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Clay and clay-supported reagents in organic synthesis

Rajender S. Varma[*]

Clean Processes Branch, National Risk Management Research Laboratory, US Environmental Protection Agency, 26 West Martin Luther King Drive, Cincinnati, OH 45268, USA

Contents

1. Introduction

Recent years have witnessed a phenomenal growth in the use of inorganic solids as reaction media for organic transformations.[1–5] Laszlo even went on to claim that the future of synthetic organic chemistry rests with heterogeneous media rather than the currently predominant homogeneous systems due to certain specific advantages of using solid surfaces.[2a] Clay minerals constitute one such medium.[2b]

Clay minerals occur abundantly in nature and their high surface area, sorptive and ion-exchange properties have been exploited for catalytic applications through decades. Solid clay catalysts[6,7] have a broad range of functions including (a) use as catalytically active agents (usually as solid acids), (b) as bifunctional or 'inert' supports, (c) as fillers to give solid catalysts with required physical properties (e.g. attrition–resistance, density, specific heat capacity etc.).

2. Structure of clay minerals

Clay minerals are made up of layered silicates. They are crystalline materials of very fine particle size ranging from 150 to less than 1 micron (colloidal form). There are two basic building blocks viz. tetrahedral and octahedral layers, which are common to clay minerals.[8–11]

2.1. Layer structure

Tetrahedral layers consist of continuous sheets of silica tetrahedra linked via three corners to form a hexagonal mesh and the fourth corner of each tetrahedron (normal to the plane of the sheet) is shared with octahedra in adjacent layers. Octahedral layers in clay mineral, on the other hand, consist of flat layers of edge-sharing octahedra, each formally containing cations at its centre (usually Mg^{2+} or Al^{3+}) and OH^- or O^{2-} at its apices. Octahedral layers may be trioctahedral or dioctahedral depending on the degree of occupancy of the octahedral sites.[2b]

These different classes of clay minerals, namely the 1:1, 2:1, etc. have a different arrangement of tetrahedral and octahedral layers. Structural units of clays therefore consist of either

(a) alternating tetrahedral or octahedral sheets (OT or 1:1 structure), e.g. kaolinite group,
(b) a sandwich of one octahedral sheet between two tetrahedral sheets (TOT or 2:1 structure), e.g. smectite clay minerals of which the most common member is montmorillonite,
(c) an arrangement in which the three layer TOT units alternate with a brucite layer (2:1:1 structure), e.g. chlorite.

2.1.1. Composition and isomorphous substitution.
Tetrahedral sites in clay minerals are mainly occupied by Si^{4+}. However, isomorphous substitution by Al^{3+} is also common. In the case of trioctahedral, octahedral sites are generally occupied by Mg^{2+}. Isomorphous substitution by other divalent cations such as Fe^{2+} or Ni^{2+} or by univalent cations such as Li^+ is common. In the case of dioctahedral clay minerals, octahedral sites are predominantly occupied by Al^{3+} and isomorphous substitution by other trivalent cations like Fe^{3+}, Cr^{3+} or divalent cations like Mg^{2+} or Fe^{2+} are common in 2:1 structures.

2.2. Smectite group minerals

This group of clay minerals has a dioctahedral or trioctahedral 2:1 layer structure, with isomorphous substitution that leads to a negative layer charge of less than 1.2 per formula unit. Interlayer spacings vary between ∼10 and 15 Å and are generally dependent on the nature of the exchangeable cation and the relative humidity.

Smectites are divided into four sub-classes depending upon

(a) the type of octahedral layer (dioctahedral or trioctahedral),
(b) the predominant location of layer charge sites (octahedral or tetrahedral).

Montmorillonite and beidellite groups shown below are dioctahedral smectites with layer charges predominantly in octahedral and tetrahedral sites, respectively.

Montmorillonite group: $(M_x^+)^{ex}[(Si_8)^{tet}(M(III)_{4-x}M(II)_x)^{oct}O_{20}(OH)_4]^{x-}$
Beidellite group: $(M_x^+)^{ex}[(Si_{8-x}Al_x)^{tet}M(III)_4^{oct}O_{20}(OH)_4]^{x-}$
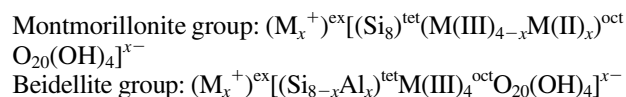
where M^+ is the exchangeable cation present in the interlayer (e.g. Na^+) and M(III) and M(II) are non-exchangeable octahedrally coordinated trivalent and divalent cations (e.g. Al^{3+} and Mg^{2+}), respectively and the layer charge is $0.5 < x < 1.2$.

Hectorite and saponite groups are trioctahedral smectites with layer charges predominantly in octahedral and tetrahedral sites, respectively. Their ideal formulae are

Hectorite group: $(M_x^+)^{ex}[(Si_8)^{tet}(M(II)_{6-x}M(I)_x)^{oct}O_{20}(OH)_4]^{x-}$
Saponite group: $(M_x^+)^{ex}[(Si_{8-x}Al_x)^{tet}(M(II)_6)^{oct}O_{20}(OH)_4]^{x-}$
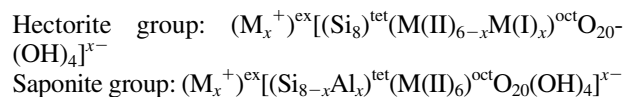
M(II) and M(I) are non-exchangeable octahedrally coordinated divalent and univalent cations (e.g. Mg^{2+} and Li^+), respectively and the layer charge is $0.5 < x < 1.2$.

Clay minerals that predominantly have properties governed by smectites are called bentonites. Montmorillonite is a major constituent of most bentonites (typically 80–90 wt%), the remainder being a mixture of mineral impurities including quartz, crystobalite, feldspar and various other clay minerals, depending upon geological origin. Bentonites containing high level of montmorillonites are the most abundant and commercially mineable forms of smectites.

2.2.1. Montmorillonites. Montmorillonite is the most important smectite used in catalytic applications. High cation-exchange capacity (CEC) and good swelling properties allow a wide variety of catalytically active forms of montmorillonite to be prepared (e.g. containing acidic cations, metal complexes, photocatalytically active cations, etc.)

Montmorillonites are most frequently used as Brönsted acid catalysts, where the exchangeable cations are either protons or polarizing cations (e.g. Al^{3+}, Cr^{3+} or Fe^{3+}). Acid site strength depends upon the type of interlayer cations present ($H_3O^+ > Al^{3+} > Ca^{2+} > Na^+$). Higher acid strength generally leads to greater catalytic activity, but poorer product selectivity. Controlling the acid site strength by choice of interlayer cations proves to be useful for 'fine-tuning' the catalyst selectivity. When treated with mineral acids under harsh conditions (e.g. refluxing), montmorillonites undergo leaching of aluminum and, to a lesser extent, silicon. This leads to increased surface area and concentration of weak acid sites, but a decrease in concentration of strong acid sites. Acid leached montmorillonite is particularly useful for catalytic applications requiring only weak acid sites, where strong acid sites give rise to poor selectivity.

3. Properties of clays

3.1. Ion exchange

Isomorphous substitution of cations in the lattice by lower-valent ions, e.g. the substitution of aluminium for silicon, magnesium and/or ferrous ion for aluminum or sometimes lithium for magnesium, leaves a residual negative charge in the lattice that is balanced by other cations.[11] These can be readily replaced by other cations when brought into contact with these ions in aqueous solution.

3.2. Swelling

Many clay minerals absorb water between their layers, which move apart and the clay swells. For efficient swelling, the energy released by cations and/or layer solvation must be sufficient to overcome the attractive forces (such as hydrogen bonding) between the adjacent layers. In 1:1 (OT) clay minerals (kaolinite), water forms strong hydrogen bonds with hydroxyl groups on hydrophilic octahedral layers, allowing swelling to occur.

With 2:1 (TOT) clay minerals, the ability to swell depends on the solvation of interlayer cations and layer charge. Clays with 2:1 structures and low layer charge (e.g. talc and pyrophyllite) have very low concentration of interlayer cations

and therefore do not swell readily. At the other extreme, those with very high layer charges (e.g. mica) have strong electrostatic forces holding alternate anionic layers and the interlayer cations together, thus preventing swelling. Those with univalent interlayer cations swell most readily and with divalent, trivalent and polyvalent cations, swelling decreases accordingly. The extent of swelling can be observed by measuring interlayer separations using powder X-ray diffraction.

3.3. Intercalation and cation-exchange

In swelling clay minerals, such as smectites, the interlayer cations can undergo exchange with cations from external solutions. The concentration of exchangeable cations is called CEC, usually measured in milliequivalents per 100 g of dried clay. Since smectites have the highest concentration of interlayer cations, they have the highest cation exchange capacities (typically 70–120 mequiv./100 g). Structural defects at layer edges give rise to additional CEC and a small amount of anion exchange capacity.

3.4. Acidity

The interlayer cations contribute to the acidity of clay minerals. Some of these cations may be protons or polarizing cations (e.g. Al^{3+}) which give rise to strong Brönsted acidity.[12] The higher the electronegativity of M^+, the stronger are the acidic sites generated. Brönsted acidity also stems from the terminal hydroxyl groups and from the bridging oxygen atoms.

In addition, clay minerals have layer surface and edge defects, which would result in weaker Brönsted and/or Lewis acidity, generally at low concentrations. The acid strength is usually expressed by the Hammett scale. On this scale, the acidity of clay minerals can be comparable to that of concentrated sulfuric acid. The surface acidity of natural clays with Na^+ or NH_4^+ as interstitial cations ranges from $+1.5$ to -3. Washing of the clay with mineral acid, such as HCl, brings down the Hammett (H_O) function from -6 to -8, which is between conc. HNO_3 (-5) and H_2SO_4 (-12).

