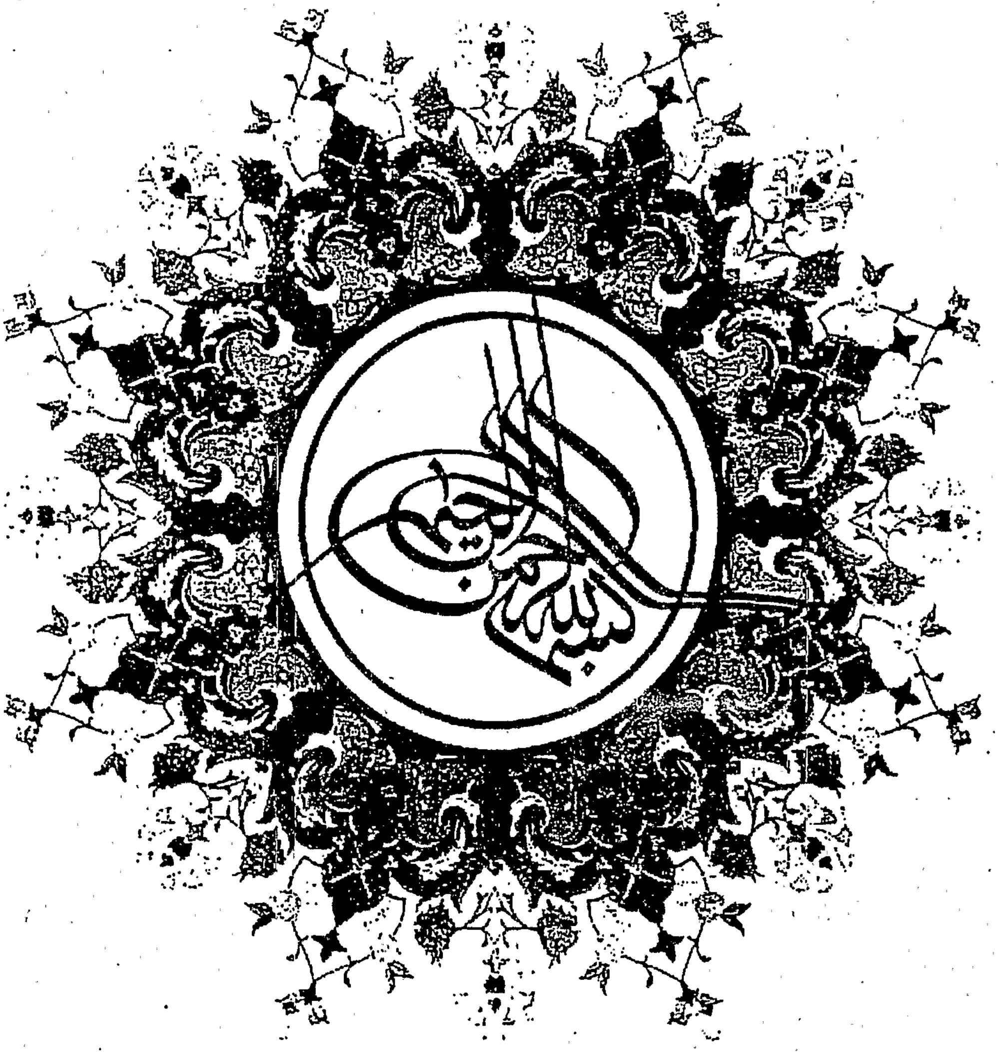

١٠٧٥٨١

دانشگاه شهید باهنر کرمان

Shahid Bahonar University of Kerman
Faculty of Science
Department of Chemistry

Microwave-assisted Synthesis of Dihydropyrimidinone, Cinnamic Acid and Imine Derivatives and Synthesis of Stable Phosphorus Ylides and Corresponding Iminophosphoranes

Supervisor:

Dr. K. Saidi

Prepared by:

H. Khabazzadeh

A Dissertation Submitted as a Partial Fulfillment of the Requrements for the Degree of Doctor of Philosophy in Chemistry (Ph. D.)

June 2008

دانشگاه شهید باهنر کرمان

دانشکده علوم

گروه شیمی

رساله برای دریافت درجه دکتری شیمی

سنتز مایکروویو مشتقات دی هیدروپیریمیدینون ها، سینامیک اسید ها و ایمین ها و سنتز ایلید های فسفر پایدار و ایمینوفسفوران های مربوطه

استاد راهنما:
دکتر کاظم سعیدی

مؤلف:
حجت ا... خباززاده

تیرماه ۸۷

Abstract

Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions. Microwave reactions under solvent-free conditions and/or in the presence of a solid support such as alumina, silica and graphite, resulting in shorter reaction times and higher product yields than those obtained by using conventional heating offer low cost together with simplicity in processing and handling.

