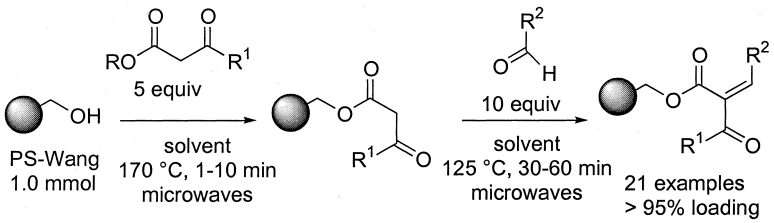
JOURNAL OF combinatorial CHEMISTRY

Article

Rapid Parallel Synthesis of Polymer-Bound Enones Utilizing Microwave-Assisted Solid-Phase Chemistry

Gernot A. Strohmeier, and C. Oliver Kappe

J. Comb. Chem., **2002**, 4 (2), 154-161• DOI: 10.1021/cc010043r • Publication Date (Web): 15 January 2002



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 5 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Rapid Parallel Synthesis of Polymer-Bound Enones Utilizing Microwave-Assisted Solid-Phase Chemistry

Gernot A. Strohmeier and C. Oliver Kappe*

Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

Received July 22, 2001

A microwave-assisted parallel solid-phase synthesis of a collection of 21 polymer-bound enones has been developed. The two-step protocol involves initial high-speed acetoacetylation of polystyrene Wang resin with a selection of seven common β-ketoesters. When microwave flash heating at 170 °C was employed, complete conversions were achieved within 1−10 min, a significant improvement over the conventional thermal method, which takes several hours for completion. Significant rate enhancements were also observed for the subsequent microwave-heated Knoevenagel condensations with a second set of 13 different aldehydes. Reaction times were reduced to 30−60 min at 125 °C in the microwave protocol compared to 1−2 days using conventional thermal conditions. Kinetic comparison studies indicate that the observed rate enhancements can be attributed to the rapid direct heating of the solvent (1,2-dichlorobenzene) by microwaves rather than to any specific microwave effect. All reactions have been carried out in commercially available parallel reactors with on-line temperature measurement, designed specifically for use in multimode microwave cavities.

Introduction

Faced with the increasing demand for novel drug targets, there is considerable current interest to accelerate the technologies associated with combinatorial chemistry and high-throughput synthesis.[1] One of the most often used techniques in combinatorial chemistry is automated solid-phase organic synthesis (SPOS) based on the original Merrifield method for peptide preparation.[2] However, one disadvantage of this methodology compared to standard solution-phase synthesis is the comparatively long reaction times that are usually required owing to the heterogeneous reaction conditions involving insoluble polymer supports. Since speed is generally recognized as an important factor in high-throughput synthesis and combinatorial chemistry, any technique that is able to accelerate the process of solid-phase organic synthesis is of considerable interest.

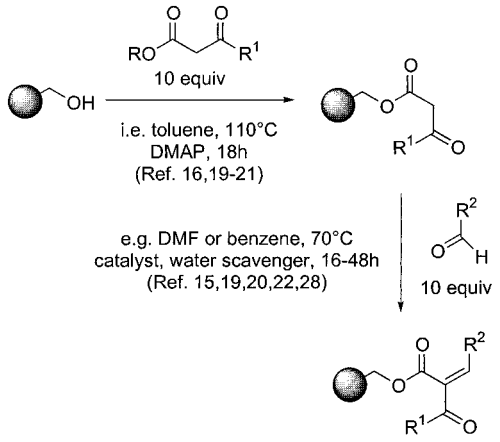
In recent years, the concept of speeding up resin-bound chemistry by microwave activation has created a lot of interest, from both the academic and industrial communities.[3−14] In a number of publications, significant rate accelerations and very high loadings for several solid-phase protocols have been reported, with reaction times being reduced in some cases from hours to a few minutes.[3−14] Despite these initial reports, the benefits associated with this new technology have not been rigorously established, since in many cases domestic household microwave ovens have been employed that do not allow the monitoring of temperature or pressure profiles during irradiation experiments. In a recent model study using dedicated microwave reactors involving the alkylation of standard Merrifield-type resins with carboxylate anions, we have demonstrated that microwave flash heating, i.e., the very rapid heating of the reaction mixture in combination with high reaction temperatures, is most likely responsible for the observed rate enhancements using this nonconventional heating method.[14] We now take our initial "proof of concept" studies a step further and (i) report on the application of this technology toward synthetically more useful resin-bound chemistry and (ii) demonstrate the feasibility of carrying out such microwave-assisted transformations in a controlled and reproducible parallel fashion, employing dedicated reactor systems.

As a suitable transformation to illustrate the concept of microwave-assisted parallel solid-phase synthesis, we have chosen the two-step preparation of polymer-bound enones. For both solid-phase reaction steps there is ample precedence in the literature.[15−29] In general, the usual pathway involves acylation of a hydroxy-functionalized resin with a β-ketoester,[15−21] followed by Knoevenagel condensation of the resulting resin-bound 1,3-dicarbonyl moiety with aldehyde building blocks (Scheme 1).[15,19,20,22,27−29] Apart from β-ketoesters, other reagents have been employed as substitutes in the first step, including diketene,[22,23] acyl meldrum acids,[19,24] *N*-hydroxysuccimidylacetoacetate,[23] and 1,3-dioxine-4-ones.[23,25,26] While some of these reagents are considerable more reactive than β-ketoesters, they either require multistep preparation (e.g., acyl meldrum acids) or provide no diversity (i.e., diketene). On the other hand, a wide range of β-ketoesters are either commercially available or easily accessible but have to be reacted with the hydroxy resins at relatively high temperatures for considerable periods of time (typically at 110 °C for several hours).[15−21] Subsequent Knoevenagel condensations with aromatic or aliphatic aldehydes have also been reported to be quite slow, sometimes

* To whom correspondence should be addressed. Phone: +43-316-3805352. Fax: +43-316-3809840. E-mail: oliver.kappe@uni-graz.at.