4. Pillared clays

Between the TOT layers of a smectite, large cationic species (e.g. aluminum chlorhydrol) can be inserted by cation exchange.[13,14] Such bulky species act like pillars, propping apart the TOT layers (typically by 0.3–1.5 nm). Slit-shaped pores are formed between pillars and TOT layers, which give rise to a uniform two-dimensional micropore system between adjacent TOT layers. Pore entry sizes are governed by the height of the pillars and the distance between them and can be designed to suit specific application.

A wide range of bulky cationic species have been used to prepare pillared smectites, including organic cations[15,16] (e.g. quaternary ammonium cations and 1,4-diazabicyclo-[2.2.2] octane, DABCO) and inorganic cations (e.g. poly-oxyhydroxides of aluminum and zirconium). Alumina

pillars derived from aluminum chlorhydrol are the most widely used. They have strong Brönsted acidity and retain a limited ability to swell. Heating at low temperature (<110°C) leads to dehydration, whereas calcination at high temperature (~450°C) leads to irreversible conversion of ACH (aluminum chlorhydrol) cations to small particles of alumina that remain between the smectite's TOT layers. Alumina pillared clays have rigid, non-swelling, interlayer micropore structures (pore volume typically 0.1 cm^3 ml^{-1}) and moderate surface areas, but considerably lower Brönsted acidity than their ACH exchanged precursors. Their salient feature, namely, the ability to retain the microporosity at high temperatures (unlike non-pillared precursors) render pillared smectites as attractive catalysts or supports, for gas phase reactions where the retention of surface area is important.

5. Supported reagents

The deliberate introduction of a reagent into or onto an inert, generally porous, inorganic support produces supported reagents.[2,3,17] There are several advantages of engaging a supported reagent in organic syntheses. They offer

(a) remarkable ease of handling and use. A simple filtration suffices to remove the contaminated by-products. The evaporation of solvent from the filtrate is often sufficient to provide the product in pure form,
(b) reduced product contamination by having the reagent fully bound to the solid support,
(c) relatively safe handling owing to the full chemisorption of the toxic chemicals,
(d) reduced environmental problems upon work-up. Many inorganic species are powerful oxidants and sometime can cause explosions. However, they can be tamed by prior adsorption onto the solid support,
(e) good thermal and mechanical stabilities, allowing higher stirring rates, if necessary,
(f) good dispersion of active (reagent) sites, which leads to significant improvement in reactivity. The higher reactivity can also arise from physical factors such as vastly enhanced collision rates between reactants due to either the reduced dimensionality on the solid reaction sites or the boost in their local concentration due to trapping in the interstitial spaces of microporous solids. Chemisorption generally activates adsorbates with respect to bond breaking, and
(g) improvement in reaction selectivity due to the constraints of the pores and the characteristics of surface adsorption.

5.1. Clay-supported reagents

Alumina, silica and aluminosilicates (clays and zeolites) are some of the most widely employed supports, where surface hydroxyl groups play a major role in these reactions. Clay-supported potassium permanganate oxidizes secondary alcohols to ketones.[18] The selective oxidation of an allylic alcohol to an unsaturated ketone is a special attribute of this oxidant. It is significant to note that, with prolonged reaction times and a very large excess of the oxidant, olefinic bonds

are also cleavable. The advantage of this method is that, unlike manganese dioxide oxidation, prior activation of the reagent is not necessary.

The oxidation potential of thallium(III) nitrate (TTN) supported on K10-montmorillonite has been established by McKillop et al.[19] Oxidations are easily performed in inert solvents such as toluene, heptane, methylene chloride and carbon tetrachloride. Some of the typical applications of TTN reagent are (a) oxidative rearrangement of alkyl aryl ketones leading to alkyl arylcarboxylates,[20] (b) conversion of alkenes to acetals, (c) oxidative rearrangement of aldehydes and esters and (d) conversion of 3-acetylpyrrole into the corresponding methoxycarbonylpyrrole.[21]

The selective oxidation of alkyl arenes to the corresponding aryl butyl peroxides (45–90%) has been accomplished with *tert*-butyl hydroperoxide (TBHP) using Ru(III)-exchanged K 10 clay.[22a] Hydrocarbons such as cyclohexane can be oxidized with 70% TBHP in the presence of Mn^{2+}-exchanged clay as catalyst with high turnover numbers.[22b]

5.1.1. 'Clayfen and claycop'. Impregnation of Fe(III) and Cu(II) nitrates onto K 10-montmorillonites produced a novel class of multipurpose reagents termed *clayfen* and *claycop*, respectively by Laszlo and co-workers.[23,24] Clayfen is utilized as an efficient oxidant for the oxidation of alcohols (~90% yield of aldehydes without over-oxidation to carboxylic acids in the case of primary alcohols),[23] oxidation of benzoin to benzil,[25] and oxidative coupling of thiols to disulfides via, thionitrite intermediates.[26] Clayfen is also used for the regeneration of carbonyls from their various protected forms such as tosylhydrazones, phenylhydrazones and semicarbazones.[27] It can be used to convert hydrazones into azides as well.

Claycop is relatively less reactive than clayfen but enjoys a greater stability.[28] It has been used for the oxidation of dihydropyridines to pyridines,[29] quantitative regeneration of carbonyl groups from the protective bisthioacetals, selenoacetals[30] and also from thiocarbonyls.[31]

Clayzic is another supported reagent that is zinc chloride 'doped' natural aluminosilicate clay.[32] It is identified as a very promising supported reagent for the Friedel–Crafts alkylation of benzenoid compounds,[33] a reaction that is facile even at room temperature. In reactions where Lewis acidity is critical, this reagent enjoys unique advantages and has numerous potential applications.

More recently, clayan, ammonium nitrate doped clay, has been introduced for similar oxidative applications including nitration of styrene under solvent-free conditions (vide infra).

6. Organic reactions in clay media

Acid-treated and cation-exchanged montmorillonites possess the ability to catalyze organic reactions.[34] During the thirties and forties, acid-treated montmorillonites were major catalysts used in petroleum processing, though they were later replaced by more thermostable zeolites. The
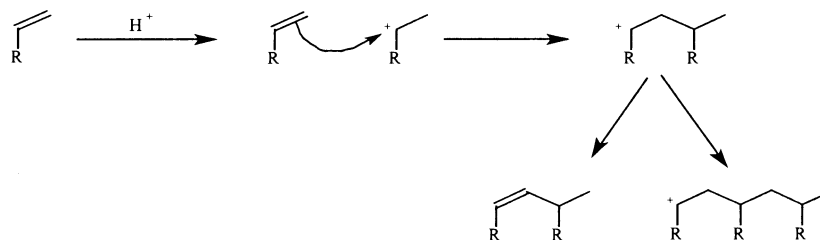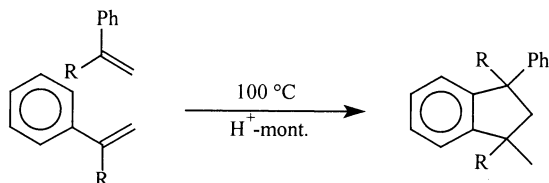
Scheme 1.

modified montmorillonites are versatile heterogeneous catalysts for a wide variety of organic reactions.

6.1. Oligomerization reactions

Alkenes undergo facile oligomerization in the presence of acid-treated or ion-exchanged montmorillonites.[35] The reaction involves protonation to generate a stabilized carbocation that, in turn, reacts with other alkene molecules to give dimers as well as oligomers after deprotonation (Scheme 1).

Styrene has been polymerized in the presence of acid-treated montmorillonite[36] and is one of the earliest reported clay-catalyzed dimerization reactions (Scheme 2).
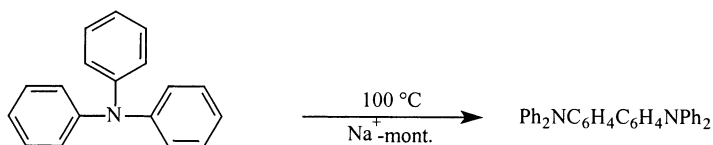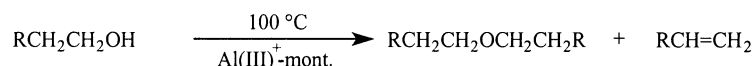

Scheme 2.

Triphenylamine readily provides *N,N,N′,N′*-tetraphenyl-benzidine.[37] The mechanism involves an initial dimerization, followed by a benzidine type rearrangement upon heating (Scheme 3).

6.2. Dehydration reactions

The intramolecular dehydration of alcohols is efficiently catalyzed by both Al(III) as well as H⁺-exchanged clays.[38] Primary alcohols afford mainly dialkyl ethers with little alkene production whereas secondary and tertiary alcohols provide alkenes almost exclusively (Scheme 4).

Ethylene glycol upon heating, with Al(III)-exchanged clay to 200°C, provides polyethylene glycol.[38] This intermolecular elimination of water from two molecules is a very common acid catalyzed reaction and can be successfully accomplished by montmorillonite. Benzyl alcohol, on the other hand, undergoes polymerization with Al(III)-exchanged montmorillonite to yield poly(phenylenemethyl-ene) by elimination of water via an electrophilic aromatic substitution reaction.[38]

Primary amines are converted to dialkylamines by loss of ammonia[39] and thiols afford dialkyl thioethers[40] by elimination of hydrogen sulfide (Scheme 5).

$$RCH_2XH \xrightarrow[Al(III)^+\text{-mont.}]{-H_2X} RCH_2XCH_2R$$
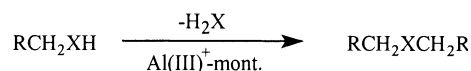
X = NH, O, S

Scheme 5.

Pyrrolidine, a cyclic secondary amine, on treatment with Al(III)-montmorillonite provides interesting products[39] which are distinct from the chemistry in the solution phase (Scheme 6).

