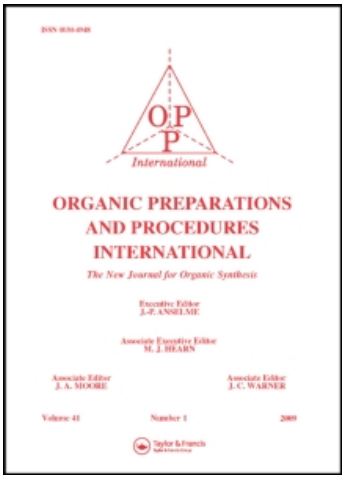

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APPLICATIONS OF MICROWAVE ENERGY IN ORGANIC CHEMISTRY. A REVIEW

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INTRODUCTION

Probably the first recorded application of microwave energy in organic synthesis is the aqueous emulsion polymerization of butyl acrylate, acrylic acid, and methacrylic acid using pulsed electromagnetic radiation.[1] The polymerization rates were substantially higher than those observed under conventional emulsion polymerization. Not much attention seems to have been paid to this patent, for it was not until 1986 that the first reports of the application of commercial microwave ovens to the synthesis of small organic molecules appeared. Indeed, the present author was using a kitchen microwave oven as early as 1977 to cure epoxy resins when he was too impatient to wait for the required 24 hrs (at that time) for curing to occur at room temperature, but he obviously did not have the imagination or foresight to do the same type of thing in his laboratory until early in 1985! Then, when a hydrosilation reaction his group was working on took 18 hrs at 180° to give a very low yield of product which was extremely tedious to work up, he remembered the epoxy glue and the hydrosilation in a kitchen microwave was attempted and resulted in remarkable improvements both in reaction time and yields (see below).

Microwave heating had been used for a wide variety of purposes such as moisture analysis,[2] the wet ashing of biological and dissolution of geological materials,[3] regeneration of activated carbon,[4] the preparation of activated carbon from carbonaceous materials,[5] the treatment of sewage and sewage sludge,[6] and the drying of spaghetti.[8d] It was, however, the pioneering papers by Gedye[16] and by Majetich[14] and their co-workers in 1986 that stimulated the interest of synthetic organic chemists in this new technique.[16]

This review will cover the recent applications of microwave radiation to effect organic chemical reactions, such as the synthesis of organic and organometallic compounds, polymerization, and depolymerizations; the use of this technique in pharmaceutical and industrial applications as well as brief coverage of what is known (including some speculations) about the mode of action of microwaves will be examined. A very brief review of the topic (combined with the use of ultrasound and high pressure) appeared in 1989; the Tilden lecture on the broader topic of microwave dielectric heating effects appeared after the present review was completed.[7b] Two articles have also appeared in

the "popular" press.[8] In addition, a book describing the principles, techniques and some of the equipment used in microwave sample preparation has been published.[9]

Remarkable decreases in the times necessary to carry out reactions (up to 3 orders of magnitude) and, in some cases, cleaner reactions with easier workup than when using conventional heating methods, have been reported with microwave irradiation. Microwave heating essentially involves microwave dielectric loss.[7b,9,10a] Microwaves are generated in a magnetron and are guided to the oven cavity. They are reflected by the walls of the oven and absorbed by suitable compounds placed in the oven. Polar molecules absorb microwave energy, non-polar ones do not. Microwave radiation interacts with dipolar compounds which try to align themselves with the external applied field. As the field alternates (from positive to negative and back), the dipolar molecules attempt to follow it and rotate to align themselves with the field. The electric field of the commonly used irradiation frequency (2450 MHz) changes sign (direction) 2.45 x 10^9 times/sec and the tortional effect on dipolar molecules rotating back and forth causes heating since the molecular rotation lags behind the changes in the electric field and the molecules then absorb energy; heating also occurs through frictional effects. The dielectric loss (ε'') measures the efficiency with which electromagnetic radiation is converted to heat, and the ratio of this to the dielectric constant ε' of the molecule (its ability to be polarized in that field) expresses the ability of these molecules to transform electromagnetic energy into thermal energy (at that temperature and frequency:[9] $\varepsilon''/\varepsilon' = \tan\delta$ where δ is the *dissipation factor* of the sample). It has been suggested that "localized superheating" occurs,[9,11] and that this accounts for the rate enhancements observed. The ability of a molecule to couple with microwave radiation is a function of its molecular polarizability (in turn, a function of its dipole moment, as given by the Debye equation), but many additional factors are involved in microwave testing. Thus, 1-propanol has a much lower dipole moment (20.1 at 25°) than does water (78.54 at 25°) but the former heats up 1.7 times faster than does the latter, which has been attributed[10b] to the lower heat capacity of propanol (2.45 J/gK) as compared with water (4.18 J/gK). Porcelains have a higher dipole moment (6.0 - 8.0) than does acetic acid (6.15 at 20°), but the latter is heated up readily in a microwave oven while the former do not, owing to the fact that the ceramic molecules cannot rotate in the alternating microwave field. Similarly, it has been reported that while some monomers undergo dielectric loss heating readily i. e. absorb microwave energy, the resulting polymer may not (so that the temperature drops as the polymerization proceeds) since the large polymer molecules are less able (or unable) to "follow" the alternating field. Finally, it has been suggested that since molecular rotation may be relatively slow, double quantum excitation may occur and lead to the "localized superheating" postulated.

Since only polar molecules interact with microwave energy, such molecules in a non-polar solvent (e. g. cyclohexane, benzene), would absorb the energy but not the solvent [or the reaction vessel if it is made of TEFLON (pertetrafluoroethylene, μ 2.1 at 22°) or a ceramic, or even Pyrex (μ 4.50 - 6.00)]; therefore, heating proceeds from the inside of the vessel and radiates out, in contrast to conventional heating which proceeds from the outside in and thus may be less economical in terms

of the energy used.

Another factor which may play a role is interfacial polarization (the Maxwell-Wagner effect)[10b] where there is a build up of charges at interfaces, as for example, when small amounts of a conducting phase are in contact with a non-conducting medium exposed to microwaves. Thus, while there seems to be no specific "microwave effect" and no superheating in pure organic solvents, such localized superheating may well occur under non-homogeneous conditions or when a dipolar molecule or reactive intermediate is formed in a non-microwave absorbing medium.

I. EQUIPMENT

Most organic chemists use ordinary kitchen microwave ovens to effect the reactions described in this review. In our laboratories, for instance, we use a Sears Kenmore oven, or a CEM Corp. model MDS-81D oven equipped with a carrousel which oscillates through 180° to ensure uniformity of heating of up to 12 reaction vessels, with automatic internal pressure control (when the internal pressure reaches a preset value the power cuts off). The CEM oven has been modified for us to incorporate rudimentary internal stirring capability, as well as automatic internal temperature control (see below). For other applications e.g. industrial, microwave "coils" have been used, as have batteries of up to 10 antenna wave guides spaced at half wavelength.[12]

For reactions that have to be carried out under pressure or in a sealed vessel, thick-walled TEFLON screw-capped vessels have been most commonly used. These may be placed in an insulating material (to absorb any liquid spilled and to prevent damage to the oven should the bottle explode) or in a specially designed PARR polyetherimide bomb. These, like the CEM vessels, have special pressure relief discs built in. Alternatively, annealed, thick-walled Pyrex sealed pressure tubes have been used, surrounded by glass wool or vermiculite, and placed in a box constructed of 1/4" Corian (a heat resistant polymer) for example.[7] We have also used thick walled Pyrex tubing sealed with a ROTAFLO valve to carry out microwave irradiations of liquids absorbed on solid supports.

Temperatures inside the sealed bombs may be measured in a variety of ways. The most convenient (but by far the most expensive) method uses a fiber optic thermocouple (Luxtron); these fiber optic thermocouples are also rather fragile. Alternatively, a fiber optic probe inside a glass support tube has been placed 1.5 mm from the sample tube coated with a phosphor paint at the point at which the temperature measurement was desired.[13] The cheapest (but most inconvenient and tedious) way of measuring the *approximate* internal temperature is by placing the number of solids of known melting points in sealed mp tubes inside the solution and determining which compound has melted and which has not. It is essential to carry out numerous runs for *each* oven, *each* power setting, *each* irradiation time, *each* total volume of bottle or tube, *each* reaction mixture and *each* volume of reaction mixture.[14] In our modified CEM-MDS-81D oven, internal temperatures are measured *and controlled* by a gold-coated thermocouple inserted in a narrow quartz well which is immersed to an appreciable extent in the reaction solution, and connected to the external regulator. It

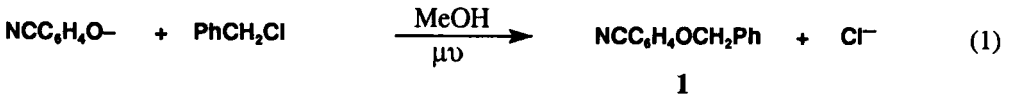
is essential that a sufficient length of the thermocouple be immersed in a solution *which absorbs microwave* (μv) *energy*, otherwise extremely erratic behavior will be observed and the thermocouple will be damaged. Recently, many reactions have been carried out in open Erlenmeyer flasks, or under reflux in modified microwave ovens. These will be discussed below.

