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Review

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J. Comb. Chem., **2002**, 4 (2), 95-105• DOI: 10.1021/cc010048o • Publication Date (Web): 13 December 2001

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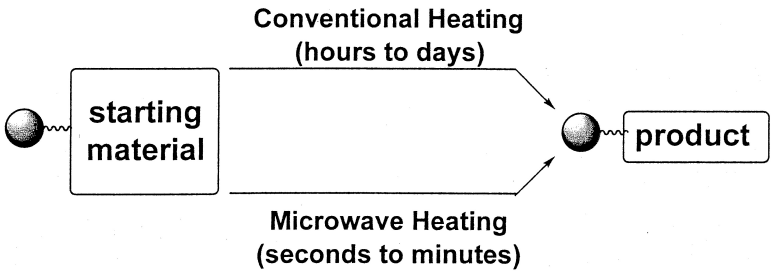

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Volume 4, Number 2 March/April 2002

Reviews

Increasing Rates of Reaction: Microwave-Assisted Organic Synthesis for Combinatorial Chemistry

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Received July 27, 2001

I. Introduction

Combinatorial chemistry,[1−6] a technique that allows for the synthesis of large numbers of molecules by varying combinations and permutations of modular components, has changed the nature of chemical discovery. Having gone from a technique that was met with skepticism in the 1970s, combinatorial chemistry not only is fashionable today but will most likely become a routine technique tomorrow. Virtually every pharmaceutical company involved in drug discovery has invested enormously in this new technology. The sheer number of journal articles dealing with new combinatorial methods for generating molecular diversity has ballooned in the past 5 years,[6,7] and it continues to grow with the launching of three new journals devoted to the subject: Molecular Diversity (1995), Combinatorial Chemistry and High Thoroughput Screening (1998), and Journal of Combinatorial Chemistry (1999). With this increasing stream of creative ideas, the limitations of combinatorial chemistry seem to be fading. Many reactions that were once limited to solution phase can now be performed on solid phase, and those that cannot may be conducted in 96-well plates to produce libraries by parallel solution synthesis. However, in this age of high-throughput drug discovery, significant limitations remain, one of which is often reaction rate. To this end, researchers have begun to employ microwaves to accelerate the pace of sometimes-sluggish solution- or solid-phase combinatorial reactions.

Microwave-assisted organic synthesis was first demonstrated independently in the research labs of Giguere[8] and Gedye.[9] Both demonstrated that the use of microwave ovens dramatically accelerated the rate of many organic reactions. Since then, microwave heating has been applied not only to reduce reaction times but also to improve yields and selectivity.[10−15] Although microwave techniques have been used to aid organic synthesis since 1984, publications reporting this nonconventional heating method in combinatorial synthesis are limited in part because combinatorial chemistry did not begin to be widely embraced until 5 years ago or so. In this paper, we will review published reactions that can be accelerated on solid support by taking advantage of microwave heating. These examples have been artbitrarily divided into two categlories: (i) reactions that are conducted in solvent and (ii) reactions that are conducted without solvent.

II. Theory Behind Microwave Heating and Its Advantages

Microwaves are a form of electromagnetic radiation (Figure 1). When molecules with a permanent dipole are placed in an electric field, they become aligned with this field.[16] If the electric field then oscillates, the orientations of the molecules will also change in response to each oscillation. International convention dictates that most microwave ovens operate at 12.2 cm (2450 mHz) so that it does not interfere with radar or other telecommunications devices. At this wavelength, oscillations occur 4.9×10^9 times per second. Consequently, molecules subjected to this wavelength of electromagnetic radiation are extremely agitated as they align and realign themselves with the oscillating field, creating an intense internal heat that can

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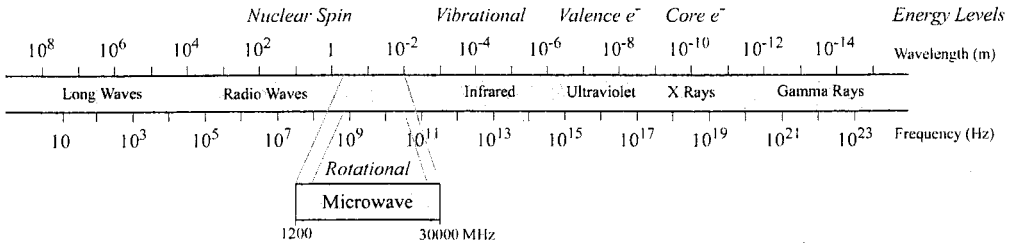


Figure 1. Microwaves are between IR and radiofrequencies. Since some bands between 1 and 25 cm are for telecommunications and radar, not all bands are available for microwave heating. International convention allows commercial and scientific microwave heating at bands of 915, 2450, 5800, and 22 125 MHz. Most ovens opperate at 2450 MHz (=12.2 cm).

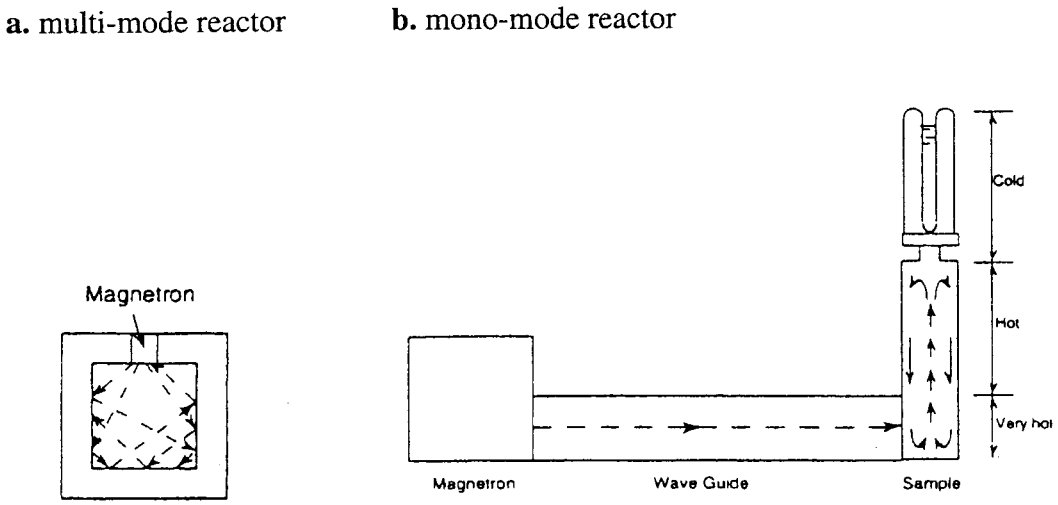


Figure 2. Multimode Reactor versus the monomode reactor.

escalate as quickly as 10 °C per second. Nonpolar molecules such as toluene, carbon tetrachloride, diethyl ether, and benzene are microwave-inactive, while polar molecules such as DMF, acetonitrile, CH_2Cl_2, ethanol, and H_2O are microwave-active (i.e., polar molecules can align themselves with the electric field).