6.3. Addition reactions

Acid-treated and cation-exchanged montmorillonites are effective catalysts for a variety of addition reactions.[41] The mechanism involves, in the first step, the addition of a proton or a Lewis acidic site and the subsequent rearrangement of the intermediate carbocation to generate the more stable forms that then combine with a nucleophile. The products are formed by the elimination of the proton or by the Lewis acidic site. Alcohols can add to alkenes in the presence of montmorillonite to afford ethers.[42,43] The

$$\xrightarrow[Na^+\text{-mont.}]{100\,°C} Ph_2NC_6H_4C_6H_4NPh_2$$

Scheme 3.

$$RCH_2CH_2OH \xrightarrow[Al(III)^+\text{-mont.}]{100\,°C} RCH_2CH_2OCH_2CH_2R \ + \ RCH=CH_2$$

Scheme 4.

Scheme 6.

Where X = S, O, OCO
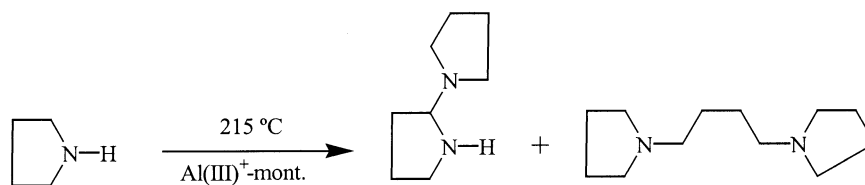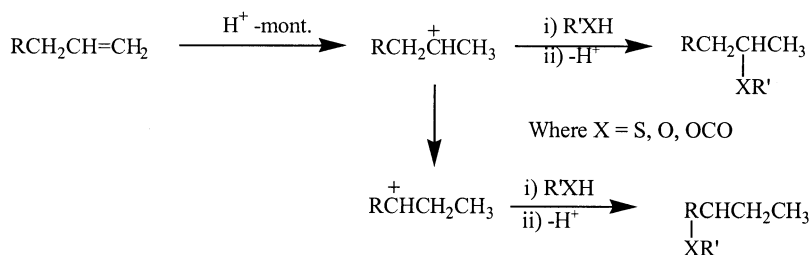
Scheme 7.

reaction with alk-1-enes, however, is slow and results in a mixture of alk-2-yl and alk-3-yl ethers (Scheme 7).

Hydrogen sulfde and thiols add to alkenes in the presence of acid-treated and Al(III)-exchanged montmorillonites at 200°C to provide dialkyl sulfides in good yields (Scheme 8).[44]

Scheme 8.

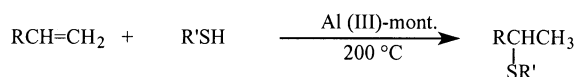Ammonia can add to ethyne over acid montmorillonite to yield both pyridine and piperidine.[34] However, no addition occurs in the case of alkenes. The addition of carboxylic acids to alkenes takes place over Al(III)-exchanged or proton-exchanged montmorillonites to provide esters (Scheme 9).[45]

6.4. Isomerization and rearrangement reactions

Pillared clays are commonly employed in alkane isomerizations.[46] As an example, Fries rearrangement can be used to prepare alkyl aryl ketones. Clays as well as their various cation-exchanged forms efficiently catalyze the Fries rearrangement of phenyl as well as naphthyl esters (acetates, benzoates and sulfonates).[47] The nature of the product depends on the size of the leaving group and is more pronounced with phenyl esters. Cation-exchanged montmorillonites are used as effective catalysts for the facile rearrangement of phenyl toluene-*para*-sulfonate to give 2- and 4-hydroxyphenyl-4-tolylsulfones.[48] Selectivity

for the *ortho*-isomer can be as high as 93% (Cu^{2+}–montmorillonite) and as low as 65% (H^+–montmorillonite).

6.5. Aromatic electrophilic substitution (Friedel–Crafts reaction)

There are numerous disadvantages in using stoichiometric amounts of aluminum chloride in the industrially significant Friedel–Crafts reaction that are associated with pollution load on the environment. Montmorillonite supported transition metal salts (zinc and nickel chlorides) are highly active and selective reagents for the catalysis of Friedel–Crafts alkylation and circumvents some of the drawbacks (Scheme 10).[49,50]
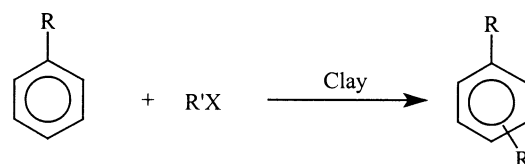
Scheme 10.

The Friedel–Crafts acylation of anisole, mesitylene and xylene by Fe(III) modified clay provides good to quantitative yields of the acyl derivatives.[51] Montmorillonite-supported cupric nitrite has been used in the regioselective nitration of aromatic hydrocarbons.[52] A vastly increased *para*-preference is reported in the nitration of halobenzenes.[53] Clay-catalyzed nitrodecarboxylation of aromatic acids (*para*-anisic acid) has also been reported.[54] The acid treated montmorillonite has been used to catalyze the electrophilic substitution of protonated formaldehyde to
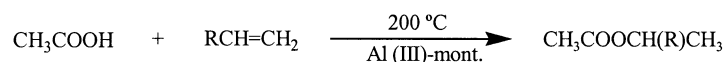
Scheme 9.
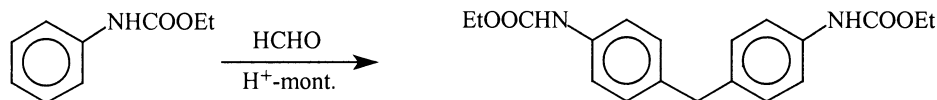
Scheme 11.

aromatic amines and phenols to produce diarylmethane derivatives of commercial interest (Scheme 11).[34]

6.6. Miscellaneous reactions (Diels–Alder, Heck and Suzuki reaction)

Fe(III)-doped K 10-montmorillonite, in combination with 4-*tert*-butylphenol, is a potent catalytic system for unactivated dienophiles in the Diels–Alder reactions.[55] The cation-exchanged K 10 montmorillonites are calcined and silylated in order to eliminate acidic sites. The solids thus obtained, promote the Diels–Alder reaction of cyclopentadiene with *trans*-anethole and cyclodimerization of *trans*-anethole.[56] Ce^{3+}-exchanged montmorillonite finds application as a useful substrate-selective acetalization catalyst.[57] Cation-exchanged montmorillonites catalyze the rearrangement of alkyl phenyl ethers to alkyl phenols.[58] The characterization of pillared clays,[59–61] study of their properties,[62–64] and their utility in chemical reactions[65] have also gained widespread attention in recent years.
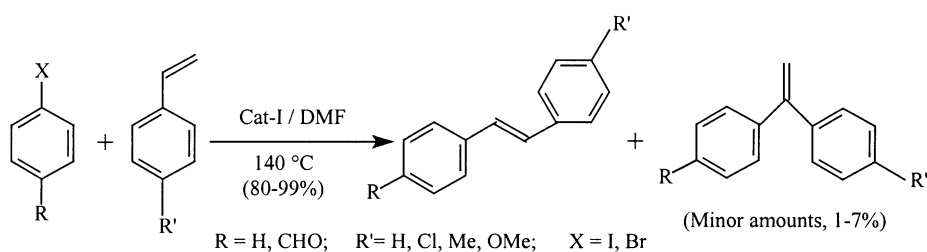
Heck reactions involving the palladium-catalyzed reaction of aryl halides with olefins are important carbon–carbon bond forming reactions.[66a–c] Recently, it has been demonstrated that $PdCl_2$ or $Pd(OAc)_2$ in the presence of tetraphenylphosphonium salts, exhibits high catalytic activity.[66d] The palladium salt employed in homogeneous reactions is reduced in situ to an active zero valent palladium species. The regenerated Pd^{II} species in these reactions have

strenuous requirements involving separation and processing before they can be reused again.[66c]

In order to improve the catalyst efficiency and its reusability, we have developed a new clay-based catalyst system, palladium chloride and tetraphenylphosphonium bromide ($PdCl_2/Ph_4PBr$) intercalated clay (Cat-I) and explored its application in the arylation of olefins.[67] The catalyst can be prepared by refluxing sodium-exchanged clay with a solution of $PdCl_2$ and tetraphenylphosphonium bromide in water for 48 h. The clay material is then filtered, washed thoroughly with water and dried overnight in an oven at 100–110°C. In a typical example, an equimolar amount (1 mmol) of aryl halide and styrene is refluxed with a mixture of catalyst and sodium acetate in dimethylformamide (Scheme 12) with continuous stirring.

The organized assembly of aluminosilicate layers leads to the formation of quantitative yields of products in a short time. The other salient features of the reactions are the manipulative ease and the separation of the catalyst by simple filtration. The subsequent reuse of the catalyst without loss in activity makes this an ideal protocol, a useful and attractive alternative to other methods.

The Suzuki coupling of aryl halides with arylboronic acids or esters provides ready access to biaryl compounds and has become a valuable tool for the organic chemists in view of the low toxicity, stability and ease of handling of boronic acids.[68a–c] We have extended the use of palladium chloride

R = H, CHO;   R'= H, Cl, Me, OMe;   X = I, Br

(Minor amounts, 1-7%)

Scheme 12.

R = H, 2-Ph, 4-Ph, 4-SMe and 4-*tert* butyl; R_1 = H, CHO
X = H, F and Cl; X_1 = I, Br

Scheme 13.