Finally, it should be pointed out that the CEM Corp., as well as the CSIRO (in partnership with Industrial Microwave Applications of Australia) have developed continuous flow systems in which an external pump drives a solution through a coil placed within the microwave oven at a predetermined rate, and the product is collected outside the oven at the other end (for a home-made version of this, see Chen, Chiou, and Wang[15]). It should be emphasized that, for reactions carried out under pressure, suitable precautions should *always* be taken since reaction vessels have been known to explode in a few isolated instances.

If it is desired to carry out a reaction under pressure in solution in a non-polar solvent in which the solvent absorbs the *thermal* energy and then transmits it to the reactants, it has been recommended[7,14] that the Pyrex reaction vessel be embedded in vermiculite (hydrous silicates of iron, aluminum, and magnesium). The water of hydration absorbs microwave energy so that the vermiculite heats up very rapidly and then transmits the heat rapidly to the solution (*by conduction* i. e. from the outside in, as with conventional heating), so that much higher temperatures are reached much more rapidly than by using conventional heating methods. In these cases, of course, "localized superheating" in the reaction solution does not play any role and the observed increased rates are induced presumably by higher solution temperatures.

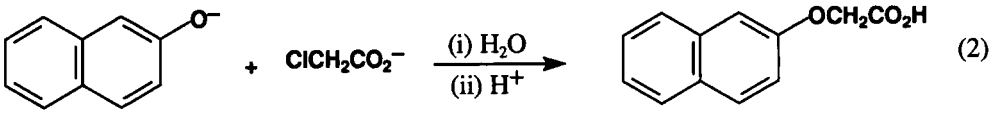
II. SYNTHESIS OF SMALL ORGANIC MOLECULES

As indicated above, the start of the explosion of activity in the application of microwave (μv) energy in organic synthesis was ignited in 1986 by a paper by Gedye, Smith, Westaway and their co-workers,[16] followed a few months later by the equally important paper by Giguere, Majetich and their co-workers.[14] Gedye and coworkers[16-17] reported rate increases of 113 to 1240-fold in a variety of reactions carried out in sealed Teflon vessels, as opposed to the same reactions carried out under reflux. These included: a) aqueous **acid-catalyzed hydrolysis** of benzamide to benzoic acid: (relative reaction times: reflux to microwave = 6); b) homogeneous (alc. NaOH) or heterogeneous (aq. NaOH) **hydrolysis** of isopropyl benzoate (2.5-3.0), methyl benzoate (24); c) **esterification** of benzoic acid: with MeOH (μ = 32.6) (96), with 1-propanol (μ = 20.1) (40), with 1-butanol (μ = 17.8)(8), with 1-pentanol (μ = 13.9)(1.3); d) **formation of benzophenone oxime** from benzophenone, hydroxylamine hydrochloride and pyridine in ethanol (60); **S_N2 etherification** of 4-cyanophenoxide ion with benzyl chloride to give **1** (240-1240, depending on the *size* of the Teflon vessel: the smaller the size - and therefore the higher the pressure, and hence the higher the temperature for the same amount of reactants and solvent - the higher the rate) and of sodium



1

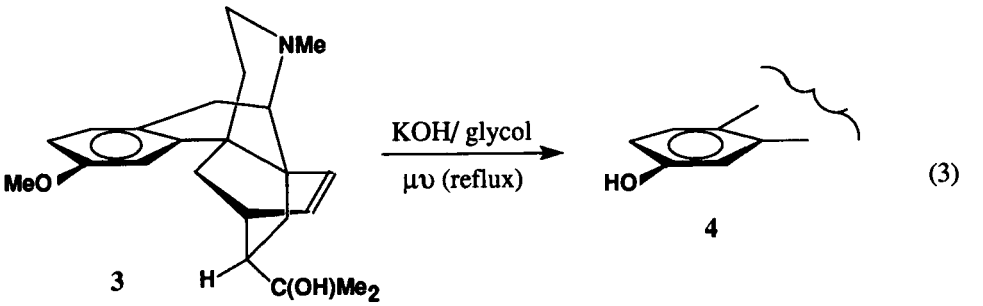
2-naphthoxide with sodium chloroacetate in water to give 2-naphthoxyacetic acid (**2**) (30).



2

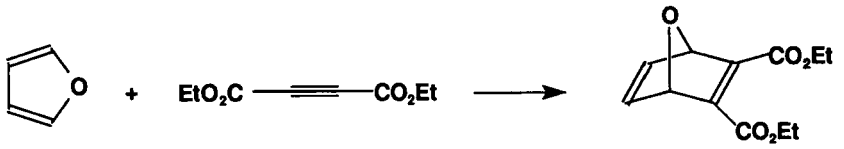
Similar results have been achieved (except on a much larger scale) by carrying out the esterifications and the S_N2 reaction of phenoxide with benzyl chloride in a kitchen microwave oven using a continuous flow system: external pump, fraction collector and internal reaction coil made of Teflon tubing (capacity ca. 10 ml).[15] Results virtually identical with those obtained in a closed vessel were realized. The **aqueous permanganate oxidation of toluene** to benzoic acid also appeared to proceed faster but these experiments had to be stopped before complete reaction because excessive pressures (explosions) developed in the Teflon vessels. It might be possible to carry out these reactions in the CEM oven with automatic pressure control (if the high pressure is not the result of an uncontrollable chain reaction).

An example of an **aryl alkyl ether cleavage** to the corresponding phenol using microwave radiation has been reported.[18] Attempted demethylation of **3** using BBr_3 gave a complex mixture, but using KOH in glycol and a small amount of water *under reflux* in a microwave oven modified for this purpose gave the desired phenol **4** (63%):



3 **4**

Diels-Alder reactions proceed much more rapidly using microwave heating.[14] Thus, the reaction of anthracene with maleic anhydride in *p*-xylene give the adduct (92%) in 3 min (internal temp. 160° < 187°), as compared to a 90% yield in 10 min under control conditions (138°). More spectacular results were obtained in the addition of anthracene with dimethyl fumarate in *p*-xylene (μv, 10 min, 87%, 325° < 361°; control, 4 hrs, 67%, 138°), and with furan (**5**) and diethyl acetylene dicarboxylate (neat) to give **6** (μv, 10 min, 66%, 325° < 361°; control, 4 hrs, 68%, 100°) since furan is known to be rather temperature sensitive.



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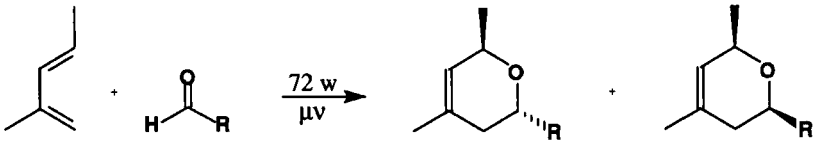
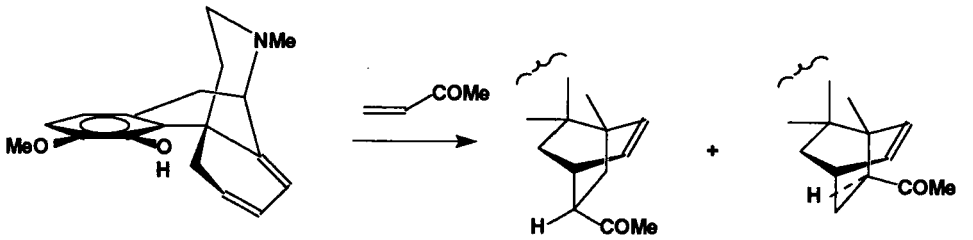
The [4+2] cycloaddition of glyoxal derivatives to 2-methyl-1,3-pentadiene using 72 w of microwave power takes place faster than under control conditions.[19a]



(82-96%) (5)

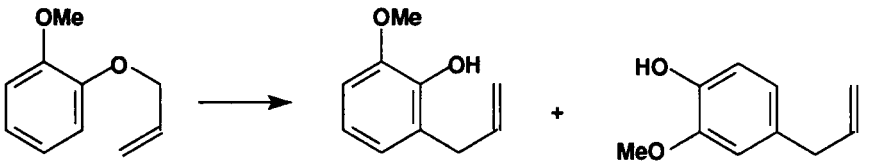
R = $CH(OMe)_2$, CO_2Me

It is appropriate at this point to mention a remarkable observation, namely that when 6-demethoxy-β-dihydrothebaine (**7**) was boiled under reflux for 60 hrs with a large excess of methyl vinyl ketone, it gave a mixture of **8** and **9** (in a 3:2 ratio), but extensive polymerization of the dienophile occurred which made work-up and product isolation difficult.[19b] On the other hand, when the cycloaddition was carried out *under reflux at atmospheric pressure* in a modified microwave oven, the reaction was complete within 24 hrs with substantially less formation of polymeric material and the products (**8**: **9** = 2.2:1) could be isolated and purified easily.[18] Since the reaction temperature of the bulk medium in both cases must be similar, this result speaks for the "localized superheating" concept of microwave action.



