Microwave-Assisted Rapid and Simplified Hydrogenation\textsuperscript{1,†}

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Catalytic transfer hydrogenation has been conducted under microwave irradiation in open vessels using high-boiling solvents such as ethylene glycol (bp 198 °C) as the microwave energy transfer agent. Reduction of double bonds and hydrogenolysis of several functional groups were carried out safely and rapidly (3–5 min) at about 110–130 °C with 10% Pd/C as an efficient catalyst and ammonium formate as the hydrogen donor. Diverse types of \( \beta \)-lactam synthons were prepared by the reduction of ring substituents containing alkene and alkylidene groups or conjugated unsaturated esters. Cleavage of the \( \beta \)-lactam ring by hydrogenolysis of the N–C\(_4\) bond of 4-aryl-2-azetidinones was a facile reaction with 10% Pd/C as the catalyst; but no ring scission occurred when Raney nickel catalyst was employed. Dehalogenation of aromatic compounds was also successful with ammonium formate and Pd/C catalyst. Hydrogenolysis of phenylhydrazone of methyl benzoformate gave the methyl ester of phenylglycine in excellent yield. The techniques described here for microwave assisted hydrogenation are safe, rapid, and efficient and are suitable for research investigation as well as for undergraduate and high school laboratory exercises.

Introduction

Laboratory-scale catalytic hydrogenation\textsuperscript{2} plays a key role in chemical research and the synthesis of organic intermediates. Any simplification of this operation is, therefore, potentially useful provided the total process is safe and ecologically friendly. Industrial-scale hydrogenation, which has special requirements, will not be considered here.

In most organic laboratories it is a common practice to conduct catalytic reduction or hydrogenolysis under 40 psi pressure in a commercially available apparatus. Pure hydrogen gas from a cylinder fitted with an appropriate valve system is required. The air in the hydrogenator has to be completely removed either by flushing the system for several minutes with hydrogen, or, by repeatedly pumping the system down to a low pressure and refilling with hydrogen. Laboratories in remote locations may not have all of these facilities available at short notice. Many teaching laboratories are often not equipped with multiple units for frequent use by groups of students.

Some hydrogenation processes are more effective under higher pressure (1000 psi or more) and thus require more elaborate equipment. Considerable amounts of hydrogen are wasted during the flushing of such equipment. Hydrogen and air mixtures are potentially hazardous if flames or sparks are produced in the neighborhood of hydrogenators.

Results and Discussion

Catalytic Transfer Hydrogenation. In recent years a few laboratories have started to employ catalytic transfer hydrogenation (CTH).\textsuperscript{3} This is a safe and simple operation in which a catalyst and hydrogen gas are replaced with a catalyst and a hydrogen donor such as cyclohexane,\textsuperscript{4} hydrazine,\textsuperscript{5} formic acid,\textsuperscript{6} ammonium formate,\textsuperscript{7} cyclohexadiene,\textsuperscript{8} and phosphinic acid,\textsuperscript{9} sodium hypophosphite.\textsuperscript{10} This type of hydrogenation is usually conducted in flasks fitted with a magnetic stirrer and a reflux condenser. Ethyl alcohol is a widely used solvent for CTH.

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Recently we\textsuperscript{11} have demonstrated that catalytic transfer hydrogenation can be conducted very rapidly and in essentially quantitative yield inside an unmodified domestic microwave oven. We present here details of our technique and indicate the scope of reduction and hydrogenolysis achieved under microwave irradiation.

**Microwave-Assisted Reactions.** Two pioneering papers\textsuperscript{12} appeared in 1986 on remarkable acceleration of many organic reactions upon irradiation with microwaves (2450 MHz). Since then, a number of laboratories, including our own, have been studying microwave-assisted chemical synthesis.\textsuperscript{13} Some research groups conduct their reactions in sealed tubes, which can withstand several atmospheres of pressures, but occasional explosions have been reported due to the high pressure from a rapid rise in temperature.

A few laboratories\textsuperscript{14a} avoid the risk of explosions by conducting microwave-assisted reactions at ambient pressure by irradiating reactants adsorbed on solid supports such as clay, alumina, or silica gel.

Special microwave ovens have been designed by some groups to prevent explosions caused by run away reactions.\textsuperscript{14b} We prefer to conduct experiments in open vessels in inexpensive, unmodified, domestic microwave ovens. A wide variety of compounds have been synthesized using our microwave-induced organic reaction enhancement (MORE) chemistry techniques.\textsuperscript{15}

These techniques are also very convenient for rapid and safe catalytic transfer hydrogenation experiments.

