De ce reactii in flux?

Overview

- Reactii mai rapide
- Reactii mai sigure
- Optimizarea reactiei mai rapida
- Conditii de reactie imposibile in sarja
- Reactii de regula mai selective
- Scale-up mai usor in flux decat in sarja
- Integrare usoara a analizei reactiei
- Reactii mai usor de finisat in flux.

Explicatii

Cum se ating in flux reactii mai rapide?

- Este mult mai usor de presurizat un reactor in flux
- Presiunile mai ridicate faciliteaza cresterea temperaturilor
- Temperaturile mai ridicate au ca rezultat viteze de reactie mai mari

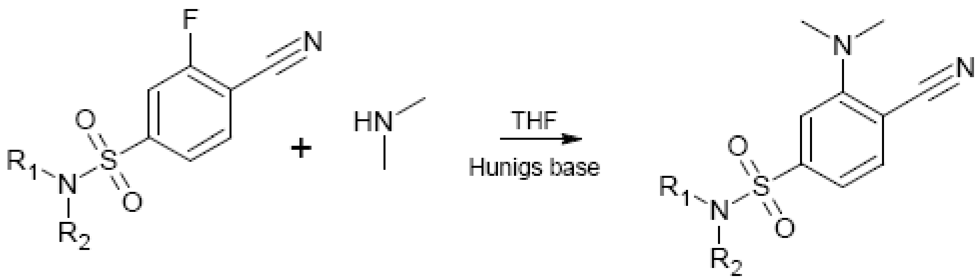
$$k = Aexp\left[-\left(\frac{E_a}{RT}\right)^{\beta}\right]$$

- Exemplu:
  - Reactorul Syrris poate fi presurizat pana la 20bar
  - Aceasta presupune o crestere a punctului de fierbere al solventior cu 100-150C

Solvent	1 bar	7 bar	17 bar
Dichloromethane	41°C	109°C	153°C
Methanol	65°C	138°C	185°C
Water	100°C	181°C	231°C

  - **Ecuatia Arrhenius spune ca viteza este de 2 x rapida pentru fiecare 10C crestere a T**
  - **Deci 100C crestere =2x2x2x2x2x2x2x2x2x2 mai rapid (peste 1000x mai rapid)**

Exemplu: supraincalzirea in flux



<u>In serie:</u>

- Reactie incompleta in reactor discontinuu dupa 1 saptamana de lucru in reflux
- Randament al reactiei foarte prost.

<u>In flux:</u>

- A fost posibila supraincalzirea THF pana la 140ºC
- Optimizari: timp de reactie, temperatura de reactie si echivalentii reactivilor au fost diferiti pentru fiecare din cele doua reactii
- 100% conversie pentru o varietate de substraturi la 140ºC cu timp de rezidenta 1 ora.

Tibotec, Johnson & Johnson (Belgium)

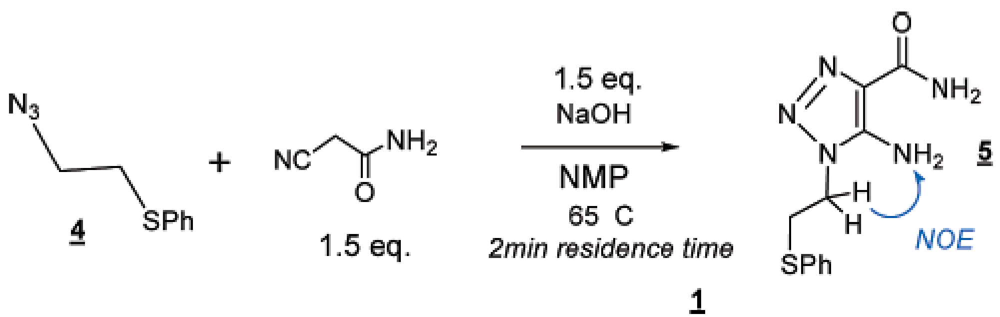
De ce permite chimia in flux reactii mai sigure?

- Cantitativ, reactia desfasurata in orice moment este minimizat
- Raportul intre suprafata si volumul de reactie este de 1000 de ori mai mare in reactorul continuu

- Exemplu:
  - Daca un reactor clasic de 10L explodeaza, consecintele vor fi serioase
  - Aceiasi 10L de reactie pot fi trecuti printr-un reactor tubular de 10ml avand astfel siguranta ca numai 10 ml reactioneaza in orice moment dat
  - Pentru o reactie mai rapida (de ex. 1 min timp de rezidenta), aceasta reactie presupune desfasurarea ei peste noapte.
  - **In acest caz riscul este de 1/1000!!!**

Examplu – reactie mai sigura in flux

- Sinteza Triazole la Wyeth



- Risc: compusi ai azidelor. Utilizarea la scara medie si mare este interzisa
- β-azidoethyl phenyl sulfide: Tf =65ºC, TSU exoterma la 155ºC
- “Continuous-flow reactions have the potential to be much safer than batch reactions, as only a small amount of reactive and potentially hazardous material is heated or converted to product at any given time.”

