Continuous Flow Synthesis of Substituted Benzo-bisimidazoles – Precursors for Cruziforms

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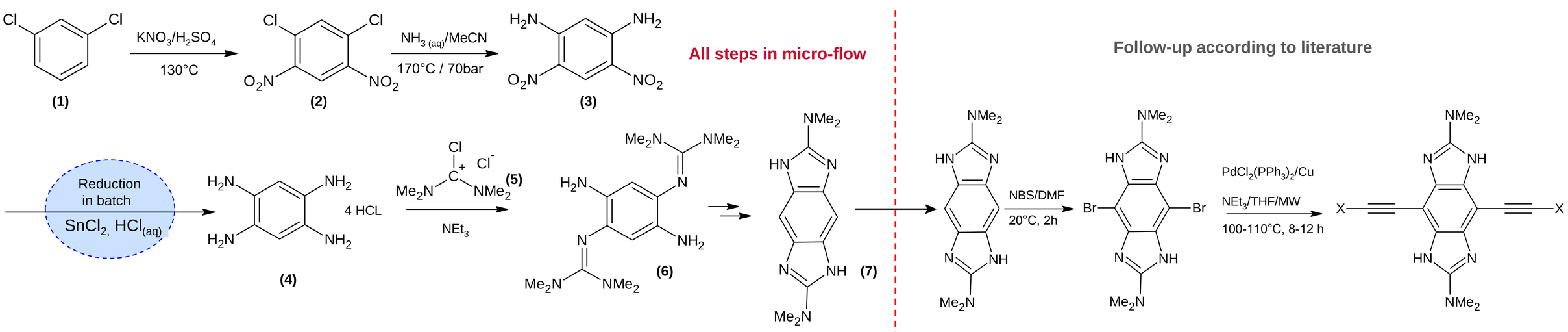
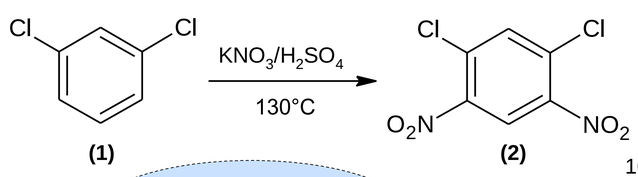
Introduction

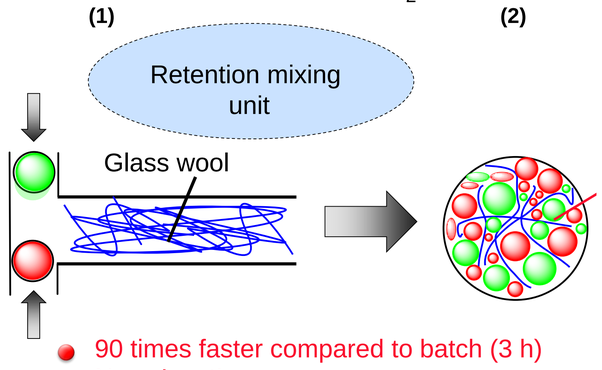
So-called “Cruciforms” are aromatic fluorophores consisting of two perpendicular conjugated π-systems, which form a cross-like structure. They are commonly used as fluorescent materials for optoelectronics.[1,2] The central aromatic core of theses substances often consists of condensed heteroaromatics, such as benzobisimidazoles.[3] Using flow chemistry, the productivity, selectivity and convenience of the underlying synthetic strategies is highly increased. The original batch synthesis of these heterocycles involves a series of inconvenient, dangerous, and unselective reactions, ranging from nitration to substrates containing multiple functional groups with little to no difference in reactivity.[4,5] The synthesis sequence starting from 1,3-dichlorobenzene **(1)** to 2,6-*N,N,N',N'*-tetramethylamino-benzobisimidazole **(7)** is shown below. In three of four cases, switching from batch to flow systems resulted in a remarkable increment in overall performance. For the first step, a glass-wool packed bed reactor was used to speed up a biphasic aromatic nitration of **(1)** to 1,3-dichloro-4,6-dinitrobenzene **(2)** from 3h to 2 min (90 times faster). The concept of Novel Process Windows was exploited in the following substitution reaction of **(2)** to 1,3-diamino-4,6-dinitrobenzene **(3)** to circumvent the use of ammonia gas in favor of the much cheaper and less toxic aqueous ammonia by applying high pressures (70 bar) and temperatures above 170 °C. The reduction of **(3)** to 1,2,4,5-tetraaminobenzene **(4)** was performed in batch. In the key step, the ring-closure to **(7)**, 1,4-bis-(tetramethylguanidino)-2,5-diaminobenzene **(6)** was selectively synthesized out of **(4)** with bis-(dimethylamino)-chlorocarbenium chloride **(5)** as a non-isolated intermediate with a vastly improved yield (54%) compared to the batch reaction (12% yield). Careful utilization of mixing strategies and kinetic effects (homogeneous versus segmented flow) made a reaction pathway for **(7)** possible, which occurred only as a byproduct in the original synthesis. The multiple addition of **(5)** to **(6)** is by far the preferred reaction. This reaction step is extremely mixing sensitive and overlain by subsequent precipitation. Therefore, a SIMM micromixer was used. Further improvement of the reaction was observed by switching to a segmented flow regime, presumably due to the superior residence time control by traveling segments or droplets resulting 65% yield **(7)**. [6]

