Cycloadditions under Microwave Irradiation Conditions: Methods and Applications

Antonio de la Hoz,*[a] Angel Díaz-Ortis,[a] Andrés Moreno,[a] and Fernando Langa[b]

Keywords: Cycloadditions / Fullerenes / Heterocycles / Microwave / Natural products

Microwave irradiation has been applied with success to cycloaddition reactions. The special characteristics of such irradiation entails the use of new methodologies, including equipment, glassware, solvents, and solid supports. All of these aspects are described in this review. Under classical heating conditions, these reactions usually require long reaction times, high temperatures, and/or Lewis acid catalysts, resulting in partial or total decomposition of sensitive compounds. This is a particularly significant problem in the synthesis of natural products. These problems have been conveniently overcome by the use of microwave irradiation. The short reaction time associated with microwave activation avoids decomposition of reagents and products, and prevents polymerization of the diene or dienophile. Heterocyclic compounds have been synthesized by cycloaddition reactions, or have been observed to react as dienes and dipoles under microwave irradiation conditions. Even those heterocyclic systems that are very reluctant to participate in cycloaddition reactions, such as pyrazoles, can be induced to react under microwave irradiation conditions. The application of this method to the chemistry of [60]fullerene has permitted derivatization of this system while avoiding the problems of polycycloaddition and cycloreversion. In most cases, spectacular accelerations and great improvements in yields and reaction conditions are observed. Finally, in some cases, changes in the chemo-, regio-, or stereoselectivity have been observed. These changes have been connected with the absolute hardness of the transition state, with the harder state being favored under microwave irradiation conditions. Microwave chemistry thus opens new possibilities for modifying the result of competitive reactions by considering the relative hardness of the transition states.

1. Introduction

Microwave radiation is an alternative to conventional heating for introducing energy into reactions. Microwave heating uses the ability of some compounds (liquids or solids) to transform electromagnetic energy into heat.

Microwave irradiation is an efficient methodology in cycloaddition reactions of compounds that are sensitive




Antonio de la Hoz (left, top) obtained his Ph. D. from the Universidad Complutense in Madrid in 1986. After postdoctoral research in 1987 with Prof. Begtrup at the Danmarks Tekniske Høskole, he joined the Faculty of Chemistry of the Universidad de Castilla-La Mancha in Ciudad Real in 1988 as an Assistant Professor. His research interests include heterocyclic chemistry, microwave activation of organic reactions, and solvent-free organic synthesis.

Angel Díaz-Ortis (right, top) was born in Tomelloso (Spain) and obtained his Ph.D. from the Institute of Medicinal Chemistry (Madrid) in 1988. After postdoctoral research at Laboratorios Alter S.A., he joined the Faculty of Chemistry of the Universidad de Castilla-La Mancha (UCLM). Presently, he is Assistant Professor of Organic Chemistry. His research interests encompass new synthetic methods, including preparation of heterocyclic compounds by cycloaddition reactions in a microwave environment.

Andrés Moreno (left, bottom) was born in 1962 in Ciudad Real (Spain). He obtained his degree in organic chemistry (1985) from the Universidad Complutense in Madrid and his Ph.D. (1990) from the Universidad de Castilla-La Mancha. He spent postdoctoral assignments in the Dyson Perrins Laboratory, University of Oxford, U.K. (1991−1992) in NMR studies of peptides in solution. He became Associate Professor/University Lecturer in 1995, and his current research interest includes NMR studies in solution and the development of environmental synthetic methodologies for organic synthesis.

Fernando Langa (right, bottom) is Assistant Professor of Organic Chemistry at the Universidad de Castilla-La Mancha at the Faculty of Environmental Sciences (Toledo). He was born in Madrid in 1954. He received his B.S. and Ph.D. degrees in chemistry in 1976 and 1981, respectively. In 1990 he joined the faculty at the UCLM. Between 1983−1989 he spent several periods as a postdoctoral fellow at the University of Dundee in Scotland. His research interests include microwave-assisted organic synthesis, as well as the chemistry and electrical and optical properties of organofullerenes.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

---

[a] Departamento de Química Orgánica, Facultad de Química, Universidad de Castilla-La Mancha,
E-14071 Ciudad Real, Spain
Fax: (internat) +34-926/295-418
E-mail: adlh@qino-cr.uclm.es
[b] Departamento de Química Orgánica, Facultad de Ciencias del Medio Ambiente,
E-45071 Toledo, Spain
Fax: (internat.) +34-925/268-840
E-mail: flanga@amb-to.uclm.es

1434−193X/00/1122−3659 $ 17.50+.50/0

and/or have low reactivities. Some examples of such are natural products, heterocycles, and fullerene derivatives.

This means of heating has many attractions in chemistry because, in contrast to conventional heating, its magnitude depends on the dielectric properties of the molecules. As a guide, compounds with high dielectric constants tend to absorb microwave irradiation while less polar substances and highly ordered crystalline materials are poor absorbers.

The use of microwave irradiation has led to the introduction of new concepts in chemistry, because the absorption and transmission of the energy is completely different from the conventional mode of heating. In addition, sample shape and size have a different influence and this has an effect on the scale-up of some reactions.

With microwaves, the energy transfer is not produced by conduction or convection, but by dielectric loss. The propensity of a sample to undergo microwave heating depends on the dielectric properties, the dielectric loss factor (ε''), and the dielectric constant (ε'). The dielectric constant represents the ability of a substance to absorb microwaves, while the dielectric loss factor represents the ability of a substance to transform this energy into heat. A high dissipation factor ($\tan\delta = \varepsilon''/\varepsilon'$) is responsible for a high susceptibility to microwave energy. Dielectric parameters relevant to microwave heating have recently been catalogued.[1]

Two important parameters in electromagnetic heating are the penetration depth and sample shape. The penetration depth depends on the wavelength of the electromagnetic radiation and the dielectric properties of the material. The wavelength in the microwave region enables entire bulk regions of the material to be heated simultaneously without any major temperature gradient, and heating is only dependent on the dielectric properties of the material. This type of heating can be performed only by electromagnetic heating in the microwave and RF region; other forms of electromagnetic radiation have a penetration depth that is too small and thermal conductivity is the limiting factor in, for instance, infrared.

The shape and size of objects have much greater, and completely different, effects on temperature distribution than they do in classical heating. Microwave energy is delivered into the interior of the heated material, so the interior can be heated without the mediation of conductive heating. The electric field enters the processed material from a different medium, so boundary conditions and object shape can affect the distribution of electromagnetic energy inside the heated object.

Spherical materials will concentrate an electromagnetic field at their center. For more complicated shapes, the distribution of the electromagnetic field inside the processed object can be highly complex, with some regions receiving much more energy than others. Cylindrical flasks, which have a higher volume to surface area ratio, are the most suitable for microwave applications.

The successful application of microwave irradiation in chemistry dates from 1975.[2] A number of examples have been described in analytical chemistry,[3] environmental chemistry,[3a] materials chemistry,[4] organometallic chemistry,[5] and organic chemistry.[6]

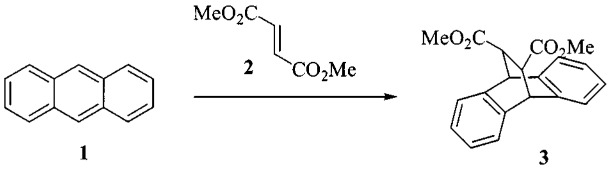
In many cases, cycloaddition reactions require the use of harsh conditions such as high temperatures and long reaction times. These conditions are not compatible with sensitive reagents or products. Moreover, the applicability of Diels−Alder cycloadditions is limited by the reversibility of the reaction when a long reaction time is required. All these problems have been conveniently solved by the rapid heating produced by microwave irradiation: a situation not accessible by classical methods. With the aid of microwave irradiation, cycloaddition reactions have been performed with great success.[7,8]

In this paper, we will review the techniques and applications of microwave irradiation in cycloaddition reactions. This mode of heating requires not only appropriate microwave equipment and glassware, but also a new experimental outlook. A special chapter will focus on modifications induced by microwaves in chemo-, regio-, and stereoselectivity, and will give possible explanations for this behavior.

2. Reactions in Solution

2.1. Reactions Under Pressure

The first examples (Scheme 1) of microwave-induced reactions were cycloadditions and pericyclic reactions performed under pressure (due to the use of domestic microwave ovens, to avoid the risk of igniting flammable solvents).[9,10]



MICROWAVE	CONTROL
10 min	4 h
p-xylene, 87%	*p*-xylene, 67%
325°<361°C	138°C

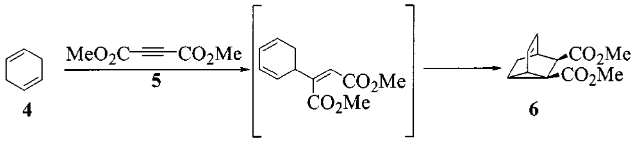
Scheme 1

These reactions using domestic microwave ovens were carried out in sealed, thick-walled glass tubes or in Teflon acid-digestion vessels.[11]

Teflon vessels can be used at up to 14 atm. of pressure and, at temperatures below 250 °C, are resistant to most commonly used chemicals. However, these digestion vessels deform at temperatures >250 °C.

The lack of control over temperature and pressure in these systems could lead to safety problems arising from overpressure due to the heating rate caused by microwaves.

These problems can be reduced by using a solvent-free methodology; this also permits the use of larger quantities of reagents. Thus, Giguere performed tandem ene/intramolecular Diels−Alder reactions of 1,4-cyclohexadiene (**4**) with dimethyl acetylenedicarboxylate (**5**) in sealed tubes in commercial microwave ovens[12] (Scheme 2) and Rao reported on the cycloaddition of furan and cyclopentadiene derivatives with (1-chloro-1,2-difluorovinyl)phenylsulfone.[13] In both cases, the yields were greatly improved and reaction times reduced in relation to conventional heating.



Conventional heating: DMF, reflux, 40 h, 14%
Microwave: DMF, 179-184°C (90 psi), 20 min, 49%

Scheme 2

2.2. Reactions at Reflux

Reactions involving a solvent at reflux require the use of modified commercial microwave ovens, in which the oven is perforated on the top to accommodate a reflux condenser and a 10 cm pipe is used to avoid microwave leakage; the rotating dish is replaced by a magnetic stirrer or by monomode reactors specially designed for chemical synthesis (Figure 1).[14]

The advantage of these reactions is that the reaction temperature is controlled by the reflux temperature of the solvent,[15] although overheating of between 13 and 26 °C above the normal boiling point of polar solvents may occur as a result of the "inverted heat transfer" effect, since boiling nuclei are formed at the surface of the liquid.[16]

Cycloadditions of C_{60} under microwave irradiation conditions require this methodology in most cases, because the reactions are performed on a very small scale and C_{60}, along with many dienophiles, does not absorb microwaves efficiently.[17]

2.3. Microwave Organic Reaction Enhancement (MORE)

Microwave Organic Reaction Enhancement (MORE) chemistry has been described by Bose as a safe and convenient alternative to pressure reactions and modified microwave ovens.[18]

In MORE chemistry, the solvent of choice absorbs microwaves in an energy-efficient manner and is therefore heated rapidly under microwave irradiation. The solvent should also have a boiling point at least 20−30 °C higher than the desired reaction temperature.[19]

High boiling polar solvents such as dimethylformamide (bp. 160 °C), chlorobenzene (bp. 132 °C), 1,2-dichlorobenzene (bp. 180°C), and 1,2,4-trichlorobenzene (bp. 214 °C) have been used. It is not necessary to employ a large volume of the reaction medium and in many cases a slurry at room temperature was found to give a clear solution during the rapid rise in temperature under microwave heating. This type of methodology is particularly valuable for medium-scale operations. Tall, loosely covered beakers with a capacity much greater than the volume of the reaction mixture were used, thus avoiding the use of closed vessels, overpressure, and explosions.[20] The main drawback of this methodology, however, is invariably the elimination of the high boiling solvent.

