Solvent-Free Heterocyclic Synthesis

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Solvent-Free Heterocyclic Synthesis

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1. Introduction

Heterocycles form, by far, the largest of the classical divisions of organic chemistry. Moreover, they are of immense importance not only biologically and industrially but also to the functioning of any developed human society as well. Their participation in a wide range of areas cannot be underestimated. The majority of pharmaceutical products that mimic natural products with biological activity are heterocycles. Therefore, researchers are on a continuous pursuit to design and produce better pharmaceuticals, pesticides, insecticides, rodenticides, and weed killers by following natural models. Heterocycles play a major part in biochemical processes and are also side groups of the most typical and essential constituents of living cells. Other important practical applications of these compounds can also be cited, for instance, their use as additives and modifiers in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators. Finally, as an applied science, heterocyclic chemistry is an inexhaustible resource of novel compounds. A vast number of combinations of carbon, hydrogen, and heteroatoms can be designed, providing

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compounds with the most diverse physical, chemical, and biological properties.[1,2] Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic, and approximately one-half are heteroaromatic.[2] It is, therefore, easy to understand why both the development of new methods and the strategic deployment of known methods for the synthesis of complex heterocyclic compounds continue to drive the field of synthetic organic chemistry. Organic chemists have been engaged in extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. Among them, cyclocondensation reactions are of the most attractive methodologies for synthesizing heterocyclic compounds,[1] and the need for improved cyclocondensation reactions is evident.

Cyclocondensation reactions generally involve the elimination of water, alcohol, or amine and have been performed with great success under solvent-free conditions. Many authors have described protocols for the solvent-free synthesis of a wide range of organic compounds, and there is a rapidly growing number of reports describing quick, selec-

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tive, and efficient transformations, that allow a high degree of conversion of reactants to products.[3−5] Such protocols merit further investigation as they may offer distinct advantages such as improved atom utilization[6] or atom economy[7] by avoidance of common derivation procedures;[8] decreased byproduct formation and, hence, decreased waste[9] resulting from purification procedures required to separate the desired product from impurities; and, in many cases, reduced energy utilization both in the reaction and purification stages as well as opportunities for process intensification. The magnitude of these advantages is clear when considering the 12 Green Chemistry Principles and the international tendency to develop green and sustainable chemical processes, with lesser generation of toxic and nontoxic waste. However, although solvent-free reactions may provide a tool for waste reduction and energy efficiency, there are evident and important questions to be answered in order to ascertain whether such procedures are hazard-free. In addition, a greater understanding of the thermal characteristics of solvent-free reactions is required.

Solvent-free conditions for heterocyclic synthesis have increased rapidly in recent years. The following graph showing the distribution of publications involving solvent-free conditions was elaborated using the Web of Science, SciFinder, and other sites with the keywords *solvent-free* and *solventless*, which were refined with *synthesis*, and from a selection of papers related to the synthesis of heterocyclic compounds (cyclocondensation reactions) (Figure 1).

The period of time covered in the search terminated in December, 2008. From the data depicted in Figure 1, it is clear that the number of papers concerning the synthesis of heterocyclic compounds under solvent-free conditions has increased markedly in recent years. Of the total of more than 900 articles published since the first publication in 1995, the greatest number of publications was found in the last three years with about 70% of total of papers. Among the types of procedures mentioned above, solvent-free reactions in the presence of solid mineral supports (blue bar) corresponded to approximately 11% of reports and reactions in the presence of catalysts (green bar) corresponded to 66% of papers. Although neat conditions represented 23% of total papers, this protocol presented the most significant and regular increase, mainly since 2001. These data underline the need for a serious study about solvent-free heterocyclic synthesis, which could demonstrate the advantages of these protocols in heterocyclic synthesis as a green and viable alternative as well as stimulate researchers in heterocyclic synthesis to adopt solvent-free conditions.

Over the past few years, there have been several reviews published in which solvent-free synthesis occupied a central theme. In these reviews, solvent-free reactions were approached in (i) the general framework of organic synthesis with examples of reactions of oxidation, addition, elimination, substitution, polymerization, and photoreaction and reactions catalyzed by enzymes;[3,10] (ii) specific syntheses such as reactions that involved asymmetric catalysis,[11] synthesis of metal complexes,[12] alcohol oxidations,[13] metathesis reactions,[14] and aldol condensation reactions;[8] (iii) methodologies coupled with microwave irradiation[15−19] involving deprotection, condensation, cyclization, rearrangement, oxidation, and reduction reactions including the rapid one-pot assembly of heterocyclic compounds from *in situ* generated intermediates.[15] Advantages and disadvantages[20] and recent advances in general aspects of solvent-free reactions have also been discussed.[21]

Thus, considering the lack in the literature of a review with a detailed approach of cyclocondensation reactions in solvent-free conditions and continuation of our research on more sustainable heterocyclic synthesis, we propose a systematic review of the use of solvent-free conditions in the synthesis of heterocyclic compounds from cyclocondensation reactions. Because the publications demonstrated in Figure 1 denote a great deal of material to be covered, it was necessary to make some limitations to the scope of this review: (i) heterocycles obtained from cycloaddition reactions were excluded and (ii) reactions on solid mineral supports, where the reactants are impregnated as neat liquids on solid supports (e.g., aluminas, silicas, zeolites, and clays), and reactions in the presence of catalysts also have been excluded. Only papers involving reactions between "neat reactants" have been considered. We emphasize that solvent-free reactions are defined as those employing <5 equiv of one reactant with respect to the substrate. The solvent-free method was compared with identical or similar reactions that involved the use of molecular solvent, when these data were available in the literature. Papers that employed other methodologies, such as solid support and catalysts, were disregarded for this comparison. The data shown in this review correspond to the period ending in December 2008. If some references are more recent, they correspond to results that became available to us during the elaboration of this manuscript. We have arranged the large volume of data in terms of the type of heterocycle formed, starting with five-, six-, and seven-membered rings, in the order of an increasing number of heteroatoms, i.e., first with one heteroatom, two heteroatoms, three heteroatoms; and the heteroatom order of N > O > S > P.

2. Organic Reactions under Solvent-free Conditions

Chemical reactions can be performed in the gaseous, liquid, or solid state, but, with reason, the vast majority of chemical transformations are usually carried out in the liquid

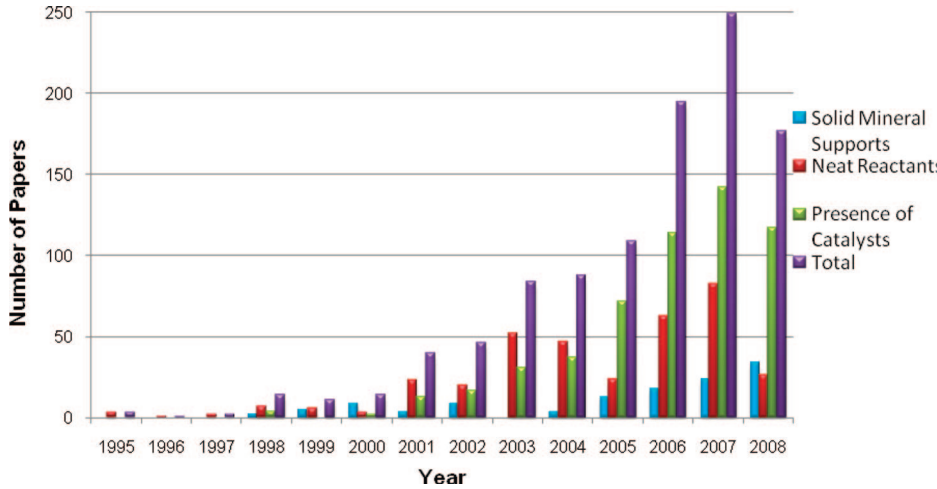


Figure 1. Distribution of papers dealing with synthesis of heterocyclic compounds under solvent-free conditions by year.

phase in solution. It is the ideal medium to transport heat to and from endo- and exothermic chemical reactions. Upon dissolution of solutes, solvents break the crystal lattice of solid reactants, dissolve liquid or gaseous reactants, and exert a considerable influence on reaction rates and on the positions of chemical equilibrium. In addition, the reactants can interact effectively if they are in a homogeneous solution, which facilitates stirring, shaking, or other forms of agitation, whereby the reactant molecules come together rapidly and continuously.[20,22] Moreover, uniform heating or cooling of the mixture in solution, if needed, can be carried out easily. However, the role of a solvent in the context of an organic reaction is much more complex than merely providing a homogeneous setting where a large number of reactants can collide. A solvent has the power to enhance or reduce the speed of a reaction, sometimes enormously. Changing the solvent can influence the rate of reaction, and it can even change the reaction course itself. This may manifest in altered yields and ratios of products. Thus, a solvent can be deeply and inseparably associated with the process of an organic reaction through the solvation of the reactants, products, transition state, or other intervening species. Such intimate interactions between the solvent and the reaction partners are due to many factors that include mainly electrostatic, steric, and conformational effects. In spite of such a strong involvement, the solvent does not become part of the product and is recovered unchanged after the reaction is over. So far, one may not envisage or plan to perform a reaction in the absence of a solvent. However, it has also been said that "the best solvent is no solvent".[11] Despite the intensity of this statement, the use and understanding of solvent-free conditions has remained undeveloped in comparison to solvent-based methods. Defining the concept of solvent-free synthesis can be difficult since various name tags are frequently employed. In the interest of clarity, Scott et al.[23] distinguish between: (i) *solid-phase reaction*, the reaction of molecules from a fluid phase with a solid substrate, e.g., polymer-supported peptide syntheses; (ii) *solvent-free reaction*, any system in which neat reagents react together, in the absence of a solvent; and (iii) *solid-state reaction* or *solid−solid reactions*, in which two macroscopic solids interact directly and form a third, solid product without intervention of a liquid or vapor phase. Other authors[3] consider *solid-state reaction* to be the same as *solvent-free reaction* and consider *solid-supported reactions* as a distinct reaction. In this review, we consider *solid−solid reactions* to be the same as *solvent-free reactions*, and we will discuss reactions in which the reactants are *liquid−liquid*, *liquid−solid*, and *solid−solid*. We have adopted these terms because, although many of the solvent-free reactions involve macroscopic organic solids, many of them proceed via a liquid or melt phase. This intriguing fact has formed the basis of detailed studies on several organic reactions.[23] These organic reactions that have been reported to proceed "in the solid phase" clearly involve the formation of a liquid phase. This melting implies the existence of a eutectic mixture with temperature fusion below the melting points of the reactants. In some cases, where heating is required, it is again clear that a phase change (from solid to liquid) occurs. Many solvent-free reactions may be accessible to all reaction types, be they simple or complicated, and to all classes of compounds. The most common and important reactions are condensation of carbonyl compounds, cycloadditions, alkylations, aromatic substitutions, additions of amines, water, and alcohols, cyclizations, eliminations, rearrangements, C−C coupling, cascade reactions, and catalyzed reactions.[3]

Advantages of solvent-free reactions, in comparison to reactions in molecular solvents, include the following: (i) there is no reaction medium to collect, purify, and recycle; (ii) the compounds formed are often sufficiently pure to circumvent extensive purification using chromatography, and in some cases there is not even the need for recrystallization; (iii) sequential solvent-free reactions are possible in high-yielding systems; (iv) the reactions are often rapid, sometimes reaching substantial completion in several minutes as compared to hours with organic solvents; (v) there is often no need for specialized equipment; (vi) energy usage may be significantly lower; (vii) there often is no need for preformed salts and metal−metalloid complexes; (viii) functional group protection−deprotection can be avoided; (ix) there may be lower capital outlay for equipment when setting up industrial processes; and (x) considerable batch-size reduction and processing-cost savings are achievable, making solvent-free protocols not only more environmentally benign but also more economically feasible.[21] There are some disadvantages to solvent-free reactions, but these can be dealt with through developments in engineering reactor technology.[24] Objections to the use of solvent-free reactions include the formation of "hot spots" and the possibility of runaway reactions. Instead of operating in the old paradigm, where a reaction medium or solvent is used as a heat sink or heat-transfer agent, it would be better to work toward developing reactors either

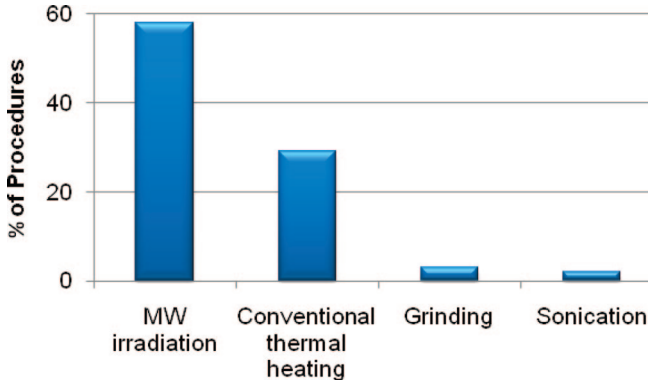


Figure 2. Percentage of procedures for each type of activation method.

for continuous flow or batch systems. Clearly, measuring the reaction heat in solvent-free reactions is as important as is effective heat dissipation. If highly exothermic reactions are shown to be suitable for solvent-free conditions, the problem could be addressed through the design of advanced reactors. Another objection involves difficulties in handling solid or highly viscous material. Again, this can be overcome by advances in engineering and innovative reactors. The choice of a solvent-free or specific molecular solvent reaction medium will depend on several issues, including selectivity, stereochemistry, yield, waste, viscosity, ease of recycling, energy usage, ease of product isolation, competing reactions, and reaction heat.[21]

2.1. Mechanistic Considerations in Solvent-free Reactions

One of the requirements for solvent-free conditions is the molecular movement of reactants. In cases in which one of the reactants is in the liquid phase at the temperature of reaction and is miscible with the other reactant(s), the molecular movement and the contact between reactants are understood based on concepts of solution reactions.[22] In cases in which all or one of the reactants are solid at the temperature of reaction, the molecular movement is more complex, but recently, evidence of this movement has been demonstrated and is considered to be the minimal requirement for the solid−solid reaction to proceed.[3] Under appropriate conditions of stirring (mechanochemistry, microwave, ultrasound, and magnetic stirring), molecules move from crystal to crystal. For a reaction in solution, one would expect the concentration of substrates A and B to be lower than that of the pure compounds, and even when two molecules collide, the reaction may not take place (depending on reactive cross section and orientation).[25] However, in the case of two solid particles, although substrate "concentration" may be high, the actual number of active substrate molecules would be low because only those molecules on the particle surface would be able to react.[26] This limitation is due to the orientation of the molecules, which is fixed in the solid state, making for a lower cross section, and therefore, considerable energy is often required to disrupt the crystal lattice, enabling the individual molecules to react.[27]

In this review, four activation mechanisms involved in solvent-free reactions will be considered: (i) mechanochemistry (grinding); (ii) microwave irradiation (MW); (iii) ultrasound irradiation (US); and (iv) conventional thermal heating. Figure 2 illustrates the percentage of procedures for each type of activation method reported in the papers collected for this review, where it can be observed that 58% of the procedures entailed MW irradiation, 29% entailed conventional thermal heating, 3% entailed grinding, and 2% entailed sonication.

2.2. Mechanochemistry (Grinding)

Mechanochemistry can be as simple as grinding two reactants in a pestle and mortar[1,28] or more complex, as with the use of ball mills.[11,29] Ball mills, however, have the advantages of requiring no physical effort, supplying greater power, being programmable, and allowing more systematic studies of the process. They are readily available commercially, and two types that are appropriate for laboratory-scale syntheses are the shaker and planetary mills. With shaker mills, a rapid (e.g., 10−50 Hz) side-to-side (or figure eight) motion of the reaction vessel causes a ball within to impact against the sides of the vessel and its contents. With planetary mills, the reaction vessel follows a circular path while simultaneously spinning in the reverse direction. The kinetic energy supplied during grinding can have several effects on a crystalline solid, including heating, reduction of particle size (with concomitant increase in surface area and the generation of fresh surfaces), formation of defects and dislocations in crystal lattices, local melting, and even phase changes to alternative polymorphs.[28,29] Importantly, grinding also provides mass transfer. Because of the high reactant concentrations and the efficient mixing, other solvent-free reactions, including those between solids with intermediate local melting and those with at least one liquid reactant, can benefit from the use of ball mills. In chemical synthesis, ball milling modifies the reaction conditions and enhances the reactivity of the reactants (mechanical activation). The latter is generally due to mechanical-induced breaking of molecular bonds (mechanochemistry), but a result of the more efficient mixing and the large increase of reactant surfaces is close contact between the starting materials on a molecular scale.[30,31] Besides that, other factors such as an increased temperature and an enhanced pressure can be responsible for the reactivity changes observed. Scott et al.[7,14,21,23] have highlighted the important fact that, in most cases, solvent-free reactions between solid reactants actually proceed through bulk liquid phases. Such liquid phases are possible due to the formation of eutectics between the reactants and product(s) and any evolution of heat.[12] In these papers, Scott et al.[7,14,21,23] pointed out that solid−solid reactions occurring between two discrete crystalline solids, without intervention of a mobile phase and which allows a large number of productive molecular collisions, would be expected to exhibit diffusion-controlled kinetics (slow reaction).[32] Thus, the rapid rates exhibited by most of the reactions studied ($\tau_{1/2\ (25\ °C)} < 60$ s in some cases) do not support the theory of two solids reacting together without intervention of a new (liquid) phase that would enable higher substrate mobility.[32] Some heat is released upon stirring of the two components, which leads to the complete melting of the mixture. Such heat may be generated by the occurrence of hot spots during initial contact of the solids, and this phenomenon should be carefully considered when high-intensity grinding techniques, such as ball milling, are employed (even in cases where a temperature-controlled apparatus is used).[33] The general mechanism for solvent-free mechanical activation involves three stages:[12,34]

(i) *Phase rebuilding*: Molecules move and there are directional long-range migrations of molecules of reactant A into

cleavage planes or channels in crystalline reactant B and vice versa. This is driven by the internal pressure that comes from the formation of product C at the interface between the reactants. This distorts the original crystal structures and results in a mixed A−B−C phase.

(ii) *Phase transformation*: Product crystals are formed, and this is the step in which crystals of product C grow from the distorted mixed A−B−C phase. During this step, the growing C crystals remain spatially discontinuous on the A and B particles.

(iii) *Crystal disintegration or detachment*: A new surface is created, and chemical and geometrical mismatch between the starting (A and B) phases and the product (C) phase causes disintegration of the particles. This in turn reveals new surfaces of the reactants, and continued agitation then serves to bring these new surfaces into contact for further reaction.

It is also interesting to consider the situation where the temperature at which the reaction is conducted is above the eutectic temperature of the reactants A and B. If A and B react in a solid−solid reaction, whether by grain-boundary diffusion or surface migration,[35] product C begins to form and, should there exist an AC, BC, or ABC eutectic that occurs below the reaction temperature, a liquid phase may again intervene. Thus, a reaction that begins as a solid−solid reaction may proceed much more rapidly by intervention of a liquid phase arising due to the existence of a lower-melting eutectic formed by the product and the reactants. In addition, in several reactions under solvent-free conditions, water is produced. Condensation reactions are the most common example, and water should be considered a fourth chemical component in the phase diagram. Indeed, the inclusion of further miscible components only serves to increase the proliferation (and likelihood of occurrence) of possible liquid phases. These reactions, therefore, should be classified together with classical liquid/liquid and liquid/solid systems that react in the absence of an added solvent.

Solvent-free reactions profit from higher reactivity because the reactants are not solvated. Thus, it is more common to work at room temperature or to cool down below eutectic temperatures than to heat up. Nonetheless, reactions require minimal energy in order to overcome activation barriers, in which case, alternative energies such as microwave and ultrasound have been successfully employed in organic reactions under solvent-free conditions.

2.3. Microwave Irradiation

In this review, it was considered of the utmost importance to discuss the effects and the mechanisms involved in microwave irradiation in solvent-free reactions. In many examples, it has been shown that the application of microwave irradiation reduces the reaction time, increases the product yield and sometimes results in a different product distribution compared to conventional thermal heating methods.[15,16,36] The rate acceleration observed in microwave irradiation is due to material-wave interactions leading to thermal and nonthermal effects. The thermal effects largely result from a more efficient energy transfer to the reaction mixture, which is known as dielectrical heating. This phenomenon relies on the ability of a substance (solvent or reactant) to absorb microwaves and convert them into heat. The reaction mixture is heated from the inside since the microwave energy is transferred directly to the molecules (solvent, reactants, and catalysts). This process is known as "volumetric core heating" and results in a temperature gradient that is reversed compared to the one resulting from conventional thermal heating.[15,16,36]

Nonthermal microwave effects result in differences in product distributions, yields, and reaction times. They may result from the orientation effects of polar species in the electromagnetic field that make a new reaction path with lower activation energy. These effects can be understood by considering Arrhenius law[21] [$k = A \exp(-\Delta G^{\ddagger}/RT)$] and may result from modifications in each of the equation terms. Thus, the increase in the pre-exponential factor A represents an increase in the probability of molecular impacts. The collision efficiency can be effectively influenced by mutual orientation of polar molecules involved in the reaction. Because this factor is dependent on the vibration frequency of the atoms at the reaction interface, it may be affected by the microwave field. It has been suggested[37] that, in some examples, MW activation could originate from hot spots generated by dielectric relaxation on a molecular scale. The new reaction path with low activation energy ($\Delta G^{\ddagger}$) is certainly a main effect. When considering the contribution of enthalpy and entropy to the value of $\Delta G^{\ddagger}$ [$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$], it may be predicted that the magnitude of the $-T\Delta S^{\ddagger}$ term would increase in a microwave-assisted reaction, which is more organized than conventional thermal heating because of dipolar polarization. In recent years, Kappe et al.[38] published a sequence of papers discussing the existence of nonthermal microwave effects in a series of synthetic transformations. The arguments presented by Kappe are based on the measurement of reaction temperature in microwave irradiation. In these reactions, both microwave dielectric heating and conventional thermal heating, the temperature was measured by fiber-optic probes. Kappe observed that the same reaction temperature and the same reaction time resulted in very similar yields.[38] Therefore, Kappe et al.[38] established that many of the hypothesized nonthermal effects could result from incorrect temperature measurements, since they were not observed when the reaction temperature was monitored using appropriate devices. Despite these results published by Kappe, the subject of "nonthermal microwave effects" remains highly controversial, because, as stated by Kappe himself, the response time of the fiber-optic sensor can be quite long depending both on the type of fiber-optic device used and on the protective shielding employed with the probe. In addition, the solvents used by Kappe had a high loss tangent ($\tan \delta$) and were employed in large amounts in relation to reactants, which could lead to dilution of microwave irradiation power, making it impossible to observe nonthermal microwave effects. Therefore, the possible nonthermal effects will also be influenced by solvents that moderate or impede the reactant interaction with the microwave irradiation. On the other hand, microwave effects are frequently expected in solvent-free reactions.[39] Reactions between neat reactants in quasi-equivalent amounts require, preferably, at least one liquid phase in heterogeneous media and lead to interfacial reactions.[3] In addition to the environmental interest of these methods in terms of use, separation and economy, and safe and clean procedures, absorption of microwave irradiation should now be limited only to the reactive species. The reactions described in this review have shown that, when the reaction is carried out under specially designed microwave irradiation, a reduction in reaction time was observed in comparison with conventional thermal heating. This finding indicates the probable existence of

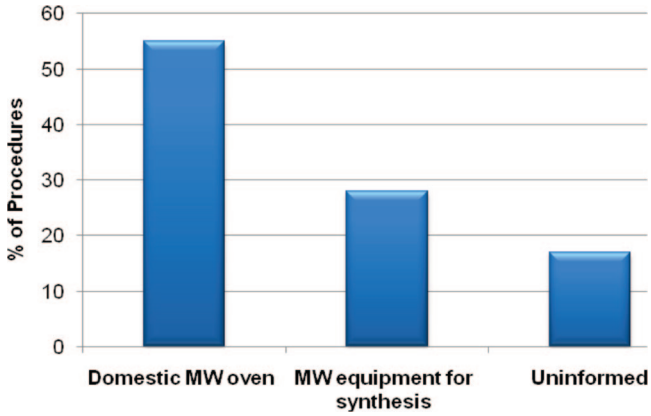


Figure 3. Percentage of procedures for each type of equipment employed for MW irradiation.

Table 1. Nominal and Reaction Power of Domestic MW Oven and Equipment for Synthesis from Papers Collected for This Review

	number of papers	
	MW domestic oven[a]	MW equipment for synthesis
authors informed only nominal power (W)	6	4
authors informed reaction power (W)	27[b]	6
power uninformed	1	1

[a] For papers that did not inform the equipment type, we consider the equipment as MW domestic oven. [b] The calibration of the MW domestic oven was informed only in two papers.

nonthermal effects of MW in cyclocondensation reactions. This hypothesis could be explained considering the conclusions made by Kappe et al.:[38] if the reaction proceeds in either conventional thermal heating or MW conditions under the same temperature (same heat amount), the reduction of reaction time from hours to minutes (with the same yields) is a result of the nonthermal effects of MW. On the other hand, from this review it was possible to observe that, in spite of the recent improvements in controlling reactions with MW, most reactions are still performed in domestic microwave ovens (without control of temperature, power, and pressure inside the reaction vessel). Figure 3 shows the percentage of solvent-free microwave procedures that used a domestic microwave oven, used a microwave equipment for synthesis, or did not inform which type of equipment was used.

A detailed analysis of the distribution shown in Figure 2 led to the construction of Table 1. Of the 28 papers whose authors reported the use of a domestic MW, 6 informed only the nominal power of the microwave equipment while 27 of them informed the microwave power irradiated during the reaction. The calibration of the domestic microwave oven was informed only in two papers (See Schemes 1 and 4). Unfortunately, these studies carried out using domestic microwave ovens present incomplete experimental information, and the reaction conditions have poor reproducibility. On the other hand, reports on reactions performed in microwave equipment for synthesis supplied more information about the experimental use of the microwave equipment: 4 of 11 authors informed only the nominal power of the microwave and 6 informed the reaction power. These data are summarized in Table 1. Another finding was that ~60% of the papers did not inform the reaction temperature, making the comparison between microwave-assisted methods and conventional thermal heating methods difficult. It was also concluded that the information provided on microwave power, temperature, and pressure in the papers covered was incomplete, regardless of whether the microwave equipment was domestic or for synthesis. This demonstrates the need for more detailed studies in this research area.

