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Real time observation of microwave-enhanced reactions via fast FTIR spectroscopy

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ABSTRACT

Microwave-enhanced reactions are very fast in comparison to thermal reactions. The determination of optimal end point often fails because conventional analytical methods are too slow. Therefore, we established a fast method using FTIR spectroscopy. The result of the reaction control analysis is obtained within less than 1 min.

1. Introduction

The concept of microwave-enhanced reactions in organic synthesis is well established for a huge variety of reactions (see for some examples[1]) which were recently summarized in reviews[2] and several books.[3] It is possible to shorten the reaction time in comparison to classical heating from days or hours to minutes. The problem of such fast reactions is to find the optimal end point of the conversion. Typical analytical methods controlling the progress of the reaction such as NMR, TLC or HPLC often take longer time than the reaction in the microwave. The time range varies from several minutes to half an hour or even more depending on the pretreatment of the sample prior to the measurement. Within this time, the reaction progresses and by- and decomposition products may develop. This decreases the yield of the major product and increases the effort to isolate the main product.

Previously, UV/vis[4] and Raman[5] spectroscopies were reported to be suitable to monitor the reaction progress. Herein, we established a fast method to observe the progress of the reaction in real time via fast FTIR spectroscopy after microwave-assisted evaporation of samples of the reaction solution. The power of the method is demonstrated by four completely different examples.

2. Results and discussion

The following syntheses were carried out in a Milestone Ethos 1600 or a Milestone Rotaprep System. The fast FTIR spectra were measured using a Bruker Alpha apparatus and Opus software. There are two procedures A[6] (Examples 1–4) and B[7] (Example 1) to prepare and measure the progress of the reaction.

2.1. Example 1: synthesis of 1-δ-sulfobutyl-2,3,3-trimethylindoleine 1

Compound **1** is a starting material for the synthesis of cyanine dyes. Cao et al.[8] synthesized **1** in dichlorobenzene within 12 h in 69% yield (see Fig. 1). We carried out the reaction in the microwave oven with and without dichlorobenzene. In the first case, the reaction lasted for 2 h and the yield was 75% (procedure A). Without solvent, the reaction was completed already (procedure B) in 45 min and the yield was quantitative (99.8%).[9] The starting materials are both liquids and they absorb the microwave irradiation properly, since their concentration is higher in absence of solvent and they react much faster.

A part of the FTIR spectrum can be seen in Figure 2. After 45 min, the peak at 1033 cm^{-1} remained unchanged indicating the quantitative conversion. The reaction mixture could be worked up.

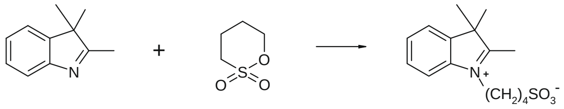

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Figure 1. Synthesis of compound **1**.

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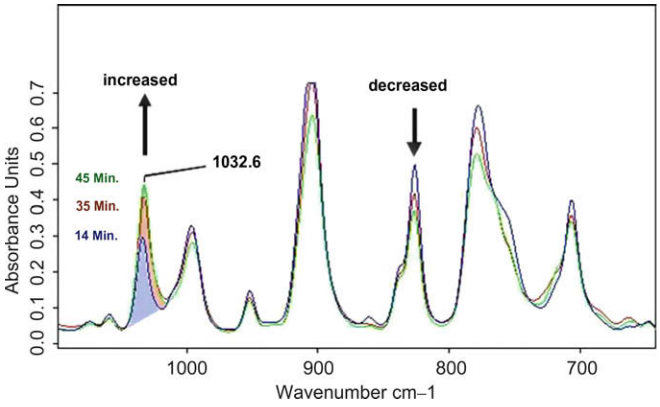

Figure 2. IR absorption bands of reaction 1.

2.2. Example 2: synthesis of 2-(3-dimethylamino-propyl)-isoindoline-1,3-dione 2

The formation of the imide **2** was published as both a thermal and a microwave-enhanced method (see Fig. 3).[1a] The reaction time was shortened (from hours to minutes) and the yield was improved with microwaves from 85% to 91%. However, the reaction was supposed to last for further 30 min applying the second method. On monitoring the reaction by means of procedure A, it was revealed that the reaction was completed within 15 min. The carbonyl signal of the imide at 1714 cm^{-1} was fully developed after 15 min (see Figs. 4 and 5) and increased only very slightly till 20 min. Additionally, the yield was augmented to 99%.

2.3. Example 3: synthesis of hexamethylenebis[dimethyl(3-phthalimidopropyl)-ammonium] dibromide (W84) 3

W84 was synthesized in the classical way (time 2 h, yield is not reported,[10] (see Fig. 6) but was found to be 80%) and in a microwave oven (time 30 min, yield 91%).[1a] IR monitoring at 694 cm^{-1} (see Fig. 7) revealed the reaction being finished after 21 min in 99% yield.

