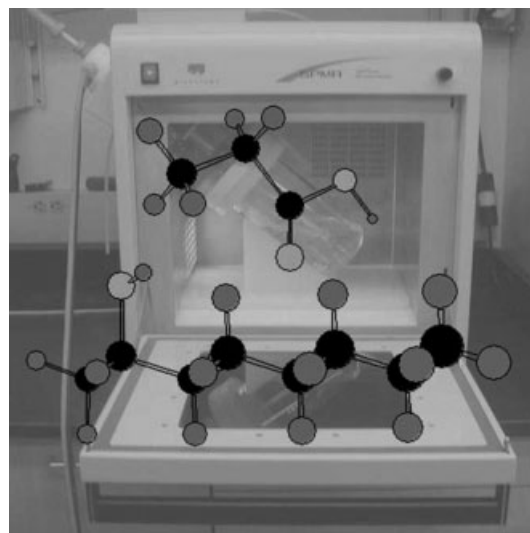


Microwave-Promoted Esterification Reactions: Optimization and Scale-Up

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Microwave heating is becoming a widely accepted tool for synthetic chemists. While many reactions have been performed on a small scale using microwave heating, few have been further developed into larger-scale syntheses. Here, a microwave-promoted esterification reaction protocol is presented. The apparatus used allows for the removal of water generated during the course of the reaction and as a result the process can be driven toward completion. Reactions have been run on scales up to 3 mol.



Introduction

Microwave heating is becoming a widely accepted tool for synthetic chemists. It is possible to improve product yields and enhance the rate of reactions as well as being a safe and convenient method for heating reaction mixtures to elevated temperatures.^[1,2] While many reactions have been performed on the small scale using microwave heating, few have been further developed into larger-scale syntheses. This clearly needs to be addressed if the technology is going to impact process chemistry.^[3,4] There are two possible scale-up options. The first is to use a continuous flow microwave cell. This technology is being used successfully for a number of different reactions.^[5,6]

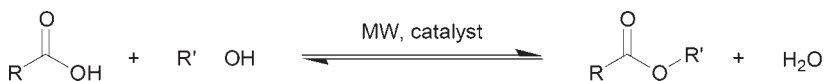
The other option is to use a batch-type process. This could either involve using one large vessel^[7-9] or parallel batch reactors.^[10,11] Recently, our group has become interested in esterification reactions since these elementary yet multifaceted reactions find wide application in organic synthesis.^[12] They are used on small and large scales in the chemical industry, in particular the fine chemicals, flavor, and fragrance businesses.^[13,14] They also have potential use in polymer synthesis. Microwave heating has been used to facilitate acid, base, and enzyme catalyzed esterification reactions.^[15,16] It has also been the subject of previous scale-up attempts.^[17-20] A problem with esterification reactions is that they are essentially equilibrium processes (Scheme 1). In order to drive the reaction to completion, either the ester product or the water generated needs to be removed as the reaction proceeds or else an excess of one of the reagents needs to be used.

A glance through the literature on microwave-promoted organic synthesis shows that the majority of the reactions

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■ Scheme 1.

are performed in sealed vessels. Although performing microwave-promoted organic synthesis in sealed vessels does allow chemists to access high temperatures and facilitates many transformations, it is often possible to get rate and yield enhancements using an open vessel attached to a simple reflux condenser. A round-bottomed flask (50–125 mL capacity) can be placed directly into the cavity of a scientific monomode microwave apparatus and reactions are run using the same level of accurate parameter control as is possible using sealed vessels. In addition, it is possible to scale up chemistry, optimized in open vessels, by moving to a multimode microwave apparatus and a larger reaction vessel. As an example, we have investigated the transfer of a Suzuki coupling protocol from sealed to open vessels.^[21] On a 1-mmol scale in a 10 mL sealed tube, the reaction is complete within 5 min of heating at 150 °C using water as a solvent and, depending on the substrate, 500 ppb to 5 ppm palladium catalyst.^[22,23] The same chemistry can be performed on the 10 mmol scale in a 100 mL open vessel, the reaction taking 20 min to reach completion. Depending on the substrate, sometimes a slightly higher catalyst loading is required (1–5 ppm).^[24] This protocol can then be scaled up to the 1 mol level, performing the reaction in a 5 L flask.

