alkoxides is an interesting nuance of asymmetric epoxidation catalysis for which future mechanistic studies will hopefully provide an adequate rationale.

Acknowledgment. We are grateful to the National Science Foundation (CHE-8903218) for financial support. We thank Professors M. G. Finn and Yasuhiro Kawanami for valuable discussions. T.H.K. acknowledges the support of NSERC (Canada) and the Alberta Heritage Scholarship Fund.

Microwave-Induced Organic Reaction Enhancement Chemistry. 2. Simplified Techniques[†,1]

Ajay K. Bose,* Maghar S. Manhas, Malay Ghosh, Mamta Shah,[‡] Vegesna S. Raju, Shamsher S. Bari,[§] Sarder N. Newaz, Bimal K. Banik, Ashok G. Chaudhary, and Khaled J. Barakat

Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Hoboken, New Jersey 07030

Received September 23, 1991

Summary: A variety of organic reactions have been conducted efficiently in a few minutes in unsealed vessels at ambient pressure in unmodified microwave ovens by using selected organic solvents.

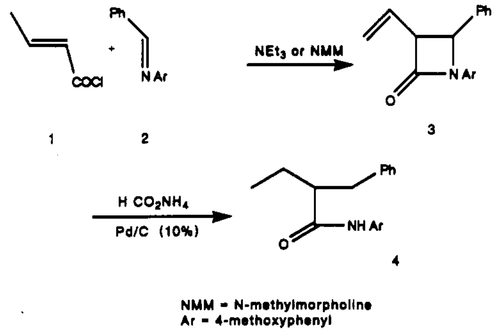
Commercial microwave ovens are now widely accepted as safe and convenient devices in the kitchen. The magnetrons in these ovens are set at a frequency of 2450 MHz for raising the temperature of water molecules through the efficient absorption of microwave energy.[2] Polar organic compounds can also be heated through dipole rotation. Hydrocarbon solvents, because of lack of dipole moment, absorb microwave energy poorly and are not heated to high temperatures in these ovens. Teflon, polystyrene, glass, and ice are nearly transparent to microwaves.[3]

In 1986, Gedye et al.[4] and Giguere et al.[5] demonstrated that many organic reactions can be conducted very rapidly under microwave irradiation. Since then, several other groups have described accelerated organic reactions in nonaqueous media.[6,7] These reactions are usually conducted on a small scale in sealed tubes or in capped Teflon vessels, and the acceleration in reaction rates is ascribed to elevated temperature and high pressure reached in a few minutes in a microwave oven.[4] Some explosions have been reported.

Giguere et al.[5] devised an explosion proof system in which a sealed reaction vessel is covered with vermiculite in a container made of a special polymer able to withstand high temperature. Even hydrocarbon solvents could be used because vermiculite, which is a hydrated silicate, absorbs microwave energy efficiently and heats the reaction vessel and contents. High pressure was avoided by some investigators by conducting solid-phase reactions with substrates absorbed on clay, silica, or alumina[8] or by modifying a domestic microwave oven.[9]

We wish to describe here practical and simple techniques for using domestic microwave ovens without alteration[10] as safe and convenient laboratory devices. We have observed that a large variety of organic reactions in nonaqueous media can be conducted on milligram to several hundred gram scale in 1–10 min in inexpensive equipment.[1] Furthermore, there is no need for sealed vessels, reflux condensers, stirrers, water separators (Dean-Stark tube), etc. We have devised a method for extending these techniques to reactions that are normally conducted in hydrocarbon solvents. The key to our "Microwave-induced Organic Reactions Enchancement" (MORE) chemistry is the proper choice of a microwave energy transfer medium and a nontraditional approach to the experimental set up for organic reactions.

Scheme I



To demonstrate the versatility of MORE chemistry, a variety of organic reactions are described here that we have conducted in domestic microwave ovens. In the course of these studies we have also uncovered an interesting aspect of the Bischler–Napieralski reaction which is reported here.

Safe Techniques. The preferred reaction vessel is a tall beaker with a loose cover of much larger capacity than the volume of the reaction mixture. A large Erlenmeyer

---

[†] Dedicated to Professor Luigi Z. Pollara.