R. Tinder, T. Storz, *Org. Process Res. Dev.*, **13**, 2009

Cum putem realiza mai repede optimizarea reactiei?

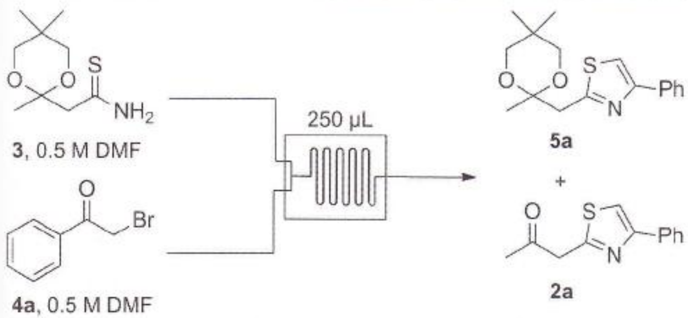
- In reactorul continuu este extrem de usor de variat:
  - Timpul de reactie
    - Variind debitul total
  - Temperatura de reactie
    - Masa putina de incalzit
  - Raportul intre reactivi
    - Variind debitele
  - Concentratia
    - Variind cursul solventului
- O reactie este evacuata de urmatoarea (separate de un solvent), de aceea se utilizeaza numai un reactor. .

- **Adica 50-100 conditii de reactie pot fi investigate in numai 15 minute de setari**

Exemplu – optimizare rapida in flux

- Optimizarea sintezei de tiazol la Institutul Burnham

Table 1. Optimization of thiazole **2a** synthesis



entry	time (min)	temp (°C)	H_2O (equiv)	ratio (**3**:**5a**:**2a**)[a]
1	2.5	50	0	0 : 8.8 : 1
2	5.0	50	0	0 : 8.6 : 1
3	2.5	100	0	0 : 1 : 1.7
4	5.0	100	0	0 : 1 : 2.9
5	2.5	150	0	0 : 1 : 8.7
6	5.0	150	0	0: 1 : 6.8
7	**5.0**	**150**	**1.0**	**0 : 1 : 11.7**
8	5.0	150	5.0	0 : 1 : 104
9	5.0	150	10	1 : 0 : 3.5

- Variind timpul de rezidenta, temperatura si echivalentul apei
- Conditii optime identificate in 9 experimente cu timp total de 37.5 min

N. Pagano, N. D. P. Cosford, *J. Flow Chem.* 2011

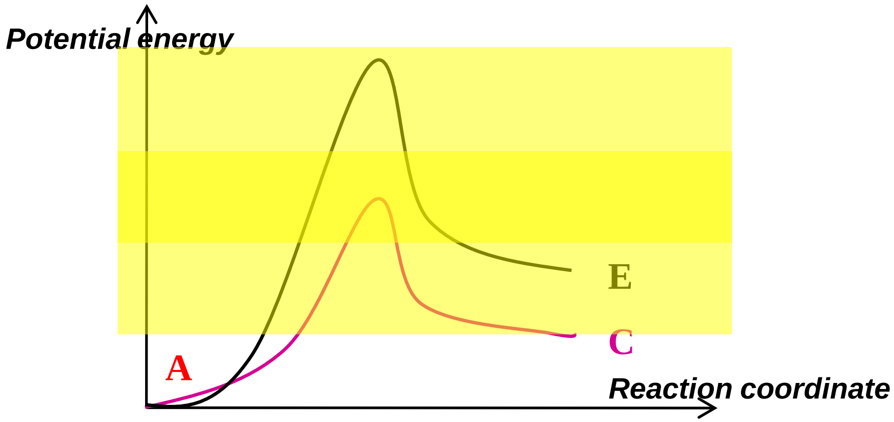
Cum se pot obtine in flux conditii de reactie de neatins in sarja?

- Mixarea se face prin difuzie.
  - Adica mult, mult mai rapid si mai sigura decat in reactorul discontinuu.

- Fiindca reactoarele sunt pre-incalzite/racite, reactia poate atinge temperatura setata aproape instantaneu
- Exemplul 1
  - Timpii de incalzire si racire sunt mult mai mici decat in microunde, deci reactii ultra incalzite si ultra rapide sunt posibile cu usurinta
- Examplul 2
  - Deprotonarea unui substrat la temperatura joasa, apoi adaugarea unui nucleofil si instantaneu incalizrea la o temperatura ridicata.

Cum poate reactia in flux sa fie mai sensibila?