In this investigation dihydropyrimidinones, cinnamic acids and imines were synthesized in solvent-free microwave and thermal conditions. The effect of various catalysts and supports were investigated in these reactions. The main goal in these reactions is introducing of new methodologies with shorter reaction times and higher product yields.

In another section of this investigation stable phosphorus ylides containing an amino group in the β position were synthesized and were converted to the corresponding iminohosphoranes.

Contents

Chapter 1
Microwave

Chapter 2
Dihydropyrimidinones

Chapter 3
Cinnamic acids

Chapter 4
Imines

Chapter 5
Phosphorus ylides

Chapter 1

Microwave

1.1. Introduction

In the electromagnetic spectrum, the microwave radiation region is located between infrared radiation and radio waves. Microwaves have wavelengths of 0.001-1 m, corresponding to frequencies between 0.3 and 300 GHz. Telecommunication and microwave radar equipment occupy many of the band frequencies in this region. In general, in order to avoid interference, the wavelength at which industrial and domestic microwave apparatus intended for heating operates is regulated to 12.2 cm, corresponding to a frequency of 2.450 (+ 0.050) GHz, but other frequency allocations do exist. In the 1970s, the construction of the microwave generator, the magnetron, was both improved and simplified. Consequently, the prices of domestic microwave ovens fell considerably, leading to them becoming a mass product. The design of the oven chamber or cavity, however, which is crucial for the heating characteristics, was not significantly improved until the end of the 1980s.

In inorganic chemistry, microwave technology has been used since the late 1970s, while it has only been implemented in organic chemistry since the mid-1980s. Gedye and Giguere first reported the use of microwave heating to accelerate organic chemical transformations [1, 2]. The development of the technology for organic chemistry has been rather slowing compared, to for example, combinatorial chemistry and computational chemistry. This slow uptake of the technology has been principally attributed to its lack of controllability and reproducibility, safety aspects and a generally low degree of understanding of the basics of microwave dielectric heating.

The short reaction times and expanded reaction range that is offered by microwave assisted organic synthesis are suited to the increased demands in industry. In particular, there is a requirement in the pharmaceutical industry for a higher number of novel chemical entities to be produced, which requires chemists to employ a number of resources to reduce the time for the production of compounds. Chemistry databases, software for diversity selection, online chemical ordering systems, open-access and high through put systems for analysis and high-speed, parallel and combinatorial synthesis equipment have all contributed in increasing the throughput. The common factors for these technical resources are automation and computer-aided control. They do not, however, speed up the chemistry itself. Developments in the chemistry have generally been concerned with novel highly reactive reagents in solution or on solid supports. In general, most organic reactions have been heated using traditional heat transfer equipment such as oil baths, sand baths and heating jackets. These heating techniques are, however, rather slow and a temperature gradient can develop within the sample. In addition, local overheating can lead to product, substrate and reagent decomposition. In contrast, in microwave dielectric heating, the microwave energy is introduced into the chemical reactor remotely and direct access by the energy source to the reaction vessel is obtained. The microwave radiation passes through the walls of the vessel and heats only the reactants and solvent, not the reaction vessel itself. If the apparatus is properly designed, the temperature increase will be uniform throughout the sample, which can lead to less by-products and/or decomposition products. In pressurized systems, it is possible to rapidly increase the temperature far above the conventional boiling point of the solvent used.

1.2. Background and theory

If two samples containing water and dioxane, respectively, are heated in a single-mode microwave cavity at a fixed radiation power and for a fixed time the final temperature will be higher in the water sample (Fig. 1).

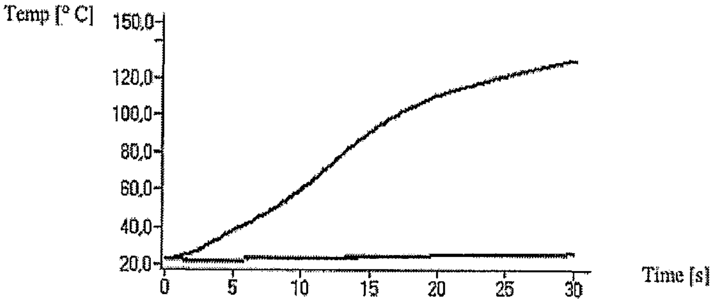

Figure 1. The temperature increases of water and dioxane, respectively, at 150W microwave irradiation. The upper curve represents water and the lower plot represents dioxane.

