Microwave–Mediated Synthesis of *N*–Containing Heterocycles: from Batch to Continuous Flow Processes

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To my parents

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ABSTRACT

Microwave–assisted organic synthesis has received increasing attention in recent years as a valuable alternative to the use of conductive heating for accelerating chemical reactions. Current technology has attempted to overcome the limited dimensions of the standing wave cavity by the use of multimode batch or continuous flow reactors that pump the reagents through the microwave chamber.

A new prototype continuous flow microwave reactor using either a 10 mL or 80 mL flow cell has been developed for use with a monomodal instrument. This system possessed a number of advantages over commercially available coils or a microreactor. New efficient methods for the microwave–assisted synthesis of pyrazoles, pyrimidines, Bohlmann–Rahtz pyridines and Hantzsch dihydropyridines were developed using ethynyl carbonyl compounds as common precursors and this batch technology was successfully transferred to continuous flow processing using the prototype microwave reactor. The use of an 80 mL tube flow cell allowed the synthesis of 8 g of product in 1 h processing time, showing its potential for the large scale application of this prototype.

ABBREVIATIONS

Ac	Acetyl
APcI	atmospheric pressure chemical ionization
aq	Aqueous
Ar	Unspecified aryl substituent
Bu	Butyl
BuLi	Butyllithium
c	Concentration
cat.	Catalytic/catalyst
CMR	Continuous microwave reactor
CF	Continuous Flow
CI	Chemical Ionisation
DCM	Dichloromethane
DHP	Dihydropyridine
DMF	*N*,*N*–Dimethylformamide
DMSO	Dimethyl sulphoxide
ε	Molar absorbtivity
EI	Electron Impact
equiv. or eq.	Equivalent
Et	Ethyl
FTIR	Fourier Transform Infra Red
g	Grams
GC–MS	Gas Chromatography Mass Spectrometry
h	hour/s
HPLC	High Pressure Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IBX	*o*-Iodoxybenzoic acid
IR	Infra Red
J	Coupling constant (in Hz)
lit.	Literature
LRMS	Low Resolution Mass Spectrometry
M	Molar

MAOS	Microwave–Assisted Organic Synthesis
MCR	Multiple Component Reaction
Me	Methyl
MHz	Megahertz
min	Minutes
μM	Micromolar
mol	Mole
Mp	Melting point
MS	Mass Spectrometry
NaPTSA	sodium p-toluene sulphonate aqueous solution
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser effect Spectroscopy
p	*Para*
Ph	Phenyl
PhMe	Toluene
ppm	parts per million
quant.	Quantitative
R	Specified substituent
R_f	Retention factor
RT	Room Temperature
Silica/SiO_2	Merck Kieselgel 60 H silica or Matrex silica 60
STA	Silicotungustic acid
Tert	Tertiary
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
UV	Ultraviolet
vs	Versus

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INTRODUCTION: Microwave Chemistry

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1.1 History

The potential of microwaves as a heat source was discovered by accident in the 1940s by Dr Percy Spencer. At that time the company he worked for was investigating the use of the magnetron for application in RADAR devices. During one of the experiments he noticed that a chocolate bar in his pocket had melted. Intrigued by this discovery, he tried other experiments confirming that microwaves can be used as a heat source and they are more efficient than conventional heating methods. The first patent on the use of microwaves to cook food is dated 1946 and one year later "Radarange", the first commercial microwave oven, was on the market. Colossal and expensive, this first model of a microwave oven did not stimulate consumer demand. However, technological advances led to a much smaller, safer and cheaper home microwave model and as fears and myths surrounding this new technology faded, the microwave oven grew to be an international phenomenon. In 1975, microwave oven sales exceeded the traditional gas oven for the first time and the following year an explosion in popularity in Japan opened the doors to the international market. By 1976, the microwave oven reached about 52 million U.S. households (nearly 60%).

The potential and versatility of microwaves were soon recognized by industry. In the 1950s food industries began to test their usefulness for food processing; for example, to dry food (such as

potato chips, roast coffee, beans and peanuts) and to defrost, precook and temper meats. Drying industries found microwave heating advantageous, applying it to processes for cork, ceramics, paper, leather, tobacco, textiles, pencils and flowers. Alternative applications include using an irradiation coil to remove pollutants, rubber vulcanization, moisture and fat analysis of food products, solvent extraction, waste remediation and wet ashing or digestion procedures for biological and geological samples as an important tool in analytical chemistry.

Organic chemists seemed to ignore the potential of microwaves until 1986 when the first paper on the use of microwave ovens for organic synthesis was published by Gedye *et al.*[1] They reported a extraordinary rate enhancement and dramatic reduction in reaction time observed for hydrolysis, oxidations, esterifications and nucleophilic substitutions. The reaction time was reduced up to 240–fold compared to classical procedures as a result of the rapid heating capability of microwaves. This very first paper also highlighted some of the problems related to the use of domestic microwave ovens in terms of safety and parameter control. The experiments described, carried out in sealed vessels without reliable control of temperature and pressure, often resulted in violent explosions. Nevertheless carrying out these procedures in domestic microwave ovens was continued until recently. Companies started designing a microwave oven for chemical laboratories in the 1980s, providing multi–mode systems equipped with corrosion–resistant cavities, reinforced doors, temperature and pressure monitoring and automatic safety controls. These dedicated microwave ovens were much safer and reliable however they were not ideal for small scale reactions. It was in the late 1990s, with the advent of mono–mode microwave ovens that microwave chemistry enjoyed a remarkable growth to become the reliable, efficient heating method used in academia and industry that it is today.

1.2 Microwave Theory

1.2.1 Introduction

Microwaves are electromagnetic waves with wavelength of approximately 0.01–1 metre corresponding to frequencies of between 0.3 GHz and 300 GHz. In the electromagnetic spectrum microwaves lie between the infrared radiations and radio waves (Figure 1). RADAR equipments use wavelengths between 1 cm and 25 cm and the remaining wavelength range is used for telecommunications. In order to avoid interferences with these utilities, most of the microwave ovens operate at 2.45 GHz (corresponding to wavelengths of 12.2 cm). The major operating

frequency for microwave heaters is 2.45 GHz. This frequency has the right penetration depth to interact with laboratory scale samples and there is the ready availability of power sources to generate microwaves at this frequency. Other frequency allocations can be used, providing efficient shielding is present to prevent radiation leakage and consequent interference.

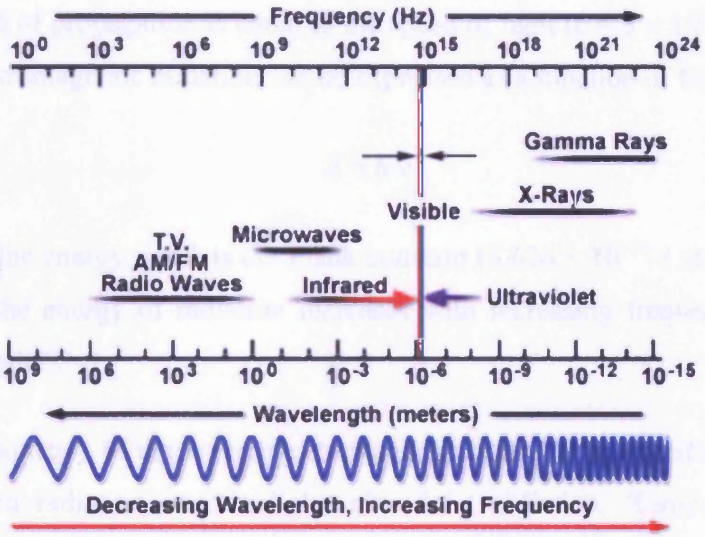


Figure 1. Electromagnetic spectrum

Electromagnetic waves are generally described as self–propagating waves in space which are composed of an oscillating magnetic and electric field. These components travel at right angles to each other and to the direction of motion as shown in Figure 2.

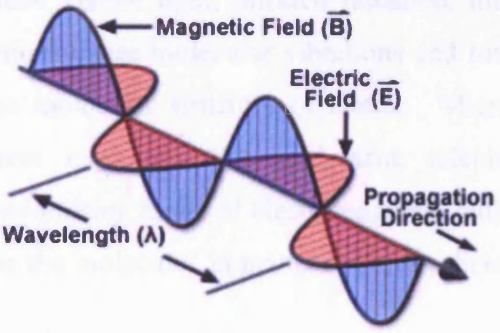


Figure 2. A plane linearly polarised electromagnetic wave

Electromagnetic waves are described by the wavelength (λ) defined as the distance between two consecutive crests, the frequency (ν) defined as the number of cycles per seconds and the speed of propagation (υ_w). They are correlated by the following relationship

$$\lambda = \upsilon_w / \nu \quad (1)$$

In vacuum the speed of propagation is equal to the speed of light ($c = 3 \times 10^8$ m s^{-1}). The energy associated with electromagnetic radiation can be expressed as a function of frequency:

$$E = h \nu \quad (2)$$

where E represents the energy and h is the Plank constant (6.626×10^{-34} J s). From eqns (1) and (2) it follows that the energy of radiation increases with increasing frequency and hence with decreasing wavelength.

According to the frequency of the wave, electromagnetic radiation is classified into radio waves, microwaves, infrared radiation, visible light, ultraviolet radiation, X–rays and gamma rays. Electromagnetic waves vary in size, from very long radio waves the size of buildings to very short gamma rays smaller than atom nuclei. Therefore they vary in energy (eqn (2)) and can be divided into ionizing radiation and non–ionizing radiation in relation to their effect on matter. Ionizing radiation is extremely powerful and penetrating. These very high frequency rays can ionize the molecular structure of matter and damage the cells of living tissues even at low levels and in sufficient dose can cause genetic mutations. Ionizing radiation is the sort of radiation associated with radioactive substances like uranium, radium, and the fall–out from atomic and thermonuclear explosions. The ionizing range of frequencies includes X–rays, gamma rays, and cosmic rays. Non ionizing radiations include visible light, infrared radiation, microwaves and radio waves. These lower frequency radiations cause molecular vibrations and rotations but they do not have enough energy to change the molecular structure of matter. Microwaves used in microwave ovens, similar to microwaves used in radar equipment, telephone, television and radio communication are in the *non–ionizing* range of electromagnetic radiation. Insufficient intensity microwaves will simply cause the molecules in matter to rotate, thereby causing frictions, which produce heat.

1.2.2 Microwave Dielectric Heating[2,3]

Chemical reactions can be driven *via* microwave dielectric heating exploiting the ability of some materials to transform electromagnetic energy into heat. The electric field exerts a force on charged particles generating an induced current if they can move freely through the substance or a dielectric polarization if the charge carriers are bound to certain regions and their motion is balanced by a counter force. Both conduction and dielectric polarization are mechanisms of microwave heating.

1.2.2.1 Dielectric Polarization

The total polarization of a substance can be expressed by the sum of diverse components:

$$\alpha_t = \alpha_e + \alpha_a + \alpha_d + \alpha_i \qquad (3)$$

where α_e represents the electronic polarization, resulting from the realignment of electrons around nuclei; α_a is the atomic polarization, arising from relative displacement of nuclei generated by an inhomogeneous charge distribution within the molecule; α_d is the dipolar polarization, due to the orientation of permanent dipoles caused by the electric field; α_i represents the interfacial polarization which occurs when there is an accumulation of charges at interfaces.

The response of a material to the electric oscillating field depends on the time of the orientation and disorientation process relative to the frequency of the radiation. α_e and α_a do not contribute to the dielectric heating effect because the timescales for their polarization and depolarization are much faster than the microwave frequencies. In contrast the timescales associated with α_d and α_i are comparable with microwave frequencies, consequently the dipolar and interfacial polarizations are the major contributors to the total polarization of materials by microwaves. Thus equation (3) can be approximated as follows:

$$\alpha_t = \alpha_d + \alpha_i \qquad (4)$$

taking into account just the dipolar polarization, α_d, and the interfacial polarization, α_i, components.

a) Dipolar Polarization. The dipolar polarization is due to the orientation of permanent dipoles under an electric field. A permanent dipole moment is caused by an electronegativity difference between bound atoms in the molecule. Mathematically it is defined as:

$$\mu = qr \tag{5}$$

where μ is the dipole moment, q represents the magnitude of the charge and r is the distance between the centres of charge; the bigger the dipole moment, the higher the ability of that molecule to couple with microwaves, generating heat.

Under an external field, dipolar molecules try to align themselves with the field by rotation using the energy provided by the applied field (Figure 3). In different physical states molecules show a different ability of motion. In gases they have motion freedom, hence the result is an instantaneous alignment with the field. In liquids their movements are reduced by the presence of other molecules and intermolecular forces, therefore the ability of the dipole to align with the field depends on the fluid viscosity.

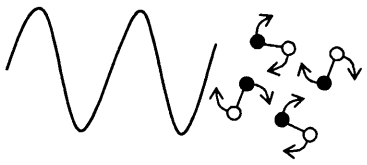


Figure 3. Dipolar polarization mechanism

Another important factor which affects the heat generating capacity is the frequency of the radiation. Polar molecules irradiated by microwaves generate heat when the frequency of the oscillating electric field gives them enough time to break the intermolecular forces existing in polar liquids and to follow the applied field. It is also important that it keeps the molecules almost in phase with the applied oscillating field, in this way there is a phase difference between the dipole orientation and the direction of the field which results in molecular collisions and frictions and hence heating (Figure 3). If the frequency applied is very high the polar molecules will not be able to make any significant motion before the field has reversed and the irradiation will result in no heat production. In the case of low frequency the molecules will move in phase with the field and the heat produced is not significant.

A more rigorous description of this phenomenon requires the introduction of some parameters which define the dielectric properties of materials: the dielectric constant ε', the dielectric loss ε''_d, the tangent delta δ, and the relaxation time τ.

Dielectric Constant and Dielectric Loss Factor. The dielectric constant, also known as relative permittivity, is the permittivity of the material related to that of free space. It expresses the ability of a molecule to be polarized by the electric field and it gives the quantity of electrical potential energy stored. In the microwave frequency range, the relative permittivity is expressed by a complex relationship:

$$\varepsilon^* = \varepsilon' - j\varepsilon''_d \tag{6}$$

where ε' is the real part of the equation (the dielectric constant) and ε''_d is the dielectric loss which reflects the conductance of the material. The latter parameter is related to the capacity of transforming electromagnetic energy into heat and it is defined as:

$$\varepsilon''_d = \sigma_d/\omega\varepsilon'_s \tag{7}$$

where σ_d is the conductivity, ω represents the angular frequency ($\omega = 2\pi\nu$) and ε'_s the static dielectric constant. At very high and low frequencies the dielectric loss factor is zero and the dielectric constant coincides with the relative permittivity. Moving from the radio waves region to the infrared radiation region the dielectric constant decreases. This is due to the increase of the loss factor contribution to the equation (6).

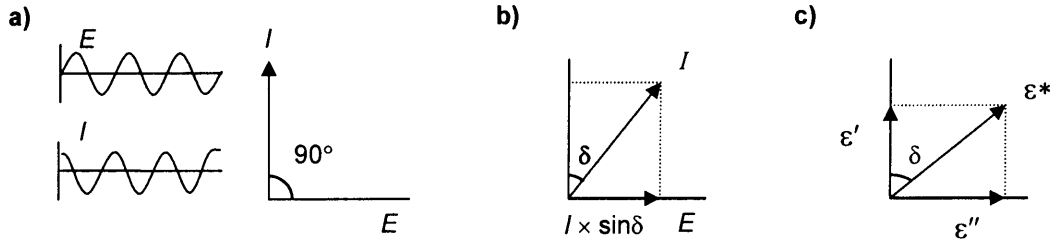


Figure 4. Phase diagram for a) an ideal dielectric; b) a phase displacement in the microwave radiation region; c) relationship between ε^*, ε' and ε''

Irradiation by radio waves corresponds to the ideal dielectrics behaviour described in Figure 4a, the dipoles can easily follow the oscillating field and the resulting induced current is 90° out of

phase with the electric field. There is no energy dissipation since the product $I \times E$ is zero and no component of I in phase with E results. In the microwave radiation region (frequencies of 10^9–10^{12} Hz) the alignment of the dipoles lags behind the direction of the electric field. This causes a phase difference, quantified by the loss angle δ (Figure 4b), that possesses a component in phase with the electric field, $I \times \sin \delta$. In this case energy is absorbed by the molecules and transformed into heat by molecular frictions and collisions in the vain attempt to follow the field. The magnitude of this phenomenon is given by the dielectric loss, ε'', that becomes important when the loss angle is significantly different from 90° (Figure 4c). Using higher frequency waves, such as infrared radiations, the dipoles are not able anymore to follow the fast reverse field and the result is a behaviour similar to non polar materials.

The variation of the dielectric constant and the dielectric loss with frequency is shown in Figure 5. The dielectric constant, ε', shows a constant value both at low and high frequencies, ε_s and ε_∞ respectively. At frequencies corresponding to the microwave region its magnitude falls from ε_s to ε_∞ while the dielectric loss increases until a maximum value is reached.

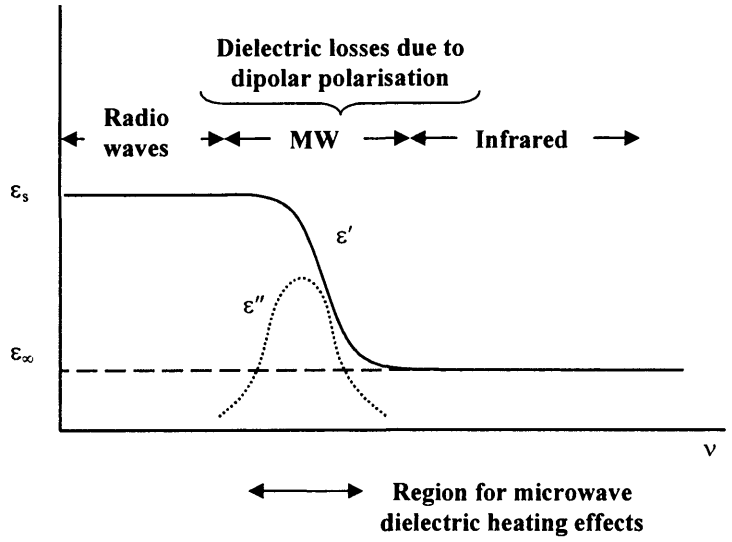


Figure 5. The dielectric constant as a function of frequency

Debye's theoretical examination demonstrates that the maximum value reached by the dielectric loss is independent of the frequency:

$$\varepsilon''_{MAX} = (\varepsilon_S - \varepsilon_\infty)/2 \qquad (8)$$

this equation defines it as the average between ε_∞, the dielectric constant at high frequency, and ε_S, the static dielectric constant.

Loss Tangent. A further important parameter in the description of dielectric properties of materials is the loss tangent. Mathematically it is defined as the ratio between the dielectric loss and the dielectric constant and it describes the ability of a material to convert electromagnetic energy into heat at a given frequency and temperature (Figure 6).

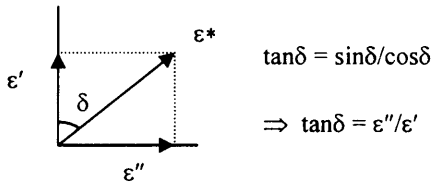


Figure 6. Relationship between ε*, ε′ and ε″ and tangent delta (δ)

Relaxation Time. The dielectric properties of matter are related to its ability to reverse orientation under an applied field. When the electric field is applied, the polar molecules in the sample orientate with the field and when the field is switched off they return to a random orientation. The time taken by a dipole to assume a randomised state once the electric field is switched off is defined as the relaxation time:

$$\tau = 1/\omega \qquad \text{with } \omega = 2\pi\nu \qquad (9)$$

where τ is the relaxation time, ω is the angular frequency and ν is the frequency of the applied field. A particular polarization mechanism becomes important when the relaxation time approaches the inverse excitation frequency. Thus, just polarizations with relaxation times of approximately 10^9 s contribute to dielectric heating effect of microwaves. Debye's interpretation of the relaxation time for spherical dipoles in liquids is given in terms of the frictional forces in the medium:

$$\tau = 4\pi r^3 \eta / kT \qquad (10)$$

where r is the radius of the dipole, η is the viscosity of the medium, k is the Boltzmann's constant and T is the temperature. From the above relationship, it follows that the magnitude of the relaxation time increases when dipole volume ($V = 4/3\pi r^3$) and medium viscosity increases and when the temperature decreases. The theoretical description of relaxation time in solids is much more complicated. In liquids a dipole can assume any position and changes direction repeatedly under the effect of thermal agitation. In contrast, interactions between dipolar molecules in a solid state generate a high number of equilibrium positions separated by potential barriers that the dipole has to overcome moving from one position to another.

b) Interfacial Polarization. The interfacial polarization is a minor mechanism of dielectric heating compared to the dipolar polarization described previously. It is important just for inhomogeneous materials having conducting inclusions in a non–conducting medium–for instance a dispersion of metal particles in a microwave transparent material. The surrounding non–conducting medium retards the conducting material polarization. Similarly to what happens in the dipolar polarization mechanism, the polarization is not instantaneous and the heat generating capacity is frequency dependent even though the interfacial polarization is due to a conducting mechanism. This is quite a complex interaction that can be considered as a combination of the two major mechanisms. The loss related to the accumulation of charges between the interfaces is known as the Maxwell–Wagner effect but its importance in the microwave region has not been well defined.

1.2.2.2 Conduction Mechanism

The conduction mechanism is the second major interaction of the electric field with matter that contributes to microwave dielectric heating effects. It is due to the behaviour of ions and charged particles under irradiation. If they have freedom of motion throughout the substance, then a current is induced by the applied field (Figure 7). This phenomenon is more efficient compared with the dipolar polarization mechanism in terms of heat generating capacity. The ions move in phase with the field generating a higher number of collisions and so a larger quantity of energy is produced.

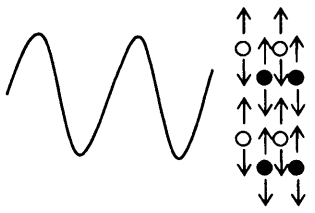


Figure 7. Conduction mechanism

Under microwave irradiation, materials containing ions show losses due to conduction in addition to dielectric losses. The complex relative permittivity for these materials can be expressed by the following equation:

$$\varepsilon^* = \varepsilon' - j(\varepsilon''_d + \varepsilon''_c) \tag{11}$$

where ε^* is the complex permittivity, ε' is the real part of the dielectric constant, ε''_d is the dielectric losses (eqn (7)) and ε''_c is the conduction losses which is given by this relationship:

$$\varepsilon''_c = \sigma_c/\omega\varepsilon'_s \tag{12}$$

where σ_c is the conductivity, ω represents the angular frequency and ε'_s the static dielectric constant. The previous equation is found to be a good approximation at low frequencies. However at high frequencies, the linear relationship diverges to experimental values and the following equation is found to be more accurate:

$$\varepsilon''_c = \text{constant} \times f^k \tag{13}$$

where k approaches unity for high concentrations of conducting material.

At room temperature losses in the microwave region are principally due to dipolar relaxation. However as the temperature increases conduction losses increase rapidly and become as important as dipolar relaxation loss in the microwave region. The increase of conduction with temperature is associated with the thermal activation of electrons from valence bands to conduction bands. The presence of material defects enhances electrical conduction by decreasing the energy gap between the valency and conduction bands.

1.2.3 Rate of Heating

A useful approximation for the power absorbed and a basic relationship between the four variables is given by the following fundamental relationship

$$P = \sigma \, |E|^2 = \omega \varepsilon_s \varepsilon'' \, |E|^2 \qquad (14)$$

$$= (\omega \varepsilon_s \varepsilon' \tan\delta) \, |E|^2$$

where P is the power dissipation per unit volume and σ is the conductivity of the material. It can be seen that the power absorbed varies linearly with frequency, the relative dielectric constant and the loss tangent, and varies with the square of the electric field.

The rate of heating can be expressed as

$$\Delta T/t = P/\rho C = \sigma \, |E|^2 / \rho C \qquad (15)$$

$$= \omega \varepsilon_s \varepsilon'' \, |E|^2 / \rho C = (\omega \varepsilon_s \varepsilon' \tan\delta) \, |E|^2 / \rho C$$

where ρ is the density and C the specific heat capacity. The temperature rise in a time interval is directly proportional to the power dissipation and inversely proportional to density and specific heat capacity. Therefore the efficiency of conversion of microwave energy into heat depends on the dielectric and thermal properties of the material.

1.2.4 Microwave Absorbing Capability of Organic Solvents

The majority of solvents used in organic synthesis can be successfully used in microwave chemistry since they have a permanent dipole moment. Table 1 shows the dielectric properties of a range of compounds (alcohols, hydrocarbons, ketones, esters, acids, nitriles, chlorinated hydrocarbons, glycols) used as common solvents in organic chemistry. They have been categorized into high, medium or low microwave absorbers. The higher the dipole moment the higher the dielectric constant and hence the higher the ability of the molecules to follow the reverse field. Water is the solvent with the highest dielectric constant shown in Table 1; nevertheless, it belongs to the medium absorber group because its dielectric loss factor and its loss tangent are relatively low. These last two parameters give a better measure of the heat generating

capacity of a solvent under microwave irradiation. Both dielectric constant and tangent loss depend on the relaxation time which represents an additional important parameter to be considered. The dielectric parameters relevant to microwave dielectric heating have been amply discussed by Mingos *et al.*[3]

The majority of microwave ovens operate at 2.45 GHz corresponding to a relaxation time of 65 ps. Compounds that show a relaxation time of this magnitude couple efficiently with microwaves, therefore an effective conversion of microwave energy into thermal energy occurs. However, solvents with relaxation times of one or two orders of magnitude different from that which corresponds to the microwave frequency applied are still an efficient medium for dielectric heating because their loss tangent and loss factor are sufficiently large. The relaxation time of water is 9 ps at 20 °C and its relaxation frequency is 18 GHz, and thus the most effective conversion of microwave energy into thermal energy will occur in this frequency region. The relaxation time of alcohols listed in Table 1 is of the order of 51–800 ps, which enable them to couple efficiently with the applied frequency and make them good solvents for dielectric heating. According to eqn 10, their relaxation time increases as the molecule volume increases due to the restricted rotation of the whole molecule. Isomeric alcohols show comparable relaxation times, suggesting that the position of the OH group does not influence the relaxation time. An anomalous behaviour is shown by those alcohols with a CH_2OH group adjacent to a double bond or a phenyl group. Their relaxation times are very short compared with those of corresponding saturated alcohols ($\Delta\tau \sim$ 400–500 ps), which suggests a localized rotation process for these molecules. Primary amines anchored to large molecules also have relaxation times which are inconsistent with the rotation of the whole molecule, for instance *ortho–*, *meta–* and *para–* methoxyaminobenzenes show a relaxation time of 25–30 ps. It has been proposed that the inversion at the nitrogen atom is responsible for such a short relaxation time instead of a local rotation. Nitriles, esters, ketones (τ = 4–68 ps) and chlorinated hydrocarbons (τ = 4–15 ps) exhibit short relaxation times and this is attributed to the absence of strong hydrogen bonds. In contrast acetic and formic acid have long relaxation times (76–177 ps) because of the strong hydrogen bonding associated with the carboxylic acid groups.

High absorbing solvents couple very efficiently with microwaves and can therefore be heated very quickly, while medium and low absorbers can be heated above their boiling point but they take longer to reach the desired temperature. The coupling efficiency of these solvent can be improved by adding salts or small amounts of polar solvent. An alternative to conventional solvents is represented by ionic liquids.[4]

Table 1. Dielectric constant, tangent delta and dielectric loss for a range of common solvents measured at 25 °C and 2.45 GHz

Absorbance level	Solvent	τ/ps[a]	tanδ[b]	ε′ [b]	ε″ [b]
	Ethylene glycol	104.6	1.358	37.0	49.950
	Formic acid	76.7	0.722	58.5	42.237
	DMSO	20.5 [c]	0.825	45.0	37.125
High	Ethanol	170 [c]	0.941	24.3	22.866
	Methanol	51.5 [c]	0.659	32.6	21.483
	Nitrobenzene	43.7 [c]	0.589	34.8	20.497
	1–Propanol	332 [c]	0.757	20.1	15.216
	2–Propanol	237 [c]	0.799	18.3	14.622
	Water	9.04 [c]	0.123	80.4	9.889
	1–Butanol	538 [c]	0.571	17.1	9.764
	NMP		0.275	32.2	8.855
	Isobutanol	644 [c]	0.522	15.8	8.248
	2–Butanol	562 [c]	0.477	15.8	7.063
	2–Methoxyethanol	23.7 [d]	0.410	16.9	6.929
Medium	DMF	13.05 [c]	0.161	37.7	6.070
	o–Dichlorobenzene		0.280	9.9	2.772
	Acetonitrile	4.47 [c]	0.062	37.5	2.325
	Nitromethane	4.51 [c]	0.064	36.0	2.304
	Methylethylketone	5.90 [c]	0.079	18.5	1.462
	1,2–Dichloroethane	11.14 [c]	0.127	10.4	1.321
	Acetone	3.54 [c]	0.054	20.7	1.118
	Acetic acid	177.4	0.174	6.2	1.079
	Chloroform	8.94 [c]	0.091	4.8	0.437
	Dichloromethane	3.12 [c]	0.042	9.1	0.382
	Ethyl acetate	4.41 [c]	0.059	6.0	0.354
Low	THF	3.49 [c]	0.047	7.4	0.348
	Chlorobenzene	12.9 [c]	0.101	2.6	0.263
	Toluene		0.040	2.4	0.096
	o–Xylene		0.018	2.6	0.047
	Hexane		0.020	1.9	0.038

[a] Gabriel, C.; Gabriel, S.; Grant E. H.; Halstead, B. S. J.; Mingos D. M. P. *Chem. Soc. Rev.* **1998**, 27, 213. [b] Hayes, B. L. *Microwave synthesis: chemistry at the speed of light;* CEM publishing: Matthews, NC, **2002**, chapter 2, p 35. [c] Relaxation time measured at 20 °C. [d] Relaxation time measured at 35 °C.

1.2.5 Thermal Runaway

The relaxation time of a solvent depends on the temperature, and according to eqn (10) it decreases as the temperature is increased. This is due to the larger translational motions of molecules at high temperature that permit them to randomise more quickly. Table 1 shows that a significant number of organic solvents which have relaxation times greater than 65 ps and thus they have a loss tangent which increases with temperature. As a result, these solvents convert more of the microwave energy into thermal energy as the temperature increases. Therefore, the heating rate augments, producing a phenomenon known as thermal runaway. There are a few cases where thermal runaway may diminish as the boiling point is approached because a rise in temperature causes a reduction in loss tangents. This behaviour is characteristic of low molecular weight solvents such as MeOH and CH_3CN, which have short relaxation times.

1.2.6 Superheating Effect

The boiling points shown by many organic solvents in a microwave cavity at atmospheric pressure is 15–25 °C higher than their conventional boiling points. This phenomenon, known as superheating, has been interpreted on the bases of the nucleate boiling model and the temperature profile for a solvent irradiated by microwaves.[5]

The conventional boiling theory considers nucleate boiling as the most likely source of boiling which relies on the existence of tiny crevices on the surface of the vessel in which vapour embryo can be trapped by solvent. When the liquid layer temperature approaches the saturation temperature of the site, bubble growth occurs until a critical size is approached. At this point the bubble is released from the cavity and boiling occurs. The superheated liquid layer, which surrounds the bubble, supplies the energy for the bubble growth.

In conventional heating, thermal energy is supplied to the vessel by an external heat source (heating mantle, oil bath, sand bath, *etc.*). Heat must pass through the vessel walls before reaching the liquid in the vessel. The result is a slow and inefficient heating process which depends on the conductivity of the different materials penetrated. In contrast, microwave heating generates an instantaneous uniform heating distribution throughout the sample. Microwaves couple directly with the molecules in the sample, since the vessel is made of microwave

transparent materials (borosilicate glass, quartz or Teflon). The consequence is an inverted temperature profile compared with conductive heating as shown in Figure 8.

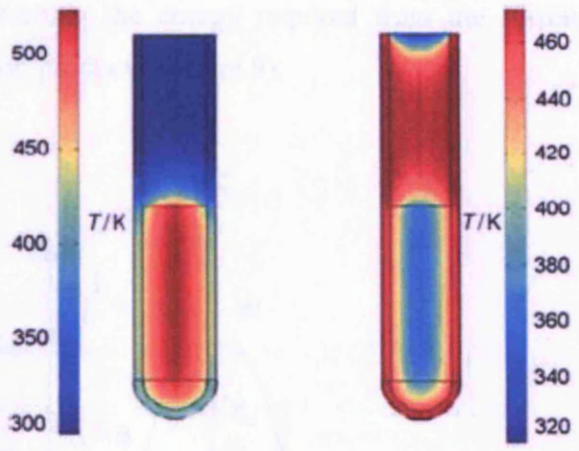


Figure 8. Temperature profiles in microwave (left) and conductive heating (right).[6]

The inversion of the temperature profile observed when the vessel is heated by microwaves explains the higher boiling point observed. In microwave heating the outer walls of the flask are continuously cooled by convective air flow, therefore the layer of solvent adjacent to the walls shows a lower temperature than the bulk liquid. As a consequence more time is required for the layer of liquid adjacent to the walls of the vessel to reach the saturation temperature and give rise to the boiling act. Wetting properties of the solvents have been demonstrated to have an important role in the superheating effect.[5]

1.2.7 Microwave Effects

Dramatic rate accelerations and yield enhancements resulting from microwave irradiation cannot be often achieved by conventional heating but are still attributed to thermal effects. They are due to the peculiarities of microwave dielectric heating, defined as specific microwave effects, arising from the heating rate (see Section 1.3), superheating (see Section 1.5), selective absorption of heterogeneous catalyst or reagents in a less polar medium that can generate the so–called "hot spots". This is a thermal effect caused by the inhomogeneous field, resulting in high temperature

zones within the sample. Hot spots may be created by the difference in dielectric properties of material in the sample, by the uneven distribution of electromagnetic field strength, or by volumetric dielectric heating under microwave conditions.[7,8]

A representative reaction coordinate shows that the reagents must reach the higher energy level of the transition state (absorbing the energy required from the surrounding environment) to be converted into the reaction products (Figure 9).

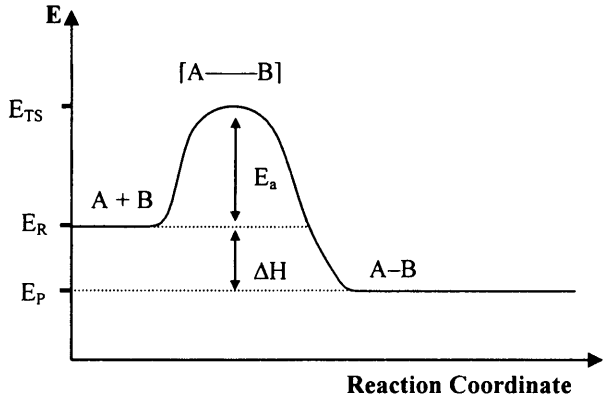


Figure 9. Typical reaction coordination for the transformation of the reagents A and B into the product A–B passing through the transition state [A——B]

The speed associated to a transformation is given by the Arrhenius equation

$$k = Ae^{-Ea/RT} \qquad (16)$$

where k is the reaction rate constant, A is the frequency of collisions with a correct geometry for a reaction to occur, E_a is the activation energy, R is the gas constant and T is the temperature. The exponential term represents the fraction of molecules with the minimum energy required to overcome the activation energy barrier. Based on the Arrhenius equation, Mingos and Baghurst calculated the rate acceleration due to an increase in temperature for a first order reaction. A rise in temperature from 77 °C to 177 °C results in a 1000–fold rate increase (13.4 h *vs* 23.4 s).[2] This suggests that many of the rate enhancements observed under microwave assisted conditions can be rationalized by thermal/kinetics effects, and they can be associated with specific microwave effects.

However, some authors have suggested the existence of non–thermal microwave effects which have been proposed to be responsible for the rate acceleration, and particular cases of altered product distribution observed. Non–thermal microwave effects are defined as acceleration in rate that cannot be rationalized by either thermal, kinetic or specific effects.[6] They have been proposed to result from a direct interaction of the electromagnetic field with specific molecules or intermediates in the reaction mixture (orientation effects) or from changes in thermodynamic parameters such as the activation energy (possibly through the entropic parameter of the system) or the Arrhenius pre–exponential factor A (due to an increase in the molecular mobility caused by the microwave field). Similar arguments are given by Loupy who asserts that a non–thermal microwave effect can take place if the polarity of the system is enhanced from the ground state to the transition state. Under these conditions, the higher stabilization of the transition state by the microwave field has been suggested to reduce the activation energy.[9]

Many authors assert that speculations on non–thermal microwave effects have been often due to uncritical considerations of published results and in many cases rate acceleration may be rationalized, taking into account the high reaction temperature and the change of physical property of the solvent.[10] However, no direct comparison with a conventional heating method was reported for most of the early experiments, leaving room for speculation about the nature of the phenomenon. Microwave effects still seems to be a controversial subject in the chemistry world,[9–11] and further investigations are required in order to support or reject some of the existing theories.[12]

1.3 Synthetic Applications

Microwave irradiation as an alternative heating method in synthetic chemistry has received increasing interest in recent years. Drastically reduced reaction times, enhancements in selectivity, improvements in yield and production of cleaner chemistries have attracted the attention of the chemical community, resulting in an exponential increase of papers since the first publication in organic synthesis in 1986 (Figure 10). Winning over the initial scepticism, due mainly to the unsafe nature and irreproducibility of experiments in domestic microwave ovens, microwave chemistry has become a reliable, efficient heating method used in academia and industries.

Despite being a relatively new technique, a large number of books[13] and reviews have been published on the application of microwaves to organic,[6,14] medicinal and combinatorial chemistry[15] and drug discovery.[16] More specific topics such as polymer synthesis,[17] heterocyclic chemistry,[18] radiochemistry,[19] homogeneous and heterogeneous catalysis,[20] synthesis of nanoporous materials,[21] and supported reagents in organic chemistry[22] under microwave assisted conditions have also been reported.

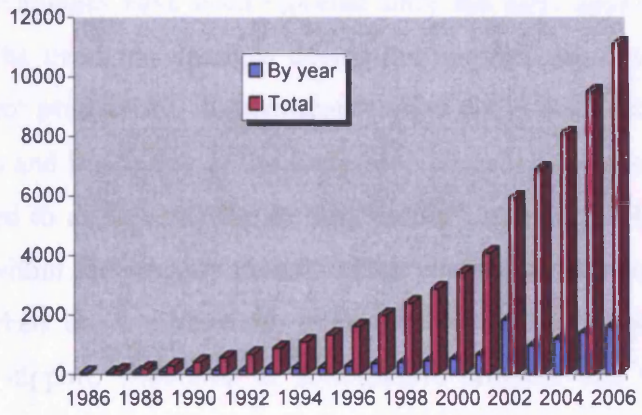


Figure 10. Number of publication identified by keywords "microwave synthesis not plasma not discharge not spectroscopy" plotted against publication year for the period 1986–2006

In theory microwave energy can accelerate all types of thermally driven chemical reactions. In particular, reactions under thermodynamic control can benefit from microwave irradiation since the activation energy required for those transformations to occur is very high and conventional heating sources are often not able to supply enough energy to promote them.[23] The high heating rate and short reaction times permit reactions to be performed that do not occur by conventional heating, for instance the preparation of isotopically labelled drugs that have a short half–live,[24] and the use of catalysts which decompose under conventional methods.[25] In addition, microwave irradiation satisfies the demand for more efficient use of energy that has become a focal point in chemical research in recent years. A comparative study of reaction techniques reported by Clark and co–workers confirmed that energy consumption is more efficient, with up to an 85–fold reduction in demand on switching from an oil bath to a microwave reactor.[26]

New perspectives for microwave chemistry may result from the combination with new technologies. The energy efficiency of microwave organic synthesis can be united with

technologies designed to simplify product isolation and purification such as solid– and fluorous–phase.[16a] Another potential field of application appears to be microwave–assisted capillary synthesis, the application of microwave heating to a microreactor (lab on–a–chip).[27]

1.4 Synthetic Techniques

Different synthetic techniques have been reported since the early application of microwaves to organic synthesis. The trend has changed during the last two decades, responding to specific needs and/or equipment availability. Experiments carried out in domestic microwave ovens often resulted in explosions and hence one of the first needs in early days was related to safety issues. The technique referred to as solvent–free or "dry media" appeared to be a solution for solvent over–pressurization within the reaction vessel, which was the main cause of reported incidents. Reagents were absorbed on a microwave transparent (alumina, silica) or microwave active (graphite) inorganic support, irradiated at atmospheric pressure and then the products were extracted from the support. This quite popular technique was claimed to be an environmentally friendly method since it enabled a reduction in waste production. Nevertheless, solvents were often used to absorb the reagents on the support and to isolate the products after irradiation. In addition, good temperature control of dry media was often troublesome, causing reproducibility problems. Many reviews have been published on this technology, which also included further solvent–free procedures under microwave-assisted conditions such as phase transfer catalysis and neat reactions.[28]

The advent of dedicated instruments for chemistry reopened the path to synthesis in solvents. Classical reflux reactions can be performed in a microwave using open vessel techniques.[29] Exploiting the superheating effect (see Section 1.6), observed in solvents irradiated with microwaves at atmospheric pressure, it is possible to achieve a rate increase up to 10–fold compared to conventional methods. The use of pressurized systems, corresponding to the conventional autoclave technique, permits a much higher enhancement in rate. The temperature can be increased far above the boiling point of the solvent resulting in extraordinary improvements in reaction rate. Therefore most of the microwave chemistry reported in recent years have been carried out in pressurized systems.

1.5 Microwave Reactors

Domestic ovens, inexpensive and easy to modify, responded to the needs of the first experiments of microwave effects on chemical transformations. Nowadays, dedicated microwave instruments have replaced domestic ovens. Designed for the needs of research laboratories, these systems are equipped with temperature and pressure monitors, automatic safety controls, built–in cooling features and automation. Currently, monomode and multimode reactors are available on the market (Figure 11).[30] The multimode apparatus has a design similar to domestic ovens, equipped with a large chamber where many samples can be irradiated at the same time, whereas the monomode (or single–mode) has been designed for small scale synthesis.

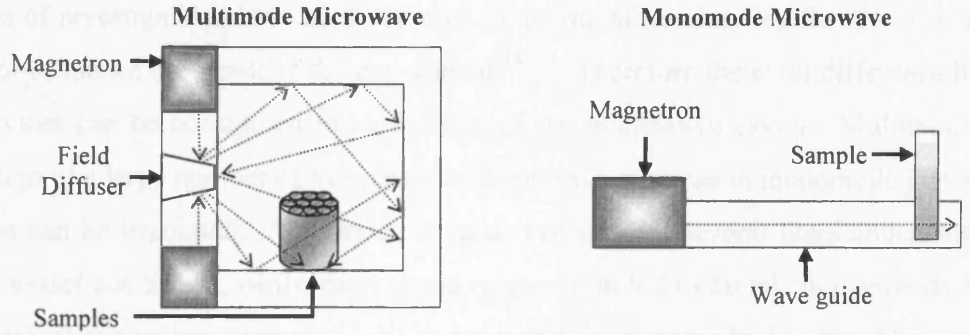


Figure 11. Schematic representation of a multimode and a monomode microwave reactor

As shown in Figure 11, in a monomode microwave device, the reactor is directly inserted into the waveguide, which has been designed to reflect microwaves in phase with the empty waveguide. The result is the generation of standing waves and the reactor (max. 100 mL) is inserted exactly where the maximum of the electric field was calculated for the dielectric material air. The sample is irradiated from the side, consequently great inhomogeneities of the electric field and high temperature differences arise. Moreover, new modes are created by refraction, reflection and interference, due to the insertion of the reactor and reaction mixture, which will eventually result in a system with high microwave power density. Every additional change leads to an increase in the amount of multimode radiation. As a result this kind of device can be better described as a multimode system with an undetermined amount of initial monomode radiation. Distinguishing

between monomode and multimode devices would be better accomplished in terms of their radiation intensity or power density.[14b]

Multimode systems have a design similar to domestic ovens, the radiation is directed through a large cavity where it is reflected by the walls. As a result, multimode radiation is developed, and in contrast stationary waves are avoided. An improvement in the field homogenization compared to domestic microwaves has been achieved using two magnetrons facing each other and a field diffuser (as shown in Figure 11). Radiation is in general homogeneously distributed and the sample is irradiated from every direction. Those instruments allow the use of pulsed (pulses at the higher available power are applied) and unpulsed (continuous) irradiation. The large microwave chamber cause a much lower power density compared to the monomode models (300 WL^{-1} *vs* 23 WL^{-1}).

A series of investigations have been reported in the literature, showing that the irradiation method does not influence the result of the experiment.[14c,31] Therefore the main difference between these two devices can be considered to be the size of the microwave cavity. Multimode permits the irradiation of a large number of samples simultaneously, whereas in monomode just one sample at the time can be irradiated. Multimode systems can process several liters under both open– and closed–vessel conditions, whilst the volume ranges from 0.2 to 50 mL in pressurized systems, up to 150 mL at atmospheric pressure, can be processed in monomode devices. However automated monomode synthesizers are equipped with robotic gripper devices which move the single vessels in and out of the microwave cavity, resulting in a high throughput.

1.6 Scale–up Technology

Mono–mode instruments have developed into a reliable systems for small scale synthesis whereas, in contrast, applications on a large scale are still troublesome. Researchers have moved towards two different approaches exploring batch type reactors and continuous flow techniques as potential methods to scale up microwave synthesis. The main problem encountered in scaling–up microwave technology is the penetration depth of microwaves into matter. The penetration depth D_p, is an important parameter in the design of a microwave experiment that can be defined by the following relation when the dielectric loss is small:

$$D_p \propto \lambda\sqrt{\varepsilon'/\varepsilon''} \qquad (17)$$

Where λ is the wave length of the applied electromagnetic field, ε′ is the dielectric constant and ε″ is the loss factor, the equation shows that D_p depends on the dielectric properties of the irradiated material. At the typical operating frequency of 2.45 GHz the penetration depth of the microwave radiation is in the order of few centimetres, therefore the maximum volume of a sample is limited to approximately 1 L. An additional problem related to the use of large microwave reactors is the need of higher powers to guarantee an adequate power density. A power output higher than 5000 W is needed to heat a 3 L sample,, requiring sophisticated and expensive cooling systems. The problems and safety issues related to the use of pressurized large volumes under microwave irradiation make it impossible to scale up microwave mediated processes in batch mode.

1.6.1 Continuous Flow Microwave Reactors

The physical limitation of microwave reactors leads to a continuous flow approach as the only feasible scale up strategy. Continuous flow microwave reactors are a synthetic platform technique resulting from the combination of microwave and continuous flow[32] enabling techniques. Recently two reviews have been published on microwave flow chemistry by Pitts[33] and Kappe.[34] Figure 12 shows a schematic representation of a simple continuous microwave reactor (CMR). Those reactors operate by passing the reagents through a flow cell inserted into the microwave cavity. The use of a back pressure regulator allows the device to reproduce the conditions of a sealed tube mode. The described set up allows large scale production in contained microwave reactors. Nevertheless, the reality of carrying out only homogeneous processes in continuous flow mode represents a great limitation of this technology.

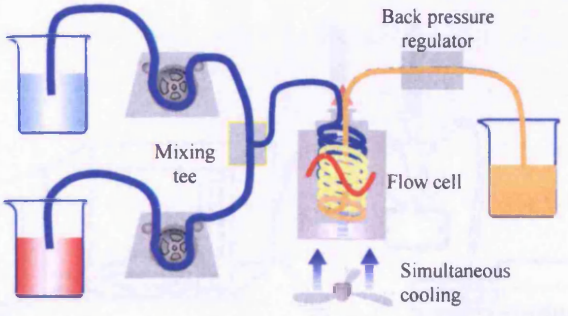


Figure 12. Simple continuous flow microwave reactor

1.6.1.1 Continuous Flow Microwave Reactor Prototypes

A number of papers have been published describing the use of custom–built microwave reactors. In early days the majority of publications reported the description of a modified domestic oven, in order to study continuous flow processes under microwave irradiation.