Where R = 2-Me, 3-Me, 4-Me, 4-NO$_2$; X = Br, Cl; X' = CN, SCN, OH
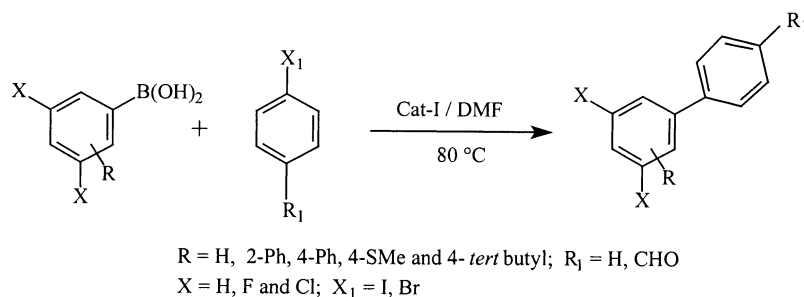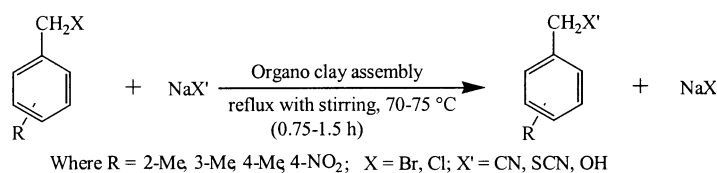
Scheme 14.

and tetraphenylphosphonium bromide intercalated clay (Cat-I) to the rapid synthesis of biaryl compounds via the cross-coupling reactions.[69]

In a typical example, an equimolar amount (1 mmol) of aryl halide and arylboronic acid is refluxed with premixed catalyst and potassium carbonate in dimethylformamide with continuous stirring (Scheme 13). The simple separation of the catalyst by filtration and its recyclability enhances the potential of this high yield reaction.

In the case of *ortho*-substituted arylboronic acid, the rate of the reaction is slower than *para* substituted acids due to large steric hindrance. The reaction rate using this heterogeneous catalyst is much faster, even at these very low concentrations of the catalyst (0.01 mmol/mmol of substrate), when compared to homogeneous reaction conditions. Interestingly, the reaction can also be conducted under environmentally benign aqueous media using ultrasound, wherein the biaryl compounds are obtained in good yields.[69]

7. Basic clays

Surface acidity of clays can be reduced substantially by introducing silylpropylethylenediamine. These modified clays are weakly basic and can be employed for base-catalyzed reactions such as Knoevenagel condensation.[70] Nucleophilic substitution reactions using quaternary ammonium salts-exchanged montmorillonite[71] and other clay-surfactants composites are also reported.[72]

The known efficiency of surfactant-pillared clays to act as a dispersed solid phase in a triphasic catalyst system[72] prompted us to prepare modified clays by introducing 3-aminopropyl-triethoxysilane and surfactants into the clay interlayer. We have extended the use of these organo-clay assemblies in some useful organic transformations. As an example, benzyl cyanides, thiocyanides and alcohols are easily accessible from the corresponding
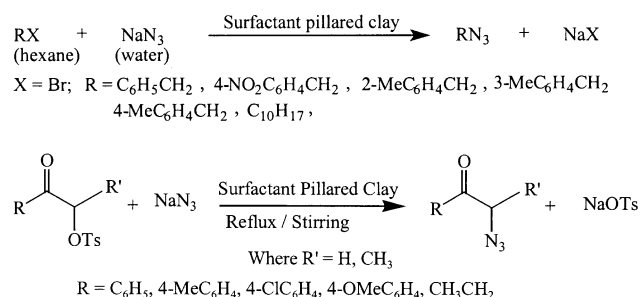
benzyl halides and sodium cyanide, thiocyanide and hydroxide, respectively (Scheme 14).[73]

The ability of crown ethers and cryptands to intercalate smectites is well known.[74] They form very stable polydentate coordination compounds in the interlayer space, replacing water molecules that belong to the hydration sphere of the exchangeable cations. Consequently, we decided to conduct the reaction by substituting 18-crown-6 in place of surfactants in the organo-clay assembly. The reaction turned out to be equally facile with this crown ether-clay material.[73] This method provides a relatively benign approach to the preparation of a variety of benzyl derivatives using triphase catalyst.
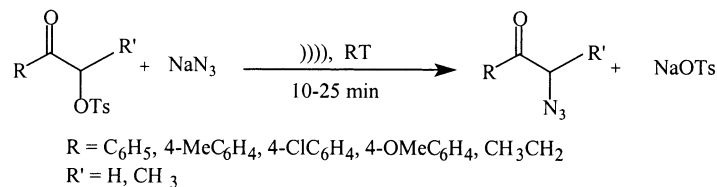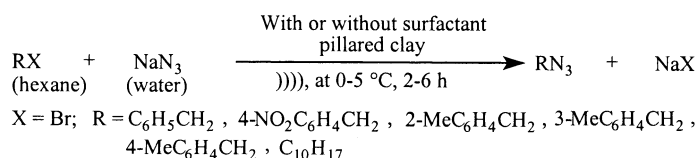
The utility of 18-crown-6 'doped' clay as a recyclable phase transfer catalyst in nucleophilic substitution reactions has been explored in our laboratory; it provides relatively improved yields of alkyl azides from alkyl bromides and sodium azide in aqueous medium.[75]

We have recently shown that alkyl halides and α-tosyloxyketones afford the corresponding azide derivatives upon treatment with aqueous sodium azide under triphase catalysis or ultrasound irradiation conditions.[76,77] The use of surfactant pillared clay materials and sonochemistry has been compared in these nucleophilic substitution reactions, culminating in a practical synthesis of azides and α-azidoketones involving triphase catalysis. A nucleophilic displacement occurs in this system that consists of a dispersed solid phase and two immiscible liquid phases containing the electrophilic and nucleophilic reagents where the reagents get transferred from the liquid phase to the solid phase.[78,79] Among the nucleophilic substitution reactions, there are only a handful of studies wherein ultrasound irradiation has been substituted for a phase transfer catalyst. In view of the paucity of the data in this field, we decided to explore the viability of ultrasound as a substitute for a phase-transfer catalyst (PTC). Interesting results have been obtained on a set of catalytic systems that include: (1) triphase catalyst under classical (reflux) condition; (2) triphase catalyst in conjunction with ultrasound irradiation at very low temperature; (3) and finally, a two-phase catalyst-free system using only ultrasound irradiation.[79]

In a typical example, the alkyl bromide (in hexane) or α-tosyloxyketones (in chloroform) and aqueous NaN$_3$ are admixed in the molar ratio 1:1.2 and refluxed with continuous stirring in the presence of organo-clay material under classical conditions or under ultrasound irradiation with or without organo-clay assembly (Schemes 15 and 16).

Under the influence of ultrasound irradiation, we have observed a favorable acceleration in reaction rates when

RX + NaN$_3$ $\xrightarrow{\text{Surfactant pillared clay}}$ RN$_3$ + NaX
(hexane) (water)

X = Br; R = C$_6$H$_5$CH$_2$, 4-NO$_2$C$_6$H$_4$CH$_2$, 2-MeC$_6$H$_4$CH$_2$, 3-MeC$_6$H$_4$CH$_2$
4-MeC$_6$H$_4$CH$_2$, C$_{10}$H$_{17}$,

Where R' = H, CH$_3$

R = C$_6$H$_5$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-OMeC$_6$H$_4$, CH$_3$CH$_2$

Scheme 15.

$$RX \underset{\text{(hexane)}}{} + NaN_3 \underset{\text{(water)}}{} \xrightarrow[\text{))))}, \text{ at } 0\text{-}5\ ^{\circ}\text{C}, \text{ 2-6 h}]{\overset{\text{With or without surfactant}}{\overset{\text{pillared clay}}{}}} RN_3 + NaX$$

X = Br; R = $C_6H_5CH_2$, $4\text{-}NO_2C_6H_4CH_2$, $2\text{-}MeC_6H_4CH_2$, $3\text{-}MeC_6H_4CH_2$,
$4\text{-}MeC_6H_4CH_2$, $C_{10}H_{17}$

R = C_6H_5, $4\text{-}MeC_6H_4$, $4\text{-}ClC_6H_4$, $4\text{-}OMeC_6H_4$, CH_3CH_2
R' = H, CH_3

Scheme 16.

Scheme 17.

Table 1. Clay-catalyzed synthesis of imines using microwaves

R	R'	Yield (%)
C_6H_5	C_6H_5	98
C_6H_5	$p\text{-}HOC_6H_4$	95
C_6H_5	$o\text{-}HOC_6H_4$	96
C_6H_5	$p\text{-}Me_2NC_6H_4$	96
C_6H_5	$p\text{-}MeOC_6H_4$	97

compared to classical conditions (i.e. under reflux). The addition of catalytic amount of surfactant-pillared clays further facilitated the reaction, thereby indicating a synergistic effect of ultrasound on triphase catalyst system. However, the successful reaction with sonication in the absence of pillared clay indicates that ultrasound can indeed substitute for a phase transfer catalyst, thereby suggesting that this is the method of choice for the nucleophilic substitution reactions.[79]

8. Microwave-accelerated solvent-free organic transformations using clay-supported reagents

In contrast to conventional homogeneous reaction procedures, the use of surface active catalysts and inorganic reagents has received much attention in recent years because of the enhanced selectivity and milder conditions.[80] Microwave (MW) irradiation, an unconventional energy source, has been used for a variety of applications including organic synthesis wherein chemical reactions are accelerated because of selective absorption of MW energy by polar molecules, non-polar molecules being inert to the MW dielectric loss.[81a] The use of microwave irradiation for the acceleration of organic reactions has profound impact on such heterogeneous reactions. The combination of the use of reactants and reagents immobilized on mineral oxide surfaces and microwave irradiation has blossomed into a

powerful technique with numerous attractive applications under relatively benign, solvent-free conditions.[81]

8.1. Synthesis of imines and enamines

The condensation reaction of aldehydes with primary amines, involving addition–elimination steps, proceeds via a polar transition state intermediate that has the propensity to couple with MW irradiation. Consequently, such reactions occurring with loss of water molecule are exquisitely positioned to benefit from exposure to MW irradiation.

