Recent Advances in Microwave-Assisted Synthesis

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Outline

1. A Brief Review of Microwave Theory

The use of microwave irradiation in organic synthesis has become increasingly popular within the pharmaceutical and academic arenas, because it is a new enabling technology for drug discovery and development.[1] By taking advantage of this efficient source of energy, compound libraries for lead generation and optimization can be assembled in a fraction of the time required by classical thermal methods.

Presently, thermally driven organic transformations take place by either of two ways: conventional heating or microwave-accelerated heating. In the first way, reactants are slowly activated by a conventional external heat source. Heat is driven into the substance, passing first through the walls of the vessel in order to reach the solvent and reactants. This is a slow and inefficient method for transferring energy into the reacting system. In the second way, microwaves couple directly with the molecules of the entire reaction mixture, leading to a rapid rise in temperature. Since the process is not limited by the thermal conductivity of the vessel, the result is an instantaneous localized superheating of any substance that will respond to either dipole rotation or ionic conduction—the two fundamental mechanisms for transferring energy from microwaves to the substance(s) being heated.[1a]

The rate of a reaction is determined by the Arrhenius equation ($k = Ae^{-Ea/RT}$), where T is the absolute temperature that controls the kinetics of the reaction. In conventionally heated reactions, this temperature is a bulk temperature (T_B). Microwave-assisted reactions are different. Microwave irradiation will directly activate most molecules that possess a dipole or are ionic. Since energy transfer occurs in less than a nanosecond (10^{-9} s), the molecules are unable to completely relax (~ 10^{-5} s) or reach equilibrium. This creates a state of nonequilibrium that results in a high instantaneous temperature (T_i) of the molecules and is a function of microwave power input. The instantaneous temperature is not directly measurable, but it is much greater than the measured T_B ($T_i >> T_B$). Thus, the greater the intensity of microwave power being administered to a chemical reaction, the higher and more consistent T_i will be. A precedence exists where the concept of instantaneous temperatures has been used to explain reactions occurring at a lower bulk temperature than expected, while using microwave irradiation.[2] In addition, in ultrasonic chemistry, extremely high and immeasurable temperatures are created that enhance the rates of chemical reactions by up to 1 million times.[3] The instantaneous temperature (T_i), not T_B, ultimately determines the kinetics of microwave reactions.

Based on experimental data from numerous studies that have been performed over the past ten years, chemists have found that microwave-enhanced chemical reaction rates can be faster than those of conventional heating methods by as much as 1,000-fold.[1] Assuming a standard first-order rate law (rate = k[A]), the Arrhenius rate equation has been used to calculate the instantaneous temperatures required to get three different reaction enhancements (10-, 100-, and 1,000-fold). The assumption was based on a desired reaction bulk temperature of 150 °C and an activation energy of 50 kcal/mol for the transformation. For a 10-fold rate increase, it was determined that a temperature enhancement of only 17 °C would be needed, relative to a bulk temperature of 150 °C. Microwave energy can provide that temperature increase instantly. Likewise, for a 100-fold rate increase, the instantaneous temperature would have to reach 185 °C—approximately a 35 °C increase over the bulk temperature. A 1000-fold enhancement would need a 56 °C increase over T_B. These instantaneous temperatures are very consistent with the temperatures that would be expected in a microwave system and are directly responsible for the enhancements in reaction rates and yields.[1m]

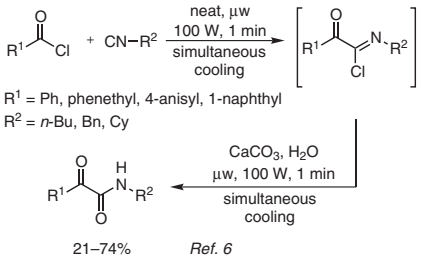
2. Enhanced Microwave Synthesis (EMS)