10.1021/cc010043r CCC: $22.00
Published on Web 01/15/2002

Scheme 1



resulting in reaction times of up to 48 h at 70 °C.[15,19,20,22,27−29] Here, we demonstrate that controlled microwave flash heating in parallel mode can be used to speed up both processes outlined in Scheme 1 significantly, providing rapid access to a diverse set of polymer-bound Knoevenagel products. These enones (as well as the intermediate 1,3-dicarbonyl compounds) are important building blocks in solid-phase synthesis for the generation of several heterocyclic privileged scaffolds such as as dihydropyridines,[18,22,25] pyridines,[18−20,22] dihydropyrimidines,[29,30] pyrazolones,[16,20,24] and benzothiazepines, etc.[31]

Results and Discussion

To be able to perform microwave irradiation experiments in a reproducible manner, we have employed a commercially available multimode microwave reactor dedicated for chemical synthesis. This instrument features a built-in magnetic stirrer, direct temperature control of the reaction mixture with the aid of fiber-optic probes and/or shielded thermocouples, and software that enables on-line temperature/pressure control by regulation of microwave power output. Importantly, the flexible modular platform allows the use of various types of parallel reactors (multiprep rotors in continuous movement) that house, for example, 50 reaction vessels that fit in the large multimode cavity (see Experimental Section). For easier handling of the resins, all experiments described herein were carried out in open PFA (Teflon perfluoroalkoxy) vessels that withstand high temperatures/organic solvents and are microwave-transparent. The use of glass vessels in microwave-assisted SPOS does not affect the chemistry, but it aggravates the handling of resins. For both reaction steps we have chosen 1,2-dichlorobenzene as the solvent. This solvent has been used earlier in microwave-assisted chemistry[32] and fulfills all the requirements for performing resin-based transformations; dichlorobenzene has (i) good swelling properties for both polystyrene and TentaGel resin,[33] (ii) a high boiling point (180 °C) if reactions are to be performed at atmospheric pressure, (iii) high chemical stability and inertness to minimize side reactions, and (iv) a high dielectric loss tangent (tan δ).[34] A high value for tan δ indicates a strong coupling with microwave energy, which means that the corresponding solvent will be heated rapidly when irradiated in a microwave cavity (microwave flash heating).[34]

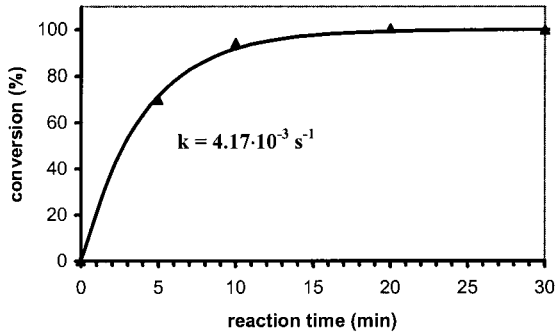


Figure 1. FTIR kinetic study of transacetoacetylation with ethyl acetoacetate at 150 °C in open PFA vessels. Absorption bands at 1743 cm^{-1} were set in relation to the 1452 cm^{-1} Wang resin band.

Microwave-Assisted Acetoacetylations. For solid support in all transformations described below, we have used standard polystyrene Wang resin (1.0 mmol OH/g, 1% DVB cross-linked) because our previous experience with this support/linker combination has demonstrated that this type of resin is unaffected even by extended microwave irradiation in solvents at 200 °C.[14] Transesterifications with acetoacetates are somewhat different compared to "normal" esters. It has been demonstrated that such acetoacetylations proceed by the initial formation of a highly reactive α-oxoketene intermediate via pseudopericyclic reaction pathways involving six-membered transition states.[35] The elimination of the alcohol component of the acetoacetic ester is therefore the rate-limiting step in this transformation. Subsequent trapping of the ketene functionality with alcohols (i.e., a hydroxy-functionalized resin) then provides the transacetoacetylated products. Generally this step is accomplished by thermolysis of the corresponding β-ketoesters.[36−38] Several kinetic studies have shown that methyl or ethyl esters are not ideal precursors because of their relatively low thermolysis rates.[36,37] *tert*-Butyl esters are significantly more reactive and show a more than 15-fold increased reactivity.[36,37] However, since most of the commercially available β-ketoesters are methyl or ethyl esters, we wanted to develop reaction conditions that would accommodate these precursors.

For an initial evaluation of microwave-assisted solid-phase acetoacetylations, we have carried out a kinetic investigation at 150 °C with ethyl acetoacetate as a representative example.[39] As shown in Figure 1, completion was observed after 20 min at a preselected maximum temperature of 150 °C, a concentration of 20 mg of resin/mL of solvent and 5 equiv of ester. The on-bead FTIR kinetic analysis[40−47] (see Experimental Section) shows a first-order profile with $k = 4.17 \times 10^{-3}$ s^{-1} ($t_{1/2} = 4$ min). Note that in this microwave-assisted process there is no need to use a catalyst such as DMAP, as often recommended in the literature for this transformation.[21] A kinetic comparison experiment demonstrated that there was no difference in the reaction rate of a DMAP-catalyzed and noncatalyzed run. To reach even shorter reaction times, we have further increased the reaction temperature to 170 °C by microwave flash heating, i.e., just below the boiling point of the solvent. This increase in reaction temperature corresponded to a decrease in the reaction time for ethyl acetoacetate to 5−10 min. Because of the high loss tangent of the solvent, such high temperatures

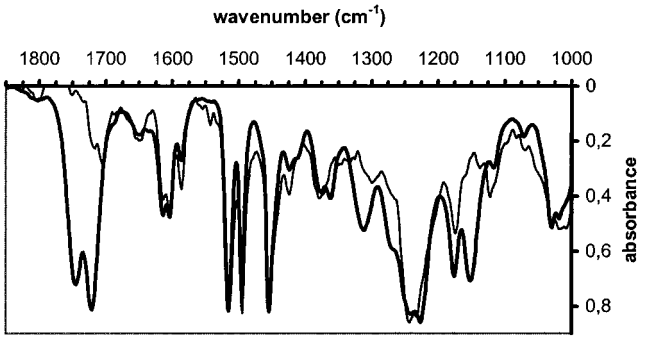


Figure 2. FTIR spectra of polymer-bound acetoacetate **1b** and Wang resin.

can be reached in less than a minute in a microwave flash heating experiment. For safety reasons a 2 min heating ramp was performed before the temperature was maintained at the selected maximum value of 170 °C (see Figure S1 in the Supporting Information for a representation of the heating profile). Although the above transesterification is an equilibrium process, here the conversion can be easily driven to completion by using the high-boiling ester component in excess and by the rapid removal of the volatile ethanol formed in the ester thermolysis. The thermal stability of the acetoacetate attached to Wang resin was confirmed by heating a sample of resin **1a** in 1,2-dichlorobenzene at 170 °C for 30 min, resulting in a loss of material of only 13%. The FTIR spectra of **1a** and Wang resin are shown in Figure 2.