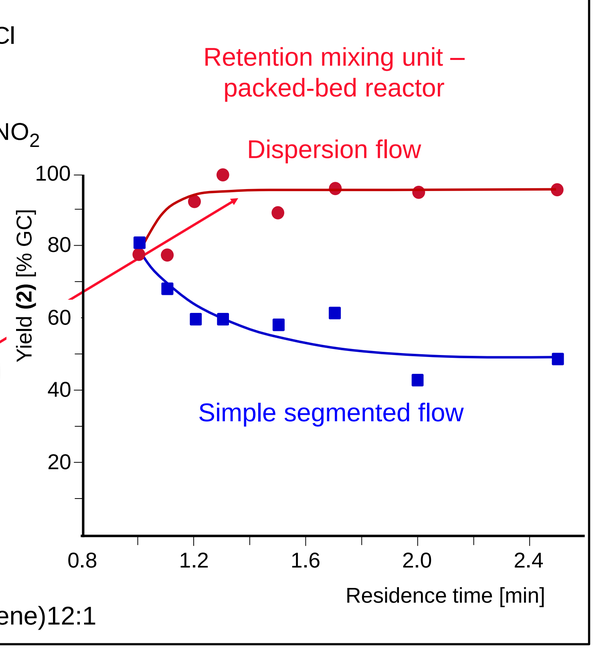
Reaction Sequence Performed in a Micro-flow Reactor



Nitration in a Micro Packed-bed Reactor

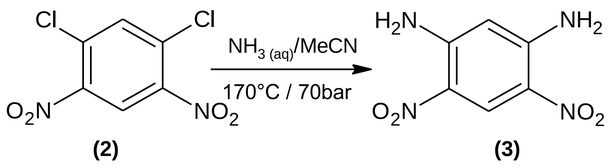


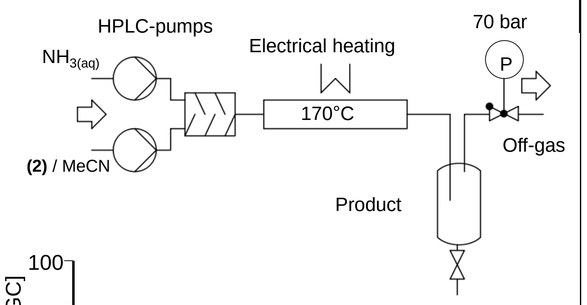




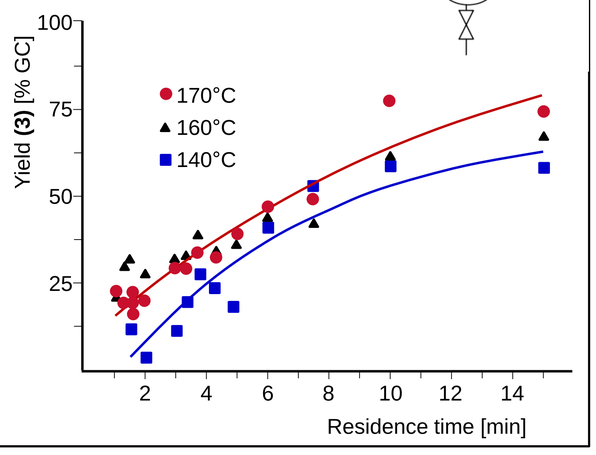
- 90 times faster compared to batch (3 h)
- No solvent!
- Reactor volume: 3.2 mL
  Overall flow rate: 1.3 – 3.4 mL min^{-1}
  Flow ratio (nitration mixture to dichlorobenzene)12:1