Recently, an alternative method for performing microwave-assisted organic reactions, termed "Enhanced Microwave Synthesis" (EMS), has been examined.[4] By externally cooling the reaction vessel with compressed air, while simultaneously administering microwave irradiation, more energy can be directly applied to the reaction mixture. In "Conventional Microwave Synthesis" (CMS), the initial microwave power is high, increasing the bulk temperature (T_B) to the desired set point very quickly. However, upon reaching this temperature, the microwave power decreases or shuts off completely in order to maintain the desired bulk temperature without exceeding it. When microwave irradiation is off, classical thermal chemistry takes over, losing the full advantage of microwave-accelerated synthesis. With CMS, microwave irradiation is predominantly used to reach T_B faster. Microwave enhancement of chemical reactions will only take place during application of microwave energy.[5] This source of energy will directly activate the molecules in a chemical reaction; therefore, it is not desirable to suppress its application. EMS ensures that a high, constant level of microwave energy is applied.

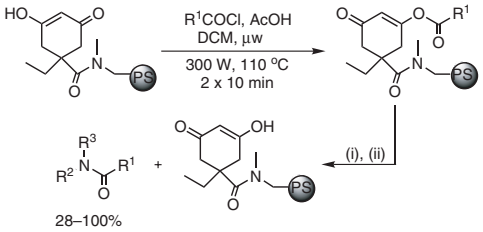
Research published very recently in leading organic synthesis journals supports the use of simultaneous cooling of reactions being heated by microwave energy.[6–8] Simultaneous cooling enables a greater amount of microwave energy to be introduced into a reaction, while keeping the reaction temperature low. This results in significantly greater yields and cleaner chemistries. EMS was employed in the synthesis of a variety of α-keto amides to support a protease inhibitor discovery project. This may eventually lead to improved treatments for stroke, Alzheimer's disease, and muscular dystrophy.[6] Following an earlier protocol from the 1960s, the authors coupled acyl chlorides with various isonitriles. α-Keto imidoyl chloride intermediates were formed, which were then converted to the α-keto amides upon hydrolysis **(Scheme 1)**. Under conventional heating conditions, this took between 2 to 6 hours for completion; whereas under optimized EMS conditions, the two steps were completed in 2 min and in 21–74% yields.

EMS has also been beneficial in producing higher release levels of the desired amides from the solid-phase resin, as compared with microwave heating alone **(Scheme 2)**.[7]

More recently, Katritzky et al. illustrated the advantages of EMS in preparing bistriazoles by the 1,3-dipolar cycloaddition reactions of 1,4-bis(azidomethyl)benzene with monoacetylenes.[8] When reacting the diazide with a carbamoylpropiolate at 120 W and 55 °C for 30 minutes, cycloaddition only occurred at one of the azido moieties. Higher temperatures and irradiation powers resulted in decomposition. By using EMS for the reaction between the diazide and butynoate at 120 W and 75 °C for 1 hour, the Katritzky group successfully synthesized the bistriazole **(eq 1)**. The major isomer was isolated in 54–65% yields.



Scheme 1. Improved Synthesis of α-Keto Amides by Enhanced Microwave Synthesis (EMS).

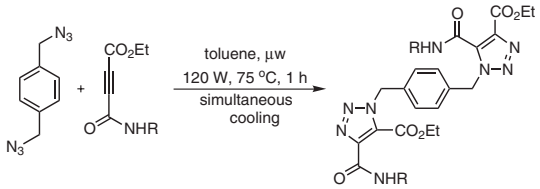


(i) R^2R^3NH, MeOH, μw, 200 W, 125 °C, 0.5 h, continuous cooling.
(ii) Dowex® 50WX resin, rt, 1 h.

R^1 = Pr, *i*-Pr, Ph, 4-$MeOC_6H_4$, 3,5-$Cl_2C_6H_3$; R^2 = *n*-Bu, Bn, Ph
R^3 = H; R^2,R^3 = $CH(CH_3)(CH_2)_4$

Ref. 7

Scheme 2. Improved Release Levels of Amides from Resin by EMS.

