MICROWAVE TECHNOLOGY—CHEMICAL SYNTHESIS APPLICATIONS

1. Introduction

Microwaves (0.3 GHz–300 GHz), with relatively large wavelengths (1 mm-1 m), lie in the electromagnetic radiation region between radiowave (rf) and infrared (ir) frequencies. Microwave (MW) energy has been used for heating food materials for almost one-half of a century (1) and now it has been realized that this technique may find potential useful applications in chemical technology.

Microwaves are a nonionizing form of radiation energy that cannot break chemical bonds but transfer energy selectively to various substances. Some materials (such as hydrocarbons, glass, and ceramics) are nearly transparent to MW, and therefore behave as good insulators in a microwave oven since they are heated only to a very limited extent; metals reflect MW; molecules with dipole moment (many types of organic compounds) and salts absorb MW energy directly. Microwaves couple directly with molecules in the reaction mixture with rapid rise in temperature; dipole rotation and ionic conduction being two most important fundamental mechanisms for transfer of energy from microwaves to the molecules being heated. Essentially, polar molecules try to align themselves with the rapidly changing electric field of the microwave and the coupling ability, among other factors, is determined by the polarity of the molecules. Therefore there are some important differences between the conventional chemical reactions in the liquid phase and the same reactions conducted under microwave irradiation.

When a liquid reaction mixture is subjected to conventional heating, the walls of the vessel are directly heated but the reaction mixture receives thermal energy by conduction/convection. The temperature of the reaction mixture cannot be higher than the temperature of the vessel walls. In contrast, microwave energy passes through glass vessels directly and is available for absorption by appropriate molecules in the reaction mixture. It is therefore possible for these molecules to be at higher energy levels and the contents of the flask to be at a high bulk temperature in a few minutes.

Another important feature of microwaves is that they penetrate several centimeters into a liquid; in contrast, radiant heat (e.g, from ir rays) raises the temperature of only the surface layer. A reaction mixture under microwave irradiation is therefore at a higher temperature in the middle than at the surface. Accordingly, the temperature profile of the reaction mixture can be quite different depending on whether there is conventional heating or microwave induced energy transfer.

In terms of microwave hardware, the initial studies used the domestic MW oven with multimode applicators. The multimode cavities have multiple pockets of energy dispersed throughout the cavity; different levels of energy intensity in these pockets are often referred to as hot and cold spots. Consequently, in order to achieve equal distribution of energy, multimode systems continuously rotate samples throughout the energy field. While the total power

generated is high (1000–1200 W), the power density of the ensuing field is low (~0.025–0.040 W/mL) in view of the total volume of the cavity. To overcome the inherent limitations of the multimode systems, instrument manufacturers have developed single-mode cavities that produce homogeneous intense pocket of energy that is highly reproducible. Although the output of the single-mode systems is low (300–400 W), their smaller cavity volume and single, focused energy pocket provides a high field density in the range of 0.90 W/mL. The recent advances in the technology have enabled greater flexibility to chemists. In addition to the traditional rectangular waveguide type applicator, circular waveguide applicators have become available that are capable of self-tuning thus allowing multiple entry points for the MW energy to enter the cavity.

In a closed system, the reaction mixture may experience high temperature as well as high pressure. The rapid reaction rates observed in microwave-assisted reactions may be entirely due to these special conditions. It is not surprising, therefore, that violent explosions have been reported in some reactions conducted in sealed systems when low boiling solvents or reactants are present.

Many instances are known now when reactions in an open system (with or without reflux condensers or without solvent) experience enhancements of various types (especially highly accelerated reaction rates and greater purity and higher yield of the product) under microwave irradiation. Such enhancement is attributed to "nonthermal microwave effects" by one school of researchers.

Although there is no consensus yet about the mechanism of microwave-enhanced reactions, MW techniques are already finding diverse types of applications in chemical technology. These include acceleration of chemical reactions (2–13); applications in waste treatment (14); alkane decomposition (15); polymer technology (16); drug release and targeting (17); ceramics (18); and the preparation of samples for analysis (19). Utilization of this technique to solid-state organic synthesis and to inorganic chemistry has shown significant advantages (20). This methodology has also found use in a wide range of decomposition processes including hydrolysis of proteins and peptides (21). Specifically, tremendous growth has been witnessed in organic synthesis (2–13) wherein chemical reactions are accelerated because of selective absorption of MW energy by polar molecules, nonpolar molecules being inert to the MW dielectric loss (22). Initially, the chemical experiments with microwave heating used high dielectric solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) where the rate enhancements are now believed to be due to rapid superheating of the polar solvents and pressure effects (22). However, the development of high pressures and the use of specialized closed vessels, are some of the challenges in these solution-phase reactions that, in part, have been addressed by newly introduced commercial MW instruments with precise temperature and pressure controls. The latest developments in dedicated MW equipment have attracted the attention of chemical and pharmaceutical companies, and their heightened interest has become obvious as exemplified recently in the application of microwaves in the combinatorial chemistry arena that generates a library of potentially useful chemical entities (23a) and several books on the microwave synthesis (23b,23c).

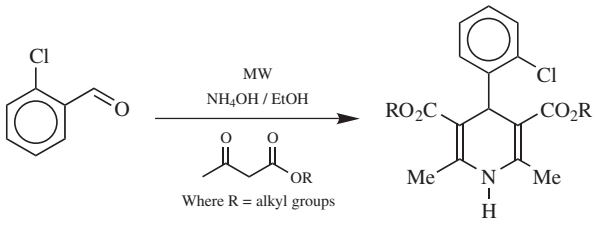
2. Microwave Assisted Organic Reactions in the Liquid Phase

The description here is by no means comprehensive but gives a flavor of the research activity in solution-phase MW chemistry. Only representative reactions in various solvents are described here and the reader is strongly advised to read the recent review articles (7–9,11) and books (23b,23c).

One of the following three possible situations may be encountered in solution-phase reactions:

1. A low-boiling solvent is used that requires a sealed system or a refluxing condenser.
2. A higher boiling solvent is used (or, no solvent if one of the reactants is a liquid) in an open reaction vessel but the bulk temperature of the reaction mixture is kept well below the boiling point of the solvent so that a reflux condenser is not needed and an unmodified domestic microwave oven is adequate.
3. The course of the reaction, in solution phase, may be modified depending on whether the solvent absorbs microwaves strongly or is nearly transparent to microwaves. If no solvent is used or the solvent is transparent to MW, the reactants absorb microwave energy directly and thus may allow "nonthermal microwave effect" to manifest. The absorbing characteristic of a solvent is determined by several factors such as dipole moment, dielectric constant, tangent delta, dielectric loss, and dielectric relaxation time.

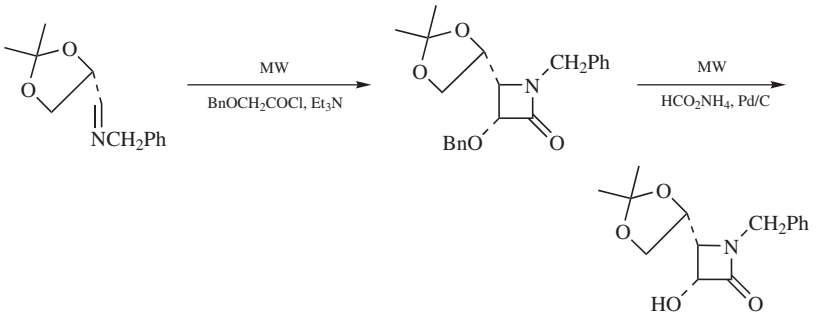
2.1. Cyclization and Cycloaddition Reactions. Alvarez-Builla and co-workers have used MW irradiation to expedite the synthesis of 1,4-dihydropyridines (24a). In this case, improved product yield are obtained and reaction time is reduced compared to conventional reactions (eq. 1). Several unsymmetrical 1,4-dihydropyridines have been prepared in excellent yields from arylmethyleneacetoacetate and β-aminocrotonate upon MW irradiation in ethanol (24b).



(1)

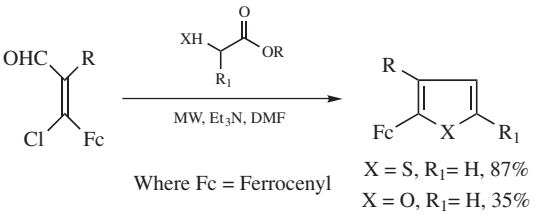
On similar lines, high speed parallel synthesis of 4-aryl-3,4-dihydropyrimidine-2(1H)-ones (DHPM) has been accomplished by heating in a MW oven a neat mixture of β-ketoesters, aryl aldehydes, and urea derivatives with polyphosphate esters (PPE) as the reaction mediator (25). In view of the readily accessible aromatic aldehydes, β-ketoesters, and urea derivatives, a large collections of DHPMs can potentially be prepared (26), applying the recently developed automated, high throughput robotic technologies for performing microwave-assisted combinatorial synthesis (27).

Enantiomerically pure β-lactams have been prepared using MW irradiation (28) (eq. 2).



(2)

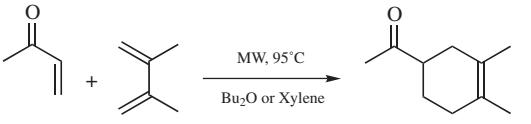
Toma and co-workers used microwaves for the synthesis of ferrocenyl (Fc) substituted heteroaromatic system (29) wherein the reaction of ferrocenyl substituted acrylaldehydes with esters provides a moderate-to-good yield of ferrocenyl-substituted heterocycles (eq. 3).



(3)

The same research group earlier reported on the MW-assisted formation of ferrocenyl oximes (30) that, in contrast to conventional thermal synthesis, affords only the thermodynamically stable isomer.

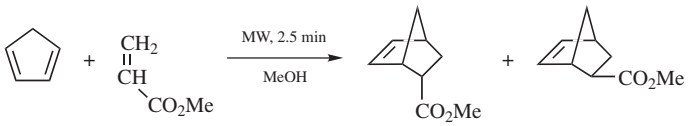
Some comparative cycloaddition reactions in xylene or dibutyl ether (31) have been conducted and the rates of the reaction are always found to be higher under MW irradiation conditions (eq. 4). This acceleration is larger in apolar solvents that show weak dielectric losses. The authors contended that this may be due to a change in the entropy of the system. Further, the existence of *hot spots* analogous to those described in ultrasound chemistry (32) may be another possible explanation.



(4)

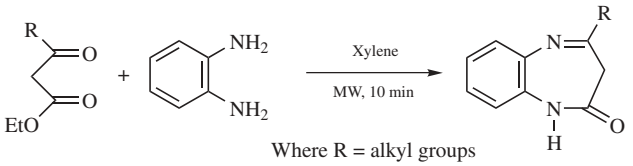
Gedye and co-workers investigated the cycloaddition reaction between cyclopentadiene and methyl acrylate (eq. 5) where the MW irradiation does not affect the endo/exo selectivity (33). The observed differences can be explained by the fact that the reaction under MW irradiation occurs at a higher temperature

than that under conventional refluxing conditions. Similarly, the research groups of Bond (34) and Strauss (35) also conclude that the reaction rates are identical in the presence or absence of MW irradiation, the final yield being dependent on the temperature profile and not on the mode of heating.



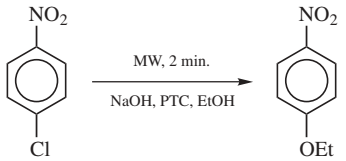
(5)

Benzodiazepin-2-ones have been prepared by the condensation of *o*-phenylenediamines with β-ketoesters in xylene under MW irradiation conditions (36) (eq. 6) and it is claimed that the classical heating mode fails to produce any product. Similarly, other diazepines have also been prepared under the influence of microwaves (37).



(6)

2.2. Aromatic Substitution Reactions. Aromatic nucleophilic substitution reactions have been enhanced (144–240 fold) using MW irradiation (38) in the presence of a small amount of phase-transfer catalyst (PTC) (eq. 7).



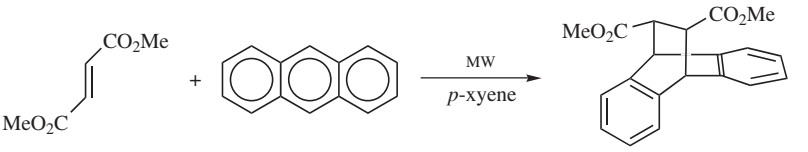
(7)

A MW-expedited S_NAr reaction of activated aromatic substrates such as chlorotoluene with a cyclic amine, piperidine, has been described (39) using potassium carbonate in refluxing ethanol (6 min) or basic alumina under solvent-free conditions (75 s); the conventional reaction by heating under refluxing conditions, however, requires 16 h for completion.

Friedel-Crafts germylation of benzene and toluene catalyzed by aluminum chloride has been modestly enhanced via MW irradiation (40) when compared to standard reflux conditions.

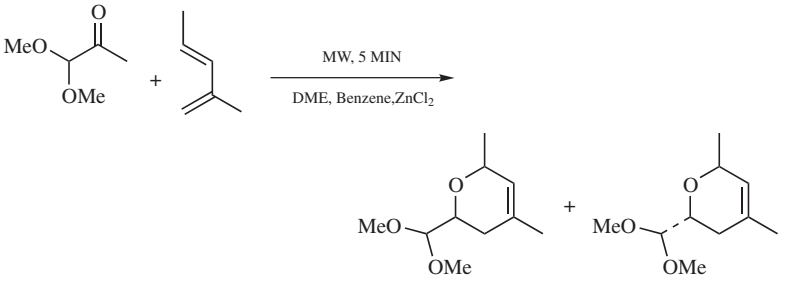
2.3. Pericyclic Reactions (Claisen, Ene, Diels-Alder Reactions). Giguere, Majetich, and co-workers have been among the first in highlighting the MW-activated Claisen, Ene, and Diels-Alder reactions (41). As an example, anthracene reacts with dimethyl fumarate within 10 min in *p*-xylene to afford 87% yield of product whereas conventional heating condition delivers

only 67% in 4 h (eq. 8).



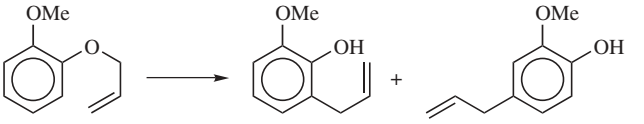
(8)

MW irradiation has been used for the cycloaddition of (*E*)-2-methyl-1,3-pentadiene with pyruvic aldehyde dimethyl acetal that leads to products in good yield (42), whereas no reaction reportedly occurs under conventional heating conditions (eq. 9).



(9)

Claisen rearrangement of allyl ether in the absence of solvent under conventional thermolysis provides the good yield of rearranged products within a short period of time (43). The same rearrangement using microwaves in the presence of *N*-methylformamide (NMF) affords 87% of the product (eq. 10).

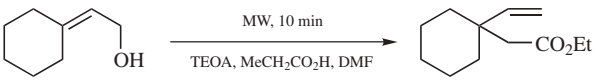


(10)

Control
At 320°C, 92%, neat, 12 min
At 265°C, 71%, neat, 45 min

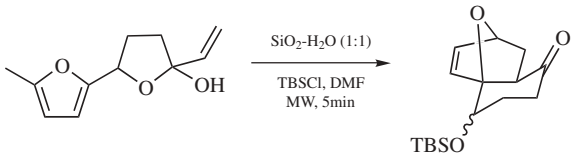
Microwave
At 370°<400°C, 71%, neat, 12 min
At 300°<315°C, 72%, DMF, 5 min
At 276°C, 87%, NMF, 90 s

Ortho ester Claisen rearrangement of the ketene–acetal derived from the alcohol proceeds readily (10 min) in an open beaker (83%) with triethyl orthoacetate (TEOA) using MW irradiation (44,45), but it requires 48 h for completion of the reaction under conventional heating in a sealed tube (eq. 11). It is worth noting that the presence of boiling chips or solid particles in reaction vessel leads to substantial evaporation of solvent culminating in the reduced yield of products.



(11)

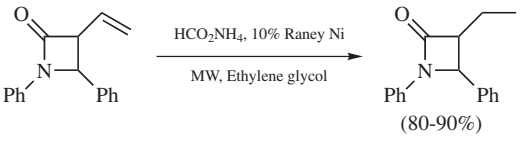
Intramolecular Diels-Alder reaction exemplified by a hemiacetal affords product (64%) under MW irradiation conditions (46a), whereas classical heating method fails to produce the product (eq. 12). Unprecedented microwave effects have been implicated in the MW-promoted cycloaddition reaction between fulvenes and a variety of alkenes and alkynes that lead to the efficient assembly of the polycyclic ring systems found in isobarbatene and alcyopterosin (46b). Interestingly, these reactions, conducted in benzene and DMSO, do not occur under conventional thermolytic conditions.