Several reactions have been performed using this methodology, including [4+2] and [2+2] cycloadditions. These were found to experience significant reductions in the reaction time and improvements in yield (Scheme 3 and Scheme 4).

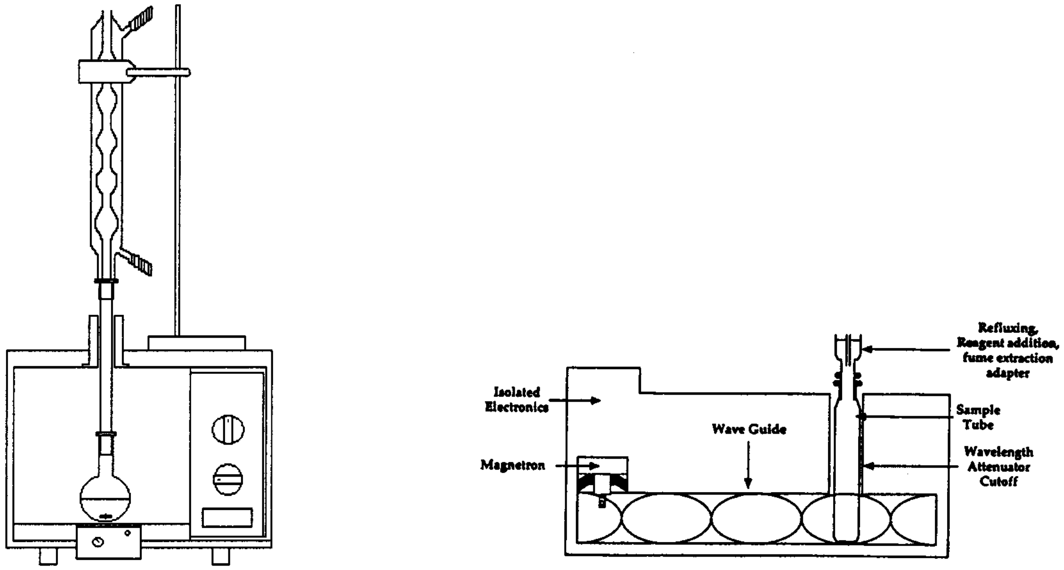
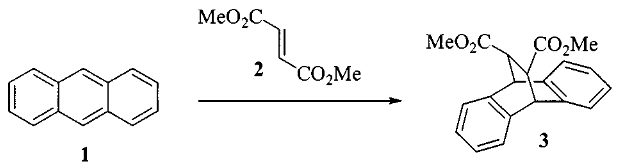


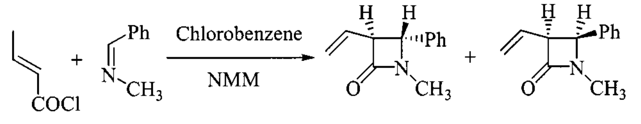
Figure 1. Scheme of a modified microwave oven and a focused monomode reactor



1 3

Solvent	Time	Yield (%)
Chlorobenzene	5 min	< 5
o-Dichlorobenzene	5 min	15-20
1,2,4-Trichlorobenzene	5-10 min	70

Scheme 3



7 8 9 10

Microwave irradiation: 30 s, 55°C, trans/cis 25/75
5 min, 108°C, trans/cis 80/20
Conventional heating: 6 h., 40°C, trans/cis 40/60
10 min, 115°C, trans/cis 80/20

Scheme 4

3. Solvent-Free Conditions

Solvent-free conditions are especially suitable for microwave activation. Several advantages are evident for this approach.[21]

- In the absence of solvent the radiation is absorbed directly by the reagents, so the effect of microwaves is more marked.
- Solid supports can be used efficiently; many mineral oxides are poor conductors of heat, while they absorb microwave radiation very efficiently.[22]
- This methodology can be used in conjunction with other synthetic methods, such as phase-transfer catalysis in the absence of solvent.[23]

The use of solvent-free methodologies is particularly interesting because environmentally benign syntheses can easily be designed:

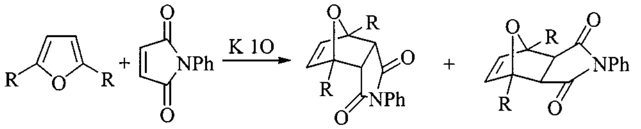
- The use of large volumes of solvent can be avoided, thus reducing solvent emissions and the necessity for redistillation.
- Workup procedures are considerably simplified, because in many cases the pure product can be obtained directly from the crude reaction mixture by simple extraction, distillation, or sublimation.
- Recyclable solid supports can be used efficiently in place of mineral acids and oxidants.
- Scale-up is facilitated by the absence of solvent.

3.1. Reactions with Supports

Alumina, silica, clays, and zeolites are increasingly used as acidic or basic supports.[24]

In many cases, cycloaddition reactions require Lewis acid catalysts to produce good yields. Clay and doped silica-gel catalysts have emerged as useful alternatives to Lewis acids.

The cycloaddition of furan (**11**) under solvent-free conditions, catalyzed by K10 montmorillonite, produced a decrease in the reaction time, although no changes in the *endo*/*exo* relationship were observed from that obtained by classical heating (Scheme 5).[25]

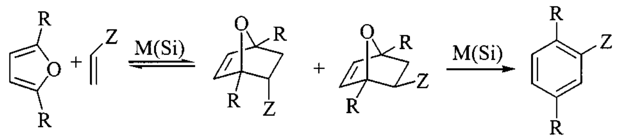


11 12 13 14

	13	14
Conventional heating	1.3	1
Microwave irradiation	1.5	1

Scheme 5

The use of silica-supported Lewis acids as catalysts for Diels−Alder reactions of 2,5-dimethylfuran leads to fairly good yields of adducts. Computational studies of the reaction mechanism show that the activation barriers are lower in the catalyzed reaction, especially when Al(Si) is used (Scheme 6).[26]



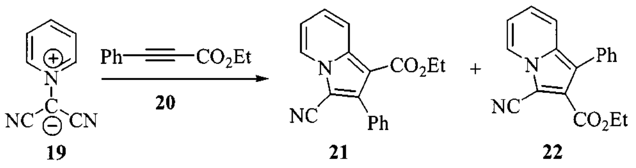
11 15 16 17 **18** 50-92%

Scheme 6

The use of microwave irradiation leads, in some cases, to good yields of aromatic products and thus constitutes a good synthetic route to polysubstituted aromatic compounds. Computational studies show that hard Lewis acids, such as aluminium derivatives, make the adduct ring-opening stage easier than the corresponding zinc derivatives do (Scheme 6).[26]

Solid supports such as silica gel[27] and alumina[28] have also been used in the generation of 1,3-dipoles and, in this way, heterocyclic compounds can be obtained in one-pot procedures. However, no changes in regioselectivity have been observed under microwave irradiation conditions in these cases.

The regioselectivity can be modified by changing the polarity of the solid support.[29] In the reaction of pyridinium dicyanomethylide (**19**) with ethyl phenylpropiolate (**20**), the selectivity changes from 88:12 to 98:2 when the support is changed from silica gel to neutral bentonite (Scheme 7).



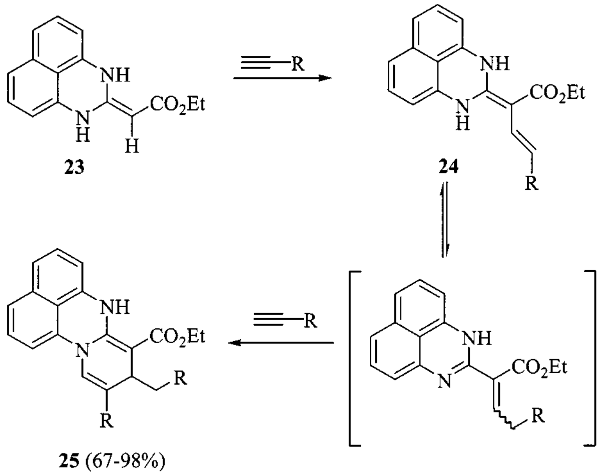
	21	22
Silicagel	88	12
Bentonite	98	2

Scheme 7

3.2. Reactions Without Support

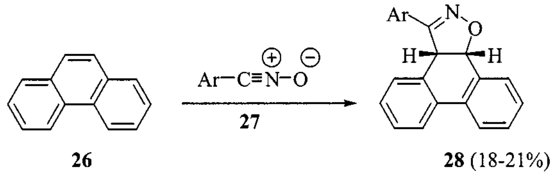
An alternative to the use of supported reagents is the use of uncatalyzed "neat reactions". Under these conditions, the radiation is absorbed directly by the reagents and this produces spectacular accelerations and improved yields and purities of the reaction products. Workup procedures are simplified and changes in the selectivity of the cycloaddition are sometimes observed.