[‡] Participant in the UPTAM (Undergraduate Projects in Technology and Medicine) program of Stevens Institute of Technology.

[§] Visiting Scientist from Panjab University, Chandigarh, India.

(1) Part 2 in this series. For part 1, see: Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Tabei, K.; Urbanczyk-Lipkowska, Z. *Heterocycles* **1990**, *30*, 741. Presented in part at the 202nd National Meeting of the American Chemical Society, New York, Aug 1991; ORGN 195.

(2) Neas, E. D.; Collins, M. J. In *Introduction to Microwave Sample Preparation*; Kingston, H. M., Jassie, L. B., Eds. American Chemical Society: Washington, 1988; Chapter 2.

(3) Previously, we[1] have described a reaction conducted in a vial enclosed in a block of ice. The reactants were heated directly by the microwave irradiation without melting much of the ice; the products that were formed were chilled immediately when the oven was turned off—a useful set up if reaction products are thermolabile.

(4) (a) Gedye, R. N.; Smith, F. E.; Westaway, K. C. *Can. J. Chem.* **1988**, *66*, 17. (b) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279.

(5) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945. (b) Giguere, R. J.; Namen, A.; Lopez, B.; Arepally, A.; Ramos, D.; Majetich, G.; Defauw, J. *Tetrahedron Lett.* **1987**, *28*, 6553. (c) Giguere, R. J. *Organic Synthesis: Theory and Applications*; JAI Press: Greenwich, 1989; Vol. 1, pp 103–172.

(6) Berlan, J.; Giboreau, P.; Lefeuvre, S.; Merchand, C. *Tetrahedron Lett.* **1991**, *32*, 2363 and references cited therein.

(7) Chen, S.-T.; Chiou, S.-H.; Wang, K.-T. *J. Chin. Chem. Soc.* **1991**, *38*, 85.

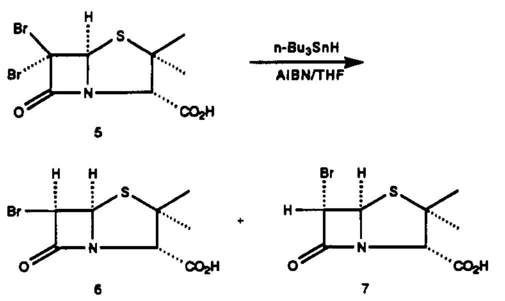
(8) (a) Alloum, A. B.; Labiad, B.; Villemin, D. *J. Chem. Soc., Chem. Commun.* **1989**, 386. (b) Gutierrez, E.; Loupy, A.; Bram, G.; Ruiz-Hitzky, E. *Tetrahedron Lett.* **1989**, *30*, 945. (c) Bram, G.; Loupy, A.; Majdoub, M.; Gutierrez, E.; Ruiz-Hitzky, E. *Tetrahedron* **1990**, *46*, 5167.

(9) Chen, S.-T.; Chiou, S.-H.; Wang, K.-T. *J. Chem. Soc., Chem. Commun.* **1990**, 807.

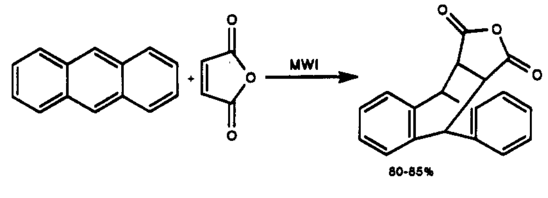
(10) Modification of commercial microwave equipment can be hazardous because of possible leakage of microwave radiation.[2]