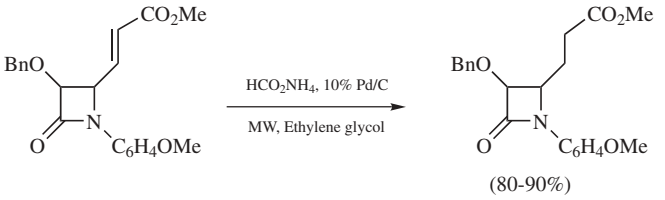
(12)

2.4. Catalytic Hydrogenation. MW-assisted hydrogenation of benzaldehyde to benzyl alcohol using $RuHCl(CO)(PPh_3)_3$ occurs under the influence of microwaves (47). A comparative study of this transformation with classical refluxing conditions revealed that the reaction is complete within 7 min under MW irradiation whereas it requires 3 h under standard reflux conditions.

Bose and co-workers have reported the MW-assisted hydrogenation of substituted β-lactams using Raney nickel or Pd/C (48a). On a small scale, the authors noted the similar reaction time using a preheated oil bath at 130°C, but the MW-assisted reaction on a large scale appear to proceed more rapidly (eq. 13a,13b).



(13a)



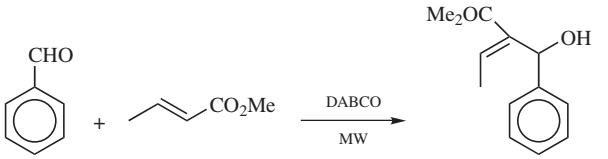
(13b)

The effect of the MW irradiation on the palladium-catalyzed transfer hydrogenation of soybean oil using aqueous sodium formate solution has been studied. Although the mechanism appears to be the same as for conventional heating (48b), there is a significant increase in the reaction rate in the case of MW experiments and it is attributed to the MW-facilitated transport processes at the catalyst and oil–water interfaces.

2.5. Oxidation Reactions. Among the first oxidative studies with MW irradiation is the oxidation of toluene with potassium permanganate (49); it provides a modest yield (40%) of benzoic acid after 5 min.

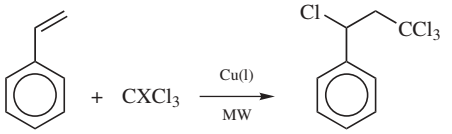
Subsequently, a wide variety of oxidative protocols have been developed that utilize, eg, manganese oxide (50) or *tert*-butylhydroperoxide (51) for the rapid oxidation of benzylic and secondary alcohols.

2.6. Alkene Functionalization. The Baylis-Hillman reaction is an important carbon–carbon bond-forming reaction utilized in the molecules bearing several functional groups. This reaction is relatively slow and can be enhanced by altering reaction conditions such as pressure, temperature, or the use of ultrasound. The use of MW irradiation improves the yield and reduces the reaction time (52). The reaction of styrene with methyl crotonate in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) leads to the required product in good yield within 10 min (eq. 14).



(14)

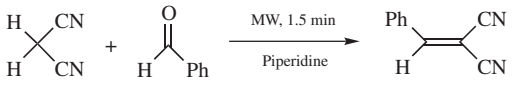
A copper-catalyzed addition of chlorinated hydrocarbons to styrenes (53) has been demonstrated (eq. 15).



(15)

Where X = Cl, O2Et

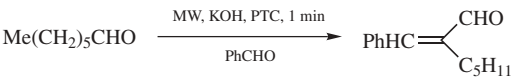
2.7. Alkene Synthesis. The Knoevenagel condensation reaction involving active methylene compounds and carbonyl groups for the synthesis of alkenes has been demonstrated using MW irradiation (eq. 16) (54). The reactions are conducted in open vessels that lead to the efficient removal of water, thus circumventing the need for the use of a Dean-Stark apparatus.



(16)

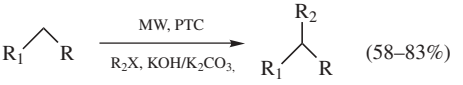
(90%)

A rapid synthesis of jasminaldehyde (~1 min) has been achieved using MW thermolysis (55), wherein the reaction of benzaldehyde with *n*-heptanal, in the presence of a phase-transfer catalyst (PTC), gives a mixture of products containing 82% of desired product (eq. 17).



(17)

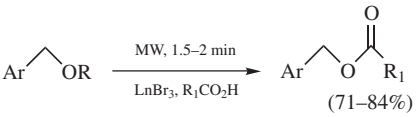
2.8. Alkylation Reactions. Phase-transfer catalysts also promote MW-assisted C-alkylation of active methylene compounds (56) (eq. 18).



(18)

Where R = SPh, MeCO; R_1 = CO_2Et; X = Cl, Br
and R_2 = alkyl, allyl, benzyl

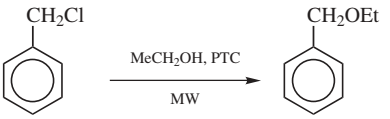
Carboxylic esters have also been prepared using MW irradiation (57) as exemplified in the reaction of benzyl ether with carboxylic acid in the presence of $LnBr_3$ (eq. 19).



(19)

Where R =alkyl; R_1 = CH_3 or n-C_5H_{11}
and Ln = La, Nd, Sm, Dy, or Er

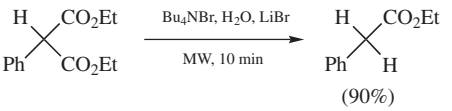
The reaction of benzyl chloride with ethanol is accelerated significantly using MW irradiation (58a) with the aid of a PTC (eq. 20).



(20)

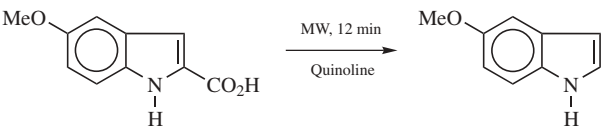
Recently, MW-assisted coupling of phenols with aryl halides has been achieved in the presence of potassium carbonate to afford diaryl ethers within a few minutes (58b); high temperature reached in DMSO solvent may be responsible for acceleration of this S_NAr reaction in the absence of any catalyst.

2.9. Decarboxylation Reactions. MW irradiation in the presence of a phase-transfer catalyst (PTC) affects the decarboxylation of malonate esters (59) (eq. 21).



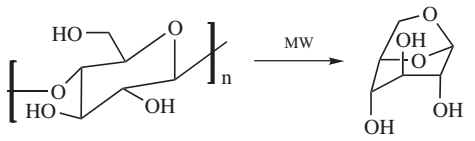
(21)

A similar decarboxylation of indole-2-carboxylic acid derivative occurs in quantitative yield (60a) when a suspension of substituted indole in quinoline is subjected to MW irradiation (eq. 22). However, an environmentally benign protocol is now available that proceeds readily in water (60b).



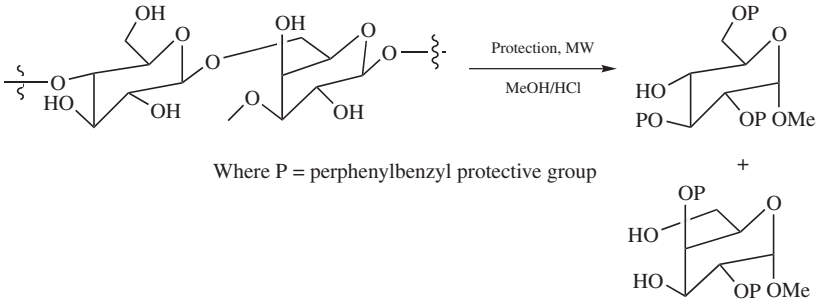
(22)

2.10. Carbohydrate Chemistry. The convenient and simple preparation of 1,6-anhydro-β-D-glucopyranose, a useful chiral synthon in organic chemistry, from starch, cellulose and related (1–4)-D-glucans has been achieved using MW irradiation (61) although yields are low (eq. 23).



(23)

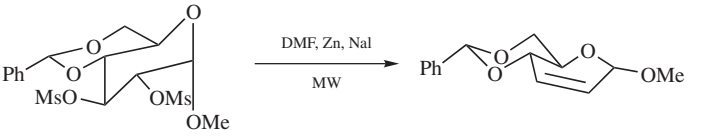
Methanolysis of oligosaccharides typically requires prolonged reflux in methanolic hydrochloric acid. The cleavage of glycosidic bonds in perphenylbenzylated derivatives requires vigorous conditions. In an interesting methanolysis protocol, suitably protected oligosaccharides upon MW irradiation lead to the generation of products with anomeric inversion (62) (eq. 24).



Where P = perphenylbenzyl protective group

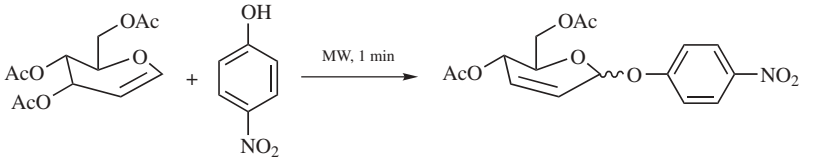
(24)

Tosylates or mesylates upon MW irradiation with sodium iodide and zinc dust in DMF lead to the improved yield of unsaturated pyranosides with reduced reaction times when compared to classical heating protocols (63) (eq. 25).



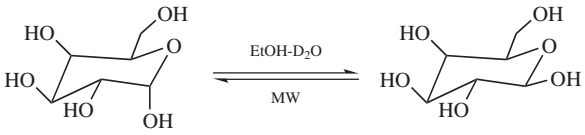
(25)

Ferrier rearrangement products are obtained in good yield by the reaction of tri-*O*-acetyl-D-glucals with phenols in sealed vessels upon MW thermolysis (64a); the products are generated in much reduced reaction time when compared to classical heating methods (eq. 26). Subsequently, the same research group has reported that montmorillonite K-10 catalyzes Ferrier rearrangement of tri-*O*-acetyl-D-galactal with a range of alcohols and phenols in open vessels with very high α-selectivity and without the formation of the 2-deoxy-D-*lyxo*-hexopyranosides (64b).



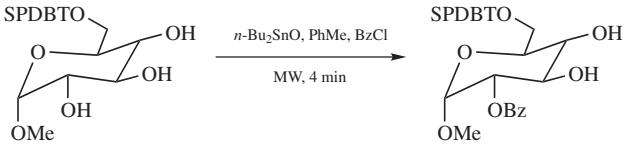
(26)

MW irradiation leads to a change of the equilibrium mixture of α-D-glucose to β-D-glucose during the mutarotation of α-D-glucose in aqueous ethanolic medium (EtOH/H_2O 1:1 ratio). More α-D-glucose is discerned than expected (65) in a rather abnormal effect that cannot be explained by classical heating effects and possible specific action created by a MW radiation field (eq. 27).



(27)

Selective benzoylation of polyols occurs under MW irradiation conditions (66a). The reaction carried out in the presence of dibutyltin oxide as solvent exclusively leads to the product that is benzoylated in the C-2 position (eq. 28). Further, it is found that only a catalytic amount of dibutyltin oxide (0.2 mol equiv.) is required for the formation of dibutylstannylene acetals from polyols or amino alcohols (66b). The selectivity of the benzoylation process can be modulated by varying the power output of MW oven or changing the nature of the solvent used.

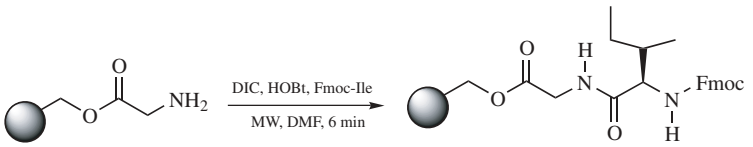


(28)

Where TBDPS = *tert*-butyldiphenylsilyl

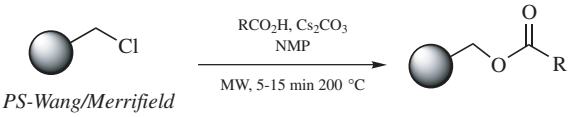
2.11. Combinatorial Chemistry. Combinatorial synthesis is the process by which a large numbers of chemical compounds can be synthesized very quickly in contrast to the traditional chemistry of the past that involves the slow and painstaking synthesis of one compound at a time. Consequently, there is interest currently to accelerate the technologies to identify novel drug targets via high throughput synthesis and combinatorial chemistry (67). Several combinatorial techniques are available wherein the ensuing products could be made as mixtures or in a parallel fashion, using either solution or solid phase techniques. Automated solid-phase organic synthesis (SPOS) based on the Merrifield method of peptide assembly is one of the most popular strategies available but is hampered by the relatively long reaction times involved and the associated degradation of the polymer support due to extended reaction periods. As mentioned in the introduction (23,25–27), speeding up resin-bound chemistry by MW activation has received widespread attention (68–70) in view of the significant rate accelerations as the reaction times are dramatically reduced from hours to a few minutes. Dedicated MW reactor systems are now available that allow such MW-expedited reactions to be performed under controlled and reproducible conditions. Polymer-bound reagents or scavengers, parallel synthesis, fluorous-phase techniques, synthesis on soluble polymer supports, and the construction of libraries in automated format are various approaches that are amenable to MW technology.

Solid-Phase Organic Synthesis (SPOS). The first report, using an unmodified domestic MW oven but a custom-made solid-phase reaction vessel, involved diisopropylcarbodiimide (DIC)-mediated solid-phase peptide couplings (71). Several 9-fluorenylmethoxycarbonyl (Fmoc)-protected amino acids and peptide fragments are coupled with glycine preloaded polystyrene Wang resin (PS-Wang) in DMF, using either the symmetric anhydride or pre-formed precursors such as *N*-hydroxybenzotriazole active esters (HOBt) under atmospheric pressure (eq. 29). Improved coupling efficiencies with MW irradiation have been observed for various peptide couplings, the rate enhancement being at least two- or three fold over traditional couplings at room temperature. In contrast to the 30-min time period for control reactions without MW irradiation, peptide bond formations are completed within 2–6 min using microwaves.



PS-Wang Resin Where Fmoc = 9-fluorenylmethoxycarbonyl (29)

Using a dedicated multimode MW reactor, the coupling of aromatic carboxylic acids to polystyrene Wang resin has been reported (72) to occur in near quantitative loadings under atmospheric pressure in 1-methyl-2-pyrrolidone (NMP) at 200°C within 10 min, as opposed to 2–3 days using conventional coupling protocols at room temperature. In a related study, the attachment of carboxylic acids to chloromethylated polystyrene resins via the cesium carbonate method has also been achieved (73) with significant rate-enhancements as compared to the conventional thermal method (eq. 30). Reaction times are reduced from 12 to 48 h with heating at 80°C to 5–15 min with MW flash heating at temperatures up to 200°C. Detailed kinetic comparison studies using fluoroptic temperature measurements, however, have shown that the observed rate enhancements can be attributed to the rapid direct heating of the solvent by microwaves rather than to a specific nonthermal microwave effect (73). Interestingly, no noticeable degradation of the polystyrene resins is observed even after prolonged exposure to MW irradiation at 200°C.



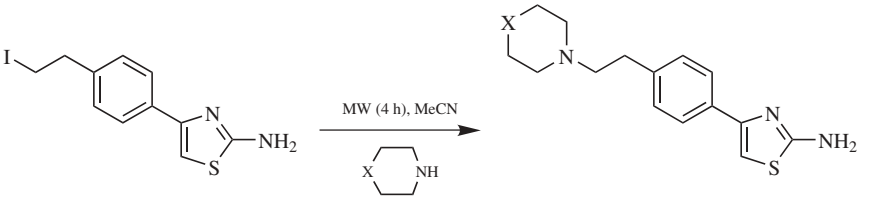
PS-Wang/Merrifield (30)

Where R = aryl, substituted aryl and alkyl groups

Parallel Synthesis. The parallel processing of synthetic sequences has been one of the central themes in combinatorial chemistry (67) wherein the assembly of library of compounds occurs using an ordered array of spatially separated small reaction vessels. The location of the compound in the array

provides the structure of the compound. The most commonly used format for parallel synthesis is the 96-well microtiter plate that enables, often in an automated fashion, the assembly of hundreds of compounds by parallel synthesis (67).