Diels–Alder reactions[30] and 1,3-dipolar cycloadditions[31,32] have been performed using this methodology. Thus, Bazureau described the cycloaddition of a 1-azadiene derived from a vinylpyrimidine (**23**) as a tandem conjugate addition/hetero-Diels–Alder reaction (Scheme 8).[33]



Scheme 8

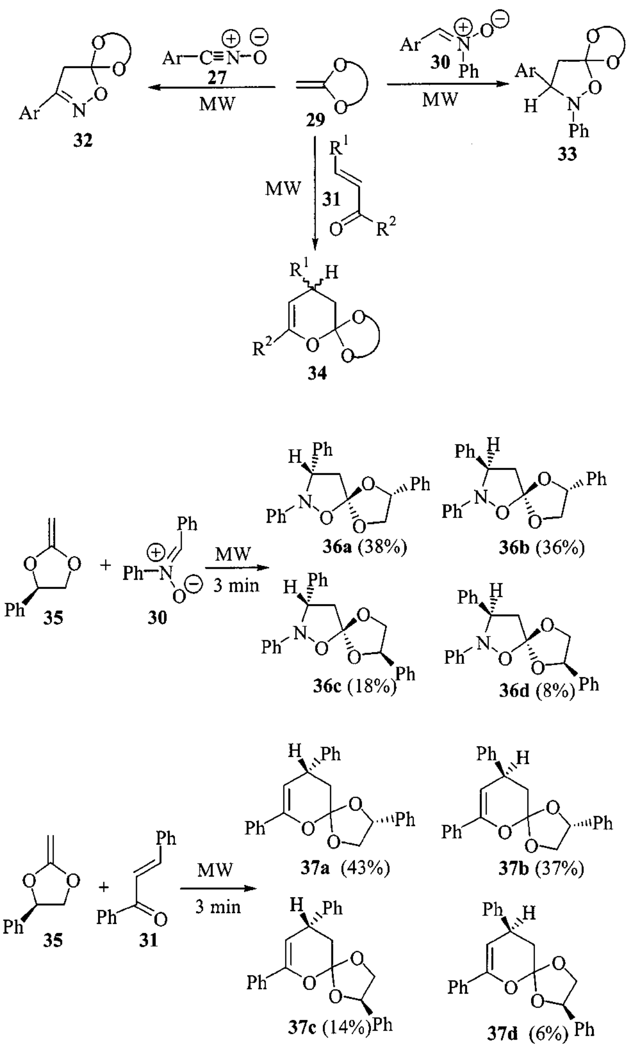
Corsaro emphasizes the importance of the solvent-free methodology in the cycloaddition of polycyclic aromatic hydrocarbons with nitrile oxides. Under solvent-free conditions, reactions were completed in 3–10 min. It was observed that the reaction failed when it was performed in refluxing decalin, due to degradation of the 1,3-dipole (Scheme 9).[34]



Scheme 9

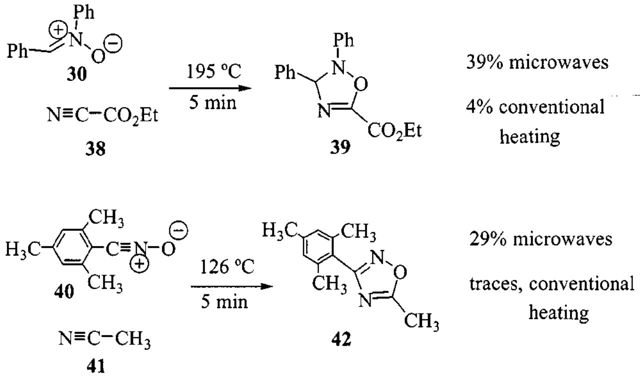
Díaz-Ortiz described the hetero-Diels–Alder and 1,3-dipolar cycloaddition of ketene acetals under these conditions. Reactions were improved and products were isolated directly from the crude reaction mixture, with no polymerization of ketene acetals occurring.[35]

When an enantiomerically pure ketene acetal **35** was used, cycloadditions with *N*,α-diphenylnitrone (**30**) and with chalcone (**31**) were achieved within 3 min; in 98 and 96% yields, respectively. Under the same reaction conditions, but using classical heating in the absence of solvent at 120–124 °C for 3 min, yields decreased to 3–4%. These results suggest that the excellent yields achieved under microwave irradiation conditions are perhaps not exclusively due to the rapid heating of the reaction mass (Scheme 10).



Scheme 10

Microwave irradiation induces 1,3-dipolar cycloaddition of aliphatic and aromatic nitriles with nitrones or nitrile oxides under solvent-free conditions. Such reactions give the corresponding 2,3-dihydro-1,2,4-oxadiazoles **39** or



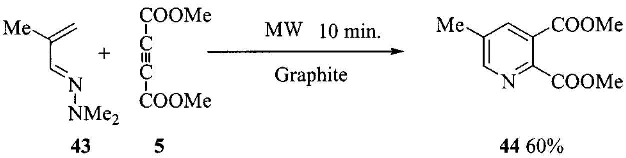
Scheme 11

1,2,4-oxadiazoles **42**, respectively (Scheme 11).[36] With microwave irradiation, the yields were always higher than those obtained with classical heating. However, the most significant differences were achieved with the less reactive nitriles. Such an observation is in keeping with Lewis's remark that "slower reacting systems tend to show a greater effect under microwave irradiation than faster reacting systems".[37]

3.3. Reactions with a Heat Captor

Garrigues described the use of graphite as a heat captor under microwave irradiation conditions. Graphite is a chemically inert support that couples strongly with microwaves by a conduction process and so is able to transmit high levels of thermal energy to the supported reagents.[38]

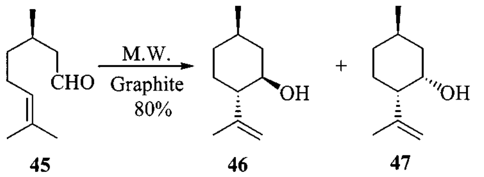
Methods involving microwave-assisted, graphite-supported dry media have been described for hetero-Diels−Alder cycloaddition reactions of anthracene, 1-azadienes, and 1,2,4,5-tetrazines with several C−C dienophiles and carbonyl compounds.[39] This technique leads to a shortening of reaction times; a situation that allows work to be undertaken at ambient pressure in an open reactor, avoiding the formation of unwanted compounds by thermal decomposition of reagents or products (Scheme 12).



Scheme 12

Similarly, higher power-input retro-Diels−Alder reactions of anthracene derivatives have been observed to occur in 3−5 min. periods.[39] This method is an alternative to the use of flash thermolysis. The use of graphite is a prerequisite for obtaining high temperatures in a short time.

This methodology has been extended by the same author to include carbonyl-ene reactions.[40] The cyclization of (+)-citronellal (**45**) to pulegols **46** and **47** is faster when performed under microwave irradiation conditions with a graphite support. The stereoselectivity was also different to that obtained using classical heating, with a greater amount of (+)-neoisopulegol (**47**) being produced (Scheme 13).



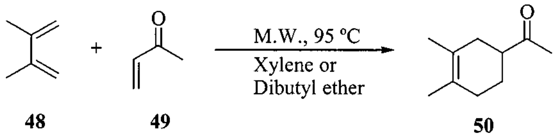
Scheme 13

4. Specific Effects in Cycloaddition Reactions

The existence of results that cannot be explained solely by the effect of rapid heating has led various authors to postulate the existence of a so-called "microwave effect". According to this, acceleration or changes in reactivity and selectivity could be explained by a specific radiation effect and not merely by a thermal effect. Several reviews have catalogued synthetic results that have been attributed to the microwave effect.[4b,41,42]

Various authors have proposed that changes in thermodynamic parameters under microwave irradiation conditions are the cause of the "microwave effect". However, when a compound absorbs microwaves, the dielectric heating causes an increase in the temperature of the system. When the internal energy of the system is raised, it is distributed between translational, rotational, or vibrational energies, independently of the mode of heating. Consequently, it was concluded that no kinetic differences should be expected between reactions heated by microwaves and by classical heating if the temperature is known and the solution is thermally homogenous.[6c,43]

Berlan found that cycloaddition reactions performed at reflux in xylene or dibutyl ether (Scheme 14) were always faster under microwave conditions than when using classical heating methods.[44] The observed acceleration is more significant in apolar solvents that show weak dielectric losses (Figure 2). Because of this, the authors proposed that a modification to $\Delta G^{\ddagger}$ is produced, possibly through a change in the entropy of the system. Subsequently, Strauss found that the kinetics of these and other reactions are similar under microwave irradiation and classical heating conditions; hence there was no specific effect.[45]



Scheme 14

Similarly, in the cycloaddition of cyclopentadiene (**51**) with methyl acrylate (**52**), described by Gedye, microwave radiation does not alter the *endo/exo* selectivity and the observed changes can be explained by the fact that the reactions under microwave conditions occur at higher temperatures than those taking place at reflux (Scheme 15).[46]

The existence of the so-called "microwave effect" has not been proved. However, it does seem to have been demon-

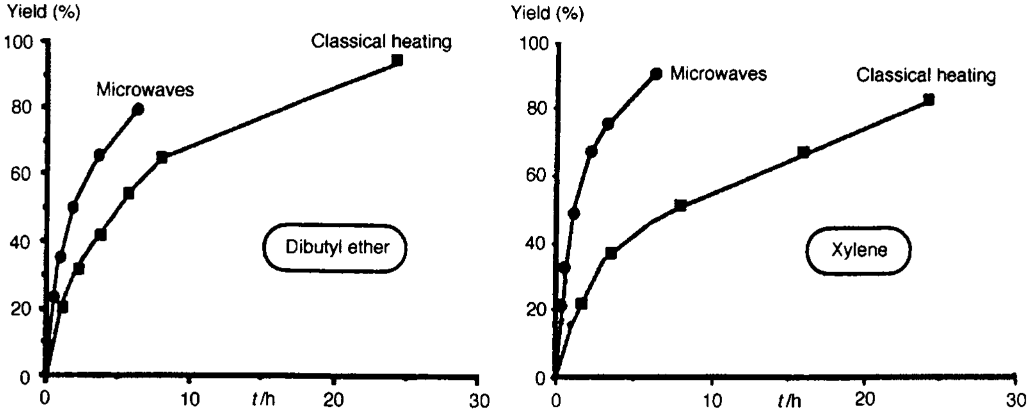
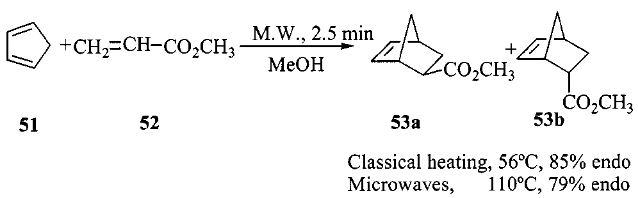


Figure 2. Yield vs. time for the reaction depicted in Scheme 14



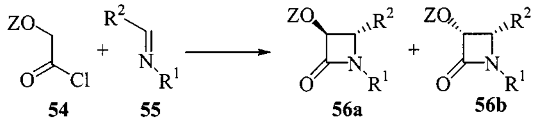
Scheme 15

strated that overheating of polar liquids[16] occurs and that "hot spots" are present in heterogeneous systems, especially at the interface.[41] Similarly, microwave irradiation produces an increase in the molecular mobility in solids.[4b]

The utility of microwaves is evident in improving numerous processes or in modifying the chemo-, regio-, or stereoselectivity. These changes seem to arise in many cases from the heating rate provided by microwaves; a situation that is not possible using classical heating. Suard considered there to be two important differences between conventional heating and microwave irradiation.[47] Firstly, under microwave irradiation conditions, the initial slope of the sample temperature is different from zero, and secondly, in contrast to the situation observed with conventional heating, conduction flow represents the major flow of the system. As a consequence, a rapid heating rate must be responsible for the effects observed.

In cycloaddition reactions, only a few instances have been described in which changes in the selectivity have been observed under microwave irradiation. In concerted processes, the regio- and stereoselectivities of the reaction are governed by frontier orbital interactions, and no changes in the selectivity are expected unless a change in the reaction mechanism occurs.