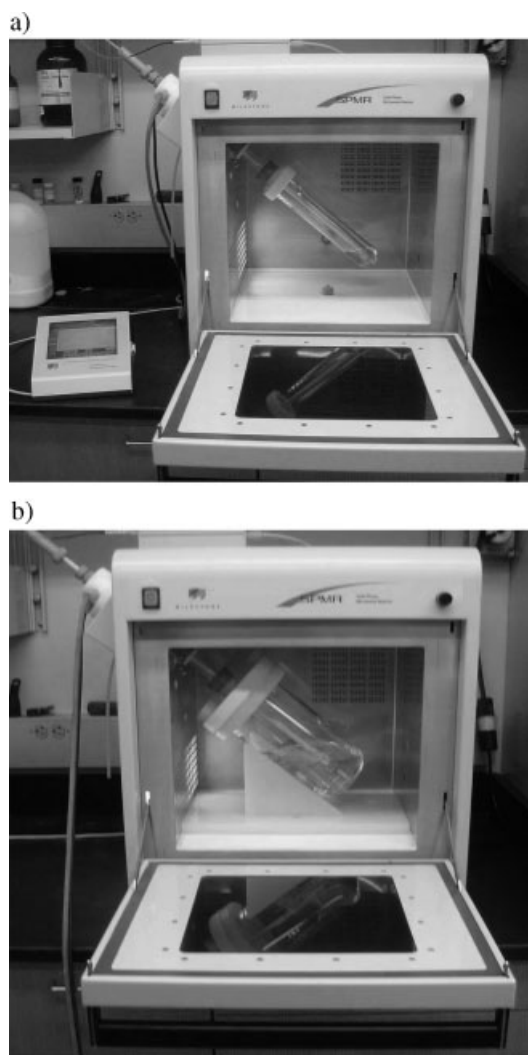
When using a sealed vessel or an open vessel reflux set-up, it would not be possible to remove either product or water during an esterification reaction. In order to address this issue while staying with an open-vessel design, we have turned our attention to a new microwave apparatus and discuss our initial results here.

Experimental Part

Materials and Apparatus

All reagents were obtained from commercial suppliers and used without further purification. ¹H and ¹³C NMR spectra were recorded at 293 K on a 400 MHz spectrometer. Reactions were performed using a Milestone solid-phase microwave reactor (SPMR) apparatus (Figure 1). The single magnetron (1 200 watt) multimode unit, with rotating diffuser for homogeneous microwave distribution in the cavity, delivers from 0 to 1 000 watts microwave power in 1 watt increments. This instrument is controlled with a touch screen terminal running Easy CONTROL software. Using this reactor system, microwave irradiation was applied using either power (wattage) control or temperature control. In the case of the latter, reaction mixtures were ramped to

the desired temperature over a time period set by the operator. Microwave power, based on a proportional-integral-derivative (PID) algorithm, is adjusted to maintain an even heating profile over this time period. Once at the desired temperature, the reaction mixture was held for a set time before cooling. Temperature measurement was either by an infrared (IR) sensor located in the right-hand wall of the microwave unit facing at the bottom of the vessel or by a fiber-optic probe inserted directly into the reaction mixture. The SPMR could also be connected to a vacuum pump on the outside of the microwave unit. On the outside of the microwave unit there is also an opening to which a tube was attached in order to add or remove liquids during the reaction. Inside the microwave cavity, a tilted glass reactor rotates in order to mix the reaction mixture effectively. Furthermore, the glass vessels have special paddles built in for more effective mixing of reaction mixtures and to ensure homogeneous heating. Different size of reaction vessels



■ Figure 1. Microwave unit used for open-vessel esterification reactions.

could be used with this system, starting from 300 mL up to 4 L. The glass vessels can work up to 200 °C and under vacuum of 300 mbar.

General Experimental Procedure

In a 3-L glass vessel, propionic acid (0.224 L, 3 mol), 1-octanol (0.472 L, 3 mol), and sulfuric acid (8.750 mL) were placed. The vessel was attached to the rotor mechanism in the microwave cavity. The mixture was heated to 100 °C over the period of 5 min and then held there for 10 min. After stopping the heating and allowing the reaction mixture to cool to 50 °C, the vessel was removed. Conversion could be determined by NMR analysis of the crude product mixture. The ester was isolated by placing the contents of the reaction vessel into a separatory funnel together with 250 mL brine and basifying the mixture using NaHCO₃. The product constituted the resultant organic layer and was isolated, characterized by comparison of NMR spectral data with that in the literature.

Results and Discussion

In a previous study we had performed the esterification of acetic acid and propanol in a 10 mL sealed tube on a 23 mmol scale using microwave heating.^[25] The reaction was run using a 1:1 stoichiometric ratio of acetic acid to propanol and sulfuric acid (0.6% by volume) added as a catalyst. The mixture was heated to 100 °C using a monomode microwave apparatus and held at this temperature for 1 min. A 63% yield of propyl acetate was obtained. Regardless of the reaction time or temperature, the yield could not be increased. We attribute this to the fact that once equilibrium has been reached. Since neither the product nor water generated could be removed, the forward reaction proceeded no further. To overcome these problems we decided to move to a multimode microwave apparatus, designed such that we could intro-