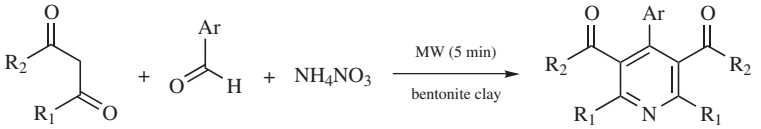
The MW-assisted approach appears to be ideally suited for rapid product generation in high yield under these uniform conditions. The nucleophilic substitution of an alkyl iodide with a variety of 60 different piperidine and piperazine derivatives (eq. 31) in individual sealed polypropylene vials has been one of the first parallel reactions conducted under multimode MW irradiation conditions (74).



(31)

Where X = NR, CR_1,R_2, (R_1 and R_2 being alkyl groups)

The first promising MW-assisted combinatorial chemistry, introduced in 1998, used the model three-component Hantzsch pyridine synthesis in 96-well polypropylene plates wherein several 1,3-dicarbonyl compounds and aryl aldehyde building blocks are dispensed using a robotic handler. The libraries of substituted pyridines are thus readily obtainable in a high throughput parallel fashion using ammonium nitrate as the ammonium source on bentonite clay support (eq. 32) (27). The desired products are extracted by organic solvents from the solid support and are devoid of any starting material.

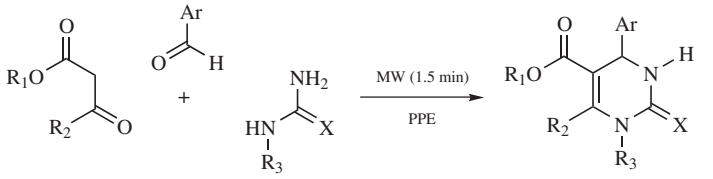


(32)

Where Ar = Phenyl or substituted phenyl
and R_1 and R_2 are alkyl groups

Using a similar format, the classical Biginelli three-component condensation products, dihydropyrimidines, have been obtained in a MW-accelerated reaction (eq. 33) (25). Neat mixtures of β-ketoesters, aryl aldehydes, and (thio)ureas with polyphosphate ester (PPE) as reaction mediator are irradiated in a domestic microwave oven for 1.5 min and the expected dihydropyrimidines (61–95%) are obtained after aqueous workup. The rapid approach has been practically demonstrated by a parallel assembly of 10 dihydropyrimidine analogues in a single MW-irradiation event. Experimentally, it simply involves subjecting to MW irradiation a set of small glass beakers containing the specific building blocks in an alumina bath that serves as a holder of small

reaction vessels and also as a heat sink.

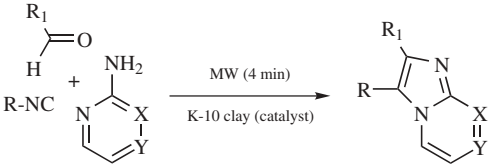


(33)

Where Ar = Phenyl or substituted phenyl
and R_1,R_2 and R_3 are alkyl groups

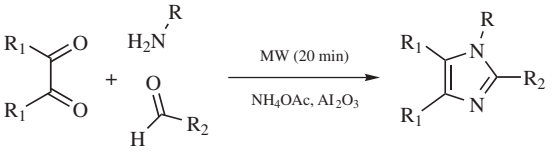
Several additional examples of solvent-free MW-accelerated processes for parallel synthesis are now known (eq. 34). As an example, imidazo-annulated pyridines, pyrazines, and pyrimidines are rapidly obtained in high yield by an Ugi-type three-component reaction using montmorillonite K-10 clay as catalyst (eq. 34a) (75). Similarly, a group of 1,2,4,5-substituted imidazoles can be assembled in 68–80% yield by condensation of 1,2-dicarbonyl compounds with amines, aldehydes and ammonium acetate on acidic alumina (eq. 34b) (76). In an analogous manner, tri-substituted imidazoles have been prepared from aldehydes and 1,2-dicarbonyl compounds in presence of ammonium acetate as nitrogen source. A library of thioamides has been prepared via thionation under solventless conditions using the Lawesson's reagent. This high yield protocol simply involves a brief MW irradiation (8 min) of a mixture of Lawesson's reagent and amide derivatives to afford the corresponding thioamides after solid-phase extraction (eq. 34c) (77).

In most of the aforementioned parallel reactions (eqs. (32–34)) rarely has any solvent been used and, very often, the starting materials or reagents are either supported on mineral solid support, such as clay, silica, or alumina or these inorganic oxides are used in catalytic amounts with reaction components.

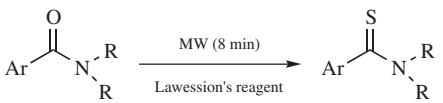


(34a)

Where X = Y = CH
X = CH, Y = N
X = N, Y = CH



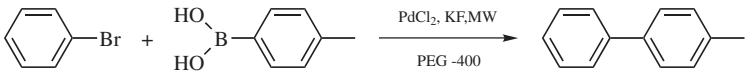
(34b)



(34c)

The initial explorations in this area have essentially utilized domestic multimode MW ovens, that at times, lack temperature and pressure control, and have uneven spatial electromagnetic field distribution (13). However, recent availability of commercially dedicated MW reactor systems has addressed some of these reproducibility issues. The increasing interest exhibited by pharmaceutical and chemical companies has prompted most of the leading MW manufacturers (78) to adopt their systems for a truly high throughput and high speed synthesis format to address the need for combinatorial synthesis.

2.12. Organometallic Chemistry. Relatively speaking, there are fewer examples of transition-metal-catalyzed MW-assisted reactions reported in the literature. However, dramatic acceleration of reactions upon exposure to microwaves has been demonstrated, the prominent being the C−C bond forming Suzuki, Heck, and Stille reactions (79–81). Polyethylene glycol (PEG) is found to be an inexpensive and non-toxic reaction medium for the MW-assisted Suzuki cross coupling of aryl halides with arylboronic acids. This environmentally friendly process offers easy access to biaryls (eq. 35) employing palladium chloride as catalyst and potassium fluoride as base including the recycling of catalyst (80). More recently, a ligand-free palladium-catalyzed Suzuki reaction has been reported in water (81) that uses low palladium loadings (0.4 mol%) in a rapid reaction (5–10 min).



(35)

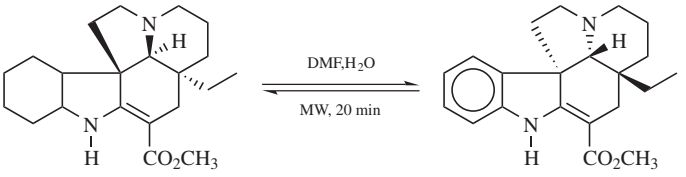
The original molybdenum-catalyzed asymmetric allylic alkylation developed by Trost and co-workers has now been transformed into a fast and efficient reaction under non-inert conditions using MW-accelerated reaction (82a). This modification has enabled the reaction to be performed in one-step employing stable precatalyst [$Mo(CO)_6$] in low concentration and under an air-stable environment. The scope of the fluorous Stille coupling with respect to both the tin and triflate/halide components has been extended using the MW protocol; the reaction is completed in 2 min in contrast to the conventional thermal reaction that requires about a day (82b).

MW irradiation strongly accelerates the rhodium-catalyzed intramolecular coupling of benzimidazole C−H bond to pendent alkenes thus affording functionalized heterocyclic products (83). The optimization of solvent mixture consisting of acetone and *o*-dichlorobenzene without drying or degassing and with minimal precautions to exclude air from the reaction vessels bodes well for the future of such MW-assisted protocols involving transition metals.

2.13. Miscellaneous Reactions. A variety of organic transformations ranging from racemization reactions to stereoselective transformations, labeling experiments to reactions in a continuous MW reactor, and environmental remediation reactions are summarized below. All exploit the unique attributes of MW irradiation.

Racemization Reactions. In two consecutive Diels-Alder cycloreversion and cycloaddition steps, a complete racemization of (−)-vincadifformine has been achieved under MW irradiation in DMF (84) (eq. 36); the (+) isomer is

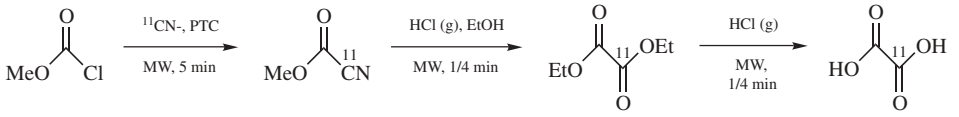
useful in the preparation of the pharmacologically important alkaloid, vincamine. Under classical conditions, the racemization requires longer times and the reaction is also accompanied by the formation of significant amounts of decomposition products.



(36)

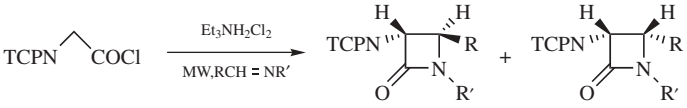
The hydrolysis of ATP (adenosine triphosphate) is reported to proceed 25 times faster under MW irradiation when compared to classical heating conditions (85). The authors attribute this to the direct absorption of radiation or to selective excitation of the water of hydration over the bulk of solution. However, the same authors have finally concluded that the rate of the reaction solely depends on the temperature of the medium and not on the mode of heating (86).

Synthesis of Isotopically Labeled Compounds. Short-lived radiolabeled compounds have been synthesized rapidly under MW irradiation conditions which otherwise could not be prepared easily by means of conventional methods. An interesting application is the preparation of isotopically labeled drugs of short half-life (^{11}C, $t_{1/2} = 20$ min, ^{122}I, $t_{1/2} = 3.6$ min, and ^{18}F, $t_{1/2} = 100$ min). This protocol is successful because it reduces reaction times by a factor of 20 and doubles the radioactivity of the final product (87). Stone-Elander and co-workers have prepared (^{11}C) diethyl oxalate and (^{11}C) oxalic acid using MW-expedited protocols (eq. 37) (88).



(37)

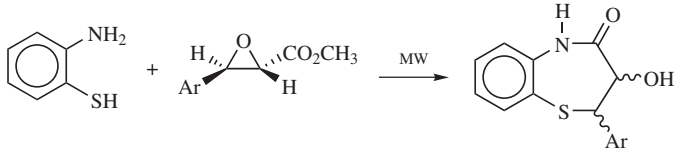
Stereoselective Additions. The stereoselective outcome of a reaction under MW or classical conditions is different when tetrachlorophthaloyl glycine chloride is reacted with base and an imine (89). The trans isomer is obtained exclusively under microwave irradiation but mixtures of the cis and trans isomers under classical conditions (eq. 38).



(38)

The addition of 2-aminothiophenol to glycidic esters is highly stereoselective under MW irradiation conditions (90). By adjusting solvent polarity, the cis/trans ratio can be modified; apolar aprotic solvents favor cis isomers while protic solvents favor trans isomers. In apolar solvents, however, gradual increase

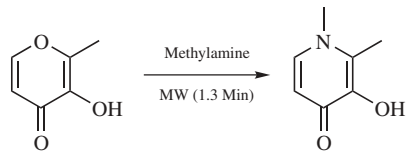
in power level leads to an increase in the proportion of trans isomer (eq. 39).



(39)

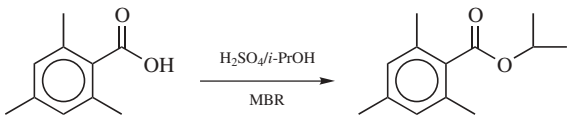
Power (390 W), PhMe, 20 min, 75%, cis/trans 9:1
Power (490 W), AcOH, 10 min, 84%, cis/trans 1:9

Reactions in Continuous (CMR) and Batch (MBR) Microwave Reactors. A laboratory-scale continuous MW reactor (CMR) has been developed by an Australian team and has been used to conduct a variety of organic reactions in a range of solvents including water. Isopropylideneglycerol has been prepared (84%) very rapidly under MW irradiation by heating a solution of glycerol in acetone in the presence of *p*-toluenesulfonic acid as catalyst in 1.2 min at 133°C (91). 1,2-Dimethyl-3-hydroxypyrid-4-one (65%) is synthesized within 1.3 min by the reaction of 3-hydroxy-2-methyl-4-pyrone with aqueous methylamine under MW irradiation conditions (eq. 40) (91). In contrast, under classical heating, the yield is only 50% after 6 h.



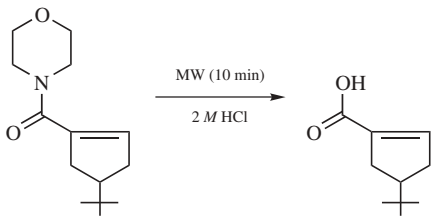
(40)

In a laboratory-scale batch reactor (MBR) developed by the same team, mesitoic acid reacts with excess of propan-2-ol in the presence of a catalytic amount of sulfuric acid under MW irradiation to afford isopropyl mesitoate (56%) (eq. 41) (92).



(41)

In general, the hydrolysis of tertiary amides is difficult to achieve even at reflux conditions. A morpholinide derivative has been successfully hydrolyzed to afford 4-*tert*-butylcyclopent-1-enoic acid (70%) in 10 min under microwave irradiation whereas only 40% product is obtainable after 4-h reflux under classical condition (eq. 42) (92).



(42)

Using this batch reactor, the ortho-Claisen rearrangement of allyl phenyl ether has been achieved in aqueous media where 2-allylphenol is obtained almost exclusively after 10 min of irradiation (92).

Environmental Remediation Using Microwaves. A laboratory scale study has been conducted to explore the *in situ* decomposition of polychlorinated biphenyls (PCBs) and aroclors in soil using microwave energy and graphite fibers in machinable ceramic bombs (93). Most of the chlorinated aromatics decomposed; none could be extracted from the soil suggesting that the dechlorinated materials are tightly bound, and possibly encapsulated, by the vitrified soil. Subsequently, the same group studied the *in situ* decomposition of polyaromatic hydrocarbons (PAHs) such as benzo[*a*]pyrene, benzo[*b*]fluoranthene, benz[*a*]anthracene, and 1-nitropyrene in soil in an open vessel using MW energy. Again, neither the PAHs nor the decomposition products could be extracted from the soil (94).

Using an integrated microwave/uv-illumination method, the photocatalytic decomposition of the cationic rhodamine-B dye has been examined in aqueous TiO_2 dispersions and the process has proven to be superior to the one using TiO_2 photocatalytic degradation alone. The enhanced efficiency, even at low concentration of molecular oxygen and low radiant excitance of the light source, is attributed to the rapid formation of the reactive oxygen species ($^{\cdot}OH$ radicals) (95). The catalytic reduction of sulfur dioxide with methane to form carbon dioxide has been examined over MoS_2/Al_2O_3 catalysts where reaction occurs under MW irradiation conditions at a temperature that is about 200°C lower than that required by conventional heating, presumably due to the formation of hot-spots within the catalyst (96). The highest conversion to carbon dioxide and sulfur, with associated minimum amount of formation of side products, is obtained when the molar ratio of sulfur dioxide to methane is two, which is the stoichiometric amount.

The catalytic decomposition of NO was studied over Fe/NaZSM-5 catalyst using MW irradiation where increased conversion of NO to nitrogen occurred with increasing amount of Fe loading with maximum conversion up to 70% (97). It is observed that the catalyst showed good endurance to excess oxygen in the MW heating mode.

3. Microwave-accelerated Solvent-free Organic Reactions

Heterogeneous reactions facilitated by supported reagents on inorganic oxide surfaces have received special attention in recent years, both in the industrial setting as well as in the laboratory. The first report of the surface-mediated chemical transformation dates back to 1924 (98), but it was not until almost one-half of a century later that the technique received widespread attention as attested by several books, reviews, and account articles (10,99–107). The use of microwave (MW) irradiation techniques for the acceleration of organic reactions had profound impact on these heterogeneous reactions since the appearance of initial reports on the application of microwaves for chemical synthesis in polar solvents (43,49). The approach has blossomed into a useful technique for a variety of applications in organic synthesis and functional group transformations, as is

testified by a large number of publications and review articles on this theme (2–6,10,12,13,23).