Imines have been conventionally prepared using several reagents such as zinc chloride,[82a] titanium(IV) chloride,[82b] molecular sieves[82c] and alumina.[82d] In a broad program to develop environmentally benign synthetic protocols utilizing MW irradiation under solvent-free conditions,[81] a simple synthetic procedure has been developed that is catalyzed by montmorillonite K 10 clay[83] for the preparation of imines and enamines (Scheme 17, Table 1).[84] This approach eliminates the need for the large excess of support usually employed in solid phase reactions[82d] and reduces, considerably, the longer reaction times and large quantities of aromatic solvents required in the conventional solution phase chemistry that entails the azeotropic removal of water using Dean–Stark apparatus.[83]

Enamines are an important class of compounds used for selective alkylation and acylation of carbonyl compounds[85] and as valuable intermediates for the synthesis of biologically active natural products.[86] Consequently, the reaction of secondary amines with carbonyl compounds has been explored using microwave irradiation (Scheme 18, Table 2). The removal of a water molecule from the intermediate, catalyzed by *p*-toluenesulfonic acid,[82b,c] is the driving force for the reaction and is normally achieved by its azeotropic removal.[87–89] The coupling of the
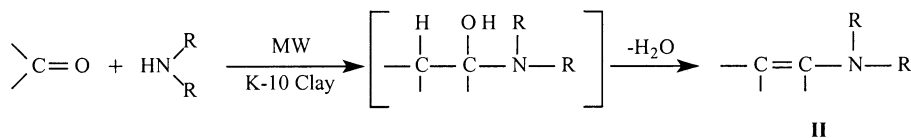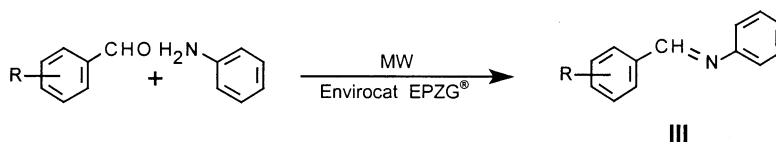
Scheme 18.

Table 2. Clay-catalyzed synthesis of enamines using microwaves

Ketone	Amine	Yield (%)	Time (min)
Cyclohexanone	Morpholine	97	8
Cyclohexanone	Piperidine	95	8
Cyclohexanone	Pyrrolidine	95	6
2-Methylcyclohexanone	Pyrrolidine	75	12
Cyclopentanone	Piperidine	96	8

heterogeneous catalyst, Envirocat EPZG[®],[90] has been examined for the synthesis of the valuable intermediates, imines and enamines, utilizing readily available carbonyl compounds and amines precursors.

This improved solventless synthesis of imines and enamines is conducted by simply mixing neat aldehydes and ketones
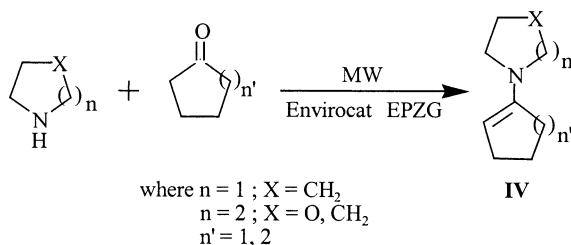

Scheme 19.

Table 3. EPZG[®] catalyzed synthesis of imines using microwaves

| R	Time (min)	Yield (%)
Hydrogen	1.0	97
o-Hydroxy	1.0	92
p-Hydroxy	3.0	91
p-Methyl	2.5	90
p-Dimethylamino	3.0	96
p-Methoxy	2.5	95

with a primary and secondary amine, respectively, and irradiating the mixture in an unmodified household microwave oven for 1–3 min in the presence of a catalytic amount of Envirocat EPZG[®]. The reaction of aldehydes and primary amines in the presence of Envirocat EPZG[®90,91] gave imines (**III**) under microwaves irradiation (Scheme 19, Table 3).[92]

Similarly, enamines (**IV**) are also prepared by reaction of ketones bearing an α-hydrogen atom with secondary amines (Scheme 20, Table 4). Some enaminoketones and acylamines have been prepared via a similar microwave-assisted approach, but the protocol requires a large excess of solid mineral support.[93] The elaboration of in situ generated enamines to heterocycles such as isoflav-3-enes has been accomplished in a one-pot method (vide infra).

microwaves with the ensuing polar intermediate transition state is presumably the key factor in expedited product formation.

8.2. Synthesis of imines and enamines using Envirocat EPZG[®] as a catalyst

An environmentally friendly and commercially available

8.3. Oxidation of sulfides to sulfoxides using clayfen

There are several oxidizing reagents that have been used to achieve sulfide to sulfoxide oxidation. Examples include hydrogen peroxide,[94] peracids,[95] chromic acid,[96] manganese dioxide,[96] nitric acid,[97] ozone,[98] sodium metaperiodate,[99] hypervalent iodine reagents,[100] and zeolites.[101] Most of these processes suffer from drawbacks, such as the use of corrosive acids, hazardous peracids, and metallic compounds that generate toxic waste streams. Earlier, iron(III) nitrate impregnated on clay (clayfen) has been used for a variety of heterogeneous reactions by Laszlo et al.[17]

where n = 1 ; X = CH$_2$
n = 2 ; X = O, CH$_2$
n' = 1, 2

IV

Scheme 20.

Table 4. EPZG[®] catalyzed synthesis of enamines using microwaves

Ketone	Amine	Yield (%)
Cyclohexanone	Morpholine	96
Cyclohexanone	Piperidine	90
Cyclohexanone	Pyrrolidine	94
Cyclopentanone	Piperidine	93
Cyclopentanone	Morpholine	94

We have provided a new and practical dimension to these reagents by using them in the solid state under microwave irradiation conditions.[102] Such a solid state reaction process
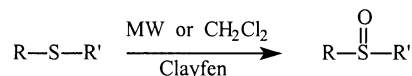
Scheme 21.

**Table 5.** Oxidation of sulfides to sulfoxides using clayfen

Entry	R	R′	CH₂Cl₂		MW (solventless)	
			Time (h)	Yield (%)	Time (s)	Yield (%)
1	(CH₃)₂CH	(CH₃)₂ CH	16	84	30	89
2	C₄H₉	C₄H₉	12	83	R.T.	86
3	CH₃	C₁₂H₂₅	18	88	30	90
4	CH₃	C₆H₅	18	90	15	91
5	C₆H₅	C₆H₅	20	72	60	75
6	C₆H₅CH₂	C₆H₅	23	84	60	85
7	C₆H₅CH₂	C₆H₅CH₂	24	10	60	15
8	Tetrahydrothiophene		11	78	R.T.	81
9	Tetrahydrothiopyran4-one		12	79	60	83

R.T. refers to reactions that are completed at room temperature.

using iron(III) nitrate impregnated on montmorillonite clay (clayfen) under the influence of microwaves (Scheme 21, Table 5) is applicable to long chain aliphatic sulfides (entry 3) which are normally insoluble in polar solvents and are therefore difficult to oxidize by conventional reactions. Sulfoxide products are accompanied by the formation of trace amount of sulfones i.e. <5% yield as confirmed by ^{1}H NMR analysis of the crude products. However, in the case of benzyl sulfide (entry 7), sulfone is the major product (~70%), both in solution as well as under solvent-free conditions. The reaction does proceed in refluxing methylene chloride solution but requires much longer reaction time (Table 5).

8.4. Oxidation of alcohols by clayfen

Oxidation of alcohols is an important transformation in organic synthesis and several methods are known for this particular conversion.[103] The use of heavy metals and peracids is very common but are detrimental to the environment.[104–106] In this context, the use of inexpensive supported reagents has received attention because of the selectivity and associated ease of manipulation[20,107] and more specifically, clay-supported reagents have found widespread acceptance in a variety of heterogeneous reactions.[2b,17] We have achieved a facile oxidation of alcohols to carbonyl compounds using clayfen, under solvent-free conditions (Scheme 22, Table 6).[108] Interestingly, primary alcohols afford aldehydes exclusively with no formation of the corresponding carboxylic acids.
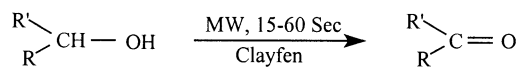
Scheme 22.

Table 6. Oxidation of alcohols by clayfen under microwave irradiation
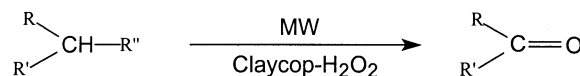
R	R′	Time (s)	Yields (%)
H	C₆H₅	15	92
CH₂CH₃	C₆H₅	30	87
C₆H₅	C₆H₅CO	60	93
H	p-CH₃C₆H₄	15	94
H	p-CH₃OC₆H₄	–	96
p-CH₃OC₆H₄CO	p-CH₃OC₆H₄	60	94
H	Tetrahydrofurfuryl	30	90
	–(CH₂)₅–	30	89

8.5. Oxidation of organic substrates by claycop and hydrogen peroxide

Metal ions are involved in oxidation reactions[109] and in biological dioxygen metabolism.[110] As an example, hydroperoxy copper(II) compound, has been produced using copper(II) acetate and hydrogen peroxide,[111] which is also obtainable from copper(II) nitrate and hydrogen peroxide (Eq. (1)).[112] The nitric acid generated in the process requires neutralization by potassium bicarbonate to maintain a pH~5.

$$2Cu(NO_3)_2 + 2H_2O + H_2O_2 \rightarrow 2CuO_2H + 4HNO_3 \quad (1)$$
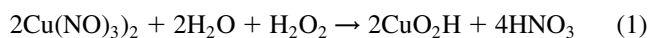
We have accomplished a MW-enhanced chemical oxidation of a variety of substrates using claycop in the presence of hydrogen peroxide (substrate:claycop:H₂O₂ ratio being 1:0.8:1) (Scheme 23, Table 7).[113] This expeditious method requires no pH control adjustments and affords higher yields of the oxidized products relative to earlier processes using copper-based reagents.[111,112]

Scheme 23.

