Microwave-Assisted Hydrogenation of Pyridines

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Abstract: Using a commercially available device for controlled introduction of hydrogen in a vial for reactions under microwave dielectric heating, we developed a protocol for the transformation of substituted pyridines into the corresponding piperidines. Complete reduction occurred in 40 minutes, or even less, on substrates that require 24–48 hours to be reduced under standard conditions. Moreover, the reduction proved to be as stereoselective as the corresponding reaction carried out at room temperature.

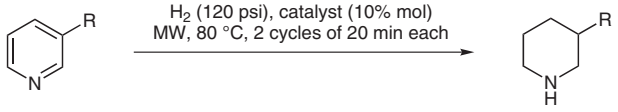
Key words: microwave, hydrogenation, piperidines, heterogeneous catalysis

The use of microwaves to heat organic reactions has gained considerable interest in the last 15 years. The main advantage of the use of microwave irradiation is the reduction of time required for chemical transformations. Moreover, the formation of byproducts is reduced, yields and often the purity of the final products are improved. Many kinds of transformations have been tested under microwave irradiation, in many instances giving better results than conventional heating.[1] Although microwave irradiation might seem simply an alternative for introducing energy into reactions, the use of this technology has launched a new concept in organic synthesis because the transmission and absorption of energy is different from conventional thermal heating. The temperature profiles achieved by microwave heating cannot easily be duplicated with traditional heating and allow kinetic control.[2–5] The success of this technique is confirmed by the number of scientific publications (and patents) that increases every year. Moreover, several reactions that use homogeneous and heterogeneous catalysis have been improved by the use of microwaves as the metal catalyst is the centre of high local dielectric microwave heating.[6]

Amongst different metal-catalyzed reactions tested inside a microwave cavity, hydrogenation can be considered as one of the most potentially useful. The highly efficient heating of the catalyst can be associated with the possibility of working under pressure, as most of the reactors for microwaves are tested to withstand the pressure developed by the solvent during heating. The microwave reaction tube can be considered as a potential small autoclave that could be used for reaction with gaseous reagents. Recently, Vanier described the use of microwaves to perform hydrogenation under moderate temperature and pressure.[7] Amongst different substrates that can be hydrogenated, pyridines are extremely interesting as the piperidines produced are important building blocks and intermediates for the synthesis of natural products or pharmacologically relevant compounds.[8] On the other hand, hydrogenation of pyridines often requires the use of high H_2 pressure with heating or long reaction times.[9]

Following our interest in microwave-assisted reactions with gaseous reagents,[10] we decided to explore the possibility to prepare differently substitued piperidines through hydrogenation of pyridines under microwave irradiation. We used the gas addition accessory for Discover Micro-

Table 1 Optimisation of the Procedure for Microwave-Assisted Hydrogenation



1 R = COOH
2 R = CH_2COOEt

3 R = COOH
4 R = CH_2COOEt

Entry	Pyridine	Solvent	Catalyst	Product, yield (%)[a]
1	**1**	EtOH	PtO_2	**3**, 98
2	**2**	EtOH	PtO_2	**4**, <5
3	**2**	THF	PtO_2	**4**, <5
4	**2**	$CHCl_3$	PtO_2	**4**, 65
5	**2**	EtOAc	PtO_2	**4**, 70
6	**2**	H_2O	PtO_2	**4**, 25
7	**2**	HCOOH	PtO_2	**4**, <5
8	**2**	AcOH	PtO_2	**4**, 98
9	**1**	AcOH	PtO_2	**3**, 98
10	**2**	AcOH	Pd/C (10 mol%)	**4**, 35
11	**2**	AcOH	$Pd(AcO)_2$	**4**, 20
12	**2**	AcOH	$Pd(OH)_2$/C (10 mol%)	**4**, 98
13	**2**	AcOH	Rh/C (5 mol%)	**4**, 98
14	**2**	H_2O	Rh/C (5 mol%)	**4**, 60
15	**2**	EtOH	$Pd(OH)_2$/C (10 mol%)	**4**, 10

[a] Isolated products.

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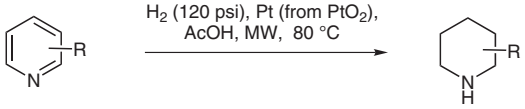
wave Synthesis System developed in collaboration with the Italian branch of CEM.[11]

As the only example of pyridine reduction described by Vanier was the hydrogenation of picolinic acid on PtO_2 in EtOH at 80 °C and under 100 psi of H_2, we started our investigation using these conditions. Picolinic acid[12] or nicotinic acid (**1**) were reduced to the corresponding piperidine carboxylic acids in very good yields after 20 minutes of exposure to microwaves (entry 1 in Table 1).