Because of this fast and homogeneous heating, microwave-assisted solid-phase combinatorial synthesis offers several advantages over traditional heating. Often, thermally demanding reactions such as certain Diels−Alder reactions take hours in solution, but up to days on solid-support, and may require repetitive treatments with excess reagents to drive them to completion. However, with microwave heating, these same reactions may be complete in minutes. The homogeneous nature of microwave heating eliminates local overheating at the reaction walls, which can lead to side products. Therefore, microwave-irradiated reactions not only are faster but proceed with higher purity and, consequently, higher yields. In an industry where time is money, the dramatic rate acceleration and increased purity and yields of microwave-assisted reactions make them attractive for high-throughput combinatorial drug discovery.

III. Equipment Needed

Two types of reactors exist for microwave-assisted organic synthesis: a multimode reactor and a monomode reactor (Figure 2). The most common apparatus used is the multimode reactor, otherwise known as the commercial kitchen microwave oven. Although this domestic oven is popular and relatively inexpensive, the distribution of the electric field is not homogeneous, creating hot spots in only parts of the oven. In addition, the temperature cannot be set, leading to poor experimental reproducibility. However, many organic syntheses have been conducted with these ovens after first calibrating the temperature corresponding to each position inside the reaction cavity by heating capillaries of compounds with known melting points.[15]

For more reproducible results, more sophisticated and expensive monomode reactors are available.[17] These reactors focus electromagnetic waves with a waveguide, leading to a homogeneous distribution of energy inside the reaction cavity. Most commercially available monomode reactors allow temperature control via variable power and temperature monitoring via preinstalled digital thermometers. Some ovens are computer-interfaced for reaction monitoring and automation, while others are designed for the ease of adding reagents under inert atmospheres with mechanical stirring. Monomode ovens are especially valuable when small amounts of reagents are used. For example, Combs found that conducting reactions on a 96-well plate in a regular domestic oven did not give consistent heating within the whole plate; i.e., significant temperature gradients were observed between the outside and inside wells.[18]

Since microwave reactions can be carried out with or without solvent, the reaction vessels required vary depending on the application. For small-scale reactions in polar solvents, screw-capped closed Teflon vessels with 5−6 mm thick walls are required to prevent evaporation, potential fire hazards, and explosions. For microwaving of large-scale reactions employing solvent, use of a custom-made pressure relief

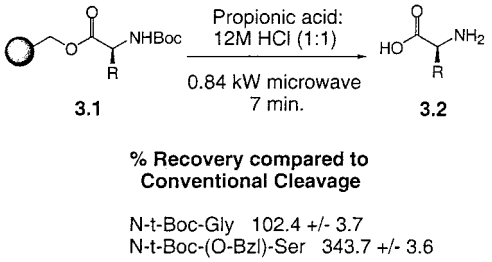


Figure 3.

vessel is recommended. Solvent-free reactions are less cumbersome and can be conducted in a standard glass round-bottomed or Erlenmeyer flask.

IV. Microwave Applications in Combinatorial Library Synthesis

Microwave-assisted organic syntheses can be divided into two major categories: (i) reactions performed in the presence of solvent and (ii) those in the absence of solvent. In reactions requiring solvent, DMF, DME, or CH_2Cl_2 is typically employed. Nonpolar solvents may be used provided that one of the reactants is polar (i.e., microwave-active) to generate heat during the irradiation. Many examples of microwave-assisted reactions have been performed on solvent-swollen polystyrene/divinylbenzene or polystyrene grafted with poly(ethylene glycol) (PEG) based beads (TentaGel) and will be reviewed in this paper ("Reactions on Solvent-Swollen Polymeric Beads", section A.1). In addition, several examples of microwave-accelerated fluorous organic reactions applied toward combinatorial chemistry are reviewed.

Because of the safety limitations inherent in microwave-assisted reactions conducted in solvent, research has focused on developing solvent-free conditions that can be performed safely in an open vessel. Within the category of solvent-free microwave synthesis are three subdivisions: (i) reaction mixtures impregnated on microwave-active mineral oxides such as clay, silica, and alumina, (ii) reactions under phase-transfer catalysis (PTC), i.e., when a reactant acts as both a reactant and an organic phase, and (iii) reactions between neat solid reactants. Examples of microwave-assisted reactions in each of these three solvent-free subdivisions will also be reviewed in this paper ("Microwave-Assisted Solvent-Free Combinatorial Synthesis", section B).

A. Microwave Reactions for Combinatorial Synthesis in the Presence of Solvent. A.1. Reactions on Solvent-Swollen Polymeric Beads. Combinatorial chemistry was first demonstrated in the synthesis of peptides. Similarly, the first microwave-assisted solid-phase reaction was conducted with peptides. The traditional method of peptide hydrolysis is to treat the peptide with 6 M HCl at 110−120 °C for 24 h. Yu et al. demonstrated that this hydrolysis alternatively can be completed in 7 min with the aid of a domestic microwave oven and Teflon screw-capped vials (Figure 3).[19] In his pioneering experiments to demonstrate the utility of microwaves, he irradiated Merrifield resin-bound *N*-Boc-protected amino acids (**3.1**) in the presence of a 1:1 mixture of propionic acid and 12 M HCl and recovered amino acids (**3.2**) in yields comparable to those obtained from traditional 24 h heating methods. In fact, a 3-fold increase in the recovery

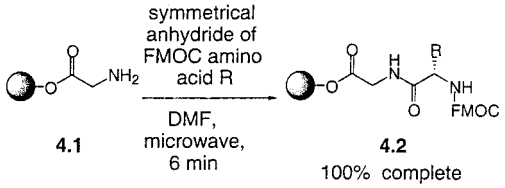


Figure 4.

