A New Microwave Reactor for Batchwise Organic Synthesis

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Received November 15, 1994[⊗]

A laboratory-scale microwave batch reactor (MBR) has been developed for organic synthesis or kinetic studies on the 20–100 mL scale, with upper operating limits of 260 °C and 10 MPa (100 atm). The MBR complements a continuous microwave reactor which was the subject of a previous report from the authors' laboratory. Microwave-assisted organic reactions were conducted safely and conveniently in the MBR, for lengthy periods when required, and in volatile organic solvents. The use of water as a solvent for organic reactions was also explored. Examples include oxidation, elimination, esterifications, hydrolysis of a tertiary amide, etherification, isomerization, Hofmann elimination, α-iodination of a carboxylic acid, Claisen rearrangement, aminoreductone formation, and Willgerodt reactions. Advantages of the new MBR include the capability for rapid heating and quenching of reaction mixtures, minimal temperature gradients within the sample, and elimination of wall effects. Safety aspects have been discussed.

Introduction

The earliest reported microwave-assisted organic reactions were carried out with domestic microwave ovens and rudimentary reaction vessels.[1] Although rate enhancements of up to 1240-fold were observed,[2] hazards associated with microwave heating of organic reactions were also apparent, including deformation of vessels and explosions.[1b,2,3] Thus, the technology was perceived as simultaneously beneficial through increased rates, yet potentially dangerous owing to the flammability of solvents.[1b,2–4]

To retain the benefits and minimize the risks, workers explored solvent-free conditions including "dry" media,[4,5] usually with open vessels in domestic microwave ovens. Several interesting applications have now been reported.[5] These techniques appear to have limited scope for scaling-up, however. Also, some procedures may be difficult to reproduce, owing to differences in performance of domestic microwave ovens, nonuniform heating, and the lack of temperature measurement.

An alternative approach involving high boiling solvents, unmodified domestic microwave ovens, and conventional beakers and flasks also has been pursued.[6] Reactions on the multigram scale were conducted in minutes rather than hours, using solvents such as chlorobenzene, 1,2-dichlorobenzene, ethylene glycol, and diglyme.

However, if the potential applications of microwave technology in organic chemistry are to be fully explored, specifically designed microwave reactors will be required, and it is essential that they operate reliably and safely on a routine basis in the presence of organic solvents.

Our group recently reported on a continuous microwave reactor (CMR) for conducting organic reactions.[7] Advantages and applications of the new technique were discussed. However, CMR may not be appropriate for kinetics studies, or when solids or highly viscous liquids are to be heated. Because of its mode of operation, it is more suitable for chemical processing or process optimization than once-only synthetic reactions on a small scale.

These aspects led us to develop a complementary laboratory-scale microwave batch reactor (MBR) for kinetics studies and synthesis.[8–10] The unit had a stirrer and facilities for monitoring temperature and pressure in the reaction vessel directly, but its upper operating limits were only 200 °C and 1 MPa.[8] It also lacked capabilities for withdrawing samples during a reaction and for postreaction cooling. We have now developed a more advanced laboratory-scale MBR, which has these facilities and can be operated at higher temperature and pressure.[11,12] This new reactor is discussed, along with examples and safety issues.

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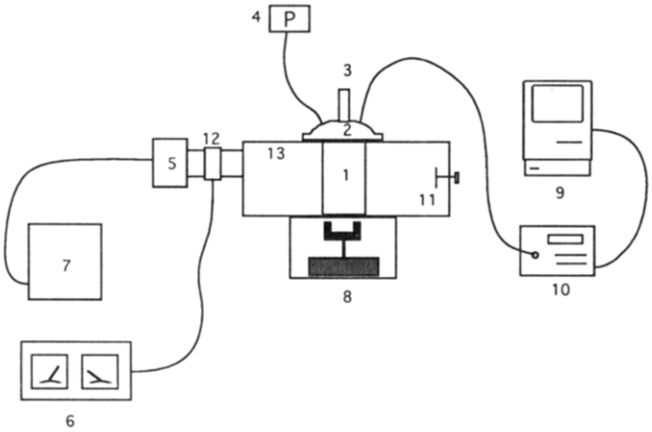

Figure 1. Schematic diagram of the MBR: 1, reaction vessel; 2, top flange; 3, cold-finger; 4, pressure meter; 5, magnetron; 6, forward/reverse power meters; 7, magnetron power supply; 8, magnetic stirrer; 9, computer; 10, optic fiber thermometer; 11, load matching device; 12, waveguide; 13, multimodal cavity (applicator).