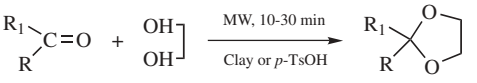
Although reactions in conventional organic solvents (7–9,11,108), ionic liquids (109–111), PEG (80) and aqueous media (91) have grown in view of the availability of commercial MW systems, the focus has remained on less cumbersome solvent-free methods. In these procedures the neat reactants, often in the presence of mineral oxides or supported catalysts (2–6,10,12,13,23), undergo facile reactions to provide high yields of pure products, thus eliminating or minimizing the use of organic solvents. The application of MW irradiation with the use of catalysts or mineral supported reagents, under solvent-free conditions, enables organic reactions to occur rapidly at ambient pressure (2–6,10), thus providing chemical processes with unique attributes such as enhanced reaction rates, high yields and ease of manipulation. These reactions conducted with the help of reagents immobilized on the porous solid supports have salient advantages such as good dispersion of active reagent sites, selectivity and easy work-up procedures. Another major factor responsible for their popularity is the ready availability of inexpensive household MW ovens that can be safely used for solventless reactions and an opportunity to work with open vessels, thus avoiding the risk of high pressure development. The reactions appear to occur at relatively low bulk temperature although higher localized temperatures may be reached during MW irradiation. Unfortunately, accurate recording of temperature has not been made in the majority of such studies. This MW strategy has been the most widely practiced approach in laboratories around the globe in spite of the relatively poor understanding of the reasons for such dramatic rate acceleration. The recyclability of some of these solid supports, in some selected processes, renders them into environmentally friendlier "green" protocols.

Since the initial report (112), a large number of MW-promoted solvent-free protocols have been illustrated for a wide variety of useful chemical transformations such as protection/deprotection (cleavage), condensation, rearrangement reactions, oxidation, reduction, and the synthesis of several heterocyclic compounds on mineral supports (2–6,10,12,13,23). These reactions have enabled the synthesis of a range of industrially significant chemical precursors such as imines, enamines, enones, nitroalkenes, sulfur compounds and heterocyclic compounds in a relatively environmentally friendlier manner (2–6,10,12,13,23). A vast majority of these solvent-free reactions have been performed using an unmodified household MW oven or commercial MW equipment usually operating at 2450 MHz in open glass containers with neat reactants. The general procedure involves simple mixing of neat reactants with the catalyst, their adsorption on mineral or "doped" supports, and subjecting the reaction mixture to MW irradiation.

Unfortunately, the comparison of MW-accelerated reactions with similar reactions in an oil bath has not been made in all the reports in the literature. Nevertheless, it is clear that this solventless approach addresses the problems associated with waste disposal of solvents that are used several fold in chemical reactions thus minimizing or avoiding the excess usage of chemicals and solvents. The discussion pertaining to the preparation of supported reagents or catalysts is not included here since several review articles are available on this theme (99–107).

3.1. Protection–Deprotection (Cleavage) Reactions. Although inherently wasteful, protection–deprotection reaction sequences constitute an integral part of organic syntheses such as the preparation of monomers, fine chemicals, and precursors for pharmaceuticals. These reactions often involve the use of acidic, basic or hazardous reagents, and toxic metal salts (113). The solventless MW-accelerated cleavage of functional groups provides an attractive alternative to conventional deprotection reactions.

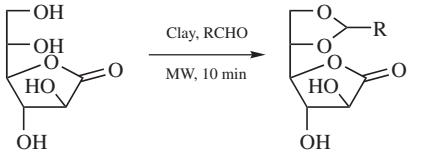
Formation of Acetals and Dioxolanes. The acetal and dioxolane derivatives of aldehydes and ketones have been prepared using orthoformates, 1,2-ethanedithiol or 2,2-dimethyl-1,3-dioxolane in acid-catalyzed reactions that proceed in the presence of *p*-toluenesulfonic acid (*p*-TsOH) or clay under solvent-free conditions (eq. 43). The yields obtained with the microwave method are better than those obtained using conventional heating in an oil bath (114).



(43)

Where R_1 = Ph: R = H

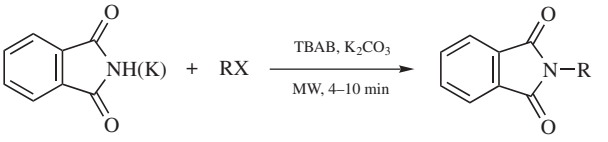
The acetals of 1-galactono-1,4-lactone have been prepared in excellent yields (115) by adsorbing the lactone and the aldehyde on montmorillonite K-10 or KSF clay followed by heating the reaction mixture in a MW oven (eq. 44).



(44)

Thioacetals have been prepared in a similar manner from active methylene compounds that are adsorbed on KF-alumina, admixed with methanesulphonothioate and irradiated in a MW oven (116).

N-Alkylation Reactions. Several solvent-free N-alkylation reactions have been reported which involve the use of the phase-transfer agent, tetrabutylammonium bromide (TBAB), under MW irradiation conditions. Some recent examples include N-alkylation of phthalimides (117) or its potassium salt (118) in the presence of potassium carbonate and TBAB (eq. 45).

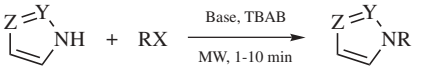


(45)

Where R = Benzyl or alkyl groups

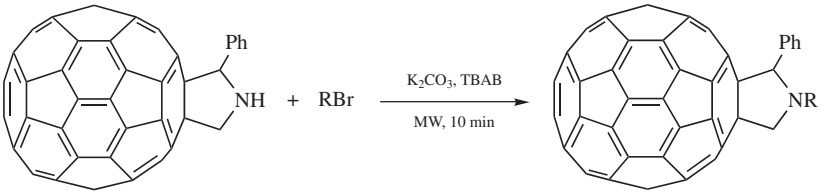
Subsequently, the approach has been extended to the derivitization of a variety of heterocycles, eg, carbazoles (119a), azaheterocycles (eq. 46) (119b)

including pyrrolidino[60]fullerenes (eq. 47) using K_2CO_3/KOH and TBAB (120).



(46)

Where X = Cl, Br I and Z, Y = C, N (58–95%)

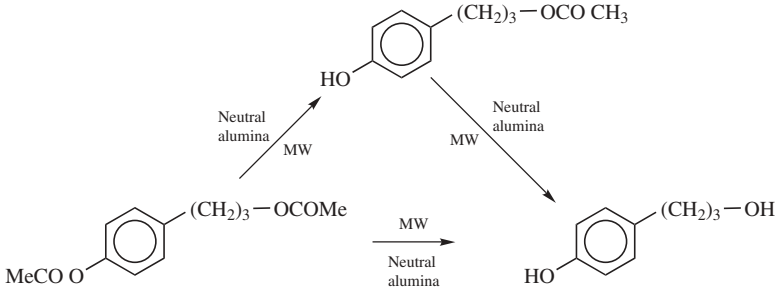


(47)

(31–70%)

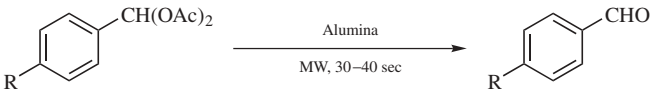
Where R = Benzyl, alkenyl or alkyl groups

Deacylation Reactions. The utility of recyclable alumina as a viable support surface for deacylation reaction is described by Varma and his colleagues (121) wherein the orthogonal deprotection of alcohols is possible under solvent-free conditions on neutral alumina surface using MW irradiation (eq. 48). Interestingly, chemoselectivity between alcoholic and phenolic groups in the same molecule has been achieved simply by varying the reaction time; the phenolic acetates are deacetylated faster than alcoholic analogues.



(48)

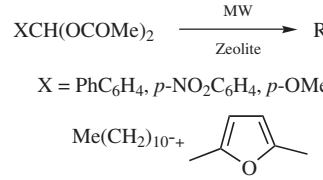
Deprotection of Aldehyde Diacetates. In a very rapid reaction, the diacetate derivatives of aromatic aldehydes upon MW irradiation on neutral alumina surface regenerate aldehydes (eq. 49) (122). The selectivity in these reactions is achieved by merely adjusting the time of irradiation. For example, the aldehyde diacetate is selectively removed in 30 s, whereas 2 min is required to cleave both the diacetate and ester groups. The protocol is applicable to compounds bearing olefinic moieties such as cinnamaldehyde diacetate (122).



(49)

Where R = H, Me CN, NO_2, OCOMe (88–98%)

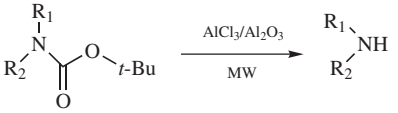
A similar reaction has been described using zeolite supports (eq. 50). It is not known whether the reactions occur on the surface of or inside the zeolite pores (123,124).



(50)

Debenzylation of Carboxylic Esters. An efficient solvent-free debenzylation process for the cleavage of carboxylic esters on alumina surface has been developed by Varma and colleagues (125). By changing the surface characteristics of the solid support from neutral to acidic, the cleavage of the Fmoc group and related protected amines can be achieved in a similar manner. The optimum conditions for cleavage of N-protected moieties require the use of basic alumina and irradiation time of 12–13 min at ~130–140°C. The hydrolysis of allyl esters has also been reported on K-10 clay (126).

Cleavage of N-tert-Butoxycarbonyl (Nboc) Group. A solvent-free deprotection of *N-tert*-butoxycarbonyl groups has been accomplished in the presence of neutral alumina that is "doped" with aluminum chloride (eq. 51) (127). This approach may find application in a typical peptide bond-forming reaction thus eliminating the use of irritating and corrosive chemicals such as trifluoroacetic acid and piperidine.



(51)

Desilylation Reactions. *Tertiary*-butyldimethylsilyl (TBDMS) ether derivatives of alcohols can be rapidly cleaved to regenerate the corresponding hydroxy compounds on alumina using MW irradiation (eq. 53) (128). This approach circumvents the use of corrosive fluoride ions that is normally employed for cleaving of such silyl protecting groups.

Deprotection of trimethylsilyl ethers has also been accomplished (88–100%) on K-10 clay (129) and oxidative cleavage (70–95%) in the presence of clay and iron (III) nitrate (130).

Dethioacetalization Reaction. Thio acetals and ketals are key protecting groups employed in organic transformations but the regeneration of carbonyl groups by cleavage of acid and base stable thioacetals and thioketals is a challenging task. Conventionally, the cleavage of thioacetals requires the use of toxic heavy metals such as Ti^{4+}, Cd^{2+}, Hg^{2+}, Tl^{3+}, or uncommon reagents such as benzeneseleninic anhydride (131). A solid-state dethioacetalization reaction has been reported by Varma and co-workers using clayfen that proceeds in high yields (eq. 52) (131), and this general reaction does not yield any by-products except for substrates bearing free phenolic groups where

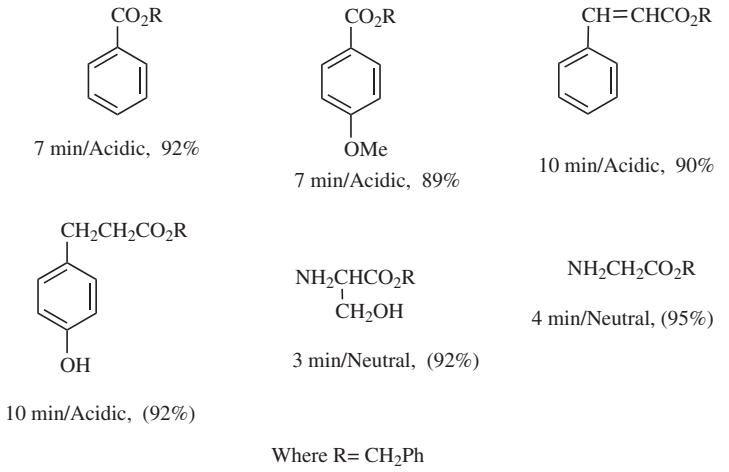


Fig. 1. Cleavage of benzylic carboxylic esters on alumina.

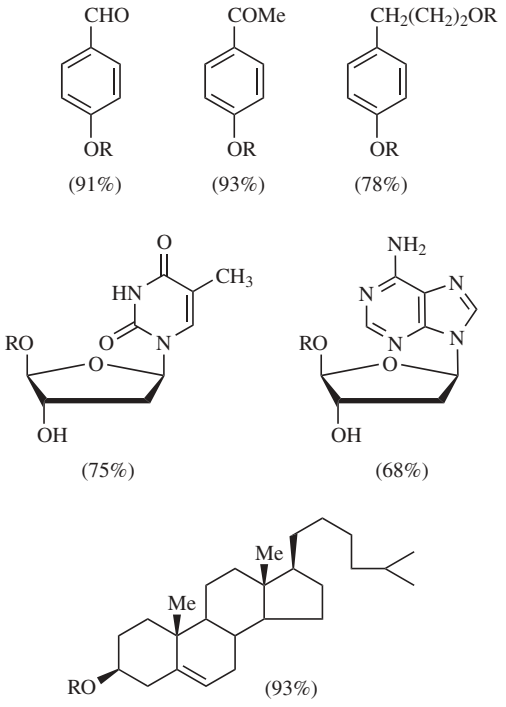
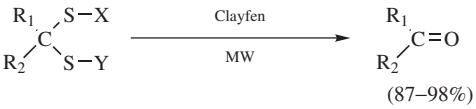


Fig. 2. Cleavage of *t*-butyldimethyl silyl (TBDMS) groups.

ring nitration is observed.



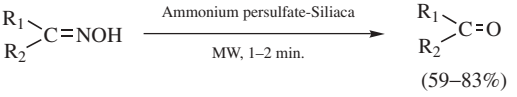
(52)

Where R_1 = Ph, *p*-$CH_3C_6H_4$, *p*-$NO_2C_6H_4$; R_2 = H ; X–Y = –$(CH_2)_2$–
$R_1 = R_2$ = Et ; X–Y = –$(CH_2)_2$– ; $R_1 = R_2$ = Ph ; X = Y = Et
R_1 = Ph ; R_2 = Me ; X–Y = –$(CH_2)_2$–
R_1–R_2 = isoflavanolyl, 2–methylcyclohexyl; X–Y = –$(CH_2)_2$–

A report on the cleavage of thioacetals with clayan (80–89%) has also appeared subsequently (132).

Deoximation Reactions. Oximes have been employed as protecting groups for carbonyl groups owing to their hydrolytic stability. The development of newer deoximation reagents has therefore continued with the availability of a wide range of such agents namely, Raney nickel, pyridinium chlorochromate, pyridinium chlorochromate-H_2O_2, triethylammonium chlorochromate, dinitrogen tetroxide, trimethylsilyl chlorochromate, Dowex-50, dimethyl dioxirane, H_2O_2 over titanium silicalite-1, zirconium sulfophenyl phosphonate, *N*-haloamides, and bismuth chloride (133).

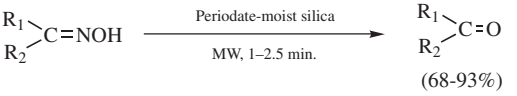
The search for a solvent-free deprotection procedure has led to the use of the relatively benign reagent, ammonium persulfate on silica, for regeneration of carbonyl compounds (eq. 53) (133). Neat oximes are simply admixed with the solid supported reagent and then irradiated in a MW oven to regenerate free aldehydes or ketones; the process is applicable to both aldoximes and ketoximes. The critical role of surface is apparent since the same reagent supported on clay surface delivers predominantly the Beckmann rearrangement products, the amides (134).



(53)

Where R_1 = Ph. *p*-ClC_6H_4, *p*-$MeOC_6H_4$; $R_2 = CH_3$
R_1 = 2-thienyl, 1-naphthyl, C_6H_5, *p*-NO_3Ph, m, *p*-$(MeO)_2C_6H_3$; R_2 = H
and $R_1 = R_2$ = cyclohexyl

A facile deoximation procedure with sodium periodate impregnated on moist silica (eq. 54) has also been introduced that is applicable exclusively to ketoximes (135).

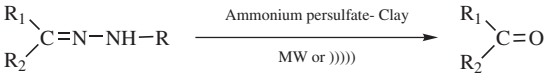


(54)

Where R_1 = Me ; R_2 = Ph, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-MeC_6H_4, *p*-MeO C_6H_4; *p*-$NH_2C_6H_4$,
$R_1 = R_2$ = Ph; $R_1 = R_2$ = cyclohexyl, tetrahydronaphthyl,
and R_1 = Et , R_2 = *n*-butyl

Aldehydes can be regenerated from the corresponding bisulfites (85–98%) on KSF clay surface (136).

Cleavage of Semicarbazones and Phenylhydrazones. Carbonyl compounds have also been rapidly regenerated from the corresponding semicarbazone and phenylhydrazone derivatives using ammonium persulfate impregnated on montmorillonite K-10 clay (eq. 55) (137). Microwave and ultrasound irradiation protocols can be employed in these solventless procedures wherein microwave exposure achieves cleavage in minutes and ultrasound-procedure reactions require 1–3 h for the regeneration of carbonyl compounds (137).