**MORE Chemistry Techniques.** We have developed an unconventional experimental set up for conducting organic reactions to take advantage of the special nature of microwave energy.

Erlenmeyer flasks or beakers with loose covers are preferred reaction vessels for ambient pressure reactions in unmodified domestic microwave ovens. The upper parts of these vessels remain cool since glass is transpar-
group and reduction of the unsaturated ester to a saturated ester side chain to give the \(\beta\)-lactam 6 which retained the N-benzyl group intact (Scheme 3).

Using conventional catalytic hydrogenation (ambient pressure of hydrogen at 50 °C in methanol with Pd/C as the catalyst), Ojima et al.\cite{16} have cleaved N–C\(_3\) bonds in 4-phenyl-2-azetidinones to produce phenylalanine derivatives (for example, see Scheme 4) in a convenient fashion and in high yield. We\cite{17} had observed earlier that, in the presence of a large excess of Raney nickel catalyst and hydrogen, 3-methoxy-1,4-diphenyl-2-azetidinone underwent \(\beta\)-lactam scission to provide a small amount of the anilide of 3-methoxy-\(\beta\)-phenylpropionic acid (Scheme 5). However, under milder conditions, cleavage of the \(\beta\)-lactams ring does not occur. For several years now mild catalytic hydrogenation (5–10% Pd/C catalyst, room temperature) under conventional conditions have been the standard method in our laboratory for the reduction of \(\alpha\)-azido-\(\beta\)-lactams to \(\alpha\)-amino-\(\beta\)-lactams (for example, see Scheme 6).

Recently we\cite{11} have studied microwave assisted catalytic transfer hydrogenolysis at 120–130 °C using 10% Pd/C as the catalyst. Rapid scission of 4-phenyl-2-azetidinones was observed in every case. The N-benzyl group of the \(\beta\)-lactam 9 was not hydrogenolysed, but the O–Bn group at C-3 was converted to an OH group; alkenes (11, 13, and 15) were reduced to alkyl groups (Scheme 7). The reduction product was obtained in high yield and in a few minutes. It is useful to note that under these conditions Ra–Ni did not cause cleavage of the \(\beta\)-lactam ring in 3 (See Scheme 2).

The hydrogenation of 4-styryl-2-azetidinones (17 and 19) showed an interesting pattern (Scheme 8): the alkene groups were reduced but there was only partial \(\beta\)-lactam ring scission under the conditions used with Pd/C catalyst. Thus, the two products (18a,b), namely, the saturated \(\beta\)-lactam and the open chain amide, were formed in approximately 6:4 ratio. It would appear that the vinylogous aryl group led to the scission of the C\(_\alpha\)=N bond, but if the styril group were reduced first, ring cleavage was of course no longer possible. The relative rates of reduction of the styril group and hydrogenolysis of the \(\beta\)-lactam ring can therefore be expected to be influenced by the level of microwave irradiation.

**Stereoselective Preparation of \(\beta\)-Lactam Synthons.** A convenient procedure has been developed in our laboratory\cite{19} for resolving hydroxy-\(\beta\)-lactams (e.g., 23) by the formation of two diastereomeric glycosides via the Ferrier reaction involving a glucal (e.g., 22) (Scheme 9). The determination of the stereochemistry of the glycosidic linkages in these compounds was necessary. The problem appeared to have a reliable solution if the unsaturation could be easily removed, and the \(^1\)H NMR spectra of the chair-shaped pyranosides could be studied. CTH reaction using 10% Pd/C was tested on 24a and found to be successful: the unsaturation in the sugar moiety was removed without ring fission of the \(\beta\)-lactam to give 25a. Allylic deacetylation also occurred to a limited extent and gave 25b.

Microwave-assisted CTH reaction of 26 resulted in the formation of a reduced and deacetylated product 27. The proton NMR spectrum of this compound was useful for assigning the stereochemistry of the glycosidic bond.

In the course of studies on carbapenem synthons, a series of monocyclic \(\beta\)-lactams were generated with an exo-alkene group at C-3,\cite{15,16}20 These conjugated double bonds could be reduced easily under microwave-assisted CTH reaction (Scheme 10). Furthermore, because of the essentially planar shape of the \(\beta\)-lactam ring and the bulk of the substituent at C4, the hydrogenation was stereo-specific: only cis \(\beta\)-lactams were obtained because the catalyst surface was always placed trans to the large substituent at C4. Such stereospecificity is of course highly desirable from the point of view of atom economy.