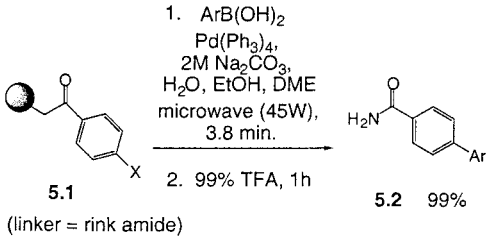


Figure 5.

of serine and threonine, amino acids notorious for their difficult recovery under traditional hydrolysis methods, was observed with the then-novel microwave heating technique.

Four years later, the same group demonstrated that not only can microwave heating accelerate peptide hydrolyses on Merrifield resin but it can also enhance peptide coupling efficiencies as well (Figure 4).[20] A number of symmetrical anhydride or HOBT activated FMOC-amino acids were coupled onto HMP-Gly resin (**4.1**) swollen in DMF using microwave irradiation at 10% power ($T = 55$ °C) for 6 min to yield the resin-bound dipeptide Gly-X (**4.2**). Subsequent hydrolysis of the dipeptides for analysis showed that the coupling reactions all went to completion, even with hindered β-branched amino acids such as Val and Ile. In comparison, without microwave heating, coupling of the same activated amino acids was only 60−70% complete after 6 min. It was also noted that no racemization occurred during the microwave irradiation. As further proof of concept, the group synthesized a heptapeptide and decapeptide, comparing microwave to nonmicrowave coupling methods. Each coupling step employing microwave irradiation for 4 min went to 99−100% completion, while the average coupling yield in the non-microwave-assisted synthesis was 80% for each step.

Despite these two landmark papers, solid-phase microwave techniques stayed in the realm of peptide synthesis until 1996, when Larhed applied microwave techniques to synthesize small druglike organic molecules on beads. In this paper, Larhed demonstrated that Suzuki couplings of polymer-bound aryl halides with arylboronic acids and a palladium catalyst could be achieved after microwave irradiations of only 3.8 min using a monomode microwave reactor at 45 W (Figure 5).[21] These reactions were conducted in DME/H_2O and sealed in a heavy-walled Pyrex tube. A total of eight compounds were synthesized separately, with all yields greater than 80%. However, unlike the Merrifield resins, microwaving of the TentaGel beads used as the solid support in these Suzuki couplings resulted in the release of a minor amount of PEG, perhaps due to the final TFA cleavage step rather than actual microwaving. In addition to the Suzuki coupling, Larhed also reported the success of a microwave-assisted Stille coupling reaction on TentaGel in this paper (Figure 6).

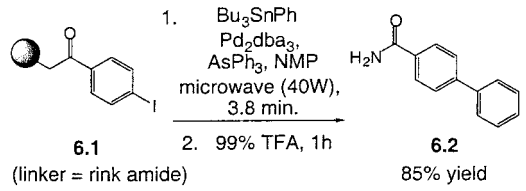


Figure 6.

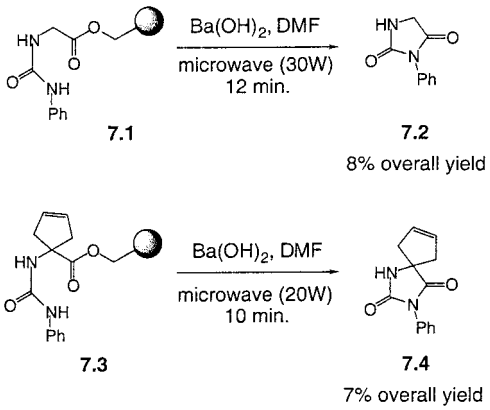


Figure 7.

Publication of the microwave-promoted Suzuki coupling on solid phase launched a number of microwave-assisted small-molecule syntheses on either TentaGel or Merrified resin. For example, through an intramolecular carbanilide cyclization, Kurth synthesized spiro heterocycles in minutes using microwave irradiation and barium hydoxide as the catalyst, a reaction that normally takes 48 h with traditional heating (Figure 7).[22] The paper focused on solution-phase carbanilide cyclizations, citing numerous examples of hydantoins synthesized using microwave assistance, with yields ranging from 40% to 98%. However, two examples were shown where microwave assistance allowed for the quick release of hydantoins off the Merrifield resin. These two reactions were done with DMF-swollen Merrifield resin (**7.1** and **7.3**) in a Teflon capped, thick-walled test tube. After irradiation at 30 W with a monomodal microwave (Microwell 10 reactor) for five or six 2 min intervals, 7−8% overall yields (after five unoptimized steps based on a starting Merrifield resin loading of 2 mequiv/g) of hydantoins **7.2** and **7.4** were released. Although these unoptimized yields do not seem impressive, they are comparable to the optimized 20% overall yields obtained after 48 h in refluxing THF.

Aside from the hydantoins, another heterocyclic reaction has benefited from microwave irradiation (Figure 8). Microwave irradiation of TentaGel-bound benzimidazoles (**8.1**) in the presence of $Cu(OAc)_2$, various aryl boronic acids, and pyridine-NMP gave N-arylated heterocycles **8.2** and **8.3** in high purity (96%) and yields (56%).[18] Traditional heating at 80 °C for 48 h gave only 30% yields. In addition, microwave irradiation of various other TentaGel bound heterocycles such as imidazoles, triazoles, and pyrazoles were also N-arylated under similar conditions, giving good yields (56−64%) and purities (73−97%). In these polymer-supported aryl−heteroaryl C−N cross-coupling reactions, Combs demonstrated that diverse libraries of potentially biologically active N-arylated heterocycles could be made in less than 5 min with a kitchen microwave oven. However, since a multi-mode domestic microwave oven (Sharp Carousel microwave, 1000 W) was employed, adaptation to 96-well microtiter plates was difficult because of nonuniform heating of the plate.

