UV Monitoring of Microwave-Heated Reactions—A Feasibility Study

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Abstract: UV/Visible spectroscopy has been used to monitor the progress of the formation of benzimidazole from the reaction between 1,2-diaminobenzene and formic acid. The reaction was performed at three concentration levels, each becoming more dilute so that at the most dilute level direct UV monitoring from the reaction sample was possible. At each level the reaction was conducted by conventional and by microwave heating. The success of the microwave reaction at the most dilute levels encourages the construction of a microwave reactor/UV/Vis spectrometer hybrid instrument for the monitoring of this and other reactions.

Keywords: cyclization · heterocycles · microwaves · nitrogen heterocycles · UV/Vis spectroscopy

Introduction

Microwave-assisted synthetic chemistry—a background: Microwave-assisted synthesis is a relatively young science. While the heating effects of microwaves were discovered in 1945,[1] and synthetic inorganic and organic chemistry have been established sciences for at least 150 years, the first microwave-enhanced organic syntheses were not published until 1986.[2, 3] Today, the number of papers published on microwave-assisted chemistry is increasing rapidly. Observations made have been summarized in a number of reviews.[4]

The signature of microwave-enhanced chemistry is that the rates of reactions involving polar components are usually very fast. Reactions that require hours or days of conventional heating may often be accomplished in minutes by microwave heating. Product distributions sometimes differ for microwave and conventional heating.[5] Reactions which otherwise give no or very small amounts of product may give good yields under microwave irradiation.[4m, 6] These improvements have often been attributed to so-called "special" microwave effects. Critical studies have, however, asserted that most of the proposed microwave effects can be explained as thermal at extreme conditions.[7] Further, detailed investigations of the microwave-enhanced chemical reactions are clearly motivated.

Macroscopic in situ probing of reactions usually involves monitoring the temperature and pressure of the reaction sample. For microwave-assisted reactions this is not as trivial as it is for conventional heating since the microwaves may interact with the monitoring device. Thermocouples or optical fiber-based thermometers that are designed for use in microwave fields, though not common, are commercially available. Various laboratory microwave devices use built-in monitoring of the IR radiation emitted from the outside of the reaction vessel for estimating the sample temperature. Such a method requires knowledge about the energy diffusion from the reaction to the vessel surface; that is standard vessels have to be used. The IR method is as reliable as the more direct fiberoptic technique if these requirements are fulfilled and is therefore often preferable since the fiberoptic probe may be sensitive to the chemicals in the reacting sample. Also any probe placed in the reaction mixture may act as a point for nucleation, thereby reducing superheating effects. Pressure in the reaction vessel may be monitored by connecting to pressure gauges through microwave-transparent lines or by measuring the mechanical movement of, for instance, a membrane connected to the vessel. We are interested in developing a method for observing the progress of the chemical reaction itself. Dynamically monitoring the changes in chemical composition would give valuable information about how a particular process develops as a function of time and how and why it may differ under various reaction conditions.

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  0947-6539/02/0810-2255 $ 20.00+.50/0

Choice of monitoring method: The method chosen should probe without essentially disturbing the process. The monitoring should be in situ and the method should utilize specific properties of the sample components that can be used to estimate relative concentrations. This led us to consider spectroscopic methods, since most compounds have characteristic microwave, IR, visible, and UV spectra.

The fact that broad-band microwave-emitting circuits coupled to solid-state microwave spectrometers are commercially available[8] makes the use of microwave spectroscopy attractive. The absorption or emission microwave spectra of a compound relate to discrete transitions between rotational states of the molecule. The spectra are characterized by sharp lines for the pure rotations in the gas phase, but quite broad bands in the liquid phase since the rotations are hindered as the molecules come closer to each other. The spectrum may be disturbed by the intense reaction-driving microwave irradiation and we therefore conclude that in situ microwave spectral characterization of a reaction may not be the best approach.