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\(\begin{align*}
(16) & \text{Ojima, I.; Suga, S.; Abe, R. Chem. Lett. 1980, 853.} \\
(17) & \text{Bose A. K.; Manhas, M. S.; Chib, J. S.; Chawla, H. P. S.; Dayal, B. J. Org. Chem. 1974, 39, 2877.}
\end{align*}\)

\(\begin{align*}
(18) & \text{Bose, A. K.; Anjanevulu, B.; Bhattacharya, S. K.; Manhas, M. S. Tetrahedron 1967, 23, 4769.} \\
(20) & \text{Banik, B. K.; Manhas, M. S.; Bose, A. K. Tetrahedron Lett. 1997, 38, 5077.}
\end{align*}\)
Dehalogenation Reaction. Rajagopal and Spatola\textsuperscript{21} have studied CTH methods for the dehalogenation of aromatic compounds. They have observed that the order of addition of reagents plays an important role in the dehalogenation process. According to them, the catalytic activity of the Pd/C catalyst is improved significantly when it is activated before the addition of the hydrogen acceptor. Thus, the dechlorination of 4-chlorotoluene is completed in 90 min at room temperature when ammonium formate is added to the catalyst after the introduction of the substrate. In contrast it required only 15 min for complete reduction if the sequence of the addition of the formate and the halo-compound were reversed.

We\textsuperscript{22} have observed, however, that when microwave-assisted CTH reactions are used for dehalogenation, the end products and the time for complete reduction are independent of the order of addition of the reactants. Several $\beta$-lactams (such as, 28 and 33) and isoquinoline derivatives (e.g., 31) were smoothly dehalogenated (Scheme 11) in a few minutes.

During microwave-assisted dehalogenation of chlorobenzene and $p$-bromoanisole, the formation of biphenyls (Scheme 12) in about 10% yield was detected. No coupling to dimeric products was observed during the dehalogenation of 1-bromonaphthalene and 9-bromoanthracene.

Rajagopal and Spatola\textsuperscript{23} studied the kinetics of the dehalogenation of o-chlorotoluene by HCO$_2$Na–EtOH–H$_2$O and DCO$_2$Na–EtOD–D$_2$O and noted a kinetic isotope effect. On the basis of these findings they suggested that transfer of the formyl hydrogen of the donor to the catalyst surface is the rate-determining step. Wiener et al.\textsuperscript{24} have observed a significant kinetic isotope effect in the decomposition of sodium formate (HCO$_2$Na–H$_2$O vs DCO$_2$Na–D$_2$O) catalyzed by 5% Pd/C at 35 °C. But, they\textsuperscript{24} concluded from their study on the reduction of nitro-toluene with formate that there was no kinetic isotope effect.

Synthesis of Amines. Hydrazones are formed in excellent yield in minutes under microwave irradiation of ketones such as 35 and with hydrazine or phenylhydrazine in ethylene glycol solution. Such hydrazones can be converted to amines by microwave-assisted CTH reaction. Thus, methyl benzoylformate (35) gave the phenylhydrazine (36) in 90% yield in 6 min. Reduction of (36) during 4 min of microwave irradiation in the presence of ammonium formate and 10% Pd/C led to the amine (37) which was acetylated to give methyl N-acetyl phenylglycinate (38) in excellent yield (Scheme 13).\textsuperscript{25}

Summary and Outlook

In summary, we have devised safe, rapid, and efficient techniques for conducting catalytic hydrogenation and hydrogenolysis using just beakers and flasks and unmodified domestic microwave ovens. Runaway reactions under microwave irradiation leading to possible explosion are prevented by operating under ambient pressure in open systems. The source of hydrogen for this catalytic transfer hydrogenation method was ammonium

formate, which is inexpensive and easy to store and transport—unlike pure hydrogen gas under pressure in cylinders.

Field tests at Stevens Institute of Technology and neighboring inner city high schools have shown that the microwave-assisted techniques described here for reduction and hydrogenolysis are safe and suitable for research investigations as well as laboratory exercises for college and pre-college students. With minor modifications these techniques could also be used for many industrial processes.

Recent publications show increasing use of catalytic transfer hydrogenation methods. Thus, Albanese et al.\(^{25}\) have found these methods to be the best for the hydrogenolysis of 4-nitrobenzyl esters of cephalosporin antibiotics without isomerizing or reducing the conjugated double bond. Knochel and co-workers\(^{26}\) have reported new efficient catalysts for enantioselective transfer hydrogenations. There is every reason to believe that these and other new developments\(^{27}\) can be enhanced by the application of microwave-assisted techniques described by us here.