In order to understand why this phenomenon occurs, it is necessary to comprehend the underlying mechanisms of microwave dielectric heating. As with all electromagnetic radiation, microwave radiation can be divided into an electric field component and a magnetic field component. The former component is responsible for the dielectric heating, which is effected via two major mechanisms.

1.2.1. Dipolar polarization mechanism

One of the interactions of the electric field component with the matrix is called the dipolar polarization mechanism. For a substance to generate heat when irradiated with microwaves it must possess a dipole moment such as dipole moment of water molecule. A dipole is sensitive to external electric fields and will attempt to align itself with the field by rotation, (Fig. 2).

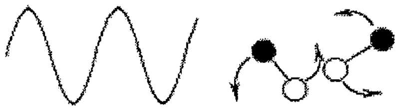

Figure 2. Dipolar molecules which try to align with an oscillating electric field.

The applied field provides the energy for this rotation. In gases, molecules are spaced far apart and their alignment with the applied field is, therefore, rapid, while in liquids instantaneous alignment is prohibited by the presence of other molecules. The ability of molecules in a liquid to align with the applied electric field will vary with different frequencies and with the viscosity of the liquid. Under low frequency irradiation, the molecule will rotate in phase with the oscillating electric field. The molecule obtains some energy by this behavior, but the overall heating effect by this full alignment is small. Alternatively, under the influence of a high frequency electric field the dipoles do not have sufficient time to respond to the oscillating field and do not rotate. Since no motion is induced in the molecules, no energy transfer takes place and therefore no heating occurs. If the applied field is in the microwave radiation region, however, a phenomenon occurs between these two extremes. In the microwave radiation region, the frequency of the applied irradiation is low enough so that the dipoles have time to respond to the alternating electric field and therefore rotate. The frequency is, however, not high enough for the rotation to precisely follow the field. Therefore, as the dipole re-orientates to align itself with the electric field, the field is already changing and generates a phase difference between the orientation of the field and that of the dipole. This phase difference causes energy to be lost from the dipole by molecular friction and collisions, giving rise to dielectric heating. Thus, in the earlier example, it becomes clear why dioxane, which lacks the dipole characteristics necessary for microwave dielectric heating, does not heat while water, which has a large dipole moment, heats readily. Similarly, this explains why gases could not be heated under microwave irradiation, since the distance between two rotating molecules is long enough for the molecules to be able to follow the electric field perfectly so that no phase difference will be generated.

1.2.2. Conduction mechanism

If two samples containing distilled water and tap water, respectively, are heated in a single mode microwave cavity at a fixed radiation power and for a fixed time, the final temperature will be higher in the tap water sample (Fig. 3).

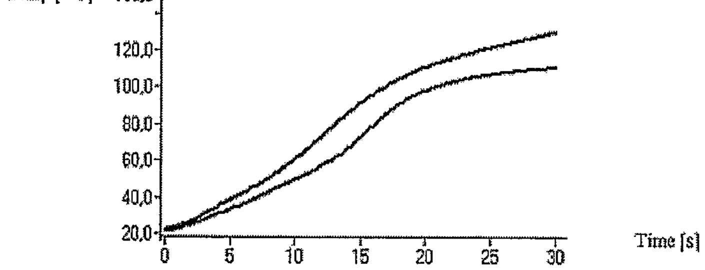

Figure 3. The temperature increases of distilled water and tap water, respectively, at 150W microwave irradiation. The upper curve represents tap water and the lower plot represents distilled water sample.

This phenomenon is due to the second major interaction of the electric field component with the sample, the conduction mechanism. A solution containing ions, or even a single isolated ion with a hydrogen bonded cluster, in the sample the ions will move through the solution under the influence of an electric field, resulting in expenditure of energy due to an increased collision rate, converting the kinetic energy to heat (Fig. 4).

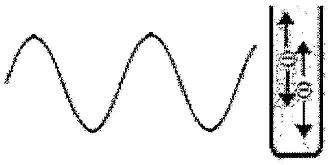

Figure 4. Charged particles in a solution will follow the applied electric field.

The conductivity mechanism is a much stronger interaction than the dipolar mechanism with regard to the heat- generating capacity. In the above example, the heat generated by the conduction mechanism due to the presence of ions adds to the heat produced through the dipolar mechanism, resulting in a higher final temperature in the tap water.

