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Microwave Technology Applied to Medicinal Chemistry

Introduction. Microwave chemistry is a versatile tool for medicinal chemists and is now being used routinely in drug discovery and in many academic laboratories. Often thermal (room temperature, oil bath or heating mantle-mediated) reactions can be speeded up and it is not uncommon to see reactions that would otherwise necessitate several hours to go to completion in an oil bath take minutes in a microwave (see note 1). How can we explain such an acceleration in reaction rates and how can we put this to use in medicinal chemistry?

First of all, microwaves are a source of electromagnetic radiation and not a heat source *per se*. Heat is generated by oscillating molecules realigning their dipoles in the electromagnetic field and creating molecular friction. Hence**, absorbed microwave energy leads to heat**. The rate of heating is crudely governed by the dipole moment and polarity of the solvent and by a term called the loss factor **tan δ** (see note 2). "Good" microwave solvents (high tan δ >0.5) will heat up quickly; these include ethanol, dimethyl sulphoxide and ethylene glycol; medium solvents (tan δ = 0.1−0.5) include water and dimethylformamide. Poor microwave solvents (tan δ <0.1) include toluene, hexane, carbon tetrachloride and dioxane.

Such a rise in temperature often enables the solvent to superheat in a microwave, especially given that most reactions are performed in a sealed tube; water, for example, can usually readily be heated to around 180 °C and aqueous phase reactions such as the Suzuki coupling depicted in scheme 2 can be complete within a few minutes rather than the several hours required under thermal conditions.

Such fast reactions usually involve less decomposition and give rise to cleaner reactions since the solvent is heated uniformly within the microwave cavity. By contrast, thermal reactions often show "cold spots" within the core solvent and "hot spots" where the solvent comes into contact with the inner wall of the reaction vessel since they rely on the relatively inefficient

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conductive heat transfer from the heat source e.g. oil bath, through the glass reaction vessel to the reaction. In thermal reactions, decomposition of the product and reactants over time can also occur.
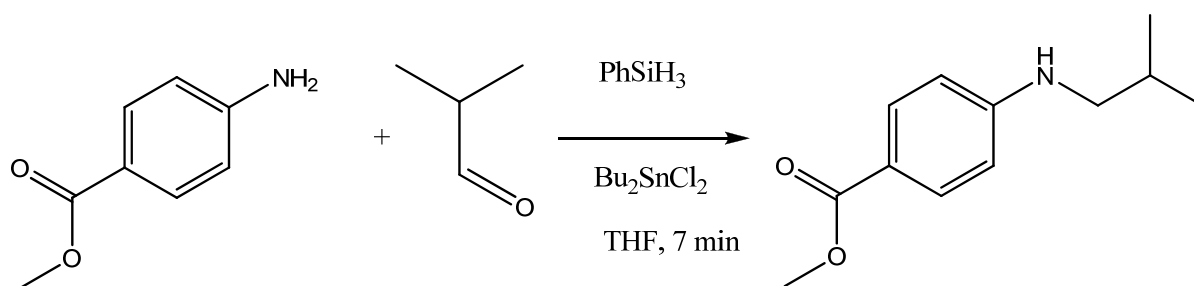
However, despite all of these apparent advantages, there are disadvantages associated with microwave assisted organic synthesis (MAOS). For example, scale-up can often be a problem: gram quantities are generally the maximum that can be handled in a microwave and so larger scale manufacturing processes would require several runs or batches to be carried out. Moreover, microwave units can be costly, running into several thousand pounds.