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**Experimental Section**

Melting points were determined with a Mel-temp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 1310 instrument. NMR spectra were recorded on a Bruker AC-20 spectrometer using TMS as an internal standard. Chemical ionization mass spectra were recorded on a Biospect instrument using CH\(_4\) as the reagent gas. Thin-layer chromatography was performed with Whatman plates, and the spots were detected by UV. Microanalyses were performed by Schwartzkopf Microanalytical Laboratory, NY. Compounds described here are racemates.

**General Procedure for \(\beta\)-Lactams.** The reaction of substituted acetyl chlorides with Schiff bases and tertiary amines (triethylamine for conventional experiments; \(N\)-methyImorpholine for reactions under microwave irradiation) was used for the synthesis of acetoxy-, benzyloxy-, methoxy-, and
phenoxy-substituted β-lactams (for example, 1, 5, 17, and 28).
For the preparation of α-vinyl-β-lactams (for example, 3 and
19), α, β-unsaturated acid chlorides were substituted for acetyl
chlorides and the reaction was conducted under microwave
irradiation.29

Schiff bases were prepared by the reaction of an aldehyde
with an amine in methylene chloride solution in the presence
of molecular sieves.29

Almost all of the β-lactams used as starting material for
this study are known compounds described in the literature.
Many of these β-lactams have been reported in our earlier
publications.30

removed from the oven. Careful decantation of the reaction mixture after cooling followed by the addition of glycol to the reaction vessel would preserve the catalyst for the next experiment.

It is customary in our laboratory to place a beaker cover or a filter funnel on top of the reaction vessel to prevent any accidental spillage. Since glass is nearly transparent to microwaves, the upper parts of the beaker of flask serves as a concentrator for the small amount of vapors formed. After the hydrogenation the reaction mixture was cooled and then filtered. The filtrate was diluted with water and extracted with ethyl acetate, and the organic layer was washed with water. Evaporation of the solvent from the organic layer (dried over anhydrous Na₂SO₄) followed by crystallization gave the pure product in 80–90% yield. We have observed that the optimal ratio of the catalyst (10% Pd/C) to substrate is 0.3:1 by weight for each reducible group. Five equivalents of ammonium formate for each reducible group gave good results.

2: yield 75%; mp 108 °C; IR (CHCl₃) 1740 cm⁻¹; 1H NMR 7.30–6.69 (m, 10H), 5.43 (d, J = 4.30 Hz, 1H), 4.93 (d, J = 4.32 Hz, 1H), 3.53–3.39 (m, 1H), 3.00–2.86 (m, 1H), 2.03–1.82 (m, 2H), 1.11 (t, J = 7.37 Hz, 3H); CIMS (CH₄ gas) m/z 282 (M + H⁺). Anal. Calcld for C₁₁H₂₀N₂O: C, 76.84; H, 6.80; N, 4.97. Found: C, 76.67; H, 6.67; N, 4.89.

4a: yield 80%; mp 118 °C; IR (CHCl₃) 1740 cm⁻¹; 1H NMR 7.35–6.99 (m, 10H), 4.67 (d, J = 2.34 Hz, 1H), 3.10–3.01 (m, 1H), 2.03–1.82 (m, 1H), 1.11 (t, J = 7.37 Hz, 3H); CIMS (CH₄ gas) m/z 282 (M + H⁺). Anal. Calcld for C₁₁H₂₀N₂O: C, 81.24; H, 6.81; N, 5.57. Found: C, 80.99; H, 6.67; N, 4.89.

4b: yield 85%; mp 109 °C; IR (CHCl₃) 1740 cm⁻¹; 1H NMR 7.32 (s, 5H), 7.15 (d, 2H), 6.69 (d, 4H), 4.54 (d, J = 2.27 Hz, 1H), 3.74 (s, 3H), 2.94–2.90 (m, 2H), 2.07–1.69 (m, 2H), 1.04 (t, 3H). Anal. Calcld for C₁₁H₂₀N₂O: C, 76.84; H, 6.80; N, 4.97. Found: C, 76.62; H, 6.92; N, 5.0.