2.4. Ultrasound Irradiation

Besides ball milling and microwave heating, ultrasound irradiation has emerged as a powerful technique for the promotion of organic reactions.[40] In order to affect chemical reactivity in liquids (power ultrasound), its frequency range must lie between microwaves and diagnostic ultrasound. The activation is caused by cavitation, which involves the creation, growth, and collapse of micrometer-sized bubbles that are formed when an acoustic pressure wave propagates through a liquid. According to the so-called "hot spot theory", extreme local conditions occur inside the cavitating bubbles and their interfaces when they collapse. These have been estimated to be in the range of 4900−5200 K[41] and 1700 atm.[40] The interactions of acoustic waves with chemical systems lead to an energy transfer that can result in enhanced mechanical effects in heterogeneous processes and induce new reactivities. In most cases, the application of ultrasound does not affect the chemical pathways. The reaction rates are often comparable to those of nonirradiated systems, and the only role of ultrasound is then to mix the phases of a heterogeneous system. Thus, the increased yields and reaction rates are due to mechanical effects associated with the sound waves. Chemical effects of ultrasound (true sonochemistry) can only be expected if high-energy species that are released after cavitational collapse act as reaction intermediates. In these cases, changes in product distribution, switching of reaction mechanisms, or changes in regio- or diastereoselectivity may occur.[40a]

2.5. Conventional Thermal Heating

Finally, it is worthwhile to consider that a significant number of papers covered by this review present reactions that are carried out in conventional thermal heating (magnetic stirring and heat energy by oil bath). However, major drawbacks of this activation method include inefficient contact between reactants during stirring and the kind of energy (direct heat) furnished to reaction media. It has been reported that, for most reactions that form products in good yields by mechanochemistry, MW, or sonochemistry, the product is either not formed or is isolated in low yields in conventional thermal heating. Generally, the reactants are decomposed or retained without reacting. It seems that conventional thermal heating is more adequate for reactions in solution. However, in this review, it was possible to observe that, in cyclocondensation reactions, conventional thermal heating is frequently employed and presents good performance. It was also possible to observe that grinding and US have been explored very little in solvent-free cyclocondensation reactions.

3. Cyclocondensation Reactions

Cyclocondensation (a kind of annulation reaction involving the formation of a ring from one or several acyclic precursors) involves a set of condensation reactions in which one-,

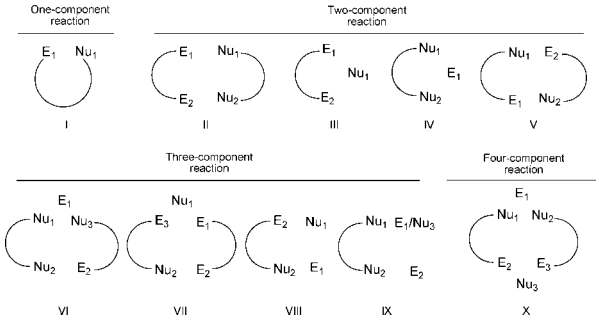


Figure 4. Number of components and reaction types in the cyclocondensation reactions discussed in this review.

two-, three-, or four-component reactants yield a single main cyclic product with the accompanying formation of some other small molecule(s).[42] In this review, the synthesis of series of five-, six-, and seven-membered heterocyclic rings obtained from cyclocondensation reactions will be described. These reactions were carried out with different numbers of components and reactions types, as summarized in Figure 4. The functional groups contained in each component can react as electrophiles (E_1, E_2, and E_3) or nucleophiles (Nu_1, Nu_2, and Nu_3). In general, the electrophiles are carbon atoms present in functional groups, such as carbonyl, imine, nitrile, β-carbon of α,β-unsaturated ketone, ethylcyanoacetate, mono- and dihalo-substituted carbons, and acetal and orthoester carbons; and the nucleophiles are either carbon atoms present in the α-position of aldehydes, ketones, enols, or enamines, or heteroatoms such as nitrogen, oxygen, and sulfur.

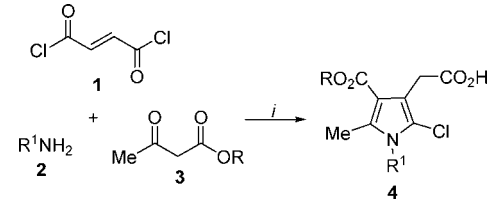
Table 2 shows the number of reaction components, building blocks, and reaction types that are found in cyclocondensation reactions described in this review. The first column demonstrates the number of reaction components, and the second column shows the reaction building blocks. So, for example, the arrangement [3 + 2] → [CCC + NN] indicates that the heterocycle was formed by two building blocks, one of which possessed three atoms ([CCC]) and the other of which possessed two atoms ([NN]). The reaction types (see Figure 4) are depicted in the third column, while the heterocycles obtained are listed in the last column. In one-component cyclocondensation reactions, the formation of either (i) one carbon−heteroatom bond or (ii) one carbon−carbon bond was observed. In two-component cyclocondensation reactions, the formation of either (i) two carbon−heteroatom bonds, (ii) one carbon−heteroatom bond and one heteroatom−heteroatom bond, or (iii) one carbon−heteroatom and one carbon−carbon bond was observed. In three-component cyclocondensation reactions, there were three possibilities: (i) the formation of three carbon−heteroatom bonds, (ii) the formation of two carbon−heteroatom bonds and one carbon−carbon bond, or (iii) the formation of one carbon−heteroatom bond and two carbon−carbon bonds. In four-component cyclocondensation reactions, the formation of two carbon−heteroatom and two carbon−carbon bonds was observed. The formation of carbon−heteroatom bonds, in general, involves either the nucleophilic addition (in most cases, with a step elimination reaction) of a heteroatom nucleophile (O, N, S, or P) to a carbonyl (imine or nitrile) carbon atom or to the β-carbon of α,β-unsaturated systems or the heteroatom nucleophilic substitution into mono- and dihalo-substituted carbons or acetal and orthoester carbons. The formation of carbon−carbon bonds, in general, involves nucleophilic addition (in most cases, followed by a subsequent elimination step) of a carbon atom nucleophile (carbonyl α-carbon) to a carbonyl (imine or nitrile) carbon atom or to the β-carbon of α,β-unsaturated systems, substituted carbons, or acetal and orthoester carbons.

4. Five-Membered Heterocycles with One Heteroatom

4.1. Pyrroles

Pyrroles are heterocycles of great importance because of their presence in numerous products such as antioxidants,[43a] antibacterial,[43b,c] antitumor,[43d] anti-inflammatory,[43e,f] and antifungal agents.[43g] Moreover, they are a highly versatile class of intermediates in the synthesis of natural products as well as in heterocyclic chemistry.[44] Many methods have been developed for their synthesis, which include Knorr,[45a] Paal−Knorr,[45b] and Hantzsch syntheses[46] and 1,3-dipolar cycloaddition reactions.[47] Alizadeh et al.[48] described the synthesis of pentasubstituted pyrroles **4**, from equimolar amounts of fumaryl chloride **1**, primary amines **2**, and alkyl acetoacetate **3**, under solvent-free conditions (Scheme 1). The cyclocondensation reaction was performed at room temperature, during 10 h, to afford **4** in 70−85% yields. This synthetic approach to obtain pentasubstituted pyrroles **4** using molecular solvents has not yet been described in the literature.

Scheme 1



R = Me, Et; R^1 = Pr, *i*-Pr, *i*-Bu, allyl
i: solvent-free, r.t., 10 h (70−85%)

4.2. Isoindolediones

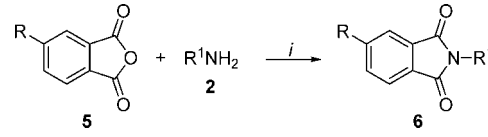
Isoindole-1,3-diones are key structural units of a variety of biologically important compounds, possessing anti-inflammatory[49,50] and antiviral[51] properties, among others. They also find important applications as synthetic intermediates in the dye,[52] pesticide,[53] and polymer[54] industries. The most common method reported in the literature for the synthesis of isoindole-1,3-diones involves the reaction of a phthalic anhydride and a primary amine.[55] Syntheses of isoindole-1,3-diones have also been reported from the ammoxidation of 2-xylenes by vanadium/titanium/oxygen catalysis and subsequent oxidation of intermediate 2-tolunitriles,[56] microwave irradiation of 2-(hydroxymethyl)isoindoline-1,3-dione with aryl amines, phthalic anhydrides with urea or anilines, microwave-induced cleavage of solid-supported 2-amidoesters,[57] palladium catalyzed carbonylation of 2-haloamides, and a combination of carbonylation and nitrogenation of 2-halophenyl alkyl ketones.[58] In this context, Barchín et al.[59] reported a microwave-assisted synthesis of isoindole-1,3-dione **6** from the reaction of equimolar amounts of phthalic anhydride **5** and substituted anilines **2**, under solvent-free conditions (Scheme 2). The mixture was irradiated in a domestic microwave oven for 8.5 min, and the products were obtained in 34−97% yields. The same reaction was accomplished in diethyl ether, where the mixture was stirred for 1 h, furnishing the intermediate *N*-phenylphthalic

Table 2. Reaction Types and Building Blocks of Cyclocondensation Reactions

no. components	building blocks	reaction type	product
One-Component Reactions			
[1 + 0]	[CCNCCC]	I	quinolines
[1 + 0]	[NCNNCC]	I	triazines
[1 + 0]	[OCCSCCC]	I	oxathiepinones
Two-Component Reactions			
[4 + 1]	[CCCC + N]	III	isoindolediones
[3 + 2]	[CCC + NN]	II	pyrazoles
[3 + 2]	[CCC + NN]	II	pyrazolines
[3 + 2]	[CCC + NN]	II	pyrazolones
[4 + 1]	[NCCN + C]	IV	imidazolidinones
[3 + 2]	[CCO + CN]	V	oxazoles
[4 + 1]	[NCCO + C]	IV	oxazolines
[4 + 1]	[NCCO + C]	IV	oxazolidines
[4 + 1]	[NCCS + C]	IV	thiazoles
[4 + 1]	[NCCS + C]	IV	thiazolines
[3 + 2]	[NCS + CC]	II	thiazolidinones
[4 + 1]	[NCNO + C]	IV	oxadiazoles
[4 + 1]	[CCNN + P]	IV	diazaphospholes
[4 + 2]	[CCCC+NC]	V	pyridines
[5 + 1]	[CCCCC+N]	III	pyridinones
[5 + 1]	[CCCCO+C]	IV	pyranones
[3 + 3]	[CCC+CCN]	II	quinolines
[3 + 3]	[CCN+CCC]	II	quinolinones
[3 + 3]	[CCO + CCC]	II	flavones
[4 + 2]	[CCCC + NN]	II	pyridazinones
[3 + 3]	[NCN + CCC]	II	pyrimidines
[3 + 3]	[NCN + CCC]	II	pyrimidinones
[4 + 2]	[NCNC+CC]	V	pyrimidinones
[4 + 2]	[NCCC+CN]	V	(thio)pyrimidinones
[4 + 1]	[NCCN + C]	IV	quinazolines
[4 + 2]	[NCCC + CN]	V	quinazolinones
[3 + 3]	[CNC+CCN]	II	quinazolinones
[4 + 2]	[NCCN + CC]	II	quinoxalines
[4 + 2]	[NCCN + CC]	II	quinoxalinediones
[4 + 2]	[NCCO + CC]	II	oxazines
[5 + 1]	[NCCCO + C]	IV	oxazinones
[4 + 3]	[NCCN + CCC]	II	benzodiazepines
[5 + 2]	[CCCNC + CN]	II	benzodiazepinediones
[5 + 2]	[SCCCO + CC]	II	oxathiepinones
Three-Component Reactions			
[2 + 2 + 1]	[CC + CC + N]	VII	pyrroles
[3 + 1 + 1]	[NCN + C + C]	IX	imidazoles
[2 + 2 + 1]	[CC + CS + N]	VII	thiazolines
[2 + 1 + 1]	[CCN + C +S]	VIII	thiazolines
[3 + 2 + 1]	[CCN + CC + C]	VI	quinolines
[3 + 2 + 1]	[CCN + CC + C]	VI	isoquinolines
[3 + 2 + 1]	[CCN + CC + C]	VI	acridines
[3 + 2 + 1]	[NCN + CC + C]	VI	(thio)pyrimidinones
[4 + 1 + 1]	[CCCN + C + N]	VIII	quinazolines
[3 + 2 + 1]	[CCCN + C + N]	VIII	quinazolinones
[3 + 2 + 1]	[NCN + CC +C]	VI	quinazolinones
[3 + 2 + 1]	[NCS + CC + C]	VI	thiazines
Four-Component Reactions			
[2 + 2 + 1 + 1]	[CC + CC + C + N]	X	pyridines
[2 + 2 + 1 + 1]	[CC + CC + C + N]	X	pyridinones
[2 + 2 + 1 + 1]	[CC + CC + C + N]	X	quinolines

acid, which suffered cyclocondensation reaction after addition of sodium acetate and acetic anhydride and heating for 30 min. The products **6** were obtained in 37−73% yields.[57e]

Scheme 2



R = H, Me

R^1 = Ph, 4-MeO-Ph, 2-MeO-Ph, 3-F_3C-Ph, 4-*i*-Pr-Ph, 2,6-$(Et)_2$-Ph, 2-F-Ph, 4-F-Ph, 2-Me-6-*i*-Pr-Ph, 2,6-$(i\text{-Pr})_2$-Ph, 2-Cl-Ph, 3-Cl-Ph, 2,4-$(Br)_2$-6-MeO_2C-Ph, 2-Me-3-Cl-Ph

i: solvent-free, MW, 550 W, 8.5 min (34−97%)

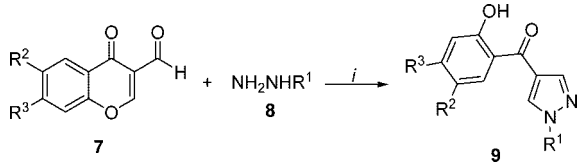
5. Five-Membered Heterocycles with Two Heteroatoms

5.1. Pyrazoles

Pyrazoles have a long history of applications in the pharmaceutical and agrochemical industries due to their herbicidal, fungicidal, insecticidal, analgesic, antipyretic, and anti-inflammatory properties.[60] The synthesis of pyrazoles by the so-called [3 + 2] atom fragments has been relatively well investigated. In this method, β-diketones or their derivatives (the three-atom fragment) are condensed with hydrazine and its derivatives (the two-atom fragment) to close

a five-membered ring.[61] There have been many attempts to develop alternative methods for pyrazole synthesis. Sabitha et al.[62] reported a microwave-assisted synthesis to obtain 4-(2-hydroxybenzoyl)pyrazoles **9** under solvent-free conditions. Compounds **9** were synthesized from the reaction of equimolar amounts of 3-formylchromones **7** with phenylhydrazine or tosylhydrazine **8** (Scheme 3). The mixture was irradiated in a domestic microwave oven for 1−4.5 min to afford the respective pyrazoles **9** in 67−89% yields. The same reaction, under microwave irradiation, using ethanol in the presence of KOH at 120 °C for 7 min, furnished similar compounds (yield not reported).[61b]

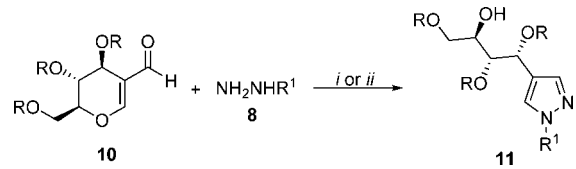
Scheme 3



R^1 = Ph, Ts; R^2 = H, Me, Cl, Br; R^3 = H, Me
i: solvent-free, MW, 600 W, 1−4.5 min (67−89%)

Yadav et al.[63] reported the synthesis of a new class of optically pure 4-substituted pyrazoles **11** from 2-formyl glycols **10** and hydrazines **8** under solvent-free conditions (Scheme 4). The reactions were carried out under both microwave irradiation and conventional thermal heating, where both protocols used the reactants **10** and **8** in a molar ratio of 1:1.2, respectively. In the first approach, the mixture was irradiated in a domestic microwave oven for 3−6 min, to afford the corresponding pyrazoles **11** in 79−87% yields. The same reaction, under conventional thermal heating, at 90 °C required 6−9 h to achieve complete conversion, furnishing the products in 65−80% yields. The authors reported that the rate enhancement under microwave irradiation may be attributed to the absorption of more microwave energy by the polar reactants, generating sufficient heat energy to promote the reaction. This method for the synthesis of pyrazoles **11** using molecular solvents has not yet been described in the literature.

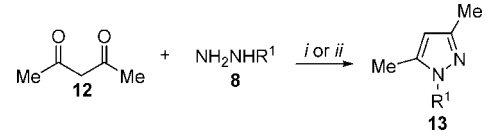
Scheme 4



R = Me, Et, Bn; R^1 = H, Ph, 2-Et-Ph, 4-Cl-Ph, 4-MeO-Ph, 3-Cl-Ph
i: solvent-free, MW, 450 W, 3−6 min (79−87%)
ii: solvent-free, oil bath, 6−9 h, 90 °C (65−80%)

Deshmukh et al.[64] reported a microwave-assisted process to synthesize 3,5-dimethylpyrazole **13** under solvent-free conditions (Scheme 5). The pyrazole **13** was obtained when the reaction was performed with equimolar amounts of 2-hydrazinobenzothiazole **8** and acetylacetone **12** in a domestic microwave oven. The mixture was irradiated for 1 min, affording **13** in 90% yield (Scheme 5, *i*). The same conversion carried out under conventional thermal heating required 3 h and furnished the products in 65% yield (Scheme 5, *ii*).[64] The reaction of 2-hydrazinobenzothiazole with different acetylacetones under refluxing ethanol in the presence of acetic acid for 3 h furnished similar products in 56−89% yields.[61g]

Scheme 5

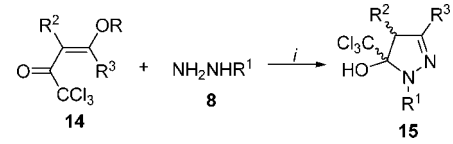


R^1 = Benzo[*d*]thiazol-2-yl
i: solvent-free, MW, 1 min, 130 °C (90%)
ii: solvent-free, oil bath, 3 h, (65%)

5.2. Pyrazolines

Pyrazolines are important five-membered heterocyclic compounds, with applications as dyestuffs, analytical reagents, and agrochemicals.[61a,b,65] In addition, these heterocycles possess important pharmacological activities such as antitumor,[66] anti-inflammatory,[67] antidiabetic,[68] and antidepressant properties.[69] Pyrazolines are quite stable and have been utilized by chemists in bioactive moieties to synthesize new compounds possessing biological activities. The synthesis of pyrazolines by the so-called [3 + 2] atom fragments has been relatively well investigated. In this method, β-diketones or their derivatives (the three-atom fragment) are condensed with hydrazine and its derivatives (the two-atom fragment) to close a five-membered ring.[61] There have been many attempts to develop alternative methods for pyrazole synthesis. Martins et al.[70] reported the synthesis of novel 4,5-dihydro-1*H*-pyrazoles **15** from the cyclocondensation reaction of enones **14** with hydrazine methyl carboxylate **8** under solvent-free conditions (Scheme 6). The reactants **14** and **8** were used in a molar ratio of 1:1.25, and this mixture was irradiated in a domestic microwave oven at a temperature range of 50−55 °C. While conventional thermal heating, using methanol as solvent, gave only moderate yields in a reaction time of 24 h, the cyclocondensation reaction carried out under solvent-free conditions and under microwave irradiation gave the expected products in a reaction time of 6 min with yields 10% higher, on average, than those obtained by conventional thermal heating under solvent conditions.[70]

Scheme 6



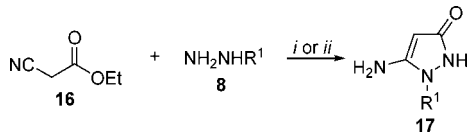
R = Me, Et; R^1 = CO_2Me; R^2 = H, Me
R^3 = H, Me, Pr, *i*-Pr, *c*-Pr, Bu, *i*-Bu, *t*-Bu, Ph, 4-O_2N-Ph
i: solvent-free, MW, 45 W, 50−55 °C, 6 min (70−98%)

5.3. Pyrazolones

Pyrazolones are appropriate precursors for the preparation of herbicides,[71] liquid crystals,[72] and dyes.[73] They are traditionally synthesized by treatment of β-ketoesters with substituted hydrazines under acidic conditions at elevated temperature.[74] Some developments include solid-phase synthesis[75] and a two-step reaction of benzoyl hydrazones with silyl enolates in the presence of a catalyst.[76] The use of more environmentally friendly protocols for the synthesis of substituted pyrazolones has been reported.[77] In this context, Deshmukh et al.[64] reported a microwave-assisted process to synthesize 5-aminopyrazolone **17** under solvent-free conditions (Scheme 7). Compound **17** was obtained from the reaction of equimolar amounts of ethyl cyanoacetate **16** and

2-hydrazinobenzothiazole **8** in a domestic microwave oven. The mixture was irradiated for 2 min, affording **17** in 88% yield (Scheme 7, *i*). The same conversion carried out under conventional thermal heating required 4 h and furnished the products in 80% yield (Scheme 7, *ii*).[64] This method for the synthesis of pyrazolone **17** using molecular solvents has not yet been described in the literature.

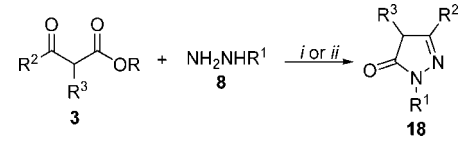
Scheme 7



R^1 = Benzo[*d*]thiazol-2-yl
i: solvent-free, MW, 2 min, 130 °C (88%)
ii: solvent-free, oil bath, 4 h, (80%)

Mojtahedi et al.[77c] reported the cyclocondensation reaction of hydrazines **8** with β-ketoesters **3** under solvent-free conditions using ultrasound irradiation (Scheme 8). The pyrazolones **18** were obtained from an equimolar mixture of the reactants **8** and **3**. The reaction was carried out in a probe sonicator for 2−20 min, affording **18** in 84−95% yields (Scheme 8, *i*). The intensity level of irradiation was adjusted at a range of 40−90% from an instrument with a frequency of 24 kHz and nominal power of 460 W. Control experiments showed the crucial role of ultrasonic irradiation for the reaction to proceed and excluded the effect of a possible simultaneous thermal activation. Pal et al.[78] also reported the synthesis of a series of pyrazolones **18** from the reaction of hydrazine **8** and β-ketoester **3**, under solvent-free conditions and microwave irradiation. In this reaction, the reactants were used in a molar ratio of 1:1.05, respectively. The mixture was irradiated in a domestic microwave oven for 2−4 min, furnishing the products in 62−89% yields (Scheme 8, *ii*). In order to compare the solvent-free conditions with the solvent conditions, the authors performed the same reaction in methanol under reflux for 10 h and compound **18** (R = Et; R^1 = Ph; R^2 = Me) was isolated in 88% yield.[78]

Scheme 8

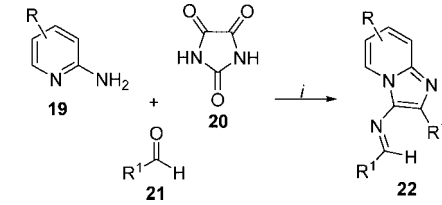


R = Et; R^1 = H, Ph, 2,4-$(O_2N)_2$-Ph, 4-Cl-Ph, $CONH_2$
R^2 = Me, Pr, *i*-Pr, Ph, CF_3, Thien-2-yl
R^3 = H, Et; R^2, R^3 = $-(CH_2)_4-$
i: solvent-free, US, 2−20 min (84−95%)
ii: solvent-free, MW, 2−4 min (62−89%)

5.4. Imidazoles

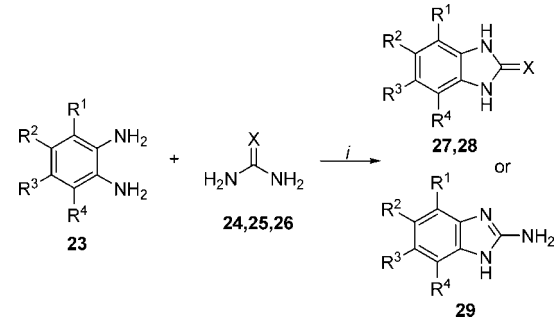
Compounds with an imidazole ring system have many pharmacological properties and can play important roles in biochemical processes.[79] Several methods of imidazole synthesis can be found in the literature, including hetero-Cope rearrangement;[80] four-component condensation of arylglyoxals; the combination of primary amines, carboxylic acids, and isocyanides on Wang resin;[81] the reaction of *N*-(2-oxo)-amides with ammonium trifluoroacetate;[82] the use of 1,2-amino alcohols in the presence of PCl_5;[83] and, finally, the combination of diketones, aldehydes, amines, and ammonium acetate in one of five possible media: phosphoric acid,[84] acetic acid,[85] acetic acid or H_2SO_4 with organocatalysts,[86] or dimethyl sulfoxide (DMSO).[87] Several assisted syntheses of imidazoles from β-diketones and aldehydes in the presence of a variety of catalysts also have been reported.[87−93] Thus, there has been great effort to develop alternative methods for the synthesis of imidazoles. Adib et al.[94] described the synthesis of imidazo[1,2-*a*]pyridines **22** via a multicomponent reaction between 2-aminopyridines **19**, imidazoline-2,4,5-trione **20**, and benzaldehydes **21** using solvent-free conditions, as shown in Scheme 9. The reactants **19**, **20**, and **21** were used in a molar ratio of 1:1.5:2.5, respectively. The desired products were obtained after a short reaction time and in 92−97% yields with both substrates with electron-donating and electron-withdrawing groups.[94] This multicomponent synthesis of imidazo[1,2-*a*]pyridines **22** using molecular solvents has not yet been described in the literature. A synthetic protocol for the synthesis of benzimidazolones **27** and **28** and benzimidazoles **29** under solvent-free conditions using microwave irradiation has also been reported by Aghapoor et al.[95] The condensation reaction of equimolar amounts of 1,2-phenylenediamine **23** with urea **24** (or thiourea **25**) or guanidine **26** was irradiated for 5−6 min to furnish the respective compounds **27**−**29** in 75−90% yields (Scheme 10). The authors did not inform the microwave equipment nor the power used in the reaction. The same reaction using solvent conditions required the use of dimethyl formamide (DMF), at 80 kPa and 150 °C for 3 h to obtain the product **27** in 98% yield.[96]

Scheme 9



R = H, 4-Me, 5-Me, 6-Me
R^1 = Ph, 4-Me-Ph, 3-Me-Ph, 4-MeO-Ph, 4-F-Ph
i: solvent-free, oil bath, 200 °C, 5 min (92−97%)

Scheme 10



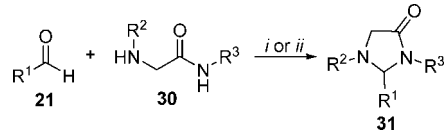
X = O (**24, 27**); X = S (**25, 28**); X = NH (**26, 29**); R^1, R^2, R^3, R^4 = H
i: solvent-free, MW, 5−6 min (75−90%)

5.5. Imidazolidinones

Imidazolidinones display a wide range of biological properties, including anticonvulsant,[97] antidepressant,[98] anti-inflammatory,[99] antiviral,[100] and antitumor.[101] The general synthetic approach to such compounds involves the condensation of α-aminoamides, with symmetrical ketones and 2-methylbenzaldehyde.[102] Despite the existence of such procedures, novel methods for imidazole synthesis are still in demand. In this sense, Pospíšil and Potáček[103] described

the synthesis of a new series of substituted imidazolidin-4-ones **31** from the reaction of equimolar amounts of *N*-substituted α-aminoamides **30** and aldehydes **21** under solvent-free conditions (Scheme 11). Products **31** were synthesized using both conventional thermal heating and microwave irradiation. The authors observed that conventional thermal heating at 200 °C required 30 min with 89−96% yields while the microwave-assisted method, which used microwave equipment for synthesis, at the same temperature required only 5 min with 68−95% yields. When the reaction was performed using solvent conditions, the use of benzene reflux for 1−48 h was required and the products were obtained with yields of 45−85%.[104]

Scheme 11

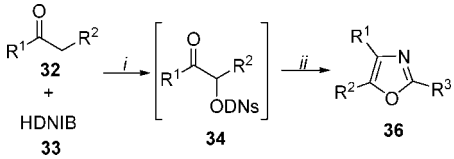


R^1 = H, Me, *i*-Pr, Ph, 4-Cl-Ph, 4-Me_2N-Ph, 4-O_2N-Ph, 2-(CH_2=$CHCH_2O$)-Ph
R^2 = Me, Bn; R^3 = *i*-Pr, *c*-Hexyl, Allyl, Bn
i: solvent-free, oil bath, 200 °C, 30 min (89−96%)
ii: solvent-free, MW, 200 °C, 5 min (68−95%)

5.6. Oxazoles

Oxazoles have attracted great interest because of their emergence as subunits of various biologically active natural products as well as their utility as valuable precursors in many useful synthetic transformations.[105] Oxazoles are commonly prepared from the Hantzsch reaction[106] or the cyclodehydration of β-ketoamides.[107] The dehydrogenation of oxazolines[108] and other processes such as aza-Wittig reactions,[109] Schmidt rearrangements,[110] the use of isocyanides,[111] toluenesulfonylmethyl isocyanide (TosMIC),[112] and intramolecular alkyne additions[113] have also been employed. Although oxazoles have widespread applications in diverse areas, there are few papers that highlight the improvement of synthetic methods to obtain these heterocycles. However, Lee et al.[114] described a one-pot method for the synthesis of multisubstituted oxazoles **36** by the reaction of amide **35** with intermediary **34** under microwave irradiation and solvent-free conditions (Scheme 12). The intermediary **34** was formed in situ from the reaction of carbonyl compounds **32** with [hydroxy-(2,4-dinitrobenzene sulfonyloxy)iodo]benzene **33** (HDNIB) in a domestic microwave oven for 1−2 min. The reactants **32** and **33** were used in a molar ratio of 1:1.2. In all cases investigated, the reactions proceeded with 58−94% yields. In addition, the formation of **36** was highly regioselective, giving only a single product without any regioisomeric oxazole.[114] This one-pot method for the synthesis of polysubstituted oxazoles **36** using molecular solvents has not yet been described in the literature.