- Selectivitatea proasta vine din instabilitatea temperaturii, concentratiei si a vitezei de aditie/agitare
- Datorita raportului mare intre suprafata si volumul de reactie si a mixarii prin difuzie, chimia in flux ofera:
  - Excelent control de temperatura



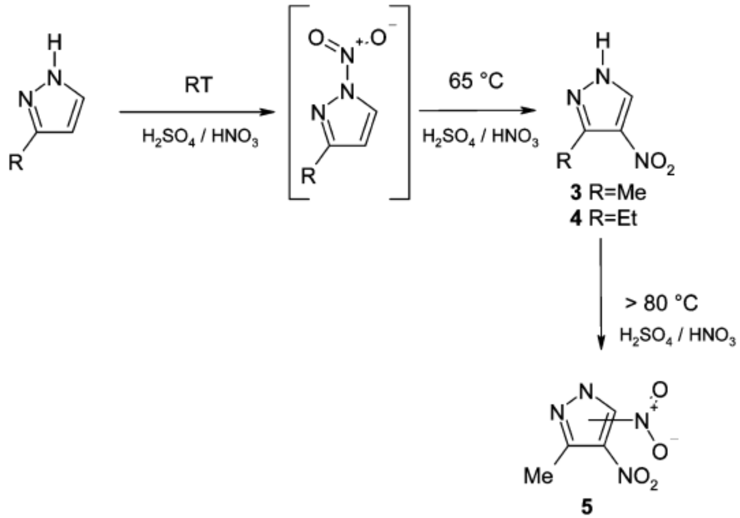
  - Gradient de concentratie minim

- **In flux se permite o mai buna selectivitate**

Exemple - reactii mai curate in flux

- Nitrare pirazol la AstraZeneca

Scheme 2. Temperature-dependent pyrazole nitration



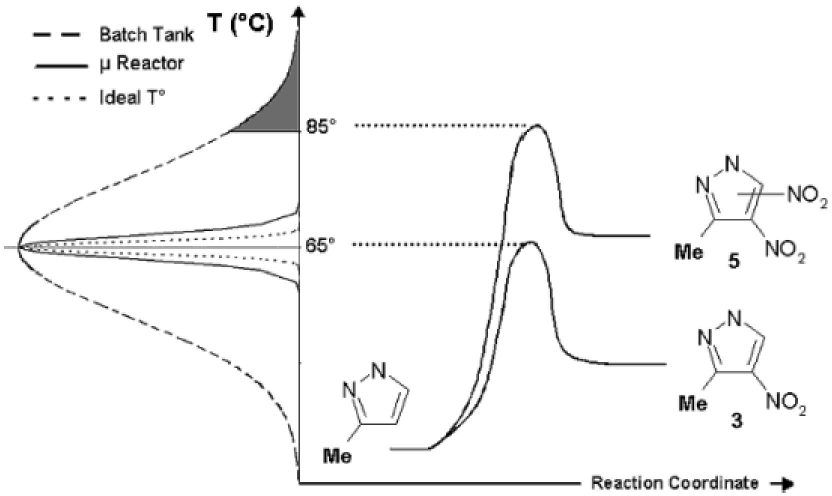


Figure 4. Temperature population in a batch reactor vs a microreactor and impact on byproduct generation.[2]

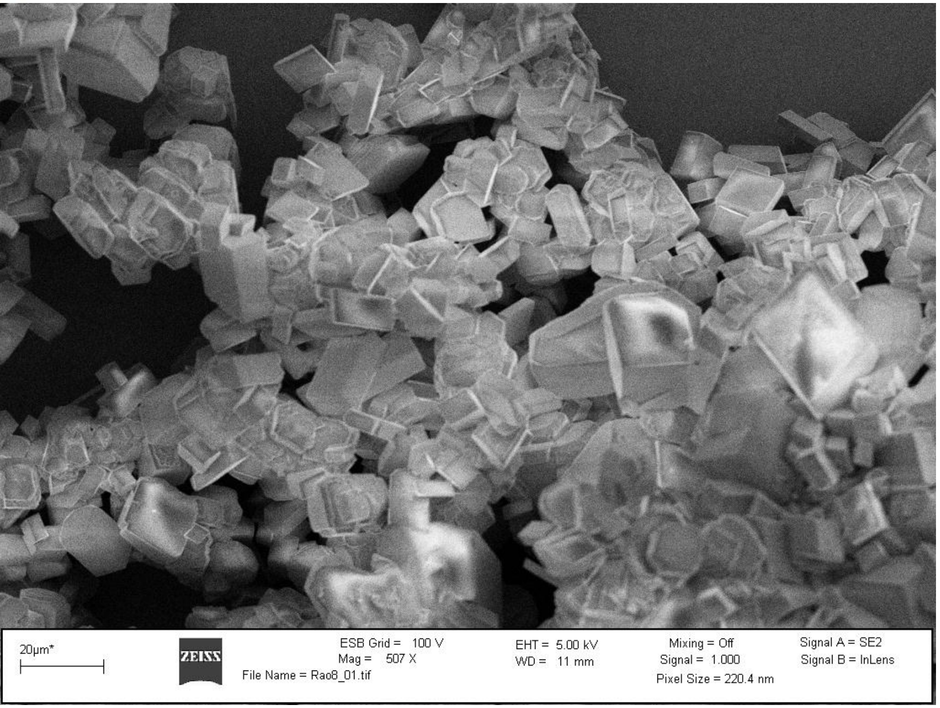
- “In cazul unei reactii cu risc, eventualitatea unui incident este minimizata pentru ca se evita acumularea de intermediari cu potential de risc.”