1.3. Loss angle

As mentioned above, polar solvents and/or ions are needed for microwave heating. How does the microwave heating effect differ for different solvents? The dielectric polarization depends primarily on the ability of the dipoles to reorientate in an applied electric field. It would seem reasonable to believe that the more polar the solvent, (i.e. the higher the dielectric constant it possesses), the more readily the microwave irradiation is absorbed and the higher the temperature obtained. This would appear to correspond well to what is observed in the case of water versus dioxane (Fig. 1). If, however, two solvents with comparable dielectric constants, ε_s, such as acetone and ethanol (Table 1), are heated at the same radiation power and for the same period of time as the water described above, the final temperature will be much higher in ethanol than in acetone (Fig. 5).

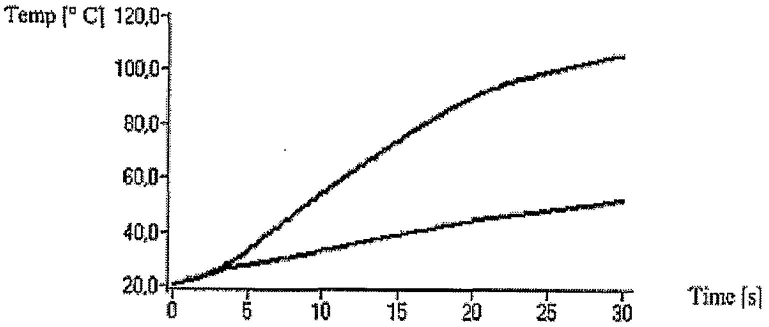

Figure 5. The temperature increase of ethanol and acetone, respectively, at 150W microwave irradiation. The upper curve represents ethanol the lower plot represents acetone.

In order to be able to compare the abilities of different solvents to generate heat from microwave irradiation, their capabilities to absorb microwave energy and to convert the absorbed energy into heat must be taken into account. These factors may be considered using the loss angle, δ, which is usually expressed in the form of its tangent (Eq. (1)).

$$\tan \delta = \varepsilon''/\varepsilon' \qquad (1)$$

The dielectric constant, or relative permittivity, ε', presents the ability of a dielectric material to store electrical potential energy under the influence of an electric field. At room temperature and under the influence of a static electric field, ε', is equal to the dielectric constant, ε_S. The loss factor, ε'', quantifies the efficiency with which the absorbed energy is converted into heat. For solvents with comparable ε' and low values of $\tan \delta$, the loss factor provides a convenient parameter for comparing the abilities of different materials to convert microwave into thermal energy. The dielectric constants of acetone and ethanol are, indeed, in the same range (Table 1), but ethanol possesses a much higher loss tangent. For this reason, ethanol couples better with microwave irradiation, resulting in a more rapid temperature increase.

Table 1. Dielectric constants and loss tangent values for some solvents relevant to organic synthesis

Solvent	Dielectric constant (ε_S)[a]	Loss tangent (tan δ)[b]
Hexane	1.9	
Benzene	2.3	
Carbontetrachloride	2.2	
Chloroform	4.8	
Acetic acid	6.1	0.091
Ethyl acetate	6.2	0.174
THF	7.6	0.059
Methylene chloride	9.1	0.047
Acetone	20.6	0.042
Ethanol	24.6	0.054
Methanol	32.7	0.941
Acetonitrile	36	0.659
Dimethylformamide	36.7	0.062
DMSO	47	0.161
Formic acid	58	0.722
Water	80.4	0.123

[a] The dielectric constant, ε_s, equals the relative permittivity, ε', at room temperature and under the influence of a static electric field.

[b] Values determined at 2.45 GHz and room temperature.

1.4. Superheating effect

The relaxation time, T, defines the time it takes for one molecule to return to 36.8% of its original situation when the electric field is switched off. The relaxation time is dependent on the temperature and decreases as the temperature is increased. Since both ε' and ε'' are dependent on T, the ability of a solvent to convert microwave energy into heat will be dependent not only on the frequency, but also on the temperature. Consequently, an organic solvent with a relaxation time >65 ps irradiated at 2.45 GHz will have a loss tangent that increases with temperature. The heating rate for these solvents will increase during microwave dielectric heating, most probably by limiting the formation of 'boiling nuclei'. This phenomenon is described as superheating and may result in the boiling points of solvents being raised by up to 26°C above their conventional values [3]. In a pure solvent, the higher boiling point can be maintained as long as the microwave irradiation is applied. Substrates or ions present in the solvent will, however, aid the formation of 'boiling nucleuses' and the temperature will eventually return to that of the normal boiling point of the solvent. The superheating phenomenon is widely believed to be responsible for many of the rate increases which often accompany solution phase microwave assisted organic reactions at atmospheric pressure [4].