Use of Microwaves in Parallel Synthesis

Parallel synthesis can be performed when automated microwave units are employed; in many cases, 24 or more reactions can be programmed in sequence (see Fig. 16.26, Patrick 4th ed; note the Radleys "Greenhouse[TM]" reactor on the right hand side is not a microwave but is used for thermal parallel synthesis). With such a rapid synthetic process, libraries of molecules can be synthesised, productivity is enhanced, and lead optimisation can be accelerated, rendering drug discovery more efficient. Selected examples of MAOS used in a medicinal chemistry setting are shown below.
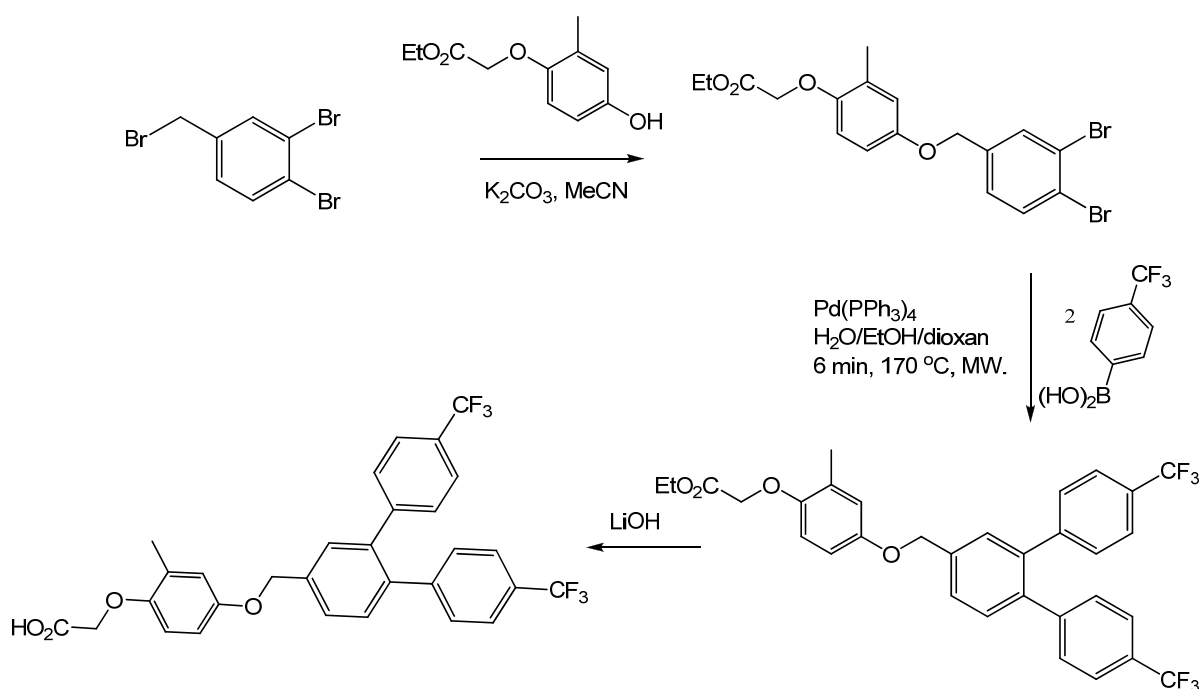
Firstly, three commonly employed reactions in library generation include amide coupling (Ch 16.9, Patrick 4th ed), peptide synthesis and reductive aminations. An example of a microwave mediated condensation between an acid and an amine has already been given in the textbook (Fig. 16.35). Water-based solid phase peptide synthesis can be performed in a microwave using Boc-protected amino acids. For example, Leu-Enkephalin could be synthesised in high yields with no racemisation.

Reductive aminations between an aldehyde and a ketone could be carried out in a microwave using a metal hydride derivative to reduce the intermediate imine derivative (Scheme 1).
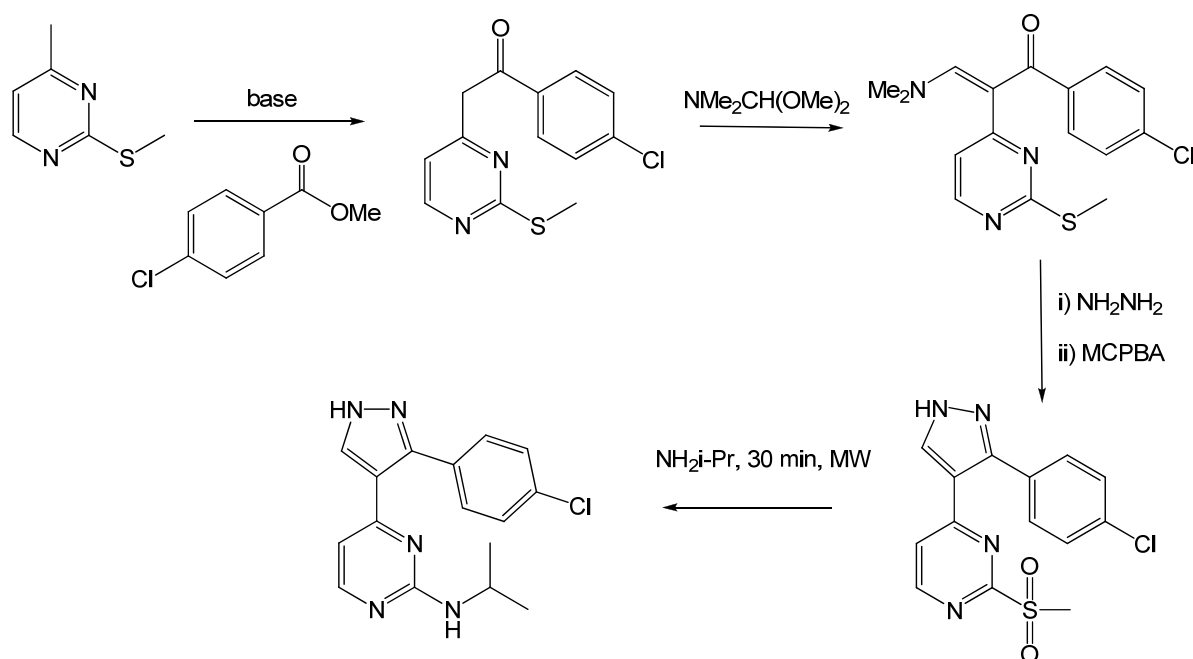
Scheme 1. Reductive aminations