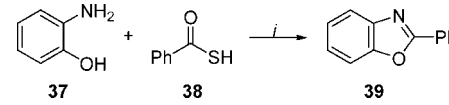
Scheme 12



R^1 = Me, Ph, 4-Me-Ph, 4-Cl-Ph
R^2 = H, Me, COMe, CO_2Et, $CONEt_2$, Ph; R^3 = Me, Ph
i: solvent-free, MW, 20−40 s
ii: solvent-free, R^3CONH_2 (**35**), MW, 1−2 min (58−94%)

In a two-component reaction, Seijas et al.[115] described the synthesis of benzoxazole **39** using microwave irradiation under solvent-free conditions. In this method, equimolar amounts of 2-aminophenol **37** were condensed with thiobenzoic acid **38** in a microwave equipment for synthesis (Scheme 13). The mixture was irradiated for 1 min (190 °C) and led to the respective product **39** in 83% yield. This method for the synthesis of oxazoles **39** using molecular solvents has not yet been described in the literature.

Scheme 13

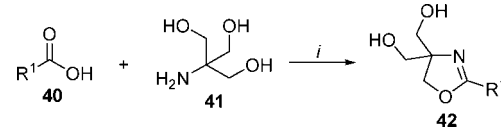


i: solvent-free, MW, 190 °C, 1 min (83%)

5.7. Oxazolines

Oxazolines are an important class of heterocycles that have held the fascination of many synthetic chemists.[116] 2-Oxazolines have been used as chiral auxiliaries, as ligands for metal entrapment, and, of particular importance, as protecting groups for carboxylic acids and amino alcohols.[117] Methods to synthesize 2-oxazolines have been extensively explored. The most commonly used methods are (i) the reaction of amino alcohols with carboxylic acids[118] or carboxylic acids derivatives (orthoesters, nitriles, imino ether hydrochlorides, and acyl benzotriazoles)[119] and (ii) the cyclodehydration of β-hydroxyamides with Burgess reagent, Vilsmeier reagent, and reactants such as DAST and PPh_3/DEAD.[108a,120] Thus, considering the importance of this class of compounds, Marrero-Terrero and Loupy[121] reported the synthesis of different oxazolines **42** under solvent-free conditions and microwave irradiation from the condensation of carboxylic acids **40** and α,α,α-tris(hydroxymethyl)methylamine **41** (Scheme 14). The reactants **40** and **41** were used in equimolar amounts, and this mixture was then irradiated in a domestic microwave oven for 2−5 min, furnishing the desired products in 80−95% yields. When this reaction was performed using the zeolite Ersorb-4 in xylene as solvent at 130 °C for 5 h, similar compounds were obtained in 90% yield.[118b]

Scheme 14



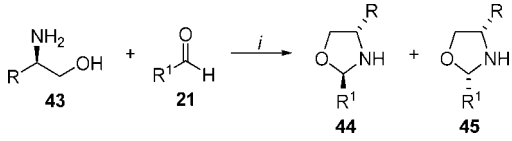
R^1 = Ph, fur-2-yl, heptadecenyl
i: solvent-free, MW, 850 W, 200−210 °C, 2−5 min (80−95%)

5.8. Oxazolidines

Oxazolidines have been investigated extensively since they exhibit many biological activities such as antibacterial, antimicrobial, and antitumor.[122] They can also be used as synthetic intermediates,[123] as chiral auxiliaries[124] and as precursors for synthetically and pharmaceutically important 1,2-amino alcohols,[125] which are present in several natural products.[126] This heterocycle can be synthesized from [3 + 2]-cycloaddition between carbonyl compounds and *N*-activated aziridines in the presence of a Lewis acid.[127] However, the most direct route to oxazolidines is the condensation of amino alcohols with either an aldehyde or acetone,[128] and such condensations of amino alcohols, including L-serine and L-cysteine methyl esters, with paraformaldehyde have been

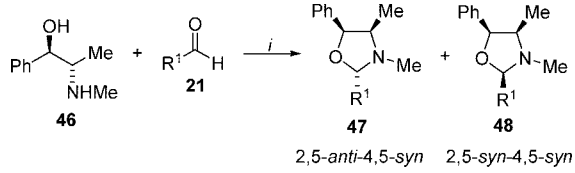
frequently employed, despite the fact that the yields are rather low.[129] Nevertheless, novel methods for oxazolidine synthesis are still needed. Therefore, Kuhnert and Danks[130] synthesized a series of 1,3-oxazolidines **44** and **45** from the condensation of enantiomerically pure amino alcohols, such as (*R*)-(2)-2-phenylglycinol, (*R*)-(2)-leucinol, and (*R*)-(2)-2-amino-3-phenylpropanol **43**, with substituted aldehydes **21**, under microwave irradiation (Scheme 15). When equimolar amounts of starting materials were used, the reaction gave the products directly in 96−99% yields in excellent purity with a diastereomeric ratio of 98:2. Because of the difficulties with the stability of these products,[131] the authors improved the reaction between (−)-ephedrine **46** (Scheme 16) or (+)-pseudoephedrine **49** (Scheme 17) and aldehydes **21**. These amino alcohols are known to form stable aminals, which are frequently used in asymmetric synthesis.[131−133] The conditions are suitable to drive the equilibrium between the two diastereomers toward the thermodynamically more stable diastereomer. The products **47**, **48** and **50**, **51** were obtained in 78−98% and 98−99% yields, respectively, with excellent diastereoselectivities. It was observed that, under focused microwave irradiation, the reaction rate increased and yields were improved in comparison to previously published procedures using conventional thermal heating.[133,134] The authors did not inform the microwave equipment used in the reaction. This method for the synthesis of oxazolidines **44**, **45**, **47**, **48**, **50**, and **51** using molecular solvents has not yet been described in the literature.

Scheme 15



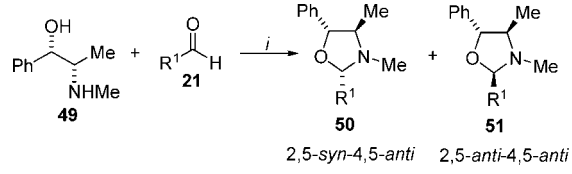
R = Ph, *i*-Bu, Bn; R^1 = 4-F-Ph, *t*-Bu
i: solvent-free, MW, 200 W, 2−3 min (96−99%)

Scheme 16



R^1 = 4-F-Ph, *t*-Bu
i: solvent-free, MW, 200 W, 160 s (78−98%)

Scheme 17

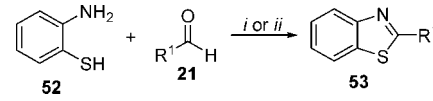


R^1 = 4-F-Ph, *t*-Bu
i: solvent-free, MW, 200 W, 140−180 s (98−99%)

5.9. Thiazoles

Many thiazoles have emerged as active pharmaceutical ingredients in several drugs due to their potential anti-inflammatory,[135] antitumor,[136] antihyperlipidemic,[137] and antihypertensive[138] properties, among several other biological properties.[139] Several methods for the synthesis of thiazoles have been developed, in particular for the 2-substituted benzothiazole.[140] The most common ones among them are the condensation of 2-aminothiophenols with substituted carboxylic acids, acyl chlorides, aldehydes, and nitriles.[140a,b] Another method employs potassium ferricyanide cyclization of thiobenzanilides (Jacobson's method).[141] Employment of solid supports for the synthesis of benzothiazole moiety is also known.[142,143] One of the methods that employs microwave techniques for the synthesis of benzothiazoles involves the use of 4-toluenesulphonic acid[144] to condense *β*-chlorocinnamaldehydes and 2-aminothiophenol. Another method uses ionic liquids[145] to condense aromatic aldehydes with 2-aminothiophenol. Much effort has been made to develop alternative methods for the synthesis of thiazoles. In this scenario, Mukhopadhyay and Datta[146] performed the two-component condensation reaction between equimolar amounts of arylaldehydes **21** and 2-aminothiophenol **52** under solvent-free conditions and microwave irradiation to obtain benzothiazoles **53** (Scheme 18). The mixture was placed in an alumina bath and irradiated in a domestic microwave oven for 3−20 min. A variety of **21** were reacted, and both electron-donating and electron-withdrawing groups on the aromatic nucleus underwent smooth reactions to furnish **53** in 83−95% yields (Scheme 18, *i*). A report describing this reaction in the presence of molecular solvent as xylene and activated carbon, under oxygen atmosphere, revealed the attainment of products **53** in 72−86% yields.[147] In another study, Seijas et al.[115] synthesized benzothiazole **53** (R^1 = Ph) from the reaction of thiobenzoic acid instead of **21** using microwave-assisted synthesis under solvent-free conditions. The reactants thiobenzoic acid and **52** were used in equimolar amounts, and the mixture was irradiated in a microwave equipment for synthesis at 190 °C for 1 min, furnishing **53** in 91% yield (Scheme 18, *ii*).

Scheme 18



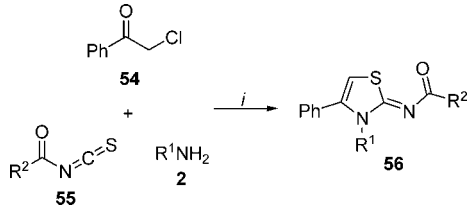
R^1 = Ph, 4-MeO-Ph, 4-HO-Ph, 4-Cl-Ph, 4-O_2N-Ph, 4-Me_2N-Ph, 3-HO-Ph, 3-O_2N-Ph, 3-Br-Ph, 2-Cl-Ph, 2-MeO-Ph, 2-HO-Ph, 3-MeO-4-HO-Ph, 2-cinnamyl
i: solvent-free, MW, 120−720 W, 3−20 min (83−95%)
ii: solvent-free, MW, 190 °C, 1 min (91%)

5.10. Thiazolines

The thiazoline ring presents interesting activities, such as anti-HIV,[148] anticancer,[149−151] and antibiotic.[152−154] General methodologies for the synthesis of this heterocycle involve the coupling of imidates or esters with aminothiols,[155−157] the cyclodehydration of hydroxy thioamides,[149,158−160] and the condensation of nitriles with mercaptoalcohols.[161,162] There have also been some reports on the use of microwaves to prepare a thiazoline ring, i.e., the irradiation of 2-aminoethanethiol with *N*-acylbenzotriazoles followed by the addition of thionyl chloride and a new irradiation step,[119e] or the preparation of 2-arylthiazolines from aryl ketonitriles and cysteamine.[163] Condensations of 2-aminothiols with nitriles,[164] carboxylic acids,[165] esters,[157] iminoethers,[166] or iminotriflates[167] are other exploitable reactions. Thiazolines have also been prepared from acylamino and thioacylamino alcohols[159,160,168,169] or by multistep conversions from oxazolines.[170] Despite these procedures, there continues to be a demand for novel methods for thiazoline synthesis. In order to meet this demand, Xia and Lu[171] developed a protocol for the synthesis of 2-acylimino-3-aryl-3*H*-thiazolines **56**.

The synthetic route to the three-component preparation of this compound is outlined in Scheme 19. In this one-pot operation, equimolar amounts of aroylisocyanates **55**, amines **2**, and ω-haloacetophenone **54** were reacted to provide the target products **56**. The straightforward route, beginning from aroylisothiocyanates instead of *N*-acylthioureas, facilitated the combinatorial construction of a library of compounds **56**. The reaction under solvent-free conditions in a domestic microwave oven was performed in 30−45 s, furnishing the products in 83−98% yields. To determine whether the microwave effect existed in this experiment, a three-component reaction under solvent-free conditions was carried out using conventional thermal heating. When the mixture was heated at 80 °C for 1 h, the products **56** were obtained in 41−77% yields, showing a clear microwave effect on the reaction. There seemed to be no obvious substituent effect on acyl moieties, since arylisocyanates with an electron-withdrawing group like NO_2 were used successfully in the three-component condensation to provide the products in 89% yield. However, a remarkable substituent effect was observed on anilines, since the reactions were only accomplished smoothly using anilines with electron-donating groups. The same reaction carried out in refluxing benzene for 3 h led to 40−53% yields of **56** and some complex byproducts were generated.[171]

Scheme 19

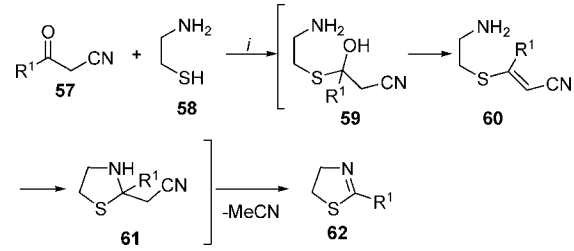


R^1 = Ph, 4-Me-Ph, 2-Me-Ph, 4-Cl-Ph, 3-Cl-Ph, 4-MeO-Ph
R^2 = Ph, 4-Cl-Ph, 4-MeO-Ph, 4-O_2N-Ph
i: solvent-free, MW, 580 W, 30−45 s (83−98%)

Kamila and Biehl[163] reported the synthesis of 2-thiazolines **62** from equimolar amounts of arylketonitrile **57** and cysteamine **58**, under solvent-free conditions and microwave irradiation (Scheme 19). The reaction mixture was irradiated in a microwave equipment for synthesis at 210 °C for 10 min to furnish **62** in 85−98% yields. According to the authors, the mechanism involves the loss of acetonitrile to give product **62**, which is demonstrated in Scheme 20. For comparison, when the reaction was carried out using conventional thermal heating at 210 °C for 10 min, product **62** (R^1 = Ph) was obtained in 55% yield. The authors suggested that the difference in the thiazoline yields reflects the rapid and volumetric heating in the microwave procedure when compared to the slow and superficial heating in the conventional thermal heating.[163] This protocol for the synthesis of thiazolines **62** using molecular solvents has not yet been described in the literature.

In another study, Seijas et al.[172] reported the synthesis of 2-thiazolines **65** from the reaction of carboxylic acids **40** and 1,2-aminoalcohols **63** in the presence of Lawesson's Reagent **64**, employing microwave irradiation, under solvent-free conditions (Scheme 21). The reactants **40**, **63**, and **64** were used in a molar ratio of 1:1.5:0.75, respectively, in a microwave equipment for synthesis, at 150 °C for 4−8 min. These reactions provided the desired products in better yields, when the aminoalcohols **63** with R^2, R^3 = H and R^2 = Me, R^3 = H were employed. However, the use of aminoalcohols

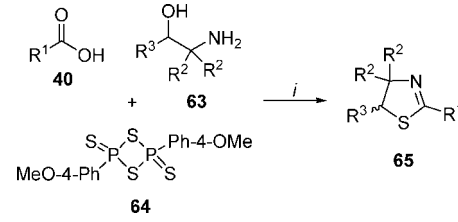
Scheme 20



R^1 = Ph, 4-F-Ph, 4-Cl-Ph, 4-Me-Ph, 4-MeO-Ph, 4-CN-Ph, 4-Br-Ph, naphth-1-yl, 2,4-$(MeO)_2$-Ph, 2,4-$(Cl)_2$-Ph
i: solvent-free, MW, 150 W, 150 psi, 210 °C, 10 min (85−98%)

63 with R^2 = H, R^3 = Ph gave poor yields.[172] This synthesis of 2-thiazolines **65** in the presence of Lawesson's Reagent using molecular solvents has not yet been described in the literature.

Scheme 21



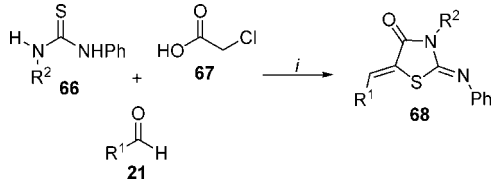
R^1 = hexyl, nonyl, $H_2OC(CH_2)_7$, Bn, Ph, 3-Me-Ph, 4-MeO-Ph, 2,3-$(MeO)_2$-Ph, 4-Cl-Ph, 4-Br-Ph, naphth-2-yl, pyrid-3-yl, thien-2-yl, fur-2-yl, R^2 = H, Me; R^3 = H, Ph
i: solvent-free, MW, 150 °C, 4−8 min (21−86%)

5.11. Thiazolidinones

Thiazolidin-4-ones constitute an important class of heterocyclic compounds for their potential pharmaceutical application as antimicrobial agents.[173−175] Consequently, a large number of synthetic protocols leading to these compounds have been reported in the literature.[176] 5-Arylidene-2-iminothiazolidin-4-ones[177] were synthesized by the reaction of 2-iminothiazolidin-4-ones and appropriate aldehydes under basic conditions in ethanol at reflux for about 24 h. The synthesis of iminothiazolines[178] was previously reported using microwave irradiation by Hantzsch cyclization. Following the same strategy, Kasmi-Mir et al.[179] described a one-pot, three-component reaction of thioureas **66**, chloroacetic acid **67**, and appropriate aldehydes **21** under solvent-free conditions and microwave irradiation, according to Scheme 22. The reactants **21**, **66**, and **67** were used in a molar ratio of 1:1:1.2, respectively, and this mixture was irradiated in microwave equipment for synthesis at 90−110 °C, for 10−20 min, furnishing 5-arylidene-2-iminothiazolidin-4-ones **68** in a range of 61−89% yields. When products were obtained by condensation of thiourea with chloroacetyl chloride in the presence of triethylamine in $CHCl_3$ at room temperature, the yield was 93% in a mixture of isomers.[177]

Darehkordi et al.[180] reported the synthesis of thiazolidin-4-ones **71** from the reaction of equimolar amounts of thiosemicarbazones **69** and dimethylacetylene dicarboxylate (DMAD) **70** under solvent-free conditions and microwave irradiation (Scheme 23). The mixture of **69** and **70** was subjected to microwave irradiation for 5 min to give **71** in 82−95% yields. The authors did not inform the type of microwave equipment used in the reaction. The effect of the electron-donor group on the progress of the reaction and on the structure of the final products was also investigated.

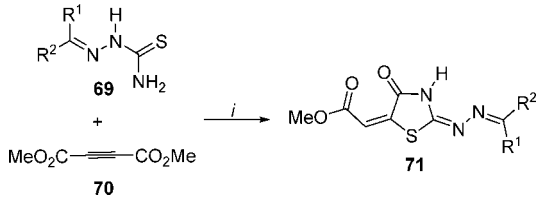
Scheme 22



R^1 = Ph, 4-MeO-Ph, 4-Me_2N-Ph, benzo[3,4]dioxan-2-yl
R^2 = Ph, 4-Me-pyrid-2-yl
i: solvent-free, MW, 30−50 W, 90−110 °C, 10−20 min (61−89%)

When an electron-donor group was present on the benzene ring, higher yields were obtained without exerting heat or refluxing the reaction mixture, and the reaction rate was also much faster. In comparison, when the reaction was carried out in ethyl acetate at room temperature for 3 h, the product was formed with 95% yield.[180]

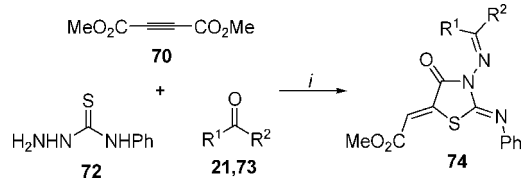
Scheme 23



R^1 = Pr, 4-Me_2N-Ph, 4-MeO-Ph, Ph, 4-Me-Ph, thien-2-yl, fur-2-yl
R^2 = H, Me, Ph
i: solvent-free, MW, 50 W, 5 min (82−95%)

Recently, Yavari et al.[181] reported a one-pot synthesis of highly functionalized thiazolidin-4-ones **74** using equimolar amounts of 4-phenylthiosemicarbazide **72** and DMAD **70** with aldehydes **21** or ketones **73** under solvent-free conditions (Scheme 24). The reactions proceeded at room temperature and were completed in 8 h, furnishing the products **74** in 70−83% yields. These products may be considered potentially useful synthesis intermediates because they possess atoms with different oxidation states. The advantage of this procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. This one-pot synthesis of thiazolidin-4-ones **74** using molecular solvents has not yet been described in the literature.

Scheme 24



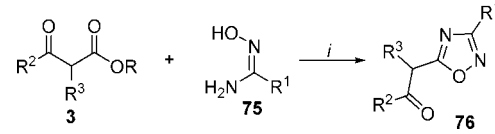
R^1 = Me, Et, Ph, 4-Me-Ph, 4-MeO-Ph, 4-O_2N-Ph, 3-O_2N-Ph, 3-Br-Ph
R^2 = H, Me
i: solvent-free, r.t., 8 h (70−83%)

6. Five-Membered Heterocycles with Three Heteroatoms

6.1. Oxadiazoles

Among a wide variety of aryl groups, 1,2,4-oxadiazole is a heteroaryl group that is often used in medicinal chemistry. It is considered to be a bioisostere of carboxylic functionalities and can be used to replace an ester group to achieve compounds that are resistant to enzyme-catalyzed hydrolysis.[182] 1,2,4-Oxadiazoles are usually synthesized by 1,3-dipolar cycloaddition of cyano compounds or dehydration of acyl amidoxime.[183] Compared to the large number of syntheses of 1,2,4-oxadiazole-containing compounds, the syntheses of α-oxadiazolo esters are quite limited. The known methods include 1,3-dipolar cycloaddition of nitrile oxides to α-cyano esters,[184] alcohololysis of 5-cyanomethyl oxadiazole,[185] and derivatization of malonic acid. The latter method is a straightforward approach since the synthesis of 1,2,4-oxadiazole by cyclization/dehydration of acyl amidoxime is well-known. Thus, considering the importance of this class of compounds, Du et al.[186,187] reported a synthesis of α-1,2,4-oxadiazolo esters and 5-β-keto-1,2,4-oxadiazoles **76** from amidoximes **75** and malonic esters or β-ketoesters **3**, respectively, under solvent-free conditions (Scheme 25). The reactants **75** and **3** were used in a molar ratio of 1:2, respectively. The mixture was gradually heated to 120−150 °C, for 2−6 h. Various substituted amidoximes **75** were reacted with β-ketoester or malonic esters **3** and gave 47−100% yields of the desired oxadiazole **76**. The electron-withdrawing or -donating group on the phenyl ring did not affect the reaction. Amidoximes **75** bearing a simple alkyl group also worked well in this reaction. The authors performed the reaction of dimethylisobutyl malonate and pyridylamidoxime in both refluxing toluene for 24 h and microwave irradiation at 130 °C for 2 h, and the desired product was obtained in 2% and trace yields, respectively. When dioxane was used under the same reaction conditions, most of the amidoxime remained unchanged. The reaction only occurred with good yields under solvent-free conditions. According to the authors, the solvent-free conditions probably contributed to the high efficiency of this reaction through two different additive effects: driving the reaction toward the desired oxadiazole product by removing other volatile products and favoring the entropy effect by achieving a high concentration of amidoxime reactants. In addition to the oxadiazole product, a molecule of alcohol and a molecule of water were also generated according to the proposed mechanism. Removal of these side products is easier under the solvent-free conditions, facilitating completion of the reaction, which was also accelerated by the high concentration of amidoxime obtained under the solvent-free conditions.[186,187]

Scheme 25



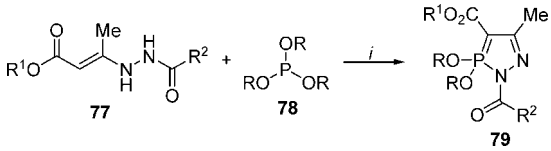
R = Me, Et, *t*-Bu; R^2 = Me, *t*-Bu, OEt, OBn; R^3 = H, *i*-Bu, *c*-Pentyl, Bn, Ph
R^1 = Me, *c*-Pr, *i*-Pr, CO_2Et, Ph, 4-MeO-Ph, 4-F_3C-Ph, 4-CO_2Me-Ph, CH_2OBn, CH_2SO_2-4-F-Ph, 2-F_3C-pyrid-4-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 5-(benzo[1,2,5]oxadiazol)oxymethyl
i: solvent-free, oil bath, 120−150 °C, 2−6 h (47−100%)

6.2. Diazaphospholes

1,2,3-Diazaphospholes are well-known[188] and have been intensively studied by many chemists.[189] Organophosphorus compounds are important naturally occurring substrates in several biochemical processes, and tetracoordinated pentavalent phosphorus compounds are well-known biologically active compounds that possess potent anticholinesterase activity.[190] The classical method for their preparation entails PCl_3 condensation of alkylketone hydrazones,[191] while 1,2,3-

diazaphosphole is best prepared from the respective 1,2-diaza-1,3-butadiene and a fused benzothiadiphosphole as the phosphorus-donating reactant.[192] Diazaphospholes are also synthesized from dipolar [3 + 2]-cycloaddition reactions.[193] Despite the synthetic methodologies available in the literature, there is a continuous demand for diazaphospholes synthesis. In this sense, Attanasi et al.[194] synthesized a series of 1,2,3-diazaphospholes **79** from the reaction of trialkyl phosphates **78** and 1,2-diaza-1,3-butadiene **77** under solvent-free conditions. The reactants **78** and **77** were used in a molar ratio of 4:1, respectively. The mixture was stirred at room temperature for 4−7.5 h, under nitrogen atmosphere, furnishing the products in 87−98% yields (Scheme 26). The authors observed that, when this protocol was carried out in the presence of atmospheric moisture, a series of hydrazonophosphonates in the *E*-isomeric form was obtained. This method to 1,2,3-diazaphospholes **79** using molecular solvents has not yet been described in the literature.

