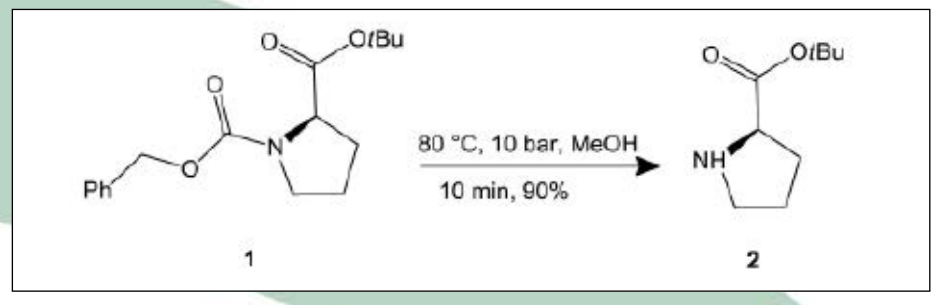
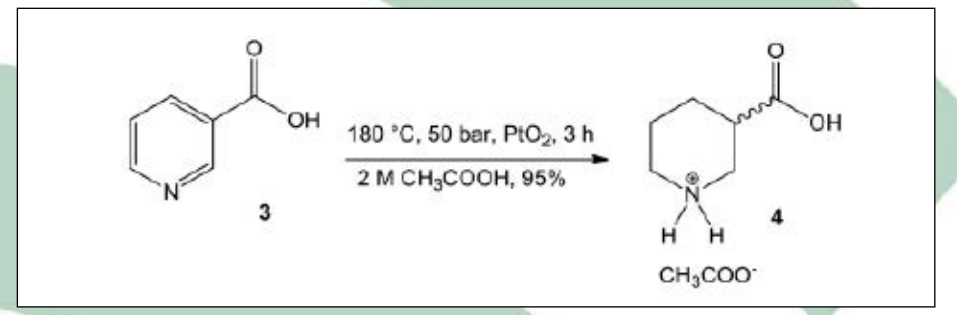
Microwave Hydrogenations

Large-Size, High Pressure Microwave Reactor

Microwave hydrogenations are a useful tool in multistep syntheses of complex organic compounds. However, in most reactors currently available, the pressure and the temperature ranges that can be applied are limited. Here we demonstrate the cleavage of a Cbz-protecting group, dearomatisations, fast hydrogenations of a double bond and the hydrogenation of a thiophene derivative using a microwave reactor.



Scheme 1: Cleavage of Cbz-protected tert.-butyl pyrrolidine carboxylate 1



Scheme 2: Hydrogenation of nicotinic acid 3

Introduction

Metal-catalyzed reactions are a common tool in the syntheses of complex organic compounds. With microwave support these reactions are often faster and result in better yields. Typical applications of metal-catalyzed reactions involve the formation of heterocyclic ring systems [1] or hydrogenations. The first hydrogenation with microwave irradiation was published in 1993 [2] using formic acid as hydrogen source, while the first work of microwave-enhanced hydrogenations with H_2 under pressure was published in 2005 [3a]. Since then, microwave supported hydrogenations have made a rapid progress [3b-g]. In this paper, we demonstrate how hydrogenations of aromatic rings and sterically hindered double bonds, as well as deprotection reactions can benefit from the application of high temperature and high pressure.

Results

The cleavage of the benzyloxycarbonyl (Cbz) protecting group can be quite a challenge requiring long reaction times. As a representative example, we have chosen the Cbz cleavage from a tert-butyl pyrrolidine carboxylate 1 which is an important intermediate for the synthesis of peptides (scheme 1) [4]. In a conventional autoclave, the reaction takes 60 min at 80 °C and 10 bar. Using the high pressure microwave reactor (synthwave, MLS = Microwave B) under the same conditions, the reaction is already completed in 10 min. In both cases the yield is 90 %.

In the second example nicotinic acid was hydrogenated using PtO_2 in acetic acid to give piperidine carboxylate 4 (scheme 2). For optimization of the conversion time the reaction was monitored by FTIR spectroscopy as described previously [5]. After 3 h the FTIR spectrum shows the complete disappearance of the =CH signal at 3070 cm^{-1} and the appearance of the NH_2^+ absorption bands at 2990 to 2400 cm^{-1}. Longer reaction times did not affect the yield.