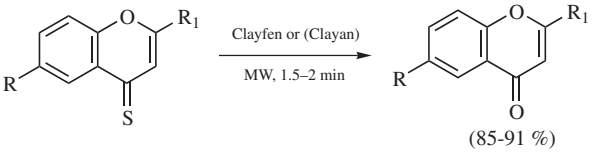


(55)

Where $R_1 = C_4H_9$, Ph, *p*-ClC_6H_4, *p*-MeC_6H_4, *p*-HOC_6H_4;
R_2 = Me; C_2H_5
and R = $CONH_2$, Ph

The carbonyl compounds have been regenerated from the corresponding hydrazones (75–98%) (138) and semicarbazones (55–90%) (139) using bismuth trichloride.

Dethiocarbonylation. Dethiocarbonylation is the transformation of thiocarbonyl to carbonyl groups and has been accomplished with several reagents namely, trifluoroacetic anhydride, CuCl/MeOH/NaOH, tetrabutylammonium hydrogen sulfate/NaOH, clay/ferric nitrate, $NOBF_4$, bromate and iodide solutions, alkaline hydrogen peroxide, sodium peroxide, thiophosgene, trimethyloxonium fluoroborate, tellurium based oxidants, dimethyl selenoxide, benzeneseleninic anhydride, benzoyl peroxide, and halogen-catalyzed alkoxides under phase-transfer conditions (140). These methods, unfortunately, have certain limitations such as the use of stoichiometric amounts of the oxidants that are often inherently toxic or long reaction times or tedious procedures. Varma and co-workers have developed an efficient dethiocarbonylation process under solvent-free conditions using clayfen or clayan (eq. 56) (140) that is accelerated by MW irradiation.

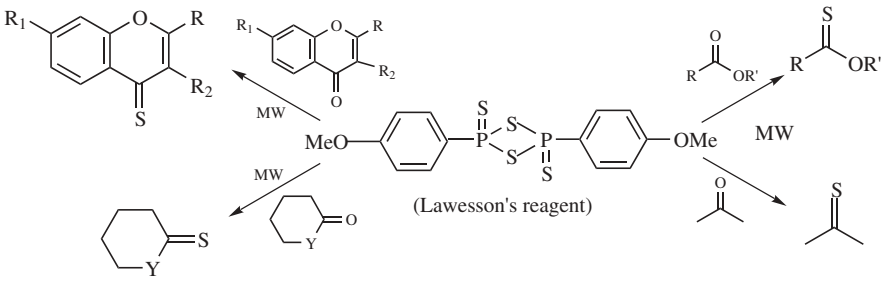


(56)

Where R = H; R_1 = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$
R = OMe; R_1 = *p*-MeC_6H_4

Thionation Reactions: Synthesis of Thioketones, Thiolactones, Thioamides, Thionoesters and Thioflavonoids. Among expeditious chemical transformations that can be accomplished under solventless conditions, the conversion of carbonyl compounds to the corresponding thio analogues is especially useful. The conventional synthesis of thioketones involves the reaction

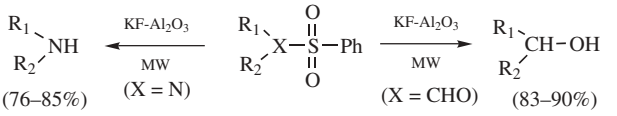
of substrates with phosphorous pentasulfide under basic conditions, hydrogen sulfide in the presence of acid or Lawesson's reagent. Using the MW approach, no acidic or basic media is used and the carbonyl compounds are simply admixed with neat Lawesson's reagent (0.5 equiv) and irradiated under solvent-free conditions. This benign approach is general and is applicable to the high yield conversion of ketones, flavones, isoflavones, lactones, amides and esters to the corresponding thio analogues (eq. 57). This ecofriendly solvent-free protocol uses comparatively much smaller amount of Lawesson's reagent and avoids the use of large excesses of dry hydrocarbon solvents such as benzene, xylene, triethylamine, or pyridine that are conventionally used (141).



(57)

Where Y= O, NH and R, R', R_1, and R_2 are aryl or alkyl groups

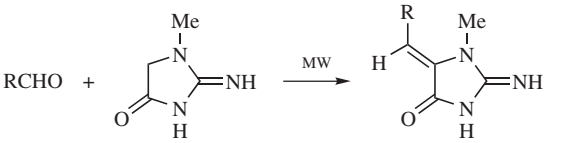
Alcohols and amines have been regenerated by MW-promoted cleavage of sulfonates (83–90%) and sulfonamides (76–85%), respectively, on basic KF-alumina (eq. 58) (142).



(58)

3.2. Condensation Reactions. Several MW-assisted aldol (143,144) and Knoevenagel reactions have been accomplished using relatively benign reagents such as ammonium acetate (145).

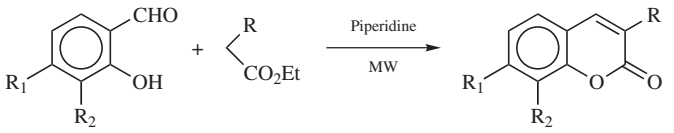
Knoevenagel Condensation Reactions–Synthesis of Coumarins. Knoevenagel condensation reactions of aldehydes with creatinine occur rapidly under solvent-free reaction conditions at 160–170°C using a focused MW oven (eq. 59) (146).



(59)

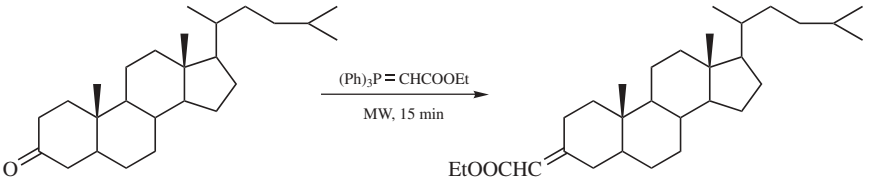
The condensation of 5-nitrofurfuraldehyde with active methylene compounds affords, under MW irradiation, 5-nitrofurfurylidines using $ZnCl_2$ and K-10 as catalysts (147).

The classical Pechmann approach for the synthesis of coumarins via the microwave-promoted reaction (148) has now been extended to solvent-free system wherein salicylaldehydes undergo Knoevenagel condensation with a variety of ethyl acetate derivatives in presence of piperidine (eq. 60) (149).



(60)

Wittig Olefination Reactions. The Wittig reaction of stable phosphorous ylides with ketones in the absence of solvent is accelerated by MW irradiation and affords improved yields when compared to the reactions carried out by conventional heating methods (eq. 61) (150).

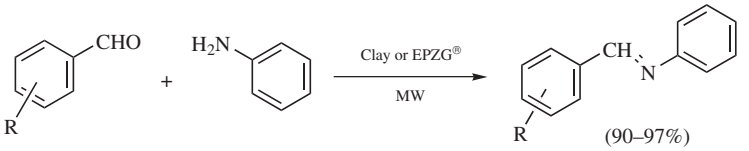


(61)

The preparation of several phosphonium salts has been reported using a domestic MW oven. In these reactions neat triphenylphosphine is reacted with organic halide in a pressurized tube and shows remarkable rate enhancement (151).

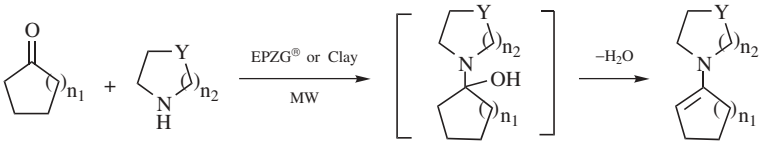
Synthesis of Imines, Enamines, Nitroalkenes, and N-Sulfonylimines. Imines, enamines, nitroalkenes, and *N*-sulfonylimines are conventionally prepared by condensation reactions that liberate water which is removed azeotropically. These reactions, usually catalyzed by *p*-toluenesulphonic acid, titanium (IV) chloride, or montmorillonite K-10 clay, require the use of a Dean Stark's apparatus and a large excess of aromatic hydrocarbons such as benzene or toluene for azeotropic water removal.

MW-expedited dehydration reactions using montmorillonite K-10 clay (152) (eqs. 64,65) or Envirocat reagent (153), EPZG®, (eqs. 62,63) have yielded a rapid synthesis of imines and enamines via the reactions of primary and secondary amines with aldehydes and ketones, respectively. The generation of polar transition state intermediates in these reactions that readily couple to microwaves is mainly responsible for these rapid imine- or enamine-forming reactions. The use of a MW oven at lower power levels or intermittent heating has been used to prevent the loss of low boiling reactants (152,153).



(62)

Where R = H, *o*-OH, *p*-OH, *p*-Me, *p*-OMe, *p*-NMe_2

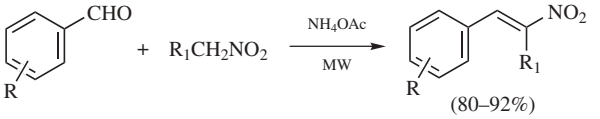


(63)

$n_1 = 1$; $n_2 = 2$; Y = CH_2 ; $n_1 = 1$; $n_2 = 2$; Y = O
$n_1 = 2$; $n_2 = 1$; Y = CH_2 ; $n_1 = 2$; $n_2 = 2$; Y = CH_2
$n_1 = 2$; $n_2 = 2$; Y = O

The Henry reaction, which is the condensation of nitroalkanes with carbonyl compounds to generate nitroalkenes, also proceeds rapidly via this MW approach in the presence of catalytic amounts of ammonium acetate, thus avoiding the use of a large excess of polluting nitrohydrocarbons usually employed as solvents in these reactions (eq. 64) (154).

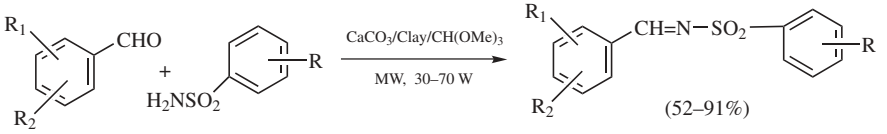
The cycloaddition, reduction and oxidation of α,β-unsaturated nitroalkenes provide easy access to a vast array of functionalized molecules such as nitroalkanes, N-substituted hydroxylamines, amines, ketones, oximes, and α-substituted oximes and ketones (155–157). Therefore, numerous possibilities exist for exploiting these *in situ* generated nitroalkenes for the preparation of valuable synthetic precursors and building blocks.



(64)

Where R_1 = H, R = H, *p*-OH, *m,p*-$(OMe)_2$, *m*-OMe-*p*-OH, 1-naphthyl, 2-naphthyl
R_1 = Me, R = H, *p*-OH, *p*-OMe, *m,p*-$(OMe)_2$, *m*-OMe-*p*-OH

The one-pot solventless synthesis of *N*-sulfonylimines from the MW heating of aldehydes with sulfonamides using relatively benign reagents, calcium carbonate and montmorillonite K-10 clay has been reported (eq. 65) (158).

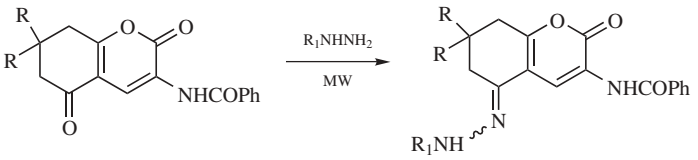


(65)

Where R = H, Me, COOMe, Cl; R_1 = H, OMe, OCOMe, Br; R_2 = H, OMe, OCOMe

The formation of hydrazones has been achieved in toluene (159). Further reaction of the hydrazones with alkali (KOH) under MW irradiation conditions accomplishes Wolff-Kichner reduction in good yield (160). However, recently it has been shown that a solvent-free and catalyst-free reaction of hydrazines with carbonyl compounds is possible upon microwave irradiation in a household MW oven (eq. 66) (161). Remarkably, the general reaction proceeds nicely even for solid reactants and is completed below the melting points of the two reactants possibly via the formation of an eutectic. The control experiments conducted concurrently in separate open beakers revealed that the reactions could be simply

followed by visual observation when a melt is obtained (162).



(66)

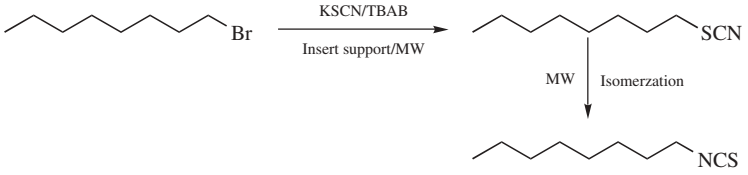
Where R = H or Me and R_1 = aryl or substituted aryl groups

A solid-state synthesis of amides from readily available starting materials, namely, nonenolizable esters and amines, has also been reported in a household MW oven using potassium *tert*-butoxide (163).

The kinetics of the acid-catalyzed esterification of 2,4,6-trimethylbenzoic acid in isopropanol have been examined under MW irradiation conditions (164). A relatively practical technique for MW-assisted synthesis of esters has been reported where the reactions can be conducted either on solid mineral supports or by using a phase-transfer catalyst (PTC) in the absence of organic solvents (165). Recently, the esterification of enols with acetic anhydride and iodine has also been reported (166).

3.3. Isomerization and Rearrangement Reactions. Numerous isomerization and rearrangement reactions have been accomplished using MW-irradiation. At times the reactions are performed in solution phase while some others occur on graphite or Lewis acids "doped" mineral supports and sometimes even by heating the neat reactants. Notable examples are the benzil–benzilic acid rearrangement (167), solventless Beckmann rearrangement on K-10 clay (134,168), Fries rearrangement on K-10 clay that affords mixture of ortho- and para-products (169), Fries rearrangement that leads to the formation of flavonones (170) and thia-Fries rearrangement of arylsulfonates using aluminum trichloride and zinc chloride on silica gel (171).

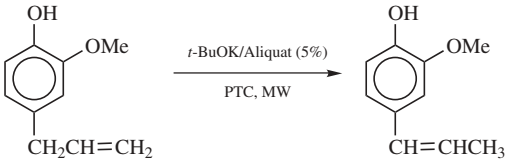
Octyl Thiocyanates–Synthesis and Isomerization. Vass and co-workers have developed nontraditional supports, which are chemically inactive and couple poorly with microwaves (118). For example, in the presence of a phase transfer catalyst, tetrabutylammonium bromide (TBAB) on sodium chloride, octyl bromide undergoes thiocyanation reaction with potassium thiocyanide (KSCN) and further isomerizes to isothiocyanate under MW irradiation (eq. 67) (118).



(67)

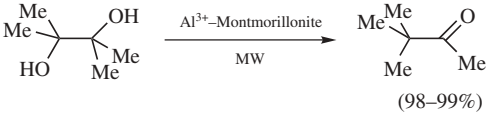
Eugenol–Isoeugenol Isomerization. Isoeugenol, an important feedstock in the manufacture of vanillin, is obtained by the base-catalysed MW-assisted isomerization of naturally occurring eugenol under solvent-free condition in the presence of potassium *tert*-butoxide, *t*-BuOK, and a catalytic amount of

phase-transfer reagent, (eq. 68) (172).



(68)

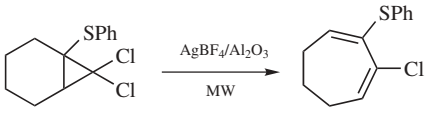
Pinacol–Pinacolone Rearrangement. A solvent-free pinacol–pinacolone rearrangement has been reported using MW irradiation. The process involves irradiation of the *gem*-diols with Al^{3+}-montmorillonite K-10 clay for 15 min to afford the rearrangement product in excellent yields (eq. 69) (112); the comparative reaction performed under conventional heating in an oil bath requires longer reaction times (15 h).



(98–99%)

(69)

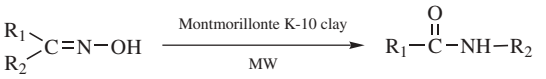
A facile ring expansion reaction under solvent-free conditions on alumina surface has also been described (eq. 70) (173); the MW protocol is superior to the one conducted in methanol.



(75%)

(70)

Beckmann Rearrangement. Montmorillonite K-10 clay surface is found to be superior among several acidic surfaces that have been used for the Beckmann rearrangement of oximes (eq. 71) (134). However, the conditions are not adaptable for the aldoximes that instead dehydrate to the corresponding nitriles under solventless conditions.



(71)

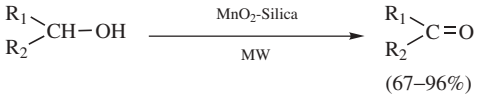
Where R_1 = Me or Ph; R_2 = Ph or substituted phenyl

The Ferrier rearrangement also occurs (72–83%) by subjecting neat reactants under solvent-free conditions to MW irradiation (174).