Scheme 26



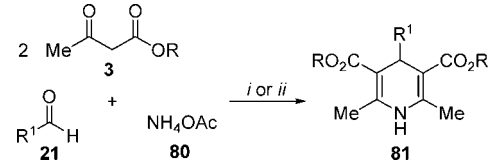
R = Me, Et; R^1 = Me, Et, *t*-Bu, Allyl, Bn
R^2 = NH_2, NHPh, O*t*-Bu
i: solvent-free, r.t., 4−7.5 h (87−98%)

7. Six-Membered Heterocycles with One Heteroatom

7.1. Pyridines

Pyridines are basic structural motifs found in numerous products with interesting medicinal properties such as antitumor, antimicrobial,[195] myasthenia gravis,[196] multiple sclerosis,[197] spinal cord injuries,[198] and botulism.[199] Numerous synthetic methodologies for the synthesis of 2-aminopyridines have been reported, including the condensation of α,β-unsaturated ketones with malononitrile in the presence of ammonium acetate,[200] nucleophilic substitution of 2-halopyridines with primary or secondary amines,[201] aminolysis of 2-alkoxypyridines, and [4 + 2]- or [3 + 3]-type ring-formation reactions.[202] Despite the numerous synthetic methodologies available in the literature, novel methods for pyridines synthesis are still in demand. Therefore, Wang et al.[203] reported a procedure for the synthesis of 1,4-dihydropyridines **81** under solvent-free conditions and ultrasound irradiation, which was designed to overcome some limitations of the Hantzsch reaction (Scheme 27). The mixture of aldehyde **21**, ethyl acetoacetate **3**, and ammonium acetate **80**, in a ratio of 1.1:2.5:1.2, respectively, was irradiated in a water bath of ultrasonic cleaner, nominal power of 250 W, at 28−35 °C for a period of 25−70 min. The condensations proceeded smoothly to afford the products **81** in 80−99% yields (Scheme 27, *i*). The condensation of various substituted aldehydes, carrying either electron-donating or -withdrawing substituents, showed an electronic and a steric effect of substituted groups on the yields of 1,4-dihydropyridines **81**. The reactivity of aldehydes with electron-withdrawing groups was higher than those with electron-donating groups in the Hantzsch condensation under solvent-free and ultrasound irradiation conditions. The position of substituents in the benzene ring of aldehyde influenced this reaction; for instance, the yield of 2-Cl−Ph−CHO reaction with ethyl acetoacetate **3** and ammonium acetate **80** under ultrasound irradiation in 25 min at 26−27 °C was lower than that of 3-Cl−Ph−CHO and 4-Cl−Ph−CHO. In an identical reaction, Zolfigol and Safaiee[204] reported the synthesis of 1,4-dihydropyridines **81** under solvent-free conditions using conventional thermal heating. The molar ratio between aldehyde **21**, ethyl acetoacetate **3** and ammonium acetate **80** was 1:2:1.5, respectively. The reactions were completed in 2 min−4.5 h at 80 °C, furnishing the products in 83−99% yields (Scheme 27, *ii*). By comparing the two solvent-free protocols, it can be concluded that the method using ultrasound irradiation led to a reduction of the reaction time (∼52%) and that both methods gave 1,4-dihydropyridines **81** in very similar yields. The same reaction carried out in refluxing ethanol during 8 h furnished a similar product in 48% yield.[205]

Scheme 27



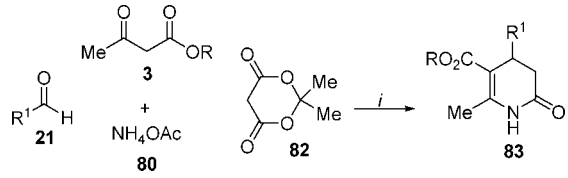
R = Et; R^1 = H, Me, Et, Pr, Ph, 2-Br-Ph, 3-Br-Ph, 4-Br-Ph, 2-O_2N-Ph, 3-O_2N-Ph, 4-O_2N-Ph, 2-MeO-Ph, 4-MeO-Ph, 3,4-OCH_2O-Ph, 2-Cl-Ph, 3-Cl-Ph, 4-Cl-Ph, 2,4-$(Cl)_2$-Ph, 4-HO-Ph, 4-HO-3-Me-Ph, Ph−CH=CH, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, fur-2-yl, thien-2-yl
i: solvent-free, US, 28−35 °C, 25−70 min (80−99%)
ii: solvent-free, oil bath, 80 °C, 2 min−4.5 h (83−99%)

7.2. Pyridinones

Pyridinones constitute an important class of heterocyclic compounds for their potential pharmaceutical applications, for example, as antibacterial and antifungal agents.[206] The synthesis of 2-pyridinones may be carried out by the oxidation of *N*-substituted pyridinium salts,[207] the reaction of β-dicarbonyl compounds or α,β-unsaturated ketones with malononitrile or similar active methylene compounds,[202,208] the reaction of α-oxoketenedithioacetals with cyanoacetamide in the presence of a base,[209] the cycloaddition of 2-azadienes with acetylenic dienophiles,[210] the reaction of lithium dienediolates and nitriles,[211] and the reaction of acyl isocyanates and trimethylsilylketene.[212] Previous syntheses of 2,3-dihydro-1*H*-pyridin-4-ones include multistep protocols commencing from β-amino-β-arylpropionic acids,[213] 4-methoxypyridine,[214] and *t*-butyl enaminoesters.[215] The syntheses of 2,3-dihydro-1*H*-pyridin-4-ones using the aza-Diels−Alder reaction and 5,6-dihydro-1*H*-pyridin-4-ones from the reaction of a ketene dithioester with methylamine have also been reported.[216] The synthesis of 3,4-dihydropyridinones **83** has been reported by Rodríguez et al.[217] in a procedure involving a one-pot condensation from Meldrum's acid **82**, methyl acetoacetate **3**, and benzaldehyde **21** in the presence of ammonium acetate **80** using microwave irradiation under solvent-free conditions (Scheme 28). In this method, equimolar amounts of the starting compounds were placed in microwave equipment for synthesis and then irradiated at 100−130 °C for 10−15 min, and the 3,4-dihydropyridinones **83** were obtained in 81−91% yields. In order to show the advantages of the microwave-assisted method, the authors compared it to conventional thermal heating under the same conditions, checking for the possibility of intervention of nonthermal microwave effects. The lower yields (20−83%)

obtained in conventional thermal heating, even after 2 h of reaction, indicate that the effect of microwave irradiation is not purely thermal. This improvement attributed to a strong nonthermal MW effect was considered to be connected to the reaction mechanism and the evolution of polarity during the course of the reaction. In comparison, when the reaction was carried out in refluxing ethanol or acetic acid for 6−10 h, the products were formed in 24−61% yields.[217]

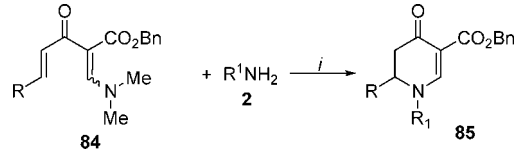
Scheme 28



R = Me; R^1 = Ph, 3-O_2N-Ph, 4-O_2N-Ph, 2-Cl-Ph, 4-Cl-Ph, 4-MeO_2C-Ph, 2,4-$(NO_2)_2$-Ph
i: solvent-free, MW, 100−130 °C, 10−15 min (81−91%)

Another solvent-free method for the synthesis of 2,3-dihydropyridin-4-ones **85** has been reported by Panunzio et al.[218] In this protocol, enaminoketones **84** in the presence of different aliphatic and aromatic amines **2** underwent ring closure under microwave irradiation (Scheme 29). The reactants **84** and **2** were used in a molar ratio of 1:1.1, respectively. The mixture was irradiated in a microwave equipment for synthesis in an open-vessel system for 5 min, furnishing **85** in 54−86% yields. Nevertheless, when R = $(CH_3)_2$CHCH(OTIPS) and R^1 = CH_2CH_2OH, *c*-Pr the intermediate secondary enaminone was isolated. These intermediates were irradiated again for 5 min, furnishing the product **85**. For comparison, the enaminone (R = $(CH_3)_2$CHCH(OTIPS), R^1 = CH_2CO_2Me) was reacted under reflux in toluene for 8 h, resulting in 46% yield.[218]

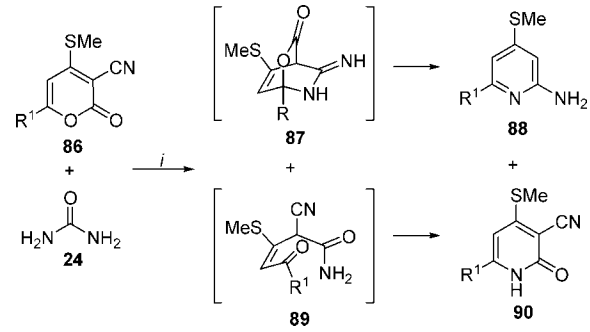
Scheme 29



R = *s*-Bu, $(CH_3)_2$CHCH(OTIPS), *c*-hexyl, Ph, 3-Me-Fur-2-yl
R^1 = *c*-Pr, CH_2CH_2OH, CH_2CO_2Me, 4-MeO-Ph
i: solvent-free, MW, 300 W, 5 min (54−86%)

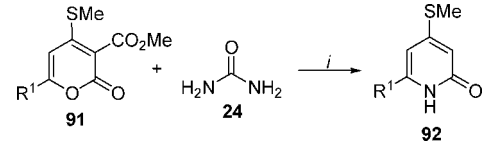
In a single work, Goel et al.[219] reported the one-pot regioselective synthesis of 2-aminopyridines **88** and 2-pyridinones **90** through nucleophile-induced ring transformation of 2-pyranone **86** with urea **24** under solvent-free conditions. The reaction proceeded at 150 °C, for 8−15 min, for the formation of a mixture of products **88** and **90** in 81−87% yields (Scheme 30). The reactants **86** and **24** were used in a molar ratio of 1:2.3, and the products were isolated in a 1:1 ratio. The authors suggested that **88** and **90** were formed through the intermediates **87** and **89**, respectively. On the other hand, the reaction of 2-pyranone **91** with urea **24** at 150 °C under solvent-free conditions afforded the 2-pyridinones **92** as the sole product in 70−80% yields (Scheme 31). The authors did not inform the molar ratio of the reactants. This one-pot regioselective synthesis of 2-aminopyridines **88** and 2-pyridinones **90** and **92** using molecular solvents has not yet been described in the literature.

Scheme 30



R^1 = Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, 4-Me-Ph, 4-MeO-Ph, fur-2-yl, thien-2-yl
i: solvent-free, oil bath, 150 °C, 8−15 min (81−87%)

Scheme 31



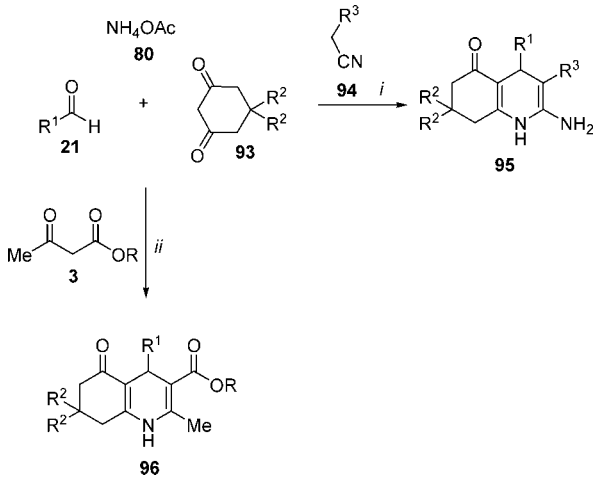
R^1 = Ph, 4-F-Ph, 4-Me-Ph, thien-2-yl, pyrid-2-yl
i: solvent-free, oil bath, 150 °C, 10−15 min (70−80%)

7.3. Quinolines

Quinolines have been found to possess useful biological activities such as antimalarial, antibacterial, antiasthmatic, antihypertensive, and anti-inflammatory.[220] A method to obtain quinolines related to the classical Hantzsch tetrahydropyrane synthesis involves the four-component reaction of an aldehyde with ethyl acetoacetate, a cyclic 1,3-diketone, and ammonia in acetic acid or refluxing alcohol.[221] Several alternative and more efficient methods have been developed and include the use of ionic liquids,[205,222] metal triflates,[223] I_2,[224] ceric ammonium nitrate,[225] polymers,[226] and organocatalysts.[227] Kumar et al.[228] reported the four-component synthesis of quinolines **95** and **96**, similar to the classical Hantzsch reaction, using aldehydes **21**, ammonium acetate **80**, dimedone **93**, and malononitrile/α-cyanoesters **94** or β-ketoesters **3** (Scheme 32) in a grinding process. The reactants **21**, **80**, **93**, and **94** or **3** were used in a molar ratio of 1:1.5:1:1, respectively. In the first case, the mixture was ground for 12−25 min to furnish the products **95** in 65−88% yields (Scheme 32, *i*). When the reaction was carried out with β-ketoesters **3**, the mixture was ground for 12−45 min to furnish the products **96** in 56−95% yields (Scheme 32, *ii*). It is evident that electron-rich and electron-deficient aldehydes reacted smoothly with β-ketoesters to produce the products in high yields. However, with aliphatic aldehydes, lower yields of the products were observed. When equimolar amounts of benzaldehyde, dimedone, ethyl acetoacetate, and ammonium acetate were heated under reflux in ethanol for 4 h, the product was obtained in 55% yield.[228]

Quiroga et al.[229] described a three-component reaction for the synthesis of benzopyrazolo[3,4-*b*]quinolines **99** and **101**, under solvent-free conditions. The procedure involved the heating of equimolar amounts of 5-aminopyrazoles **98**, aromatic aldehydes **21**, and β-tetralone **97** at 120 °C for 1.5−7 min to afford **99** in 48−74% yields (Scheme 33). A similar reaction was performed with equimolar amounts of **98**, **21**, and α-tetralone **100** at 120 °C fir 1.5−3.5 min to furnish **101** in 55−80% yields (Scheme 34). The lower reactivity of α-tetralone compared to that of β-tetralone is

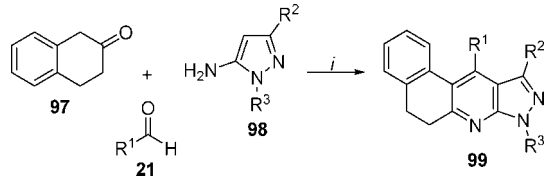
Scheme 32



R = Me, Et; R^1 = Pr, Ph, 4-HO-Ph, 4-MeO-Ph, 4-Cl-Ph, 4-Me_2N-Ph, 3-Br-Ph, 2-Cl-Ph, 4-Me-Ph, 4-Me_2N-Ph, 3-MeO-4-HO-Ph, 4-O_2N-Ph, 3,4,5-$(MeO)_3$-Ph, thien-2-yl, thien-3-yl, benzo[3,4]dioxan-2-yl
R^2 = Me; R^3 = CN, CO_2Et
i: solvent-free, grinding, r.t., 15−25 min (65−88%)
ii: solvent-free, grinding, r.t., 12−45 min (56−95%)

due to the fact that α-tetralone did not participate in a three-component reaction, since the previous formation of an intermediate from the reaction of α-tetralone with aldehydes was necessary in order to obtain compounds **101**. The solvent conditions required heating in ethanol for 10−12 h to afford **99** in 40−45% yields or 20−22 h to afford **101** in 38−44% yields.[229]

Scheme 33

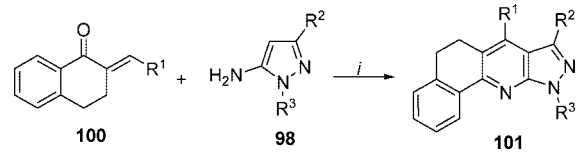


R^1 = Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, 4-F_3C-Ph, 4-Me-Ph, 4-MeO-Ph, pyrid-4-yl; R^2 = Me, *t*-Bu; R^3 = Ph, 4-Cl-Ph
i: solvent-free, oil bath, 120 °C, 1.5−7.0 min (48−74%)

7.4. Quinolinones

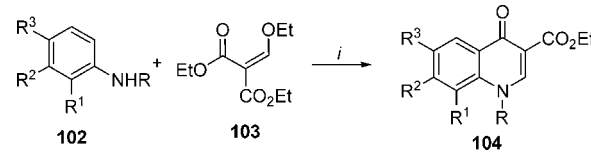
Quinolinones are the most important class of synthetic human and veterinary antibiotics. They are effective in controlling a wide range of bacteria, both gram positive and gram negative, and are often used in the treatment of a range of illnesses.[230] In particular, quinolinones have attracted considerable interest in a number of pharmacological applications, including in the treatment of Parkinson's and Alzheimer's diseases.[231] Quinolinones have been synthesized by cyclization of *N*-acetylanthranilic acids,[232] condensation of malonates/malonic acid with anilines using $ZnCl_2$ and $POCl_3$,[233] and cyclization of malonodianilides using $AlCl_3$,[234] PPA,[235] and CH_3SO_3H/P_2O_5.[236] One of the well-known syntheses of quinolinones is the Gould−Jacobs reaction in which an aromatic amine reacts with diethyl ethoxymethylenemalonates (EMME).[237] Dave and Joshipura[238] reported the study of the Gould−Jacobs reaction to obtain quinolin-4-ones **104** under microwave-assisted synthesis and solvent-free conditions (Scheme 35). The reactants, aromatic amine **102** and EMME **103**, were used in equimolar amounts, and the reaction was performed in a domestic microwave oven for 2−14 min, furnishing the product **104** in 75−92% yields. Similarly, Nadaraj and Selvi[239] presented a microwave-assisted process under solvent-free conditions to obtain quinolin-4-ones **106**. In this process, the β-enamino ester **105** underwent an intramolecular cyclocondensation by irradiation using a domestic microwave oven for 2−4 min and the products **106** were obtained in 74−96% yields (Scheme 36). Considering the similarity of this reaction with that described by Dave and Joshipura,[238] comparison of the reaction performed using molecular solvents was analogous, where the molecular solvents such as paraffin or diphenyl oxide required a time of 0.25−1 h and furnished the products in 55−91% yields.[237,240]

Scheme 34



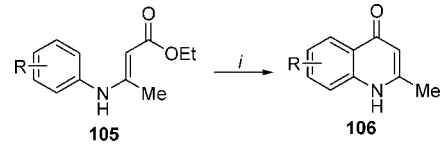
R^1 = Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, 4-F_3C-Ph, 4-Me-Ph, 4-MeO-Ph, pyrid-4-yl; R^2 = Me, *t*-Bu; R^3 = Ph, 4-Cl-Ph
i: solvent-free, oil bath, 120 °C, 1.5−3.5 min (55−80%)

Scheme 35



R = H; R^1 = H, Me; R^2 = H, Cl; R^3 = H, F, Cl, Br, I, Me, NO_2
i: solvent-free, MW, 560−700 W, 2−14 min (75−92%)

Scheme 36



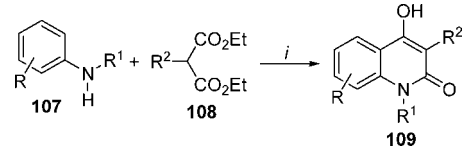
R = H, 2-Me, 2-NO_2, 2−OH, 2-OMe, 4-Cl, 4-Br, 4-OMe, 4-Me
i: solvent-free, MW, 320 W, 2−4 min (74−96%)

Lange et al.[241] described the synthesis of 4-hydroxyquinolin-2-ones **109** using anilines **107** and malonic ester **108** as starting material, under solvent-free conditions (Scheme 37). The synthetic procedure involved the irradiation of the mixture using microwave equipment for synthesis for 15 min to give the products **109** in 8−94% yields. The reactants **108** and **107** were used in a molar ratio of 2:1, respectively. The presence of the electron-withdrawing trifluoromethyl group on the aniline ring had a deactivating effect on the final electrophilic aromatic cyclization. *N*-Substituted anilines reacted nicely; however, the sterically bulky cyclohexyl group led to a low yield. Malonates (where R^2 = butyl, *t*-butyl, or benzyl) did not react with 2-chloroaniline under these conditions. This synthetic route to 4-hydroxyquinolin-2-ones **109** using molecular solvent has not yet been described in the literature.

7.5. Isoquinolines

Isoquinolines are a pharmacologically interesting class of heterocycles with potent antitumoral[242,243] and antifungal[244] properties. The most commonly used approach for the synthesis of isoquinolines involves generation of the pyridone core through the Curtius rearrangement of the corresponding

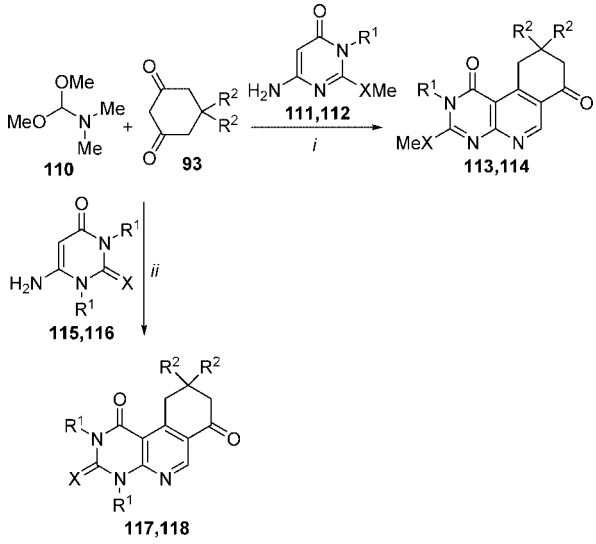
Scheme 37



R = H, 2-MeO, 3-MeO, 4-MeO, 3-Cl, 4-Cl, 3-F, 3-CF_3
R^1 = H, Me, Pr, Bu, *c*-hexyl
R^2 = Ph, 4-MeO-Ph, 4-Me-Ph, 3-PhO-Ph, thien-3-yl
i: solvent-free, MW, 500 W, 15 min (8−94%)

α,β-unsaturated cinnamoyl azide followed by thermally induced cyclization of the isocyanate intermediate.[245] Another route entails the conversion of phthalic anhydride to *N*-substituted imide and a base-promoted rearrangement of ethyl phthalimidoacetate into the corresponding 1,4-dihydroxybenz[*f*]isoquinoline.[246] In this context, many researchers have experienced the need for an efficient methodology for the synthesis of isoquinolines and have shown interest in the possibility of using solvent-free conditions. Quiroga et al.[244] reported a microwave-assisted process to synthesize pyrimido[4,5-*c*]isoquinolines **113** or **114** from the reaction of aminopyrimidine **111** or **112**, dimedone **93**, and *N*,*N*-dimethylformamide dimethylacetal **110** under solvent-free conditions (Scheme 38). The reactants **93**, **110**, **111**, or **112** were used in a molar ratio of 1:1.2:1, respectively. The mixture was irradiated in a domestic microwave oven for 2−6 min to furnish the products **113** or **114** in 55−75% (Scheme 38, *i*). The authors also synthesized a series of pyrimido[4,5-*c*]isoquinolines **117** or **118**, using the same conditions described previously, from the reaction of **110**, **93**, and **115** or **116**, which were obtained in similar yields (55−70%, Scheme 38, *ii*). The reaction to obtain **113**, **114**, **117**, and **118** was also carried out by heating in ethanol for 4−6 h; however, the products were obtained in 21−70% yields.[244]

Scheme 38

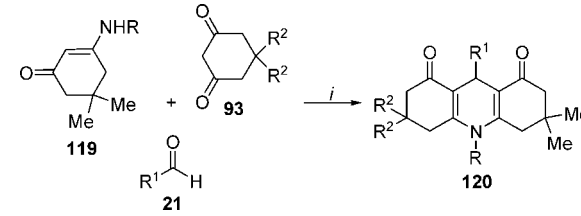


X = O (**111, 113, 115, 117**); X = S (**112, 114, 116, 118**)
R^1 = H, Me; R^2 = H, Me
i: solvent-free, MW, 600 W, 2−6 min (55−75%)
ii: solvent-free, MW, 600 W, 2−6 min (55−70%)

