Solvent-free organic syntheses

using supported reagents and microwave irradiation

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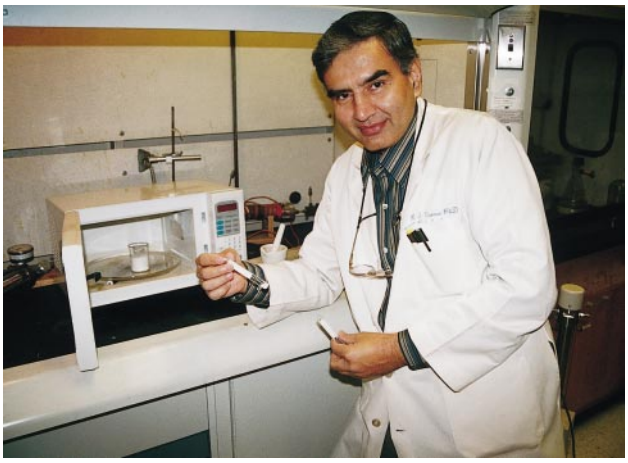
Summary

Recent developments in microwave-accelerated solventless organic syntheses are summarised. This expeditious and solvent-free approach involves the exposure of neat reactants to microwave (MW) irradiation in conjunction with the use of supported reagents or catalysts which are primarily of mineral origin. The salient features of these high yield protocols are the enhanced reaction rates, greater selectivity and the experimental ease of manipulation. Among other reagents recently described in the literature on this eco-friendly green approach, the use of recyclable mineral oxides or supported reagents from our laboratory such as $Fe(NO_3)_3$–clay (clayfen), $Cu(NO_3)_2$–clay (claycop), NH_4NO_3–clay (clayan), NH_2OH–clay, $PhI(OAc)_2$–alumina, $NaIO_4$–silica, CrO_3–alumina, MnO_2–silica, $NaBH_4$–clay, *etc*. are highlighted in MW-promoted deprotection, condensation, cyclization, rearrangement, oxidation and reduction reactions including the rapid one-pot assembly of heterocyclic compounds from *in situ* generated intermediates.



Raj Varma was born in India and obtained his Ph.D. from Delhi University in 1976. After postdoctoral research at Robert Robinson Laboratories, Liverpool, UK and Univ. of Tennessee, Knoxville, TN, USA, he was a faculty member at Baylor College of Medicine and Houston Advanced Research Center. Presently, he is Research Professor of Chemistry at Sam Houston State University, Huntsville, TX, USA, with an appointment at the Texas Research Institute for Environmental Studies. His research interests encompass natural product chemistry, new synthetic methods, bioelectronics and environmental sciences which includes the development of eco-friendly solvent-free synthetic methods using microwave or ultrasound irradiation. Further details of the multidisciplinary activity may be found at his home page, http://www.shsu.edu/~chm_rsv/

1. Introduction

Heterogeneous organic reactions have proven useful to chemists in the laboratory as well as in the industrial context. These reactions are effected by the reagents immobilized on the porous solid supports and have advantages over the conventional solution phase reactions because of the good dispersion of active reagent sites, associated selectivity and easier work-up. The recyclability of some of these solid supports renders these processes into truly eco-friendly green protocols. Although the first description of surface-mediated chemistry dates back to 1924,[1] it was not until the late 1970s that the technique received genuine attention with the appearance of two reviews,[2] followed by a series of books and account articles.[3]

A related development that had a profound impact on these heterogeneous reaction is the use of microwave (MW) irradiation techniques for the acceleration of organic reactions. Since the appearance of the first article on the application of microwaves for chemical synthesis in polar solvents,[4] the approach has blossomed into a useful technique for a variety of applications in organic synthesis and functional group transformations.[5–34] The focus has lately shifted to less cumbersome solvent-free methods[7–35] wherein the neat reactants, often in the presence of mineral oxides or supported catalysts, undergo facile reactions to provide high yields of pure products thus eliminating or minimizing the use of organic solvents.

Microwave reactions involve selective absorption of MW energy by polar molecules, non-polar molecules being inert to MW dielectric loss. The initial experiments with microwave techniques centered around the use of high dielectric solvents

Green Context

The combination of supported reagents and microwave irradiation can be used to carry out a wide range of reactions in short times and with high conversions and selectivity, without the need for solvents. This approach can prove beneficial since the recovery of solvents from conventional reaction systems always results in some losses. Recovery of both products and inorganic support/catalyst is generally possible, leading to an efficient and low waste route to a range of products. ***SJT***

such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF). The rate enhancements in such reactions are now believed to be due to rapid superheating of the polar solvents. However, in these solution-phase reactions, the development of high pressures and the use of specialized Teflon vessels and sealed containers are some of the limitations. During recent years, a practical dimension to the microwave heating protocols has been added by accomplishing reactions on solid supports under solvent-free conditions. In these reactions, the organic compounds adsorbed on the surface of inorganic oxides, such as alumina, silica and clay, or 'doped' supports absorb microwaves whereas the solid support does not absorb or restrict their transmission. The bulk temperature is relatively low in such solvent-free reactions although higher localized temperatures may be reached during microwave irradiation. These solvent-free MW-assisted reactions provide an opportunity to work with open vessels thus avoiding the risk of high pressure development and increasing the potential of such reactions to upscale.

2. Microwave accelerated solvent-free organic reactions

The practical feasibility of microwave assisted solvent-free protocols has been demonstrated in useful transformations involving protection/deprotection, condensation, oxidation, reduction, rearrangement reactions and in the synthesis of various heterocyclic systems on inorganic solid supports. Herein, we describe our results on this environmentally benign microwave approach for the synthesis of a wide variety of industrially important compounds and intermediates, namely enones, imines, enamines, nitroalkenes, oxidized sulfur species and heterocycles which, obtained otherwise by conventional procedures, contribute to the burden of chemical pollution. Recent work in this area by other research groups is also included. Most of the reactions described herein are performed in open glass containers (test tubes, beakers and round-bottomed flasks) using neat reactants under solvent-free conditions in an unmodified household MW oven or a focused MW oven operating at 2450 MHz. In many cases, the comparisons of the MW-accelerated reactions have been made by conducting the same reaction in an oil bath at the same bulk temperature. The problems associated with waste disposal of solvents (used many-fold in chemical reactions) and excess chemicals are avoided or minimized. Some of the supported reagents, namely clay-supported iron(III) nitrate (clayfen), and copper(II) nitrate (claycop), are prepared according to the literature procedure.[36]

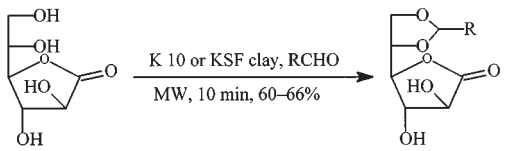
The general procedure involves simple mixing of neat reactants with the catalyst/promoter or their adsorption on mineral or 'doped' supports.

2.1. Protection/deprotection reactions

The protection/deprotection reaction sequences form an integral part of organic manipulations such as the preparation of monomer building blocks, fine chemicals and precursors for pharmaceuticals and these reactions often involve the use of acidic, basic or hazardous and corrosive reagents and toxic metal salts. In this section, the MW-accelerated protection/deprotection of functional groups that have been carried out under solvent-free conditions are highlighted.

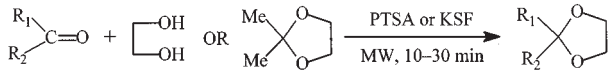
2.1.1. Formation of acetals and dioxolane.

Loupy and coworkers have efficiently prepared acetals of 1-galactono-1,4-lactone in excellent yields by adsorbing the lactone and the aldehyde on montmorillonite K 10 or KSF clay followed by exposing the reaction mixture to microwave irradiation (Scheme 1).[34e]



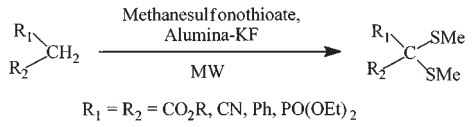
Scheme 1

Hamelin *et al.* have successfully protected aldehydes and ketones as acetals and dioxolanes using orthoformates, 1,2-ethanedithiol or 2,2-dimethyl-1,3-dioxolane.[37] This acid-catalysed reaction proceeds in the presence of *p*-toluenesulfonic acid (PTSA) or KSF clay under solvent-free conditions (Scheme 2). The yields obtained with the microwave method are better than those obtained using the conventional heating mode (oil bath).



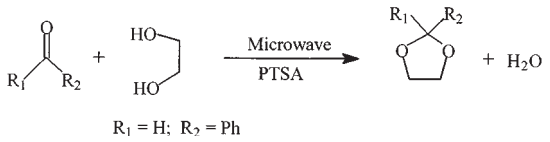
Scheme 2

Villemin *et al.* have prepared thioacetals using an essentially similar technique.[34f] The active methylene compounds are adsorbed on alumina–KF, mixed with methanesulfonothioate and are irradiated in a microwave oven to generate thioacetals in good yields (Scheme 3).



Scheme 3

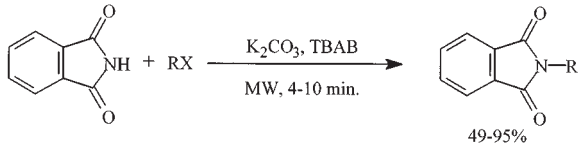
In the presence of ethylene glycol and *p*-toluenesulfonic acid, a mixture of ketone and aldehyde leads to the formation of dioxolane upon exposure to microwaves (Scheme 4).[37]



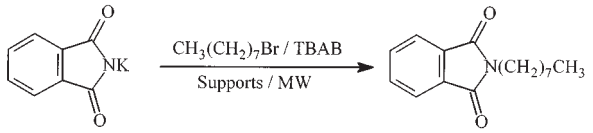
Scheme 4

2.1.2. N-Alkylation reactions.

A variety of solvent-free N-alkylation reactions have been reported which entail the use of phase transfer agents such as tetrabutylammonium bromide (TBAB) under microwave irradiation conditions. The important recent examples are N-alkylation of phthalimides (Scheme 5)[38] or its potassium salt (Scheme 6)[39] in the presence of potassium carbonate and TBAB.