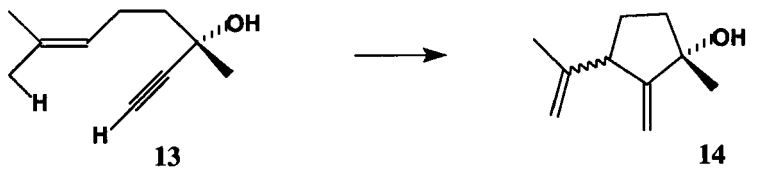
7 8 9 (6)

Claisen rearrangements also proceed somewhat faster under microwave irradiation (sealed tubes surrounded by vermiculite). For example, allyl ether **10** rearranged to the *ortho* (**11**) and *para* products (**12**) in 12 min at 370° < 400° in 71% yield, compared with a 71% yield at 265° under conventional heating (but 92% yield in 12 min at 320°), whereas the rearrangement in *N*-methylformamide solution at 276° < 300° gave an 87% of product in 90 sec.[14] An **"ene" reaction** was greatly improved by microwave heating: **13** gave **14** in 15 min (neat, 62%, 400° < 425°) as



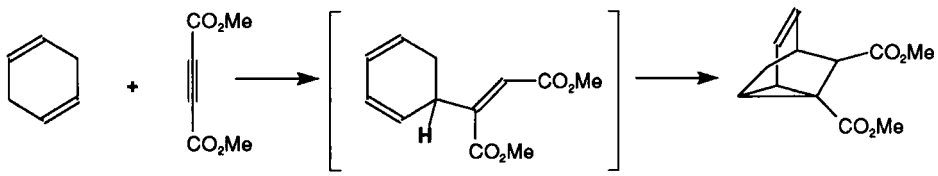
10 11 12 (7)

compared with 12 hrs (neat, 60%, 180°) for the control reaction.[14] This was then extended to tandem "ene"/intramolecular Diels-Alder reactions[20] of 1, 4-cyclohexadiene and mono- or di-activated acetylenes. The di-activated acetylene reactions proceeded faster and in higher yields under



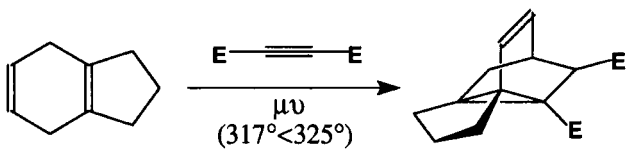
13 14 (8)

microwave conditions than under control conditions but the mono-activated ones, while reacting faster than under control conditions, did not give as good a yield when $ZnCl_2$ was added as a catalyst.



(9)

Bicyclic dienes reacted well with dimethyl acetylenedicarboxylate under microwave conditions (sealed tube in vermiculite, no solvent) e. g. 15 to 16.[20] In all cases, a large excess (10-15 fold) of "ene" over enophile had to be used.

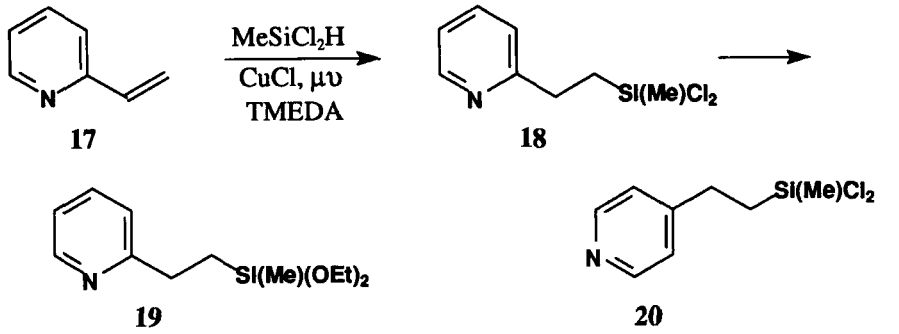


15 16 (10)

The stereochemistry of an intramolecular Diels-Alder reaction to yield a mixture of octahydronaphthalenes has been shown to be the same whether carried out under conventional or microwave (vermiculite insulated) heating.[7,21] Hence, there is either no *direct* coupling of microwave energy with the triene substrate, or such interaction affects all the relative transition states equally.

Hydrosilylation of alkenes proceeds very conveniently under pressure in a microwave

oven.[22] The hydrosilyation of 2-vinylpyridine (**17**) with methyldichlorosilane and CuCl in the presence of TMEDA (18 hrs at 180°) (with or without Et_3N) is, as reported,[23] a very dirty reaction whose extremely tedious workup produces a very low yield (5%) of product **18** (shorter reaction times lead to lower yields). The same reaction in a Parr 23 ml microwave digestion bomb in a kitchen microwave oven (750 w) (six 30 sec bursts of energy at full power, separated by 30 min cooling down periods), followed by work-up and isolation of the product as the diethoxysilane derivative **19** (75%) was very facile. This represents a 360-fold decrease in reaction time and a considerable improvement in yield and work-up. 4-Vinylpyridine gave **20** (71%) (μv, 10 min), as opposed to a 50% yield after 16 hrs of conventional heating.[24]



17 **18** **19** **20** (11)

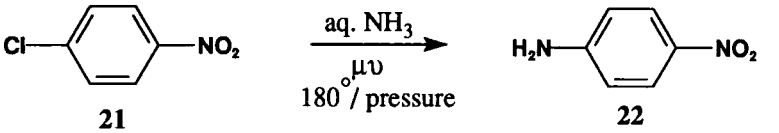
Cyclizations of 1,4-butanediol to tetrahydrofuran and of diethylene glycol to dioxane occur with the same efficiency either in a closed vessel or during continuous flow in a microwave oven;[15] similarly, the hydrolysis of sucrose to glucose and fructose (using an acid cation-exchange resin), and the racemization of L-amino acids in acetic acid are much more efficient under these conditions.

The **hydrolysis of proteins** proceeds very rapidly and quantitatively in a sealed Teflon vessel in the microwave oven; this permits rapid amino acid analysis. Hydrolysis of insulin B and oxidized ribonuclease A with 6N HCl or 1:1 propionic acid - 12N HCl took place in 3-7 min with microwave heating (>150°) compared with 24 hrs at 110° under conventional conditions and gave almost identical amounts of the individual amino acids.[25] A 72 hrs hydrolysis time is needed to ensure complete hydrolysis of peptide bonds, adjacent to some hydrophobic amino acids such as valine or isoleucine under normal heating conditions. Subsequently, the procedure was modified and 4M methanesulfonic acid was used, and a reusable Pyrex hydrolysis tube (4 mm I.D) with PTFE cap containing three sealing O-rings to ensure leak-free operation during high-temperature heating was employed.[26] N-*t*-BOC amino acids attached to Merrifield solid phase resins can be hydrolyzed in a microwave oven using propionic acid - 12M HCl (1:1, v/v) for 7 min at 70% power (ca. 180°) (Teflon bombs) 2-5 times faster than by using conventional heating.[27]

Polypeptide synthesis has also been achieved using microwave energy. Amino acid amides, e.g. a mixture of glycinamide, alaninamide, valinamide, and aspartic acid α-amide produced polypeptides (MW 1000-4000) on microwave heating during repeated hydration-dehydration cycles. Amino acids were incorporated in proportion to their starting concentrations, except that glycinamide

reacted 1.5 times faster. The polypeptides had definite secondary structures: α-helix and β-sheet in aqueous solution.[28] Examples of polymerizations leading to macromolecules are discussed below.

