Flow Synthesis Using Gaseous Ammonia in a Teflon AF-2400 Tube-In-Tube Reactor: In-Line Titrations and Fanetizole Synthesis

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Flow Chemistry

Flow chemistry has received a great deal of attention from the scientific community over the last decade. Continuous-flow techniques can often provide better mixing and heat transfer, precise control over concentrated or hazardous reaction streams, reduced solvent waste and synthetic shortcuts.[1] Moreover, the rapid process optimization of synthetic steps on a small scale, combined with the telescoping of steps together in a continuous mode, enables more elaborate multistep sequences to be performed, leading directly to drug molecules or even natural products.[2]

Efficient Temperature Control

Fig. 1. The Polar Bear Plus Flow.

To date, a number of flow reactors and devices are available for lab scale preparations. The Polar Bear Plus Flow is a compact, state of the art temperature control module for both heated and cooled flow-through chemistry applications. The unit uses proprietary heating/cooling technology to deliver temperatures from 150 ºC down to -40 ºC

Ley's Group in the Innovative Technologies Centre (ITC).[4]

Gas-Liquid Phase Chemistry in Flow

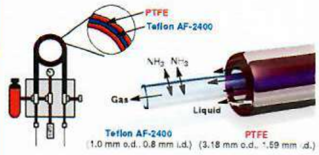

Fig. 2. The tube-in-tube reactor.

The development of a permeable membrane based tube-in-tube gas flow reactor has facilitated the transfer of gases into a liquid stream, in a controlled and safe manner.[3] Indeed, several applications from our group demonstrate with success the use of O_2, O_3, H_2, CO, CO_2, NH_3, C_2H_4 and Syngas in a range of organic transformations.

Flow Synthesis of Thioureas

Evaluation of the scalability and throughput:

(a) segmented mode

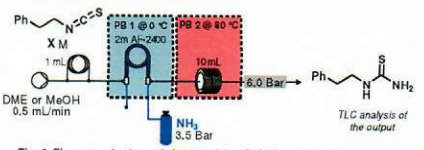

Fig. 6. Flow setup for the optimisation of the alkyl-thiourea synthesis.

✓ DME
full conversion - up to 1.2 M
($[NH_3]$ = 1.10 M)
✓ MeOH
full conversion - up to 1.4 M
($[NH_3]$ = 1.58 M), low levels of thiocarbamate by-product formation

(b) continuous mode

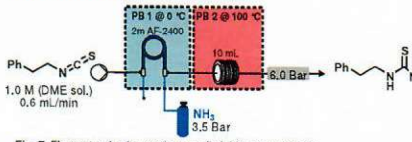

Fig. 7. Flow setup for the continuous alkyl-thiourea synthesis.

✓ full conversion

✓ quantitative yield

✓ up to 156 g per day

Ammonia Measurement– In-Line Titrations[5]

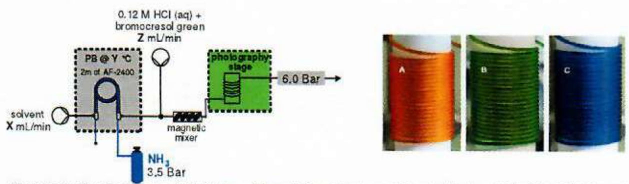

Fig. 3. In-line flow titration setup (left). Pictures of the outlet from the mixer at different pH values (right): (A) acidic (pH <3.8); (B) intermediate pH; (C) pH > 5.4.

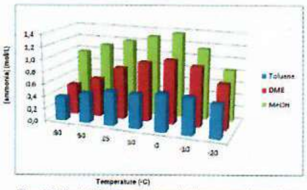

Fig. 4. Effect of the temperature in the ammonia uptake.

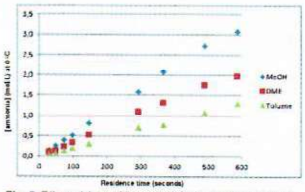

Fig. 5. Effect of the residence time in the ammonia uptake.

Telescoped Process – Fanetizole Synthesis

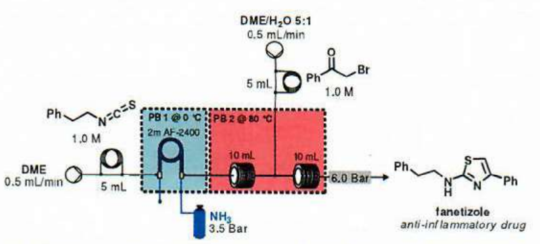

Fig. 8. Flow setup for the multistep process consisting of thiourea synthesis followed by the Hantzsch preparation of fanetizole.

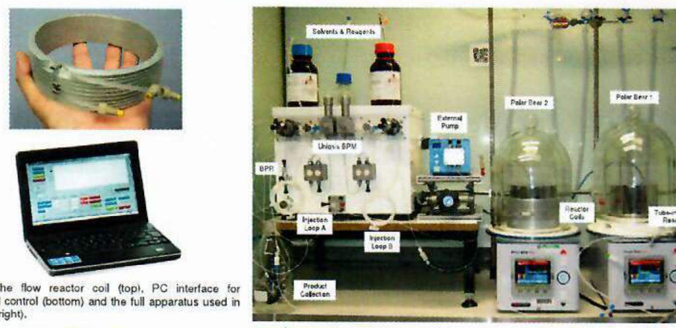

Fig. 9. The flow reactor coil (top), PC interface for automated control (bottom) and the full apparatus used in this work (right).

[1] Ley, S. V.; Baxendale, I. R. *Chimia* **2008**, *62*, 162. [2] Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K. *Chem. Commun.* **2006**, 2566. [3] (a) O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596. (b) Polyzos, A.; O'Brien, M.; Petersen, T. P.; Baxendale, I. R.; Ley, S. V. *Angew. Chem. Int. Ed.* **2011**, *50*, 1190 and references contained therein. [4] (a) Browne, D. L.; Baumann, M.; Harji, B. H.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2011**, *13*, 2011. (b) Desai, A. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 9223. [5] Browne, D. L.; O'Brien, M.; Koos, P.; Cranwell, P. B.; Polyzos, A.; Ley, S. V. *Synlett* **2012**, *23*, 1402.

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