Hydrogenolytic dearomatisation of an aromatic ring containing no heteroatoms is a challenging organic transformation. We explored the hydrogenation of phenylalanine 5 by means of Rh/C as a catalyst to give (2S)-amino-cyclohexylacetic acid 6 (scheme 3). Using the high-pressure reactor, at 180 °C and 60 bar hydrogen pressure, 6 could be obtained in nearly quantitative yield (99 %) in only 3 h reaction time.

Strychnine 7 contains an indoline ring system in addition to a separated double bond in the oxepine ring and can be theoretically hydrogenated in both functionalities (scheme 4). We aimed to explore the influence of different catalysts, reaction times, and hydrogen pressures on the selectivity of hydrogenation. However, no matter which conditions were chosen (table 1), only the double bond was hydrogenated, and the aromatic ring was left untouched. The best yield of dihydrostrychnine 8 was achieved at 180 °C, 55 bar hydrogen pressure and 6 min reaction time using Pd/C as catalyst. Replacing Pd/C by Ru/C, Rh/C

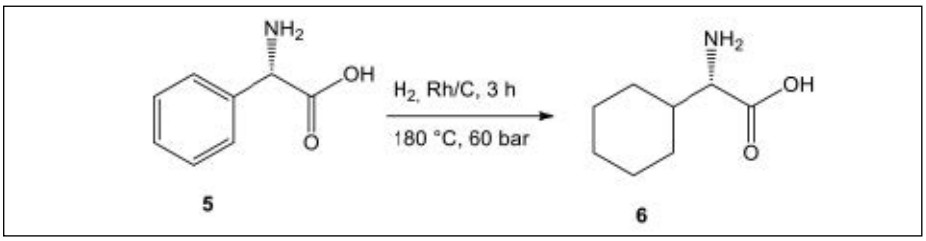
Table 1: Reaction conditions for the hydrogenation of strychnine 7

reactor	catalyst	temp./pressure [°C]/[bar]	Time [h]	Yield [%] / compound
Autocleavea	H_2, Pd/C	25/5	48	94/8
Microwave A	H_2, Pd/C	90/20	2	98/8
Microwave B	H_2, Pd/C	180/55	0.1	99/8
Microwave B	H_2, Ru/C	180/55	1	96/8
Microwave B	H_2, Rh/C	180/55	1	95/8
Microwave B	H_2, Pt/C	180/55	1	96/8
Microwave B	H_2, PtO_2	200/60	3	90/8
Microwave B	H_2, PtO_2	270/60	4.5	52/9

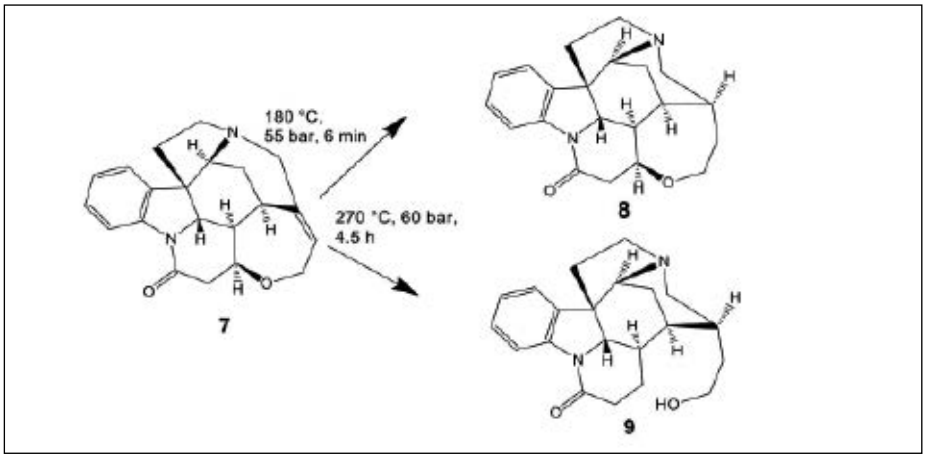
[a] ref.5, Microwave A = Ethos 1600, MLS, ref. 2a. Microwave B = Synthwave MLS

and Pt/C and prolonging the reaction time to 1 h slightly reduced the yield. Of note, at temperatures higher than 250 °C decomposition of dihydrostrychnine could be observed. For example, using PtO_2 at 270 °C and 60 bar hydrogen pressure, tetrahydroisostrychnine 9, resulting from the cleavage of the hexahydrooxepine ring of 8, was isolated as a major product. In comparison to the previously reported multi-step synthesis of 9 [6], our one-step procedure is demonstrably more efficient at providing gram quantities of the product in higher yield.

