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Ultrasound in heterocycles chemistry

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1. Introduction

The importance of heterocycles in many fields of science (including organic, inorganic, bioorganic, agricultural, industrial, pharmaceutical, and medicinal chemistry, as well as material science) can hardly be overemphasized,[1] and justifies a long lasting effort to work out new synthetic protocols for their production. A particularly attractive approach is based on ultrasound-promoted heterocyclization reactions of suitably functionalized substrates, which can allow the regioselective synthesis of highly functionalized heterocycles using readily available starting materials under mild and selective conditions.

The use of ultrasound to promote chemical reactions is called sonochemistry. The effects of ultrasound observed during organic reactions are due to cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid. Cavitation induces very high local temperatures and pressures inside the bubbles (cavities), leading to turbulent flow of the liquid and enhanced mass transfer.

One of the most fascinating areas of sonochemistry in organic chemistry is sonochemical switching. In some cases, application of ultrasound may completely change the distribution of products or even cause the formation of different substances. The first example in which ultrasound induced a divergent pathway relative to thermal conditions was reported by Ando and co-workers more than 30 years ago.[2] Herein, we will also discuss some cases of sonochemical switching. Sonochemistry shares some aims with green chemistry, as it also uses smaller quantities of hazardous chemicals and solvents, reduces energy consumption, and increases product selectivity.

Recently, ultrasound has been utilized to accelerate a wide number of synthetically useful organic reactions.[3,4] In addition to the field of organic chemistry, sonochemistry has also been used in the preparation of micro and nanomaterials, i.e., protein microspheres.[5] Ultrasound also has many therapeutic and diagnostic applications, i.e., medical ultrasonography and teeth cleaning; however, a higher frequency (1–10 MHz) is used in these cases than in sonochemistry (20–100 kHz) (Fig. 1).

The availability of many publications, reviews, and books[3,4] clearly indicates the impact of ultrasound on organic synthesis in

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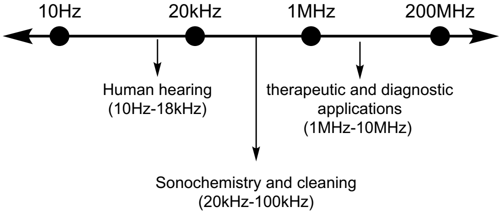


Figure 1. Ultrasound range diagram.

the past 30 years. However, to the best of our knowledge, there is only one review, dated 1989, that exclusively describes the use of ultrasound in heterocyclic chemistry.[6] In this review, we will discuss only the synthesis of heterocyclic compounds using ultrasound energy and, in some cases, show comparisons with conventional conditions. The methodology for the functionalization of heterocycles or their side chains will not be discussed. From now on we will abbreviate ultrasound as US and, when examining conventional conditions, we will be referring to reactions under stirring and/or thermal conditions.

2. Historical background

Most modern ultrasonic devices rely on transducers (energy converters), which are composed of piezoelectric materials. The basis for present-day generation of US devices was established around 1880, with the discovery of the piezoelectric effect by the brothers Pierre and Jacques Curie. Piezoelectric materials respond to the application of an electrical potential across opposite faces with a small change in dimension. If the potential is alternated at high frequencies, the crystal converts the electrical energy to mechanical vibration energy; at sufficiently high alternating potential, high frequency sound (ultrasound) is generated. However, cavitation as a phenomenon was first identified and reported in 1895[7] by Thorneycroft and Barnaby. During field tests of high-speed torpedo boats, they observed that the formation and collapse of large bubbles caused erosion of ship's propeller.

In 1927,[8] Richards and Loomis noticed the first chemical effects of US. With some exceptions, the field was quite forgotten for nearly 60 years. However, in the 1980s, sonochemistry was reborn and began to be widely used in many different areas. The reason for this growth was the availability of inexpensive and appropriate laboratory equipment, such as ultrasonic cleaning baths (low intensity) or ultrasonic probes (high intensity) (Fig. 2).

3. Cavitation: origin and theories

Since US (waves of compression and expansion) is generated by a piezoelectric ceramic in a probe or cleaning bath, it will pass through a liquid, with the expansion cycles exerting negative pressure on the liquid. If this applied negative pressure is strong enough to break down the intermolecular van der Waals force of the liquid, small cavities or gas-filled microbubbles are formed. Cavitation is considered as a nucleated process, meaning that these micrometer-scale bubbles will be formed at pre-existing weak points in the liquid, such as gas-filled crevices in suspended particulate matter or transient microbubbles from prior cavitation events. Most liquids are sufficiently contaminated by small particles that cavitation can be readily initiated at moderate negative pressures.

As microbubbles are formed, they absorb energy from US waves and grow. However, it will reach a stage where it can no longer absorb energy efficiently. Without the energy input, the cavity can no longer sustain itself and implodes. It is this implosion of the cavity that creates an unusual environment for chemical reactions.[3]

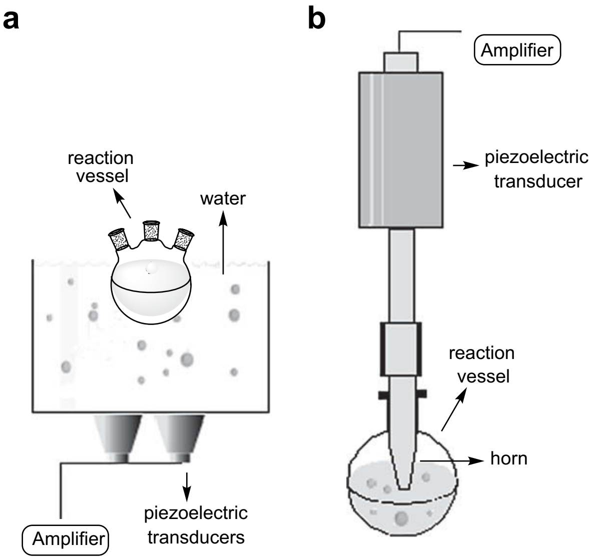


Figure 2. (a) Ultrasonic cleaning bath. (b) Ultrasonic probe.

There are a few factors that can affect the efficiency of bubble collapse, such as:[9] (1) vapor pressure; (2) temperature; (3) thermal conductivity; (4) surface tension and viscosity; (5) the US frequency; and (6) acoustic intensity.

Since the wavelength of US between successive compression waves measures approximately from 10 to 10^{-3} cm, it does not directly interact with molecules to induce chemical change. So, how do reactions occur under US irradiation? Basically, two theories have been proposed to explain the effect of cavitation on chemical reactions: the 'hot spot'[10] and electrical microdischarge[11] theories. Because the latter is not well established, it will not be discussed in this review; however, it cannot be entirely ruled out due to the complex nature of cavitation.

The 'hot spot' theory relies on bubble collapse in the liquid to produce enormous amounts of energy from conversion of the kinetic energy of liquid motion into heating of the bubble contents. Compression of the bubbles during cavitation is more rapid than thermal transport, resulting in the generation of short-lived localized hot spots. Experimental results have shown that these bubbles have temperatures around 5000 K, pressures of approximately 1000 atm, and heating and cooling rates above 10^{10} K/s. Three classes of sonochemical reactions exist:[3]

(1) Homogeneous sonochemistry: homogeneous systems that proceed via radical or radical-ion intermediates. This implies that sonication is able to affect reactions proceeding through radicals and, furthermore, that it is unlikely to affect ionic reactions. In the case of volatile molecules, the bubbles (or cavities) are believed to act as a microreactor; as the volatile molecules enter the microbubbles and the high temperature and pressure produced during cavitation break their chemical bonds, short-lived chemical species are returned to the bulk liquid at room temperature, thus reacting with other species. Compounds of low volatility, which are unlikely to enter bubbles and thus be directly exposed to these extreme conditions, still experience a high energy environment resulting from the pressure changes associated with the propagation of the acoustic wave or with bubble collapse (shock waves);

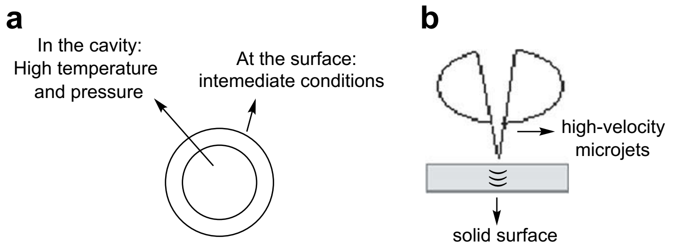


Figure 3. (a) cavitation bubble in a homogeneous system; (b) cavitation bubble in a heterogeneous system.

alternatively, they can react with radical species generated by sonolysis of the solvent.

(2) Heterogeneous sonochemistry (liquid–liquid or solid–liquid systems): heterogeneous systems that proceed via ionic intermediates. Here, the reaction is influenced primarily through the mechanical effects of cavitation, such as surface cleaning, particle size reduction, and improved mass transfer. When cavitation occurs in a liquid near a solid surface, the dynamics of cavity collapse change dramatically. In homogeneous systems, the cavity remains spherical during collapse because its surroundings are uniform (Fig. 3a). Close to a solid boundary, cavity collapse is very asymmetric and generates high-speed jets of liquid (with velocities of approximately 400 Km/h; Fig. 3b). These jets hit the surface with tremendous force. This process can cause harsh damage at the point of impact and produce newly exposed highly reactive surfaces.

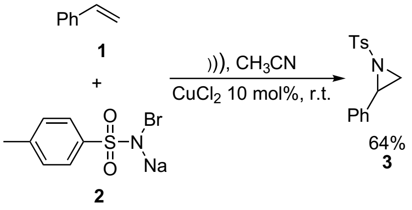
(3) Sonocatalysis (overlap homogeneous and heterogeneous sonochemistry): heterogeneous reactions that include a radical and ionic mechanism. Radical reactions will be chemically enhanced by sonication, but the general mechanical effect described above may very well still apply. If radical and ionic mechanisms lead to different products, US should favor the radical pathway, potentially leading to a change in the nature of the reaction products.

4. Three- and four-membered rings

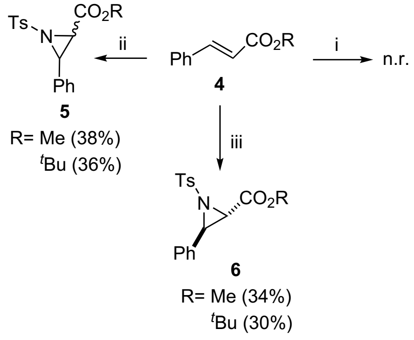
In 2001,[12] the first aziridination of olefins under US and microwave irradiation was reported. Styrene **1** underwent aziridination under US irradiation in the presence of bromoamine-T **2** and $CuCl_2$ (Scheme 1). A good yield of aziridine **3** was obtained in just 20 min at room temperature.

The authors also performed a comparison study of different energy sources. As can be seen in Scheme 2, when cinnamates **4** were subjected to conventional conditions, no reaction was observed. However, when microwave (MW) irradiation was employed, the products were obtained as a mixture of cis and trans isomers of aziridines **5**. Finally, when **4** were irradiated with US, only *trans*-aziridines **6** were observed.

Fluoroaziridines were successfully synthesized by reaction of *N*-alkyl-*N*-benzhydrylideneamines **7** with monofluorocarbene **9** (Scheme 3).[13] The carbene was generated in situ from dibromofluoromethane **8** in the presence of Pb and tetrabutylammonium bromide under US irradiation at 40 °C. The reaction proceeds via azomethine ylide intermediates **10** and aziridines **11** were obtained in low yields (Scheme 3).



Scheme 1.



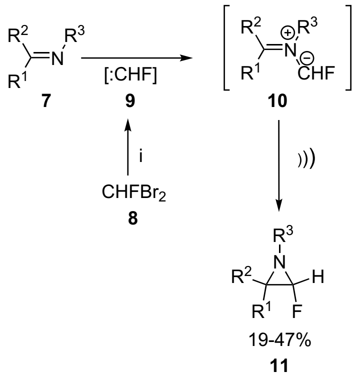
i: **2**, CH_3CN, $CuCl_2$ 10 mol%, r.t., stirring conditions.
ii: **2**, CH_3CN, $CuCl_2$ 10 mol%, MW irradiation.
iii: **2**, CH_3CN, $CuCl_2$ 10 mol%, r.t.,))).

Scheme 2.

When imine derivatives of arenecarbaldehydes **12** were subjected to the same conditions, in the presence of Pb and tetrabutylammonium bromide under US irradiation at 40 °C, stereoisomeric aziridines **13a** and **13b** were obtained (Scheme 4). The configurations of **13a** and **13b** were delineated from the values of J_{HF}. Under conventional conditions, some of compounds **12** (when R^2 is aliphatic) were unable to form aziridines **13a** and **13b**; although the yields were low, this demonstrates the power of US in performing reactions that do not normally occur under other conditions.

Bartsch and co-workers[14] have reported the synthesis of β-lactams **15** via the US-promoted Reformatsky reaction using 'not activated' zinc dust and a catalytic amount of iodine. The reactions were subjected to high-intensity ultrasound (HIU) from a direct immersion horn.

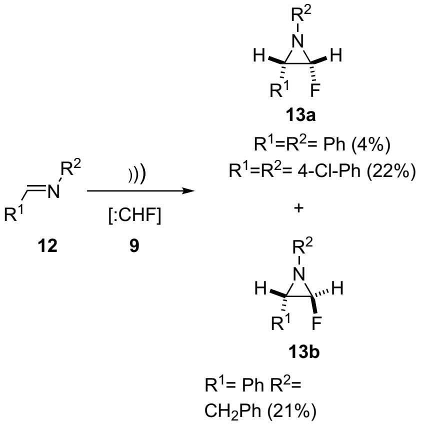
The Reformatsky reaction utilizing imines **12** as electrophiles can provide β-lactams **15**, as well as the corresponding β-amino esters **16** (Scheme 5). When ethyl bromoacetate **14** was used, the



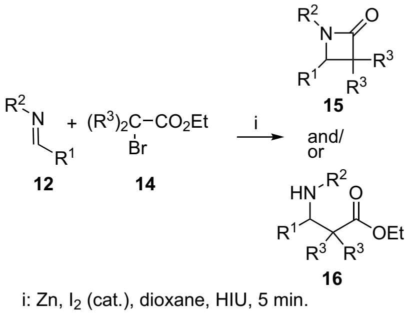
R^1=R^2= Ph or 2,2'-biphenylene
R^3= Me, CH_2Ph, CH_2CO_2Me, CH_2CH_2Ph

i: Pb*, n-Bu_4NBr, 40 °C,))).

Scheme 3.



Scheme 4.



Scheme 5.

reaction was not very selective. However, when ethyl α-bromoisobutyrate was employed, the reaction was more selective. Electron-withdrawing substituents attached to the nitrogen atom favored the formation of β-amino esters.