3.4. Oxidation Reactions—Oxidation of Alcohols and Sulfides. Metal-based reagents have found extensive use as oxidants in organic synthesis. Potassium permanganate ($KMnO_4$), manganese dioxide (MnO_2), chromium trioxide (CrO_3), potassium dichromate ($K_2Cr_2O_7$), potassium chromate (K_2CrO_4), peracids, and peroxides are some of the oxidizing reagents employed (175–177).

The utility of such reagents in oxidation processes is compromised for several reasons including potential danger in handling of metal complexes, inherent toxicity, cumbersome product isolation and waste disposal problems. Immobilization of metallic reagents on solid supports has addressed some of these limitations and provided an attractive alternative in organic synthesis because of the enhanced selectivity and the metals are not leached into environment.

Silica Supported Activated Manganese Dioxide. Silica supported manganese dioxide (MnO_2) provides a rapid and high yield route for the oxidation of alcohols to aldehydes and ketones. Benzyl alcohols are selectively oxidized to carbonyl compounds using 35% MnO_2 "doped" silica under MW irradiation conditions (eq. 72) (178).

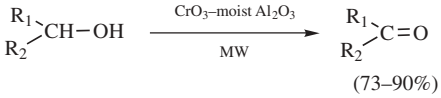


(67–96%)

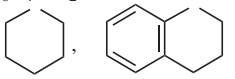
Where R_1 = H; R_2 = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, PhCH=CH
R_1 = Et, Ph, PhCO; R_2 = Ph
R_1 = *p*-$MeOC_6H_4CO$; R_2 = *p*-$MeOC_6H_4$ (72)

Clay-supported manganese dioxide (bentonite) has also been used for the oxidation of phenols to quinones (30–100%) (179) and MnO_2 on silica effects the dehydrogenation of pyrrolodines (58–96%) (180).

Chromium Trioxide Supported on Wet Alumina. The use of chromium(VI) reagents as oxidants is limited due to their inherent toxicity, their preparation in various complex forms (with acetic acid or pyridine) and complicated work-up procedures. Chromium trioxide (CrO_3) immobilized on premoistened alumina affords efficient oxidation of benzyl alcohols to carbonyl compounds by simple mixing (eq. 73). Remarkably, neither the overoxidation to carboxylic acids nor the usual formation of tar, a typical occurrence in many CrO_3 oxidations, is observed (181).



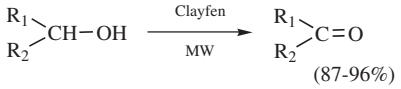
(73–90%)

Where R_1 = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$; R_2 = H
R_1 = Ph ; R_2 = Me, Ph, PhCO; R_1 - R_2 =  (73)

The reagent system is also used for the preparation of acyclic α-nitro ketones by the oxidation of nitroalkanols under solvent-free conditions (182).

Selective Solvent-Free Oxidation with Clayfen. A rapid MW oxidation protocol for the oxidation of alcohols to carbonyl compounds has been reported by Varma and co-workers using montmorillonite K-10 clay-supported iron(III) nitrate (clayfen) under solvent-free conditions (183) which proceeds via the intermediacy of nitrosonium ions. Interestingly, no carboxylic acids are formed in the oxidation of primary alcohols. The simple solvent-free experimental procedure

involves mixing of neat substrates with clayfen and a brief MW irradiation for 15–60 s. This fast, manipulatively simple and selective protocol avoids excess use of solvents and toxic oxidants (eq. 74) (183). The solid-state utility of clayfen [iron(III) nitrate on clay] as an oxidant has afforded higher yields and the amounts used in these protocols are half of that used by Laszlo and co-workers (101,102).



(74)

Where R_1 = H; R_2 = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, 2-tetrahydrofuranyl

R_1 = Me, PhCO; R_2 = Ph ; R_1 - R_2 = cyclohexyl

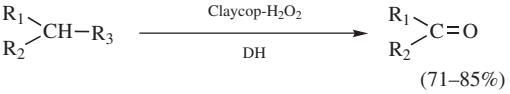
R_1 = *p*-$MeOC_6H_4CO$; R_2 = *p*-$MeOC_6H_4$

Iron(III) nitrate has been used with HZSM-5 zeolite, both in dichloromethane solution and in solid state, under MW irradiation conditions (184). More recent studies point out attractive alternatives that avoid the use of any solid supports in the oxidative conversions with nitrate salts (185,186).

Oxidation Reactions with Claycop-Hydrogen Peroxide. Metal ions play a central role in several oxidation reactions including biological dioxygen metabolism. For example, copper(II) acetate and hydrogen peroxide react to produce a stable oxidizing agent, hydroperoxy copper(II) compound. The same oxidant can also be prepared from copper(II) nitrate and hydrogen peroxide (eq. 75) (187) although the reaction requires the neutralization of ensuing nitric acid by potassium bicarbonate to maintain a pH ∼5.

$$2\,Cu(NO_3)_2 + H_2O_2 + 2\,H_2O \longrightarrow 2\,CuO_2H + 4\,HNO_3 \qquad (75)$$

Copper(II) nitrate immobilized on K-10 clay (claycop) plus hydrogen peroxide is an effective oxidant for a variety of substrates and provides excellent yields (eq. 76) (188); the maintenance of pH of the reaction mixture is not required.



(76)

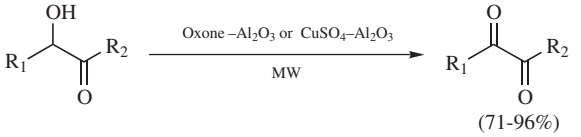
Where R_1 = Ph, *p*-$NO_2C_6H_4$; R_2 = H, Ph; R_3 = H, Br, CN, NH_2, COOH

Aqueous hydrogen peroxide (30%) has also been used for the oxidation of primary alcohols (60–84%) (189). In the presence of acetonitrile, hydrogen peroxide provides easy access to epoxides from olefinic substrates on hydrotalcites (190).

Oxidations with Copper Sulfate or Oxone®–Alumina. Benzoins, both symmetrical and unsymmetrical, have been rapidly oxidized to benzils in high yields using the solid reagent, copper(II) sulfate-alumina (191) or Oxone-moist alumina (192,193) upon exposure to microwaves (eq. 77). Normally, these oxidative transformations employ reagents such as nitric acid, Fehling's solution,

thallium(III) nitrate, ytterbium(III) nitrate, ammonium chlorochromate-alumina and clayfen. In addition to extended reaction times, most of these processes suffer from the use of corrosive acids and toxic metallic compounds that generate undesirable waste products.

The process, however, is applicable only to α-hydroxyketones as exemplified by mixed benzylic–aliphatic α-hydroxyketones or 2-hydroxypropiophenone that delivers the corresponding vicinal diketone (192,193).



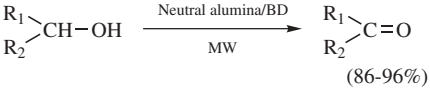
(77)

Where $R_1 = R_2$ = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4

R_1 = Ph; R_2 = *p*-MeC_6H_4, *p*-$MeOC_6H_4$ and R_1 = Me; R_2 = Ph

Nonmetallic Oxidants: Alumina Supported Iodobenzene Diacetate (IBD). Organohypervalent iodine reagents such as iodoxybenzene, *o*-iodoxybenzoic acid (IBX), bis(trifluoroacetoxy)iodobenzene (BTI), and Dess-Martin periodinane have been used for the oxidation of alcohols and phenols. Most of these reactions are conducted in high boiling DMSO or relatively toxic acetonitrile that increase the burden on the environment. Further, the use of inexpensive iodobenzene diacetate (IBD) as an oxidant, however, has not been fully exploited.

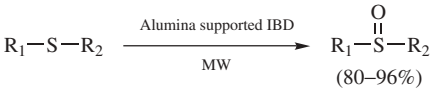
Varma and co-workers reported for the first time the use of supported iodobenzene diacetate as an oxidant. In this novel oxidative protocol, alumina-supported IBD under solvent-free conditions rapidly converts alcohols to the corresponding carbonyl compounds in almost quantitative yields (194). The use of alumina as a support improved the yields markedly as compared to neat IBD (eq. 78). 1,2-Benzenedimethanol, however, undergoes cyclization to afford 1(3H)-isobenzofuranone.



(78)

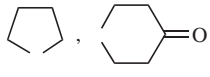
Where R_1 = Ph, substituted Ph and R_2 = H, Et, COPh

Oxidation of Sulfides to Sulfoxides by Alumina Supported Iodobenzene Diacetate. The solid oxidizing reagent, IBD-alumina, has been used for the rapid, high yielding and selective oxidation of alkyl, aryl and cyclic sulfides to the corresponding sulfoxides upon MW irradiation (eq. 79) (195).

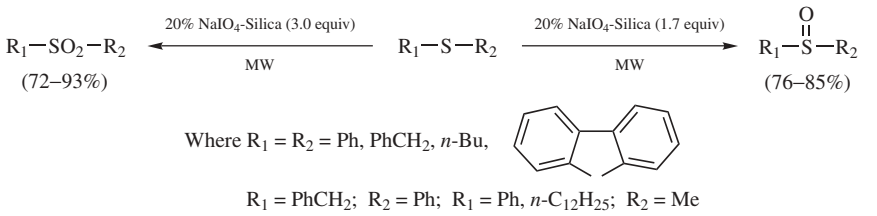


(79)

where $R_1 = R_2$ = i-Pr, *n*-Bu, Ph, $PhCH_2$; R_1 = Ph ; R_2 = Me, $PhCH_2$

R_1 = *n*-$C_{12}H_{25}$; R_1 = Me ; R_1 - R_2 = 

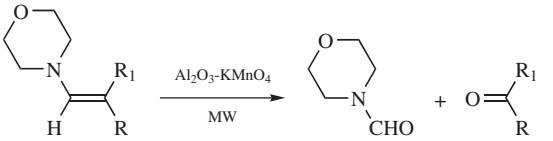
Oxidation of Sulfides to Sulfoxides and Sulfones: Sodium Periodate–Silica. The conventional reaction conditions for the oxidation of sulfides to the corresponding sulfoxides and sulfones are rather strenuous, requiring oxidants such as nitric acid, hydrogen peroxide, chromic acid, peracids, and periodate. The oxidation of sulfides to sulfoxides and sulfones is achieved in a selective manner using MW irradiation under solvent-free conditions with desired selectivity to either sulfoxides or sulfones over sodium periodate ($NaIO_4$) on silica (eq. 80) (196). A reduced amount of the active oxidizing agent, 20% $NaIO_4$ on silica, is employed that is safer and easier to handle.



(80)

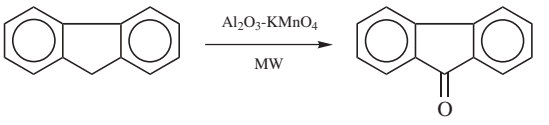
Several refractory thiophenes can be oxidized under these conditions, eg, benzothiophenes are oxidized to the corresponding sulfoxides and sulfones using ultrasonic and microwave irradiation, respectively, in the presence of $NaIO_4$–silica (196). A noteworthy feature of the protocol is its applicability to long chain fatty sulfides that are insoluble in most solvents and are consequently difficult to oxidize.

Oxidation of Enamines and Arenes: Potassium Permanganate ($KMnO_4$)–Alumina. β,β-Disubstituted enamines have been successfully oxidized under solvent-free conditions into carbonyl compounds by alumina supported KMnO4 in both domestic (255 W, 82°C) and focused microwave ovens (330 W, 140°C) (197); the yields are better in the latter case. No carbonyl compounds are formed when the same reactions are conducted in an oil bath at 140°C, (eq. 81).



(81)

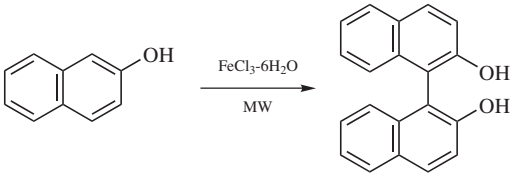
$KMnO_4$–Al_2O_3 oxidizes arenes to ketones within 10–30 min under solvent-free conditions using focused microwaves (eq. 82) (198).



(82)

Miscellaneous Oxidation Reactions. A rapid oxidative coupling of β-naphthols occurs in the presence of iron(III) chloride, ($FeCl_3.6H_2O$) using a

focused MW-oven under solvent-free conditions; the procedure is superior to conventional heating (eq. 83) (199).

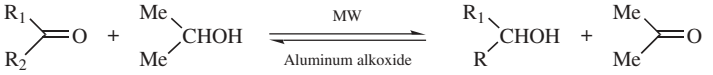


(83)

MW-assisted oxidations have been used for the oxidation of benzylic bromides to the corresponding aldehydes using pyridine N-oxides (15–95%) (200). The catalyst system, V_2O_5/TiO_2, and modified forms thereof by addition of an effective MW coupling dielectric such as MoO_3, WO_3, Nb_2O_5, or Ta_2O_5, have been used for the selective oxidation of toluene to benzoic acid under MW irradiation. When conventional heating is used, such additives display no positive influence on catalyst's performance (201).

3.5. Reduction Reactions. MW-assisted reduction reactions were among the last to be studied. The kinetics of catalytic-transfer hydrogenation of soybean oil in MW and thermal field have been examined and reaction rates are found to be eight times greater in MW than the conventional heating at the same temperature (202). Ammonium formate has been used for the allylic reduction (203) and the protocol has been subsequently adapted for the reduction of imines and in the dehalogenation of aryl halides in presence of 10% Pd/C (204).

Reduction of Carbonyl Compounds with Aluminum Alkoxides. The reduction of carbonyl compounds with isopropyl alcohol and alumina (205) has now been adapted for an expeditious solvent-free reduction process that utilizes aluminum alkoxides under MW irradiation conditions (eq. 84) (206).



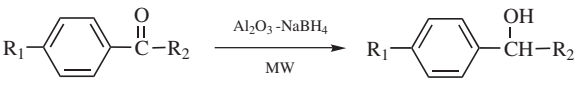
(84)

Reduction of Carbonyl Compounds with Alumina–Sodium Borohydride. The relatively inexpensive and safe sodium borohydride ($NaBH_4$) has been extensively used as a reducing agent because of its compatibility with protic solvents. The solid-state reduction of carbonyl compounds has been accomplished by mixing them with $NaBH_4$ and storing the reaction mixture in a dry box for 5 days. The disadvantage in the usual reduction reaction with $NaBH_4$ is that the solvent slows down the reaction rate while in the solid-state reactions, the required time (5 days) is too long for it to be of any practical utility (207).

In a first example of its kind under solvent-free conditions, Varma and coworkers reported a simple method for the expeditious reduction of aldehydes and ketones that uses alumina-supported $NaBH_4$ and proceeds in the solid state using microwaves (208). The process involves simple mixing of carbonyl compounds with 10% $NaBH_4$ supported on alumina and exposure of the reaction mixture to microwaves in a household MW oven for 0.5–2 min (eq. 85).

The useful chemoselective feature of the reaction is apparent from the reduction of *trans*-cinnamaldehyde (cinnamaldehyde/$NaBH_4$-alumina, 1:1 mol

equiv); olefinic moiety remains intact and only the aldehyde functionality is reduced in a facile reaction.



(62–93%)

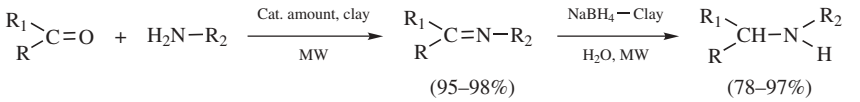
Where R_1 = Cl, Me, NO_2 ; R_2 = H ; R_1 = H ; R_2 = Me, Ph

R_1 = Ph ; R_2 = PhCH(OH) ; $R_1 = R_2$ = Me,

$R_1 = p$-$MeOC_6H_4$; $R_2 = p$-$MeOC_6H_4CH(OH)$ (85)

The reaction rate improves in the presence of moisture and the reaction does not proceed in the absence of alumina. The alumina support can be recycled and reused for subsequent reduction, repeatedly, by mixing with fresh borohydride without any loss in activity. In terms of safety, the air used for cooling the magnetron ventilates the microwave cavity, thus preventing any ensuing hydrogen from reaching explosive concentrations. The process has been nicely utilized for the MW-enhanced solid-state deuteriation reactions using sodium borodeuteride impregnated alumina (209). Subsequent extension of these studies to specific labeling has been explored (210) including deuterium exchange reactions for the preparation of reactive intermediates (211).