Wang and co–workers published the first prototype of a continuous microwave reactor in 1990 in response to safety issues and consequent scalability problems exhibited by domestic microwave ovens for organic synthesis.[35] The reactor consisted of a modified domestic oven equipped with a Teflon coil (~10 mL) and the reactions were carried out by pumping the reagents into the flow cell and then out to a product collector. They investigated five different organic transformations: (i) the esterification of *p*–hydroxybenzoic acid with butanol and methanol, (ii) the racemization of optically pure amino acids in acetic acid, (iii) the acid hydrolysis of sucrose to glucose and fructose, (iv) the S_N2 reaction of phenoxide with benzyl chloride, and (v) the cyclization of butane–1,4–diol and diethylene glycol. All reactions were run by irradiating the reaction mixture for 1–10 min at full power (650 W) under atmospheric pressure. A heterogeneous process was also described: the hydrolysis of sucrose was carried out by packing the flow cell with a cation–exchange resin. Most of the reactions investigated showed a higher efficiency compared to experiments carried out in closed vessel systems under microwave irradiation.

Another example of a modified microwave oven was reported by Khadikar.[36] An omega–shaped glass coil (65 mL) was used as a flow cell and the reaction was carried out in a closed loop mode (Figure 13).

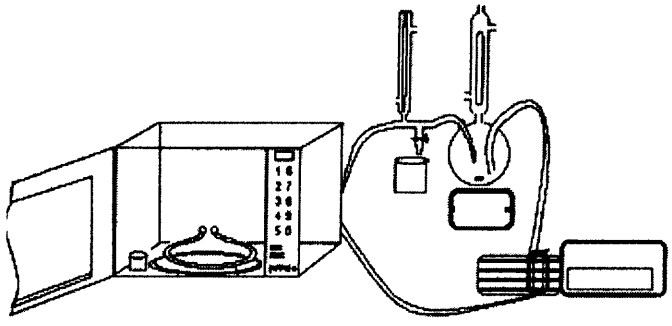
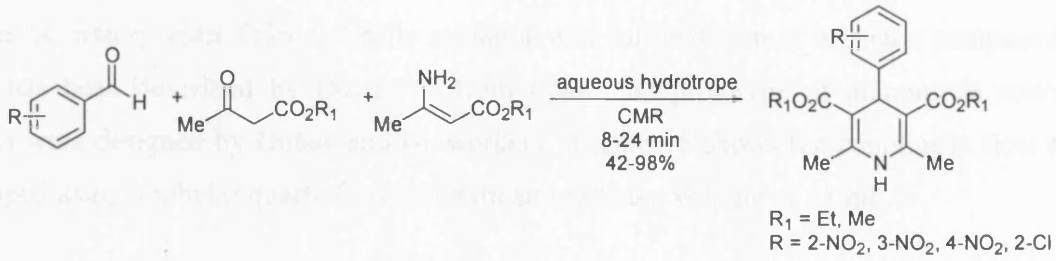


Figure 13. Simple continuous flow microwave reactor (from ref. 36)

The Hantzsch dihydropyridine synthesis using a hydrotrope solution of 50% sodium p-toluene sulphonate aqueous solution (NaPTSA) as a solvent was first optimized in batch mode. Then, the synthesis of five dihydropyridines was carried out in a continuous flow regime, resulting in excellent yields and short reaction times (Scheme 1).



Scheme 1. Synthesis of Hantzsch dihydropyridines using an omega–shaped flow cell in a modified domestic oven

In order to study the kinetics of heterogeneous systems under microwave irradiation, Kabza *et al.* designed a CMR, by modifying a domestic multimode microwave oven (Figure 14).[37]

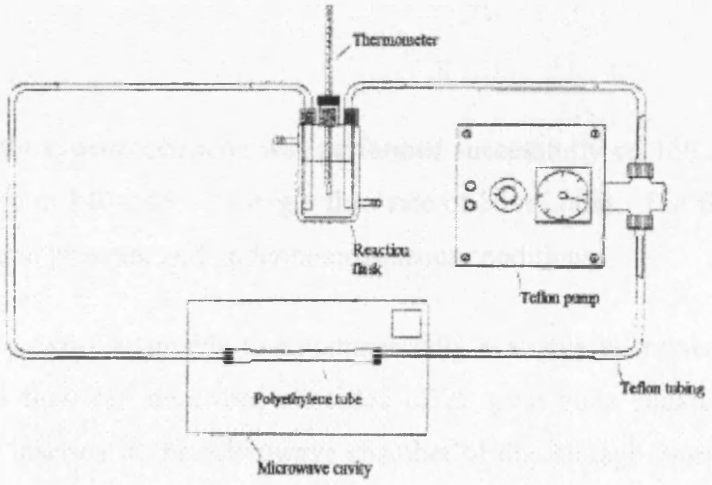


Figure 14. Continuous flow cell set–up for heterogeneous processes under microwave radiation (from ref. 37)

The acid–catalysed Fisher–type esterification of isopentyl alcohol and acetic acid was chosen as a model system. The polyethylene tube flow cell was packed with Amberlyst–15 cation exchange resin. The reaction was performed at atmospheric pressure, the temperature was recorded in the external reaction vessel and kept constant at 40 °C. The model system behaved comparably under both microwave and thermal conditions, indicating no energy–source preference for optimum reaction kinetics.

A large laboratory scale Friedel–Crafts acylation and sulfonylation of aromatic compounds in a CMR has been described by Dubac.[38] Both CMR and prototype of monomode microwave devices were designed by Dubac and co–workers. Figure 15 shows the continuous flow reactor developed using a tubular quartz flow cell with an irradiated volume of 11 mL.

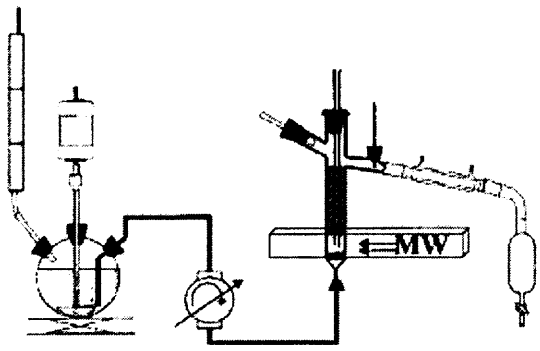
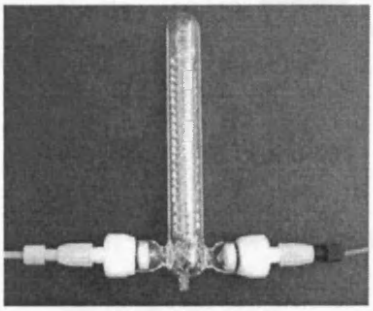


Figure 15. CMR developed for large laboratory scale synthesis (from ref. 38)

The synthesis of methoxybenzophenone was performed successfully on 150 g scale; the reaction mixture was irradiated at 140–145 °C using a flow rate of 20 mL/min. The flow–through system operated at atmospheric pressure and under homogeneous conditions.

A flow cell prototype easily adaptable to a commercially available instrument was described by Wilson *et al.*[39] The flow cell described consisted of 22 glass coils encased in a glass sheath (Figure 16) and was inserted in the microwave chamber of the Biotage Emrys Synthesizer from underneath the instrument by removing the cleaning tray.



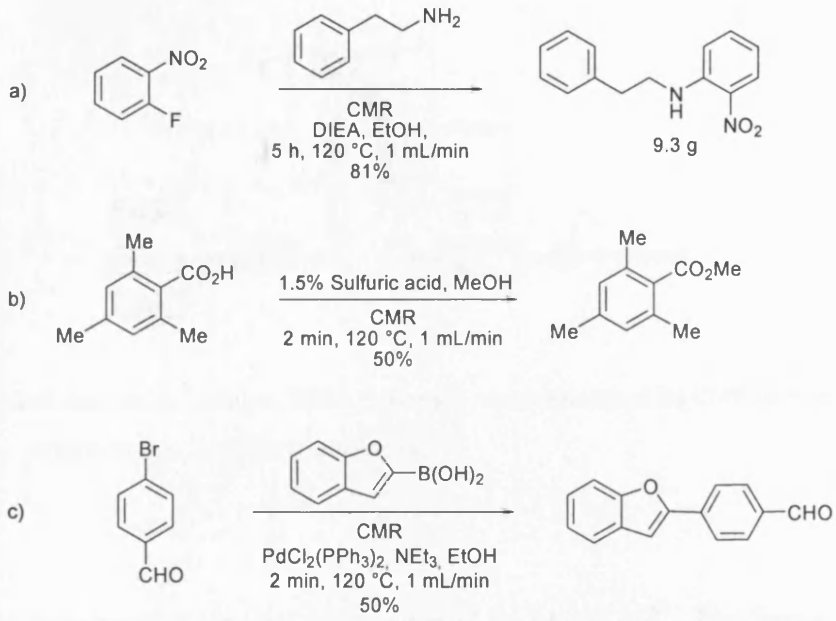
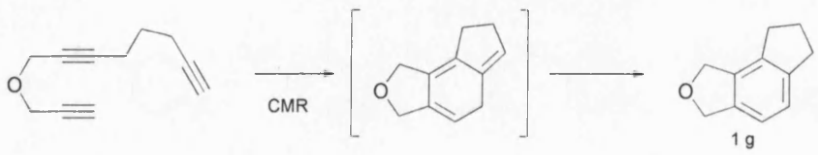


Figure 16. Glass coiled flow cell (from ref. 39) on the left. Reactions investigated in the glass coil flow cell on the right. a) Nucleophilic aromatic substitution of 2–fluoro–3–nitrobenzene with phenethylamine; b) Esterification of 2,4,6–trimethylbenzoic acid with methanol; c) Suzuki coupling of 4–bromobenzaldehyde

Aromatic nucleophilic substitution, esterification and Suzuki cross coupling were chosen as representative reactions resulting in yields comparable to or greater than those obtained under thermal heating conditions. However, product crystallization was reported to cause line clogging during one of the experiments, highlighting one major limitations of CMRs. The CMR prototype as described by Wilson was used to carry out a non–metal–catalysed intramolecular alkyne cyclotrimerization reaction by Ley and co–workers.[40] Cyclotrimerization of oxygen–bridged triyne was carried out in a flow mode on a 1 g scale (Scheme 2).



Scheme 2. Cyclotrimerization of oxygen–bridged triyne in a glass coiled flow cell (see Figure 15)

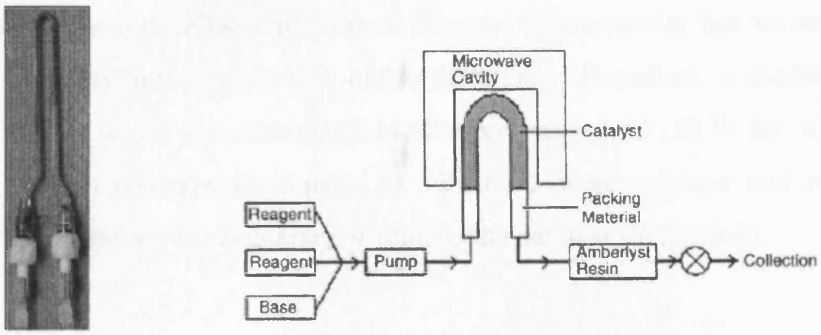
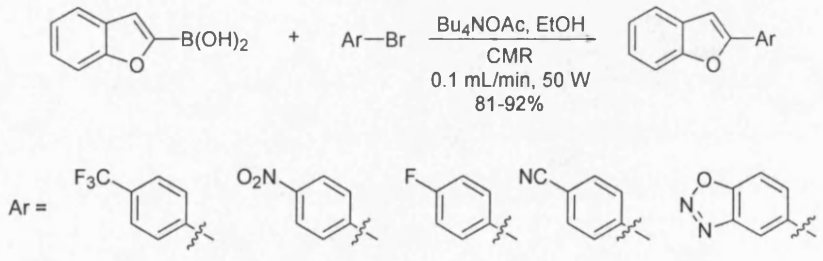


Figure 17. Left: U–tube flow cell packed with EnCat® catalyst. Right: Schematic representation of the CMR used to perform Suzuki reactions (from ref. 41)

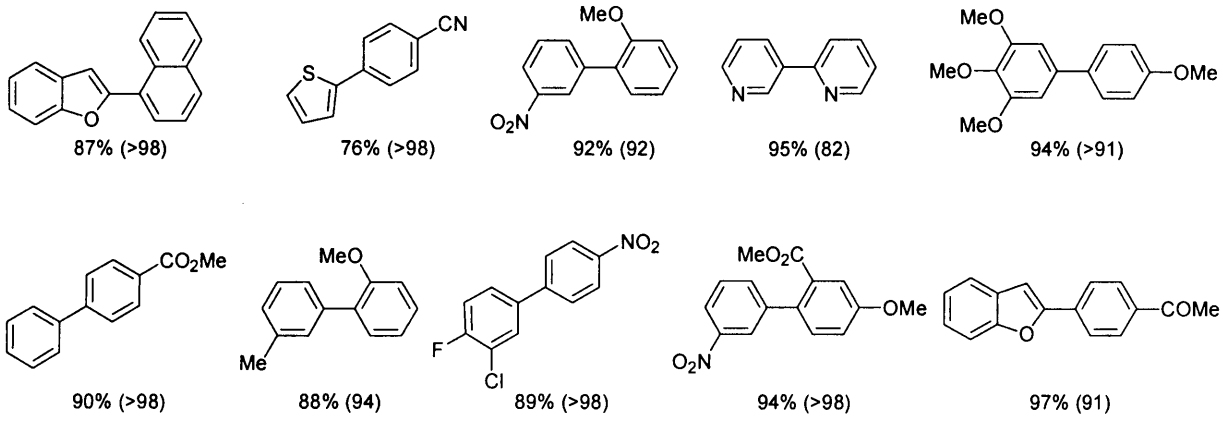
An example of a heterogeneous flow type process has been reported by Ley *at al.*[41] The Suzuki cross–coupling reaction, mediated by a palladium–encapsulated catalyst (EnCat®) was first investigated in batch mode and the optimized protocol was then transferred to continuous flow application. A commercially available U–tube flow cell packed with EnCat ® catalyst was placed in the microwave chamber of the Biotage Emrys Synthesizer (Figure 17).

A flow rate of 0.1 mL/min was employed corresponding to the residence time of 65 s and a back pressure regulator (40 psi) maintained a constant flow profile. As the reaction mixture left the microwave chamber, it passed through a column of Amberlyst 15 sulfonic acid resin to remove any residual base or boronic acid salts. Five different aryl bromides were successfully tested in a continuous flow process using a constant power of 50 W (Scheme 3).



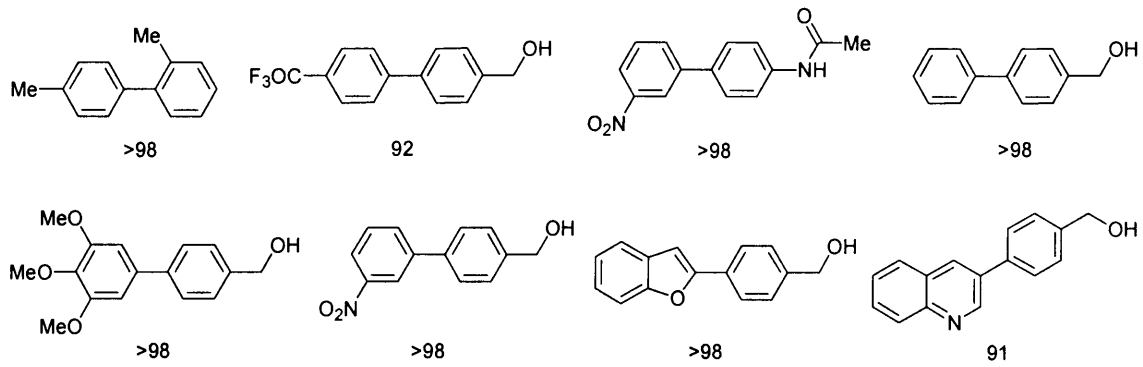
Scheme 3. Flow–based microwave Suzuki reaction performed at a constant power level of 50 W

However, it was noted that the palladium catalyst became exponentially hot under prolonged irradiation, causing the polymer to melt and block the tube. Therefore, a modified heating protocol was established in which the microwave irradiation was pulsed (50 W for 30 s followed by 18 s of cooling). Ten representative pairs of substrates were selected and reacted in a sequential fashion without having to regenerate or replace the catalyst (Scheme 4).



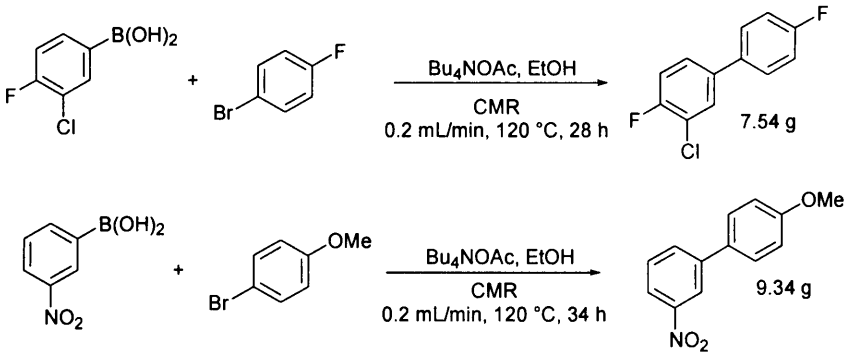
Scheme 4. Yields of microwave–assisted Suzuki reactions in flow performed in a pulsed irradiation regime (percentage purities given in parentheses)

In the attempt to further enhance the flow–mode reactions, the utilization of concurrent heating and cooling was investigated resulting in an enhanced level of functional selectivity and capability (Scheme 5).



Scheme 5. Percentage purities of biaryl compounds synthesised in flow processing. Reactions performed at 50 W using a power setting with simultaneous cooling

Finally two separate coupling reactions were undertaken on a larger scale (Scheme 6). The reactions progressed efficiently for many hours: the mass of product obtained in a single operation was an 80–fold increase on that produced in a single batch reaction.



Scheme 6. Large scale continuous production of biaryl compounds in a CMR at 50 W using a power setting with simultaneous cooling

The first dedicated large–scale multimode microwave device set up for continuous flow processing was developed by Strauss and co–workers in 1994.[42] A schematic diagram of this CMR is shown in Figure 18; a coil flow cell fabricated from a microwave transparent material was placed into the microwave chamber of a multimode microwave. The reaction mixture was rapidly cooled after it exited the microwave device and the temperature was monitored in different zones before and after the irradiation zone. Feedback microprocessor control was introduced, allowing the operator to preset temperature, flow rate and cooling of the reaction mixture. A number of safety parameters were incorporated into the reactor software allowing a maximum pressure of 1400 kPa and maximum temperature of 200 °C. The potential of this prototype was demonstrated in the successful completion of a wide range of chemical transformations including nucleophilic substitutions and additions, esterification, transesterification, acetalization, amidation, base– and acid–catalysed hydrolysis, isomerization, decarboxylation, elimination, Michael addition, Hofmann degradation, Williamson ether synthesis, Mannich, Finkelstein, Baylis–Hillman and Knoevenagel reactions.

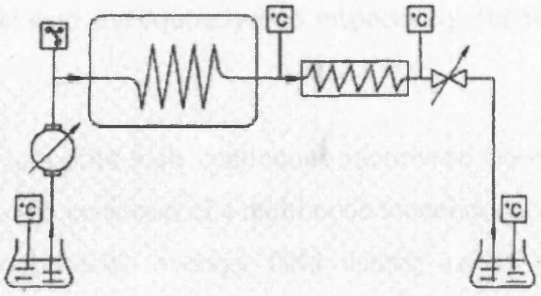


Figure 18. First dedicated continuous flow microwave reactor (from ref. 42)

Esterification of benzoic acid in a microwave tubular flow reactor was reported by Pipus and co–workers (Figure 19).[43]

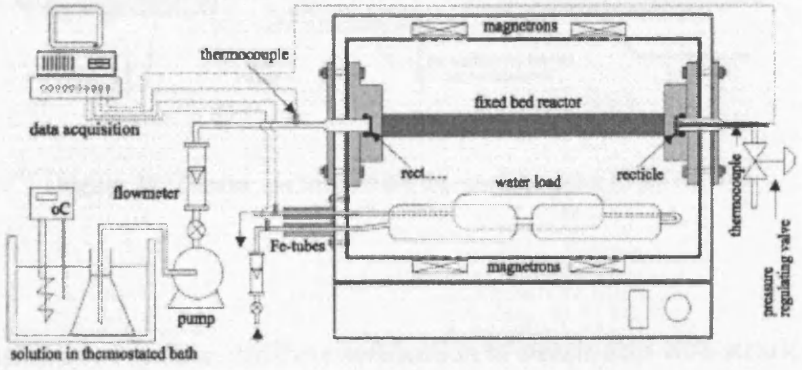


Figure 19. Microwave tubular flow reactor (from ref. 43)

The Pyrex glass tube used as a flow cell (inner diameter 1.07 cm, length 42 cm) was placed in a domestic microwave oven and a continuous water flow system was added to absorb the excess of radiation. The temperature of the inlet and outlet flow was measured with NiCr–Ni thermocouples and a back pressure regulator (100 psi) was placed at the outlet of the reactor. A mathematical model was proposed to describe temperature profiles and to predict the conversion of a reaction in a tubular flow reactor. The CMR was designed to verify the agreement between experimental and calculated data. Acid–catalysed esterification of benzoic acid with ethanol was chosen as a model reaction, and both homogeneous and heterogeneous processes were

investigated using sulphuric acid and Amberlyst 15 respectively, running reactions at 140 °C at a flow rate of 1 L/h.

The design and modelling of a pilot scale continuous microwave dry–media reactor was reported by Esveld *et al.*[44,45] This CMR consisted of a multimode tunnel microwave cavity (0.6 m^2) with a net microwave power of 4.4 kW (average field density of 15 kV/m) providing reaction temperatures up to 250 °C. The solid reaction mixture was transported to the oven in low open Pyrex supports closely packed on a Teflon–coated glass fibre web conveyor, moving at 17 cm/min (Figure 20).

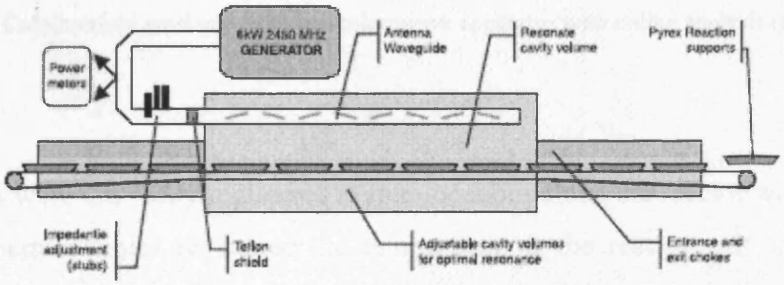


Figure 20. Continuous microwave dry–media reactor (from ref. 44)

To study the feasibility of scaling–up, the esterification of stearic acid with stearicyl alcohol under solvent free conditions catalysed by montmorillonite type KSF was chosen as a model reaction. A 95% yield of the ester product was obtained by irradiating the reaction mixture for 30 min at 170 °C which resulted in a production of about 100 kg per day.

Microwave apparatus at miniplant scale with online analysis was reported by Ondruschka *et al.*[46] The experimental set up is shown in Figure 21: a multimode microwave device (maximum power 2000 W) was equipped with a tubular reactor (0.88 L), the pumping rates amounted to 0.5–20 L/h and a filter system was used to prevent the capillary system from clogging.

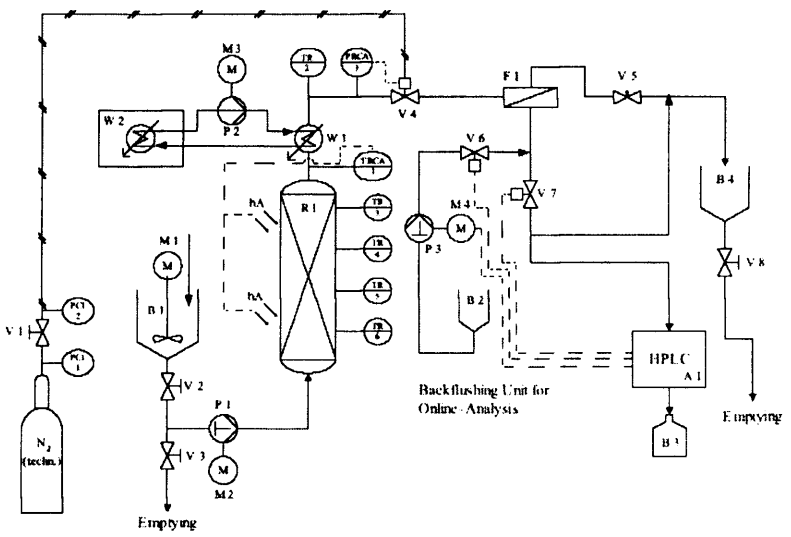


Figure 21. Continuously working miniplant microwave apparatus with online analysis (from ref. 46)

The temperatures were indirectly registered at four locations along the reactor with IR sensors and two Ni–Cr/Ni thermocouples registered the temperature at the reactor exit and after the heat exchanger. The hydrolysis of saccharose was investigated as a model reaction for the development of an online HPLC analysis method.

1.6.1.2 Commercially Available CMR

Two models of CMRs are on the market. CEM produces the Voyager CF®, based on the CEM Discover batch microwave unit equipped with two HPLC pumps, which allows laboratory scale production. A number of flow cells with different volumes and shapes are available: a Teflon and a glass coil flow cell (5 and 10 mL), a range of U–shaped flow cells (up to 30 mL) and tube flow cells (10 and 80 mL). Milestone offers a large scale reactor, the FlowSYNTH®, with a reactor volume of 200 mL and flow rate up to 130 mL/min, which thus has the potential of processing 8 L/h (Figure 22).

Figure 22. CEM Voyager CF® (left), Milestone FlowSYNTH® (centre) and ETHOS CFR® (right)

A Dimroth rearrangement was performed in the CEM Voyager CF®, as described by Kappe and Orru.[47] Figure 23 shows the commercially available flow cell that was used. It consisted of a 10 mL glass tube filled with 2 mm–sized glass beads. The reaction mixture was introduced into the flow cell at the bottom of the vial *via* a Teflon tube. A 17 bar back pressure regulator connected to the end of the outlet tubing ensured the system remained under pressure throughout the process and the built–in IR sensor allowed the temperature to be monitored at the bottom of the flow cell.

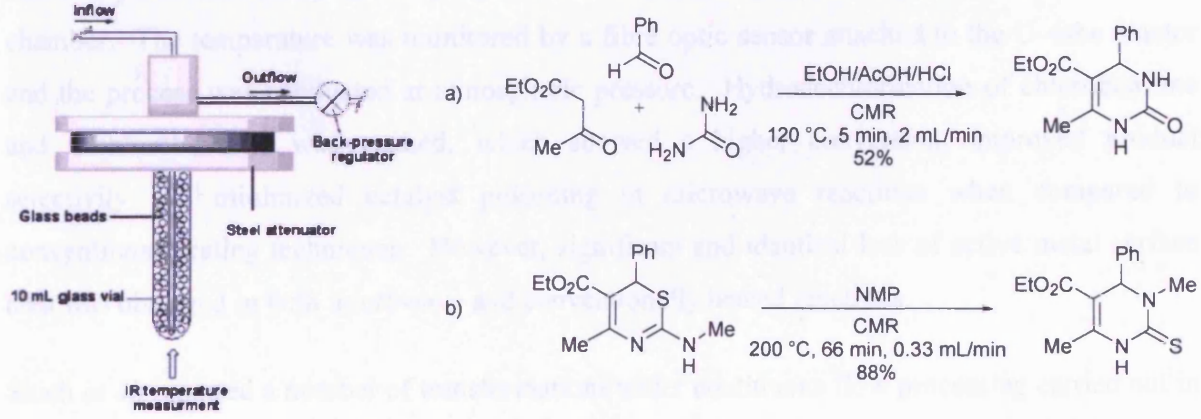


Figure 23. Tube flow cell (left–from ref. 47). Biginelli reaction (a) and Dimroth rearrangement (b) performed in a tube flow cell

The Biginelli reaction was chosen as a test reaction for the described set–up, and continuous flow processing showed comparable efficiency to the batch experiment, allowing the preparation of

product on a 25 g/h scale. To this end, the Dimroth rearrangement previously optimised batch wise was studied under continuous flow microwave conditions, allowing the isolation of product in 88% yield (compared to 93% in the batch process).

Sahle–Demessie and co–workers investigated the hydrodechlorination of chlorinated benzenes over Pd/Al_2O_3 catalyst in the CEM Voyager CF® (Figure 24).[48]

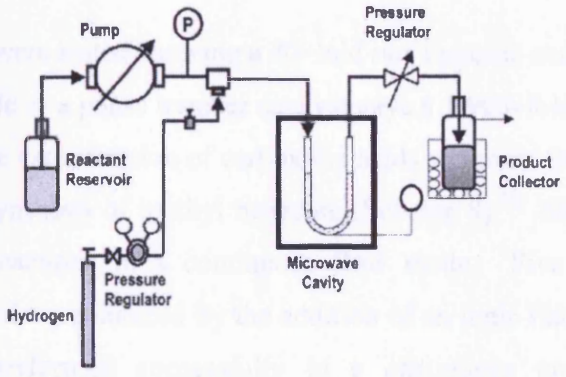
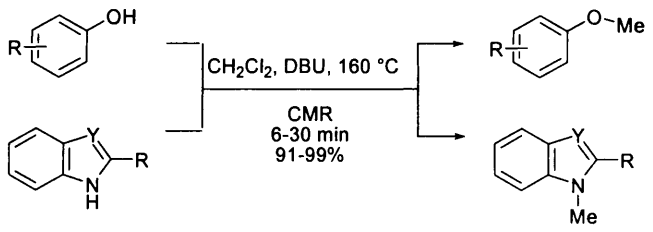


Figure 24. Continuous phase microwave reactor used for hydrodechlorination reaction (from ref. 48)

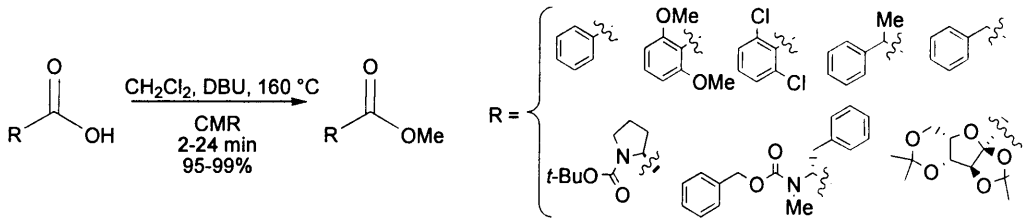
The catalyst (0.5% Pd/Al_2O_3) was packed in a 15 mL quartz U–tube and placed in the microwave chamber. The temperature was monitored by a fibre optic sensor attached to the U–tube reactor and the process was conducted at atmospheric pressure. Hydrodechlorination of chlorobenzene and trichlorobenzene was studied, which showed a higher conversion, improved product selectivity and minimized catalyst poisoning in microwave reactions when compared to conventional heating techniques. However, significant and identical loss of active metal surface area was observed in both microwave and conventionally heated reactions.

Shieh *at al.* reported a number of transformations under continuous flow processing carried out in the Milestone ETHOS–CFR®. An environmentally friendly protocol for methylation of phenols and *NH*–containing heteroaromatic compounds was provided using 1,8–diazobicyclo[5.4.0]undec–7–ene (DBU) as a nucleophilic catalyst, which was further enhanced by the use of microwave irradiation (Scheme 7).[49]



Scheme 7. Methylation of phenols and *NH*–containing heteroaromatic compounds in the Milestone ETHOS–CFR®

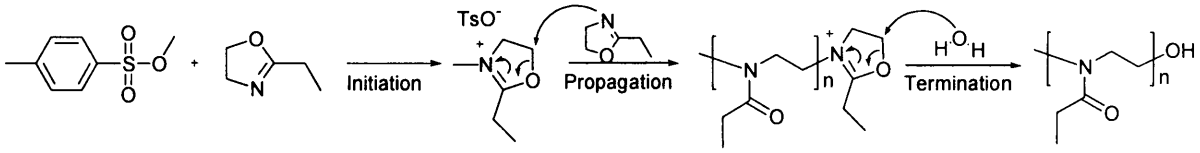
Eight different substrates were tested showing a 80–fold rate increase and, interestingly, the use of tetrabutylammonium iodide as a phase transfer catalyst gave a 1,900–fold rate increase. The same protocol was applied to the esterification of carboxylic acids where its feasibility for scale up was shown by a 100 g scale synthesis of methyl benzoate (Scheme 8).[50] Shieh and co–workers also reported *N*–benzylation reactions in a continuous flow mode. Five examples of DABCO–catalyzed benzylation reactions enhanced by the addition of an ionic liquid (tetrabutylammonium chloride TBAC) were performed successfully in a continuous process under microwave irradiation.[51]



Scheme 8. Esterification of carboxylic acids with DBU in the Milestone ETHOS–CFR®

Scale up of the microwave–assisted polymerization of 2–ethyl–2–oxazoline by cationic ring–opening in a continuous–flow reactor was reported by Schubert and co–workers (Scheme 9).[52] Polymerizations were performed in the CEM Voyager CF® monomode instrument using two different flow coils (CEM Teflon and glass coil) and in a small tube (10 mL), and in the Milestone FlowSYNTH® multimode instrument (200 mL). Monomer (at 4 M concentration) in acetonitrile at 140 °C and a monomer–to–initiator ratio of around 100 was irradiated for 1000 s in

four different CMRs and in a batch mode using the Biotage Emrys Liberator® monomode microwave synthesizer.



Scheme 9. Living cationic ring–opening polymerization of 2–ethyl–2–oxazoline with methyl tosylate as initiator

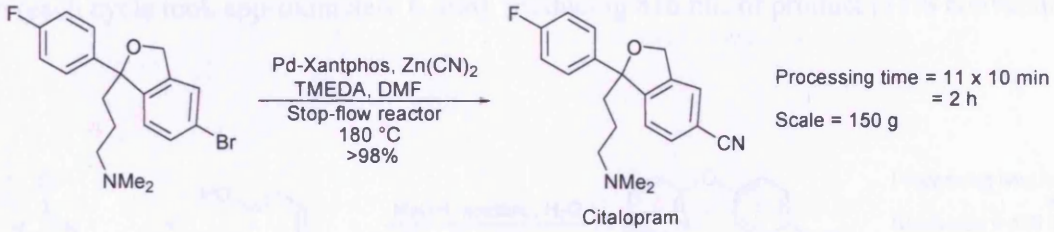
The polymerizations in the batch reactor and the two coil reactors reached close to full conversion, whereas the tube reactor reached 80% conversion and the Milestone reactor 60% conversion. Additionally it was found that all the continuous flow processes resulted in a broader molecular weight distribution compared to microwave polymerization in batch mode. It was proposed that this may be caused by the different flow profile in the different type of reactors, namely laminar in the flow coils and in the tube reactor and turbulent in the Milestone reactor. Investigation of the residence time distribution of the different reactors revealed a larger deviation of the data points from the sigmoidal fit for the tube reactor and the Milestone reactor, which might explain the broader molecular weight distribution observed.

1.6.2 Stop–Flow Microwave Reactors

Current research revealed that microwave assisted synthesis can be performed on a large scale by exploiting continuous flow techniques. However the practical difficulties of carrying out heterogeneous processes under continuous flow mode necessitates alternative solutions for this kind of transformation. CEM proposes a stop–flow reactor, also referred to as automatic continuous batch wise production, as the solution. This design automatically fills the 80 mL vessel with reagents, seals the vessel, performs a microwave experiment, releases the vessel, removes the reaction mixture and cleans it with solvents (Figure 25).

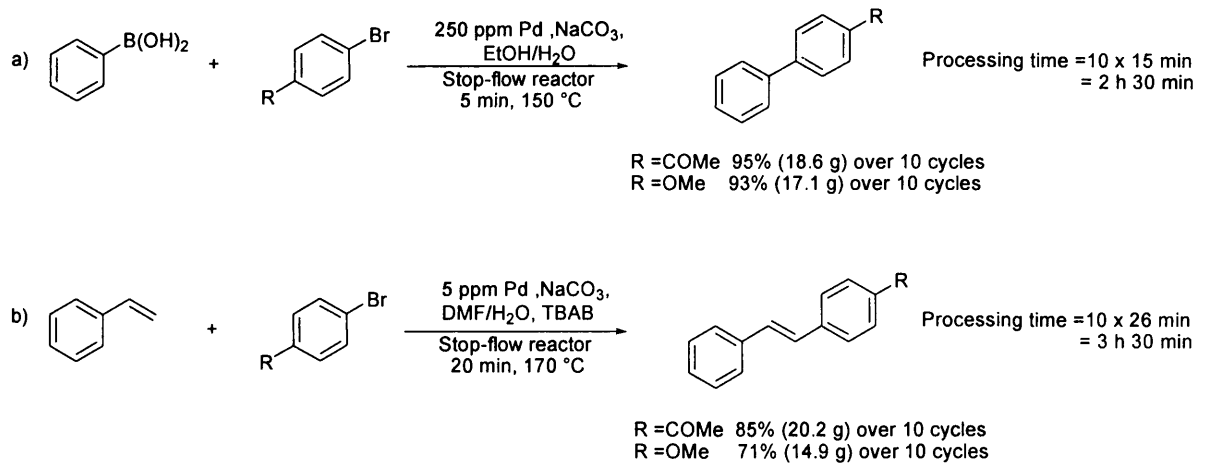
Figure 25. CEM Voyager SF® based on stop–flow technology

A large scale synthesis of citalopram by microwave enhanced palladium catalysed cyanation procedure in a stop–flow continuous process was reported by Pitts and co–workers.[53] The process was first optimized on small scale and then transferred to larger scale in a CEM Voyager SF®. A cycle time of 10 min produced 14 g of product, a longer run provided 150 g in 11 cycles (2 h) (Scheme 10).



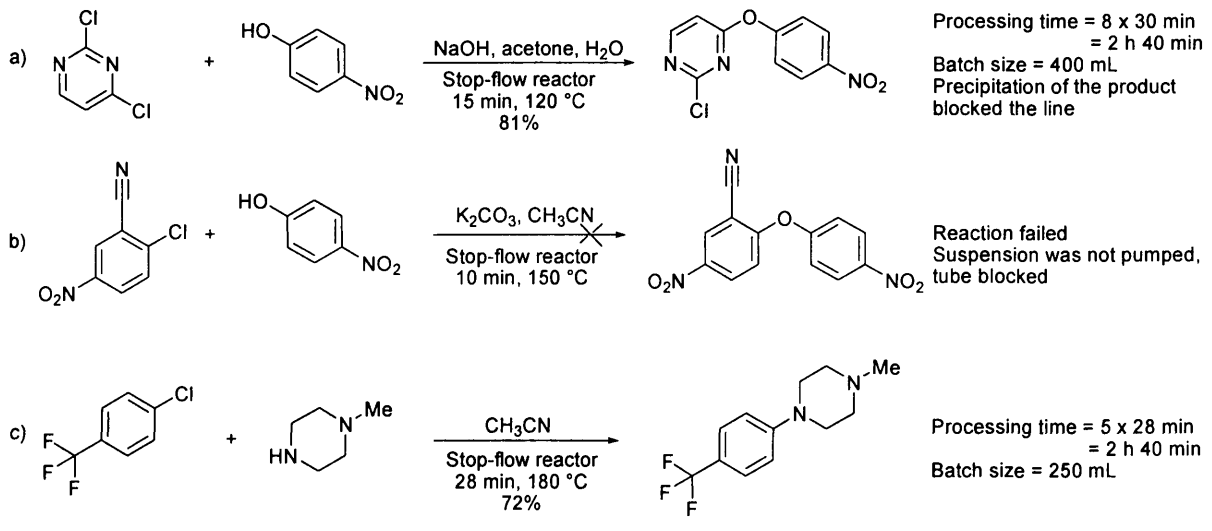
Scheme 10. Large scale synthesis of citalopram by palladium catalysed cyanation in a stop flow microwave reactor

Scale–up of microwave promoted Suzuki and Heck reactions in the CEM stop–flow apparatus was reported by Leadbeater and co–workers.[54] The reactions previously optimized in small scale were easily scaled up from 1 to 10 mmol, then adapted to the automated stop–flow Voyager apparatus with few, if any, modifications (Scheme 11).



Scheme 11. Scale–up of microwave promoted Suzuki and Heck reactions in the CEM stop–flow apparatus

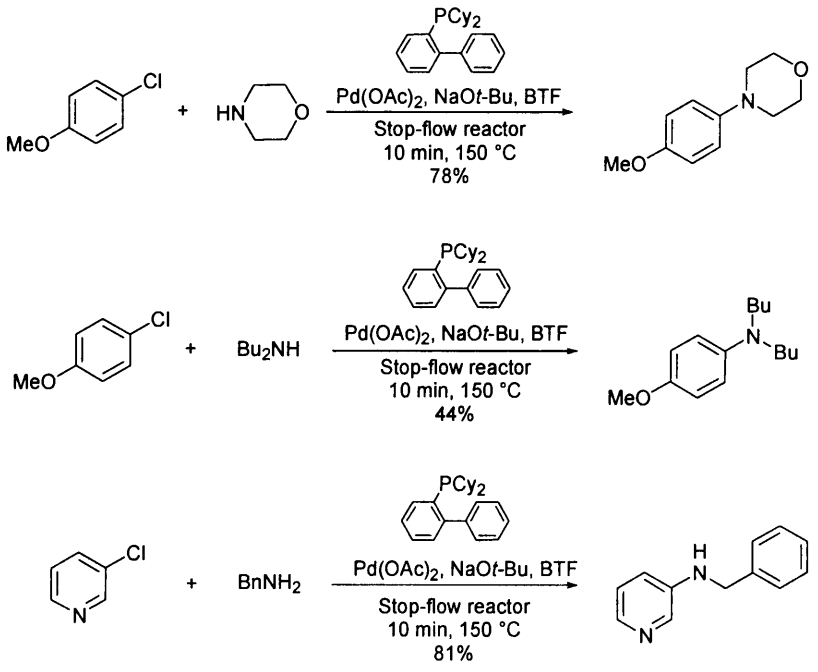
Combination of automated stop–flow apparatus and *in situ* Raman monitoring was reported by the same research group.[55] Esterication of acetic acid with butanol using sulphuric acid as the catalyst was chosen as a model reaction. Raman spectra were recorded approximately every 6 s during the reaction, permitting the conversion of starting material to product to be monitored, showing that the reaction went to completion in just 74 s when irradiated at 150 °C (300 W). To scale up the reaction the apparatus was set to run 22 cycles for a total processing time of 2 h 12 min (each cycle took approximately 6 min), producing 816 mL of product (71% conversion).



Scheme 12. Large scale microwave–assisted transformations in a stop–flow reactor

Lehmann and co–workers reported their evaluation of microwave reactors for large scale synthesis.[56] The efficiency of the CEM Voyager SF was tested for three different reactions, two homogeneous and one heterogeneous processes (Scheme 12). This stop–flow system offered the advantage of automation and a low–safety risk related to the small reaction volume (50 mL). On the other hand relatively long processing times and critical issues related to the handling of suspensions and precipitated product represented a limitation of this stop–flow technique.

A similar evaluation of large scale microwave reactors was reported by Loones and co–workers.[57] Scale–up of Buchwald–Hartwig aminations under microwave irradiation was investigated using commercially available batch reactors and the CEM stop–flow reactor. The reactions showed in Scheme 13 were successfully transferred to large scale (60 mmol) in a stop–flow mode without yield decrease; even the heterogeneous mixture (NaO*t*–Bu in BTF) was pumped by the Voyager without any clogging. The authors outlined the different heating efficiency of the device they used and the importance of the choice of the solvent in a large scale microwave process. Toluene used in the small scale reactions had to be replaced with Benzotrifluoride (BTF), a higher absorber solvent which permitted the desired temperature to be reached.



Scheme 13. Large scale microwave–assisted Buchwald–Hartwig aminations in a stop–flow reactor

1.7 New Perspectives: Microwave–Mediated Microfluidic Technology

While microwave technology is moving towards large scale synthesis, new devices have been tested for microscale production. Microreactors have shown enhanced performance compared to traditional reactors and they have the advantage of minimal waste production. Microwave irradiation can be successfully combined with microfluidic technology.[58] An increasing number of papers on this field open new perspectives for an efficient microscale production appropriate for biological screening.

Haswell *et al.* illustrated the study of microwave heating of heterogeneously catalysed Suzuki reactions in a microreactor.[59] The reactions were conducted in a glass microreactor (Figure 26), with inlet and outlet reservoirs located in the top plate, and a central port was designed to introduce the catalyst in the microreactor channel. In design A (left), a monolayer of catalyst particles was deposited over the entire catalyst channel area, whilst in design B (right) the catalyst was located in the form of a plug. The limited absorption of microwave energy directly by the channel contents was overcome by coating the outside of the bottom plate corresponding to the region of catalyst packing with a thin gold film.

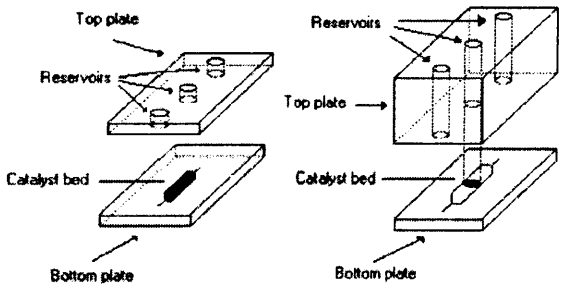
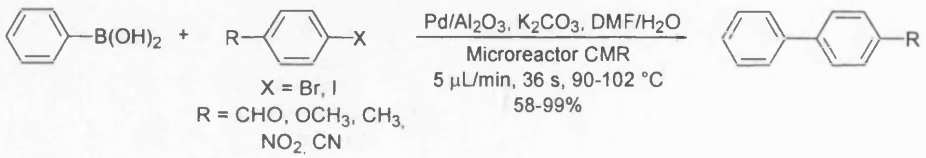


Figure 26. Linear channel microreactor and catalyst packing strategies (from ref. 59)

The microreactor was heated in the cavity of a CEM Discover®. The first set of experiments was carried out in microreactor design B and conversion for a range of aryl halides is shown in Scheme 14. It was observed that the gold film appeared to evaporate during the MW exposure, becoming less efficient at absorbing microwaves. A comparison between the two catalyst packing modes showed that more efficient heating was achieved using design A.



Scheme 14. Microwave–assisted heterogeneous Suzuki coupling reaction in a linear microreactor

Microwave–assisted Suzuki reaction in a continuous flow capillary reactor was reported by the same group.[60] The flow reactor consisted of a U–shaped glass capillary mounted within the cavity of a CEM Discover® microwave synthesizer. The catalyst particles were loaded along the tube by insertion of a glass rod at the end of the catalyst bed as shown in Figure 27. In order to prevent the low absorption of microwaves that will occur due to the small volumes of material present, the bottom section of the U–tube was sputter–coated with gold.