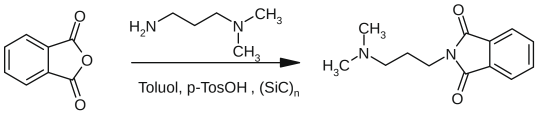

Figure 3. Synthesis of compound **2**.

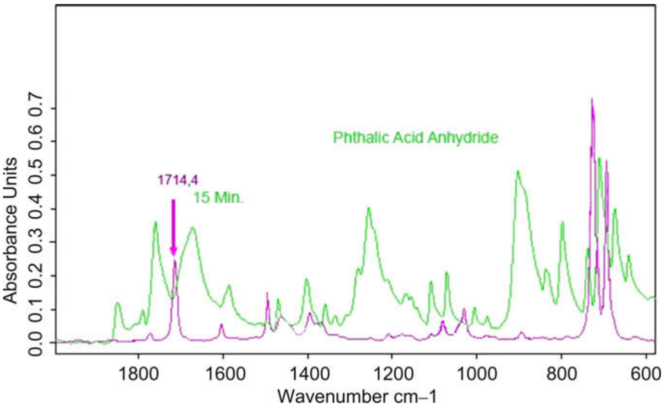

Figure 4. IR absorption bands of phthalic acid anhydride (green) and reaction mixture (magenta) after 15 min.

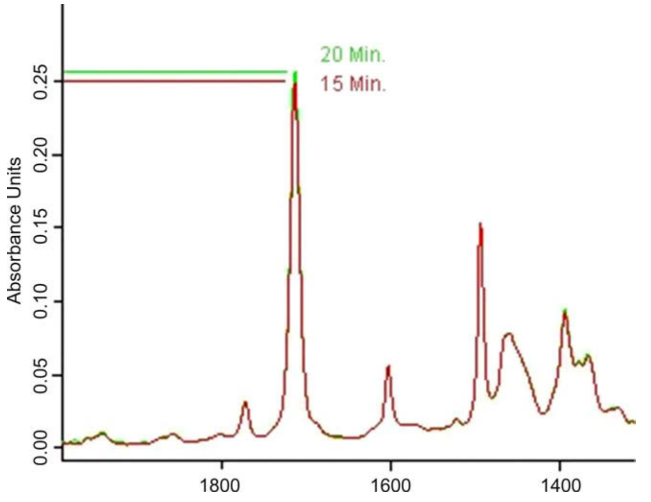

Figure 5. Extension of the IR absorption bands of the reaction mixture after 15 and 20 min.

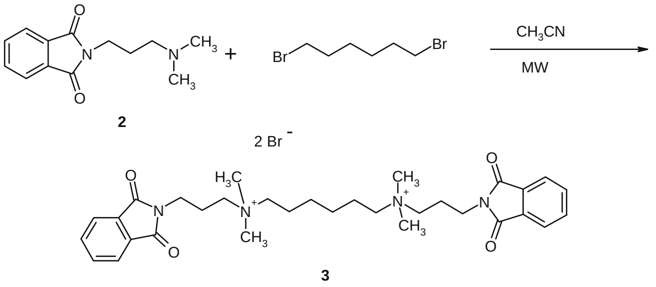

Figure 6. Synthesis of W84.

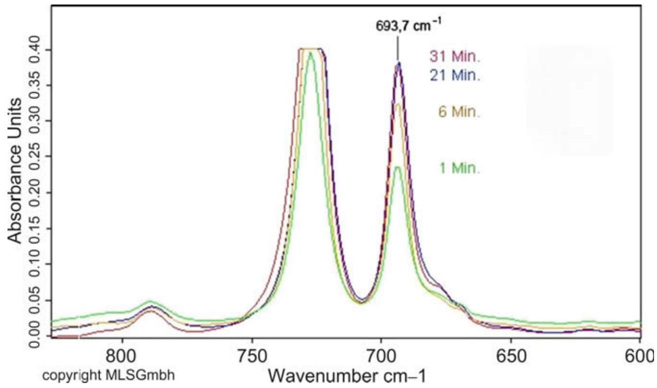

Figure 7. IR absorption bands after 1, 6, 21 and 31 min.

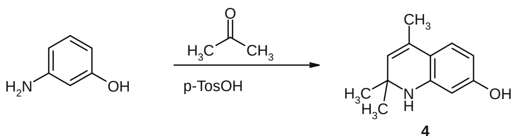

Figure 8. Synthesis of compound **4**.