7.6. Acridines

Acridines are of considerable interest because of the diverse range of their biological properties, for example, antibacterial[247] and antiparasitic.[248] Moreover, their anticancer properties[249] have also been studied, for instance, their inhibitory activity against topoisomerases and telomerases.[250] These heterocycles are usually constructed via harsh conditions that appear unsuitable for the synthesis of functionalized acridines. For example, high temperatures and strongly basic or acidic media are required for synthesizing acridines via some previously described methods: modification of acridone intermediates,[251] the Bernthsen reaction,[252] cyclization of diphenylamine-2- carboxaldehyde, or adaptation of the Pfitzinger quinoline synthesis.[253] Despite the availability of these procedures, novel methods for acridine synthesis are still in demand. In this scenario, Wang and Miao[254] reported the synthesis of unsymmetrical acridine-1,8-diones **120** through the reaction of preformed enaminones **119** with dimedone **93** and aldehydes **21** (Scheme 39). The reaction was performed from the mixture of equimolar amounts of reactants stirred under solvent-free conditions at 160 °C for 2−5 min, affording **120** in 70−87% yields. Comparable product yields (71−87%) were achieved under reflux in water for 3−10 h. To demonstrate the advantages using the solvent-free conditions and water, selected reactions were carried out in organic solvents for comparison. The reaction was performed in dioxane (reflux), toluene (100 °C), and ethanol (reflux) and furnished the products with yields 40−50% lower, on average, than those obtained under solvent-free conditions. In the solvent-free reactions, it was reported that the reaction mixtures first turned into a uniform liquid phase and then into the solid products. This phenomenon may be related with the melting points of the starting materials, except those that are lower than 160 °C. Therefore, the uniform liquid phase formed at 160 °C, because either a simple melt or a eutectic melt facilitated the reaction, leading to higher reaction rates and higher yields than those found with organic solvents.[254]

Scheme 39



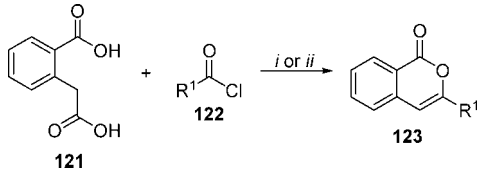
R = H, Me, 4-Me-Ph; R^1 = H, Cl, OMe
R^2 = H
i: solvent-free, oil bath, 160 °C, 2−5 min (70−87%)

7.7. Pyranones

Pyranones display a wide range of biological activities[255] such as antifungal,[256] cytotoxic,[257] antimicrobial,[258] antiallergic, and antimalarial[259] effects. Recently, several methods have been reported for the synthesis of pyranones such as palladium-catalyzed reactions, electrophilic aromatic substitution, and cyclization of 2-allyl- and alkenylbenzoic acid.[260] Tajudeen and Khan[261] developed a microwave-assisted process for the preparation of benzopyrans **123** by the reaction of homophtalic acid **121** and acid chlorides **122** under solvent-free conditions. The reactants **121** and **122** were used in a molar ratio of 4:1, respectively. The mixture was irradiated at 200 °C for 4−8 min, and the products were obtained in 70−94% yields (Scheme 40). The authors did not inform the microwave equipment used for the reaction. This reaction was also performed in conventional thermal

heating, at the same temperature; however, it required 4 h, and the products were obtained in 69−80% yields.[261]

Scheme 40

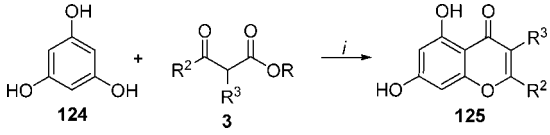


R^1 = Bu, *c*-Hexen-1-yl, Ph, 4-Me-Ph, 4-O_2N-Ph, 4-Cl-Ph, 4-MeO-Ph
i: solvent-free, MW, 900 W, 200 °C, 4−8 min (70−94%)
ii: solvent-free, oil bath, 200 °C, 4 h (69−80%)

7.8. Flavones

Flavones are interesting biological markers,[262] and there is increasing importance of their multiple biological activities: leishmanicidal,[263] anti-HIV,[264] antioxidants,[265] bactericidal,[266] and antiallergic activity.[267] Despite having been present in organic chemistry for quite some time, there continues to be interest in the isolation of new constituents[268] and the development of new synthetic approaches.[269] Despite the high number of steps involved, most of the current syntheses for new flavones are based on the pioneer work developed by Robinson[270] and Venkataraman.[271] Seijas et al.[272] reported a microwave-assisted procedure to synthesize flavones **125** by mixing β-ketoester **3** and phenol **124**, which were used in a molar ratio of 2:1, respectively, under solvent-free conditions (Scheme 41). The reactions were accomplished in microwave equipment for synthesis for 2−12 min, leading to respective flavones **125** in 66−96%. Reactions were performed either under wattage control or temperature control (240 °C) with no significant differences in reaction times or yields. To discover whether there were nonthermal microwave effects in this reaction, the reaction temperature was reduced both under conventional thermal heating and microwave conditions. Both experiments were carried out using the same time (10 min) and the same temperature ramp (25−152 °C), and the yield was 4-fold in the microwave reaction. When the reaction was performed under microwave irradiation with $CuCl_2$ as catalyst in refluxing ethanol, during 5 min, the yield for similar products was 89%.[273]

Scheme 41



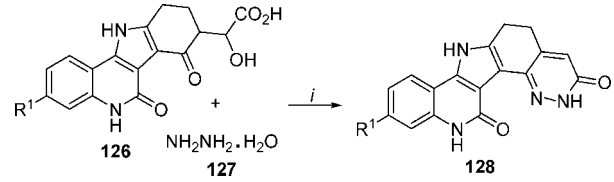
R = Et; R^2 = Ph, 2-MeO-Ph, 3-MeO-Ph, 3,4-$(MeO)_2$-Ph, 2,3,4-$(MeO)_3$-Ph, 2,3-OCH_2O, 4-HO-Ph, 4-Cl-Ph, 4-NO_2−Ph, 4-Me-Ph; R^3 = H
i: solvent-free, MW, 800 W, 240 °C, 2−12 min (66−96%)

8. Six-Membered Heterocycles with Two Heteroatoms

8.1. Pyridazinones

Pyridazinones have been reported to possess a wide range of biological activities, such as anticancer,[274] antituberculosis,[275] antihypertensive,[276] and antimicrobial.[277] Moreover, since the early 1980s, it has been proven that pyridazinones possess various biological activities including platelet aggregation and antihypertensive,[278] antisecretory, antiulcer,[279] antidepressant and tranquilizing,[280] antibacterial, and antifungal.[281] In general, the synthesis of pyridazinones proceeds via reaction of γ-ketoacids and their derivatives with alkylhydrazines or phenylhydrazines to give the corresponding hydrazones, which may be converted by a simple condensation reaction to pyridazinones. Other syntheses of pyridazinones are based, for example, on condensation of Wittig reagents with arylhydrazones or condensation of α-ketoesters with hydrazinocarbonylacetic acid esters.[282] Thus, considering the importance of pyridazinones, Dandia et al.[283] described the synthesis of pyridazinodiones **128** from the reaction of compound **126** and hydrazine hydrate **127** under solvent-free conditions (**Scheme 42**). The reactants **127** and **126** were used in a molar ratio of 3:1, respectively. The mixture was irradiated in a domestic microwave oven for 3−5 min to furnish the products in 85−88% yields. The authors also performed the reaction using molecular solvents by refluxing compound **126** and hydrazine hydrate **127** (70−80 mL) for 50−52 h; however, this reaction furnished the desired products in 30−40% yields.[283]

Scheme 42



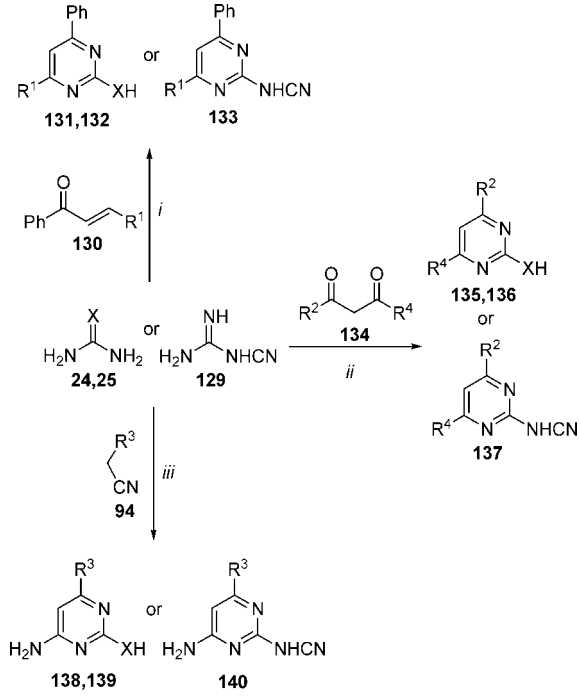
R^1 = OMe, Cl
i: solvent-free, MW, 700 W, 3−5 min (85−88%)

8.2. Pyrimidines

Pyrimidines are of chemical and pharmacological interest and compounds containing the pyrimidine ring system have been shown to possess antitumor, antibacterial, antifungal, antimalarial, and anticonvulsant activities.[284−288] Pyrimidines have been synthesized using various procedures including the reaction of amidines with α,β-unsaturated ketones;[289] dimerization−oxidative fragmentation of β-arylvinylimines;[290] condensation of phenacyldimethylsulfonium salts, aldehydes, and ammonia;[291] reaction of alkynes and nitriles in the presence of TfOH;[292] rearrangement of 2,4,5-trisubstituted imidazolines;[293] one-pot, three-component reaction of aryl halides, terminal propargyl alcohols, and amidinium salts based upon a coupling−isomerization−cyclocondensation sequence;[294] arylation of halogenated pyrimidines via a Suzuki coupling reaction;[295] reaction of α,α-dibromo oxime ethers with Grignard reagents;[296] microwave-assisted reaction of amidines and alkynones;[297] and sequential assembly of aryl groups onto a pyrimidine core (2-methylthiopyrimidine).[298] Much effort has been made to develop alternative methods for the synthesis of pyrimidines. The use of solvent-free conditions and microwave irradiation in the synthesis of pyrimidines was studied by Goswami et al. (Scheme 43).[299] First, the reaction of chalcones **130** with urea **24** (or thiourea **25**) or cyanoguanidine **129** was performed. The mixture was irradiated in a domestic microwave oven for 7−30 min, and the desired substituted pyrimidines **131**−**133** were obtained in 50−70% yields (Scheme 43, *i*). Later, the authors carried out the reaction of β-diketones **134** with urea **24** (or thiourea **25**) or cyanoguanidine **129** under microwave irradiation for 2−20 min to result in pyrimidines **135**−**137** in 55−96% yields (Scheme 43, *ii*). Finally, the authors performed the reactions between cyano compounds **94** and urea **24** (or thiourea **25**) or cyanoguanidine **129** under microwave irradiation for 5−10 min to obtain

the amino pyrimidines **138**−**140** in 60−80% yields (Scheme 43, *iii*). All reactions were performed with equimolar amounts of reactants. When the same reaction was carried out in sodium ethoxide and ethanol under reflux, the reaction time was 2.5 h.[300]

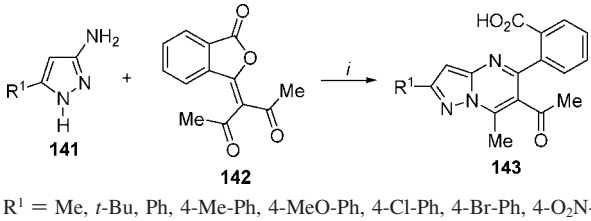
Scheme 43



X = O (**24, 131, 135, 138**); X = S (**25, 132, 136, 139**)
R^1 = Ph, 3-Br-Ph; R^3 = CO_2Et, CN; R^2, R^4 = Me, Ph
i: solvent-free, MW, 450 W, 7−30 min (50−70%)
ii: solvent-free, MW, 300−700 W, 2−20 min (55−96%)
iii: solvent-free, MW, 300−450 W, 5−10 min (60−80%)

Quiroga et al.[301] reported a one-pot method for the synthesis of polyfunctionally substituted pyrazolo[1,5-*a*]pyrimidines **143** under solvent-free conditions (Scheme 44). The use of a biselectrophilic reactant provided a highly regioselective cyclocondensation along with the introduction of a 2-benzoic acid residue into a single molecule. The synthetic protocol involved the use of a fusion method between aminopyrazoles **141** and β-diketone **142** in equimolar amounts by heating in an oil bath at 150 °C, which afforded **143** after just a few minutes and in 82−92% yields. In addition, compounds **143** were prepared in a regioselective method that allowed the synthesis of polyfunctionalized pyrazolo[1,5-*a*]pyrimidines, and no evidence of another regioisomer was found. This one-pot method for the synthesis of pyrazolo[1,5-*a*]pyrimidines **143** using molecular solvents has not yet been described in the literature.

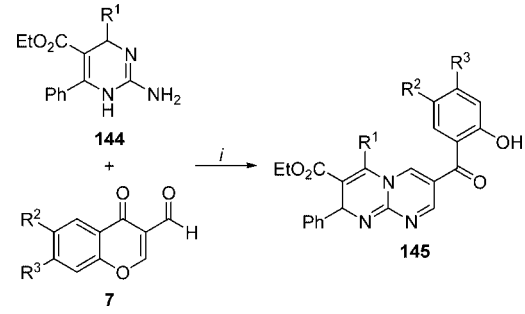
Scheme 44



R^1 = Me, *t*-Bu, Ph, 4-Me-Ph, 4-MeO-Ph, 4-Cl-Ph, 4-Br-Ph, 4-O_2N-Ph
i: solvent-free, oil bath, 150 °C, 1.5−2 min (82−92%)

Eynde et al.[302] demonstrated that 2-aminopyrimidines **144** reacted with 3-formylchromones **7**, in equimolar amounts, to furnish only one series of pyrimido[1,2-*a*]pyrimidine **145** (Scheme 45). The product **145** was obtained through microwave irradiation in a domestic microwave oven for 20 min. The same reaction was performed in ethanol under reflux for 4 h; however, the products were obtained in lower (60−80%) yields when compared with the solvent-free method (>95%).[302]

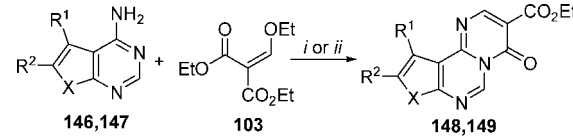
Scheme 45



R^1 = Ph, 4-Me-Ph, 4-MeO-Ph, 4-Cl-Ph, thien-2-yl; R^2, R^3 = H
i: solvent-free, MW, 20 min (>95%)

Desai[303] applied the Gould−Jacobs type of reaction for the synthesis of pyrimido[1,2-*c*]pyrrolo[3,2-*e*]pyrimidines **148**, using a domestic microwave oven under solvent-free conditions (Scheme 46). The reaction of equimolar amounts of 4-aminopyrrolo[2,3-*d*]pyrimidines **146** and EMME **103** provided the products in 10−12 min with 65−75% overall yields (Scheme 46, *i*). The authors also carried out the reaction using conventional thermal heating in two steps, where 4-aminopyrrolo[2,3-*d*]pyrimidines **146** were condensed with EMME **103** at 130−140 °C for 3.5−4.5 h to obtain an intermediate, which, through cyclocondensation reaction in boiling diphenyl oxide at 250 °C for 2−3 h, provided 1,4-dihydropyrimido[1,2-*c*]pyrrolo[3,2-*e*]pyrimidine **148** in 50−65% overall yields.[303] Similar to Desai,[303] Dave and Shah[304] applied the Gould−Jacobs type of reaction for the synthesis of thieno[3,2-*e*]pyrimido[1,2-*c*]pyrimidinones **149** using a domestic microwave oven under solvent-free conditions. The reaction of 4-aminothieno[2,3-*d*]pyrimidines **147** with EMME **103**, in a single step, provided the products **149** in 7−10 min in 80−83% yields (Scheme 46, *ii*). On the other hand, using a two-step conventional thermal heating protocol, compounds **147** were condensed with EMME **103** at 130−140 °C for 3.5−4.0 h to obtain an intermediate, which, through cyclocondensation reaction in boiling diphenyl oxide at 250 °C for 1.5−2.0 h, provided **149** in 42−61% overall yields.[304]

Scheme 46



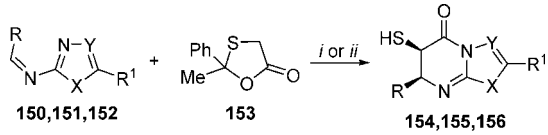
X = NR (**146, 148**); (R = Ph, 4-MeO-Ph, 4-Cl-Ph, 4-F-Ph, 3-Cl-4-F-Ph)
X = S (**147, 149**)
R^1 = Me, Ph, 4-MeO-Ph, 4-Cl-Ph; R^2 = H, Me
R^1, R^2 = $-(CH_2)_3-$, $-(CH_2)_4-$
i: solvent-free, MW, 700 W, 10−12 min (65−75%)
ii: solvent-free, MW, 700 W, 7−10 min (80−83%)

8.3. Pyrimidinones

Pyrimidinones are of considerable interest both in the industry and in academia because of their promising biologi-

cal activities as calcium channel blockers, antihypertensive agents, and anticancer drugs.[305] Thus, synthesis of this heterocyclic nucleus is of great importance, and quite a number of synthetic procedures based on the modifications of the century-old Biginelli's reaction,[306] involving an acid-catalyzed three-component condensation of a 1,3-dicarbonyl compound, aldehyde, and urea, have been developed during the past few years.[305,307] Basically, these methods are all similar, using different Lewis acid catalysts such as BF_3,[307a] $FeCl_3$,[307b] $InCl_3$,[307c] $BiCl_3$,[307d] $LaCl_3$,[307e] $LiClO_4$,[307f] Mn(OAc),[307g] and CAN[307h] in a solvent such as CH_3CN, CH_2Cl_2, or tetrahydrofuran (THF). Recently, a number of procedures under solvent-free conditions using $Yb(OTf)_3$,[307i] montmorillonite,[307j] and ionic liquid[307k] as catalysts have also been reported. Many of these catalysts and solvents are not at all acceptable in the context of green synthesis. In this sense, Yadav et al.[308] developed a synthetic approach to azolopyrimidines **154**−**156** incorporating a thiol function at C-6 under solvent-free conditions and microwave irradiation (Scheme 47). The annulation was successful with an intimate mixture of equimolar amounts of 1,3-oxathiolan-5-one **153** and azole Schiff bases **150**−**152** in a microwave equipment for synthesis for 8−12 min to furnish **154**−**156** in 75−89% yields (Scheme 47, *i*). The reactions were also carried out using a thermostatted oil bath at the same temperature (80 °C) for 12−14 h to ascertain whether the MW method improved the yields or simply increased conversion rates. It was found that significantly lower yields (40−52%, Scheme 47, *ii*) were obtained using oil bath heating as compared to the MW-activated method. The authors rationalized this observation on the basis of the formation of a dipolar transition state (TS) from an uncharged ground state (GS) and the greater stabilization of the more polar TS by dipole−dipole interactions with the electric field of microwaves as compared to the less polar GS, which may reduce the activation energy ($\Delta G^{\ddagger}$), resulting in the rate enhancement. This synthetic approach to obtain azolopyrimidines **154**−**156** using molecular solvents has not yet been described in the literature.

Scheme 47

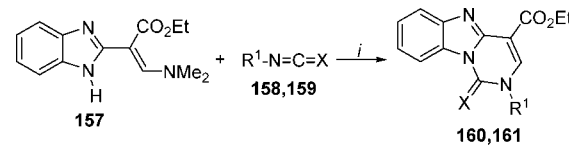


X = O, Y = N (**150, 154**); X = S, Y = N (**151, 155**); X = S, Y = C-Ph (**152, 156**)
R = Ph, 4-Cl-Ph, H; R^1 = Ph, 4-Cl-Ph, 4-MeO-Ph
i: solvent-free, MW, 100 W, 80 °C, 8−12 min (75−89%)
ii: solvent-free, oil bath, 80 °C, 12−14 h (40−52%)

Another synthetic approach to obtain pyrimidinones was demonstrated by Meziane et al.[309] This method involves annulation of isocyanates **158** (or isothiocyanates **159**) with benzoimidazol-2-yl-*N*,*N*-dimethylethenamine **157** under solvent-free conditions (Scheme 48). The reactants **158** or **159** and **157** were used in a molar ratio of 2:1, respectively. The mixture was heated at 48 °C under nitrogen and gave the pyrimido[1,6-*a*]benzimidazol-1-ones **160** and **161** in yields ranging from 52 to 82% after 1 h. This synthetic approach to obtain pyrimidinones **160** and **161** using molecular solvents has not yet been described in the literature.

In a multicomponent method, Ranu et al.[310] discovered that Biginelli's reaction proceeded very efficiently, requiring no solvent and producing 3,4-dihydropyrimidin-2-ones **162**

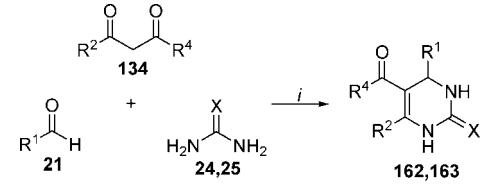
Scheme 48



X = O (**158, 160**); X = S (**159, 161**)
R^1 = Me, Et, EtO_2CCH_2, Ph, 4-Cl-Ph, 4-O_2N-Ph
i: solvent-free, oil bath, 48 °C, 1 h (52−82%)

and **163** in 78−85% yields (Scheme 49). In a typical experimental procedure, a mixture of 1,3-dicarbonyl compound **134**, aldehyde **21**, and urea **24** (or thiourea **25**) in a molar ratio of 1:1:1.5, respectively, was heated at 100−105 °C in neat conditions and was completed in 1 h. A wide variation of alkyl groups in 1,3-dicarbonyl compounds **134**, as well as in aldehydes **21**, are tolerated in this procedure, providing a library of 3,4-dihydropyrimidin-2-ones **162** and **163**. The same reaction was performed using molecular solvents such as ethanol or DMF, under reflux, with trichloroisocyanuric acid as catalyst and required 8−12 h, furnishing the products in 85−95% yields.[307l]

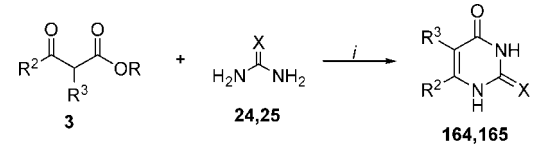
Scheme 49



X = O (**24, 162**); X = S (**25, 163**)
R^1 = Pr, *i*-Pr, hexyl, Ph, 4-O_2N-Ph, 4-Cl-Ph, 4-MeO-Ph, 3-MeO-Ph, PhCH=CH, 4-HO-3-MeO-Ph, naphth-2-yl, benzo[3,4]dioxan-2-yl, pyrid-2-yl, fur-2-yl; R^2 = Me, Et; R^4 = Me, Ph, OEt, OMe
i: solvent-free, oil bath, 100−105 °C, 1 h (78−85%)

Mojtahedi et al.[311] also reported the preparation of pyrimidinones **164** and thiopyrimidinones **165** in solvent-free and microwave-assisted conditions (Scheme 50). The method involved the cyclocondensation reaction between methyl or ethyl β-ketoester **3** and urea **24** (or thiourea **25**) in a domestic microwave oven to furnish **164** and **165** in 53−81% yields. The reactants **3** and **24** or **25** were used in equimolar amounts. The same rection was performed in refluxing ethanol, containing metallic sodium, for 6−7 h, furnishing the products in 4−78% yields.[312]

Scheme 50

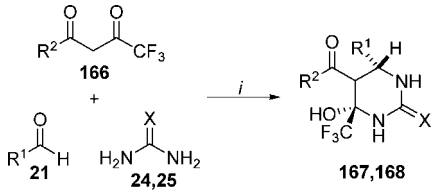


X = O (**24, 164**); X = S (**25, 165**)
R = Me, Et; R^2 = Et, H; R^3 = Me, Ph, CH_2Cl
i: solvent-free, MW, 2−6 min (53−81%)

Recently, Khunt et al.[313] developed a microwave-assisted process for the fast preparation of tetrahydropyrimidines **167** and tetrahydrothiopyrimidines **168** employing equimolar amounts of neat 1,3-dicarbonyl compounds **166**, different aromatic aldehydes **21**, and urea **24** (or thiourea **25**) (Scheme 51). The reaction was carried out in microwave equipment for synthesis, and the products **167** and **168** were obtained in high purity (>90%), in 78−85% yields, and without any side products in every run. This procedure can be compared

with the conventional thermal heating method, which involves the use of THF as solvent, $InCl_3$ as catalyst, during 6−9 h, and furnishes similar products with 75−95% yields.[307c]

Scheme 51

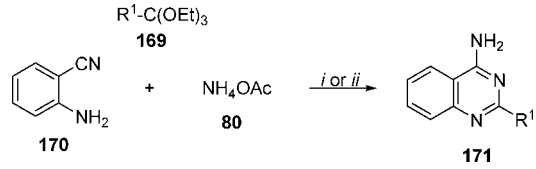


X = O (**24, 167**); X = S (**25, 168**); R^2 = 4-MeO-Ph
R^1 = Ph, 4-MeO-Ph, 2-MeO-Ph, 3,4-$(MeO)_2$Ph, 2,5-$(MeO)_2$Ph, 3-O_2N-Ph, 4-O_2N-Ph, 4-Cl-Ph, 3-HO-Ph
i: solvent-free, MW, 600 W, 110−120 °C, 1.5−6.5 min (78−85%)

8.4. Quinazolines

Quinazoline compounds are well-known for their anticonvulsant,[314,315] antihypertensive,[316,317] anti-inflammatory,[318] and phosphodiesterase inhibitor properties.[319] Interest in the quinazolinic structure[320] has led to a number of different synthetic pathways (e.g., Niementowski's synthesis,[321] Bischler's synthesis,[322] and Riedel's synthesis).[323] Quinazolines can also be synthesized from anthranilic acid[324−326] and benzonitrile.[327] Thus, considering the importance of this class of compounds, Rad-Moghadam and Samavi[328] developed both a microwave-assisted and a conventional thermal heating protocol for the preparation of quinazolines **171** from a mixture of 2-aminobenzonitrile **170**, orthoester **169**, and ammonium acetate **80** under solvent-free conditions (Scheme 52). The authors did not inform the microwave equipment used in the reaction. The reactants **169**, **170**, and **80** were used in a molar ratio of 2:1:1, respectively. The excess of orthoester was necessary to diminish the side reactions. The microwave-assisted synthesis furnished products **171** in 82−89% yields and for 5−7 min (Scheme 52, *i*), and in the conventional thermal heating method it was observed that the yields were slightly superior (83−92%), although it required 30−80 min (Scheme 52, *ii*). The authors also performed the reaction in refluxing ethanol for 180−240 min to furnish the products in 71−81% yields.[328]