A number of simple organic reactions of industrial importance have been carried out under the influence of microwave irradiation in sealed vessels.[22] For example, sulfonation of naphthalene and anthraquinone and amination of *p*-chloroaniline (**21**) have been studied. Reaction of **21** with aq. ammonia[29a] takes place in a Teflon bomb (microwave), but at the high (180°) internal temperatures and pressures necessary the Teflon is gradually destroyed and begins to leak.[22] In thick-walled Pyrex tubes irradiation at low power (2 - 2.5 min, followed by a cooling period - process repeated 15-20 times) led to occasional violent explosions. A variety of catalysts were tried and the only one found to be useful was Cu_2O. Using it, the reaction proceeded faster and more safely, and a 93% yield of product (**22**) could be obtained after a total heating time of 1 hr, compared with a 95% yield reported[29a] after 10 hrs of conventional heating (a ten-fold decrease in reaction time). Clearly, however, this procedure is not a practical one and the technology of heating and temperature (or pressure) control in sealed glass vessels will have to be developed if it is to become so.

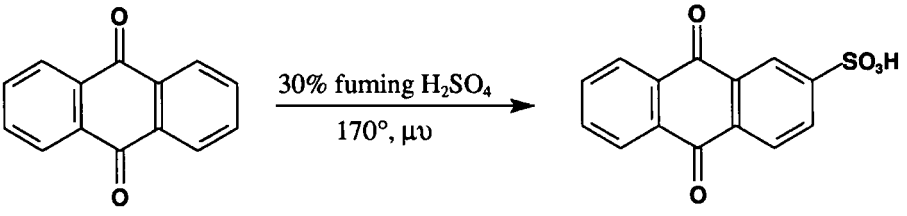


21 **22** (12)

The synthesis of the industrially important naphthalenesulfonic acids with conc. H_2SO_4 takes place in good yields at 163° for 4 hrs.[30] Using conventional microwave bombs, temperature control was difficult, and pressure control (as in the CEM Corp. model MDS-81D microwave oven) could not be used, since conc. H_2SO_4 has a negligible vapor pressure at the temperatures used. Sulfonation of anthraquinone with fuming sulfuric acid (18% SO_3 at 135° for 3 hrs and then 66% SO_3 at 110° for 4 hrs) takes place conventionally and gives a 49% yield of anthraquinone-2-sulfonic acid.[29b] In principle, pressure control of microwave power should be possible in this case. Unfortunately, the SO_3 is consumed as the reaction proceeds, the pressure drops, and the internal temperature rises so as to restore the set pressure, and disulfonation now predominates. These problems can be overcome using a modified CEM-MDS-81D microwave oven with both internal pressure and temperature controllers, and with some stirring capability (see earlier section on "Equipment"). Thus, when the desired internal temperature is reached the power is cut off. Using such equipment sulfonations could be effected very efficiently. Naphthalene and 98% H_2SO_4 at 160° (3 min) gave a 93% yield of sulfonic acids (β-:α- = 87.7: 4.7). Anthraquinone-2-sulfonic acid (**24**) was formed (54%) from anthraquinone (**23**) and 30% fuming H_2SO_4 in 6 min at 170°.

Cyclohexanone phenylhydrazone gives good yields of tetrahydrocarbazole on heating in acid and piperidine-2,3-dione 3-*p*-nitrophenylhydrazone gives the corresponding 1-oxo-1,2,3,4-tetrahydro-β-carboline in formic acid, both in a Teflon bomb under microwave irradiation for 1-2 min.[31]

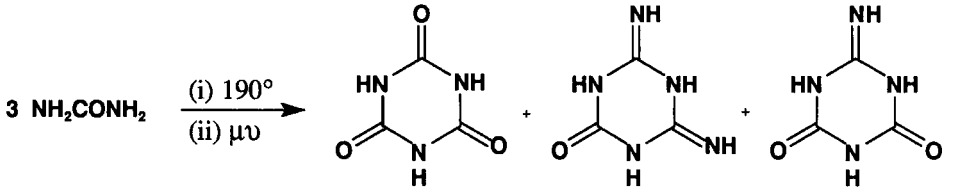
A few examples of microwave-induced reactions in open vessels, i.e. not under pressure, have been mentioned above. Many new examples have been reported in the last two years and the



(13)

23 **24**

technique is becoming quite popular. An early example was the synthesis of cyanuric acid (**25**) from urea.[32] Thus, urea was heated until turbid at 190° and then placed in a microwave oven (household, 750 w) for 6.5 min to give a product mixture (78-87%) containing 65% of **25** and 35% of a mixture of ammelin (**26**) and ammelide (**27**).

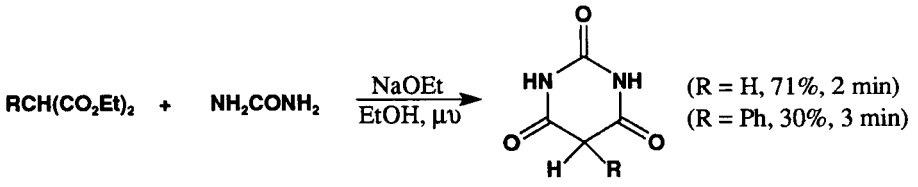


(14)

25 **26** **27**

A number of heterocycles have been synthesized in solution, often in ordinary open Erlenmeyer flasks.[33] Thus, *N*-phthaloylation of α-amino acids was effected using phthalic anhydride, the amino acid and Et_3N in dimethylformamide solution in a micro reaction vial with a septum cap. Heating in a microwave oven for 1-8 min (depending on the scale of the reaction - up to 200 g could be used, in which case an Erlenmeyer flask covered with a watch glass was used) at low power gave the *N*-phthalimido derivative in high yield. That no conventional thermolysis was involved was established by placing the reaction vial in a beaker of water, the water was frozen and the tube encased in the block of ice was irradiated for 3 min in the microwave oven, after which the outer surface of the ice had melted slightly. Formation of phthalimidoacetic acid took place in good yield.

Some reactions described in **Organic Syntheses** were duplicated in a microwave oven; in



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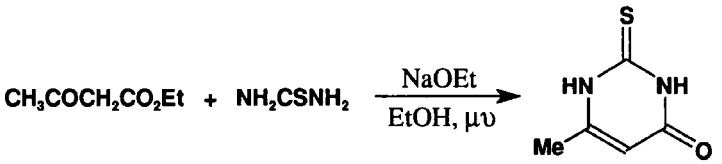
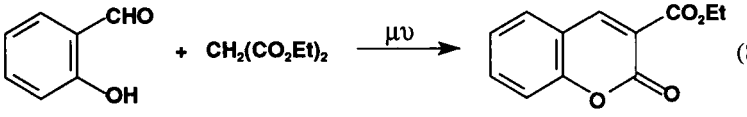


(16)

29

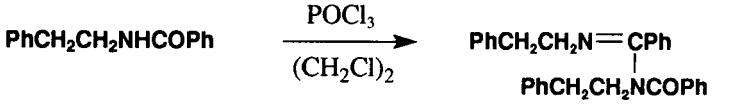
each case, the reaction was highly accelerated and the yields and purity were comparable.[32] The reactions reported included the synthesis of barbituric acid derivatives (**28**), the reaction of ethyl acetoacetate with thiourea to give 2-thio-6-methyluracil (**29**), the synthesis of benzimidazole from *o*-phenylenediamine and formic acid and the Knoevenagel-type condensation of ethyl malonate and salicylaldehyde in the absence of solvent to give ethyl coumarin-3-carboxylate (**30**). When *N*-benzoyl-2-phenethylamine and $POCl_3$ in DMF were heated in a microwave oven, no Bischler-



(82%, 3 min) (17)

30

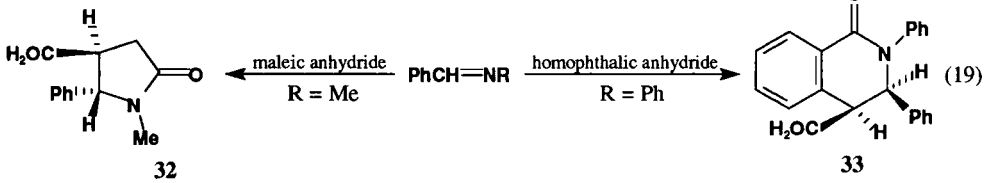
Napieralski product was isolated and only intractable tars were formed. When the solvent was changed to 1,2-dichloroethane, amidine **31** was obtained in near quantitative yield.[33b] Heating



(18)

31

succinic anhydride and *N*-methybenzaldimine in DMF in a microwave oven for 5 min gave **32** (*trans*-isomer only; 59% yield). The same reaction carried out in refluxing benzene for 36 hrs gave **32** (major product), together with the *cis*-isomer (83% overall yield).[34] Homophthalic anhydride and benzylideneaniline afforded tetrahydroisoquinoline **33** (3 min, 67%, mn); (15 min, 40%, Δ [35b]).[33b]



(19)

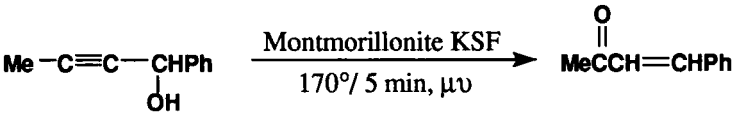
32 **33**

The improvements of a Diels-Alder reaction carried out under reflux in a microwave oven and in the cleavage of an aryl ether have been mentioned above already,[18] as have reactions carried out under flow conditions.[15] Under microwave irradiation, sulfonation of naphthalene with conc. H_2SO_4 can be carried out as readily and as well in an Erlenmeyer flask as in a sealed bomb.[36]

Microwave heating techniques for "dry" organic reactions have been developed very recently, mainly by Villemin and his coworkers,[37] and by Mingos and his coworkers (the latter work will be discussed below in the Synthesis of Organometallic and Related Compounds Section).

