Drug Discovery at the Speed of Light

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Microwave synthesis is an idea whose time has come: an emerging technology that will have a major impact on drug discovery and development over the next 3-5 years.

Although there have been major advancements in the last 5 years in the methodology of synthetic chemistry, one element of the process has not changed since its inception - the use of conductive heating to perform chemical reactions. Conductive heating is still the primary method used for chemical transformations. However, with the advent of microwave synthesis, there is for the first time, a technology that will dramatically change the way chemical synthesis is performed by offering a new energy source, powerful enough to complete reactions in minutes, instead of hours or even days. With recent advances in technology and the development of an applications base, the organic chemist is now presented with the tools and knowledge to be able to effectively apply microwave synthesis to any routine.

A microwave (figure 1) is a form of electromagnetic energy, which falls at the lower end of the electromagnetic spectrum and is defined in a measurement of frequency as 300 to 300,000 megahertz. This includes the region that will affect molecular rotation, though the preferred frequency of 2450 MHz, chosen by some microwave instrumentation manufacturers, falls below any of the rotational transitions that will occur in molecules. One of the four available frequencies for industrial, scientific or medical applications, 2450 MHz is preferred because it has the right penetration depth to interact with laboratory scale samples and has become the standard for bench top systems.

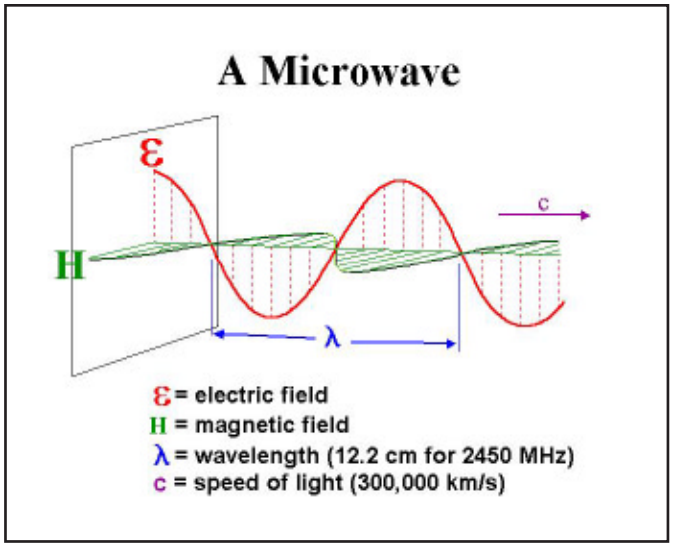

Figure 1

Microwave energy (figure 2) consists of an electric field and a magnetic field, though only the electric field transfers energy to heat a substance.[1] Any interaction from the magnetic field is insignificant. The energy in microwave photons (.03 kcal/mole) is very low relative to the typical energies of 80-120 kcal/mole for chemical bonds. Thus, microwaves will not directly affect molecular structure. In the excitation of molecules, the effect of microwave absorption is purely increased kinetic energy.

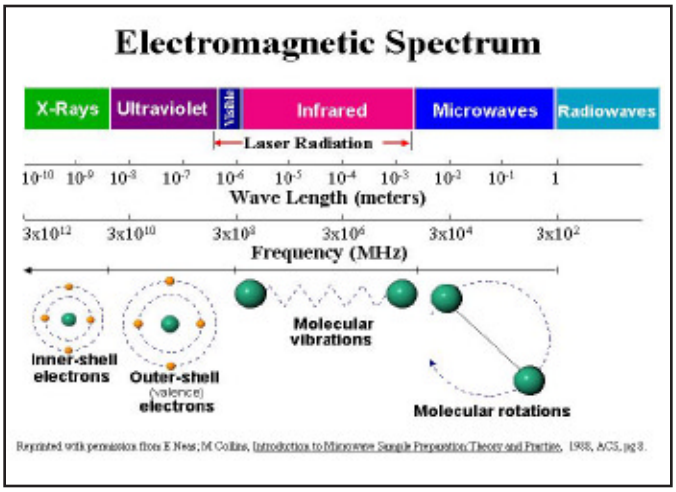

Figure 2

Traditionally, chemical synthesis has been achieved through conductive heating with an external heat source, where the temperature is elevated and heat is driven into the substance, passing first through the wall of the vessel in order to reach the solvent and reactants. This is a slow and inefficient method for transferring energy into the system,

because it depends on the thermal conductivity of the various materials that must be penetrated. It also results in a higher external temperature than the final internal temperature, which is problematic as the required internal temperature can only be reached by sufficiently increasing the surface temperature of the material over the desired temperature.