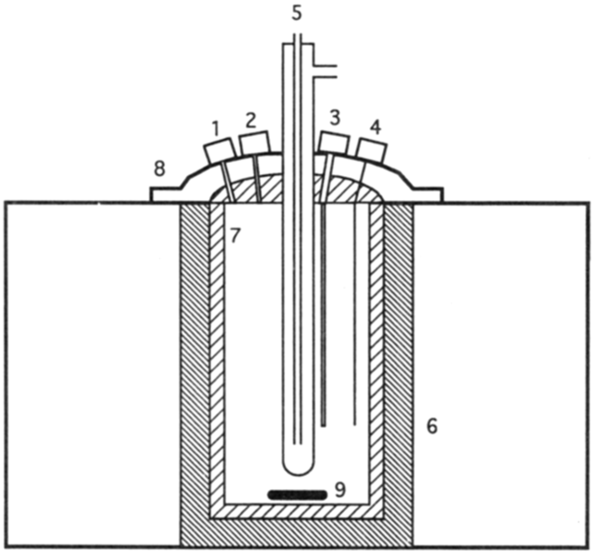

Figure 2. Schematic diagram of reaction vessel and associated components: 1, pressure transducer; 2, pressure relief valve; 3, sample addition/removal port; 4, optic fiber thermometer; 5, cold-finger; 6, retaining cylinder; 7, PTFE reaction vessel; 8, top flange; 9, magnetic stirrer bar.

Results and Discussion

The Microwave Batch Reactor. The features of the new MBR are illustrated schematically in Figures 1 and 2. Microwave power was generated with a 1.2 kW magnetron and regulated by an infinitely variable power supply. Microwaves were directed *via* the waveguide[13] into the multimodal cavity,[13] which was fabricated from plate steel. Forward and reflected power[13] were measured within the waveguide. Reflected power was minimized by a load matching device.[13] The reaction vessel, of 20–100 mL operating capacity, was equipped with a magnetic stirrer bar and was retained by microwave-transparent fittings within the cavity. The optic fiber thermometer, cold-finger cooler, pressure transducer, pressure relief valve, and sample withdrawal tube/inert gas inlet were all attached to a stainless steel flange which formed a gas-tight seal with the reaction vessel. Wettable surfaces were fabricated from poly(tetrafluoroethylene) (PTFE), poly(ether ether ketone) (PEEK), or quartz. A stainless steel or quartz cold-finger was used. Access to the reaction vessel was *via* the removable top flange. In contrast with reported systems,[3b,8,14,15] the MBR could operate up to 260 °C and 10 MPa.

Examples. Details of reactions are presented in Table 1. Examples include oxidation (entry 7), elimination (entry 8), esterification (entries 1, 2, and 10), hydrolysis of a tertiary amide (entry 12), etherification (entries 3 and 4), isomerization (entry 15), Hofmann elimination (entry 9), α-iodination of a carboxylic acid (entry 6), Claisen rearrangement in water (entry 5), aminoreductone formation (entry 11), and Willgerodt reactions (entries 13 and 14). Despite an earlier prediction to the contrary,[4a] the results establish that with appropriate monitoring and control, microwave-assisted organic reactions can be conducted safely and conveniently at elevated temperatures, even for lengthy periods, and in volatile organic solvents.

Since microwaves heat by irradiation rather than by conduction, rapid heating rates are possible. This is a significant advantage of the MBR over conventional methods. However, for microwave chemistry, the vessels are usually made from materials which are good thermal insulators (*e.g.*, PTFE) and the benefits of rapid heating can be partially negated if long cooling times are required at the end of the reaction. Decomposition of thermally labile products can occur during periods of gradual cooling, and the time needed to complete reactions is extended under such circumstances. Therefore, cessation of heat input should be followed by rapid quenching if necessary. The cold-finger cooling system developed here has proven to be highly effective in this regard. Typically, a reaction carried out on the 100 mL scale at 200 °C for 5 min in the MBR could be worked up after a total time of only 10 min, the heating and cooling processes each requiring only *ca.* 2.5 min.

Rapid cooling is not always necessary, but for the thermal preparation of unstable compounds, it is essential. In the Hofmann elimination (entry 9), for example, a two-phase water/$CHCl_3$ solvent system was used. Immediately after the starting salt had reacted, the product aryl vinyl ketone was extracted (and diluted) into the poorly microwave-absorbing, and thus cooler, organic phase. The mixture was then subjected to rapid postreaction cooling. These measures prevented polymerization and afforded near quantitative yields of the monomer.