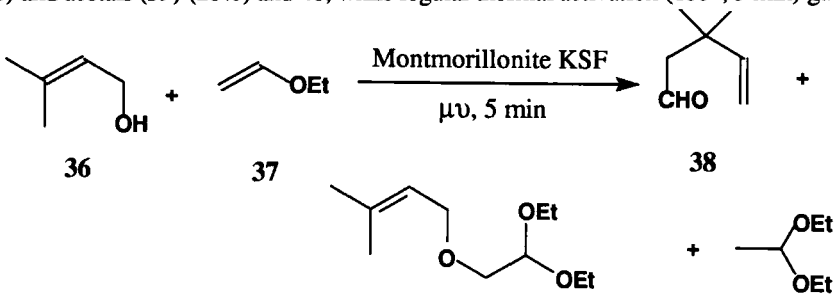
Inorganic oxides (alumina, silica) do not absorb microwaves at 2450 MHz and, therefore, do not hinder their transmission. In "dry" organic reactions, hydroxyl groups, water, fluoride ions and organic compounds present on the surface of these oxides do absorb microwaves and are activated by them. Acidic clays - montmorillonite K10 or KSF - have also been shown to be very useful in such "dry" organic reactions.

Thus, 1-phenyl-2-butynol (**34**) absorbed on montmorillonite KSF had not reacted after 2 days at room temperature. Irradiation with microwaves (270 w) for 5 min (170°) in a sealed Teflon vessel gave the rearranged α, β-unsaturated ketone (**35**) in 92% yield. On the other hand, conventional heating of the adsorbed **34** at 170° for 5 min gave < 2 % of **35**. Other acetylenic



34 **35** (20)

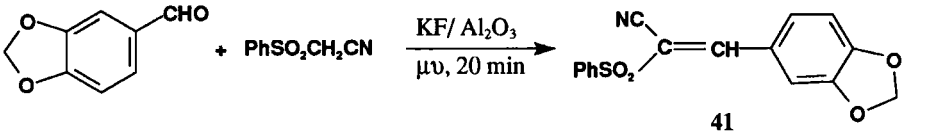
alcohols behaved similarly.[37] The pinacol rearrangement of 1,2-diphenylethyleneglycol to diphenylacetaldehyde (98%) was also facile,[37] as was that of pinacol to pinacolone.[38] A combination of acid-catalysis, surface activation of a [3,3]-sigmatropic shift[39] and microwave activation of a mixture of **36** and ethyl vinyl ether (**37**) (2 equiv.) on KSF (μν, 160 w, 5 min) gave 3,3-dimethyl-4-pentenal (**38**) (75%) and acetals (**39**) (20%) and **40**, while regular thermal activation (135°, 5 min) gave no **38**.



36 **37** **38** (21)

39 **40**

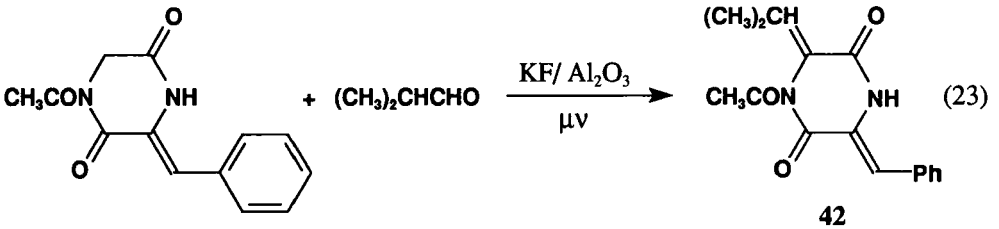
Aldol-type condensations could also be carried out efficiently using potassium fluoride on alumina in microwave-induced reactions. Thus, while piperonal and benzenesulfonylacetonitrile on KF/alumina at room temperature gave a poor yield of condensation product **41**, microwave irradiation (55 w, 20 min) of the mixture gave a 95% yield of **41**.[37,40] Other examples of aldol-type



41 (22)

condensations include those of 1,4-diacetylpiperazine-2,5-dione with aldehydes on $KF/Al_2O_3/\mu\nu$ to give albonursin (**42**) and analogues *via* the 1-acetyl derivatives, of tetronic acid with aldehydes to give 3-(arylmethylene)-2,4-(3H,5H)-furandiones[41] and of 3-methyl-1-phenylpyrazol-5-one with

aldehydes on montmorillonite KSF/μv to give **43**.[42] Barbituric acid condensed similarly with



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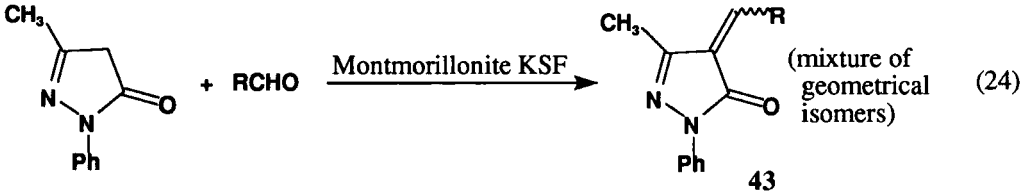
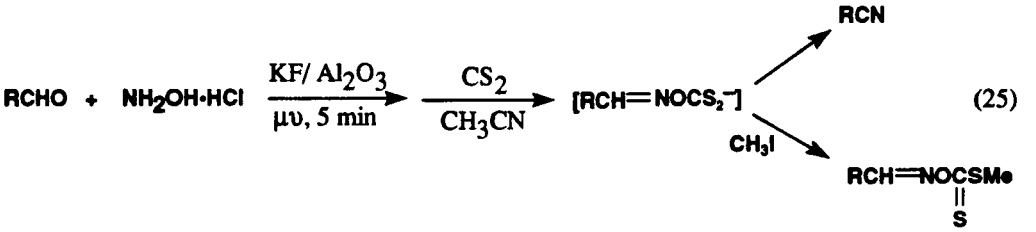


43 (24)

aldehydes,[43] as did rhodamine and anthrone.[37] Microwave irradiation on KF/Al_2O_3 has also been used to convert aldehydes to the corresponding nitriles in 52-89% yield. In this procedure, the aldehyde was treated with hydroxylamine hydrochloride, then KF/Al_2O_3 was added and the solvent evaporated; the residue was then irradiated with 350 w of microwave energy for 5 min, after which CS_2 in acetonitrile was added and the mixture kept at room temperature for 16-48 hrs. Work-up gave the desired nitrile.[44]



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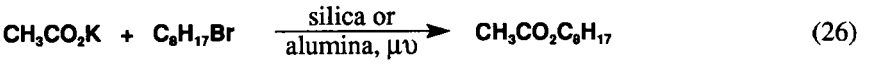
S_N2 substitution (reaction of potassium acetate with 1-bromooctane) to give the ester **44** has also been carried out on silica or alumina without solvent ("dry media" reactions) by microwave