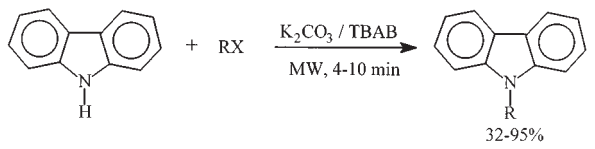


Scheme 5

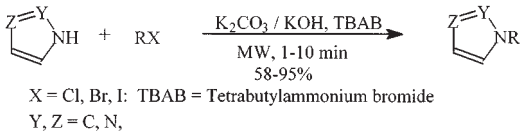


Scheme 6

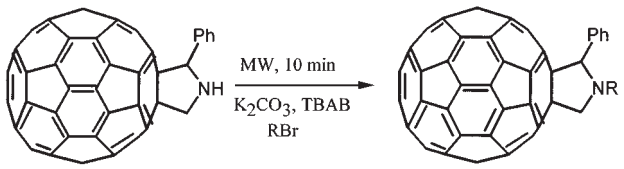
The approach has been extended to a variety of heterocyclic systems, namely carbazole (Scheme 7),[40] other azaheterocycles using K_2CO_3/KOH and TBAB (Scheme 8)[41] including pyrrolidino[60]fullerenes (Scheme 9).[42]



Scheme 7



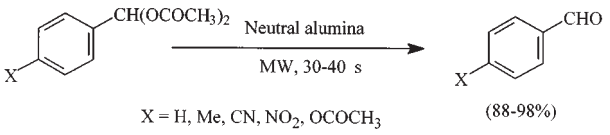
Scheme 8



Scheme 9

2.1.3. Cleavage of aldehyde diacetates.

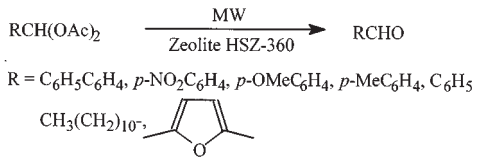
The diacetate derivatives of aromatic aldehydes are rapidly cleaved on a neutral alumina surface upon brief exposure to MW irradiation (Scheme 10).[11] The selectivity in these deprotection reactions is achievable by simply adjusting the time of



Scheme 10

irradiation. As an example for molecules bearing an acetoxy functionality (R = $OCOCH_3$), the aldehyde diacetate is selectively removed in 30 s, whereas an extended period of 2 min is required to cleave both the diacetate and ester groups. The yields obtained are better than those possible by conventional methods and the protocol is applicable to compounds encompassing olefinic moieties such as cinnamaldehyde diacetate.

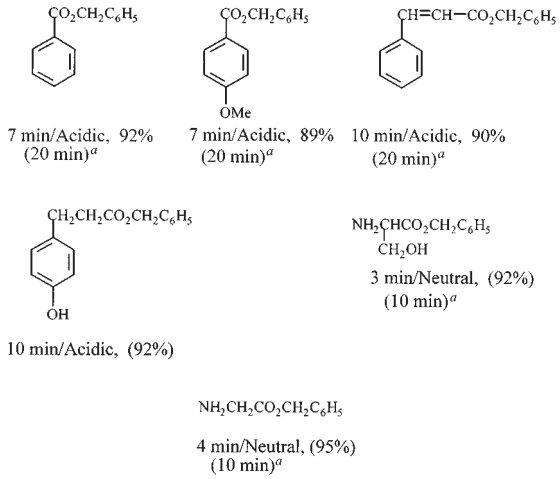
Essentially, a similar reaction has been reported using zeolites wherein 1,1-diacetates undergo deprotection under microwave irradiation in solvent-free conditions (Scheme 11).[43] However, it was not reported whether the reaction occurs on the surface or inside the zeolite pore structures.



Scheme 11

2.1.4. Debenzylation of carboxylic esters.

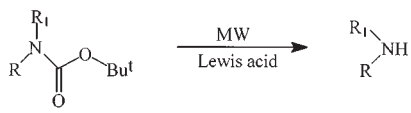
The promising solvent-free debenzylation of esters (Scheme 12)[13] paves the way for the cleavage of the 9-fluorenylmethoxy



Scheme 12 [a] Times in parentheses refer to deprotection in an oil bath at the same temperature.

carbonyl (Fmoc) group that can be extended to protected amines by changing the surface characteristics of the solid support. 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.

This approach may find application in peptide bond formation that would eliminate the use of irritating and corrosive chemicals such as trifluoroacetic acid and piperidine, as has been demonstrated recently for the deprotection of N-boc groups (see Scheme 13).



Scheme 13

2.1.5. Selective cleavage of N*-tert-butoxycarbonyl group.*

The solventless cleavage of the *N-tert*-butoxycarbonyl (Nboc) group is achieved readily in the presence of aluminium chloride 'doped' neutral alumina upon exposure to microwave irradiation (Scheme 13).[44]

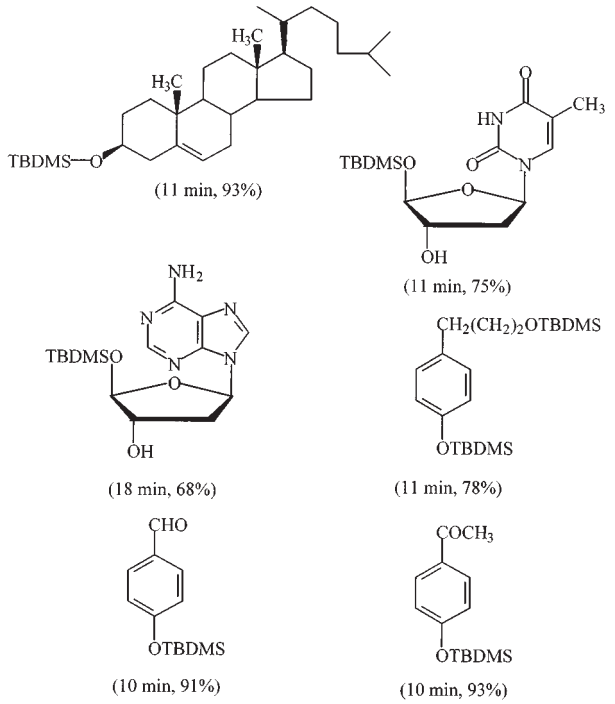
2.1.6. Desilylation reactions.

tert-Butyldimethylsilyl (TBDMS) ether derivatives of a variety of alcohols are rapidly deprotected to regenerate the corresponding hydroxy compounds on alumina surface under MW irradiation conditions (Scheme 14).[12] This approach circumvents the use of corrosive fluoride ions which are conventionally employed for cleaving the silyl protecting groups.[12]

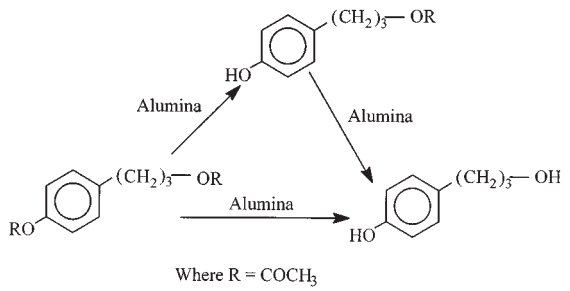
2.1.7. Deacylation reactions.

The orthogonal deprotection of alcohols is possible on a neutral alumina surface using microwave irradiation (Scheme 15). Interestingly, chemoselectivity between alcoholic and phenolic groups in the same molecule can be achieved simply by varying the reaction time; the phenolic acetates are deacetylated faster than alcoholic analogues.[10]

The optimization of relevant parameters with an unmodified household microwave oven such as the power level of microwaves employed and pulsed techniques (multistage, discontinuous irradiation to avoid the generation of higher tempera tures) has been used to obtain good results.[10]



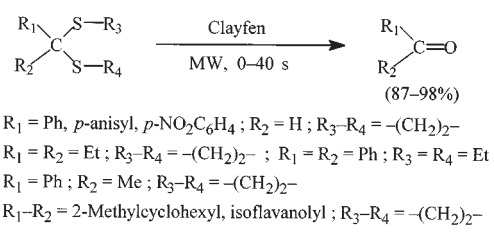
Scheme 14



Scheme 15

2.1.8. Dethioacetalization reaction.

Among the processes for the regeneration of carbonyl compounds, the cleavage of acid and base stable thioacetals and thioketals is quite challenging; the deprotection of thioacetals invariably requires the use of toxic heavy metals such as Hg^{2+}, Ag^{2+}, Ti^{4+}, Cd^{2+}, Tl^{3+}, or reagents such as benzeneseleninic anhydride.[9] We have accomplished the dethioacetalization reaction in high yield and in solid state using clayfen (Scheme 16).[9]

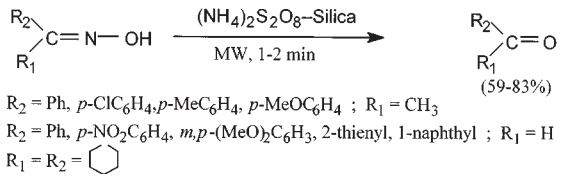


Scheme 16

2.1.9. Deoximation reactions.

The important role of oximes as protecting groups owing to their hydrolytic stability has provided motivation for the development of newer deoximation reagents such as 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.[8]

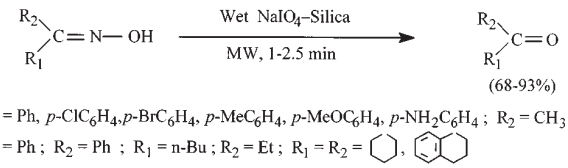
The solvent-free deprotection of protected carbonyl compounds has been successfully demonstrated using relatively benign ammonium persulfate on silica (Scheme 17).[8] Neat



Scheme 17

oximes are admixed with a solid supported reagent and the contents are irradiated at full power in a MW oven to regenerate free aldehydes or ketones in a process that is applicable to both aldoximes and ketoximes. The role of the surface is critical since the same reagent supported on a clay surface delivers predominantly the Beckmann rearrangement products, the amides.[34k]

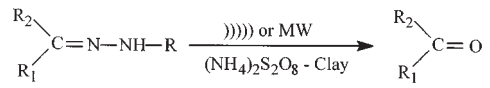
A facile deoximation protocol with sodium periodate impregnated moist silica (Scheme 18) has been introduced that is applicable exclusively to ketoximes[14]



Scheme 18

2.1.10. Cleavage of semicarbazones and phenylhydrazones.

Aldehydes and ketones are also rapidly regenerated from the corresponding semicarbazones and phenylhydrazones using ammonium persulfate impregnated on montmorillonite K 10 clay (Scheme 19) under either microwave or ultrasound irradiation



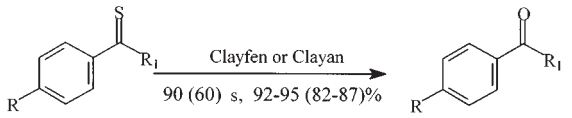
Scheme 19

conditions.[15] However, in these solventless procedures microwave exposure achieves results in minutes whereas ultrasound-promoted reactions require 1–3 h for completion of the deprotection reaction.