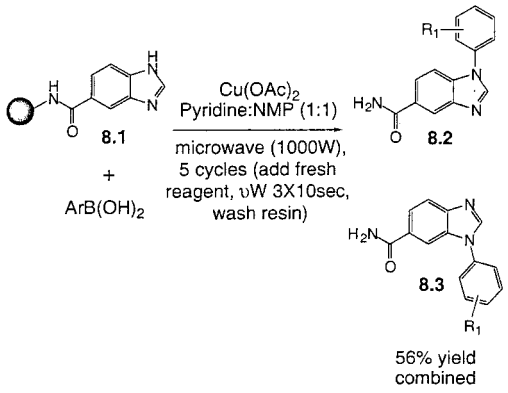
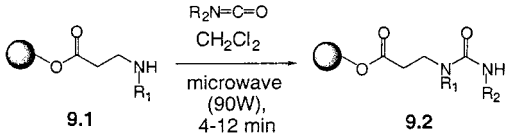


Figure 8.



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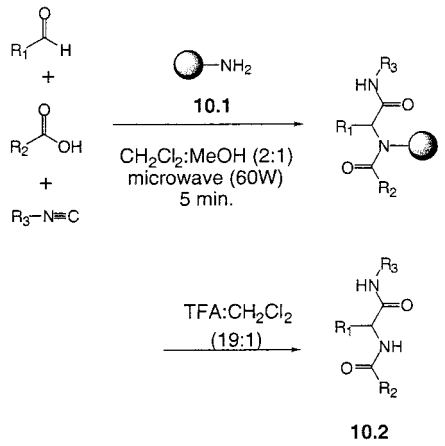

Figure 10.

In the same year, two other examples of microwave-assisted solid-phase syntheses of small molecules were reported: isocyanate additions and the UGI four-component coupling reaction. In the first paper, Yu added Wang resin bound amines (**9.1**) swollen in CH_2Cl_2 to various isocyanates under microwave irradiation with a monomode reactor (Prolabo Soxwave 100 microwave cavity) to synthesize substituted ureas **9.2** in less than 12 min (Figure 9).[23] Although this short communication only reported five examples, it was the first to show a side by side comparison of the reaction progression under microwave irradiation versus room temperature by direct monitoring with KBr pellet/FTIR (12 min, microwave vs 210 min, room temperature).

The second paper deals with the UGI four-component coupling reaction.[24] The UGI reaction has been widely used to prepare combinatorial libraries both in solution and on solid phase because of the immense product diversity available through variations in the starting materials. However, solid-phase UGI reactions take 24 h to several days for completion. Nielson demonstrated that this coupling on

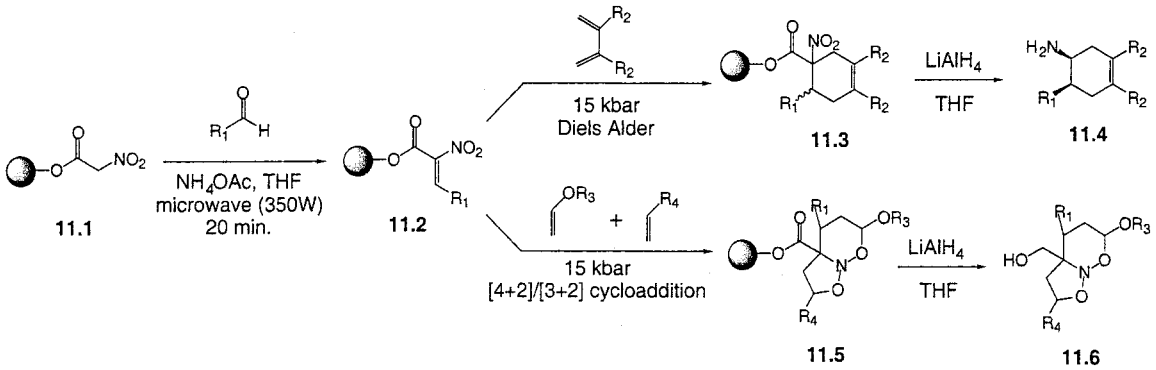

Figure 11.

solid phase could be achieved in 5 min with microwave irradiation (Figure 10). Mixtures of various aldehydes, carboxylic acids, and isocyanides in CH_2Cl_2/MeOH (2:1) were added to TentaGel resin-bound amines (**10.1**) and were irradiated for 5 min at 60 W using a monomodal microwave (Microwell 10) and 10 mL Teflon screw-capped vials. The 18 α-acylaminoamides (**10.2**) were isolated in 24−96% yields, but with greater than 95% purity, and in a fraction of the time required under traditional heating conditions. Although some of the yields are low, they are comparable to those obtained from normal UGI solid-phase reactions. As with the aforementioned Suzuki reaction on TentaGel, the UGI reaction also resulted in a minor amount of PEG leakage during the TFA cleavage step. The successful application of microwave technology to the UGI reaction demonstrates the potential of microwave assistance in other multicomponent coupling reactions for the construction of large libraries.

More recently, the synthesis of a common intermediate with potential for generating diversity was achieved using microwave assistance. A Knoevenagel condensation between various aldehydes and the Wang resin bound nitroacetic acid **11.1** gave a variety of nitroalkenes (**11.2**) that were then further functionalized by a Diels−Alder reaction (**11.3**) or a one-pot tandem [4 + 2]/[3 + 2] cycloaddition (**11.5**) to generate additional diversity (Figure 11).[25] A $LiAlH_4$ reductive cleavage off the Wang resin then afforded a variety of cis cyclic amines (**11.4**) and bicyclic nitrosoacetals (**11.6**), respectively. Although both of the cycloadditions were achieved under high pressure rather than with microwave assistance, the synthesis of the building block, resin-bound nitroalkene **11.2**, was accelerated using a 20 min microwave irradiation at 350 W. Surprisingly, the reaction was conducted in a volatile solvent (THF) without the use of special reaction vessels. Regardless of the technical parameters, the efficient synthesis of the resin-bound nitroalkene **11.2** and applications of the resin for molecular diversity are impressive.