IR spectroscopy is used to characterize vibrations of functional groups in molecules. These spectra have a rich structure of more or less broad peaks describing various normal modes characteristic for the molecule. However, the intensity of the vibrational transitions varies with the temperature of the sample. Most IR instruments have an energy range that corresponds to 1500 – 1900 cm^{-1}. The fact that we want to use this technique for in situ studies in a sample with temperatures ranging from 25 to 350 °C with blackbody temperature peaks between 5 to 10 micrometer makes the use of IR spectroscopy as the probe less feasible.

Raman spectra arise from inelastic collisions between molecules and photons that are usually in the visible energy range. The emitted Stokes or anti-Stokes lines are in the same energy region as the exciting radiation. Raman spectra are unaffected by the presence of blackbody type radiation. The weakness of the observed Raman lines suggests the use of a laser as an excitation source. However, the laser light may, in unfavorable cases, excite a significant fraction of the molecules in the reaction to be studied. For this reason Raman spectroscopy may not be a good choice for a general monitoring method.

UV/Vis spectra are the result of electronic excitations of molecules and are characteristic for the molecules. A normal, broad-band, background light source with a continuous or semicontinuous spectrum is not usually intense enough to excite more than a small fraction of the molecules in the absorption cell. The spectra may or may not be affected by the temperature of sample. Even though spectra of the absorbances by various compounds in a reaction sample may overlap, we find UV/Vis spectroscopy to be most suitable for in situ spectroscopy of microwave-irradiated reacting samples.

Realistic requirements: The purpose of this study was to examine whether or not it is feasible to monitor a microwave-assisted reaction by using UV/Vis spectroscopy. The UV/Vis spectra of the reactants and products should be characterized by relatively sharp peaks, which are easily identifiable. Product peaks should preferably not overlap with those of the reactants. The peak positions should not significantly vary with temperature. Spectral changes caused by the environment (solvent, sample pH, etc.) should be small or predictable.

The model reaction: Imidazoles and benzimidazoles are basic structures in endogenous compounds such as the amino acid histidine and the purines and pyrimidines of the nucleic acids. They serve as an important biostere for the catechol structure in medicinal chemistry and are important building blocks in combinatorial chemistry directed toward new pharmaceutical agents. According to Meth-Cohn,[9] one third of the pages of the *Drug Compendium of the Comprehensive Medicinal Chemistry*[10] contain imidazole or benzimidazole units.

As early as 1963, Wagner and Millet[11] described that the heterocyclization reaction forming benzimidazole (**3**) (Figure 1 a) proceeds to give 85 % yields after conventionally heating at 100 °C for 2 h. A commercial microwave oven has been used to reduce the times for this reaction.[12] Though the conditions were not specified in detail, yields of 70 % were obtained when the sample in an Erlenmeyer flask was heated for 3 min at a low power setting.

As shown in Figure 1 b – d, the spectral characteristics of the components of this reaction are quite favorable for the planned feasibility study. The major features of the spectrum of 1,2-diaminobenzene (**1**; Figure 1 b) are the broad shoulder at 230 – 240 nm and the broad peak between 256 and 304 nm with a maximun at 293 nm. On addition of formic acid (**2**) (= reaction mixture at t_o, Figure 1 c,), the shoulder becomes a defined peak at 230 nm, the absorbance of the second peak decreases significantly and its maximum shifts slightly to 280 nm. Benzimidazole in dilute formic acid (Figure 1 d) has a