2.1.11. Dethiocarbonylation.

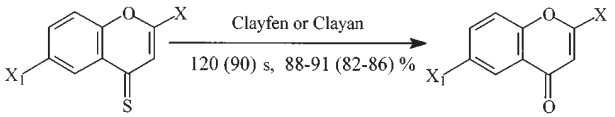
Several reagents such as trifluoroacetic anhydride, CuCl/MeOH/NaOH, tetrabutylammonium hydrogen sulfate/NaOH, clay/ferric nitrate, $NOBF_4$, bromate and iodide solutions, alkaline hydrogen peroxide, sodium peroxide, bases *e.g.* KOBu, thiophosgene, DMSO, trimethyloxonium fluoroborate, tellurium based oxidants, photochemical transformations, dimethyl selenoxide, benzeneseleninic anhydride, benzoyl per-

oxide, halogen-catalyzed alkoxides under phase transfer conditions, $NaNO_2$/HCl, $Hg(OAc)_2$, $SOCl_2/CaCO_3$, and singlet oxygen have been used for dethiocarbonylation.[16] However, these methods have certain limitations such as the use of the stoichiometric amounts of the oxidants which are often inherently toxic or require longer reaction time or involve tedious procedures. In a process that is accelerated by microwave irradiation, we have accomplished efficient dethiocarbonylation wherein a variety of thioketones are readily converted into the corresponding ketones under solvent-free conditions using clayfen or clayan (Schemes 20, 21).[16]



R_1 = Me ; R = H ; R_1 = Ph ; R = H, Br, Me

Scheme 20



X = Ph, p-MeC_6H_4, p-$MeOC_6H_4$; X_1 = H
X = p-MeC_6H_4 ; X_1 = OMe

Scheme 21

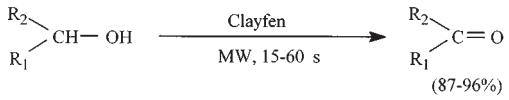
2.2. Oxidation reactions: oxidation of alcohols and sulfides

The conventional oxidizing reagents employed for organic functionalities are peracids, peroxides, manganese dioxide (MnO_2), potassium permanganate ($KMnO_4$), chromium trioxide (CrO_3), potassium chromate (K_2CrO_4), and potassium dichromate ($K_2Cr_2O_7$),[45a] though these reagents have their own limitations in terms of toxicity, work-up and associated waste disposal problems.

Metal-based reagents have been extensively used in organic synthesis. The utility of such reagents in the oxidative transformation is compromised due to their inherent toxicity, cumbersome preparation, potential danger (ignition or explosion) in handling of their complexes, difficulties in terms of product isolation and waste disposal. Introduction of metallic reagents on solid supports has circumvented some of these problems and provided an attractive alternative in organic synthesis because of the selectivity and associated ease of manipulation. Further, the immobilization of metals on the surface avoids their leaching into the environment.

2.2.1. Selective and solvent-free oxidation with clayfen.

We have developed a facile method for the oxidation of alcohols to carbonyl compounds wherein montmorillonite K 10 clay-supported iron(III) nitrate (clayfen) is used under solvent-free conditions. The process is accelerated tremendously by exposure to MW irradiation[17] and the reaction presumably proceeds *via* the intermediacy of nitrosonium ions. Remarkably, no carboxylic acids are formed in the oxidation of primary alcohols. The experimental procedure simply involves mixing of neat alcohols with clayfen and a brief irradiation of the reaction mixtures in a MW oven for 15–60 s in the absence of solvent. This extremely rapid, manipulatively simple, inexpensive and selective protocol avoids the use of excess solvents and toxic oxidants. Using clayfen [iron(III) nitrate] in the solid state and in amounts that are half that of used by Balogh and Laszlo[36] we have achieved a rapid synthesis of carbonyl compounds in high yields (Scheme 22).[17]

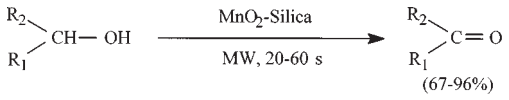


R_1 = Ph, p-MeC_6H_4, p-$MeOC_6H_4$, ; R_2 = H
R_1 = Ph ; R_2 = Et, PhCO ; R_1– R_2 =
R_1 = p-$MeOC_6H_4$; R_2 = p-$MeOC_6H_4CO$

Scheme 22

2.2.2. Activated manganese dioxide–silica.

Using manganese dioxide–silica, an expeditious and high yield route to carbonyl compounds is developed. Benzyl alcohols are selectively oxidized to carbonyl compounds using 35% MnO_2 'doped' silica under MW irradiation conditions (Scheme 23).[18]



R_1 = Ph, p-MeC_6H_4, p-$MeOC_6H_4$, PhCH=CH ; R_2 = H
R_1 = Ph ; R_2 = Et, Ph, PhCO ; R_1 = R_2 = hydroquinone
R_1 = p-$MeOC_6H_4$; R_2 = p-$MeOC_6H_4CO$

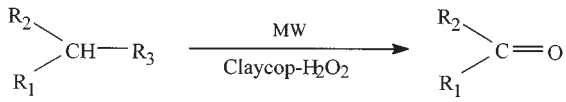
Scheme 23

2.2.3. Claycop–hydrogen peroxide.

Metal ions play a significant role in many of these oxidative reactions as well as in biological dioxygen metabolism. Copper(II) acetate and hydrogen peroxide have been used to produce a stable oxidizing agent, a hydroperoxy copper(II) compound, which is also obtainable from copper(II) nitrate and hydrogen peroxide [eqn. (1)]. The resulting nitric acid, however, requires neutralization by potassium bicarbonate to maintain a pH ≈5.

$$2Cu(NO_3)_2 + 2H_2O + H_2O_2 \longrightarrow 2CuO_2H + 4HNO_3 \qquad (1)$$

Copper(II) nitrate impregnated on K 10 clay (claycop)–hydrogen peroxide is an effective reagent for the oxidation of a variety of substrates and provides excellent yields (Scheme 24)[19] wherein the maintenance of pH of the reaction mixture is not required.

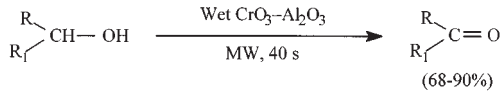


R_1 = Ph , p-$NO_2C_6H_4$
R_2 = H, Ph
R_3 = H, Br, COOH, CN, NH_2

Scheme 24

2.2.4. Chromium trioxide impregnated wet alumina.

The utility of chromium(VI) reagents in the oxidative transformation is compromised due to toxicity, involved preparation of its various complexes and cumbersome work-up and disposal problems. Chromium trioxide (CrO_3) impregnated pre-moistened alumina is an efficient oxidising system which converts benzyl alcohols to carbonyl compounds by simply admixing the substrates with the reagent at room temperature (Scheme 25). The reactions



R = Ph, p-MeC_6H_4, p-$MeOC_6H_4$, p-$NO_2C_6H_4$; R_1 = H
R = Ph ; R_1 = Me, Ph, PhCO ; R = R_1 = ,

Scheme 25

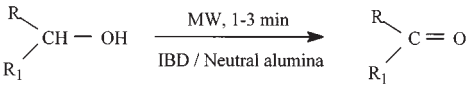
are relatively clean with no tar formation, typical of many CrO_3 oxidations. Interestingly, no overoxidation to carboxylic acids is observed.[20]

Acyclic α-nitro ketones are obtained in one-pot operation *via* a solvent-free approach that utilizes *in situ* oxidation of the nitroalkanols with premoistened alumina supported chromium trioxide.[43b]

2.2.5. Nonmetallic oxidants—iodobenzene diacetate (IBD) 'doped' alumina.

Iodoxybenzene, *o*-iodoxybenzoic acid (IBX), bis(trifluoroacetoxy)iodobenzene (BTI), and Dess–Martin periodinane are some of the common organohypervalent iodine reagents which have been used for the oxidation of alcohols and phenols, but the use of iodobenzene diacetate (IBD) in this area, in spite of its low cost, has not been fully exploited. Most of these reactions, however, are conducted in high boiling DMSO and toxic acetonitrile media that result in an environmental pollution load. Also, IBX has been reported to be explosive under heavy impact and heating over 200 °C.

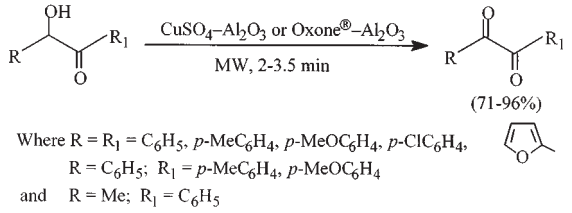
A facile oxidation of alcohols to carbonyl compounds occurs rapidly with alumina-supported IBD under solvent-free conditions and MW irradiation, in quantitative yields.[21] The advantage of using alumina as a support is apparent in marked improvements in yields obtained with the alumina–IBD system as compared to neat IBD (Scheme 26). Interestingly, 1,2-benzenedimethanol undergoes cyclization to afford 1(3*H*)-isobenzofuranone.