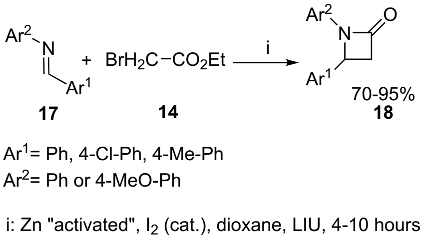
A previous work[15] also demonstrated the formation of β-lactams **18**, but under low intensity ultrasound (LIU) (Scheme 6). However, in this case the zinc dust was activated by washing with nitric acid in order to achieve high yields. The reactions were performed in a cleaning bath in the presence of catalytic I_2 in dioxane, and products **18** were obtained in 70–95% yields. Under these conditions the formation of β-amino esters was not observed.

Comparing this work with that described by Bartsch and coworkers,[14] the importance of the intensity of US in sonochemistry becomes clear; zinc activation was not necessary in HIU, however, inactivated zinc leads to an almost 50% reduction in yield using LIU. Another remarkable difference between the uses of different intensity US is the reaction time; in HIU, the reaction requires only 5 min, while 4–10 h are necessary in LIU.

β-Lactones **21** were synthesized by reaction of aryl chromium carbene complexes **19** with propargylic alcohols **20** (Scheme 7).[16,17] The reaction was carried out in the presence of triethylamine in benzene using US irradiation under thermal conditions. Although the yields in both cases were comparable, the reaction under US irradiation proved to be faster than conventional conditions.

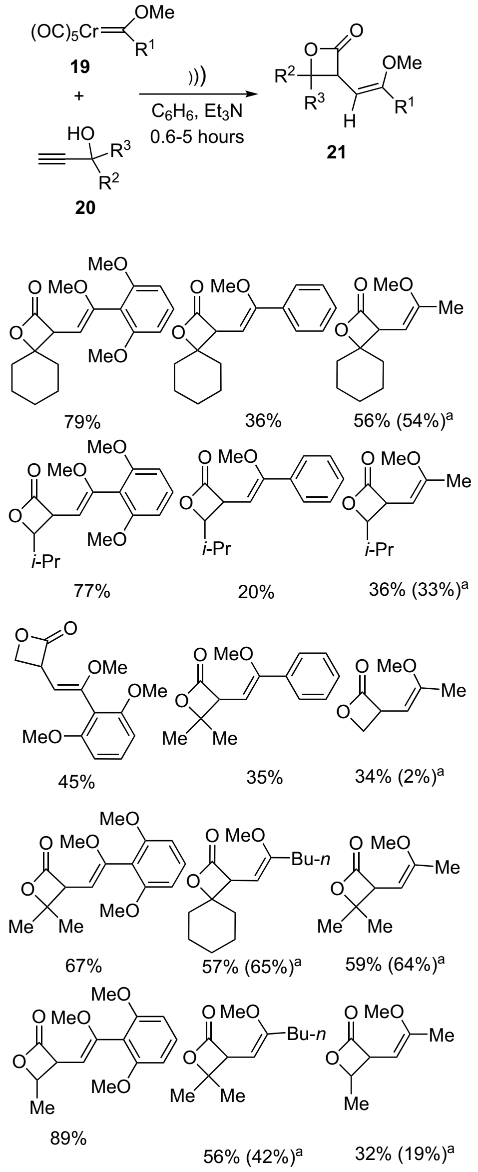
5. Five-membered rings

Previously, we described the synthesis of aziridines by reaction of a fluorocarbene with imines under US irradiation.[13] This reaction proceeds by the formation of an azomethine ylides **10**, which can be trapped with dimethyl maleate **22**, to produce pyrrolidines **23** or pyrrole rings **24** in moderate yields (Scheme 8).



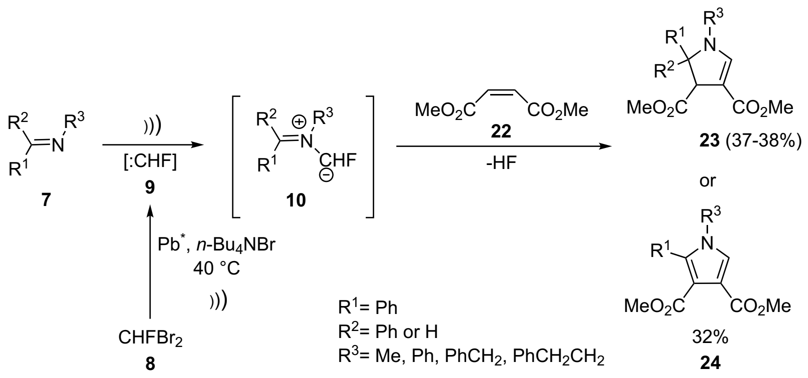
Scheme 6.

A difluorocarbene **26** can be generated in the same way that fluorocarbene **9** was formed, but from dibromodifluoromethane **25**; compound **26** has been also used in reactions with *N*-furfurylideneanilines **27** to form azomethine ylides **28** (Scheme 9).[18] This undergoes a 1,5-electrocyclization into



a Yields in parentheses of the reactions were carried out under thermal condition (1-7 hours).

Scheme 7.



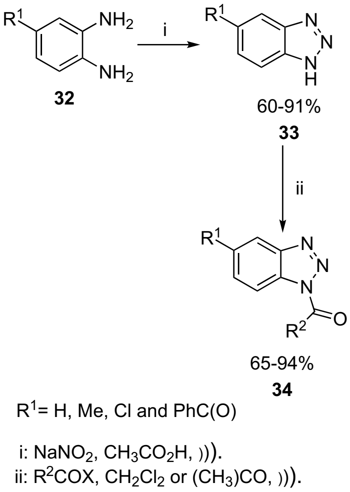
Scheme 8.

a furan ring to afford intermediate **29**, which reacts with a second equivalent of carbene to form the tetrafluoride compound **30**. After purification or by simple treatment with silica, compound **30** was hydrolyzed to bicyclic compound **31** in moderate yields.

Synthesis of 1*H*-benzotriazoles **33** from *o*-phenylenediamine **32** with sodium nitrite in acetic acid (Scheme 10) was recently reported.[19] The products were obtained in good to excellent yields after 10–15 min of sonication at 5 °C. Products **33** were then subjected to an acylation reaction under US irradiation to obtain 1-acylbenzotriazoles **34** (Scheme 10).

The 1,4-disubstituted 1,2,3-triazoles **37** have been successfully synthesized from sodium azide, terminal alkynes **35**, and alkyl/aryl halides **36** (Scheme 11).[20] The reactions were catalyzed by 10 mol % of CuI in an aqueous medium under US irradiation at room temperature for 15–30 h. All products were obtained in good to excellent yields, with high regioselectivity.

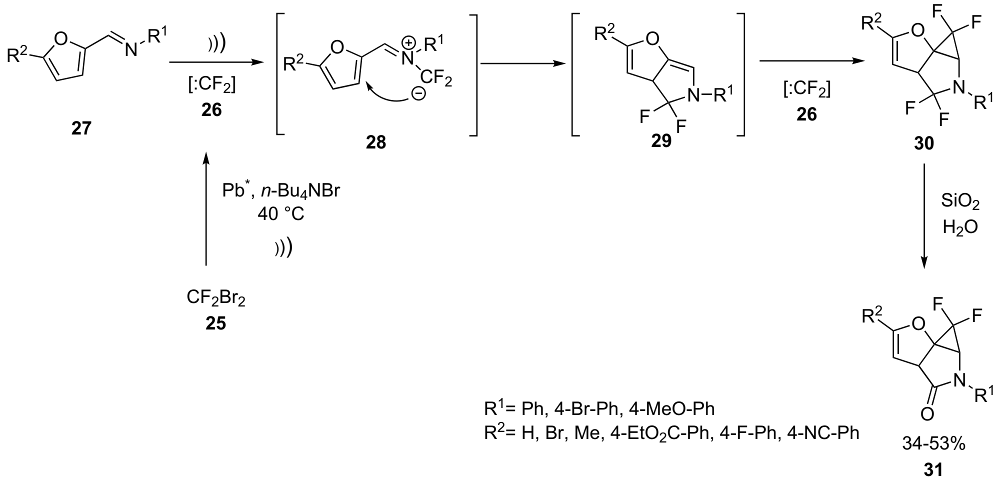
Martins and co-workers[21] reported the US-promoted synthesis of dihydroisoxazoles **39** from a variety of 1,1,1-trihalomethyl-4-alkoxy-3-alken-2-ones **38** and hydroxylamine hydrochloride (Scheme 12). The reaction proceeds in the presence of pyridine in an aqueous medium at 45 °C and has a short reaction time.



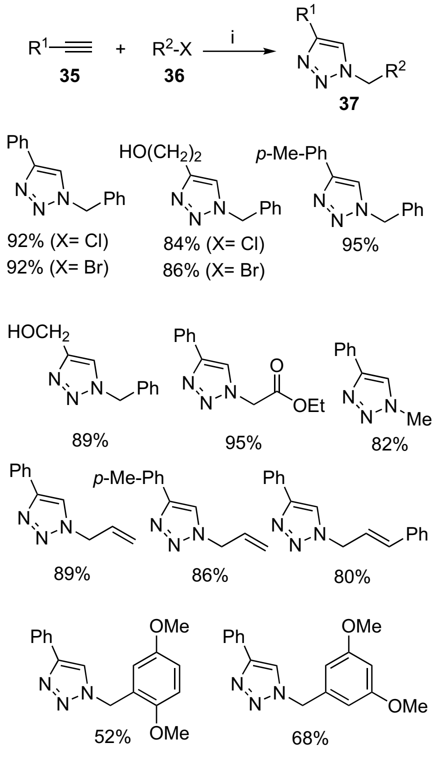
Scheme 10.

Conjugated nitrones **40** and unactivated alkenes **41** undergo a cycloaddition reaction under US irradiation to afford isoxazolidines **42** (Scheme 13).[22] The reactions were carried out using a direct immersed sonic horn, and the products were obtained in good yields and excellent regioselectivity. A comparison study showed that US irradiation increases the reaction rate 20–30 times over thermal conditions.

The cycloaddition reaction between nitrile oxide **43** and different alkenes produces 4,5-dihydroisoxazoles under US irradiation (Scheme 14).[23–25] The reaction was complete in 10–90 min at room temperature, with good yields and excellent regioselectivity.



Scheme 9.



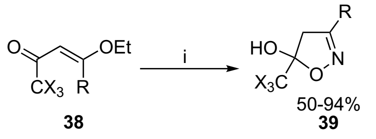
i: NaN_3, H_2O, r.t., CuI (10 mol%),))).

Scheme 11.

Nitrile oxide **43** was generated in situ via a US-mediated reaction of 1-arylaldoxime **54** with $NaOCl/H_2O/CH_2Cl_2$,[23,24] $Ca(OCl)_2/H_2O/CH_2Cl_2$,[24] or sodium dichloroisocyanurate/Al_2O_3/CH_2Cl_2[25] (Scheme 15). The chloro intermediate **55** undergoes the loss of an HCl molecule to produce nitrile oxide **43**.

Braibante and co-workers[26,27] reported that β-enamino ketones **56** and β-enamino esters **57** react with hydrazine compounds under US irradiation in the presence of the solid support K-10 to produce pyrazoles **58** and pyrazolinones **59**, respectively (Scheme 16). β-Enamino ketones **56** reacted with hydrazine to afford only one of the possible regioisomers in moderate yields. Unfortunately, the exact regioisomer was not identified. When β-enamino ketones **56** were reacted with methylhydrazine, the regioselectivity showed a dependence on the substituent present on the aromatic ring.

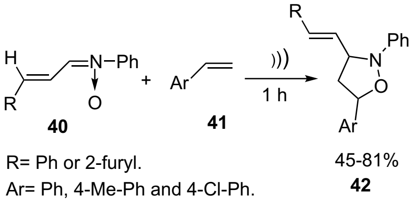
β-Enamino esters **57** also reacted with methylhydrazine under US irradiation in the presence of K-10 to produce the pyrazolinones **59** in good yields (Scheme 16). As for compounds **56**, the regioselectivity depended on the interaction of the substituent on the aromatic ring with the solid support K-10.



X= F or Cl
R= H, aryl or alkyl

i: NH_2OH HCl, Py, H_2O, r.t., 15-30 minutes,))).

Scheme 12.



R= Ph or 2-furyl.
Ar= Ph, 4-Me-Ph and 4-Cl-Ph.

Scheme 13.

The same group[28] extended their study of β-enamino compounds **56** to the use of hydroxylamine hydrochloride under US and K-10 conditions to obtain isoxazoles and isoxazolones. When β-enamino ketones **56** were subjected to reaction with hydroxylamine in dichloromethane using K-10 as a solid support, isoxazoles **60** were obtained in excellent yields (Scheme 17). The reaction showed excellent regioselectivity in most cases.

The reaction between β-enamino esters **57** and hydroxylamine was also evaluated under the same conditions. Under US conditions, a mixture of *E*- and *Z*-isoxazolylidenes **61** were obtained in good yields (Scheme 18, path A). However, when the same substrate **57** was subjected to the reaction in dichloromethane under reflux, the expected isoxalones **62** were formed (Scheme 18, path B). The formation of 5-oxoisoxazolylidene **61** probably occurs due to the initial formation of **62**, followed by condensation with a second equivalent.

Pyrazole rings **65** or **66** were prepared from α-oxo thioxoester **63** or from α-oxoketene *O*,*N*-acetals **64**, respectively, and hydrazine derivatives using Montmorillonite K-10 as a solid support under US irradiation (Scheme 19).[29] Regiospecific pyrazoles were obtained in low to moderate yields.

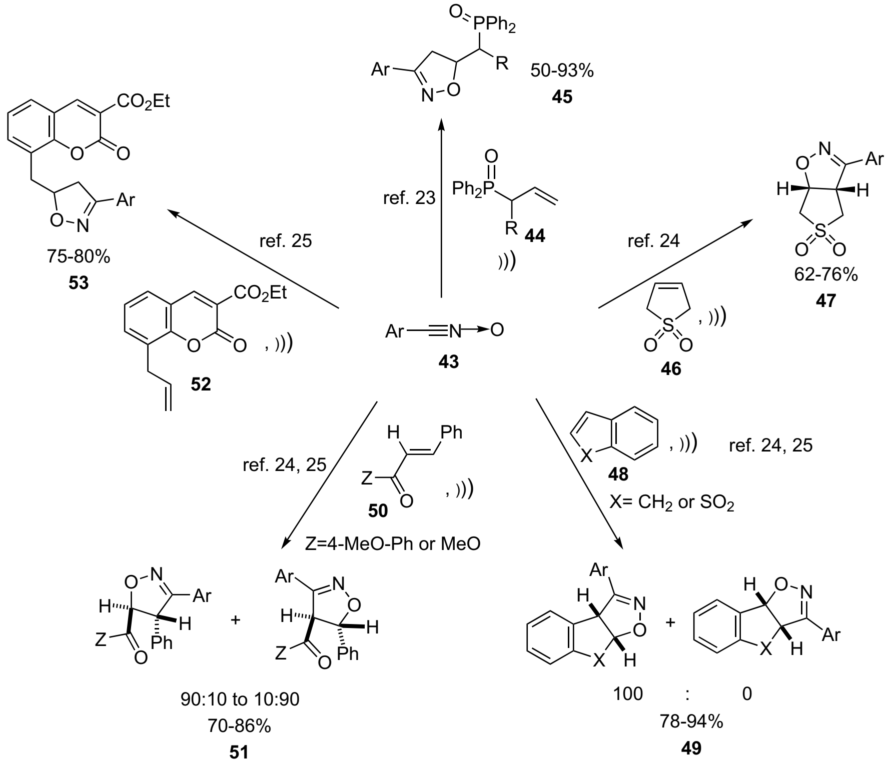
When α-oxoketene *O*,*N*-acetals **64** were subjected to acidic conditions, 3(5)-ethoxy-5(3)-phenyl-1*H*-pyrazole derivative **65** was obtained via loss of an amino group. However, when the same substrates were subjected to neutral conditions, 3-amino-substituted 1,5-diphenyl pyrazoles **66**, derived from the loss of an ethoxy group, were obtained.

