Chapter 3

Microwave assisted synthesis of heterocycles - an overview

3.1 Microwave-Assisted Organic Synthesis (MAOS) – A Brief History

While fire is now rarely used in synthetic chemistry, it was not until Robert Bunsen invented the burner in 1855 that the energy from this heat source could be applied to a reaction vessel in a focused manner. The Bunsen burner was later superseded by the isomantle, the oil bath or the hot plate as a means of applying heat to a chemical reaction. In the past few years, heating and driving chemical reactions by microwave energy has been an increasingly popular theme in the scientific community [1, 2].

Microwave energy, originally applied for heating foodstuffs by Percy Spencer in the 1940s, has found a variety of technical applications in the chemical and related industries since the 1950s, in particular in the food-processing, drying and polymer industries. Other applications range from analytical chemistry (microwave digestion, ashing and extraction) [3] to biochemistry (protein hydrolysis, sterilization) [3], pathology (histoprocessing, tissue fixation) [4] and medical treatments (diathermy) [5]. Somewhat surprisingly, microwave heating has only been implemented in organic synthesis since the mid-1980s. The first reports on the use of microwave heating to accelerate organic chemical transformations (MAOS) were published by the groups of Richard Gedye (Scheme 3.1) [6] and Raymond J. Giguere/George Majetich [7] in 1986.

Scheme 3.1 Hydrolysis of benzamide: The first published example (1986) of microwave-assisted organic synthesis.
In those early days, experiments were typically carried out in sealed teflon or glass vessels in a domestic household microwave oven without any temperature or pressure measurements. The results were often violent explosions due to the rapid uncontrolled heating of organic solvents under closed-vessel conditions. In the 1990s, several groups started to experiment with solvent-free microwave chemistry (so-called dry-media reactions), which eliminated the danger of explosions [8]. Here, the reagents were pre-adsorbed onto either an essentially microwave-transparent (i.e., silica, alumina or clay) or strongly absorbing (i.e., graphite) inorganic support, that additionally may have been doped with a catalyst or reagent. Particularly in the early days of MAOS, the solvent-free approach was very popular since it allowed the safe use of domestic microwave ovens and standard open-vessel technology. While a large number of interesting transformations using “dry-media” reactions have been published in the literature [8], technical difficulties relating to non-uniform heating, mixing and the precise determination of the reaction temperature remained unresolved, in particular when scale-up issues needed to be addressed.

Alternatively, microwave-assisted synthesis has been carried out using standard organic solvents under open-vessel conditions. If solvents are heated by microwave irradiation at atmospheric pressure in an open vessel, the boiling point of the solvent typically limits the reaction temperature that can be achieved. In order to nonetheless achieve high reaction rates, high-boiling microwave-absorbing solvents have been frequently used in open-vessel microwave synthesis [9]. However, the use of these solvents presented serious challenges in relation to product isolation and recycling of the solvent. Because of the recent availability of modern microwave reactors with on-line monitoring of both temperature and pressure, MAOS in dedicated sealed vessels using standard solvents—a technique pioneered by Christopher R. Strauss in the mid-1990s [10]—has been celebrating a comeback in recent years. This is clearly evident surveying the recently published (since 2001) literature in the area of controlled microwave-assisted organic synthesis (MAOS). It appears that the combination of rapid heating by microwaves with sealed-vessel (autoclave) technology will most likely be the method of choice for performing MAOS on a laboratory scale in the future. Importantly, recent innovations in microwave reactor technology now allow controlled parallel and automated sequential
processing under sealed-vessel conditions, and the use of continuous- or stop-flow reactors for scale-up purposes.