Claisen rearrangements on solid phase can also be accelerated with microwave heating (Figure 12). Kumar was able to convert Merrifield resin derivatized with *O*-allyl phenolic ethers (**12.1**) into ortho-allylic phenols (**12.2**) with microwave irradiation using a domestic microwave oven and an open Erlenmeyer flask.[26] This microwave-accelerated Claisen rearrangement was complete in 4−6 min in K_2CO_3 and DMF but took 15−20 min under the same conditions without DMF. Although the reaction was conducted in an

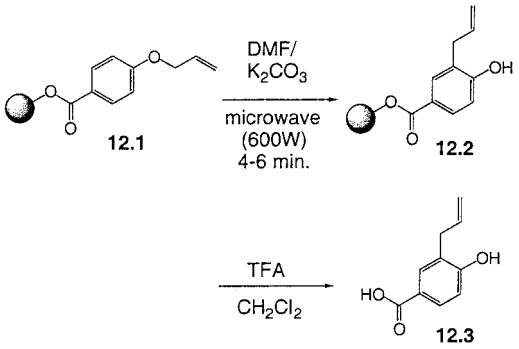

Figure 12.

open flask, the solvent evaporation and reaction temperature was controlled via pulse irradiation (1 min with 20 s intervals). Yields between 84% and 92% were observed for these minute-long microwave reactions, comparable to the yields obtained after 10−16 h of traditional heating at 140 °C.

Microwave-assisted reactions on solid phase are not confined to Merrified or TentaGel resin; they can also be performed on cellulose or polypropylene membranes. Scharn generated 8000 cellulose-bound 1,3,5-triazines in parallel using a microwave-assisted nucleophilic substitution reaction (Figure 13).[27] For generation of this spatially addressed parallel library, amino-functionalized membranes (**13.1**) were first dipped in 4 M cyanuric chloride in CH_2Cl_2 at room temperature for 15 min to give membrane **13.2**. Diversity was then introduced by pipetting various secondary amines dissolved in NMP directly onto individual squares drawn out in pencil on the cellulose membrane (**13.3**). Although the first nucleophilic substitution was complete at room temperature in 30 min, harsh conditions (80 °C for 5 h) were needed to achieve complete substitution of the last chlorine atom in the subsequent step. Consequently, Scharn reduced the substitution time to under 6 min with microwave irradiation (**13.4**). In addition, yields for this difficult second coupling were increased from 50% to greater than 95%.

In all the aforementioned examples of microwave-promoted solid-phase synthesis reactions, dramatic rate accelerations were observed. However, none of these papers sought an explanation for this rate enhancement nor were temperatures and pressures during the microwave irradiation period measured. Several months ago, however, Stadler reported on a comprehensive study of the rate enhancements observed in solid-phase microwave reactions.[28] By use of

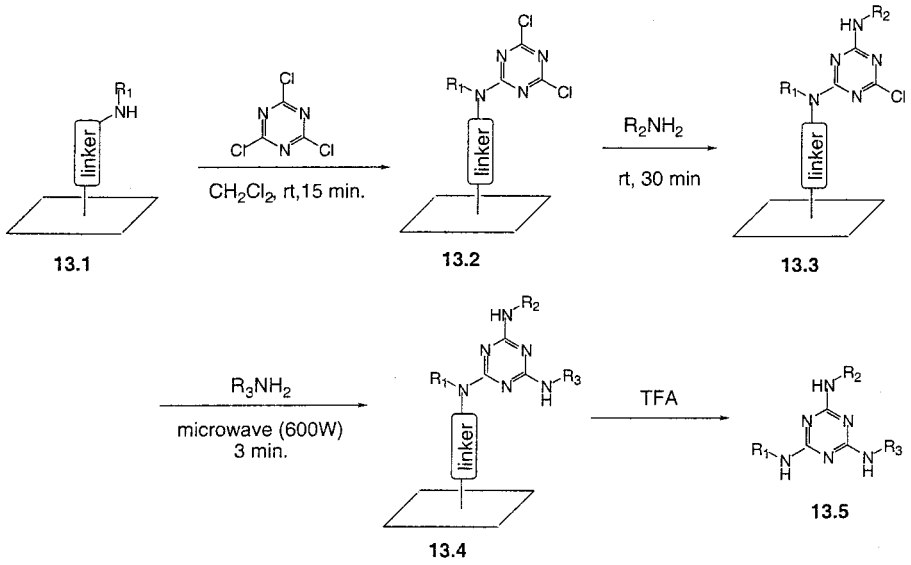

Figure 13.

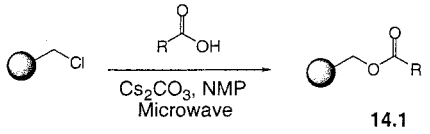

Figure 14.

state-of-the-art microwave reactors equipped with a built-in magnetic stirrer and temperature and pressure controls, temperature and pressure profiles were mapped for the coupling of 33 substituted aromatic, heterocyclic, and alkylcarboxylic acids to the Merrified resin (Figure 14). These studies showed that the dramatic rate increases were due to the direct rapid "in-core" heating of the solvent, not by "nonthermal" microwave effects as some have postulated.[29] In addition, examination of the beads under a microscope after a 700 W 20 min irradiation showed that neither the physical appearance nor the swelling behavior of the beads had changed. These in-depth studies further confirm the feasibility of microwave technology for solid-supported combinatorial synthesis.

A.2. Reactions with Fluorous Compounds. Solid-phase reactions allow for easy separation but typically suffer from slow rates of reaction due to heterogeneity. Researchers seek to bridge that gap with microwave-assisted reactions as shown in the above examples. Larhed, the pioneer of microwave-assisted small-molecule solid-phase synthesis, added yet another novel twist to microwave-assisted reactions by coupling microwave technology with fluorous organic reactions.

Highly fluorinated compounds are insoluble in organic solvents and water at room temperature, but when heated, they can become soluble. Consequently, the ability to conduct homogeneous reactions with fluorous reagents at high temperatures, yet have insoluble fluorous byproducts at room temperature, allows reasearchers to benefit from the advantages of both solid-phase and solution-phase chemistry.

