Synthesis of Pharmacologically Active Compounds Using Microwave Assisted Chemistry

Katinka Ruda, Martins Katkevics, Ilga Mutule*, Vita Ozola*, Edgars Suna**
Personal Chemistry, Hamnesplanaden 5, SE-753 23 Uppsala, Sweden
Katinka.Ruda@personalchemistry.com
**Latvian Institute of Organic Synthesis, Aizkraukles 21, LV-1006 Riga, Latvia*

Introduction

Microwave-assisted organic synthesis has been used for over 10 years, which has resulted in more than 1000 publications. Unfortunately virtually all reactions performed so far have been accomplished in ordinary multimode domestic ovens.

The disadvantages with these kinds of equipments are the lack of temperature and pressure control and, more seriously, the lack of reproducibility and safety. The last aspects have prevented the extensive use of this technique in the drug discovery industries.

The introduction of single-mode, focused microwave systems with temperature (T) and pressure (P) control and T/P regulation possibilities designed for organic synthesis has revolutionized the way medicinal and organic chemistry can be performed. In closed systems which allows pressures up to 20 bars, the organic solvents can be heated up to temperatures 2-3 times the respective boiling points which allows much shorter reaction times than those obtained in open microwave systems.

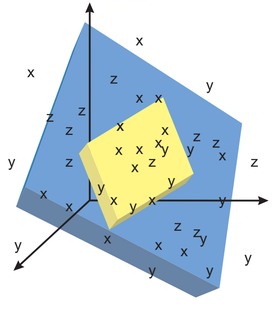
Coherent Synthesis™

Coherent Synthesis is a complete range of instrumentation, knowledge-based systems, optimized reagents and software.

SmithSynthesizer™

- Part of Coherent Synthesis
- Designed for organic synthesis
- Highly reproducible results
- Safe system
- Reaction volumes up to 5.0 mL
- Specially designed vials and caps
- Precise temperature and pressure control
- Automated for overnight runs
- Stirring

Major advantages



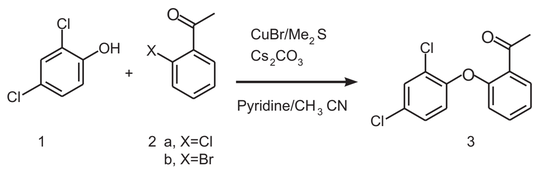
- Expanded reaction diversity
- "Impossible" reactions possible
- Rapid testing of creative ideas
- Shorter reaction times
- Higher yields, improved purity
- Less amount of reagents
- Less reactive reagents
- Increased productivity
- Reproducible results

Synthesis

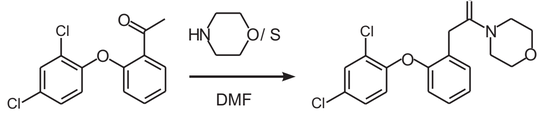
Using the automated SmithSynthesizer™, several pharmacologically active compounds have been synthesized in order to show the versatility of microwave heating, high temperature reactions, and high pressure reactions. Compared to conventional methods, microwave heating often gave higher reaction yields due to e.g. less degradation of reaction components and less formation of bi-products. Furthermore, sensitive reagents could be replaced with less reactive ones, and the amount of reagents needed could often be reduced. Synthesis of Atenolol[1,2], Fenclofenac[3,4], Fluoxetine[5-7], and Fenbufen[8] involved for example the Willgerodt-Kindler, Mitsunobu, and Friedel-Crafts reactions. The Mitsunobu reaction was also performed using a solid supported reagent.

Fenclofenac

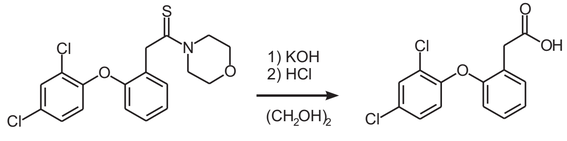
Fenclofenac, is an anti-inflammatory agent.