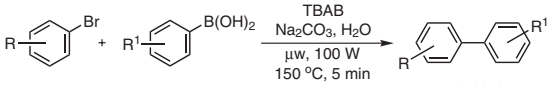


eq 1

1,3-Dipolar Cycloaddition

R	Major Isomer
C_6H_5	54%
4-MeC_6H_4	65%

Ref. 8



eq 2

R = H, 2-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 4-Ac, 4-CHO, 4-NO_2, 4-NH_2, 4-CO_2H, 4-CO_2Me, 2,6-Me_2, 2-Pyr
R^1 = H, 4-Me, 4-Ac

Pd-Catalyst-Free Suzuki Coupling

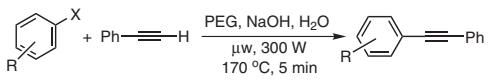
Ref. 9b

3. New Synthetic Applications

The recent publication of several major reviews on microwave-assisted organic synthesis notwithstanding,[1a,b,l] a plethora of very recent articles describing a variety of new chemistries performed with microwave irradiation have appeared. This section will document many of these synthetic applications. **Table 1**, at the end of this section, provides an in-depth summary of the wide range of microwave-assisted applications that are not discussed here in detail.[2,4,5e,6–246]

In organometallic chemistry, two of the most phenomenal recent discoveries are transition-metal-free Suzuki and Sonogashira couplings.[9] Leadbeater and coworkers have shown that reacting an activated aryl bromide with an arylboronic acid in water, using tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst, results in a successfully coupled biaryl Suzuki product without the aid of a palladium catalyst **(eq 2)**.[9b] In addition, a transition-metal-free Sonogashira reaction between an aryl bromide or iodide and phenylacetylene results in respectable yields **(eq 3)**.[9c] In this case, poly(ethylene glycol) is used as the phase-transfer agent.

Buchwald–Hartwig chemistry has become a powerful method for synthesizing arylamines. Conventionally, this reaction requires high temperatures and long reaction times. Many fast and highly efficient applications have been developed in conjunction with



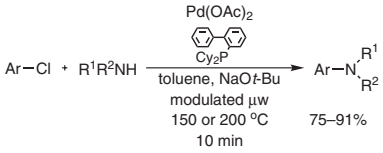
X = Br, I
R = H, 4-Me, 4-Ac, 4-MeO

9–92% yields
10–100% conversions

eq 3

Transition-Metal-Free Sonogashira Reaction

Ref. 9c



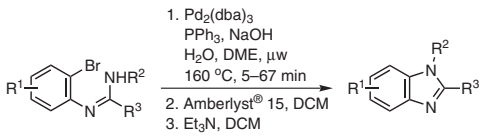
75–91%

eq 4

R^1 = H, Me; R^2 = Ph, 4-tolyl; R^1R^2 = $(CH_2)_2O(CH_2)_2$
Ar = 2-pyridinyl, 3-pyridinyl, 2-quinolinyl, 2-pyrazinyl, 4-tolyl, 2-anisyl

Intermolecular Buchwald–Hartwig Amination of Aryl Chlorides

Ref. 11



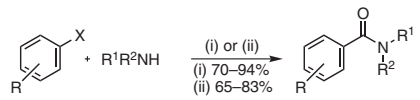
66–98%

eq 5

R^1 = 3-Me, 5-H, 5-OMe, 5-NO_2
R^2 = Me, *i*-Pr, Ph
R^3 = Me, Ph

Intramolecular Buchwald–Hartwig Amination of Aryl Bromides

Ref. 10

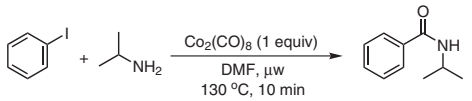


(i) $Pd(OAc)_2$, dppf, imidazole, KO*t*-Bu, DMF
μw, 180–190 °C, 15–20 min (*Ref. 21*).
(ii) [Pd], K_2CO_3(aq), $Mo(CO)_6$, diglyme, μw, 150 °C, 15 min (*Ref. 19*).

eq 6

(i) X = Br; R = H, 2-Me, 4-Me, 4-MeO
R^1R^2NH = aniline, benzylamine, morpholine.
(ii) X = Br, I; R = 4-Me, 4-MeO, 4-CF_3, 4-Ac
R^1R^2NH = *n*-$BuNH_2$, piperidine.