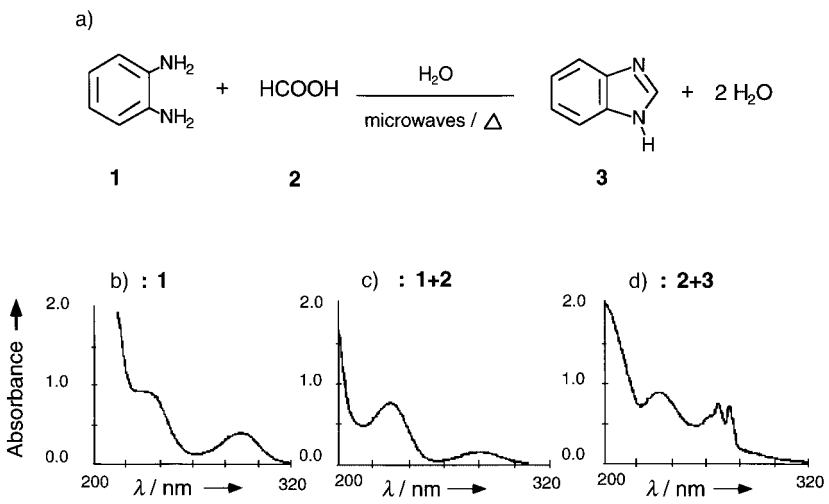

Figure 1. Model reaction with UV profiles at key stages.

  0947-6539/02/0810-2256 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 10

peak at 233 nm, which was not separable from that of the starting material with the spectrometer used here. However, the two distinct peaks at 267 and 274 nm were easily distinguishable from that of the starting mixture.

Results and Discussion

Calibration of UV absorbance to concentration of 3: The UV absorbance was calibrated for the product concentration by adding, in a stepwise fashion, aliquots (5 μL) of an acidified stock solution (7.1×10^{-3} M) of **3** to a cuvette containing water (3 mL) and acquiring the spectrum between each addition. The absorbances corresponding to 100% yields of **3** across the concentration ranges of interest are depicted in Figure 2. During the progress of a reaction, plots acquired of the absorbances of the peaks at 267 and 274 nm (Figure 3) follow a similar trend, indicating that either can be used in monitoring the progress of the reaction.

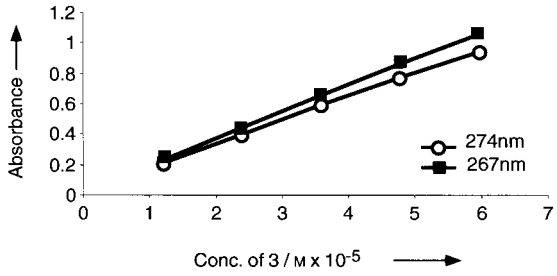

Figure 2. Calibration plot used to quantify 100% yield for a known concentration of benzimidazole.

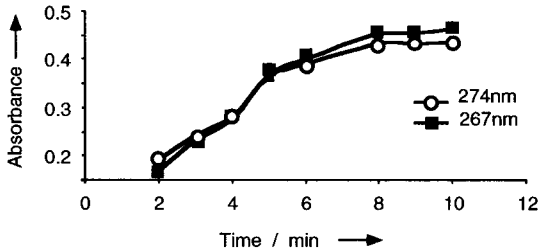

Figure 3. Absorbance of chromophores at 267 and 274 nm versus time during experiment 6 (Table 1).

Effect of temperature on the sample UV: We were concerned about the influence of reaction temperature on the UV spectra and, consequently, the conclusions drawn about the course of a reaction being heated. To assess the size of this effect, we heated samples of different compositions to 60 °C in the microwave and allowed them to cool to room temperature in a cuvette placed inside the spectrophotometer. The sample temperature was measured with a thermometer every minute immediately prior to acquisition of the spectrum. The blank for acetone was acetone at room temperature, for the other two (both aqueous solutions) water (at room temperature). In Figure 4, the spectral changes for the most dilute reaction mixture used here (see Table 1) were examined and are compared with changes for other typical solvents, neat acetone and DMSO/H_2O (1:6, v/v). The UV absorbance