Unfortunately, when a differently substituted pyridine such as **2** was submitted to the same procedure, no reduction was observed even after 80 minutes of microwave irradiation. With the aim of finding more general reaction conditions, we explored different solvents and catalysts mantaining the same H_2 pressure, temperature, and time (see Table 1). Amongst standard solvents for reduction, acetic acid gave the best results in terms of conversion, yields, and purity of the reduced products. We tried also different heterogenous catalysts (see entries 10–15 in Table 1) and found that PtO_2, $Pd(OH)_2/C$ (10 mol%) and Rh/C (5 mol%) gave comparable results. However, the use of acetic acid as solvent was critical in order to have good yields of products (see entries 14 and 15, Table 1). Thus, we decided to investigate the hydrogenation of different pyridine substrates using the less expensive and more easily recoverable PtO_2 as the catalyst.

During the study on compounds **5**–**18** (Table 2) we observed that reaction reproducibility was low, as piperidine products were obtained in very different yields when repeating the reduction without any obvious change in the reaction conditions. Thus, we turned our attention to the nature of the catalyst finding that reduction conditions were completely reproducible if PtO_2 was reduced to Pt prior to addition of the pyridine substrate. This 'prereduction' was carried out in AcOH under H_2 (120 psi) and microwave dielectric heating at 50 °C for 15 minutes. To this mixture, the substrate dissolved in AcOH was added and, after refilling the vial with H_2, the reduction was carried out under standard conditions to give the required piperidines with more reproducible yields.[13]

Table 2 Reduction of Different Pyridine Substrates



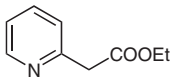
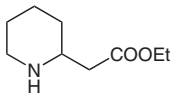
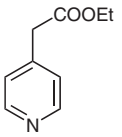
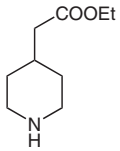
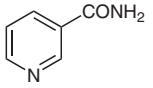
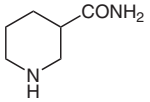
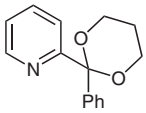
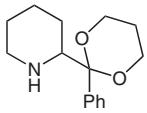
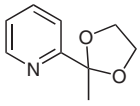
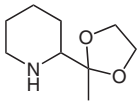
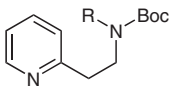
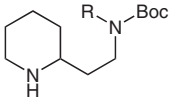
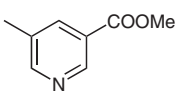
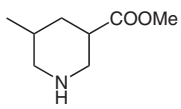
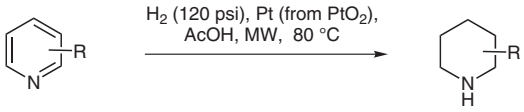
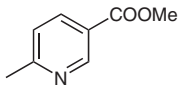
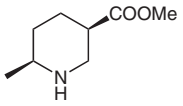
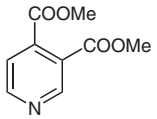
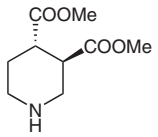
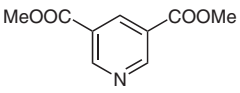
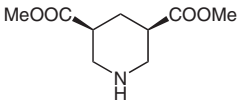
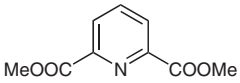
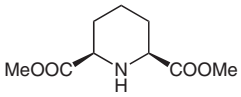
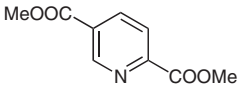
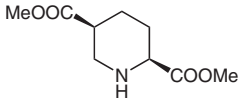
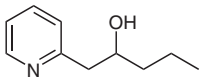
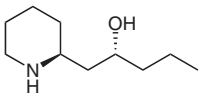
Entry	Pyridine		Conditions	Product (conversion)[a]		Yields (%)
1	**5**		20 min (1 cycle)		**19** (98%)	95
2	**6**		20 min (1 cycle)		**20** (98%)	94
3	**7**		20 min (1 cycle)		**21** (98%)	95
4	**8**		40 min (2 cycles, 20 min each)		**22** (98%)	95
5	**9**		20 min (1 cycle)		**23** (98%)	95
6	**10** R = H **11** R = Me		R = H: 40 min (2 cycles, 20 min each) R = Me: 20 min (1 cycle)		**24** (98%) **25** (98%)	93 95
7	12		40 min (2 cycles, 20 min each)		**26** (98%) (dr = 1:1)[b]	95

Table 2 Reduction of Different Pyridine Substrates (continued)