Pd-Catalyzed Amidation Using in situ Generated CO

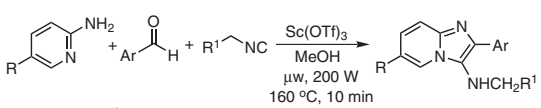


63%

eq 7

Palladium-Free Amidation Using $Co_2(CO)_8$ as the Only CO Source

Ref. 22a



R = Me, Br; R^1 = Ph, CO_2Et
Ar = 2-pyridinyl, 2-naphthyl

50–93%

eq 8

A Three-Component Ugi Reaction

Ref. 24

microwave irradiation.[10–16] One interesting example is the palladium-catalyzed amination of (azahetero)aryl chlorides. Aryl chlorides are known to be quite unreactive due to the C–Cl bond strength, but with microwave heating for 10 minutes, these aminations proceed nicely **(eq 4)**.[11] **Equation 5** shows a microwave-assisted, improved intramolecular amination of aryl bromides to benzimidazoles.[10]

Another organometallics area of interest is carbonyl-insertion reactions. Multiple examples of palladium-catalyzed ester synthesis,[17] both palladium-[18–21] and nonpalladium[22]-facilitated amidations, and diaryl ketone synthesis[23] have been published. Carbon monoxide can be generated in situ by reaction of a formamide with potassium *t*-butoxide, or it can be generated from metal carbonyl complexes such as $Mo(CO)_6$ or $Co_2(CO)_8$. **Equation 6** illustrates palladium-catalyzed amidations using both carbon monoxide sources.[18–21] Using EMS, an amidation was successfully executed directly from an aryl halide and an amine with only $Co_2(CO)_8$ and no palladium catalyst or additional CO source **(eq 7)**.[22] To the author's knowledge, this has never been achieved with either CMS or conventional heating.

One-pot, multicomponent reactions receive much attention because of their efficient access to complex molecules. In the past year or so, there have been many different microwave-assisted multicomponent applications examined. Some of these include Ugi,[24,25] Mannich,[26–29] and other heterocycle-forming reactions.[30–51] The Ugi condensation can be either a three-component or a four-component, one-pot reaction. A three-component example—utilizing a 2-aminopyridine, an aldehyde, and an isocyanide—successfully leads to fused 3-aminoimidazoles in 10 minutes under microwave irradiation **(eq 8)**.[24] Ugi reaction products are generally difficult to purify at the end of the reaction because of the multiple reactants. When one reagent is attached to a solid-phase resin, however, the purification bottleneck is removed. **Scheme 3** shows a four-component Ugi reaction example in which the solid-phase resin acts as a protecting group for one of the amino groups on the diaminobenzene. After the condensation is completed, cleavage of the resin with trifluoroacetic acid (TFA) provides a primary amine that can then undergo cyclization to form the quinoxalinone ring system. By changing either the isocyanide or the aldehyde component, a diverse library can be synthesized.[25]

Mannich reactions are some of the best methods to synthesize β-amino ketones. This one-pot, three-component condensation traditionally utilizes a substituted methyl ketone, an aldehyde, and an amine. In the Petasis boronic-Mannich reaction, the methyl ketone is replaced with a boronic acid and the aldehyde components most commonly used are glyoxylic acid and salicylaldehyde. This yields α-amino acids and aminoalkylphenols, respectively. **Equation 9** illustrates a microwave-assisted, boronic-Mannich reaction run in dichloromethane at 120 °C for 10 minutes.[26] Reaction of glyoxylic acid with different boronic acids and amines provided moderate-to-good yields.