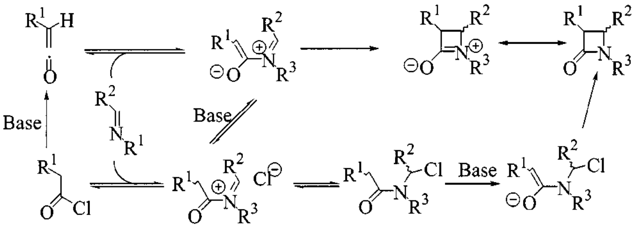
Bose has described reactions of acid chlorides **54** with Schiff bases **55**, in which the stereoselectivity depends on the order of addition of the reagents (Scheme 16).[48,49] When the condensation was conducted by a "normal addition" sequence (i.e. acid chloride last), only the *cis*-β-lactam (**56b**) was formed. However, if the "inverse addition" technique (triethylamine last) was used, 30% *cis*- and 70% *trans*-β-lactams were obtained under the same conditions. When the reaction was conducted in a microwave oven using chlorobenzene, the ratio of *trans*- and *cis*-β-lactams was 90:10, irrespective of the order of addition. Moreover, there was no isomerization to the thermodynamically more stable *trans*-β-lactam (**56a**).



Z = $COCH_3$, Ph, $R_1 = CH_2Ar$, R_2 = Ar

Scheme 16

This effect has recently been rationalized by postulating that, under microwave irradiation conditions, the route involving direct reaction between the acyl chloride and the imine competes efficiently with the ketene–imine reaction pathway (Scheme 17).[50]

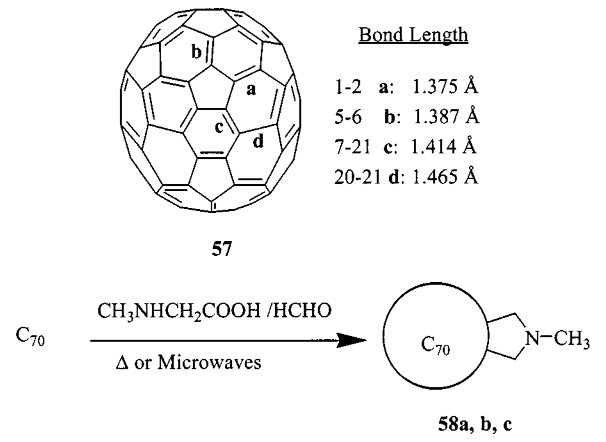


Scheme 17

Langa described the cycloaddition of *N*-methylazomethine ylides to C_{70} to give three regioisomers (**58a–c**), by attack at the 1–2, 5–6, and 7–21 bonds (Scheme 18).[51]

Using conventional heating conditions, the 7–21 (**58c**) isomer was formed only as a low proportion of the total, and the 1–2 (**58a**) isomer was found to predominate. Under microwave irradiation conditions and on using ODCB, which absorbs microwaves efficiently, significant changes were observed. Unlike under the classical conditions, **58c** was never formed under microwave irradiation conditions, regardless of the power of irradiation, and isomer **58b** was predominant under higher power conditions (Scheme 18 and Figure 3).

A computational study on the mode of cycloaddition showed that the reaction is stepwise, the first step consisting



57

58a, b, c

Scheme 18

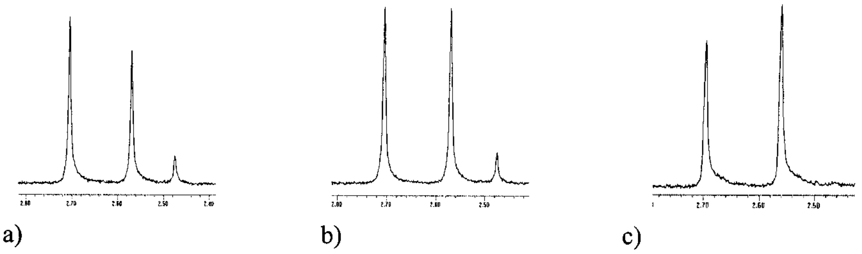


Figure 3. ^1H NMR spectra (methyl groups) of the adducts **58a**, **58b**, and **58c** (Scheme 18) from left to right. a) classical heating in toluene; b) classical heating in ODCB; c) microwave irradiation at 180 W in ODCB

of a nucleophilic attack on the azomethine ylide. The most highly negative charge on the fullerene moiety in the transition states **a** and **b** is located at the carbon adjacent to the carbon–carbon bond being formed. In transition state **c**, however, the negative charge is delocalized all around the C_{70} subunit. The relative ratio of isomers **58a–c** is related to the hardness, and so the formation of **58b** should be favored under microwave irradiation conditions. It is noteworthy that purely thermal arguments predict the predominance of **58c** under microwave irradiation; and this is opposite to the result found experimentally.

5. Applications

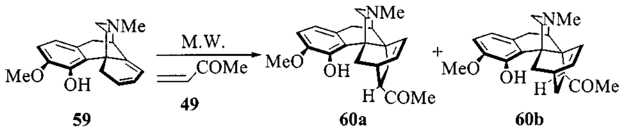
5.1. Applications in the Synthesis of Natural Products

Cycloaddition reactions increase molecular complexity by formation of a cyclic compound and, simultaneously, formation of two C–C bonds.[52] Such reactions are also regio- and stereoselective. For these reasons, cycloaddition reactions are, in most cases, the key step in multistep syntheses of natural products.

These reactions usually require long reaction times, high temperatures, and/or Lewis acid catalysts; conditions that result in partial or total decomposition of sensitive compounds. This is particularly important in the synthesis of natural products, and these problems have in many cases been conveniently solved by the use of microwave irradiation conditions. The short reaction times associated with microwave activation avoid the decomposition of reagents and products and prevent polymerization of the diene or dienophile.

In an attempt to prepare new diprenorphine analogs, Linders, in one of the first examples of microwave-induced organic reactions, reported on the reaction of methyl vinyl ketone with 6-demethoxy-β-dihydrothebaine (**59**).[53] Attempts to perform the Diels–Alder reaction under classical conditions resulted in extensive polymerization of the dienophile. A dramatic improvement was achieved when the cycloaddition was carried out using a modified microwave oven to perform the reaction at the reflux temperature of methyl vinyl ketone. Under these conditions, the two adducts **60a** and **60b** were obtained in a 3:2 ratio according to HPLC (Scheme 19).

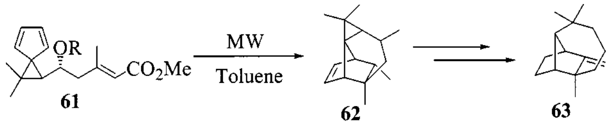
Fallis, in the synthesis of the bridged sesquiterpene longifolene (**63**), performed the intramolecular cycloaddition of compound **61** as a key reaction for the construction of the bridged system (Scheme 20).[54]



59 **49** **60a** **60b**

Microwaves, 32%, 3 : 2 ratio

Scheme 19



61 **62** **63**

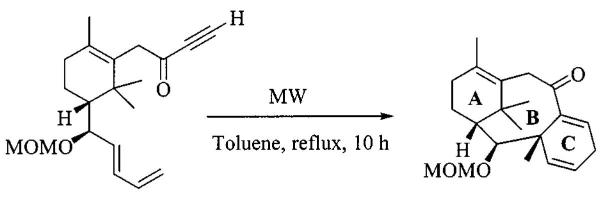
R = $SiMe_2{}^tBu$

62 Conventional heating, 10%
Microwave irradiation, 92%

Scheme 20

The cycloaddition reaction afforded 10% of the cycloadduct **62** after 24 h at reflux in toluene, while decomposition predominated at higher temperatures. When the triene was heated in a sealed glass vessel in a modified microwave oven, however, the adduct was obtained in 92% yield.

The same author used this strategy for the synthesis of tricyclic taxoide skeleton **65**; an intramolecular Diels–Alder approach that proceeds in the direction from left to right (ring A to BC) (Scheme 21).[55] Once again, microwave irradiation was necessary to perform the required cycloaddition in good yield.



64 **65**, 40%

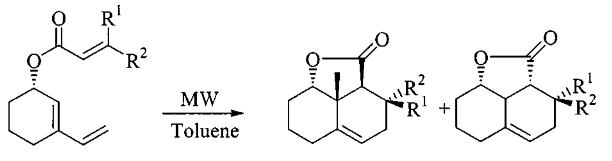
Scheme 21

The cycloaddition of ketone **64** could be effected in a sealed glass tube in a modified microwave oven, to afford the tricyclic system stereoselectively. This major adduct arose via the preferred transition state, in which the nonbonded interactions were minimized by the alignment of the dienophile beneath the triene unit remote from the MOM substituent. This pattern of π-facial selectivity implies that, with the "natural" C2 stereoselectivity, the preferred geometry should provide the relative stereochemistry required for taxol itself.

A synthesis of the decalin unit of compactin (**68**) — a potent competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which acts as an effective hypocholesterolemic agent — was planned around an intramolecular Diels−Alder reaction (Scheme 22).[56]

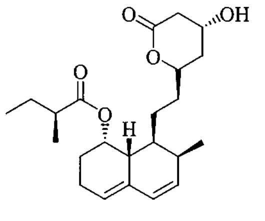
The reaction was carried out by heating the reagents at 150 °C for 10 h in *o*-xylene. The desired *exo* adduct was obtained with high stereoselectivity, and formation of the diastereoisomer **67b** was considered to occur by isomerization of the *exo* adduct.

Under microwave irradiation conditions, the reaction was dramatically accelerated and the carboxylic acid was obtained after 45 min, with a small increase in the stereoselectivity (Scheme 22).[56]



66 **67a** **67b**

a $R_1 = CO_2Et$, $R_2 = H$; Conventional heating: exo/endo: 91/9
Microwave irradiation: exo/endo: 94/6
b $R_1 = CO_2H$, $R_2 = H$; Conventional heating: exo/endo: 82/18
Microwave irradiation: exo/endo: 85/15



Compactin **68**

Scheme 22

5.2. Applications in Heterocyclic Chemistry

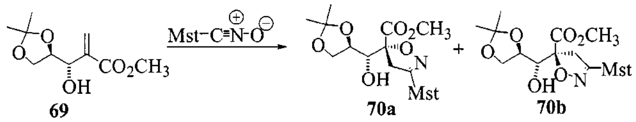
5.2.1. Synthesis of Heterocyclic Compounds by Cycloaddition Reactions

Cycloaddition reactions, in contrast to classical cyclization reactions, have recently become a powerful tool for the construction of heterocyclic rings. Microwave irradiation has been used to increase the reaction rate, to perform difficult cycloadditions, and to obtain temperature-sensitive compounds.

Thus, [2+2] cycloadditions have commonly been used to obtain β-lactam derivatives.[18−20,48,49] Bose described the synthesis of the thienamycin side chain using this methodology,[57] with the first step a [2+2] cycloaddition under microwave irradiation conditions. Likewise, Khajavi described the reaction of trichloroacetic anhydride with imines.[58] Using classical heating conditions, the reaction required the use of $Fe_2(CO)_9$ as a catalyst, whereas under microwave irradiation conditions no catalyst was required.

1,3-Dipolar cycloadditions have been used to produce heterocyclic five-membered rings; microwave irradiation was used to facilitate the cycloaddition and even to prepare the 1,3-dipole in situ, by elimination,[27−28] thermal ring opening[31b] and thermally induced tautomerization.[59]

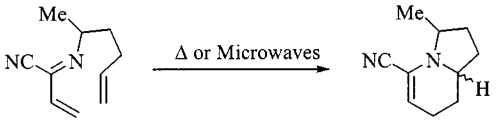
Loupy described the preparation of trifluoromethyl-substituted isoxazolines by cycloaddition of nitrones to fluorinated dipolarophiles, and considerable improvements in yields and experimental conditions were achieved.[60] Fišera described the effect of the addition of methylmagnesium bromide on the stereoselectivity of reactions of mesitonitrile oxide with Baylis−Hillman adducts **69** (Scheme 23).[61] In this case, microwave irradiation produced a decrease in reaction time for both the chelated and the non-chelated cycloadditions, without any loss of stereoselectivity for noncatalyzed cycloadditions and with only a small change in the stereoselectivity for the chelated reaction.