Another example (not included in Table 1) involved the degradation of cellulose in dilute sulfuric acid, where high temperatures were required in order to cleave the glycosidic bonds, but the glucose so formed was susceptible to decomposition. In this context, excellent results were obtained when the temperature was raised from ambient to 215 °C within 2 min, maintained at 215 °C for 30 s, and then rapidly decreased to 50 °C. Only 1 min was spent above 200 °C, and the conversion to glucose was 39%.[16]

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Table 1. Example Reactions and Conditions

entry no.	reaction	temp (°C)	mean press. (kPa)	time (min)	product	yield (%)	lit. ref
1	PhCOOH + MeOH/2 M HCl	200	1300	20	PhCOOMe	96	
2	2,4,6-trimethylbenzoic acid + *i*-PrOH/H_2SO_4	148	1000	60	isopropyl 2,4,6-trimethylbenzoate	56	8, 9
3	$PhCH_2CH_2Br$ + MeOH	140	1000	120[a]	$PhCH_2CH_2OMe$	78[b]	7, 29
4	$PhCH_2CH_2Br$ + MeOH	170	2100	20	$PhCH_2CH_2OMe$	75[b]	7, 29
5	$PhOCH_2CH{=}CH_2$ in water	240	3300	10	2-allylphenol	84	1b
6	dry HOAc + $I_2/Bi(OAc)_3$	200	570[c]	20	ICH_2COOH	83	17
7	4-*tert*-butylcyclohexanols + $CrO_3/HOAc/H_2O$	25−28, then 110	100	60, then 15	4-*tert*-butylcyclohexanone	61	26
8	$Br(CH_2)_6Br$ + HMPA	200	100	10	$Br(CH_2)_4CH{=}CH_2$	49	25, 32
9	$[4\text{-}EtOPhCO(CH_2)_2NMe_3]^+ I^-$ in water/$CHCl_3$	110[d]	350	1	$4\text{-}EtOPhCOCH{=}CH_2$	97	
10	3-hydroxy-2-methyl-4-pyrone with $Ac_2O/NaOAc$ in $CHCl_3$	125	300	15	3-acetoxy-2-methyl-4-pyrone	75	30
11	3-hydroxy-2-methyl-4-pyrone in 25% aqueous NH_3	130	nr[e]	30	3-hydroxy-2-methylpyrid-4-one	69	31
12	4-[(4-*tert*-butyl-1-cyclopenten-1-yl)-carbonyl]morpholine in 2 M HCl	200	3000	10	4-*tert*-butylcyclopentene-1-carboxylic acid	70	18
13	PhCOMe + S_8 in pyridine and 28% aqueous NH_3	185	1840[f]	10	$PhCH_2CONH_2$	72	19, 20
14	$PhCH{=}CH_2$ + S_8 in pyridine and 28% aqueous NH_3	170	1600[f]	10	$PhCH_2CONH_2$	51	19, 20
15	carvone + TsOH in PhCl/dioxane	180	330	35	carvacrol	85	7, 10

[a] Samples were withdrawn at 10 min intervals during the heating. [b] Percent conversion. [c] Initially purged with N_2 and then pressurized to 170 kPa with N_2 before heating. [d] Temperature of the aqueous phase. [e] Not recorded. [f] Maximum pressure attained.

Microwave heating can also offer an alternative to the use of aggressive reagents at lower temperatures. For example, attempted Williamson syntheses of 2-phenylethyl ethers from 2-phenylethyl halides and alkoxides give mainly styrene instead of the desired product.[7] Here though, methyl 2-phenylethyl ether was prepared from MeOH and 2-(bromoethyl)benzene in the absence of catalyst. Although both reactions (entries 3 and 4) afforded comparable conversions, the more vigorous conditions required considerably less time. This etherification showed that when elevated temperatures are not detrimental to chemoselectivity or product stability, such conditions can be highly beneficial. Because routine laboratory glassware is not designed for pressurized operation, however, higher boiling solvents are conventionally employed to increase reaction temperature. This can introduce difficulties for subsequent removal of solvent. Since reactions can be conducted safely at elevated pressures in the MBR, low-boiling solvents can be used in high temperature reactions, and the product can be readily concentrated.

