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Solvent-free accelerated organic syntheses using microwaves*

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Abstract: A solvent-free approach for organic synthesis is described which involves microwave (MW) exposure of neat reactants (undiluted) either in the presence of a catalyst or catalyzed by the surfaces of inexpensive and recyclable mineral supports such as alumina, silica, clay, or "doped" surfaces, namely, $Fe(NO_3)_3$-clay (clayfen), $Cu(NO_3)_2$-clay (claycop), NH_2OH-clay, $PhI(OAc)_2$-alumina, $NaIO_4$-silica, MnO_2-silica, and $NaBH_4$-clay. A variety of deprotection, condensation, cyclization, oxidation, and reduction reactions are presented including the efficient one-pot assembly of heterocyclic molecules from *in situ* generated intermediates such as enamines and α-tosyloxyketones. The application of this solvent-free MW approach to multicomponent reactions is highlighted that can be adapted for high-speed parallel synthesis of the library of dihydropyrimidine-2(1*H*)-ones and imidazo [1,2-a]annulated pyridines, pyrazines, and pyrimidines.

INTRODUCTION

In the electromagnetic radiation spectrum, microwaves (0.3 GHz–300 GHz) lie between radiowave (Rf) and infrared (IR) frequencies with relatively large wavelength. Microwaves, a nonionizing radiation incapable of breaking bonds, are a form of energy and not heat and are manifested as heat through their interaction with the medium or materials wherein they can be reflected (metals), transmitted (good insulators that will not heat) or absorbed (decreasing the available microwave energy and rapidly heating the sample).

Microwave (MW) irradiation, an unconventional energy source, has been used for a variety of applications including organic synthesis [1–10], wherein chemical reactions are accelerated because of selective absorption of MW energy by polar molecules, nonpolar molecules being inert to the MW dielectric loss. Heterogeneous reactions facilitated by supported reagents on inorganic oxide surfaces have received attention in recent years [11]. The application of microwave irradiation in conjunction with the use of catalysts or mineral-supported reagents, under solvent-free conditions, enables organic reactions to occur expeditiously at ambient pressure [1–5,9,10], thus providing unique chemical processes with special attributes such as enhanced reaction rates, higher yields, and the associated ease of manipulation.

The results from our laboratory on this MW-expedited approach are described for the synthesis of a variety of industrially significant compounds and intermediates, namely, imines, enamines, enones, nitroalkenes, oxidized sulfur species, and heterocycles. This methodology is exemplified by a concise synthesis of flavones, tetrahydroquinolones, 2-aroylbenzofurans, and thiazole derivatives and demonstrates the exploitation of *in situ* generated reactive intermediates in one-pot synthesis of heterocyclic compounds. The adaptability of the protocols to rapid and parallel synthesis in solvent-free multicom-

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ponent reactions is demonstrated in the assembly of imidazo[1,2-a]annulated pyridines, pyrazines, and pyrimidines (Ugi reaction) and dihydroprimidine-2(1*H*)-ones (Biginelli reaction).

FUNCTIONAL GROUP TRANSFORMATIONS

Synthesis of thioketones, thiolactones, thioamides, thionoesters, and thioflavonoids

Cleavage reactions are expedited by MW exposure of protected molecules on mineral oxides or benign "doped" reagents, as has been shown in the regeneration of alcohols, acids, and carbonyl compounds [12–15].

Among several expeditious chemical transformations that can be accomplished under these solvent-free conditions, the conversion of carbonyl compounds to the corresponding thio analogs is especially useful. The usual synthesis of thioketones involves the reaction of substrates with hydrogen sulfide in the presence of acid, phosphorous pentasulfide under basic conditions, or Lawesson's reagent. Using our approach, the carbonyl compounds are simply admixed with neat Lawesson's reagent (0.5 equiv.) and irradiated under solvent-free conditions that do not require any acidic or basic media. This benign approach is general and is applicable to the high-yield conversion of ketones, flavones, isoflavones, lactones, amides, and esters to the corresponding thio analogs (Fig. 1). This eco-friendly, solvent-free protocol uses comparatively much smaller amount of Lawesson's reagent and avoids the use of large excess of dry hydrocarbon solvents such as benzene, xylene, triethylamine, or pyridine that are conventionally used [16].

OXIDATION REACTIONS

The introduction of metallic reagents on solid supports have solved some of the associated toxicity problems and provides an attractive alternative to the conventional oxidation reactions in view of the selectivity and ease of manipulation. We have developed several MW-assisted oxidative protocols [17–20] using an array of supported reagents applicable to both alcohols and sulfides (Fig. 2).