A comparative study between the use of conventional conditions and US irradiation using substrate **67** was reported by Karale and co-workers.[30] Substrate **67** produced thiadiazole rings **68** in acidic medium and triazole rings **69** in basic medium (Scheme 20). US-mediated synthesis was concluded to be superior to the conventional method as a consequence of decreased reaction time, better yields, and the ability to carry out reactions at room temperature.

Pyrazole fatty esters **71** have been synthesized by treating 1,3-diketo fatty ester **70** with hydrazine, methyl, phenyl, or 4-nitrophenylhydrazine in water under US irradiation at 60 °C (Scheme 21).[31] This reaction did not show significant regioselectivity. Compound **70** was also treated with 1,2-dimethylhydrazine to produce compound **72** in 79% yield (Scheme 21).

The same research group extended the synthesis of pyrazole fatty esters using keto-allenic ester **73**.[32] Compound **73** was treated with different hydrazines in methanol under US irradiation at room temperature to give rise to the corresponding pyrazoles **74** (Scheme 22). In contrast to the reaction described above, this reaction appears to be quite regiospecific, resulting in a single regioisomer.

1,3,5-Triaryl-2-pyrazolines **76** were synthesized under ultrasonic conditions by the reaction of chalcones **75** and phenylhydrazine in the presence of sodium acetate using water as the solvent (Scheme 23).[33] Again, the use of US irradiation proved to be more effective when compared with conventional conditions (stirring and reflux). The reaction under US irradiation required less

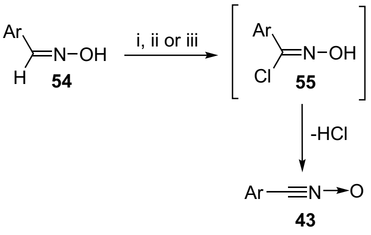


Scheme 14.

reaction time, and the products generated were regiospecific and produced in better yields.

Recently,[34] Khosropour described the synthesis of 2,4,5-trisubstituted imidazoles **79**. The reaction between aldehydes **77** and 1,2-dicarbonyl compound **78** was carried out in the presence of ammonium acetate and 20 mol % of $Zr(acac)_4$ at room temperature (Scheme 24). Both reactants tolerated electron-withdrawing and electron-donor groups. The reaction time under US was 3–4 times less than when the reaction was carried out under thermal conditions.

A cascade Sonogashira coupling–cyclization reaction was reported for the synthesis of 2-substituted indoles **82**.[35] The reaction of *o*-iodoanilines **80** with 1-alkynes **81** in the presence of $Pd(OAc)_2$ under US irradiation afforded a 'one-pot' synthesis of indole rings **82** in moderate to good yields (Scheme 25). An important feature of this methodology is that the use of copper, ligand, and amine was not necessary. US irradiation resulted in a significant enhancement in the reaction rate. Under conventional conditions, the reaction requires more than 30 h, whereas only 5 h were needed to complete the reaction under US irradiation.



i= $NaOCl/H_2O/CH_2Cl_2$ (ref. 23-24).
ii= $Ca(OCl)_2/H_2O/CH_2Cl_2$ (ref. 24).
iii=sodium dichloroisocyanurate/Al_2O_3/CH_2Cl_2 (ref. 25).

Scheme 15.

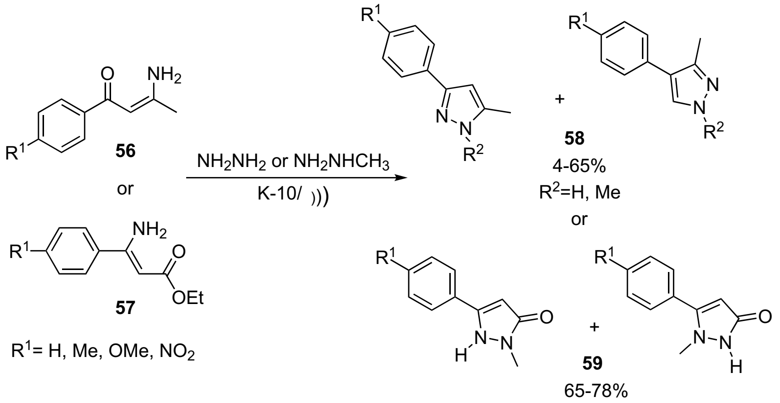
Using the same conditions, the authors were able to synthesize benzo[*b*]furans **84** by replacing *o*-iodoanilines **80** with *o*-iodophenols **83** (Scheme 26).[36] The reaction was highly tolerant to electron-rich and electron-poor, as well as aromatic and aliphatic alkynes **81**. Interestingly, when diiodophenols were used, a second Sonogashira coupling was observed (Scheme 27). By transmission electron microscopy (TEM) analysis, the authors showed that Pd(0) nanoparticles produced by US irradiation are the active species in the reaction and are extremely important for obtaining good yields. When reactions were carried out under conventional conditions, the yields dropped significantly.

A US-promoted Bishler–Napieralski synthesis of indoles was described by Haroutounian and Koulocheri.[37] Substrates **85** were irradiated for a period of 8–20 h at 35 °C in the presence of polyphosphoric acid (PPA) to produce moderate yields of indoles **86** (Scheme 28).

Lactones **90** were prepared by reaction of olefins **87** and the carboxyalkyl radical **89** generated from the corresponding carboxylic acid **88** under US irradiation in the presence of $Mn(OAc)_3$ (Scheme 29).[38] All lactones **90** were obtained in good yields and shorter reaction times when compared with thermal conditions.

Under thermal conditions, this reaction only occurred in the presence of a stoichiometric amount of $Mn(OAc)_3$, but the authors showed that, under US irradiation, the reaction can be carried out in the presence of a catalytic amount of $Mn(OAc)_3$. They believe that the Mn(II) acetate formed during the reaction could be reoxidized to Mn(III) salt; this could be due to the formation of powerful oxidizing species as a consequence of the effects of US irradiation on the solvent (acetic acid).

Toma and co-workers[39] reported that dimethyl α-(3-phenylpropyl)malonate **91** can react in different ways in the presence of



Scheme 16.

manganese(III) triacetate, with or without sonication. Compound **91** in the presence of 2 equiv of $Mg(OAc)_3$ under thermal conditions produced bicyclic compound **92** in 29% yield (Scheme 30). However, when the same reaction took place in an ultrasonic probe, three other products were obtained in addition to product **92**, including the furan ring-containing product **94** with a yield of 13%. The formation of these compounds **94**–**96** requires the presence of oxygen in the medium, resulting in the hydroxyl radical intermediate **93**, which can produce all of products **94**–**96** (Scheme 30).

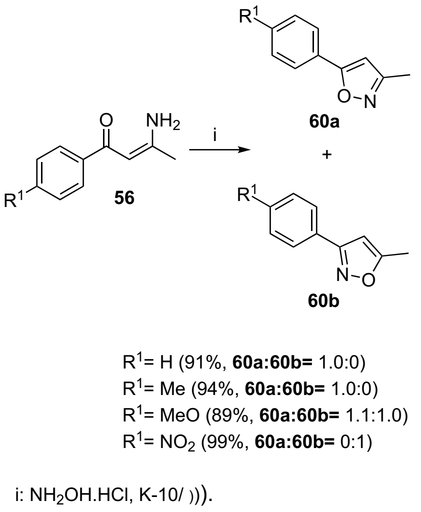
Sá e Melo and co-workers[40,41] reported the formation of tetrahydrofuran rings **98** by sonolysis of steroid compounds containing bromohydrins **97**. Halohydrins **97** were subjected to US irradiation at 45 °C in the presence of (diacetoxy-iodo)-benzene (DIB) and an iodine system to produce tetrahydrofuran steroid in excellent yields (Scheme 31). This reaction occurs via the formation of an alkoxyl radical that allows intramolecular hydrogen abstraction at the methyl group leading to cyclic-ethers **98**.

The same reaction conditions have been used for functionalization of 1β*H*-laurenan-2α-ol **99** (Fig. 4).[42] The author transformed four isomeric alcohols of structure **99** to their corresponding tetrahydrofuran rings in an attempt to investigate conformational twisting of the [5.5.5.7]fenestrane ring system.

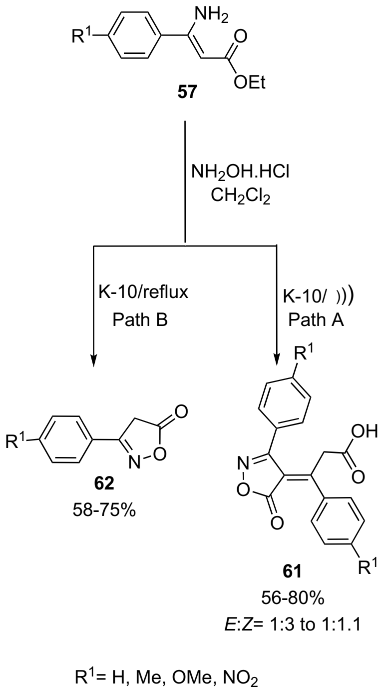
It was recently demonstrated that aryl substituted α-bromocarbonyl alkynes **100** in the presence of a stoichiometric amount of indium(I) iodide in acetonitrile solvent under US irradiation undergo a radical cyclization to afford stereospecific substituted tetrahydrofuran rings **101**[43] (Scheme 32). The authors found that an aryl substituent with an electron-donating group and α-bromocarbonyl moiety was essential for an effective reaction. When the same reaction was subjected to room temperature or refluxing with stirring, no reaction or the formation of unidentified by-products was observed, respectively.

US-promoted synthesis of imidazolidine-2-thione **104** was reported by Entezari and co-workers,[44] and the heterocycle was obtained from the reaction between ethylenediamine **102** and carbon disulfide **103** in a methanol and water solvent system (Scheme 33). The reaction occurs in the presence of an acid catalyst (HCl) or in the absence of any catalyst, and the yield depends on the reaction temperature.

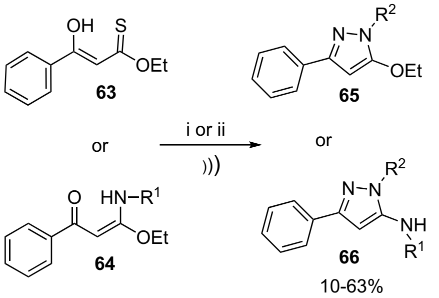
The authors suggest that the reaction occurs even in the absence of catalyst due to the acidic conditions produced by



Scheme 17.



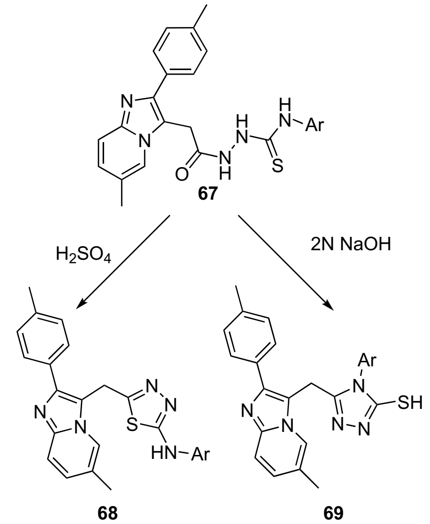
Scheme 18.



R^1= Me, Ph, Bn, CHMePh (*R*) or (*S*)
R^2= H or Ph

i= NH_2NHPh, K-10
ii= $NH_2NHR^2.HCl$, K-10

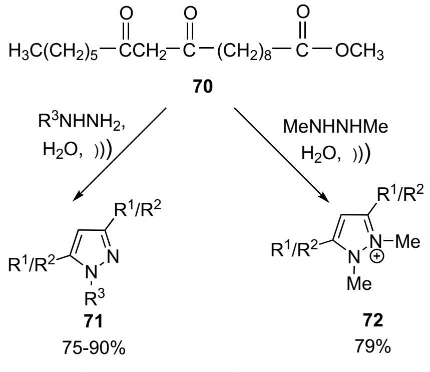
Scheme 19.



)))= 76-88% (25 min).)))= 76-88% (25 min.)
C.C.= 58-69% (150 min.) C.C.= 58-69% (150 min.)

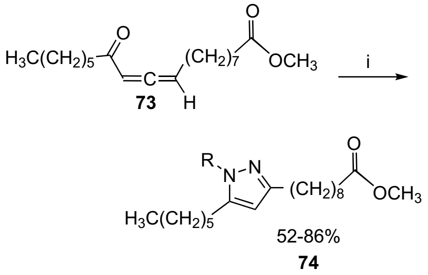
Ar= Ph; 2,3 or 4-MeO-Ph; 2,3 or 4-Me-Ph;
3 or 4-Cl-Ph; 4-Br-Ph

Scheme 20.



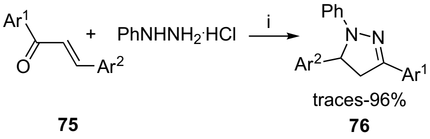
R^1= $H_3C(CH_2)_5$- ; R^2= $-(CH_2)_8C(O)OCH_3$
R^3= H, CH_3, Ph, 4-NO_2-Ph

Scheme 21.



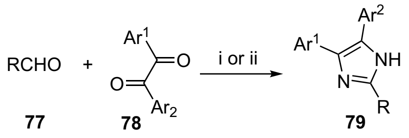
i: $RNHNH_2$, MeOH, r.t.,))).
R= H, Me or Ph

Scheme 22.



i: CH_3CO_2Na,))).
Ar^1= Ph, 4-Cl-Ph, 3-NO_2-Ph
Ar^2= Ph, 4-MeO-Ph, 4-Me-Ph, 4-Cl-Ph, 3-NO_2-Ph

Scheme 23.

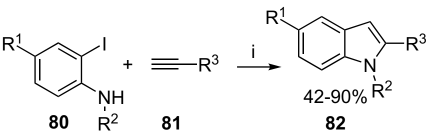


R= aryl, heteroaryl, alkene, aliphatic.
Ar^1= Ph, 4-CH_3O-Ph, 4-NO_4-Ph, 4-F-Ph.
Ar^2= Ph, 4-CH_3O-Ph, 4-F-Ph.

i: $Zr(acac)_4$ 20 mol%, NH_4OAc, EtOH, r.t., 20-45 minutes,))). (81-96%)
ii: $Zr(acac)_4$ 20 mol%, NH_4OAc, EtOH, r.t., 1-5 hours, reflux. (72-95%)

Scheme 24.