1.5. Solvents in microwave assisted organic synthesis

Since the frequency for most types of microwave apparatus is set at 2.45 GHz, the dielectric constant can only change with temperature. When a solvent is heated, the dielectric constant decreases as the temperature increases. Water has a dielectric constant which decreases from 78 at 25°C to 20 at 300°C (Fig. 7), the latter value being comparable to that of solvents such as acetone at ambient temperature [5]. Water can, therefore, behave as a pseudo-organic solvent at elevated temperatures, but this property is only valid in pressurized systems. It was mentioned earlier that nonpolar solvents are not heated under microwave irradiation. The addition of small amounts of a polar solvent with a large loss tangent, however, usually leads to higher heating rates for the whole mixture. The energy transfer between the polar molecules that couple with the microwave radiation and the non-polar solvent bulk is rapid. This method provides an effective means of using non-polar solvents in microwave organic synthesis. Another way of increasing heating rates is the addition of salts to the solvent. Unfortunately, a solubility problem in many organic solvents results in heterogeneous mixtures. In microwave-assisted synthesis, a homogeneous mixture is preferred to obtain a uniform heating pattern. Ionic liquids have recently been reported as novel environmentally friendly and recyclable alternatives to dipolar aprotic solvents for organic synthesis [6]. The excellent dielectric properties of these ionic liquids offer large advantages when used as solvents in microwave assisted organic synthesis.

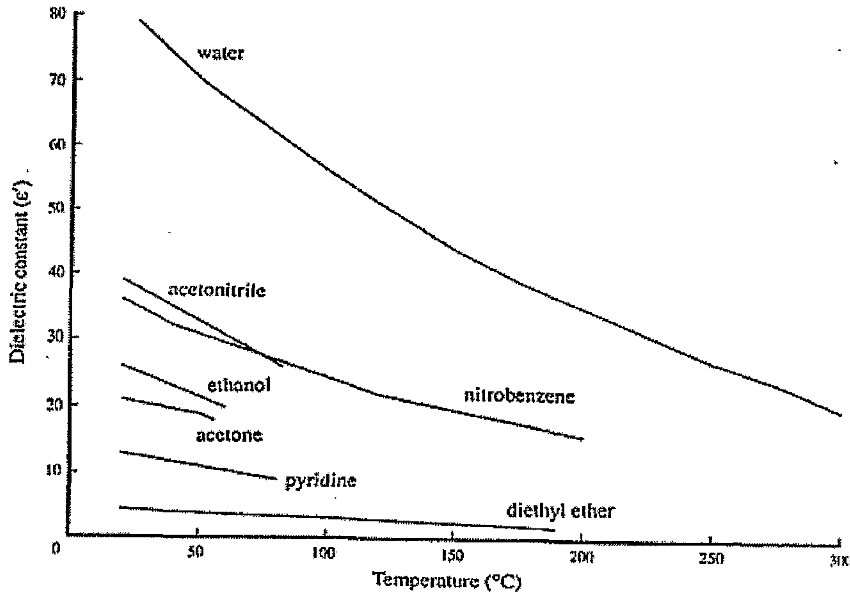

Figure 7. Plots of dielectric constants against temperature for various solvents.

Ionic liquids absorb microwave irradiation in a very efficient manner and, additionally, they exhibit a very low vapour pressure, thereby enhancing their suitability even further for microwave heating. Despite ionic liquids being salts, they dissolve to an appreciable extent in a wide range of organic solvents as compared to water and alcohols. Some ionic liquids are also soluble in many non-polar organic solvents and can therefore be used as microwave coupling agents when microwave transparent solvents are employed (Fig. 8).

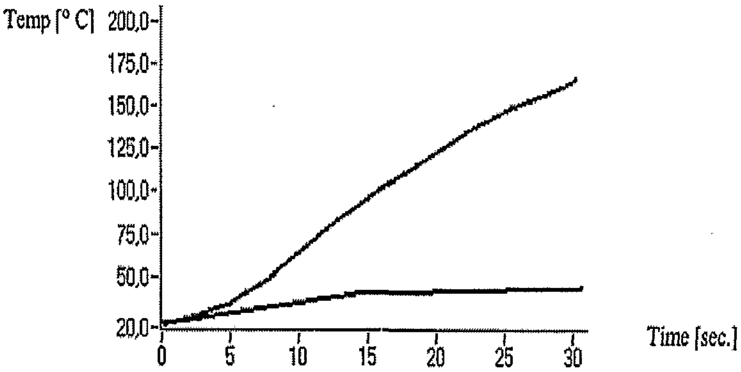

Figure 8. The impact of the addition of ionic liquids on the temperature increase of dioxane at 300 W microwave irradiation.