Microwave heating (figure 3) is a very different process: the microwaves couple directly with the molecules that are heating, leading to a rapid rise in temperature. Because the process is not dependent upon the thermal conductivity of the materials, the result is an instantaneous heating of anything that will react to either dipole rotation or ionic conduction, the two fundamental mechanisms for transferring energy from microwaves to the substance being heated.

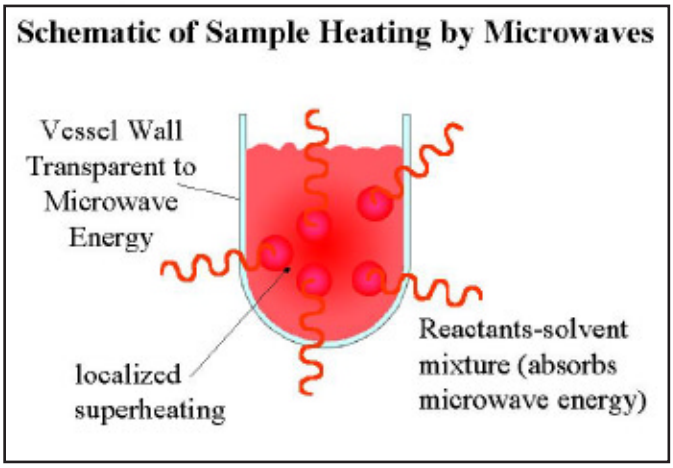

Figure 3

Dipole rotation is an interaction in which polar molecules or polar species try to align with the rapidly changing electric field of the microwave. The motion of the molecule as it tries to orient to the field results in a transfer of energy. The coupling ability of this mechanism is related to the polarity of the molecules and their ability to align with the field and relax to their initial state. Though there are a number of factors that will ultimately determine the dipole rotation coupling efficiency, in essence, any polar species that are present will encounter this mechanism of energy transfer.

The second way to transfer energy is ionic conduction, which results if there are free ions or ionic species present in the substance being heated. The electric field generates ionic motion as the molecules try to orient to the field, causing rapid heating. The temperature of the substance also affects ionic conduction; as the temperature increases, the transfer of energy becomes more efficient.

In a typical reaction coordinate, the process begins with reactants, which have a certain potential energy level. In order to complete the transformation, these reactants must be activated to a transition state. Once there, they quickly react and return to a lower energy state - the product for the reaction. Microwave energy provides the momentum to overcome the activation energy barrier and complete the reaction.

Typically, activation energy for drug discovery and development work is 50 kcal/mole. A typical process would involve 30 mg each of reactant and product with an average molecular weight of 300 g/mole (300-350 is characteristic of drug compounds). As shown in figure 4, five calories of energy are required for the full transformation of the reactants. Microwave hardware commercially available today typically delivers 300 watts of power. Translated into calories, this indicates that 72 cal/sec of energy are available from the 300 watts of microwave, assuming a 100% efficiency of the microwave heating. Clearly, the amount of microwave energy being introduced to the system is very large relative to the energy needed to achieve the activation energies required for the transformation, which contributes to the increase in speed and the higher yields that result.

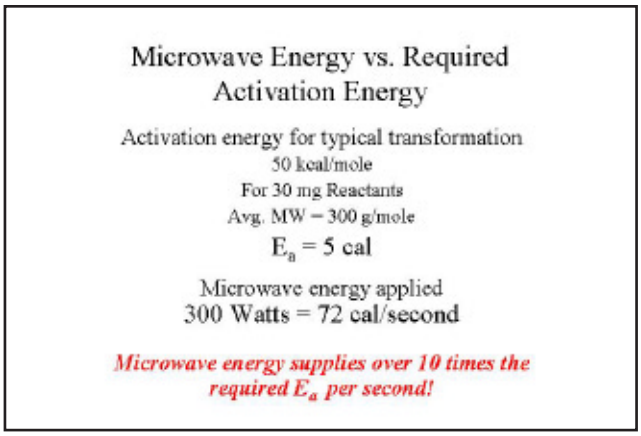

Figure 4

One of the most important aspects of microwave energy is the rate at which it heats. (Figure 5) Microwaves will transfer energy in 10^{-9} seconds, with each cycle of the electromagnetic energy. The kinetic molecular relaxation from this energy is approximately 10^{-5} seconds. The energy transfers faster than the molecules can relax, resulting in a non-equilibrium condition and high instantaneous temperatures that affect the kinetics of the system. This enhances the reaction rate, as well as the yields. Activated complexes do not normally exist long enough to have an opportunity to absorb microwave energy, although there are a number of stabi-