Reductive Amination of Carbonyl Compounds. The eco-friendlier processes developed by Varma and co-workers for imine formation (152,153) have been extended to a solvent-free reductive amination protocol for carbonyl compounds using sodium borohydride supported on moist montmorillonite K-10 clay that is facilitated by MW irradiation (eq. 86) (212). Conventionally, sodium cyanoborohydride (213), sodium triacetoxyborohydride (214), and $NaBH_4$ coupled with sulfuric acid (215) are reagents used for the reductive amination of carbonyl compounds; the use of corrosive acids or cyanide-based reagents results in toxic waste generation.



(95–98%) (78–97%)

Where R = *i*-Pr, Ph, *o*-HOC_6H_4, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$; R_1 = H ; R_2 = Ph

R - R_1 = –$(CH_2)_5$– ; R_2 = Ph ; R - R_1 = –$(CH_2)_6$– ; R_2 = *n*-Pr

R = *p*-ClC_6H_4 ; R_1 = H ; R_2 = *o*-HOC_6H_4 ; R = R_1 = Et ; R_2 = Ph

R = *n*-C_5H_{11} ; $R_1 = CH_3$; R_2 = morpholine, piperidine ; R = *i*-Pr ; R_1 = H ; R_2 = *n*-$C_{10}H_{21}$ (86)

The solid-state reductive amination of carbonyl compounds on alumina, clay, silica, and especially K-10 clay surface rapidly affords secondary and tertiary amines (212). Clay behaves as a Lewis acid and also provides water from its interlayers thus enhancing the reducing ability of $NaBH_4$ (10a). Thus practical applications of $NaBH_4$ reductions on mineral surfaces for *in situ* generated Schiff's bases have been successfully demonstrated.

Solid-State Crossed Cannizzaro Reaction. The classical Cannizzaro reaction is the disproportionation of an aldehyde to an equimolar mixture of primary alcohol and carboxylic salt (216,217) and is restricted to aldehydes that lack α-hydrogens. This oxidation–reduction reaction is normally conducted under strongly basic conditions and has the inherent disadvantage of lower yields of desired products (218,219). The popularity of Cannizzaro reaction in synthetic organic chemistry dwindled considerably after the discovery of lithium aluminum hydride, $LiAlH_4$, in 1946. The crossed Cannizzaro reaction (218), using a scavenger and inexpensive paraformaldehyde, however, has provided improved yields of alcohols prior to the introduction of hydride reducing agents.

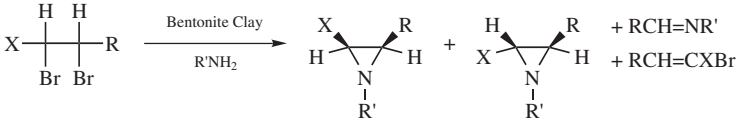
The reaction does not proceed under solventless MW-irradiation conditions on an alumina surface with calcium hydroxide or in the presence of a strong base such as sodium hydroxide. The reaction remains incomplete with concomitant formation of several unidentified products and is reminiscent of earlier described observations on basic alumina surface (220). Finally, Varma and coworkers discovered that the reaction proceeds rapidly on a barium hydroxide ($Ba(OH)_2.8H_2O$) surface, which constitutes the first application of this reagent in a solvent-free crossed Cannizzaro reaction (221). In a typical experimental procedure, a mixture of benzaldehyde (1 mmol) and paraformaldehyde (2 mmol) is mixed with barium hydroxide octahydrate (2 mmol) and irradiated in a MW oven (100–110°C) or heated in an oil bath (100–110°C) (eq. 87). These studies have generated additional interest and the general utility of this reaction has been further explored using microwaves (222,223).

$$\mathrm{RCHO} + (\mathrm{CH_2O})_n \xrightarrow[\mathrm{MW}]{\mathrm{Ba(OH)_2 \cdot 8H_2O}} \underset{(80\text{–}99\%)}{\mathrm{RCH_2OH}} + \underset{(1\text{–}20\%)}{\mathrm{RCOOH}} \qquad (87)$$

3.6. Microwave-Assisted Synthesis of Heterocyclic Compounds.

Heterocyclic chemistry has been a major beneficiary of MW-expedited solvent-free chemistry utilizing mineral supported reagents developed over the last decade (224). A few examples are shown below.

Aziridines. The synthesis of aziridines has been achieved under solvent-free conditions wherein elimination predominates over the Michael addition under MW irradiation when compared to the classical heating under the same conditions (eq. 88) (225).

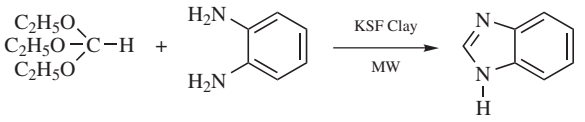


(88)

Where X = electron withdrawing group

Benzimidazoles. The condensation of *o*-phenylenediamines with ortho esters in the presence of KSF clay under either refluxing conditions in toluene

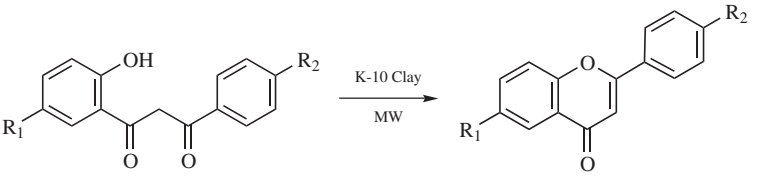
or solvent-free condition using MW irradiation affords benzimidazoles (eq. 89) (226).



(89)

Flavones. Flavonoids constitute an important class of naturally occurring oxygen heterocyclic compounds in the plant kingdom, the most abundant being the flavones. These phenolic compounds display a wide variety of biological activities and have proven useful in the treatment of various diseases (227,228). The commonly followed approach for the preparation of flavones involves the Baker-Venkataraman rearrangement, wherein an *o*-hydroxyacetophenone is benzoylated to form the benzoyl ester followed by the treatment with base (KOH/pyridine) to effect acyl migration, forming a 1,3-diketone (229). The ensuing diketone is then cyclized using strong acids such as sulfuric acid and acetic acid to afford flavone.

A solvent-free synthesis of flavones has been reported that involves the MW irradiation of *o*-hydroxydibenzoylmethanes adsorbed on montmorillonite K-10 clay for 1–1.5 min. A rapid and exclusive formation of cyclized flavones occurs in good yields (eq. 90) (230). The intramolecular Michael addition of *o*-hydroxychalcones on silica gel surface has been reported (231). A similar cyclization reaction of 2′-aminochalcone derivatives on clay surface readily affords 2-phenyl-1,2,3,4-tetrahydroquinolones (232).



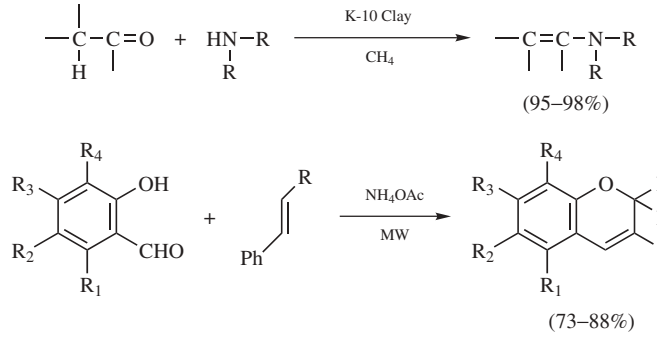
(90)

Where R_1 = H ; R_2 = H, Me, OMe, NO_2

R_1 = OMe; R_2 = H, Me, OMe

2-Amino Substituted Isoflav-3-enes. The estrogenic properties displayed by isoflav-3-ene derivatives have attracted the attention of medicinal chemists. Varma and co-workers have uncovered a useful enamine-mediated pathway to this class of compounds (233–235). The same group has now discovered a facile and general method for the MW-assisted synthesis of isoflav-3-enes substituted with basic moieties at the 2-position (eq. 91) (236). This convergent one-pot approach to 2-substituted isoflav-3-enes exploits the *in situ* generated enamine derivatives that are subsequently reacted with *o*-hydroxyaldehydes in the

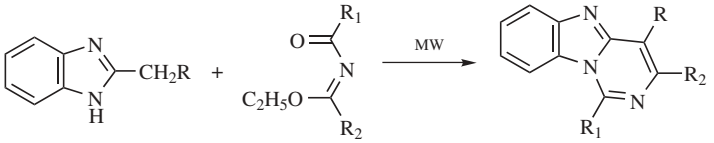
same pot (eq. 91) (236).



(91)

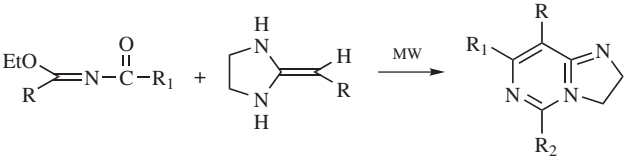
Where R = morpholinyl, piperidinyl or pyrrolidinyl
and $R_1 = R_3 = R_4$ = H, Cl, NO_2

Bridgehead Nitrogen Heterocyclic Compounds. The rapid MW-assisted synthesis of bridgehead nitrogen heterocycles has been achieved under solvent-free conditions as exemplified by the synthesis of pyrimidino[1,6-*a*] benzimidazoles (eq. 92) and 2,3-dihydroimidazo[1,2-*c*]pyrimidines (eq. 93) from *N*-acylimidates and activated 2-benzimidazoles or imidazoline ketene aminals, respectively (237,238).



(92)

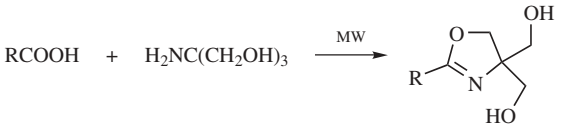
Where R = CN, CO_2Me, CO_2Et and
R_1, R_2 = alkyl, aryl



(93)

Where R_1, R_2 = alkyl; R = CN, CO_2Et

Synthesis of 2-Oxazolines. Oxazolines are conveniently accessible from α,α,α-tris(hydroxymethyl)methylamine and carboxylic acids under microwave irradiation conditions (eq. 94) (239).

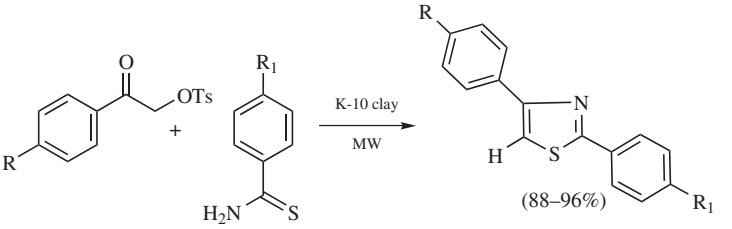


(94)

Where R = heptadecenyl, phenyl and 2-furyl

Synthesis of Substituted Thiazoles. The Hantzsch protocol that is normally used for the preparation of thiazoles, requires the use of lachrymatory

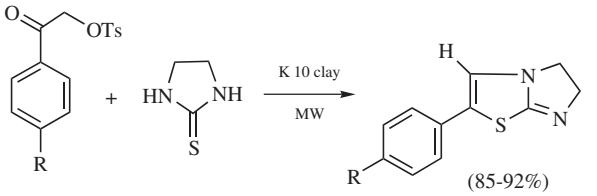
α-haloketones and thioureas (or thioamides) (240). In a process which eliminates this problem, Varma and co-workers have synthesized the title compounds by the simple solvent-free reaction of thioamides, in the presence of K-10 clay, with α-tosyloxyketones that is generated *in situ* from arylmethyl ketones and [hydroxy(tosyloxy)iodo]benzene (HTIB) under MW irradiation conditions (eq. 95) (241).



(95)

Where R = H, Me, OMe, Cl and R_1 = Cl, OMe

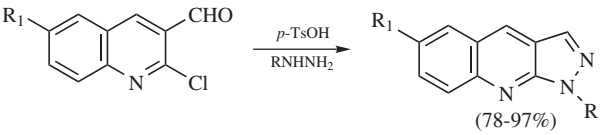
The MW-accelerated synthesis of the corresponding bridgehead heterocycles is finished in a short time (eq. 96), whereas using a conventional heating approach, the reactions of α-tosyloxyketones with ethylenethioureas remain incomplete in an oil bath for hours at 130°C (224,241).



(96)

Where R = H, Me, OMe, Cl

Pyrazolo[3,4-*b*]quinolines and pyrazolo[3,4,-*c*]pyrazoles have been synthesized by MW irradiation of β-chlorovinylaldehydes and hydrazines in presence of *p*-toluenesulfonic acid (*p*-TsOH) (eq. 97) (242).

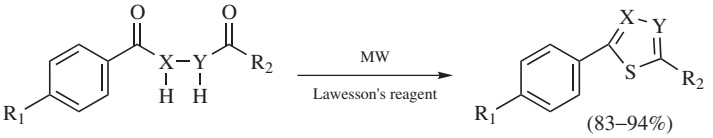


(97)

Where R_1 = H, Me, OMe and R = H, Ph

The MW-mediated ring closure of several 1,4-dicarbonyl compounds has resulted in the synthesis of useful *S*-heterocycle-containing liquid crystalline targets. The new ring-closure methodology affords higher yields than an earlier synthesis of a liquid crystal; some of these newer reactions have been scaled

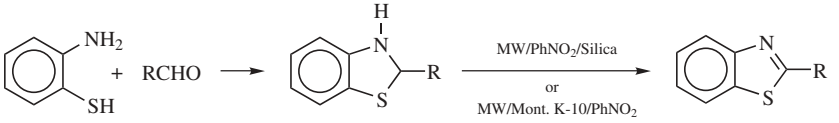
up to several grams without compromising the yield (eq. 98) (243).



(98)

Where R1 = h, OMe, Br; R2 = Ph, O-alkyl
and X = Y = CH or N

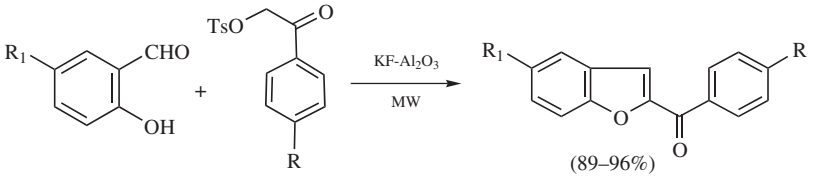
2-Arylbenzothiazoles have been synthesized in high purity by the condensation of aldehydes with *o*-aminothiophenol using silica gel/nitrobenzene or montmorillonite K-10/nitrobenzene under MW irradiation (eq. 99) (244).



(99)

Where R = aryl, substituted aryl, heteroaryl group

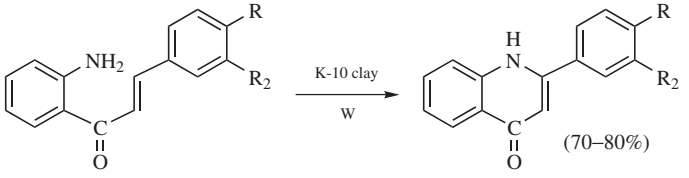
Synthesis of 2-Aroylbenzofurans. Pharmacologically important 2-aroylbenzofurans are obtained under basic solvent-free conditions from α-tosyloxyketones and salicylaldehydes in the presence of potassium fluoride doped alumina using MW irradiation (eq. 100) (224,241).



(100)

Where R = H, Me, OMe, Cl and R_1 = H, Cl

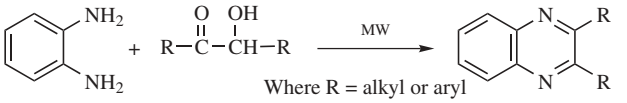
Synthesis of Quinolones, Quinolinones, Quinazolines and Quinolines. As mentioned earlier, readily available 2′-aminochalcones provide easy access to medicinally important 2-aryl-1,2,3,4-tetrahydro-4-quinolones in a solvent-free cyclization reaction on K-10 clay under MW irradiation (eq. 101) (232).



(101)

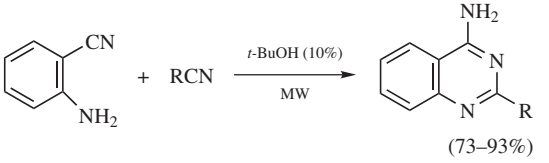
Where R_1 = Cl, Br, Me, OCH_3, NO_2; R_2 = H
and R_1 = R_2 = H, OMe

2,3-Disubstituted quinoxalines have been synthesized by subjecting aryl or alkyl acyloins and *o*-phenylenediamine under microwave irradiation for 3–6 min (eq. 102) (245).



