Scalability in Microwave-Assisted Organic Synthesis

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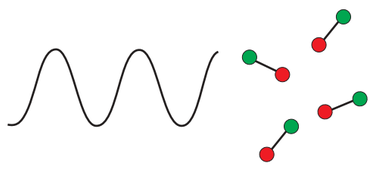
Introduction

Microwave-assisted organic synthesis has been used for over 10 years, resulting in over 1000 publications. The introduction of Coherent Synthesis™ enabled temperature and pressure control, and – more importantly - reproducibility and safety. In closed systems allowing the development of high pressures, the organic solvents can be heated to temperatures 2-3 times their respective boiling points, which allows for much (a hundredfold) shorter reaction times than those obtained in open microwave systems. Compared to conventional methods, microwave heating often provides higher reaction yields as a result of, for example, less degradation of reaction components and the formation of fewer bi-products.

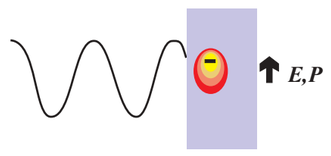
Mechanisms of microwave heating

Dipolar oscillation



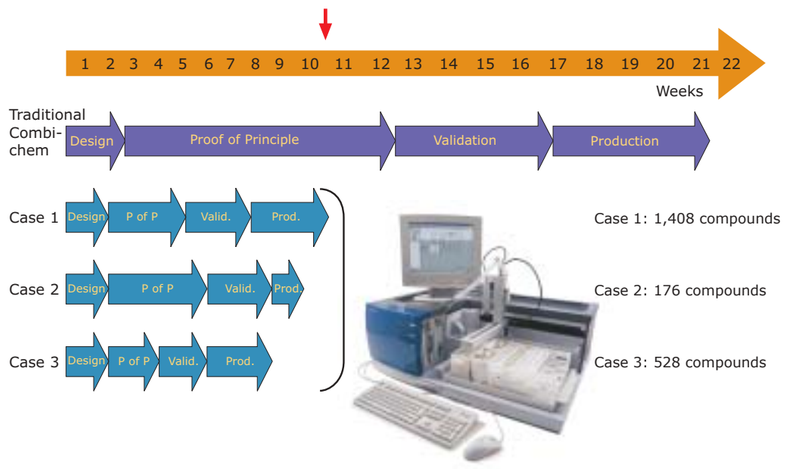
The phase difference between the field and dipole polarizations causes energy to be lost from the dipole. The energy is converted to heat by random collisions.

Ionic conduction



The electric field component of the wave forces the charged particles in the material to move back and forth. The energy is again converted to heat by random collisions.

High quality libraries in half the time



Source: Background data was presented by Dr. Chris Sarko, Boehringer Ingelheim at ACS National Meeting, San Diego, April 2001.

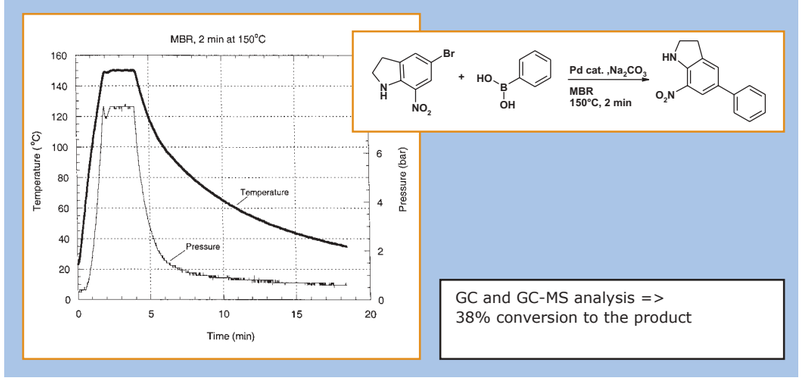
Scalability

In order to demonstrate the feasibility of scaling up SmithSynthesizer™ reactions through duplication of the heating regimen, five different reactions were carried out on a Microwave Batch Reactor (MBR) prototype. The results shown here indicate the scalability of Coherent Synthesis™.