lized intermediates, resident stabilized intermediates and other intermediates that are much longer lived. Many of these have lifetimes longer than 10^{-9} seconds, so the opportunity exists for them to couple directly with the microwave and be further enhanced. Most intermediates are highly polar species and many of them are even ionic in character, making them excellent candidates for microwave energy transfer.

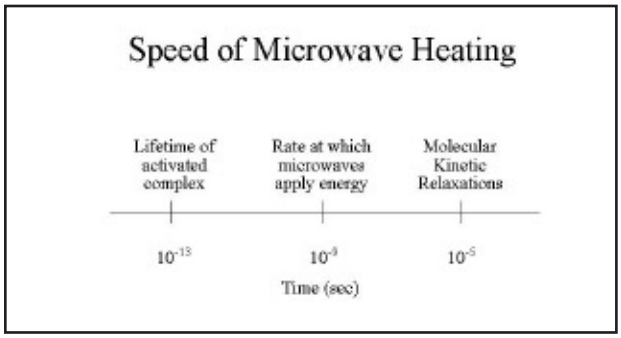

Figure 5

In the basic rate equation (figure 6), the reaction rate constant is dependent on two factors: the frequency of collisions that have the correct geometry for a reaction to occur and the fraction of those molecules that have the minimum energy required to overcome the activation energy barrier. Though there has been some speculation that microwaves affect the orientation of the molecular collisions and/or activation energies, there is no direct evidence to support either of these ideas.[2,3] Microwave energy affects the temperature parameter in this equation, due to the high instantaneous heating of the substance above the normal bulk temperature. This is the primary factor in the observed rate enhancements.

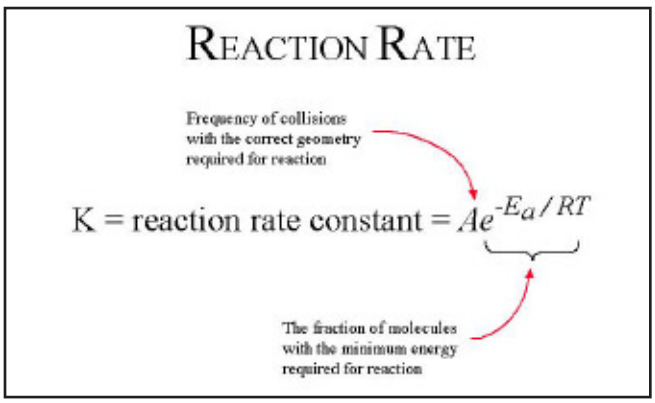

Figure 6

Microwave-enhanced chemical reactions can be faster by as much as 1,000-fold. This is based on experimental data, from numerous works, that have been performed over the last 15 years.[4,5,6,7,8,9,10,11] Using the rate equation, calculations were performed to determine the temperatures required to get these reaction enhancements. For a 1000-fold rate increase, it was determined that a temperature enhancement of approximately 55 °C would be needed. For a 100-fold rate increase the temperature would reach 185 °C and require approximately a 35 °C increase over the bulk temperature. For a 10-fold enhancement, a 15-20 °C increase would be required. Thus, these instantaneous temperatures are very consistent with the temperatures that would be expected in these systems and can fully account for the reaction rate and yield enhancement. These calculations were also performed over a range of temperatures and, as expected, the lines are essentially parallel, predicting the instantaneous versus bulk temperatures.