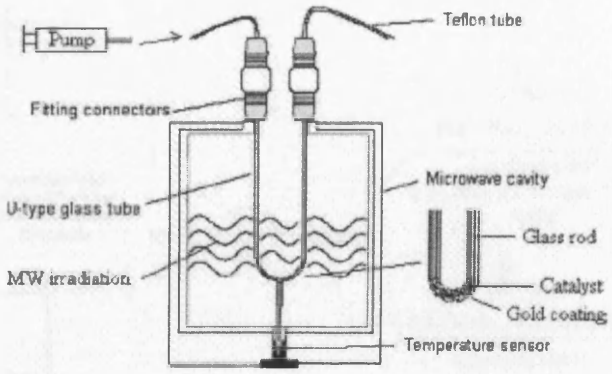
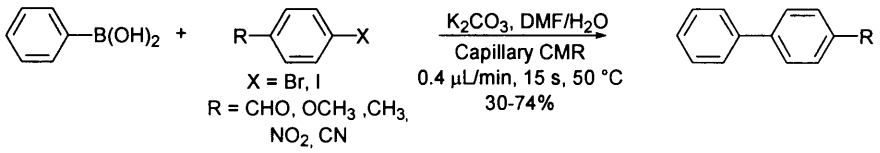


Figure 27. Continuous flow microwave capillary reactor (from ref. 60)

Two supported Pd catalysts were tested, Pd/SiO_2 and Pd/Al_2O_3. The former showed aggregation of the catalyst particles at around 80 °C which in turn deactivated the catalyst. The latter was successfully used: neither condensation between alumina particles nor deactivation of the catalyst over a short number of runs was observed. A range of different aryl halides were evaluated, Scheme15 shows that good conversions were achieved in just 15 s.



Scheme 15. Microwave–assisted heterogeneous Suzuki coupling reaction in a continuous flow capillary reactor

Another prototype of a microreactor for microwave–assisted capillary continuous flow synthesis was developed by Organ *et al.*[61] The flow reactor design consisted of a stainless steel holding/mixing chamber with three inlet ports that merge into one outlet (Figure 28) placed into the microwave cavity of the Biotage Smith Creator Synthesizer. The Suzuki coupling was chosen as the reaction of study. Six examples of diaryl compounds were synthesised using $Pd(OAc)_2$ or $Pd(Ph_3P)_4$ as catalyst, and a range of different solvents and bases were tested.

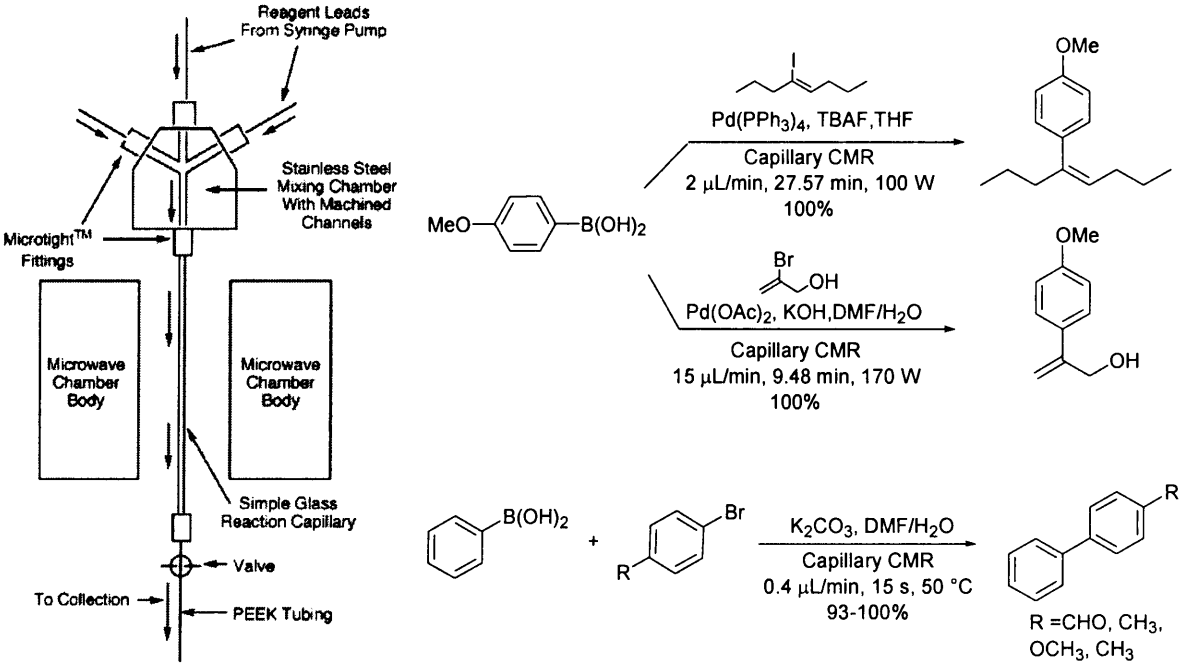
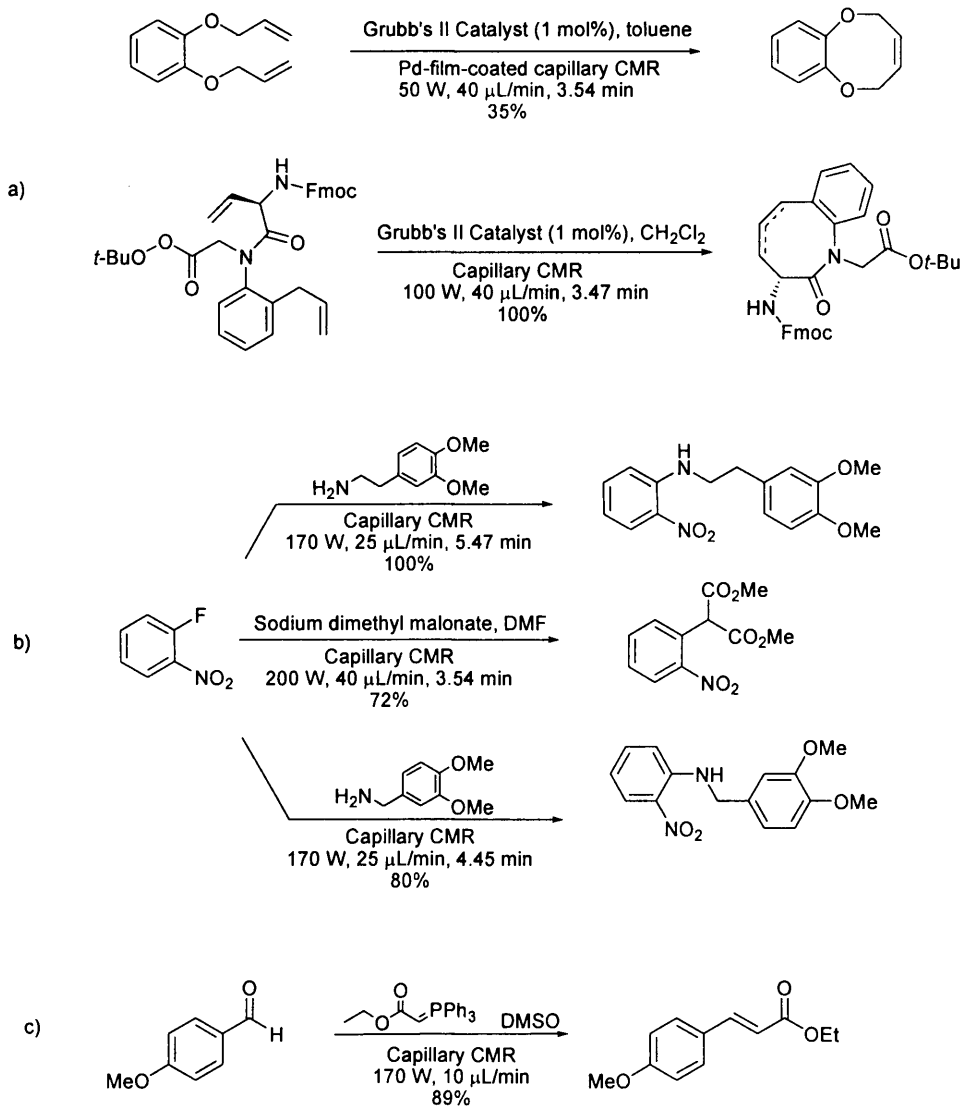


Figure 28. Continuous flow microwave microreactor (from ref. 61) on the left. Microwave–assisted Suzuki coupling in a continuous flow microreactor

In accordance with Haswell's observations, it was noted that the use of a Pd film deposited inside the capillary resulted in an improved heating phenomenon. In addition, it was demonstrated that the deposited metal itself was capable of catalyzing the Suzuki coupling without any additional catalyst. Excellent conversions were also observed in ring closing metathesis, another metal–catalysed process, and in nucleophilic aromatic substitutions and Wittig reactions, two examples of non–organometallic–mediated transformations (Scheme 16).



Scheme 16. Microwave–assisted transformations in a continuous flow capillary reactor a) ring closing metathesis; b) nucleophilic aromatic substitution; c) Witting reaction

No sign of poor kinetics due to laminar flow was observed and in 37 min 20 mg of product was obtained, illustrating that this method provided useful quantities of product to conduct further

studies upon, such as biological screening. A parallel capillary reactor system, based on the capillary microreactor described previously, was reported by the same group.[62,63] In this improved design four pairs of two inlet ports afforded four outlet ports allowing the parallel synthesis of four different substrates simultaneously (Figure 29).

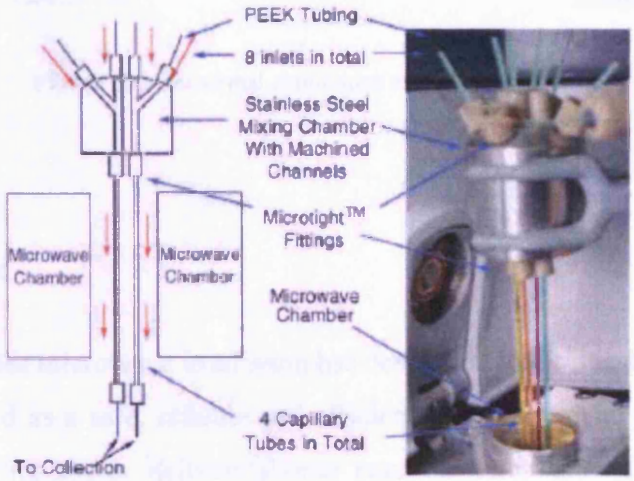


Figure 29. Parallel capillary multireactor system (from ref. 62)

The performance of a microreactor capable of operating isothermally in a microwave field was reported by Jachuck and co–workers.[64] The microreactor consisted of an aluminium section and a polytetrafluoroethylene (PTFE) section, used for the heat transfer side and the reaction side respectively (Figure 30). The heat generated on the reaction side was rapidly absorbed by the heat transfer fluid (H_2O) on the heat transfer side. Experiments were carried out in a domestic microwave oven. Oxidation of benzyl alcohol to benzaldehyde catalysed by $Fe(NO_3)_3 \cdot 9H_2O$ was performed using the continuous isothermal reactor over a range of residence times (3–17 s) corresponding to different flow rates (1–5 mL/min) and different microwave intensities (0–39 W), and the heat transfer fluid was circulated at 120 mL/min.

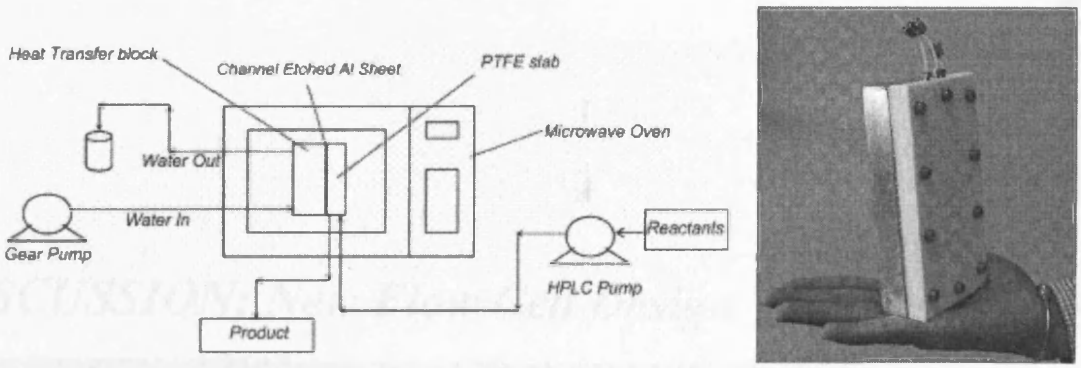


Figure 30. Isothermal continuous micro reactor (from ref. 64)

1.8 Conclusion

In the last two decades microwave irradiation has developed into a steady heating method and it is nowadays considered as a safe, reliable and efficient technique. The peculiar characteristics of this alternative heating source delivers shorter reaction times and enhanced yields and allows reactions to be carried out under conditions not achievable by conventional techniques opening up new perspectives. Safety issues, which were the main problem encountered in early experiments, have essentially been completely overcome with the advent of dedicated instruments. These reactors enable either small or large laboratory scale reactions, some of them offering sequential whereas others parallel synthesis, and it possible to choose between batch and continuous flow devices. However, the challenge of carrying out reaction on large scale appropriate for the chemical industry represents a great limitation of this technique.

DISCUSSION: New Flow Cell Design

2

2.1 Introduction

Microwave–assisted organic synthesis (MAOS) has received increasing attention in recent years as a valuable alternative to the use of conductive heating for accelerating chemical reactions. With no direct contact between the chemical reactants and the energy source, microwave–assisted chemistry is energy efficient, provides fast heating rates and enables rapid optimization of procedures. From the early experiments in domestic ovens to the use of multimodal or monomodal instruments designed for organic synthesis, this technology has been implemented worldwide and continues to be developed. However, although modern monomodal instruments dedicated for MAOS are very successful in small scale operations, efforts to process this technology on large scale are frustrated by the physical limitations of microwave heating, with a penetration depth of only a few centimeters and the limited dimensions of the standing wave cavity. Current technology has attempted to overcome these obstacles with conventional instruments by the use of continuous flow (CF) reactors that pump the reagents through a flow cell in and out of the cavity. We set out to address this challenge and establish a new method for carrying out MAOS under CF processing using a commercially available monomodal microwave synthesizer.

2.2 A Simple Continuous Flow Microwave Reactor

2.2.1 Flow Cell Design

A new simple continuous microwave reactor has been developed for use in a monomodal microwave synthesizer with direct but non intrusive temperature control using an IR sensor. This makes optimum use of the standing wave cavity, in order to improve the energy efficiency of microwave–assisted flow reactions. The principal design of our flow cell featured the need to make optimum use of the cavity and to be able to monitor the temperature of reaction directly using the instrument's in–built IR sensor. Figure 31 shows in detail the tube flow cell set up. A standard 10 mL Pyrex tube was fitted with a custom built steel head, filled with sand (~12 g) held between two drilled frits and sealed using PTFE washers.

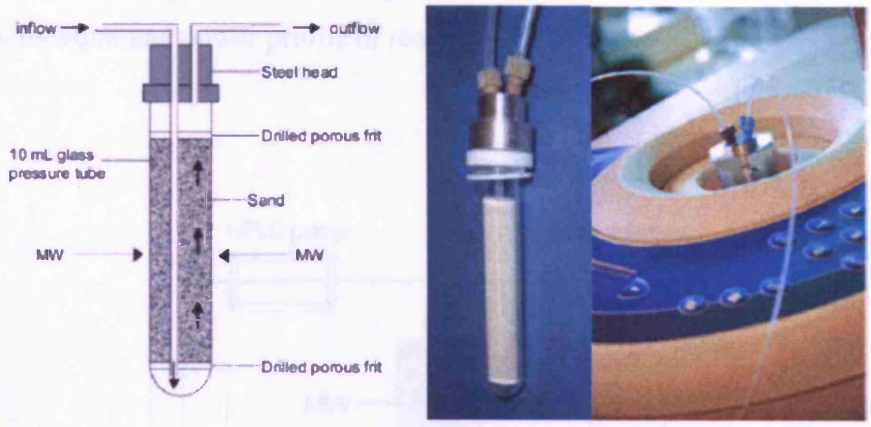


Figure 31. New tube flow cell set up

It was anticipated that the use of a packing agent would minimize dispersion and effectively create a lattice of microchannels for efficient energy transfer. The reaction mixture was pumped from the bottom of the flow cell and forced to move upwards through the sand layer, ensuring a reliable residence time of the reaction mixture into the microwave chamber. Figure 32 shows how a compound passes through the flow cell, reaching the top of the tube. It was demonstrated that the same behaviour was maintained during irradiation; in fact interruption of a microwave experiment showed the reaction mixture progressed through the tube flow cell in the form of a compact band.

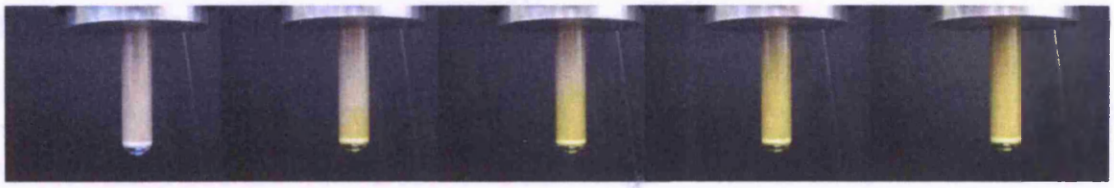


Figure 32. Effect of sand as a packing agent on the residence time of reactants into the microwave chamber

A diagram of the continuous microwave reactor (CMR) set up is shown in Figure 33. The inlet tube of the flow cell is connected to a HPLC pump and a back pressure regulator (100 psi) is connected to the outlet tube, allowing experiments to be run under pressure. The flow cell was inserted into the cavity of the CEM Discover® microwave synthesizer and the temperature monitored using the instrument's in–built IR sensor, situated at the bottom of the microwave chamber. Feedback microprocessor control was connected to the CEM Discover® microwave synthesizer, thereby allowing the operator to preset temperature, power, cooling and to monitor the temperature–pressure and power profile of reactions.

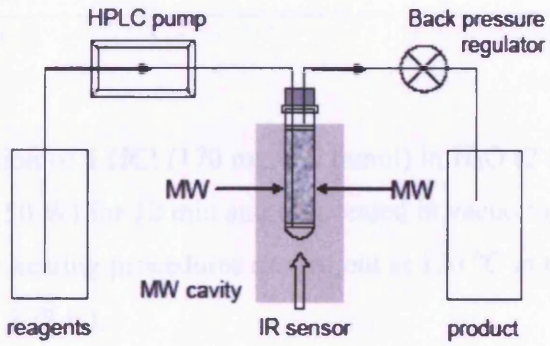


Figure 33. Diagram of flow cell apparatus

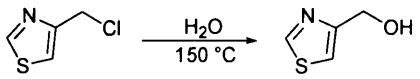
Experiments were performed by priming the reactor with the solvent system, which was then irradiated and stabilized at the required reaction temperature through moderation of microwave power before the introduction of reagents into the reactor.

2.2.2 Test Reactions

Our tube flow cell was first tested using two well–known microwave–assisted reactions operating under continuous flow (CF) conditions: the hydrolysis of (chloromethyl)thiazole **1** to give hydrochloride **2**[65] (Table 2) and the Fischer indole synthesis[66] of **5** (Table 3).

Table 2 shows the results obtained for the hydrolysis of (chloromethyl)thiazole **1.** The reaction was performed under continuous flow mode (entry 1) in the CMR prototype and gave the product **2**.HCl in 85% yield after 3 min of irradiation at 150 °C, processing 1 g in 15 min.

Table 2. Hydrolysis of (chloromethyl)thiazole performed in the CMR*



1.HCl **2**.HCl

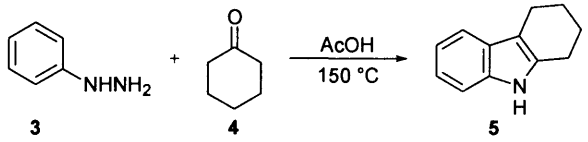
Entry	Heating Method	Mode	Conditions	Yield%
1	MW	CMR	1mL/min	85
2	MW	Sealed tube	10 min	>98
3	Conductive	Sealed tube	12 min	90

For comparison, a solution of **1**.HCl (170 mg, 1.0 mmol) in H_2O (2 mL) was irradiated at 150 °C in a sealed glass tube (150 W) for 10 min and evaporated in vacuo to give **2**.HCl (151 mg, >98%). Comparable conductive heating procedures carried out at 150 °C in a sealed tube for 12 min gave thiazole **2**.HCl (90% by HPLC).

The results obtained for the Fischer indole synthesis of **5** from phenyl hydrazine **3** and cyclohexanone **4** in acetic acid at 150 °C are shown in Table 3. A flow rate of 0.5 mL/min corresponding to a residence time of 6 min in the microwave chamber was used in the continuous flow process. A total processing time of 30 min gave the target molecule **5** in 91% yield (entry 1).

Table 3. Hydrolysis and Fischer indole synthesis performed in the CMR†

* Experiments were carried out by Robin Wood



3 4 5

Entry	Heating Method	Mode	Conditions	Yield%
1	MW	CMR	0.5 mL/min	91
2	MW	Sealed tube	10 min	62
3	Conductive	Sealed tube	10 min	94

For comparison, a solution of **3** (220 mg, 2.2 mmol) and cyclohexanone **4** (196 mg, 2 mmol) in AcOH (4 mL) was irradiated at 150 °C in a sealed glass tube (150 W) for 10 min giving **5** in 62% yield (entry 2). Entry 3 shows the comparable conductive heating procedure, carried out at 150 °C in a sealed tube for 10 min, which gave compound **5** in 94% yield.

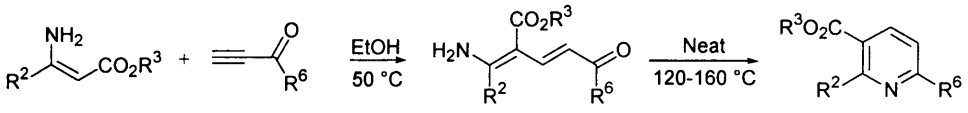
Both test reactions were easily transferred to CF process without the need of further modification showing comparable results in batch and CF mode.

2.3 Flow Cell Efficiency

2.3.1 Bohlmann–Rahtz Pyridine Synthesis

Following the success of the test flow reactions, efforts were made to develop a new microwave–assisted process for the synthesis of pyridines based upon the Bohlmann–Rahtz (B–R)[67] reaction. This regioselective synthesis of trisubstituted pyridines by the reaction of enamines and alkynyl ketones or aldehydes, was first reported in 1957 (Scheme 17). This two–step process proceeds by Michael addition to give an aminodienone intermediate which can be isolated in high yield. In a subsequent procedure, the aminodienone intermediate undergoes cyclodehydration at a temperature of 120–160 °C, to give 2,3,6–trisubstituted pyridines in excellent overall yield and with total regiocontrol.

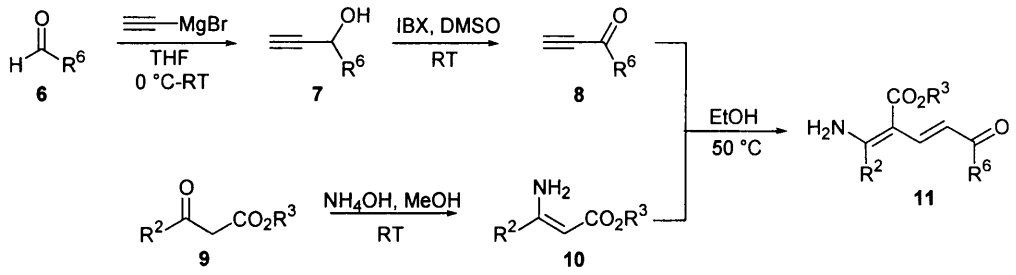
† Experiments were carried out by Robin Wood



Scheme 17. Traditional Bohlmann–Rahtz pyridine synthesis

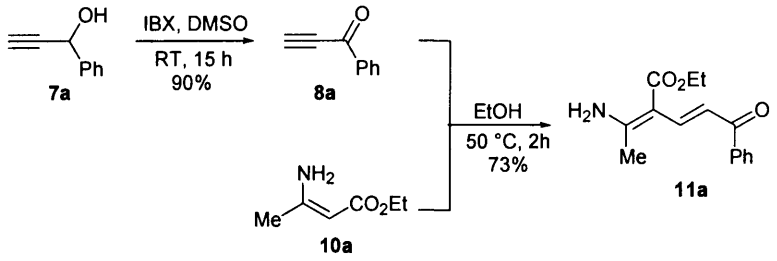
Previous work within the Bagley group has shown that the cyclodehydration of aminodienones can be effected using conductive heating,[68] and with a Lewis[69] or Brønsted[70] acid catalyst, to give 2,3,6–trisubstituted pyridines directly and with total regiocontrol. This transformation has been applied in the synthesis of pyridine–containing thiopeptide antibiotics[71] and their derivatives,[72] as well as pyrido[2,3–*d*]pyrimidines,[73] heterocyclic amino acids,[74] nonsteroidal anti–inflammatory agents,[75] and combinatorial pyridine libraries.[76] Cyclodehydration of aminodienones to access the target pyridine (Scheme 17) represents a relatively simple transformation and as such should be ideal to investigate the effect of a scale up system on the course of an heteroannulation reaction.

Aminodienones were synthesized by condensation of the alkynone **8** and enamine **10** in ethanol under conductive heating following the general strategy shown in Scheme 18. Non commercially available alkynones **8** were obtained in two steps: aldehyde **6** was reacted with ethynyl magnesium bromide affording the propargylic alcohol **7** which was then oxidized to the corresponding ketone **8**. Non commercially available enamine **10** was synthesised from the corresponding β–ketoester **9**.



Scheme 18. General synthetic approach used for the synthesis of aminodienones **11**

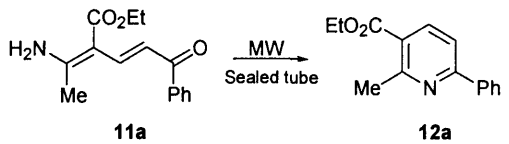
The synthesis of 2–methyl–6–phenylpyridine–3–carboxylate **12a** by cyclodehydration of 2–amino–3–ethoxycarbonyl–6–phenylhexa–2,4–dien–6–one **11a** was chosen as a model reaction to verify the efficiency of our new tube flow cell.



Scheme 19. Synthesis of 2–amino–3–ethoxycarbonyl–6–phenylhexa–2,4–dien–6–one **11a**

To this end 2–amino–3–ethoxycarbonyl–6–phenylhexa–2,4–dien–6–one **11a** was prepared, by condensation of 1–phenyl–2–propyn–1–one **8a** and ethyl aminocrotonate **10a** in ethanol, in 73% yield after purification by column chromatography on silica (Scheme 19).

Table 4. Microwave–assisted cyclodehydration of 2–amino–3–ethoxycarbonyl–6–phenylhexa–2,4–dien–6–one **11a** in a sealed tube



Entry	Solvents	Conditions [a]	Results
1	DMSO	20 min, 170 °C	98%
2	EtOH	40 min, 130 °C	**12a** and starting material
3	Toluene–AcOH	20 min, 50 °C	>98%
4	Toluene–AcOH	10 min, 70 °C	>98%
5	Toluene–AcOH	2 min, 100 °C	>98%

[a] Reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 150 W)

Propargylic ketone **8a** was synthesised by oxidation of the commercially available 1–phenyl–2–propyn–1–ol **7a** using *o*–iodoxybenzoic acid (IBX) as the oxidizing agent.

The microwave–mediated B–R synthesis of pyridine **12a** was first investigated in batch mode in order to find the optimum conditions for transfer to flow–through processing (Table 4). Particular attention was given to the solvent choice as homogeneous conditions are an essential requirement for many CF processes to avoid a number of technical difficulties. Table 4 shows that the use of an acid catalyst accelerates the process, achieving quantitative conversion under mild conditions. The optimum conditions for this heteroannulation reaction were found to be in toluene, catalyzed by acetic acid, at 100 ° C for just 2 minutes (entry 5).

2.3.2 Effect of a CF System on Cyclodehydration of Aminodienones

2.3.2.1 Coil Flow Cell

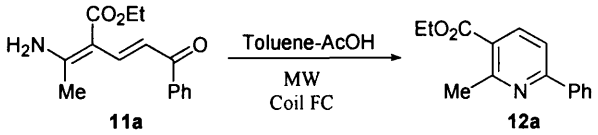
The cyclodehydration of aminodienone **11a** was transferred to the CMR in order to investigate the effect of scale up and continuous processing on the course of this transformation. The reaction was first tested in a CMR using a commercially available flow cell, the CEM Teflon coil flow cell (3 mL) shown in Figure 34. All the experiments were carried out under atmospheric pressure with external temperature monitoring using a fibre optic sensor. The residence time of the reaction mixture in the microwave irradiation zone was taken as the reaction time.

Figure 34. Commercially available coil flow cell

The CMR operated by passing the reaction mixture through the microwave cavity. First of all the CMR was primed with solvent (toluene–acetic acid (5:1)) and irradiated at the initial power of 300 W until stable conditions were reached, then a solution of aminodienone **11a** in toluene–acetic acid was passed through the continuous flow system and washed with further batches of solvent. The reaction mixture was quenched in a solution of saturated aqueous $NaHCO_3$.

Table 5 outlines the different conditions investigated. The reaction was first investigated at 50 °C for comparison with experiments carried out batch wise. Effect of concentration and irradiation time was studied in order to verify if the flow process was more efficient compared to the corresponding batch reaction.

Table 5. Continuous flow cyclodehydration of aminodienone **11a** in the coil flow cell



Entry	Molarity	Flow rate (mL/min)	Conditions [a]	Ratio of **11**:**12** [b]
1	0.1028	1	3 min, 50 °C, cooling	1:1
2	0.0617	1	3 min, 50 °C, cooling	1.2:1
3	0.1028	0.5	6 min, 50 °C, cooling	3:1
4	0.1028	0.25	12 min, 50 °C, cooling	18:1
5	0.0617	1.53	2 min, 90 °C	14:1
6	0.1028	1.14	2.5 min, 90 °C	17:1
7	0.1028	1.53	3 min, 90 °C	20:1
8	0.1028	1.53	2 min, 100 °C	1:11
9	0.1028	1	3 min, 100 °C	>98% [c]
10	0.1028	1	RT	1:2

[a] Reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 150 W).
[b] Ratio determined by ^1H NMR analysis of crude reaction mixture.
[c] Yield of pure isolated product

The results obtained suggest the two processes have comparable efficiency (entries 1–4). To this end, the transfer of the optimized cyclodehydration of aminodienone **11a** (entry 5, Table 4) to CF mode was examined. Disappointingly, the transformation did not go to completion under CF mode, and the yield based upon ^{1}H NMR analysis of crude reaction mixture was 85% (entry 8). In addition, reaching the desired temperature of 100 °C using a flow rate of 1.5 mL/min (corresponding to a residence time of 2 min) required, when possible, incredibly long irradiation time in order for the system to reach equilibrium. Quantitative conversion of aminodienone **11a** to the target pyridine **12a** was achieved by decreasing the flow rate to 1 mL/min, corresponding to a reaction time of 3 min (entry 9). Finally, a blank experiment was conducted, showing the continuous flow process itself gives a modest contribution to the cyclodehydration (entry 10).

Flow–based Bohlmann–Rahtz synthesis of pyridine **12a** using a coil flow cell proved to be less efficient in terms of time–consumption compared to the batch–wise experiment. The problems encountered in reaching the required temperature represents a great limitation of this system.

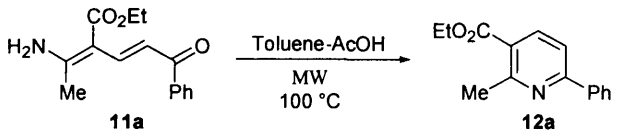
2.3.2.2 Tube Flow Cell

2.3.2.2.1 Homogeneous Cyclodehydration of Aminodienones

In order to verify if the results obtained were due to the CF process itself or to the flow cell used, the same transformation was studied using the tube flow cell we developed. Aminodienone **11a** was cyclodehydrated with CF processing under homogeneous conditions in toluene–acetic acid (5:1) over sand, comparing the results to batch experiments carried out in a sealed tube and to the corresponding homogeneous CF process with a Teflon heating coil (Table 6). The process was successfully transferred to continuous flow process using our tube flow cell without the need for further modifications. Reaction temperature was reached within a few minutes even with simultaneous cooling (Appendix A).

Our tube flow cell proved to be more efficient compared to the coil flow cell. To this end, further investigations were conducted on the tube flow cell, in particular different packing agents were tested in the glass tube reactor in order to verify their effect on a continuous flow process. The optimized B–R pyridine synthesis of **12a** (entry 3, Table 6) was performed in the tube flow cell using sand (with and without concurrent heating and cooling), glass beads and without any packing agent (Table 7).

Table 6. Cyclodehydration of aminodienone **11a**



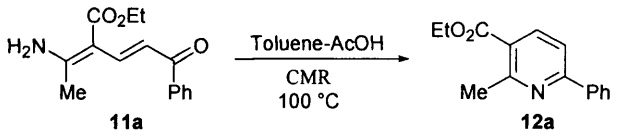
11a **12a**

Entry	Mode	Conditions[a]	Flow rate (mL/min)	Yield%
1	Sealed tube	2 min[b]	–	>98
2	Coil flow cell	3 min, cooling	1	>98
3	Tube flow cell	2 min, cooling	1.5	>98

[a] Reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 300 W). [b] Initial power = 150 W

For comparison the two experiments carried out in the coil flow cell have been also included in the table. The total energy reported in Table 7 represents the energy delivered by the magnetron in each experiment, obtained by integrating the power versus time profile. The first four entries show experiments carried out in the tube flow cell. The experiment performed using sand as the packing agent without the use of simultaneous cooling was found to be more efficient in terms of energy used. Initial power of 200 W was sufficient to reach the reaction temperature and this resulted in more than 500 kJ saved (Entries 1 and 2). The flow cell packed with glass beads has a 4 mL volume, and hence a 2 mL flow rate was required to guarantee a residence time of 2 min in the microwave chamber (entry 3); in the absence of packing agents a flow rate of 3.5 mL was applied (entry 4). The tube flow cell filled with sand was found to be more energy efficient using less magnetron energy. In contrast, flow reactions performed in the coil flow cell were problematic. Entry 5 shows one attempt to transfer the optimized conditions (2 min, 100 °C) to the coil flow cell reactor. With the required 1.5 ml/min flow rate the maximum temperature reached was 90 °C and the conversion under those conditions was 85%. Decreasing the flow rate to 1 ml/min (corresponding to 3 min residence time), it was possible to achieve the desired temperature and quantitative conversion but with a much longer processing time.

Table 7. Effect of different packing agents on cyclodehydration of aminodienone **11a**



Entry	Volume (mL)	Flow rate (mL/min)	Flow cell	Packing agent	Initial Power (W)[a]	Total energy (kJ)[b]	Yield%
1	3	1.5	Tube	Sand	300[c]	735	>98
2[f]	3	1.5	Tube	Sand	200	204	>98
3	4	2.0	Tube	Glass beads	200	245	>98
4	7	3.5	Tube	–	300	352	>98
5	3	1.5	Coil	–	300[d]	762	85
6[g]	3	1.0	Coil	–	300[e]	1411	>98

[a] Reaction conditions: toluene– acetic acid (5:1), 2 min, 100 °C. [b] Energy delivered by the magnetron in a flow reactor, obtained by integrating the power versus time profile. [c] Experiment carried out with simultaneous cooling. [d] Reaction temperature 90 °C. [e] Reaction time: 3 min. [f] Temperature–Power profile shown in Figure 34. [g] Temperature–Power profile shown in Figure 34

The glass tube reactor charged with sand, irradiated at an initial power of 200 W without simultaneous cooling, was found to be the most energy efficient system using less magnetron energy (entry 2). Pressure temperature profile for this transformation is shown in Figure 35 (top graphic).

The graphic shows the desired temperature of 100 °C was reached within 300 s using a total energy of 204 kJ. In contrast the most efficient process performed in the coil flow cell used 1411 kJ (entry 6, Table 7). This huge difference in energy required is due to the need to use full power (300 W) to reach the reaction temperature (bottom graphic, Figure 35), in addition this step was almost 4–times longer, compared to the experiment in the tube flow cell set up (1100 s *vs* 300 s). This was attributed to be a direct consequence of the improved heating efficiency for reactions in the glass tube, as heating coils by design wind in and out of the optimum space.

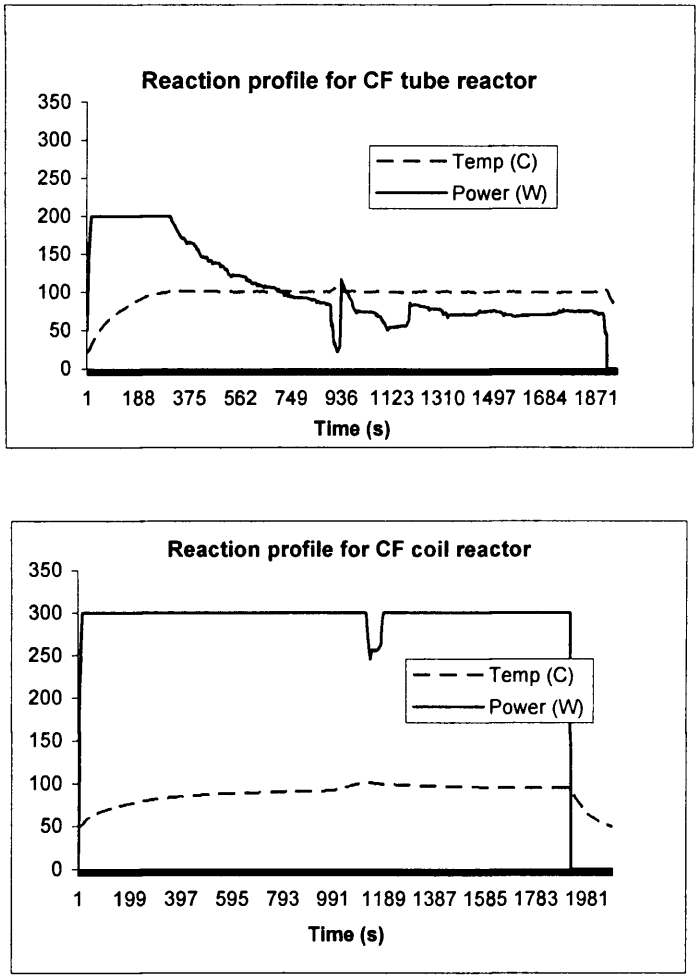
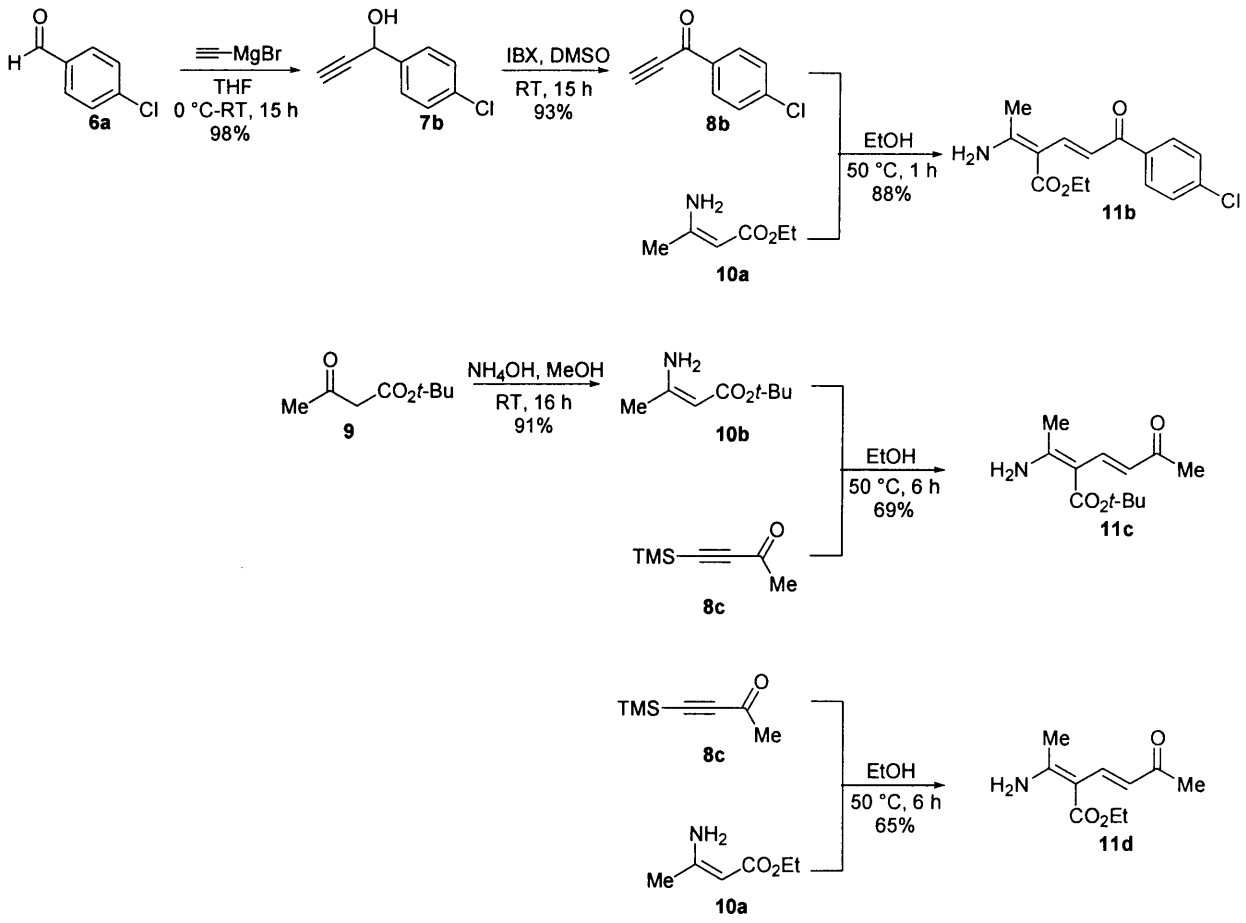


Figure 35. Temperature–Power profiles for continuous flow microwave experiments in the new tube flow cell (top) and in the CEM commercially available coil flow cell (bottom)

Since the glass tube was filled with standard quartz sand (40–100 mesh, suitable for use in chromatography), two experiments were carried out to verify if the sand promotes the transformation under investigation. When aminodienone **11a** was irradiated in toluene (without acetic acid) in the presence and absence of sand in a sealed tube, no appreciable difference was observed (13% versus 5% conversion, respectively), indicating that the sand has a negligible (if any) effect on the cyclodehydration.

In order to study the performance of different substrates under flow through processing, a range of aminodienones were synthesized (Scheme 20) and cyclodehydrated with CF processing under homogeneous conditions in toluene–acetic acid (5:1) over sand.



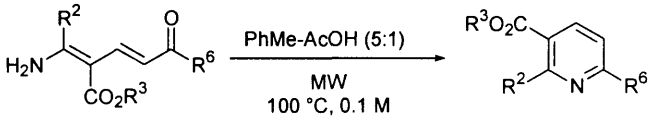
Scheme 20. Synthesis of aminodienones **11b**, **11c** and **11d**

The results were compared to batch experiments carried out in a sealed tube and to the corresponding homogeneous CF process with a Teflon heating coil (Table 10). Aminodienones **11b–d** were synthesised by condensation of enamine **10a–b** and propargylic ketone **8b–c** in EtOH under conductive heating. Non commercially available 1–(4–chlorophenyl)–2–propyn–1–one **8b** was obtained in two steps, by the reaction of 4-chlorobenzaldehyde **6a** with ethynyl magnesium bromide to give the 1–(4–chlorophenyl)–2–propyn–1–ol **7b,** which was then converted to the corresponding ethynyl ketone **8b** using IBX as oxidizing agent. *tert*–Butyl β–aminocrotonate **10b** was prepared by amination of *tert*–butyl acetoacetate **9**.

The B–R pyridine synthesis was then tested both in a batch and in a continuous flow mode, comparing the efficiency of the coil and the tube flow cell (Table 8). The four substrates were

irradiated with microwaves in a sealed tube and converted into the corresponding pyridines in 2 min.

Table 8. Comparison of B–R syntheses of 2,3,6–trisubstituted pyridines **12a–d** in batch and CF mode



11a-d **12a-d**

Entry	R^2	R^3	R^6	Sealed tube [a] Yield%	CF coil [b] Yield%	CF glass tube [c] Yield%
1	Me	Et	Ph	>98	>98	>98
2	Me	Et	*p*–C_6H_4Cl	98	>98	>98
3	Me	Et	Me	80	85	96
4	Me	*t*–Bu	Me	82	88	98

[a] Sealed tube: 2 min, initial power = 150 W. [b] CF coil: 3 min, 300 W. [c] CF glass tube filled with sand: 2 min, 200 W.

All the transformations were successfully transferred to the CMR, giving the product in a slightly higher yield compared to the corresponding reactions in a sealed tube. However the cyclodehydration performed using the coil flow cell went to completion after 3 min, demonstrating the improved performance of the glass tube reactor over a commercial Teflon heating coil.

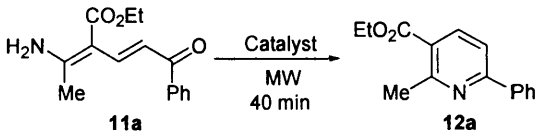
In conclusion, under conditions that gave efficient conversion to pyridine **12a–d**, the processing rates of material using the glass tube reactor were considerably higher. Additionally, CF reactions run at the same flow rate used less magnetron energy in a glass tube than in the heating coil, demonstrating that a glass tube CF reactor offers improved heating efficiency and improved performance over commercial Teflon heating coils. A higher processing rate is possible with a glass tube reactor as a faster flow rate can be maintained without compromising the reaction temperature and yield. This was attributed to be a direct consequence of the improved heating efficiency for reactions in the glass tube, as heating coils by design wind in and out of the optimum space.

2.3.2.2.2 *Heterogeneous Cyclodehydration of Aminodienones*

A further advantage of the tube flow cell over commercially available coils is in the potential to carry out heterogeneous as well as homogeneous reactions by immobilizing a catalyst on the support in the Pyrex tube.

The initial investigation involved the use of a range of supported acid catalysts in batch experiments in order to find the best conditions for transfer to a continuous flow process. Table 9 shows the results obtained using an ion exchange resin (Amberlyst 15) and sulfonic acid on silica (SiO_2–OSO_3H). A mixture of starting material and products or the presence of side products was detected by ^{1}H–NMR spectroscopic analysis of the crude reaction mixture, showing these catalysts were not ideal for this transformation.

Table 9. Effect of different supported acid catalysts on the cyclodehydration of aminodienone **11a** in sealed tube experiments



11a **12a**

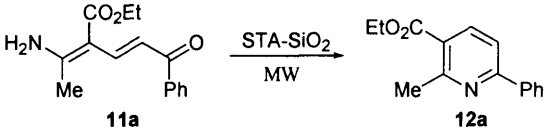
Entry	Catalyst [a]	Solvent	Temperature [b]	Results [c]
1	Amberlyst 15	EtOH	120 °C	**12a**, **11a** (9:1)
2	Amberlyst 15	Toluene	100 °C	**12a**, **11a** (1.4:1)
3	SiO_2–OSO_3H	Toluene	100 °C	**12a**, **11a** (1:1.7)
4	SiO_2–OSO_3H	Toluene	120 °C	**12a**, by–products

[a] In each experiment 20 wt% of supported acid catalyst was used. [b] Reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 150 W). [c] Ratio determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture

Thus, the synthesis of pyridine **12a** was studied using a supported heteropolyacid, silicotungstic acid on silica (STA–SiO_2), as catalyst.[77] The reaction was first investigated at room temperature and at reflux in ethanol or dichloromethane, which showed that even after long reaction times no trace of product was observed (entries 1–4). Encouragingly, the use of microwave irradiation enormously improved the transformation (entries 5–10). Optimum conditions were found to be

irradiation of the reaction mixture for 40 min at 100 °C in ethanol (entry 9), or at 120 °C in dibromoethane (entry 10), giving the product in quantitative yield.