REDUCTION REACTIONS

The solid-state selective reduction of carbonyl compounds occurs readily with alumina-supported sodium borohydride ($NaBH_4$) in a reaction that is accelerated by moisture [21]. The alumina support can be reused repeatedly by simply washing off the product—a process that hydrates the alumina surface to facilitate subsequent reduction reactions. Our earlier optimized imine-forming (Schiff bases) reaction using catalytic amount of clay [22] can be adapted for the borohydride reduction in the same pot, thus providing a simple route to secondary and tertiary amines [23]. Clay serves the dual purpose of a Lewis acid and also provides water from its interlayers, which enhances the reducing ability of $NaBH_4$ (Fig. 3).

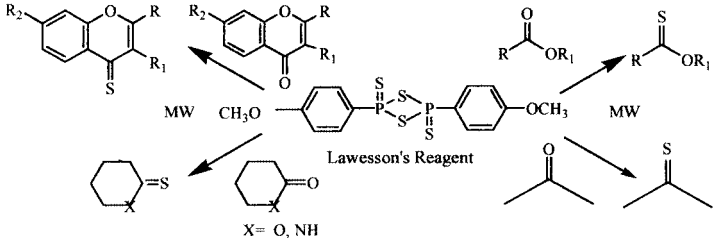

Fig. 1 Solvent-free synthesis of thioketones, thiolactones, thioamides, and thionoesters.

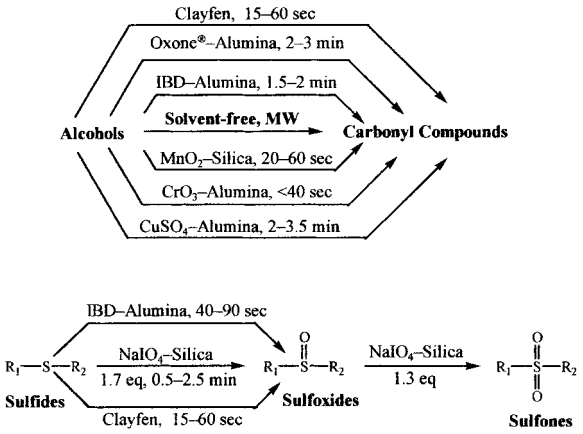

Fig. 2 Oxidation of alcohols to carbonyl compounds and oxidation of sulfides to sulfoxides and sulfones. (Reproduced with permission from R. S. Varma, *McGraw-Hill 2002 Year Book of Science and Technology*,

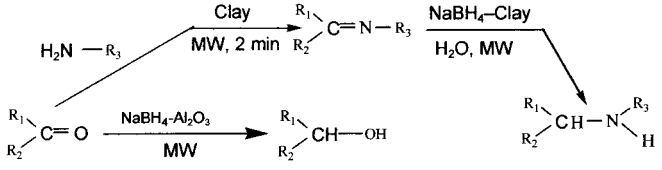

Fig. 3 Borohydride reduction of carbonyl compounds and reductive amination reactions. (Reproduced with permission from R. S. Varma, *McGraw-Hill 2002 Year Book of Science and Technology*, 2000.)

The air used for cooling the magnetron ventilates the microwave chamber, thus preventing build-up of any explosive concentrations of hydrogen.

SYNTHESIS OF HETEROCYCLIC COMPOUNDS

A variety of heterocyclic compounds can be rapidly assembled employing this solvent-free approach as demonstrated by the synthesis of flavonoids using Baker–Venkataraman rearrangement and related cyclization of 2′-aminochalcones to 2-aryl-1,2,3,4-tetrahydro-4-quinolones on clay [24]. A concise one-pot method can be used to synthesize isoflav-3-enes bearing basic amino substituents at 2 position via the intermediacy of *in situ* generated enamine derivatives followed by reaction with *o*-hydroxy-aldehydes [25].

This convergent strategy has been extended to the synthesis of naturally occurring and pharmacologically active 2-aroylbenzo[b]furans that proceeds rapidly via the condensation of *in situ* generated α-tosyloxyketones with a variety of salicylaldehydes on potassium fluoride "doped" alumina (Fig. 4); the process avoids the use of lachrymatory starting materials [26].

Similarly, thiazoles can be readily obtained by the reaction of thioamides with α-tosyloxyketones in a clay-catalyzed reaction (Fig. 4). A typical experimental procedure entails mixing thioamides in an open glass container with *in situ* generated α-tosyloxyketones and montmorillonite K 10 clay. The reaction mixture is irradiated in a microwave oven for 3–6 min with intermittent irradiation to afford substituted thiazoles in 88–96% yields. The versatility of the MW approach becomes apparent in the synthesis of bridgehead heterocycles when reactants are cyclic thioureas (Fig. 4).