Microwave heating allows chemical reactions to be shifted from kinetic control to thermodynamic control because of the high energy available. As shown in figure 7, this can change the product for a particular transformation. This mechanism is a probable explanation for some of the work that has been done concerning selected stereo-isomers, which were generated using microwave versus conventional heating.[12]

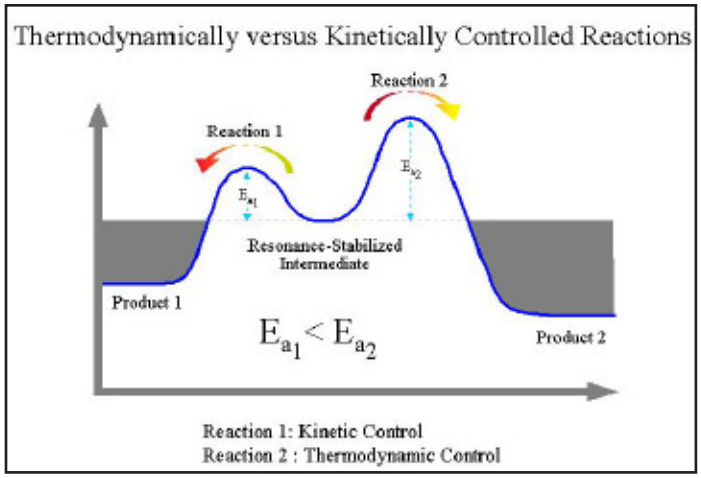

Figure 7

Clearly, microwave heating is extremely useful in slower reactions where high activation energies are required to do various transformations. With the elevated molecular energy generated by the transfer of microwave energy, reactions that required many hours or even days to complete have been accomplished in minutes. It is also possible to use non-polar solvents to actually reduce the bulk heating and directly energize the molecule. The solvent acts as a heat sink to pull energy away. The use of non-polar

solvents in this manner will open opportunities to perform temperature sensitive reactions that were not possible with conventional heating.

Historically, microwave instruments have been multimode systems. With their larger cavities, these systems have been used successfully to process multiple sample formats, microtiter plates and larger scale reactions (more than a liter). Due to their design, multimode cavities have hot and cold spots, which become problematic for chemists trying to perform repeatable chemistry on a small scale. In addition, though the total power generated may be high, the power density in the cavity is quite low; therefore, trying to heat the small individual samples characteristic of drug discovery is difficult.

In the last ten years, single mode cavities with more consistent and predictable energy patterns have become available.[13] These cavities typically offer good uniform energy distribution and the ability to couple more efficiently with small samples, because the higher power density allows the energy to be more focused. However, if the sample size or the polarity of the sample varies in a single mode cavity, it can dramatically affect the ability of the applicator to couple with the sample. Due to this concern, single mode cavities have generally required some type of mechanical tuning device in the system.

In the original single mode design (figure 8), there is a waveguide (the microwave cavity), a power source, a sample positioned at a maximized energy point from the magnetron, and then normally, some type of mechanical tuning device in the system that will adjust it for variations in the sample.[14,15,16,17]

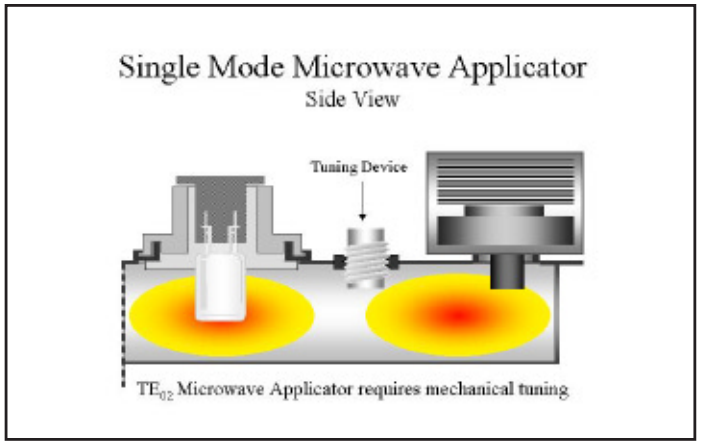

Figure 8

Recent advances in single mode microwave technology now offer greater flexibility to the organic chemist. There is now a single mode applicator, which incorporates a circular cavity and waveguide, that is capable of self-tuning (figure 9). This type of system features multiple entry points for microwaves into the cavity itself, compensating for variations in the sample and the size of the sample placed in the cavity. This single mode cavity is also larger than its predecessors, offering flexibility in terms of sample volume. It can also accept sample containers from 10 mL up to 125 mL in size.