69	**70a**	**70b**
r.t., 48 h	95	5
MW, 4 min	78	22

Scheme 23

The hetero-Diels−Alder reaction is one of the most important methods for the synthesis of heterocycles. Microwave irradiation has been used to improve reactions of heterodienophiles[40,62] and heterodienes[33,35,38,63] with low reactivities. Motorina described the intramolecular hetero-Diels−Alder reaction of *N*-alkyl-2-cyano-1-azadienes (**71**) (Scheme 24);[63] although the reaction had already success-



71 **72**

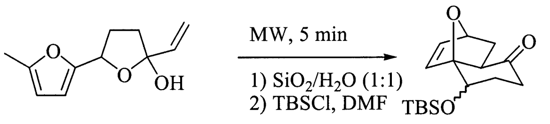
Scheme 24

fully been performed by heating the reactants in benzene overnight in a sealed tube at 110 °C, it was found that reaction time could be reduced to 14 min in a microwave oven.

5.2.2. Reactivity of Heterocyclic Compounds in Cycloaddition Reactions

Only a few examples of the reaction of heterocyclic dipoles under microwave irradiation conditions have been described.[29] The use of heterocycles in [4+2] cycloadditions is more common and such reactions of pyrones,[64] furan,[25,26,65] and pyrazoles[66−68] have been described, along with retro-Diels−Alder reactions.[12]

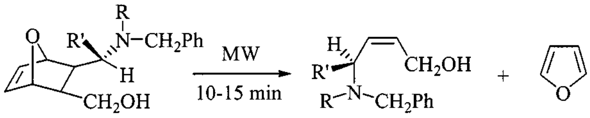
The intramolecular Diels−Alder reaction of furan **73** fails to take place using classical heating conditions (Scheme 25).[65] However, the reaction has been successfully carried out, in 64% yield, by using microwaves and absorbing the product onto silica gel/water.



73 **74** 64 %

Scheme 25

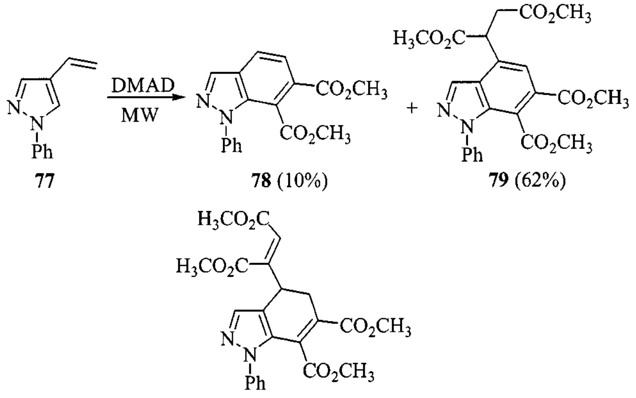
Bortolussi described the synthesis of unsaturated amino alcohols **76** by thermolysis of furan adducts **75**, with a significant reduction in reaction time observed when using microwaves (Scheme 26).[69]



75 **76** (98%) **11**

Scheme 26

Diels−Alder cycloadditions of vinylpyrazoles under classical conditions require highly reactive dienophiles and extreme conditions; i.e. high pressures and temperatures (8−10 atm. and 120−140 °C) for long reaction times (several days), to obtain, in most cases, only moderate yields.[70] The main obstacle in these reactions is the extensive polymerization of the reagents. 1-Phenyl-4-vinylpyrazole (**77**) reacted with dimethyl acetylenedicarboxylate (DMAD) within 6 min under microwave irradiation conditions, to afford the adducts **78** and **79** in 72% overall yield (Scheme 27).[66] The cycloaddition was performed in a Teflon vessel in a domestic microwave oven. The clean nature of the reaction allowed intermediate **80** to be characterized, although this compound is not detected when classical heating is used; as it rearranges spontaneously in a few minutes at the reaction temperature to give the aromatic compound.

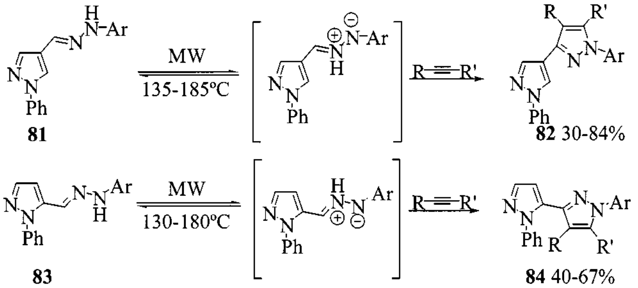


77 **78** (10%) **79** (62%) **80**

Scheme 27

The reaction proceeds even with a very poor dienophile such as ethyl phenylpropiolate, which does not react under classical conditions.

Bipyrazolyl derivatives can be prepared by 1,3-dipolar cycloadditions under microwave irradiation conditions.[67] The irradiation results in thermal isomerization of the pyrazolyl hydrazones **81** and **83** to the corresponding azomethine imines, to afford [4,3′] or [5,3′] bipyrazolyl adducts **82** and **84** in 10−45 min in 30−84% yields (Scheme 28).



81 **82** 30-84% **83** **84** 40-67%

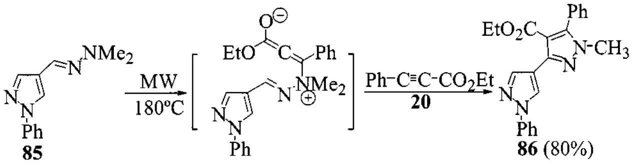
Scheme 28

Microwave irradiation was required to obtain the adducts in good yield. Under microwave irradiation conditions, the hydrazones underwent a 1,3-dipolar cycloaddition with dimethyl fumarate to afford the corresponding adducts in 84 and 56% yield. When classical heating in an oil bath under the same reaction conditions (temperature and reaction time) was used, yields decreased to 17 and 25%, respectively.

Although pyrazolyl hydrazones could theoretically undergo a [4+2] cycloaddition by reacting as 1-azadienes, no example could be found in which cycloaddition gave [4+2] adducts.

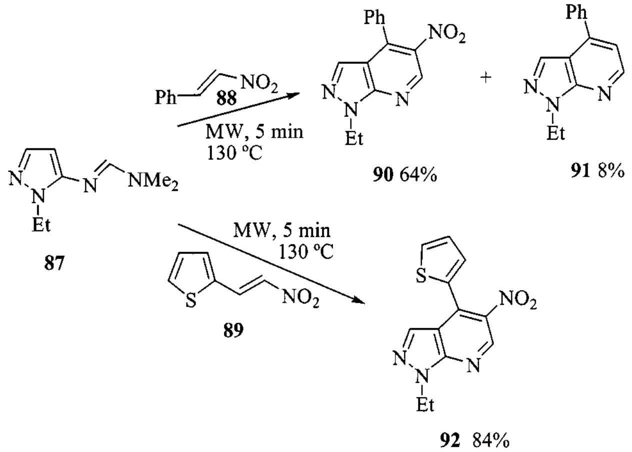
Computational studies on model systems, at the B3LYP/6-31G* level, were performed in order to ascertain the reasons for the preferential [3+2] periselectivity. The data on the transition structures corresponding to the [4+2] and [3+2] reactions predicted the preferential formation of the [3+2] cycloadducts. Moreover, inclusion of thermal and entropic factors resulted in an enhancement in the energy differences in favor of the [3+2] process.

The corresponding dimethyl hydrazone **85**, which cannot undergo a thermal 1,2-hydrogen shift to afford an azomethine imine, gave the (4,3′) bipyrazole **86** in 80% yield under microwave irradiation conditions (Scheme 29). These reactions could occur through a Michael-type intermediate that could give bipyrazole **86** by cyclization, or a cyanopyrazole by fragmentation. Classical heating in these cases did not give rise to these compounds.



Scheme 29

Pyrazole derivatives are very reluctant to participate as dienes in Diels−Alder cycloadditions that involve the pyrazole ring, due to the associated loss of aromaticity.[71] However, microwave irradiation under solvent-free conditions induces pyrazolyl 2-azadienes **87** to undergo Diels−Alder cycloadditions with nitroalkenes **88−89** within 5−10 min, to give good yields of pyrazolo[3,4-*b*]pyridines (Scheme 30).[68] Under classical heating conditions, only traces of the cycloadducts were detected.



Scheme 30

This is the first example of a [4+2] cycloaddition involving a pyrazole ring and it represents a new, interesting, and versatile approach to the preparation of pyrazolo[3,4-*b*]pyridines.

However, the reaction of vinylpyrazoles and pyrazolylimines with *N*-trichloroethylidenecarbamate, a reactive aza-dienophile, did not produce the expected pyrazolopyridines.[72]

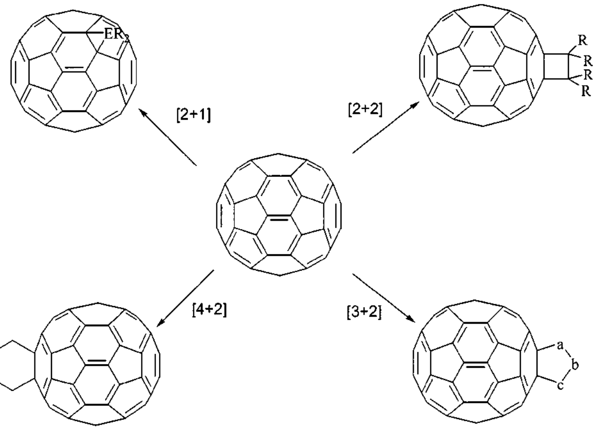
Reaction between vinylpyrazoles and *N*-trichloroethylidenecarbamate occurs though the exocyclic double bond to give Michael addition to the conjugated system. This reaction must be considered as an electrophilic substitution on the exocyclic bond, which is activated by conjugation with the pyrazole ring. On the other hand, 5-pyrazolylimine reacted by a substitution at the activated 4-position of the pyrazole ring, while 4-pyrazolylimine − in which position 4 is blocked − did not react after 15 min of microwave irradiation and the only process observed was the decomposition of the reagents.

With conventional heating under similar conditions, no reaction occurs with either vinylpyrazoles or pyrazolylimines; only decomposition of the starting material takes place. These results show that the introduction of a nitrogen in the exocyclic double bond reduces its nucleophilicity.