Scheme 26

2.2.6. Copper sulfate–alumina or oxone®–wet alumina.

The oxidative transformation of α-hydroxyketones to 1,2-diketones has been accomplished by a variety of reagents namely nitric acid, Fehling's solution, thallium(III) nitrate (TTN), ytterbium(III) nitrate, clayfen, and ammonium chlorochromate–alumina.[22] In addition to the extended reaction time, most of these processes suffer from drawbacks such as the use of corrosive acids and toxic metallic compounds that generate undesirable waste materials. Consequently, there is room for the development of an eco-friendly solvent-free protocol for the oxidation of benzoins. Recently, we have found that both symmetrical and unsymmetrical benzoins can be rapidly oxidized to benzils in high yields using solid reagent systems, copper(II) sulfate–alumina[22] or Oxone®–wet alumina[23] under the influence of microwaves (Scheme 27).

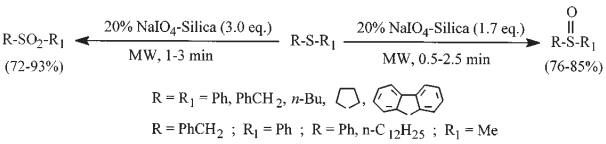


Scheme 27

Interestingly, under these solvent-free conditions, primary alcohols *e.g.* benzyl alcohol and secondary alcohols *e.g.* 1-phenylpropan-1-ol undergo only limited oxidative conversion which is of little practical utility. Apparently, the process is applicable only to α-hydroxyketones as exemplified by various substrates including a mixed benzylic/aliphatic α-hydroxyketone, 2-hydroxypropiophenone, that affords the corresponding vicinal diketone.[23]

2.2.7. Sodium periodate on silica—oxidation of sulfides to sulfoxides and sulfones.

Sulfides are usually oxidized to sulfoxides under strenuous conditions using strong oxidants like nitric acid, hydrogen peroxide, chromic acid, peracids, and periodate.[24] Using MW irradiation this oxidation is achievable with the desired selectivity, to either sulfoxides or sulfones, using silica 'doped' with 10% sodium periodate under reduced power and reaction time (pulsed techniques).[24] Consequently, a much reduced amount of the active oxidizing agent is employed which is safer and easier to handle (Scheme 28).

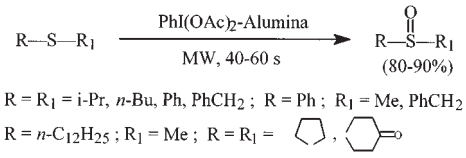


Scheme 28

Importantly, various refractory thiophenes that are often not reductively removed by conventional refining processes can be oxidized under these conditions, *e.g.* benzothiophenes are oxidized to the corresponding sulfoxides and sulfones using ultrasonic and microwave irradiation, respectively, in the presence of $NaIO_4$–silica.[24] A noteworthy feature of the protocol is its applicability to long chain fatty sulfides which are insoluble in most solvents and are consequently difficult to oxidize.

2.2.8. Iodobenzene diacetate–alumina.

As described earlier (section 2.2.5), the solid reagent system IBD–alumina is a useful oxidizing agent and its use is extendable to the expeditious, high yield and selective oxidation of alkyl, aryl and cyclic sulfides to the corresponding sulfoxides upon microwave activation (Scheme 29).[25a]



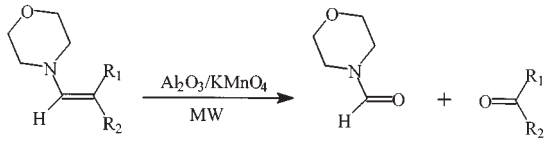
Scheme 29

In a solid state reaction with clayfen, a variety of alkyl, aryl and cyclic sulfides are rapidly oxidised to the corresponding sulfoxides in high yield upon microwave thermolysis.[25b]

2.3 Other oxidation reactions

2.3.1. Oxidation of enamines.

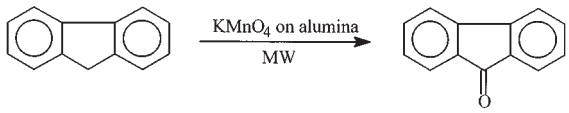
Under solvent-free conditions, Hamelin's group[34g] has successfully oxidized β,β-disubstituted enamines into carbonyl compounds with $KMnO_4$–Al_2O_3 in domestic (255 W, 82 °C) as well as in focused (330 W, 140 °C) microwave ovens. The yields are better in the latter case whereas no ketone formation is observed when the same reactions are conducted in an oil bath at 140 °C (Scheme 30).



Scheme 30

2.3.2. Oxidation of arenes with permanganate ($KMnO_4$)–alumina.

$KMnO_4$ impregnated alumina oxidises arenes to ketones within 10–30 minutes in solvent-free conditions using focused microwaves (Scheme 31).[45b]



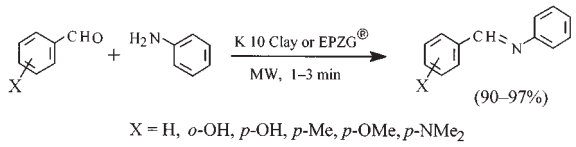
Scheme 31

2.4. Condensation reactions

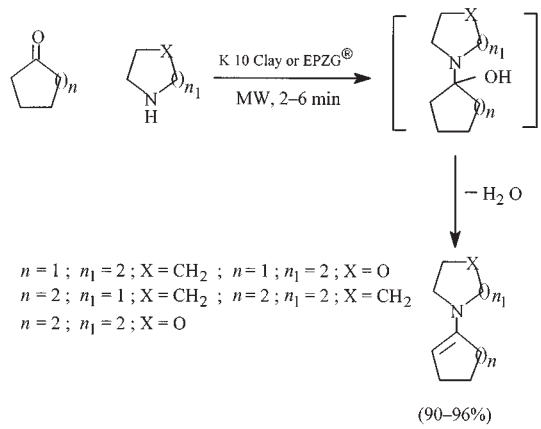
2.4.1. Synthesis of imines, enamines and nitroalkenes.

The driving force in the preparation of imines, enamines and nitroalkenes is the azeotropic removal of water from the intermediate, which is normally catalyzed by *p*-toluenesulfonic acid, titanium(IV) chloride, and montmorillonite K 10 clay. Conventionally, a Dean–Stark apparatus is used which requires a large excess of aromatic hydrocarbons such as benzene or toluene for azeotropic water elimination.

MW-induced acceleration of such dehydration reactions using montmorillonite K 10 clay[26] (Schemes 32, 33) or Envirocat reagent,[27] EPZG® (Schemes 32, 33) has been demonstrated in a facile preparation of imines and enamines *via* the reactions of primary and secondary amines with aldehydes and ketones, respectively.



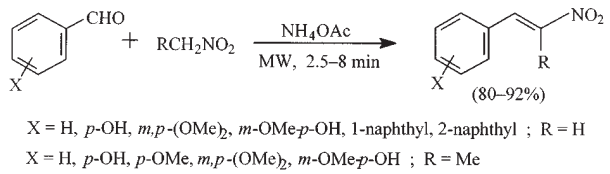
Scheme 32



Scheme 33

Microwaves, generated at the usual frequency of 2450 MHz, are ideally suited to remove water in imine or enamine forming reactions. For low boiling starting materials, reduced power intensities of microwaves coupled with pulsed techniques have been used.[26,27]

The Henry reaction, condensation of carbonyl compounds with nitroalkanes to afford nitroalkenes, also proceeds rapidly *via* this MW approach and requires only catalytic amounts of ammonium acetate involving neat reactants thus avoiding the use of a large excess of polluting nitrohydrocarbons normally employed (Scheme 34).[28]

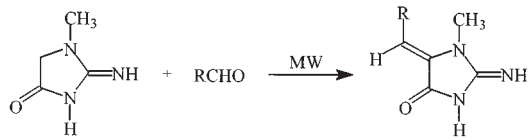


Scheme 34

The reduction, oxidation and cycloaddition reactions emanating from α,β-unsaturated nitroalkenes provide easy access to a vast array of functionalities that include nitroalkanes, N-substituted hydroxylamines, amines, ketones, oximes, and α-substituted oximes and ketones.[46] Consequently, there are numerous possibilities of using these *in situ* generated nitroalkenes for the preparation of valuable building blocks and synthetic precursors.

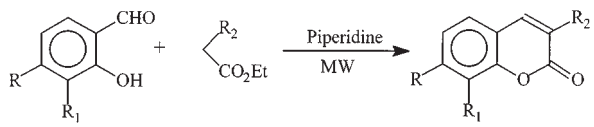
2.4.2. Knoevenagel condensation reactions—Coumarin synthesis.

An expeditious Knoevenagel condensation of creatinine with aldehydes has been achieved using focused microwave irradiation (40–60 W) under solvent-free reaction conditions at 160–170 °C (Scheme 35).[47]



Scheme 35

Villemin and Martin[34l] have synthesized 5-nitrofurfurylidine by the condensation of 5-nitrofurfuraldehyde with active methylene compounds under microwave irradiation using K 10 and $ZnCl_2$ as a catalyst. The useful synthesis of coumarins *via* the microwave promoted Pechmann reaction[48a] has been extended to solventless systems wherein salicylaldehydes undergo Knoevenagel condensation with a variety of ethyl acetate derivatives under basic conditions (piperidine) to afford coumarins (Scheme 36).[48b]



Scheme 36

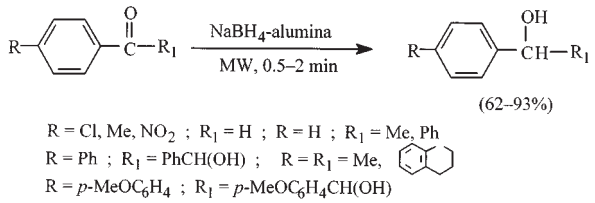
2.5 Reduction reactions

2.5.1. Borohydride reduction of carbonyl compounds to alcohols.

Relatively inexpensive sodium borohydride ($NaBH_4$) has been extensively used as a reducing agent in view of its compatibility with protic solvents and safer nature. The solid state reduction of

ketones has also been achieved by mixing them with $NaBH_4$ and storing the mixture in a dry box for five days. The major disadvantage in the heterogeneous reaction with $NaBH_4$ is that the use of solvent slows down the reaction rate while in the solid state reactions the time required is too long (5 days) for it to be of any practical utility.[32]

We have developed a rapid method for the reduction of aldehydes and ketones that uses alumina supported $NaBH_4$ and proceeds in the solid state using microwaves.[32] The process in its entirety involves a simple mixing of carbonyl compound with (10%) $NaBH_4$–alumina in the solid state and irradiating the mixture in a MW oven for 0.5–2 min (Scheme 37).