To this end, Larhed demonstrated microwave-accelerated Stille couplings of fluorinated tin reagents as a method of high-throughput combinatorial synthesis. A variety of fluorinated aryltin, heteroaryltin, and allyltin reagents (**15.1**) were coupled with organic halides and triflates (**15.2**) in the presence of LiCl and catalytic amounts of $PdCl_2(PPh_3)_2$ in DMF (Figure 15).[30] The reaction mixtures were irradiated to completion with a monomode microwave (MicroWell 10) at 50−70 W in less than 2 min, whereas analogous solution-phase reactions took 24 h at 80 °C. After a three-phase extraction with fluoroheptanes (FC-84), CH_2Cl_2, and H_2O, good yields of Stille coupled products were isolated (**15.3**). Also of note is the decrease in the homocoupled biaryl side product observed when microwave heating was employed as opposed to conventional thermal heating. A more highly fluorinated tin compound $PhSn(CH_2CH_2C_{10}F_{21})_3$ has also been employed to increase partitioning into the fluorous phase during product isolation.[31]

B. Microwave-Assisted Solvent-Free Combinatorial Synthesis. B.1. Reaction Mixtures Adsorbed onto Mineral Oxides. One way to perform a microwave-promoted solvent-free reaction is to first impregnate a solid support capable of absorbing microwave irradiation (i.e., silica, clay, or alumina) with a solution of reactants dissolved in a volatile solvent. The solvent is then removed via evaporation, and the dry mixture is irradiated by microwaves. After irradiation, the product is extracted with the appropriate solvent. Because there is no solvent during the microwave irradiation, fire and explosion hazards are minimized and the reactions can be performed in open vessels. Currently, two groups have reported using this method of solvent-free microwave reactions for combinatorial synthesis.

Khmelnitsky et al. reported the first practical application of microwave technology in combinatorial chemistry using solvent-free conditions. In this 1998 paper, a three-component Hantzsch synthesis of substituted pyridines was performed in 96-well plates suitable for high-throughput synthesis (Figure 16).[32] Each step, from addition of reagents to the final product recovery was automated. For example, each well of the plate was filled with 100 mg of bentonite (clay)/ammonium nitrate (5:1 w/w) and various 1,3-dicarbonyl compounds and aldehydes using a Cyberlab C-200 robotic liquid handler. The plates were irradiated for 5 min with a domestic Kenmore 1300 W microwave oven at 70%

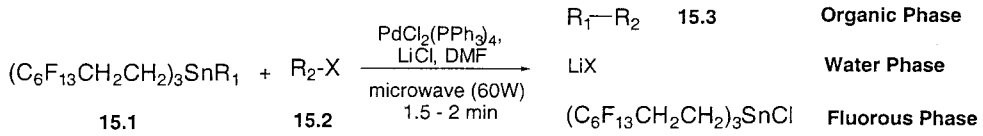

Figure 15.

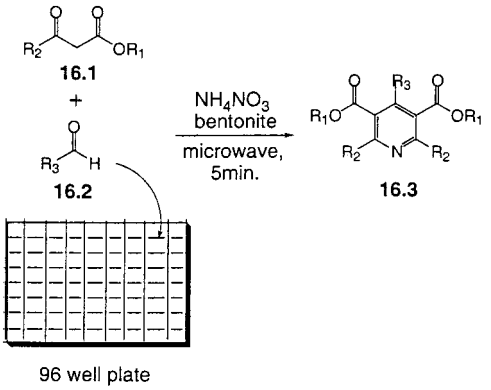

Figure 16.

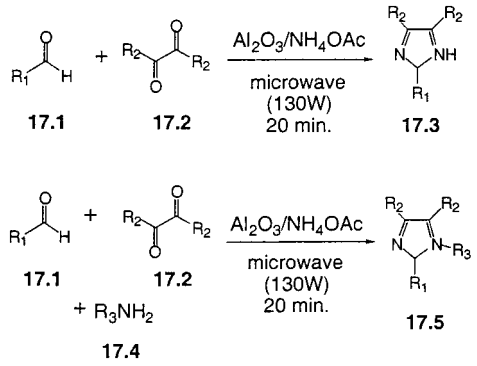

Figure 17.

power, and the resultant products were extracted with ethyl acetate and analyzed by high-throughput HPLC/MS. Although yields were not reported, the solvent-free parallel Hantzsch synthesis successfully provided a large number of substituted pyridines in greater than 70% purity in a relatively short amount of time. The success is owed largely to solvent-free conditions, allowing 96-well plates to be microwave-irradiated in open wells without the problems associated with solvents (i.e., evaporation, explosions, and cross contamination).

Two years later, the same group reported the synthesis of a library of diversely substituted imidazoles under solvent-free conditions (Figure 17).[33] This time, rather than utilizing 96-well plates, they opted for traditional glass round-bottomed flasks. Various aldehydes and 1,2-dicarbonyl compounds were adsorbed onto acidic alumina impregnated with ammonium acetate and then were irradiated for 20 min with a household microwave oven (130 W, 10% power). The products were then extracted with a mixture of acetone and triethylamine to give a variety of substituted imidazoles in 67−82% yields and 75−85% purity. In contrast, traditional methods required heating in acetic acid for 4 h.

Another group working on developing methods for microwave-assisted solvent-free combinatorial chemistry is Kidwai's group in India. Kidwai's laboratory has published three papers on the microwave synthesis of biologically

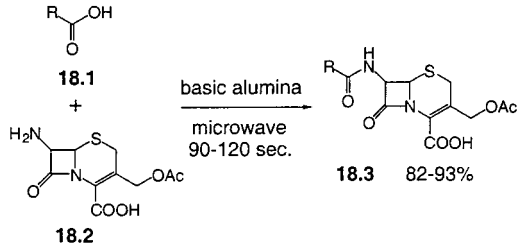

Figure 18.

active molecules. In the first paper, 10 Cephalosporin derivatives were made with the aide of microwave irradiation and then were screened for antibacterial activity (Figure 18).[34] Various heterocyclic carboxylic acids (**18.1**) and 7-aminocephalosporanic acid (**18.2**) were adsorbed onto basic alumina and microwave-irradiated for 90−120 s to afford N-acylated cephalosporin analogues (**18.3**) in good yields (82−93%). Traditional heating not only took 2−6 h but gave diminished yields (63−76%) compared to microwave heating.