2.4. Example 4: synthesis of 2,2,4-trimethyl-1,2-dihydroquinolin-7-ol 4

Yi et al.[11] synthesized the dihydroquinoline **4** with propyne and $Ru_3(CO)_{12}/HBF_4 \times OEt_2$ (see Fig. 8). They achieved only 38% yield

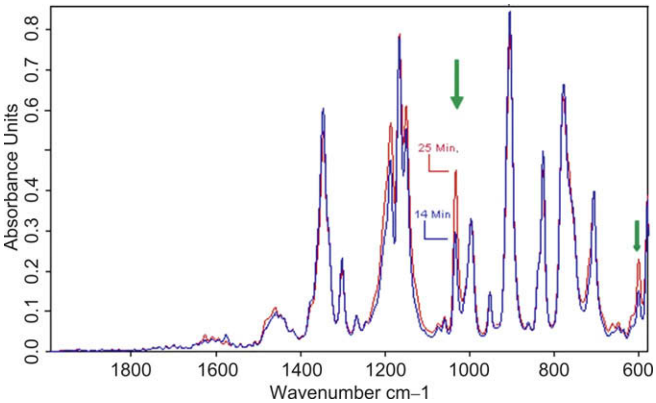

Figure 9. IR absorption bands of the reaction mixture after 14 and 25 min.

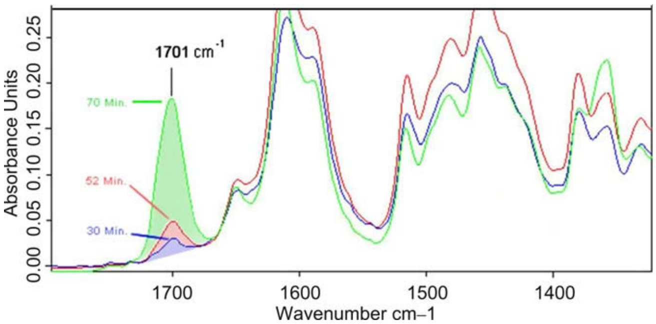

Figure 10. Extension of the IR absorption bands of the reaction mixture after 30, 52 and 70 min.

within 24 h. We carried out the reaction with a large excess of acetone. Ninety percent of **4** could be isolated after 18 h at 25 °C. When the reaction mixture was heated up classically to 50 °C, acetone polymers were formed which were very difficult to be separated from the desired product. In the microwave, the reaction was completed after 25 min at 55 °C (see Fig. 9). Only small amounts of by-product (acetone polymer) were formed after 30 min. The extension of the reaction time leads to higher amounts of the by-product (cf., Fig. 10 showing IR absorption bands after 30, 52 and 70 min) as can be seen from the growing signal at 1701 cm^{-1} (see Figs. 9 and 10). The arrows indicate the formation of the reaction product **4**.

Monitoring of microwave-enhanced reactions by fast FTIR spectroscopy allows the observation of conversion progress for nearly any chemical reaction. There is always a change in the IR spectra of the starting materials and the product especially in the finger print area. This is a big advantage in comparison to in situ monitoring by UV/vis spectroscopy where only concentrations in the range of 10^{-4} to 10^{-5} M can be observed. The FTIR method is superior to the Raman assay because many common solvents are Raman active.

The drawback of the FTIR method is applied to highly boiling and microwave transparent solvents (e.g., xylene, decaline). They cannot be evaporated in reasonable time.

3. Conclusion

The examples clearly demonstrate that monitoring of the fast microwave-supported reactions is possible via the FTIR method because the preparation of the samples to be measured IR-spectroscopically takes normally less than 1 min. However, pretreatment of the reaction samples for NMR or HPLC measurements can take up to half an hour in addition to the measurement itself. TLC does not need a sample preparation but the development time is mostly at least 10 min. Thus, the fast FTIR method presented here is optimal for the identification of the end point of the fast microwave-enhanced reaction. Over-reactions occurring during the course of NMR-, HPLC- or TLC monitoring can be avoided. Taken together, monitoring a reaction by fast FTIR spectroscopy is a useful tool to save human and material resources which can be used for other scientific challenges.

Acknowledgement

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6. Procedure A: The starting materials were dissolved in the reaction solvent and a few drops of the solution were placed on a Weflon® plate. The plate was treated with microwaves until the solvent was completely evaporated. A FTIR spectrum was monitored with the plate. The microwave oven was switched on until the reaction temperature was reached. For monitoring purposes reaction samples were prepared in the same way, after 1 min, after 2, 3 or more minutes until no change in the last two spectra were observed or until by- or decomposition products appeared. The reaction mixture was immediately cooled down to 25 °C in an air stream within 15 min and worked up.
7. Procedure B: The starting materials were mixed well without any solvent and a FTIR spectrum of one of the starting materials was monitored. The microwave oven was switched on until the reaction temperature was reached. The reaction mixture was monitored as described above without evaporating the solvent. The reaction was stopped, cooled down to 25 °C in an air stream within 15 min and worked up.
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