Since the early days of microwave synthesis, the observed rate accelerations and sometimes altered product distributions compared to oil-bath experiments have led to speculation on the existence of so-called “specific” or “non-thermal” microwave effects [11]. Historically, such effects were claimed when the outcome of a synthesis performed under microwave conditions was different from that of the conventionally heated counterpart at the same apparent temperature. Reviewing the present literature [12], it appears that today most scientists agree that in the majority of cases the reason for the observed rate enhancements is a purely thermal/kinetic effect, i.e., a consequence of the high reaction temperatures that can rapidly be attained when irradiating polar materials in a microwave field, although effects that are caused by the unique nature of the microwave dielectric heating mechanism (“specific microwave effects”) clearly also need to be considered. While for the medicinal chemist in industry this discussion may seem largely irrelevant, the debate on “microwave effects” is undoubtedly going to continue for many years in the academic world. Regardless of the nature of the observed rate enhancements, microwave synthesis has now truly matured and has moved from a laboratory curiosity in the late 1980s to an established technique in organic synthesis, heavily used in both academia and industry.

The initially slow uptake of the technology in the late 1980s and 1990s has been attributed to its lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating. The risks associated with the flammability of organic solvents in a microwave field and the lack of available dedicated microwave reactors allowing for adequate temperature and pressure control were major concerns. Important instrument innovations now allow for careful control of time, temperature and pressure profiles, paving the way for reproducible protocol development, scale-up and transfer from laboratory to laboratory and from scientist to scientist. Today, microwave chemistry is as reliable as the vast arsenal of synthetic methods that preceded it. Since 2001, therefore, the number of publications related to MAOS has increased dramatically, to such a level that it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale [1, 2]. Not only is
direct microwave heating able to reduce chemical reaction times significantly, but it is also known to reduce side reactions, increase yields and improve reproducibility. Therefore, many academic and industrial research groups are already using MAOS as a technology for rapid reaction optimization, for the efficient synthesis of new chemical entities or for discovering and probing new chemical reactivity.

3.2 Applications of microwaves in heterocyclic ring formation

3.2.1 Five-membered heterocyclic rings

3.2.1.1 Pyrroles
The classical Paal-Knorr cyclization of 1,4-diketones to give pyrroles is dramatically speeded-up under microwave irradiation and high yields are obtained as shown in Scheme 3.2 [13].

![Scheme 3.2]

3.2.1.2 Pyrazoles
Another recent application of microwaves in cyclization is the preparation of pyrazoles from hydrazones using the Vilsmeier cyclization method by treatment with

![Scheme 3.3]
POCl₃ and DMF [14]. As shown in Scheme 3.2, once again the reaction is speeded-up by factors of several 100-fold.

### 3.2.1.3 Imidazoles
An important classical preparation of imidazoles is from an α-diketone, an aldehyde and ammonia. Here again, excellent yields can be obtained in reaction times of a few minutes as shown in Scheme 3.4 [15].

![Scheme 3.4](image)

### 3.2.1.4 Oxazolines
The example of Scheme 3.5, the preparation of oxazolines shows that partially saturated five-membered rings can also be prepared advantageously using microwaves [16].

![Scheme 3.5](image)

### 3.2.1.5 Triazoles and Tetrazoles
Schemes 3.6 and 3.7 show the overview of five-membered rings with illustrations of the advantageous preparation of 1,2,4-triazoles [17] and tetrazoles [18] respectively using microwaves. Notice that in Scheme 3.6 the starting aryl cyanides are also made
by a Pd-catalyzed but microwave-enhanced replacement of aryl bromides using zinc cyanide.

$$\text{Ar-CN} \xrightarrow{\text{NH}_2\text{NH}_2\text{-2HCl}} \xrightarrow{\text{NH}_2\text{NH}_2\text{-H}_2\text{O}} \text{Ar-C} \equiv \text{N}$$

MW: 60 W, 130 °C, 36-96%
Conventional: 60 min., 130 °C, 45-60%

Ar = C₆H₅; 4-OCH₃C₆H₄, 4-NH₂C₆H₄,
4-OHClC₆H₄, 4-CH₂C₆H₄ etc.