0022-3263/91/1956-6968$02.50/0 © 1991 American Chemical Society

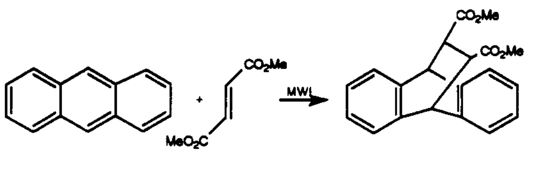
Scheme II



Scheme III



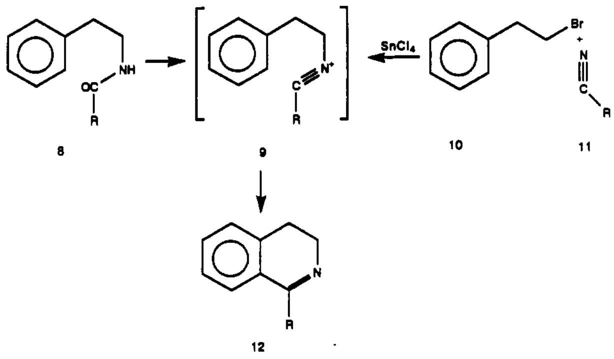
Solvent	Time	Yield (%)
Chlorobenzene	2-3 min	40
0-Dichlorobenzene	2 min	80-85
Diglyme	1 min	90



Solvent	Time	Yield (%)
Chlorobenzene	5 min	< 5
0-Dichlorobenzene	5 min	15-20
1,2,4-Trichlorobenzene	5-10 min	70

MWI = Microwave irradiation

Scheme IV



flask with a funnel as a loose top can be used in place of the beaker. For the reaction medium (energy-transfer medium) a solvent is selected which is polar (with high dielectric constant and therefore heated rapidly under microwave irradiation) and which has a boiling point that is 20–30 °C higher than the desired reaction temperature.[11] The strategy is to control the energy input from the microwave oven into the reaction mixture so as to keep the reaction temperature substantially below the boiling point of the energy-transfer medium. Superheating of liquids is common under microwave irradiation.[12]

An excellent energy-transfer medium for many types of reactions in a domestic microwave oven is *N,N*-dimethylformamide (DMF): a good solvent with high bp (160 °C) and high dielectric constant ($\epsilon = 36.7$). This solvent can retain water formed in a reaction, thus obviating the need for a water separator.[1] The reaction temperature can be raised to about 140 °C without noticeable vaporization.[13] Other solvents which are suitable for particular reactions are discussed below.

I. α-Vinyl β-Lactams. In 1971, we[14] described the synthesis of α-vinyl β-Lactams **3** by the reaction of an α,β-unsaturated acyl chloride **1** with a Schiff base **2** and triethylamine in refluxing benzene for a few hours. For the MORE version of this reaction, benzene is not suitable since it does not absorb microwave energy readily.

We have now observed that by replacing benzene with chlorobenzene (polar, bp 131 °C) α-vinyl β-lactam formation can be achieved in 65–70% yield in about 5 min. The controls in the microwave oven are set to keep the temperature of the reaction mixture below 110 °C to prevent chlorobenzene from approaching its boiling point too closely. For reactions on a small scale (less than 5 g), finer control on energy transfer to the reaction mixture is attained by using a "heat sink" (a beaker of water or DMF) which absorbs a major part of the microwave energy entering the oven space. Higher boiling *N*-methylmorpholine has been found to be better than triethylamine as the base (see Scheme I).

II. Catalytic Hydrogenation. To a solution of α-vinyl β-lactams **3** in ethylene glycol (bp 196–198 °C) were added ammonium formate and Pd/C (10%) catalyst, and this mixture was irradiated in a microwave oven. Reduction of the double bond and cleavage of the β-lactam by hydrogenolysis to give the amide **4** were complete in less than 45 s at a temperature of about 110 °C. Such rapid catalytic hydrogenation should be of great practical value in syntheses involving short-lived radiopharmaceuticals.[15]

III. Free-Radical Reaction. α-Halo β-lactams undergo stereoselective dehalogenation by a free-radical reaction in dry tetrahydrofuran with tributyltin hydride in the presence of 2,2-azobisisobutyronitrile.[16] 6,6-Dibromopenicillanic acid (**5**) was converted to the *cis*-6β-bromo compound **6** with minor amounts of the *trans*-6α-bromo isomer **7** in about 3 min of heating at low energy in a microwave oven (see Scheme II).