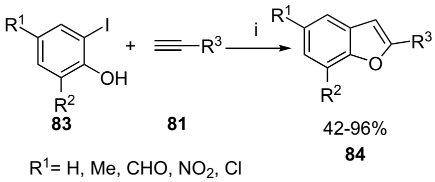
sonication of the medium during the cavitation process; dissolved gas, such as oxygen and nitrogen, in water can lead to an acidic medium resulting from the production of nitrate and nitrite ions.



R^1= H, Me, CO_2Me, COMe
R^2= Ts, Ms
R^3= Ph, 4-Me-Ph, 4-MeO-Ph, 3-F-Ph, 1-naphthyl

i: $Pd(OAc)_2$ (2 mol%), Bu_4NOAc, CH_3CN,))).

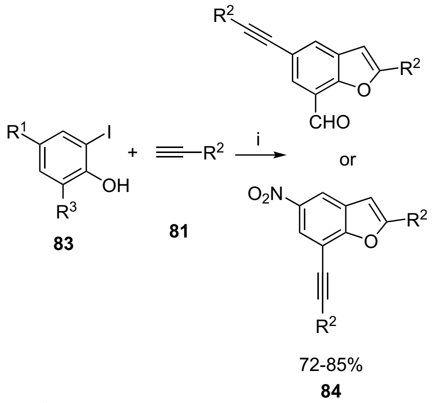
Scheme 25.



R^1= H, Me, CHO, NO_2, Cl
R^2= H or MeO
R^3= Ph, 4-Me-Ph, 3-F-Ph, CH_2OH,
$CH(OH)CH_3$, $C(CH_3)_2OH$

i: $Pd(OAc)_2$ (2 mol%), Bu_4NOAc, CH_3CN,))).

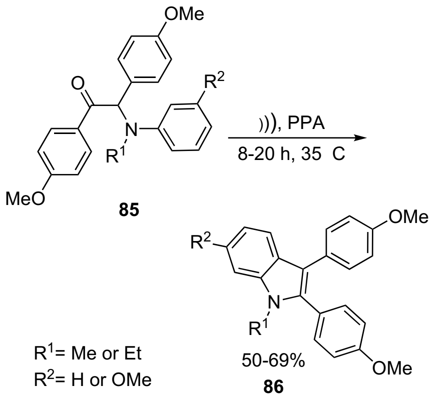
Scheme 26.



R^1= NO_2 or I.
R^2= Ph, 4-Me-Ph, 4-MeO-Ph, 3-F-Ph.
R^3= I or CHO

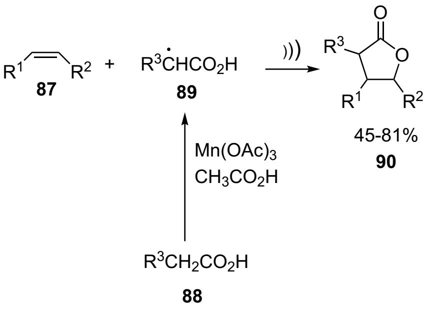
i: $Pd(OAc)_2$ (2 mol%), Bu_4NOAc, CH_3CN,))).

Scheme 27.



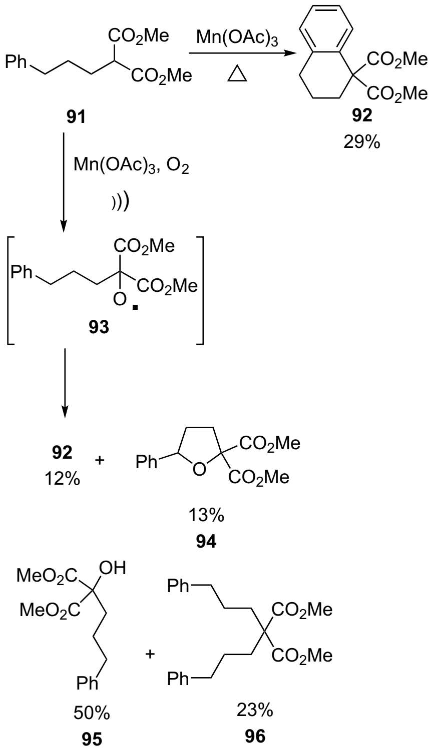
R^1= Me or Et
R^2= H or OMe

Scheme 28.

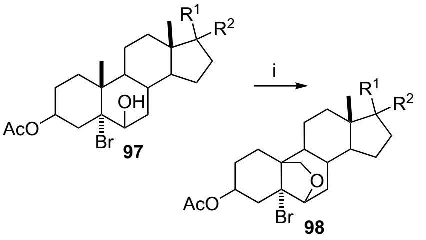


Alkene= cyclooctene, cyclohexene, norbene,
styrene, 2,3-dihydrofuran,....
R^3= CO_2Me or CN

Scheme 29.



Scheme 30.

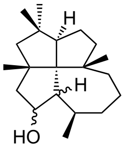


R^1 =R^2 = O (92%)
R^1 = C_8H_{17} R^2 = H (90%)
R^1 = $C(O)CH_3$ R^2 = H (90%)
R^1 = $C(O)CH_2OAc$ R^2 = O (99%)

i: DIB/ I_2, 45 °C,))).

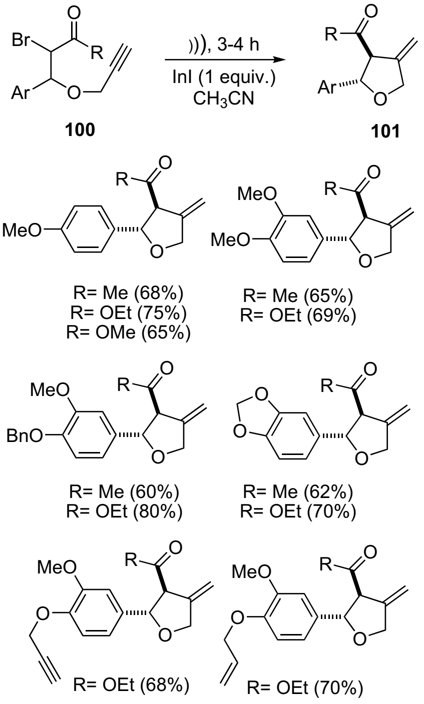
Scheme 31.

The synthesis of five-membered heterocycles containing sulfur, selenium, and tellurium has been reported by Šibor and Pazdera.[45] Two different kinds of heterocycles **106–108** can be prepared by reaction of substrates **105**, a chalcogen atom, and isothiocyanate or ketones in the presence of triethylamine under US conditions (Scheme 34). Beyond the utilization of US, the authors studied the use of conventional conditions, as well as microwave irradiation and found that although US accelerated



99

Figure 4. 1β*H*-Laurenan-2α-ol.

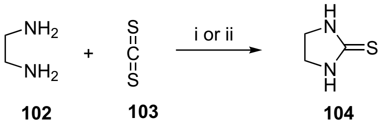


Scheme 32.

the reaction described, the microwave effect was more significant.

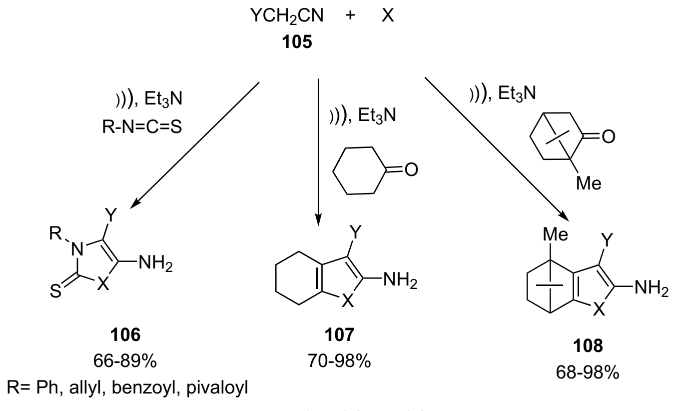
The highly substituted 4-piperidone **109** was employed as a synthon for spiro-heterocycles.[46] When compound **109** was treated with thiobenzoylhydrazide, methylhydrazine carbodithioate, or thiosemicarbazide in the presence of piperidine under US irradiation, the corresponding piperidino-thiadiazoles **110**–**112** were obtained in good yields (Scheme 35).

Pyrazoles **114** have been obtained from the aromatization reaction of pyrazolines **113**.[47] The reaction was performed in the presence of claycop (K-10 clay-supported copper nitrate), and pyrazoles **114** were produced in excellent yields (Scheme 36). The use of US irradiation enhanced the reaction rate; when conventional conditions were employed, the reaction required 1–6 h; however, under ultrasonic waves, the reactions were completed within 10–15 min.



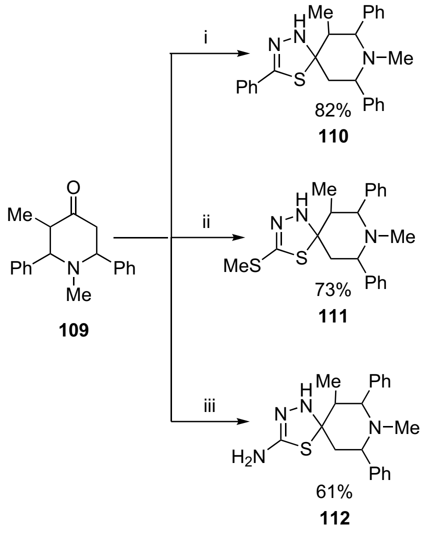
i= EtOH/H$_2$O, HCl,))) (51-93%)
ii= EtOH/H$_2$O,))) (29-92%)

Scheme 33.



Y= CN, CO$_2$Et, CONH$_2$
X= S, Se or Te

Scheme 34.

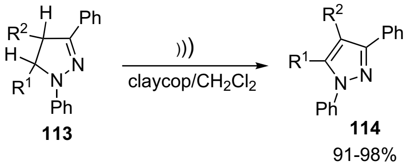


i: Piperidine, EtOH, PhC(S)NHNH$_2$,))).
ii: Piperidine, EtOH, MeC(S)NHNH$_2$,))).
iii: Piperidine, EtOH, NH$_2$C(S)NHNH$_2$,))).

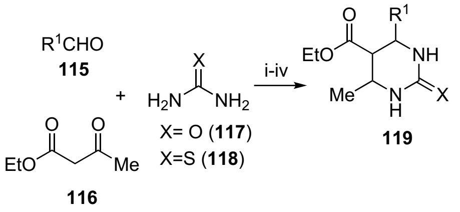
Scheme 35.

6. Six-membered rings

Zhidovinova and co-workers[48] showed that the classical Biginelli reaction[49] (EtOH and HCl) is accelerated by a factor of 40 times or more as a result of US irradiation. The three-component reaction among aldehydes **115**, ethyl acetoacetate **116**, and urea **117** or thiourea **118** in the presence of a catalytic



Scheme 36.



R^1= H, aryl, heteroaryl, aliphatic or cynnamyl.
i= EtOH, HCl (drops),))), 2-5 min. (90-95%, ref. 48)
ii= solvent-free, HCl (1 mol%),))), 15-45 min. (72-97%; ref. 50)
iii= solvent-free, TFA (5 mol%),))), 45-90 min. (67-92%; ref. 50)
iv= [Hbim]BF$_4$,))), 40-90 minutes (83-97%; ref. 51)

Scheme 37.

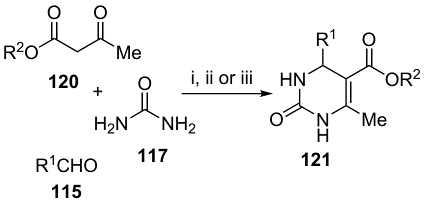
amount of HCl was completed within 2–5 min at room temperature, and Biginelli adducts **119** were obtained in excellent yields (Scheme 37).

Dihydropyrimidin-2-ones (thiones) (DHPM) **119** were also recently prepared under US irradiation in solvent-free conditions.[50] The Biginelli reaction was catalyzed by HCl (1 mol %) or trifluoroacetic acid (5 mol %) and completed within 15–45 min in reactions involving urea **117** and 60–90 min in reactions involving thiourea **118** (Scheme 37).

Srinivasan and co-workers[51] discovered that Biginelli reactions can also be performed in the absence of any catalyst. The reaction between aldehydes **115**, ethyl acetoacetate **116,** and urea **117** or thiourea **118** was carried out in 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF$_4$), a non-volatile ionic liquid, in the presence of sonic waves in a very short reaction time (Scheme 37).

DHPM(s) **119** were easily isolated and in high yield, by a simple dilution and filtration procedure. The aqueous filtrate was then distilled to remove water and leave behind quantitative yields of [Hbim]BF$_4$. The recovered ionic liquid could be reused in the same reaction at least three times without a decrease in yield. Based on the spectral data, the authors were able to postulate that the ionic liquid plays an important role in this multicomponent reaction, acting as an inherent Brønsted acid.

Li and co-workers[52,53] used US to promote the Biginelli reaction between aldehydes **115**, β-keto esters **120**, and urea **117** to obtain DHPM **121** in good to excellent yields (Scheme 38). The reaction was catalyzed by aminosulfonic acid[52] or iodine[53] and, in both cases, the reaction was very tolerant of aromatic aldehydes carrying either electron-withdrawing or electron-donating substituents. However, when aliphatic aldehydes were employed, the iodine-catalyzed reaction was not very successful.



R^1= H, aryl, heteroaryl, aliphatic or cynnamyl.
R^2= Me or Et

i= NH2SO$_3$H, EtOH,))), 40-60 min. (85-97%, ref. 52)
ii= I$_2$, CH$_3$CN,))), 2-4 h (19-95%; ref. 53)
iii= CAN, MeOH,))), 3-7 h. (88-92%; ref. 54)

Scheme 38.

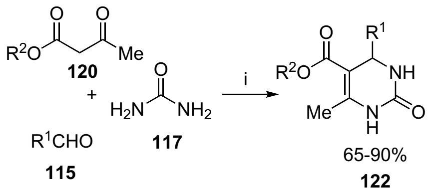
Yadav and co-workers[54] showed that ceric ammonium nitrate (CAN) can also be used as a catalyst in US-promoted Biginelli reaction (Scheme 38). The reaction was carried out in methanol under ultrasonic waves. Heteroaryl, aromatic (electron poor or electron rich), aliphatic, and α,β-unsaturated aldehydes were used and, in all cases, compounds **121** were obtained in high yields and with high purity. The authors suggest a radical mechanism for the reaction, in which a single-electron transfer from CAN to the β-keto esters and latter radical adds to the imine intermediate.

DHPM(s) **122** have been produced by utilization of inexpensive ammonium chloride as a mediator of the reaction under US irradiation (Scheme 39).[55] The Biginelli reaction was carried out in methanol and irradiated for 3–5 h in a cleaning bath. The antioxidant activity of these DHPM(s) **122** was evaluated, and some of these compounds exhibited strong activity against lipid peroxidation induced by Fe and EDTA.