Table 10. Cyclodehydration of 2–amino–3–ethoxycarbonyl–6–phenylhexa–2,4–dien–6–one **11a** using STA–SiO_2 as catalyst



11a **12a**

Entry	Solvent	Conditions[a]	Heating method	Results
1	EtOH	RT, 48 h	–	**11a**
2	CH_2Cl_2	RT, 48 h	–	**11a**
3	EtOH	reflux, 48 h	Conductive	**11a**
4	CH_2Cl_2	reflux, 48 h	Conductive	**11a**
5	EtOH	20 min, 100 °C	MW	**12a**, **11a** (7:1)[b]
6	EtOH	15 min, 120 °C	MW	**12a**, **11a** (6:1)[b]
7	EtOH	30 min, 120 °C	MW	**12a**, **11a** (31:1)[b]
8	EtOH	40 min, 120 °C	MW	**12a** (>98%)
9	EtOH	40 min, 100 °C	MW	**12a** (>98%)
10	$BrCH_2CH_2Br$	40 min, 120 °C	MW	**12a** (>98%)

[a] Microwave–assisted reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 150 W). [b] Ratio determined by ^1H NMR spectroscopic analysis of the crude reaction mixture

Based on the results obtained with STA it was decided to study the effect of a different support on the efficiency of the model reaction. Thus, silicotungstic acid on carbon–silica (STA–C/SiO_2) was tested under microwave irradiation (Table 11).

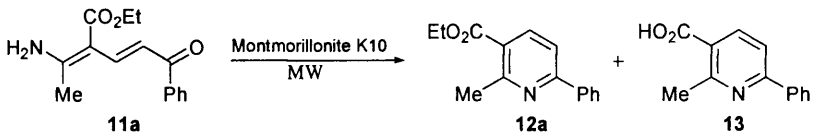
Table 11. Cyclodehydration of aminodienone **11a** using STA–C/SiO_2 as catalyst

Entry	Solvent	Conditions [a]	Results
1	Toluene	40 min, 100 °C	**12a**, **11a** (1.2:1) [b]
2	$CHCl_3$	40 min, 60 °C	**12a**, **11a** (1:16) [b]
3	$BrCH_2CH_2Br$	40 min, 120 °C	**12a** (>98%)

[a] Microwave–assisted reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 150 W)
[b] Ratio determined by ^1H NMR analysis of crude reaction mixture

Pyridine **12a** was isolated in quantitative yield after irradiation at 120 °C for 40 min (entry 3), demonstrating that STA–C/SiO_2 showed comparable efficiency to STA–SiO_2.

Table 12. Cyclodehydration of aminodienone **11a** using montmorillonite K10 as catalyst



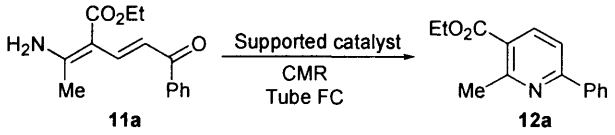
Entry	Solvent	Conditions [a]	Results [b]
1	$CHCl_3$	20 min, 50 °C	**12a**, **11a** (1:3.2), **13** (trace)
2	EtOH	40 min, 60 °C	**12a**, **11a** (1:1.3), **13** (trace)
3	EtOH	40 min, 70 °C	**12a**, **11a** (3.8:5), **13** (trace)
4	Toluene	40 min, 100 °C	**12a**, **13** (trace)
5	Toluene	20 min, 100 °C	**12a**, **13** (trace)
6	Toluene	10 min, 100 °C	**12a**, **13** (trace)
7	Toluene	3 min, 100 °C	**12a**, **13** (trace)
8	Toluene	2 min, 100 °C	**12a**, **13** (trace)
9	EtOH	40 min, 70 °C	**12a** (>98%) [c]
10	Toluene	2 min, 100 °C	**12a** (>98%) [c]

[a] Reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 150 W). [b] Ratio determined by ^1H NMR spectroscopic analysis of crude reaction mixture. [c] Reactions were performed using a dry catalyst. Yield of pure isolated product

Despite showing excellent conversion, the process required a relatively long reaction time. Therefore a different acid supported catalyst, montmorillonite K10, was tested in the attempt to achieve good yields in a shorter time. Table 12 shows the different conditions investigated; surprisingly the carboxylic acid **13** was also formed during the experiments. It was assumed that the amount of water retained by the hygroscopic catalyst was enough to catalyze the hydrolysis of the ester group under the acidic reaction conditions. The use of dry catalyst eliminated side product formation and quantitative conversion was obtained in 40 min in ethanol (entry 9), and in just 2 min using toluene as solvent (entry 10).

The latter results represented an ideal process for the CMR. However, low solubility of the aminodienone in toluene made it impossible to run a flow reaction. To this end, an equally efficient but relatively prolonged reaction had to be considered. Cyclodehydration of aminodienone **11a** catalyzed by STA–SiO_2 in ethanol was transferred to the CMR. The batch wise experiment gave quantitative convertion at 70 °C in 40 min (entry 9, Table 10). Because of this long reaction time it was necessary to carry out the experiment in a closed–loop mode: the intake line to the HPLC pump was placed in the reaction mixture along with the outtake line from the flow cell, creating a closed–loop system. The tube flow cell was charged with STA–SiO_2 (3.7 g) and the reaction mixture was passed through the microwave chamber. Mainly unreacted starting material was recovered after 40 min of irradiation (entry 1, Table 13). Further investigation revealed that this unsuccessful result was due to catalyst leaching in ethanol. Thus, dibromoethane was chosen as an alternative solvent for the flow–based transformation. Aminodienone showed good solubility in dibromoethane and no catalyst leaching was detected using this solvent. In addition, batch experiments carried out in dibromoethane using both STA–SiO_2 (entry 10, Table 10) and STA–C/SiO_2 (entry 3, Table 11) were found to be efficient. Despite the good presumption, the catalyst decomposed under the reaction conditions (entries 2–4). The last option suitable for flow through experiments was the use of montmorillonite K10 as the supported catalyst in ethanol. Performing the experiment in a sealed tube afforded the product in excellent yield after 40 min of irradiation (entry 10, Table 12). The flow cell was fitted with montmorillonite K10 (4.5 g) and the reactor was set up to operate in a closed–loop mode. Entry 5 shows that the first experiment gave the target pyridine in 16% yield (due to the low mass of the crude product recovered after irradiation). The use of a higher flow rate did not enhance the process, so a second experiment was carried out, passing a basic solution (NH_3/MeOH) through the flow cell after the irradiation step. In this case the total yield was 97%, confirming our hypothesis that under the acidic reaction conditions the target pyridine was protonated and immobilized on the catalyst.

Table 13. Heterogeneous cyclodehydration of aminodienone **11a** in our tube CFR



11a **12a**

Entry	Catalyst	Solvent	Conditions [a]	Flow rate (mL/min)	Results
1	STA–SiO_2	EtOH	40 min, 70 °C	1	**12a**, **11a** (1:11) [b]
2	STA– SiO_2	$BrCH_2CH_2Br$	9 min, 120 °C	0.3	Decomposition
3	STA–C/SiO_2	$BrCH_2CH_2Br$	9 min, 120 °C	0.3	Decomposition
4	STA–C/SiO_2	$BrCH_2CH_2Br$	3 min, 120 °C	1	Decomposition
5	K10	EtOH	40 min, 70 °C	0.5	**12a** (16%)
6	K10	i) EtOH ii) NH_3/MeOH	45 min, 70 °C	1.5	**12a** (97%)

[a] Reactions were performed at the required reaction temperature through moderation of microwave power and using simultaneous cooling. [b] Ratio determined by ^1H NMR spectroscopic analysis of crude reaction mixture

In conclusion, many problems were encountered such as catalyst leaching (entry 1), the insolubility of the reactant in toluene which prevented the use of this solvent in a continuous flow process, product decomposition (entry 2, 3 and 4) and the protonation/immobilization of the product under the acidic reaction conditions (entry 5 and 6). The protonated pyridine could be recovered by passing a basic solution through the flow cell in a sort of batch process. However, these difficulties are very much related to the particular process investigated and hence the prospect of performing heterogeneous reaction using the tube flow cell was considered to be feasible and in evidence in our study. Pitts reported the use of this tube flow cell developed by us for heterogeneous Suzuki reactions using encapsulated palladium (Pd EnCat™) as catalyst. The flow process was successful compared to commercially available U–shaped flow cells and this showed the potential of this apparatus in large scale synthesis.[78]

2.4 Microreactor *vs* CMR

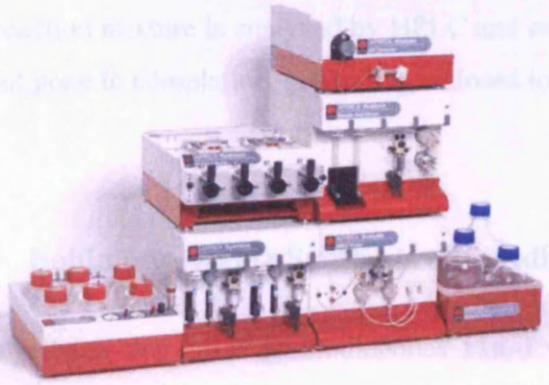
2.4.1 Definition and Properties of Microreactors

Microreactors are reactors with three-dimensional structures, the inner dimensions of which are between ten and a hundred micrometers in size. The main feature of these reactors, in comparison

to conventional chemical reactors, is the high surface-area-to-volume ratio. This allows for fast heating and cooling in reaction mixtures within the microstructures. The result in many cases is higher selectivity, yield and product quality. In addition to heat transport, mass transport is also improved in microstructured reactors. Mixing times, down to several milliseconds, are generally smaller than in conventional systems and the diffusion times are very short, hence the influence of mass transport on the speed of a reaction can be considerably reduced. The flows are mostly laminar, directed, and highly symmetric. The multiphase flows often exhibit high order between the phases, allowing to simulate and model systems to develop microprocess engineering apparatus by rational design. The hazard potential of strongly exothermic or explosive reactions can also be drastically reduced. Higher safety is also achieved in reactions with toxic substances or higher operating pressures. Microreactors allow the operator to optimize processes in a short time and with improved safety in a scale appropriate for biological screening.[58]

2.4.2 The Syrris AFRICA® Microreactor

The AFRICA® microreactor is an example of commercially available automated microreactor proposed by Syrris. Figure 36 shows a picture of the reactor and a schematic description of the different modules available.



- **Pressurization Module** up to 7 bar
- **Reagent Feed Module (RFM)**
- **Reagent Injection Module (RIM)**
- **Chip Reactor Module**
- **Product Collection Module (PCM)**
- **Sample & Dilutor** which injects diluted sample onto HPLC column
- **HPLC**
- **UV Detector**
- **Flow Manager software**
- **Flow Liquid-Liquid Extraction (FLLEX)**

Figure 36. The Syrris AFRICA® microreactor

Microreactors have a volume of 60 µL – 1000 µL, although 4 mL and 16 mL tube reactors are also available for larger scale synthesis, and reaction time can vary from 1 min to 2 h. The typical production rate for this apparatus ranges from 0.5 mg to 2 g product/h.

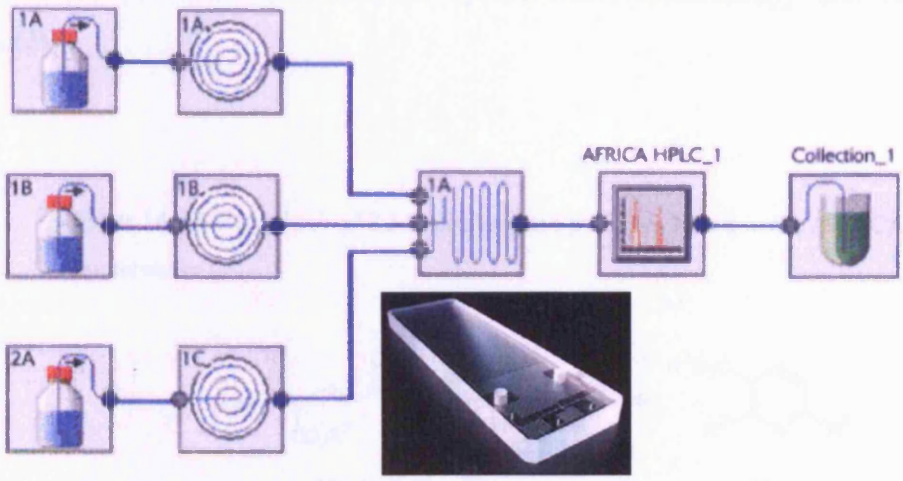


Figure 37. Schematic representation of automated flow process in the Syrris AFRICA® microreactor

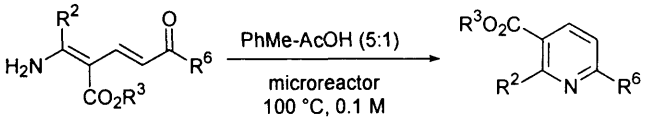
Figure 36 shows a schematic representation of an automated flow process in the Syrris AFRICA® microreactor. Up to three different reagents can be injected contemporarily into the microreactor. The reaction mixture is analyzed by HPLC and collected or reinserted into the chip if the reaction has not gone to completion, generating a closed loop system.

2.4.3 Bohlmann–Rahtz Synthesis of Pyridines in the AFRICA® Microreactor

The cyclodehydration of aminodienones **11a-d** was carried out in the AFRICA® microreactor consisting of a number of basic units comprising pressurization module, reagent feed module (RFM), reagent injection module (RIM), chip reactor module and product collection module (PCM). In order to compare the efficiency of the microreactor with the CMR, the experiments were performed under the same conditions used for the microwave–assisted continuous flow processes. A 0.1 M solution of aminodienones **11a-d** in toluene–acetic acid was passed through the chip reactor at a temperature of 100 °C (Table 14). After a reaction time of 1 min and 2 min,

TLC analysis showed a mixture of product and starting material was present. Heating the reaction mixture for 4 min gave complete conversion to the corresponding pyridine product. Product precipitation occurred during the cyclodehydration of aminodienone **11c**, causing line blockage. Therefore, the synthesis of pyridine **12c** was performed using a 0.05 M solution of aminodienone **11c** (entry 3). This instrumental setup allowed the production of samples of just a few milligrams, hence the crude products were analysed by ^{1}H NMR spectroscopy and GC-MS analysis (Appendix B).

Table 14. B–R synthesis of 2,3,6–trisubstituted pyridines **12a–d** in the AFRICA® microreactor



11a-d **12a-d**

Entry	R^2	R^3	R^6	Results		
				1 min[a]	2 min[a]	4 min[b]
1	Me	Et	Ph	**11a** and **12a**	**11a** and **12a**	**12a**
2	Me	Et	*p*–C_6H_4Cl	**11b** and **12b**	**11b** and **12b**	**12b**
3	Me	Et	Me	**11c** and **12c**	**11c** and **12c**	**12c**[c]
4	Me	*t*–Bu	Me	**11d** and **12d**	**11d** and **12d**	**12d**

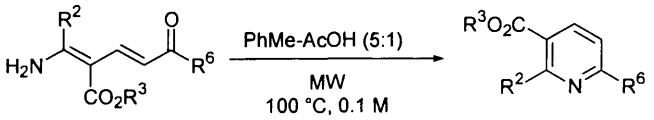
[a] Reaction monitored by TLC analysis

[b] Products were analysed by ^{1}H NMR spectroscopy and GC-MS analysis

[c] Reaction performed using a 0.05 M solution of aminodienone **11c**.

For comparison, the results obtained for the B–R syntheses of 2,3,6–trisubstituted pyridines **12a–d** under continuous flow processing in a microreactor and in a CMR (see Section 2.3.2.2) are shown in Table 15. The table outlines the difference in the required reaction time for efficient conversion found using the two different continuous flow reactors. This observation could be due to more accurate temperature measurement in the microreactor rather than in the tube flow cell, where an IR sensor monitors the temperature at the bottom of the flow cell, as the temperature inside the flow cell may be higher than that recorded at the bottom of the tube. Further investigation is necessary to verify if the difference in reaction rate is due to a measurement error or because of the improved efficiency of the microwave heated CMR over the microreactor.

Table 15. Comparison of B–R synthesis of 2,3,6–trisubstituted pyridines **12a–d** in a microreactor and in a CMR



11a-d **12a-d**

Entry	R^2	R^3	R^6	Microreactor	CMR[b]
1	Me	Et	Ph	4 min	2 min
2	Me	Et	*p*–C_6H_4Cl	4 min	2 min
3	Me	Et	Me	4 min [c]	2 min
4	Me	*t*–Bu	Me	4 min	2 min

[a] Reaction performed in the Syrris AFRICA® microreactor.

[b] Reaction performed in the tube flow cell filled with sand.

[c] Reaction performed using a 0.05 M solution of aminodienone **11c**.

In conclusion, the B–R synthesis of 2,3,6–trisubstituted pyridines **12a–d** by cyclodehydration of aminodienones **11a-d** was successfully performed in the Syrris AFRICA® microreactor. However complete conversion to the corresponding pyridines was achieved after 4 min, which equates to a doubling of the reaction time compared to the same transformation performed in a microwave heated CF tube reactor. Therefore, the CMR using the tube flow cell demonstrated improved performance over the commercially available microreactor.

2.5 Conclusions

In conclusion, a CF microwave reactor has been developed for use with a monomodal instrument that enables the direct measurement of flow cell temperature using an IR sensor. This system shows the potential to carry out heterogeneous as well as homogeneous reactions by immobilizing a catalyst on the support in the glass tube. It was demonstrated that the tube CF reactor offers the potential for operation on a large scale, successful transfer from batch to CF processing and improved performance over commercial Teflon heating coils and a commercially available microreactor.

DISCUSSION: Microwave–Mediated Synthesis of N–Containing Heterocycles in Batch Mode

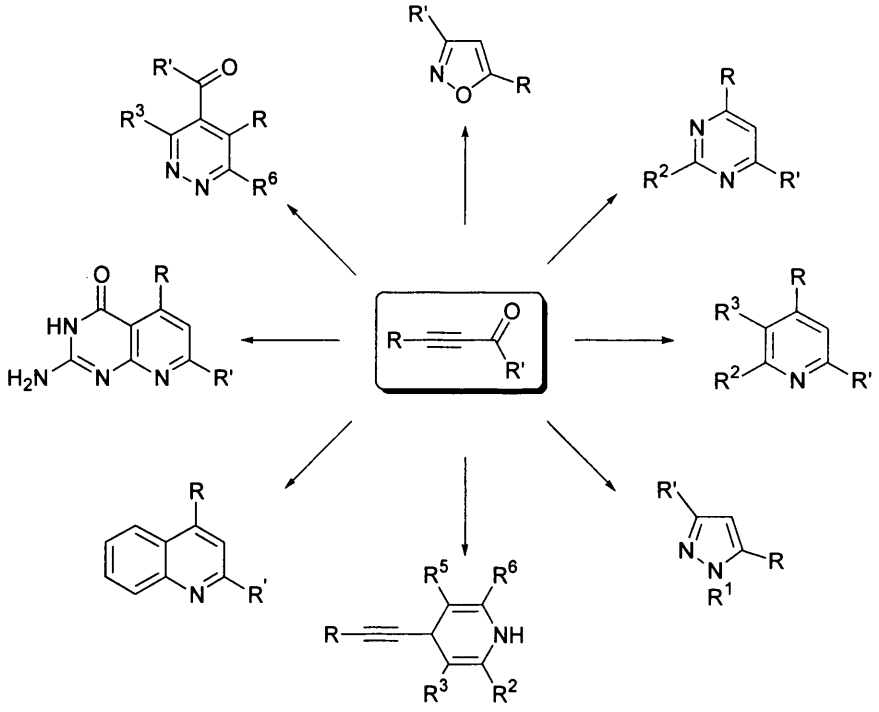
3

3.1 Introduction

The development of new methods for the rapid synthesis of heterocyclic compounds continues to attract considerable attention for the preparation of diverse structural motifs of biological and pharmaceutical importance. A high proportion of modern pharmaceutical agents, fine chemicals and agrochemicals are heterocyclic compounds. The Bagley group seeks to establish new methods for the rapid assembly of heterocycles, designed to incorporate great diversity in the shortest number of preparative steps so that the synthesis of different heterocyclic targets from a single starting library becomes feasible. This can be achieved by the development of new heteroannulation procedures, combined with *in situ* preparation of common intermediates. This methodology has been found to be more efficient, in terms of yield and energy used, under microwave–assisted conditions; however the development of large scale synthetic procedures under microwave irradiation, appropriate for the chemical industries, has until now been problematic with current technology. With the advent of new scale–up technologies for flow–through systems in a monomodal microwave instrument this study now becomes possible and lays the groundwork for the development of clean and efficient large–scale technologies for the future.

Alkynones are important intermediates used in the synthesis of a range of simple nitrogen–containing heterocycles. Pyridazines,[79] pyridines,[67] quinolines,[80] triazoles,[81] isoxazoles,[81,82] pyrazoles,[81,83] and pyrimidines[82,84,85] have all been prepared from these substrates (Scheme 21), in applications ranging from access to non–proteinogenic amino acids[85] to the total synthesis of

complex natural products.[71a] The Bagley research group has reported a number of new one–step methods for the synthesis of pyridines,[68,70,86] pyrimidines[87] and pyrido[2,3–*d*]pyrimidines[69a,73b] by cyclocondensation of an alkynone and either an enamine, β–ketoester or amidine under either thermal or microwave–assisted conditions that gave the target heterocycle in good yield and, where appropriate, with total control of regiochemistry.



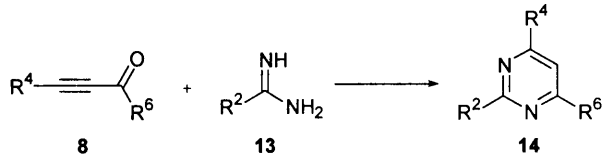
Scheme 21. *N*–Containing hetrocycles accessible from alkynone

We report herein new efficient methods to access pyrimidines, pyrazoles, Hantzsch dihydropyridines and Hantzsch pyridines under microwave–assisted conditions in batch–mode. Efforts were made to find optimum condition for transfer to a continuous flow microwave reactor in order to evaluate the versatility of the tube flow cell developed within the group (see Chapter 2). This study will expand the scope and versatility of microwave–assisted chemistry and provide an assortment of new tandem processes for the heterocyclic chemist of value in total synthesis, methodology work, medicinal chemistry, combinatorial chemistry, for access to useful heterocyclic building blocks in organic chemistry and more importantly, for clean and efficient large–scale synthesis and process research.

3.2 Pyrimidine Synthesis

3.2.1 Introduction

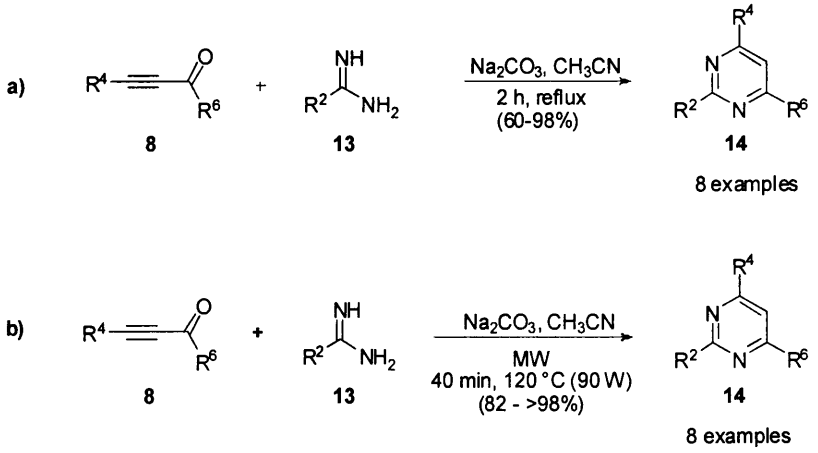
Pyrimidines can be synthesized from alkynone **8** using an amidine **13** nucleophile. It likely proceeds by 1,4–addition followed by cyclodehydration to yield the target 2,4,6–trisubstituted pyrimidine (Scheme 22). This tandem process represents a relatively simple transformation and as such it is ideal to investigate the effect of a continuous flow system on the course of a heteroannulation reaction.



8 **13** **14**

Scheme 22. Pyrimidine synthesis from alkynone and amidine

Previous work within the Bagley group showed that the cyclocondensation between alkynone **8** and amidine **13** in acetonitrile in the presence of sodium carbonate as base (to liberate **13** from the corresponding hydrochloride salt) proceeds in 2 h under conductive heating and in 40 min under microwave–assisted conditions (Scheme 23).



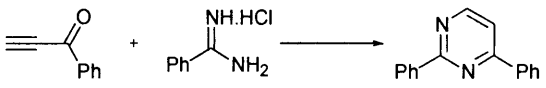
Scheme 23. Pyrimidine synthesis from alkynone and amidine under conductive and microwave heating

The use of microwave irradiation reduced the reaction time from 2 h to 40 min and also resulted in improved yields without the need for chromatographic purification. Although these results were very encouraging, in terms of reaction efficiency and facility, the relatively long reaction time was prohibitive for a flow–through process. Thus efforts were made to reduce the reaction time further by carrying out experiments under homogeneous conditions in an alternative solvent, to establish a system that had the potential for transfer to flow processing.

3.2.2 Microwave-Assisted Synthesis of Pyrimidines

The synthesis of 2,4–diphenylpyrimidine **14a** by cyclocondensation of 1–phenyl–2–propyn–1–one **8a** and benzamidine **13a** (used as its hydrochloride salt) was chosen as a reaction of study. Table 16 shows the different conditions investigated for this transformation in order to find a fast and efficient method for transfer to continuous flow processing.

Table 16. Synthesis of 2,4–diphenylpyrimidine **14a** from alkynone **8a**



8a **13a** **14a**

Entry	Conditions[a]	Solvent	Reagents	Results[b]
1	40 min, 120 °C	CH_3CN	Na_2CO_3	**14a** (87%)[c]
2	40 min, 120 °C	EtOH	Na_2CO_3	**14a** and starting materials
3	15 min, 120 °C	Toluene	AcOH	**14a** and starting materials
4	20 min, 120 °C	Toluene	AcOH	**14a** and starting materials
5	30 min, 120 °C	Toluene	AcOH	**14a** and starting materials
6	20 min, 70 °C	MeOH	MeONa	**14a** (97%)[c]
7	10 min, 70 °C	MeOH	MeONa	**14a** (92%)[c]
8	2 min, 100 °C	MeOH	MeONa	**14a** (>98%)[c]

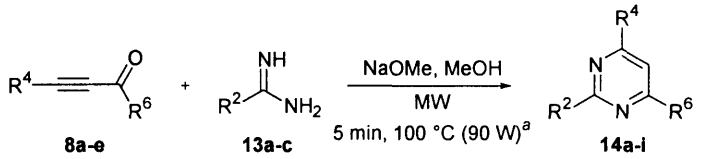
[a] Reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 90 W).

[b] Results determined by ^1H NMR analysis of crude reaction mixture.

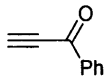
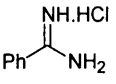
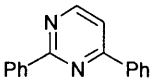
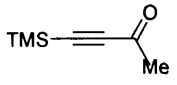
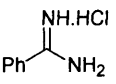
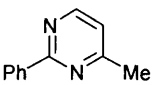
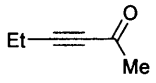
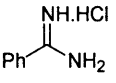
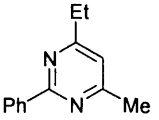
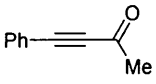
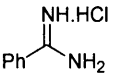
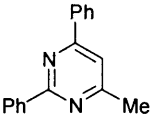
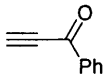
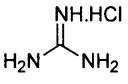
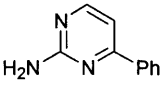
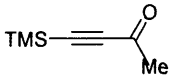
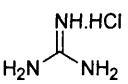
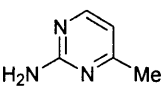
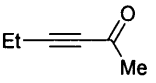
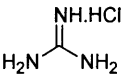
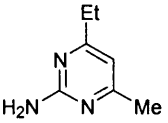
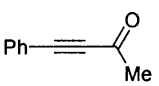
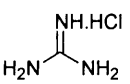
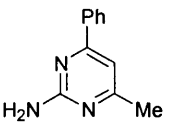
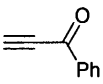
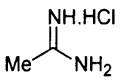
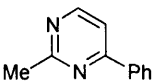
[c] Yield of pure isolated product.

The experiment performed in ethanol using sodium carbonate as the base was less efficient than the reaction carried out in acetonitrile (entries 1 and 2). Comparable results were obtained using toluene–acetic acid as the solvent system, as a mixture of product and starting materials was recovered even after 30 min of irradiation at 120 °C (entries 3–5).

Table 17. Synthesis of 2,4,6–trisubstituted pyrimidines **14a–i** from alkynones



8a-e **13a-c** **14a-i**

Entry	Alkynone **8a–d**	Amidine **13a–c**·HCl	Product **14a–i**	Yield%
1				>98[b]
2				91
3				84
4				75
5				90
6				85
7				62
8				69
9				90

[a] Initial MW irradiation power of 90 W was moderated throughout the course of the reaction in order to maintain the required temperature. [b] Reaction time = 2 min

Replacing the sodium carbonate by pre–treatment with a stronger base such as sodium methoxide gave almost a quantitative yield in 20 min at 70 °C. Further investigation revealed that increasing the reaction temperature to 100 °C yielded the product in quantitative yield in just 2 min after a simple aqueous work up (entry 8). In order to provide an homogeneous procedure for the rapid synthesis of pyrimidines appropriate for flow processing, a mixture of benzaldehyde hydrochloride **13a**·HCl and sodium methoxide was stirred in methanol at room temperature and filtered. Phenylpropynone **8a** was added and the homogeneous solution was irradiated in a monomodal microwave synthesiser.

Based on these findings a range of different readily–available ethynyl ketones **8a–e** and amidines **13a–c** were used to establish substrate variability for the optimum microwave–assisted reaction (Table 17). Although the efficiency of this procedure was comparable or lower than the corresponding thermal experiments, this method allows rapid access to pyrimidines under ideal condition for continuous flow processing (Appendix C). In addition, 2–aminopyridines have been shown to exhibit cardiotonic activity[88] and the analogous series of 2,4,6–trisubstituted pyridines bind to both estrogen receptor alpha and delta, with modest selectivity for the former,[89] and so the reported method could provide rapid access to non–steroidal libraries for potential application as selective estrogen receptor modulators or ligands for the nuclear receptor superfamily of ligand–regulated transcription factors.[90]

3.2.3 Conclusion

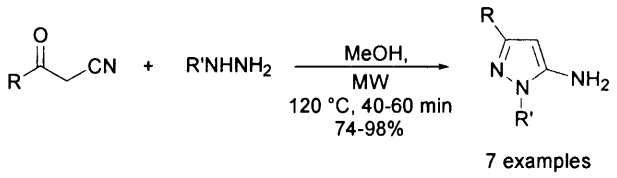
In conclusion a new efficient procedure for the synthesis of pyrimidines from alkynones was described under microwave irradiation. It was found that the use of a strong base such as NaOMe to liberate the free amidine facilitates the process giving the target pyrimidine in very good yield after 2–5 min of irradiation.

3.3 Pyrazole Synthesis

3.3.1 Introduction

Previous work within the Bagley group showed that microwave irradiation of substituted hydrazines and β–ketonitriles gives 5–aminopyrazoles in excellent yield.[91] The experiments were performed irradiating a mixture of hydrazine and β–ketonitriles in MeOH at 120 °C for 40–60

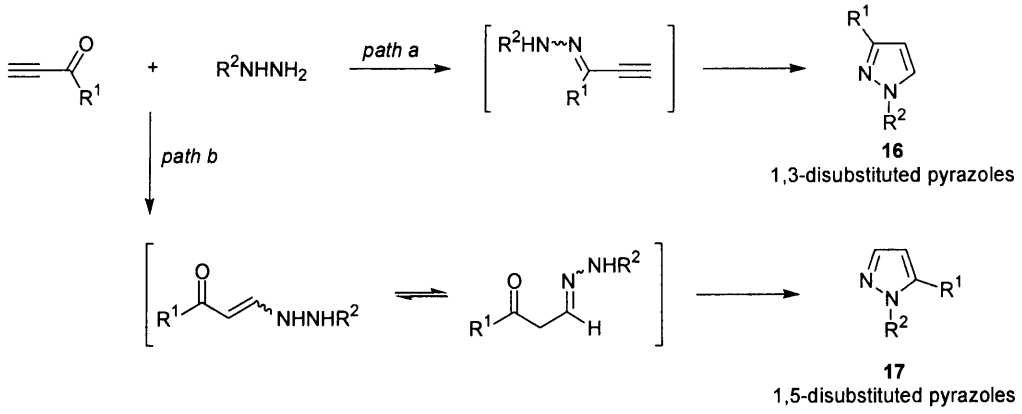
min to give 5–aminopyrazoles in 74–98% yield (Scheme 24). Although the yields for experiments were comparable to those obtained using conductive heating, the reaction times were dramatically reduced from 18 h to 40–60 min.



Scheme 24. Microwave–assisted synthesis of 5–aminopyrazoles from substituted hydrazines and β–ketonitriles

The reported method for the synthesis of 5–aminopyrazoles was applied in the synthesis of the *N*–pyrazole urea BIRB 796, a potent and selective inhibitor of p38α mitogen–activated protein kinase that was used for the study of accelerated ageing in Werner syndrome cells.

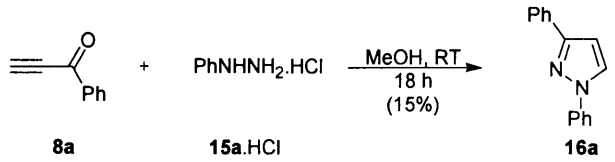
Pyrazoles can also be accessed from alkynones using hydrazines as the nucleophile. This transformation proceeds efficiently under well established conditions,[92] nevertheless the regioselectivity of reactions can be poor and is often contradictory in the literature. Our investigation was directed to the regiochemical control of this heteroannulation process, resolving any literature ambiguities and finding optimum conditions for transfer to continuous flow processing. This pyrazole synthesis can give rise to two different regioisomeric products, 1,3–diphenyl– or 1,5–diphenylpyrazole, **16** or **17** respectively (Scheme 25).



Scheme 25. Competitive pathways for the regioselective synthesis of disubstituted pyrazoles from ethynyl ketones

The first step of the reaction produces hydrazones followed by ring closure giving the target heterocycle. In accordance with the mechanistic findings of Miller and Reiser[83] and Coispeau and Elguero,[93] the variation in regioisomer composition can be rationalized by the competition of hydrazone formation by 1,2– and 1,4–addition of the hydrazine derivative (Scheme 25). 1,2–Addition generates the hydrazone intermediate which leads to the 1,3–disubstituted pyrazole by cyclodehydration (*path a*), whereas 1,4–addition generates the enamine intermediate in tautomeric equilibrium with the hydrazone which gives the 1,5–disubstituted isomer (*path b*).

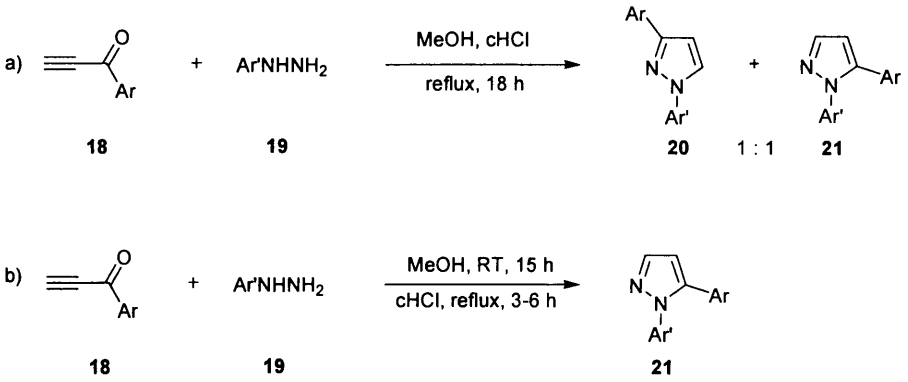
Different procedures have been reported in the literature for the synthesis of pyrazoles by condensation of alkynones and hydrazines. Kirmse reported the isolation of 1,3–diphenyl pyrazole **16a** as a single regioisomer by stirring a solution of **8a** and the hydrazine hydrochloride **15a**·HCl in methanol overnight, however the product was obtained in very poor yield (Scheme 26). The transformation was suggested to proceed through conjugate addition of the anilino amine followed by cyclodehydration under the reaction conditions.[94]



8a **15a**.HCl **16a**

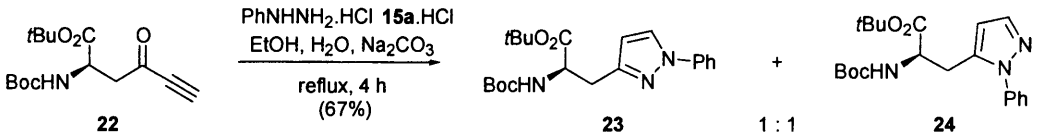
Scheme 26. Pyrazole syntheses reported by Kirmse *et al*

Miller and Reiser reported the synthesis of a variety of 1,3– and 1,5–donor–acceptor substituted pyrazole derivatives by cyclocondensation of α,β–ethynyl ketones with substituted phenyl hydrazines. The ratio of the two isomers was controlled by varying the reaction conditions in a manner consistent with competitive 1,2– and 1,4–addition followed by ring closure. The authors observed that when a solution of an electron–rich arylpropynone **18** and hydrazine derivative **19** was heated at reflux in methanolic hydrochloric acid for 18 h, both pyrazole regioisomers were obtained in equal amounts in high yield. An alternative two step procedure afforded only the 1,5–disubstituted pyrazole **21** when a solution of **18** and **19** was stirred in methanol at room temperature for 15 h and then heated at reflux on addition of concentrated hydrochloric acid (Scheme 27).



Scheme 27. Regioselectivity in pyrazole syntheses reported by Miller *et al.*

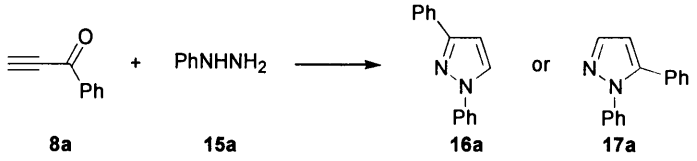
Baldwin and co–workers studied a related cyclocondensation of ethynyl ketone **22** and phenylhydrazine **15a**, as a route to non–proteinogenic pyrazole amino acids, using Na_2CO_3 to liberate the free base of the hydrazine. Stirring the reaction mixture at reflux in ethanol, an inseparable mixture of 1,3– and 1,5–regioisomers, **23** and **24** respectively, was obtained in a ratio of 1:1 (Scheme 28).[81]



Scheme 28. Pyrazole synthesis reported by Baldwin *et al*

3.3.2 Microwave-Assisted Synthesis of Pyrazoles

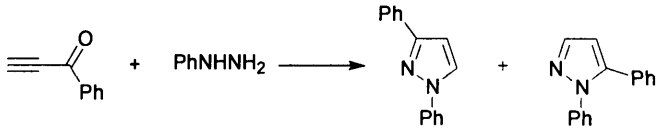
The heterocyclization of phenylpropynone **8a** and phenylhydrazine **15a** was chosen as a model reaction (Scheme 29).



Scheme 29. Heterocyclization of propynone **8a** and phenyl hydrazine **15a**

In order to compare the contradictory results reported in literature, a solution of phenylpropynone **8a** and phenylhydrazine **15a** was submitted to the four alternative procedures. Table 18 shows that in all cases a mixture of the two regioisomers was obtained. In accordance with Baldwin's findings, the experiment performed under basic conditions gave a ratio of 1:1 of the two regioisomers (entry 2), whereas under acidic conditions the 1,3–regioisomer **16** was formed preferentially (entries 1, 3 and 4).

Table 18. Reinvestigating the cyclocondensation of propynone **8a**



8a **15a** **16a** **17a**

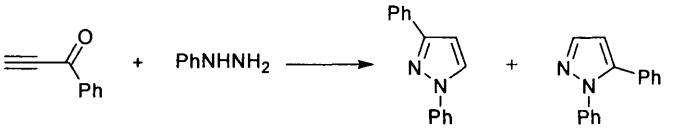
Entry	Solvent	Reagents and Conditions	Method[a]	Yield%[b]	
				16a	**17a**
1	MeOH	**15a**·HCl, RT, 18 h	94	53	10
2	EtOH	**15a**·HCl, H_2O, Na_2CO_3, reflux, 4 h	81	39	41
3	MeOH	**15a**, RT, 15 h; then cHCl, reflux, 2 h	83	81	14
4	MeOH, cHCl	**15a**, reflux, 15 h	83	76	15

[a] Literature reference for the experimental procedure. [b] Isolated yield of pyrazoles **16a** and **17a** after chromatographic purification on silica

These results suggested that acid–mediated conditions were necessary to facilitate regioselective reaction. In order to test this hypothesis, a range a different solvents and acids both under conductive and microwave heating were investigated for the reaction of propynone **8a** and the phenylhydrazine **15a** (Table 19). The regioselectivity of each experiment was examined by ^1H NMR spectroscopic analysis of the crude reaction mixture. It was observed that microwave irradiation in toluene (entry 1) or toluene–acetic acid (entry 2) at 120 °C gave both pyrazoles after 40 min with no regioselectivity. A two step process, with initial condensation in toluene followed by heating at reflux on addition of acetic acid (entry 3), silicotungstic acid on silica (STA–SiO_2) (entry 4) or montmorillonite K 10 (entry 5) did improve the regioselectivity but not above and beyond the two step process using a stronger Brønsted acid (entry 6). One and two step processes gave a comparable ratio of regioisomers (entries 6 and 8, respectively) and the experiment carried

out in dioxane–HCl gave the same result (entry 9). Without the acidification step (entry 7) the presence of intermediates was observed in the crude ^{1}H NMR spectrum and both pyrazole regioisomers were present in equal amounts. Of greatest interest was the reaction carried out under microwave dielectric heating at 120 °C (entry 10), which demonstrated that a 5:1 ratio of pyrazoles **16a** and **17a** could be obtained under acidic conditions in only 2 min.

Table 19. Modified conditions for the synthesis of pyrazoles **16a** and **17a**



8a **15a** **16a** **17a**

Entry	Solvent	Conditions	Heating method	Ratio of **16a**:**17a** [b]
1	Toluene	40 min, 120 °C	MW [a]	1:1
2	Toluene–AcOH	40 min, 120 °C	MW [a]	1:1
3	Toluene	15 h, RT; then AcOH, 4 h, reflux	Conductive	3:1
4	Toluene	15 h, RT; then STA–SiO_2, 4 h, reflux	Conductive	2:1
5	MeOH	15 h, RT; then K10, 4 h, reflux	Conductive	5:1
6	MeOH	15 h, RT; then cHCl, 4 h, reflux	Conductive	6:1 [c]
7	MeOH	15 h, RT	None	1:1
8	MeOH, cHCl	15 h, reflux	Conductive	6:1 [c]
9	HCl (4 M) in dioxane	8 h, reflux	Conductive	5:1
10	MeOH, cHCl	2 min, 120 °C	MW [a]	5:1

[a] Reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 90 W).

[b] Ratio determined by ^{1}H NMR analysis of crude reaction mixture.

[c] Miller conditions. Ratio is taken from the isolated yields of pyrazoles **16a** and **17a** after chromatographic purification on silica (as reported in Table 18).

In an attempt to improve the regioselectivity of this transformation, experiments at sub–ambient temperature were investigated under microwave irradiation using concurrent dielectric heating and cooling.[95] The reactions were carried out in the CEM Discover® CoolMate™ apparatus, which consists of two units, a monomodal microwave synthesizer and the CoolMate™ unit (Figure 38). A jacketed reaction vessel, that consists of a reaction cell inserted into a jacket through

which a cooling fluid is passed, allows the reaction to be held at a low temperature during microwave irradiation. The cooling fluid is stored in the CoolMate™ unit where it is cooled down to the desired temperature and passed through the vessel. The jacketed reaction vessel and cooling media are both microwave transparent, ensuring full energy transmission directly to the reactants. The temperature is measured with a fibre optic probe inserted directly into the reaction mixture to ensure fast, accurate and convenient reaction control. The range of temperatures attainable with this apparatus is between –80 °C and 35 °C.

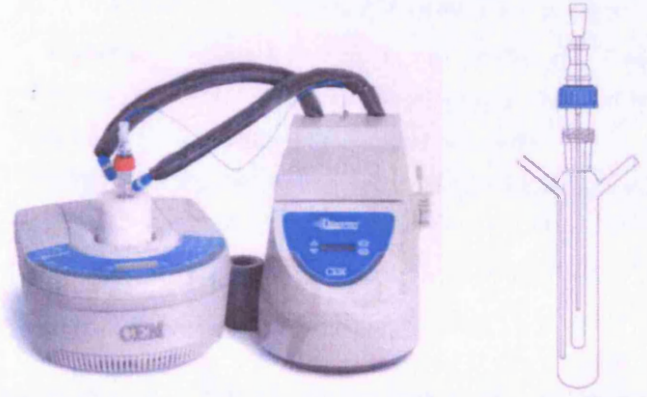
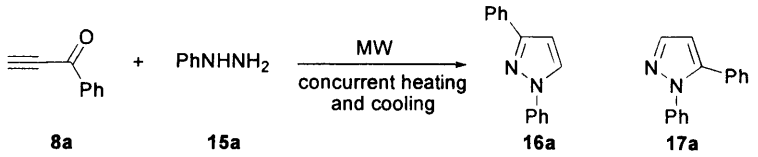


Figure 38. Discover® CoolMate™ (left) and jacketed reaction vessel (right)

Table 20 shows the different conditions that were investigated using concurrent heating and cooling in the CEM Discover® CoolMate.™ The pyrazole synthesis was carried out at –20 °C in MeOH to give a 4:1 regioisomeric ratio (entry 1), and the addition of HCl to the reaction mixture did not enhance the regioselectivity (entry 2). The experiment carried out at 0 °C in MeOH gave poorer regioselectivity (entry 3) whereas an improvement was obtained by performing the reaction at the same temperature in the presence of the acid (entry 4). A two step process carried out by irradiating the reaction mixture for 30 min at 0 °C followed by addition of acid and stirring at reflux did not result in any improvements (entry 5).

Table 20. Microwave–assisted synthesis of pyrazoles **16a** and **17a** with concurrent heating and cooling



8a **15a** **16a** **17a**

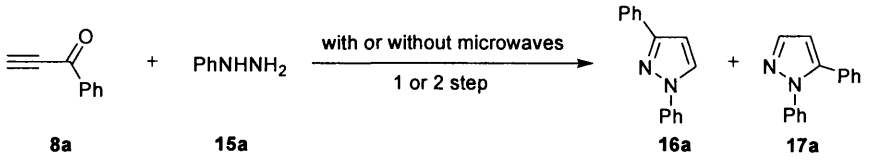
Entry	Solvent	Conditions[a]	Ratio of **16a**:**17a**[b]
1	MeOH	20 min, -20 °C	4:1
2	MeOH, HCl	30 min, -20 °C	4:1
3	MeOH	20 min, 0 °C	1.4:1
4	MeOH, HCl	20 min, 0 °C	7:1
5	MeOH	30 min, 0 °C, then HCl, 4 h, reflux	5:1

[a] Concurrent heating and cooling was carried out using the CEM Discover® Coolmate™ apparatus by irradiating at 60 W power whilst circulating a coolant through the microwave cavity.

[b] Ratio determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture.

These findings suggest that the condensation of alkynone and hydrazine is a much more facile transformation that was originally believed and the target pyrazole can be generated in a short reaction time by exploiting concurrent heating and cooling technique. Thus in order to properly quantify the advantages of this methodology, a solution of **8a** and **15a** was submitted to reaction at 0 °C either in cHCl–methanol (1.5% v/v) for 30 min (entry 1, Table 21) or in a two step process in methanol with the addition of cHCl after 15 min (entry 2, Table 21). The isolated yields of pyrazoles **16a** and **17a** after purification on silica were compared for experiments with and without concurrent heating and cooling (Table 21). It was found that the two step process (entry 2) showed no benefits through concurrent heating and cooling, whereas the yield of pyrazole **16a** was slightly but significantly improved by microwave irradiation at 0 °C in cHCl–methanol (entry 1). The differences in chemical yield that was observed were attributed to the supply of extra energy by the oscillating field, which under acidic conditions must have led to an increase in the reaction rate.