**Scheme 3.6**

$$\begin{align*}
\text{Ar-Br} & \xrightarrow{\text{Zn(CN)}_2} \text{Ar-CN} \\
& \xrightarrow{\text{Pd(PPh)}_3} \text{NaN₃} \\
& \xrightarrow{\text{NH}_2\text{Cl}} \text{R} \\
\text{MW: 60 W, 175 °C, 2 min., DMF, 78-93%} \\
\text{Conventional: 2-16 h, 71-97%} \\
\text{R = OCH₃, NO₂, CH₃ etc.}
\end{align*}$$

**Scheme 3.7**

### 3.2.1.6 Oxadiazoles

The dehydration of unsymmetrical diacylhydrazines (themselves prepared by a conventional Mitsunobu reaction) using Burgess's reagent is shown in Scheme 3.8 to give 1,3,4-oxadiazoles rapidly under microwave irradiation [19].

$$\begin{align*}
\text{R}_1\text{O} & \xrightarrow{\text{H}_2\text{NNCONH}} \text{R}_2 \\
& \xrightarrow{\text{DDC}} \text{R}_1\text{O} \\
& \xrightarrow{\text{MeO}} \text{N} \equiv \text{N} \\
\text{MW: 150 °C, 5 min., DMF} \\
\text{Conventional: 90 min., 150 °C} \\
\text{R = alkyl, aryl; R₂ = Cl, OMe}
\end{align*}$$

**Scheme 3.8**
3.2.1.7 Isoxazolines and pyrazolines
The acceleration of 1,3-dipolar cycloaddition reactions to give isoxazolines and pyrazolines by the addition of activated olefins to nitrile oxides or nitrile imides, respectively, is illustrated in Scheme 3.9; the resulting compounds are obtained in far high yield than under conventional conditions [20].

3.2.2 Benzo-derivatives of five-membered rings
3.2.2.1 Benz-imidazoles, -oxazoles, and -thiazoles
Ring closure reactions of appropriate o-substituted anilines to give benzimidazoles, benoxazoles, and benzthiazoles takes place much faster and in significantly high yield under microwave conditions than conventionally [21] as shown in Scheme 3.10.

3.2.2.2 Indoles
The classical Fischer-indole synthesis from an aryl hydrazine and a ketone is speeded-up by several 100-fold as documented in Scheme 3.11 [22].
### 3.2.2.3 γ-Carbollines

The Graebe-Ullmann synthesis which converts 1-arylbenzotriazoles into carbazoles or their heterocyclic analogs is also accelerated under microwave conditions as shown in Scheme 3.12 where the 1-(4-pyridyl)benzotriazole is converted into a γ-carboline [23].

### 3.2.3 Six-membered rings

#### 3.2.3.1 Dihydropyridines

![Scheme 3.13](image-url)
The Hantzsch dihydropyridine synthesis remains one of the most important routes to pyridine ring systems. Under conventional conditions long periods of heating are required and yields are poor to moderate. Microwaves dramatically reduce the heating times and also significantly increase the yields as shown in Scheme 3.13 [24].

3.2.3.2 Dihydropyridopyrimidinones
Dihydropyridopyrimidinones have been produced by ring annulations of aminopyrimidinones. Once again the reaction time is dramatically reduced and yields are much better with the solvent-free microwave conditions (Scheme 3.14) [25].

![Scheme 3.14](image)

3.2.3.3 Dihydropyrimidines
The Biginelli reaction is important for the preparation of dihydropyrimidine derivatives and excellent results are found for reactions carried out with microwave enhancement (Scheme 3.15) [19].