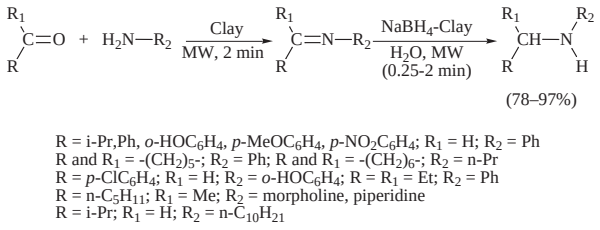
Scheme 37

The useful chemoselective feature of the reaction is apparent from the reduction of *trans*-cinnamaldehyde (cinnamaldehyde/$NaBH_4$-alumina, 1:1 mol equivalent); the olefinic moiety remains intact and only the aldehyde functionality is reduced in a facile reaction that occurs at room temperature.

No side product formation is observed in any of the reactions investigated and reaction does not take place in the absence of alumina. Further, the reaction rate improves in the presence of moisture. Alumina absorbs enough moisture during the recovery of the product that it can be recycled again by mixing with fresh borohydride and reused for subsequent reductions without any loss of activity. The air used for cooling the magnetron ventilates the microwave cavity thus preventing any ensuing hydrogen from reaching explosive concentrations.

2.5.2. Reductive alkylation of amines.

Reductive amination of carbonyl compounds has been well documented using sodium cyanoborohydride, sodium triacetoxyborohydride or $NaBH_4$ coupled with sulfuric acid. These reagents either produce waste stream or involve the use of corrosive acids. The environmentally benign methods developed in our laboratory have now been extended to a solvent-free reductive amination procedure for carbonyl compounds using wet montmorillonite K 10 clay supported sodium borohydride that is facilitated by microwave irradiation (Scheme 38).[33]

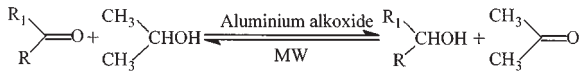


Scheme 38

These practical applications of $NaBH_4$ reductions on mineral surfaces for *in situ* generated Schiff bases have been successful.[33] The studies pertaining to the solid state reductive amination of carbonyl compounds on various inorganic solid supports such as alumina, clay, silica, *etc*., and especially on K 10 clay surface deliver secondary and tertiary amines rapidly.[33] Clay not only behaves as a Lewis acid but provides water from its interlayers that enhances the reducing ability of $NaBH_4$.

2.5.3. Reduction of carbonyl compounds with aluminium alkoxides.

The efficient reduction of carbonyl compounds using isopropyl alcohol and alumina, as demonstrated in a series of papers by Posner,[49a] has now been translated to a solventless and expeditious reduction scheme that utilises aluminium alkoxides under microwave irradiation conditions (Scheme 39).[49b]

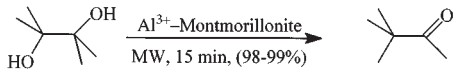


Scheme 39

2.6. Rearrangement reactions

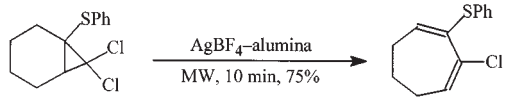
2.6.1. Pinacol–pinacolone rearrangement.

Loupy and colleagues have reported a solventless pinacol–pinacolone rearrangement using microwave irradiation.[34i] The process involves the irradiation of the *gem*-diols with Al^{3+}-montmorillonite K 10 clay for 15 min to afford the rearrangement product in excellent yields (Scheme 40). These results are compared to conventional heating in an oil bath where the reaction times are too long (15 h).



Scheme 40

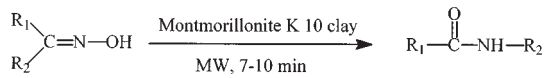
An efficient ring expansion transformation is described by Villemin and Labiad under solventless conditions (Scheme 41).[34j] This solvent-free microwave protocol is superior than the reactions conducted in conventional methanolic solution.



Scheme 41

2.6.2. Beckmann rearrangement.

Bosch *et al*. have achieved the Beckmann rearrangement of ketoximes with montmorillonite K 10 clay in 'dry' media in good yields (Scheme 42).[34k]

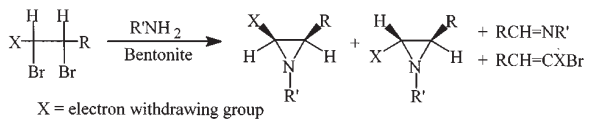


Scheme 42

2.7. Synthesis of heterocylic compounds

2.7.1. Aziridines.

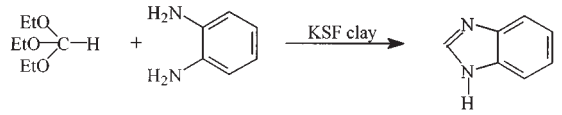
Among the various protocols known for the synthesis of the title compounds, the focused microwave approach under 'dry' conditions is especially notable in view of the observation that elimination predominates over the Michael addition under MW irradiation when compared to the classical heating under the same conditions (Scheme 43).[50]



Scheme 43

2.7.2. Benzimidazoles.

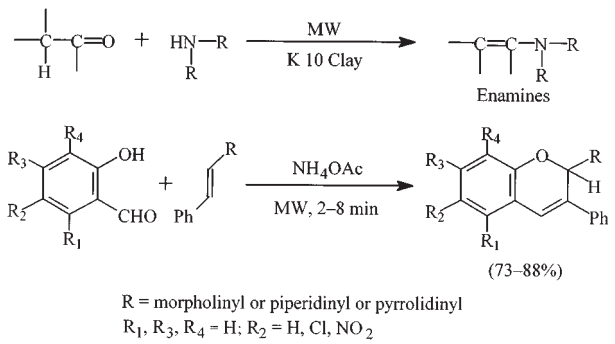
Benzimidazoles are prepared rapidly by condensation reaction of *ortho*-esters with *o*-phenylenediamines in the presence of KSF clay under either refluxing conditions in toluene or solvent-free conditions using focused microwave irradiation (Scheme 44).[51]



Scheme 44

2.7.3. Isoflav-3-enes.

Isoflav-3-enes, possessing the chromene nucleus, are well known oestrogens and several derivatives of these oxygen heterocycles have attracted the attention of medicinal chemists. Despite the availability of several methods for the synthesis of chromene derivatives, there is demand for the development of eco-friendly synthetic methods for these derivatives. We have discovered a facile and general method for the synthesis of isoflav-3-enes substituted with basic moieties at the 2 position (Scheme 45).[29] The results are especially promising in view of the convergent one-pot approach to the

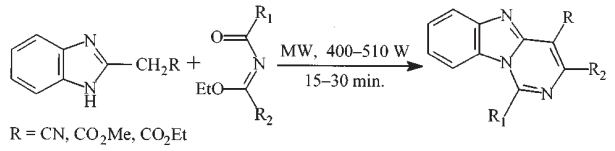


Scheme 45

heterocyclic systems such as 2-substituted isoflavenes wherein the generation of the enamine derivatives *in situ* and inducing subsequent reactions with *o*-hydroxyaldehydes in the same pot is the key feature (Scheme 45).

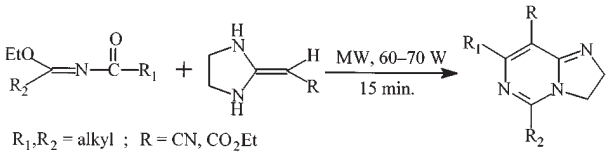
2.7.4. Bridgehead nitrogen heterocycles.

Microwave energy has found application in the rapid synthesis of bridgehead nitrogen heterocycles under solvent-free conditions. Rahmouni *et al*. have synthesised pyrimidino[1,6-*a*]benzimidazoles (Scheme 46) and 2,3-dihydroimidazo[1,2-*c*]pyrimidines (Scheme 47) under focused microwave



Scheme 46

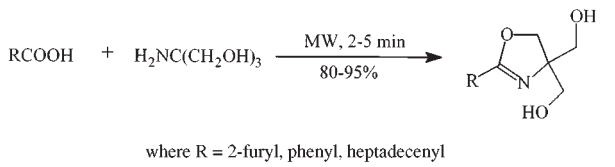
irradiation in moderate yields from *N*-acylimidates and activated 2-benzimidazoles and imidazoline ketene aminals, respectively.[34h]



Scheme 47

2.7.5. Synthesis of 2-oxazolines.

Oxazolines are readily prepared from carboxylic acids and α,α,α-tris(hydroxymethyl)methylamine under microwave irradiation conditions (Scheme 48).[52]

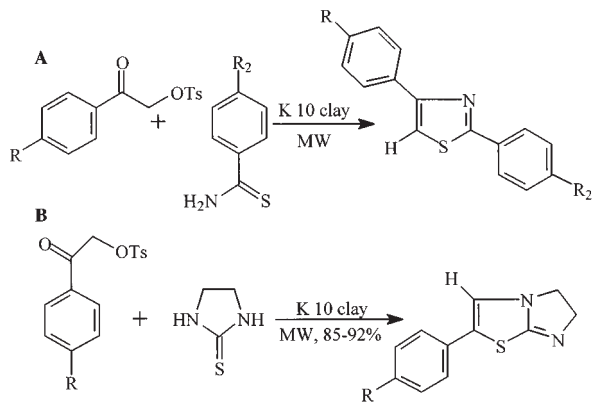


Scheme 48

2.7.6. Substituted thiazoles.

Thiazole and its derivatives are simply obtained by the reaction of α-tosyloxyketones, which are generated *in situ* from arylmethyl ketones and [hydroxy(tosyloxy)iodo]benzene (HTIB) with thioamides in the presence of K 10 clay using microwave irradiation (Scheme 49A) in a process that is solvent-free in both steps.[53]