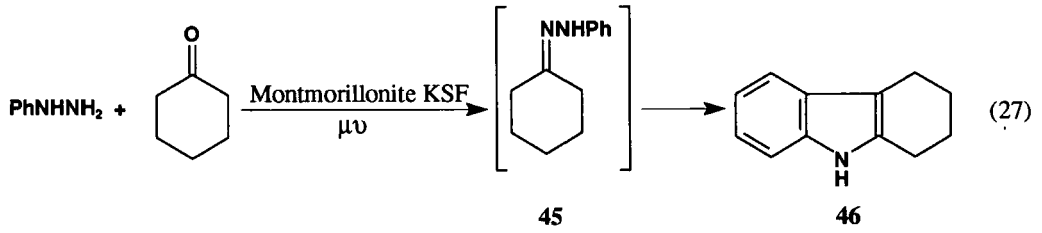


44 (26)

irradiation, with appreciable time savings. Thus, when potassium acetate was heated conventionally (100°) with 1-bromooctane and alumina for 5 hrs a 93% yield of **44** was obtained. The same reaction in an open Pyrex flask with microwave irradiation (600 w) gave a 91% yield of **44** in 10 min. When silica was used as the support instead of alumina the corresponding results were: 70% (100°, 5 hrs); 82 ± 12% (600 w, 10 min).[38] Combined use of microwave irradiation and of solid-liquid phase transfer

catalysis without solvent lead to great improvements in S_N2 reactions.[45] Thus, alkylation of 1-bromooctane with CH_3CO_2K in the presence of Aliquat 336 in the absence of solvent (μv, 600 w, 1-2 min) lead to a 98% yield of **44**. The final temperature reached was 176-187° (depending on the scale (10-500 mmol of bromide) used in the reaction). Other halides (octyl chloride, iodide, hexadecyl bromide, chloride) gave similar results. Conventional heating for 2-6 hrs at 60-85° gave comparable yields, so that the rate enhancements observed seem to be due to the high temperatures achieved very rapidly on microwave irradiation. Dehydration of its hydroxylated precursor on silica gel by irradiation with microwaves gave an 83% of dihydroaclinidiolide.[46]

A one-pot synthesis of indoles (Fischer cyclization) catalyzed by montmorillonite KSF on microwave irradiation was achieved.[47] Thus, irradiation of a mixture of phenylhydrazine, a ketone, and montmorillonite KSF in an open Pyrex flask in a commercial microwave oven (160 w, 5 min) afford the corresponding indole. Heating preformed **45** in acetic acid in a Parr bomb for 2 min

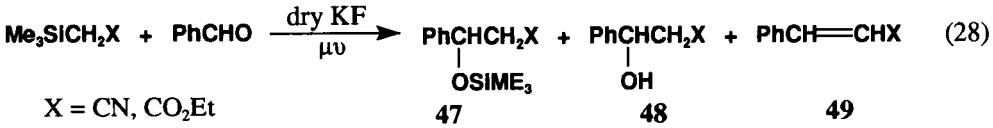


(27)

45 **46**

similarly gave **46** in high yield.[31] This latter method might be useful in those cases in which the phenylhydrazones can only be made *via* the Japp-Klingemann reaction and not from the ketones and arylhydrazines.

A Reformatsky-type reaction (silyl-Reformatsky) can be carried out conveniently by condensation of trimethylsilylacetonitrile or ethyl trimethylsilyacetate with benzaldehyde in the presence of dried KF on microwave irradiation (with or without a solid support - Al_2O, MgO or a K10 clay). Depending on the exact reaction conditions,[48] either **47**, **48**, or **49** (or mixtures) can be obtained.



(28)

III. POLYMER SYNTHESIS

As indicated in the Introduction, emulsion polymerization of acrylates was probably the first recorded application of microwave energy in organic synthesis.[1] Since then, many examples of the use of microwave irradiation in synthetic polymer chemistry have been recorded. Thus, wood-plastic composites were manufactured by using microwave (2450 and 915 MHz) irradiation.[49]

Conversions for styrene as well as for methacrylates were quite high (51.8-89.1%), but low (4.3-8.2%) for vinyl acetate.

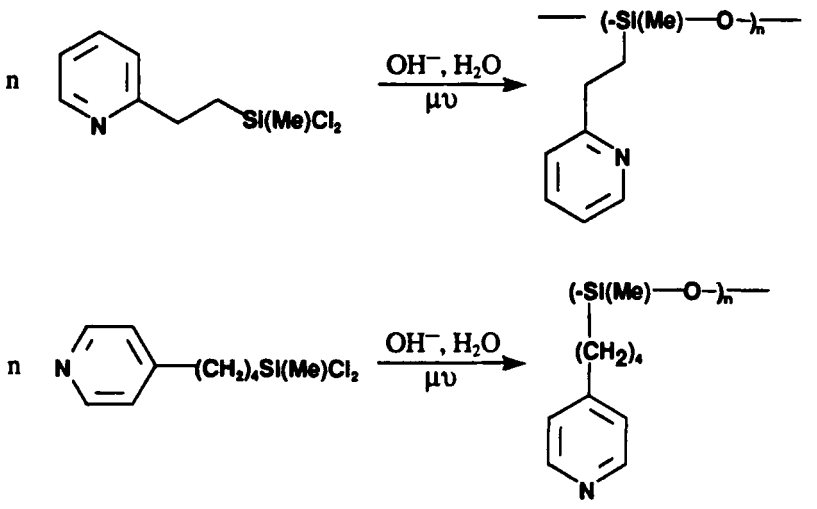
Cross-linking of polyolefins by microwave irradiation has been reported,[50] and adhesion of molded polyethylene using polyethylene gels by microwave heating has been described.[51] Polyimide foams have been prepared by microwave irradiation,[52a] and their cure kinetics studied.[52b] A polarized microwave beam (2450 MHz) has been used to polymerize 2-hydroxyethyl methacrylate in bulk in absence of any radical initiator,[53] and this report followed earlier communications on the step-growth polymerization of epoxy resins,[54,55] and of radical polymerization of unsaturated polyesters/styrene mixtures.[54,56] More detailed studies of curing of epoxy resins under the influence of continuous or pulsed microwaves have appeared subsequently.[57,58] It was shown that the discontinuous process is more efficient than the continuous one in effecting the step-growth polymerization, but that the final polymers had very similar chemical structures. Indeed, microwave polymerization of epoxy resins has been used as a rapid processing technique in ultrastructural pathology for fixing specimens (60 sec rather than 24 hrs conventionally).[59]

The synthesis[60] and curing[61] of polyurethanes using microwaves, as well as polyethertriol prepolymers[60] have been described. Comparison studies have been carried out on the microwave polymerization of denture base acrylic resins and the conventional water bath curing systems. Resins cured by microwave irradiation for 3-8 min showed better physical properties than conventional heat-cured ones and were suitable for clinical applications.[62] On the other hand, another study[63] reported that while MW values using microwave and water-bath heating were essentially the same, minimal residual monomer levels attainable with the water-bath system were not achieved using microwave because of porosity problems. These authors, unlike the Japanese workers, concluded that microwave curing offered no advantage in time saving over rapid water curing systems. The positive features of curing acrylic resins (by microwave) for denture bases have been reviewed.[64]

The application of microwave heating to the bonding of wood,[65a] to the curing of synthetic resin impregnated wood,[65b] and to wood adhesives using acid-catalyzed vinyl polymerization to which were added thermosets such as phenol-formaldehyde or urea-formaldehyde resins (which lead to improvement of bonding quickly on the edge joint)[66] have been described; the start up of a large scale plant in the US based on such technology has recently been announced in the popular press.

The manufacture of ladder siloxanes by microwave irradiation has been patented.[66] Siloxane oligomer from $PhSiCl_3$ was mixed with KOH, biphenyl ether and biphenyl and irradiated to give ladder silsesquioxanes having $\underline{M}_N$ 45,000 and polydispersity 2.5. We have polymerized a number of dichloro(methyl)pyridylalkylsilanes either with NH_4OH or with KOH in a microwave oven, and the resulting polymers were then end-capped:[67]

Finally, the microwave-vulcanization of rubber should be mentioned. Rubbers containing vulcanizers and accelerators are mixed with 5-25% powdered spinel-type ferrite (Ni-Zn-ferrite) and irradiated (2450 MHz) to be hot-vulcanized in a short period of time.[68] If the ferrite is omitted, the



(29)

temperature rise is slow as expected.