Table 21. Comparing the isolated yields[a] of pyrazoles **16a** and **17a** with and without concurrent heating and cooling



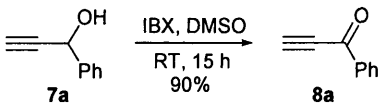
Entry	Solvent	Reagents and conditions	No irradiation		MW [b]	
			16a	**17a**	**16a**	**17a**
1	cHCl–MeOH	0 °C, 30 min	75	13	84	15
2	MeOH	0 °C, 15 min; then cHCl, 0 °C, 15 min.	83	13	82	11

[a] Isolated yields after chromatographic purification on silica.

[b] Concurrent heating and cooling was carried out using the CEM Discover® Coolmate™ apparatus by irradiating at 60 W power whilst circulating a coolant through the microwave cavity.

The experiments performed at sub–ambient temperature (with and without concurrent heating and cooling) gave only a slight improvement, if any, in the regioselectivity of reaction compared to the optimum microwave–assisted procedure (entry 10, Table 19).

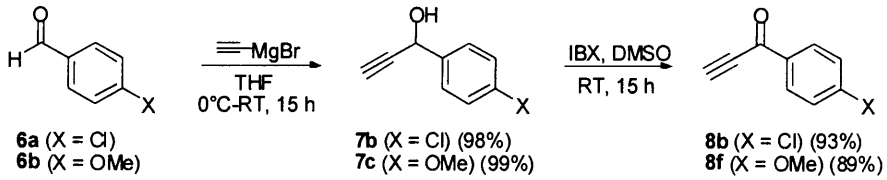
With conditions established for the microwave–assisted synthesis of pyrazoles in only 2 min, efforts were made to establish the scope of this new methodology. To this end a range of different alkynones and hydrazines were reacted to create a small library of pyrazoles. Non–commercially available aromatic alkynones were synthesized according to Scheme 30 and 31. Alkynone **8a** was obtained by oxidation of the corresponding propargylic alcohol **7a** according to the procedure described in Chapter 2 (Scheme 30).



Scheme 30. Synthesis of 1–phenyl–2–propyn–1–one **8a**

1–(4–Chlorophenyl)–2–propyn–1–one **8b** and 1–(4–methoxyphenyl)–2–propyn–1–one **8f** were obtained in two steps, by reacting the aromatic aldehyde (**6a** and **6b,** respectively) with ethynyl

magnesium bromide to give the corresponding propyn–1–ol (**7b** and **7c**, respectively), which was then converted to the corresponding propargylic ketone using IBX as the oxidizing agent.

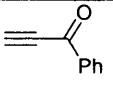
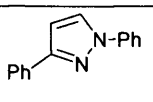
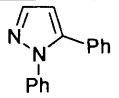
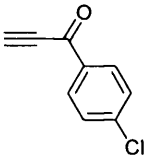
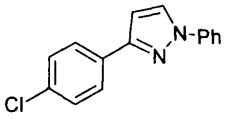
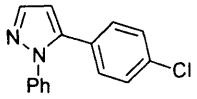
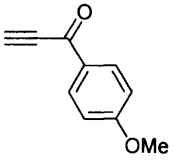
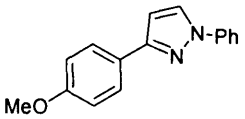
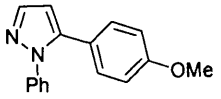
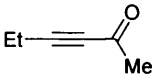
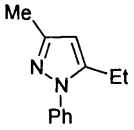
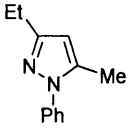
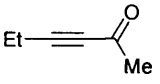
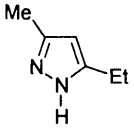
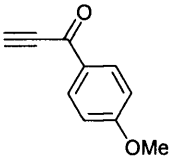
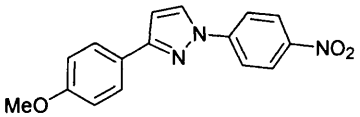
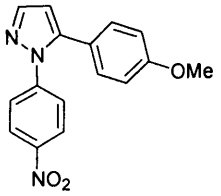
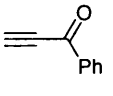
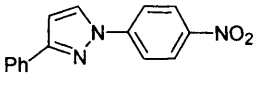
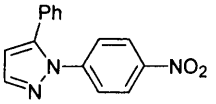
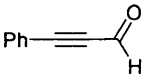
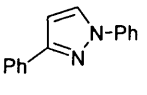
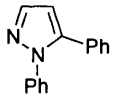
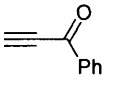
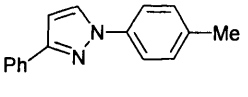
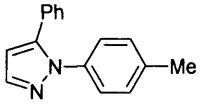


Scheme 31. Synthesis of propynones **8b** and **8f**

Hydrazine derivatives were reacted with either an ethynyl ketone or phenylpropargyl aldehyde by microwave irradiation at 120 °C for 2 min in cHCl–MeOH (1.5% v/v) and the pyrazole products separated by column chromatography (Table 22, Appendix D). All pyrazoles exhibited satisfactory spectroscopic and spectrometric data, by ^{1}H NMR, ^{13}C NMR, IR, MS and HRMS techniques.

A mixture of the two regioisomers was obtained in all experiments with the exception of 3–methyl–5–ethylpyrazole (entry 5) where a fast proton exchange takes place between the nitrogen atoms. Table 22 shows that reasonable overall yields were obtained but the regioselectivity of reaction varied considerably with substrate. 1,3–Regioisomers, which were always obtained as the major products, were identified with a downfield shift in the resonance of the pyrazole ring protons[83] by ^{1}H NMR spectroscopic analysis and by a red shift in their long wavelength absorption maxima, relative to the corresponding 1,5–isomers, presumably as a consequence of unfavourable steric interactions in the latter.[83] Qualitative NOESY effects were seen for 1,3–disubstituted pyrazoles (Table 22: entries 1, 6 and 8) between the aryl *ortho*–methine resonances and the pyrazole methine signals, the latter of which were well separated in chemical shift in the ^{1}H NMR spectrum of both pyrazole regioisomers. The trisubstituted pyrazoles (entry 4) showed NOESY effects between the aryl *ortho*–methine resonances and protons on the pyrazole 5–substituent.

Table 22. Microwave irradiation of hydrazine derivatives and ethynyl carbonyl compounds in cHCl–MeOH (1.5% v/v) at 120 °C for 2 min

Entry	Hydrazine	Alkynone	Isolated yields (%) of product(s)			
1	$PhNHNH_2$			76		15
2	$PhNHNH_2$			64		22
3	$PhNHNH_2$			50		30
4	$PhNHNH_2$			61		9
5	NH_2NH_2			83		
6 [a]	$4\text{-}O_2NC_6H_4NHNH_2$			58		23
7 [a]	$4\text{-}O_2NC_6H_4NHNH_2$			52		31
8	$PhNHNH_2$			58		28
9	$4\text{-}MeC_6H_4NHNH_2$			47		40

[a] Irradiation at 120 °C for 5 min (initial power 120 W).

The variation in regioisomer composition that was observed can be rationalized in accordance with the mechanistic findings of Miller and Reiser and Coispeau and Elguero (Scheme 25), and involves increased competition under acidic conditions of hydrazone formation by 1,2–addition which leads preferentially to the 1,3–disubstituted products. This preference would appear to be

less pronounced for the cyclocondensation of electron–rich ethynyl ketones at high temperature or in the absence of a strong acid, both of which promote the Michael addition–heterocyclization pathway. This mechanistic interplay is supported by earlier observations (Schemes 27 and 28) and would appear to be highly substrate dependent, although it can be controlled to give reasonable regioselectivities through the use of a strong Brønsted acid under microwave irradiation.

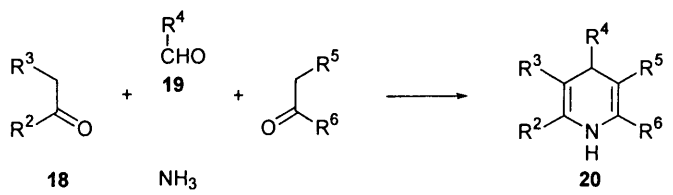
3.3.3 Conclusion

In conclusion, it was demonstrated that microwave irradiation of hydrazine derivatives and ethynyl ketones gives the corresponding pyrazoles in good yield with the major regioisomer generated according to the mechanistic rationale of Miller and Reiser. The process can be effected in one or two steps using concurrent heating and cooling and is complete in only 2 min in cHCl–methanol at 120 °C. With such short reaction times, this procedure offers an opportunity for facile transfer to a microwave flow reactor with continuous processing.

3.4 Hantzsch Pyridine Synthesis

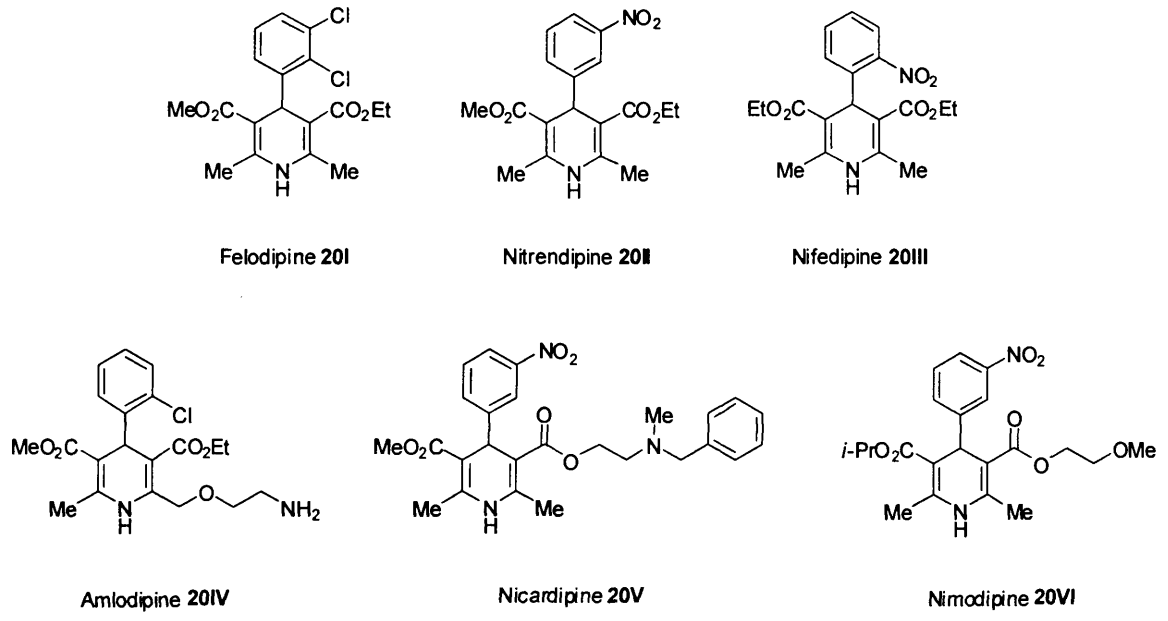
3.4.1 Introduction

The Hantzsch pyridine synthesis is a four component condensation reaction, that generates 1,4–dihydropyridine–3,5–dicarboxylate (1,4–DHP) derivatives **20** by condensation of an aldehyde **19**, β–keto ester **18** and ammonia (Scheme 32).



Scheme 32. Hantzsch dihydropyridine synthesis

First reported in 1881,[96] this multicomponent condensation reaction represents an important pathway to access 1,4–DHP derivatives with pharmacological activity.[97] The 1,4–DHP motif is found in a number of chemotherapeutic agents for the treatment of cardiovascular disease such as hypertension and angina pectoris.[98]



Scheme 33. Chemotherapeutic agents based upon 1,4–DHP derivatives for the treatment of cardiovascular disease

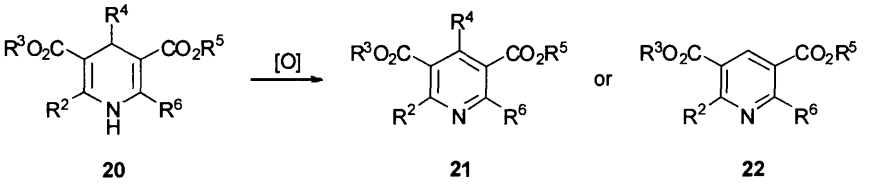
Examples of commercialized 1,4–DHP derivatives with chemotherapeutic activity include the 4–(2–chlorophenyl) derivatives felodipine **20I** and amlodipine **20IV**, 4–(2–nitrophenyl) DHP derivative nifedipine **20III** and 4–(3–nitrophenyl) derivatives nitrendipine **20II,** nicardipine **20V** and nimodipine **20VI**, amongst others[97] (Scheme 33). This important class of calcium channel antagonists has been proven to act by decreasing the passage of the transmembrane calcium current on binding, causing a long lasting relaxation in smooth muscle and reduction of contractility throughout the cardiac muscle.[99]

3.4.2 Oxidative Aromatization of Hantzsch 1,4–DHP Derivatives

3.4.2.1 Introduction

Aromatization of Hantzsch 1,4–DHP derivatives has attracted considerable attention since the discovery that the metabolism of these drugs involves an oxidation step catalyzed in the liver by cytochrome P–450.[100] The corresponding 1,4–dehydro derivatives, which are not pharmacological active, are further transformed by additional modification. The 1,4–DHP motif also features in hydride transfer biotransformations from the reduced nicotinamide adenine dinucleotide (NADH and NADPH) coenzymes, that mediate hydrogen transfer reactions in biological systems.[101] In addition, the oxidative aromatization of 1,4–DHP is also a useful synthetic approach to polysubstituted pyridines.

A wide variety of oxidants have been studied in the oxidative aromatization of 1,4-DHP derivatives, including urea nitrate and peroxydisulfate–Co(II),[102] clay supported ferric and cupric nitrate,[103] ceric ammonium nitrate,[104] pyridinium chlorochromate (PCC),[105] $BrCCl_3$/hv,[106] nitric acid,[107] nitric oxide,[108,109] *N*–methyl–*N*–nitroso–*p*–toluenesulfonamide,[109] 2,3–dichloro–5,6–dicyano–1,4–benzoquinone (DDQ),[110] $Bi(NO_3)_3$,[111] $Zr(NO_3)_4$,[112] $Mn(OAc)_3$,[113] Pd/C,[114] I_2/MeOH,[115] $KMnO_4$,[114b,116] *tert*–butyl hydroperoxide,[117] Co(II)–catalyzed auto oxidation,[118] CrO_3,[119] and nitrous acid,[120] amongst others.[121]

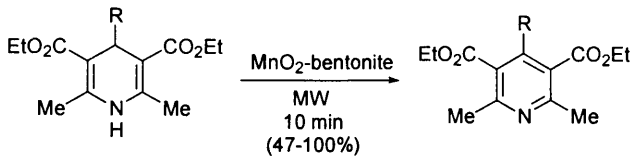


20 21 22

Scheme 34. Oxidative aromatization of 1,4–DHP derivatives

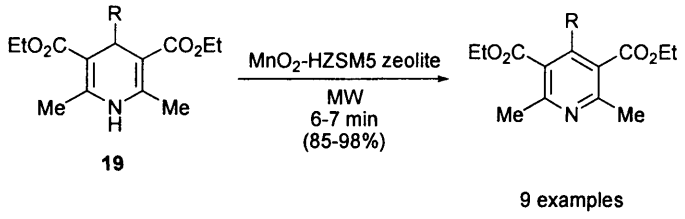
However, prolonged reaction times, poor yields and the competing oxidative dealkylation of 4–benzyl– and *sec*–alkyl–substituted DHP substrates,[120] generating the tetrasubstituted pyridine **22** (Scheme 34), have been observed and this has led to the investigation of many alternative procedures,[97,122] such as solvent free conditions,[107,111,121h] the use of sonication[103,110] and microwave heating,[97,102,107,110,111,114e,114h,123] in particular with MnO_2 as oxidant.[124,125] Alvarez and co-workers reported the first microwave–assisted method utilizing MnO_2 supported on Mexican

bentonite clay in a domestic oven (Scheme 35), giving the corresponding pyridines in 10 min and reasonable yield (47–100%).[124]



Scheme 35. Oxidative aromatization of 1,4–DHP derivatives with MnO_2 reported by Alvarez

A few years later, Heravi *et al.* reported the use of immobilized MnO_2 on HZSM–5 zeolite[125] as the oxidizing agent. The experiments were carried out by irradiating the reaction mixture for 6–7 min in a domestic microwave oven and after irradiation the mixture was washed with CH_2Cl_2 to recover the product. It was found that in the absence of an inorganic solid support incomplete reactions and alternative products were obtained (Scheme 36).

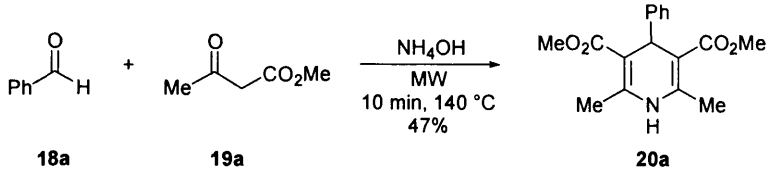


Scheme 36. Oxidative aromatization of 1,4–DHP with MnO_2 reported by Haravi

We now wish to report our own findings on new methods for the oxidative aromatization of 1,4–DHP derivatives that overcame these difficulties and prioritized the need for excellent yields using cheap, commercially available reagents coupled with microwave irradiation, to dramatically reduce reaction times.

3.4.2.2 Microwave–Assisted Aromatization of DHP Derivatives

The oxidative aromatization of 1,4–DHP **20a** was chosen as a model reaction. The substrate was synthesized by irradiating a mixture of benzaldehyde **18a**, methyl acetoacetate **19a** and aqueous ammonia for 10 min at 140 °C according to the conditions of Öhberg and Westman (Scheme 37).[126d]

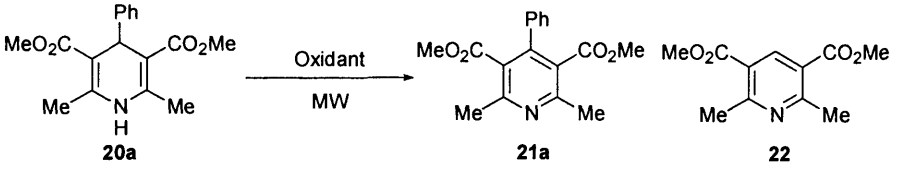


18a **19a** **20a**

Scheme 37. Microwave–assisted synthesis of 1,4–DHP **20a**

A range of different oxidants were investigated in order to find a rapid procedure for the oxidative aromatization of 1,4–DHP **20a** (Table 23).

Table 23. Exploring methods for the oxidative aromatization of 1,4–DHP



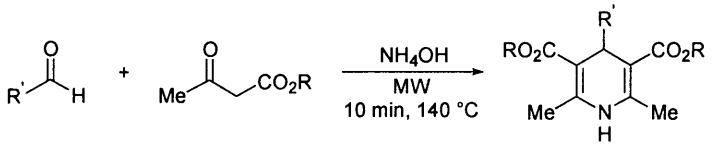
20a **21a** **22**

Entry	Oxidant	Solvent	Conditions [a]	Heating method	Results[b]
1	I_2	MeOH	24 h, reflux	Conductive	**21a** and **20a** (trace)
2	I_2	MeOH	20 min, 100 °C	MW	**21a** (trace)
3	Pd/C	AcOH	24 h, 80 °C	Conductive	**21a** and **20a** (trace)
4	Pd/C	AcOH	10 min, 120 °C	MW	**20a** and **21a** (trace)
5	Pd/C	AcOH	10 min, 180 °C	MW	**21a** and **22** (trace)
6	IBX	DMSO	1 min, 180 °C	MW	**21a** and by–products
7	IBX	$[Bmim]BF_4$	1 min, 150 °C	MW	**21a** and **20a** (17:1)
8	MnO_2	CH_2Cl_2	18 h, reflux	Conductive	**21a** (>98%)[c]
9	MnO_2	CH_2Cl_2	1 min, 100 °C	MW	**21a** (>98%)[c]

[a] Reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 150 W). [b] Results determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [c] Yield of pure isolated product

In accordance with Yadav's findings,[115] heating a methanolic solution of **20a** at reflux in the presence of iodine for 24 hours gave almost a complete conversion to pyridine **21a** (entry 1), whereas the use of microwaves failed to generate the product (entry 2). Similar results were obtained using Pd/C as oxidizing agent, where irradiation in acetic acid at 120 °C for 10 minutes gave only a trace of product (entry 4), in contrast to the high conversion observed under conductive heating methods as reported by Nakamichi *et al.* (entry 3).[114] However, increasing the temperature to 180 °C (entry 5) did promote the transformation but at these high temperatures a small amount of oxidative dealkylation also occurred, giving a mixture of products. The use of *o*–iodoxybenzoic acid (IBX) in DMSO was also investigated, but at 180 °C a mixture of products was obtained (entry 6). Carrying out the reaction at a lower temperature in the ionic liquid 1–butyl–3–methylimidazolium tetrafluoroborate ([Bmim]BF4) did overcome some of these difficulties (entry 7), but failed to effect complete conversion to pyridine **21a**.

Table 24. Synthesis of 1,4–DHP derivatives under microwave–assisted conditions



18a-i **19a,b** **20a-m**

Entry	R'	R	Product	Yield (%)[a]
1	Me	Ph	**20a**	47
2	Me	*p*–$C_6H_4NO_2$	**20b**	15
3	Me	*p*–C_6H_4Cl	**20c**	45
4	Me	*p*–C_6H_4OMe	**20d**	27
5	Et	Ph	**20e**	39
6	Et	*p*–$C_6H_4NO_2$	**20f**	36
7	Et	*p*–C_6H_4Cl	**20g**	45
8	Et	*p*–C_6H_4OMe	**20h**	23
9	Et	H	**20i**	54[b]
10	Et	Me	**20j**	21
11	Et	Et	**20k**	68
12	Et	*i*–Pr	**20l**	21
13	Et	CH_2Ph	**20m**	25

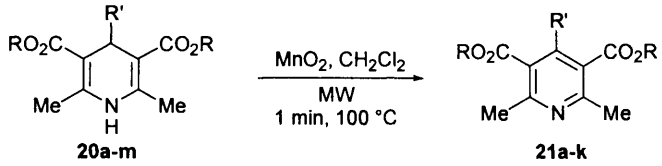
[a] Isolated yield of pure **20** after recrystallization. [b] A 3.5:1 crude mixture of 1,4-DHP **20i** and pyridine **21i** was obtained by 1H NMR spectroscopic analysis, which was then used directly without purification.

However, manganese dioxide was found to be a very efficient oxidant for this transformation either at reflux overnight under conductive heating (entry 8) or at 100 °C for 1 minute in a monomodal microwave synthesizer (entry 9). Under both conditions, pyridine **21a** was isolated in quantitative yield without the need for further purification. Our finding demonstrates that no inorganic support is required for efficient conversion, despite previous reports.[124,125]

In order to test substrate variability, a range of 1,4–DHP derivatives **20a–m** were irradiated under the same reaction conditions. The 1,4–DHP derivatives required for this study were obtained by microwave–assisted Hantzsch synthesis,[126] according to the conditions of Öhberg and Westman.[126d] A mixture of the aldehyde, β–keto ester and aqueous ammonia was irradiated at 140 °C to give the pure 1,4–DHP derivatives **20a–m** in poor to average yields following recrystallization (Table 24). Although the yields for these transformations were disappointing (15–68%) next to Öhberg's report,[126d] they did compare reasonably with those obtained using equivalent conductive heating procedures and gave the product in high purity, on the basis of a comparison of physical and spectroscopic properties with literature data. Interestingly, the irradiation of ethyl acetoacetate **19b**, formaldehyde **18i** and aqueous ammonia (entry 9) gave a mixture of 1,4–DHP **20i** and the corresponding pyridine **21i**, in a ratio of 3.5:1, respectively, indicating that for this substrate spontaneous oxidative aromatization occurs at least in part under the reaction conditions.

To this end, microwave–assisted oxidative aromatization was investigated on the range of DHPs synthesized in this fashion and in all cases an excellent yield of the corresponding pyridine **21** was obtained as shown in Table 25 (Appendix E). In the case of DHP derivative **20i**, which was generated in the Hantzsch reaction along with the corresponding pyridine **21i**, irradiating the crude mixture in the presence of MnO_2 completed the conversion to tetrasubstituted pyridine **21i**, which was isolated in 51% overall yield over the two steps. The 4–*i*Pr and 4–benzyl derivatives, **20l** and **20m** respectively, gave the product of oxidative dealkylation **21i** (entries 12 and 13). This observation is in accordance with the reported behavior of these derivatives under oxidative conditions.[97]

Table 25. Synthesis of pyridines **21a–k** by oxidative aromatization of 1,4–DHP derivatives **20a–m** using MnO_2 under microwave irradiation[a]



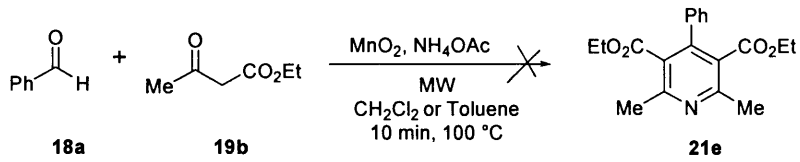
Entry	Substrate	Product	R	R'	Yield (%)[b]
1	**20a**	**21a**	Me	Ph	>98
2	**20b**	**21b**	Me	*p*–$C_6H_4NO_2$	99
3	**20c**	**21c**	Me	*p*–C_6H_4Cl	97
4	**20d**	**21d**	Me	*p*–C_6H_4OMe	96
5	**20e**	**21e**	Et	Ph	99
6	**20f**	**21f**	Et	*p*–$C_6H_4NO_2$	93
7	**20g**	**21g**	Et	*p*–C_6H_4Cl	94
8	**20h**	**21h**	Et	*p*–C_6H_4OMe	99
9	**20i**	**21i**	Et	H	94[c]
10	**20j**	**21j**	Et	Me	97
11	**20k**	**21k**	Et	Et	98
12	**20l**	**21i**	Et	H	91
13	**20m**	**21i**	Et	H	98

[a] Initial MW irradiation power of 150 W was moderated throughout the course of the reaction in order to maintain the required temperature.

[b] Isolated yield of pure **21.**

[c] A mixture of **20i** and **21i** was used (51% overall yield over 2 steps).

As an extension of this methodology, a one–pot tandem oxidation–heteroannulation process was investigated using MnO_2 as the oxidant. A mixture of benzaldehyde **18a**, ethyl acetoacetate **19b**, ammonium acetate and manganese dioxide in CH_2Cl_2 or toluene was irradiated for 10 min at 100 °C in order to access pyridine **21e** but no trace of product or DHP intermediate **20e** were observed (Scheme 38).



18a 19b 21e

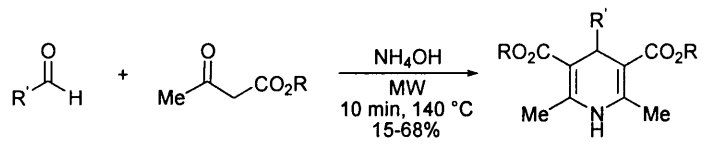
Scheme 38. Attempted one–pot synthesis of pyridine **21e**

3.4.2.3 Conclusion

In conclusion, microwave irradiation of 1,4–DHP derivatives at 100 °C in CH_2Cl_2 provides tetra– or pentasubstituted pyridines in only one minute without the use of an inorganic solid support. The reaction proceeds by either oxidative aromatization, for 4–aryl or linear primary 4–alkyl substrates, or oxidative dealkylation for 4–*sec*–alkyl or 4–benzyl substrates. This extremely facile and rapid process provides the target pyridines without the need for further purification and in excellent yield.

3.4.3 Hantzsch Dihydropyridine Synthesis

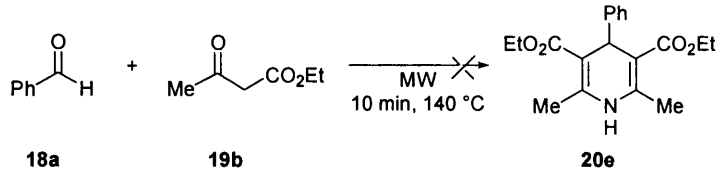
As previously reported (Table 24, Section 3.4.2.2), the Hantzsch 1,4–DHPs required for the oxidative aromatization study were obtained by microwave–assisted Hantzsch synthesis according to the conditions of Öhberg and Westman. Scheme 39 summarizes the results obtained irradiating a mixture of aldehyde **18a-i**, β–keto ester **19a,b** and aqueous ammonia at 140 °C. The pure 1,4–DHP derivatives **20a–m** were isolated in poor to average yields following recrystallization.



18a-i 19a,b 20a-m

Scheme 39. Microwave–assisted Hantzsch 1,4–DHP synthesis

In the search for a rapid and efficient procedure for Hantzsch dihydropyridine synthesis, a range of different conditions were studied. The addition of a Lewis acid ($ZnBr_2$) in toluene or the use of butylmethylimidazolium tetrafluoroborate ([Bmim]BF_4) as the solvent gave a mixture of product, starting materials and side products (Scheme 40).



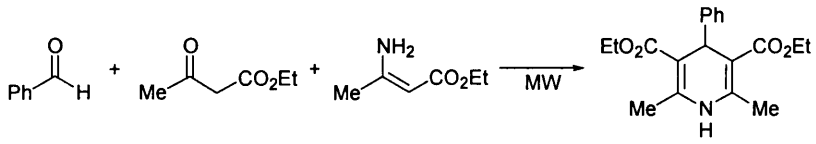
18a **19b** **20e**

Reagent and conditions: (a) NH_4OAc, $ZnBr_2$, Toluene; (b) NH_4OAc, [Bmim]BF_4

Scheme 40. Attempted optimization of the Hantzsch dihydropyridine synthesis

In order to simplify the transformation, one equivalent of keto ester **19b** was replaced with the corresponding enamine **10a** and the reaction time and temperature was varied but none of the conditions that were tried gave a cleaner reaction compared to the Öhberg–Westman conditions (Table 26).

Table 26. Attempted optimization of the Hantzsch 1,4-DHP synthesis

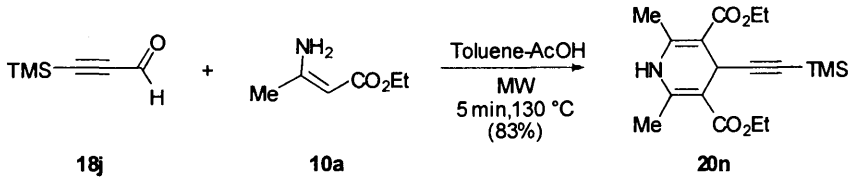


18a **19b** **10a** **20e**

Entry	Reagents and Conditions [a]	Result [b]
1	50 min, 120 °C	**20e** and starting materials
2	10 min, 140 °C	**20e** and side products
3	NH_4OAc, 10 min, 140 °C	**20e,** starting materials and side products
4	5 min, 140 °C	**20e** and starting materials
5	NH_4OAc, 5 min, 140 °C	**20e,** starting materials and side products
6	10 min, 130 °C	**20e** and starting materials
7	15 min, 140 °C	**20e** and starting materials
8	10 min, 150 °C	**20e** and starting materials
9	20 min, 140 °C	**20e** and starting materials

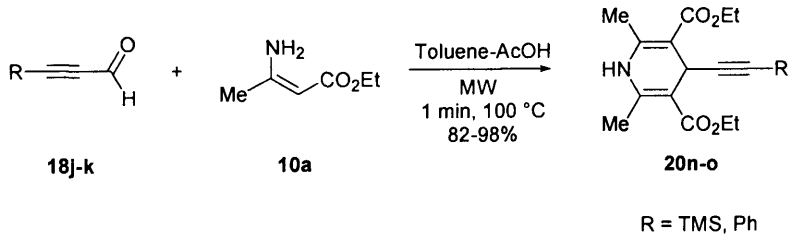
[a] Reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 150 W). [b] Results determined by ^1H NMR spectroscopic analysis of the crude reaction mixture

Following our own interest in the use of alkynones in synthesis, the condensation between propargylic aldehydes and an enamine was investigated. Then, a mixture of TMS–propargylic aldehyde **18j** and enamine **10a** was irradiated in toluene–acetic acid (5:1) for 5 min at 130 °C giving the Hantzsch DHP as the sole product in good purity (Scheme 41). This result was in accordance with the findings reported by Bohlmann and Rahtz in their description of a method for pyridine synthesis.[67] These authors observed that using phenyl propargyl aldehyde, the Hantzsch DHP was isolated as the product in high yield, whereas the Bohlmann–Rahtz pyridine was obtained using ethynyl ketones. Even when the reaction was tried under the classical Bohlmann–Rahtz conditions (EtOH, reflux, overnight) the only product provided was the Hantzsch DHP.



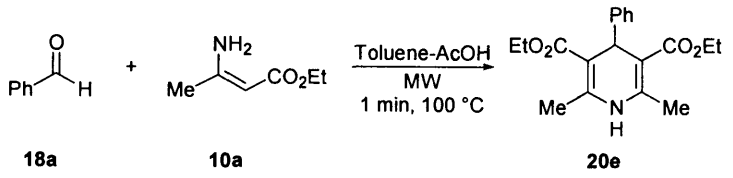
Scheme 41. Synthesis of Hantzsch DHPs from propargyl aldehyde **18j**

Our investigation supported this finding and showed that the reaction goes to completion in 1 minute providing DHP **20n** without the need for further purification in 82% yield (Scheme 42). Comparable results were obtained using phenyl propargyl aldehyde **18k**, where the corresponding DHP **20o** was isolated in 98% yield.



Scheme 42. Synthesis of Hantzsch DHPs under Bolhmann–Rahtz conditions

This procedure was then tested for the synthesis of DHP **20e**. A mixture of benzaldehyde **19a** and two equivalents of ethyl aminocrotonate **10a** in toluene–acetic acid (5:1) was irradiated for 1 minute at 100 °C (Scheme 43).

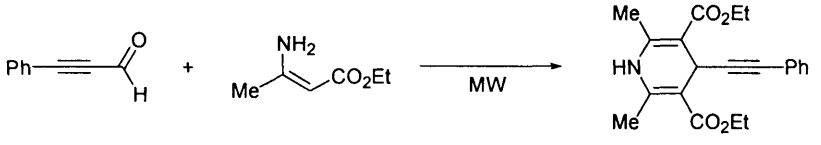


18a **10a** **20e**

Scheme 43. Attempted optimization of Hantzsch dihydropyridines synthesis

The result was a mixture of product **20e**, starting materials (**18a** and **10a**) and by–products, showing the use of a propargylic aldehyde rather than an aromatic or aliphatic aldehyde is responsible for the very high yield in this transformation.

Table 27. Investigation of new solvent for the synthesis of 1,4-DHP **20o** under homogeneous conditions



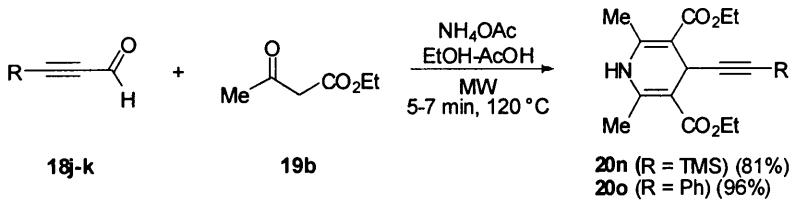
18k **10a** **20o**

Entry	Solvent	Conditions [a]	Solubility	Results
1	EtOH	15 min, 120 °C	Good	**20o** and starting materials[b]
2	AcOH	–	Poor	–
3	EtOH–AcOH	1 min, 100 °C	Good	**20o** (>98%)

[a] Reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 150 W)

[b] Results were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture

However the optimum conditions found for the synthesis of DHPs **20n** and **20o** were not transferable to a continuous flow process because of the insolubility of the starting materials in the solvent system. Thus different solvent systems were investigated, including ethanol, acetic acid and ethanol–acetic acid (Table 27). The first solvent tried was ethanol, the classic solvent for Hantzsch dihydropyridine synthesis, in which both starting materials and the product are soluble, but the reaction was not as clean and efficient as in toluene–acetic acid: after 15 minutes at 120 °C the reaction had not gone to completion (entry 1). The use of acetic acid as the solvent was not feasible because of the insolubility of the starting materials in this system (entry 2). Finally ethanol–acetic acid (5/1) was used giving the product in excellent yield and purity (entry 3). Hantzsch dihydropyridine synthesis in the latter solvent system showed the same efficiency as in toluene–acetic acid with the advantage of the homogeneous conditions required for a continuous flow process. Based on these findings the four component reaction was investigated by replacing the enamine **10a** with the corresponding β–keto ester **19b** and ammonium acetate (Scheme 44). The target DHP was obtained in a very short reaction time and excellent yield without the need for further purification.



18j-k **19b** **20n** (R = TMS) (81%)
20o (R = Ph) (96%)

Scheme 44. Four–component Hantzsch dihydropyridine synthesis

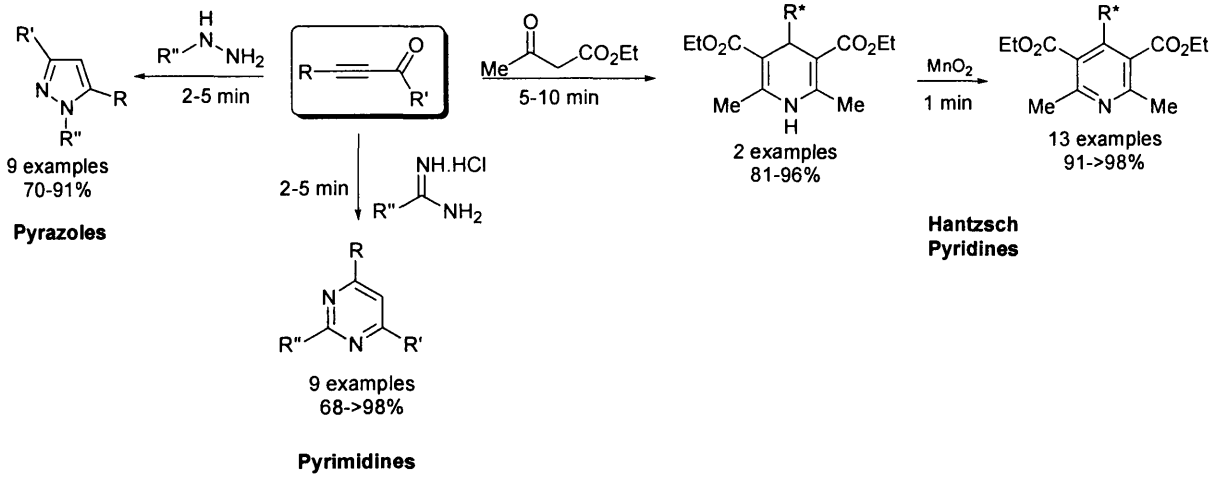
Scheme 44 shows the synthesis of 4–ethynyldihydropyridines **20n** and **20o** from two commercially available propargylic aldehydes, TMS–propargyl aldehyde **18j** and phenylpropargyl aldehyde **18k**. Diethyl 4–(TMS–ethynyl)–2,6–dimethyl–1,4–dihydro–3,5–pyridine dicarboxylate **20n** was obtained in 81% yield in 7 minutes by irradiating a solution of TMS-propargyl aldehyde **18j**, ethyl acetoacetate **19b**, ammonium acetate in ethanol–acetic acid (5:1) at 120 °C and diethyl 4–(phenylethynyl)–2,6–dimethyl–1,4–dihydro–3,5–pyridine dicarboxylate **20o** was obtained in 96% yield after 5 minutes of irradiation.

3.4.4 Conclusion

In conclusion it was found that phenylpropargyl aldehyde **18j** and TMS–propargyl aldehyde **18k** react very efficiently under microwave–assisted conditions to give the corresponding 1,4-DHPs **20n–o**. Furthermore, this transformation is ideal for transfer to continuous flow processing using our tube flow cell.

3.5 Conclusion

The use of ethynyl ketones in the synthesis of simple *N*–containing heterocycles was successfully applied to the synthesis of pyrimidines, pyrazoles and 1,4-dihydropyridines under microwave–assisted conditions (Scheme 45).



Scheme 45. Microwave-assisted synthesis of heterocycles

It was found that microwave irradiation of ethynyl ketones and hydrazine derivatives gives the corresponding pyrazoles in good yield with the 1,3–regioisomer generated as major product. In a one pot procedure, complete conversion to pyrazoles **16a-h** and **17a-h** was achieved within 2 min of irradiation at 120 °C. Using amidines as the nucleophile the same range of alkynones gives easy access to pyrimidines. The use of a strong base to liberate the free amidine facilitates the

process, giving the target pyrimidine **14a-i** in very good yield after 2–5 min of irradiation. In addition, from a preliminary study it would appear that propargylic aldehydes react more efficiently than aliphatic and aromatic aldehydes with enamines to form 1,4-DHP derivatives. Two examples of 4–ethynyldihydropyridines **20n** and **20o** were prepared using commercially available precursors. In an investigation of oxidants for the one-pot synthesis of Hantzsch pyridines, it was also found that MnO_2 is an excellent oxidizing agent for the oxidative aromatization of 1,4–DHP derivatives to the corresponding penta- or tetrasubstituted pyridines **20a–m**.

In conclusion, new efficient methods to access pyrimidines, pyrazoles, Hantzsch dihydropyridines and Hantzsch pyridines under microwave–assisted conditions in batch mode have been described. Efforts were made to find optimum condition for transfer to a continuous flow microwave reactor in order to evaluate the versatility of the tube flow cell developed within the group (see Chapter 2). This study will provide new procedures for access to useful heterocyclic building blocks in organic chemistry and more importantly, for clean and efficient large–scale synthesis and process research.

DISCUSSION: Microwave–Mediated Synthesis of N–Containing Heterocycles under CF Processes

4

4.1 Introduction

Following our own interest in the direct transfer of reactions from small to large scale, a prototype of a continuous flow cell was developed for use in a single–mode microwave synthesizer with direct temperature control using the instrument's in–built IR sensor. This design makes optimum use of the standing wave cavity to improve the energy efficiency of microwave assisted flow reactions. The cyclodehydration of aminodienones to access the Bohlmann–Rahtz pyridines was successfully transferred to continuous flow processing (see Chapter 2). To this end, new efficient procedures for the syntheses of pyrimidines, pyrazoles and 1,4–dihydropyridines were developed in batch mode under microwave–assisted conditions using ethynyl ketones as a common intermediate or precursor (see Chapter 3).

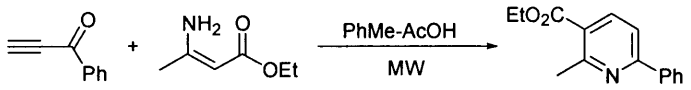
The direct transfer of these reactions from batch mode (carried out in a sealed tube in a monomodal microwave synthesizer) to continuous flow processing using the flow cell developed within the group and the transfer of this processing technology to laboratory large scale operations in a 80 mL flow cell are reported herein.

4.2 Synthesis of Heterocycles under Continuous Flow Processing

4.2.1 Bohlmann–Rahtz Pyridine Synthesis

In previous work, the cyclodehydration of aminodienones to access the Bohlmann–Rahtz pyridines has been optimized under microwave–assisted conditions in a sealed tube giving the product in quantitative yield in just two minutes using toluene as the solvent and acetic acid as the catalyst (see Chapter 2). In order to determine if a more direct process could be established, the condensation of enamine and alkynone, with *in situ* formation of aminodienone, has been investigated in order to find the optimum conditions for transfer to continuous flow microwave reactor. The effect of temperature on the 2–component Bohlmann–Rahtz pyridine synthesis is shown in Table 28. The synthesis of pyridine **12a** from alkynone **8a** and enamine **10a** was chosen as a test reaction for this process.

Table 28. Effect of temperature on the 2–component Bohlmann–Rahtz pyridine synthesis



8a **10a** **12a**

Entry	Conditions[a]	**8a**:**10a** ratio	Results[b]
1	10 min, 100 °C	1:1.2	**12a** and starting materials (trace)
2	15 min, 100 °C	1:1.2	**12a** and starting materials (trace)
3	1 min, 140 °C	1:1.2	**12a** and starting materials (trace)
4	3 min, 140 °C	1:1.2	**12a** and starting materials (trace)
5	5 min, 140 °C	1:1	**12a** and starting materials (trace)
6	5 min, 140 °C	1:1.2	**12a** (74%)[c]

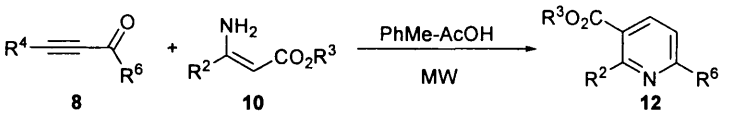
[a] Reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 120 W).

[b] Results determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

[c] Yield of pure isolated product.

Entry 6 shows the reaction goes to completion in 5 minutes at 140 °C providing the pyridine in 74% yield after chromatographic purification. These conditions were then applied to a range of different alkynones and enamines (Table 29).

Table 29. Effect of alkynone and enamine structure on the Bohlmann–Rahtz pyridine synthesis



Entry	R^4	R^6	R^2	R^3	Conditions [a]	Results [b]
1	H	Ph	Me	Et	5 min, 140 °C	**12a**, (74%) [c]
2	H	4–C_6H_4Cl	Me	Et	5 min, 140 °C	Product, intermediate and starting materials
3	H	4–C_6H_4Cl	Me	Et	7 min, 140 °C	Product and intermediate
4	H	4–C_6H_4OMe	Me	Et	5 min, 140 °C	Product, intermediate and starting materials
5	H	4–C_6H_4OMe	Me	Et	7 min, 140 °C	Product and side products
6	H	Ph	Ph	Et	5 min, 140 °C	Product, intermediate and starting materials
7	H	Ph	Ph	Et	7 min, 140 °C	Product and side products
8	TMS	Me	Me	Et	5 min, 140 °C	Starting materials, by–products and trace of product
9	TMS	Me	Me	Et	10 min, 140 °C	Starting materials, by–products and trace of product
10	TMS	Me	Me	*t*–But	5 min, 140 °C	Side products and trace of product
11	TMS	Me	Me	*t*–But	10 min, 140 °C	Side products and trace of product

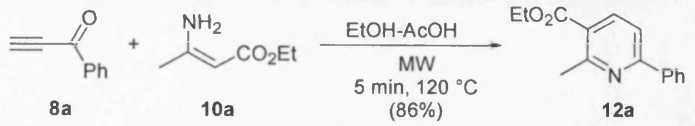
[a] Reactions were performed at the required reaction temperature through moderation of microwave power (initial power = 120 W).

[b] Results determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

[c] Yield of pure isolated product

None of the reagents tried give a clean and fast reaction with potential for transfer to a continuous flow process using the tube flow cell. It was also observed that the use of 4–(TMS)–3–butyn–2–one did not give the desired pyridine as major product, the crude ^{1}H–NMR spectrum showing just a trace of the corresponding pyridine and many side products (entries 8–11).

Consequently, a reinvestigation of the reaction conditions was deemed to be necessary. Based on the previous result obtained in the Hantzsch dihydropyridine synthesis (Scheme 44), ethanol–acetic acid (5:1) was selected as the solvent system of choice.



Scheme 46. Bohlmann–Rahtz pyridine synthesis in ethanol–acetic acid

Scheme 46 shows the target pyridine was obtained in a better yield compared to the same reaction carried out in toluene–acetic acid (Table 29). To this end, these conditions were investigated in the tube flow cell charged with sand using the set up shown in Figure 39 (see also Chapter 2), connecting a back pressure regulator (100 psi) to the outlet tube to perform the experiment under pressure.