5.3. Applications in C_{60} Chemistry

Since Krätschmer and Huffmann discovered a procedure for preparing bulk quantities of C_{60},[73] the chemistry and derivatization of fullerene has continued to attract attention aimed at preparing derivatives with interesting physical properties and biological activities.[74][75] In addition, new materials based on C_{60} derivatives show promise for solar energy conversion,[76] nonlinear optical behavior,[77] superconductivity,[78] ferromagnetism,[79] or HIV-1 protease inhibition.[80]

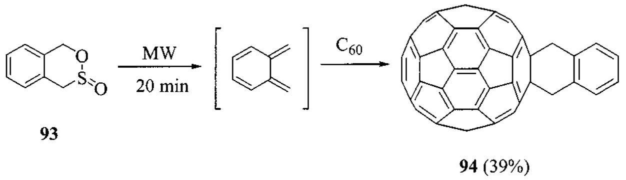
C_{60} reacts as an electron-deficient polyolefin and, consequently, one of the main ways of functionalizing fullerenes involves cycloaddition reactions,[81] in which C_{60} is a reactive 2π component. In this context, [1+2], [2+2], [3+2], and [4+2] cycloadditions have been performed (Scheme 31); and the conditions for cycloadduct formation strongly depend on the gap between the controlling orbitals. For this reason it is frequently necessary to use conditions involving several hours (or days) under reflux in high boiling solvents. Thus, it was interesting to investigate the potential of microwave irradiation in the preparation of fullerene derivatives when this type of reaction is involved. The characteristics of [60]fullerene, i.e. the absence of a dipole moment and the necessity of working on a very small scale, entail the use of a solvent in these reactions.



Scheme 31

[4+2] Cycloadditions selectively afford the 6,6-ring junction adducts,[82] which in some cases undergo a facile retro-Diels−Alder reaction as a consequence of the low thermodynamic stability of the adduct. However, very stable Diels−Alder cycloadducts have been prepared by using different substituted *o*-quinodimethanes, thanks to stabilization of the adducts by aromatization.[83]

Langa et al. described the microwave-induced Diels–Alder reaction with *o*-quinodimethane – generated in situ from 4,5-benzo-3,6-dihydro-1,2-oxathiin-2-oxide (**93**) (sultine)[84,85] – leading to cycloadduct **94** (Scheme 32).[86] This reaction was the first application of microwave irradiation to the preparation of a functionalized C_{60} derivative.



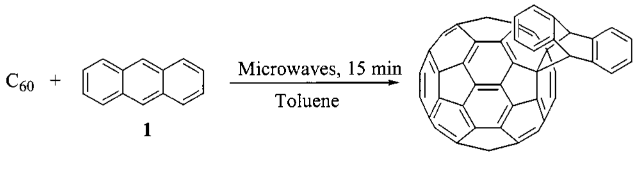
93

94 (39%)

Scheme 32

In order to avoid explosion hazards,[87] a modified domestic microwave oven was used (Figure 1). Higher yields were obtained in shorter periods of time when using microwave irradiation (39% yield after 20 min of irradiation) than under conventional thermal conditions. Longer irradiation times produced a decrease in the yield of **94** due to increased bisadduct formation.

The scope of the microwave technique in the preparation of fullerene derivatives was demonstrated in the well known Diels–Alder reaction of C_{60} with anthracene,[88] which had been reported to form cycloadduct **95** under thermal conditions (13%,[88a] reflux, toluene, three days; 25%[88b] reflux, benzene, 12 h) (Scheme 33), in addition to multiply-substituted adducts that underwent cycloreversion to the starting materials.



1

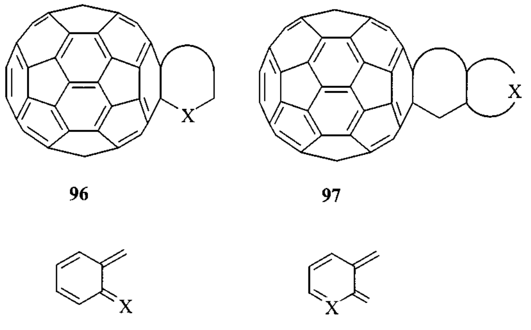
95 (35%)

Scheme 33

Under microwave irradiation conditions, with toluene as a solvent, cycloadduct **95** was formed in 35% yield after 15 min at 800 W,[89] constituting an improvement on the yields obtained by conventional heating. This case also demonstrates how this methodology not only reduces the reaction times to minutes, as one would expect, but also leads to improvements in the yields. This fact is probably due to a decrease in the degree of reversion of the cycloadduct in the shorter period of time needed for the microwave reaction. It is remarkable that under microwave conditions no formation of bis adducts was observed in these reactions.

Fullerene derivatives functionalized with heterocycles (fulleroheterocycles) are of particular interest because:[90] (a) even a simple combination of fullerenes with structurally diverse heterocycles provides a multitude of derivatives, (b) heterocycles are themselves intriguing and important functional groups, (c) functional conversions can be carried out with relative ease by heterocyclic modification and heterocyclic ring-opening, and (d) bond formation between fullerene carbons and various heteroatoms provides a new aspect of functionalization.

Fullerene derivatives fused with heterocycles by bonds between fullerene carbons and heterocycle heteroatoms (**96**) (fused heterocycles) by means of hetero-Diels–Alder reactions, and fullerene derivatives (Scheme 34) covalently linked with heterocycles by bonds between fullerene carbons and heterocycle ring carbons (**97**) (covalently linked heterocycles) by Diels–Alder processes have been prepared by cycloaddition of heterocyclic *o*-quinodimethanes **98** and **99**, respectively, using microwave irradiation conditions.

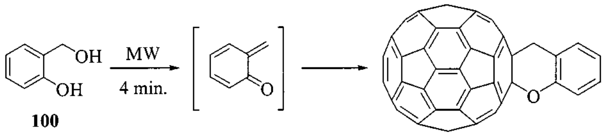


96 **97**

98 **99**

Scheme 34

The reaction of C_{60} with *o*-quinone methide, prepared from *o*-hydroxybenzyl alcohol (**100**) (Scheme 35), was performed in a modified domestic microwave oven at 800 W and gave **101** in only 4 min and with a 27% yield.[89] Although Eguchi et al.[91] reported a slightly better yield (31%) for this reaction using thermolysis in a sealed vessel, the microwave approach to this adduct offers the simplicity of its procedure, avoiding the risk of high pressure conditions.



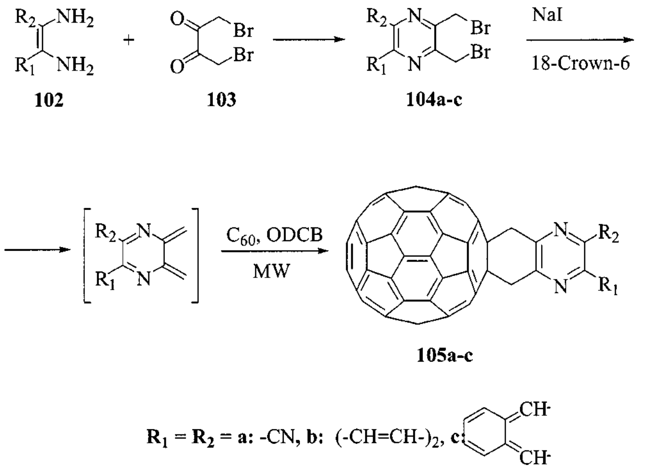
100

101 (27%)

Scheme 35

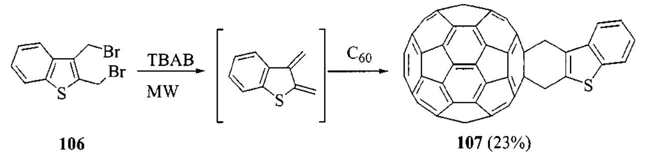
Novel pyrazine-containing cycloadducts **105a–c** were synthesized by Diels–Alder reaction of [60]fullerene with the corresponding 2,3-bis(bromomethyl)pyrazine derivatives **104a–c** (Scheme 36);[92] the 2,3-pyrazinoquinodimethanes were trapped as the Diels–Alder adducts by reaction with [60]fullerene in refluxing ODCB as solvent under classical heating conditions and under microwave irradiation conditions in a focused microwave reactor (Figure 1). Once again, the use of microwave irradiation led to higher yields than those produced by classical heating for **105a** and **105b** (up to 4.5 times) and reaction times were significantly reduced from 24 h to 0.5 h. In the case of **105c**, large quantities of polyadducts were detected under microwave irradiation, causing a decrease in the yield.

Interestingly, in the syntheses of thiophene cycloadducts **107**, the use of microwave irradiation led to lower yields[92]



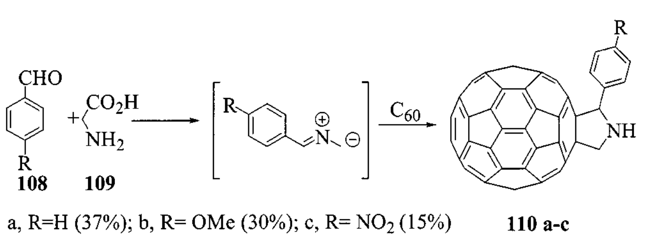
Scheme 36

(Scheme 37) than those obtained from conventional heating (23% versus 43%), although reaction times were significantly reduced.[93]



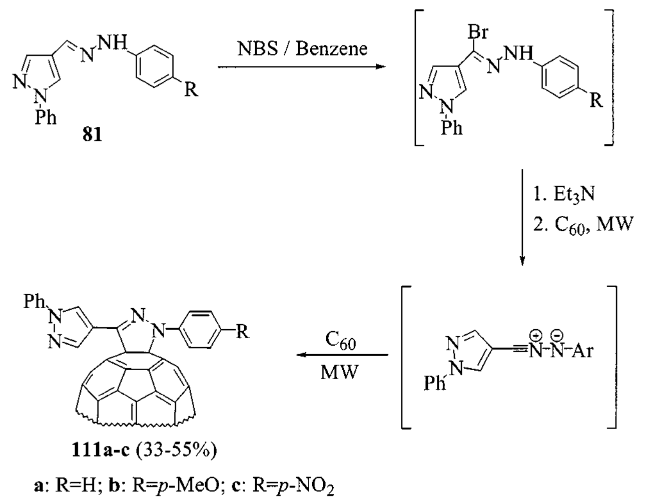
Scheme 37

A general method for the functionalization of C_{60} is the 1,3-dipolar cycloaddition of azomethine ylides, which was first described by Prato[94] and leads to fulleropyrrolidines. Several fulleropyrrolidines (**110a−c**) have been prepared under microwave irradiation conditions by Langa et al.[51] These authors observed that microwave irradiation again competes favorably and, thus, **110a** was prepared in 37% yield using a focused microwave reactor, and **110b** and **110c**, which had not previously been reported, were also prepared in 30% and 15% yield, respectively (Scheme 38). The dipolar cycloaddition of azomethine ylides to C_{70} under microwave irradiation conditions has also been studied, and these experiments showed interesting changes in regioselectivity (vide supra).