J. Pelleter, F. Renaud, *Org. Process Res. Dev.*, 2009

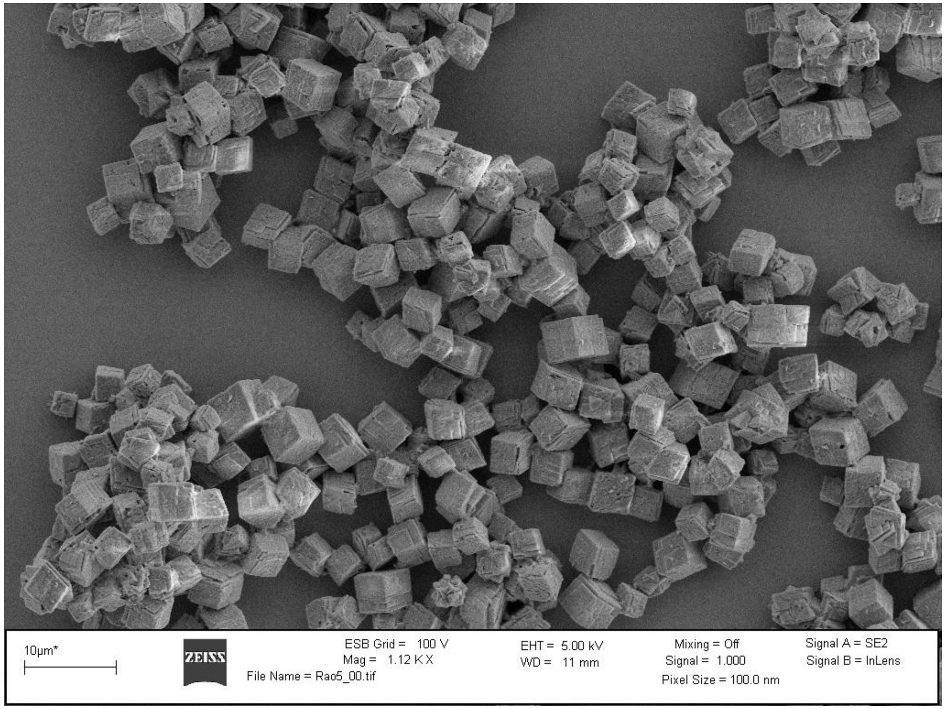
Exemplu – control mai bun in flux

- Reactie $CaCl_2$ cu Na_2CO_3 pentru sinteza $CaCO_3$ continuu si discontinuu
- Exactl aceeasi concentratie, temperatura si timp de reactie/rezidenta
- Calitate si reproductibilitate clar mai buna in flux decat in sarja

Batch



Flow



De ce este reducerea/marirea la scara mai usoara in flux?

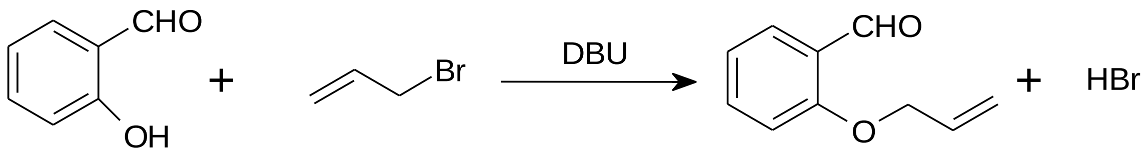
- Pentru ridicare la scara de 10x sau 100x
  - Este posibila producerea oricarei cantitati
  - Dintr-un robinet pot umple o cana sau o cada.

- Pentru 1000x +
  - Principiile fundamentale ale unui raport suprafata/volum mai mare inseamna ca marirea la scala in flux va reduce efectele transferului termic
  - Abilitatea de a utiliza mixere statice inseamna ca mixarea este mai rapida si mai reproductibila.