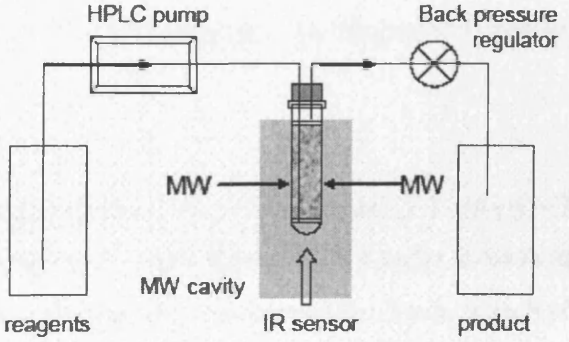
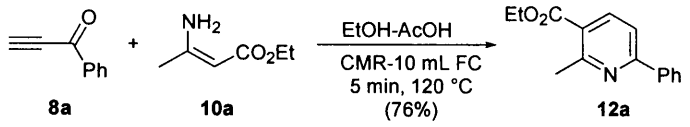


Figure 39. Diagram of the tube flow cell apparatus

The experiment was performed by priming the reactor with the solvent system, which was then irradiated and stabilized at the required reaction temperature through moderation of microwave power before the introduction of reagents into the reactor.



8a 10a 12a

Scheme 47. Bohlmann–Rahtz pyridine synthesis in the tube flow cell under CF processing

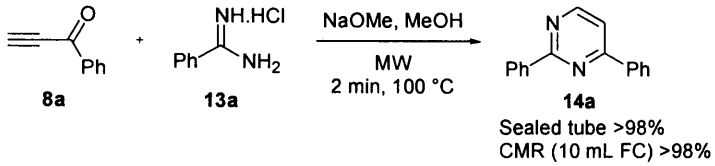
A flow rate of 0.6 mL/min ensured a residence time of 5 min in the microwave chamber (the volume of the tube FC filled with sand is 3 mL). Following the irradiation, the flow cell was washed with batches of solvent to recover the reaction mixture. The pyridine **12a** was obtained in 76% yield after chromatographic purification (Scheme 47), showing a slightly reduction in efficiency compared to the batch experiment (86%, see Scheme 46).

4.2.2 Pyrimidines, Pyrazoles and 1,4–Dihydropyridines

In previous work, new efficient procedures for the synthesis of pyrimidines, pyrazoles and 1,4–dihydropyridines were developed in batch mode under microwave–assisted conditions using ethynyl ketones as a common intermediate or precursor (see Chapter 3). In order for efficient transfer, efforts were made to find the optimum conditions for a continuous flow process.

4.2.2.1 Pyrimidines

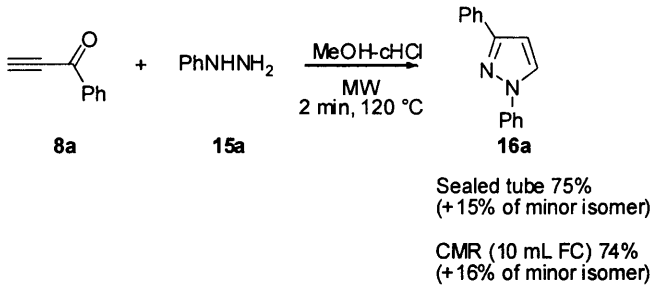
The synthesis of diphenylpyrimidine **14a** from 1–phenyl–1–propyn–2–one **8a** and benzamidine **13a** in MeOH was transferred to the tube flow cell. In order to have a homogeneous solution the benzamidine hydrochloride salt **13a**·HCl was stirred for 5 min with NaOMe, the resulting salt was filtered off and the solution was diluted with MeOH. The alkynone was added and the solution was passed through the microwave chamber using a flow rate of 1.5 mL/min. Pyridine **14a** was obtained in quantitative yield in both batch and continuous flow processes (Scheme 48).



Scheme 48. Comparison between batch and CF processes for the synthesis of pyrimidine **14a**

4.2.2.2 Pyrazoles

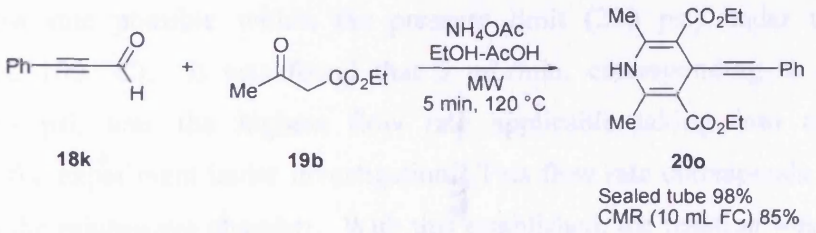
The synthesis of 1,5–diphenylpyrazoles was chosen as the next experiment for study. The process optimized in batch mode involved irradiating the reaction mixture for 2 min in MeOH–cHCl at 120 °C giving the pyrazole **16a** in 75% yield (plus 15% of the minor isomer **17a**). These conditions were then investigated in the CF tube reactor and were found to give the product with near identical efficiency and regioselectivity (Scheme 49).



Scheme 49. Comparison between batch and CF processes for the synthesis of pyrazole **16a**

4.2.2.3 Hantzsch 1,4–Dihydropyridines

The last process tested was the four–component Hantzsch 1,4–dihydropyridine **20o** synthesis. Scheme 50 shows that even if the product was obtained in good yield the reaction does not perform as efficiently as in batch mode in a similar fashion to the results obtained by study of the Bohlmann–Rathz pyridine synthesis (see Scheme 47).



18k 19b 20o

Sealed tube 98%
CMR (10 mL FC) 85%

Scheme 50. Comparison of the four–component Hantzsch DHP synthesis in a sealed tube and CMR

4.3 Towards Large Scale Processes

Based on the promising results obtained with the 10 mL tube flow cell developed within the group it was decided to set up an 80 mL flow cell in order to perform these reactions on a larger scale. Figure 40 shows the 80 mL flow cell filled with sand (left) and the flow cell inserted into the microwave chamber of the CEM Discover® (centre). The temperature was monitored using a fibre optic sensor inserted in the centre of the flow cell and the pressure device (Figure 40, right) allowed to monitor the pressure in the flow cell, generated by the back pressure regulator (100 psi) which was connected to the outlet tube. The volume of the cell filled with sand was found to be 16.5 mL and the maximum pressure was 200 psi.

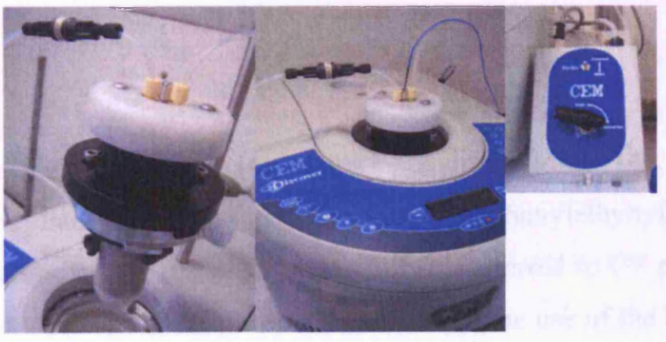
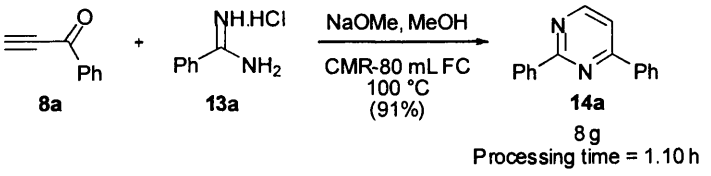


Figure 40. 80 mL flow cell set up (left and centre) and pressure device (right)

Among the different reactions performed in the 10 mL tube flow cell, the 2,4–diphenylpyrimidine **14a** synthesis was chosen as reaction of study because of its high efficiency, short reaction time and ease of work–up. The first course of study in the use of this new flow cell was to investigate

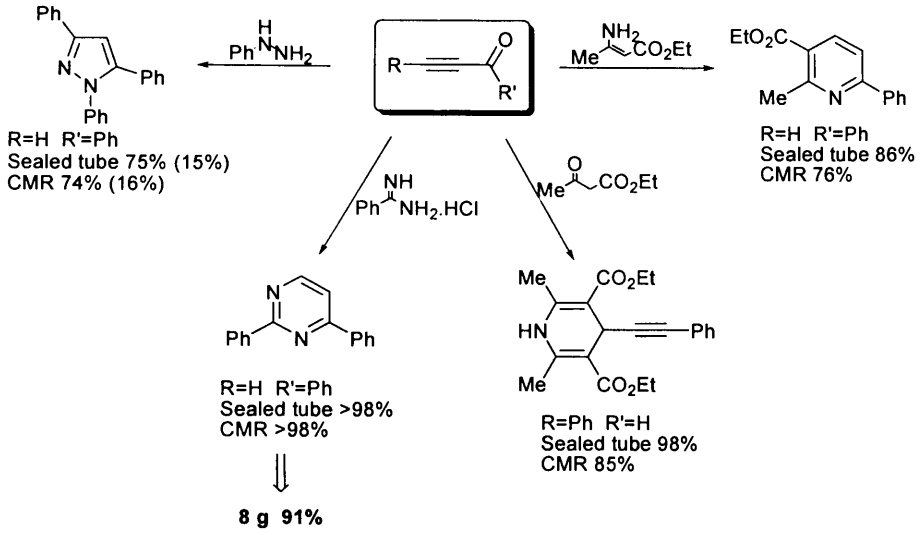
the maximum flow rate possible within the pressure limit (200 psi) under these reaction conditions (MeOH, 100 °C). It was found that 5 mL/min, corresponding to a pressure of approximately 150 psi, was the highest flow rate applicable taking into account safety considerations for the experiment under investigation. This flow rate corresponds to a residence time of 3.5 min in the microwave chamber. With this established, the reaction was transferred to the 80 mL flow cell keeping the same concentration used in the small scale experiment. During the experiment the pressure raised to 200 psi and the safety device halted the irradiation. Blockage was detected neither in the lines nor in the back pressure regulator. The raise in pressure was due to product crystallization in the flow cell that presumably blocked the microchannels through the sand. The experiment was then repeated diluting the sample and under these conditions the reaction was successfully performed on an 8 g scale, giving pyrimidine **14a** in 91% yield after a total processing time of 1.10 h (Scheme 51).



Scheme 51. Large scale synthesis of pyrimidine **14a** in an 80 mL tube flow cell

4.4 Conclusion

The synthesis of 1,3–diphenylpyrazole **16a**, 2,4-diphenylpyrimidine **14a**, ethyl 2–methyl–6–phenylpyridine–3–carboxylate **12a** and diethyl 4–(phenylethynyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20o** was successfully transferred to CF process using the CF microwave reactor developed within the group (Scheme 52). The use of the 80 mL tube flow cell allowed the synthesis of 8 g of product in 1 h processing time showing the potential for large scale application of this prototype reactor.



Scheme 52. Comparison between batch and CF processes

CONCLUSION

5

In conclusion, a new prototype CF microwave reactor (based on both a 10 mL and 80 mL flow cell) was developed for use with a monomodal instrument. It was demonstrated that the glass tube CF reactor offers higher processing rates and improved performance over commercial Teflon heating coils and a microreactor. New efficient methods for the microwave–assisted synthesis of pyrazoles, pyrimidines, B–R pyridines and Hantzsch DHPs were developed using alkynones as a common precursor and then successfully transferred to CF processing using the CF microwave reactor developed within the group. The use of the 80 mL tube flow cell allowed the synthesis of 8 g of product in 1 h processing time, demonstrating its potential in the large scale application of this prototype. All the reactions were directly transferred from batch to CF process with little if any modification.

This study provided an assortment of new processes for the synthesis of structural motifs of biological and pharmaceutical importance and expanded the versatility of microwave–assisted chemistry showing the feasibility of direct scaling up from batch to continuous flow processing.

EXPERIMENTAL

6

6.1 Experimental Techniques

Commercially available reagents were used without further purification; solvents were dried by standard procedures. Light petroleum refers to the fraction with b.p. 40–60 °C. Column chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Analytical thin layer chromatography was carried out using aluminium–backed plates coated with Merck Kieselgel 60 GF_{254} that were visualised under UV light (at 254 and/or 360 nm) and/or potassium permanganate stain. Melting points (mp) were determined on a Kofler hot stage apparatus and are uncorrected. Infra–red (IR) spectra were recorded in the range 4000–600 cm^{-1} on a Perkin–Elmer 1600 series FTIR spectrometer using nujol mull for solid samples and thin films between NaCl plates for liquid samples. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ at 25 °C unless stated otherwise using a Bruker DPX 400 instrument operating at 400 MHz for ^1H spectra and 100 MHz for ^{13}C spectra and were reported in ppm; *J* values were recorded in Hz and multiplicities were expressed by the usual conventions (s = singlet, d = doublet, t = triplet, app = apparent, m = multiplet). Low–resolution mass spectra (MS) were determined using a Fisons VG Platform II Quadrupole instrument using atmospheric pressure chemical ionization (APcI) unless otherwise stated. ES refers to electrospray ionization, CI refers to chemical ionization (ammonia) and EI refers to electron impact. High–resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at Swansea, UK using the ionisation methods specified. *In vacuo* refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump. Microwave experiments were carried out in a CEM Discovery® microwave synthesizer at the temperature and initial power stated.

6.2 General Experimental Procedures

6.2.1 General procedure for the synthesis of propargylic alcohols from aldehydes. A solution of aldehyde (5.0 mmol) in dry THF (10 mL) was added dropwise to a stirred solution of ethynylmagnesium bromide in THF (0.5 M; 15 mL, 7.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h, warmed to room temperature and stirred overnight. Saturated aqueous NH_4Cl solution (2 mL) was added, the mixture was evaporated *in vacuo* and partitioned between Et_2O (30 mL) and saturated aqueous NH_4Cl solution (30 mL). The ethereal layer was washed with brine (30 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the crude *aldehyde*.

6.2.2 General procedure for the oxidation of propargylic alcohols to alkynones using IBX. A solution of *o*–iodoxybenzoic acid (IBX) (9.9 mmol) in DMSO (150 mL) was stirred for 15 min at room temperature until homogeneous. A solution of propargylic alcohol (7.6 mmol) in DMSO (10 mL) was added and the mixture was stirred for 16 h. H_2O (30 mL) was added and the mixture was stirred at room temperature for 10 min, cooled in ice and partitioned between H_2O (100 mL) and Et_2O (80 mL). The mixture was filtered through Celite® and the aqueous layer was further extracted with Et_2O (40 mL). The organic extracts were combined, washed sequentially with H_2O (3 x 40 mL), saturated aqueous $NaHCO_3$ (60 mL) and brine (60 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the crude *alkynone*.

6.2.3 General procedure for the synthesis of aminodienones by Michael addition of enamines and alkynones. A solution of enamine (5.8 mmol) and alkynone (7.5 mmol) in EtOH (80 mL) was stirred at 50 °C for 1–7 h, cooled and evaporated *in vacuo* to give the crude *aminodienone*.

6.2.4 General procedure for the microwave–assisted cyclodehydration of aminodienones in a sealed tube. A solution of aminodienone (0.31 mmol) in toluene–glacial acetic acid (5:1; 3 mL) was irradiated for 2 min at 100 °C in a CEM Discover® microwave synthesizer at an initial power of 150 W. The solution was allowed to cool and partitioned between saturated aqueous $NaHCO_3$ (25 mL) and AcOEt (25 mL). The aqueous layer was further extracted with AcOEt (2 x 15 mL), the combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the crude *pyridine*.

6.2.5 General procedure for the microwave–assisted cyclodehydration of aminodienone in a heating coil reactor. The Teflon heating coil flow cell was primed with toluene–glacial acetic acid (5:1) at a flow rate of 1.0 mL/min, irradiated at an initial power of 300 W and stabilized

at100 °C. A flask was charged with a solution of aminodienone (0.31 mmol) in toluene–glacial acetic acid (5:1, 3 mL), which was then passed through the cavity at the given flow rate and washed with further batches of solvent. The reaction mixture was quenched in a solution of saturated aqueous $NaHCO_3$, extracted with AcOEt (3 x 30 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the crude *pyridine*.

6.2.6 General procedure for the microwave–assisted cyclodehydration of aminodienones in a glass tube reactor. The glass tube flow cell (10 mL) filled with sand (~12 g) was primed with toluene–glacial acetic acid (5:1) at a flow rate of 1.5 mL/min, irradiated at an initial power of 200 W and stabilized at 100 °C. A flask was charged with a solution of aminodienone (0.31 mmol) in toluene–glacial acetic acid (5:1, 3 mL), which was then passed through the cavity at the given flow rate, washing with further batches of solvent. The reaction mixture was quenched in a solution of saturated aqueous $NaHCO_3$, extracted with AcOEt (3 x 30 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the crude *pyridine*.

6.2.7 General procedure for the cyclodehydration of aminodienones in a microreactor. A solution of aminodienone (0.1 M) in toluene–glacial acetic acid (5:1) was flowed through a microfluidic reaction chip using a Syrris AFRICA® microreactor, heated at 100 °C for 4 min. The reaction mixture was quenched in a solution of saturated aqueous $NaHCO_3$, extracted with AcOEt (3 x 30 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the crude *pyridine*.

6.2.8 General procedure for the microwave–assisted pyrimidine synthesis: A mixture of amidine hydrochloride salt (1.2 mmol) and sodium methoxide (25 wt%; 1.3 mmol) was stirred for 5 min at room temperature then diluted with MeOH (5 mL). Ethynyl ketone (1.0 mmol) was added and the mixture was irradiated for 2–5 min at 100 °C in sealed tube using a self–tunable CEM Discover® microwave synthesizer at an initial power of 150 W. The solution was evaporated under reduced pressure and the crude residue partitioned between H_2O and AcOEt and the aqueous layer was further extracted with AcOEt. The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give the crude *pyrimidine*.

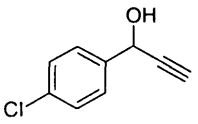
6.2.9 General procedure for the microwave–assisted pyrazole synthesis: A solution of hydrazine (0.46 mmol) and ethynyl ketone (0.46 mmol) in cHCl–MeOH (1.5% *v/v*) (3 mL) was irradiated in a sealed tube at 120 °C for 2 min using a CEM Discover single–mode microwave synthesizer, by moderating the initial microwave power (120 W). After cooling in a stream of compressed air, the solution was evaporated *in vacuo* to give the crude *pyrazole*.

6.2.10 General procedure for the microwave–assisted Hantzsch dihydropyridine synthesis.[126d] A mixture of aldehyde (2.5 mmol), β–ketoester (12.5 mmol) and 35% aqueous ammonium hydroxide (10.0 mmol) was irradiated for 10 min at 140 °C in a CEM Discover® microwave synthesizer at an initial power of 150 W. The mixture was allowed to cool and evaporated *in vacuo* to give the crude *dihydropyridine*.

6.2.11 General procedure for the microwave–assisted Hantzsch dihydropyridine aromatization using manganese dioxide. A mixture of 1,4–dihydropyridine (0.2 mmol) and manganese dioxide (2 mmol) in CH_2Cl_2 (1 mL) was irradiated for 1 min at 100 °C in a CEM Discover microwave synthesizer at an initial power of 150 W. The solution was allowed to cool, filtered though Celite® and evaporated *in vacuo* to give the crude *Hantzsch pyridine*.

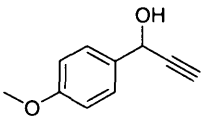
6.3 Experimental Procedures

1–(4–Chlorophenyl)–2–propyn–1–ol (7b)



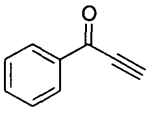
4–Chlorobenzaldehyde **6a** (1 g, 7.3 mmol) and a solution of ethynylmagnesium bromide in THF (0.5 M; 22 mL, 11 mmol) were reacted according to general procedure **6.2.1** to give the *title compound*[69b] as a pale yellow oil (1.21 g, 98%) (Found: $M^{\cdot+}$, 166.0180. C_9H_7ClO [$M^{\cdot+}$] requires 166.0180); R_f = 0.27 (CH_2Cl_2); IR (film)/cm^{-1} 3422, 2891, 2124, 1642, 1597, 1495, 1411, 1262, 1198, 1090, 1011, 953, 909, 846, 799, 737, 654; ^1H NMR (400 MHz; $CDCl_3$) δ 7.52 (2H, app d, *J* 8.4, *o*–Ph*H*), 7.35 (2H, app d, *J* 8.4, *m*–Ph*H*), 5.42 (1H, s, 1–H), 2.66 (1H, s, 3–H), 2.31 (1H, s, OH); ^{13}C NMR (100 MHz; $CDCl_3$) δ 139.1 (C), 134.0 (C), 128.6 (CH), 128.2 (CH), 83.5 (CH), 75.2 (C), 64.2 (CH); *m/z* (EI) 166 ($M^{\cdot+}$, 11%), 164 (25), 111 (15), 53 (100).

1–(4–Methoxyphenyl)–2–propyn–1–ol (7c)



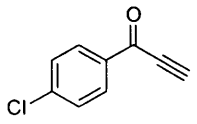
p–Anisaldehyde **6b** (1 g, 7.3 mmol) and a solution of ethynylmagnesium bromide in THF (0.5 M; 22 mL, 11 mmol) were reacted according to general procedure **6.2.1** to give the *title compound* [127] as a pale yellow oil (1.17 g, 99%) (Found: $M^{\cdot+}$, 161.0595. $C_{10}H_{11}O_2$ [$M^{\cdot+}$] requires 161.0597); R_f = 0.10 (CH_2Cl_2); IR (film)/cm^{-1} 3442, 3003, 2940, 2831, 1617, 1509, 1466, 1444, 1302, 1251, 1179, 1111, 1033, 952, 831, 768; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.52 (2H, app d, *J* 8.5, *o*–Ph*H*), 6.86 (2H, app d, *J* 8.5, *m*–Ph*H*), 5.44 (1H, s, 1–H), 3.82 (3H, s, OCH_3), 2.61 (1H, s, 3–H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 160.1 (C), 135.2 (C), 128.4 (CH), 115.0 (CH), 84.3 (CH), 74.5 (C), 64.7 (CH), 55.0 (CH_3); *m/z* (EI) 162 ($M^{\cdot+}$, 100%), 161 (50), 145 (32), 131 (42), 89 (60), 53 (45).

1–Phenyl–2–propyn–1–one (8a)



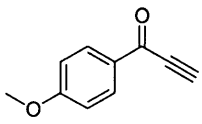
1–Phenyl–2–propyn–1–ol **7a** (2.8 g, 21 mmol) was reacted according to general procedure **6.2.2** to give the *title compound* as a pale yellow solid (2.5 g, 90%), mp 48–50 °C (MeOH) (lit.[68] mp 47–48 °C) (Found: $M^{\cdot+}$, 130.0411. C_9H_6O [$M^{\cdot+}$] requires 130.0413); R_f = 0.44 (CH_2Cl_2); IR (nujol)/cm^{-1} 1647, 1591, 1583, 1452, 1314, 1269, 1170, 1004, 696; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.09 (2H, m, *o*–Ph*H*), 7.56 (1H, m, *p*–Ph*H*), 7.40 (2H, m, *m*–Ph*H*), 3.37 (1H, s, CH); ^{13}C NMR (100 MHz; $CDCl_3$) δ 177.5 (C), 136.1 (C), 134.6 (CH), 129.7 (CH), 128.7 (CH), 80.9 (C), 80.3 (CH); *m/z* (EI) 130 ($M^{\cdot+}$, 156%), 102 (21), 77 (32), 53 (100), 51 (40).

1–(4–Chlorophenyl)–2–propyn–1–one (8b)



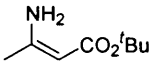
1–(4–Chlorophenyl)–2–propyn–1–ol **7b** (2.8 g, 21 mmol) was reacted according to general procedure **6.2.2** to give the *title compound* as a pale yellow solid (2.50 g, 93%), mp 67–68 °C (MeOH) (lit.[76a] mp 68–69 °C) (Found: M^+, 164.0023. $C_9H_5{}^{35}ClO$ [M^+] requires 164.0023); R_f = 0.45 (CH_2Cl_2); IR (nujol)/cm^{-1} 1661, 1470, 1383, 1250, 1090, 1012, 729; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.01 (2H, app d, *J* 8.5, *o*–Ph*H*), 7.40 (2H, app d, *J* 8.5, *m*–Ph*H*), 3.41 (1H, s, CH); ^{13}C NMR (100 MHz; $CDCl_3$) δ 176.8 (C), 141.1 (C), 135.2 (C), 131.5 (CH), 129.0 (CH), 81.1 (C), 78.0 (CH); *m/z* (EI) 166 ([$C_9H_5{}^{37}ClO$]$^{\cdot+}$, 10%), 164 ([$C_9H_5{}^{35}ClO$]$^{\cdot+}$, 23), 138 (12), 136 (34), 113 (3), 111 (12), 75 (38), 53 (100).

1–(4–Methoxyphenyl)–2–propyn–1–one (8f)



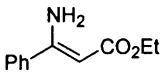
1–(4–Methoxyphenyl)–2–propyn–1–ol **7c** (2.8 g, 21 mmol) was reacted according to the general procedure **6.2.2** to give the *title compound* as a pale yellow solid (2.24 g, 89%), mp 85–86 °C (MeOH) (lit.[128] mp 81–83 °C) (Found: MH^+, 161.0599. $C_{10}H_9O_2$ [M^+] requires 161.0597); R_f = 0.29 (CH_2Cl_2); IR (nujol)/cm^{-1} 2120, 1640, 1603, 1570, 1517, 1429, 1250, 1167, 1122, 1022, 851, 762, 711, 689; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.07 (2H, app d, *J* 8.8, *o*–Ph*H*), 6.89 (2H, app d, *J* 8.8, *m*–Ph*H*), 3.86 (3H, s, OCH_3), 3.31 (1H, s, CH); ^{13}C NMR (100 MHz; $CDCl_3$) δ 176.0 (C), 164.8 (C), 132.2 (CH), 129.6 (CH), 114.0 (CH), 80.4 (C), 80.1 (C), 55.7 (CH_3); *m/z* (APcI) 161 (MH^+, 100%), 145 (13).

(*Z*)–*tert*–Butyl β–aminocrotonate (10b)



Ammonium hydroxide solution (35%, 40 mL) was added to a mixture of *tert*–butyl acetoacetate **9a** (4 ml, 24.2 mmol) in MeOH (40 mL) and stirred at room temperature for 16 h. After cooling, the solution was evaporated *in vacuo* and partitioned between water (20 mL) and Et_2O (20 mL). The aqueous layer was further extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound*[129] as a pale yellow oil (3.44 g, 91%) (Found: MH^+, 158.1177. $C_8H_{16}NO_2$, [MH^+] requires 158.1176); R_f = 0.14 (light petroleum–EtOAc, 3:1); IR (film)/cm^{-1} 3550, 3344, 2983, 2923, 1662, 1621, 1569, 1455, 1394, 1360, 1294, 1152, 987, 788; ^1H NMR (400 MHz; $CDCl_3$) δ 8.12 (1H, br s, NH*H*), 4.70 (1H, br s, N*H*H), 4.45 (1H, s, CH), 1.84 (3H, s, CH_3), 1.49 (9H, s, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (C), 158.8 (C), 85.9 (CH), 78.2 (C), 28.6 (CH_3), 22.3 (CH_3); *m/z* (APcI) 158 (MH^+, 82%).

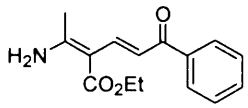
(*Z*)–Ethyl 3–amino–3–phenylpropenoate (10c)



Ammonium acetate (6.71 g, 85 mmol) was added to a solution of ethyl benzoylacetate **9b** (2.78 g, 14.4 mmol) and the mixture was heated at reflux in toluene–glacial acetic acid (5:1; 20 mL) for 16 h. After partitioning between water (50 mL) and Et_2O (30 mL), the aqueous layer was further extracted with Et_2O (2 x 15 mL) and the combined organic extracts were washed sequentially with saturated aqueous sodium hydrogen carbonate solution (25 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound*[130] as a pale yellow oil (2.37 g, 86%) (Found: MH^+, 192.1023. $C_{11}H_{14}NO_2$, [MH^+] requires 192.1025); R_f = 0.11 (light petroleum–

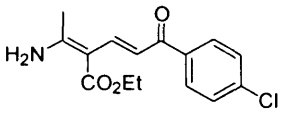
EtOAc, 3:1); IR (film)/cm^{-1} 3444, 3332, 2977, 2938, 1659, 1621, 1555, 1494, 1366, 1175, 1091, 1032, 798, 774, 695; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.42 (1H, br s, NH*H*), 7.35–7.11 (5H, PhH), 7.03 (1H, br s, N*H*H), 4.77 (1H, s, CH), 3.97 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 1.07 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (C), 160.4 (C), 137.7 (C), 130.2 (CH), 128.9 (CH), 126.2 (CH), 84.6 (CH), 59.0 (CH_2), 14.5 (CH_3); *m/z* (APcI) 192 (MH^+, 100%), 146 (22).

(2*Z*,4*E*)–2–Amino–3–ethoxycarbonyl–6–phenylhexadien–6–one (11a)



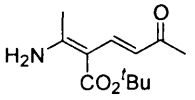
Ethyl β–aminocrotonate **10a** (1.65 g, 5.8 mmol) and 1–phenyl–2–propyn–1–one **8a** (2.0 g, 7.5 mmol) were reacted for 1 h according to general procedure **6.2.3**. Purification by column chromatography on SiO_2, eluting with EtOAc–light petroleum (8:2), gave the *title compound* as a yellow solid (2.83 g, 73%), mp 159–161 °C (light petroleum–EtOAc) (lit.[131] mp 164 °C) (Found: MH^+, 260.1279. $C_{15}H_{18}NO_3$, [MH^+] requires 260.1281); R_f = 0.38 (EtOAc–light petroleum, 8:2); IR (nujol)/cm^{-1} 3339, 1625, 1584, 1537, 1499, 1379, 1350, 1322, 1287, 1223, 1207, 1178, 1111, 1058, 1036, 1022, 982, 848, 707, 628; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.71 (1H, br s, NH*H*), 7.95 (2H, m, *o*–Ph*H*), 7.88 (1H, d, *J* 15.1, 4–H), 7.45 (3H, *m,p*–Ph*H*), 7.42 (1H, d, *J* 15.1, 5–H), 5.73 (1H, br s, N*H*H), 4.22 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 2.31 (3H, s, CH_3), 1.37 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 191.0 (C), 169.8 (C), 166.7 (C), 141.0 (CH), 139.7 (C), 131.8 (CH), 128.3 (CH), 128.1 (CH), 115.8 (CH), 95.5 (C), 60.0 (CH_2), 22.6 (CH_3), 14.5 (CH_3); *m/z* (APcI) 260 (MH^+, 100%), 243 (26), 214 (18).

(2*Z*,4*E*)–2–Amino–3–ethoxycarbonyl–6–(4–chlorophenyl)hexadien–6–one (11b)



Ethyl β–aminocrotonate **10a** (0.6 g, 4.7 mmol) and–(4–chlorophenyl)–2–propyn–1–one **8b** (1.0 g, 6.1 mmol) were reacted for 1 h according to general procedure **6.2.3**. Purification by column chromatography on SiO_2, eluting with with EtOAc–light petroleum (8:2), gave the *title compound* as a yellow solid (1.2 g, 88%), mp 164–165 °C (light petroleum–EtOAc) (Found: MH^+, 294.0892. $C_{15}H_{17}ClNO_3$, [MH^+] requires 294.0891); R_f = 0.51 (EtOAc–light petroleum, 8:2); IR (nujol)/cm^{-1} 3348, 1655, 1628, 1596, 1570, 1542, 1488, 1353, 1321, 1289, 1224, 1175, 1122, 1089, 1058, 1040, 1011, 976, 855, 823, 745, 717, 646, 588, 537, 501; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.68 (1H, br s, NH*H*), 7.86 (1H, d, *J* 15.0, 4–H), 7.86 (2H, app d, *J* 8.4, 2',6'–Ph*H*), 7.35 (2H, app d, *J* 8.4, 3',5'–Ph*H*), 7.31 (1H, d, *J* 15.0, 5–H), 5.81 (1H, br s, N*H*H), 4.23 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 2.27 (3H, s, CH_3), 1.35 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 189.6 (C), 169.7 (C), 167.0 (C), 141.6 (CH), 138.1 (C), 138.0 (C), 129.5 (CH), 128.6 (CH), 115.1 (CH), 95.6 (C), 60.1 (CH_2), 22.6 (CH_3), 14.5 (CH_3); *m/z* (APcI) 296 (MH^+, 32%), 294 (MH^+, 100), 277 (17), 260 (18).

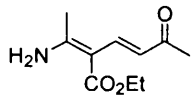
(2*Z*,4*E*)–2–Amino–3–*tert*–butoxycarbonylheptadien–6–one (11c)



tert–Butyl β–aminocrotonate **10b** (0.5 g, 3.2 mmol) and 4–(trimethylsilyl)–3–butyn–2–one **8c** (0.89 g, 6.4 mmol) were reacted for 6 h according to general procedure **6.2.3**. Purification by column chromatography on SiO_2, eluting with light petroleum–EtOAc (1:1), gave the *title compound* as a pale yellow solid (47 mg, 65%), mp 142–144 °C (light petroleum–EtOAc) (Found:

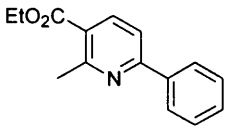
MH^+, 226.1441. $C_{12}H_{20}NO_3$, [MH^+] requires 226.1438); R_f = 0.26 (light petroleum–EtOAc, 1:1); IR (nujol)/cm^{-1} 3344, 1654, 1543, 1488, 1442, 1360, 1321, 1289, 1221, 1161, 1103, 1031; ^1H NMR (400 MHz; $CDCl_3$) δ 9.65 (1H, br s, NH*H*), 7.47 (1H, d, *J* 15.3, 4–H), 6.41 (1H, d, *J* 15.3, 5–H), 5.41 (1H, br s, N*H*H), 2.19 (3H, s, CH_3), 2.20 (3H, s, CH_3), 1.46 (9H, s, CMe_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 199.2 (C), 169.6 (C), 165.3 (C), 139.5 (CH), 121.3 (CH), 96.0 (C), 81.1 (C), 28.3 (CH_3), 28.2 (CH_3), 22.4 (CH_3); *m/z* (APcI) 226 (MH^+, 98%), 209 (56), 170 (83), 153 (100).

(2*Z*,4*E*)–2–Amino–3–ethoxycarbonylheptadien–6–one (11d)



Ethyl β–aminocrotonate **10a** (1.0 g, 7.74 mmol) and 4–(trimethylsilyl)–3–butyn–2–one **8c** (1.63 g, 0.01 mol) were reacted for 6 h according to general procedure **6.2.3**. Purification by column chromatography on SiO_2, eluting with EtOAc–light petroleum (8:2), gave the *title compound* as a pale yellow solid (1.1 g, 69%), mp 135–137 °C (light petroleum–EtOAc) (lit.[68] mp 135 °C) (Found: MH^+, 198.1127. $C_{10}H_{16}NO_3$, [MH^+] requires 198.1125); R_f = 0.29 (EtOAc–light petroleum, 8:2); IR (nujol)/cm^{-1} 3332, 1648, 1554, 1489, 1443, 1352, 1310, 1277, 1200, 1183, 1111, 1023; ^1H NMR (400 MHz; $CDCl_3$) δ 9.62 (1H, br s, NH*H*), 7.52 (1H, d, *J* 15.4, 4–H), 6.49 (1H, d, *J* 15.4, 5–H), 5.53 (1H, br s, N*H*H), 4.20 (2H, q, *J* 7.1, OCH_2CH_3), 2.22 (3H, s, CH_3), 2.15 (3H, s, CH_3), 1.27 (3H, t, *J* 7.1, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 199.4 (C), 169.3 (C), 165.9 (C), 139.2 (CH), 121.1 (CH), 94.5 (C), 60.1 (CH_2), 28.2 (CH_3), 22.8 (CH_3), 14.2 (CH_3); *m/z* (APcI) 198 (MH^+, 100%), 180 (57).

Ethyl 2–methyl–6–phenylpyridine–3–carboxylate (12a)



I. Cyclodehydration of aminodienone using toluene–acetic acid as solvent system. (2*Z*,4*E*)–2–Amino–3–ethoxycarbonyl–6–phenylhexadien–6–one **11a** (80 mg, 0.31 mmol) was reacted according to general procedures **6.2.4**, **6.2.5**, **6.2.6** and **6.2.7** to give the *title compound* as a pale yellow solid (74 mg, >98%; 74 mg, >98%; 74 mg, >98%; respectively).

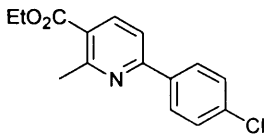
II. Cyclodehydration of aminodienone using ethanol–acetic acid as the solvent system under microwave irradiation. A solution of (2*Z*,4*E*)–2–amino–3–ethoxycarbonyl–6–phenylhexadien–6–one **11a** (80 mg, 0.31 mmol) in ethanol–glacial acetic acid (5:1; 3 mL) was irradiated for 2 min at 100 °C in a CEM Discover microwave synthesizer at an initial power of 90 W. The solution was evaporated under reduced pressure and the residue partitioned between saturated aqueous $NaHCO_3$ solution (25 mL) and DCM (25 mL). The aqueous layer was further extracted with DCM (2 x 15 mL), the combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound* as a pale yellow solid (74 mg, >98%)

III. Cyclodehydration of aminodienone catalysed by montmorillonite K–10 in a glass tube microwave reactor. A glass tube flow cell (10 mL) filled with montmorillonite K–10 (~4.5 g) was primed with ethanol at a flow rate of 1.5 mL/min, irradiated at an initial power of 150 W and stabilized at 70 °C. A flask was charged with a solution of (2*Z*,4*E*)–2–amino–3–ethoxycarbonyl–6–phenylhexadien–6–one **11a** (0.42 g, 1.60 mmol) in ethanol (20 mL), which was then passed through the cavity at the given flow rate for 40 min. The inlet line to the HPLC pump was placed in the reaction mixture along with the outlet line from the flow cell, creating a closed–loop system. The reaction mixture was irradiated for 40 min and then a saturated solution of NH_3 in MeOH was passed through the flow cell. The reaction mixture was evaporated under reduced pressure and partitioned between H_2O (25 mL) and ethyl acetate (25 mL). The aqueous layer was further extracted with ethyl acetate (2 x 15 mL), dried (Na_2SO4) and evaporated *in vacuo* to give the *title compound* as a yellow solid (0.38 g, 97%).

IV. Two–component Bohlmann–Rahtz pyridine synthesis in a sealed tube. A solution of ethyl β–aminocrotonate **10a** (52 mg, 0.40 mmol) and 1–phenyl–2–propyn–1–one **8a** (40 mg, 0.31 mmol) in ethanol–glacial acetic acid (5:1; 3 mL) was irradiated for 5 min at 120 °C in a CEM Discover® microwave synthesizer at an initial power of 90 W. The solution was evaporated under reduced pressure and the residuum partitioned between saturated aqueous $NaHCO_3$ (25 mL) and AcOEt (25 mL). The aqueous layer was further extracted with AcOEt (2 x 15 mL), the combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the crude *pyridine*. Purification by column chromatography on SiO_2, eluting with light petroleum–EtOAc (8:2), gave the *title compound* as a pale yellow solid (64 mg, 86%).

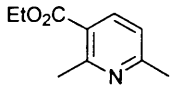
V. Two–component Bohlmann–Rahtz pyridine synthesis in a glass tube microwave reactor. The pressure–rated glass tube flow cell (10 mL) filled with sand (~12 g) was primed with ethanol–glacial acetic acid (5:1) at a flow rate of 0.6 mL/min, irradiated at an initial power of 100 W and stabilized at 120 °C. A flask was charged with a solution of ethyl β–aminocrotonate **10a** (52 mg, 0.40 mmol) and 1–phenyl–2–propyn–1–one **8a** (40 mg, 0.31 mmol) in ethanol–glacial acetic acid (5:1; 3 mL), which was then passed through the cavity at the given flow rate, washing with further batches of solvent. The reaction mixture was quenched in a solution of saturated aqueous $NaHCO_3$, extracted with dichloromethane (3 x 30 mL), dried ($NaSO_4$) and evaporated *in vacuo* to give the crude compound. Purification by column chromatography on SiO_2, eluting with light petroleum–EtOAc (8:2), gave the *title compound* as a pale yellow solid (56 mg, 76%), mp 44–45 °C (aq. EtOH) (lit.[67] mp 44 °C); (Found: MH^+, 242.1176. $C_{15}H_{16}NO_2$ [MH^+] requires 242.1176); R_f = 0.47 (light petroleum–EtOAc, 8:2); IR (nujol)/cm^{-1} 1717, 1581, 1476, 1277, 1090 and 1022; ^1H NMR (400 MHz; $CDCl_3$) δ 8.21 (1H, d, *J* 8.2, 4–H), 8.00 (2H, m, *o*–Ph*H*), 7.59 (1H, d, *J* 8.2, 5–H), 7.41 (3H, m, *m.p*–Ph*H*), 4.28 (2H, q, *J* 7.1, OCH_2CH_3), 2.85 (3H, s, CH_3), 1.35 (3H, t, *J* 7.1, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ(ppm) 165.7 (C), 159.1 (C), 158.1 (C), 138.5 (CH), 137.6 (C), 128.7 (CH), 128.0 (CH), 127.6 (CH),122.8 (C), 116.5 (CH), 60.3 (CH_2), 24.6 (CH_3), 13.5 (CH_3); *m/z* (APcI) 242 (MH^+, 100%), 214 (50).

Ethyl 2–methyl–6–(4–chlorophenyl)pyridine–3–carboxylate (12b)



(2*Z*,4*E*)–2–Amino–3–ethoxycarbonyl–6–(4–chlorophenyl)hexadien–6–one **11b** (91 mg, 0.31 mmol) was reacted according to general procedures **6.2.4**, **6.2.5**, **6.2.6** and **6.2.7** to give the title compound as a pale yellow solid (85 mg, >98%; 85 mg, >98%; 85 mg, >98%; respectively); mp 46–47 °C (aq. EtOH) (lit.[76a] mp 47–48 °C) (Found: MH^+, 276.0787. $C_{15}H_{15}ClNO_2$ [MH^+] requires 276.0786); R_f = 0.68 (light petroleum–EtOAc, 1:1); IR (nujol)/cm^{-1} 1725, 1588, 1497, 1465, 1362, 1258, 1185, 1163, 1091, 1015, 899, 828, 784, 742, 701; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.31 (1H, d, *J* 8.0, 4–H), 7.98 (2H, app d, *J* 8.4, 2',6'–Ph*H*), 7.49 (1H, d, *J* 8.0, 5–H), 7.43 (2H, app d, *J* 8.4, 3',5'–Ph*H*), 4.42 (2H, q, *J* 7.1, OCH_2CH_3), 1.63 (3H, s, CH_3), 1.37 (3H, t, *J* 7.1, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.4 (C), 160.8 (C), 158.2 (C), 139.1 (CH), 134.2 (C), 136.0 (C), 128.9 (CH), 128.3 (CH), 124.4 (C), 117.8 (CH), 60.7 (CH_2), 24.6 (CH_3), 14.5 (CH_3); *m/z* (APcI) 278 (MH^+, 33%), 276 (MH^+, 100), 250 (18), 248 (56).

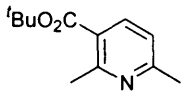
Ethyl 2,6–dimethylpyridine–3–carboxylate (12c)



(2*Z*,4*E*)–2–Amino–3–ethoxycarbonylheptadien–6–one **(11c)** (81 mg, 0.41 mmol) was reacted according to general procedures **6.2.4**, **6.2.5**, **6.2.6** and **6.2.7** to give the *title compound* as a pale yellow solid (59 mg, 80%; 63 mg, 85%; 71 mg, 96%; respectively), mp 59–60 °C (ethanol) (lit.[67] mp 60 °C) (Found: MH^+, 180.1020. $C_{10}H_{14}NO_2$, [MH^+] requires 180.1019); R_f = 0.44 (light petroleum–EtOAc, 1:1); IR (nujol)/cm^{-1} 1730, 1593, 1272, 1236, 1148, 1079, 770, 722; ^{1}H NMR

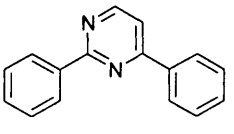
(400 MHz; $CDCl_3$) δ 8.05 (1H, d, *J* 8.1, 4–H), 7.05 (1H, d, *J* 8.1, 5–H), 4.33 (2H, q, *J* 7.1, OCH_2CH_3), 2.78 (3H, s, CH_3), 2.52 (3H, s, CH_3), 1.34 (3H, t, *J* 7.1, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.9 (C), 161.5 (C), 159.0 (C), 138.3 (CH), 122.5 (C), 120.9 (CH), 61.8 (CH_2), 25.1 (CH_3), 24.4 (CH_3), 13.7 (CH_3); *m/z* (APcI) 180 (MH^+, 95%), 152 (100), 134 (20).

tert–Butyl 2,6–dimethylpyridine–3–carboxylate (12d)



(2*Z*,4*E*)–2–Amino–3–*tert*–butoxycarbonylheptadien–6–one **(11d)** (86 mg, 0.38 mmol) was reacted according to general procedures **6.2.4**, **6.2.5**, **6.2.6** and **6.2.7** to give the title compound as a pale yellow oil[68] (65 mg, 82%; 69 mg, 87%; 79 mg, >98%; respectively); (Found: MH^+, 208.1329. $C_{12}H_{18}NO_2$, [MH^+] requires 208.1332); R_f = 0.59 (light petroleum–EtOAc, 1:1); IR (film)/cm^{-1} 2925, 2850, 1721, 1598, 1464, 1377, 1281, 1177, 1140, 1083, 775, 722; ^1H NMR (400 MHz; $CDCl_3$) δ 7.94 (1H, d, *J* 8.0, 4–H), 6.89 (1H, d, *J* 8.0, 5–H), 2.71 (3H, s, CH_3), 2.44 (3H, s, CH_3), 1.56 (9H, s, CMe_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.9 (C), 161.2 (C), 158.4 (C), 139.3 (CH), 124.1 (C), 120.8 (CH), 82.0 (C), 27.9 (CH_3), 25.4 (CH_3), 24.8 (CH_3); *m/z* (APcI) 208 (MH^+, 10%), 152 (100), 134 (10).

2,4–Diphenylpyrimidine (14a)



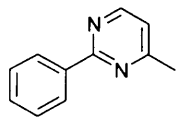
I. Synthesis in a sealed tube under microwave irradiation. Benzamidine hydrochloride salt **13a** (0.19 g, 1.2 mmol), sodium methoxide (25 wt%; 71 mg, 1.3 mmol) and 1–phenyl–2–propyn–1–

one **8a** (0.13 g, 1.0 mmol) were reacted for 2 min according to general procedure 6.2.8 to give the title compound as a pale yellow solid (0.12 g, 99%).

II. Synthesis in a glass tube microwave reactor. The glass tube flow cell (10 mL) filled with sand (~12 g) was primed with methanol at a flow rate of 1.5 mL/min, irradiated at an initial power of 200 W and stabilized at 100 °C. A flask was charged with a solution of benzamidine hydrochloride salt **13a** (0.19 g, 1.2 mmol), sodium methoxide (25 wt%; 71 mg, 1.3 mmol) and 1–phenyl–2–propyn–1–one **8a** (0.13 g, 1.0 mmol) in methanol (3 mL), which was then passed through the cavity at the given flow rate, washing with further batches of solvent. The reaction mixture was evaporated and the residue partitioned between H_2O and ethyl acetate. The aqueous layer was further extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound* as a pale yellow solid (0.12 g, >98%).