Entry	Pyridine	Conditions	Product (conversion)[a]	Yields (%)
8	**13** 	20 min (1 cycle)	 **27** (68%) (dr = 5:1)[b]	48
9	**14** 	60 min (3 cycles, 20 min each)	 **28** (98%) (dr = >99:1)[b]	94
10	**15** 	20 min (1 cycle)	 **29** (82%) (dr = 2:1)[b]	80
11	**16** 	40 min (2 cycles, 20 min each)	 **30** (80%) (dr = >99:1)[b]	78
12	**17** 	40 min (2 cycles, 20 min each)	 **31** (98%) (dr = 9:1)[b]	94
13	**18** 	40 min (2 cycles, 20 min each)	 **32** (92%) (dr = 2:1)[b]	85

[a] Conversion was determined by ^{1}H NMR analysis (COSY experiments) of the crude mixture. The value 98% indicates complete disappearance of the aromatic pyridine signals.
[b] Diastereomeric ratio was determined after transformation of the crude products into the corresponding tosylates that were separated by column chromatography.

The products prepared following this method (**19**–**32**) are listed in Table 2. The use of AcOH in connection with microwave dielectric heating gave remarkably selective results.[14] Acid-labile groups, such as 1,2-dioxolane and 1,2-dioxetane, were not deprotected (entries 4 and 5) and even the thermally and acid-labile Boc group survived (entry 6). In order to compare microwave dielectric heating with traditional heating, we reduced pyridine **11** in an autoclave under the same conditions used in the microwave experiments. After heating the solution for 20 minutes at 80 °C under 120 psi of H_2 on preformed Pt, we observed a conversion of 40% whereas 24 hours were required to reach a complete conversion when thermal heating was applied.[15]

Microwave-assisted hydrogenation was also stereoselective. Compounds **28** and **30** (entries 9 and 11 in Table 2) were obtained as a single diasteromer (*trans* and *cis*, respectively) and compounds **27** and **31** (entries 8 and 12, Table 2) were formed with a good diasteromeric ratio in favour of the *cis* isomer.[16] This result is comparable with the stereoselectivity observed when the same pyridines were submitted to hydrogenation at room temperature for longer time.[17] Analogously, the poor stereoselectivity observed in the formation of piperidines **26** and **29** was previously observed under standard conditions.[18] This stereochemical trend is consistent with a first reduction of the protonated C=N bond, likely protonated in the reaction medium, followed by rapid hydrogenation of the resulting more stable C=C bonds.[19]

In conclusion we have demonstrated that it is possible to achieve hydrogenation of the pyridine ring contained in different substrates in less than one hour of exposure to H_2 and microwave irradiation in AcOH. These conditions are compatible with the presence of acid-labile functional groups present on the molecule (as acetals or *tert*-butyl carbamate protection). Moreover, the microwave-assisted reaction was as stereoselective as the corresponding transformations carried out at room temperature[20] encouraging the extension of microwave dielectric heating to reactions that proceed through a substrate-controlled stereochemical path.