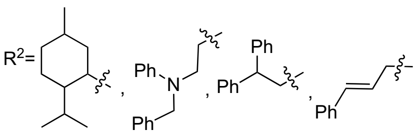
Podands containing substituted DHPM(s) **124**, **126**, and **128** were synthesized by US-promoted Biginelli reaction.[56] The DHPM(s) were obtained in two different ways: (1) the condensation of formyl podands **123**, ethyl acetoacetate **116**, and urea **117**, thiourea **118**, or aminoazoles **125** (Scheme 40); (2) the reaction of ureido-podands **127**, ethyl acetoacetate **116**, and aldehydes **115** (Scheme 41). In both cases, ethanol was used as the solvent, the reactions were completed within 5–10 min of US irradiation, and the products were obtained in moderate to good yields.

Silica-catalyzed Biginelli and Hantzsch reactions were recently reported.[57] The condensation of aromatic aldehydes **115**, ethyl (methyl) acetoacetate **120**, and urea **117** or thiourea **118** in the presence of silica under US irradiation produced DHPM(s) **129** in very good yields (Scheme 42). 4-Aryl pyridines **130** were obtained by the same procedure, but replacing (thio)urea with concentrated ammonia solution (Scheme 42).

Some pyrazoles containing DHPM(s) rings **133** attached at position 4 were synthesized from US-promoted Biginelli reactions in the presence of Mg(ClO$_4$)$_2$ as a catalyst (Scheme 43).[58] The condensation of 4-formylpyrazoles **131**, β-keto carbonyl **132**, and (thio)urea **117** or **118** in the presence of 10 mol % of Mg(ClO$_4$)$_2$ was performed in refluxing ethanol and irradiated for 2–3 h. The catalyst proved to be recyclable; it was able to catalyze the reaction three times with little loss in yield.

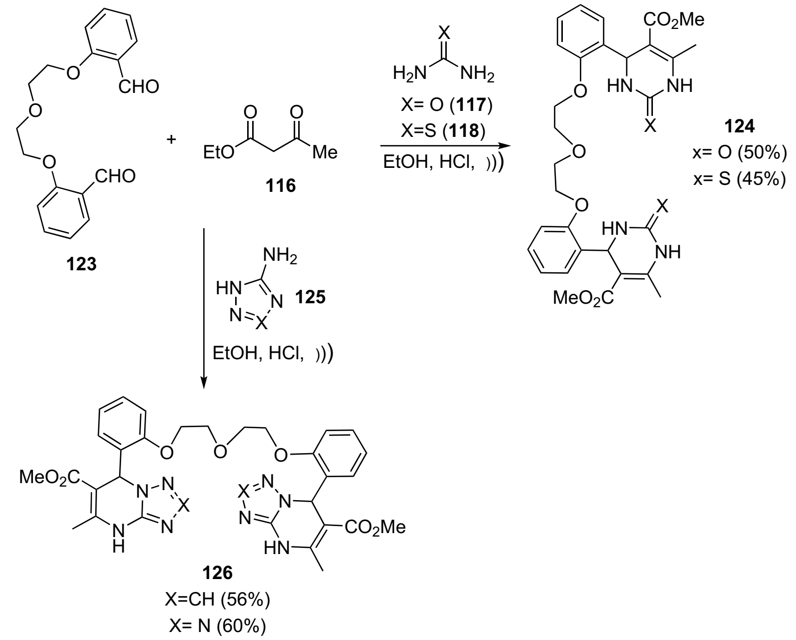


R^1= Ph or 3-NO$_2$-Ph



i: NH$_4$Cl, MeOH,))).

Scheme 39.



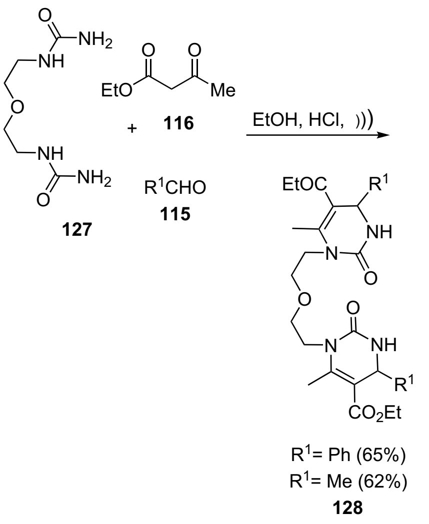
Scheme 40.

Li and co-workers[59,60] extended their earlier study of multicomponent reactions,[52,53] and achieved US-mediated synthesis of 4-oxo-2-thioxohexahydropyrimidines **135**. One-pot condensation of aromatic aldehydes **115** with ethyl cyanoacetate **134** and thiourea **118** was performed in the presence of potassium carbonate and ethanol, leading to compounds **135** in low to high yields (Scheme 44). The reaction was affected by electron-poor aldehydes, and the products were obtained in lower yields, for example, *p*-nitrobenzaldehydes produced their corresponding pyrimidines with a yield of only 20%.

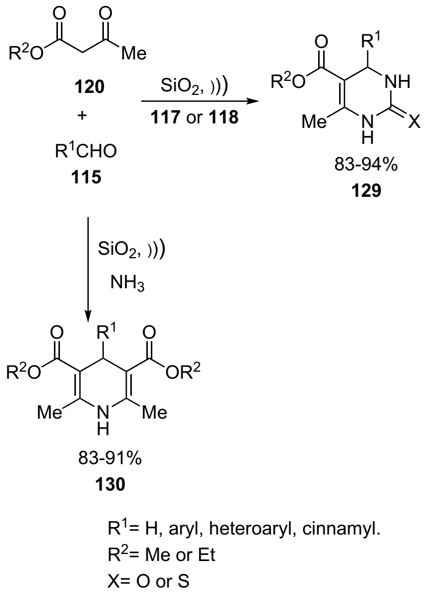
A US-mediated Ullmann condensation between 2-chlorobenzoic acid **136** and 2-aminopyridine derivatives **137** has been described.[61,62] The reaction was carried out in the presence of anhydrous potassium carbonate and copper powder using DMF as solvent (Scheme 45). In comparison with conventional conditions (stirring for 6 h at reflux temperature), the US irradiated reaction demonstrated a shorter reaction time (20 min) and greater yields (Scheme 45).

Pellón and co-workers,[63] continuing their studies of the US-mediated Ullmann reaction, reported the condensation of 2-chlorobenzoic acids **136** with aminothiazoles **139** or aminobenzothiazole **141** (Scheme 46). They used the same procedure described above and, in this case, US again enhanced the reaction rate and yields.

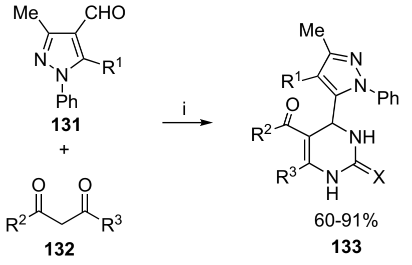
In 1995,[64] Vanden Eynde and co-workers demonstrated that Hantzsch 1,4-dihydropyridines **143** could be aromatized to their corresponding pyridines **144** and/or **145** in the presence of manganese dioxide (Scheme 47). The reaction rate was enhanced by US irradiation, and the reaction yields were comparable to those obtained with conventional conditions.



Scheme 41.



Scheme 42.



R^1= Cl or OPh
R^2= OEt, Me or Ph
R^3= Me or Ph
X= O or S

i: $Mg(ClO_4)_2$ (10 mol%), EtOH, **117** or **118**,))).

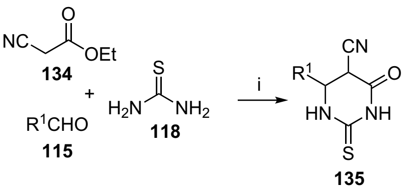
Scheme 43.

When the group in the 4-position was *i*-Pr or benzyl, 4-position unsubstituted pyridines were obtained via a dealkylation process (Scheme 47). However, when 2,3-dichloro-5,5-dicyano-1,4-benzoquinone was employed instead of MnO_2, these groups remained in the pyridine products.

The same research group showed[65] that claycop can also be used in the aromatization reaction of Hantzsch 1,4-dihydropyridines **143** under US irradiation (Scheme 47). Surprisingly, these conditions were not efficient for the aromatization of Hantzsch 1,4-dihydropyridines **143** bearing an alkyl group in 4-position (Scheme 47), and the authors showed that reaction rates were significantly enhanced by sonic waves.

The US-promoted aromatization of Hantzsch 1,4-dihydropyridines **143** was also performed using I_2 as an oxidant (Scheme 47).[66] Using **12** as an oxidant 1,4-dihydropyridines **143** containing an *i*-Pr group in the 4-position produced a complete dealkylation product **144** as in the method A (using MnO_2; Scheme 47).

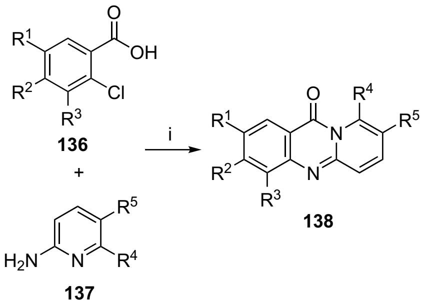
Unsymmetrical 1,4-dihydropyridines **146** were oxidized to their corresponding pyridines **147** and **148** by a US-assisted photochemical reaction (Scheme 48).[67] This photochemical oxidation is



i: K_2CO_3, EtOH, r.t.,))).

R^1	Yield (%)
Ph	90
4-$(CH_3)_2$N-Ph	90
4-CH_3-Ph	80
3,4-(OCH_2O)-Ph	77
4-CH_3O-Ph	68
2,4-Cl_2-Ph	74
2-Cl-Ph	69
3-Cl-Ph	52
4-Cl-Ph	48
3-Br-Ph	33
3-NO_2-Ph	70
4-NO_2-Ph	20

Scheme 44.

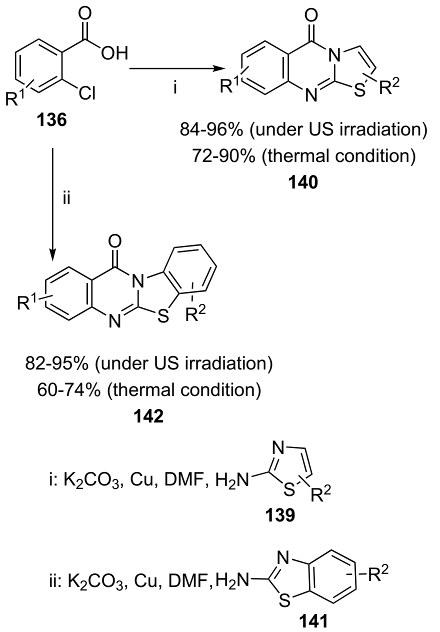


i: Cu, K_2CO_3, DMF,))).

R^1	R^2	R^3	R^4	R^5	Yield (%)[a]
H	H	H	H	H	75 (64)
H	H	H	CH_3	H	82 (77)
H	H	H	H	CH_3	69 (48)
OCH_3	H	H	H	H	79 (72)
H	Cl	H	H	H	65 (49)
H	H	NO_2	H	H	67 (52)
NO_2	H	H	H	H	78 (72)
NO_2	H	NO_2	H	H	89 (84)
H	NO_2	H	H	H	63 (25)

[a] Yields in parenthesis are under stirring and 6 hours of reflux.

Scheme 45.



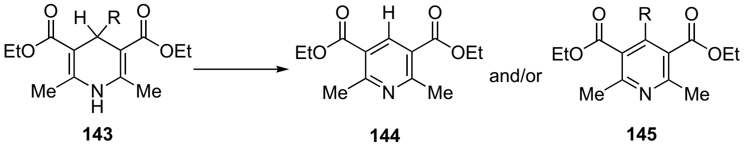
84-96% (under US irradiation)
72-90% (thermal condition)
140

82-95% (under US irradiation)
60-74% (thermal condition)
142

i: K_2CO_3, Cu, DMF, H_2N– **139**

ii: K_2CO_3, Cu, DMF, H_2N– **141**

Scheme 46.



Method A - MnO_2, CH_2Cl_2, r.t., 5 minutes,))) (ref. 64).
Method B - Claycop, CH_2Cl_2, r.t., 5-60 minutes,))) (ref. 65).
Method C - I_2, CH_3CN, r.t., 15-45 minutes,))) (ref. 66).

R	Product	Method A (%)	Method B (%)	Method C (%)
H	**144**	81	98	–
Et	**145**	95	–	–
i-Pr	**144**	83	–	98
$PhCH_2$	**144**	80	–	–
Ph	**145**	91	85	98
3-NO_2-Ph	**145**	85	78	95
4-Cl-Ph	**145**	92	83	–
4-MeO-Ph	**145**	90	–	94
2-furyl	**144** + **145**	78 (**145**)	–	30 (**144**) + 70 (**145**)

Scheme 47.

well known, but the reaction rates showed a significant increase when US irradiation was employed. They also demonstrated that when the same reaction is carried out in the absence of US conditions, no reaction is observed.

The proposed mechanism of this reaction involves an electron-transfer process in which the solvent (chloroform) is also involved in the reaction. According to the proposed mechanism, the excited singlet or triplet of 1,4-dihydropyridines (PyH_2^*) **149** donates an electron to chloroform to form $PyH_2^{\bullet+}$ **150** and $CHCl_3^{\bullet-}$ **151** (Scheme 49); elimination of HCl from both species leads to the formation of the radical pair $PyH^\bullet$ **152** and $^\bullet CHCl_2$ **153**. Hydrogen abstraction by radical **154** completes the reaction by the formation of pyridine **147** and dichloromethane **155**. The presence of the latter, **155**, in the reaction mixture was observed by GC analysis.

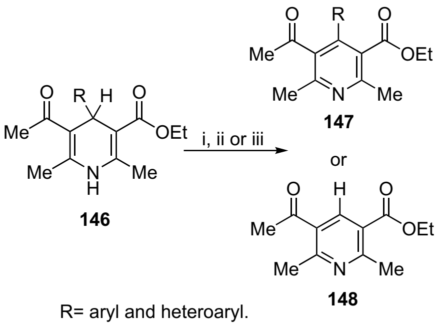
Ramakrishnan and co-workers[68] studied the US-accelerated condensation of aromatic aldehydes **156** with β-aminocrotonate **157** and cyclohexane-1,3-dione **158** or cyclopentane-1,3-dione **160** to achieve tetrahydroquinolines **159** or tetrahydrocyclopenteno[*b*]pyridines **161**, respectively (Scheme 50). Under US irradiation, the reaction requires 20–30 min for completion, while up to 8 h are required under thermal conditions.

Tetrahydropyrimidines **165** or **166** were synthesized by a US-promoted multicomponent cyclocondensation.[69] Reactions between chalcones **162**, ammonia, and carbonyl compound **163** or **164** were completed at room temperature in methanol within 90 min (Scheme 51). All products were obtained after a simple filtration/wash protocol in good yields.

Two 1,2,4,5-tetrazines **168** were prepared from the US-promoted decomposition of sydnone compound **167** in THF (Scheme 52).[70] When the reaction was carried out in DMF, this decomposition was not observed.