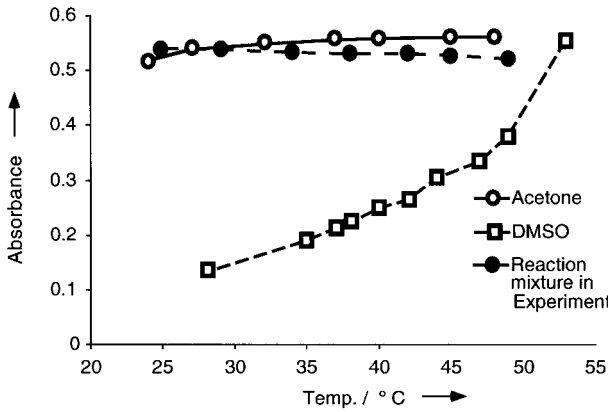

Figure 4. Effects of temperature on UV absorbance (experiment 9).

change for this reaction mixture and for acetone were negligible, while that of DMSO was 0.4 over a 30 °C range. These differences illustrate that temperature effects on the UV spectra need to be assessed for the reaction systems/solvents used. Here, to completely eliminate any possible contributions from temperature on these results, we took the extra precaution of cooling the sample to room temperature before each UV measurement. However, in an in situ monitoring situation, this would probably not have been necessary with this particular reaction mixture.

Reaction of 1 with 2 to yield 3: Literature procedures for the cyclization reaction have been performed at or around the boiling point of **2** (101 °C for the concentration used). For our microwave/conventional heating comparisons we performed the conventional heating at both 70 and 100 °C. The latter was just at the boiling point of water and just below that of **2** so that the fastest heating could be achieved without having to use pressurized vessels or reflux equipment to avoid concentration changes due to evaporation during prolonged heating. One lower temperature, 70 °C, was chosen for its reasonable separation from the maximum conventional temperature and from the average temperature in the microwave heated samples.

To prevent loss of reaction sample by evaporation, closed vessels were used throughout. When using a closed vessel, a balance needs to be reached between sample volume and headspace in the reaction vessel, to give as long a reaction time as possible before the vessel integrity is compromised. The smaller the reaction sample is, the quicker it is heated, evaporates, and pressure builds up. However, with larger reaction samples the headspace available for evaporation is smaller. For our vessels (11 mL) we found that heating for 60 s at 150 W gave a useful heating time at a reasonably high power setting. If heated for longer times at the same input power, the septum usually blew after an additional 10–15 s.

The monomodal microwave equipment used here was not equipped with built-in temperature monitoring which could continually adjust the microwave power so that a constant reaction temperature could be maintained. So we independently measured a sample temperature every second during the heating and subsequent cooling. As can be seen in Figure 5, the temperature very rapidly increased and achieved a

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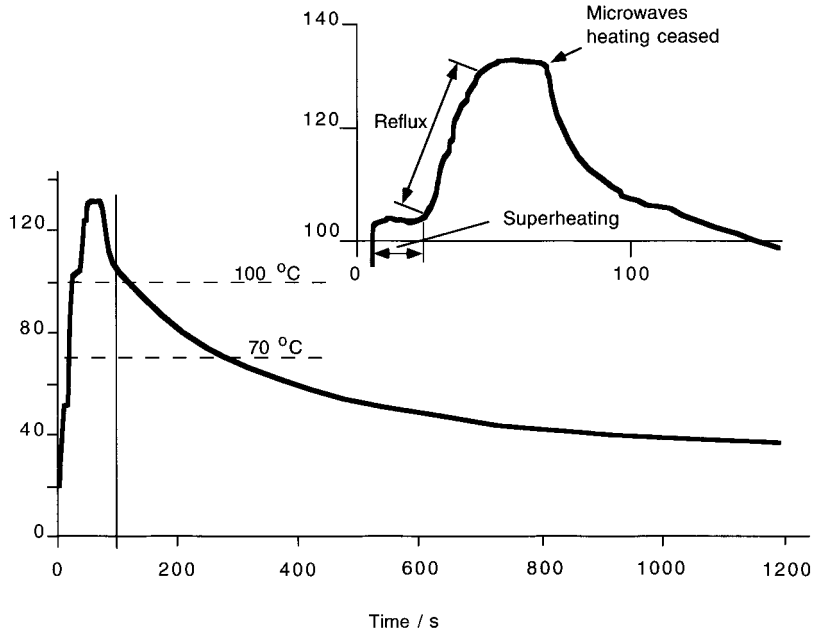

