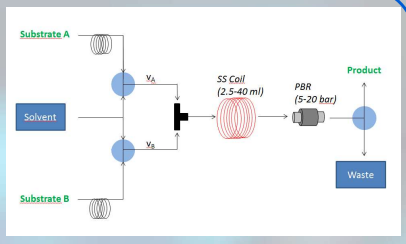
Flow chemistry applications at Orion Medicinal Chemistry as part of the IMI Chem21 Project.[1]

Anniina Vesalainen*, Hertta Karjalainen*, A. John Blacker†
*Medicinal Chemistry, Orion Corporation, Tengströminkatu 8, 20101 Turku, Finland; †iPRD, University of Leeds, UK
contact: anniina.vesalainen@orionpharma.com

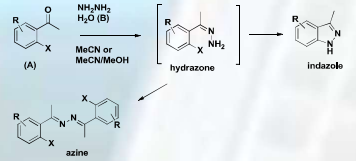
Introduction

- Flow chemistry is having an impact in medicinal chemistry because it can speed up development and lower the costs.
- Flow synthesis can reduce environmental burden through process intensification. It also offers a safe means to perform traditionally risky chemistry where hazardous reagents, intermediates or extreme conditions are used.
- In this regard the indazole moiety is a useful building block in a variety of bioactive molecules but the synthesis often requires harsh conditions, long processing times and hazardous reagents or intermediates. We report here robust, versatile and safe synthesis of indazoles in a flow reactor.
- SnAr reactions of amines with activated aryl fluorides often require long processing times at high temperatures. Moreover, the generation of hydrofluoric acid is detrimental to glass-lined reactors.[2] Our preliminary studies with trimethyl silylacetate as a trapping agent in a flow system show a lot of promise and at the same time allowing us to develop a method with remarkably reduced reaction times.



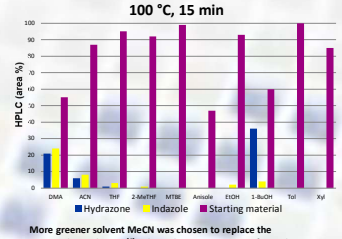
Reactor configuration of flow synthesis with indazole and SnAr reactions.

3-Me-*1H*-indazole synthesis optimization in flow reactor for pharmaceutical building blocks



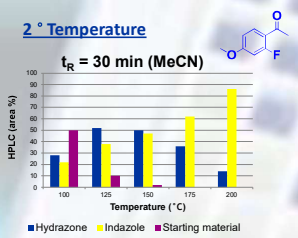
Indazole synthesis proceeds via hydrazone intermediate[3]. Azine formation is a typical side reaction.

1° Solvent Screen

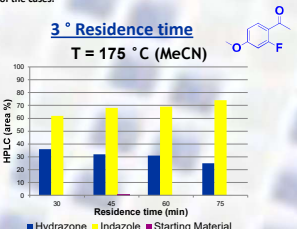


More greener solvent MeCN was chosen to replace the previously used DMA.[4] Sideproduct azine was not formed in any of the cases.

2 ° Temperature



3 ° Residence time



0.5 M Acetophenone stock solution was used. Hydrazine excess increased the conversion and it was raised up to ~4.5-5.4 eq. The effect of temperature and residence time were investigated. 175 °C with 75 min residence time was used with other substrates and scale up.

4 ° Substrate scope and Scale up

- Scale-up of the indazole with acetonitrile was difficult due to pressure rise during prolonged residence times.
- Hydrazine hydrate forms a biphasic system with acetonitrile.
- Gas bubbles were formed during the reaction, which may be caused by decomposition of hydrazine.[5]
- Addition of methanol to the hydrazine solution avoided over-pressure albeit with lower conversion.
- Substrate scope showed moderate to excellent conversions but suprisingly poor yields in some cases.
- Some indazoles are volatile which may explain inconsistencies between conversions (HPLC area %) and isolated yields.

