formation and reductive ring opening in a single combined two tube-in-tube flow reactor was not successful. However, flow rates of 3 - 8 mL/h in each step enabled reactions times of only 1 - 3 h in total thus, significantly shorter than performed by traditional methods in batch.

Acknowledgment

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