As can be seen from inspection of the data presented in Table 1, analogous acetoacetylation reactions with a variety of β-ketoesters can be performed successfully within 1−10 min using the above microwave protocol. Methyl or ethyl aceto- and benzoylacetates require 5−10 min for completion as judged by FTIR monitoring, more or less independent of the substitution in the γ-position. Methyl esters are the preferred precursors, since they undergo a well-defined thermolysis process to the anticipated α-oxoketene intermediates. Ethyl esters instead, although also successfully applied in our experiments, are known to sometimes eliminate ethylene in preference to ethanol, resulting in the formation of undesired decomposition products.[38] In agreement with literature data on solution-phase reactions, *tert*-butyl esters are significantly more reactive,[36,37] providing polymer-bound acetoacetates in only 1 min at 170 °C (Table 1, entry h). To rapidly access a collection of the corresponding polymer-bound β-ketoesters **1a**−**g** (Scheme 2, Table 1), the seven products were also obtained from a single microwave irradiation experiment (10 min, 170 °C), employing a multiprep rotor system (see Experimental Section). Complete conversion (>99%) was achieved in all cases.

Microwave-Assisted Solid-Phase Knoevenagel Condensations. Knoevenagel condensations on solid support have been described for several types of β-dicarbonyl components. This includes not only β-ketoesters,[15,19,20,22] but also malonic esters/amides[27−29] and cyanoacetamides.[48] Although several different reaction mechanisms have been discussed, differing in the catalyst employed, the crucial step in all cases is to initiate enolization of the CH acidic component.[49,50] Therefore, piperidine, piperidinium acetate, and ethylenediamine

Scheme 2

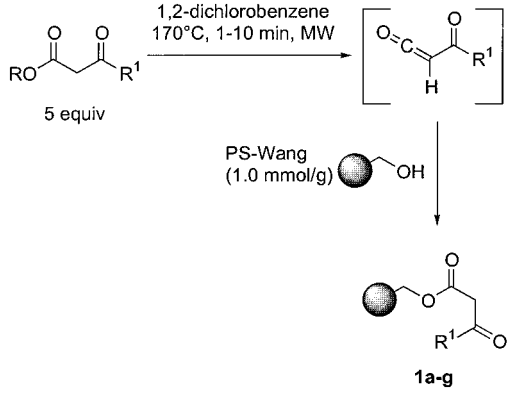


Table 1. Preparation of Polymer-Bound Acetoacetates **1**[a]

compd	R	R^1	time (min)
1a	Et	Me	10
1b	Et	iPr	10
1c	Et	Ph	5
1d	Et	Bu	5
1e	Me	Cl−CH_2−	5
1f	Me	Et	10
1g	Me	4-F−Ph	5
1h	t-Bu	Me	1

[a] Yields are >99% (as determined by on-bead FTIR monitoring and weight gain of the resin; see Experimental Section).

diacetate (EDDA) have found widespread application as distinct and efficient catalysts for solution- and solid-phase Knoevenagel condensations. Initial attempts were made to carry out microwave-assisted Knoevenagel condensations with 0.3 equiv of piperidinium acetate using the same conditions as for the acetoacetylation step (170 °C, 1,2-dichlorobenzene). Disappointingly, the result was a more or less complete cleavage of all material from the resin (FTIR). Sealed vessel conditions as reported by Kuster and Scheeren[9] for related Knoevenagel condensations of polymer-bound nitroacetic acid gave the same unsatisfactory result.

By systematic variation of the reaction conditions, we have ultimately discovered that Knoevenagel condensations with piperidinium acetate can be carried out at up to 125 °C under atmospheric conditions in 1,2-dichlorobenzene, employing 10 equiv of aldehyde (Scheme 3; also, see Figure S2 in the Supporting Information for a representative heating profile). Higher temperatures led to significant cleavage of material from the resin, which can be explained by the noninertness of the catalyst. The application of other solvents or catalysts (e.g., ethylenediamine diacetate) did not provide better results; indeed, most of the alternative catalysts sometimes used in conventional solution-phase chemistry such as DBU,[51] 1,8-dimethylaminonaphthalene,[52] benzylamine acetate,[53] sodium acetate or lithium acetate[54] refused to promote condensations. Note that in the microwave protocol the use of a water scavenger is not necessary because of the high reaction temperature, being well above the boiling point of water. We have investigated the kinetic profile of the reaction of polymer-bound acetoacetate **1a** with 3-nitrobenzaldehyde as a model system. As shown in Figure 3, the Knoevenagel condensation proceeds sufficiently quickly with a first-order kinetic profile and $k = 2.78 \times 10^{-3}$ s^{-1} ($t_{1/2} = 6$ min). Therefore, a nearly complete conversion is obtained after

Scheme 3

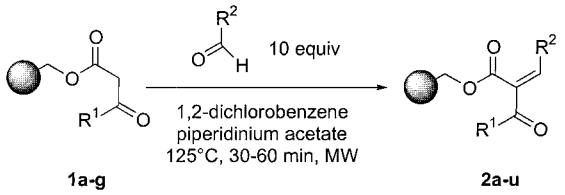


Table 2. Preparation of Polymer-Bound Enones[a]

compd	starting resin	R^2
2a	**1a/1h**	Ph
2b		3-(NO_2)Ph
2c		3,4-(F)Ph
2d		2-(CF_3)Ph
2e		2,3-(Cl)Ph
2f		3-(MeO)−4-(OH)Ph
2g		1-naphthyl
2h	**1b**	Ph
2i		4-(F)Ph
2j		4-(NMe_2)Ph
2k	**1c**	2-(Ph)−ethen
2l	**1d**	3-(MeO)−4-(OH)Ph
2m		3,4-(F)Ph
2n		4-(Me)Ph
2o	**1e**	2-(CF_3)Ph
2p		2-(Cl)Ph
2q	**1f**	2-(Cl)Ph
2r		2,3-(Cl)Ph
2s		3,4-(MeO)Ph
2t		1-naphthyl
2u	**1g**	Ph

[a] Yields are >95% (as determined by on-bead FTIR monitoring, weight gain of the resin, and cleavage of products; see Experimental Section).