- **Salvati timp si bani marind la scala in flux**

Exemplu de marire la scala

- Sinteza de 2-alil-oxibenzaldehida
- Reactie efectuata in cadrul grulupui Ley pentru a demonstra utilitatea Micro Capillary Flow Disc Reactor si FRX FLLEX (Flow Liquid-Liquid EXtraction)

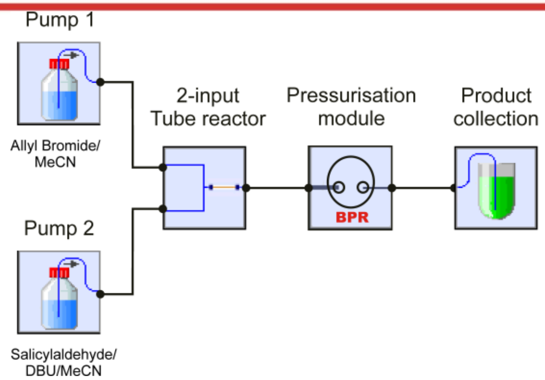


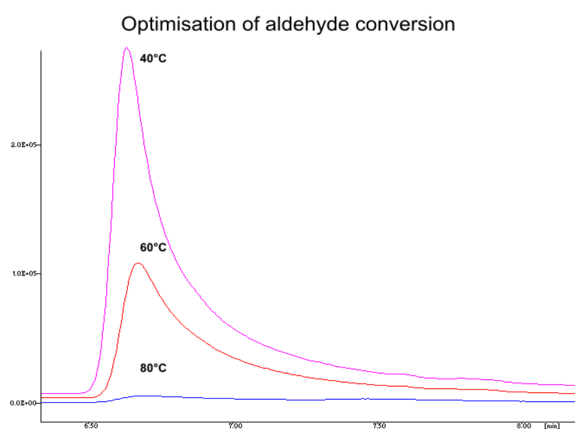
- Conditiile de reactie publicate: temperatura camerei, Reactin MeCN 113min
- Dilutie cu EtOAC si spalare cu $HCl_{(aq)}$ utilizand FRX FLLEX

[1] Ley et al. Org. *Process Res. Dev*, 2007, **11** (3), 399-405.

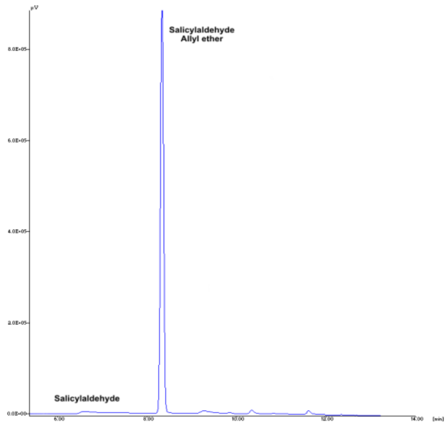
Optimizare si marire la scala

- Reactia a fost optimizata si redusa la un reactor de 16ml
  - Timp rezidenta redus de la 113 ore la 13.3 ore
  - Conversa a ramas mare (97%)
  - Reactia a decurs peste noapte





Parent depletion during optimizaton



Product Formation

- **Rezultat: 376g de produs (randament 97% conform HPLC)**

Cum se face analiza mai facil?

- Pentru a analiza multiple reactii in sarja presupune utilizarea a mai multor senzori (unul per reactor).

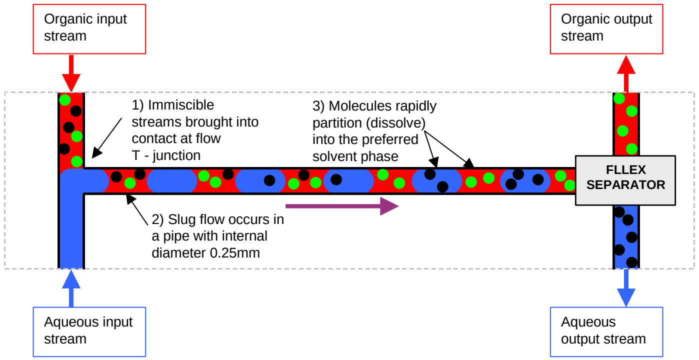
- In flux, multe reactii total diferite pot “curge” in acelasi senzor.
  - Sampler and Dilutor poate trimite spre analiza o cantitate de produs in orice moment

- In flux, reactia curge automat spre sistemul de analiza

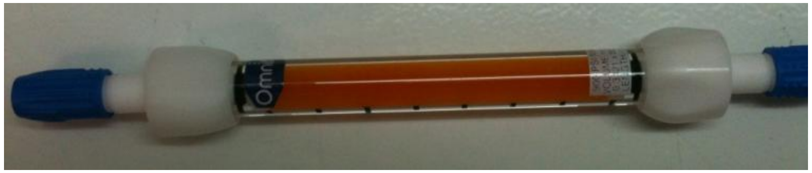
De ce este finisarea reactiei mai usoara in flux?