Novel Process Windows – High T,p - Substitution

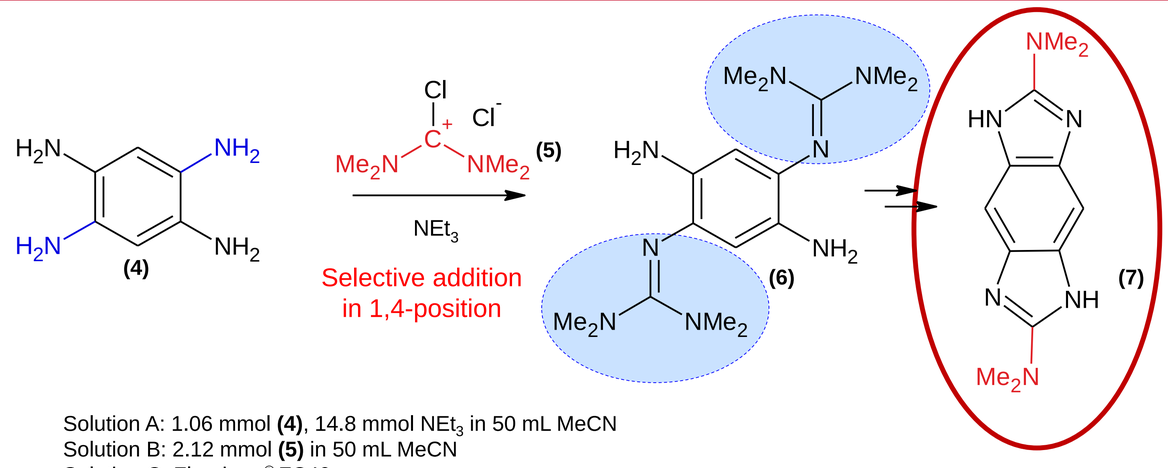




- Reaction is performed with aqueous ammonia
- Temperature (170°C) above the boiling point ($NH_{3(aq)}$ / MeCN)
- Reactor volume: 4 mL
  Overall flow rate: 0.27 – 2.5 mL min^{-1}
  Flow ratio: 1:1
- Batch process takes 24 h

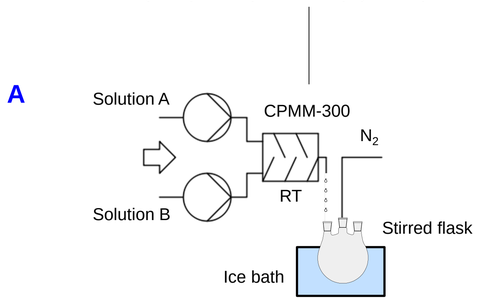


Addition and Ring Closure under Micro Flow Conditions

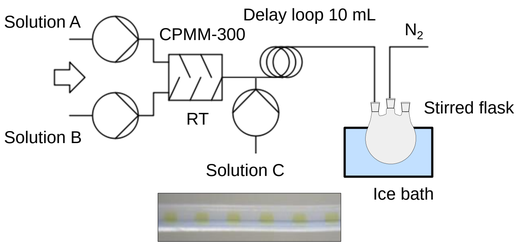


Solution A: 1.06 mmol **(4)**, 14.8 mmol NEt_3 in 50 mL MeCN
Solution B: 2.12 mmol **(5)** in 50 mL MeCN
Solution C: Fluorinert® FC40

Flow rates (A, B): 500 µL each, (C): 300 µL min^{-1}

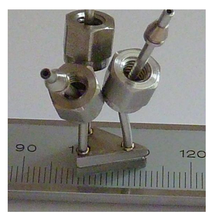


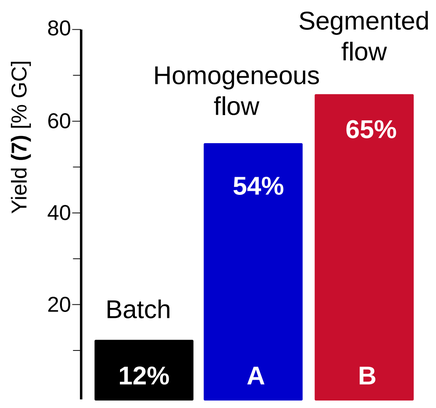
Residence time (mixer and tube) ≪ 1 sec



Residence time 7.7 min

- Very fast reaction
- Superior mixing is essential (favors kinetic product) !
- Backmixing is avoided
- Over-addition is supressed
- CPMM-300 micro mixer (IMM) with very small inner volume - 0.055µL
- Instantaneous precipitation





Summary

- A four step batch synthesis was adapted for microfluidic applications and considerably improved.
- Biphasic reactions (e.g. nitration) were performed in a segmented flow regime as well as in a packed-bed column. The continuously redispersion in a backed-bed increases the interfacial area between the two phases repeatedly resulting in much higher yield compared to a segmented flow procedure.
- Novel Process Windows allow to perform a substitution reaction with unusual reaction conditions, e.g. processing aqueous ammonia at 170°C and 70 bar. Compared to the conventional batch process the reaction becomes nearly 100 times faster.
- Highly reactive Vilsmeier salts were successfully used to synthesize benzobisimidazole directly from 1,2,4,5-tetraaminobenzene. This reaction is strongly mixing sensitive and overlain by instantaneous precipitation. Both drawbacks can be reduced by using an efficient micromixer with very small internal volume and either dripping the reaction mixture in a stirred vessel or transfer it to a segmented flow regime.

References

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