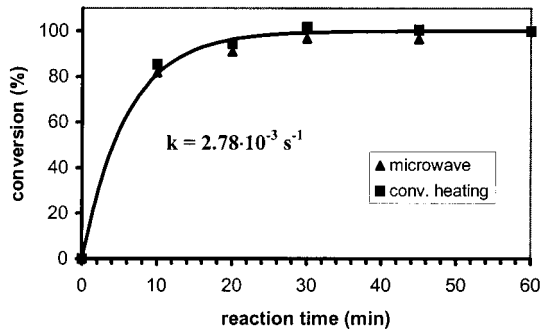


Figure 3. FTIR kinetic study of the Knoevenagel condensation between 3-nitrobenzaldehyde (10 equiv) and polymer-bound acetoacetate **1a** at 125 °C in open PFA vessels using 0.3 equiv of piperidinium acetate as catalyst. Absorption bands at 1531 cm^{-1} (NO_2) were set in relation to the 1452 cm^{-1} Wang resin band.

30 min. Nevertheless, we have conducted all of the following parallel synthesis using a set of 13 aldehydes and the 7 different polymer-bound ketoesters (see above), using an irradiation time of 1 h to ensure complete conversions in all cases. Again, the multiprep rotor was employed to generate the 21-member library of polymer-bound Knoevenagel products in a single irradiation experiment (Table 2).

Despite the different properties of polymer-bound acetoacetates and the diverse nature of the aldehydes used, Knoevenagel condensations went to near completion (>95%) in every investigated case. These results were confirmed by on-bead FTIR analysis, accurate weight gain measurements of scrupulously washed and dried resins, and postcleavage

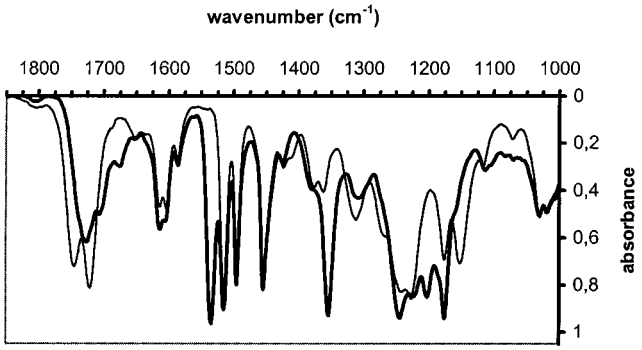
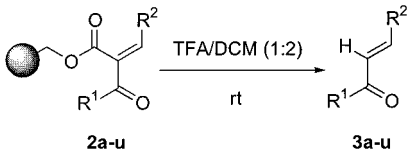


Figure 4. FTIR spectrum of polymer-bound β-ketoester **1b** and enone **2b**.

Scheme 4



analysis of the resulting enones **3a**−**u** by GC−MS and ^{1}H NMR measurements (Scheme 4). The FTIR spectra of polymer-bound acetoacetate **1b** and enone **2b** (Figure 4) show characteristic changes in the regions of carbonyl absorptions, represented by the disappearance of both the original β-ketoester bands (1743 and 1718 cm^{-1}) and evolution of a new centered enone band (1725 cm^{-1}), as well as characteristic absorptions due to the aromatic nitro substituent (1531 and 1351 cm^{-1}) of the aldehyde component. Similar measurements have been performed for all examples (see Experimental Section). Cleavage with trifluoroacetic acid (TFA) provided directly the corresponding enones **3** as mixtures of *E*/*Z* isomers resulting from decarboxylation of the corresponding intermediate β-ketoacids.[55] GC−MS and ^{1}H NMR analyses confirmed their chemical identity, although in some cases further decomposition due to the strongly acidic cleavage conditions took place.

In recent years the possible existence of so-called nonthermal microwave effects has been the subject of intense discussions.[56] Many early claims of the existence of such effects in homogeneous systems have been reinterpreted after appropriate experimentation with temperature monitoring, as, for example, the effect of superheating and the elevated temperatures that are usually generated in microwave chemistry experiments. For solid-phase organic transformations performed with the aid of microwave irradiation, recent evidence points in the same direction.[14] Despite these facts, we have carried out a thermal comparison experiment for the reaction of **1a** and 3-nitrobenzaldehyde. The reaction conditions were identical in every respect to the microwave run except that heating was performed in a preheated oil bath at 125 °C. As can be seen in Figure 3, the kinetics of the microwave and the conventional run are virtually identical. A nonthermal microwave effect therefore could not have been observed. An exact kinetic comparison between microwave and conventional heating for the corresponding acetoacetylation reactions presented above is somewhat more difficult because of the extremely rapid reactions at 170 °C and the associated fast heating. One has

to keep in mind, however, that in our experiments a comparatively polar solvent was used (1,2-dichlorobenzene), which strongly interacts with microwaves. We cannot exclude the possibility of nonthermal effects in these reactions employing nonpolar solvents (i.e., 1,4-dimethylbenzene), where the reactant molecules could absorb microwave energy directly.[56]