- In reactorul discontinuu finisarea reprezinta o operatiune separata: purificare apoasa, filtrare sau separare in faza solida

- Fiindca reactia este deja in miscare chimia in flux ofera finisare integrata in-line:
  - Flow liquid-liquid extraction (FLLEX)

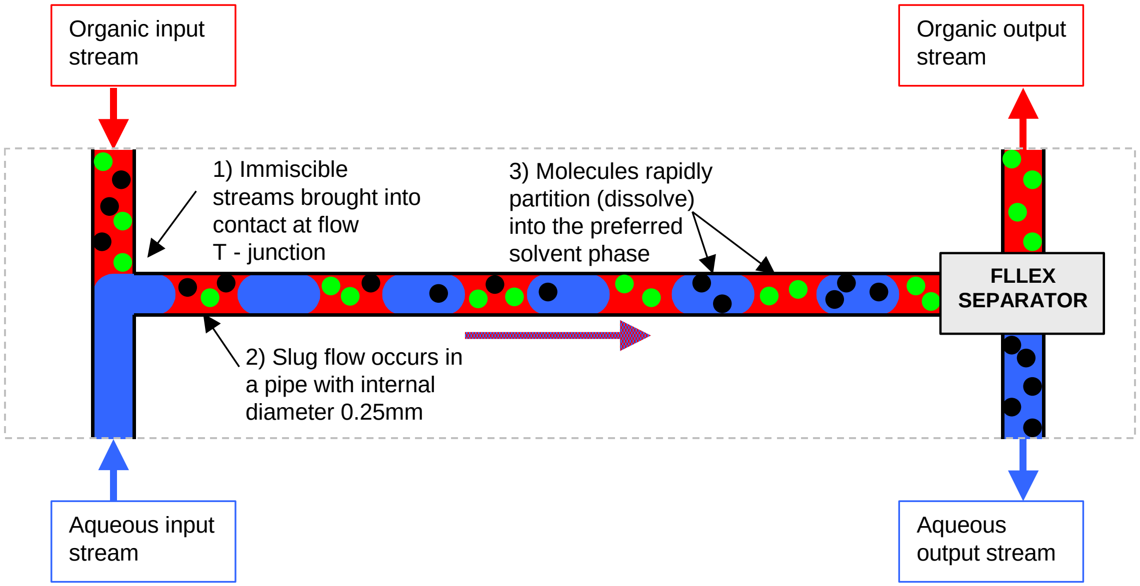


  - Reactivi in faza solida/scavengeri/filtrare



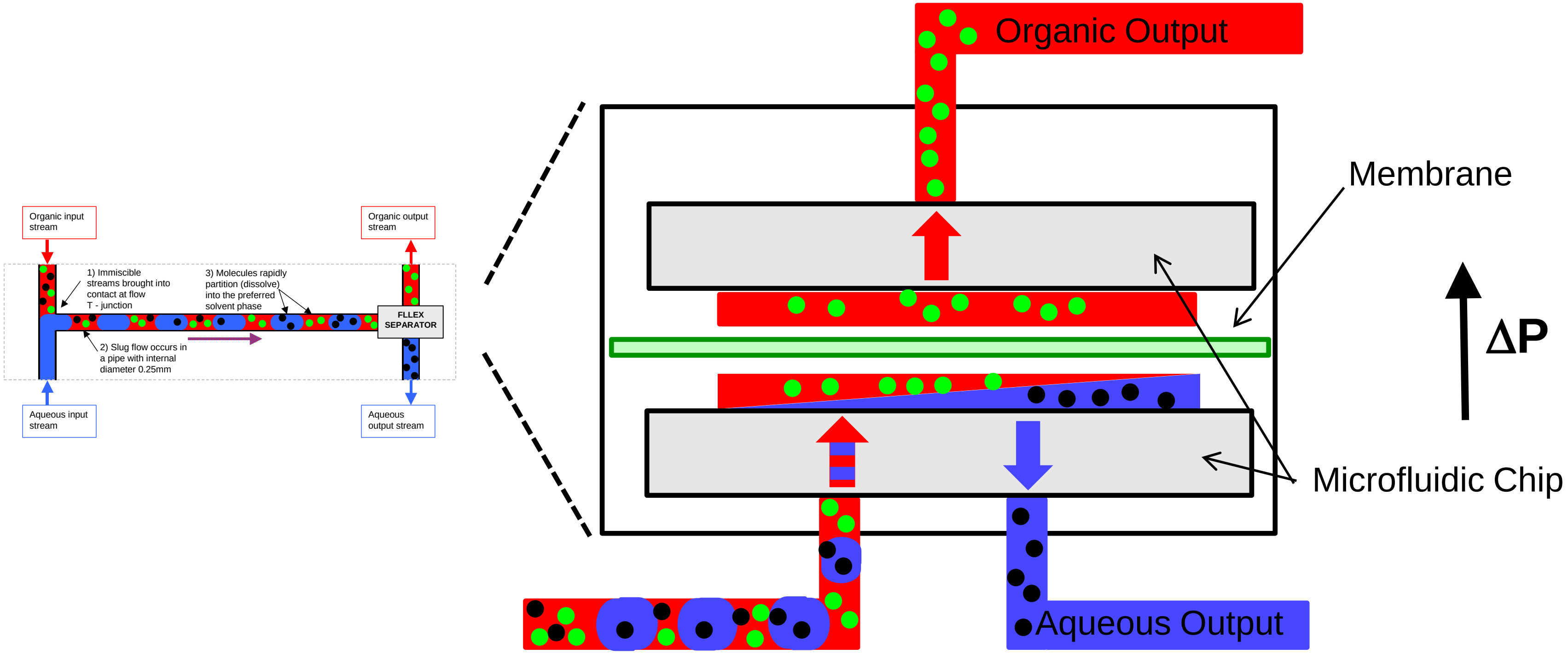
Liquid Liquid Extraction (FLLEX)