Proof of principles 1(5): 50-fold scale-up

Suzuki Reaction of a bromodihydroindole with phenyl boronic acid

The MBR was charged with phenylboronic acid (0.61 g; 5 mmol) dissolved in 1,2-dimethoxyethane / water / ethanol (7:3:2; 15 ml), 5-bromo-7-nitroindoline (1.46 g; 6 mmol) dissolved in 1,2-dimethoxyethane (43.8 ml), stock solvent system [ethanol / water (2:3); 31.3 ml], sodium carbonate (0.64 g; 6 mmol) in water (3 ml), and bis(triphenylphosphine)-palladium (II) chloride (37 mg). The vessel was purged with nitrogen and the reaction mixture heated at 150°C for 2 minutes, with stirring. After cooling, the product mixture was filtered through celite, extracted with 5 M HCl (50 ml) and extracted with diethyl ether (150 ml).

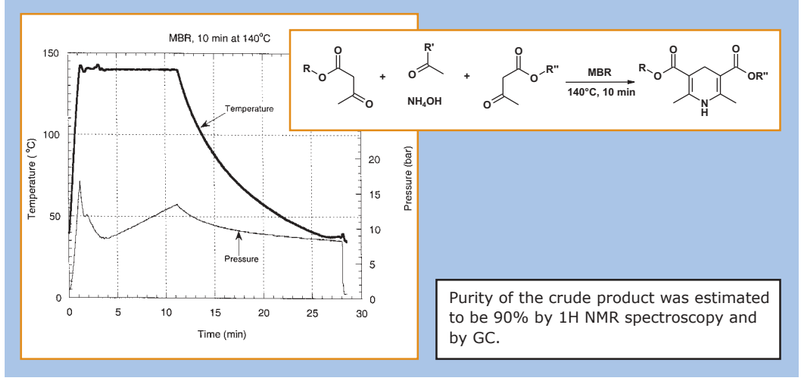


GC and GC-MS analysis =>
38% conversion to the product

Proof of principles 2(5): 50-fold scale-up

The Hantzsch Reaction of benzaldehyde with ethyl acetoacetate and 25% aqueous ammonium hydroxide

The MBR was charged with benzaldehyde (13.0 g, 0.123 mol), ethyl acetoacetate (80.0 g, 0.615 mol) and ammonium hydroxide (25% in H_2O, 8.6 g, 0.246 mol). The reaction mixture was irradiated and kept for 10 minutes at 140°C. After cooling (the vessel was vented before opening), pale yellow solid was filtered off (20.0 g). The mother liquor, on standing, gave two more crops of crystalline product which were filtered off (6.4 g).

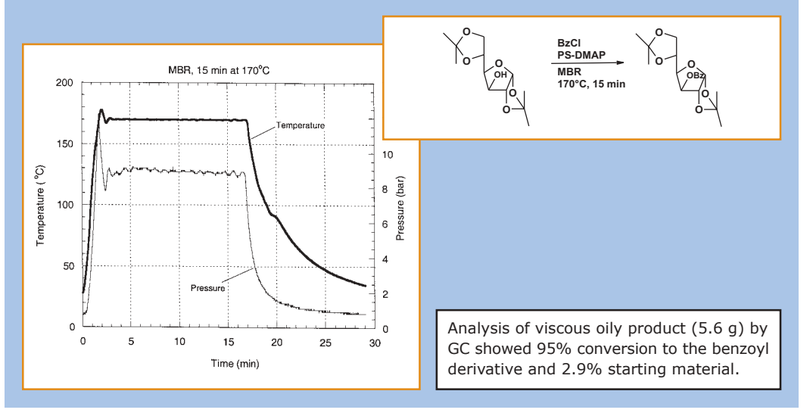


Purity of the crude product was estimated to be 90% by 1H NMR spectroscopy and by GC.

Proof of principles 3(5): 40-fold scale-up

Benzoylation of diacetone glucose with benzoyl chloride catalysed by polystyrene linked dimethylaminopyridine

The MBR was charged with diacetone-D-glucose (4.0 g, 15.4 mmol), benzoyl chloride (4.3 g, 30.4 mmol), polystyrene-linked dimethylaminopyridine (20.5 g, 61.6 mmol) and acetonitrile (80 ml). The reaction mixture was microwave-irradiated for 15 minutes at 170°C. After cooling, the resin was filtered off and the solvent evaporated.