Concluding Remarks

In conclusion, it has been demonstrated that controlled microwave flash heating can be used as an effective tool to speed up solid-phase organic synthesis. For acetoacetylation reactions involving β-ketoesters and standard polystyrene Wang resin, reaction times could be reduced from hours using conventional thermal heating to only 1−10 min using microwave flash heating. Similar, but less dramatic, effects were also found for the subsequent Knoevenagel condensations where conventional reaction times of 1−2 days could be reduced to 30−60 min without affecting the purity of the resin-bound material or unintentional cleavage from the support. Although the observed rate accelerations are not due to any specific effects of the microwave irradiation, but rather are a consequence of the direct rapid and intense heating of the solvent together with the unconventionally high reaction temperatures, the convenience and flexibility of microwave heating are evident. The combination of modern microwave reactor technology and combinatorial chemistry applications is a logical consequence of the increased speed and effectiveness offered by microwave heating.[57] In particular, the possibility of running several solid-phase reactions in parallel using dedicated multimode microwave reactors and specifically designed reaction vessels for parallel synthesis is of considerable interest. One has to stress that modern multimode reactors ensure a more homogeneous distribution of energy within the cavity than is possible with a domestic household oven. In the latter case significant temperature gradients are usually observed, e.g., using 96-well microtiter plates, which makes the reproducibility of more subtle chemistries troublesome.[13,58] Current developments in reactor technology and vessel design include systems where several 96-well plates can be irradiated rapidly and simultaneously in a multimode microwave cavity[59] and microwave reactors for automated sequential microwave processing.[60] The use of these systems will increase the possible throughput in combinatorial synthesis significantly. We are currently evaluating a variety of different polymeric supports and chemistries for use in microwave-assisted combinatorial synthesis.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded in deuteriochloroform on Bruker AMX360 and AMX500 instruments operating at 360 and 500 MHz, respectively. On-bead FTIR spectra were recorded on a Unicam Galaxy series FTIR 7000 (Mattson Instruments, Inc.) using mashed resin beads in KBr pellets. GC−MS measurements were performed on a Hewlett-Packard model 6890 instrument equipped with an HP 5973 mass selective detector.

Microwave Irradiation Experiments. Milestone MLS ETHOS 1600 Reactor (Figure S3 in the Supporting Information).[61,62] The multimode microwave reactor has a twin magnetron (2 × 800 W, 2455 MHz) with a maximum delivered power of 1000 W in 10 W increments (pulsed irradiation). A rotating microwave diffuser ensures homogeneous microwave distribution throughout the plasma-coated PTFE cavity (35 cm × 35 cm × 35 cm). All experiments were carried out in open PFA vessels with a 30 mL volume, with the vessels positioned in a continuously moving multi-PREP 50 rotor system for parallel synthesis (Figure S4 in the Supporting Information). A magnetic stirring bar (Teflon coated, 2 cm) was used in every vessel to guarantee optimal energy distribution and mixing of solvent. In all irradiation experiments, rotation of the multi-PREP rotor, irradiation time, temperature, and power were monitored/controlled with the ''easy-WAVE" software package (version 3.2.). Temperature was monitored with the aid of a shielded thermocouple (ATC-300) inserted into one of the reaction containers. In the case of parallel reactions, we have confirmed, by standard temperature measurements performed immediately after the irradiation period, that the resulting end temperature in each vessel was the same within ±2 °C.

Reaction Monitoring by FTIR.[40−47] FTIR spectra of resin samples were measured in transmission mode. Absorbance spectra were obtained by conversion of the crude transmission data and subsequent baseline correction. For comparison of equal amounts of the solid support involved, linear standardization of spectra was done using the 1452 cm^{-1} band of Wang resin, which we found was unaffected by chemical transformations. All spectra were analyzed with respect to the intensity of appearing or disappearing bands and by comparison with reference samples resulting from a conventional heating experiment. Since absorbance is in a direct relationship with concentration (Lambert−Beer's law), conversion rates can be calculated from a given intensity and a reference sample of known conversion (in our case >99%). To ensure quantitative conversion in the reference sample, kinetic experiments (determination of the end point in a synthetic transformation), weight gain, and cleavage (in the case of enones) were used.

General Procedure for the Preparation of Resin-Bound β-Ketoesters 1a−h (Example for 1a). To 1.5830 g (1.583 mmol) of Wang resin (Fluka, Buchs, Switzerland, 1.0 mmol/g, 200−400 mesh, catalog no. 13611, lot no. 392831/1, 1% DVB) in a PFA vessel (multi-PREP rotor) was added 10 mL of 1,2-dichlorobenzene and 1.03 g (7.91 mmol, 5 equiv) of ethyl acetoacetate. After the mixture was stirred at room temperature for 10 min to allow complete swelling of the resin, the vessel was irradiated with a maximum power of 200 W at the preselected 170 °C for 10 min (Figure S1). Then the mixture was allowed to cool for 3 min. The resin was filtered, washed with acetone (3 × 20 mL), THF (2 × 15 mL), MeOH (2 × 15 mL), and dichloromethane (3 × 10 mL), and dried (40 °C, 10 mbar, 14 h). The yield was 1.7155 g (weight gain of 8.370%, >99% conversion relative to a loading of 1.000 mmol/g). FTIR (KBr pellets): 3083, 3060, 3026, 2921, 1743 (C═O), 1718 (C═O) cm^{-1}. Comparison

with the conventional published protocol using diketene gave the same results in terms of weight gain and FTIR spectrum.

General Procedure for the Preparation of Resin-Bound Enones 2a−u (Example for 2b). To 248.6 mg (229.3 μmol) of acetoacetylated Wang resin **1a** in a PFA vessel (multiPREP rotor) was added 10 mL of 1,2-dichlorobenzene, 10.1 mg (69.7 μmol, 0.30 equiv) of piperidinium acetate, and 340 mg (2.25 mmol, 10 equiv) of 3-nitrobenzaldehyde. After the mixture was stirred at room temperature for 10 min to allow complete swelling of the resin, the vessel was irradiated with a maximum power of 200 W at the preselected 125 °C for 60 min (Figure S2). Then the mixture was allowed to cool for 5 min. After that, the hot resin was filtered, washed with acetone (3 × 5 mL), THF (3 × 5 mL), MeOH (2 × 5 mL), and dichloromethane (3 × 5 mL), and dried (40 °C, 10 mbar, 14 h). The yield was 278.5 mg (weight gain of 12.03%, 98% conversion relative to acetoacetylated Wang resin). FTIR (KBr pellets): 3025, 2922, 1725 (C═O), 1531 (NO_2), 1351 (NO_2) cm^{-1}. Comparison with the conventional thermal protocol (90 °C, 60 h) gave the same results in terms of weight gain and FTIR spectrum.