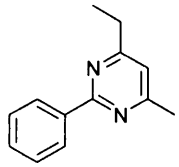
III. Synthesis in an 80 mL glass tube microwave reactor. The glass tube flow cell (80 mL) filled with sand (~86g) was primed with methanol at a flow rate of 5 mL/min, irradiated at an initial power of 200 W and stabilized at 100 °C. A flask was charged with a solution of benzamidine hydrochloride salt **13a** (7.35g, 46.2 mmol), sodium methoxide (25 wt%; 2.7 g, 50 mmol) and 1–phenyl–2–propyn–1–one **8a** (5 g, 38.5 mmol) in methanol (350 mL), which was then passed through the cavity at the given flow rate, washing with further batches of solvent. The reaction mixture was evaporated and the residue partitioned between H_2O and ethyl acetate. The aqueous layer was further extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were dried ($NaSO_4$) and evaporated *in vacuo* to give the *title compound* as a pale yellow solid (8.03 g, 91 %), mp 72–73 °C (aq. MeOH) (lit.[132] mp 71 °C); (Found: MH^+, 233.1074. $C_{16}H_{12}N_2$, [MH^+] requires 233.1073); R_f = 0.35 (light petrol–Et_2O, 1:1); IR (nujol)/cm^{-1} 1585, 1542, 1490, 1421, 1276, 1168, 1072, 1026, 747, 689; ^1H NMR (400 MHz; $CDCl_3$) δ 8.75 (1H, d, *J* 5.2 Hz, 4–H), 8.52 (2H, m, *o*–Ph*H*), 8.12 (2H, m, *o*–Ph*H*), 7.47 (1H, d, *J* 5.2 Hz, 5–H), 7.40 (6H, m, Ph*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ 165.0 (C), 164.3 (C), 158.3 (CH), 138.3 (C), 137.3 (C), 131.4 (CH), 131.1 (CH), 129.4 (CH), 129.0 (CH), 128.7 (CH), 127.6 (CH), 115.0 (CH); *m/z* (APcI) 233 (MH^+, 100%).

2–Phenyl–4–methylpyrimidine (14b)



Benzamidine hydrochloride salt **13a** (0.19 g, 1.2 mmol), sodium methoxide (25 wt%; 71 mg, 1.3 mmol) and 4–trimethylsilyl–3–butyn–2–one **8c** (0.14 g, 1.0 mmol) were reacted for 5 min according to general procedure **6.2.8** to give the *title compound* as a yellow oil[133] (0.155 g, 91%), (Found: MH^+, 171.0918. $C_{11}H_{11}N_2$, [MH^+] requires 171.0917); R_f = 0.40 (light petroleum–Et_2O, 1:1); IR (film)/cm^{-1}3065, 3040, 2922, 1587, 1572, 1458, 1423, 1385, 1290, 1249, 1172, 1070, 1028, 830, 750, 694; ^1H NMR (400 MHz; $CDCl_3$) δ 8.58 (1H, d, *J* 5.1 Hz, 4–H), 8.34 (2H, m, *o*–Ph*H*), 7.41 (3H, m, *m,p*–Ph*H*), 6.96 (1H, d, *J* 5.1 Hz, 5–H), 2.52 (3H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.7 (C), 164.8 (C), 157.2 (CH), 138.2 (C), 130.9 (CH), 128.9 (CH), 128.5 (CH), 119.0 (CH), 24.9 (CH_3); *m/z* (ES) 171 (MH^+, 100%).

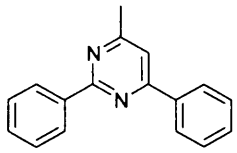
2–Phenyl–4–ethyl–6–methylpyrimidine (14c)



Benzamidine hydrochloride salt **13a** (0.19 g, 1.2 mmol), sodium methoxide (25 wt%; 71 mg, 1.3 mmol) and 3–hexyn–2–one **8d** (96 mg, 1.0 mmol) were reacted for 5 min according to general procedure **6.2.8** to give the *title compound* as a yellow oil[133] (0.167 g, 84%), (Found: MH^+, 199.1232. $C_{13}H_{15}N_2$, [MH^+] requires 199.1230); R_f = 0.64 (light petroleum–Et_2O, 1:1); IR (film)/cm^{-1}3064, 2971, 2995, 1591, 1574, 1543, 1440, 1373, 1173, 1068, 1028, 919, 863, 752, 696; ^1H NMR (400 MHz; $CDCl_3$) δ 8.37 (2H, m, *o*–Ph*H*), 7.40 (3H, m, *m,p*–Ph*H*), 6.84 (1H, s,

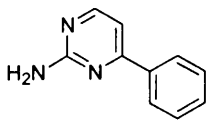
CH), 2.77 (2H, q, *J* 7.6 Hz, C*H*$_2$CH$_3$), 2.46 (3H, s, CH$_3$), 1.26 (3H, t, *J* 7.6 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; CDCl$_3$) δ 172.0 (C), 167.3 (C), 164.5 (C), 138.7 (C), 130.6 (CH), 128.8 (CH), 128.6 (CH), 117.1 (CH), 31.3 (CH$_3$), 24.7 (CH$_2$), 13.2 (CH$_3$); *m/z* (ES) 199 (MH$^+$, 100%).

2,4–Diphenyl–6–methylpyrimidine (14d)



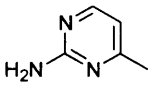
Benzamidine hydrochloride salt **13a** (0.19 g, 1.2 mmol), sodium methoxide (25 wt%; 71 mg, 1.3 mmol) and 4–phenyl–3–propyn–2–one **8e** (0.11 g, 1.0 mmol) were reacted for 5 min according to general procedure **6.2.8** to give the *title compound* as a pale yellow solid (0.185 g, 75%), mp 94–95 °C (aq. MeOH) (lit.[134] mp 92–94°C); (Found: MH$^+$, 247.1232. $C_{17}H_{15}N_2$, [*MH*$^+$] requires 247.1230); R_f = 0.56 (light petroleum–Et$_2$O, 1:1); IR (nujol)/cm^{-1} 1590, 1572, 1534, 1212, 1175, 1071, 1027, 856, 778, 748, 694; ^{1}H NMR (400 MHz; CDCl$_3$) δ 8.53 (2H, m, *o*–Ph*H*), 8.13 (2H, m, *o*–Ph*H*), 7.49–8.41 (7H, m, *m,p*–Ph*H* and CH), 2.55 (3H, s, CH$_3$); ^{13}C NMR (100 MHz; CDCl$_3$) δ 168.2 (C), 164.7 (C), 164.1 (C), 138.5 (C), 137.6 (C), 131.1 (CH), 130.9 (CH), 129.3 (CH), 128.9 (CH), 128.8 (CH), 127.6 (CH), 114.4 (CH), 25.1 (CH$_3$); *m/z* (ES) 247 (MH$^+$, 100%).

2–Amino–4–phenylpyrimidine (14e)



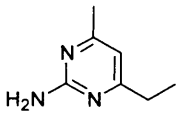
Guanidine hydrochloride salt **13b** (0.11 g, 1.2 mmol), sodium methoxide (25 wt%; 71 mg, 1.3 mmol) and 1–phenyl–2–propyn–1–one **8a** (0.13 g, 1.0 mmol) were reacted for 5 min according to general procedure **6.2.8** to give the *title compound* as a yellow solid (0.154 g, 90%), mp 160–161 °C (aq. MeOH) (lit.[135] mp 162–163 °C); (Found: MH^+, 172.0869. $C_{10}H_{10}N_3$, [MH^+] requires 172.0869); R_f = 0.38 (AcOEt); IR (nujol)/cm^{-1} 3309, 3156, 1652, 1558,1334, 1296, 1217, 823, 768, 702; ^{1}H NMR (400 MHz; MeOD) δ 8.18 (1H, d, *J* 5.3 Hz, 4–H), 7.95 (2H, m, *o*–Ph*H*), 7.38 (3H, m, *m,p*–Ph*H*), 7.03 (1H, d, *J* 5.3 Hz, 5–H), ^{13}C NMR (100 MHz; $CDCl_3$) δ 165.9 (C), 163.7 (C), 159.2 (CH), 137.6 (C), 131.0 (CH), 129.2 (CH), 127.4 (CH), 108.2 (CH); *m/z* (ES) 172 (MH^+, 100%).

2–Amino–4–phenylpyrimidine (14f)



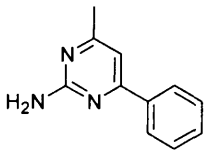
Guanidine hydrochloride salt **13b** (0.11 g, 1.2 mmol), sodium methoxide (25 wt%; 71 mg, 1.3 mmol) and 4–trimethylsilyl–3–butyn–2–one **8c** (0.14 g, 1.0 mmol) were reacted for 5 min according to general procedure **6.2.8** to give the *title compound* as a yellow solid (93 mg, 85%), mp 158–160 °C (aq. MeOH) (lit.[135] mp 155–157 °C); (Found: MH^+, 110.0713. $C_5H_8N_3$, [MH^+] requires 110.0713); R_f = 0.15 (AcOEt); IR (nujol)/cm^{-1} 3316, 3160, 1666, 1561; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.07 (1H, d, *J* 5.1 Hz, 4–H), 6.41 (1H, d, *J* 5.1 Hz, 5–H), 5.18 (2H, br s, NH_2), 2.25 (3H, m, CH_3), ^{13}C NMR (400 MHz; $CDCl_3$) δ 168.7 (C), 163.3 (C), 158.3 (CH), 111.5 (CH), 24.4 (CH_3); *m/z* (ES) 110 (MH^+, 100%).

2–Amino–4–methyl–6–ethylpyrimidine (14g)



Guanidine hydrochloride salt **13b** (0.11 g, 1.2 mmol), sodium methoxide (25 wt%; 71 mg, 1.3 mmol) and 3–hexyn–2–one **8d** (96 mg, 1.0 mmol) were reacted for 5 min according to general procedure **6.2.8** to give the *title compound* as a yellow solid (85 mg, 62%), mp 118–120 °C (aq. MeOH); (Found: MH^+, 138.1027. $C_{11}H_{12}N_3$, [MH^+] requires 138.1026; R_f = 0.17 (AcOEt); IR (nujol)/cm^{-1} 3310, 3175, 1650, 1558, 1347, 1303, 1265, 1222, 1050, 910, 844, 803; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.33 (1H, s, CH), 5.05 (2H, br s, NH_2), 2,47 (2H, q, *J* 7.6 Hz, CH_2CH_3), 2.24 (3H, s, CH_3), 1.14 (3H, t, *J* 7.6 Hz, CH_2CH_3), ^{13}C NMR (100 MHz; $CDCl_3$) δ 173.2 (C), 168.3 (C), 163.2 (C), 109.6 (CH), 31.0 (CH_2), 24.2 (CH_3), 13.2 (CH_3); *m/z* (APcI) 138 (MH^+, 100%).

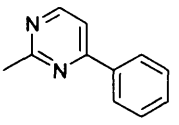
2–Amino–4–methyl–6–phenylpyrimidine (14h)



Guanidine hydrochloride salt **13b** (0.11 g, 1.2 mmol), sodium methoxide (25 wt%; 71 mg, 1.3 mmol) and 4–phenyl–3–propyn–2–one **8e** (0.11 g, 1.0 mmol) were reacted for 5 min according to general procedure **6.2.8** to give the *title compound* as a pale yellow solid (0.127 g, 69%), mp 175–177 °C (aq. MeOH) (lit.[134] mp 174–175 °C); (Found: MH^+, 186.1026. $C_{11}H_{12}N_3$, [MH^+] requires 186.1026; R_f = 0.38 (AcOEt); IR (nujol)/cm^{-1} 3313, 3187, 1636, 1576, 1548, 1351, 1223, 1117, 1074, 770, 705; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.92 (2H, m, *o*–Ph*H*), 7.38 (3H, m,

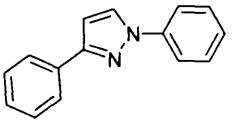
m,p–Ph*H*), 6.85 (1H, s, CH), 5.04 (2H, br s, NH_2), 2.32 (3H, m, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.0 (C), 165.8 (C), 163.6 (C), 137.9 (C), 130.8 (CH), 129,1 (CH), 127.4 (CH), 107.8 (CH), 24.6 (CH_3); *m/z* (ES) 186 (MH^+, 100%).

2–Methyl–4–phenylpyrimidine (14i)



Acetamidine hydrochloride salt **13c** (0.11 g, 1.2 mmol), sodium methoxide (25 wt%; 71 mg, 1.3 mmol) and 1–phenyl–2–propyn–1–one **8a** (0.13 g, 1.0 mmol) were reacted for 5 min according to general procedure **6.2.8** to give the *title compound* as ayellow solid (0.153 g, 90%), mp 49 °C (aq. MeOH) (lit.[135] mp 50–51 °C); (Found: MH^+, 171.0916. $C_{11}H_{11}N_2$, [MH^+] requires 171.0917); R_f = 0.14 (light petroleum–Et_2O, 1:1); IR (nujol)/cm^{-1} 1574, 1549, 1312, 1074, 995, 841, 791, 752, 598; ^1H NMR (400 MHz; $CDCl_3$) δ 8.60 (1H, d, *J* 5.3 Hz, 4–H), 7.99 (2H, m, *o*–Ph*H*), 7.41 (4H, m, *m,p*–Ph*H* and 5–H), 2.75 (3H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.9 (C), 164.5 (C), 157.9 (CH), 137.3 (C), 131.2 (CH), 129.4 (CH), 127.6 (CH), 114.4 (CH), 26.7 (CH_3); *m/z* (ES) 171 (MH^+, 100%).

1,3–Diphenylpyrazole (16a)



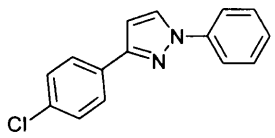
I. Synthesis in a sealed tube under microwave irradiation. Phenylhydrazine **15a** (0.05 g, 0.46 mmol) and 1–phenyl–2–propyn–1–one **8a** (0.06 g, 0.46 mmol) were reacted according to general

procedure **6.2.9**. Purification by flash column chromatography over silica, eluting with methylene, gave the *title compound* as a colourless solid (77 mg, 76%).

II. Synthesis using concurrent heating and cooling under microwave irradiation in a CEM Discover® Coolmate.™ A solution of phenylhydrazine **15a** (0.05 g, 0.46 mmol) and 1–phenyl–2–propyn–1–one **8a** (0.06 g, 0.46 mmol) in cHCl–MeOH (1.5% v/v) (3 mL) was irradiated for 30 min at 0 °C in a CEM Discover® CoolMate™ microwave synthesizer at a power of 60 W. The reaction mixture was evaporated *in vacuo*. Purification by column chromatography on silica, eluting with methylene chloride, gave the *title compound* as a colourless solid (85 mg, 84%).

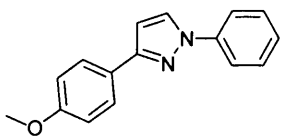
III. Synthesis in a glass tube microwave reactor. The glass tube flow cell (10 mL) filled with sand (~12 g) was primed with cHCl–MeOH (1.5% v/v) at a flow rate of 1.5 mL/min, irradiated at an initial power of 150 W and stabilized at a temperature of 100 °C. A flask was charged with a solution of phenylhydrazine **15a** (0.05 g, 0.46 mmol) and 1–phenyl–2–propyn–1–one **8a** (0.06 g, 0.46 mmol) in cHCl–MeOH (1.5% v/v) (3 mL), which was then passed through the cavity at the given flow rate, washing with further batches of solvent. The reaction mixture was quenched in a solution of saturated aqueous $NaHCO_3$, evaporated under reduced pressure and the residue partitioned between saturated aqueous $NaHCO_3$ solution (25 mL) and CH_2Cl_2 (25 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 x 15 mL), the combined organic extracts were washed with brine (15 mL), dried ($NaSO_4$) and evaporated *in vacuo*. Purification by column chromatography on silica, eluting with methylene chloride gave the *title compound* as a colourless solid (75 mg, 74%), mp 81–83 °C (MeOH) (lit.[136] mp 84–85 °C); (Found: MH^+, 221.1074. $C_{15}H_{13}N_2$, [MH^+] requires 221.1073); R_f = 0.61 (CH_2Cl_2), IR (nujol)/cm^{-1} 1598, 1526, 1504, 1360, 1264, 1114, 1061, 1046, 954, 755 and 686; ^1H NMR (400 MHz; $CDCl_3$) δ 7.89 (1H, d, *J* 2.5 Hz, 5–H), 7.85 (2H, m, *o*–Ph*H*), 7.71 (2H, m, *o*–Ph'*H*), 7.38 (4H, m, *m*–Ph*H* and *m*–Ph'*H*), 7.24 (2H, m, *p*–Ph*H* and *p*–Ph'*H*), 6.71 (1H, d, *J* 2.5 Hz, 4–H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 153.3 (C), 140.6 (C), 133.5 (C), 129.8 (CH), 129.1 (CH), 128.5 (CH), 128.4 (CH), 126.7 (CH), 126.2 (CH), 119.5 (CH), 105.4 (CH); UV (dichloromethane) λ_{MAX} (ε) 284 (17959), 224 (6189); MS (APcI) *m/z* (rel intensity) 221 (MH^+, 100%), 194 (5), 118 (10).

1–Phenyl–3–(4–chlorophenyl)pyrazole (16b)



Phenylhydrazine **15a** (83 mg, 0.77 mmol) and 1–(4–chlorophenyl)–2–propyn–1–one **8b** (0.13 g, 0.77 mmol) were reacted according to general procedure **6.2.9**. Purification by flash column chromatography on silica, eluting with methylene chloride, gave the *title compound* as a pale yellow solid (0.125 g, 64%), mp 79 °C (MeOH) (lit.[137] mp 76–77 °C); (Found: MH^+, 255.0683. $C_{15}H_{12}ClN_2$, [MH^+] requires 255.0684); R_f = 0.83 (CH_2Cl_2); IR (nujol)/cm^{-1} 1596, 1505, 1443, 1411, 1259, 1173, 1111, 1073, 1044, 952, 909, 839, 758, 689; ^1H NMR (400 MHz; $CDCl_3$) δ 7.88 (1H, d, *J* 2.5 Hz, 5–H), 7.78 (2H, d, *J* 8.5 Hz, 2'',6''–Ar*H*), 7.69 (2H, m, *o*–Ph*H*), 7.41 (2H, m, *m*–Ph*H*), 7.31 (2H, d, *J* 8.5 Hz, 3'',5''–Ar*H*), 7.22 (1H, m, *p*–Ph*H*), 6.67 (1H, d, *J* 2.5 Hz, 4–H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 152.2 (C), 140.4 (C), 134.1 (C), 131.9 (C) 129.9 (CH), 129.2 (CH), 128.6 (CH), 127.5 (C), 126.9 (CH), 119.5 (CH), 105.4 (CH); UV (dichloromethane) λ_{MAX} (ε) 288 (20760), 224 (5190); MS (ES) *m/z* (rel intensity) 255 (MH^+, 100%), 187 (70).

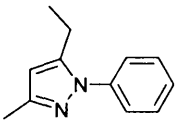
1–Phenyl–3–(4–methoxyphenyl)pyrazole (16c)



Phenylhydrazine **15a** (83 mg, 0.77 mmol) and 1–(4–methoxyphenyl)–2–propyn–1–one **8f** (0.12 g, 0.77 mmol) were reacted according to general procedure **6.2.9**. Purification by flash column chromatography on silica, eluting with methylene chloride, gave the *title compound* as a yellow solid (96 mg, 50%), mp 92–93 °C (MeOH) (lit.[137] mp 94–96 °C); (Found: MH^+, 251.1178.

$C_{16}H_{15}N_2O$, [MH^+] requires 251.1179); R_f = 0.58 (CH_2Cl_2); IR (nujol)/cm^{-1} 1597, 1514, 1358, 1296, 1247, 1176, 1113, 1027, 953, 834, 758, 690; ^1H NMR (400 MHz; $CDCl_3$) δ 7.87 (1H, d, *J* 2.5 Hz, 5–H), 7.78 (2H, d, *J* 9.5 Hz, 2'',6''–Ar*H*), 7.70 (2H, m, *o*–Ph*H*), 7.39 (2H, m, *m*–Ph*H*), 7.21 (1H, m, *p*–Ph*H*), 6.90 (2H, d, *J* 9.5 Hz, 3'',5''–Ar*H*), 6.63 (1H, d, *J* 2.5 Hz, 4–H), 3.80 (3H, s, OCH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 159.9 (C), 153.1 (C), 140.6 (C), 129.8 (CH) 128.4 (CH), 127.5 (CH), 126.6 (CH), 126.2 (C), 119.4 (CH), 114.4 (CH), 104.9 (CH), 55.7 (CH_3); UV (dichloromethane) λ_{MAX} (ε) 289 (18824) 257 (4572), 224 (5432); MS (CI) *m/z* (rel intensity) 251 (MH^+, 100%).

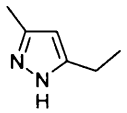
1–Phenyl–3–methyl–5–ethylpyrazole (16d)



Phenylhydrazine **15a** (0.10 g, 0.77 mmol) and 3–hexyn–2–one **8d** (74 mg, 0.77 mmol) were reacted according to general procedure **6.2.9.** Purification by flash column chromatography on silica, eluting with methylene chloride, gave the *title compound* as a colourless oil[i] (88 mg, 61%); (Found: MH^+, 187.1230. $C_{12}H_{15}N_2$, [MH^+] requires 187.1230); R_f = 0.16 (CH_2Cl_2); IR (film) 3063, 2971, 2936, 2877, 1599, 1552, 1503, 1458, 1429, 1382, 1366, 1326, 1128, 1072, 1022, 975, 911, 773, 695; ^1H NMR (400 MHz; $CDCl_3$) δ 7.48–7.35 (5H, Ph*H*), 6.06 (1H, s, CH), 2.66 (2H, q, *J* 7.5 Hz, CH_2CH_3), 2.34 (3H, s, CH_3), 1.22 (3H, t, *J* 7.5 Hz, CH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 148.9 (C), 146.0 (C), 139.8 (C), 129.0 (CH), 127.5 (CH), 125.2 (CH), 104.8 (CH), 19.8 (CH_2), 13.6 (CH_3), 13.2 (CH_3); UV (dichloromethane) λ_{MAX} (ε) 252 (9515); MS (ES) *m/z* (rel intensity) 187 (MH^+, 100%).

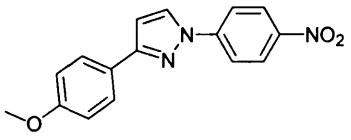
[i] Structure confirmed by NOESY effects between the *ortho*-phenyl protons and the ethyl group.

3–Methyl–5–ethylpyrazole (16e)



Hydrazine hydrate **15b** (39 mg, 0.77 mmol) and 3–hexyn–2–one **8d** (74 mg, 0.77 mmol) were reacted according to general procedure **6.2.9.** Purification by flash column chromatography on silica, eluting with AcOEt, gave the *title compound* as a colourless oil[138] (70 mg, 83%); (Found: MH^+, 110.0917. $C_6H_{11}N_2$, [MH^+] requires 110.0917); R_f = 0.35 (AcOEt); IR (film) 3197, 2970, 1579, 1478, 1455, 1377, 1342, 1319, 1244, 1148, 1051, 1031, 1009, 960, 801, 728; ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.81 (1H, s, CH), 5.41 (1H, br s, NH), 2.58 (2H, q, *J* 7.6 Hz, CH_2CH_3), 2.22 (3H, s, CH_3), 1.19 (3H, t, *J* 7.6 Hz, CH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 150.6 (C), 144.5 (C), 102.7 (CH), 20.2 (CH_2), 13.6 (CH_3), 12.3 (CH_3); UV (dichloromethane) λ_{MAX} (ε) 229 (3120); MS (APcI) *m/z* (rel intensity) 111 (MH^+, 100%).

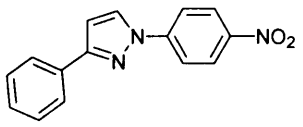
1–(4–Nitrophenyl)–3–(4–methoxyphenyl)pyrazole (16f)



4–Nitrophenylhydrazine **15c** (30% water; 0.11 g, 0.51 mmol) and 1–(4–methoxyphenyl)–2–propyn–1–one **8f** (76 mg, 0.46 mmol) were reacted for 5 min according to general procedure **6.2.9**. Purification by flash column chromatography on silica gel uluting with methylene chloride, gave the *title compound* as a yellow solid (79 mg, 58%), mp 199 °C (MeOH) (lit.[83] mp 197–198 °C); (Found: MH^+, 296.1030. $C_{16}H_{14}N_3O_3$ requires MH^+, 296.1030); R_f = 0.75 (CH_2Cl_2); IR (nujol)/cm^{-1} 1595, 1516, 1329, 1311, 1244, 1177, 1107, 1027, 948, 850, 829, 750, 719; ^{1}H NMR

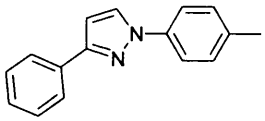
(400 MHz; $CDCl_3$) δ 8.28 (2H, d, *J* 9.2 Hz, 3',5'–Ar*H*), 8.01 (1H, d, *J* 2.7 Hz, 5–H) , 7.88 (2H, d, *J* 9.2 Hz, 2',6'–Ar*H*), 7.80 (2H, d, *J* 8.8 Hz, 2'',6''–Ar*H*), 6.93 (2H, d, *J* 8.8 Hz, 3'',5''–Ar*H*), 6.74 (1H, d, *J* 2.7 Hz, 4–H) 3.82 (3H, s, OCH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 161.5 (C), 154.3 (C), 146.5 (C), 144.8 (C), 128.6 (CH), 127.7 (CH), 125.8 (CH), 125.3 (C), 118.5 (CH), 114.6 (CH), 106.9 (CH), 55.8 (CH_3); UV (dichloromethane) λ_{MAX} (ε) 358 (16857), 234 (7094); MS (ES) *m/z* (rel intensity) 296 (MH^+, 50%), 141 (100), 126 (35), 118 (38).

1–(4–Nitrophenyl)–3–phenylpyrazole (16g)



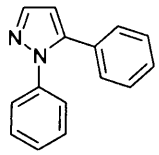
4–Nitrophenylhydrazine **15c** (30% water; 0.11 g, 0.51 mmol) and 1–phenyl–2–propyn–1–one **8a** (76 mg, 0.46 mmol) were reacted for 5 min according to general procedure **6.2.9**. Purification by flash column chromatography on silica, eluting with methylene chloride, gave the *title compound* as a yellow solid (63 mg, 52%), mp 173 °C (MeOH) (lit.[139] mp 170–171 °C); (Found: MH^+, 266.0922. $C_{15}H_{12}N_3O_2$, [MH^+] requires 266.0930); R_f = 0.79 (CH_2Cl_2); IR (nujol)/cm^{-1} 1595, 1520, 1500, 1442, 1342, 1218, 1108, 958, 925, 855, 802, 772, 702; ^1H NMR (400 MHz; $CDCl_3$) δ 8.27 (2H, d, *J* 9.2 Hz, 3',5'–Ar*H*), 7.95 (1H, d, *J* 2.6 Hz, 5–H), 7.87 (4H, 2',6'–Ar*H* and *o*–Ph*H*), 7.38 (2H, m, *m*–Ph*H*), 7.30 (1H, m, *p*–Ph*H*), 6.81 (1H, d, *J* 2.6 Hz, 4–H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 154.9 (C), 145.6 (C), 144.8 (C), 132.6 (C), 129.2 (CH), 129.1 (CH), 128.7 (CH), 126.4 (CH), 125.8 (CH), 118.7 (CH), 107.3 (CH); UV (dichloromethane) λ_{MAX} (ε) 344 (20305), 235 (9188); MS (ES) *m/z* (rel intensity) 266 (MH^+, 100%), 224 (18).

1–(4-Tolyl)–3–phenylpyrazole (16h)



p–Tolylhydrazine hydrochloride salt **15d** (73 mg, 0.46 mmol) and 1–phenyl–2–propyn–1–one **8a** (0.06 g, 0.46 mmol) were reacted according to general procedure **6.2.9.** Purification by flash column chromatography on silica, eluting with methylene chloride, gave the *title compound* as a yellow solid (50 mg, 47%), mp 113 °C (MeOH) (Found: MH^+, 235.1229. $C_{16}H_{15}N_2$, [MH^+] requires 235.1235); R_f = 0.67 (CH_2Cl_2); IR (nujol)/cm^{-1} 1607, 1526, 1363, 1311, 1284, 1262, 1124, 1042, 956, 937, 813, 756, 702; ^1H NMR (400 MHz; $CDCl_3$) δ 7.85 (3H, *o*–Ph*H* and 5–H), 7.58 (2H, d, *J* 8.3 Hz, 2',6'–Ar*H*), 7.34 (2H, m, *m*–Ph*H*), 7.23 (1H, m, *p*–Ph*H*), 7.17 (2H, d, *J* 8.3 Hz, 3',5'–Ar*H*), 6.46 (1H, d, *J* 2.4 Hz, 4–H), 2.32 (3H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 153.0 (C), 138.4 (C), 136.6 (C), 133.6 (C), 130.3 (CH), 129.0 (CH), 128.3 (CH), 127.2 (CH), 126.2 (CH), 119.4 (CH), 105.1 (CH), 21.4 (CH_3); UV (dichloromethane) λ_{MAX} (ε) 289 (19831), 223 (5266); MS (ES) *m/z* (rel intensity) 235 (MH^+, 100%), 217 (12).

1,5–Diphenylpyrazole (17a)



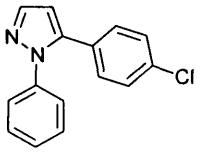
I. Synthesis in a sealed tube under microwave irradiation. Phenylhydrazine **15a** (0.05 g, 0.46 mmol) and 1–phenyl–2–propyn–1–one **8a** (0.06 g, 0.46 mmol) were reacted according to general

procedure **6.2.9**. Purification by flash column chromatography over silica, eluting with methylene chloride, gave the *title compound* as a pale yellow solid (16 mg, 15%).

II. Synthesis using concurrent heating and cooling under microwave irradiation in a CEM Discover® Coolmate.™ A solution of phenylhydrazine **15a** (0.05 g, 0.46 mmol) and 1–phenyl–2–propyn–1–one **8a** (0.06 g, 0.46 mmol) in cHCl–MeOH (1.5% v/v) (3 mL) was irradiated for 30 min at 0 °C in a CEM Discover® CoolMate™ microwave synthesizer at a power of 60 W. The reaction mixture was evaporated *in vacuo*. Purification by column chromatography on silica, eluting with methylene chloride gave the *title compound* as a colourless solid (15 mg, 15%).

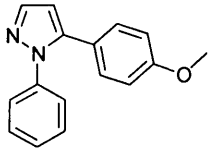
III. Synthesis in a glass tube microwave reactor. The glass tube flow cell (10 mL) filled with sand (~12 g) was primed with cHCl–MeOH (1.5% v/v) at a flow rate of 1.5 mL/min, irradiated at an initial power of 150 W and stabilized at a temperature of 100 °C. A flask was charged with a solution of phenylhydrazine **15a** (0.05 g, 0.46 mmol) and 1–phenyl–2–propyn–1–one **8a** (0.06 g, 0.46 mmol) in cHCl–MeOH (1.5% v/v) (3 mL), which was then passed through the cavity at the given flow rate, washing with further batches of solvent. The reaction mixture was quenched in a solution of saturated aqueous $NaHCO_3$, evaporated under reduced pressure and the residue partitioned between saturated aqueous $NaHCO_3$ solution (25 mL) and CH_2Cl_2 (25 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 x 15 mL), the combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by column chromatography on silica, eluting with methylene chloride, gave the *title compound* as a pale yellow solid (18 mg, 17%), mp 52–55 °C (MeOH) (lit.[136] mp 55–56 °C); (Found: MH^+, 221.1072. $C_{15}H_{13}N_2$, [MH^+] requires 221.1073); R_f = 0.18 (CH_2Cl_2); IR (nujol)/cm^{-1} 1596, 1541, 1502, 1450, 1385, 1224, 1158, 1130, 1068, 960, 761, 695; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.66 (1H, d, *J* 1.5 Hz, 3–H), 7.28–7.22 (8H, *o,m*–Ph*H* and *o,m*–Ph'*H*), 7.19–7.15 (2H, *p*–Ph*H* and *p*–Ph'*H*), 6.45 (1H, d, *J* 1.5 Hz, 4–H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 143.0 (C), 140.3 (CH), 140.1 (C), 130.6 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 127.4 (CH), 125.2 (CH), 107.9 (CH); UV (dichloromethane) λ_{MAX} (ε) 252 (14493); MS (APcI) *m/z* (rel intensity) 221 (MH^+, 100%), 194 (10), 152 (5), 103 (5).

1–Phenyl–5–(4–chlorophenyl)pyrazole (17b)



Phenylhydrazine **15a** (83 mg, 0.77 mmol) and 1–(4–chlorophenyl)–2–propyn–1–one **8b** (0.13 g, 0.77 mmol) were reacted according to general procedure **6.2.9**. Purification by flash column chromatography on silica,eluting with methylene chloride, gave the *title compound* as a pale yellow solid (43 mg, 22%), mp 65–67 °C (MeOH) (lit.[140] mp 68–70 °C); (Found: MH^+, 255.0683. $C_{15}H_{12}ClN_2$, [MH^+] requires 255.0684); R_f = 0.58 (CH_2Cl_2); IR (nujol)/cm^{-1} 1597, 1502, 1442, 1405, 1226, 1174, 1134, 1089, 1068, 1018, 960, 925, 842, 790, 760, 691; ^1H NMR (400 MHz; $CDCl_3$) δ 7.67 (1H, d, *J* 1.8 Hz, 3–H), 7.41–7.12 (9H, Ph*H* and Ar*H*), 6.45 (1H, d, *J* 1.8 Hz, 4–H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 142.2 (C), 140.8 (CH), 140.2 (C), 134.7 (C) 130.4 (CH), 129.5 (CH), 129.4 (C), 129.2 (CH), 128.1 (CH), 125.6 (CH), 108.4 (CH); UV (dichloromethane) λ_{MAX} (ε) 256 (13606); MS (ES) *m/z* (rel intensity) 255 (MH^+, 100%).

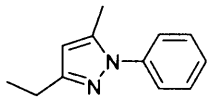
1–Phenyl–5–(4–methoxyphenyl)pyrazole (17c)



Phenylhydrazine **15a** (83 mg, 0.77 mmol) and 1–(4–methoxyphenyl)–2–propyn–1–one **8f** (0.12 g, 0.77 mmol) were reacted according to general procedure **6.2.9**. Purification by flash column chromatography on silica, eluting with methylene chloride, gave the *title compound* as a yellow oil[140] (57 mg, 30%); (Found: MH^+, 251.1181. $C_{16}H_{15}N_2O$, [MH^+] requires 251.1179); R_f = 0.30

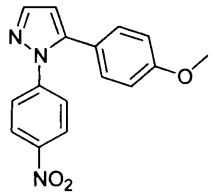
(CH_2Cl_2); IR (film) 3064, 3002, 2937, 2836, 1613, 1598, 1547, 1501, 1449, 1382, 1290, 1247, 1179, 1132, 1072, 1031, 961, 925, 836, 787, 764, 694; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.64 (1H, d, *J* 1.8 Hz, 3–H), 7.31–7.22 (5H, m, Ph*H*), 7.18 (2H, d, *J* 9.5 Hz, 2'',6''–Ar*H*), 6.76 (2H, d, *J* 9.5 Hz, 3'',5''–Ar*H*), 6.39 (1H, d, *J* 1.8 Hz, 4–H), 3.72 (3H, s, OCH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 159.9 (C), 147.5 (C), 144.2 (C), 140.5 (CH) 130.4 (CH), 129.3 (CH), 127.8 (CH), 125.6 (CH), 123.3 (C), 114.3 (CH), 107.7 (CH), 55.7 (CH_3); UV (dichloromethane) λ_{MAX} (ε) 252 (14014); MS (ES) *m/z* (rel intensity) 251 (MH^+, 100%).

1–Phenyl–3–ethyl–5–methylpyrazole (17d)



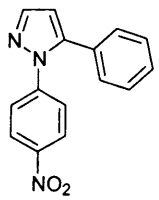
Phenylhydrazine **15a** (0.10 g, 0.77 mmol) and 3–hexyn–2–one **8d** (74 mg, 0.77 mmol) were reacted according to general procedure **6.2.9.** Purification by flash column chromatography on silica, eluting with methylene chloride, gave the *title compound* as a colourless oil (13 mg, 9%); (Found: MH^+, 187.1231. $C_{12}H_{15}N_2$, [MH^+] requires 187.1230); R_f = 0.21 (CH_2Cl_2); IR (film)/cm^{-1} 3063, 2971, 2936, 2877, 1597, 1599, 1552, 1503, 1458, 1429, 1382, 1366, 1325, 1128, 1072, 1022, 911, 773, 695; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.37 (5H, Ph*H*), 5.99 (1H, s, CH), 2.62 (2H, q, *J* 7.6 Hz, C*H*$_2$CH$_3$), 2.25 (3H, s, CH_3), 1.21 (3H, t, *J* 7.6 Hz, CH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 155.4 (C), 140.4 (C), 139.6 (C), 129.4 (CH), 127.6 (CH), 125.2 (CH), 105.7 (CH), 21.9 (CH_2), 14.4 (CH_3), 12.9 (CH_3); UV (dichloromethane) λ_{MAX} (ε) 251 (8727); MS (APcI) *m/z* (rel intensity) 187 (MH^+, 100%).

1–(4–Nitrophenyl)–5–(4–methoxyphenyl)pyrazole (17f)



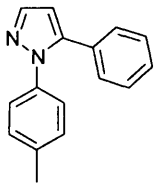
4–Nitrophenylhydrazine **15c** (30% water; 0.11 g, 0.51 mmol) and 1–(4–methoxyphenyl)–2–propyn–1–one **8f** (76 mg, 0.46 mmol) were reacted for 5 min according to general procedure **6.2.9**. Purification by flash column chromatography on silica, eluting with methylene chloride, gave the *title compound* as a yellow solid (31 mg, 23%), mp 98–100 °C (MeOH) (lit.[83] mp 101–103 °C); (Found: MH^+, 296.1027. $C_{16}H_{14}N_3O_3$, [MH^+] requires 296.1030); R_f = 0.42 (CH_2Cl_2); IR (nujol)/cm^{-1} 1613, 1603, 1548, 1497, 1338, 1295, 1253, 1175, 1108, 1022, 956, 919, 856, 835, 810, 746; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.14 (2H, d, *J* 9.0 Hz, 3',5'–Ar*H*), 7.71 (1H, d, *J* 1.6 Hz, 3–H) , 7.43 (2H, d, *J* 9.0 Hz, 2',6'–Ar*H*), 7.09 (2H, d, *J* 8.8 Hz, 3'',5''–Ar*H*), 6.82 (2H, d, *J* 8.8 Hz, 2'',6''–Ar*H*), 6.44 (1H, d, *J* 1.6 Hz, 4–H) 3.77 (3H, s, OCH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 160.5 (C), 146.5 (C), 145.1 (C), 143.9 (C) 142.1 (CH), 130.6 (CH), 125.0 (CH), 124.8 (CH), 122.6 (C), 114.7 (CH), 109.6 (CH), 55.7 (CH_3); UV (dichloromethane) λ_{MAX} (ε) 313 (11848), 234 (13852); MS (ES) *m/z* (rel intensity) 296 (MH^+, 100%), 207 (50), 141 (80).

1–(4–Nitrophenyl)–5–phenylpyrazole (17g)



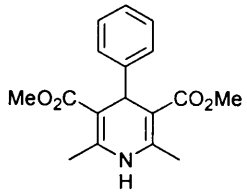
4–Nitrophenylhydrazine **15c** (30% in water; 0.11 g, 0.51 mmol) and 1–phenyl–2–propyn–1–one **8a** (76 mg, 0.46 mmol) were reacted for 5 min according to general procedure **6.2.9**. Purification by flash column chromatography on silica, eluting with methylene chloride, gave the *title compound* as a yellow solid (38 mg, 31%), mp 114–115 °C (MeOH) (lit.[141] mp 117–118 °C); (Found: MH^+, 266.0938. $C_{15}H_{12}N_3O_2$, [MH^+] requires 266.0930); R_f = 0.56 (CH_2Cl_2); IR (nujol)/cm^{-1} 1596, 1520, 1500, 1442, 1343, 1218, 1164, 1108, 1071, 958, 925, 855, 802, 772, 702; ^1H NMR (400 MHz; $CDCl_3$) δ 8.11 (2H, d, *J* 9.1 Hz, 3',5'–Ar*H*), 7.72 (1H, d, *J* 1.7 Hz, 3–H), 7.39 (2H, d, *J* 9.1 Hz, 2',6'–Ar*H*), 7.30 (3H, *o,p*–Ph*H*), 7.17 (2H, m, *m*–Ph*H*), 6.49 (1H, d, *J* 1.7 Hz, 4–H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 146.3 (C), 145.3 (C), 144.0 (C), 142.2 (CH) 130.4 (C), 129.4 (CH), 129.3 (CH), 129.2 (CH), 125.1 (C), 124.9 (CH), 110.1 (CH); UV (dichloromethane) λ_{MAX} (ε) 315 (10100), 235 (11636); MS (ES) *m/z* (rel intensity) 266 (MH^+, 100%), 232 (55), 188 (25).

1–(4-Tolyl)–5–phenylpyrazole (17h)



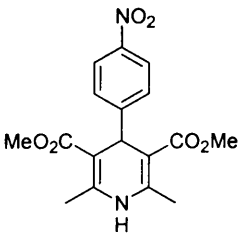
p–Tolylhydrazine hydrochloride salt **15d** (73 mg, 0.46 mmol) and 1–phenyl–2–propyn–1–one **8a** (0.06 g, 0.46 mmol) were reacted according to general procedure **6.2.9.** Purification by flash column chromatography over silica gel using methylene chloride as the eluant gave the *title compound* as a yellow solid (43 mg, 40%), mp 76–77 °C (MeOH); (Found: MH^+, 235.1227. $C_{16}H_{15}N_2$, [MH^+] requires 235.1235); R_f = 0.30 (CH_2Cl_2); IR (nujol)/cm^{-1} 1612, 1516, 1335, 1223, 1178, 1127, 1106, 1070, 957, 925, 819, 764 and 702; ^1H NMR (400 MHz; $CDCl_3$) δ 7.87 (1H, d, *J* 2.0 Hz, 3–H), 7.22–7.13 (9H, *J* 9.0 Hz, Ar*H* and Ph*H*), 6.21 (1H, d, *J* 2.0 Hz, 4–H), 2.29 (3H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 143.1 (C), 140.5 (C), 137.7 (C), 131.3 (C) 129.9 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 127.3 (CH), 125.4 (CH), 107.9 (CH), 21.5 (CH_3); UV (dichloromethane) λ_{MAX} (ε) 252 (13741); MS (ES) *m/z* (rel intensity) 235 (MH^+, 100%).

Dimethyl 4–phenyl–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20a).



1,4–Dihydropyridine **20a** was prepared according to general procedure **6.2.10** using benzaldehyde **18a** (0.27 g, 2.5 mmol), methyl acetoacetate **19a** (1.45 g, 12.5 mmol) and 35% aqueous ammonium hydroxide (0.17 g, 10.0 mmol). Purification by recrystallization (aq. EtOH) gave the *title compound* as a pale yellow solid (0.35 g, 47%), mp 199–200 °C (aq. EtOH) (lit.[142] mp 198–199 °C) (Found: MH^+, 302.1387. $C_{17}H_{20}NO_4$, [MH^+] requires 302.1387); R_f = 0.39 (light petroleum–EtOAc, 1:1); IR (nujol)/cm^{-1} 3341, 1700, 1648, 1433, 1344, 1300, 1222, 1121, 1101, 1053, 1018, 764, 700; ^1H NMR (400 MHz; $CDCl_3$) δ 7.26 (2H, m, *o*–Ph*H*), 7.22 (2H, m, *m*–Ph*H*), 7.13 (1H, m, *p*–Ph*H*), 5.74 (1H, br s, NH), 5.04 (1H, s, CH), 3.67 (6H, s, OCH_3), 2.35 (6H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.0 (C), 147.4 (C), 144.2 (CH), 128.0 (CH), 127.6 (CH), 126.2 (C), 103.9 (C), 51.0 (CH_3), 39.3 (CH), 19.6 (CH_3); *m/z* (APcI) 302 (MH^+, 49%), 270 (100).

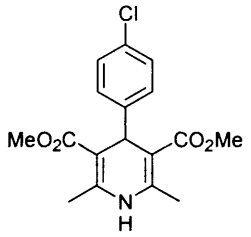
Dimethyl 4–(4–nitrophenyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20b)



1,4–Dihydropyridine **20b** was prepared according to general procedure **6.2.10** using *p*–nitrobenzaldehyde **18b** (0.38 g, 2.5 mmol), methyl acetoacetate **19a** (1.45 g, 12.5 mmol) and 35%

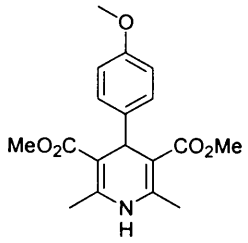
aqueous ammonium hydroxide (0.17 g, 10.0 mmol). Purification by recrystallization (aq. EtOH) gave the *title compound* as a yellow solid (0.13 g, 15%), mp 198–200 °C (aq. EtOH) (lit.[142] mp 198–199 °C) (Found: MH^+, 347.1237. $C_{17}H_{19}N_2O_6$, [MH^+] requires 302.1387); R_f = 0.2 9 (light petroleum–EtOAc, 1:1); IR (nujol)/cm^{-1} 3341, 1704, 1650, 1519, 1345, 1216, 1123, 1097, 1016, 830; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.03 (2H, d, *J* 8.8 Hz, *m*–Ar*H*), 7.36 (2H, d, *J* 8.8 Hz, *o*–Ar*H*), 5.68 (1H, br s, N*H*), 5.03 (1H, s, CH), 3.58(s, 6H, OCH_3), 2.29 (s, 6H, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.8 (C), 155.1 (C), 146.8 (C), 145.3 (C), 129.0 (CH), 123.9 (CH), 103.4 (C), 51.6 (CH_3), 40.2 (CH), 20.1 (CH_3); *m/z* (ES) 347 (MH^+, 32%), 315 (100), 207 (56), 141 (78).

Dimethyl 4–(4–chlorophenyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20c)



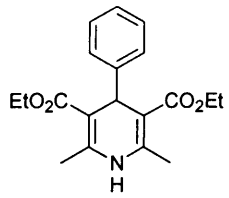
1,4–Dihydropyridine **20c** was prepared according to general procedure **6.2.10** using *p*–chlorobenzaldehyde **18c** (0.35 g, 2.5 mmol), methyl acetoacetate **19a** (1.45 g, 12.5 mmol), and 35% aqueous ammonium hydroxide (0.17 g, 10.0 mmol). Purification by recrystallization (aq. EtOH) gave the *title compound* as a yellow solid (0.38 g, 45%), mp 198 °C (aq. EtOH) (lit.[142] mp 194–196 °C); (Found: MH^+, 336.0997. $C_{17}H_{19}NO_4$, [MH^+] requires 336.1003); R_f = 0.37 (light petroleum–EtOAc, 1:1); IR (nujol)/cm^{-1} 3333, 1697, 1650, 1345, 1306, 1210, 1121, 1020, 842; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.23 (4H, m, Ar*H*), 5.70 (1H, br s, NH), 5.00 (1H, s, CH), 3.68 (6H, s, OCH_3), 2.37 (6H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.9 (C), 146.0 (C), 144.3 (C), 131.8 (C), 129.1 (CH), 128.2 (CH), 103.7 (C), 51.1 (CH_3), 38.9 (CH), 19.7 (CH_3); *m/z* (ES) 336 (MH^+, 40%), 306 (38), 304 (100), 224 (42), 196 (44), 115 (36).