Acknowledgment

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References and Notes

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(10) Petricci, E.; Taddei, M. *Chemistry Today* **2007**, *25(3)*, 45.
(11) Petricci, E.; Mann, A.; Rota, A.; Schoenfelder, A.; Taddei, M. *Org. Lett.* **2006**, *8*, 3725; with this device it is possible to carry standard reactions in sealed tube, under nitrogen atmosphere, and under a reactive gas pressure up to 200 psi; see http://www.cem.com.
(12) Pipecolinic acid was obtained in 95% by reduction of picolinic acid with H_2 (100 psi) on PtO_2 in EtOH at 80 °C for 20 min as reported in ref. 7.
(13) ***N*-Methyl-2-(piperidin-2-yl)ethanamine (25) – General Procedure**
A suspension of PtO_2 (0.045 mmol, 10.3 mg, 10%mol) in AcOH (1.5 mL) was placed in the vial of a Discover Microwave Synthesizer and purged three times with H_2 (120 psi). The vial was submitted to microwave irradiation (200 W) at 50 °C for 15 min. The vial was vented, flushed with nitrogen, and then opened to introduce *N*-Boc-*N*-methyl-2-(pyridin-2-yl)ethanamine (**11**, 107 mg, 0.45 mmol). The vial was closed and purged again with H_2 (120 psi). The reaction mixture was then heated under microwave irradiation (200 W) at 80 °C (applying pulse cooling of the vial with a steam of air to avoid overheating) for 20 min. During this period we observed absorption of H_2 as the internal pressure of the vial decreased to 70 psi. After cooling to r.t. the reaction mixture was filtered through Celite®. The filter was washed with MeOH (2 mL) and the solution concentrated under reduced pressure. The crude was mixed with EtOAc (10 mL) and to this mixture solid Cs_2CO_3 (1.2 mmol, 390 mg) was added. The suspension was stirred at r.t. for 10 h, then filtered again through Celite® and the filter washed with additional EtOAc. The collected fractions were evaporated to give pure *N*-methyl-2-(piperidin-2-yl)ethanamine (**25**, 107 mg, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.16 (m, 2 H, CH_2N), 2.89 (m, 1 H, CH-6), 2.7 (s, 3 H, CH_3), 2.53–2.37 (m, 2 H, CH-6, CH-3), 2.32 (m, 1 H, CH-2), 1.70 (m, 1 H, CH-4), 1.56 (m, 1 H, CH-4), 1.50–1.17 (m, 13 H, CH_2CHN, CH-3, CH-5, CH_3C), 1.06–0.91 (m, 1 H, CH-5). ES-MS: *m/z* = 243.2 $[M+1]^+$.
Characterisation of piperidines that are not previously described:
Compound **24**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.75 (br s, 1 H, NHCO), 2.30–2.85 (m, 3 H, CH_2N, CH-6), 2.51–2.85 (m, 2 H, CH-6, CH-2), 1.66 (m, 1 H, CH-4), 1.54 (m, 1 H, CH-4), 1.45–1.16 (m, 14 H, CH_2CHN, CH-3, CH-5, CH_3C), 0.96 (m, 1 H, CH-5). ES-MS: *m/z* = 229.2 $[M + 1]^+$.
Compound **28**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.7 (s, 6 H, CH_3O), 3.36 (dd, 1 H, J_1 = 4 Hz, J_2 = 12.4 Hz, CH-2), 3.05–2.86 (m, 3 H, CH-2, CH-3, CH-6), 2.78–2.71 (m, 1 H, CH-6), 2.70–2.62 (m, 1 H, CH-4), 2.01–1.92 (m, 1 H, CH-5), 1.87–1.78 (m, 1 H, CH-5). ES-MS: *m/z* = 202.2 $[M + 1]^+$.
Compound **26** (as a *cis–trans* mixture): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66 (s, 3 H, CH_3O), 3.62 (s, 3 H, CH_3O), 3.32 (m, 1 H, CH-2), 3.26 (m, 1 H, CH-2), 3.04 (m, 1 H, CH-6), 2.94 (m, 1 H, CH-6), 2.75 (dd, 1 H, J_1 = 3.6 Hz, J_2 = 13.2 Hz, CH-2), 2.65–2.55 (m, 2 H, CH-2, CH-3), 2.27 (t, 1 H, *J* = 8 Hz, CH-6), 2.16 (t, 1 H, *J* = 12 Hz, CH-6), 2.06 (m, 2 H, CH-3, CH-4), 1.68 (m, 2 H, CH-5), 1.34 (m, 1 H, CH-4), 1.12 (2 H, m, CH-4), 0.83 (m, 6 H, CH_3). ES-MS: *m/z* = 158.2 $[M + 1]^+$.
(14) For analogous examples, see: Alongi, M.; Minetto, G.; Taddei, M. *Tetrahedron Lett.* **2005**, *46*, 7069.
(15) In this experiment we observed the formation of about 25% of the expected acetamide. This kind of product was never observed under microwave dielectric heating.
(16) The ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. The stereochemistry was determined after purification of the corresponding tosylates prepared under standard conditions. The isomeric tosylates were separated by flash chromatography on silica gel and the relative stereochemistry of the substituents assigned by comparison of the coupling constants determined through gDQCOSY.
(17) Except for compound **28** that is not reported in the literature, the other products have been previously obtained by hydrogenation of the corresponding pyridines over heterogeneous catalysts under higher pressure for longer times:
(18) (a) Compound **29** – conditions: r.t., 15 h, 45 psi, only *cis* isomer isolated: Chênevert, R.; Dickman, M. *J. Org. Chem.* **1996**, *61*, 3332. (b) Compound **31** – conditions: 110 °C, 60 h, 50 psi of H_2, ratio 3:1: Urban, F. J. *J. Heterocycl. Chem.* **1995**, *32*, 857.
(19) Curran, T. P.; Smith, M. B.; Pollastri, M. P. *Tetrahedron Lett.* **1994**, *35*, 4515.
(20) In the case of compound **32** we were expecting a good selectivity, relying on the possibility of an intramolecular hydrogen bond between the OH, the N, and the Pt catalyst. Surprised of finding a 2:1 ratio, we repeated the reduction reported to give a high dr (EtOH, PtO_2, 400 psi for 24 h at r.t.). However, we still observed the formation of **32** as a 2:1 mixture of diastereoisomers (^{13}C NMR analysis), the same ratio observed by us under microwave irradiation. See:
(a) Jones, T. H. *Tetrahedron Lett.* **1990**, *31*, 1535.
(b) Cooke, G. A.; Fodor, G. *Can. J. Chem.* **1968**, *46*, 1105.