Cleavage of Enones (Example for 2b). A total of 251.8 mg (206.9 μmol) of polymer-bound 2-acetyl-3-(3-nitrophenyl)acrylic acid (**2b**) was treated with 2 mL of cleavage cocktail (TFA/DCM 1:2). After the mixture was shaken at room temperature for 30 min, the resin was filtered off and washed two times each with 1 mL of DCM followed by 1 mL of methanol. The combined filtrates were evaporated to dryness, yielding 37.9 mg (198.2 μmol, 96%) of 4-(3-nitrophenyl)-but-3-en-2-one. ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H), 6.84 (d, 1H, J = 16.3 Hz), 7.55 (d, 1H, J = 16.3 Hz), 7.61 (t, 1H, J = 8.0 Hz), 7.86 (d, 1H, J = 7.7 Hz), 8.25 (dd, 1H, J = 8.2 Hz, J = 1.2 Hz), and 8.41 (s, 1H). GC−MS, *m*/*z*: 191 (M^+, 22), 176 (100), 129 (23), 102 (43).

Kinetics of Acetoacetylation. To 210 mg (210 μmol) of Wang resin in a PFA vessel was added 10 mL of 1,2-dichlorobenzene and 140 mg (1.07 mmol, 5 equiv) of ethyl acetoacetate. After the mixture was stirred at room temperature for 10 min to allow complete swelling of the resin, the vessel was irradiated with a maximum power of 200 W at the preselected 150 °C for 40 min. Resin samples taken at 5, 10, 20, 30, and 40 min were washed with acetone, THF, and DCM (see above), and dried (40 °C, 10 mbar, 14 h). FTIR spectra were analyzed by comparison of bands at 1743 cm^{-1} (C═O) and 1452 cm^{-1} (resin).

Kinetics of Knoevenagel Condensation. To 190 mg (175 μmol) of acetoacetylated Wang resin (**1a**) in a PFA vessel was added 10 mL of 1,2-dichlorobenzene, 8.0 mg (55 μmol, 0.31 equiv) of piperidinium acetate, and 264 mg (1.75 mmol, 10 equiv) of 3-nitrobenzaldehyde. After the mixture was stirred at room temperature for 10 min to allow complete swelling of the resin, the vessel was irradiated with a maximum power of 200 W at the preselected 125 °C for 60 min. An identical setup was immersed in a preheated oil bath, but catalyst and aldehyde were added when the temperature had reached the desired 125 °C. Resin samples from both experiments were taken at 10, 20, 30, 45, and 60 min. After being washed with acetone, THF, and DCM (see above), the samples were dried (40 °C, 10 mbar, 14 h). FTIR spectra were analyzed by comparison of bands at 1531 cm^{-1} (NO_2 asymmetric) and 1452 cm^{-1} (resin).

Acknowledgment. This work was supported by BASF AG, Ludwigshafen, Germany.

Supporting Information Available. Representativeheating profiles for microwave-assisted acetoacetylations and Knoevenagel condensations, graphical illustrations of the microwave equipment used, FTIR data for selected polymer-bound ketoesters **1** and enones **2**, and GC−MS data for cleavage products **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Sucholeiki, I. *High-Throughput Synthesis. Principles and Practices*; Marcel Dekker: New York, 2001.
(2) Zaragoza Dörwald F. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, 2000.
(3) Yu, H.-M.; Chen, S.-T.; Wang, K.-T. Enhanced Coupling Efficiency in Solid-Phase Peptide Synthesis by Microwave Irradiation. *J. Org. Chem.* **1992**, *57*, 4781−4784.
(4) Larhed, M.; Lindeberg, G.; Hallberg, A. Rapid Microwave-Assisted Suzuki Coupling on Solid-Phase. *Tetrahedron Lett.* **1996**, *37*, 8219−8222.
(5) Hoel, A. M. L.; Nielsen, J. Microwave-Assisted Solid-Phase Ugi Four-Component Condensations. *Tetrahedron Lett.* **1999**, *40*, 3941−3944.
(6) Yu, A.-M.; Zhang, Z.-P.; Yang, H.-Z.; Thang, C.-Y.; Liu, Z. Wang Resin Bound Addition Reactions under Microwave Irradiation. *Synth. Commun.* **1999**, *29*, 1595−1599.
(7) Chandrasekhar, S.; Padmaja, M. B.; Raza, A. Solid Phase−Solid State Synthesis of *N*-Alkyl Imides from Anhydrides. *Synlett* **1999**, 1597−1599.
(8) Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. Solid Supported Aryl/Heteroaryl C−N Cross-Coupling Reactions. *Tetrahedron Lett.* **1999**, *40*, 1623−1626.
(9) Kuster, G.; Scheeren, H. W. The Preparation of Resin Bound Nitroalkenes and Some Applications in High Pressure Promoted Cycloadditions. *Tetrahedron Lett.* **2000**, *41*, 515−519.
(10) Alterman, M.; Hallberg, A. Fast Microwave-Assisted Preparation of Aryl and Vinyl Nitriles and the Corresponding Tetrazoles from Organo-halides. *J. Org. Chem.* **2000**, *65*, 7984−7989.
(11) Scharn, D.; Wenschuh, H.; Reineke, U.; Schneider-Mergener, J.; Germeroth, L. Spatially Addressed Synthesis of Amino- and Amino-Oxy-Substituted 1,3,5-Triazine Arrays on Polymeric Membranes. *J. Comb. Chem.* **2000**, *2*, 361−369.
(12) Stadler, A.; Kappe, C. O. The Effect of Microwave Irradiation on Carbodiimide-Mediated Esterifications on Solid Support. *Tetrahedron* **2001**, *57*, 3915−3920.
(13) Glass, B. M.; Combs, A. P. Rapid Parallel Synthesis Utilizing Microwave Irradiation. In *High-Throughput Synthesis. Principles and Practices*; Sucholeiki, I., Ed.; Marcel Dekker: New York, 2001; pp 123−128.
(14) Stadler, A.; Kappe, C. O. High Speed Couplings and Cleavages in Microwave Heated, Solid-Phase Reactions at High Temperatures. *Eur. J. Org. Chem.* **2001**, 919−925.
(15) Tietze, L. F.; Hippe, T.; Steinmetz, A. Solid-Phase Three-Component Domino Reactions: Combinatorial Approach to Substituted 3,4-Dihydro-2H-pyrans. *Synlett* **1996**, 1043−1044.
(16) Tietze, L. F.; Steinmetz, A. A General and Expedient Method for the Solid-Phase Synthesis of Structurally Diverse 1-Phenylpyrazolone Derivatives. *Synlett* **1996**, 667−668.