1.6. Why does microwave irradiation speed up in the chemical reactions?

Since the introduction of microwave assisted organic synthesis in 1986, the main debate has dealt with the question of what actually alters the outcome of the synthesis. Is it merely an effect of the thermal heat generated by the microwaves or is it an effect specific for microwave heating?

In most examples, the specific microwave effects claimed, can be attributed to thermal effects. Microwave heating can be very rapid, producing heat profiles not easy accessible by other heating techniques. Experiments performed using microwave assisted organic synthesis may therefore result in a different outcome when compared to conventionally heated reactions, even if the final temperature is the same. It has been shown, for example, that the heating profile can alter the regioselectivity in the sulfonation of naphthalene [7]. In poorly designed single mode systems, 'hot spots' may be encountered, which is frequently a problem in multi-mode systems. In these systems, the problem can give rise to local temperatures which are higher than the temperature measured in the bulk. Similarly, this superheating effect can also result in temperatures much higher than expected when performing reflux reactions in microwave ovens. These effects can sometimes give rise to unexpected results. Additionally, the accuracy of temperature measurements when performing microwave assisted organic synthesis can appear to be uncontrolled. These inaccuracies in temperature measurement often occur when performing the reactions in domestic ovens with microtitre plates or on solid supports, where there are inherent difficulties in measuring the temperature accurately [8]. Even if there is a, 'specific microwave effect', the effect would appear to be less important than stated in earlier publications.

1.7. Microwave assisted synthesis techniques

1.7.1. Domestic household ovens-'solvent-free' open vessel reactions

Most of the papers published in chemistry journals have been performed using domestic microwave ovens. The key reasons for using a device intended for heating food items to perform syntheses are that they are readily available and inexpensive. These types of experiments are conducted with an increased risk to the user, and the use of domestic microwave ovens for microwave chemistry should be considered to be entirely at the risk of the operator, any equipment guarantees being invalidated.

The lack of control in domestic microwave ovens when performing microwave assisted synthesis has led to a vast number of incidents, including explosions, being reported. One method for avoiding this problem has been to omit the solvent from the reaction and perform the reactions on solid supports such as various clays, aluminum oxides and silica. A number of very interesting syntheses have been performed using this technique and a majority of the publications contain work conducted in this manner [9, 10]. The solvent-free technique has been claimed to be particularly environmentally friendly, since it avoids the use of solvents and offers a simpler method of workup. Various clays and other solid supports have been extensively employed in both solvent-free and solution phase techniques. It may be very difficult to obtain a good temperature control at the surface of the solids if the solvent-free technique is used. This would inevitably lead to problems regarding reaction predictability, reproducibility and controllability. There are, however, still benefits from using solvent-free approaches, which include improved safety by avoiding low-boiling solvents that would otherwise cause undesirable pressure increases during heating.

1.7.2. Reflux systems

A number of reflux systems have been developed in an effort to use solvents in microwave assisted organic synthesis without the risk of explosion. Some systems are modified domestic ovens, while others have been designed with single mode cavities. There is little risk of explosions with reflux systems, since the systems are at atmospheric pressure and flammable vapours cannot be released into the microwave cavity. The temperature, however, cannot be increased by more than 13-26°C above the normal boiling point of the solvent and only for a limited time. Although this particular superheating effect will, of course, speed up the reactions to some extent, it will not result in the same effects that can be achieved at much higher temperatures [11].

1.7.3. Pressurized systems

Reactions performed under pressure in a microwave cavity also benefit from the rapid heating rates and remote heating of microwave dielectric heating. These types of experiments led to one of the very early developments using microwave assisted organic synthesis [1]. The lack of control, however, could make these reactions very unpredictable, often resulting in explosions. Nowadays, modern apparatus for running organic synthesis under pressure has overcome these problems. Most apparatus is now equipped with good temperature control and pressure measurement, which avoids a great deal of the failures due to thermal runaway reactions and poor heating (Fig. 9). The technique offers a simple method of performing rapid syntheses and is the most versatile of the approaches presented above, but has so far not been extensively explored [11].