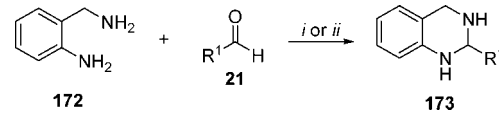
Scheme 52



R^1 = H, Me, Et, Pr, Bu
i: solvent-free, MW, 180 W, 5−7 min (82−89%)
ii: solvent-free, oil bath, 120 °C, 30−80 min (83−92%)

Correa et al.[329] described the synthesis of 1,2,3,4-tetrahydroquinazolines **173** from the reaction of 2-aminobenzylamine **172** and benzaldehydes **21** using two different methods, grinding and oil bath (Scheme 53). In the first method, the reactants **172** and **21** were used in a molar ratio of 1:1.1, respectively, while in the second, equimolar amounts were used. In both methodologies used, the conversion of the reactants into the products was similar (grinding = 71−99%, oil bath = 75−99%); however, the time required in the oil bath method was lower than that in the grinding method. The authors also reported this synthetic route using water as solvent, for which a longer reaction time was necessary when compared with both of the earlier methods.[329]

Scheme 53

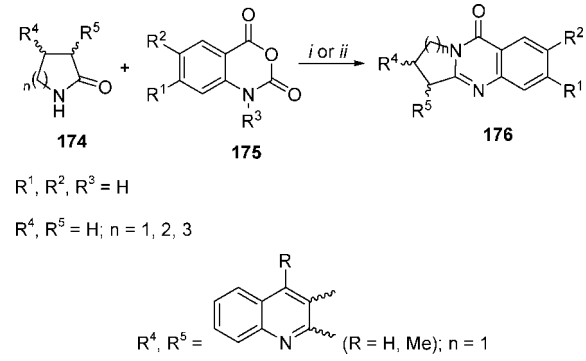


R^1 = Ph, 2-O_2N-Ph, 3-O_2N-Ph, 4-O_2N-Ph, 2-HO-Ph, 4-HO-Ph, 2,3-$(HO)_2$-Ph, 2-HO-3-Br-Ph, 2-HO-3-MeO-Ph, 3,4-$(MeO)_2$-Ph, 4-Br-Ph, 3-Cl-Ph, 2,3-$(Cl)_2$-Ph
i: solvent-free, grinding, 3 min−48 h
ii: solvent-free, oil bath, 50−80 °C, 2 min−4 h

8.5. Quinazolinones

Quinazolin-4-ones have various biological activities, including anticancer,[330] antidiuretic,[331] and anticonvulsant[332] properties. Several methods have been reported for the synthesis of quinazolinones, and common synthetic methods for aryl-substituted quinazolinone compounds include cyclization of *O*-acylaminobenzamides,[333] amidation of 2-aminobenzonitrile followed by oxidative ring closure,[334] solid-phase synthesis of 2-arylamino-substituted quinazolinones,[335] reduction of the azide functionality,[336] preparation from isatoic anhydrides and Schiff bases,[337] and Pd-catalyzed heterocyclization of nitroarenes.[338] Despite numerous synthetic methodologies available in the literature, novel methods for quinazolinone synthesis are still in demand. In this sense, Yadav and Reddy[339] reported a novel microwave-assisted synthesis of *Luotonin A* **176** from the reaction of equimolar amounts of 3-oxo-1*H*-pyrrolo[3,4-*b*]quinoline **174** and isatoic anhydride **175** (Scheme 54). The mixture was irradiated in a domestic microwave oven and furnished the products **176** in a short reaction time (6−7 min) and in 85−87% yields. The authors used other lactams **174** such as 2-pyrrolidinone, δ-valerolactam, and ε-caprolactam that reacted with isatoic anhydride **175** to afford the corresponding **176**. The products were obtained in 89−92% yields and in a short reaction time (6−8 min). The reaction was also carried out under conventional thermal heating at 120 °C (the highest observed temperature during microwave irradiation), which required longer time (5−8 h) and afforded **176** in 60−75% yields. The authors also performed the reaction in CH_2Cl_2 with $BF_3 \cdot OEt_2$ at room temperature during 48 h; the product **176** was obtained in 32% yield.[339]

Scheme 54

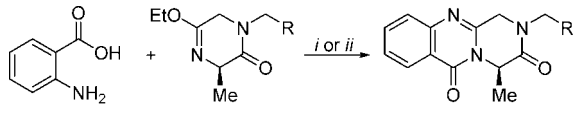


i: solvent-free, MW, 450 W, 6−7 min (85−87%)
ii: solvent-free, MW, 450 W, 6−8 min (89−92%)

Later, Cledera et al.[340] synthesized a series of pyrazino[2,1-*b*]quinazoline-3,6-diones **179** from the cyclocondensation

reaction of iminoethers **178** and anthranilic acid **177** in both conventional thermal heating and microwave-assisted methods (Scheme 55). The reactants **178** and **177** were used in a molar ratio of 1:1.1, respectively. The authors observed that the latter, which was performed in a domestic microwave oven, led to the products in higher yields. In the same study, the reaction of pyrazino[1′,2′:1,5]pyrrolo[2,3-*b*]indol-4-one **180** with anthranilic acid **177** was accomplished in both oil bath heating and microwave irradiation to synthesize the products **181**−**183** (Scheme 56). The reactants **180** and **177** were used in a molar ratio of 1:1.1, respectively. For compounds **181**−**183** (Scheme 56), it was observed that, besides the improved yields and shorter reaction time, the results were much better in terms of stereochemical integrity than those obtained using conventional thermal heating (compound **181** = 23% yield, compound **182** = 8% yield, and compound **183** = 3% yield), since the microwave-assisted method produced only two isomers (compound **181** = 41% yield and compound **182** = 7% yield).[341] This synthetic approach to obtain products **179** and **181**−**183** using molecular solvents has not yet been described in the literature.

Scheme 55



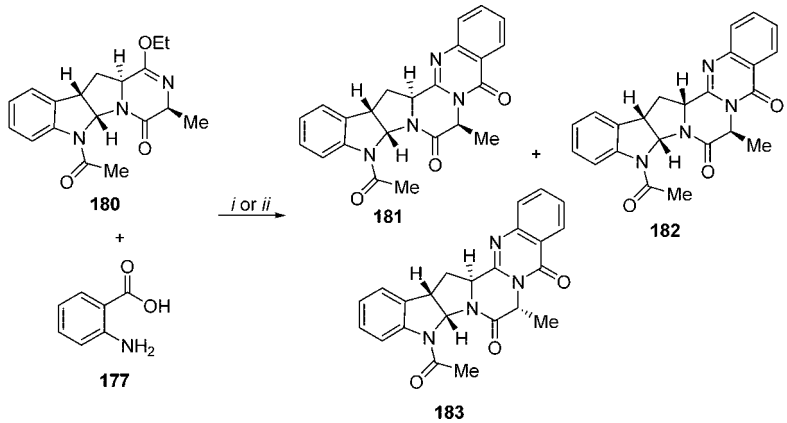
R = H, Bn, 4-MeO-Ph, naphth-2-yl, indol-3-yl
i: solvent-free, oil bath, 120−200 °C, 1−2 h (16−54%)
ii: solvent-free, MW, 600 W, 3−6 min (48−89%)

Cledera et al.,[342] in another publication, also reported the synthesis of pyrazino[2,1-*b*]quinazoline-3,6-dione **185**, under solvent-free conditions, employing iminoethers **184** that contained an attached conjugated and exocyclic double bond (Scheme 57). The reactants **184** and **177** were used in a molar ratio of 1:1.1, respectively. The reaction of these substrates with anthranilic acid **177** was found to be troublesome for conventional thermal heating (Scheme 57, *i*).[343] Conversely, in a domestic microwave oven, compounds **185** were obtained, although in 19−26% yields (Scheme 57, *ii*). This reaction required a longer reaction time when compared with previous results obtained by these authors, due to the lowered reactivity of the iminoether function associated with its conjugation. The same report also presented the use of other iminoethers such as pyrrolo[1,2-*a*][1,4]diazepin-5-one **186** (Scheme 57, *iii*) and pyrazino[1′,2′:1,5]pyrrolo[2,3-*b*]indol-4-one **188** (Scheme 56, *iv*) in cyclocondensation reactions with compound **177**. The reactants **186** and **177** were used in a molar ratio of 1:1.1, respectively, while the reactants **177** and **188** were used in a molar ratio of 3:1, respectively. The authors observed that the products **187** and **183** were obtained in 40−58% yields by the microwave-assisted synthesis. However, this method was better than that reported in the literature, where **187** and **183** were obtained in poor yields or in a product mixture.[344] Finally, they reported the reaction, under microwave irradiation, using 2 equiv of compound **177** with 2,5-dihydropyrazine **189** (Scheme 58), furnishing the product **190** in better yield (89%) when compared with other reports in the literature (54%).[345] This synthetic approach to obtain products **185**, **187**, and **183** using molecular solvents has not yet been described in the literature.

Chichetti et al.[346] investigated a solvent-free and microwave-assisted protocol to prepare quinazoline-2,4-diones **195**−**198** using bis(pentafluorophenyl)imidodicarbonate **191** and substituted anilines **102** or heterocyclic amines **192**−**194** (Scheme 59). The authors also used the amine **199** to obtain cyanoquinazoline-2,4-diones **200** (Scheme 60). In both cases, the authors did not inform the microwave equipment used in the reaction. The reactants **191** and either **102**, **192**−**194**, or **199** were used in a molar ratio of 2:1, respectively, and only one regioisomer was attained. The products were obtained in 44−84% yields. This protocol to prepare quinazoline-2,4-diones **195**−**198** and **200** using molecular solvents has not yet been described in the literature.

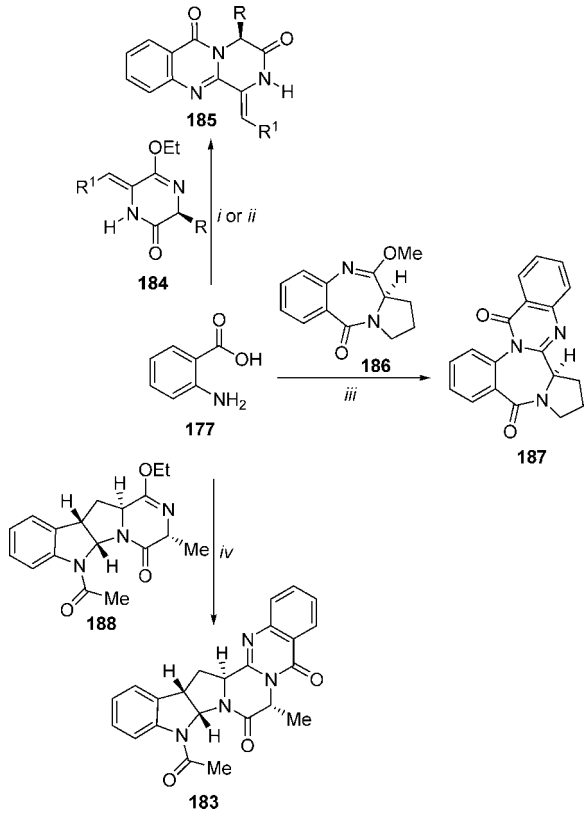
Dandia et al.[347] synthesized a series of disubstituted quinazolin-4-ones **202** from a multicomponent cyclocondensation reaction between equimolar amounts of anthranilic acid **177**, phenyl acetyl chloride **201**, and substituted anilines **2**, under solvent-free conditions and using a domestic microwave oven (Scheme 61). Products **202** were obtained in 87−92% yields and in a short reaction time (4−5 min). The conventional thermal heating protocol for the synthesis of disubstituted quinazolin-4-ones involved two steps.[348] First, the cyclodehydration of 2-benzamidobenzoic acid with acetic anhydride gave benzoxazin-4-one; and subsequently, the reaction of benzoxazin-4-one with amines in refluxing glacial acetic acid and pyridine for 10−12 h furnished the products **202** in moderate yields.[349]

Scheme 56



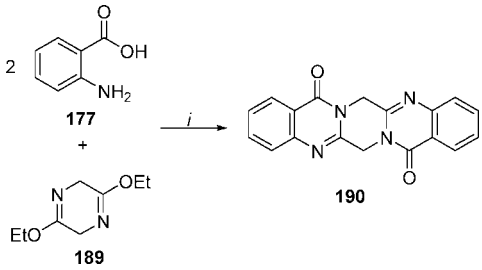
i: solvent-free, oil bath, 140 °C, 6 h
ii: solvent-free, MW, 600 W, 3 min

Scheme 57



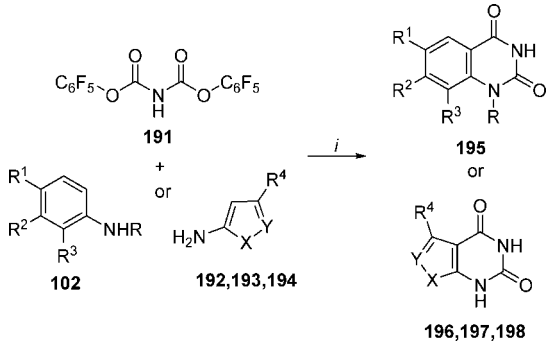
R = Me, *i*-Pr; R^1 = 4-MeO-Ph, 1-tosyl-1*H*-indol-3-yl
i: solvent-free, oil bath, 120 °C, 2 h (R = Me, 15%)
ii: solvent-free, MW, 600 W, 9 min (19−26%)
iii: solvent-free, MW, 600 W, 5 min (40%)
iv: solvent-free, MW, 600 W, 3 min (58%)

Scheme 58



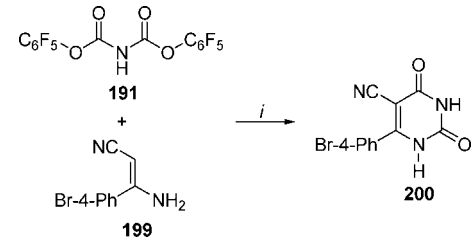
i: solvent-free, MW, 600 W, 6 min (89%)

Scheme 59



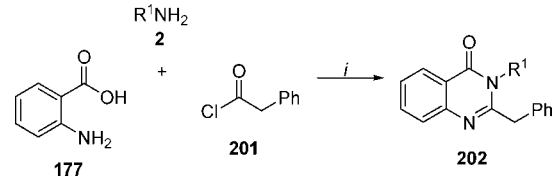
X = O, Y = CCO_2Me (**192, 196**); X = NMe, Y = N (**193, 197**)
X = NPh, Y = N (**194, 198**); R = Me, Ph
R^1 = H, Me; R^2 = OMe, OPr, OPh, SMe
R^3 = H; R^4 = H, Me; R^2, R^3 = $-O(CH_2)_2O-$
i: solvent-free, MW, 250 °C, 20 min (44−78%)

Scheme 60



i: solvent-free, MW, 250 °C, 20 min (84%)

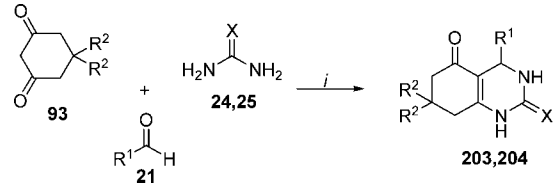
Scheme 61



R^1 = 2-F-Ph, 2-F_3C-Ph, 3-F-Ph, 3-F_3C-Ph, 3-F_3C-4-Cl-Ph
i: solvent-free, MW, 640 W, 150−165 °C, 4−5 min (87−92%)

Kidwai et al.[350] reported a microwave-assisted process for the preparation of quinazolin-5-ones **203** and **204** in a classical Biginelli reaction from equimolar amounts of aldehyde **21**, dimedone **93**, and urea **24** (or thiourea **25**) (Scheme 62). The mixture was irradiated in a domestic microwave oven for 1.8−3.5 min, and the products **203** and **204** were obtained in 85−92% yields. When this reaction was performed in refluxing ethanol, the use of the catalyst nafion-H (100 mol %) was required and the reaction took place after 10 h, leading to compound **203** (R^1 = 4-Cl-Ph) in 72% yield.[351]

Scheme 62



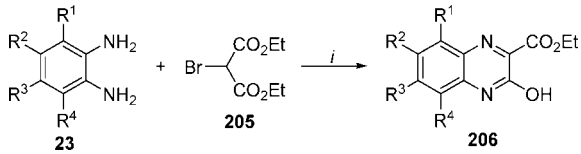
X = O (**24**, **203**); X = S (**25**, **204**)
R^1 = Ph, 4-Cl-Ph, benzo[3,4]dioxan-2-yl, 2-Cl-quinol-3-yl
R^2 = Me
i: solvent-free, MW, 95−105 °C, 1.8−3.5 min (85−92%)

8.6. Quinoxalines

Quinoxalines are an important class of benzoheterocycles[352] that constitute the building blocks of some organic semiconductors[353] and a wide range of pharmacologically active compounds including anticancer[354] and antimicrobial agents.[354,355] 2,3-Disubstituted quinoxalines are usually synthesized by condensation of aryl-1,2-diamines with epoxides[356] or dicarbonyl compounds or their equivalents.[357] Difunctional quinoxalines can also be prepared by cyclization of α-aryliminooximes with α-dicarbonyl compounds[358] and by $POCl_3$-mediated heteroannulation of α-nitroketene *N*,*S*-anilinoacetals.[359] Recently, a report appeared describing an efficient protocol for the synthesis of quinoxalines at room temperature using cupric sulfate pentahydrate as catalyst in water.[360] Nevertheless, there is still a need to develop improved methods for the synthesis of quinoxalines that avoid toxic reactants and solvents and strive toward economic viability and operational simplicity. In this context, Haldar et al.[361] described a one-pot protocol to synthesize a series

of substituted quinoxalines **206** from equimolar amounts of 1,2-phenylenediamine **23** and diethyl bromomalonate **205** under solvent-free conditions (Scheme 63). The mixture of **23** and **205** was kept under vacuum at room temperature, and the reaction was completed after 6−8 h, furnishing **206** in 44−78% yields. This one-pot strategy to synthesize quinoxalines **206** using molecular solvents has not yet been described in the literature.

Scheme 63



R^1 = H, Me; R^2 = H, Cl, PhCO, NO_2, Me; R^3 = H, Cl, Me; R^4 = H, Me
i: solvent-free, r.t., 6−8 h (44−78%)

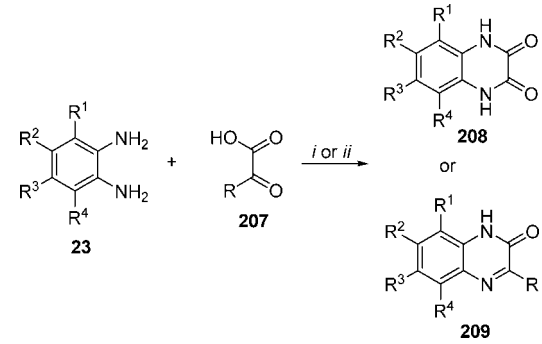
8.7. Quinoxalinediones

Quinoxalinediones have been used extensively in the treatment of epilepsy, Parkinson's disease, schizophrenia, and pain.[362−368] The Hinsberg reaction,[369] although known for over a century, is still the most useful method for the preparation of such type of compounds. By heating 1,2-phenylenediamines with α-ketoacids, quinoxalinones were obtained, though yields were never above 50−65%.[370] Much effort has been made to develop alternative methods for the synthesis of quinoxalinediones. In this context, Thakuria and Das[371] reported simple solid-phase grinding of equimolar amounts of 1,2-phenylenediamine **23** and α-ketoacids **207** at room temperature in open atmosphere to obtain the 1,4-dihydroquinoxaline-2,3-dione **208** or quinoxalin-2-one **209** in 76−98% yields (Scheme 64, *i*). The procedure was performed by grinding with a pestle in a mortar at room temperature until the mixture turned into a melt. A wide range of 1,2-phenylenediamines **23** was screened in order to ascertain the scope of this reaction protocol. The presence of electron-withdrawing groups in diamine starting materials gave lower yields with longer reaction times. Gris et al.[372] also described the synthesis of quinoxalin-2-ones **209** from the condensation reaction of equimolar amounts of 1,2-phenylenediamine or 2,3-diaminenaphthalene **23** with α-ketoacids **207** under solvent-free conditions and microwave irradiation (Scheme 64, *ii*). The mixture was irradiated in a domestic microwave oven for 3−13 min, furnishing the products in 70−91% yields. When the reaction was performed in refluxing HCl 2 M solution, the reaction time was 2.5 h and the similar product yield was 94%.[373]

8.8. Oxazines

Oxazines have attracted special attention as pharmaceutical drug candidates and are amply represented in patent literature.[374] In particular, 1,4-oxazines show promising properties, including antidepressant, anticancer, and anti-inflammatory activities, that explain the constant interest of synthetic chemists.[375] One method to synthesize the oxazine core, called the Mitsunobu reaction, involves a diol cyclization.[376] Novel methods for oxazine synthesis are still in demand. Therefore, Régnier et al.[377] reported the synthesis of 2-aminomorpholines **213** under solvent-free and microwave-assisted conditions from a straightforward four-component reaction between 1,2-aminoalcohols **211**, glyoxal **207**, boronic acids **210**, and aliphatic or aromatic amines **212**

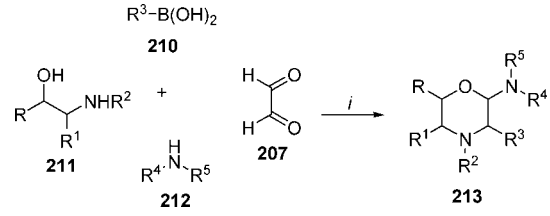
Scheme 64



R = OH (**208**); R = Me, Et, $(CH_2)_2-CO_2H$, CH_2-CO_2H, CH_2-Ph (**209**)
R^1, R^4 = H; R^2 = H, Cl; R^3 = H, NO_2, Cl, Me, Pr, Ph, Cl
R^2, R^3 = −CH=CH−CH=CH−
i: solvent-free, grinding, r.t., 0.5−3 h (76−98%)
ii: solvent-free, MW, 650−750 W, 3−13 min (70−91%)

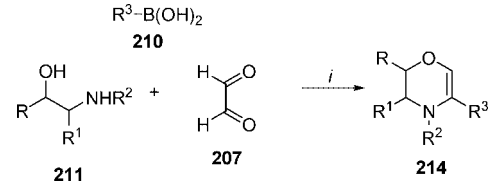
(Scheme 65). The reaction was carried out in microwave equipment for synthesis, and the reactants **207**, **210**, **211**, and **212** were used in a molar ratio of 1:1:1:1.5, respectively. The neat reactants were submitted to microwave irradiation during 15 min at 110 °C, and the products **213** were obtained with higher purity and in 43−77% yields. The reactions were also conducted under solvent conditions in refluxing toluene. If the expected products were effectively present, this method was unsatisfactory in terms of yields and purity. The authors reported that *N*-alkylaminoethanol associated with aryl boronic acids gave the best results with a decrease in yield in the case of a primary aliphatic or aromatic amines compared to a secondary one. A similar observation was made with styrylboronic acid, while the presence of substituents was better tolerated in position 2 on the aminoalcohol than in position 1.[377] The authors also performed the same reaction with similar conditions using equimolar amounts of 1,2-aminoalcohols **211**, glyoxal **207**, and boronic acids **210**, in the absence of amine (Scheme 66). The dehydrated products **214** were obtained in 84% yield. When this reaction was performed in ethanol, at room temperature, for 12 h, similar products were obtained in 86% yield.[378]

Scheme 65



R = H, Me; R^1 = H, Ph; R^2 = Me, Bn
R^3 = Ph, 4-MeO-Ph, CH=CH-Ph; R^3, R^4 = $-(CH_2)_5-$
R^4 = Me, Et, pentyl, Ph, 4-Br-Ph, 2-furanemethyl
R^5 = H, Ph, Bn
i: solvent-free, MW, 110 °C, 15 min (43−77%)

Scheme 66

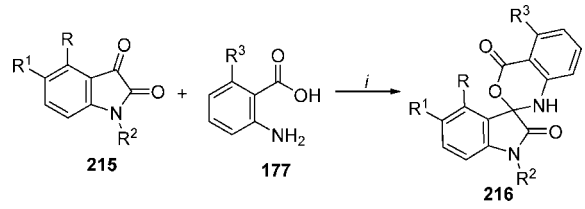


R = H; R^1 = H; R^2 = Me; R^3 = Ph
i: solvent-free, MW, 100 °C, 30 min (85%)

8.9. Oxazinones

The heterocyclic ring systems 1,3-oxazin-2-ones are present in many biologically important natural products, and they have been used as key intermediates in the synthesis of aminoalcohols and as chiral auxiliaries.[379,380] The preparation of *trans*-5-hydroxy-1,3-oxazin-2-ones and *cis*- and *trans*-5-hydroxymethyl-1,3-oxazolidin-2-ones from (2,3-*anti*)-3-amino-1,2-diols was also reported.[381] Saxena et al.[382] published the synthesis of the 1,3-oxazin-2-ones **216** through reaction of equimolar amounts of indole-2,3-diones **215** with anthranilic acid **177** using microwave irradiation under solvent-free conditions (Scheme 67). The mixture was irradiated in a domestic microwave oven for 2−6 min, furnishing the products in 92−98% yields. The reaction of **215** with **177** under varied conditions failed to give the desired spiro compounds **216**. The presence of C-6 methyl was considered crucial for the reaction to take place. To confirm this hypothesis, the reaction was carried out with different anthranilic acids **177**, in order to study the effect of alkyl groups with different chain lengths and unsaturation sites at the C-6 position in anthranilic acid. The authors reported the traditional method for preparing product **216** using EtOH for 2−4 h at room temperature, which yielded 91−97%.[382]

Scheme 67

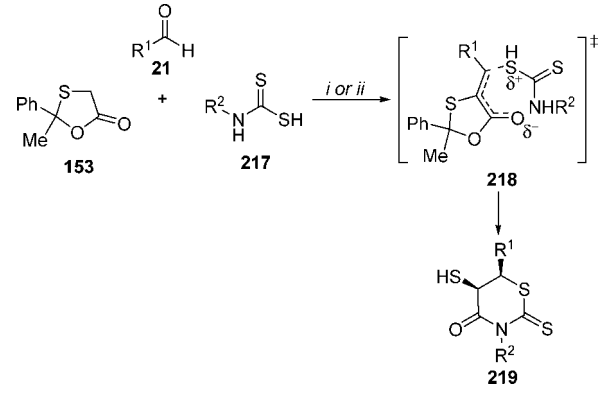


R = H, Cl; R^1 = H, Me, Br, F; R^2 = H, Me
R^3 = Me, decyl, octadecanyl, dec-3-ynyl, octadec-9-enyl
i: solvent-free, MW, 200 W, 2−6 min (92−98%)

8.10. Thiazines

The 1,3-thiazine nucleus is the active core of cephalosporins, which are among the most widely used β-lactam antibiotics. Because of their chemical and biological interest, syntheses of various 1,3-thiazines have been reported in the literature,[383−390] but 1,3-thiazines incorporating a thiol function were hitherto unreported and were not accessible through any of the known synthetic routes for 1,3-thiazines.[383−390] In order to investigate new methods, Yadav et al.[391] reported the synthesis of 1,3-thiazines **219** from the reaction of equimolar amounts of 1,3-oxathiolan-5-one **153**, aromatic aldehydes **21**, and an *N*-aryl dithiocarbamic acid **217** under microwave irradiation and solvent-free conditions (Scheme 68, *i*). Although the authors did not inform the microwave equipment used in the reaction, they reported that the mixture was irradiated for 8−10 min, affording the 1,3-thiazines **219** in 76−90% yields with >96% diastereoselectivity. The reactions were also carried out using a thermostatted oil bath at the same temperature (85 °C) for 3−5 h, which led to the respective 1,3-thiazines **219** in 40−54% yields (Scheme 68, *ii*). The authors reported that significantly lower yields (42−54%) were obtained using conventional thermal heating, on average 20% lower than the MW-activated method. A diastereomeric ratio of 96:4 was found for the reactions performed with MW activation, while that of 55:45 was found for conventional thermal heating. The authors suggested that the high diastereoselectivity in favor of *cis* isomers was due to reaction paths occurring by the more polar transition states **218** (TS).[392] This one-pot strategy to synthesize 1,3-thiazines **219** using molecular solvents has not yet been described in the literature.