Li and co-workers[71] reported the US-mediated one-pot synthesis of 4*H*-benzo[*b*]pyran derivatives **171**. The three-component condensation of aromatic aldehydes **115** with 1,3-cyclohexanedione **169** and cyanoacetic esters **170** proceeds in the presence of KF/basic Al_2O_3 in ethanol to produce excellent yields of compounds **171** (Scheme 53). The reaction was highly tolerant of both electron-poor and electron-rich aromatic aldehydes. The authors showed that the catalyst KF/Al_2O_3 could be recycled without any loss in catalyst activity.

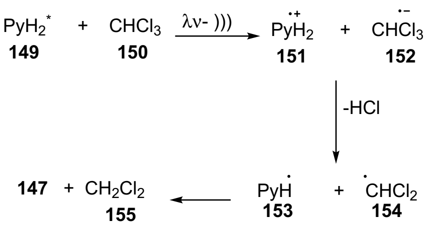
The synthesis of 1,8-dioxo-octahydroxanthene derivatives **172** has been described by Jin and co-workers.[72] US-mediated



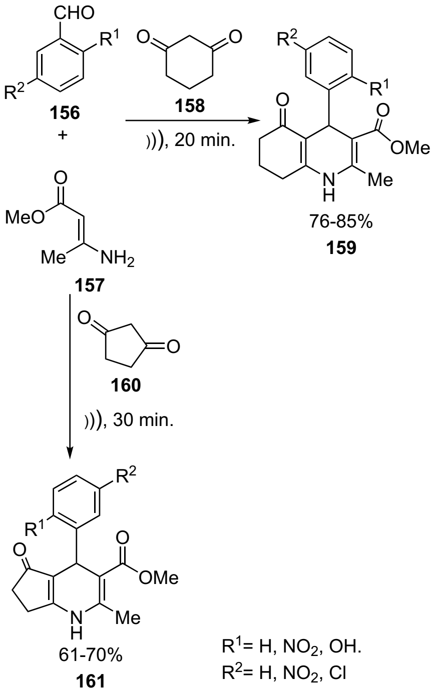
R= aryl and heteroaryl.

i: λν, 0.25-5.5 hours, in chloroform.
ii: λν-))), 0.1-2.3 hours, in chloroform.
iii:))) no reaction.

Scheme 48.

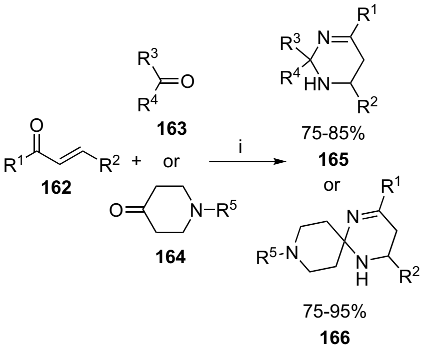


Scheme 49.



R^1= H, NO_2, OH.
R^2= H, NO_2, Cl

Scheme 50.

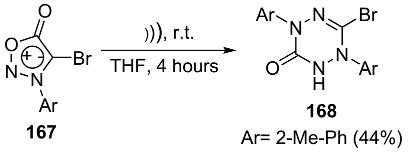


R^1= R^2= aryl
R^3= H, aryl, heteroaryl, alkyl
R^4= H or CH_3
R^5= benzyl, *i*-Pr, Me, Et, CO_2Me, C(O)Me

i: NH_3, MeOH, r.t.,))).

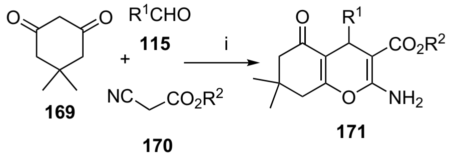
Scheme 51.

reactions between aromatic aldehydes **115** and 2 equiv of 1,3-cyclohexanedione **169** were carried out in water and resulted in products **172** in excellent yields and high purity (Scheme 54). *p*-Dodecylbenzenesulfonic acid (DBSA) was employed as a catalyst (10 mol %), and aromatic aldehydes possessing either electron-donating or electron-withdrawing substituents all reacted very well.



Ar= 2-Me-Ph (44%)
Ar= 4-MeO-Ph (25%)

Scheme 52.

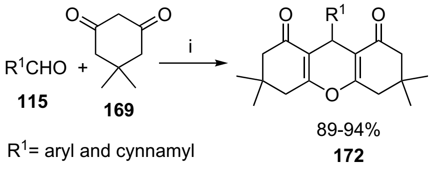


i: KF/Al_2O_3,))), EtOH, r.t.

R^1	R^2	Yield (%)
Ph	Me	81
	Et	86
2-Cl-Ph	Me	97
	Et	84
4-Cl-Ph	Me	96
	Et	98 (97)[a]
4-Me-Ph	Me	94
	Et	93
3-NO_2-Ph	Me	85
	Et	98
4-NO_2-Ph	Et	84
2,4-Cl_2-Ph	Et	94
3,4-(OCH_2O)-Ph	Et	90

[a] Using recycled KF/Al_2O_3 as catalyst.

Scheme 53.

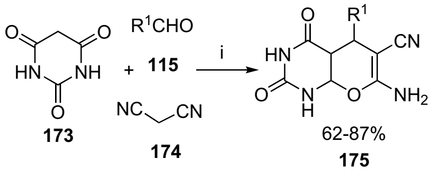


R^1= aryl and cynnamyl

i:))), H_2O, r.t., DBSA (10 mol%).

Scheme 54.

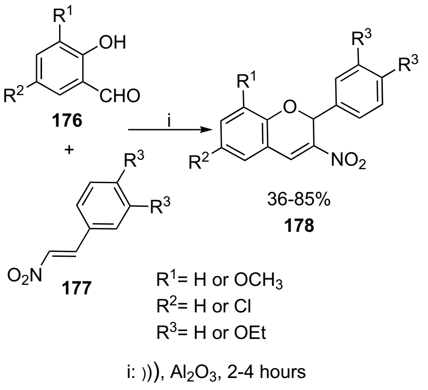
Bicyclic compounds of type **175** have been synthesized by a US-promoted three-component reaction between aromatic aldehydes **115**, barbituric acid **173**, and malonitrile **174** (Scheme 55).[73] The reaction was performed in an aqueous medium without the use of any catalyst, and the products **175** were obtained in good yields after recrystallization.



R^1= aryl

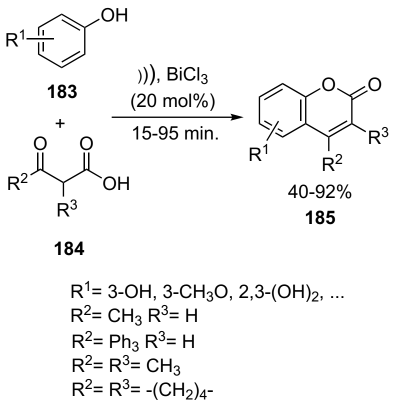
i:))), H_2O, r.t., 1 to 3 hours.

Scheme 55.



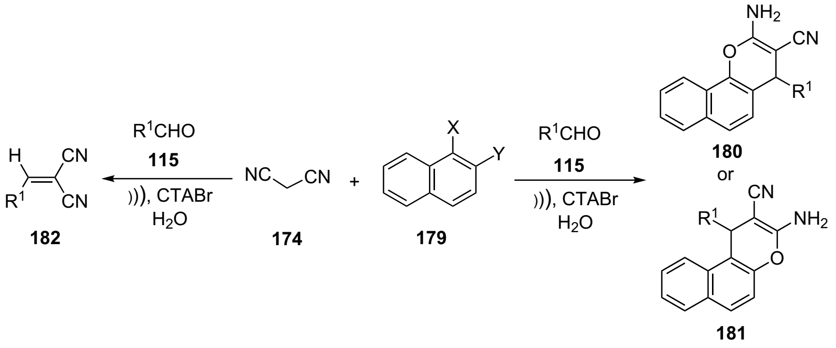
Scheme 56.

Kabalka and Varma[74] applied US in the synthesis of 3-nitro-2*H*-chromenes **178** from *o*-hydroxybenzaldehydes **176** and β-nitrostyrenes derivatives **177** (Scheme 56). The reaction was performed using basic alumina as a solid support in the absence of any solvent, and the products were obtained after simple washing of the solid support with acetone or dichloromethane.



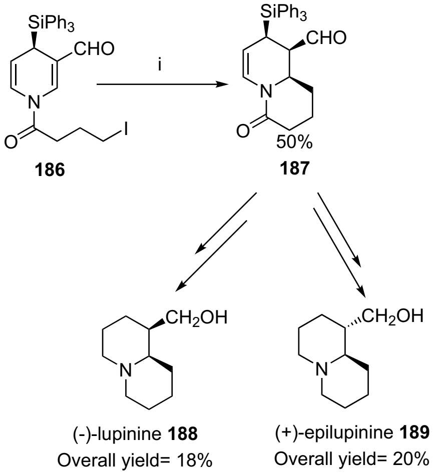
Scheme 58.

Jin and co-workers[75] reported the US-assisted synthesis of 2-amino-2-chromenes **180** and **181**. The multicomponent reaction was carried out in water using a catalytic amount of cetyltrimethylammonium bromide (CTAB) (Scheme 57). The reaction afforded the desired product **180** or **181** when benzaldehydes and electron-poor aromatic aldehydes were employed. However, when



R^1	X	Y	Product	Yield (%)
Ph	OH	H	**180**	92
2-Cl-Ph	OH	H	**180**	86
3-Cl-Ph	OH	H	**180**	88
4-Cl-Ph	OH	H	**180**	95
3-NO_2-Ph	OH	H	**180**	91
4-NO_2-Ph	OH	H	**180**	94
2,4-Cl_2-Ph	OH	H	**180**	85
Ph	H	OH	**181**	78
4-NO_2-Ph	H	OH	**181**	80
4-Cl-Ph	H	OH	**181**	83
2-Cl-Ph	H	OH	**181**	72
4-HO-Ph	OH	H	**182**	90
4-CH_3O-Ph	OH	H	**182**	88
3,4-OCH_2O-Ph	OH	H	**182**	83
3-CH_3O-4-HO-Ph	OH	H	**182**	85
4-Me_2N-Ph	OH	H	**182**	84
3,4-OCH_2O-Ph	H	OH	**182**	78
4-CH_3O-Ph	H	OH	**182**	82

Scheme 57.



i:))), Zn/CuI, *i*-PrOH, H_2O.

Scheme 59.

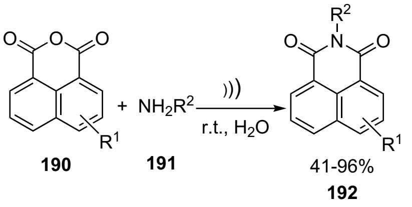
aromatic aldehydes carrying electron-rich substituents were used, α-cyanocinnamonitrile derivatives **182** were produced (Scheme 57).

Some coumarin compounds **185** have been successfully produced via a US-assisted Pechmann condensation.[76] The reactions between phenols **183** and 1,3-carbonyl carboxylic acids **184** were catalyzed by bismuth(III) chloride (20 mol %) in the absence of any solvent (Scheme 58).

The cyclization reaction of 1,4-dihydropyryidine **186** under US irradiation afforded the bicyclic compound **187**, and this compound was used in the synthesis of two natural alkaloids, (−)-lupinine **188** and (+)-epilupinine **189** (Scheme 59).[77] The reaction under US irradiation was carried out in the presence of zinc/cupric iodide, and product **187** was obtained in 50% yield as a unique and stable cis diastereomer.

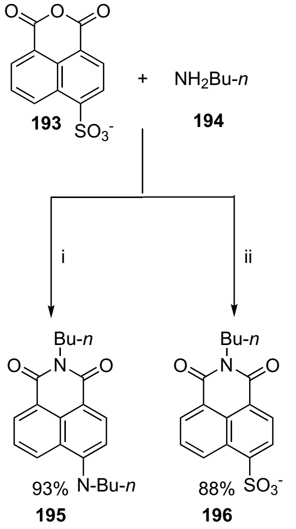
Some *N*-alkyl-1,8-naphthalimides **192** were prepared by reaction of anhydrides **190** and primary amines **191** (Scheme 60).[78] The reaction was performed under US irradiation in an aqueous medium. The products were obtained in good to excellent yields without the need for purification, in most of the cases.

When 4-sulfonic-1,8-naphthalic anhydride **193** is reacted with *n*-butylamine **194**, the final product depends on the ultrasonic specifications. Using an ultrasonic cleaner at 50 W and 45 KHz, compound **195** was obtained in 93% yield (Scheme 61).[78] However, when the same reaction took place in an ultrasonic cleaner at 150 W and 25 KHz, the final product **196** was isolated in 88% yield (Scheme 61). Although the authors did not offer an explanation for this behavior, it is clear that different frequencies can act in different ways.



R^1= H, 4-NO_2, 4-Cl, 3-NO_2
R^2= alky or allyl

Scheme 60.



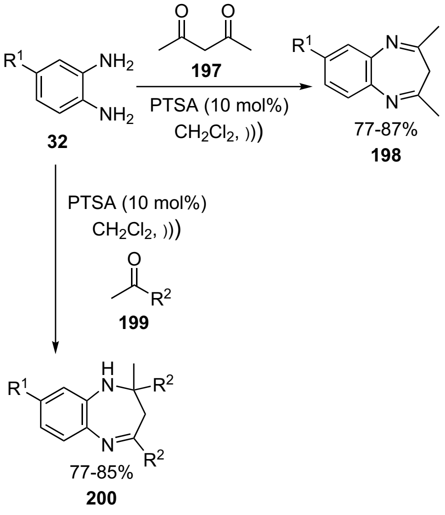
i: 50 W/ 45 KHz,))), r.t., H_2O.
ii: 150 W/ 25 KHz,))), r.t., H_2O.

Scheme 61.

7. Seven-membered rings

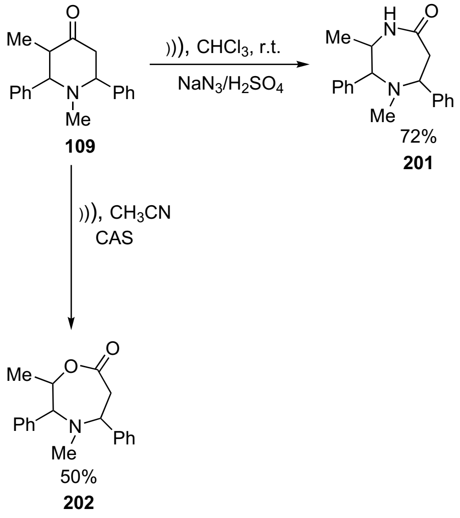
We recently reported that 1,5-benzodiazepinic rings **198** or **200** could be synthesized by a US-promoted condensation of *o*-phenylenediamine derivatives **32** with 2,4-pentadione **197** or ketones **199**, respectively[79] (Scheme 62). The reaction was catalyzed by 10 mol % of *p*-toluenesulfonic acid (PTSA), and the products were obtained in good yields, containing either electron-withdrawing or electron-donating groups attached to diamine **32**.