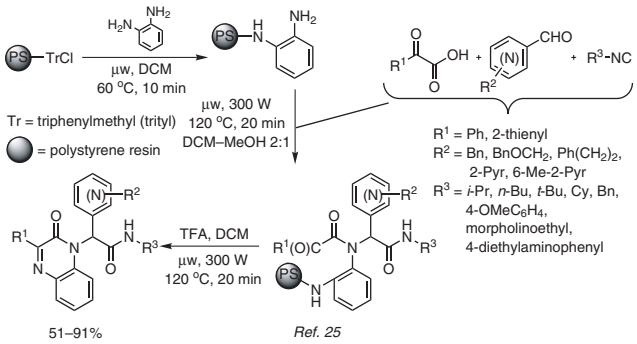
Ring-closing metathesis (RCM) has become a powerful synthetic tool for the construction of ring systems. Utilizing Grubbs' catalyst (a metal carbene complex) carbon-, oxygen-, nitrogen-, and sulfur-containing dienes can cyclize to form functionalized cycloalkenes. When carried out conventionally, this reaction can be plagued by long reaction times, and it can also have limited success due to unfavorable substitution patterns. Use of microwave irradiation has allowed greatly enhanced reaction and conversion rates, as well as opened up new, previously inaccessible, ring-system possibilities.[52–57] **Equation 10** illustrates a survey of microwave-assisted RCM reactions in both solvent and solvent-free conditions.[54]

Table 1. Recent Applications of Microwave-Assisted Organic Synthesis

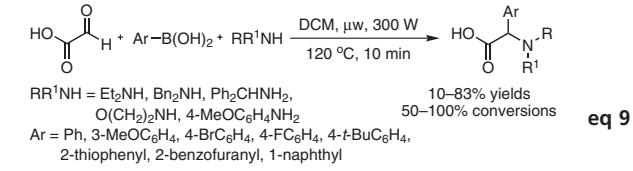
Reaction Type	Reference No.
Alkylations, Acetylations	36,60,83–93
Asymmetric Reactions	58–60,83,85,94
Carbohydrates	92,95–99
CO Insertions	17–24
Condensations	28–31,100–104
Cyanations	105–111
Cycloadditions	8,76,107,112–119,127c,g,128,224
Heterocycle Synthesis	5e,8,25–27,32–57,72,74,76,78,79,81,101,107,108, 112, 114,116,118,120–150
Reactions Involving Ionic Liquids	41,105c,127g,151–161
Michael Reactions	94,127f,162–165
Multicomponent Synthesis	25–51
Nucleoside Synthesis	49,166–169
General Organometallics	17–24,52–57,60,80,83,85,115,127d,170–179
Buchwald-Hartwig	10–16
Heck, Suzuki, Sonogashira	9,116,161,166b,180–184
Fischer Carbenes	185
Pauson-Khand	186–188
Oxidations	189–196
Peptides, Proteins	2,197–203
Photochemistry	65,170,204–205
Polymers	61,63,64,67,68,70,206–212
Protections/Deprotections	213–217
Radicals	61–70
Rearrangements	69,99,153,194,200b,218–223
Ring-Closing Metathesis (RCM)	52–57
Scavengers	7,73,127a,b,224
Simultaneous Cooling (EMS)	4,6,7,8
Solid-Phase Reactions	7,18,23,26,39,42,67,71–82,93b,100,123e,125, 127b,e,133,168,197,198a,b,202,225–231
Solvent-Free Reactions	31,33,34,48–50,84,89,91,98,102,104,122,128, 131,132,135,136,139,142,145,191,192,195,196
C–H Bond Activation	232
Dye Synthesis	233,234
Halide Exchange	235
Halogenation	166a,236–238
Macrocycles	58,59
Nitration	239,240
SNAr	241
Phosgenation	242
Polymerase Chain Reaction (PCR)	243
Trypsin Digestion	244
Wittig Reaction	245,246

Macrocyclic ring systems are of key interest to many natural product chemists. One emerging area for these chemists is library synthesis of diversity-oriented templates that resemble natural products. These molecules can have therapeutic potential that is greater than the natural products themselves. Microwave-assisted asymmetric macrocyclic syntheses provide a fast and efficient route to these compounds.[58–60] Utilizing a distannoxane catalyst, an effective, microwave-assisted (200 °C, 7 min) cyclodimerization of a chiral hydroxy ester led to a 60% yield of the macrodiolide product **(eq 11)**.[58]