Scheme 68



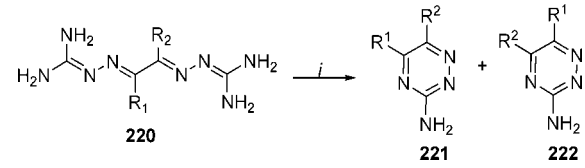
R^1 = Ph, 4-Cl-Ph, 4-MeO-Ph; R^2 = Ph, 2-Me-Ph, 4-MeO-Ph
i: solvent-free, MW, 480 W, <85 °C, 8−10 min (76−90%)
ii: solvent-free, oil bath, 85 °C, 3−5 h (42−54%)

9. Six-Membered Heterocycles with Three Heteroatoms

9.1. Triazines

Triazines are compounds endowed with selective anticonvulsant, antibacterial,[393] and antimalarial activity.[394] The main route employed for the synthesis of 1,2,4-triazines involves the reaction of an acylnitrile with aminoguanidine bicarbonate in the presence of nitric acid and DMSO. However, Matikainen and Elo[395] reported the synthesis of 3-amino-1,2,4-triazines **221** and **222** from the heating of bis(amidinohydrazone) **220** under solvent-free conditions under *vacuum* (Scheme 69). The reactions were accomplished in oil bath using a sealed ampule that was heated at 210 °C for 1−3 h. The products were easily isolated, being sublimed off from the starting material and forming single crystals. When unsymmetrical bis(amidinohydrazones) were used, two isomeric products were obtained; however, the authors did not inform the molar ratio. This method to synthesize 3-amino-1,2,4-triazines **221** and **222** using molecular solvents has not yet been described in the literature.

Scheme 69



R^1 = H, Me, Et; R^2 = H, Me
i: solvent-free, oil bath, 210 °C, 1−3 h

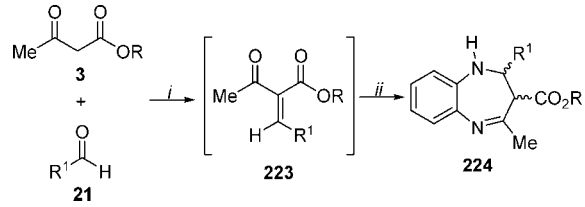
10. Seven-Membered Heterocycles with Two Heteroatoms

10.1. Benzodiazepines

Benzodiazepines are an important class of bioactive molecules and are widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressant, anti-inflammatory, and hypnotic agents.[396,397] Methods reported in the literature for the synthesis of 1,5-benzodiazepines include condensation

reactions of 1,2-phenylenediamine with α,β-unsaturated carbonyl compounds,[398] β-haloketones,[399] or ketones in the presence of $BF_3 \cdot OEt_2$,[400] $NaBH_4$,[401] polyphosphoric acid, or SiO_2,[402] MgO/PCl_3,[397a] Yb(OTf)$_3$.[397b] Another method involves the reductive cyclization of nitro and azido proline esters.[403] Considering the importance of this class of compounds, Kidwai and Mothsra[404] described a two-step synthesis of 1,5-benzodiazepines **224** using a microwave-assisted protocol under solvent-free conditions. Initially, a mixture of equimolar amounts of ethyl acetoacetate **3** and aromatic aldehydes **21** was irradiated in a domestic microwave oven to furnish the adduct **223** (Scheme 70). Then, 1,2-phenylenediamine **23** was added and the mixture was irradiated again to yield the 1,5-benzodiazepines **224** in 86−97% yields. The same reaction carried out by heating in ethanol gave only trace amounts of the product even after 4−5 h of heating.[404]

Scheme 70



R = Et; R^1 = Ph, 4-Cl-Ph, 4-MeO-Ph, 4-HO-Ph, fur-2-yl, indo-3-yl, benzo[3,4]dioxan-2-yl

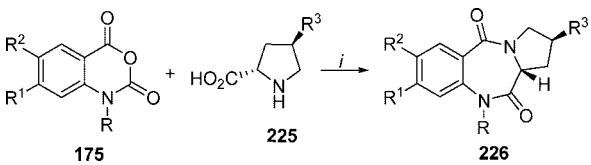
i: solvent-free, MW, 130−150 °C

ii: solvent-free, 1,2-phenylediamine (**23**), MW, 130−150 °C, 2−3.5 min (86−97%)

10.2. Benzodiazepinediones

Benzodiazepinediones are antithrombotics, antitumor and ethanol intoxication antagonists, and antibiotic agents with potential application as enzyme inhibitors and herbicides.[405−411] The synthetic pathways to these compounds are varied and have involved polymer-supported amino acids cyclization with 2-nitrobenzoic acids or protected anthranilic acids,[412] cyclization of certain dipeptides derived from Boc anthranilic acid and α-amino acid methyl esters or by reaction of *N*-carboxy-α-amino acid anhydrides with Boc anthranilic acid,[413] and liquid-phase combinatorial synthesis.[406] Another route is directly converted isatoic anhydride to 1,4-benzodiazepine-2,5-diones through cyclocondensation with amino acids at room temperature or by fusion of their uncyclized intermediates at high temperature.[414] In this sense, Kamal et al.[415] presented a microwave-assisted process under solvent-free conditions to obtain pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones **226** (Scheme 71). Equimolar amounts of isatoic anhydride **175** and L-proline **225** were irradiated for 2−3 min with 1 min intervals, furnishing the products **226** in 80−92% yields. The authors did not inform the microwave equipment used in the reaction. The traditional method for preparing benzodiazepinediones is to reflux DMSO or DMF for 5 h, which affords similar yields.[416]

Scheme 71



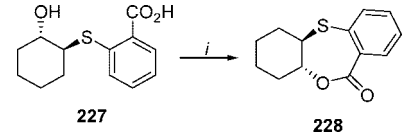
R = H, Me; R^1 = H, OH; R^2 = H, Me, OH, OMe; R^3 = H, OH

i: solvent-free, MW, 2−3 min (80−92%)

10.3. Oxathiepinones

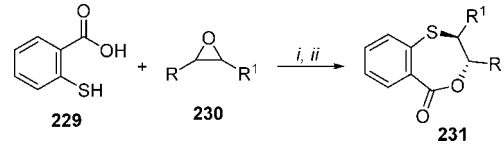
Oxathiepinones, related isosterically to thiazepinones, are a very interesting class of compounds with a wide spectrum of biological activity.[417] There is no efficient synthetic method for their preparation. One of the few synthetic methods available is via thiolysis of styrene oxide by thiosalicylic acid.[418] Taking this into account, Fringuelli et al.[419] studied methodologies to synthesize 1,4-benzoxathiepin-5-ones **228** from the lactonization of β-hydroxy arylsulfides **227**, which were obtained from thiolysis of 1,2-epoxides. In these studies, the authors evaluated the lactonization process under various reaction conditions: (i) under solvent-free conditions; (ii) in the presence of a reaction medium; and (iii) in the presence and absence of a Brønsted acid catalyst. The transformation required 24 h in refluxing water under acidic conditions to furnish the product in 70% yield.[420] The use of Ti(IV) and Hf(IV) chlorides as catalysts (in stoichiometric or catalytic amounts) in the presence of dichloromethane 50 °C was not effective, resulting in the formation of a 4:1 mixture of *cis*- and *trans*-β-chloro sulfides. The best result was obtained under solvent-free conditions without using any Lewis acid catalyst or dehydrating agent. The lactonization of an example of β-hydroxy arylsulfides **227**, induced by simply heating at 200 °C in an open vial to facilitate the elimination of water, resulted in 95% yield of product **228** (Scheme 72). Only 30% conversion was reached when the temperature was lowered to 50 °C and when the reaction was carried out in the presence of molecular sieves and In(OTf)$_3$ at 50 °C. In any cases, the cyclization temperature used under solvent-free conditions is quite low considering that a temperature of 150 °C is usually required after anhydride activation of the carboxylic functionality and in many other esterification protocols. The authors also performed a one-pot protocol involving equimolar amounts of 1,2-epoxides **230** and thiosalicylic acid **229**, which were initially heated at 30−65 °C for 2−8 h in a closed vial, and then heating was continued at 100−200 °C for 1−8 h in the open vial, affording the 1,4-benzoxathiepin-5-ones **231** with high diasteroselectivity and in 43−90% yields (Scheme 73).

Scheme 72



i: solvent-free, oil bath, 200 °C, 1 h (95%)

Scheme 73



R = H; R^1 = Hexyl, $CH_2OCH_2CH{=}CH_2$, Ph, CH_2OPh, benzo[3,4]dioxan-2-yl; R, R^1 = $-(CH_2)_3-$, $-(CH_2)_4-$

i: solvent-free, oil bath, closed vial, 30−65 °C, 2−8 h

ii: solvent-free, oil bath, open vial, 100−200 °C, 1−8 h (43−90%)

11. Environmental Aspects

In the chemical sciences, there is a need to develop benign synthetic pathways that, in addition to being high yielding (historically the most important measure of the success of a

reaction), are safe, environmentally acceptable, and simple, exhibiting high atom efficiency and hence a reduced number of steps and no waste.[4] Removing organic solvents in chemical synthesis is important in the drive toward benign chemical technologies. Organic solvents are high on the list of toxic or otherwise damaging compounds because of the large volumes used in the industry and difficulties in containing volatile compounds. The number of protocols for the solvent-free synthesis of a wide range of organic compounds and the number of reports of rapid, selective, and efficient transformations, with a high degree of conversion of reactants to products, grow daily.[3,4] Such protocols bear further investigation as they may offer distinct advantages such as improved atom utilization[5] by avoidance of common derivation procedures;[7] decreased byproduct formation and, hence, decreased waste resulting from purification procedures required to separate the desired product from the impurities; and, in many cases, reduced energy utilization both in the reaction and purification stages as well as opportunities for process intensification. This indicates that solvent-free reaction conditions may provide a tool for addressing waste-reduction and energy efficiency. Sustainability is an increasingly important issue in the wider context of population, health, the environment, energy, technology, and renewable resources, and, in chemical sciences, as an integral part of the rapidly emerging field called *green chemistry*.[3,4]

11.1. Reaction Metrics for Green Chemistry

Nowadays, it is widely accepted that no solvent is a priori green; rather, its greenness strongly depends on the specific application, its toxicological properties, and the environmental impact resulting not only from the production process but also from its whole life cycle.

In order to evaluate the environmental impact of a synthetic organic process, a set of metrics that would enable an assessment of the initial developmental process and allow environmental improvements to be monitored during its developmental stages has been proposed by co-workers in the green chemistry area.[8,421] These measures increase the awareness of green chemistry, emphasize key issues, and provide information to assist chemists to choose between alternative routes. The measures are a mixture of qualitative and quantitative assessments of inputs and outputs for a particular process.[8,421] Although the majority is designed specifically for use within pharmaceutical and chemical industries, these measures should find wider relevance within the academy. The main parameters are briefly discussed as follows:

(i) *Atom economy*:[421a,b] This parameter is the ratio of the molecular weight of the target molecule to the sum total of the molecular weights of all the substances produced in the stoichiometric equation for the reaction involved. It allows for the amount of the reactants incorporated into the end product. Cycloadditions are examples of transformations with 100% atom economy. For other reactions (e.g., substitution reaction), a 100% economy can never be reached due to the nature of the reaction. The main use of this parameter is to adapt reaction sequences such that transformations with low atom economy are limited to a minimum.

(ii) *Environmental factor (E-factor)*:[8,421c−f] The E-factor is designated as weight of waste generated *per* weight of product. Waste is defined as everything produced in the process except the desired product. It takes the chemical yield into account and includes reactants, solvent losses, all process aids and, theoretically, even fuel (although this is often difficult to quantify).

(iii) *Environmental quotient (EQ)*:[421g,h] The value of the E-factor is limited as it does not take into account the nature and environmental impact of the waste generated. In order to arrive at a more meaningful prediction, the E-factor is multiplied by an environmentally hazardous quotient Q. For example, a Q value of 1 can be attributed to NaCl, while heavy metals can be assigned a value between 100−1000 based on their toxicity.

(iv) *Effective mass yield*:[421i] This parameter is defined as the percentage of the mass of the desired product relative to the mass of all nonbenign materials used in the synthesis. It introduces the important issue of (eco)toxicity.

(v) *Mass intensity (MI)*:[421j] Mass intensity is defined as the ratio of the total mass used in a process (step) and the mass of the end product. It takes into account the yield, stoichiometry, solvent, and the reactants used in synthesis. The total mass also includes chemicals (except water) used in workup procedures such as washes with acid, base, salt solution, or organic solvent, as well as extractions and/or crystallizations. Also, a few unified metrics have been developed that combine some of the above-mentioned individual parameters with relevant factors for specific purposes.

(vi) *Process profile*:[421k] Intended primarily as a management tool for economic evaluation, it takes into account all important factors involved in large-scale production. These include process parameters, raw material cost, yield, throughput time, throughput volume, number of steps in synthetic sequence, special equipment requirements, reproducibility, tolerance to abuse, linearity of sequence, environmental abuse potential, potential occupational health and safety hazards, raw material availability, susceptibility to regulatory changes, and patent protection.

(vii) *Life cycle analysis (LCA)*:[421l,m] In this methodology, all stages of the life cycle of a chemical as well as environmental impacts of byproduct and auxiliaries (solvents, coreactants, and technical facilities) are considered. It consists of three domains: the analysis of the starting material, the analysis of the impact, and the analysis of the improvements. It can be used to evaluate existing processes and/or design new processes.

(viii) *EcoScale*:[421n] This is a semiquantitative tool to select an organic procedure based on economical and ecological parameters. Six general parameters that influence the quality of reaction conditions are analyzed (yield, price of reaction components, safety, technical setup, temperature/time, and workup). Within each of these parameters, individual penalty points of various relative weights are assigned that take into account all possible situations when setting up an organic chemistry experiment. The penalty points are cumulative for all components of the preparation. In order to simplify the EcoScale design, the usual differentiation between solvents (usually present in >10 equiv), reactants, auxiliary or coreactants, and catalysts (usually present in <0.1 equiv) is not made. An ideal reaction has the EcoScale value of 100. The EcoScale score for a particular preparation of the product in a high-purity state (>98%) is calculated by subtracting any applicable penalty points from the maximum value of 100.

More recently, Reinhardt et al.[421o] developed a set of measures to evaluate the greenness of a product or process; the method includes three main criteria: the energy factor

(EF), the environmental and human health factor (EHF), and the cost factor (CF), which characterizes the energy demand, toxicity and cost of chemicals, auxiliaries, and energies and equipment used during the life cycle stages of a product or process.

The above analyses often show that the cost of waste, including effluent treatment, waste disposal, loss of raw materials, etc., can amount to up to 40% of the overall production costs.[421j] This has led to several governmental (e.g., Green Chemistry Program of the U.S. Environmental Protection Agency[422]) and corporate initiatives to develop their own set of qualitative and semiquantitative green parameters. For example, GlaxoSmithKline has published a set of metrics including carbon efficiency (CE) and reaction mass efficiency (RME), which enables the assessment of batch processes in terms of waste, energy usage, and chemistry efficiency.[423] These metrics are based on the number of chemistry steps, number of purification steps, number of isolated intermediates, total yield, nature of solvents, use of extreme conditions, and use of reactants with known environmental, safety, or health problems, among others. Another new reaction metric, the stoichiometric factor (SF), assesses reactions run under nonstoichiometric conditions. This metric proposes a general algorithm for reaction mass efficiency based on four competing factors (reaction yield, atom economy, stoichiometric factor, and the reaction and postreaction solvent and/or catalyst recovery).[424a] This approach was followed by the introduction of minimum atom economy (AE) and maximum environmental impact factor (E-factor), which have been applied to over 400 named reactions.[424b] The search and implementation of appropriate metrics for assessing the quality of a chemical process clearly can be complex, time-consuming, problematic (unclear definitions), or restricted to only one topic (waste, safety, etc.). In particular, the lack of transparency of the life cycle analysis, the lack of objectivity in assigning the Q value for a reactant, or the unclear definition of "nonbenign" for the calculation of effective mass yield can be noted.

11.2. E-Factor

The E-factor will be discussed in detail in this review due to our novel proposal to evaluate it on a laboratory scale. Recently, the Green Chemistry Institute Pharmaceutical Round Table used the Process Mass Intensity (P) MI, which is the same as Mass Intensity, to benchmark the environmental acceptability of processes used by its members (see the Green Chemistry Institute Web site).[421j] This Institute joins several leading pharmaceutical companies (Eli Lilly, GlaxoSmithKline, Pfizer, Merck, AstraZeneca, Schering-Plough, and Johnson & Johnson). The aim was to use this data to drive the greening of the pharmaceutical industry. This alternative metric offers an advantage over the E-factor as it gives a mental picture of how wasteful a process is.[425] The ideal (P) MI is 1, whereas the ideal E-factor is 0, which more clearly reflects the ultimate goal of zero waste (eqs 1−5). The E-factor is the actual amount of waste produced in the process, defined as everything besides the desired product.[425] There is one exception: water is generally excluded from the calculation of the E-factor. For example, when considering an aqueous waste stream, only the inorganic salts and organic compounds contained in the water are counted, while the water itself is excluded. Note that this method of calculation will automatically exclude water used in the process but not water formed. Inclusion of water

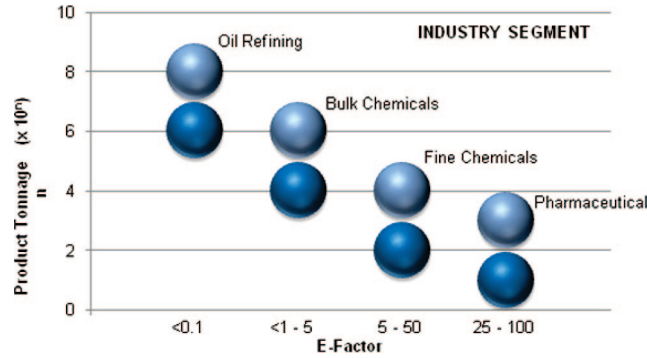


Figure 5. E-factor by industry segment.

used in the process (as solvent and in workup) can lead to an exceptionally high E-factor.[426] A higher E-factor means more waste and, consequently, greater negative environmental impact. In theory, the E-factor is derived directly from atom efficiency. For example, an atom efficiency of 40% corresponds to an E-factor of 1.5. In practice, the E-factor can be much higher as the yield is not always 100%, an excess of reactant(s) is often used, and solvent losses and salt generation in subsequent neutralization steps have to be taken into account.[425]

The calculation and definition of the E-factor is simple: quantity of input (raw materials), minus quantity of desired product, divided by weight of product output. It can be easily calculated from the quantity of tons of raw material purchased and tons of product sold, for a particular product or a production site or even a whole company, as shown in eqs 1−5.

$$\text{Reactants} \rightarrow \text{Product} + \text{Waste} \tag{1}$$

$$\text{E-factor} = \frac{m_{\text{waste}}}{m_{\text{products}}} \tag{2}$$

$$\text{E-factor} = \frac{m_{\text{reactants}} - m_{\text{products}}}{m_{\text{products}}} \tag{3}$$

$$\text{Mass Intensity} = \frac{m_{\text{reactants}}}{m_{\text{products}}} \tag{4}$$

$$\text{E-factor} = \text{Mass Intensity} - 1 \tag{5}$$

It is interesting to note that, based on literature data,[425] the waste problem in chemical manufacturing is enormous, and it may be concluded that the larger the scale of the particular chemical industry (with respect to volume of production), the smaller is the amount of waste generated *per* weight of product. Thus, the E-factor regularly decreases as the yearly production volume of the given chemical industry increases, in the order: pharmaceutical industry, low-tonnage chemical industry, basic chemical synthesis industry, petrochemical industry (Figure 5). In fact, the production of pharmaceuticals, which demands a greater degree of advanced technologies, nevertheless generates the largest amount of wastes *per* production unit. This is especially due to the need for multiple-step processes for synthesis and purification with significant volumes of solvents, which then generally cannot be reused due to the high demands made on the purity of the end product.

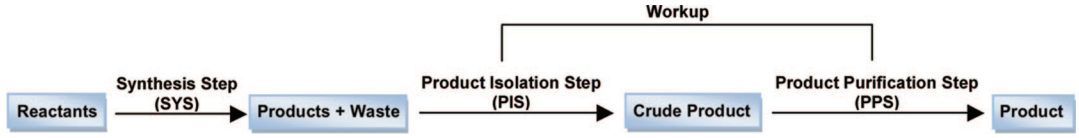


Figure 6. Synthetic procedure steps to obtain product.

11.3. Workup of Solvent-free Reactions

For the preparation of an organic product to be considered acceptable, it must both be relatively efficient and offer easy workup and purification steps. Although many reactions performed in solvent-free conditions do not require the extraction of the product, they do require extensive purification, especially in catalyzed reactions. One topic that is often neglected in the context of solvent-free synthesis is the effort necessary to remove the reactants or products during the workup procedure, generally consuming a large amount of organic solvent and energy, respectively. The solvent extraction volume can exceed the volume of water by factors of up to 30.[425] Despite the importance of the reaction workup in the environmental impact of an organic process, few papers present information about the exact amount of solvents used in this step. This deficiency in the literature prevents the complete application of the set of metrics that evaluate the actual environmental impact of any given synthetic organic process.

11.4. Cyclocondensation Reactions under Solvent-free Conditions

As discussed above, solvents play a large role in the waste generated from synthetic processes, leading to negative environmental impacts. In order to evaluate this impact, a set of metrics has been proposed. These green metrics furnish information to assist chemists in order to choose between alternative routes and obtain cleaner and more sustainable processes. Quantitative and qualitative assessments of input and output for a particular process have been defined by Sheldon et al.[8,421c−e,427] with the introduction of the E-factor and the environmental quotient. As already discussed in this review, the E-factor is designated as the weight of waste generated *per* weight of product, whereas waste is defined as everything produced in the process except the desired product (eqs 1−5).

In this review, the E-factor was applied to evaluate the magnitude of waste generated in cyclocondensation reactions at a laboratorial scale. This environmental metric was calculated for the solvent-free reactions reported in this review and, when possible, for the same reactions accomplished in the presence of molecular solvents, allowing for a comparison of the solvents' effect on the magnitude of waste generated in cyclocondensation reactions. In order to calculate the E-factor, it was necessary to consider all the data involved in each synthetic procedure, such as amount of reactants and volume of solvents used in the synthesis or in the workup. This information may be obtained (i) only for the synthesis step (SYS); (ii) for the synthesis and product isolation steps (SYS + PIS); (iii) for the synthesis and product purification steps (SYS + PPS); (iv) or for the synthesis and workup steps (SYS + PIS + PPS) (Figure 6).

After analyzing the papers considered in this review, it was observed that most procedures entailed a workup step. The papers were divided in accordance with the type of synthetic procedure and are classified as SYS; SYS + PIS; SYS + PIS + PPS; or SYS + PPS. This distribution is illustrated in Figure 7. Only 3% of the protocols required no workup step and allowed the attainment of products through the synthesis step alone (SYS). On the other hand, 10% of the synthetic procedures involved the synthesis and isolation of compounds (SYS + PIS) without requiring any method of purification. The use of synthesis, isolation, and purification steps (SYS + PIS + PPS) was employed in 39% of the procedures reported in this review. Finally, 48% of the procedures required no isolation step and compounds were purified directly after the synthesis step (SYS + PPS).

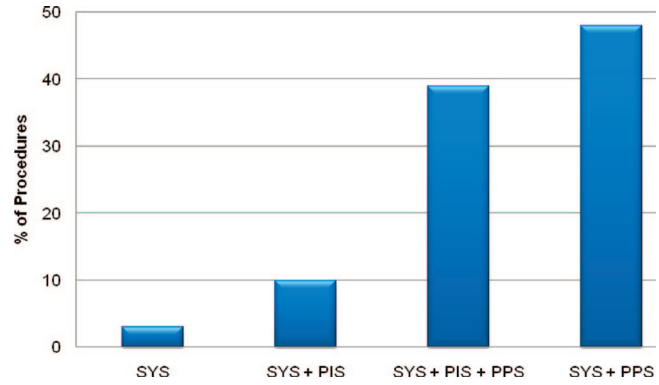


Figure 7. Percentage of procedures using different synthetic steps for cyclocondensation reactions.

Although the majority of procedures used some workup step, it is important to note that a great many of the synthetic procedures did not inform the amount of solvent used in their protocols. Only 33% of the solvent-free methodologies informed the volume of solvent used for the isolation of compounds (SYS + PIS). Moreover, none of the reported methodologies informed the volume of solvent loss in the purification of products (SYS + PIS + PPS or SYS + PPS).

In the calculation of E-factors for this review, when the solvent volume used in the isolation of compounds was mentioned, the E-factor encompassed the isolation step (SYS + PIS). However, when the solvent volume used in the workup (PIS or PPS) was not reported, the E-factor was considered only for the synthesis step (SYS).