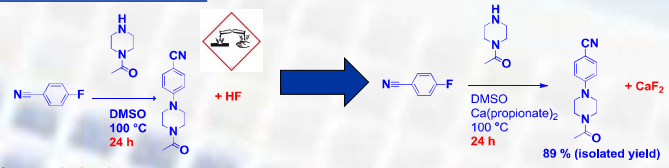
Entry	Product	Solvent	HPLC area %	Isolated yield (%)
1		MeCN[1] MeCN/MeOH MeCN/MeOH[2] DMSO[3]	72 67 55 56	68 28 18 N/A
2		MeCN MeCN[4,5] MeCN/MeOH[4,5] MeCN/MeOH[2,4,5,6]	100 90 88 95	N/A 78 60 78
3		MeCN MeCN/MeOH	95 83	44 69
4		MeCN MeCN/MeOH	100 99	73 99
5		MeCN MeCN/MeOH	91 91	26 63
6		MeCN MeCN/MeOH	92 93	51 70
7		MeCN	17	N/A
8		MeCN	91	32
9		MeCN[7]	66	N/A
10		MeCN	56	13

All reactions at 175 °C unless stated; Reactions in MeCN done in 20 ml coil with residence time 75 min and in MeCN/MeOH done in 10 ml coil with residence time 71 min unless stated.

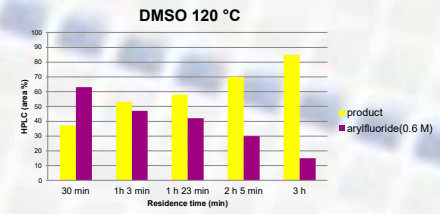
1) 10 ml coil
2) 40 ml coil
3) Temperature 120 °C
4) Temperature 150 °C
5) Residence time 15 min
6) Antisolvent crystallization
7) Cl as leaving group in starting material

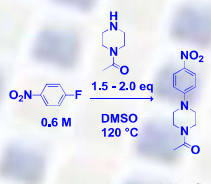
SnAr-reaction in flow: Fluoride trapping

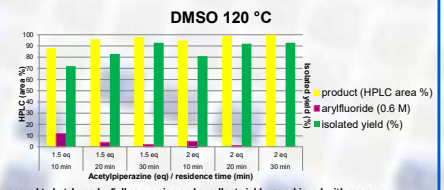
Backround: Batch reaction[2]



Flow optimization

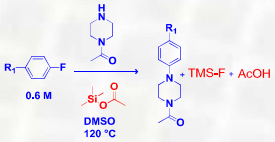






Residence time was reduced remarkably in flow system compared to batch mode. Full conversion and excellent yield was achieved with more reactive substrate 1-Fluoro-4-nitrobenzene already in 30 minutes.

Fluoride trapping in flow



Trimethylsilyl acetate forms heterogeneous mixture with DMSO and substrate unlike eg. ethoxytrimethyl silane (TMSOEt) or 1,2-Bis-(trimethylsiloxy)ethane.
*Theoretical fluoride level 5700 mg/l

Entry	R_1	Residence time	Amine (eq)	Trapping agent (eq)	Isolated yield (%)	Fluoride level (mg/l)*	Fluoride level in aqueous phase (mg/l)
1	CN	3 h	1.5	0	65	4845	355
2	CN	62 min	1.5	1	55	2850	29
3	NO_2	29 min	2	1	91	2320	13
4	NO_2	29 min	2	2	92	1140	0.6
5	NO_2	29 min	2	5	88	500	0.2

ACKNOWLEDGEMENTS

We are grateful for all our partners within CHEM21 for rewarding interactions and collaborations. The research for this work has received funding from the Innovative Medicines Initiative joint undertaking project CHEM21 (https://www.chem21.eu/) grant agreement n°115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies in kind contribution.

References: [1] www.chem21.eu; [2] Blacker et al. Development of an SnAr Reaction: Calcium Sequestration of Fluoride , *in preparation*; [3] Lukin et al. *J. Org. Chem.* 2006, *71*, 8166 [4] Wheeler et al. *Org. Proc. Res. & Dev.* 2011, *15*, 565 [5] Lucien H. *Journal of Chemical Engineering Data* 1961, *6*, 584