An efficient and fast procedure for the Hantzsch dihydropyridine syntheses using Coherent Synthesis™

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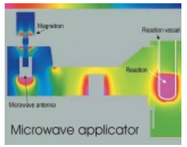
Introduction

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.

Single-mode focused microwave cavity

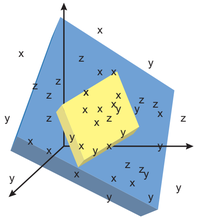


The Smith Synthesizer

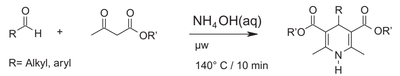
- Designed for organic synthesis
- Highly reproducible results
- Safe system
- Reaction volumes up to 5.0 mL
- Specially designed vials and caps
- Precise temperature and pressure control
- Automated for overnight runs
- Stirring

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



Hantzsch synthesis



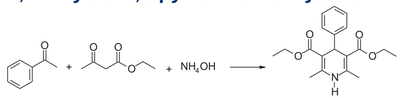
The preparation of 1,4-dihydropyridines by classical Hantzsch synthesis[1], a one-pot condensation of an aldehyde with alkyl acetoacetate and ammonia was developed more than hundred years ago. In the forties the interest for this substance class increased due to their pharmacological activity[2]. 4-Aryl-1,4-dihydropyrdines form an important class of calcium channel antagonists[3].

When sterically hindered aldehydes are employed in classical Hantzsch synthesis, long hours of reflux are needed, but still the yields are generally low[4],[5]. Reactions assisted with microwave dielectric heating usually gives shorter reaction times and often higher yields compared to conventional methods[6] and has lately become a popular method. In order to evaluate the possibility to increase the yield we used a Smith Synthesizer™ from Personal Chemistry, a mono-mode microwave synthesizer with both temperature and pressure control.

Microwave assisted Hantzsch synthesis has been described earlier by Alajarin *et al*[7] using a domestic microwave oven and sealed teflon bombs and the reaction times were decreased from more than 12 hours to 4 minutes but the yields were not improved compared to those obtained by conventional heating. In domestic microwave ovens, lacking temperature control, the temperature will increase with time when the power is constant. Increased temperature also implies increased pressure, which could induce a risk for explosion when sealed tubes are used. Heating at a fixed power of 400 W for 4 min, appeared for Alajarin *et al* to be the best compromise between efficiency and safety. The teflon bombs used were deformed when running at 500 W.

Our results show that for microwave assisted synthesis of 1,4-dihydropyridines temperature control is essential. The use of the Smith Synthesizer made it possible to both increase the yields and still have a short reaction time.

Optimisation of reaction condition for the synthesis of 4-phenyl-2,6-dimethyl-1,4-dihydro-3,5-pyridinecarboxylates

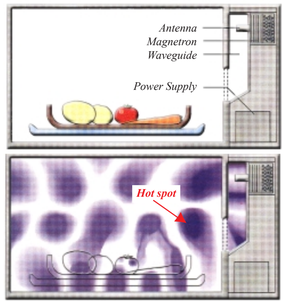


eq.	eq.	eq.	temp/time	yield(%)
1	2.2	1.2	110° / 10 min	55 [a]
1	2.2	1.2	120° / 20 min	65 [a]
1	3.0	2.0	120° / 20 min	70 [a]
1	5.0	2.0	120° / 20 min	86 [a]
1	5.0	2.0	140° / 10 min	84 [b]
1	5.0	2.0	160° / 10 min	76 [a]

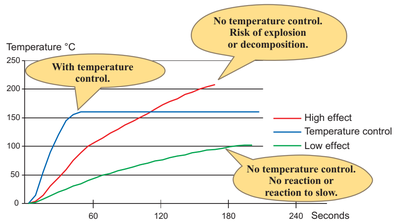
[a] tot.volym 2.6 mL, solvent: 25% NH_4OH_{aq}, [b] tot.volym 5.0 mL, solvent: 25% NH_4OH_{aq}, [c] tot.volym 5.0 mL, solvent: ethanol.

Problems with the use of domestic microwave oven in organic chemistry

- No temperature control or pressure control
- The heating pattern in a multi mode cavity
- Low reproducibility

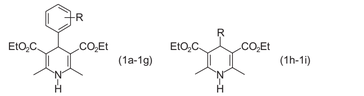


The effect of temperature control



The function of the aldehyde

To study the function of the aldehyde in this reaction, various substituted benzaldehydes and some aliphatic aldehydes were treated with ethyl acetoacetate and aqueous ammonium hydroxide under the condition found for entry V, Table 1.

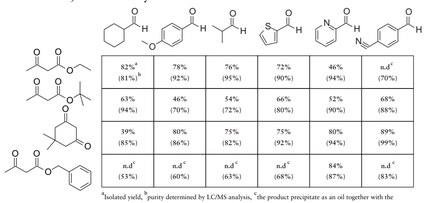


Compound	R	Smith Synth.[a] temp °C	time (min)/yield	dom. microwave[b] time (min)/yield	reflux[c] time (min)/yield	autoclave[d] time (min)/yield
1a	H	140	10 / 84%	4 / 52%	720 / 50%	—
1b	2-NO_2	150	10 / 63%	4 / 34%	720 / 50%	—
1c	2-OCH_3	150	10 / 68%	4 / 21%	720 / 15%	—
1d	2-Cl	140	10 / 81%	4 / 55%	720 / 39%	1020 / 92%
1e	2-CH_3	140	15 / 66%	—	720 / 72%	1500 / 70%
1f	2-Br	140	10 / 51%	—	—	—
1g	3,4,5-OCH_3	140	15 / 63%	—	—	—
1h	cyclohexyl	140	10 / 71%	—	720 / 38%	—
1i	$CH_3(CH_2)_5$	140	10 / 97%	—	720 / 26%(n-Hexyl)	—

[a] tot. volume ~2.5 mL, solvent: 25% NH_4OH_{aq}, [b] effect 400 W, solvent: ethanol, [c] solvent: ethanol, [d] temp: 110° C, solvent: ethanol

Library production

Since short reaction times, high yield and easy work-up procedure is our ambition we used the developed protocol to synthesize a small library of 24 compound. In order to increase the diversity we used 6 different aldehydes and 4 different β-keto esters or 1,3 dicarbonyls substrate.



82%[a] (81%)[b]	78% (92%)	76% (95%)	72% (90%)	46% (94%)	n.d[c] (70%)
63% (94%)	46% (70%)	54% (72%)	66% (80%)	52% (90%)	68% (88%)
39% (85%)	80% (86%)	75% (82%)	75% (92%)	80% (94%)	89% (99%)
n.d[c] (53%)	n.d[c] (60%)	n.d[c] (63%)	n.d[c] (68%)	84% (87%)	n.d[c] (83%)

[a]Isolated yield, [b]purity determined by LC/MS analysis, [c]the product precipitate as an oil together with the starting material giving a yield higher than 100%

After the reaction the samples were evaporated in a Savant Speed-vac. The residues were recrystallised from ethanol and water. All 24 compounds were formed in moderate to good yield (39%-89%, found after recrystallisation) and with low to excellent purity (53%-99% determined by LC/MS).

Conclusions

Microwave Assisted Organic Synthesis will have an impact on both Medicinal Chemistry and on Combinatorial Synthesis [8].

Characteristic

- Applicability to a wide range of organic reactions
- Simple reaction setup, uniform conditions
- Very short reaction times
- Increased yields, no excess reagents, decreased side products

Impact

- Increased diversity of libraries
- Simplified automation
- Dramatically increased synthetic throughput
- Simplified purification

References

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