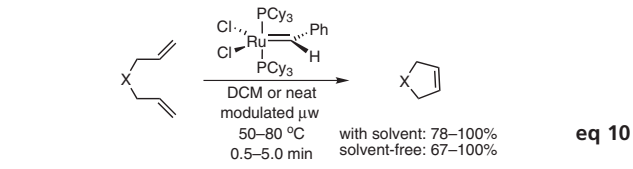
There are many organic transformations that proceed via radical chemistry. As chemists wonder if microwave irradiation can promote radical formation, microwave-assisted free-radical chemistry is increasingly being explored.[61–70] **Scheme 4** shows a microwave-assisted, tin-free, radical carboaminoxylation of substituted alkenes by the persistent radical effect (PRE).[62] Mechanistically, the alkoxyamine generates 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) and a stable malonyl radical, which subsequently reacts with the alkene. Diverse malonates were synthesized in 10 minutes in DMF at 180 °C.



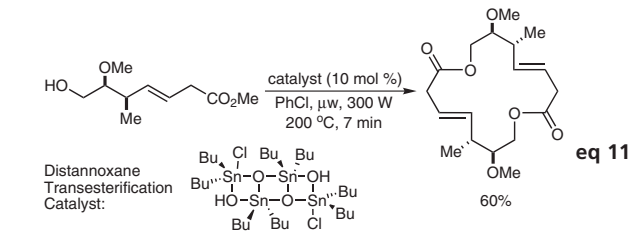
Scheme 3. A Four-Component Ugi Reaction Facilitated by Microwave Irradiation.



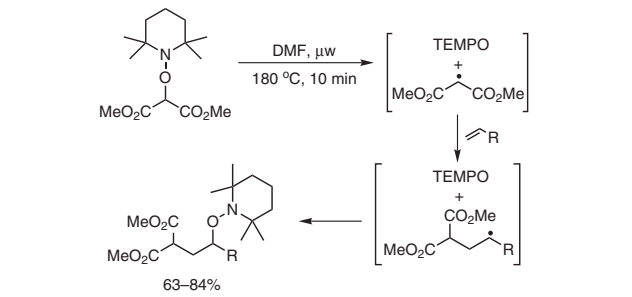
eq 9



eq 10



eq 11



Scheme 4. Tin-Free, Radical Carboaminoxylation of Substituted Alkenes.

As shown earlier in this section, microwave irradiation is very applicable not only to solution-phase chemistry, but also to solid-phase organic synthesis.[7,26,39,42,71–82] There are many different supports, including polystyrene (PS), polyamide, poly(ethylene glycol)–polystyrene (PEG-PS) graft resins, poly(ethylene glycol)–polyacrylamide (PEGA) resins, and even silica, to name a few. The choice of resin depends on its chemical and physical properties with respect to the particular chemistry to be performed. One interesting application is the use of cellulose beads for preparing pyrazole and isoxazole libraries. Cellulose swells nicely in both polar and aqueous solvents and is biodegradable. **Scheme 5** shows a two-step, open-vessel application, which produces excellent yields of the corresponding heterocycles.[74]

4. Use of Microwave Irradiation in Biochemical Applications

Microwave irradiation is fast becoming a source of energy for biochemical applications. The hesitancy of its onset, compared to organic synthesis, is most likely due to the high temperatures associated with microwave-assisted transformations. Many of the biochemical molecules are temperature-sensitive. Now, with current technology, temperatures as low as 35–40 °C can be maintained by precise power input (additional accessories allow temperatures as low as –100 °C[247]), which permits a much wider range of chemistries to be explored. At present, there have been relevant studies published on carbohydrates,[92,95–99] nucleosides[49,166–169] peptides,[197–200,203] proteins,[2,201] peptoids,[202] the polymerase chain reaction (PCR),[243] and trypsin digestion.[244]