![Scheme 3.15](image)
3.2.3.4 Tetrazines

The Diels-Alder reaction between aza-olefins and aza-dicarboxylic ester to give tetrazines is speeded-up by a factor of 1000 by microwave enhancement as shown in Scheme 3.16 [26].

\[
\begin{align*}
\text{Ph} & \quad \text{EtO}_2C-N=N-CO_2Et \\
\text{R} & \quad \text{Ph} \quad \text{N} \quad \text{N} \quad \text{CO}_2\text{Et}
\end{align*}
\]

\(R = \text{Carbohydrate}\)

MW: 300 W, 15 min., 80-96%
Conventional: 30 days

Scheme 3.16

3.2.4 Polycyclic six-membered rings

3.2.4.1 Quinolines

The Skraup synthesis has a bad reputation as it involves very messy conditions and gives only low yields of quinolines when carried out conventionally. Recently, it has been reported that microwave enhancement reduces the reaction time to a few minutes and allows high yields to be isolated (Scheme 3.17) [27].

\[
\begin{align*}
\text{R} & \quad \text{NH}_2 \\
\text{R}_1 & \quad \text{R}_2 \quad \text{R}_3 \quad \text{InCl}_3/\text{SiO}_2
\end{align*}
\]

\(R = \text{H}, \ \text{o-CH}_3, \ \text{m-CH}_3, \ \text{p-CH}_3, \ \text{o-OMe}, \ \text{p-OMe}, \ \text{m-OH}, \ \text{m-Cl} \text{ etc.}\)

\(R_1 = \text{H}, \ \text{CH}_3, \ \text{n-C}_3\text{H}_7; \ R_2 = \text{H}, \ \text{C}_2\text{H}_5; \)

\(R_3 = \text{CH}_3, \ \text{p-MeOC}_6\text{H}_4\)

MW: 600 W, 5-12 min., Solvent-free, 80-87%
Conventional: \(\text{H}_2\text{SO}_4/150^\circ\text{C}, \ \text{low yields}\)

Scheme 3.17

3.2.4.2 Pyrimido[1,2-\(a\)]pyrimidines

Pyrimido[1,2-\(a\)]pyrimidines are prepared from dihydroaminopyrimidines and chromone-3-aldehydes as is shown in Scheme 3.18 [28]. Although the conventional reaction must proceed in refluxing ethanol, reactions are much faster and better yields have been obtained with microwaves.
3.2.5 Nucleophilic Substitutions

3.2.5.1 Heterocyclic C-alkylations

Nucleophilic substitution reactions can be speeded-up very considerably as is illustrated in Scheme 3.19 for a chloro-naphthyridine derivative [29].
3.2.5.2 Heterocyclic N-alkylations

Another class of nucleophilic substitution is involved in heterocyclic N-alkylation which we have illustrated in Scheme 3.20. This shows that nucleophilic substitution on the nitrogen atom of saccharin is significantly speeded-up by microwave irradiation [19].

![Scheme 3.20]

3.2.5.3 Selective-alkylation

In Scheme 3.21, the results presented indicate that selectivity is achieved in the N alkylation of 1,2,4-triazole under microwave conditions where only the N₁-alkyl derivative was formed in contradistinction to the conventional conditions which give a considerable amount of the di-1,4-benzylated compound [30].

![Scheme 3.21]

3.2.5.4 Transition metal cross-coupling

An important type of nucleophilic substitution reactions which are recently much exploited are comprised of transition metal cross-coupling. A Suzuki coupling is shown at the top of Scheme 3.22 to give significantly better yield in the presence of
microwave irradiation [31]. At the bottom of Scheme 3.22 another Suzuki coupling is shown, which was speeded-up by a factor of 100 [32].

![Scheme 3.22](image)

3.2.6 Hetero-Diels–Alder reactions

3.2.6.1 Intramolecular reactions

We have already seen one example of a hetero-Diels–Alder reaction involving acyclic components. Hetero-Diels–Alder reactions involving cyclic components which lead to polycyclic ring systems are of great importance. An intramolecular example shown in Scheme 3.23 indicates that the reaction was accelerated by a factor of around 1000 by microwave irradiation [33].