For example, isopropyl mesitylate was produced from mesitoic acid with excess *i*-PrOH and catalytic amounts of sulfuric acid, in less than 3% conversion after refluxing for 28 h. At 148 °C in the MBR, however, the yield was 56% after only 1 h (entry 2).[8] Furthermore, a suspension of $Bi(OAc)_3$ and I_2, when heated at reflux for 40 h in excess glacial HOAc, gave iodoacetic acid in 89% yield.[17] With the MBR, a comparable yield of the product was obtained after heating for only 20 min at 200 °C (entry 6). Hydrolysis of the morpholide (entry 12) under reflux conditions in 2 M aqueous HCl gave the corresponding acid in only 48% yield after 4 h,[18] yet at 200 °C in the MBR, it was obtained in 70% yield within 10 min. The benefits were also demonstrated in straightforward esterifications (entries 1 and 10).

The Willgerodt reaction typically involves heating alkyl aryl ketones with sulfur and aqueous ammonia with or without an organic solvent to form carboxylic acid amides with the same number of carbon atoms.[19] The reactions are normally conducted over several hours in an autoclave or bomb. DeTar and Carmack[20] obtained $PhCH_2CONH_2$ in varying yields from PhCOMe at 160−190 °C over 4−6 h. With the MBR, $PhCH_2CONH_2$ was prepared by heating PhCOMe, sulfur, and aqueous ammonia in pyridine within this temperature range, but for considerably less time (entry 13). The same product was also prepared from $PhCH{=}CH_2$ in minutes (entry 14).

Recently, there has been increasing interest in the use of water as a medium for organic applications.[21,22] Temperatures of 100 °C and below have been commonly used in synthesis.[21] At higher temperatures, however, the polarity of water approaches that of solvents such as Me_2CO at room temperature.[22] This, combined with the need to minimize organic solvent usage for environmental reasons,[23] prompted us to study organic reactions in water. The convenience and operating parameters of the MBR made it ideal for these investigations.

Although White and Wolfarth[24] found that the reaction rate of the Claisen rearrangement was enhanced in polar solvents, Grieco *et al.*,[21b,d] who explored the rearrangement of allyl vinyl ethers, were the first to demonstrate the benefits of water. In the present work, allyl phenyl ether was heated at 200, 219, and 240 °C, each for 10 min, under aqueous conditions. Only 10% conversion to 2-allylphenol was obtained at 200 °C, but this increased to 48% at 219 °C and 84% at 240 °C (entry 5). To our

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knowledge this is the first example of a Claisen rearrangement of an allyl aryl ether in water.

In all of the above examples, the MBR was used as a closed system, mostly under pressurized conditions. For the preparation of 6-bromohex-1-ene from 1,6-dibromohexane (entry 8), however, it was essential to remove the monobromo olefin from the reaction medium before a second elimination of HBr could occur. Hence, the MBR was set up with an outlet tube connected to the cover assembly. 1,6-Dibromohexane was heated in the reaction vessel to 150 °C, and a small amount of HMPA was added by means of a syringe, through a second tube attached to the cover assembly. The mixture was then rapidly heated to 200 °C and further HMPA added dropwise through the syringe as the crude product was distilled through the exit tube. An advantage of using the MBR for this application was the rapid but controlled distillation of product which was made possible by the high heating rate and temperature control afforded by the MBR. The procedure was completed within 10 min, and in comparable yield with that of a recent report.[25]

Microwave reaction vessels typically are fabricated from poor thermal conductors, and this results in low rates of heat dissipation from the sample. Hence, highly exothermic reactions can present difficulties when performed without careful monitoring and adequate control.[1a,2] Microwave irradiation does not cause the chamber to heat significantly, however, and when the power is turned off heat input immediately ceases. These aspects, combined with the facility for cooling, were particularly beneficial when exothermic reactions (*e.g.*, entry 7) were conducted in the MBR.

Safety. Safety guidelines for microwave systems in the analytical laboratory have been discussed.[27] These also apply for microwave-assisted organic chemistry.

Although high rates of heating are possible under microwave conditions, a potential hazard appears when the material being irradiated possesses a dielectric loss tangent[13,27] that increases with temperature. Microwaves are then absorbed with increasing efficiency as the temperature increases, and a thermal runaway[13] can result unless the temperature is monitored and the microwave input controlled.