Figure 5. Heating profile of reaction 6 in the microwave at 150 W for 60 s.

nucleation-limited boiling temperature of 105–106 °C, which is in good agreement with that previously reported for water.[7h][13] When boiling started after about 40 s, the pressure in the vessel increased and the temperature rapidly rose to a maximum temperature of 132 °C, which was maintained for 10 s. As soon as the microwave was turned off, the temperature immediately and rapidly decreased. After 4 min at room temperature, the sample temperature was below 70 °C. The average temperature during those 5 min was 87 °C.

Three concentrations (Table 1) were investigated. In section A, the reagents were undiluted. In section B, the reagents were diluted to a concentration, which permitted an independent, direct qualification and quantification with the available GC. In section C, the reagents were diluted to a concentration, which here allowed a direct UV analysis with the available spectrophotometer (i.e. no dilution before measurement). Since in this type of reaction the liquid acid also usually serves as the solvent, a molar excess of **2** ($\geq$15-fold) was used in all experiments.

In the undiluted reactions (section A, Table 1), the times required for completion are close to, but are less than those in the conventional and microwave-heated literature syntheses. However, since the published microwave procedure[12] did not specify the scale for this particular reaction, the differences cannot be strictly compared. The yields estimated here by the UV monitoring are in good agreement with the yields of isolated product previously reported[11] and we were therefore encouraged to dilute to concentrations more appropriate for our feasibility study.

The reaction dynamics for the microwave heating of a sample diluted 70-fold (section B, Table 1) is shown in Figure 6. Yields increased rapidly for the initial 6–7 min of heating. Further heating did increase the yield slightly but changes were very slow after the endpoint taken here as 8 min. The similarity in the three graphs demonstrates the reproducibility of the microwave treatments. With reactions at these concentrations we were able to corroborate our UV results with qualification and quantification by the independent (non-UV based) GC method. The changing amounts of reaction components at expected retention times, the endpoints and

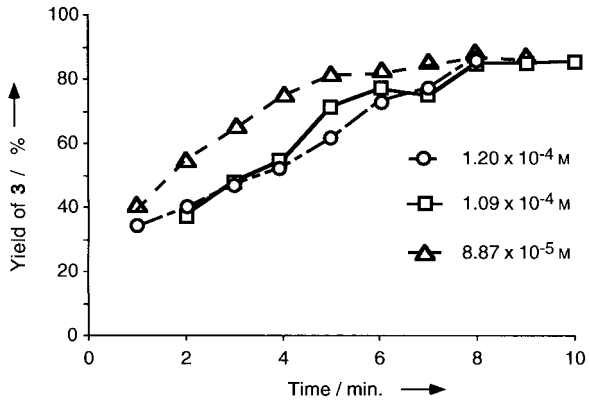

Figure 6. Progress of three typical microwave reactions from section B, Table 1.

Table 1. Experimental conditions and yields of the model reaction.

Experiment section	Number	Heating method	Conc. of **1** [mol]	Max. yield of **2** [%]	Time to completion
	1	conventional/70 °C	0.7	> 80	2 h
A	2	conventional/100 °C	0.7	> 80	45 min
	3	microwave/150 W[a]	0.7	> 80	< 2 min[b]
	4	conventional/70 °C	1.07E-02	85	22 h
B	5	conventional/100 °C	1.01E-02	79	4 h 20 min
	6	microwave/150 W[a]	1.04×10^{-2}	85	8 min[b]
	7	conventional/70 °C	8.87×10^{-5}	no reaction after 7 days	
C	8	conventional/100 °C	8.87×10^{-5}	< 30	3 days
	9	microwave/150 W[a]	8.87×10^{-5}	66	20 min[b]

[a] Maximum temperature measured 132 °C. [b] Heating periods of 1 min with intermediate cooling.

  0947-6539/02/0810-2258 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 10

the reaction trend all mirrored those observed with the UV measurements.