In the second paper, Kidwai et al. synthesized 10 novel thiadiazolyl- and oxadiazolyl-substituted quinolones (**19.6**) in good yields and screened them for antibacterial activity (Figure 19).[35] These compounds were synthesized in three steps, each taking advantage of microwave heating for rapid synthesis. For example, coupling of neat chlorofluoroaniline (**19.1**) and malonate **19.2** was accomplished with 40 s of microwave irradiation to give anilinomethylene malonate **19.3** (conventional heating took 6−7 h). Then, absorption of malonate **19.3** onto acidic alumina followed by irradiation for 60−90 s gave quinolone **19.4** without the traditional use of polyphosphoric acid. Last, microwave irradiation of quinolone **19.4** with various thiadiazoles and oxadiazoles (**19.5**) on basic alumina afforded the desired substituted quinolones (**19.6**) in 60−90 s, eliminating the use of strong bases such as NaOH and K_2CO_3. The paper compares the reaction times and yields among (a) conventional heating, (b) microwave heating in solution phase, and (c) microwave heating with reagents adsorbed onto alumina, with the end result demonstrating that microwave heating on solid phase was far superior. This was quite an impressive use of microwave heating, since a linear three-step synthetic sequence was completed in under 5 min!

In their third paper, Kidwai's group employed microwaves to synthesize thiadiazepines (**20.3**) in order to test them for antibacterial and antifungal activity (Figure 20).[36] A reaction that takes 10−18 h with traditional heating methods, microwave irradiation of 2-mercapto-1-amino substituted triazoles (**20.1**) and substituted chalcones **20.2** adsorbed into basic alumina gave various thiadiazapines **20.3** in 60−120 s. In addition to the reduced reaction time, the yields of thiadiazapines were significantly better as well (conventional heating, 57−73% versus microwave heating, 90−97%).

B.2. Phase-Transfer Catalysis. Another method of per-

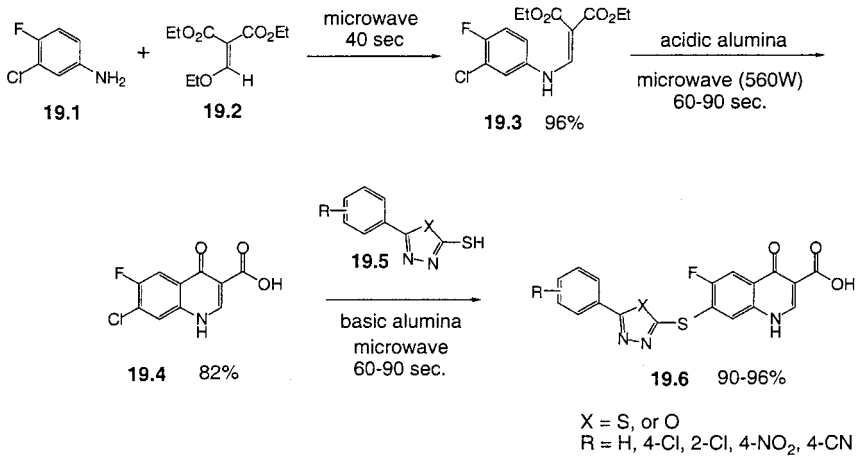

Figure 19.

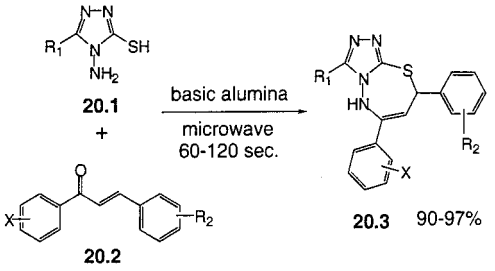

Figure 20.

forming solvent-free microwave reactions is to add a phase-transfer catalyst (PTC) to the reaction mixture in which the reactant can also act as the organic phase. PEG has been shown to be a thermally stable and inexpensive PTC. As opposed to TentaGel, which is a beaded *solid* support with a cross-linked polystyrene core grafted with linear PEG, a medium to high molecular weight PEG (MW of 3000−6000) can be, and has been, used as a *soluble* polymeric support for small-molecule synthesis.[37] The use of medium to high molecular weight PEG as a polymer support has gained popularity in combinatorial synthesis because high molecular weight PEG is a solid at room temperature but melts at 45−50 °C. Consequently, reactants linked to PEG and used at temperatures above 45 °C benefit from the advantages of solution-phase chemistry, but when cooled to room temperature, they possess the ease of purification inherent to solid-phase synthetic reactions. Only recently has high molecular weight PEG been employed as both a PTC and soluble polymeric support in microwave-assisted combinatorial synthesis.

A small library of PEG esterified biaryls was synthesized rapidly under phase-transfer catalysis via a microwave-irradiated Suzuki coupling (Figure 21).[38] PEG (MW 6000) esterified benzoates (**21.1**) were mixed with various arylboronic acids (**21.2**), water/potassium carbonate, and catalytic amounts of palladium acetate before microwave irradiation (75 W, 2−4 min), affording the polymer-bound biaryl **21.3**. The recovery of products required only precipitating with ice-cold ether. No ester cleavage occurred with microwave heating; in contrast, traditional heating for the Suzuki coupling not only took 2 h at 70 °C but also prematurely cleaved the ester linkage (up to 45%).

Palladium-catalyzed Suzuki coupling was also accelerated by microwave-assisted PTC. Although quantitative conversion of the substituted benzoic acid **21.4** to biaryl **21.5** was achieved with microwave irradiation at 200 W for 8 min, a dramatic decrease in yield compared to the PEG-bound products was observed. However, no explanation of this decrease in yield was offered.

A lower molecular weight PEG (PEG 3400) was employed as a PTC in the microwave-assisted synthesis of α-amino acid derivatives (Figure 22).[39] PEG-bound **22.1** was mixed with a variety of electrophiles and inorganic bases such as K_2CO_3 or Cs_2CO_3. Microwave irradiation of the dry mixture in an open Pyrex glass vessel in a domestic microwave oven (850 W) for 45 min afforded the alkylated products **22.2**. Interestingly, no dramatic reduction in reaction rate was observed when compared to traditional heating with acetonitrile as the solvent.

A useful variant of microwave-assisted PTC reactions is to employ poly(styrene-*co*-allyl alcohol) **23.1**, a support similar to TentaGel with properties of both polystyrene and PEG. However, polymer **23.1** can be used as a PTC in the microwave synthesis of various heterocycles and then recycled. For example, microwave-assisted coupling (domestic microwave oven) of neat *β*-keto esters and the polymer **23.1**, followed by a condensation with 5-amino-3,4-dihydro-2-phenyl-2*H*-pyrazole-3-one in refluxing acetic acid, affords the heterocycle **23.3** and the acylated polymer **23.4** in a few minutes (Figure 23).[40] The heterocyclic product was collected by filtration, while the remaining filtrate was mixed with water to precipitate the acyclated polymer **23.4**. The acylated polymer can then be recycled to the parent polymer **23.1** in 65% yield by saponification with NaOH.