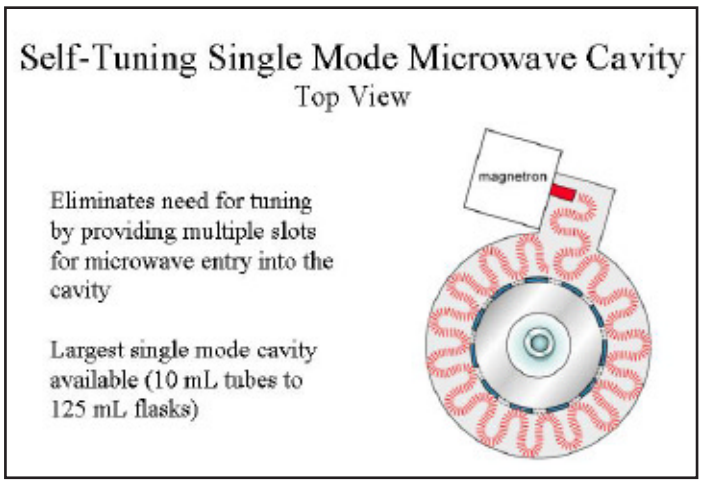

Figure 9

In addition, the technology can be used with open vessels for performing traditional atmospheric work. This provides an open system in which the chemist can perform refluxing, adding reagents to the sample while it heats. This new technology has incorporated all of the desirable capabilities of conventional heating methods into a microwave system offering the additional benefits of greatly increased speed and improved yields. This innovative single mode cavity design is not only applicable to solution phase work, but to solid phase and solvent-free systems as well.

Dr. Anil Vasudevan of Abbott Laboratories performed a number of chemical transformations with the new self-tuning, single mode cavity. The reaction shown in figure 10 is a nucleophilic aromatic substitution. An amine with various ligands attached on a center scaffold was the basis for eight different transformations. These reactions displayed a quantitative conversion with LCMS with reaction times of approximately 10 minutes at 175 °C. Compared to conventional methods the results are very impressive.

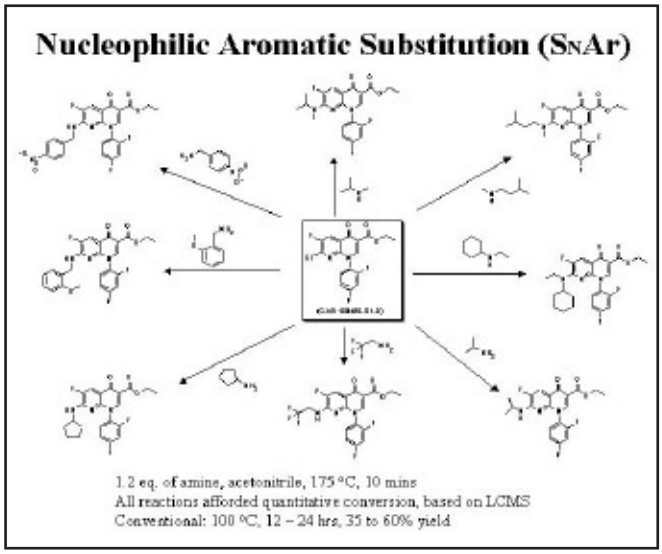

Figure 10

Another reaction Dr. Vasudevan explored was an O-alkylation of phenols using polymer-supported reagents. (Figure 11) This was a demonstration of the use of microwave energy for solid phase reactions. As with the previous transformation, he realized increased yields and reduced reaction times (from 10-30 minutes compared to more than 22 hours from earlier published works).

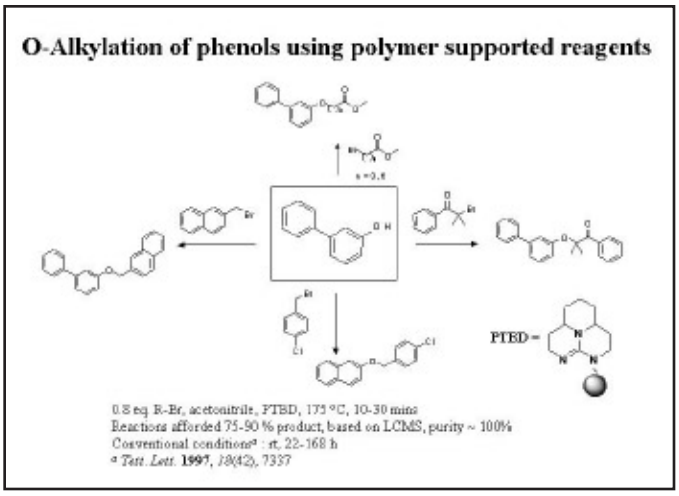

Figure 11

The Biginelli synthesis of tetrahydropyrimidines (figure 12) is a three-component reaction that, again, was successfully completed in a microwave with reaction times of 5 minutes at 170 °C with good yields for the product.