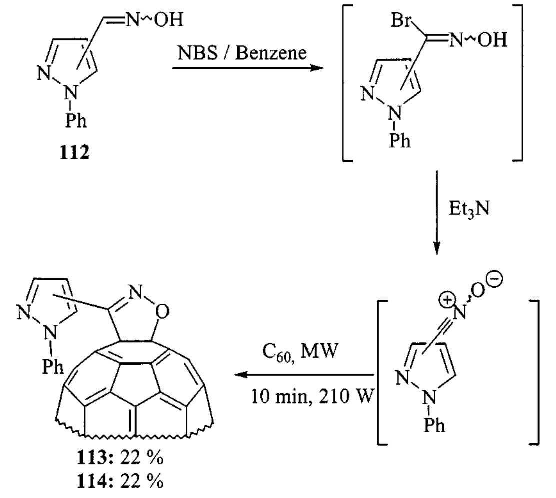
Scheme 38

The formation has been described of several 1-aryl-3-(1-phenylpyrazol-4-yl)pyrazolo[60]fullerene adducts (**111a−c**) from nitrile imines, generated in situ from the corresponding hydrazone and NBS in the presence of Et_3N and allowed to react with C_{60} under microwave irradiation conditions (Scheme 39).[95] This approach to a 2-pyrazoline ring fused to C_{60} is simpler than the previously described method, that involved cycloaddition to nitrile imines generated in situ from the corresponding *N*-chlorobenzylidene derivatives.[96]



Scheme 39

Under similar conditions, 3′-(*N*-phenylpyrazolyl)isoxazolo[60]fullerene dyads **113** [R = 4-(*N*-phenyl)pyrazolyl] and **114** [R = 5-(*N*-phenyl)pyrazolyl] have been prepared in 22% yield from the corresponding nitrile oxides (Scheme 40).[97] Longer reaction times afforded larger amounts of bis adducts. The same reactions under thermal conditions produced lower yields (**113**: 14%; **114**: 17%). A significant accelerating effect (10 minutes vs 24 hours) occurs under microwave irradiation conditions. These new isoxazoline-fused organofullerenes show an improved acceptor ability over the parent C_{60}, as the values of reduction potential show an anodic shift in relation to the C_{60} parent.



Scheme 40

6. Conclusions

We have shown that microwave irradiation is an efficient methodology in cycloaddition reactions. The special characteristics of the irradiation, dielectric properties, energy transfer, penetration depth, etc. are completely different from those in conventional heating and have led to new laboratory techniques, equipment, glassware, etc. and to a different perspective on chemical reactions. Several procedures have been designed, to work both in solution and under solvent-free conditions, and the selection of one of these methods depends on the nature of the reagents and the reaction, although solvent-free conditions using solid supports are especially suited to microwave conditions.

The application of microwave irradiation to the synthesis of natural products, heterocyclic systems, and fullerene derivatives shows that the effect of microwaves on the yield is particularly important for compounds of low reactivity and for highly sensitive reagents and products, due to the fact that mild reaction conditions, shorter reaction times, and/or lower temperatures can be used.

In some cases, modifications of the selectivity, compared with that observed in classical heating, have been observed. These modifications have been ascribed to changes in the reaction pathway; under microwave irradiation the more polar path will be favored. Computational studies have shown that the harder transition state must be favored under microwave irradiation conditions. This result opens new possibilities for the application of microwave irradiation to organic and inorganic synthesis, as dramatic modifications in the selectivity of competitive reactions can be expected if the transition states have different hardness.

Acknowledgments

Financial support from the Spanish DGICyT (project PB97-0429) is gratefully acknowledged. This work was undertaken as part of the EU-sponsored D10 COST Program (Innovative Methods and Techniques for Chemical Transformations).

---

[1] C. Gabriel, S. Gabriel, E. H. Grant, B. S. J. Halstead, D. M. P. Mingos, *Chem. Soc. Rev.* **1998**, *27*, 213−223.

[2] D. M. P. Mingos, A. G. Whittaker, *Microwave Dielectric Heating Effects in Chemical Synthesis*, in *Chemistry under Extreme or non Classical Conditions* (Eds.: R. van Eldik, C. D. Hubbard), John Wiley and Sons, **1997**, 479−545.

[3] [3a] A. Zlotorzynski, *Critical Rev. Anal. Chem.* **1995**, *25*, 43−76. − [3b] Q. Jin, F. Liang, H. Zhang, L. Zhao, Y. Huan, D. Song, *Trends Anal. Chem.* **1999**, *18*, 479−484.

[4] [4a] D. E. Clark, W. H. Sutton, *Annu. Rev. Mater. Sci.* **1996**, *26*, 299−331. − [4b] J. Jacob, L. H. L. Chia, F. Y. C. Boey, *J. Mat. Sci.* **1995**, *30*, 5321−5327.

[5] R. Van Eldik, C. D. Hubbard, *New J. Chem.* **1997**, *21*, 825−838.

[6] [6a] S. Caddick, *Tetrahedron* **1995**, *52*, 10403−10432. − [6b] A. K. Bose, M. J. Manhas, B. K. Banik, E. W. Robb, *Res. Chem. Intermed.* **1994**, *20*, 1−11. − [6c] C. R. Strauss, R. W. Trainor, *Aust. J. Chem.* **1995**, *48*, 1665−1692.

[7] C. J. Dell, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3873−3905.

[8] L. F. Tietze, G. Kettschau, *Hetero Diels−Alder Reactions in Organic Chemistry*, in *Topics in Current Chemistry*, Vol. 190, **1998**, 1−121.

[9] R. Gedye, F. Smith, K. Westaway, A. Humera, L. Baldisera, L. Laberge, L. Rousell, *Tetrahedron Lett.* **1986**, *26*, 279−282.

[10] R. J. Giguere, T. L. Bray, S. M. Duncan, G. Majetich, *Tetrahedron Lett.* **1986**, *27*, 4945−4948.

[11] G. Majetich, R. Hicks, *Radiat. Phys. Chem.* **1995**, *45*, 567−579.

[12] R. J. Giguere, A. M. Namen, B. O. Lopez, A. Arepally, D. E. Ramos, G. Majetich, G. Defauw, *Tetrahedron Lett.* **1987**, *28*, 6553−6556.

[13] M. Sridar, K. L. Krishna, K. Srinivas, J. M. Rao, *Tetrahedron Lett.* **1998**, *39*, 6529−6532.

[14] Monomode reactors: PROLABO SYNTHEWAVE S402. CEM STAR system 2 and 6.

[15] Temperature measurement is one of the main problems in microwave-assisted reactions. See ref.[2] for temperature measurement systems.

[17] D. R. Baghurst, D. M. P. Mingos, *J. Chem. Soc., Chem. Commun.* **1992**, 674−675.

[17] P. de la Cruz, A. de la Hoz, F. Langa, B. Illescas, N., Martín, C. Seoane, *Synth. Metals* **1997**, *87*, 2283−2284.

[18] [18a] A. K. Bose, M. S. Manhas, M. Ghosh, M., Shah, V. S. Raju, S. S. K. Tabey, Z. Urbanczyck-Lipkkowska, *Heterocycles* **1990**, *30*, 741−744. − [18b] A. K. Bose, M. S. Manhas, M. Ghosh, M. Shah, V. S. Raju, S. S. Bari, S. N. Newaz, B. K. Banik, A. G. Chaudhary, K. J. Barakat, *J. Org. Chem.* **1991**, *56*, 6968−6970. − [18c] B. K. Banik, M. S. Manhas, E. W. Robb, A. K. Bose, *Heterocycles* **1997**, *44*, 405−415. − [18d] A. K. Bose, B. K. Banik, N. Lavlinskaia, M. Jayaraman, M. S. Manhas, *Chemtech* **1997**, 18−24.

[19] A. K. Bose, M. S., Manhas, B. K. Banik, E. W. Robb, *Res. Chem. Intermed.* **1994**, *20*, 1−11.

[20] M. S. Manhas, B. K. Banik, Z. Kaluza, K. J. Barakat, A. K. Bose, *Tetrahedron Lett.* **1992**, *33*, 3603−3606.

[21] [21a] A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault, D. Mathé, *Synthesis* **1998**, 1213−1234. − [21b] R. S. Varma, *Green Chem.* **1999**, *1*, 43−55.

[22] A. Loupy, G. Bram, J. Sansoulet, *New J. Chem.* **1992**, *16*, 233−242.

[23] [23a] A. Loupy, J. L. Luche, *Sonochemical and Microwave Activation in Phase Transfer Catalysis*, in *Handbook of Phase Transfer Catalysis* (Eds.: Y. Sasson, R. Neumann), Blackie **1996**, 369−404. − [23b] S. Deshayes, M. Liagre, A. Loupy, J. L. Luche, A. Petit, *Tetrahedron* **1999**, *55*, 10851−10870.

[24] *Solid Supports and Catalysts in Organic Synthesis* (Ed.: K. Smith), Prentice Hall, Chichester **1992**.

[25] A. Avalos, R. Babiano, J. L. Bravo, P. Cintas, J. L. Jiménez, J. C. Palacios, *Tetrahedron Lett.* **1998**, *39*, 9301−9304.

[26] J. M. Fraile, J. I. García, M. A. Gómez, A. de la Hoz, J. A. Mayoral, A. Moreno, P. Prieto, L. Salvatella, E. Vázquez, *Eur. J. Org. Chem.*, Submitted.

[27] B. Touaux, B. Klein, F. Texier-Boullet, J. Hamelin, *J. Chem. Res. (S)* **1994**, 116−117.

[28] [28a] B. Syassi, K. Bougrin, M. Soufiaoui, *Tetrahedron Lett.* **1997**, *38*, 8855−8858. − [28b] K. Bougrin, M. Soufiaoui, A. Loupy, P. Jacquault, *New J. Chem.* **1995**, *19*, 213−219.

[29] A. Díaz-Ortiz, E. Díez-Barra, A. de la Hoz, A. Loupy, A. Petit, L. Sánchez, *Heterocycles* **1994**, *38*, 785−792.

[30] Z. Rongshun, H. Pinjie, D. Shushan, *Synth. Commun.* **1994**, *24*, 2417−2421.

[31] [31a] B. Baruah, D. Prajapati, A. Boruah, J. S. Sandhu, *Synth. Commun.* **1997**, *27*, 2563−2567. − [31b] A. Boruah, B. Baruah, D. Prajapati, J. S. Sandhu, A. C. Ghosh, *Tetrahedron Lett.* **1996**, *37*, 4203−4204.

[32] D. Karmakar, D. Prajapati, J. S. Sandhu, *Synth. Commun.* **1998**, *28*, 2415−2420.

[33] F. Cado, P. Jacquault, M. J. Dozias, J. P. Bazureau, J. Hamelin, *J. Chem. Research (S)* **1997**, 176−177.

[34] A. Corsaro, U. Chiacchio, V. Librando, S. Fisichella, V. Pistarà, *Heterocycles* **1997**, *45*, 1567−1572.

[35] [35a] A. Díaz-Ortiz, E. Díez-Barra, A. de la Hoz, P. Prieto, A. Moreno, *J. Chem. Soc., Perkin Trans. 1* **1994**, 3595−3598. − [35b] A. Díaz-Ortiz, E. Díez-Barra, A. de la Hoz, P. Prieto, A. Moreno, F. Langa, T. Prangé, A. Neuman, *J. Org. Chem.* **1995**, *60*, 4160−4166.

[36] A. Díaz-Ortiz, E. Díez-Barra, A. de la Hoz, A. Moreno, M. J. Gómez-Escalonilla, A. Loupy, *Heterocycles* **1996**, *43*, 1021−1030.