IV. BIOMASS CONVERSION AND WASTE TREATMENT

Much work has been carried out on the effect of microwave irradiation upon enzymic degradation of lignocellulosic material[69] and the solvatopulping of wood. This latter subject will be reviewed in a forthcoming publication. The conversion of *Euphorbria lathyris* to fuels by pyrolysis at 1060°K has been carried out by fluidized bed microwave heating of the biomass.[71]

Microwave energy has also been used in recycling and in disposing of organic wastes. Thus, disposal of livestock wastes by carbonization to the crude activated carbon of livestock excrement by microwave irradiation,[72] regeneration of activated carbon[73a] and solidification of carbon-containing waste solids[73b] have been reported. Toxic chlorinated organic wastes can be safely and efficiently disposed of by irradiation of a mixture of these substances and a finely divided para- or ferromagnetic material (such as a fluidized bed of powdered iron).[74] Polychlorinated biphenyls in soil can be decomposed with moist sodium hydroxide by microwave irradiation in a Parr bomb for two minutes.[75]

A number of papers have appeared on coal desulfurization with molten caustics on microwave irradiation,[76a] and a patent has been granted for the microwave-induced hydrodesulfurization of hydrocracked pitch.[76]

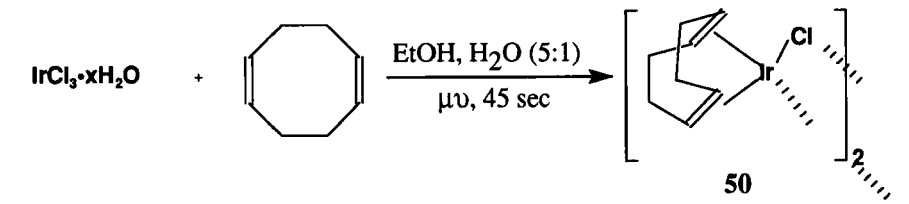
V. ORGANOMETALLIC AND RELATED COMPOUNDS

Microwave dielectric loss heating has recently been applied to inorganic synthesis[77] (including superconducting ceramics[78]) and then to the synthesis of organometallic[80,81] and

coordination compounds[82,83] by Mingos and his co-workers at Oxford.

Intercalation compounds of α-$VO(PO_4)$•$2H_2O$ with pyridine, 4-methylpyridine, and 4-phenylpyridine were synthesized two orders of magnitude more quickly (and more efficiently) using microwave compared to conventional thermal energy methods, and the samples retained a high degree of crystallinity (again in contrast to conventional heating methods).[79] For example, heating α-$VO(PO_4)$•$2H_2O$ and 4-methylpyridine (in xylene) in a Parr Teflon bomb for 3 min (max. temp. 200°) in a microwave oven gave $VO(PO_4)$•$4Mepy_{0.86}$, compared with a product $VO(PO_4)$•$4Mepy_{0.60}$ when the reaction was carried out in a sealed glass ampule in a conventional oven (12 hrs/140°). The $VOPO_4$•$2H_2O$ was shown not to absorb microwaves strongly, but the intercalated product and the pyridine and substituted pyridine solutions showed rapid heating when exposed to microwaves. Thus, it is the pyridines which are heated rapidly initially, but in later stages of the reaction autocatalytic effects associated with the absorption of microwaves by the intercalated compounds may play a role. There would be no analogous autocatalytic effect in conventional heating processes.

Diolefin-rhodium (I) and -iridium (I) complexes could be obtained in excellent yields in less than 1 min compared with many hours by conventional reflux techniques.[81] For example, heating $IrCl_3$• xH_2O with 1,5-cyclooctadiene gave $[Ir(C_8H_{12})Cl]_2$ (**50**) in 72% yield.



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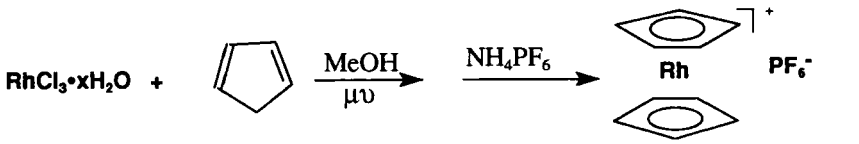
50

$RhCl_3$• xH_2O gave the corresponding product with octadiene (50 sec, 91%) and norbornadiene (35 sec, 68%), and $[Ru(\eta\text{-}C_6H_6)Cl_2)_2]$ was obtained (89%) from $RuCl_3$•xH_2O and 1,3-cyclohexadiene in aqueous ethanol (35 sec). Conventional reactions take 4-36 hrs to complete.

Interestingly, cyclopentadiene reacted with $RhCl_3$•xH_2O under microwave irradiation to give the sandwich cation $[Rh(\eta\text{-}C_6H_5)_2]^+$ [isolated as the PF_6^- salt **51** (62% yield)], rather than the chloro-bridged dimer:



(31)

51

Using conventional techniques the synthesis of **51** had only been previously possible by employing the Grignard reagent C_5H_5MgBr.[84] On the other hand, with cyclooctene and cyclooctatetraene the complexes were not isolated and rhodium metal was formed as a major product, probably owing to

the olefin complex not being stable under the reaction conditions.[81]

The synthesis of related organometallic compounds has also been achieved[80] in a commercial microwave oven so modified that solutions could be heated under reflux in it, the reflux condenser being outside the oven and connected to the reaction flask *via* a tube passing through the oven wall. (It is necessary, however, that the connecting glass tube pass through an earthed copper tube bolted to the outside of the microwave oven. These copper "chokes" prevent efficiently any microwaves from leaking outside the oven.) In this way, reactions could be carried out in solution under reflux (see also the earlier work on Diels-Alder reactions using the same technique - ref. 19b) using 250-350 w of microwave power. The reactions were slower than those carried out in a sealed Teflon vessel (higher temperatures achieved in the latter) but frequently much faster than those achieved with conventional heating techniques, which, once again, speaks in favor of the localized superheating effect under microwave irradiation. For example, the above mentioned reaction of cyclohexadiene with $RuCl_3 \cdot xH_2O$ in EtOH took less than 1 min in a sealed vessel (95% yield),[81] 30 min under reflux (85% yield),[80] and 4 hrs under conventional reflux conditions. In each case, the same product, $[Ru(\eta\text{-}C_6H_6)Cl_2]_2$ was obtained. In this manner, $RuCl_2(PPh_3)_3$ could be prepared (85%) from $RuCl_3 \cdot xH_2O$ and PPh_3 in MeOH, $[RuCl_2(\eta\text{-cymene})]_2$ (67%) from reaction with α-phellandrene, $[RhCl(cod)]_2$ (87%) from $RhCl_3 \cdot xH_2O$ and cyclooctadiene in aq. EtOH, and $[ReOCl_3(PPh_3)_2]$ (94%) from $KReO_4$ and Ph_3P in aq. EtOH.

The preparation of metallated aromatic rings by ligand redistribution reactions and reactions with metal alkoxides proceeded much faster when microwave dielectric loss heating, rather than conventional heating was used,[85] but the yields were of the same order as shown below.

$$Ph_3BI + 3\,BICl_3 \underset{1\text{-propanol}}{\overset{6\text{ min, }\mu\upsilon}{\rightleftharpoons}} 3\,PhBICl_2\ (46\%) \qquad (32)$$

Coordination compounds have been made in a sealed Teflon container using 2450 MHz microwaves (500-650 w).[82] For example, the ruthenium crown thioether complex $[Ru(9S3)_2]\,(PF_6)_2$ cannot be made directly from $RuCl_3 \cdot xH_2O$ under conventional reflux conditions,[85] but the latter reagent has to be first converted to the labile $Ru(SO_3CF_3)_3$ or $[Ru(DMSO)_6]^{2+}$. Using microwave energy the complex could be made (49%) directly from $RuCl_3 \cdot xH_2O$ after 6 x 25 sec. irradiation sequences. In another example $[Cr(DPM)_3]$ was prepared (70%) from $CrCl_3 \cdot 3H_2O$, urea and dipivaloylmethane in aqueous ethanol by 40 sec irradiation, compared to the 24 hrs required by conventional heating. $[PtCl(terpy)]Cl \cdot 3H_2O$ (from K_2PtCl_4 and terpy), $[AuCl(terpy)]Cl_2 \cdot 3H_2O$ (from $HAuCl_4$ and terpy), $[RuCl(CO)(bipy)_2]Cl$ (from $RuCl_3 \cdot xH_2O$ and bipy in DMF),[82] and ruthenium(II) polypyridine complexes[83] have all been prepared readily by microwave irradiation.

VI. PHARMACEUTICAL (BIOMEDICAL) APPLICATIONS

A number of biomedical applications of microwave energy such as the curing of acrylate denture base resins and the rapid curing of epoxy resins in fixing tissue sections, have already been alluded to.

The natural product (-)-vincadifformine has been racemized by microwave heating a DMF solution in a small sealed tube (the reaction involved a *retro*-Diels-Alder reaction to give the *seco*-derivative which then recyclizes to a mixture of enantiomers) for 20 min using 500 w of power.[87] The (+)-enantiomer is then used in the synthesis of biologically desirable (+)-vincamine.

It has been reported that microwave irradiation eliminates circadian rhythm in whole mouse brain serotonin but facilitates quantitation of bound and free serotonin.[88] It was suggested that the increased serotonin levels observed in microwaved brain could result from an increased amount of free vs. bound serotonin.