Coherent Synthesis™: 88% (2b, 150 °C/30 min)
Conventional heating: 45% (2a, Cu (s), 125 °C/24 h)



Coherent Synthesis™: 66% (150 °C/30 min)
Conventional heating: 75% (morpholine, 129 °C/24 h)

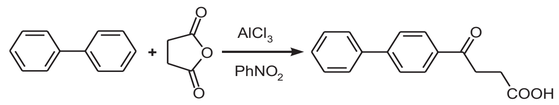


Coherent Synthesis™: 89% (200 °C/30 min)
Conventional heating: 93% (MeOH, 65 °C/72 h)

	Overall yield	Total time
Coherent Synthesis™:	52%	1.5 h
Conventional heating:	37%	4 days

Fenbufen

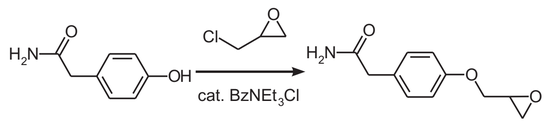
Fenbufen, is an anti-inflammatory and analgesic agent.



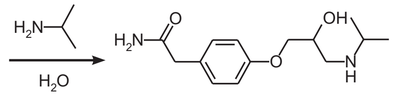
Coherent Synthesis™: 61% (80 °C/20 min)
Conventional heating: 70% (23 °C/4 days)

Atenolol

Atenolol is a b_1-selective (cardioselective) adrenoreceptor blocking agent and is used for treatment of hypertension and angina.



Coherent Synthesis™: 70% 180 °C/5 min)
Conventional heating: ref 1 (95-100 °C/6 h)
ref 2 (90 °C/3 h)

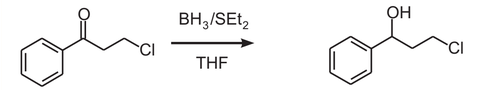


Coherent Synthesis™: 93% (130 °C/10 min)
Conventional heating: ref 1 (110 °C/12 h)
ref 2 (40 °C/2 h)

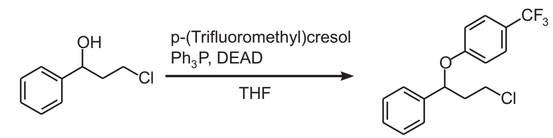
	Overall yields	Total time
Coherent Synthesis™:	65%	15 min
ref 1	-	18 h
ref 2	62%	5 h

Fluoxetine

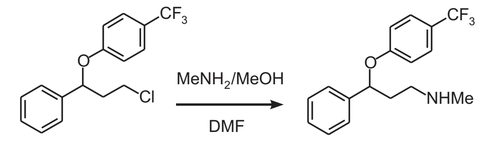
Fluoxetine, is a selective serotonin re-uptake inhibitor used as an anti-depressant.



Coherent Synthesis™: 99% (100 °C/2 min 20 s)
Conventional heating: 85%[6]



Coherent Synthesis™: 78% (120 °C/5 min)[7]
Conventional heating: 65% (23 °C/18 h)



Coherent Synthesis™: 69% (150 °C/5 min)
Conventional heating: 93% (130 °C/3 h)

Conclusion

From the syntheses described here, using microwave heating, it has been shown that ;

- **Higher yields in shorter times are achieved compared to conventional heating - minutes instead of hours**
- **Lesser amount of reagents can often be used**
- **The microwave technology is compatible with the use of solid supported reagents**

personalchemistry

References

1. Barret, A. M., *et al.* US patent US 3,934,032, Jan 20, **1976**. Barret, A. M., *et al.* US patent US 3,836,671, Sept 17, **1974**.
2. Jang, S. M. *et al.* US patent US 5,290,958, Mar 1, **1994**.
3. Atkinson, D. C., Godfrey, K. E., *et al. J. Med. Chem.*, **1983**, 26, 1353-1360.
4. German Patent 2,117,826 (Reckit&Colman) **1971**.
5. Brown, H. C., *et al. J. Org. Chem.*, **1988**, 53, 2916-2920.
6. A different reduction method was used compared to reaction using microwave heating, see ref 5.
7. The use of polymer supported triphenylphosphine yielded 1-chloro-3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propane in 64% over the first two steps. Conditions: 120 °C/300s.
8. Tomcufcik, A. S., *et al.* US patent US 3,784,701, Jan 8, **1974**.