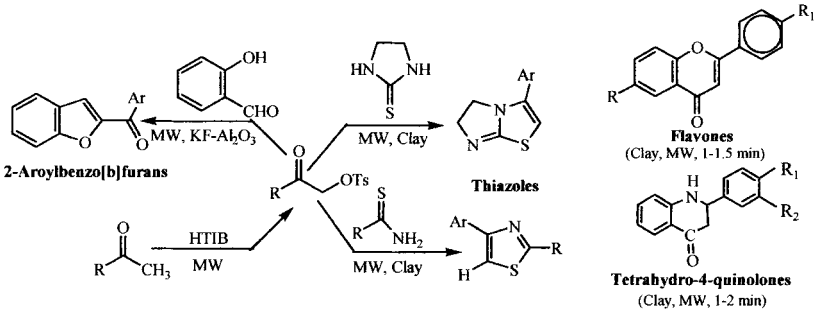

Fig. 4 Synthesis of thiazoles and aroylbenzofurans via α-tosyloxyketones. (Reproduced with permission from R. S. Varma, *McGraw-Hill 2002 Year Book of Science and Technology*, 2000.)

Microwave-accelerated multicomponent reactions

Combinatorial chemistry has gained significant importance as a tool for the synthesis of a wide variety of useful compounds, including pharmaceuticals. In this context, the multiple component condensation (MCC) approach is especially appealing in view of the fact that products are formed in a single step, and the diversity can be readily achieved simply by varying the reacting components. The generation of small-molecule libraries requires the development of efficient methodologies with special emphasis on manipulative ease of the reaction. Such a facile protocol is developed 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 [27] under solvent-free conditions using MW irradiation (Fig. 5). The conventional two-component synthesis requiring lachrymatory α-haloketones and 2-amino-heterocycles restricts the generation of a diverse library of these molecules.

This solvent-free one-pot method involves MW irradiation of mixture of aldehydes and corresponding 2-amino-pyridine, pyrazine, or pyrimidine 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 at a reduced power level (50%) to afford the corresponding imidazo[1,2-a]pyridines, imidazo[1,2-a]pyrazines, and imidazo[1,2-a]pyrimidines (Fig. 5). Further, the protocol is general for all the three components involved, 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 simply varying the three components [27].

In collaboration with Dr. Kappe, the strategy has been extended to the parallel synthesis of 4-aryl-3,4-dihydropyrimid-2(1*H*)-ones (DHPM), employing a solvent-free Biginelli multicomponent condensation reaction. The method uses neat mixtures of aryl aldehydes, β-ketoesters, and urea derivatives in presence of polyphosphate ester (PPE) as a reaction mediator [28]. In view of the readily available aromatic aldehydes, β-keto esters, and urea derivatives, a large collections of DHPMs can be potentially

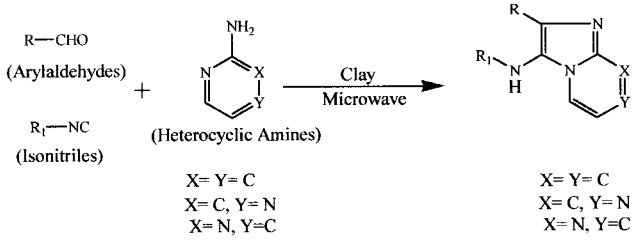

Fig. 5 Three-component condensation reaction using microwaves. (Reproduced with permission from R. S. Varma, *McGraw-Hill 2002 Year Book of Science and Technology*, 2000.)

prepared, applying the recently developed automated, high-throughput robotic technologies for performing microwave-assisted combinatorial synthesis [29].

MISCELLANEOUS REACTIONS

Several other reagents can be used under these solvent-free conditions to expedite organic reactions; for example, hydroxylamine on clay directly converts aldehydes to nitriles [30]. A general protocol that is applicable to the oxidation of dihydropyridine derivatives utilizes elemental sulfur [31]. Several nonmetallic hypervalent iodine oxidants can be used without solvents [31], and the crossed Cannizzaro reaction can be accomplished with paraformaldehyde on barium hydroxide surface [32].

In conclusion, this eco-friendly, solvent-free microwave approach opens up numerous possibilities for conducting rapid organic synthesis and functional group transformations more efficiently. Additionally, 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". The chemo-, regio- or stereoselective synthesis [33] of high-value chemical entities and parallel synthesis to generate a library of small molecules [27–29] will add to the growth of microwave-enhanced reactions in the near future.

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