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Microwave-enhanced hydrogenations at medium pressure using a newly constructed reactor

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Abstract—The newly constructed reactor for hydrogenations in microwave fields allows to work out the syntheses up to 25 bar. This is shown for the synthesis of intermediates of active agents. In order to demonstrate the superiority of the microwave-assisted hydrogenation, the reactions are compared with classical hydrogenations. The following reactions were carried out: dearomatization, debenzylation, azide hydrogenation and the hydrogenation of strychnine.

The concept of microwave-assisted organic synthesis is well established for a huge variety of reactions which were recently summarized in Microwaves in Organic Synthesis.[1] However, only a few microwave-enhanced hydrogenations were reported, for example,[2–6] whereas Yanagida and co-workers[4a] and Pillai et al.[4b] used hydrogen gas at normal air pressure for the reaction, other authors applied solid hydrogen donors. In this paper we want to report on hydrogenation reactions performed in a newly constructed reactor with hydrogen gas at medium pressure (up to 25 bar). In order to demonstrate the superiority of the microwave-assisted hydrogenation reaction temperature, time and yield will be compared to the results obtained under classical conditions. The following hydrogenations were carried out: dearomatization, debenzylation, azide hydrogenation and hydrogenation of strychnine. All synthesized compounds are intermediates on the synthesis pathway to pharmacologically active agents, which were synthesized in our laboratory both by the classical way and by microwave irradiation.

The reactors that are commercially available for pressure reactions in the microwave field cannot be used for this purpose. Thus, a new hydrogenation reactor, taking this reactor as a starting point, was constructed and optimized in collaboration with MLS/Milestone for a Milestone Ethos 1600 during the course of the described reactions. The reactor consists of a polytetrafluoroethylene (PTFE) tube (4.0 cm inner diameter, 25.5 cm length) which is covered by a polyetheretherketone (PEEK) tube to protect the system from explosions. The gas inlet including a back pressure valve, preventing the back flow of the reaction mixture into the hydrogen tube is on the bottom side of the microwave oven outside of the reaction room. On the top of the tube again outside of the reaction room, a pressure sensor, a temperature sensor, an excess pressure valve (30 bar) and an outlet valve are located. The Ethos 1600 system is equipped with a solvent sensor (QP-sensor). If there is a leakage in the vessel and solvent vapour penetrates into the cavity the microwave heating will stop immediately.[7] The minimum volume of the solution is 20 mL and the maximum 200 mL.

Dearomatization: pyridine-2-carboxylic acid **1** was hydrogenated to give pipecolic acid **2**, which is used as starting material in the synthesis of AFDX 384 derivatives[8] which are allosteric modulators of the muscarinic M_2-receptor. The conditions of the microwave-assisted reaction (25 bar, 125 °C and 1 h) were different from the conditions classically described in Ref. 9 (2.5–60 bar, 25–160 °C, 2–24 h). However, a 99% yield was achieved (85–100%[9]) and the reaction time was substantially shortened.

The piperidinium compound **4** is a key intermediate for the synthesis of a series of acetylcholinesterase inhibitors of the oxime type.[10] Compound **4** can be obtained by

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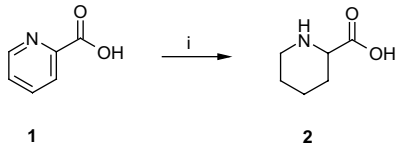
hydrogenation of the corresponding pyridinium bromide **3**. Whereas 72 h are needed at 50 bar hydrogen and 25 °C for quantitative reaction (85% yield), the reaction is completed after 1.5 h at 20 bar and 60 °C. In addition an almost 100% of **4** was obtained and logically no working-up procedure was necessary.

Debenzylation: within the same reaction pathway leading to the AFDX 384 derivatives,[8a] a deprotecting step is necessary. *N*-Debenzylation is usually performed at 50 bar H_2 and 60 °C. After 18 h a quantitative debenzylation could be observed.[8a] Carrying out the reaction in the microwave reactor the deprotection is already complete after 2 h.[16]

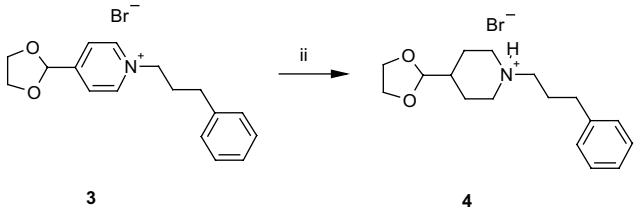
Azide hydrogenation: (*S*)-5-hydroxy-2-piperidone **8** is a key intermediate in the synthesis of pipecolic acids of interest as GABA antagonists.[11] As reported by Herdeis,[12] **8** can be obtained by a catalytic hydrogenation of azide **7**. After 3 h at 30 °C and a pressure of 3 bar, **8** could be isolated in 77% yield. Applying microwave-assisted hydrogenation resulted in 90% of the piperidone **8** already after 25 min.

