

Sophisticated synthesis of monosubstituted piperazines

– from a batch reaction vessel to a flow (microwave) reactor

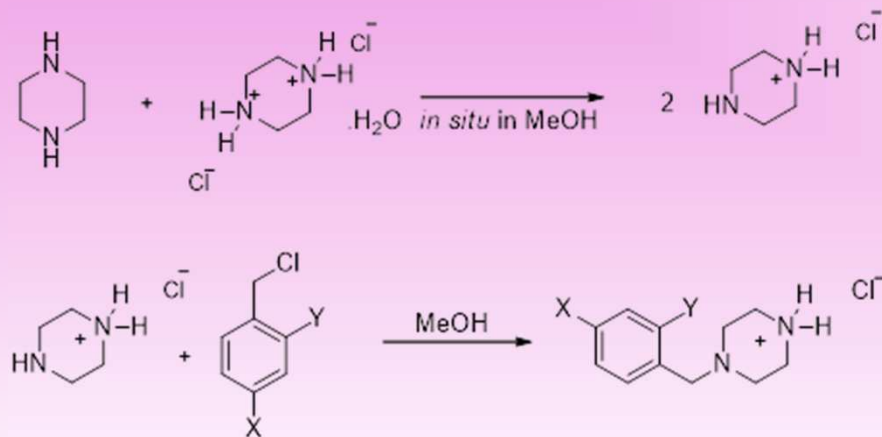
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General procedure of one-step synthesis of monosubstituted piperazine derivatives

- based on a **one-step reaction** of a piperazine (free or HCl salt) with an appropriate compound (chloride, chloroderivative, ester, unsaturated compounds, anhydride etc.)¹⁻³
- proceeds at **room or higher temperature** in common solvents (methanol, acetic acid)
- **catalyzed by metal ions supported** on commercially available polymeric resins^{4,5}



Comparison of classic and microwave-assisted processes

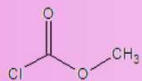
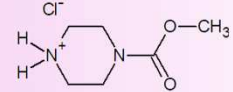
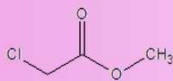
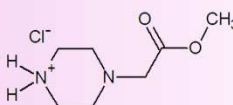
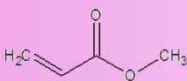
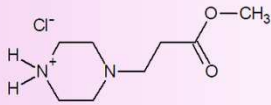


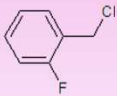
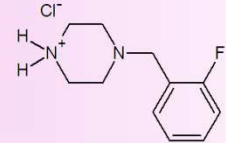
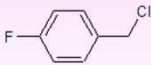
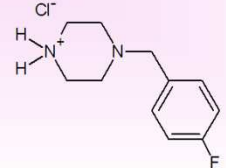
A - classic synthetic procedure¹⁻³

B - batch microwave procedure

C - flow microwave reactor procedure

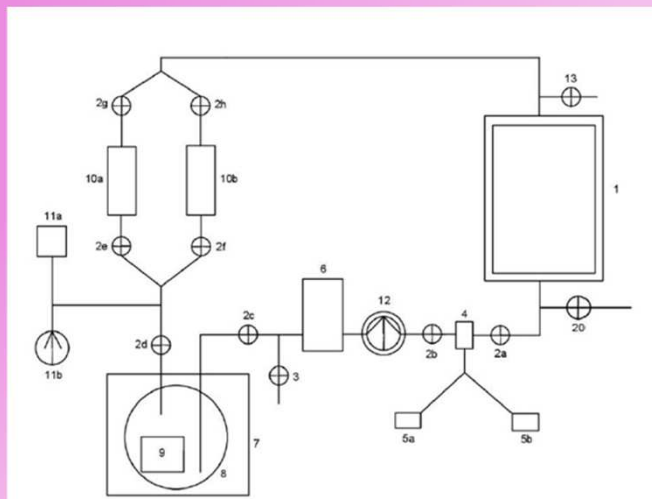
Microwave assisted procedures **accelerate** the course of reactions while keeping comparable yields.

Microwave reactor flow processes show the biggest decreases in reaction times, moreover a flow reactor allows processing of larger volumes.

| Reactant | Catalyst | Procedure ¹ | Time (hr) | Product | Yield ² (%) |
|---|----------|------------------------|-----------|---|------------------------|
|  | Cu(I) | A | 24 |  | 59-78 |
| | - | B ³ | - | | - |
| | Ce(III) | C ³ | 0.58 | | 61 |
|  | Ce(III) | A | 19 |  | 53-60 |
| | Cu(II) | B | 5-6 | | 48-54 |
| | Cu(II) | C | 2.17 | | 64 |
|  | Ce(III) | A | 7 |  | 57-62 |
| | | B | 4 | | 42-50 |
| | | C | 0.17 | | 55-61 |
|  | Cu(II) | A | 8 |  | 67-75 |
| | | B | 1.83 | | 72 |
| | | C | - | | - |
|  | Cu(II) | A | 13 |  | 84 |
| | | B | 2.5 | | 67 |
| | | C | - | | - |
|  | Cu(II) | A | 14 |  | 88 |
| | | B | 1 | | 69 |
| | | C | - | | - |

Flow reactor with microwave unit and/or catalytic bed⁶

- variable design
- large volume processing
- speed and efficiency at affordable price



Scheme of a flow microwave/catalytic bed reactor system



Draft of an outer design of a flow reactor

Three working modes possible:

- 1) Microwave assisted flow mode
- 2) Microwave assisted flow mode combined with a catalytic bed
- 3) Simple flow mode with a catalytic bed

Monosubstituted piperazine derivatives are now commercially available for research and development, please visit:

www.entwickchemicals.com
www.fichema.cz

Patents:

- 1) Pazdera, P.; Zberovská, B.; Němečková, D. (2014). *Czech patent No. CZ 304520*. IPO Prague, Czech Republic.
- 2) Pazdera, P.; Zberovská, B.; Herová, D. (2015). *Czech patent No. CZ 305317*. IPO Prague, Czech Republic.
- 3) Pazdera, P.; Zberovská, B.; Herová, D. (2016). *Czech patent No. CZ 305854*. IPO Prague, Czech Republic.
- 4) Pazdera, P.; Zberovská, B.; Procházková, M. (2013) *Czech patent No. CZ 303987*. IPO Prague, Czech Republic.
- 5) Pazdera, P.; Zberovská, B.; Herová, D.; Datinská, V.; Šimbera, J. (2015) *Czech patent No. CZ 305277*. IPO Prague, Czech Republic
- 6) Pazdera, P.; Němečková, D.; Havránková, E.; Šimbera, J.; Ševčík, R. (2018) *Czech utility model No. CZ 32201*. IPO Prague, Czech Republic.