IV. Diels–Alder Reaction. Giguere et al.[5] have conducted several Diels–Alder reactions in hydrocarbon solvents using sealed systems surrounded by vermiculite. We have tested the reaction between anthracene and maleic anhydride in open systems in a microwave oven employing chlorobenzene, *o*-dichlorobenzene, or diglyme as the en-

---

(11) Approximate avarage reaction temperature can be estimated by turning off the oven and using a thermometer to note immediately the temperature of the reaction mixture. If the energy level of the oven is properly adjusted and heating is discontinued after every 2 or 3 min, there is little vaporization and the upper part of the flask or beaker is cool enough to be held by hand upon removing from the microwave oven.

(12) Hoopes, T.; Near, E.; Majetich, G. 201st National Meeting of the American Chemical Society: Atlanta, GA, April 1991; ORGN 231.

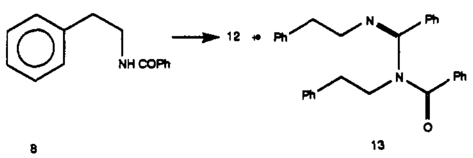
(13) Microwave ovens are equipped with fans which remove hot air and vapors from inside the oven. No safety problems were experienced when a reaction mixture with DMF as the solvent was overheated for several mixtures in a beaker with a loose cover such that the reaction mixture boiled and vapors escaped from the beaker. Metallic objects (such as a spatula) must not be placed inside a microwave oven since arcing would result.

(14) (a) Bose, A. K.; Spiegelman, G.; Manhas, M. S. *Tetrahedron Lett.* **1971**, 3167. (b) Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575.

(15) Hwang, D. R.; Moerlein, S. M.; Lang, L.; Welch, M. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1799.

(16) See, for example: Manhas, M. S.; Khajavi, M. S.; Bari, S. S.; Bose, A. K. *Tetrahedron Lett.* **1983**, *24*, 2323 and references cited therein.

Scheme V



ergy-transfer medium. The yield of the Diels–Alder adduct was about 40% in the lower boiling chlorobenzene (bp 130 °C). In *o*-dichlorobenzene (bp 178 °C) the yield was 80–85%. About the same yield (90%) was obtained when diglyme (bp 162 °C) was used as a solvent. The reaction between anthracene and dimethyl fumarate proceeded in low yield (<20%) in *o*-dichlorobenzene and diglyme. To provide a higher reaction temperature, 1,2,4-trichlorobenzene (bp 214 °C) was used as the energy-transfer medium when 70% yield of the diene adduct was obtained after 10 min of irradiation (see Scheme III).

V. The Bischler–Napieralski Reaction. Discovered nearly a century ago, the Bischler–Napieralski reaction[17] involves the conversion of an amide **8** of β-phenylethylamine to a 3,4-dihydroisoquinoline **12** in high yield. Most literature procedures prescribe heating of the amide under reflux in toluene or xylene for several hours in the presence of $POCl_3$ and/or P_2O_5. It has been suggested that the reaction intermediate is **9**, which is also considered to be the intermediate for the formation of **12** by the interaction of **10** and **11** in the presence of stannic chloride[18] (Scheme IV).

We have reported previously[1] that we attempted to conduct the Bischler–Napieralski reaction under microwave irradiation using solvents other than aromatic hydrocarbons. In DMF, tarry material was produced but in ethylene dichloride (bp 80 °C) the *N*-acylamidine **13** was formed in very high yield (Scheme V).

When a toluene solution of the amide **8** and $POCl_3$ was irradiated in a microwave oven for several min the temperature of the reaction mixture failed to rise above 80 °C. The reaction mixture was found to contain mostly the acylamidine **13** and only trace amounts of the desired 3,4-dihydroisoquinoline along with unreacted amide. For the MORE version of this traditional reaction we used chlorobenzene and irradiated the reaction mixture for 2–4 min, reaching a temperature of 110–120 °C. The product now was 40:60 mixture of the 3,4-dihydroisoquinoline **12** (R = Ph) and *N*-acylamidine **13**. To reach a higher temperature level (about 140–150 °C) we employed *o*-dichlorobenzene as the reaction medium. After about 3 min of irradiation, the ratio of **12** to **13** was 90:10 and the 3,4-dihydroisoquinoline was isolated in 72% yield. Even higher reaction temperature can be attained by utilizing 1,2,4-trichlorobenzene (bp 214 °C) as the reaction medium.