The use of 4-piperidone **109** was previously described in the synthesis of some five-membered heterocyclic rings.[46] The same authors reported that compound **109** can also react with NaN_3/H_2SO_4 under US irradiation to afford the corresponding



R^1= Cl, Me, MeO, PhC(O), 4-F-Ph-C(O)
R^2= Me, Et or Pr

Scheme 62.



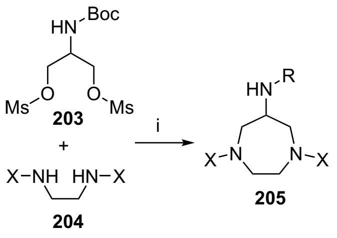
Scheme 63.

diazepanone **201** in 72% yield (Scheme 63);[80] alternately, 4-piperidone **109** can undergo a Baeyer–Villiger reaction in the presence of ceric ammonium sulfate (CAS) and ultrasonic waves to afford an oxazepanone ring **202** in 50% yield (Scheme 63).

Cravatto and co-workers recently described the US/microwave-promoted synthesis of 6-aminoperhydro-1,4-diazepine **205** (Scheme 64).[81] The reaction between *N*-Boc-serinol dimesylate **203** and protected ethylenediamine **204** in the presence of Cs_2CO_3 or K_2CO_3 was first irradiated with US for 3 min, and then microwave irradiated for an additional 2 h. The use of US irradiation plays an important role in the dispersion of solid alkali carbonate; however, no reaction was observed when US alone was used. Boc group loss was observed in small-scale reactions.

Cycloheptane rings **208** have been synthesized by a zinc/copper-promoted reductive cyclocoupling of α,α′-dibromo[82] or α,α′-diiodoketones[83] **206** with 1,3-dienes **207** (Scheme 65). The reaction was performed under US irradiation, and products **208** were obtained in moderate to good yields. Use of Me_3SiCl as a mediator is known to assist this type of reaction,[84] but its presence was not necessary using this methodology.

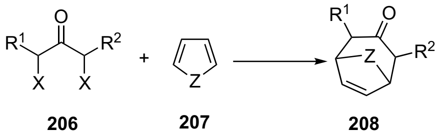
Recently, Mihovilovic and co-workers used the same approach to prepare these bicyclic ketones **208**[85] (Scheme 65), which were subsequently subjected to ring-opening cross-metathesis (ROCM) to produce six-membered rings **209** (Scheme 66).



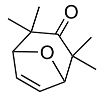
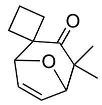
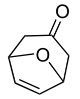
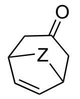
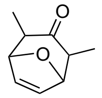
X= Tosyl (93%) or *p*-nosyl (60%).
R= Boc or H.

i: MeCN, Cs_2CO_3 or K_2CO_3,))) 3 minutes,
MW 2 hours.

Scheme 64.



Method A : Zn dust (3 equiv.), CuCl (30 mol%),
dioxane,))).
Method B : Zn-Cu pair (3 equiv.) CH_3CN,))).

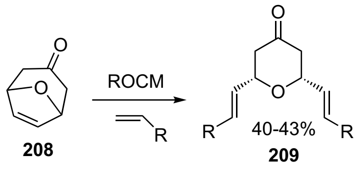
X	Z	Method	Product	Yield (%)
Br	O	A		91
Br	O	A		88
Br	O	B		60
Br	NCO_2Me	B		45
I	O	B		90

Scheme 65.

The heterocyclic oxabicyclic compound **208** synthesized by this [4+3] cycloaddition of furan and a ketone has also been used in the synthesis of several precursors for natural products containing a tetrahydrofuran structural cores **210**–**212** (Fig. 5).[86]

8. Diels–Alder reaction

Cintas and co-workers explored the synthesis of some bicycle[2.2.2]octenones **216** via US-mediated Diels–Alder reaction[87–89] (Scheme 67). The reaction between furan derivatives **215** as dienophiles and masked *o*-benzoquinones (MOB) **214** as dienes resulted in a single regio and stereoisomer in low to moderate yields. The cycloaddition reaction proved to be extremely sensitive to steric hindrance, and only the unsubstituted double bond of the furan ring reacted. An inherent limitation of this reaction is the instability of the MOB(s), which are prone to dimerization, requiring in situ preparation by oxidation of the corresponding phenol **213** with (diacetoxyiodo)benzene (DAIB) in the presence of furan (Scheme 67).



R= H, Me or Et

Scheme 66.

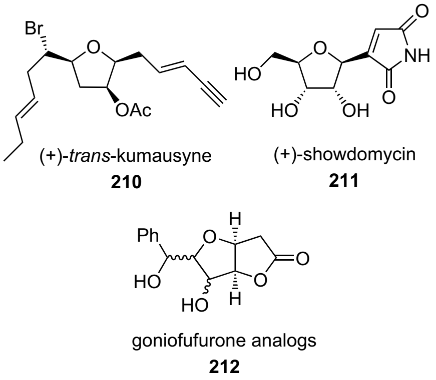
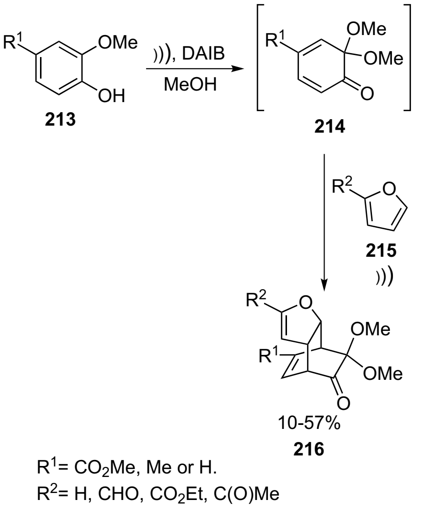
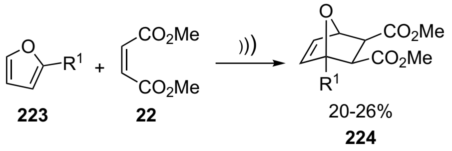


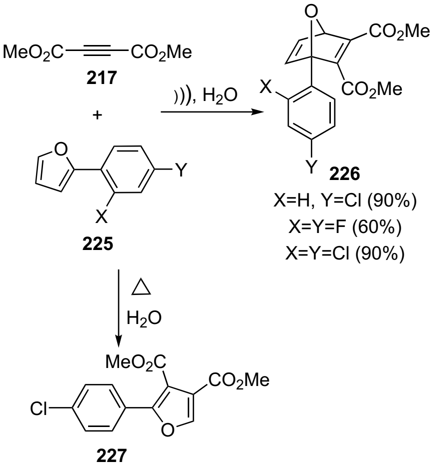
Figure 5. Natural products containing a tetrahydrofuran structural core.



Scheme 67.



Scheme 69.

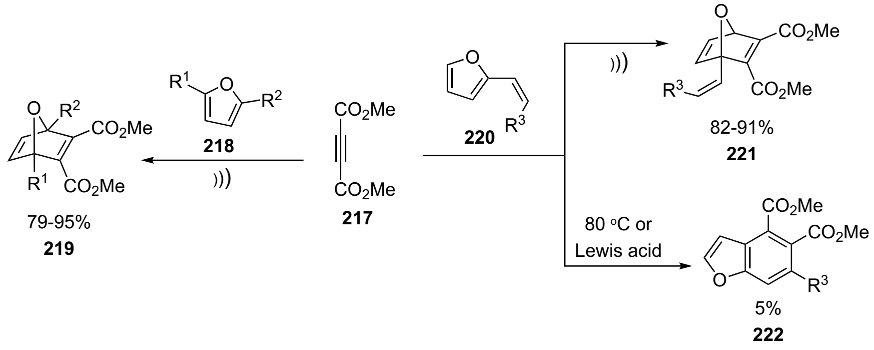


Scheme 70.

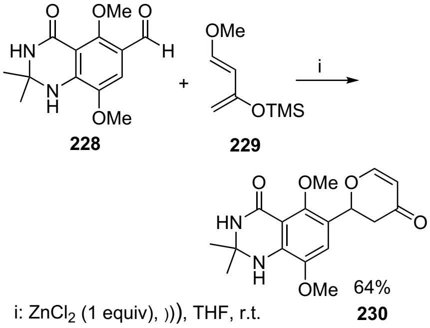
Li and co-workers showed that furan derivatives can also act as dienes in Diels–Alder reactions under US irradiation.[90] When a mixture of furans **218** and dimethyl acetylenedicarboxylate (DMAD) **217** in the absence of solvent was subjected to US irradiation, the respective oxabicyclic compounds **219** were obtained in good to excellent yields (Scheme 68). Interestingly, when 2-vinylic furans **220** were used as dienes during cycloaddition of DMAD **217** under US irradiation, only cyclic furan diene cycloadducts were obtained **221** (Scheme 68). However, under thermal conditions the only product formed in a low yield was the *exo*-cyclic diene **222** (Scheme 68).

Reaction of furan derivatives **223** with dimethyl maleate **22** under US irradiation produced only [4+2] cycloadducts **224** (Scheme 69).[90] The reaction was very slow, and the oxabicyclic adducts **224** were obtained in low yield due to the facile retro-Diels–Alder process. Although the conversion and isolated yields were relatively low under US irradiation, the *exo*/*endo* selectivities were very high (>50:1). Typically, in non-US conditions, these reactions require harsh conditions, such as high temperature in a sealed tube or Lewis acids.

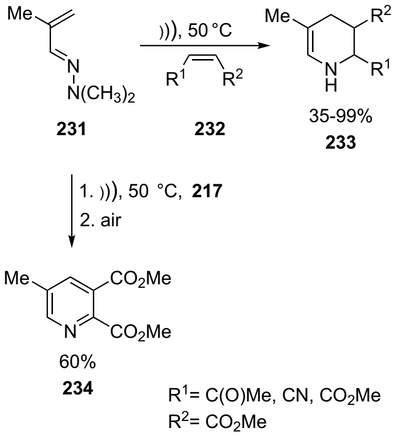
Saksena and co-workers reported US-mediated Diels–Alder reactions in an aqueous medium.[91] Reactions of 2-aryl substituted furan **225** with DMAD **217** in water in the presence of sonic waves yielded the Diels–Alder adduct **226** (Scheme 70). When substrate **225** was treated with DMAD **217** under thermal conditions, compound **227** was obtained, the product of a retro-Diels–Alder process (Scheme 70).[92,93]



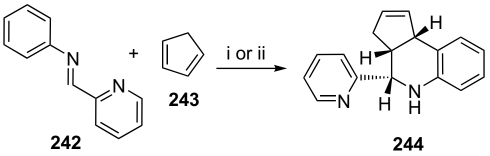
Scheme 68.



Scheme 71.



Scheme 72.



i= ZnI_2 (1 equiv.), 40 °C, 2h,))) (10%).
ii= BF_3 OEt_2, dichloromethane, -50 °C, 2h, stirring (43%).

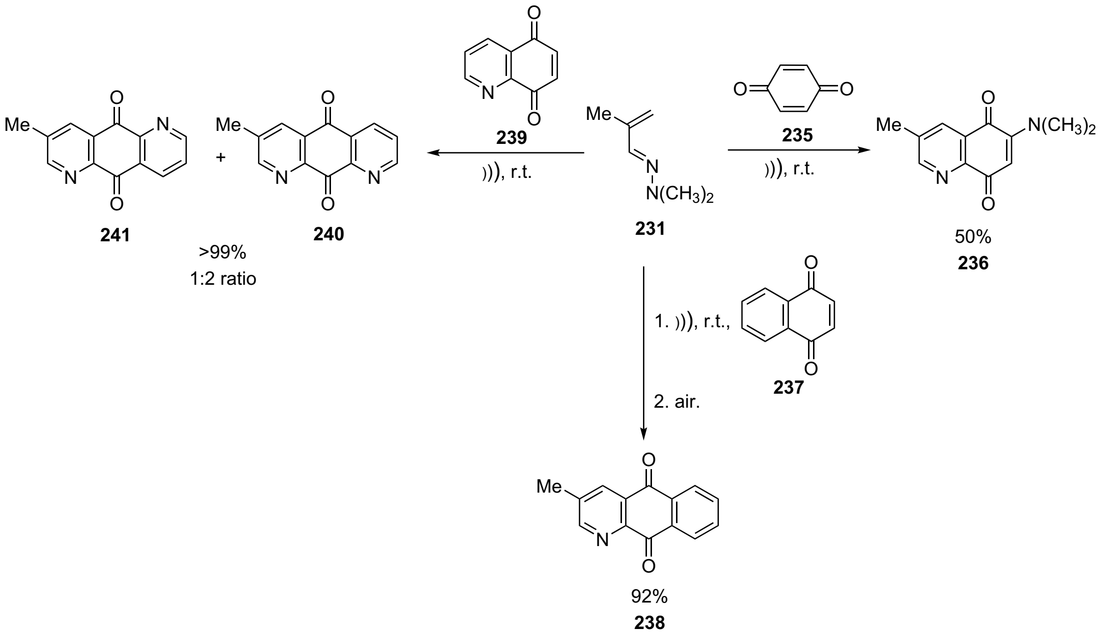
Scheme 74.

US-promoted hetero Diels–Alder has also been investigated.[94,95] Cyclization of aldehydes **228** with Danishefsky's diene **229** to provide product **230** only worked under US irradiation in the presence of zinc(II) chloride as a mediator in THF at room temperature (Scheme 71). The same reaction did not occur under conventional conditions, even in the presence of different Lewis acids, i.e., $BF_3\cdot OEt_2$.

The reaction between methacrolein dimethylhydrazine **231** and several α,β-unsaturated carbonyl compounds **232** produced the desired Diels–Alder adduct **233** in good to excellent yields (Scheme 72).[96] A trisubstituted pyridine **234** was obtained from the Diels–Alder reaction of compound **231** with DMAD **217** following air oxidation (Scheme 72).

Substrate **231** was also subjected to the Diels–Alder reaction with quinines. Reaction of **231** with benzoquinone **235** under US irradiation provided product **236** in 50% yield (Scheme 73); reaction with naphthoquinone **237** afforded product **238** in 92% yield after air oxidation (Scheme 73); finally, reaction of **231** with 5,8-quinolinequinone **239** afforded two regioisomers **240** and **241** at a 2:1 ratio (Scheme 73).

The zinc/US-promoted cycloaddition reaction between *N*-phenyl-2-(pyrid-2-yl)imine **242** and cyclopentadiene (CPD) **243** has been described (Scheme 74).[97] Normally, CPD represents the diene component and the imine reacts as a dienophile; however, in this case, CPD represents the dienophile and aryl imine **242** acts as the diene to yield cyclopenta[*c*]quinoline **244** instead of a norbornenyl ring. The same reaction catalyzed by $BF_3\cdot OEt_2$ under conventional conditions afforded the same product **244** (Scheme 74); it is remarkable that, in this case, conventional conditions proved to be milder and the product was obtained in better yield.



Scheme 73.