Table 7. Oxidation of organic substrates by claycop and hydrogen peroxide

R	R′	R″	Mole ratio	Time (s)	Yield (%)
Ph	H	COOH	1:0.8:1	60	83
Ph	Ph	COOH	1:0.8:1	90	82
Ph	H	CN	1:1.6:2	45	80
Ph	H	NH₂	1:0.8:1	30	76
Ph	H	Br	1:0.8:1	30	75
p-NO₂–Ph	H	H	1:1.6:2	90	69
Hydroquinone			1:0.8:1	30	71
Triphenylphosphine			1:0.8:1	15	85

8.6. Solvent-free reductive amination of carbonyl compounds using sodium borohydride on wet clay

Reductive amination is one of the most popular reactions for the synthesis of amines and their derivatives.[114–118] These are important precursors to a variety of agents that are of interest in pharmaceutical and agricultural industries[119] and compounds in this class are known to possess herbicidal and
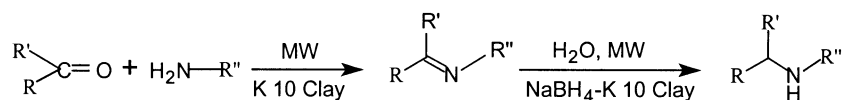
Scheme 24.

Table 8. Reductive amination of carbonyl compounds using K 10 clay supported NaBH$_4$

Entry	Amines	Carbonyl compounds	Time[a] (min)	Yield (%)
1	Aniline	Benzaldehyde	R.T.	97
2	*n*-Heptylamine	Benzaldehyde	R.T.	94
3	Tyramine	Benzaldehyde	1.50	90
4	Aniline	Salicylaldehyde	R.T.	96
5	*p*-Nitroaniline	Salicylaldehyde	1.00	88
6	Aniline	*p*-Chlorobenzaldehyde	0.50	90
7	*o*-Aminophenol	*p*-Chlorobenzaldehyde	0.75	84
8	Aniline	*p*-Anisaldehyde	0.25	93
9	*p*-Aminophenol	*p*-Anisaldehyde	0.75	81
10	Aniline	*p*-Nitrobenzaldehyde	1.25	78
11	*p*-Chloroaniline	3,4-Dimethoxybenzaldehyde	0.50	91
12	Aniline	Isobutyraldehyde	1.00	78
13	Aniline	2-Ethylbutyraldehyde	0.75	87
14	*n*-Decylamine	2-Ethylbutyraldehyde	1.50	86
15	3,4-Dimethoxy phenethylamine	Pyrrole-2 carboxyldehyde	1.50	81
16	Aniline	Acetophenone	1.50	92
17	Benzylamine	Acetophenone	2.00	66
18	Aniline	Cyclohexanone	1.00	89
19	Benzylamine	4-Methylcyclohexanone	2.00	85
20	Propylamine	Cycloheptanone	0.75	79
21	Benzylamine	1,4-Cyclohexanedione monoethylene ketal	1.50	91
22	Aniline	3-Pentanone	1.00	83
23	Morpholine	2-Heptanone	2.00	81
24	Piperidine	2-Heptanone	2.00	78

[a] Time for the reduction of in situ generated Schiff's bases in microwave oven; R.T. refers to the reductions at room temperature that are completed on simple mixing of the Schiff's base with NaBH$_4$–wet clay.

fungicidal activities.[120] Two methods are routinely used to achieve this reduction: Borch reduction using sodium cyanoborohydride [NaBH$_3$CN][121] and reductive amination using sodium triacetoxyborohydride [NaBH(OAc)$_3$].[122] The first method has the risk of leaving residual cyanide in the products or in the work-up waste stream whereas the latter involves the use of corrosive acetic acid. Inherently safer sodium borohydride (NaBH$_4$) has been extensively used as a reducing agent in view of its compatibility with protic solvents[123] and a variety of carbonyl compounds can be reduced to the corresponding hydroxy derivatives under solvent-free conditions using NaBH$_4$ impregnated on alumina.[124]

Our earlier studies targeted the rapid synthesis of imines and enamines via clay-catalyzed reactions[84,92] and prompted us to extend the use of these microwave irradiation protocols to

the reduction of carbonyls and in situ generated Schiff's bases employing NaBH$_4$-wet clay.[125]

The reductive amination, carried out on various inorganic solid supports such as alumina, clay, silica etc. revealed that clay afforded the best results.[125] No side-product formation is observed in any of the reactions investigated and the dehalogenation of the compounds (entries 6, 7 and 11) is not observed under these conditions (Scheme 24, Table 8).[126] The reaction mixture is irradiated intermittently to avoid the loss of low boiling *n*-propylamine (entry 20).

The general procedure employed is very simple and involves mixing equimolar amounts of aldehyde and amine in the presence of catalytic amount of montmorillonite K 10 clay contained in a glass container and irradiating the contents in a microwave oven for 2 min. This in situ

Where R = H, R' = H, OMe, NO$_2$, OH, Br, Me
R = R' = OMe
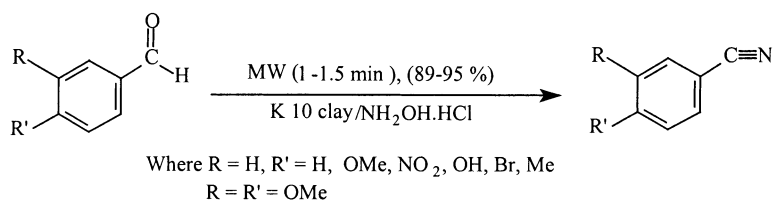
Scheme 25.

Table 9. Cleavage of semicarbazones and phenylhydrazones with ammonium persulfate and clay using microwave or ultrasonic irradiation

R	R_1	R_2	Ultrasound		Microwave	
			Time (h)	Yield (%)	Time (min)	Yield (%)
$CONH_2$	C_6H_5	Me	0.75	77	0.6	72
$CONH_2$	p-Cl–C_6H_4	Me	3.00	90	1.8	82
$CONH_2$	p-OH–C_6H_4	Me	1.00	94	1.0	85
$CONH_2$	p-Me–C_6H_4	Me	3.00	68	2.0	69
$CONH_2$	p-OMe–C_6H_4	Me	3.00	88	0.9	78
$CONH_2$	p-NH$_2$–C_6H_4	Me	1.50	62	1.0	65
$CONH_2$	p-OMe–$C_6H_4CH_2CH_2$	Me	3.00	71	1.6	75
$CONH_2$	$CH_3CH_2CH_2CH_2$	Et	2.50	79	1.3	70
C_6H_5	C_6H_5	Me	1.50	82	0.5	71
C_6H_5	$CH_3CH_2CH_2CH_2$	Et	1.00	71	1.3	65
$CONH_2$	–Cyclohexyl–		1.50	69	0.7	68

generated Schiff's base is mixed thoroughly with pre-moistened and freshly prepared $NaBH_4$–clay and reaction mixture is irradiated further for 30 s (65°C). Upon completion of the reaction, monitored by TLC, the product is extracted into an organic solvent and the solvent is removed under reduced pressure to afford the amine derivative.

8.7. One-pot conversion of aromatic aldehydes to nitriles using hydroxylamine–clay

Aldehyde to nitrile conversion is a useful chemical transformation.[127–130] In most cases, the aldoxime is prepared first and then dehydrated using a wide variety of reagents such as chloramine/base,[131] O,N-bis-(trifluoroacetyl)hydroxylamine or trifluoroacetohydroximic acid,[132] triethylamine/dialkyl hydrogen phosphinates,[133] p-chlorophenyl chlorothionoformate/pyridine,[134] $TiCl_4$/pyridine,[135] and triethylamine/phosphonitrilic chloride.[136]

The dehydration of an aldoxime generally proceeds at a much slower rate requiring long reaction times in most of the conventional methods: e.g. montmorillonite KSF (110°C, 13–19 h)[137] or elevated temperatures: e.g. zeolite (350°C).[138] Montmorillonite K 10 clay supported hydroxylamine hydrochloride provides a facile conversion of aldehydes to nitriles (89–95%) under solvent-free conditions upon brief exposure to microwaves (Scheme 25).[139]

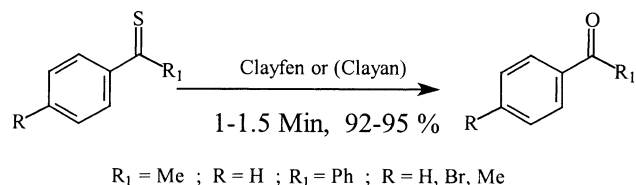### 8.8. Cleavage of semicarbazones and phenylhydrazones with ammonium persulfate–clay

Semicarbazones and hydrazones are important derivatives

in organic synthesis and find use in the protection[140–146] and purification[142] of the carbonyl compounds. Deprotection of these derivatives has been carried out using various catalysts such as copper(II) chloride,[143] cation exchange resin Dowex-50,[144] clayfen,[27] potassium bromate,[145] and zirconium sulfophenyl phosphonate,[146] usually requiring higher temperatures[143,144] and involving toxic metal ions as catalysts which are detrimental to the environment.