(17) Tietze, L. F.; Hippe, T.; Steinmetz, A. Palladium-Catalyzed Allylic Substitution on Solid Support. *Chem. Commun.* **1998**, 793−794.
(18) Bhandari, A.; Li, B.; Gallop, M. A. Solid-Phase Synthesis of Pyrrolo[3,4-b]pyridines and Related Pyridine-Fused Heterocycles. *Synthesis* **1999**, 1951−1960.
(19) Tadesse, S.; Bhandari, A.; Gallop, M. A. Solid-Phase Synthesis of Highly Functionalized 2,2′-Bipyridines. *J. Comb. Chem.* **1999**, *1*, 184−187.
(20) Grosche, P.; Holtzel, A.; Walk, T. B.; Trautwein, A. W.; Jung, G. Pyrazole, Pyridine and Pyridone Synthesis on Solid Support. *Synthesis* **1999**, 1961−1970.
(21) MacDonald, A. A.; DeWitt, S. H.; Hogan, E. M.; Ramage, R. A Solid Phase Approach to Quinolones using the DIVERSOMER Technology. *Tetrahedron Lett.* **1996**, *37*, 4815−4818.
(22) Gordeev, M. F.; Patel, D. V.; Wu, J.; Gordon, E. M. Approaches to Combinatorial Synthesis of Heterocycles: Solid Phase Synthesis of Pyridines and Pyrido[2,3-d]pyrimidines. *Tetrahedron Lett.* **1996**, *37*, 4643−4646.
(23) Trautwein, A. W.; Sussmuth, R. D.; Jung, G. Hantzsch Pyrrole Synthesis on Solid Support. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381−2384.
(24) Tietze, L. F.; Steinmetz, A.; Balkenhohl, F. Solid-Phase Synthesis of Polymer-Bound β-Ketoesters and Their Application in the Synthesis of Structurally Diverse Pyrazolones. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1303−1306.
(25) Breitenbucher, J. G.; Figliozzi, G. Solid-Phase Synthesis of 4-Aryl-1,4-dihydropyridines via the Hantzsch Three Component Condensation. *Tetrahedron Lett.* **2000**, *41*, 4311−4315.
(26) For an example involving soluble polymers, see the following. Far, A. R.; Tidwell, T. T. Ketenes in Soluble Polymer Bound Synthesis: Preparation of Succinamides and 4-Pyridones. *J. Org. Chem.* **1998**, *63*, 8636−8637.
(27) Tietze, L. F.; Steinmetz, A. Stereoselective Solid-Phase Synthesis of Cyclopentane and Cyclohexane Derivatives by Two-Component Domino Reactions: Generation of Combinatorial Libraries. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 651−652.
(28) Hamper, B. C.; Snyderman, D. M.; Owen, T. J.; Scates, A. M.; Owsley, D. C.; Kesselring, A. S.; Chott, R. C. High-Throughput ^{1}H NMR and HPLC Characterization of a 96-Member Substituted Methylene Malonamic Acid Library. *J. Comb. Chem.* **1999**, *1*, 140−150.
(29) Hamper, B. C.; Gan, K. Z.; Owen, T. J. Solid Phase Synthesis of Dihydropyrimidinones and Pyrimidinone Carboxylic Acids from Malonic Acid Resin. *Tetrahedron Lett.* **1999**, *40*, 4973−4976.
(30) Robinett, L. D.; Yager, K. M.; Phelan, J. C. Solid-Phase Synthesis of Dihydropyrimidine Combinatorial Libraries by the Atwal Modification of the Biginelli Reaction. *Abstracts of Papers*, 211th National Meeting of the American Chemical Society, New Orleans, LA, 1996; American Chemical Society: Washington, DC, 1996; ORGN 122.
(31) Micheli, F.; Degiorgis, F.; Feriani, A.; Paio, A.; Pozzan, A.; Zarantonello, P.; Seneci, P. A Combinatorial Approach to [1,5]Benzothiazepine Derivatives as Potential Antibacterial Agents. *J. Comb. Chem.* **2001**, *3*, 224−228.
(32) Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S. MORE Chemistry in a Microwave. *CHEMTECH* **1997**, *27*, 18−24.
(33) Santini, R.; Griffith, M. C.; Qi, M. A Measure of Solvent Effects on Swelling of Resins for Solid Phase Organic Synthesis. *Tetrahedron Lett.* **1998**, *39*, 8951−8954.
(34) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. Dielectric Parameters Relevant to Microwave Dielectric Heating. *Chem. Soc. Rev.* **1998**, *27*, 213−223.
(35) Birney, D. M.; Xu, X.; Ham, S.; Huang, X. Chemoselectivity in the Reaction of Acetylketene and Acetimidoylketene: Confirmation of Theoretical Predictions. *J. Org. Chem.* **1997**, *62*, 7114−7120.
(36) Witzeman, J. S. The Transacetoacetylation Reaction: Mechanistic Implications. *Tetrahedron Lett.* **1990**, *31*, 1401−1404.
(37) Witzeman, J. S.; Nottingham, W. D. Transacetoacetylation with *tert*-Butyl Acetoacetate: Synthetic Applications. *J. Org. Chem.* **1991**, *56*, 1713−1718.
(38) Freiermuth, B.; Wentrup, C. Direct Observation of α-Oxo Ketenes Formed from 1,3-Dioxin-4-ones and the Enols of β-Keto Esters. *J. Org. Chem.* **1991**, *56*, 2286−2289.
(39) For an example of a microwave-assisted acetoacetylation involving soluble polymers, see the following. Vanden Eynde, J. J.; Rutot, D. Microwave-Mediated Derivatization of Poly(styrene-*co*-allyl)alcohol, a Key Step for the Polymer-Assisted Synthesis of Heterocycles. *Tetrahedron* **1999**, *55*, 2687−2694.
(40) Yan, B. Monitoring the Progress and the Yield of Solid-Phase Organic Reactions Directly on Resin Supports. *Acc. Chem. Res.* **1998**, *31*, 621−630.
(41) Li, W. B.; Xiao, X. Y.; Czarnik, A. W. Kinetic Comparison of Amide Formation on Various Cross-Linked Polystyrene Resins. *J. Comb. Chem.* **1999**, *1*, 127−129.
(42) Li, W.; Yan, B. Effects of Polymer Supports on the Kinetics of Solid-Phase Organic Reactions: A Comparison of Polystyrene- and TentaGel-Based Resins. *J. Org. Chem.* **1998**, *63*, 4092−4097.
(43) Gallop, M. A.; Fitch, W. L. New Methods for Analyzing Compounds on Polymeric Supports. *Curr. Opin. Chem. Biol.* **1997**, *1*, 94−100.
(44) Pivonka, D. E. On-Bead Quantitation of Resin Bound Functional Groups Using Analogue Techniques with Vibrational Spectroscopy. *J. Comb. Chem.* **2000**, *2*, 33−38.
(45) Gosselin, F.; DiRenzo, M.; Ellis, T. H.; Lubell, W. D. Photoacoustic FTIR Spectroscopy, a Nondestructive Method for Sensitive Analysis of Solid-Phase Organic Chemistry. *J. Org. Chem.* **1996**, *61*, 7980−7981.
(46) Yan, B.; Yan, H. B. Combination of Single Bead FTIR and Chemometrics in Combinatorial Chemistry: Application of the Multivariate Calibration Method in Monitoring Solid-Phase Organic Synthesis. *J. Comb. Chem.* **2001**, *3*, 78−84.
(47) de Miguel, Y. R.; Shearer, A. S. Infrared Spectroscopy in Solid-Phase Synthesis. *Biotechnol. Bioeng.* **2000**, *71*, 119−129.
(48) Zaragoza, F. Carbon−Carbon Bond Formation on Solid Support: Synthesis of Monoacyl Piperazines by Knoevenagel-Type Condensation Reactions. *Tetrahedron Lett.* **1995**, *36*, 8677−8678.
(49) Tietze, L. F.; Beifuss, U. The Knoevenagel Condensation. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 341−390.
(50) Jones, G. The Knoevenagel Condensation. *Org. React.* **1967**, *15*, 204−599.
(51) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley-Interscience: New York, London, Sydney, Toronto, 1977; Vol. 6, p 158.
(52) Rodriguez, I.; Sastre, G.; Corma, A.; Iborra, S. Catalytic Activity of Proton Sponge−Application to Knoevenagel Condensation-Reactions. *J. Catal.* **1999**, *183*, 14−23.
(53) Archibald, J. L.; Bradley, G.; Opalko, A.; Ward, T. J.; White, J. C.; Ennis, C.; Shepperson, N. B. Design of an Antithrombotic Antihypertensive Agent (Wy-27569). Synthesis and Evaluation of a Series of 2-Heteroaryl-Substituted Dihydropyridines. *J. Med. Chem.* **1990**, *33*, 646−652.
(54) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons, Inc.: New York, Chichester, Brisbane, Toronto, 1967; Vol. 1, pp 1024−1027.