9. Conclusions

Synthetic organic reactions performed under non-traditional conditions (microwave and US) are gaining popularity, primarily to circumvent growing environmental concerns. The features of US-assisted organic transformations, namely the selectivity, ease of experimental manipulation, and enhanced reaction rates, were highlighted. The use of this non-traditional tool aids in overcoming many of the difficulties associated with conventional reactions, and offers both process-related and environmental advantages in the synthesis of heterocyclic compounds.

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References and notes

1. Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, 2nd ed.; Wiley-VCH: Weinheim, 2003.
2. Ando, T.; Sumi, S.; Kawate, T.; Ichihara, J.; Hanafusa, T. *J. Chem. Soc., Chem. Commun.* **1984**, 439.
3. (a) Suslick, K. S. *Science* **1990**, *247*, 1439; (b) Mason, T. J. *Chem. Soc. Rev.* **1997**, *26*, 443; (c) Cravotto, G.; Cintas, P. *Chem. Soc. Rev.* **2006**, *35*, 180.
4. Fillion, H.; Luche, J.-L. In *Synthetic Organic Sonochemistry*; Luche, J.-L., Ed.; Plenum: New York, NY, 1998; and references therein.
5. For review: (a) Peters, D. *J. Mater. Chem.* **1996**, *6*, 1605; (b) Suslinck, K. S.; Price, G. J. *Annu. Rev. Mater. Sci.* **1999**, *29*, 295; (c) Gedanken, A. *Ultrason. Sonochem.* **2004**, *11*, 47; (d) Gedanken, A. *Chem.—Eur. J.* **2008**, *14*, 3840.
6. Goldberg, Y.; Sturkovich, R.; Lukevics, E. *Heterocycles* **1989**, *29*, 597.
7. Thorneycroft, J.; Barnaby, S. W. *Inst. Civil Eng.* **1895**, *122*, 51.
8. Richards, W. T.; Loomis, A. L. *J. Am. Chem. Soc.* **1927**, *49*, 3086.
9. (a) Sehgal, C. M.; Wang, S. Y. *J. Am. Chem. Soc.* **1981**, *103*, 6606; (b) Donaldson, D. J.; Farrington, M. D.; Kruss, P. *J. Phys. Chem.* **1979**, *83*, 3130.
10. (a) Suslick, K. S.; Hammerton, D. A.; Cline, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 5641; (b) Flint, E. B.; Suslick, K. S. *Science* **1991**, *253*, 1397.
11. Margulis, M. A. In *Advances in Sonochemistry*; Mason, T. J., Ed.; JAI: London, 1990; Vol. 1.
12. Chanda, B. M.; Vyas, R.; Bedekar, A. V. *J. Org. Chem.* **2001**, *66*, 30.
13. Konev, A. S.; Novikov, M. S.; Khlebnikov, A. F. *Tetrahedron Lett.* **2005**, *46*, 8337.
14. Ross, N. A.; MacGregor, R. R.; Bartsch, R. A. *Tetrahedron* **2004**, *60*, 2035.
15. Bose, A. K.; Gupta, K.; Manhas, M. S. *J. Chem. Soc., Chem. Commun.* **1984**, 86.
16. Caldwell, J. J.; Harrity, J. P. A.; Heron, N. M.; Kerr, W. J.; McKendry, S.; Middlemiss, D. *Tetrahedron Lett.* **1999**, *40*, 3481.
17. Caldwell, J. J.; Kerr, W. J.; McKendry, S. *Tetrahedron Lett.* **1999**, *40*, 3485.
18. Voznyi, I. V.; Novikov, M. S.; Khlebnikov, A. F. *Synlett* **2005**, 1006.
19. Pereira, C. M. P.; Stefani, H. A.; Guzen, K. P.; Orfão, A. T. G. *Lett. Org. Chem.* **2007**, *4*, 43.
20. Sheedhar, B.; Reddy, P. S. *Synth. Commun.* **2007**, *37*, 805.
21. Martins, M. A. P.; Pereira, C. M. P.; Cunico, W.; Moura, S.; Rosa, F. A.; Peres, R. L.; Machado, P.; Zanatta, N.; Bonacorso. *Ultrason. Sonochem.* **2006**, *13*, 364.
22. Borthakur, D. R.; Sandhu, J. S. *J. Chem. Soc., Chem. Commun.* **1988**, 1444.
23. Armstrong, S. K.; Collington, E. W.; Knight, J. G.; Naylor, A.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1433.
24. Bougrin, K.; Lamiri, M.; Soufiaoui, M. *Tetrahedron Lett.* **1998**, *39*, 4455.
25. Syassi, B.; El Bakkali, B.; Benabdellah, G. A.; Hassikou, A.; Dinia, M. N.; Rivière, M.; Bougrin, K.; Soufiaoui, M. *Tetrahedron Lett.* **1999**, *40*, 7205.
26. Valduga, C. J.; Braibante, H. T.; Braibante, M. E. F. *J. Heterocycl. Chem.* **1997**, *34*, 1453.
27. Valduga, C. J.; Braibante, H. T.; Braibante, M. E. F. *J. Heterocycl. Chem.* **1998**, *35*, 189.
28. Valduga, C. J.; Santis, D. B.; Braibante, H. T.; Braibante, M. E. F. *J. Heterocycl. Chem.* **1999**, *36*, 505.
29. Braibante, M. E. F.; Braibante, H. T.; Tavares, L. C.; Rohte, S. F.; Costa, C. C.; Morel, A. F.; Stüker, C. Z.; Burrow, R. A. *Synthesis* **2007**, 2485.
30. Narwade, S. K.; Halnor, V. B.; Dalvi, N. R.; Gill, C. H.; Karale, B. K. *Ind. J. Chem.* **2006**, *45B*, 2776.
31. Lie Ken Jie, M. S. F.; Kalluri, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1205.
32. Lie Ken Jie, M. S. F.; Lau, M. M. L. *Chem. Phys. Lipids* **1999**, *101*, 237.
33. Li, J.-T.; Zhang, X.-H.; Lin, Z.-P. *Beilstein J. Org. Chem.* **2007**, *3*, 13.
34. Khosropour, A. R. *Ultrason. Sonochem.* **2008**, *15*, 659.
35. Palimkar, S. S.; Kumar, P. H.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron* **2006**, *62*, 5109.
36. Palimkar, S. S.; More, V. S.; Srinivasan, K. V. *Ultrason. Sonochem.* **2008**, *15*, 853.
37. Koulocheri, S. D.; Haroutounian, S. A. *Eur. J. Org. Chem.* **2001**, 1723.
38. Allegretti, M.; D'Annibale, A.; Trogolo, C. *Tetrahedron* **1993**, *49*, 10705.
39. Meciarova, M.; Toma, S.; Luche, J.-L. *Ultrason. Sonochem.* **2001**, *8*, 119.
40. Sá e Melo, M. L.; Moreno, M. J. S. M.; da Costa, S. P.; Salvador, J. A. R.; Campos Neves, A. S. *Ultrason. Sonochem.* **1994**, *1*, S37.
41. Costa, S. C. P.; Moreno, M. J. S. M.; Sá e Melo, M. L.; Campos Neves, A. S. *Tetrahedron Lett.* **1999**, *40*, 8711.
42. Weavers, R. T. *J. Org. Chem.* **2001**, *66*, 6453.
43. Ranu, B. C.; Mandal, T. *Tetrahedron Lett.* **2006**, *47*, 2859.
44. Entezari, M. H.; Asghari, A.; Hadizadeh, F. *Ultrason. Sonochem.* **2008**, *15*, 119.
45. Šibor, J.; Pazdera, P. *Molecules* **1996**, *1*, 157.
46. Padmavathi, V.; Ramana Reddy, T. V.; Audisesha Reddy, K. *Ind. J. Chem.* **2007**, *46B*, 818.
47. Mallouk, S.; Bougrin, K.; Doua, H.; Benhida, R.; Soufiaoui, M. *Tetrahedron Lett.* **2004**, *45*, 4143.
48. Zhidovinova, M. S.; Fedorova, O. V.; Rusinov, G. L.; Ovchinnikova, I. G. *Russ. Chem. Bull.* **2003**, *52*, 2527.
49. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
50. Singh, K.; Singh, S.; Kaur, P. *Lett. Org. Chem.* **2006**, *3*, 201.
51. Gholap, A. R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Green Chem.* **2004**, *6*, 147.
52. Li, J.-T.; Han, J.-F.; Yang, J.-H.; Li, T.-S. *Ultrason. Sonochem.* **2003**, *10*, 119.
53. Wang, J.-S.; Li, J.-T.; Lin, Z.-P. *Lett. Org. Chem.* **2006**, *3*, 523.
54. Yadav, J. S.; Subba Reddy, B. V.; Bhaskar Reddy, K.; Raj, K. S.; Prasad, A. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1939.
55. Stefani, H. A.; Oliveira, C. B.; Almeida, R. B.; Pereira, C. M. P.; Braga, R. C.; Cella, R.; Borges, V. C.; Savegnago, L.; Nogueira, C. W. *Eur. J. Med. Chem.* **2006**, *41*, 513.
56. Zhidovinova, M. S.; Fedorova, O. V.; Rusinov, G. L.; Ovchinnikova, I. G. *Mol. Divers.* **2003**, *6*, 323.
57. Chattejee, N. R.; Sharma, D. C.; Choudhary, Y. D.; Deshpande, A. D. *Indian J. Heterocycl. Chem.* **2007**, *16*, 293.
58. Zhang, X.; Li, Y.; Wang, J. *J. Mol. Catal. A: Chem.* **2006**, *253*, 207.
59. Li, J.-T.; Lin, Z.-P.; Han, J.-F.; Li, T.-S. *Synth. Commun.* **2004**, *34*, 2623.
60. Li, J.-T.; Han, J.-F.; Lin, Z.-P.; Li, T.-S. *Chin. J. Org. Chem.* **2004**, *24*, 675.
61. Docampo, M. L.; Pellón, R. F. *Synth. Commun.* **2003**, *33*, 1777.
62. Pellón, R. F.; Docampo, M. L.; Kunakbaeva, Z.; Gómez, V.; Castro-Vélez, H. *Synth. Commun.* **2006**, *36*, 481.
63. Pellón, R. F.; Docampo, M. L.; Fascio, M. L. *Synth. Commun.* **2007**, *37*, 1853.
64. Vanden Eynde, J.-J.; Delfosse, F.; Mayence, A.; Van Haverbeke, Y. *Tetrahedron* **1995**, *51*, 6511.
65. Maquestiau, A.; Mayence, A.; Vanden Eynde, J.-J. *Tetrahedron Lett.* **1991**, *32*, 3839.
66. Zeynizadeh, B.; Dilmaghani, K. A.; Roozijoy, A. *J. Chin. Chem. Soc.* **2005**, *52*, 1001.
67. Memarian, H. R.; Abdoli-Senejani, M. *Ultrason. Sonochem.* **2008**, *15*, 110.
68. Thirumalai, D.; Murugan, P.; Ramakrishnan, V. T. *Ind. J. Chem.* **2006**, *45B*, 335.
69. Muravyova, E. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Shishkina, S. V.; Shishkin, O. V.; Chebanov, V. A. *J. Comb. Chem.* **2007**, *9*, 797.
70. Yeh, M.-Y.; Huang, C.-Y. *Acta Crystallogr.* **1994**, *C50*, 1781.
71. Li, J.-T.; Xu, W.-Z.; Yang, L.-C.; Li, T.-S. *Synth. Commun.* **2004**, *34*, 4565.
72. Jin, T.-S.; Zhang, J.-S.; Wang, A.-Q.; Li, T.-S. *Ultrason. Sonochem.* **2006**, *13*, 220.
73. Jin, T.-S.; Liu, L.-B.; Zhao, Y.; Li, T.-S. *J. Chem. Res.* **2005**, 162.
74. Varma, R. S.; Kabalka, G. W. *Heterocycles* **1985**, *23*, 139.
75. Jin, T.-S.; Xiao, J.-C.; Wang, S.-J.; Li, T.-S. *Ultrason. Sonochem.* **2004**, *11*, 393.
76. Patil, S. B.; Bhat, R. P.; Raje, V. P.; Samant, S. D. *Synth. Commun.* **2006**, *36*, 525.
77. Mangeney, P.; Hamon, L.; Raussou, S.; Urbain, N.; Alexakis, A. *Tetrahedron* **1998**, *54*, 10349.
78. Triboni, E. R.; Berci Filho, P.; Berlinck, R. G. S.; Politi, M. J. *Synth. Commun.* **2004**, *34*, 1989.
79. Guzen, K. P.; Cella, R.; Stefani, H. A. *Tetrahedron Lett.* **2006**, *47*, 8133.
80. Padmavathi, V.; Ramana Reddy, T. V.; Audisesha Reddy, K.; Padmaja, A.; Bhaskar Reddy, D. *Ind J. Chem.* **2005**, *44B*, 2527.
81. Barge, A.; Füzerová, S.; Upadhyaya, D.; Garella, D.; Aime, S.; Tei, L.; Cravotto, G. *Synthesis* **2008**, 1879.
82. Joshi, N. N.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1986**, *27*, 687.
83. Montaña, A. M.; Grima, P. M. *Tetrahedron Lett.* **2001**, *42*, 7809.
84. Giguere, R. J.; Rawson, D. I.; Hoffmann, H. M. R. *Synthesis* **1978**, 902.
85. Mihovilovic, M. D.; Grötzl, B.; Kandioller, W.; Snajdrova, R.; Muskotál, A.; Bianchi, D. A.; Stanetty, P. *Adv. Synth. Catal.* **2006**, *348*, 463.
86. Mihovilovic, M. D.; Bianchi, D. A.; Rudroff, F. *Chem. Commun.* **2006**, 3214.
87. Avalos, M.; Babiano, R.; Bravo, J. L.; Cabello, N.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *Tetrahedron Lett.* **2000**, *41*, 4101.
88. Avalos, M.; Babiano, R.; Cabello, N.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *J. Org. Chem.* **2003**, *68*, 7193.
89. Cabello, N.; Cintas, P.; Luche, J.-L. *Ultrason. Sonochem.* **2003**, *10*, 25.
90. Wei, K.; Gao, H.-T.; Li, W.-D. Z. *J. Org. Chem.* **2004**, *69*, 5763.
91. Saksena, A. K.; Girijavallabhan, V. M.; Chen, Y.-T.; Jao, E.; Pike, R. E.; Desai, J. A.; Rane, D.; Ganguly, A. K. *Heterocycles* **1993**, *35*, 129.
92. Johnson, A. W. *J. Chem. Soc.* **1946**, 895.
93. Ayres, D. C.; Smith, J. R. *J. Chem. Soc. C* **1968**, 2737.
94. Gould, S. J.; Eisenberg, R. L.; Hillis, L. R. *Tetrahedron* **1991**, *47*, 7209.
95. Alfaro, R.; McClusky, J. V. *Synth. Commun.* **2001**, *31*, 2513.
96. Villacampa, M.; Pérez, J. M.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **1994**, *50*, 10047.
97. Wurst, K.; Buchmeiser, M. R. *Heterocycl. Commun.* **1999**, *5*, 37.

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