The synthesis of PPAR (peroxisome proliferator-activated receptor) agonists (potential antidiabetics) illustrates an impressive use of microwave chemistry. The double Suzuki reaction, involving a Pd catalysed C-C bond forming reaction between an arylboronic acid and a dibromide, illustrated in Scheme 2, took only 6 minutes in a microwave. Note that a reaction temperature of 170 °C was achievable.
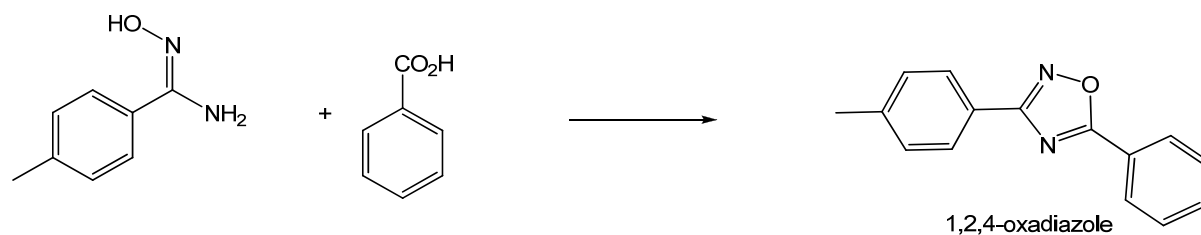

Scheme 2. PPAR agonist synthesis using MAOS

c-Jun N-terminal kinase (JNK) inhibitors are potentially useful for the treatment of obesity and insulin resistance (type 2 diabetes). Scheme 3 shows a MAOS leading to 2-substituted pyrimidine analogues by an amine displacement of a methane sulphone.[3]
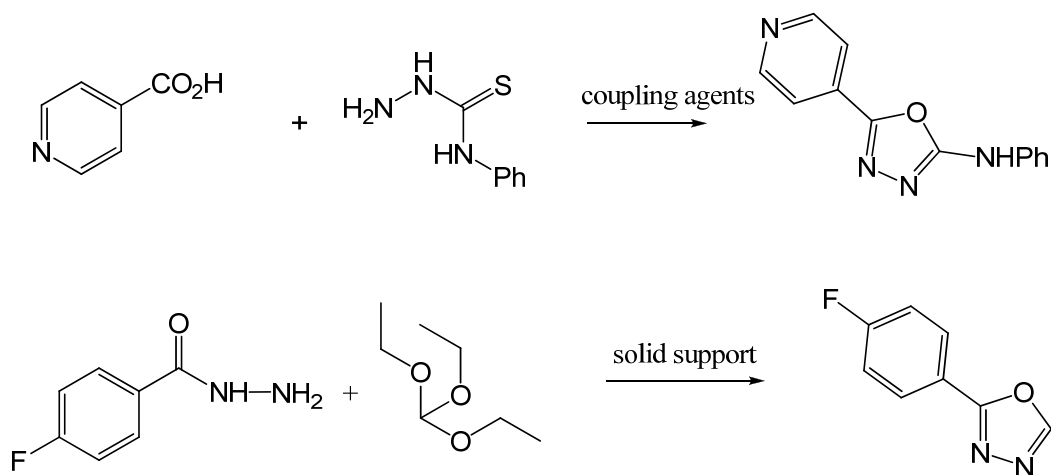
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Scheme 3. Kinase inhibitors *via* MAOS