(102)

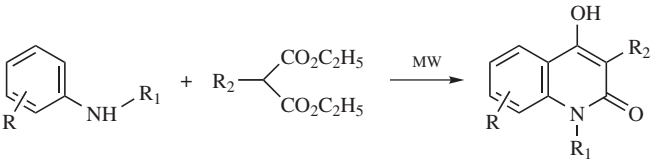
4-Aminoquinazolines have been prepared rapidly, and in good yields, in a MW reaction of cyanoaromatics and anthranilonitriles in the presence of 10% *t*-BuOH (eq. 103) (246).



(103)

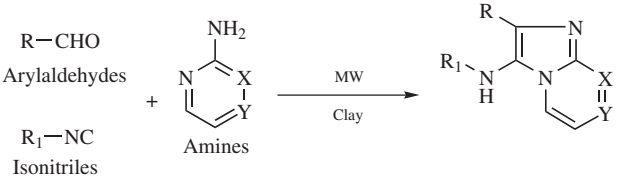
Where R = aryl, substituted aryl and heteroaromatic groups

A one-pot MW-enhanced synthesis of selective glycine receptor antagonists, 3-aryl-4-hydroxyquinolin-2(1H)-ones, has been developed via the amidation of malonic ester derivatives with anilines and subsequent cyclization of the ensuing intermediate, malondianilides (eq. 104) (247).



(104)

Multicomponent Reactions (Ugi and Biginelli Reactions). A multiple component condensation (MCC) strategy enables the creation of diverse molecules in a single step by varying the reacting components. The generation of small-molecule libraries is facilitated when the ease of reaction manipulation is coupled with efficient protocols. As described in Section 2.11. Combinatorial Chemistry, such a facile protocol is amenable to the generation of a library of imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines, and imidazo[1,2-*a*]pyrimidines under solvent-free conditions using MW irradiation (eq. 105) (75). This is a remarkable improvement over the conventional two-component synthesis that requires the use of lachrymatory α-haloketones, which restricts the generation of a diverse library of these molecules.



(105)

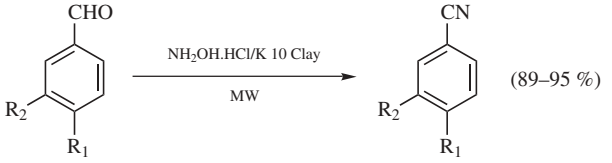
Where X= Y= C;X= C, Y= N; X= N, Y=C and R, R1= alkyl, aryl

Experimentally, aldehydes and the corresponding 2-aminopyridine, pyrazine, or pyrimidine are admixed in the presence of a catalytic amount of clay (50 mg) to generate iminium intermediates to which isocyanides are subsequently added in the same reaction vessel. The reactants are exposed to MW irradiation to afford the corresponding imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines, and imidazo[1,2-*a*]pyrimidines (eq. 107). The process is general for all three components, eg, aldehydes (aliphatic, aromatic, and vinylic), isocyanides (aliphatic, aromatic, and cyclic), and amines (2-aminopyridine, 2-aminopyrazine, and 2-aminopyrimidine). Thus, a library of imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines, and imidazo[1,2-*a*]pyrimidines can be readily obtained by varying the three components (75).

A similar MW strategy has been used to synthesize a set of pyrimidinones (65–95%) via the Biginelli condensation reaction in a household MW oven (25) and has been successfully applied to combinatorial synthesis. More recent examples describe convenient synthesis of pyrroles (60–72%) on silica gel using readily available enones, amines and nitro compounds (248a), preparation of multifunctionalized pyrido[2,3-*d*]pyrimidines in one-pot cyclocondensation of α,β-unsaturated esters, malononitriles and amidines (248b), and utility of neat reactants under solvent-free conditions to generate Biginelli and Hantzsch reaction products (249).

3.7. Miscellaneous Reactions. Several useful MW-accelerated reactions have been developed that have enabled efficient functional group transformations, very often under solvent-free conditions.

Transformation of Arylaldehydes to Nitriles. The conversion of arylaldehydes to nitriles is an important chemical transformation (250). The reaction proceeds via an aldoxime intermediate that is subsequently dehydrated using a wide variety of reagents such as chloramine/base, *O,N*-bis-(trifluoroacetyl) hydroxylamine or trifluoroacetohydroximic acid, *p*-chlorophenyl chlorothionoformate/pyridine, triethylamine/dialkyl hydrogen phosphinates, TiCl4/pyridine, triethylamine/phosphonitrilic chloride, and 1,1′-dicarbonylbiimidazole. The dehydration of aldoxime is a time consuming process even for one-pot reactions (251). Varma and co-workers showed that clay-supported hydroxylamine hydrochloride reduces the entire operation to a one-pot synthesis using microwaves wherein arylaldehydes are rapidly converted into nitriles in good yields (89–95 %) in the absence of solvent (193,252). In this general reaction, a variety of aldehydes undergo this facile conversion to the corresponding nitriles in a short time (1–1.5 min) upon MW irradiation (eq. 106).



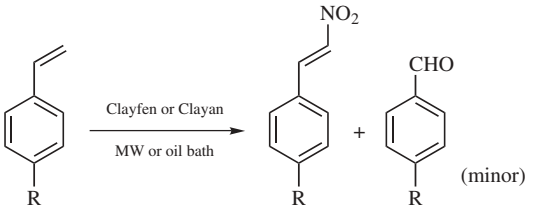
(106)

Where R_1 = H, R_2 = H, OMe, NO_2, OH, Br, Me
and $R_1 = R_2$ = OMe

Several variations of the above-mentioned transformations have been reported using silica as surface (253–255). The nitriles have been obtained

from carboxylic acids (20–93%) on alumina support (256) and from the corresponding amides (80–95%) in toluene (257).

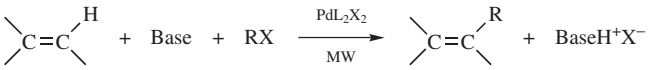
Preparation of β-Nitrostyrenes by Nitration of Styrenes. Varma and co-workers developed a solid-state synthesis of β-nitrostyrenes that uses readily available styrenes and inexpensive clay-supported nitrate salts, clayfen and clayan (eq. 107) (258). In a simple experiment, styrene mixed with clayfen or clayan is irradiated in a MW oven (~100–110°C, 3 min) or heated in an oil bath (~100–110°C, 15 min) to afford predominantly β-nitrostyrenes. In the case of clayan (clay supported ammonium nitrate), intermittent heating is recommended with 30-s intervals to maintain temperature < 60–70°C. Remarkably, the reaction proceeds only in solid state and leads to the formation of polymeric products in organic solvent.



(107)

Where R = H, Cl, Me, OMe

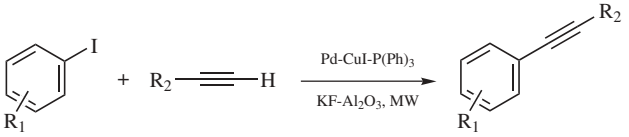
Organometallic Reactions (C–C Bond Forming Reactions). Several organometallic reactions in solution have been described earlier (Section 2.12 Organometallic chemistry), mostly palladium-catalyzed reaction of aryl halides and olefins (259) for C–C bond formation (260). The commonly used catalyst is palladium acetate, although other palladium complexes have also been used. A solvent-free Heck reaction has been conducted in excellent yields using a household MW oven and palladium acetate as catalyst and triethylamine as base (eq. 108) (261). A comparison study revealed that the longer reaction times and deployment of high pressures, typical of classical heating methods, are avoided using this MW protocol.



(108)

A rapid MW-assisted palladium-catalyzed coupling of heteroaryl and aryl boronic acids with iodo- and bromo-substituted benzoic acids, anchored on TentaGel, has been achieved (262). An environmentally friendly Suzuki cross-coupling reaction has been developed that uses a small amount of recyclable PEG as the reaction medium and palladium chloride as a catalyst (80). A solvent-free Suzuki coupling has also been reported on palladium-doped alumina in the presence of potassium fluoride as a base (263), which has been extended to Sonogashira coupling reaction, wherein terminal alkynes couple readily with aryl or alkenyl iodides on palladium-doped alumina in the presence of

triphenylphosphine and cuprous iodide (eq. 109) (264).

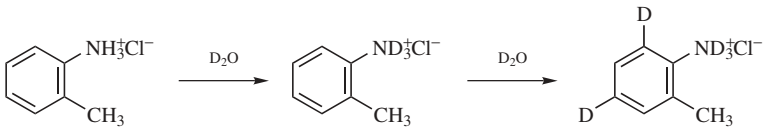


(109)

Where R_1 =H, Me, OMe, NMe_2, F, I
and R_2 = C_8H_{17}, C_6H_{13} and Ph

The intermolecular hydroacylation of 1-alkenes with aldehydes has been presented as a greener alternative to the classical approach using a homogeneous catalyst in toluene. This general reaction uses Rh(I) complex (Wilkinson catalyst) under solvent-free conditions and the MW protocol considerably enhances the reaction rate presumably as a result of the formation of polar transition states (265).

Synthesis of Radiolabeled Compounds. The MW-expedited borohydride reduction reaction described earlier (208) has been adapted for the efficient deuteration and tritiation reactions using MW irradiation and solid hydrogen–deuterium–tritium donors with minimal radioactive waste generation, a contrast from the classical tritiation efforts (266). Jones and co-workers addressed the traditional disadvantages associated with tritium labeling techniques as demonstrated in deuterated and tritiated borohydride reductions (209), based on similar MW-expedited reduction executed on alumina surface (208). The hydrogen exchange reactions that require prolonged reaction time (24 h) (267) and elevated temperatures are the primary beneficiaries of this microwave approach (eq. 110) (209). The high purity of labeled materials, efficient insertion, and excellent regioselectivity are some of the advantages of this emerging technology.

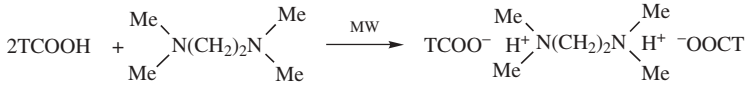


(110)

Selective, fast, and clean applications of the MW-accelerated reactions have been demonstated by Stone-Elander and co-workers in the synthesis of a variety of radiolabeled (^{3}H-, ^{11}C-, and ^{19}F-) organic compounds via nucleophilic aromatic and aliphatic substitution reactions, esterifications, condensations, hydrolysis, and complexation reactions using monomodal MW cavities on a microscale (210). Thus, a substantially reduced level of radioactive waste is generated in these protocols.

Hydrogenation reactions in which H_2–D_2–T_2 gases are replaced by labeled formates proceed very rapidly under MW irradiation conditions (eq. 111) (268). The pattern of labeling can be easily modified and the advantages are especially noteworthy in the case of tritium where high specific activity tritiated water is

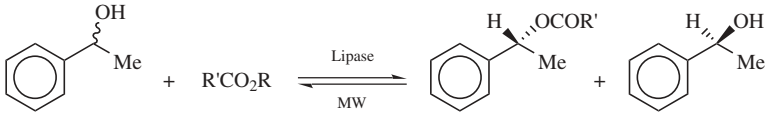
hazardous to use.



(111)

Enzyme-Catalyzed Reactions. In traditional synthetic transformations, enzymes are normally used in aqueous or organic solvent at moderate temperatures to preserve the activity of enzymes. Therefore, it is not surprising that some of these reactions require long reaction times. In view of the newer developments that immobilize enzymes on solid supports (269), they are now amenable to operate at relatively higher temperature reaction with adequate pH control. The application of MW irradiation has been investigated with two enzyme systems, namely, *Pseudomonas* lipase dispersed in Hyflo Super Cell that essentially consists of diatomeous silica around pH 8.5–9.0 and commercially available SP 435 Novozym (*Candida antarctica* lipase grafted on an acrylic resin) (270).

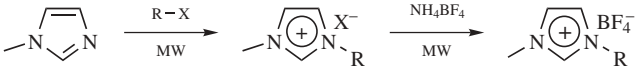
The solvent-free resolution of racemic 1-phenylethanol has been achieved under MW irradiation conditions by transesterification using the above enzymes (eq. 112) (270). A comparison of the MW-assisted reaction with that by conventional heating revealed an enhanced enantioselectivity for the former presumably due to the efficient removal of low molecular weight alcohols or water upon exposure to microwaves or alternatively an entropic effect due to dipolar polarization that induces a previous organization of the system. Thermostable enzymes such as crude homogenate of *Sulfolobus solfataricus* and recombinant β-glucosidase from *Pyrococcus furiosus* have been successfully applied to transglycosylation reactions where recycling of the biocatalyst is feasible (271).



(112)

Solvent-Free Preparation of Ionic Liquids. Room temperature ionic liquids (RTILs), consisting predominantly of dialkylimidazolium cations (272) and various anions, have received wide attention due to their potential in a variety of commercial applications such as electrochemistry (273), heavy metal ion extraction (274), phase-transfer catalysis, polymerization (275), and as substitutes for traditional volatile organic solvents (276). Most of these polar ionic salts are good solvents for a wide range of organic and inorganic materials and consist of poorly coordinating ions and provide a polar alternative for biphasic systems. Other significant attributes of these ionic liquids include barely measurable vapor pressure, potential for recycling, compatibility with various organic compounds and organometallic catalysts, and ease of separation of products from reactions (277–280). Unfortunately, most of the initial preparations of ionic liquids involve heating several hours in refluxing solvents and use of a large excess of alkyl halides–organic solvents that diminish their true potential as "green" solvents.

Ionic liquids, being polar and ionic in character, couple to MW irradiation very efficiently, and therefore are ideal microwave absorbing candidates (281) for expediting chemical reactions. An efficient preparation of the 1,3-dialkylimidazolium halides via microwave heating has been described by Varma and co-workers; it reduces the reaction time from several hours to minutes and avoids the use of a large excess of alkyl halides/organic solvents as the reaction medium (109–111,279). The efficiency of this approach has been extended to the preparation of other ionic salts bearing tetrafluoroborate anions that involves exposing *N, N'*-dialkylimidazolium chloride and ammonium tetrafluoroborate salt to MW irradiation (eq. 113) (110).



(113)

This solvent-free approach requires only a few minutes of reaction time using an unmodified household MW oven in contrast to several hours needed under conventional heating conditions (eq. 115) (280,282). The process precludes the usage of volatile organic solvents, is faster, more efficient, and ecofriendly. A general use of these ionic liquids in the protection and deprotection of alcohols has been demonstrated in a facile tetrahydropyranylation reaction (111) and significant rate enhancements are reported in the 1,3-dipolar cycloaddition reactions including the use of covalently grafted dipolarophiles on the ionic liquids (283). A recent improvement over the MW approach has been reported that involves the preparation of ionic liquids almost at room temperature under ultrasonic irradiation conditions (284). The surge of interest continues with this class of solvents especially under MW irradiation conditions where potential recycling of the catalyst is enhanced as demonstrated for a high speed Heck reaction in ionic liquid media with controlled MW heating (285).

4. Conclusions

Microwave heating, being specific and instantaneous, is unique and has found a place for expeditious chemical syntheses. Specifically, the solvent-free reactions are convenient to perform and have advantages over the conventional heating protocols as summarized in the previous sections. A wide range of selective functional group transformations have been accomplished expeditiously and efficiently using a variety of supported reagents on mineral oxides as catalysts. Although a large body of work has been performed around the world using an unmodified household MW oven (multimode applicator), more recent work does involve increasing use of commercial systems wherein not only improved temperature–power control is possible but also relatively large-scale reactions can be conducted (286) with added options for a continuous operation. The engineering and scale-up aspects for the chemical process development have also been discussed (287). Additionally, novel and, at times, rather unusual MW applications continue to appear in the chemical literature as exemplified by a recent report on the removal of organic templates of meso- and macroporous

silicious materials within minutes by MW digestion (288) that results in highly ordered inorganic frameworks with higher surface area, larger pore volumes and richer silanol groups compared with those obtained by conventional methods.

The ecofriendly advantages of these solvent-free protocols can be found in instances where catalytic amounts of reagents or supported agents are used since they provide reduction or elimination of solvents, thus preventing pollution "at source". Although not delineated completely, the reaction rate enhancements achieved in these methods may be ascribable to nonthermal effects. The rationalization of microwave effects and mechanistic considerations possibly involve the intermediacy of polar transition states that couple to microwaves more readily and are discussed in detail elsewhere (13a). The dramatic increase in the number of publications, books (23b,23c,289), and a growing body of patent literature on MW-accelerated processes (290–299) bodes well for microwave-enhanced chemical syntheses.

5. Disclaimer

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