Ammonium persulfate is commonly used in industry for bleaching[147] and for the treatment of waste water[148] with limited applications in organic synthesis.[149] Initial explorations on the oxidative cleavage of the imine-type moieties and semicarbazones using ammonium persulfate failed even after prolonged reaction periods in the absence of mineral supports. However, a simple oxidative cleavage of semicarbazones and phenylhydrazones occurs with ammonium persulfate in the presence of montmorillonite K 10 clay under microwave irradiation or ultrasound activation (Table 9).[150] The mechanism of the above transformation probably involves the decomposition of ammonium persulfate on clay under the influence of microwaves, thus generating O_2 and NH_4HSO_4 (Eq. 2). The imino nitrogen of the semicarbazone or phenylhydrazone is protonated followed by the nucleophilic attack of sulfate ion on the imino carbon. The elimination of semicarbazide and sulfur trioxide liberates the carbonyl compound (Scheme 26).

$$2(NH_4)_2S_2O_8 \xrightarrow[2H_2O]{\Delta} 4NH_4HSO_4 + O_2 \qquad (2)$$
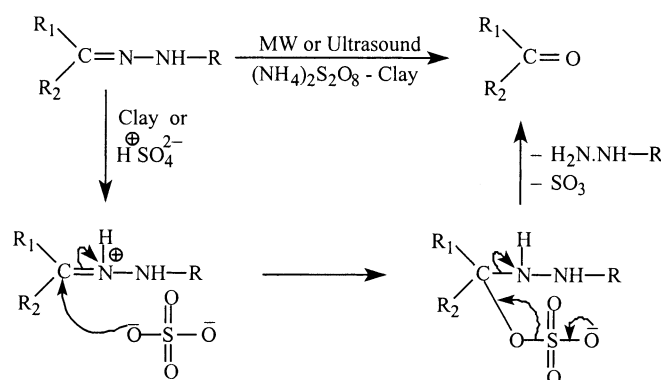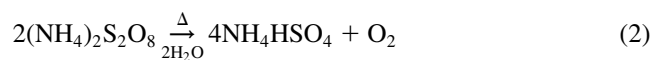
Scheme 26.

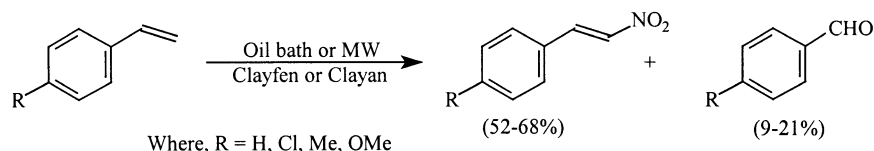**Scheme 27.**

R₁ = Me ; R = H ; R₁ = Ph ; R = H, Br, Me

8.9. Dethioacetalization—regeneration of ketones from thioketones using clay supported nitrate salts

Transformation of thioketones to ketones[31,151–154] has been achieved using several reagents such as trifluoroacetic anhydride,[151] CuCl/MeOH/NaOH,[152] tetrabutylammonium hydrogen sulfate/NaOH,[153] clay/ferric nitrate,[31] and NOBF₄.[154] These methods, however, have certain limitations such as the use of the stoichiometric amounts of the oxidants that are often inherently toxic or require longer reaction times or involve tedious procedures. Clay-supported nitrate salts [iron(III) nitrate (clayfen) or ammonium nitrate (clayan)] accomplish this high-yield transformation rapidly and under solvent-free conditions (Scheme 27).[155]
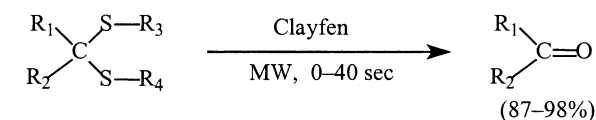
R₁ = Ph, p-anisyl, p-NO₂C₆H₄ ; R₂ = H ; R₃–R₄ = –(CH₂)₂–
R₁ = R₂ = Et ; R₃–R₄ = –(CH₂)₂– ; R₁ = R₂ = Ph ; R₃ = R₄ = Et
R₁ = Ph ; R₂ = Me ; R₃–R₄ = –(CH₂)₂–

Scheme 28.

In our laboratory, we have accomplished the solvent-free dethioacetalization of thio acetals and ketals to regenerate the corresponding carbonyl compounds using clayfen,[156] a process that is environmentally benign when compared to the conventional solution phase or heterogeneous reactions. No side products are formed during this deprotection protocol except for substrates bearing free hydroxyl moieties, where ring nitration is observed. This extremely rapid (<1 min) and manipulatively simple process involves mixing of clayfen with various substrates (Scheme 28). In some cases, a gentle warming via microwave irradiation is required.[156]

## 8.10. Nitration of aromatics and selective nitration of styrenes with clayfen and clayan

Cupric nitrate impregnated montmorillonite clay, claycop, has been used for one-pot nitration of aromatics with improved selectivity compared to reactions carried out under homogeneous conditions.[157] Several electron-rich aromatic compounds have been selectively mononitrated by claycop[158] and phenols have been nitrated using ferric nitrate or cupric nitrate on fluoridated clay (tonsil).[159] The optimization and enhancement of *para* selectivity have been demonstrated employing pillard clay with transition metals Fe(III), Cr (III) and Mn (III).[160] The porous nature of the montmorillonite affords shape-selective nitration,[161] a study that is corroborated with nitration of toluene and chloro-benzene.[162]

β-Nitrostyrene and its derivatives, valuable synthetic precursors in organic synthesis, are generally prepared by direct nitration of styrenes[163–167] or by the condensation of appropriate aldehydes with nitromethane.[168] However, it is quite challenging to achieve nitration of styrenes due to the

Where, R = H, Cl, Me, OMe

Scheme 29.

Table 10. Product distribution in solventless nitration of styrenes with clayfen and clayan

Substrate	Yields (%)		
	β-Nitrostyrene	Aldehyde	Polymer/others
With clayfen			
Styrene	68(56)	21(35)	11(09)
p-Methylstyrene	52(41)	11(24)	37(35)
p-Methoxystyrene	14(14)	09(15)	77(71)
p-Chlorostyrene	52(41)	10(22)	38(37)
With clayan			
Styrene	59(47)	20(35)	21(18)
p-Methylstyrene	44(35)	15(26)	41(39)
p-Methoxystyrene	13(12)	12(15)	75(73)
p-Chlorostyrene	49(37)	11(23)	40(40)

Clayfen, in oil bath (15 min) or in microwave, MW, (3 min) at 100–110°C; clayan, in oil bath (15 min) or in MW (3 min) at 60–70°C). Results in the parentheses refer to the yields obtained using MW irradiation.

highly sensitive nature of the vinylic side chain. The reported protocols involve the reaction of styrene with nitrate salts in polyphosphoric acid,[169] nitrohalogenation with nitryl halides (NO₂X) and dehydrohalogenation with triethylamine,[170] the treatment of styrene with tetranitromethane (TNM) in presence of pyridine[171–173] or with nitric acid (98%) in concentrated sulfuric acid.[174] Nitration with HgCl₂–NaNO₂ leads to varying degrees of ring nitration[175] while nitrogen monoxide is required in large excess with activated acidic alumina.[176] A direct conversion of styrenes to β-nitrostyrenes using clay doped with nitrate salts has been explored. Clayfen in various solvents failed to generate β-nitrostyrenes but the solid state neat reactions readily provided the desired side chain nitrated styrenes.[177] Additionally, we found that the related clayan is equally useful for nitration of styrene and its p-substituted derivatives (Scheme 29, Table 10).[177,178]

8.11. Rearrangement reactions (pinacol–pinacolone and Beckmann)

Loupy and colleagues have reported a solvent-free pinacol–pinacolone rearrangement using microwave irradiation.[179] The method involves the irradiation of *gem*-diols with Al^{3+}–montmorillonite K 10 clay to afford the rearrangement product in excellent yields (Scheme 30). The comparison of these results with the conventional oil bath heating protocols revealed that the reaction times are too long (15 h) for the latter.
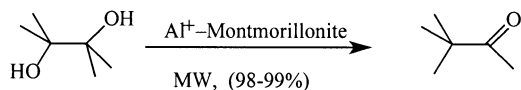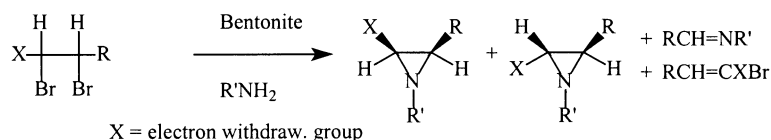

Scheme 30.

Bosch et al. have accomplished the Beckmann rearrangement of ketoximes with montmorillonite K 10 clay in 'dry' media in good yields (Scheme 31).[180]
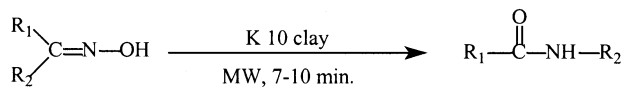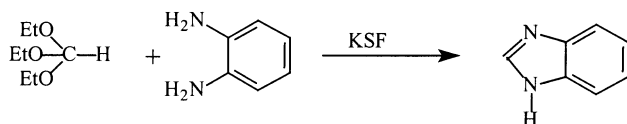

Scheme 31.