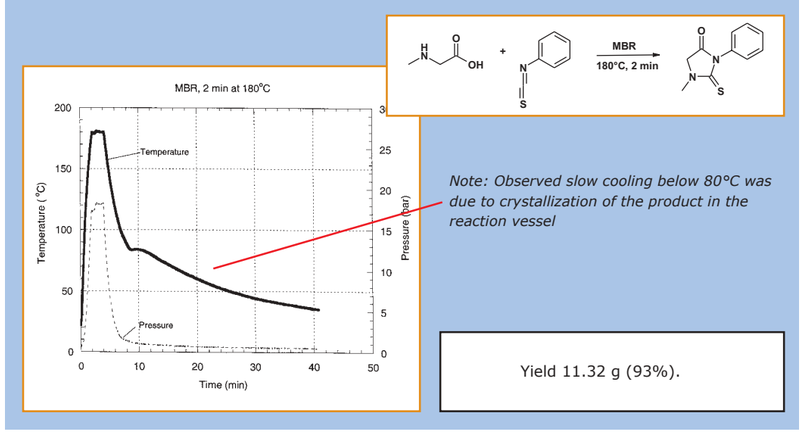


Analysis of viscous oily product (5.6 g) by GC showed 95% conversion to the benzoyl derivative and 2.9% starting material.

Proof of principles 4(5): 60-fold scale-up

Synthesis of a Thiohydantoin

Sarcosin (5.35 g, 60.05 mmol) and phenyl isothiocyanate (9.49 g, 70.2 mmol) were dissolved in ethanol (120 ml) and placed in an MBR vessel. The reaction mixture was irradiated for 2 minutes at 180°C. After cooling, the product was filtered and washed with ethanol/water mixture then dried under vacuum.



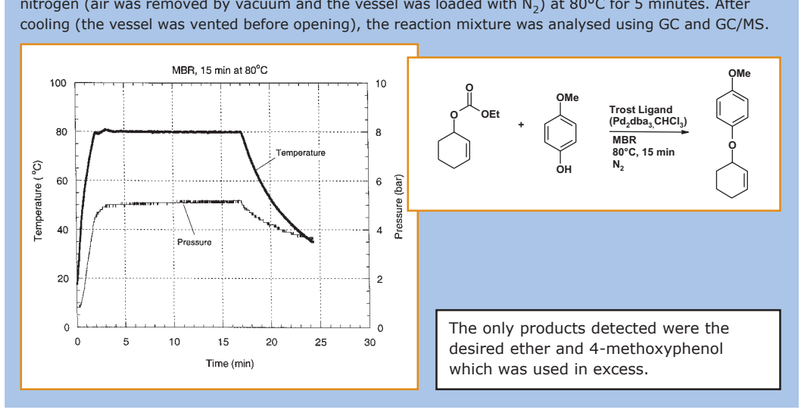
Note: Observed slow cooling below 80°C was due to crystallization of the product in the reaction vessel

Yield 11.32 g (93%).

Proof of principles 5(5): 40-fold scale-up

Palladium catalysed asymmetric alkylation of 4-methoxyphenol with cyclohex-2-enyl carbonate in the presence of Trost's catalyst

Pd_2dba_3-$CHCl_3$ (0.1068 g, 0.104 mmol), Trost's ligand (0.2132 g, 0.308 mmol) and ethyl 3-cyclohexenyl carbonate (7.56 g, 44.4 mmol) were dissolved in CH_2Cl_2 (40 ml) and stirred at room temp, under nitrogen for 15 minutes. Then a solution of 4-methoxyphenol (8.0 g, 64.4 mmol) in CH_2Cl_2 (40 ml) was prepared, and the solutions were mixed and loaded into a vessel for the MBR. The reaction was performed under nitrogen (air was removed by vacuum and the vessel was loaded with N_2) at 80°C for 5 minutes. After cooling (the vessel was vented before opening), the reaction mixture was analysed using GC and GC/MS.



The only products detected were the desired ether and 4-methoxyphenol which was used in excess.

SmithSynthesizer™

- Part of Coherent Synthesis™
- Designed for organic synthesis
- Highly reproducible results
- Automated for overnight control
- Reaction volumes up to 5.0 ml
- Specifically designed vials and caps

The First Prototype of the Batch Reactor

Specifications

- 350 ml
- 260°C
- 100 Bar
- 100-1200W
- Overshoot <3°C
- Stability <0.5°C
- Safety valves, Safety Interlocks

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