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"Some Like it Hot" - Continuous Flow Chemistry at High Temperatures and Pressures

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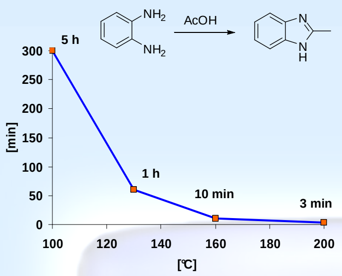
❶ The Unique Features of Flow Chemistry at High Temperatures and Pressures

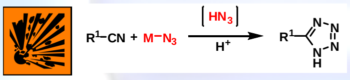
From Hours to Minutes/Seconds The superheating of solvents (+100 °C above bp) leads to a *dramatic* reduction of reaction times e.g. *from days to hours or minutes to seconds (Arrhenius Law)*.

Novel Process Windows The mechanical robustness of stainless steel reactors enable the exploration of genuine high-temperature / -pressure applications requiring exotic or harsh conditions such as the *use of supercritical solvents*.

Reaction Time vs. Temperature



Inherently Safe The low volume capillary design enables the safe handling of extremely dangerous substances.



Hessel, V. *Chem. Eng. Technol.*, ***2009***, 32, 1655; Razzaq, T; Kappe, C.O. *Chem. Asian J.* **2010**, *5*, 1274.

❷ Capillary Steel Reactor for High T/p Chemistry

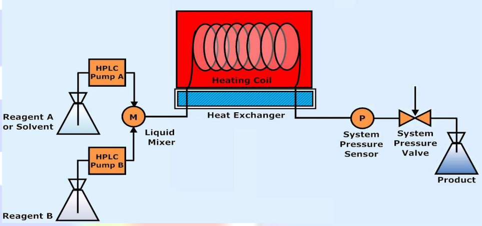
Process Intensification: Equipment for a "+100" Flow Chemistry

Stainless steel reactors allow to conduct reactions at temperatures and pressures being around ***100 °C*** and ***100 bar*** **beyond** the operating limit of most Teflon-tubing, or glass-chip based reactors.

X-Cube Flash (XCF)

www.thalesnano.com

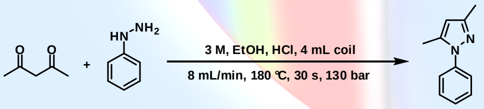
Temperature	**<350 °C**
Pressure	**<180 bar**
Flow rates	**0.5-10 ml/min**
Changeable residence coils	**4, 8, 16 mL**



Razzaq, T. ; Glasnov, T. N.; Kappe, C. O. *Chem. Eng. Technol.* **2009**, *32,* 1702.

❸ Scale Up - MW vs. Flow Space Time Yields

Space Time Yields [kg/m³s] in a Pyrazole Formation



226 g/h

Microwave Batch (Synthos 3000)	Pyrazole Synthesis		Continuous Flow (XCF)	Pyrazole Synthesis	
Temperature (°C)		180	Temperature (°C)		180
Hold Time (s)		1*	Residence Time (min)		0.5
Processing Time (min)		43	Flow Rate (mL/min)		8
Concentration (mol/L)		3	Concentration (mol/L)		3
Reactor Volume (mL)		960	Reactor Volume (mL)		4
Yield (g)		468	Yield/Hour (g)		226
Space-Time Yield (kg/m³s)		**0.19**	**Space-Time Yield (kg/m³s)**		**15.7**

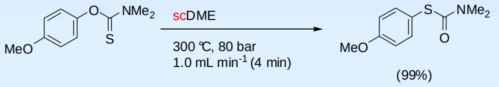
* the run was stopped after reaching the hold temperature of 180 °C, and cooled with air.

Space-Time Yield (Flow) ~ 80 x Space-Time Yield (Batch) !

Damm, M.; Glasnov, T. N.; Kappe, C. O. *Org. Process Res. Dev.* **2010**, *14*, 215.

❹ Chemistry Examples

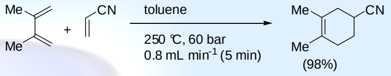
Newman-Kwart Rearrangement



supercritical (sc)

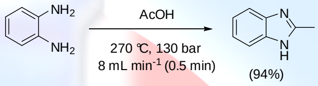
Razzaq, T. ; Glasnov, T. N.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, 1321.

Diels Alder Reaction



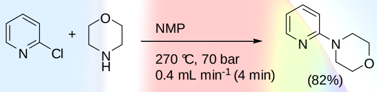
Razzaq, T. ; Glasnov, T. N.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, 1321.

Benzimidazole Formation



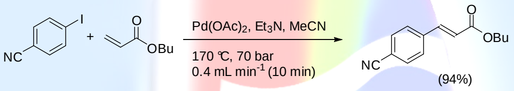
Damm, M.; Glasnov, T. N.; Kappe, C. O. *Org. Process Res. Dev.* **2010**, *14*, 215.

Nucleophilic Aromatic Substitution (SN$_{Ar}$)



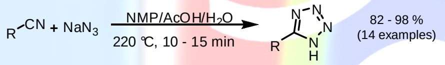
Razzaq, T. ; Glasnov, T. N.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, 1321.

Mizoroki-Heck Coupling



Glasnov, T. N.; Findening, S.; Kappe, C. O. *Chem. Eur. J.* **2009**, *15*, 1001.

Tetrazole Synthesis from Nitriles and Hydrazoic Acid

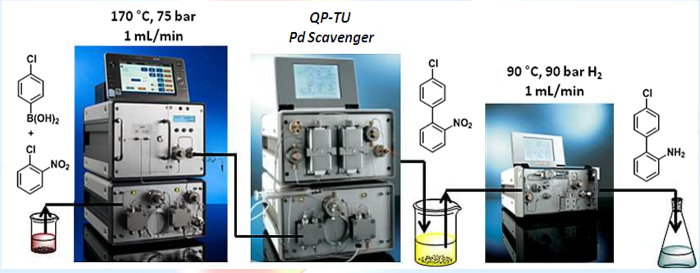


82 - 98 %
(14 examples)

Explosion hazard under batch conditions

Gutmann, B.; Roduit, J. P.; Roberge, D.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2010**, *49*, 7101.

2-Step One-Flow Synthesis of Boscalid® (BASF)



Glasnov, T. N.; Kappe, C. O. *Adv. Synth. Catal.* **2010**, *352*, 3089.

❺ Summary

- More and more recently published chemistry examples in glass-chip- and Teflon based microreactors begin to exploit the possibility of superheating solvents for process intensification leading to drastically shortened reaction times. Hence, a further increase of reaction temperatures (e.g. moving from 150 to 250°C) using a suitable reactor environment (e.g. stainless steel) leads to even shorter reaction times, according to the Arrhenius law.
- Working in a high-temperature/high-pressure continuous flow regime, many reactions requiring unusually harsh, exotic or extremely dangerous reaction conditions or the use of supercritical solvents are easily accessed and safely controlled in the microreactor environment.
- A recent example of a two-step synthesis in stainless steel equipment is the synthesis of the pesticide Boscalid (BASF) in a Suzuki-Miyaura cross coupling - hydrogenation sequence.

Acknowledgements

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