(55) For another solid-phase synthesis of enones **3**, see the following. Hird, N. W.; Irie, K.; Nagai, K. Solid Phase Synthesis of 2-Aminobutadienes Using a Piperazine Linker. *Tetrahedron Lett.* **1997**, *38*, 7111−7114.
(56) For a recent review, see the following. Perreux, L.; Loupy, A. A Tentative Rationalization of Microwave Effects in Organic Synthesis According to the Reaction Medium, and Mechanistic Considerations. *Tetrahedron* **2001**, *57*, 9199−9223.
(57) For recent reviews on this theme, see the following. (a) Larhed, M.; Hallberg, A. Microwave-Assisted High-Speed Chemistry: A New Technique in Drug Discovery. *Drug Discovery Today* **2001**, *6*, 406−416. (b) Kappe, C. O. High-Speed Combinatorial Synthesis Utilizing Microwave Irradiation. *Curr. Opin. Chem. Biol.*, in press. (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. Increasing Rates of Reaction: Microwave-Assisted Organic Synthesis for Combinatorial Chemistry. *J. Comb. Chem.* **2002**, *4*, XXXX−XXXX.
(58) Cotterill, I. C.; Usyatinsky, A. Y.; Arnold, J. M.; Clark, D. S.; Dordick, J. S.; Michels, P. C.; Khmelnitsky, Y. L. Microwave-Assisted Combinatorial Chemistry. Synthesis of Substituted Pyridines. *Tetrahedron Lett.* **1998**, *39*, 1117−1120.
(59) For a brief description, see the following. Nüchter, M.; Lautenschläger, W.; Ondruschka, B.; Tied, A. Parallelsynthesen im Mikrowellenfeld (Parallel Syntheses in Microwave Fields). *LaborPraxis* **2001**, *25* (January), 28−31.
(60) Stadler, A.; Kappe, C. O. Automated Library Generation Using Sequential Microwave-Assisted Chemistry. Application toward the Biginelli Multicomponent Condensation. *J. Comb. Chem.* **2001**, *3*, 624−630.
(61) Kappe, C. O. Speeding Up Solid-Phase Chemistry by Microwave Irradiation: A Tool for High-Throughput Synthesis. *Am. Lab.* **2001**, *33* (10), 13−19.
(62) Milestone, Inc., 160B Shelton Road, Monroe, CT 06468. Phone: +1-203/261-6175. Fax: 1 1-203/261-6592. Web site: http://www.milestonesci.com/. E-mail: mwave@milestonesci.com.

CC010043R