It is well documented that microwave irradiation is applicable to solid-phase synthesis (see references in Table 1). The majority of peptide synthesis is performed on a solid phase, and it has been shown that microwave irradiation can enhance deprotection, coupling, and cleavage reactions.[197,198a,b] Traditionally, solid-phase peptide synthesis (SPPS) is run at room temperature and can be very time consuming. It is also plagued with inherent difficulties due to intermolecular aggregation, β-sheet formation, steric hindrance from protecting groups, and premature termination of the sequence. Microwave-assisted peptide synthesis, that is run at elevated temperatures up to 60 °C, enhances coupling rates and efficiency in difficult sequences due to the thermal disruption of peptide aggregation.[197] **Scheme 6** shows the microwave-assisted synthesis of the well-known acyl carrier peptide, ACP (65–74), which was initiated on a preloaded, glycine-functionalized, Fmoc-Wang resin.[197] After conventional cleavage, the peptide was recovered in greater than 95% yield.

The onset of proteomics has created a huge need for protein-binding molecules. Building libraries of protein-like compounds has become an increasingly important goal. Unlike native proteins, peptidomimetic compounds are resistant to proteases and other modifying enzymes. Peptoids, one class of these molecules, are oligo(*N*-alkylglycines). They differ from peptides in that the side chain is connected to the amide nitrogen rather than the α-carbon atom. Standard methods for peptoid synthesis require long coupling times. With microwave irradiation, each coupling is reduced to 1 minute (**Scheme 7**).[202] Upon cleavage, both homo- and hetero-oligomers are synthesized with respectable yields varying between 43 and 95%.

Another area of biochemical interest is nucleoside chemistry. These important monomers make up nucleic acids, or DNA and RNA. The synthesis of nucleosides can assist in the development of therapeutic drugs, be used as precursors to fluorescent compounds for automated DNA synthesis, and facilitate the determination of nucleic acid metabolism. The hydroxymethyl-

ation of uracil rings with paraformaldehyde is one microwave-assisted application, which gives excellent yields (> 93%) in only 3 minutes **(Scheme 8)**.[167]

Carbohydrate chemistry is another area that can benefit from microwave irradiation. Carbohydrates are notoriously heat-sensitive. Carbohydrate derivatives are valuable intermediates in the synthesis of diverse natural products and their analogues. **Scheme 9** shows an example of an efficient route to 1,6-anhydrosugars via microwave irradiation.[98] Performing this reaction under solvent-free conditions leads to respectable yields (45–80%) in 7 minutes.

5. Conclusions and Future Trends

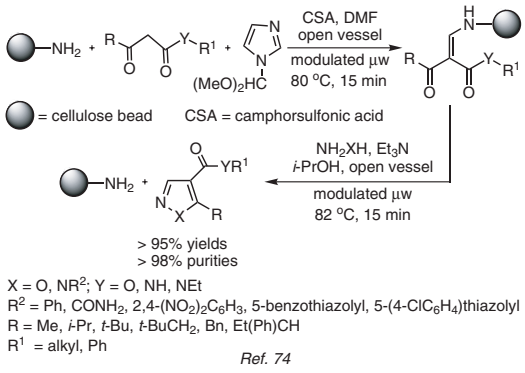
Microwave technology is emerging as an alternative energy source powerful enough to accomplish chemical transformations in minutes, instead of hours or even days. For this reason, microwave irradiation is presently seeing an exponential increase in acceptance as a technique for enhancing chemical synthesis. A growing number of investigators are adopting microwave-assisted synthesis as a means to increase their productivity.

Enhanced Microwave Synthesis (EMS) provides the ability to cool a reaction vessel externally while simultaneously administering microwave irradiation, allowing more energy to be directly applied to a chemical reaction. A higher microwave power input results in substantially enhanced chemistry while maintaining a desired bulk temperature (T_B). Reactions with large activation energies will benefit greatly from this new technology. In addition, as seen in the previous section, a whole new arena of biochemical applications can now be explored.