Pasul 1. Extractia



- Difuzia moleculelor (extractia) intre “trenuri” apare rapid, < 3 sec
- Separatorul, bazat pe o membrana hidrofoba, are ca rezultat curgerea continua a produsului finisat

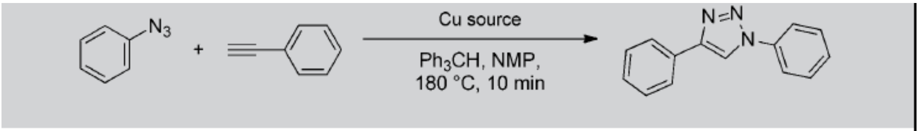
Liquid Liquid Extraction (FLLEX). Pasul 2: Separarea



- Difuzia moleculelor (extractia) intre “trenuri” apare rapid, < 3 sec
- Separatorul, bazat pe o membrana hidrofoba, are ca rezultat curgerea continua a produsului finisat

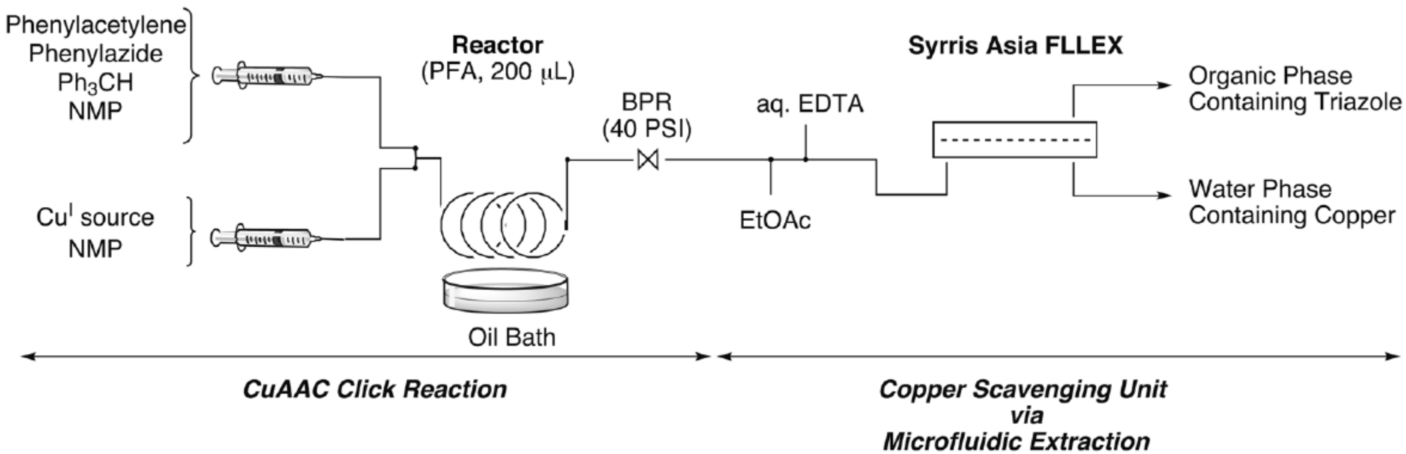
Syrris FLLEX utilizat ca unitate de separare a Cu

- Cicloaditie azide-alchene catalizata cu Cupru (CuAAC) (Click Chemistry)



Entry	Reactor type[b]	Cu catalyst (amount)	Yield [%][c]
1	Cu tube	–	51
2	PFA tube	$Cu(CH_3CN)_4BF_4$ (2.5 mol%)	91
3	PFA tube	$[Cu(phen)(PPh_3)_2]NO_3$ (1 mol%)	92 (88)[d]
4	PFA tube	$[Cu(phen)(PPh_3)_2]NO_3$ (0.5 mol%)	73

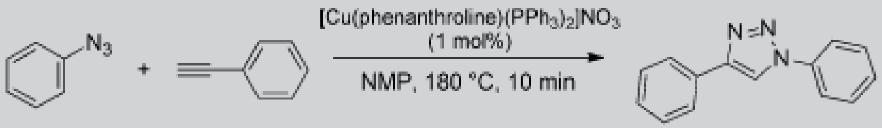
- Reactia CuAAC este candidatul ideal pentru chimia in flux deoarece temperatura mare solicitata si azida intermediara ce se formeaza reprezinta un risc de explozie.