![Scheme 3.23](image)

3.2.6.2 Intermolecular reactions

Scheme 3.24 shows two impressive examples of rate enhancement for intermolecular hetero-Diels–Alder reactions [33]. In the first example on the top of Scheme 3.24 the
initial reaction is followed by elimination thus involving the conversion of a pyrazine derivative into a pyridine. Perhaps more impressive is the lower example in Scheme 3.24 where an autoclave is required under conventional conditions but which can be dispensed with when microwave acceleration is utilized.

![Scheme 3.24](image)

3.2.7 1,3-Dipolar cycloaddition reactions

3.2.7.1 Synthesis of C-carbamoyl-1,2,3-triazoles

![Scheme 3.25](image)
There is one recent report which has involved microwave induced 1,3-dipolar cycloaddition of organic azides to acetylenic amides. As shown in Scheme 3.25, these reactions were achieved under microwave conditions in a reasonable time at temperatures of around 70±15 °C [34]. Under conventional conditions the times were roughly 100 times as long and the temperature had to be taken up to 120 °C [35].

### 3.2.8 Oxidation

The osmium-catalyzed dihydroxylation reaction, the addition of osmium tetroxide to olefins to produce a vicinal diol, is one of the most selective and reliable organic transformations. Recent work by Sharpless, Fokin, and coworkers [36] has uncovered that electron-deficient olefins can be converted into the corresponding diols much more efficiently when the reaction medium is kept acidic (Scheme 3.26).

![Scheme 3.26](image)

### 3.3. Concluding remarks

For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry. The presence of heterocycles in all kinds of organic compounds of interest in biology, pharmacology, optics, electronics, material sciences, and so on is very well known. Among them, sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers and their unique structures led to several applications in different areas.

The presence of heteroatoms results in significant changes in the cyclic molecular structure, due to the availability of unshared pairs of electrons, and in the reactivity, compared with the parent aromatic hydrocarbons. In contrast to the number and variety of such heterocycles, the number of synthetic methods to afford sulfur and nitrogen-containing molecules is, in practice, restricted to the availability of the
appropriate sulfur or nitrogen reagent. Sometimes the preparation of these heterocyclic systems by conventional ways is difficult work that implies many synthetic steps and extensive starting material.

For all these reasons, the various possibilities offered by the microwave technology are particularly attractive where fast, high-yielding protocols and the avoidance or facilitation of purification are highly desirable. Despite the area of microwave-assisted chemistry being about 20 years old, the technique has only recently received widespread global acceptance of microwave-assisted synthesis of sulfur and nitrogen-containing heterocycles in the academic and industrial communities [37]. This is a consequence of the recent availability of commercial microwave systems specific for synthesis, which offers improved opportunities for reproducibility, rapid synthesis, rapid reaction optimization and the potential discovery of new chemistries. The beneficial effects of microwave irradiation are finding an increased role in process chemistry, especially in cases when usual methods require forcing conditions or prolonged reaction times. Microwaves have also shown an advantage where processes involve sensitive reagents or when products may decompose under prolonged reaction conditions.

All above observations led us to explore microwave-assisted synthesis of our aimed heterocyclic scaffolds viz. acridine-1,8-diones, 5,6,7,8-tetrahydroquinolines and 7,8-dihydroquinolines. The results are described in the following chapters:

**Chapter 4: Studies on Microwave Assisted Synthesis of Acridines**

**Chapter 5: Studies on Microwave Assisted Synthesis of Polyhydroquinolines**
3.4 References and notes


Chapter 3

Microwave-assisted synthesis of heterocycles


[19] Single-mode cavities offer more consistent and predictable energy distribution. Single-mode instruments produce one homogeneous, intense pocket of energy that is highly reproducible. Due to their uniform energy distribution and higher power density, these systems typically couple more efficiently with small samples. Hayes, B. L. Microwave Synthesis: Chemistry at the Speed of Light; CEM Publishing: Matthews, NC, 2002.


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