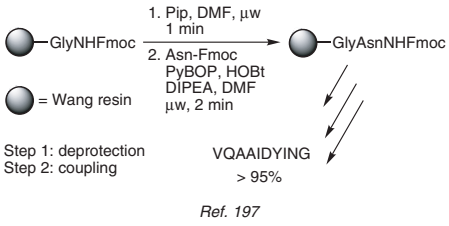
The obvious next step in microwave technology is scale-up for chemical development. Scaling up syntheses from gram quantities to kilograms is essential for drug development, as this is a discouraging bottleneck for present-day process chemists. Many milligram- and gram-scale syntheses cannot be replicated, or even attempted for safety reasons, on larger scales. Development chemists often must start from the beginning. Microwave technology provides the possibility that the same chemistries used in the initial route can be safely scaled up, enabling chemists to spend their valuable time creating novel synthetic methods, not recreating them.

Instrumentation is currently available for kilogram-scale synthesis. One application area that is being examined for scale-up microwave-assisted synthesis is flow-through technology. This allows for the continuous reaction of reagents and, therefore, the continuous on-line production of material. Another parallel technology involves a stop-flow process. Reagents are pumped into a vessel as a batch, reacted, and then pumped out into a collection container. This cycle is repeated as necessary to achieve the scale desired. This, too, allows for a continuous production of material. These two types of systems would allow the pharmaceutical laboratory to produce large quantities of final products in a safe and efficient manner. As a result, the process chemist would have access to all of the advantages of microwave synthesis without having to forfeit the scale of material production that is needed.

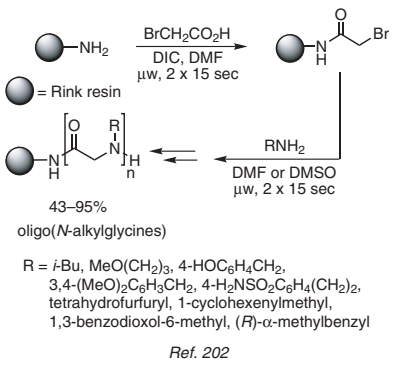
Clearly, microwave irradiation has emerged as a powerful tool for organic synthesis. In concert with a rapidly expanding applications base, microwave synthesis can be effectively applied to any type of chemistry, resulting in faster reaction times and improved product yields. In addition, microwave synthesis creates new possibilities in performing chemical reactions. Because microwaves can transfer energy directly to the reactive species, they can promote transformations that are currently not possible



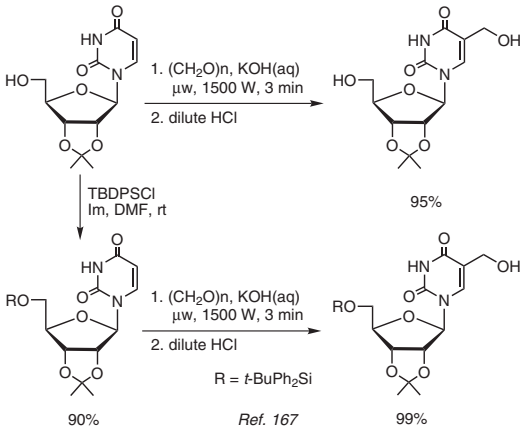
Scheme 5. Microwave-Assisted, Regiospecific, Solid-Phase Library Synthesis of Pyrazoles and Isoxazoles.



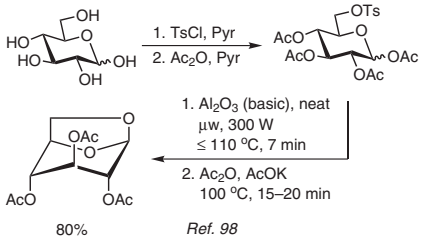
Scheme 6. Microwave-Assisted, Solid-Phase Synthesis of the Acyl Carrier Peptide, ACP (65-74).



Scheme 7. Microwave-Assisted, Solid-Phase Synthesis of Peptoids.



Scheme 8. Microwave-Assisted Hydroxymethylation of the Uracil Ring.



Scheme 9. Microwave-Assisted Synthesis of 1,6-Anhydrosugars.

using conventional heat, creating a new realm in synthetic organic chemistry.

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7. References

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