Heterocycles are present in many clinically important pharmaceuticals, hence efficient routes to such cyclic compounds are desirable. The 1,2,4-oxadiazole unit is often used as an amide bioisostere (see Chapter 13.3.7, Patrick 4th ed) and can be made in a microwave from aldoximine and carboxylic acid precursors (Scheme 4). This represents another common feature of microwave chemistry: reactions can be performed under *solventless conditions*, in this case, over alumina and within 4 min. Hence, in many cases, MAOS can be considered to be a *green chemistry* method.
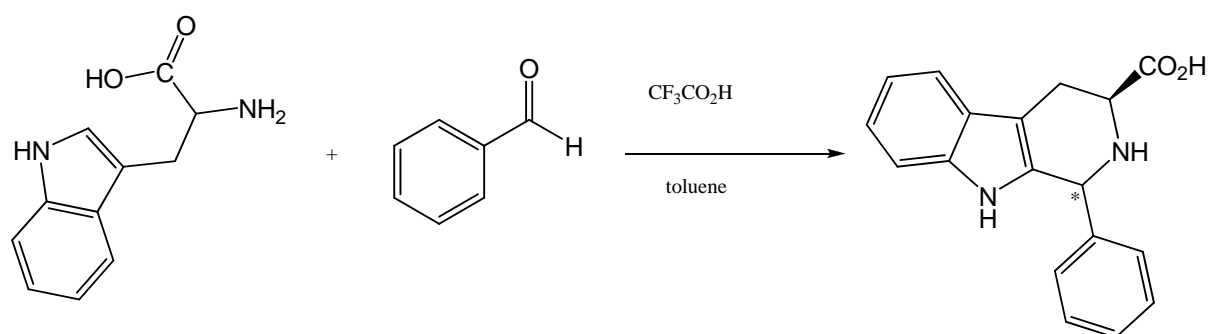

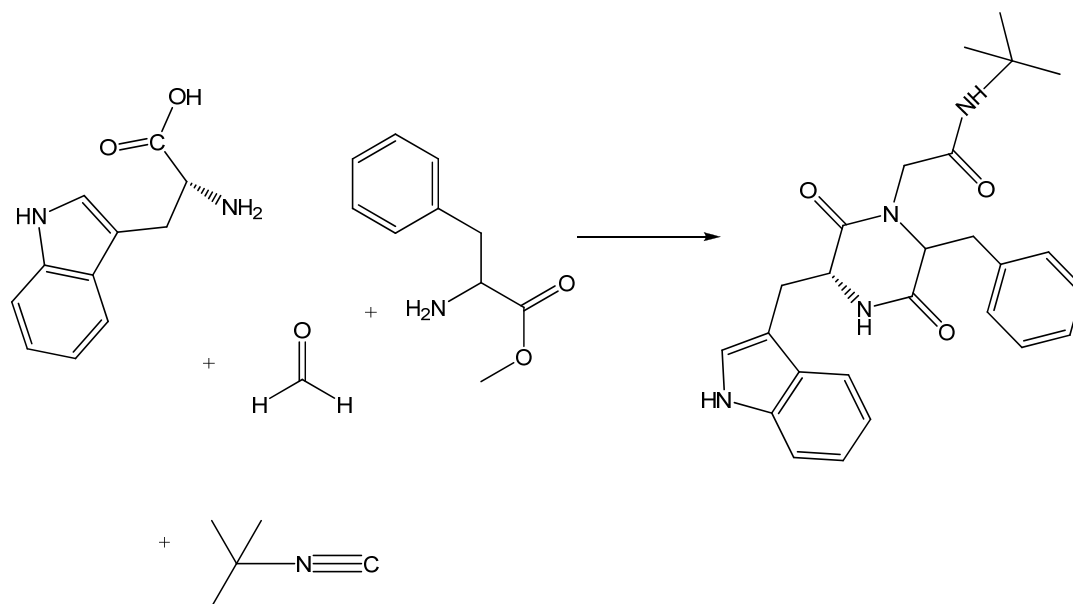## Scheme 4. 1,2,4-Oxadiazole syntheses mediated by coupling agents in a microwave.

Isomeric 1,3,4-oxadiazoles can also be made employing MAOS via a variety of methods (Scheme 5).