8.12. Synthesis of heterocylic compounds

Solvent-free microwave protocols have found useful application in the rapid assembly of biologically significant heterocyclic molecules. Notable among them are the methods that can exploit the in situ generated reactive intermediates at ambient pressure, thus rendering some tasks to essentially one-pot operation. The extension of some of these themes to multi-component reactions has provided a unique approach to generate a library of heterocycles via high-speed parallel synthesis.[81b]
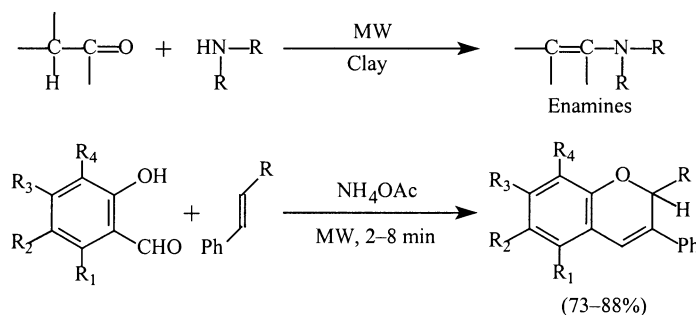
8.12.1. Aziridines and benzimidazoles. A unique method is described for the synthesis of aziridines using a focused microwave approach under solvent-free conditions where it is observed that the elimination predominates over the Michael addition under MW irradiation unlike classical heating under the same conditions (Scheme 32).[181]

In an analogous manner, benzimidazoles are prepared rapidly by condensation reaction of ortho esters with *o*-phenylenediamines in the presence of KSF clay under both refluxing conditions in toluene or solventless condition using focused microwave irradiation (Scheme 33).[182]

8.12.2. Isoflav-3-enes and flavones. Isoflav-3-enes, encompassing the chromene nucleus, are well known estrogens and consequently these heterocycles have attracted the attention of medicinal chemists. We have extended our solventless approach to enamines[84,92] and uncovered a rapid and general method for the synthesis of isoflav-3-enes substituted with basic moieties at the 2-position (Scheme 34).[183] The results are significant in view of the convergent one-pot approach to the above heterocyclic system, wherein the generation of the enamine derivatives in situ and inducing subsequent reactions with *o*-hydroxy-aldehydes in the same pot are the key features (Scheme 34).

Scheme 32.

Scheme 33.

Naturally occurring phenolic compounds widely distributed in plant kingdom belong to a class termed, flavonoids, the most abundant being the flavones. Members of this class are associated with a broad range of biological activities including cancer chemoprevention.[184] Flavones have been

R = morpholinyl, piperidinyl, pyrrolidinyl
R_1, R_3, R_4 = H ; R_2 = H, Cl, NO_2

Scheme 34.

X = H ; X$_1$ = H, Me, OMe, NO$_2$

R = OMe ; X$_1$ = H, Me, OMe

Scheme 35.

prepared by a variety of methods such as Allan–Robinson synthesis, synthesis from chalcones via an intramolecular Wittig strategy.[185] The most prevalent approach, however, involves the Baker–Venkataraman rearrangement, wherein *o*-hydroxyacetophenone is benzoylated to form the benzoyl ester followed by the treatment with base (pyridine/KOH) to effect an acyl group migration, forming a 1,3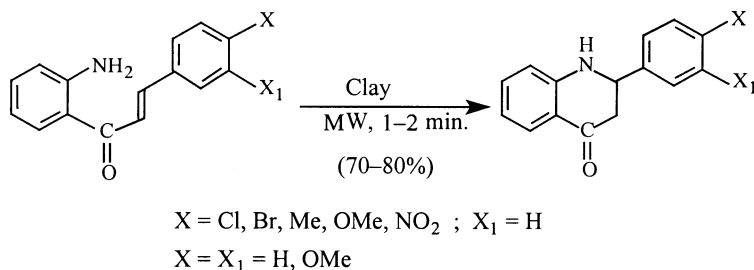-diketone.[185] The ensuing diketone is then cyclized under strongly acidic conditions with sulfuric acid and acetic acid to deliver the flavone.

A solvent-free synthesis of flavones has been achieved which simply involves the microwave irradiation of *o*-hydroxydibenzoylmethanes adsorbed on montmorillonite K 10 clay for 1–1.5 min. A rapid and exclusive formation of cyclized flavones occurs in good yields (Scheme 35).[185]

8.12.3. Quinolones. Montmorillonite K 10 clay under microwave irradiation conditions enables yet another solvent-free cyclization reaction wherein readily available 2′-aminochalcones provide easy access to 2-aryl-1,2,3,4-tetrahydro-4-quinolones[186] which are useful precursors for the medicinally important quinolones (Scheme 36).

8.12.4. Bridgehead nitrogen heterocycles-substituted thiazoles. Thiazole and its derivatives are synthesized by the simple reaction of in situ generated α-tosyloxyketones, from arylmethyl ketones and [hydroxy(tosyloxy)iodo]-
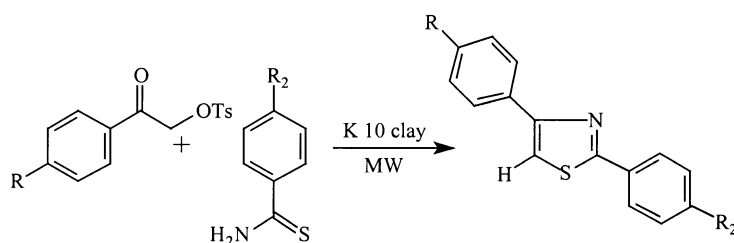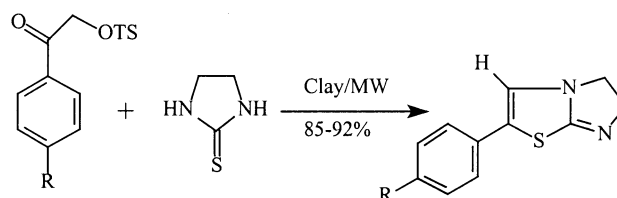
Scheme 38.

benzene (HTIB), with thioamides in the presence of K 10 clay using microwave irradiation (Scheme 37). The two-step operation is solvent-free in both the steps and can be conducted in the same pot.[187]

The bridgehead heterocycles are difficult to obtain by conventional heating methods since the reactions of α-tosyl-oxyketones with ethylenethioureas remain incomplete in an oil bath. The microwave-accelerated process, on the other hand, stands out as it gets completed in a short time (Scheme 38).[187]

8.12.5. Multi-component reactions (imidazo[1,2-*a*] annulated pyridines, pyrazine and pyrimidines—Ugi reaction). Multiple component condensation (MCC) approach is exciting in view of the fact that products are formed in a single step and the diversity can be conveniently achieved simply by varying the reacting components. The generation of small-molecule libraries requires the development of

X = Cl, Br, Me, OMe, NO$_2$; X$_1$ = H

X = X$_1$ = H, OMe
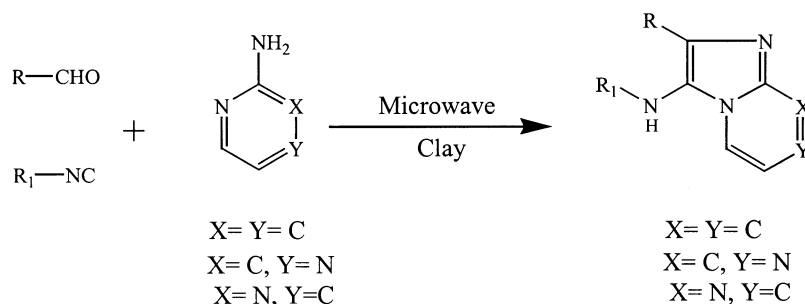
Scheme 36.

Scheme 37.

Scheme 39.

efficient protocols with special emphasis on the ease of manipulation of the reaction. We succeeded in developing such a facile protocol which is amenable to the generation of a library of imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines and imidazo[1,2-*a*]pyrimidines under solvent-free conditions using MW irradiation.[188] This is a marked improvement over the conventional two-component synthesis that requires lachrymatory α-haloketones and restricts the generation of a diverse library of these molecules.

Aldehydes and the corresponding 2-amino-pyridine, pyrazine or pyrimidine are admixed in presence of a catalytic amount of clay (50 mg) to generate iminium intermediate. Subsequently, isocyanide is added to the same container and the reactants are further exposed to MW to afford the corresponding imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines and imidazo[1,2-*a*]pyrimidines (Scheme 39). The process is general for all the three components, e.g. aldehydes (aliphatic, aromatic and vinylic), isocyanides (aliphatic, aromatic and cyclic) and amines (2-aminopyridine, 2-aminopyrazine and 2-aminopyrimidine). Thus, a library of imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines and imidazo[1,2-*a*]pyrimidines can be readily obtained by varying the three components.[188]

9. Conclusions

Commercially available clays (or their modified forms) can provide environmentally friendly alternatives for liquid Brönsted acids such as concentrated nitric or sulfuric acids and substitution of Lewis acids such as AlCl₃. The relative ease of modification of clay materials by exchanging or pillaring with various metal-cations, their reuse, and simple recovery from reaction mixtures bodes well for the future of clay-based catalysts in which their properties can be fine-tuned for specific chemical transformations. For success in the industrial context, more studies need to be conducted in continuous or vapor-phase reactors using clay 'microreactors'.

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Biographical sketch
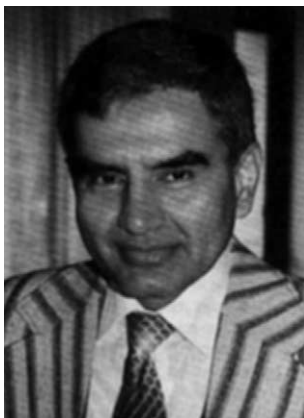
Rajender (Raj) Varma was born in India and obtained his Ph.D. from Delhi University in 1976. After postdoctoral research at Robert Robinson Laboratories, University of Liverpool, UK, he was the faculty member at Baylor College of Medicine, Senior Scientist at Houston Advanced Research Center and Research Professor at Sam Houston State University in Texas prior to joining the Clean Processes Branch at National Risk Management Research Laboratory, US EPA in 1999. He has over 25 years of research experience in management of multi-disciplinary research programs ranging from natural products chemistry, pulp and paper technology and therapeutics, to development of genosensor technology, specifically the applications and interface of chemical science with biology, solid state chemistry, bioelectronics, and development of environmentally friendlier alternatives for synthetic methods using supported reagents, molten salts, microwaves, ultrasound etc. The primary focus of his research at EPA is to evaluate novel and safer environmental protocols in industrial chemistry and its impact in human health and environmental sciences. He has published over 175 scientific peer-reviewed papers and has been awarded six US patents. He enjoys reading and jogging.