Hydrogenation of strychnine: the natural product strychnine **9**, a starting material for the synthesis of caracurine compounds, which attract interest as highly potent allosteric modulators for the M_2-receptor, was hydrogenated to dihydrostrychnine **10** by Zlotos et al.[13] The hydrogenation was accomplished classically at 5 bar, 25 °C and 48 h to obtain 94% of **10**. By microwave heating the yield was even better (98%) and the reaction time was decreased to 2 h.

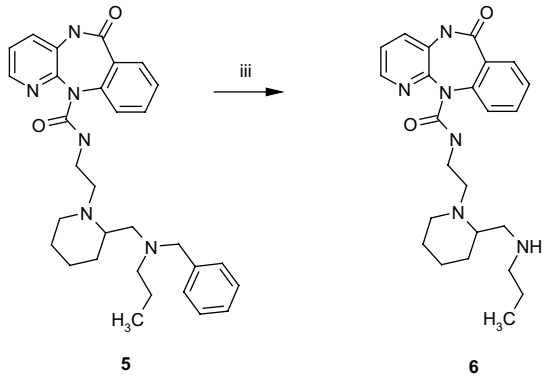
All the examples described herein clearly demonstrate that hydrogenations under microwaves led to substantially shorter reaction times (Schemes 1–5) and often better yields (Schemes 1–4). This cannot be explained by the higher temperatures applied in the microwave enhanced hydrogenations only, because hydrogenations



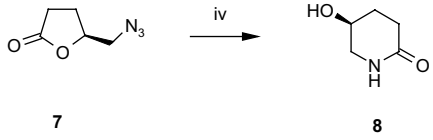
Scheme 1. Reagents and conditions: (i) EtOH, PtO_2, H_2, 25 bar, 125 °C, 1 h.



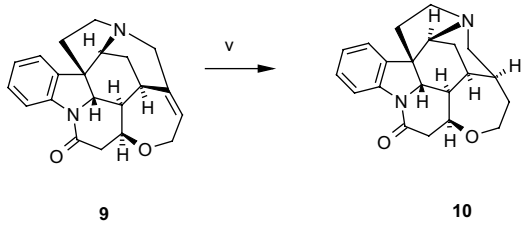
Scheme 2. Reagents and conditions: (ii) EtOH, PtO_2, H_2, 20 bar, 60 °C, 1.5 h.



Scheme 3. Reagents and conditions: (iii) EtOH, Pd–C, H_2, 25 bar, 125 °C, 2 h.



Scheme 4. Reagents and conditions: (iv) MeOH, Pd–C, H_2, 15 bar, 90 °C, 25 min.



Scheme 5. Reagents and conditions: (v) 10% acetic acid, Pd–C, H_2, 20 bar, 90 °C, 2 h.

using microwaves are not directly comparable to the classical way. Microwaves interact with the surface of the catalyst and create 'hot spots'. The catalyst surface is much hotter than the surrounding medium.[14] One may argue that microwaves interact only with reagents having a dipole moment. Even though the hydrogen in gaseous phase does not have a dipole moment, however, binding to the catalyst surface in a monomolecular layer a dipole moment can be induced.[15] Thus, the microwaves are able to interact with the hydrogen and catalyze the reaction.

We showed with these examples that catalytic hydrogenations at medium pressure with microwaves are new useful tools in the multi-step synthesis of active agents.

References and notes

1. *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002.
2. Al-Qahtani, M. H.; Cleator, N.; Danks, T. N.; Garman, R. N.; Jones, J. R.; Stefaniak, S.; Morgan, A. D.; Simmonds, A. J. *J. Chem. Res.* **1998**, 400–401.