Scheme 5. 1,3,4-Oxadiazoles via MAOS.

Pictet Spengler reactions (Scheme 6) can be performed in a microwave, as in the synthesis of tetrahydro-β-carbolines, with moderate diasteroeselectivity (new chiral centre denoted by *).
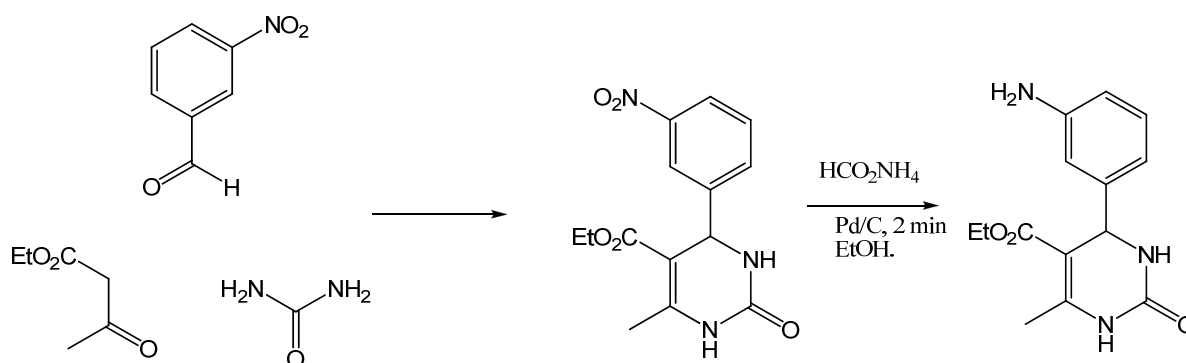

Scheme 6. Pictet Spengler reactions.

Multicomponent reactions such as the Ugi four component condensation (4-CR) can be performed rapidly in a microwave as in the synthesis of diketopiperazines (DKPs) (Scheme 7).
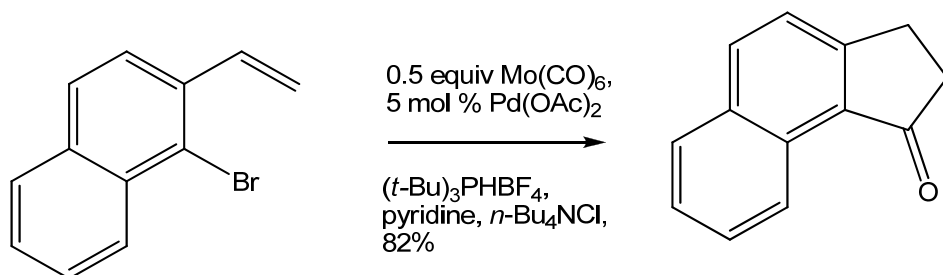
Scheme 7. Ugi 4-CR reaction via MAOS.

Finally, microwave-mediated reactions employing gases would appear at first glance to be impractical in terms of pressure, gas leakage and safety. However, there are now gas addition systems that enable the microwave tube to be pre-pressurised by the gas and then isolated from the gas source. This has uses in hydrogenation and carbonylation chemistries. Other ways of employing gases in a microwave include those that generate the gas *in situ*, such as transfer hydrogenation seen in the synthesis of a dihydropyrimidine (Scheme 8), which employed a multicomponent Biginelli reaction followed by the use of ammonium formate in the presence of a palladium catalyst.

Scheme 8. Biginelli reaction followed by transfer hydrogenation.

Carbon monoxide liberation is possible via the use of metal carbonyls in a microwave. For example, $Mo(CO)_6$ liberates CO at around 150 °C, which participates in palladium-catalysed carbonylation.

Scheme 9. Carbonylation chemistry in a microwave.

Conclusion. Microwaves are now a common tool in medicinal chemistry and have been used to significantly speed up chemistry in drug discovery and lead optimisation programmes, increasing efficiency/productivity as a result.

Notes

Note 1 Please note! Domestic microwaves are termed multimode instruments and have been optimised for much larger scale "cooking" (water is heated up in the food). Attempting reactions in such units is often dangerous and capricious. Modern single mode units are now the units of choice.

Note 2 Delta (δ) is a quantity known as the loss angle, which is usually given in the form of its tangent (tan δ). It is related to the dielectric properties of a solvent and its polarisability in an electric field.

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