When the reaction mixture was diluted 170-fold (section C, Table 1), a clear advantage with microwave treatment became apparent. The reaction actually happened and in a reasonable time. A clear endpoint was reached after heating for 19–20 min (Figure 7), while the conventionally heated samples reacted very slowly or apparently not at all. The microwave conditions and UV estimations were highly reproducible, as judged by the near superimposibility of the curves. This concentration range for this model reaction should be feasible for a direct implementation in the planned in situ monitoring system.

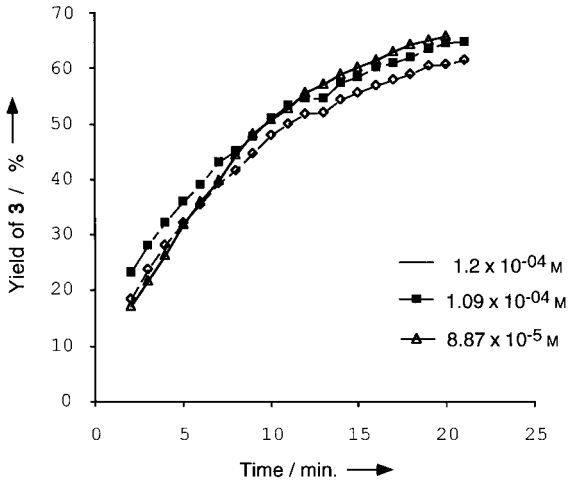

Figure 7. Progress of three typical microwave reactions from section C, Table 1.

According to the Arrhenius law, a reaction should proceed twice as quickly for every 10 °C increase in the sample temperature. For the two samples conventionally heated at 70 and 100 °C in levels A and B, the changes in speed are essentially as expected. However, the microwave heating does not fit the same pattern—the reaction is faster than would be expected using the above rule of thumb, independently of whether you consider the time at maximum temperature or at the average temperature, or the time at or above 110 or 70 °C. For section B, the temperature during the microwave reactions should have instead been 150 °C. Observations similar to these have previously been attributed to, for example, "special" microwave effects, to the rapid rate of heating, to elevated solvent boiling temperatures, to local "hot spots", and to increased mobility of the reactants.[7]

In Figure 8, predicted results for the planned in situ monitoring system are simulated from the spectral monitoring performed here. All these six spectra were taken from one microwave experiment of intermediate dilution (1.64×10^{-3}). Both the decrease of starting materials (peak at 226 nm) and the increase in product peaks at 267 and 274 nm give clear indications of the progress of reaction. The reaction endpoint is easily ascertained. The promising results from this feasibility study can be directly used to road test the new microwave/UV equipment and its implementation in monitoring the rapid reactions promoted by exposure to oscillating electromagnetic fields.

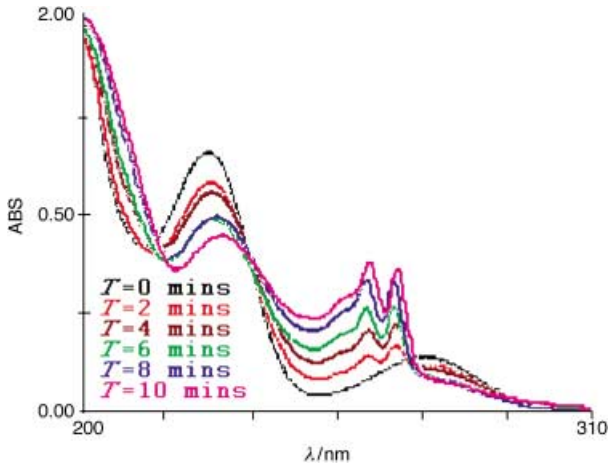

Figure 8. Simulation of the type of output we aim to produce from in situ monitoring with the microwave/UV hybrid instrument.