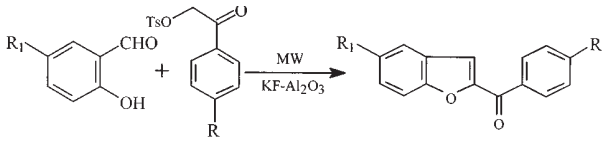
The case of corresponding bridgehead heterocycles, however, is a special one where microwave effects really become apparent since the reactions of α-tosyloxyketones with ethylenethioureas remain incomplete in an oil bath whereas in a microwave oven they are completed in a short time (Scheme 49B).[53]



Scheme 49

2.7.7. Synthesis of 2-aroylbenzofurans.

Naturally occurring and pharmacologically important 2-aroylbenzofurans are easily obtainable in the solid state from α-tosyloxyketones and salicylaldehydes in the presence of a base such as potassium fluoride doped alumina using microwave irradiation (Scheme 50).[53]

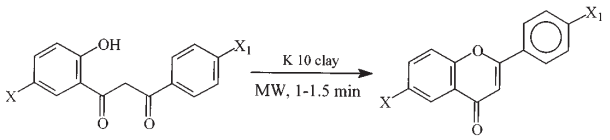


Scheme 50

2.7.8. Flavones.

Flavonoids are a class of naturally occurring phenolic compounds widely distributed in the plant kingdom, the most abundant being the flavones. Members of this class display a wide variety of biological activities and have been useful in the treatment of various diseases. Flavones have been prepared by a variety of methods such as Allan–Robinson synthesis and synthesis from chalcones *via* an intramolecular Wittig strategy.[30] The most prevalent approach, however, involves the Baker–Venkataraman rearrangement, wherein *o*-hydroxyacetophenone is benzoylated to form the benzoyl ester followed by treatment with base (pyridine/KOH) to effect an acyl group migration, forming a 1,3-diketone.[30] The diketone formed is then cyclized under strongly acidic conditions using sulfuric acid and acetic acid to deliver the flavone. Therefore, opportunities exist for the development of an expedient approach using benign and readily available starting materials.

We have achieved a solvent-free synthesis of flavones which simply involves the microwave irradiation of *o*-hydroxydibenzoylmethanes adsorbed on montmorillonite K 10 clay for 1–1.5 min. Rapid and exclusive formation of cyclized flavones occurs in good yields (Scheme 51).[30]

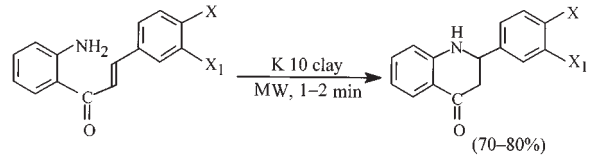


X = H ; X_1 = H, Me, OMe, NO_2
R = OMe ; X_1 = H, Me, OMe

Scheme 51

2.7.9. Synthesis of 2-aryl-1,2,3,4-tetrahydro-4-quinolones.

In yet another solventless cyclization reaction using montmorillonite K 10 clay under microwave irradiation conditions, readily available 2′-aminochalcones provide easy access to 2-aryl-1,2,3,4-tetrahydro-4-quinolones[31] which are valuable precursors for the medicinally important quinolones (Scheme 52).



X = Cl, Br, Me, OMe, NO_2 ; X_1 = H
X = X_1 = H, OMe

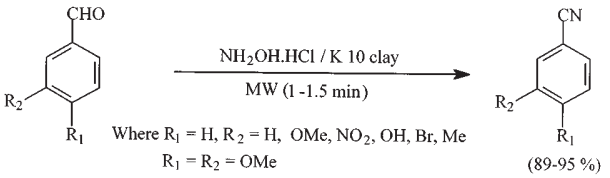
Scheme 52

2.8. Miscellaneous reactions

2.8.1. Transformation of aromatic aldehydes to nitriles.

The preparation of nitriles from aldehydes is an important chemical transformation.[54] However, in most cases the aldoxime is first prepared and subsequently dehydrated using a wide variety of reagents such as *O,N*-bis(trifluoroacetyl) hydroxylamine or trifluoroacetohydroximic acid,[55a] chloramine/base,[55b] (H_2SO_4/SiO_2),[55c] *p*-chlorophenyl chlorothionoformate/pyridine,[55d] triethylamine/dialkyl hydrogen phosphinates,[55e] $TiCl_4$/pyridine,[55f] triethylamine/phosphonitrilic chloride[55g] and 1,1′-dicarbonylbiimidazole.[55h] These conventional methods entail the dehydration of aldoxime which is a time demanding process even for one-pot reactions.[55i] We envisaged the application of hydroxylamine 'doped' on K10 clay to effect the above conversion in a one-pot synthesis using microwaves.

Arylaldehydes are rapidly converted into nitriles in good yields (89–95%) with hydroxylamine hydrochloride supported on montmorillonite K 10 clay in the absence of solvent.[55j,k] The reaction is a general one as exemplified by a variety of aldehydes (Scheme 53) that undergo this facile conversion to afford high yields of the corresponding nitriles (89–95%) within a short



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

Scheme 53

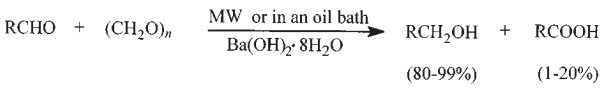
MW irradiation time (1–1.5 min).[55j,k] In the case of aliphatic aldehydes, however, only poor yields of nitriles (10–15%) are obtained with complex byproduct formation.

2.8.2. Conversion of aldehydes to alcohols—Solid state Cannizzaro reaction.

The title reaction is the disproportionation of an aldehyde to an equimolar mixture of primary alcohol and carboxylic salt[56] and is restricted to aldehydes that lack α-hydrogens and therefore can not undergo aldol condensation. Several investigations[57] have been made on this oxidation–reduction reaction, which is usually carried out in homogeneous and strongly basic conditions. The relative importance of the Cannizzaro reaction in synthetic organic chemistry decreased considerably after the discovery of lithium aluminium hydride, $LiAlH_4$, in 1946. The lower yields of the desired products has been another limitation of this reaction. However, the crossed Cannizzaro reaction,[57a] using a scavenger and inexpensive paraformaldehyde to produce alcohol in higher yields, had been another choice prior to the introduction of hydride reducing agents.

Normally conducted in solution, we explored this reaction on a variety of mineral oxide surfaces.[58a] The reaction under microwave irradiation conditions failed completely with calcium hydroxide and in the presence of a strong base such as sodium hydroxide, the reaction remains incomplete with concomitant formation of several unidentified products reminiscent of our earlier observations on basic alumina surface.[58b] Interestingly, we discovered that the reaction proceeds rapidly on a barium hydroxide, $Ba(OH)_2 \cdot 8H_2O$, surface which demonstrates the first application of this reagent in a solvent-free crossed Cannizzaro reaction.[58a] Barium hydroxide has been previously used as a catalyst in a variety of organic syntheses[59] including the Wittig–Horner reaction,[60] the reaction of chalcones with hydroxylamine[61] and the synthesis of isooxazolines and pyrazolines.[62] In a typical experiment, a mixture of benzaldehyde (1 mmol) and paraformaldehyde (2 mmol) is mixed with barium hydroxide octahydrate (2 mmol) and then irradiated in a microwave oven (100–110 °C) or heated in an oil bath (100–110 °C) (Scheme 54).

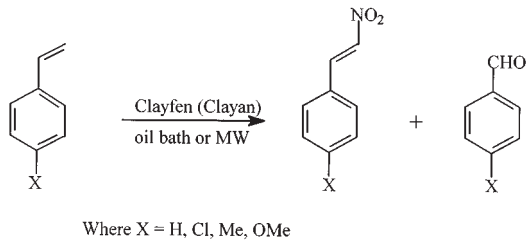
In general, aldehydes bearing an electron withdrawing substituent undergo reaction at a much faster rate than aldehydes with electron releasing groups appended.



Scheme 54

2.8.3. Side chain nitration of styrenes—preparation of β-nitrostyrenes.

We have recently described a facile solid state synthesis of β-nitrostyrenes from readily available feedstock, styrene and its substituted derivatives using inexpensive 'doped' clay reagents, clayfen and clayan (Scheme 55).[63] In a typical experiment, the neat reagent, styrene and clayfen or clayan are mixed in a glass



Scheme 55

container and the solid mixture is heated in an oil bath (≈100–110 °C, 15 min) or irradiated in a microwave oven (≈100–110 °C, 3 min). In the case of clayan, intermittent warming is recommended at 30 s intervals to maintain the temperature below 60–70 °C. Interestingly, we observed the reaction proceeds only in the solid state and leads to the formation of polymeric products in solution phase reactions.

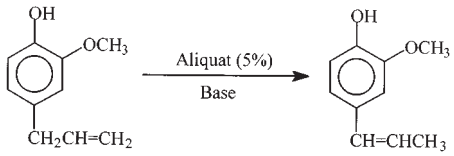
2.8.4 Oxidative coupling of β-naphthols.