B.3. Neat Solid Reagents. Several solventless microwave-assisted reactions have been reported for combinatorial synthesis in which neat reagents are mixed and microwaved in the absence of mineral oxides or a phase-transfer catalyst. For example, Varma made a 15-compound "library" via a Biginelli condensation by simply microwaving a dry mixture of various *β*-keto esters, aryl aldehydes, and urea derivatives with polyphosphate ester (PPE) as an acid catalyst for 90 s in a domestic microwave oven (Figure 24).[41] The authors speculate that the reaction is accelerated compared to the traditional Biginelli reactions conducted in refluxing THF

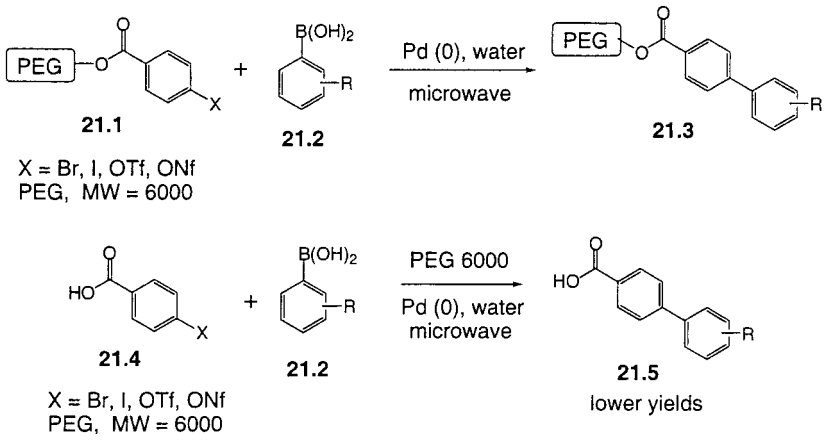

Figure 21.

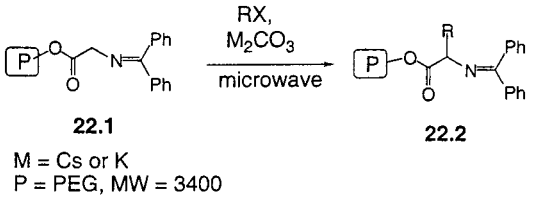

Figure 22.

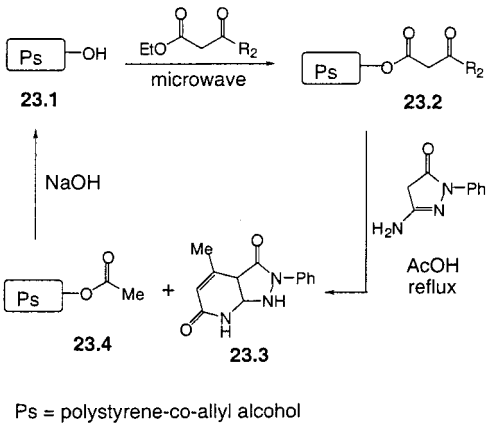

Figure 23.

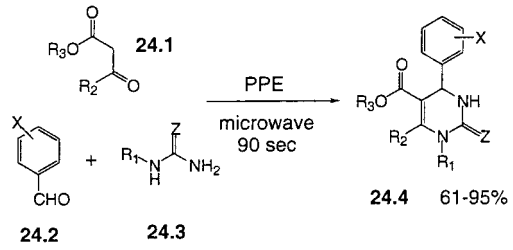

Figure 24.

and PPE for 24 h because "in-core" heating of the water byproduct is possible with microwaves.

In another interesting example of microwave-promoted reactions in the absence of solvent or a phase-transfer catalyst, a Merrified resin-bound amine (**25.1**) is throughly mixed with dry Lewis acid adsorbed silica gel and various anhydrides (**25.2**) and microwaved for 5 min in a domestic microwave oven (450 W) to prepare *N*-alkylimides **25.3** (Figure 25).[42] With the appropriate mesh size, Merrifield resin can be physically separated from silica gel, and then the product can be cleaved with TFA/CH_2Cl_2.

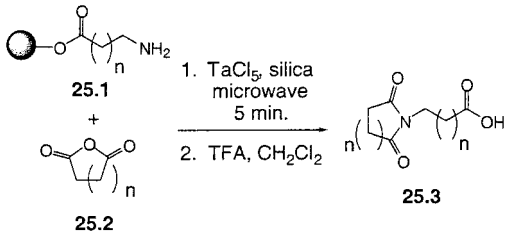

Figure 25.

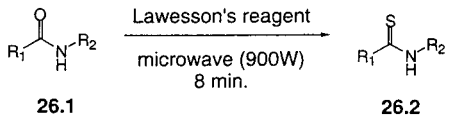

Figure 26.

Finally, microwave irradiation of solvent-free mixtures of amides and Lawesson's reagent gave the corresponding thioamides **26.2** (Figure 26).[43] Irradiation for 8 min in a domestic microwave oven (900 W) consistently gave a 96:4 mixture of the thioamide to amide, with no detection of other side products. The major obstacle in most solvent-free reactions was the ability to obtain a homogeneous mixture of the reactants.

V. Summary

Prior to combinatorial chemistry, medicinal chemists synthesized only a few compounds per week. Combinatorial chemistry revolutionized the drug industry such that the standard now is to synthesize hundreds or thousands of compounds per week. However, the bottleneck in many of these solid-phase reactions is the reaction rate. In all but 1 of the 24 examples reviewed above, microwave heating reduced the reaction time for solid-phase combinatorial synthesis from hours/days to minutes. These rate reductions are speculated to arise from the rapid "in-core" heating of polar solvents and reagents, although debate over the existence of nonthermal effects continues. Clearly, more research is needed to be able to fully incorporate microwave technology for high-throughput combinatorial synthesis, but the examples thus far demonstrate the potential of microwave technology in revolutionizing the combinatorial chemistry industry.

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