Certain ceramics or polymers which could be used to fabricate microwave reaction vessels are microwave-transparent at low temperatures but become strongly microwave-absorbing as the temperature rises. Thus, reaction vessels also have the potential for thermal runaway under microwave conditions. It is essential therefore, that the vessels have suitable dielectric properties across the intended operating-temperature range. Obviously, the materials must not be porous or soluble in the solvents used, at elevated temperature.

Another effect concerns the decrease in dielectric constant of solvents with temperature. This property reduces the efficiency of microwave absorption as the temperature rises and leads to poor matching[13,27] of the microwave load, particularly as the fluid approaches the supercritical state. Solvents and reaction temperatures should be selected with these considerations in mind, as excess input microwave energy can lead to electrical discharge.[13,27,28] Arcing could result in vessel rupture and/or an explosion if flammable compounds are involved. Therefore, it is essential in microwave-assisted organic reactions that the forward and reverse power can be monitored and the energy input reduced (or the load matching device adjusted) if the reflected power becomes appreciable.[13]

Although the applicator[13] of plate steel was an important safety feature in the possible event of vessel rupture or explosion, several hundred reactions have been conducted in the MBR without accident. Temperature and pressure measurements, stirring, infinitely variable control of microwave power input, the cold-finger, as well as a pressure relief valve, have all contributed significantly to the safety and reliability of the present system. They should be viewed as the minimum requirements for MBRs. Microwave-assisted organic chemistry is in its infancy, however, and our investigations to enhance safety are continuing.

Conclusion

A laboratory-scale MBR has been developed for conducting microwave-assisted organic reactions under controlled conditions. The unit could be operated at temperatures up to 260 °C, at pressures up to 10 MPa, and in the presence of organic solvents. An advantage of the new MBR is the ability to heat and quench reaction mixtures rapidly. Additionally, with the MBR there are minimal temperature gradients within the sample, and wall effects are eliminated. Examples demonstrate the capabilities of the MBR for carrying out a diverse range of reactions, some of which have proven difficult by conventional techniques. The MBR complements a continuous microwave reactor, which was the subject of a recent report. Without such equipment, microwave-assisted organic synthesis would be largely limited to the use of open vessels and "dry" conditions.[4,5b,6]

Experimental Section

General. The MBR[12] was fabricated in the CSIRO workshops and was employed in a fume hood. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, and chemical shifts are in ppm relative to TMS. Elemental analyses were performed by Australian Microanalytical Service, Melbourne. Electron impact (EI) mass spectra were obtained at 70 eV; chemical ionization (CI) mass spectra were recorded with methane as the reagent gas. Physical data for known compounds listed in Table 1 agreed with literature values.

Example Preparations. Oxidation of 4-*tert*-Butylcyclohexanols (Entry 7, Table 1). A solution of CrO_3 (10 g) in HOAc (50 mL) and water (10 mL) was placed in the microwave reaction vessel. Coolant (−35 °C) was circulated through the stainless steel cold-finger. When the temperature of the contents of the vessel reached *ca.* −5 °C, a solution of 4-*tert*-butylcyclohexanols (10 g) in HOAc (25 mL) was added. Circulation of coolant was maintained through the cold-finger, and the temperature of the reaction was increased to 25 °C by the application of microwave power. The reaction was controlled by circulating coolant at −35 °C through the cold-finger, while simultaneously applying and varying the micro-

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wave power, to hold the temperature at 25−28 °C over 1 h. The cooling flow was turned off, and the contents of the reaction vessel were heated to 110 °C for 15 min and then cooled to 20 °C. MeOH (5 mL) and water (50 mL) were then added. The product was steam distilled, the distillate extracted with CH_2Cl_2 (1 × 50 mL; 2 × 25 mL), the combined organic phase was washed with water (2 × 25 mL) and dried ($MgSO_4$), and the solvent removed to afford 4-*tert*-butylcyclohexanone (5.5 g; 61%) as a waxy, white solid.

For comparison, a solution of 4-*tert*-butylcyclohexanols (4.5 g) in HOAc (15 mL) was added to a solution of CrO_3 (5 g) in water (5 mL) and HOAc (25 mL) at rt, in an open vessel, without cooling. A vigorous exothermic reaction ensued, and the temperature increased to 105 °C within 10 s.