β-Naphthols undergo a quick and efficient self coupling reaction in the presence of iron(III) chloride, $FeCl_3 \cdot 6H_2O$, under focused microwave irradiation in solvent-free conditions when compared to classical heating mode (Scheme 56).[64]

Scheme 56

2.8.5. Eugenol isomerization.

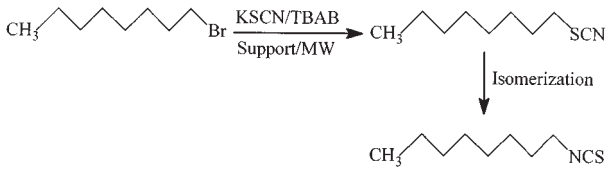
Isoeugenol, an important feedstock for the flavor industry to manufacture vanillin, is normally prepared by base-catalysed isomerization of naturally occurring eugenol. In the presence of potassium *tert*-butoxide, *t*-BuOK, and a catalytic amount of phase transfer reagent, eugenol undergoes isomerization to isoeugenol under solvent-free conditions (Scheme 57).[65]



Scheme 57

2.8.6. Synthesis and isomerization of octylthiocyanate.

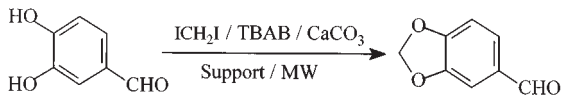
Vass and coworkers have examined various non-traditional supports which, although they are chemically inactive and couple poorly with microwaves, produce some useful chemistry. As an example, octylbromide undergoes thiocyanation reaction with potassium thiocyanide, KSCN, in the presence of a phase transfer catalyst, tetrabutylammonium bromide (TBAB) on sodium chloride surfaces and it further isomerizes to isothiocyanate (Scheme 58).[39]



Scheme 58

2.8.7. Methylenation of 3,4-dihydroxybenzaldehyde.

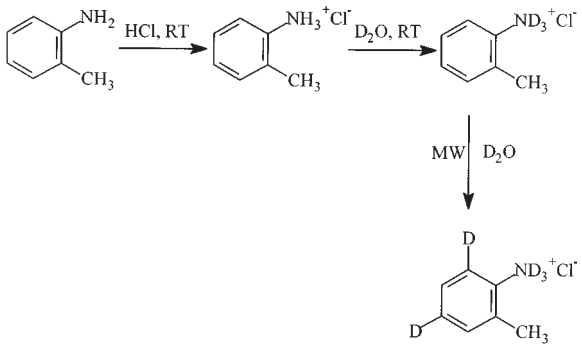
3,4-Dihydroxybenzaldehyde undergoes methylenation rapidly in the presence of a phase transfer catalyst on a benign calcium carbonate surface; presumably the bonding of the vicinal hydroxyl groups is low thereby enhancing the reaction with the alkylating agent under solvent-free microwave irradiation (Scheme 59).[39]



Scheme 59

2.8.8. Synthesis of radiolabelled compounds—exchange reactions.

Jones and coworkers[66b–d] have added a new dimension to the classical tritiation efforts of Wilzbach[66a] using microwave irradiation and solid hydrogen/deuterium/tritium donors with minimal radioactive waste generation. The group has nicely circumvented the traditional disadvantages associated with tritium labeling techniques as exemplified with deuteriated and tritiated borohydride reductions,[66b] based on similar MW-expedited reduction accomplished on alumina surfaces.[32] The hydrogen exchange reactions that require elevated temperatures and extended reaction time (24 h)[66c] are the real beneficiaries of this microwave approach.[66d] The high purity of labeled materials, efficient insertion and excellent regio-selectivity are some of the salient features of this emerging technology (Scheme 60).



Scheme 60

In an elegant application of the microwave-accelerated reactions, Stone–Elander and co-workers have synthesised radiolabelled organic compounds *via* nucleophilic aromatic and aliphatic substitution reactions, esterifications, condensations, hydrolysis and complexation reactions using microwaves.[67] The use of monomodal cavities on microscale organic reactions are real success stories of MW-expedited reactions.

3. Conclusion

This article summarizes the recent activity and eco-friendly features of the solvent-free reactions that are activated by exposure to microwave irradiation. The solventless approach opens up numerous possibilities for conducting selective organic functional group transformations more efficiently and expeditiously using a variety of supported reagents on mineral oxides. The author's own work, performed using an unmodified household microwave oven (multimode applicator), demonstrates the immediate practical applications in laboratory scale experiments. Some of the more recent work does point out the advantages of using monomode systems with focused electromagnetic waves (Prolabo) wherein not only improved temperature/power control is possible but also relatively large scale reactions (1 litre capacity) can be conducted[68] with additional options available for continuous operation. The engineering and scale-up aspects for the chemical process development have already been discussed.[69] The major industrial applications of MW-enhanced clean chemistry include the preparation of hydrogen cyanide, a chlorination plant, drying of pharmaceutical powders and pasteurization of food products.

There are distinct advantages of these solvent-free protocols since they provide reduction or elimination of solvents thereby preventing pollution in organic synthesis 'at source'. Although not delineated completely, the reaction rate enhancements achieved in these methods may be ascribable to non-thermal effects. The chemo-, regio- or stereo-selective synthesis of high value chemical entities may see the translation of these laboratory 'curious' experiments to large-scale operations pending the design of bigger microwave reactors and the participation of equally enthusiastic teams of chemical and electrical engineers to harness the true potential of this clean technology.

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5. References

1 Using chemical reagents on porous carriers, *Akt.-Ges. Fur Chemiewerte, Br. Pat.*, 1924, 231,901; *Chem. Abstr.*, 1925, **19**, 3571.
2 (*a*) G. H. Posner, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 487; (*b*) A. McKillop and K. W. Young, *Synthesis*, 1979, 401 and 481.
3 (*a*) A. Cornelis and P. Laszlo, *Synthesis*, 1985, 909; (*b*) P. Laszlo, *Preparative Chemistry Using Supported Reagents*, Academic Press, Inc., San Diego, 1987; (*c*) K. Smith, *Solid Supports and Catalyst in Organic Synthesis*, Ellis Horwood, Chichester, 1992; (*d*) M. Balogh and P. Laszlo, *Organic Chemistry Using Clays*, Springer-Verlag, Berlin, 1993; (*e*) J. H. Clark, *Catalysis of Organic Reactions by Supported Inorganic Reagents*, VCH Publishers, Inc., NY, 1994; (*f*) J. H. Clark and D. J. Macquarrie, *Chem. Commun.*, 1998, 853; (*g*) G. W. Kabalka and R. M. Pagni, *Tetrahedron*, 1997, **53**, 7999.
4 R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge and J. Rousell, *Tetrahedron Lett.*, 1986, **27**, 279.
5 For recent reviews on microwave-assisted chemical reactions see: (*a*) R. A. Abramovich, *Org. Prep. Proc. Int.*, 1991, **23**, 683; (*b*) A. G. Whittaker and D. M. P. Mingos, *J. Microwave Power Electromagnetic Energy*, 1994, **29**, 195; (*c*) S. Caddick, *Tetrahedron*, 1995, **51**, 10403; (*d*) C. R. Strauss and R. W. Trainor, *Aust. J. Chem.*, 1995, **48**, 1665; (*e*) A. K. Bose, B. K. Banik, N. Lavlinskaia, M. Jayaraman and M. S. Manhas, *CHEMTECH*, 1997, **27**, 18; (*f*) R. S. Varma, *Clean Products and Processes*, 1999, in press.
6 R. J. Giguere, A. M. Namen, B. O. Lopez, A. Arepally, D. E. Ramos, G. Majetich and J. Defrauw, *Tetrahedron Lett.*, 1987, **28**, 6553.
7 R. S. Varma, in, *Microwaves: Theory and Application in Material Processing IV*, ed. D. E. Clark, W. H. Sutton and D. A. Lewis, American Ceramic Society, Westerville, OH, 1997, pp. 357–365.
8 R. S. Varma and H. M. Meshram, *Tetrahedron Lett.*, 1997, **38**, 5427.
9 R. S. Varma and R. K. Saini, *Tetrahedron Lett.*, 1997, **38**, 2623.
10 R. S. Varma, M. Varma and A. K. Chatterjee, *J. Chem. Soc., Perkin Trans. 1*, 1993, 999.
11 R. S. Varma, A. K. Chatterjee and M. Varma, *Tetrahedron Lett.*, 1993, **34**, 3207.
12 R. S. Varma, J. B. Lamture and M. Varma, *Tetrahedron Lett.*, 1993, **34**, 3029.
13 R. S. Varma, A. K. Chatterjee and M. Varma, *Tetrahedron Lett.*, 1993, **34**, 4603.
14 R. S. Varma, R. Dahiya and R. K. Saini, *Tetrahedron Lett.*, 1997, **38**, 8819.
15 R. S. Varma and H. M. Meshram, *Tetrahedron Lett.*, 1997, **38**, 7973.
16 R. S. Varma and D. Kumar, *Synth. Commun.*, 1999, **29**, in press.
17 R. S. Varma and R. Dahiya, *Tetrahedron Lett.*, 1997, **38**, 2043.
18 R. S. Varma, R. K. Saini and R. Dahiya, *Tetrahedron Lett.*, 1997, **38**, 7823.
19 R. S. Varma and R. Dahiya, *Tetrahedron Lett.*, 1998, **39**, 1307.
20 R. S. Varma and R. K. Saini, *Tetrahedron Lett.*, 1998, **39**, 1481.
21 R. S. Varma, R. Dahiya and R. K. Saini, *Tetrahedron Lett.*, 1997, **38**, 7029.
22 R. S. Varma, D. Kumar and R. Dahiya, *J. Chem. Res.* (*S*), 1998, 324.
23 R. S. Varma, R. Dahiya and D. Kumar, *Molecules Online*, 1998, **2**, 82.
24 R. S. Varma, R. K. Saini and H. M. Meshram, *Tetrahedron Lett.*, 1997, **38**, 6525.
25 (*a*) R. S. Varma, R. K. Saini and R. Dahiya, *J. Chem. Res. (S)*, 1998, 120; (*b*) R. S. Varma and R. Dahiya, *Synth. Commun.*, 1998, **28**, 4087.
26 R. S. Varma, R. Dahiya and S. Kumar, *Tetrahedron Lett.*, 1997, **38**, 2039.
27 R. S. Varma and R. Dahiya, *Synlett*, 1997, 1245.
28 R. S. Varma, R. Dahiya and S. Kumar, *Tetrahedron Lett.*, 1997, **38**, 5131.
29 R. S. Varma and R. Dahiya, *J. Org. Chem.*, 1998, **63**, 8038.
30 R. S. Varma, R. K. Saini and D. Kumar, *J. Chem. Res.* (*S*), 1998, 348.
31 R. S. Varma and R. K. Saini, *Synlett*, 1997, 857.
32 R. S. Varma and R. K. Saini, *Tetrahedron Lett.*, 1997, **38**, 4337.
33 R. S. Varma and R. Dahiya, *Tetrahedron*, 1998, **54**, 6293.
34 (*a*) D. Villemin and B. Labiad, *Synth. Commun.*, 1990, **20**, 3333; (*b*) D. Villemin and A. B. Alloum, *Synth. Commun.*, 1990, **20**,