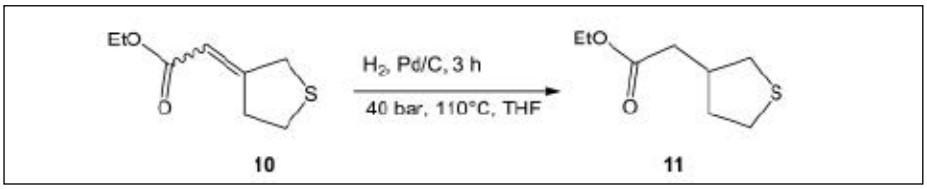
Catalytic hydrogenations of sulphur containing compounds often fail because of the poisoning of the metal catalyst surface. For instance, attempts to reduce the exocyclic double bond of the thiophene analog 10 by catalytic hydrogenation were reported to be unsuccessful, and only an alternative procedure employing *in situ* generated nickel boride gave the desired product 11 in 64–68 % yield [9] (scheme 5). We examined the latter reaction comparing the yields of the conventional autoclave hydrogenation to those achieved in our microwave reactor in different solvents at different temperatures and hydrogen pressures. The results are compiled in Table 2. While in the conventional autoclave hydrogenation in ethanol at 15 bar hydrogen pressure and 70 °C, a very long reaction time of 116 h was required to obtain 11 in 77 % yield, a comparable yield could be achieved in only 3 hours reaction time in a microwave reactor at 110 °C and 40 bar H_2 pressure using THF as solvent. These findings might be caused by the following effects: The poisoning of the metal catalyst is reversible at the beginning of the reaction, [8a] but becomes irreversible during the course of the reaction because no reactivation of the catalyst is possible in a conventional batch autoclave. If a hydrogenation is carried out in a microwave reactor there is an interaction between the metallic catalyst and the microwave irradiation. When a microwave photon meets a metal particle, the particle becomes very hot [8b]. It may be speculated that the metal poisoned surface is cleaned at the high temperatures and is reactivated, resulting in shorter reaction times. Moreover, THF is a solvent which absorbs less microwave radiation than EtOH and MeOH, respectively [10]. That means that the penetration depth of microwave radiation in THF is higher than in alcohols and thus more poisoned catalyst particles are able to interact with the irradiation. Hence, possibly more poisoned particles are reactivated. This finding can be regarded as a direct microwave effect, but further investigation is needed to prove this effect.



Scheme 3: Hydrogenation of (L)-phenylalanine 5



Scheme 4: Hydrogenation of strychnine 7



Scheme 5: Hydrogenation of ethyl 2-(dihydrothiophen-3(2H)-ylidene)-acetate 10

Taken together, these results show the large-size, high pressure microwave reactor employed here for several applications, was found to be useful for hydrogenations which are difficult to carry out in a conventional batch reactor. The reaction times were always shorter and the obtained yields higher in the majority of cases.

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References are available from the author
E. Heller: eheller@pharmazie.uni-wuerzburg.de

Table 2: Reaction conditions for the hydrogenation of ethyl 2-(dihydrothiophen-3(2H)-ylidene)-acetate 10 using H_2, Pd/C

reactor	solvent	temp./pressure [°C]/[bar]	Time [h]	Yield of 10 [%]
Autoclave	EtOH	70 / 15	18	40
Autoclave	EtOH	70 / 15	116	77
Autoclave	MeOH	70 / 15	23	33*
Microwave B	EtOH	110 / 40	10.5#	53
Microwave B	MeOH	110 / 40	10#	55*
Microwave B	THF	110 / 40	3	71

*Due to transesterification, a mixture of methoxy and ethoxyester was obtained.
Fresh catalyst was added after 2 h, 5 h and 8 h

Authors
Eberhard Heller[a,c], Amelie Gutmann[a], Georg Hiltensperger[a], Werner Lautenschläger[b], Martin J. Lohse[c], Caroline Schad[a], Tanja Schirmeister[d], Florian Seufert[a], Darius P. Zlotos[e], Ulrike Holzgrabe[a]
[a] Institute for Pharmacy and Food Chemistry, University of Würzburg, Germany
[b] Mikrowellenlaborsysteme, Leutkirch, Germany
[c] Institute for Pharmacology and Toxicology , University of Würzburg, Germany
[d] Institute for Pharmacy and Biochemistry, University of Mainz, Germany
[e] The German University in Cairo, Egypt

Contact
Institute for Pharmacy and Food Chemistry
University of Würzburg, Germany
Tel.: 0931-3185467
Fax: 0931/3185494
eheller@pharmazie.uni-wuerzburg.de