4c: yield 85%; oil; IR (neat) 1740 cm⁻¹; 1H NMR 7.37 (brs, 1H), 7.25 (d, J = 8.9 Hz, 2H), 6.7 (d, J = 8.9 Hz, 2H), 6.38–6.29 (m, 2H), 4.66 (d, J = 2.38 Hz, 1H), 3.71 (s, 3H), 3.30–3.31 (m, 1H), 2.01–1.72 (m, 2H), 1.05 (t, J = 7.41 Hz, 3H); CIMS (CH₄ gas) m/z 272 (M + H⁺). Anal. Calcld for C₁₁H₂₀N₂O: C, 70.83; H, 6.31 N, 5.16. Found: C, 70.59, H, 6.11; N, 5.02.

6a: yield 90%; mp 109–110 °C; IR (Nujol) 3300, 1730 cm⁻¹; 1H NMR 7.41 (d, 2H), 6.92 (d, 2H), 5.04 (d, J = 4.9 Hz, 1H), 4.37 (m, 3H), 3.82 (s, 3H), 3.72 (s, 3H), 2.61 (m, 2H), 2.12 (m, 2H); CIMS (NH₃ reagent gas) m/z 297 (M + 18)⁺. Anal. Calcld for C₁₁H₂₁N₂O: C, 60.20; H, 6.10; N, 5.01. Found: C, 59.61, H, 6.26, N, 5.00.

6b: yield 85%; oil; IR (Nujol) 3350, 1730 cm⁻¹; 1H NMR 7.40 (s, 5H), 5.23 (m, 1H), 4.94 (t, 1H), 4.67 (d, J = 15.4 Hz, 1H), 4.20 (d, J = 15.4 Hz, 1H), 3.75 (s, 3H), 3.24 (m, 1H), 2.41 (m, 2H), 2.0 (m, 2H); CIMS (NH₃ reagent gas) m/z 428 (M + 18)⁺. Anal. Calcld for C₁₁H₂₂N₂O: C, 75.29; H, 6.66; N, 5.49. Found: C, 75.13, H, 6.69; N, 5.58.

10b: yield 80%; mp 128 °C; IR (Nujol) 3300, 1640 cm⁻¹; 1H NMR 8.20 (brs, 1H), 7.51–6.80 (m, 9H), 4.4 (m, 1H), 3.85 (s, 3H), 3.42 (dd, J₁ = 7.80 Hz, J₂ = 7.80 Hz, 1H), 3.09 (dd, J₁ = 8.30 Hz, J₂ = 14.10 Hz, 1H), 2.63 (d, J = 8.30 Hz, 1H); CIMS (NH₃ reagent gas) m/z 289 (M + H⁺). Anal. Calcld for C₁₁H₁₇N₂O : C, 66.43; H, 6.51; N, 4.48. Found, C, 66.65; H, 6.54; N, 4.76.

12a: yield 83%; mp 113–115 °C; IR (Nujol) 1640 cm⁻¹; 1H NMR 7.10–6.65 (m, 9H), 3.73 (s, 3H), 2.82 (m, 2H), 2.21 (m, 1H), 1.75 (m, 2H), 0.90 (t, 3H); CIMS (NH₃ reagent gas) m/z 301 (M + H⁺). Anal. Calcld for C₁₁H₁₈N₂O: C, 76.32; H, 7.42; N, 4.84. Found: C, 75.80; H, 7.79; N, 4.84.
Microwave-Assisted Hydrogenation

(5 mL) were placed in an Erlenmeyer flask (125 mL). The mixture was heated for 6 min at low power setting. The desired phenyl hydrazone (36) precipitated out on scratching under ice cold condition. It was filtered, washed with hexane, and dried (yield 90%, mp 86–88 °C).

Ammonium formate (200 mg) and 10% Pd/C (100 mg) were added to phenylhydrazone (36) (2 mmol) in ethylene glycol (5 mL). The mixture was irradiated for 4 min. After the usual workup, the amine (37) was isolated (92%): 1H NMR (CDCl3) 7.40 (s, 5H), 4.6 (s, 1H), 3.61 (s, 3H), 2.0 (bri, 2H): 13C NMR 174.19, 140.11, 128.56, 127.77, 126.69, 59.15, 52.11; CIMS (NH3 reagent gas) m/z 183 (M + 18)°. A portion of (37) was acetylated with acetic anhydride and pyridine to afford (38): mp 85–86 °C; IR (Nujol) 1700 cm⁻¹; 1H NMR 8.9 (bri, 1H), 7.31 (s, 5H), 5.60 (d, J = 8.24 Hz, 1H), 3.70 (s, 3H), 2.0 (s, 3H); 13C NMR 168.79, 138.02, 128.83, 127.15, 119.98, 61.90, 56.56, 24.33; CIMS (NH3 reagent gas) m/z 225 (M + 18)°.

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