3325; (*c*) D. Villemin and A. B. Alloum, *Synth. Commun.*, 1991, **21**, 63; (*d*) J. M. Lerestif, J. P. Bazureau and J. Hamelin, *Synlett*, 1995, 647; (*e*) M. Csiba, J. Cleophax, A. Loupy, J. Malthete and S. D. Gero, *Tetrahedran Lett.*, 1993, **34**, 1787; (*f*) D. Villemin, A. B. Alloum and F. Thibault-Starzyk, *Synth. Commun.*, 1992, **22**, 1359; (*g*) H. Benhaliliba, A. Derdour, J.-P. Bazureau, F. Texier-Boullet and J. Hamelin, *Tetrahedron Lett.*, 1998, **39**, 541; (*h*) M. Rahmouni, A. Derdour, J.-P. Bazureau, J. Hamelin, *Tetrahedron Lett.*, 1994, **35**, 4563; *Synth. Commun.*, 1996, **26**, 453; (*i*) E. Gutierrez, A. Loupy, G. Bram and E. Ruiz-Hitzky, *Tetrahedron Lett.*, 1989, **30**, 945; (*j*) D. Villemin and B. Labiad, *Synth. Commun.*, 1992, **22**, 2043; (*k*) A. I. Bosch, P. de la Cruez, E. Diez-Barra, A. Loupy and F. Langa, *Synlett*, 1995, 1259; (*l*) D. Villemin and B. Martin, *J. Chem. Res.* (*S*), 1994, 146.

35 D. A. Nelson, C. Devin, S. Hoffmann and A. Lau, Division of Chemical Education, ACS National Meeting, San Francisco, April 13–17, 1997, Abstract no. 101.

36 M. Balogh and P. Laszlo, *Organic chemistry using clays*, Springer, Berlin, 1993.

37 B. Perio, M. J. Dozias, P. Jacquault and J. Hamelin, *Tetrahedron Lett.*, 1997, **38**, 7867.

38 D. Bogdal, J. Pielichowski and A. Boron, *Synlett*, 1996, 873.

39 A. Vass, J. Toth and E. Pallai-Varsanyi, *Effect of inorganic solid support for microwave assisted organic reactions*, OR 19, presented at the International Conference on Microwave Chemistry, Prague, Czech Republic, Sept. 6–11, 1998.

40 D. Bogdal, J. Pielichowski and K. Jaskot, *Synth. Commun.*, 1997, **27**, 1553.

41 D. Bogdal, J. Pielichowski and K. Jaskot, *Heterocycles*, 1997, **45**, 715.

42 P. de la Cruz, A. de la Hoz, L. M. Font, F. Langa and M. C. Perez-Rodriguez, *Tetrahedron Lett.*, 1998, **39**, 6053.

43 (*a*) R. Ballini, M. Bordoni, G. Bosica, R. Maggi and G. Sartori, *Tetrahedron Lett.*, 1998, **39**, 7587; (*b*) R. Ballini, G. Bosica and M. Parrini, *Tetrahedron Lett.*, 1998, **39**, 7963.

44 D. Subhas Bose and V. Lakshminarayana, *Tetrahedron Lett.*, 1998, **39**, 5631.

45 (*a*) *Comprehensive Organic Synthesis (Oxidation)*, ed. B. M. Trost, Pergamon, New York, 1991, vol 7; (*b*) A. Oussaid and A. Loupy, *J. Chem. Res. (S)*, 1997, 342.

46 (*a*) R. S. Varma and G. W. Kabalka, *Heterocycles*, 1986, **24**, 2645; (*b*) G. W. Kabalka and R. S. Varma, *Org. Prep. Proc. Int.*, 1987, **19**, 283; (*c*) G. W. Kabalka, L. H. M. Guindi and R. S. Varma, *Tetrahedron*, 1990, **46**, 7443.

47 D. Villemin and B. Martin, *Synth. Commun.*, 1995, **25**, 3135.

48 (*a*) V. Singh, J. Singh, P. Kaur and G. L. Kad, *J. Chem. Res. (S)*, 1997, 58; (*b*) D. Bogdal, *J. Chem. Res. (S)*, 1998, 468.

49 (*a*) G. H. Posner, A. W. Runquist and M. J. Chapdelaine, *J. Org. Chem.*, 1977, **42**, 1202 and references cited therein; (*b*) D. Barbry and S. Torchy, *Tetrahedron Lett.*, 1997, **38**, 2959.

50 A. Saoudi, J. Hamelin and H. Benhaoua, *J. Chem. Res. (S)*, 1996, 492.

51 D. Villemin, M. Hammadi and B. Martin, *Synth. Commun.*, 1996, **26**, 2895.

52 A. L. Marrero-Terrero and A. Loupy, *Synlett*, 1996, 245.

53 R. S. Varma, D. Kumar and P. J. Liesen, *J. Chem. Soc., Perkin Trans. 1*, 1998, 4093.

54 M. Miller and G. Loudon, *J. Org. Chem.*, 1975, **40**, 126.

55 (*a*) J. H. Pomeroy and C. A. Craig, *J. Am. Chem. Soc.*, 1959, **81**, 6340; (*b*) D. T. Mowry, *Chem. Rev.*, 1948, **42**, 250; (*c*) H. M. Sampath Kumar, P. K. Mohanty, M. Suresh Kumar and J. S. Yadav, *Synth. Commun.*, 1997, **27**, 1327; (*d*) D. L. Clive, *Chem. Commun.*, 1970, 1014; (*e*) P. J. Foley, *J. Org. Chem.*, 1969, **34**, 2805; (*f*) W. Lehnert, *Tetrahedron Lett.*, 1971, **6**, 559; (*g*) G. Rosini, G. Baccolini and S. Cacchi, *J. Org. Chem.*, 1973, **38**, 1060; (*h*) H. G. Foley and D. R. Dalton, *J. Chem. Soc., Chem. Commun.*, 1973, 628; (*i*) D. Villemin, M. Lalaoui and A. B. Alloum, *Chem. Ind. (London)*, 1991, 176 (*j*) R. S. Varma and K. P. Naicker, *Molecules Online*, 1998, **2**, 94; (*k*) R. S. Varma, K. P. Naicker, D. Kumar, R. Dahiya and P. J. Liesen, *J. Microwave Power Electromagnetic Energy*, 1999, in press.

56 (*a*) S. Cannizzaro, *Ann.*, 1853, **88**, 129; (*b*) T. A. Geissman, *Org. React.*, (*NY*), 1944, **II**, 94.

57 (*a*) C. G. Swain, A. L. Powell, W. A. Sheppard and C. R. Morgan, *J. Am. Chem. Soc.*, 1979, **101**, 3576; (*b*) S. K. Chung, *J. Chem. Soc., Chem. Commun.*, 1982, 480; (*c*) E. C. Ashby, D. T. Coleman III and M. P. Gamasa, *Tetrahedron Lett.*, 1983, **24**, 851.

58 (*a*) R. S. Varma, K. P. Naicker and P. J. Liesen, *Tetrahedron Lett.*, 1998, **39**, 8437; (*b*) R. S. Varma, G. W. Kabalka, L. T. Evans and R. M. Pagni, *Synth. Commun.*, 1985, **15**, 279.

59 (*a*) J. Barrios, R. Rojas, A. R. Alcanrara and J. V. Sinisterra, *J. Catal.* 1988, **112**, 528; (*b*) J. V. Sinisterra, J. M. Marinas, F. Riquelme and M. S. Arias, *Tetrahedron* , 1988, **44**, 1431.

60 J. V. Sinisterra, A. Fuentes and J. M. Marinas, *J. Org. Chem.*, 1987, **52**, 3875.

61 J. V. Sinisterra and J. M. Marinas, *Bull. Soc. Chim. Belg.*, 1987, **96**, 293.

62 J. V. Sinisterra, *React. Kinet. Catal. Lett.*, 1986, **30**, 93.

63 R. S. Varma, K. P. Naicker and P. J. Liesen, *Tetrahedron Lett.*, 1998, **39**, 3977.

64 D. Villemin and F. Sauvaget, *Synlett*, 1994, 435.

65 A. Loupy and Le Ngoc Thach, *Synth. Commun.*, 1993, **23**, 2571.

66 (*a*) K. E. Wilzbach, *J. Am. Chem. Soc.*, 1957, **79**, 1013; (*b*) J. R. Jones, *Development of new microwave enhanced tritiation procedures*, OR 9, presented at the International Conference on Microwave Chemistry, Prague, Czech Republic, Sept. 6–11, 1998; (*c*) N. H. Werstiuk, in *Isotopes in the physical and biological sciences*, ed. E. Buncel and J. R. Jones, Elsevier, Amsterdam, 1987, vol. 1A, pp. 124–155; (*d*) S. Anto, J. R. Jones and S. Y. Lu, *Microwave enhanced acid-catalysed hydrogen/deuterium exchange reactions*, P 34, presented at the International Conference on Microwave Chemistry, Prague, Czech Republic, Sept. 6–11, 1998.

67 S. Stone-Elander, N. Elander, J.-O. Thorell, P. Johnstrom, H. Ehrsson, A. Andersson and S. Kalhori, *Monomodal microwave techniques in microscale organic chemistry*, OR 2, presented at the International Conference on Microwave Chemistry, Prague, Czech Republic, Sept. 6–11, 1998 and references cited therein.

68 M. Liagre, A. Loupy, A Oussaid, A. Petit and J. Cleophax, *Scaling-up of some typical organic reactions under focused microwaves*, presented at the International Conference on Microwave Chemistry, Prague, Czech Republic, Sept. 6–11, 1998.

69 M. Mehdizadeh, *Engineering and scale-up considerations for microwave induced reactions*, in *Proceedings: Microwave-Induced Reactions Workshop*, Electric Power Research Institute, Palo Alto, CA, 1993, p. A-7.

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