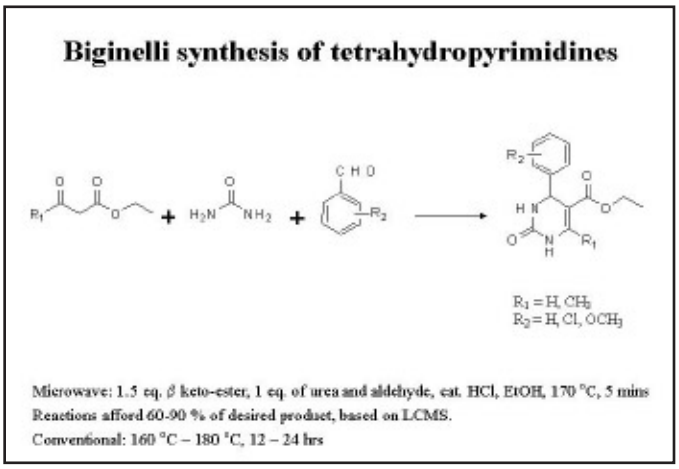

Figure 12

A 1,3,4 oxadiazole synthesis with the second stage accomplished by the use of microwave energy is represented in figure 13. This reaction was performed with conventional heating methods at 150 °C for an hour and a half, with the second stage completed at the same temperature utilizing microwave energy. The microwave-enhanced reaction was 100-fold faster, even though the measured bulk temperatures were the same. Based on the previous calculation, the instantaneous temperatures achieved with microwave heating were 15-20 °C higher than the measured bulk temperature.

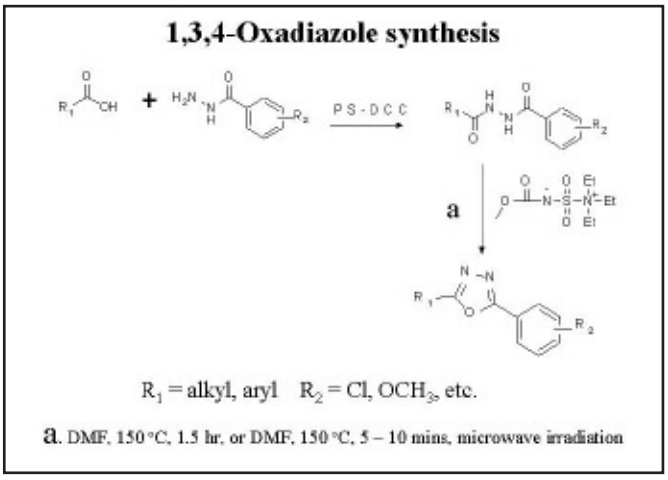

Figure 13

Another important chemistry for drug discovery is palladium coupling reactions. These reactions are a convenient way to achieve carbon-carbon bonds to decorate scaffolds. The first microwave work on the subject was performed in India in 1994 and 1995. It was done in a multimode cavity and reported by Professor Wali and his group in a publica-

tion in 1995.[18] He performed a Heck reaction with iodobenzene and 1-decene (figure 14) and was able to get a complete reaction in approximately 10 minutes compared to 14 hours with conventional methods.

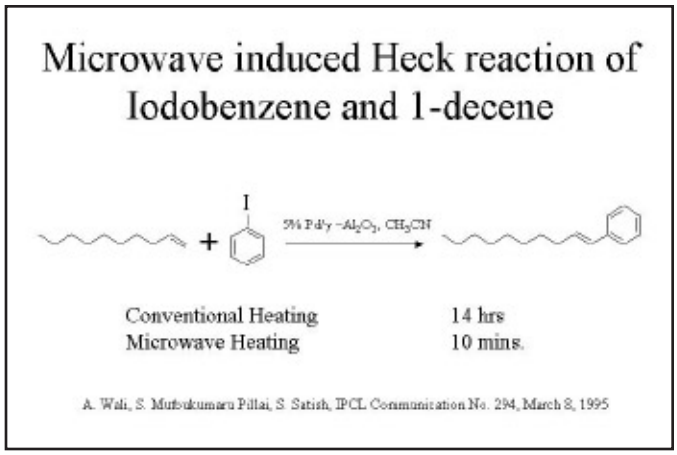

Figure 14

The next microwave work in palladium chemistry was done by Professor Villemin in France and presented in 1995 at a conference in Spain.[19] His palladium catalyzed Heck reaction (figure 15) was the first reported work in a single mode cavity. Like Dr. Wali's group, his work yielded results in about 10 minutes, using only 140 watts of power.