Preparation of 6-Bromohex-1-ene (Entry 8, Table 1). The MBR was fitted with an exit tube to allow volatile products to be collected. 1,6-Dibromohexane (48 g) was heated to 150 °C, and then HMPA (3 mL) was added through the sampling port. The temperature was rapidly raised to 200 °C, and the product began to distill through the exit tube and was collected in a chilled flask. The dehydrobromination was maintained at a steady rate by dropwise addition of HMPA (42 mL) through the sampling port. 6-Bromohex-1-ene (15.9 g; 49%) was obtained as a colorless liquid after redistillation.

4′-Ethoxyphenyl Vinyl Ketone (Entry 9, Table 1). *N*-(4′-Ethoxy-2-benzoylethyl)-*N,N,N*-trimethylammonium iodide was prepared as follows. A mixture of 4′-ethoxyacetophenone (40.0 g), paraformaldehyde (7.3 g), and $Me_2NH{\cdot}HCl$ (19.9 g) in EtOH (160 mL) was heated to reflux with vigorous stirring. Concentrated HCl (1 mL) was added, and the mixture became clear. After 1 h, a further addition of paraformaldehyde (7.3 g) was made, and heating was continued for 1 h. This procedure was repeated twice more. The mixture was then heated at reflux for a further 2 h. The EtOH was evaporated and the residual solid dissolved in water (200 mL) and extracted with Et_2O (3 × 60 mL) to remove starting ketone. The aqueous phase was basified to pH 10 with 30% w/v aqueous K_2CO_3, the resultant mixture was extracted with Et_2O (3 × 100 mL), and the combined organic phases were dried ($MgSO_4$). The solvent was removed, and the residue (42.0 g) was redissolved in Et_2O (250 mL), treated dropwise with MeI (29.5 g) over 30 min at rt and then stirred for 48 h. The iodide (50.4 g; 74%), an unstable white solid, was collected by filtration and washed with Et_2O: IR (mineral oil) 1670(s), 1350(s), 785(m) cm^{-1}; ^{1}H NMR (DMSO) δ 1.41 (t, 3H, J = 6.0 Hz), 3.22 (s, 9H), 3.62 (m, 2H), 3.79 (m, 2H), 4.1 (q, 2H, J = 6.7 Hz), 6.98 (m, 2H), 8.03 (m, 2H); ^{13}C NMR (DMSO) δ 14.4, 44.2, 52.5, 61.0, 63.6, 114.2, 128.6, 130.5, 162.7, 194.4. Anal. Calcd for $C_{14}H_{22}O_2NI$: C, 46.3; H, 6.1; N, 3.9; O, 8.8; I, 34.9. Found: C, 45.9; H, 6.5; N, 4.2; O, 9.0; I, 34.8.

A suspension of *N*-(4′-ethoxy-2-benzoylethyl)-*N,N,N*-trimethylammonium iodide (5.0 g) and hydroquinone (10 mg) in water/chloroform (1:1 by vol; 90 mL) was purged with N_2 for 30 min. The suspension was placed in the MBR and heated rapidly to 110 °C (temperature of aqueous phase), held at this temperature for 1 min, then cooled (quartz cold-finger) to 50 °C within 2 min. The organic phase was removed and the aqueous layer was extracted with $CHCl_3$ (2 × 25 mL). The combined organic phase was washed with water (2 × 25 mL), dried ($MgSO_4$), and concentrated to give 4′-ethoxyphenyl vinyl ketone (2.4 g; 97%) as an unstable oil: IR (thin film) 710 (m), 785 (s), 920 (m), 985 (m), 1600 (s), 1660 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, 3H, J = 7.0 Hz), 4.07 (q, 2H, J = 6.7 Hz), 5.83 (dd, 1H, J = 10.4, 1.9 Hz), 6.39 (dd, 1H, J = 17.0, 1.9 Hz), 6.91 (m, 2H), 7.15 (dd, 1H, J = 17.0, 10.6 Hz), 7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.7, 63.8, 114.3, 129.1, 130.0, 131.0, 132.2, 163.0, 189.2; MS (CI) m/z (relative intensity) 177 (MH$^+$, 100), 149 (35), 121 (18); high-resolution MS calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0839.

Acknowledgment. Hydrolysis of the amide (entry 12, Table 1) was carried out collaboratively with S. Middleton and J. S. Borham and the Hofmann elimination (entry 9, Table 1) with G. W. Simpson and K. L. Walsh. P. I. Somlo is thanked for helpful suggestions.

Supplementary Material Available: Copies of the ^{1}H and ^{13}C NMR spectra of 4′-ethoxyphenyl vinyl ketone (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9419293