duce or remove liquids during the course of a reaction. The apparatus, pictured in Figure 1, incorporates a tilted glass vessel inside the microwave cavity in which the reaction takes place. The rotation of the vessel assures temperature homogeneity of even large amounts of material. On the outside of the microwave unit is an opening to which a tube or a pump can be attached and product distilled out during the course of a reaction. We wanted to use this to remove the water formed during esterifications and, in doing so, drive the reactions to completion. Using a 300 mL capacity reaction vessel we chose the reaction of propionic acid and 1-octanol to test the apparatus and optimize reaction conditions. Working on a 171 mmol scale, we heated the mixture to 120 °C over the period of 5 min and held it at this temperature for 10 min, collecting water as it was evolved during the course of the reaction. Using 4% sulfuric acid by volume based on propionic acid (1.25% based on entire volume) as a catalyst we obtained an 86% yield of octylpropanoate (Table 1, entry 1). Reducing the catalyst loading from 4% to 0.8% had a deleterious effect on product yield (Table 1, entry 2). Increasing the catalyst concentration to 8% resulted in significant decomposition (Table 1, entry 3). Increasing the reaction temperature to 150 °C had a negligible effect on product yield (Table 1, entry 4). As we wanted to be able to perform the chemistry using lower boiling substrates, we felt it important to determine the effects of decreasing the temperature on the esterification reaction. Running the reaction at 100 °C, we obtained an 83% yield of the product, indicating that it was possible to operate efficiently at lower temperatures (Table 1, entry 5). The reaction could be scaled up to the 0.3 mol level using the same reaction vessel and same reaction conditions with negligible decrease in product yield (Table 1, entry 6).

With reaction conditions in hand, we screened other alcohols in the esterification reaction with propionic acid. The results are shown in Table 2. Working on the 0.3 mol

Table 1. Effect of reaction conditions on the esterification of propionic acid with 1-octanol.^{a)}

Entry	Conditions ^{b)}	Product yield
		%
1	Heat to 120 °C in 5 min and hold for 10 min, 4% H ₂ SO ₄	86
2	Heat to 120 °C in 5 min and hold for 10 min, 0.8% H ₂ SO ₄	75
3	Heat to 120 °C in 5 min and hold for 10 min, 8% H ₂ SO ₄	Decomposition
4	Heat to 150 °C in 5 min and hold for 10 min, 4% H ₂ SO ₄	87
5	Heat to 100 °C in 5 min and hold for 10 min, 4% H ₂ SO ₄	83
6 ^{c)}	Heat to 100 °C in 5 min and hold for 10 min, 4% H ₂ SO ₄	85

^{a)}Reactions performed on a 171-mmol scale using a 1:1 stoichiometric ratio of propionic acid to 1-octanol; ^{b)}Sulfuric acid measured by volume based on propionic acid; ^{c)}Reactions performed on a 300 mmol scale using a 1:1 stoichiometric ratio of propionic acid to 1-octanol.

Table 2. Preparation of esters from propionic acid using microwave heating (reactions were performed using a 1:1 stoichiometric ratio of propionic acid to alcohol and 4 wt.-% H₂SO₄ as catalyst (based on propionic acid); reaction mixtures were heated to 100 °C in 5 min and held at this temperature for 10 min; water was collected as it was generated).

Entry	Alcohol substrate	Scale	Product yield
		mol	%
1	1-octanol	0.3	85
2	1-butanol	0.3	85
3	1-propanol	0.3	90
4	2-propanol	0.3	50
5 ^{a)}	2-octanol	0.3	70
2 ^{a)}	1-octanol	3.0	83
3	1-butanol	3.0	82
4	1-propanol	3.0	94
5 ^{a)}	2-octanol	3.0	71

^{a)}Reaction performed at 120 °C.

scale, using 1-butanol we obtained propylbutanoate in 85% yield (Table 2, entry 2). With 1-propanol, a 90% yield of ester product was obtained (Table 2, entry 3). Traditionally, using secondary alcohols in esterification reactions results in lower product yields than when using their primary analogs. We find that the same is true in our methodology. With 2-propanol, a 50% yield of the desired ester was formed (Table 2, entry 4). Using 2-octanol, a 70% yield of propyl octanoate was obtained when performing the reaction at 120 °C (Table 1, entry 5).

We next wanted to run the reactions on a larger scale. To do this, we used a 2 L capacity vessel but kept the reaction time the same as that for the smaller-scale reactions. With 1-octanol as a substrate, we performed the esterification with propionic acid using 3 mol of each. We obtained an 83% yield of octylpropanoate (Table 2, entry 5). This equates to approximately 0.5 kg (0.6 L) of product. The reaction was repeated using 1-propanol, 1-butanol, and 2-octanol (Table 2, entries 6–8).

In summary, we offer here a multi-gram scale microwave-promoted esterification reaction protocol. The apparatus used gives us the ability to remove the water generated during the course of the reaction and as a result the process can be driven toward completion. Success in this reasonably simple reaction shows the potential of the apparatus for use in other reactions that either liberate water as a by-product or else yield an easily distillable product; thus driving equilibrium reactions to completion or allowing for facile product isolation.

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