Noel, Hessel (Technical University of Eindhoven)
***ChemSusChem*, *2012*,** *703–1707*

University of Eindhoven – FLLEX - Copper Scavenging Unit

Table 2. Copper scavenging by extraction with aq. EDTA in copper(I)-catalyzed azide-alkyne cycloaddition.[a]



Entry	Extraction[b]	Cu content[c] [ppm]
1	–	3156
2	flow (single extraction stage)	159 ± 9
3	1 × off-line	226 ± 51
4	2 × off-line	124 ± 4
5	3 × off-line	39 ± 1
6	flow (second extraction stage)	97 ± 3
7	flow (third extraction stage)	14 ± 1

[a] Reaction conditions: phenyl acetylene (0.225 M), phenyl azide (0.24 M), $[Cu(phen)(PPh_3)_2]NO_3$ (1 mol %), NMP, 180 °C. [b] For more details, see Supporting Information. [c] Measured by ICP–OES analysis of the product, average of two independent experiments.

<u>RESULTS</u>:

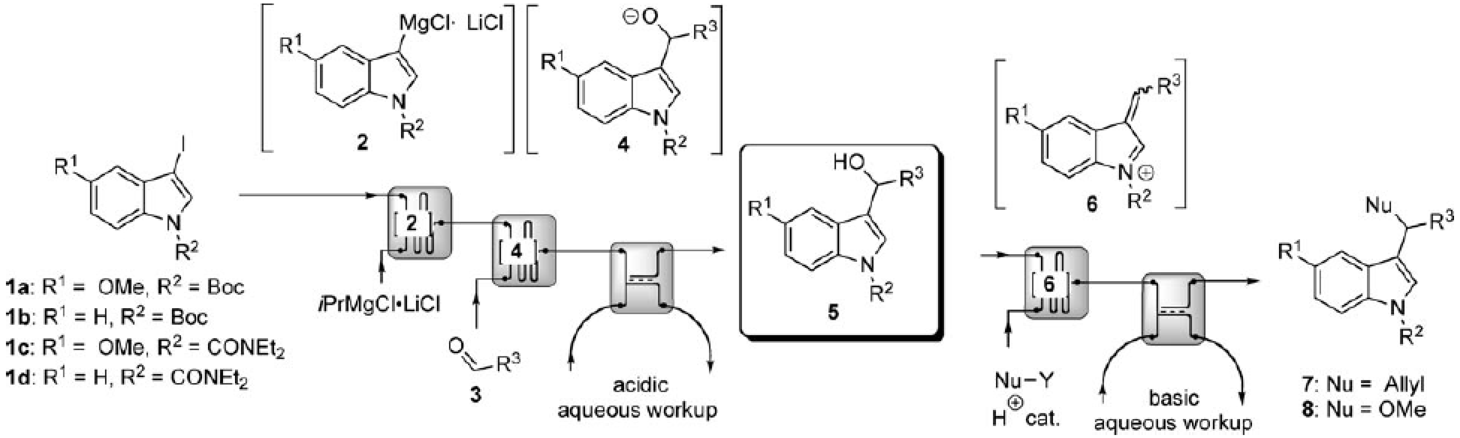
- The copper content could be effectively reduced to 119ppm in a single equilibrium extraction stage using Reaction flow/aq EDTA/EtOAc = 1/7/5

Figure 5. Collection of the two phases after phase separation in continuous flow: aqueous phase containing EDTA, copper, and NMP (left vial), and the organic phase containing triazole (right vial).

Note: The amount of copper allowed in API is 15ppm.

Exemplu – finisare in flux

- Sinteza 3-Hidroxi-metil-indoli la grupul O'Shea.



Scheme 1. Multi-step strategy for the continuous-flow synthesis of 3-hydroxymethylindoles **5** and their conversion to **7** and **8** by acid-catalysed nucleophilic substitution.

- "Our current goal is to develop automated, sequentially performed homogeneous reactions with in-line continuous liquid–liquid extraction of the products"

T. Tricotet, D. F. O'shea, *Chem. Eur. J.* 2010,

Sumar beneficii chimie in flux

- Reactii mai rapide
- Reactii mai sigure
- Optimizarea reactiei mai rapida
- Conditii de reactie imposibile in sarja
- Reactii de regula mai selective
- Scale-up mai usor in flux decat in sarja
- Integrare usoara a analizei reactiei
- Reactii mai usor de finisat in flux.

Intrebari?