3. Banik, B. K.; Barakat, K. J.; Wagle, D. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1999**, *64*, 5746–5763.
4. (a) Wada, Y.; Yin, H.; Kitamura, T.; Yanagida, S. *Chem. Lett.* **2000**, 632–633; (b) Pillai, U. R.; Sahle-Demessie, E.; Varma, R. S. *Green Chem.* **2004**, *6*, 295–298.
5. Desai, B.; Danks, T. N. *Tetrahedron Lett.* **2001**, 5965–5965.
6. Chappelle, M. R.; Kent, B. B.; Jones, S. R.; Lu, S.-Y.; Morgan, A. D. *Tetrahedron Lett.* **2002**, 5117–5118.
7. http://www.milestonesci.com/synth-tech.php.
8. (a) Holzgrabe, U.; Heller, E. *Tetrahedron* **2003**, *59*, 781–787; (b) Mohr, M.; Heller, E.; Ataie, A.; Mohr, K.; Holzgrabe, U. *J. Med. Chem.* **2004**, *47*, 3324–3327.
9. (a) Freifelder, M.; Robinson, R. M.; Stone, G. R. *J. Org. Chem.* **1962**, *27*, 284–286; (b) Shuman, R. T.; Ornstein, P. L.; Pascal, J. W.; Gesellchen, P. D. *J. Org. Chem.* **1990**, *55*, 738–741(c) Ito, K.; Mashiba, Y. *Jpn. Kokai Tokkyo Koho*, **1991**, JP 03002162 A2 19910108.
10. Alptuezuen, V.; Kapkova, P.; Baumann, K.; Erciyas, E.; Holzgrabe, U. *J. Pharm. Pharmacol.* **2003**, *55*, 1397–1404.
11. (a) Herdeis, C.; Heller, E. *Tetrahedron: Asymmetry* **1993**, *4*, 2085–2094; (b) Herdeis, C.; Heller, E. *Tetrahedron: Asymmetry* **1997**, *8*, 1115–1121.
12. Herdeis, C. *Synthesis* **1986**, 232–233.
13. Zlotos, P. D.; Buller, S.; Holzgrabe, U.; Mohr, K. *Bioorg. Med. Chem.* **2003**, *11*, 2627–2634.
14. *Microwaves in Organic Synthesis*; (a) Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; pp 366–368; (b) Zhang, X.; Hayward, D. O.; Mingos, D. M. P. *Chem. Commun.* **1999**, 975–976.
15. (a) Schlosser, E.-G.. *Heterogene Katalyse*; Verlag Chemie: Weinheim, 1972; pp 21–27; 114–124; (b) *Catalysis in Organic Syntheses*; Rylander, P. N., Greenfield, H., Eds.; Academic: New York, London, San Francisco, 1976; pp 1–48; (c) Tamaru, K. *Dynamic Heterogenous Catalysis*; Academic: New York, London, San Francisco, 1978; pp 34–37.
16. *Typical hydrogenation procedure in the microwave reactor*: 10 mmol (3.50 g) of the pyridinium compound **2** and 0.1 g of platinum on activated carbon (5% Pt) were diluted in 150 mL methanol. The solution was flushed with argon for 5 min to remove the oxygen. Hydrogen was filled until the reaction pressure of 20 bar was reached. The mixture was heated to 60 °C within 3 min. The temperature was kept constant for 1.5 h. The solution was cooled to 25 °C, the catalyst was filtered off and the solvent was evaporated to yield 3.55 g (100%) of 4-(1,3-dioxolan-2-yl)-*N*-(3-phenylpropyl)piperidine hydrobromide **4** as a colorless solid. The compound can be recrystallized from acetone/diisopropylether. However, this was not necessary for the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.29 (br, 1H, NH^+), 7.30–7.16 (m, 5H, aromat.), 4.79 and 4.64 (d, J = 5.6 Hz, 1H, O–CH–O), 3.70–3.60 (m, 2H, 7-H), 3.07–2.71 (m, 4H, 2-H, 6-H), 4.08–3.99 (m, 4H, O–$(CH_2)_2$–O), 2.68–2.16 (m, 7H, 3-H, 4-H, 5-H, 9-H), 1.76–1.69 (m, 2H, 8-H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 139.5 and 139.4 (C-10), 128.8 and 128.4 (C-11, C-12, C-14, C-14), 126.8 and 126.7 (C-13), 105.3 and 103.5 (O–CH–O), 65.2 and 65.1 (O–$(CH_2)_2$–O), 57.3 (C-7), 53.3 and 52.6 (C-2, C-6), 38.7 (C-4), 32.9 (C-9), 24.9 (C-8), 23.9 (C-3, C-5).