The reported study shows that the formation of benzimidazole from 1,2-diaminobenzene and formic acid is another of the ever expanding group of reactions which have been enhanced under microwave acceleration. The aim of the study was to decide whether it would be 1) practical and 2) useful to use UV/Vis spectroscopy as a tool for in situ monitoring of reactions in a microwave.

The results of our study show that UV/Vis spectroscopy is unaffected by the mechanics of heating by microwaves and it itself does not impinge on the methods of heating. While certain variables (i.e. temperature) of the reaction mixture may have an effect on the appearance of the UV spectrum, we are aware of these factors and their minimal nature can be negated.

So to the question of the usefulness and the feasibility of a microwave/UV hybrid instrument. The study demonstrates that this would be an excellent analytical tool for monitoring the progress of a reaction, determination of endpoints, and derivation of quantitative and kinetic data. The concentration of reactants in the section C experiments were low, but we were still able to observe the reaction proceeding across a short time frame. The easiest way to use higher concentrations and still see absorbance in the customary 0–2 range would be to shorten the path length. It may also be possible to digitally process the data in a way which reduces the level of absorbance seen. We have in this feasibility study not found any physical impediments for the construction of a hybrid microwave, UV/Vis spectrometer instrument. On the contrary, our results indicate that such an instrument would be a valuable tool for those interested in studying microwave enhancement of chemical reactions.

Experimental Section

General: 1,2-Diaminobenzene (**1**) and benzimidazole (**3**) were commercially available from Aldrich, and formic acid (85 %) (**2**) was purchased from Apoteksbolaget. Chemicals were used without further purification. UV analyses were performed with a Shimadzu 160 spectrophotometer.

Chromatographic analyses were carried out on a Shimadzu GC14A (flame ionization detector) coupled to a C-R5A integrator. All GC analyses were run on a SGE BP1 dimethyl polysiloxane capillary column with injector and detector at 250 °C and helium as the carrier gas (flow 9 mL min^{-1}). The temperature program was as follows: isocratic at 60 °C for 4 min, increase 20 °C min^{-1} to 240 °C, isocratic for 5 min followed by cooling for 7 min to 60 °C. The retention times were 4.2 and 7.1 min for **1** and **3**, respectively. For the microwave treatment, a monomodal cavity, Microwell 10 (Personal Chemistry AB, Uppsala, Sweden) was used. The reaction vessels, described previously in reference [14] were Pyrex tubes (11 mL) fitted with a screw cap and a silicone/teflon septum. Temperature measurements were made with a Nortech NoEMI TS-Series fibreoptic thermometer with a TP-21 probe.

Synthesis of 3 (Table 1): Initial experiments (A) were performed by using **1** (300 mg) in **2** (4 mL). In the second group of experiments (B) **1** (4.4 – 4.6 mg) was dissolved in water (4 mL). To this solution **2** (30 μL) was added. For the final group of experiments (C) **1** (0.96 mg) was dissolved in water (100 mL). To a 4 mL sample of this solution **2** (3 μL) was added. Conventional experiments were performed in a magnetically stirred oil bath. Microwave experiments were run at 150 W for 1 min. Between each period of heating the vessel was allowed to cool to room temperature.

Analyses of reaction mixtures: For all UV analyses 3 mL samples were analyzed against water references. For analysis of experiments from A, a sample from the reaction mixture (1.5 μL) was dissolved in water (100 mL). For experiments from section B, a reaction sample (20 μL) was taken and diluted in water (3 mL). For section C a sample of the reaction mixture (3 mL) was analyzed without dilution. This sample was recombined with the rest of the reaction mixture before heating was resumed. For GC analysis (section B) a 5 μL sample was taken directly from the reaction mixture for injection.

Acknowledgement

Support from the Swedish National Board for Technical Research (210 – 1997 – 494) and Personal Chemistry AB are gratefully acknowledged. This project was, in part, initiated through the EU sponsored D10 COST program (Innovative Methods and Techniques for Chemical Transformations).

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Received: November 22, 2001 [F3700]

  0947-6539/02/0810-2260 $ 20.00+.50/0