Table 3 compares the *Procedure E-factors* from protocols carried out under solvent-free conditions and using molecular solvents for the same reaction and the same product. Table 4 shows the *Procedure E-factors* for all procedures described in this review. The E-factor calculation was performed by using eq 3 defined by Sheldon[425] with adaptations in accordance with the data available. The E-factor was performed for each individual compound, and the *Procedure E-factor* was obtained as an average value for a series of individual E-factors. Thus, in order to minimize *Procedure E-factor* variations, it was necessary to make some statistical delimitations: (i) for the reaction step alone (SYS) and/or both the reaction and isolation steps (SYS + PIS) in the presence of solvents, the E-factor calculations were obtained considering a standard deviation lower than 5% of the mean individual E-factors; (ii) for the synthesis step (SYS) under solvent-free conditions, a standard deviation lower than 25%

Table 3. *Procedure E-factors*[a] in Solvent-free and Solvent Conditions Reported in This Review

sch./prod.	solvent-free conditions			solvent conditions		
	N^b	E-factor	refs	N^b	E-factor	refs
6/**15**	5	(SYS) 0.32 ± 0.04	70	5	(SYS) 52.28 ± 1.52	70
	8	(SYS + PIS) 114.77 ± 4.53		5	(SYS + PIS) 188.85 ± 5.44	
8/**18**	6	(SYS) 0.49 ± 0.09[c]	77c	2	(SYS) 15.96 ± 0.93	74c
				2	(SYS + PIS) 109.96 ± 5.04	
8/**18**	7	(SYS) 0.80 ± 0.12	78	1	(SYS) 40.20	74c
				1	(SYS + PIS) 276.85	
10/**27**	1	(SYS) 0.36	95	1	(SYS) 4.09	96
18/**53**	7	(SYS) 0.22 ± 0.04	146	2	(SYS) 9.22 ± 0.28	147
23/**71**	7	(SYS) 0.19 ± 0.04	180	5	(SYS) 74.78 ± 1.15	180
46/**148**	13	(SYS) 0.74 ± 0.10	303	7	(SYS) 2.91 ± 0.11	303
49/**162**, **163**	26	(SYS) 0.37 ± 0.06[c]	310	4	(SYS) 8.17 ± 0.33[c]	3071
52/**171**	5	(SYS) 3.69 ± 0.30[d]	328	5	(SYS) 13.77 ± 1.90	328
	5	(SYS + PIS) 4.48 ± 0.33[e]				
62/**203**, **204**	8	(SYS) 0.25 ± 0.02	350	1	(SYS) 9.79[c]	351
67/**206**	7	(SYS) 0.14 ± 0.02	382	6	(SYS) 8.12 ± 0.34	382

[a] *Procedure E-factors* ± standard deviation (eq 5) are an average value of the individual *Procedure E-factor* obtained from the data of one compound. [b] Number of procedures used for *Procedure E-factor* calculations. [c] Procedures which carried out isolation with water. [d] Procedures carried out by microwave irradiation. [e] Procedures carried out by conventional thermal heating.

of the mean individual E-factors was considered. Therefore, some compounds that presented values outside of these parameters were excluded from the E-factor calculations.

In general, in protocols using water as solvent, the amount of water was excluded from the E-factor calculations, while the amount of water formed in the reaction was normally computed.[426] In order to evaluate the impact of excluding the mass of water formed in solvent-free cyclocondensations reactions on the *Procedure E-factor*, the E-factor was calculated both considering the mass of water formed as part of the waste generated and also excluding this mass. The data obtained showed that the exclusion of the mass of water from E-factors for cyclocondensation reactions that led to the formation of water in the reaction medium brought about a reduction in the range of 0.01−1 units in *Procedure E-factors*. It can thus be concluded that, while the calculation of water formed during the reaction did not significantly alter the E-factor values in protocols using molecular solvent (<1%), under solvent-free conditions the E-factor values were changed by up to 24%. In Table 3 and in the following discussions, the mass of water formed in the reaction was computed in the *Procedure E-factor* values. Table 4 shows the *Procedure E-factors* for all reactions described in this review. In all cases, the mass of water formed in the reaction was also computed in the E-factor values.

The data presented in Table 3 were used in the elaboration of Figure 8, which shows the percentage of E-factors falling in the ranges of <0.1, 0.1−0.9, 1.0−4.9, 5.0−49.9, 50.0−100.0, and >100.0. These ranges were based on the data presented in Figure 5.[425] It is noteworthy that the data utilized in Figure 8 were obtained from procedures carried out under solvent-free conditions with the correspondent process accomplished in solvent condition and considering only the synthesis step (SYS).

From the data presented in Figure 8, it can be concluded that all E-factors from solvent-free conditions showed values in the range of 0.1−4.9, which is very close to values of waste found in the bulk chemical industry segment (<1−5). It is noteworthy that these segments work with volumes of ca. 10^4−10^6 tons, which leads to low E-factors.[425] Another factor that contributes to lower E-values is that almost all the solvent-free reactions involved only one synthetic step or were performed in one-pot procedures. On the other hand, most of the reactions using molecular solvents showed E-factors ranging between 5.0−49.9 and 50.0−100.0. These elevated values are similar to those for fine chemical (5−50) and pharmaceutical industries (25−100) and have been attributed to the classical use of stoichiometric reactants with low atom utilization.[425] In addition, these industries perform multistep syntheses involving large expenditures of solvents in the workup steps. Interestingly, only solvent-free procedures that used solvent in the isolation step showed E-factors higher than 20. Table 5 illustrates the difference in the ranges of *Procedure E-factors* obtained for solvent-free protocols that entail SYS and SYS + PIS.

In general, solvent-free reactions involving the synthesis and isolation steps of compounds (SYS + PIS) showed E-factors in the range of 24.2−388.9. On the other hand, in those protocols that either did not carry out an isolation step (PIS) or did not inform the amount of solvent used in PIS, the E-factors were dramatically reduced to a range of 0.1−4.0 (Table 5). This denotes the power of solvents in the waste generated in the reactions carried out at the laboratorial scale, since the mass of solvent is much larger than the mass of products obtained. In addition, the low E-factors obtained for cyclocondensation reactions are not related with the low volume employed in the reaction or with the low atom utilization but with the absence of solvents in the reaction medium. However, when the volumes of solvents used in SYS + PIS protocols were calculated into the E-factors, values close to those reported by pharmaceutical industries were obtained. Thus, it can be said that most researchers did not use a quality system that accounted for environmental and economic impacts of synthetic procedures.

Another important issue is related with the kind of solvent used for isolation and the kind of purification method. From data reported in this review, it was found that 47% of the procedures mentioned the use of organic solvents in the isolation of compounds, regardless of whether its volume was informed. Approximately 25% of the protocols used a combination of organic solvents and water in the isolation of products, and about 28% isolated the product by precipitation in water or a mixture of ice and water. Recrystallization was the purification method employed in 63% of the reports, while purification by chromatographic column, a process that uses large amounts of solvent, was accomplished by 37% of reports. Nevertheless, the lack of data concerning the

Table 4. *Procedure E-factors*[a] in Solvent-free Conditions Reported in This Review

sch./prod.	N^b	E-factor	refs	Sch./Prod.	N^b	E-factor	refs
1/**4**	8	(SYS) 0.55 ± 0.13	48	38/**113,114**	3	(SYS) 1.15 ± 0.09	244
2/**6**	17	(SYS) 0.18 ± 0.04	59	38/**117,118**	4	(SYS) 1.39 ± 0.26	244
3/**9**	5	(SYS) 0.33 ± 0.07	62	39/**120**	9	(SYS) 0.39 ± 0.09	254
					6	(SYS + PIS) 31.06 ± 1.52	
4/**11**	4	(SYS) 0.33 ± 0.06	63	40/**123**	7	(SYS) 3.40 ± 0.84[d]	261
	10	(SYS + PIS) 39.65 ± 0.66			7	(SYS) 3.79 ± 0.83[e]	
5/**13**	1	(SYS) 0.28	64	41/**125**	10	(SYS) 1.52 ± 0.33	272
					4	(SYS + PIS) 69.64 ± 2.05	
6/**15**	5	(SYS) 0.32 ± 0.04	70	42/**128**	2	(SYS) 0.74 ± 0.02[c,d]	283
	8	(SYS + PIS) 114.77 ± 4.53			2	(SYS) 2.56 ± 0.35[c,e]	
7/**17**	1	(SYS) 0.04[c]	64	43/**131,132**	6	(SYS) 0.80 ± 0.20	299
8/**18**	6	(SYS) 0.49 ± 0.09[c]	77c	43/**138,139**	2	(SYS) 0.64 ± 0.04	299
8/**18**	7	(SYS) 0.80 ± 0.12	78	44/**143**	6	(SYS) 0.16 ± 0.03	301
9/**22**	10	(SYS) 0.81 ± 0.06	94	46/**148**	13	(SYS) 0.74 ± 0.10	303
10/**27**	1	(SYS) 0.36	95	46/**149**	6	(SYS) 0.56 ± 0.05	304
10/**28**	1	(SYS) 0.57	95	47/**154**	12	(SYS) 0.70 ± 0.10[c]	308
10/**29**	1	(SYS) 0.67	95	48/**160,161**	4	(SYS) 1.30 ± 0.28	309
					2	(SYS + PIS) 36.64 ± 1.36	
11/**31**	9	(SYS) 0.18 ± 0.03	103	49/**162,163**	26	(SYS) 0.37 ± 0.06[c]	310
12/**36**	18	(SYS) 4.05 ± 0.8	114	50/**164,165**	4	(SYS) 0.95 ± 0.15[c]	311
	8	(SYS + PIS) 388.93 ± 17.49					
13/**39**	1	(SYS) 0.27	115	51/**167,168**	15	(SYS) 0.28 ± 0.03[c]	313
	1	(SYS + PIS) 224.62					
15/**44**, **45**	8	(SYS) 0.10 ± 0.02	130	52/**171**	5	(SYS) 3.69 ± 0.30[d]	328
					5	(SYS + PIS) 4.48 ± 0.33[e]	
18/**53**	7	(SYS) 0.22 ± 0.04	146	52/**171**	5	(SYS) 4.48 ± 0.33[d]	328
					5	(SYS) 3.68 ± 0.30[e]	
19/**56**	11	(SYS) 0.71 ± 0.09	171	53/**173**	3	(SYS) 0.14 ± 0.03[f]	329
					8	(SYS + PIS) 0.09 ± 0.01[e]	
20/**62**	11	(SYS) 0.39 ± 0.08	163	54/**176**	2	(SYS) 0.41 ± 0.03	339
					2	(SYS + PIS) 24.22 ± 1.23	
21/**65**	20	(SYS) 2.63 ± 0.63	172	54/**176**	3	(SYS) 0.45 ± 0.01	339
	4	(SYS + PIS) 345.48 ± 24.58			3	(SYS + PIS) 34.50 ± 1.21	
22/**68**	7	(SYS) 0.65 ± 0.08	179	55/**179**	5	(SYS) 1.20 ± 0.19	340
23/**71**	7	(SYS) 0.19 ± 0.04	180	56/**181-183**	1	(SYS) 1.49	340
24/**74**	8	(SYS) 0.46 ± 0.07	181	57/**185**	3	(SYS) 4.21 ± 0.75	342
25/**76**	7	(SYS) 1.80 ± 0.21	186	57/**187**	1	(SYS) 1.99	342
25/**76**	9	(SYS) 1.16 ± 0.19	187	59/**195-198**	10	(SYS) 7.54 ± 1.67	346
26/**79**	8	(SYS) 1.72 ± 0.25	187	60/**200**	1	(SYS) 1.77	346
27/**81**	12	(SYS) 0.73 ± 0.13	209	61/**202**	6	(SYS) 0.34 ± 0.04	347
27/**81**	28	(SYS) 0.64 ± 0.11[c]	204	62/**203,204**	8	(SYS) 0.25 ± 0.02	350
28/**83**	7	(SYS) 0.72 ± 0.08	217	63/**206**	2	(SYS) 1.22 ± 0.05	361
29/**85**	7	(SYS) 0.67 ± 0.15	218	64/**209**	4	(SYS) 0.28 ± 0.06	371
31/**92**	5	(SYS) 1.50 ± 0.15	219	64/**209**	8	(SYS) 0.34 ± 0.06	372
32/**95**	12	(SYS) 0.81 ± 0.11[c]	228	65/**213**	6	(SYS) 1.39 ± 0.24	377
32/**96**	17	(SYS) 0.69 ± 0.14[c]	228	67/**216**	7	(SYS) 0.14 ± 0.02	382
33/**99**	17	(SYS) 1.00 ± 0.25	229	68/**219**	8	(SYS) 0.67 ± 0.12[c,d]	391
					8	(SYS) 1.94 ± 0.30[c,e]	
34/**101**	12	(SYS) 0.49 ± 0.05	229	70/**224**	7	(SYS) 0.21 ± 0.05	404
35/**104**	7	(SYS) 0.69 ± 0.17	238	71/**226**	7	(SYS) 0.49 ± 0.08	415
36/**106**	9	(SYS) 0.59 ± 0.12	239	73/**231**	5	(SYS) 0.24 ± 0.04	419
37/**109**	16	(SYS) 1.76 ± 0.23	241				

[a] *Procedure E-factors* ± standard deviation (eq 5) are an average value of the individual *Procedure E-factor* obtained from the data of one compound. [b] Number of procedures used for *Procedure E-factor* calculations. [c] Procedures which carried out isolation with water. [d] Procedures carried out by microwave irradiation. [e] Procedures carried out by conventional thermal heating.

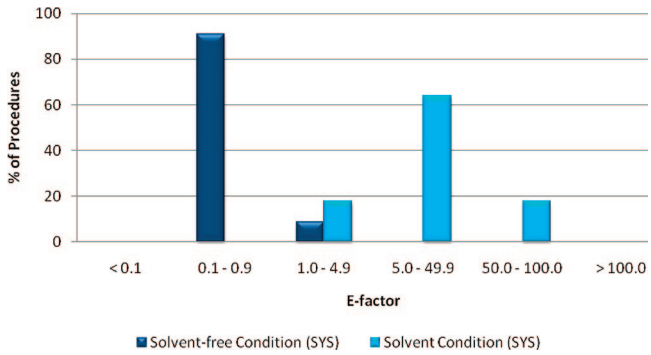


Figure 8. Percentage of procedures performed under solvent-free and solvent conditions considering the synthesis step (SYS).

Table 5. E-Factor Ranges Obtained for Solvent-free Procedures SYS and SYS + PIS

solvent-free procedures	number of procedures	E-factor ranges
SYS	59	0.1−4.0
SYS + PIS	9	24.2−388.9

volume of solvent expended in purification led us to think that E-factors may be even greater.

Therefore, the E-factor is a powerful tool for quantitative assessments of input and output for a given process and has played a major role in calling the attention of the worldwide chemical industry to the problem of waste generation in chemical manufacturing. In this review, this green metric was used to determine the waste generated in cyclocondensation reactions at a laboratory scale, both under solvent-

free conditions and when possible also in the presence of solvents. From the data obtained, it was possible to affirm that most of the waste generated in these reactions comes from the use of organic solvents in the reaction medium and/or workup step. An alarming finding was that most of the publications did not give a complete report informing all of the data involved in the synthetic procedures. For the workup, little information was reported, a fact that hindered the assessment of the E-factor and the determination of the greenness of a given protocol. In addition, many solvent-free protocols involved the use of organic solvents in the workup step, leading to elevated E-factors. Unfortunately, as most of the papers in this review used *solvent-free* and/or *green chemistry* as the main keywords, it is possible that some authors used these keywords only as buzzwords to get their papers published. However, if we truly intend to work toward the sustainability of all chemical processes developed, an urgent change is needed in the manner that we report findings. With the paradigm shifting from the traditional concepts of process efficiency and optimization, which focused exclusively on chemical yield of the desired product, to one that accounts for eliminating waste and avoiding the use of toxic and/or hazardous chemicals, it will be necessary to provide complete information for synthetic processes, reporting the amount of all chemicals used.

12. Solvent-Free Conditions and Economic Perspectives

Chemical products are generally created using energy-intensive processes and nonrenewable, petroleum-based resources as feedstocks in which solvents play a great role. They have been estimated to represent 85% of the total mass of chemicals involved in pharmaceutical manufacturing[428] and more than 90% of the hazardous waste in drug development.[429] Thus, the reduction of solvent consumption has become very interesting not only from environmental but also economic viewpoints.

The synthesis of fine chemicals or pharmaceuticals, widely carried out in batch processes, implies many successive steps: reaction, separation, isolation, and purification. The solvent is chosen according to the reactants and the reaction characteristics. Each reaction thus has a given optimal solvent that satisfies at the same time objectives of selectivity and solubility, safety constraints, and economic and environmental criteria. Therefore, the solvent generally differs from one reaction step to another. Consequently, the solvent often has to be switched before beginning a new reaction step. In the industry, solvent replacements are usually carried out by evaporation or distillation operations in the batch reactor used during the reaction. The detailed procedure depends on the reactor equipment in terms of the overhead distillation column and control loops but generally imitates the laboratory methodology developed by the chemist. Consequently, the industry can count on procedures that are robust and reliable but that are also slow and consume large amounts of solvent. Cost distribution studies have shown that the operating costs, which include mainly time, energy, equipment, and personnel, represent the main part of the global cost for an industrial process.[430] Costs involved in solvents and waste treatment appear to be lower since these chemicals are relatively cheap (0.15−2.5 euro·kg^{-1}) and burning costs (waste treatment) do not exceed 0.06 euro·kg^{-1}.[430] It is noteworthy, however, that these aspects are linked: minimizing the amount of solvent used will lead to a decrease in the cost of raw material, the operating time and the amount of waste must be treated, thus reducing the global cost.[430] If a company can significantly reduce these expenditures, then these funds can be spent in more productive areas. In addition, by avoiding the generation of pollution, industries can reduce or eliminate the costs of regulation, reduce materials use, and significantly reduce the risks associated with manufacturing and the use of chemical processes and products.[431] Moreover, companies may benefit from these approaches when a clean product or process is essential for remaining cost competitive with global rivals or when global industry standards require it.[432] Furthermore, it has been demonstrated that greener products create new markets and help industries increase or maintain market share.[433]

In fact, several companies have incorporated solvent reduction in chemical production. Two examples illustrate this tendency. The first is the redesign of the sertraline manufacturing process.[434] Pfizer streamlined the three-step synthesis of the original manufacturing process to a single step and cut its use of three starting materials to between 20−60% as a result. Additionally, the process changes eliminated the need to use, distill, and recover four toxic solvents (dichloromethane, tetrahydrofuran, toluene, and hexane) from the original synthesis, since ethanol became the sole solvent. It is worth noting that the redesign of the sertraline manufacturing process received a Presidential Green Chemistry Challenge Award in 2002.[434] Similarly, impressive improvements in solvent usage have also been reported in the process for sildenafil (Viagra) manufacture, where solvent usage was reduced from 1700 to 7 L·kg^{-1}, with a future target of 4 L·kg^{-1}.[421f] These examples denote the growth of interest in technologies that reduce solvent utilization and, thus, the environmental impact of chemical processes. In the United States, between 1983 and 2001 there were over 3200 green chemistry patents awarded, of which 61% were related with chemical manufacture, and solvent-free protocols are among the issues encompassed.[435] The United States is the leader in green chemistry patents, with 65% of all green chemistry patents. Europe is the second largest region, holding 24% of patents, followed by Japan (8%) and the rest of the world (2%).[435] An important data point shown was that universities hold 11% of these patents, while the pharmaceutical industries, a sector intensely oriented toward chemistry, hold 8%.[435] The green chemistry emphasis in universities may reflect the growing emphasis on sustainable development in the research strategies of many developed nations[436] and highlights the importance of this sector as a source of innovation in an emerging area of research. From an academic point of view, the efforts to eliminate, replace, recycle, or minimize the use of solvents should begin in the earliest stage of product/process development.[421o] A number of scientific groups have already published solvent selection/replacement tools in order to support the decision-making process.[437] Solvent selection allows for consideration of environmental, health, and safety aspects at the R&D stage, and partial consideration of life cycle aspects (life cycle assessment),[438] as well as economic criteria.[439] Kralisch et al.[440,441] suggested a holistic evaluation and optimization approach considering ecological and economic aspects. The ECO (ecological and economic optimization) method was designed to accompany and optimize early-stage development work in chemical R&D regarding the principles of ecological and economic sustainability.[440,441] To evaluate the greenness of a product or process, the method

uses three main criteria: the cost factor, the environmental and human health factor, and the energy factor, describing the cost, toxicity, and energy demand, e.g., chemicals, auxiliaries, energies, disposal, equipment, and personnel, as well as process expenditures during the life cycle stages of a product or process.[440,441] The cost factor takes into account economic factors in order to allow for a comparison of the profitability of different process/product alternatives. In regard to costs involved in laboratory-scale syntheses, it has been shown that conventional solvents are easy to obtain and relatively cheap, making the global costs mainly defined by the supply of the starting materials and dependent on the performance of the reaction media.[421o,441] From data reported by these tools, it has been proposed that solvent-free reactions provide the best environmental and cost-effective methods because of their good efficiency and reduced reaction and workup times, leading to energy savings.[421o,441]

There is no doubt that green chemistry, and, consequently, solvent-free synthesis, is being adopted around the world as a way of ensuring not only environmental improvements but also economic profits. Larger companies budget close to U.S.$ 1 billion *per* year for environmental compliance.[442] Managing synthesis wisely with the use of solvent-free conditions can help companies reduce their operating costs, comply with environmental legislation, reduce the need for pollution-abatement equipment, and enhance their market share.

13. Conclusions

After having examined all the cyclocondensation reactions described in this review, it is necessary to return to some central issues: (i) whether solvent-free conditions are better than molecular solvents for cyclocondensation reactions; (ii) whether the chemical mechanistic aspects of solvent-free reactions discussed in the literature are associated with cyclocondensation reactions; (iii) whether solvent-free cyclocondensation reactions are truly green. We hope to have shed some light on these issues. The data from the papers reviewed here clearly show that the use of solvent-free conditions in heterocyclic synthesis generally leads to similar or higher yields and a reduction in the reaction time when compared to the same reaction performed in the presence of molecular solvents. The cyclocondensation reactions reported in this review involve liquid/liquid, liquid/solid, and solid/solid media, and for all of these types of media, molecular movement was shown to occur and the reactions proceeded satisfactorily. In many of the reactions, microwave equipment was used as the activation mechanism, and this raises several polemic issues: the type of equipment used for reaction, the device used to measure the reaction temperature, the reproducibility of results, and the existence of nonthermal microwave effects. We concluded that all reactions performed in MW, both domestic oven and synthesis equipment, presented better yields and shorter reaction times than those not carried out in MW. However, the advantages of microwave domestic ovens are undermined by their poor reproducibility. In terms of temperature measurements and the existence of nonthermal effects, we believe that more research is necessary, and at present we consider that the existence of nonthermal effects cannot be excluded.

In regard to the environmental aspects of cyclocondensation reactions under the solvent-free conditions described in this review, some of the reports described as solvent-free protocols used organic solvents in the isolation step, and it is possible to affirm that most of the waste generated in these reactions came from the use of organic solvents in the workup step.

The E-factor for solvent-free reactions presented in this review showed values in a range of 0.1−4.9 for reactions performed under solvent-free conditions considering only the synthetic steps and a range of 5.0−49.9 and 50.0−100.0 for reactions accomplished using molecular solvents. This leads us to conclude that, even considering only the synthetic steps, the use of solvent-free conditions contributed to the reduction of total waste generated during a given synthetic process. It was not possible to obtain the complete E-factor calculations due to the lack of information about the synthetic method used in the workup of reactions (SYS + PIS + PPS). Only a few of the papers presented information about the exact amount of solvents used in product isolation. None of the papers informed the amount of solvent expenditure in the purification of compounds. This deficiency impedes a complete evaluation of the actual environmental impact of specific synthetic organic processes, denoting that most researchers did not operate with a quality system that encompassed the environmental impact of synthetic procedures. In this sense, there is an urgent need for changes in the manner that papers are reported to avoid the risk of green chemistry and solvent-free becoming nothing more than buzzwords for publishing papers in the academic medium.

From an economic perspective, the use of solvent-free conditions may lead to a decrease in the total cost of synthetic processes. Industrially speaking, one of the main costs involved in a process is related to the use of solvents. Moreover, reducing the amount of solvent usage can reduce the costs involved in waste treatment. In addition, by reducing the use of solvents, industries may reduce or eliminate the cost of regulation and material use and significantly reduce the risks associated with the manufacture and use of chemicals, giving rise to the production of clean products or processes in a cost-competitive manner.

Moreover, considering the importance of the cyclocondensation reaction, the main reaction employed in heterocyclic synthesis, the information presented in this review clearly illustrates the substantial advances achieved over the past decade in solvent-free reactions, good reactivities and selectivities, simplified workup steps, and generally cleaner, more economical, and safer protocols.

An investigation on the Web of Science showed a proliferation of papers in which the topic solvent-free appeared. We found 6880 papers published up to December 2008, of which more than 89% were published after the year 2000. This demonstrates the increase in new researchers in the area. On the other hand, 13% of these papers dealt with the application of solvent-free conditions in heterocyclic synthesis from cyclocondensation reactions.

We hope to have given a clear idea of the applicability of solvent-free conditions in cyclocondensation reactions to obtain heterocyclic compounds. We would like to conclude with an optimistic view for the future expansion of synthetic procedures in solvent-free media. This positive outlook comes from the certainty that the results reported here will be but the beginning of a great advance in this promising field in the near future.

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15. List of Abbreviations

AE	atom economy
Boc	*tert*-butoxycarbonyl
CAN	ceric ammonium nitrate
CE	carbon efficiency
CF	cost factor
DAST	diethylaminosulfurtrifluoride
DEAD	diethyl azodicarboxylate
DMAD	dimethyl acetylene dicarboxylate
DNs	2,4-dinitrobenzenesulfonyl
ECO	ecological and economic optimization
EF	energy factor
E-factor	environmental factor
EHF	environmental and human health factor
EMME	diethyl ethoxymethylenemalonates
EQ	environmental quotient
GS	ground state
HDNIB	[hydroxy-(2,4-dinitrobenzenesulfonyloxy)iodo] benzene
LCA	life cycle analysis
MI	mass intensity
MW	microwave irradiation
OTIPS	triisopropylsilyloxy
PIS	product isolation step
(P) MI	process mass intensity
PPA	polyphosphoric acid
PPS	product purification step
RME	reaction mass efficiency
SF	stoichiometric factor
SYS	synthesis step
TosMIC	toluenesulfonylmethyl isocyanide
TS	transition state
US	ultrasound irradiation

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