Interestingly, when the *N*-acylamidine **13** and P_2O_5 (or $POCl_3$) in chlorobenzene solution were heated for a few minutes, only a small amount of the 3,4-dihydroisoquinoline was formed at a slow rate. The addition of a few drops of water to the reaction mixture before irradiation led to a rapid conversion to **12** and a small amount of the amide **8**. The amide and acylamidine are obviously interconverted in a reversible fashion at relative rates dependent on reaction conditions.

To obtain further insight about the Bischler–Napieralski reaction, ^1H NMR spectroscopy was used for monitoring the sequence of events when the pure acylamidine **13** and P_2O_5 were heated in toluene-d_8 solution in an oil bath. No changes occurred until a drop of water was added. After a few more minutes it was observed that the reaction mixture contained substantial amounts of amide **8** and amidine **13** in about equal amounts with only traces of the 3,4-dihydroisoquinoline. It would appear from these observations that although the acylated amidine is formed at the very beginning, it need not be a direct intermediate for the 3,4-dihydroisoquinoline. The acylamidine appears to be hydrolyzed to the amide, a part of which is transformed into the dihydroisoquinoline.

Our preferred method for conducting the Bischler–Napieralski reaction is to use *o*-dichlorobenzene as the energy-transfer medium and $POCl_3$ (3 molar) as the condensing agent.

Concluding Remarks

There is a difference of opinion regarding specific activating effect of microwaves on organic reactions. Several authors[8] have reported that solid-phase reactions are very much accelerated when conducted in a microwave oven.[19] Evidence for acceleration of some homogeneous reactions under microwave irradiation has been presented recently by Berlan et al.[6]

We have studied the cycloaddition of anthracene and dimethyl fumarate in trichlorobenzene solution using ^1H NMR spectroscopy for monitoring the progress of the reaction. The reaction temperature (190–200 °C) was deduced by placing melting point capillaries filled with various substances and noting which ones melted during the reaction[5] (5 min, 2-g scale) in a microwave oven. With a preheated oil bath at 190–200 °C the same reaction was conducted under thermal activation for 5 min. The yield of the addition product was the same (28–30%) under both conditions.

For reactions on a large scale (e.g., 50 g or more) such comparison would be very difficult to make since it would take several minutes just to raise the temperature of the reaction vessel and the reactants to the planned level. In the case of reactions under microwave irradiation, only the reactants are heated rapidly and fairly uniformly without the need for a stirrer. Thus, MORE chemistry is energy efficient and cost efficient as well as very convenient to conduct—especially on a large scale.

We have observed that most organic reactions can be run safely and rapidly in a domestic microwave oven. The saving in expenses for equipment can be substantial for conducting an undergraduate organic laboratory course or setting up a research laboratory. We have tested with success the feasibility of having high school chemistry students perform selected organic reactions (preparation of *N*-phthaloylglycine and α-vinyl β-lactams) in the limited time available to them (50–90 min) for laboratory exercises.

Acknowledgment. The development of improved curricular material involving MORE chemistry for undergraduate and high school laboratory exercises was funded by a grant from the Howard Hughes Medical Institute in support of our "Chemical Biology Education Enhancement" program. We wish to thank Dr. H. Raveche', Dr. E. W. Robb, and Dr. R. J. Giguere for valuable discussions, Keiko Tabei for TLC-CIMS data, and Kavita Mistry[20] for technical assistance.

---

[17] Bischler, A.; Napieralski, B. *Chem. Ber.* **1893**, *26*, 1903.

[18] Lora-Tamayo, M.; Madronero, R.; Munoz, G. G. *Chem. Ind.* **1959**, 657.

[19] For example, Alloum et al.[8a] have reported that an acetylenic alcohol adsorbed on KSF clay gave a rearranged product in 95% yield under microwave irradiation. The same experiment under thermal activation at the same temperature (170 °C) produced less than 2% of the product.

[20] Undergraduate research participant.