[37] D. A. Lewis, *Mat. Res. Soc. Symp. Proced.* **1992**, *269*, 21.

[38] B. Garrigues, C. Laporte, R. Laurent, A. Laporterie, J. Dubac, *Liebigs Ann.* **1996**, 739−741.

[39] P. Garrigues, B. Garrigues, *C.R. Acad. Sci. Paris Ser. II* **1998**, 545−550.

[40] B. Garrigues, R. Laurent, C. Laporte, A. Laporterie, J. Dubac, *Liebigs Ann.* **1996**, 743−744.

[41] X. Zhang, D. O. Hayward, D. M. P. Mingos, *Chem. Commun.* **1999**, 975−976.

[42] F. Langa, P. de la Cruz, A. de la Hoz, A. Díaz-Ortiz, E. Díez-Barra, *Contemporary Org. Synth.* **1997**, *4*, 373−386.

[43] R. Laurent, A. Laporterie, J. Dubac, J. Berlan, S. Lefeuvre, M. Audhuy, *J. Org. Chem.* **1992**, *57*, 7099−7102.

[44] J. Berlan, P. Giboreau, S. Lefeuvre, C. Marchand, *Tetrahedron Lett.* **1991**, *32*, 2363−2366.

[45] K. D. Raner, C. R. Strauss, F. Vyskoc, L. Mokbel, *J. Org. Chem.* **1993**, *58*, 950−953.

[46] R. N. Gedye, W. Rank, K. C. Westaway, *Can. J. Chem.* **1991**, *69*, 706−711.

[47] C. Suard, R.M. Mourel, B. Cerdan, G. Bart, M. H. Feinberg, *Anal. Chim. Acta* **1996**, *318*, 261−273.

[48] A. K. Bose, B. K. Banik, M. S. Manhas, *Tetrahedron Lett.* **1995**, *36*, 213−216.

[49] A. K. Bose, M. Jayaraman, A. Okawa, S. S. Bari, E. W. Robb, M. S. Manhas, *Tetrahedron Lett.* **1996**, *37*, 6989−6992.

[50] A. Arrieta, B. Lecea, F. P. Cossío, *J. Org. Chem.* **1998**, *63*, 5869−5876.

[51] F. Langa, P. de la Cruz, A. de la Hoz, E. Espíldora, F. P. Cossío, B. Lecea, *J. Org. Chem.* in press.

[52] W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford **1990**.

[53] J. T. M. Linders, J. P. Kokje, M. Overhand, T. S. Lie, L. Mant, *Recl. Trav. Chim. Pays Bas* **1988**, *107*, 449−454.

[54] B. Lei, A. G. Fallis, *J. Org. Chem.* **1993**, *58*, 2186−2195.

[55] [55a] Y. F. Lu, A. G. Fallis, *Tetrahedron Lett.* **1993**, *34*, 3367−3370. − [55b] Y. F. Lu, A. G. Fallis, *Can. J. Chem.* **1995**, *73*, 2239−2252.

[56] K. Takatori, K. Hasegawa, S. Narai, M. Kajigawa, *Heterocycles* **1996**, *42*, 525−528.

[57] A. K. Bose, B. K. Banik, S. N. Newaz, M. S. Manhas, *Synlett* **1993**, 897−899.

[58] M. S. Khajavi, F. Sefidon, S. S. S. Hosseini, *J. Chem. Research (S)* **1998**, 724−725.

[59] [59a] J. M. Lerestif, J. Perrocheau, F. Tonnard, J. P. Bazureau, J. Hamelin, *Tetrahedron* **1995**, *51*, 6757−6774. − [59b] J. M. Lerestif, S. Feuillet, J. P. Bazureau, J. Hamelin, *J. Chem. Research (S)* **1999**, 32−33.

[60] A. Loupy, A. Petit, D. Bonnet-Delpon, *J. Fluorine Chem.* **1995**, *75*, 215−216.

[61] P. Mičúch, L. Fišera, M. K. Cyrański, T. M. Krygowski, *Tetrahedron Lett.* **1999**, *40*, 167−170.

[62] A. Stambouli, M. Chastrette, M. Soufiaoui, *Tetrahedron Lett.* **1991**, *32*, 1723−1724.

[63] I. A. Motorina, F. W. Fowler, D. S. Grierson, *J. Org. Chem.* **1997**, *62*, 2098−2105.

[64] C. R. Kamath, S. D. Samant, *Indian J. Chem.* **1996**, *35B*, 256−259.

[65] W. B. Wang, E. J. Roskamp, *Tetrahedron Lett.* **1992**, *33*, 7631−7633.

[66] A. Díaz Ortiz, J. R. Carrillo, E. Díez-Barra, A. de la Hoz, M. J. Gómez-Escalonilla, A. Moreno, F. Langa, *Tetrahedron* **1996**, *52*, 9237−9248.

[67] A. Arrieta, J. R. Carrillo, F. P. Cossío, A. Díaz Ortiz, M. J. Gómez-Escalonilla, A. de la Hoz, A. Moreno, F. Langa, *Tetrahedron* **1998**, *54*, 13167−13180.

[68] A. Díaz Ortiz, J. R. Carrillo, M. J. Gómez-Escalonilla, A. de la Hoz, A. Moreno, P. Prieto, *Synlett* **1998**, 1069−1070.

[69] M. Bortolussi, R. Bloch, A. Loupy, *J. Chem. Research (S)* **1998**, 34−35.

[70] [70a] B. Abarca González, R. A. Jones, M. Medio Simón, J. Sepúlveda Arqués, H. M. Dawes, M. B. Hursthouse, *J. Chem. Res. (S)* **1985**, 84−85. − [70b] M. Medio Simón, J. Sepúlveda Arqués, *Tetrahedron* **1986**, *42*, 6683−6686. − [70c] M. Medio Simón, M. J. Alvarez Laviada, J. Sepúlveda Arqués, *J. Chem. Soc., Perkin Trans. 1* **1990**, 2749−2750.

[71] J. Elguero, *Pyrazoles and their Benzoderivatives*, in *Comprehensive Heterocyclic Chemistry*, Vol 5 (Ed.: A. R. Katritzky), Pergamon Press, Oxford **1985**.

[72] A. Díaz Ortiz, J. R. Carrillo, A. de la Hoz, M. J. Gómez-Escalonilla, A. Moreno, P. Prieto, *Tetrahedron* **1999**, *55*, 9623−9630.

[73] W. Krätschmer, L. D. Lamb, K. Fostiropoulos, D. R. Huffmann, *Nature* **1990**, *347*, 354−357.

[74] F. Diederich, C. Thilgen, *Science* **1996**, *271*, 317−323.

[75] M. Prato, *J. Mat. Chem.* **1997**, *7*, 1097−1109.

[76] Y. P. Sun, J. E. Riggs, Z. Guo, H. W. Rollins, *Optical and Electronic Properties of Fullerenes and Fullerene-Based Materials.* (Eds.: J. Shinar, Z. V. Vardeny, Z. H. Kafafi), Marcel Dekker, Inc. **2000**, chapter 3.

[77] L. W. Tutt, A. Kost, *Nature* **1992**, *356*, 225−226.

[78] K. Tanigaki, *Handbook of Organic Conductive Molecules and Polymers* (Ed.: H. S. Nalwa), John Wiley & Sons, **1997**, Vol. 1, chapter 6.

[79] P. M. Allemand, K. C. Khemani, A. Koch, F. Wudl, K. Holczer, S. Donovan, G. Gruner, J. D. Thompson, *Science* **1991**, *253*, 301−303.

[80] S. H. Friedman, D. L. Decamp, R. P. Sijbesma, G. Srdanov, F. Wudl, G. L. Kenyon, *J. Am. Chem. Soc.* **1993**, *115*, 6506−6509.

[81] W. Sliwa, *Fullerene Sci. & Techno.* **1995**, *3*, 243−281.

[82] [82a] A. Hirsch, in *The Chemistry of the Fullerenes*, Thieme, **1994**. − [82b] A. Hirsch, *Synthesis* **1995**, 895−913.

[83] [83a] Y. Rubin, S. Khan, D. I. Freedberg, C. Yeretzian, *J. Am. Chem. Soc.* **1993**, *115*, 344−345. − [83b] P. Belik, A. Gügel, J. Spickerman, K. Müllen, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 78−80.

[84] J. L. Segura, N. Martín, *Chem. Rev.* **1999**, *99*, 3199−3246.

[85] W. F. Jarvis, M. D. Hoey, A. L. Finocchio, D. C. Dittmer, *J. Org. Chem.* **1991**, *56*, 1947−1948.

[86] B. Illescas, N. Martín, C. Seoane, P. de la Cruz, F. Langa, F. Wudl, *Tetrahedron Lett.* **1995**, *36*, 8307−8310.

[87] H. M. Kingston, P. J. Walter, W. G. Engelhart, P. J. Parsons, in *Microwave-Enhanced Chemistry* (Eds.: H. M. (Skip) Kingston, S. J. Haswell), American Chemical Society **1997**, chapter 16.

[88] [88a] J. A. Schlueter, J. M. Seaman, S. Taha, H. Cohen, K. R. Lykke, H. H. Wang, J. M. Williams, *J. Chem. Soc., Chem. Commun.* **1993**, 972−974. − [88b] M. Tsuda, T. Ishida, T. Nogami, S. Kurono M. Ohashi, *J. Chem. Soc., Chem. Commun.* **1993**, 1296−1298. − [88c] K. Komatsu, Y. Murata, N. Sugita, K. Takeuchi, T. S. M. Wan, *Tetrahedron Lett.* **1993**, *34*, 8473−8476.

[89] P. de la Cruz, A. de la Hoz, F. Langa, B. Illescas, N. Martín, *Tetrahedron* **1997**, *53*, 2599−2608.

[90] S. Eguchi, *Fullerene Sci. & Techno.* **1997**, *5*, 977−987.

[91] M. Ohno, T. Azuma, S. Eguchi, *Chem. Lett.* **1993**, 1833−1834.

[92] U. M. Fernandez-Paniagua, B. Illescas, N. Martín, C. Seoane, P. de la Cruz, A. de la Hoz, F. Langa, *J. Org. Chem.* **1997**, *62*, 3705−3710.

[93] U. M. Fernandez-Paniagua, B. Illescas, N. Martín, C. Seoane, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1077−1079.

[94] M. Maggini, G. Scorrano, M. Prato, *J. Am. Chem. Soc.* **1993**, *115*, 9798−9799.

[95] P. de la Cruz, A. Díaz-Ortiz, J. J. García, M. J. Gómez-Escalonilla, A. de la Hoz, F. Langa, *Tetrahedron Lett.* **1999**, *40*, 1587−1590.

[96] Y. Matsubara, H. Tada, S. Nagase, Z. Yoshida, *J. Org. Chem.* **1995**, *60*, 5372−5373.

[97] P. de la Cruz, E. Espíldora, J. J. García, A. de la Hoz, F. Langa, N. Martín, L. Sánchez, *Tetrahedron Lett.* **1999**, *40*, 4889−4892.

Received March 13, 2000
[O00123]