When 5-fluorouracil (5-FU) was incorporated in an implantable polymer such as a sustained release copolymer made from ethylene-vinyl alcohol (32 mol% of ethylene units) it was shown that the 5-FU was released into water in a slow continuous manner, but that when the polymer was irradiated with microwave energy (100-200 w) the rate of 5-FU release increased dramatically. The release rate returned to the baseline level when the microwave irradiation was discontinued. This increase in release rate was attributed to a temperature rise from 37° to slightly over 45° in the polymer matrix (thus, presumably, increasing its porosity), while the temperature of the stirred bulk water in which it was immersed remained relatively constant.[89] It was pointed out[89] that the application of microwave irradiation in humans, both for diagnostic and therapeutic purposes, has been extensively studied and is considered a safe practice. (*SEE HOWEVER, HEALTH WARNING, REF. 8b!).* Indeed, in cancer chemotherapy, microwave irradiation has been used to produce local hyperthermia,[90] so that such a localized microwave-controlled-release system could have potential use in such chemotherapy, with the possible additional effect of inducing hyperthermia.

Physical targeting of drug-administration by microwave irradiation has been proposed.[91] Thus, when a polymeric prodrug of the anticancer agent methotrexate coupled with biodegradable poly(hydroxypropyl)-L-glutamine (PHPG) was irradiated with 433 MHz microwaves its temperature rise was greater than that of neutral PHPG. Thus, localized drug administration induced by selective microwave irradiation, i.e. physical targeting, may be possible if the macromolecular prodrug in a polyelectrolyte system is utilized. (It was shown that polyelectrolytes showed large values of the relative dielectric loss factor (ε") and were easy to heat selectively by external microwave irradiation when injected in simulated muscle tissue).

Radiopharmaceuticals labelled with short-lived radionuclides need to be synthesized as rapidly as possible so that they may be used before their activity decays too much. This is particularly the case with ^{122}I ($t_{1/2}$ 3.6 min), ^{11}C ($t_{1/2}$ 20 min), and ^{18}F ($t_{1/2}$ 110 min) which emit positrons. The conventional and microwave heating methods have been compared for the

nucleophilic substitution of activated *p*-nitro- and *p*-fluorobenzenes with ^{18}F-fluoride, and exchange reactions of activated and deactivated haloarenes with ^{131}I-iodide.[92]

$$^{18}F^- + p\text{–}XC_6H_4\text{–}Y{=}Z \longrightarrow p\text{–}^{18}FC_6H_4\text{-}Y{=}Z + X^- \quad (33)$$

(X = NO_2, F)

The reactions were carried out in sealed 3ml Reacti-vials (Alltech Associates) in a commercial microwave oven (or in an aluminum heating block at 135° for conventional heating). No-carrier-added (NCA) ^{18}F-fluoride was produced by the ^{18}O(p,n) ^{18}F nuclear reaction on enriched ^{18}O-water in a cyclotron and was dissolved in DMSO in the presence of *t*-Bu_4NOH. In most cases, reactions proceeded in 5 min under microwave irradiation to the same extent as took 30 min on conventional heating when -Y=Z was an electron-withdrawing group. When it was electron-donating poor labelling yields resulted by both methods (as was to be expected). On the other hand, iodination with ^{131}I-iodide in 1mM NaOH catalyzed by CuCl (in DMSO) took place much faster under microwave irradiation conditions with both *p*-$IC_6H_4NO_2$ *and* *p*-IC_6H_4OMe *provided* the Reacti-vial was preheated in the microwave oven for 30 min. Isotopic exchange of ^{131}I-iodide then reached completion within 5 min (iodination yields exceeding 80% obtained within 1 min) showing that this technique should be useful for both ^{122}I as well as with the γ-emitting ^{123}I ($t_{1/2}$ 13.2 hrs). We suspect that the use of Cu_2O as the catalyst might lead to even better results (see ref. 22).

The potential for the introduction of ^{11}C in organic radio-pharmaceuticals was also examined. Thus, reductive amination of *N*-methylaniline with acetone gave a 64% yield of *N*-isopropyl-*N*-methylaniline (used in the synthesis of ^{11}C-pindolol[93]) within 90 sec using microwave heating, whereas a 67% yield of that product was obtained after conventional heating at 110° for 10 min. While an 8.5 min decrease in reaction time may appear trivial to the average organic chemist it would correspond to 25% less decay of the 20 min half-life compound.[92]

$$C_6H_5NHMe + CH_3COCH_3 \xrightarrow{[H]} C_6H_5N(Me)CHMe_2 \quad (34)$$

The most important large scale application of microwave energy in the pharmaceutical industry at present, however, is in drying pellets![94]

VII. C_1-TYPE CHEMISTRY

Some very interesting preliminary work for the functionalization of methane over suitable catalysts using continuous, but preferably pulsed, microwave energy has been reported.[95] In the latter technique, short duration pulses of microwave irradiation are focused on a surface or bed of solid catalyst which contains a ferromagnetic metal. The microwaves interact strongly with the surface

metal sites heating them to > 1400°. The organic substrate in the reactor is not heated directly by the microwaves but reacts when it comes in contact with the excited surface sites. Control of the surface temperature is achieved by gating the microwave pulses and unwanted side reactions can, in principle, be controlled by adjusting pressures and flow rates. The bulk of the reaction medium is at, or near, room temperature. The catalyst can also function by influencing the course of the reaction by the selectivity of its interaction with the organic substrate(s). In practice, the authors used a moderately high power (3 Kw) magnetron with pulsewidth gated for a few ms. Products were analyzed by gas chromatography.

The decomposition of methane occurs very rapidly over a variety of catalysts under microwave irradiation. Nickel catalysts were found to be the most efficient (e.g. Ni-1404 pellets, Ni powder, or Ni/silicon catalyst). Substantial conversions to CH_2=CH_2, CH_3CH_3 and CH≡CH occurred, with cooler, more controlled conditions, favoring higher proportions of ethylene. The following scheme was proposed to account for the products formed.[95] Evidence that methylene was

$$\begin{aligned} CH_4 &\longrightarrow :CH_2 + H_2 \\ 2\,CH_2 &\longrightarrow CH_2{=}CH_2 \\ 2\,CH_2 &\longrightarrow CH{\equiv}CH + H_2 \\ CH_2{=}CH_2 + H_2 &\longrightarrow C_2H_6 \\ C_2H_6 + :CH_2 &\longrightarrow CH_3CH_2CH_3 \end{aligned} \qquad (35)$$

the primary intermediate formed came from the formation of cyclopropane. The product mixture

$$:CH_2 + CH_2{=}CH_2 \longrightarrow \triangle \qquad (36)$$

formed in a microwave oven (continuous) reactor was much more complex than that formed in the waveguide pulsed reaction. Under the more vigorous conditions of the latter, benzene and toluene were also formed.

Oxidation of methane, propane, propylene, *n*-hexane and cyclohexane by microwave-induced catalytic reactions (Ni powder, Ni-1404, CuO, V_2O_5) with water (generation of OH and H from water adsorbed on the catalyst) gave alcohols, ketones, and ethers. Conversion efficiencies were low (ca. 5%), as were product selectivities, but these preliminary experiments showed that water could indeed be used as an oxidant in such systems.[95]

CONCLUSIONS

This review has provided a brief look at microwave methodology as applied to organic synthesis and reactions (broadly defined). In addition, some of the theories put forward to explain the observed rate enhancements were discussed. For reactions carried out in homogeneous solutions both

under pressure and under reflux, conflicting opinions have been expressed. Thus, hydrolysis of adenosine triphosphate in a sealed tube has been shown to proceed at the same rate when effected either by conventional or microwave heating.[13] The rate of the reaction of 1-propanol and acetic acid was no different when performed under microwave radiation compared to conventional heating.[96] On the other hand, marked rate accelerations by microwave irradiation have been noted repeatedly in this review over conventional heating. In some cases, this is caused by a very rapid rise in the temperature of the medium under microwave conditions, or a much higher temperature than is possible under conventional heating being reached rapidly under pressure vessel conditions. Yet, numerous cases have been documented of faster reactions under reflux conditions, and in these cases the localized superheating concept may be applicable. In some instances, dramatic rate enhancements are observed while in others there are none. It has been suggested[22] that if the microwave energy is absorbed by the solvent (e. g. H_2SO_4) and not by the substrate, only modest rate increases will result relative to those observed with conventional energy use. If, on the other hand, the microwave energy is absorbed selectively by a reactant (e. g. vinylpyridine or its copper complex, a reactant absorbed on a clay or a surface metal site) or by a complex or an intermediate on the way to the rate-determining transition state then large rate increases will result. This hypothesis requires testing.

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