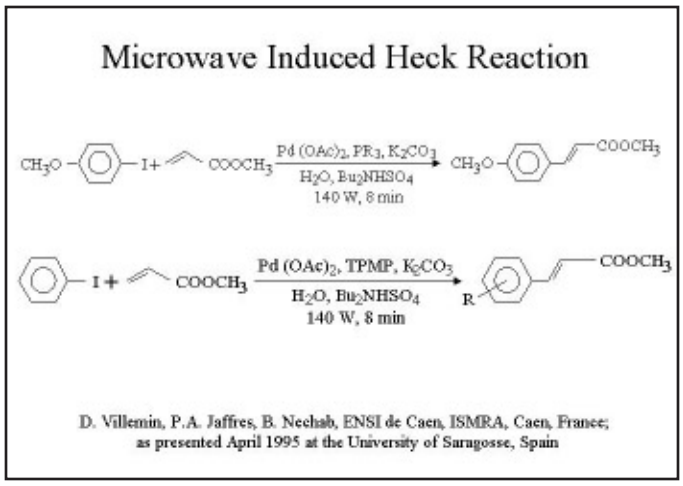

Figure 15

More recently, palladium coupling reactions have been explored by Drs. Larhed and Hallberg from the University of Upsalla. They published their initial findings in 1996 and have subsequently published additional work.[20] Their work, which has been quite exhaustive, shows major advantages in using microwaves to do palladium chemistry. (Figure 16)

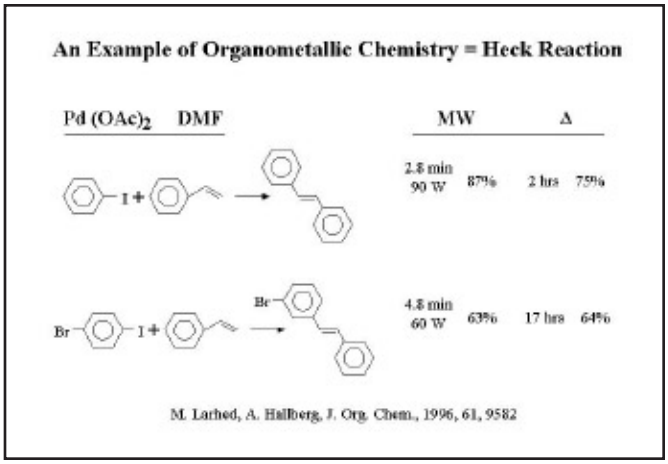

Figure 16

Microwave heating offers yet another exciting new opportunity, the possibility of returning to a sequential rather than a parallel format. In the last several years, there has been a shift to parallel synthesis, primarily due to the reaction times required for conventional heating. Microwave systems provide the opportunity to complete reactions in minutes, offering the option to return to more sequential formats. It is advantageous for the chance it affords the chemist to analyze a reaction before conducting the next step, enabling him to optimize his reactions and reduce the use of valuable substrate.

The role of microwave synthesis in drug discovery and development should dramatically increase over the next few years. There is a need for a very simple, flexible, small footprint microwave system that can be used in synthesis laboratories. As with most new technology, various levels of automation will be demanded and introduced to the market to support needs in drug discovery and library generation. This technology will eventually replace hot plates and block heaters, allowing chemists to begin using microwave energy on a broad scale, as affordable instrumentation becomes readily available. Academia, drug discovery and lead optimization are the areas expected to receive the most benefit from this new technology. As microwave synthesis instrumentation continues to evolve, new applications will be developed for a variety of chemistries and processing needs. This will naturally accelerate as the technology is adopted. Undoubtedly, microwave-enhanced synthesis will be a valuable tool for chemists in a variety of fields and specialties for many years to come.

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