Dimethyl 4–(4–methoxyphenyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20d)



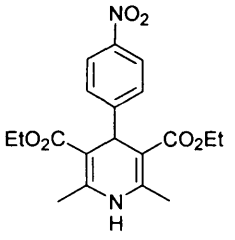
1,4–Dihydropyridine **20d** was prepared according to general procedure **6.2.10** using *p*–anisaldehyde **18d** (0.34 g, 2.5 mmol), methyl acetoacetate **19a** (1.45 g, 12.5 mmol) and 35% aqueous ammonium hydroxide (0.17 g, 10.0 mmol). Purification by column chromatography on SiO_2, eluting with light petroleum–EtOAc (7:3), followed by recrystallization (aq. EtOH), gave the *title compound* as a pale yellow solid (0.22 g, 27%); mp 184–185 °C (aq. EtOH) (lit.[143] mp 181–183 °C); (Found: MNa^+, 354.1309. $C_{17}H_{19}NO_4Na$, [MNa^+] requires 354.1312); R_f = 0.31 (light petroleum–EtOAc, 1:1); IR (nujol)/cm^{-1} 3345, 1694, 1650, 1303, 1271, 1212, 1174, 1121, 1094, 1049, 1026, 820; ^1H NMR (400 MHz; $CDCl_3$) δ 7.11 (2H, d, *J* 8.7 Hz, 2',6'–Ar*H*), 6.69 (2H, d, *J* 8.7 Hz, 3',5'–Ar*H*), 5.61 (1H, br s, NH), 4.88 (1H, s, CH), 3.69 (3H, s, OCH_3), 3.58 (6H, s, OCH_3), 2.27 (6H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.1 (C), 157.9 (C), 144.0 (C), 139.9 (C), 128.6 (CH), 113.4 (CH), 104.1 (C), 55.2 (CH_3), 51.1 (CH_3), 38.4 (CH), 19.7 (CH_3); *m/z* (ES) 354 (MNa^+, 78%), 332 (MH^+, 35%), 272 (100).

Diethyl 4–phenyl–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20e)



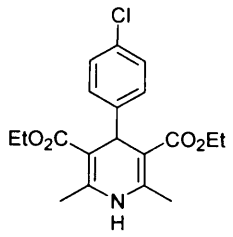
1,4–Dihydropyridine **20e** was prepared according to general procedure **6.2.10** using benzaldehyde **18a** (0.34 g, 2.5 mmol), ethyl acetoacetate **19b** (1.63 g, 12.5 mmol) and 35% aqueous ammonium hydroxide (0.17 g, 10.0 mmol). Purification by recrystallization (aq. EtOH) gave the *title compound* as a pale yellow solid (0.64 g, 39%); mp 158–160 °C (aq. EtOH) (lit.[144] mp 156–157 °C); (Found: MH^+, 330.1700. $C_{19}H_{24}NO_4$, [MH^+] requires 330.1700); R_f = 0.41 (light petroleum–EtOAc, 1:1); IR (nujol)/cm^{-1} 3340, 1688, 1650, 1298, 1212, 1124, 1090, 1018, 827; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.20–7.02 (5H, PhH), 5.74 (1H, br s, NH), 4.92 (1H, s, CH), 4.03 (4H, m, OCH_2CH_3), 2.25 (6H, s, CH_3), 1.18 (6H, t, *J* 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.7 (C), 147.8 (C), 143.9 (C), 128.0 (CH), 127.9 (CH), 126.1 (CH), 104.2 (C), 59.8 (CH_2), 39.6 (CH), 19.7 (CH_3), 14.3 (CH_3); *m/z* (APcI) 330 (MH^+, 100%), 284 (44).

Diethyl 4–(4–nitrophenyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20f)



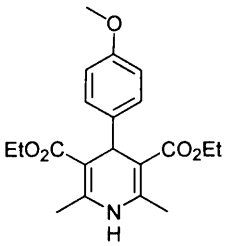
1,4–Dihydropyridine **20f** was prepared according to general procedure **6.2.10** using *p*–nitrobenzaldehyde **18b** (0.38 g, 2.5 mmol), ethyl acetoacetate **19b** (1.63 g, 12.5 mmol) and 35% aqueous ammonium hydroxide (0.17 g, 10.0 mmol). Purification by column chromatography on SiO_2, eluting with light petroleum–EtOAc (7:3) (R_f = 0.15), followed by recrystallization (aq. EtOH), gave the *title compound* as a yellow solid (0.34 g, 36%); mp 131–132 °C (aq. EtOH) (lit.[145] mp 129–130 °C); (Found: MH^+, 375.1548. $C_{19}H_{23}N_2O_6$, [MH^+] requires 375.1551); IR (nujol)/cm^{-1}: 3315, 1702, 1646, 1517, 1348, 1302, 1212, 1119, 1094, 1019 824; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.01 (2H, d, *J* 8.8 Hz, 3',5'–Ar*H*), 7.38 (2H, d, *J* 8.8 Hz, 2',6'–Ar*H*), 5.65 (1H, br s, NH), 5.04 (1H, s, CH), 4.03 (4H, m, OCH_2CH_3), 2.30 (6H, s, CH_3), 1.17 (6H, t, *J* 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.1 (C), 155.1 (C), 146.3 (C), 144.6 (C), 129.0 (CH), 123.3 (CH), 103.2 (C), 60.1 (CH_2), 40.1 (CH), 19.8 (CH_3), 14.3 (CH_3); *m/z* (APcI) 375 (MH^+, 100%), 146 (15), 139 (49).

Diethyl 4–(4–chlorophenyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20g)



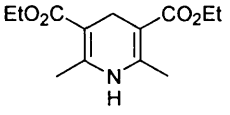
1,4–Dihydropyridine **20g** was prepared according to general procedure **6.2.10** using *p*–chlorobenzaldehyde **18c** (0.35 g, 2.5 mmol), ethyl acetoacetate **19b** (1.63 g, 12.5 mmol) and 35% aqueous ammonium hydroxide (0.17 g, 10.0 mmol). Purification by column chromatography on SiO_2, eluting with light petroleum–EtOAc (7:3) (R_f = 0.18), followed by recrystallization (aq. EtOH), gave the *title compound* as a pale yellow solid (0.41 g, 45%); mp 147–148 °C (aq. EtOH) (lit.[110] mp 144–146 °C); (Found: MH^+, 364.1309. $C_{19}H_{23}NO_4Cl$, [MH^+] requires 364.1310); IR (nujol)/cm^{-1} 3354, 1695, 1650, 1334, 1298, 1213, 1169, 1086, 1015, 830; ^1H NMR (400 MHz; $CDCl_3$) δ 7.16 (2H, d, *J* 8.6 Hz, 3',5'–Ar*H*), 7.11 (2H, d, *J* 8.6 Hz, 2',6'–Ar*H*), 5.55 (1H, br s, NH), 4.89 (1H, s, CH), 4.03 (4H, m, OCH_2CH_3), 2.26 (6H, s, CH_3), 1.15 (6H, t, *J* 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.5 (C), 146.3 (C), 144.0 (C), 131.7 (C), 129.5 (CH), 128.0 (CH), 103.9 (C), 59.9 (CH_2), 39.3 (CH), 19.7 (CH_3), 14.3 (CH_3); *m/z* (APcI) 364 (MH^+, 100%), 318 (66).

Diethyl 4–(4–methoxyphenyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20h)



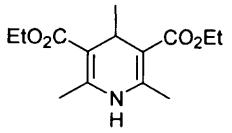
1,4–Dihydropyridine **20h** was prepared according to general procedure **6.2.10** using anisaldehyde **18d** (0.34 g, 2.5 mmol), ethyl acetoacetate **19b** (1.63 g, 12.5 mmol) and 35% aqueous ammonium hydroxide (0.17 g, 10.0 mmol). Purification by column chromatography on SiO_2, eluting with light petroleum–EtOAc (7:3) (R_f = 0.15) followed by recrystallization (aq. EtOH), gave the *title compound* as a pale yellow solid (0.21 g, 23%), mp 159–161 °C (aq. EtOH) (lit.[146] mp 159 °C); (Found: MH^+, 360.1806. $C_{20}H_{26}NO_5$, [MH^+] requires 360.1805); IR (nujol)/cm^{-1} 3339, 1690, 1649, 1301, 1253, 1213, 1121, 1088, 1030, 834; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.12 (2H, d, *J* 8.7 Hz, 2',6'–Ar*H*), 6.68 (2H, d, *J* 8.7 Hz, 3',5'–Ar*H*), 5.48 (1H, br s, NH), 4.87 (1H, s, CH), 4.03 (4H, m, OC*H*$_2$CH$_3$), 3.69 (3H, s, OCH_3), 2.26 (6H, s, CH_3), 1.15 (6H, t, J 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.7 (C), 157.9 (C), 143.5 (C), 140.3 (C), 129.0 (CH), 113.2 (CH), 104.4 (C), 59.7 (CH_2), 55.2 (CH_3), 38.7 (CH), 19.7 (CH_3), 14.3 (CH_3); *m/z* (APcI) 360 (MH^+, 22%), 252 (100).

Diethyl 2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20i)



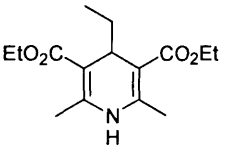
Formaldehyde **18e** (37 wt% solution in H_2O, 0.20 g, 2.5 mmol), ethyl acetoacetate **19b** (1.63 g, 12.5 mmol) and 35% aqueous ammonium hydroxide (0.17 g, 10.0 mmol) were reacted according to general procedure **6.2.10** to give a 3.5:1 crude mixture of 1,4–dihydropyridine **20i** (42%) and pyridine **21i** (12%) by ^{1}H NMR spectroscopic analysis as a pale yellow solid;[96b] ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.18 (1H, br s, NH), 4.24 (4H, q, *J* 7.1 Hz, OC*H*$_2$CH$_3$), 3.35 (2H, s, CH_2), 2.27 (6H, s, CH_3), 1.37 (6H, t, *J* 7.1 Hz, OCH_2CH_3).

Diethyl 4–methyl–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20j)



1,4–Dihydropyridine **20j** was prepared according to general procedure **6.2.10** using acetaldehyde **18f** (0.11 g, 2.5 mmol), ethyl acetoacetate **19b** (1.63 g, 12.5 mmol) and 35% aqueous ammonium hydroxide (0.17 g, 10.0 mmol). Purification by column chromatography on SiO_2, eluting with light petroleum–EtOAc (8:2) (R_f = 0.17), followed by recrystallization (aq. EtOH) gave the *title compound* as a colourless solid (70 mg, 21%); mp 130–131 °C (aq. EtOH) (lit.[96b] mp 131 °C); (Found: MH^+, 268.1543. $C_{14}H_{22}NO_4$, [MH^+] requires 268.1546); IR (nujol)/cm^{-1} 3343, 1697, 1641, 1493, 1299, 1224, 1099, 1061; ^1H NMR (400 MHz; $CDCl_3$) δ 5.41 (1H, br s, NH), 4.13 (4H, m, OCH_2CH_3), 3.75 (1H, q, *J* 6.5 Hz, CH), 2.21 (6H, s, CH_3), 1.24 (6H, t, *J* 6.9 Hz, OCH_2CH_3), 0.90 (3H, d, *J* 6.5 Hz, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.2 (C), 144.6 (C), 105.1 (C), 60.0 (CH_2), 28.9 (CH), 22.6 (CH_3), 20.0 (CH_3), 14.8 (CH_3); *m/z* (ES) 268 (MH^+, 17%), 222 (100).

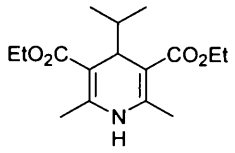
Diethyl 4–ethyl–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20k)



1,4–Dihydropyridine **20k** was prepared according to general procedure **6.2.10** using propionaldehyde **18g** (0.15 g, 2.5 mmol), ethyl acetoacetate **19b** (1.63 g, 12.5 mmol) and 35% aqueous ammonium hydroxide (0.17 g, 10.0 mmol). Purification by column chromatography on SiO_2, eluting with light petroleum–EtOAc (8:2) (R_f = 0.17) followed by recrystallization (aq.

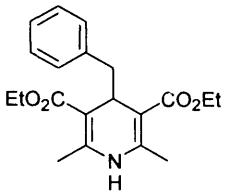
EtOH) gave the *title compound* as pale yellow solid (0.48 g, 68%); mp 111–112 °C (aq. EtOH) (lit.[147] mp 110 °C); (Found: MH^+, 282.1699. $C_{15}H_{24}NO_4$, [MH^+] requires 282.1700); IR (nujol)/cm^{-1} 3312, 1699, 1651, 1302, 1211, 1133, 1072, 999; ^1H NMR (400 MHz; $CDCl_3$) δ 5.48 (1H, br s, NH), 4.11 (4H, m, OCH_2CH_3), 3.86 (1H, t, *J* 5.5 Hz, CH), 2.10 (6H, s, CH_3), 1.29 (2H, m, CH_2CH_3), 1.22 (6H, t, *J* 7.2 Hz, OCH_2CH_3), 0.67 (3H, d, *J* 7.5 Hz, CH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.6 (C), 145.2 (C), 103.1 (C), 60.0 (CH_2), 34.4 (CH), 29.6 (CH_2), 19.9 (CH_3), 14.8 (CH_3), 9.6 (CH_3); *m/z* (ES) 282 (MH^+, 18%), 236 (100).

Diethyl 4–isopropyl–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20l)



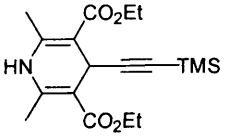
1,4–Dihydropyridine **20l** was prepared according to general procedure **6.2.10** using isobutyraldehyde **18h** (0.18 g, 2.5 mmol), ethyl acetoacetate **19b** (1.63 g, 12.5 mmol) and 35% aqueous ammonium hydroxide (0.17 g, 10.0 mmol). Purification by column chromatography on SiO_2, eluting with light petroleum–EtOAc (8:2) (R_f = 0.16), followed by recrystallization (aq. EtOH), gave the *title compound* as yellow solid (0.16 g, 21%); mp 95–97 °C (aq. EtOH) (lit.[147] mp 97 °C); (Found: MH^+, 296.1854. $C_{16}H_{26}NO_4$, [MH^+] requires 296.1856); IR (nujol)/cm^{-1} 3342, 1694, 1650, 1298, 1216, 1089, 1049; ^1H NMR (400 MHz; $CDCl_3$) δ 5.42 (1H, br s, N*H*), 4.12 (4H, m, OCH_2CH_3), 3.85 (1H, d, *J* 5.4 Hz, CH), 2.24 (6H, s, CH_3), 1.53 (1H, m, $CH(CH_3)_2$), 1.24 (6H, t, *J* 7.2 Hz, OCH_2CH_3), 0.67 (6H, d, *J* 6.8 Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.1 (C), 144.8 (C), 102.2 (C), 60.0 (CH_2), 39.2 (CH), 35.9 (CH), 19.8 (CH_3), 18.9 (CH_3), 14.5 (CH_3); *m/z* (ES) 296 (MH^+, 14%), 250 (100).

Diethyl 4–benzyl–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20i)



1,4–Dihydropyridine **20i** was prepared according to general procedure **6.2.10** using phenylacetaldehyde **18j** (0.30 g, 2.5 mmol), ethyl acetoacetate **19b** (1.63 g, 12.5 mmol) and 35% aqueous ammonium hydroxide (0.17 g, 10.0 mmol). Purification by column chromatography on SiO_2, eluting with light petroleum–EtOAc (8:2), followed by recrystallization (aq. EtOH) gave the *title compound* as pale yellow solid (0.22 g, 25%); mp 112–114 °C (aq. EtOH) (lit.[110] mp 114–116 °C); (Found: MH^+, 344.1848. $C_{20}H_{26}NO_4$, [MH^+] requires 344.1862); R_f = 0.45 (light petroleum–EtOAc, 1:1); IR (nujol)/cm^{-1} 3330, 1694, 1656, 1299, 1241, 1214, 1099, 1054, 750, 699; ^1H NMR (400 MHz; $CDCl_3$) δ 7.07 (3H, m, *o,p*–Ph*H*), 6.93 (2H, m, *m*–Ph*H*), 5.15 (1H, br s, NH), 4.12 (1H, t, *J* 5.5 Hz, CH), 3.99 (4H, m, OCH_2CH$_3$), 2.51 (2H, d, *J* 5.5 Hz, CH_2Ph), 2.11 (6H, s, CH_3), 1.18 (6H, t, *J* 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.2 (C), 145.7 (C), 139.7 (C), 130.5 (CH), 127.7 (CH), 126.0 (CH), 102.2 (C), 60.0 (CH_2), 42.7 (CH_2), 35.9 (CH), 19.6 (CH_3), 14.7 (CH_3); *m/z* (APcI) 344 (MH^+, 17%), 252 (100).

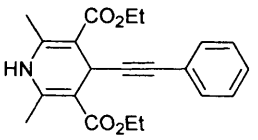
Diethyl 4–(trimethylsilylethynyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20n)



I. Two–component Hantzsch dihydropyridine synthesis using toluene–acetic acid as solvent system under microwave irradiation. A mixture of 3–(trimethylsilyl)propynal **18j** (50 mg, 0.53 mmol) and ethyl β–aminocrotonate **10a** (0.14 g, 1.05 mmol) in toluene–glacial acetic acid (5:1; 2 mL) was irradiated for 1 min at 100 °C in a sealed tube using a CEM Discover microwave synthesizer at an initial power of 70 W. The reaction mixture was allowed to cool and partitioned between saturated aqueous $NaHCO_3$ solution (25 mL) and ethyl acetate (25 mL). The aqueous layer was further extracted with ethyl acetate (2 x 15 mL) and the combined organic extracts were washed with brine (15 mL), dried ($NaSO_4$) and evaporated *in vacuo* to give the *title compound* as a yellow solid (0.15 g, 82%).

II. Four–component Hantzsch dihydropyridine synthesis using ethanol–acetic acid as solvent system under microwave irradiation. A solution of 3–(trimethylsilyl)propynal **18j** (50 mg, 0.53 mmol), ethyl acetoacetate **19b** (0.14 g, 1.1 mmol) and ammonium acetate (0.12 g, 1.6 mmol) in ethanol–glacial acetic acid (5:1; 2 mL) was irradiated for 7 min at 120 °C in a sealed tube using a CEM Discover microwave synthesizer at an initial power of 90 W. The solution was evaporated under reduced pressure and the residue partitioned between saturated aqueous $NaHCO_3$ solution (25 mL) and CH_2Cl_2 (25 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic extracts were washed with brine (15 mL), dried ($NaSO_4$) and evaporated *in vacuo* to give the *title compound* as a pale yellow solid (0.16 g, 84%).; mp 137–138 °C (aq. EtOH); (Found: MH^+, 350.1783. $C_{18}H_{27}NO_4Si$, [MH^+] requires 350.1782); R_f = 0.47 (light petroleum–EtOAc, 1:1); IR (nujol)/cm^{-1} 3302, 3244, 3107, 1699, 1661, 1636, 1503, 1328, 1301, 1208, 1120, 1095, 1026, 840; ^1H NMR (400 MHz; $CDCl_3$) δ 5.69 (1H, br s, NH), 4.72 (1H, s, CH), 4.11 (2H, m, $OCH\mathit{H}CH_3$), 4.08 (2H, m, $OCH\mathit{H}CH_3$), 2.20 (6H, s, CH_3), 1.21 (6H, t, *J* 7.1 Hz, $OCH_2C\mathit{H}_3$), 0.00 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.0 (C), 144.9 (C), 109.8 (C), 100.2 (C), 82.5 (C), 59.8 (CH_2), 27.6 (CH), 19.5 (CH_3), 14.4 (CH_3), 0.22 (CH_3); MS (APcI) *m/z* (rel intensity) 350 (MH^+, 100%), 252 (15), 178 (15), 113 (10).

Diethyl 4–(phenylethynyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate (20o)



I. Two–component Hantzsch dihydropyridine synthesis using toluene–acetic acid under microwave irradiation. A mixture of phenyl propargyl aldehyde **18k** (68mg, 0.53 mmol) and ethyl β–aminocrotonate **10a** (0.14 g, 1.05 mmol) in toluene–glacial acetic acid (5:1; 2 mL) was irradiated for 1 min at 100 °C in a sealed tube using a CEM Discover™ microwave synthesizer at an initial power of 70 W. The reaction mixture was allowed to cool and partitioned between saturated aqueous $NaHCO_3$ solution (25 mL) and ethyl acetate (25 mL). The aqueous layer was further extracted with ethyl acetate (2 x 15 mL) and the combined organic extracts were washed with brine (15 mL), dried ($NaSO_4$) and evaporated *in vacuo* to give the *title compound* as a yellow solid (0.183 g, 98%).

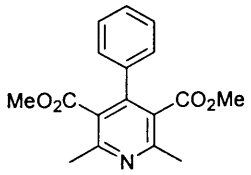
II. Two–component Hantzsch dihydropyridine synthesis using ethanol–acetic acid under microwave irradiation. A solution of phenyl propargyl aldehyde **18k** (68 mg, 0.53 mmol) and ethyl β–aminocrotonate **10a** (0.14 g, 1.05 mmol) in ethanol–glacial acetic acid (5:1; 2 mL) was irradiated for 1 min at 100 °C in a sealed tube using a CEM Discover™ microwave synthesizer at an initial power of 70 W. The solution was evaporated under reduced pressure and the residue partitioned between saturated aqueous $NaHCO_3$ solution (25 mL) and CH_2Cl_2 (25 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 x 15 ml), the combined organic extracts were washed with brine (15 mL), dried ($NaSO_4$) and evaporated *in vacuo* to give the *title compound* as a yellow solid (0.190 g, >98%).

III. Four–component Hantzsch dihydropyridine synthesis using ethanol–acetic acid under microwave irradiation. A solution of phenyl propargyl aldehyde **18k** (50 mg, 0.53 mmol), ethyl acetoacetate **19b** (0.14 g, 1.1 mmol) and ammonium acetate (0.12 g, 1.6 mmol) in ethanol–glacial acetic acid (5:1; 2 mL) was irradiated for 5 min at 120 °C in a sealed tube using a CEM Discover™ microwave synthesizer at an initial power of 90 W. The solution was evaporated under reduced pressure and the residue partitioned between saturated aqueous $NaHCO_3$ solution (25 mL) and CH_2Cl_2 (25 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 x 15 mL)

and the combined organic extracts were washed with brine (15 mL), dried ($NaSO_4$) and evaporated *in vacuo* to give the *title compound* as a yellow solid (0.180 g, 96%)

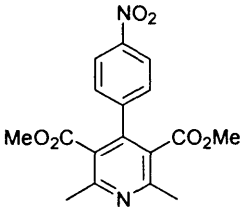
IV. Four–component Hantzsch dihydropyridine synthesis in a glass tube microwave reactor. A pressure–rated glass tube flow cell (10 mL) filled with sand (~12 g) was primed with ethanol–glacial acetic acid (5:1) at a flow rate of 0.6 mL/min and irradiated at an initial power of 100 W, stabilizing at 120 °C. A flask was charged with a solution solution of phenyl propargyl aldehyde **18k** (50 mg, 0.53 mmol), ethyl acetoacetate **19b** (0.14 g, 1.1 mmol) and ammonium acetate (0.12 g, 1.6 mmol) in ethanol–glacial acetic acid (5:1; 2 mL), which was then passed through the cavity at the given flow rate, washing with further batches of solvent. The reaction mixture was quenched in a solution of saturated aqueous $NaHCO_3$, evaporated under reduced pressure and the residue partitioned between saturated aqueous $NaHCO_3$ solution (25 mL) and CH_2Cl_2 (25 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 x 15 ml), the combined organic extracts were washed with brine (15 mL), dried ($NaSO_4$) and evaporated *in vacuo* to give the *title compound* as a yellow solid (0.13 g, 70%) mp 190–192 °C (aq. EtOH) (lit.[67] mp 192 °C); (Found: MH^+, 354.1700. $C_{21}H_{24}NO_4$, [MH^+] requires 354.1696); R_f = 0.39 (light petroleum–EtOAc, 1:1); IR (nujol)/cm^{-1} 3336, 1693, 1649, 1329, 1299, 1215, 1124, 1095, 761, 693; ^1H NMR (400 MHz; $CDCl_3$) δ 7.35 (2H, m, *o*–Ph*H*), 7.18 (3H, m, *m,p*–Ph*H*), 5.67 (1H, br s, NH), 5.20 (1H, s, CH), 4.32–4.10 (4H, m, OCH_2CH_3), 2.28 (6H, s, CH_3), 1.27 (6H, t, *J* 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.1 (C), 145.1 (C), 131.7 (CH), 128.0 (CH), 127.4 (CH), 124.1 (C), 100.3 (C), 93.1 (C), 79.2 (C), 59.1 (CH_2), 23.1 (CH), 19.6 (CH_3), 14.5 (CH_3), MS (APcI) *m/z* (rel intensity) 354 (MH^+, 52%), 252 (100).

Dimethyl 2,6–dimethyl–4–phenylpyridine–3,5–dicarboxylate (21a)



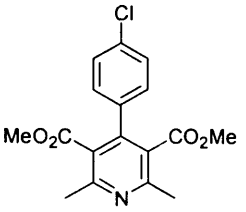
Dimethyl 4–phenyl–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20a** (60 mg, 0.2mmol) was reacted according to general procedure **6.2.11** to give the the *title compound* as a colourless solid (60 mg, >98%), mp 137 °C (EtOH) (lit.[148] mp 135–136 °C); (Found: MH^+, 300.1230. $C_{17}H_{18}NO_4$, [MH^+] requires 300.1230); R_f = 0.28 (light petroleum–Et_2O, 1:1); IR (nujol)/cm^{-1} 1732, 1556, 1288, 1113, 1036, 825; ^1H NMR (400 MHz; $CDCl_3$) δ 7.30 (3H, m, *o,p*–Ph*H*), 7.18 (2H, m, *m*–Ph*H*), 3.46 (6H, s, OCH_3), 2.52 (6H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.4 (C), 154.6 (C), 145.2 (C), 135.4 (C), 127.5 (CH), 127.2 (CH), 126.7 (CH), 125.7 (C), 51.2 (CH_3), 22.0 (CH_3); *m/z* (APcI) 300 (MH^+, 27%), 141 (100).

Dimethyl 2,6–dimethyl–4–(4–nitrophenyl)pyridine–3,5–dicarboxylate (21b)



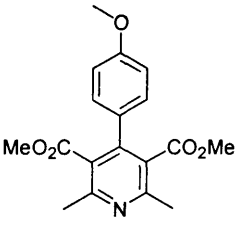
Dimethyl 4–(4–nitrophenyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20b** (60 mg, 0.17 mmol) was reacted according to general procedure **6.2.11** to give the *title compound* as a pale yellow solid (59 mg, 99%), mp 150–152 °C (EtOH) (lit.[118] mp 148 °C); (Found: MH^+, 345.1079. $C_{17}H_{17}N_2O_6$, [MH^+] requires 345.1081); R_f = 0.20 (light petroleum–Et_2O, 1:1); IR (nujol)/cm^{-1} 1721, 1602, 1558, 1516, 1346, 1303, 1231, 1099, 1048, 834; ^1H NMR (400 MHz; $CDCl_3$) δ 8.19 (2H, d, *J* 8.8 Hz, 3',5'–Ar*H*), 7.35 (2H, d, *J* 8.8 Hz, 2',6'–Ar*H*), 3.50 (6H, s, OCH_3), 2.56 (6H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.7 (C), 155.3 (C), 146.8 (C), 143.1 (C), 142.2 (C), 128.1 (CH), 125.0 (C), 122.4 (CH), 51.5 (CH_3), 22.2 (CH_3); *m/z* (ES) 345 (MH^+, 30%), 141 (100).

Dimethyl 2,6–Dimethyl–4–(4–chlorophenyl)pyridine–3,5–dicarboxylate (21c)



Dimethyl 4–(4–chlorophenyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20c** (60 mg, 0.18 mmol) was reacted according to general procedure **6.2.11** to give the *title compound* as a colourless solid (58 mg, 97%), mp 138–140 °C (EtOH) (lit.[118] mp 137–139 °C); (Found: MH^+, 334.0840. $C_{17}H_{17}NO_4Cl$, [MH^+] requires 334.0841); R_f = 0.28 (light petroleum–Et_2O, 1:1); IR (nujol)/cm^{-1} 1731, 1556, 1241, 1211, 1098, 1039, 832; ^1H NMR (400 MHz; $CDCl_3$) δ 7.28 (2H, d, *J* 8.9 Hz, 2',6'–Ar*H*), 7.12 (2H, d, *J* 8.9 Hz, 3',5'–Ar*H*), 3.50 (6H, s, OCH_3), 2.53 (6H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.6 (C), 156.1 (C), 145.3 (C), 136.1 (C), 135.2 (C), 129.6 (CH), 128.9 (CH), 127.0 (C), 52.7 (CH_3), 23.4 (CH_3); *m/z* (ES) 334 (MH^+, 42%), 141 (100).

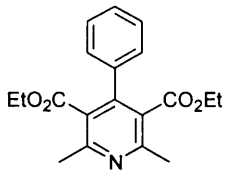
Dimethyl 2,6–dimethyl–4–(4–methoxyphenyl)pyridine–3,5–dicarboxylate (21d)



Dimethyl 4–(4–methoxyphenyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20d** (60 mg, 0.18 mmol) was reacted according to general procedure **6.2.11** to give the *title compound* as a pale yellow solid (57 mg, 96%), mp 115–117 °C (EtOH) (lit.[118] mp 115 °C); (Found: MH^+, 330.1338. $C_{18}H_{20}NO_5$, [MH^+] requires 330.1336); R_f = 0.20 (light petroleum–Et_2O, 1:1); IR

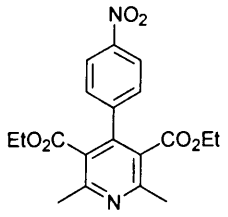
(nujol)/cm^{-1} 1731, 1609, 1562, 1513, 1292, 1245, 1180, 1111, 1030, 829; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.09 (2H, d, *J* 8.7 Hz, 2',6'–Ar*H*), 6.83 (2H, d, *J* 8.7 Hz, 3',5'–Ar*H*), 3.77 (3H, s, OCH_3), 3.51 (6H, s, OCH_3), 2.51 (6H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.1 (C), 160.1 (C), 155.8 (C), 146.2 (C), 129.5 (CH), 128.9 (C), 127.4 (C), 114.4 (CH),55.6 (CH_3), 52.7 (CH_3), 23.3 (CH_3); *m/z* (ES) 330 (MH^+, 100%), 272 (21), 141 (34).

Diethyl 2,6–Dimethyl–4–phenylpyridine–3,5–dicarboxylate (21e)



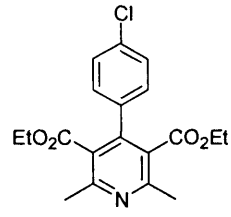
Dimethyl 4–phenyl–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20e** (0.12 g, 0.36 mmol) was reacted according to general procedure **6.2.11** to give the *title compound* as a colourless solid (0.118 g, 99%), mp 63 °C (EtOH) (lit.[120] mp 63–64 °C); (Found: MH^+, 328.1542. $C_{19}H_{22}NO_4$, [MH^+] requires 328.1543); R_f = 0.33 (light petroleum–Et_2O, 1:1); IR (nujol)/cm^{-1}: 1730, 1556, 1289, 1229, 1098, 1041, 754, 704; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.30–7.18 (5H, m, Ph*H*), 3.94 (4H, q, *J* 7.1 Hz, OCH_2CH_3), 2.53 (6H, s, CH_3), 0.82 (6H, t, *J* 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.3 (C), 155.8 (C), 146.5 (C), 136.9 (C), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.3 (C), 61.8 (CH_2), 23.3 (CH_3), 13.9 (CH_3); *m/z* (APcI) 328 (MH^+, 100%).

Diethyl 2,6–dimethyl–4–(4–nitrophenyl)pyridine–3,5–dicarboxylate (21f)



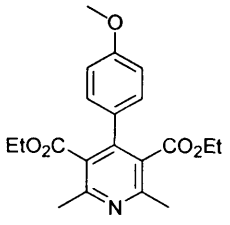
Dimethyl 4–(4–nitrophenyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20f** (0.13 g, 0.36 mmol) was reacted according to general procedure **6.2.11** to give the *title compound* as a pale yellow solid (0.126 g, 93%), mp 115–117 °C (EtOH) (lit.[110] mp 114–116 °C); (Found: MH^+, 373.1395. $C_{19}H_{21}N_2O_4$, [MH^+] requires 373.1394); R_f = 0.24 (light petroleum–Et_2O, 1:1); IR (nujol)/cm^{-1} 1723, 1601, 1556, 1518, 1349, 1295, 1230, 1105, 1045, 842; ^1H NMR (400 MHz; $CDCl_3$) δ 8.18 (2H, d, *J* 8.7 Hz, 3',5'–Ar*H*), 7.38 (2H, d, *J* 8.7 Hz, 2',6'–Ar*H*), 3.97 (4H, q, *J* 7.2 Hz, OCH_2CH_3), 2.57 (6H, s, CH_3), 0.92 (6H, t, *J* 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.5 (C), 156.5 (C), 148.2 (C), 144.4 (C), 143.7 (C), 129.8 (CH), 126.6 (C), 123.6 (CH), 62.1 (CH_2), 23.5 (CH_3), 14.1 (CH_3); *m/z* (ES) 373 (MH^+, 87%), 141 (100).

Diethyl 2,6–dimethyl–4–(4–chlorophenyl)pyridine–3,5–dicarboxylate (21g)



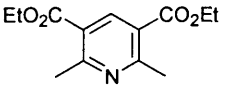
Dimethyl 4–phenyl–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20g** (0.12 g, 0.36 mmol) was reacted according to general procedure **6.2.11** to give the *title compound* as a pale yellow solid solid (0.118 g, 99%), mp 64–65 °C (EtOH) (lit.[110] mp 65–67 °C); (Found: MH^+, 362.1156. $C_{19}H_{21}NO_4Cl$, [MH^+] requires 362.1154); R_f = 0.28 (light petroleum–Et_2O, 1:1); IR (nujol)/cm^{-1} 1731, 1556, 1231, 1103, 1044, 835; ^1H NMR (400 MHz; $CDCl_3$) δ 7.28 (2H, d, *J* 8.9 Hz, 2',6'–Ar*H*), 7.12 (2H, d, *J* 8.9 Hz, 3',5'–Ar*H*), 3.99 (4H, q, *J* 7.1 Hz, OCH_2CH_3), 2.54 (6H, s, CH_3), 0.91 (6H, t, *J* 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.0 (C), 156.0 (C), 145.2 (C), 135.3 (C), 135.1 (C), 129.9 (CH), 128.8 (CH), 127.2 (C), 61.9 (CH_2), 23.4 (CH_3), 14.1 (CH_3); *m/z* (APcI) 362 (MH^+, 100%), 316 (48).

Diethyl 2,6–dimethyl–4–(4–methoxyphenyl)pyridine–3,5–dicarboxylate (21h)



Dimethyl 4–(4–methoxyphenyl)–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20h** (0.13 g, 0.36 mmol) was reacted according to general procedure **6.2.11** to give the *title compound* as a colourless solid; (0.129 g, 99%), mp 49 °C (EtOH) (lit.[146] mp 51–53 °C); (Found: MH^+, 358.1650. $C_{20}H_{23}NO_4$, [MH^+] requires 358.1649); R_f = 0.24 (light petroleum–Et_2O, 1:1); IR (nujol)/cm^{-1} 1730, 1610, 1556, 1515, 1292, 1250, 1180, 1106, 1028, 832; ^1H NMR (400 MHz; $CDCl_3$) δ 7.13 (2H, d, *J* 8.7 Hz, 2',6'–Ar*H*), 6.82 (2H, d, *J* 8.7 Hz, 3',5'–Ar*H*), 3.97 (4H, q, *J* 7.1 Hz, OCH_2CH_3), 2.52 (6H, s, CH_3), 0.93 (6H, t, *J* 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.1 (C), 158.7 (C), 154.1 (C), 144.7 (C), 128.4 (CH), 127.6 (C), 126.2 (C), 112.5 (CH), 60.3 (CH_2), 54.3 (CH_3), 21.8 (CH_3), 12.7 (CH_3); *m/z* (APcI) 358 (MH^+, 57%), 141 (100).

Diethyl 2,6–dimethylpyridine–3,5–dicarboxylate (21i)

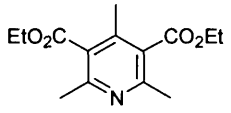


Diethyl 4–benzyl–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20m** (0.125 g, 0.36 mmol), diethyl 2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20i** (92 mg[ii]) and diethyl 4–isopropyl–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20l** (0.108 g, 0.36 mmol) were reacted according to general procedure **6.2.11** to give the the *title compound* as a colourless

[ii] A 3.5:1 crude mixture of 1,4-DHPy **X** (42%) and pyridine **Y** (12%), obtained using the general procedure **6.2.8**, was used directly without purification.

solid (89.7 mg, 98%; 86.8 mg, 94%[iii]; 83.2 mg, 91% respectively), mp 72–73 °C (EtOH) (lit.[113] mp 70–71 °C); (Found: MH^+, 252.1230. $C_{13}H_{18}NO_4$, [MH^+] requires 252.1230); R_f = 0.48 (light petroleum–Et_2O, 1:1); IR (nujol)/cm^{-1} 1721, 1591, 1555, 1298, 1254, 1223, 1107, 1045, 772; ^1H NMR (400 MHz; $CDCl_3$) δ 8.60 (1H, s, CH), 4.33 (4H, q, *J* 7.2 Hz, OCH_2CH_3), 2.78 (6H, s, CH_3), 1.34 (6H, t, *J* 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.3 (C), 162.6 (C), 141.3 (CH), 123.5 (C), 61.8 (CH_2), 25.3 (CH_3), 14.7 (CH_3); *m/z* (APcI) 252 (MH^+, 24%), 141 (100).

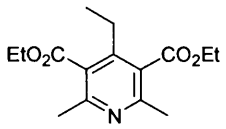
Diethyl 2,6–dimethyl–4–methylpyridine–3,5–dicarboxylate (21j)



Dimethyl 4–methyl–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20j** (97 mg, 0.36 mmol) was reacted according to general procedure **6.2.11** to give the *title compound* as a colourless oil[120] (93 mg, 97%); (Found: MH^+, 266.1387. $C_{14}H_{20}NO_4$, [MH^+] requires 266.1387); R_f = 0.33 (light petroleum–Et_2O, 1:1); IR (film)/cm^{-1} 2981, 1727, 1567, 1446, 1285, 1220, 1106, 1042; ^1H NMR (400 MHz; $CDCl_3$) δ 4.34 (4H, q, *J* 7.1 Hz, OCH_2CH_3), 2.46 (6H, s, CH_3), 2.19 (3H, s, CH_3), 1.32 (6H, t, *J* 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 174.6 (C), 166.4 (C), 155.3 (CH), 127.3 (C), 62.0 (CH_2), 23.3 (CH_3), 17.3 (CH_3), 14.6 (CH_3); *m/z* (APcI) 266 (MH^+, 58%), 141 (100).

[iii] 51% overall yield over 2 steps.

Diethyl 2,6–dimethyl–4–ethylpyridine–3,5–dicarboxylate (21k)



Dimethyl 4–ethyl–2,6–dimethyl–1,4–dihydropyridine–3,5–dicarboxylate **20k** (0.10 g, 0.36 mmol) was reacted according to general procedure **6.2.11** to give the *title compound* as a colourless oil[147] (0.10 g, 98%); (Found: MH^+, 280.1543. $C_{15}H_{22}NO_4$, [MH^+] requires 280.1543); R_f = 0.35 (light petroleum–Et_2O, 1:1); IR (film)/cm^{-1} 2979, 1729, 1568, 1447, 1414, 1384, 1278, 1236, 1208, 1106, 1040, 860; ^1H NMR (400 MHz; $CDCl_3$) δ 4.34 (4H, q, *J* 7.1 Hz, OCH_2CH_3), 2.52 (2H, q, *J* 7.6 Hz, CH_2CH_3), 2.45 (6H, s, CH_3), 1.32 (6H, t, *J* 7.1 Hz, OCH_2CH_3), 1.11 (3H, t, *J* 7.6 Hz, CH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.8 (C), 155.4 (C), 131.9 (C), 127.5 (C), 62.0 (CH_2), 25.2 (CH_2), 23.2 (CH_3), 15.6 (CH_3), 14.6 (CH_3); *m/z* (APcI) 280 (MH^+, 97%), 141 (100).

APPENDIX A: ^1H NMR and GC-MS of Pyridine 12a-d

Inlet Method report MassLynk 4.0 SCN540

Method File: **c:\masslynx\analysis.pro\acqdb\caterina**

HP6890 GC Column 1	
Column lenght (m)	30.00
Column Diameter	250.00
Film thickness(um)	0.25
Carner Gas	helium
Mode	constant flow
Inlet	back inlet
HP6890 GC Column 2	
Column lenght (m)	25.00
Column Diameter	250.00
Film thickness(um)	0.25
Carner Gas	helium
Mode	constant pressure
Inlet	back inlet
HP6890 GC Oven Parameters	
Maximum oven temperature(°C)	350.0
Equilibrium time(min)	0.0
HP6890 GC Oven Ramp	
Initial temperature(°C)	40.0
Time at initial temperature (min)	5.0

Time(min)	Rate(°C/min)	Temp(°C)
5.0	10.0	250.0
0.0	0.0	0.0
0.0	0.0	0.0
0.0	0.0	0.0
0.0	0.0	0.0
0.0	0.0	0.0

HP6890 GC Pressure 1

Initial Pressure(kPa) 1.0

Time(min)	Rate(kPa/min)	Final Pres(kPa)
0.0	0.0	0.0
0.0	0.0	0.0
0.0	0.0	0.0

HP6890 GC Pressure 2

Initial Pressure(kPa) 1.0

Time(min)	Rate(kPa/min)	Final Pres(kPa)
0.0	0.0	0.0
0.0	0.0	0.0
0.0	0.0	0.0

HP6890 PTV Inlet Cryogenic Parameters

Back inlet

Split/Splitless: Split mode

Initial temperature(°C)	200.0
Initial Pressure(kPa)	1.0
Split ratio	5

CTL PAL Method Parameters

MacroValues = GC-Inj(0,0,2,2,5,1,GC Inj1,50,500,500,2,2)

Syringe size = 10ul

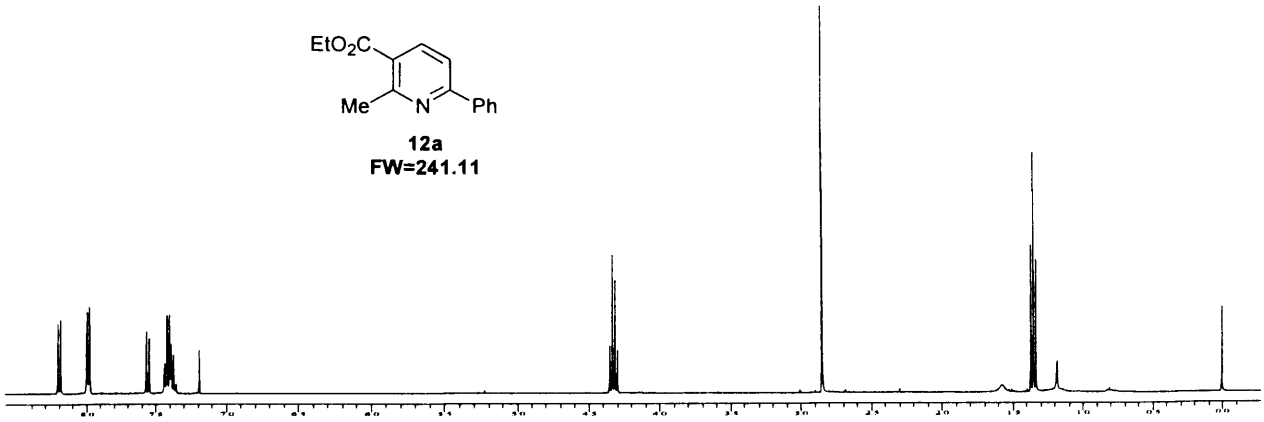
Macroline
001:Air volume (µl);0;0;SYR.Max Volume
002: Pre Clean with solvent 1 ();0;0;99
003: Pre Clean with solvent 2 ();0;0;99
004: Pre Clean with solvent ();0;0;99
005. Filling Speed (µl/s); SYR.Inject Speed; SYR.Min Speed; SYR.Max Speed
006: Filling stokes ();1;0;99
007: Inject to;INJECTOR
008: Injection Speed (µl/s); SYR.Inject Speed; SYR.Min Speed; SYR.Max Speed
009: Pre Inject Delay (ms);500;0;99000
010: Post Inject Delay (ms);500;0;99000
011: Post Clean with solvent 1();1;0;99
012: Post Clean with solvent 2();1;0;99

ATOM
001: LOCK_TERMINAL(On)
002: WAIT_FOR_DS()
003: WAIT_SYNC_SIG(Start.)
004:CLEANUP(Wash1,Off,Off,On,Off,On,Off,Off,)
005. CLEAN_SYR(Wash1, Pre Clean with solvent 1,,,,,)
006: CLEAN_SYR(Wash2, Pre Clean with solvent 2,,,,,)
007: REPEAT(Pre Clean with Sample,)
008: GET_SAMPLE(SL.Tray,SL.Index,SL.Volume,,,,Filling Speed,,,0,Off,,,)
009: PUT SAMPLE(Waste,1,,,,,)
010: END()
011: GET_SAMPLE(SL.Tray,SL.Index,SL.Volume,Air Volume,,,Filling Speed,,,,Filling Stokes,Off...)
012: INJ_SAMPLE(Inject to,Inject, Injected,,,Pre Inject Delay,Injection Speed,Post Inject Delay,1,)
0.13: SET_INJECTED()
0.14: CLEAN_SYR(Wash1,Post Clean with Solvent 1,,,,,,,)
0.15: CLEAN_SYR(Wash2,Post Clean with Solvent 2,,,,,,,)
0.16: CLEANUP(Wash1,Off,Off,Off,Off,Off,Off,On,)
0.17: LOCK TERMINAL(Off,)

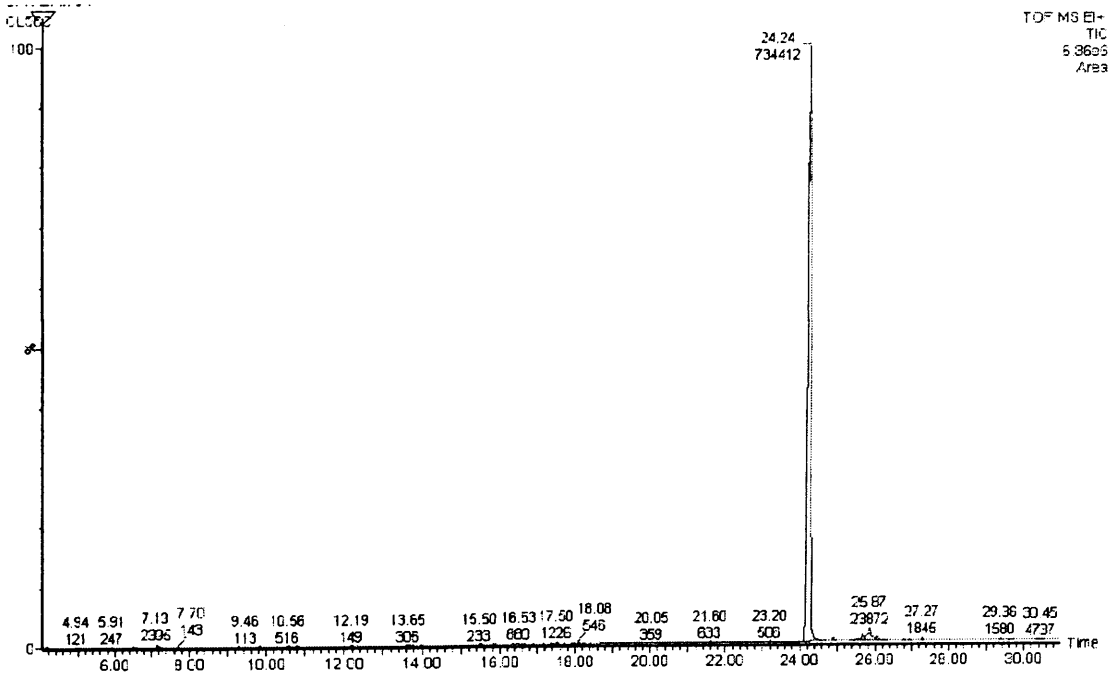
End Of Report

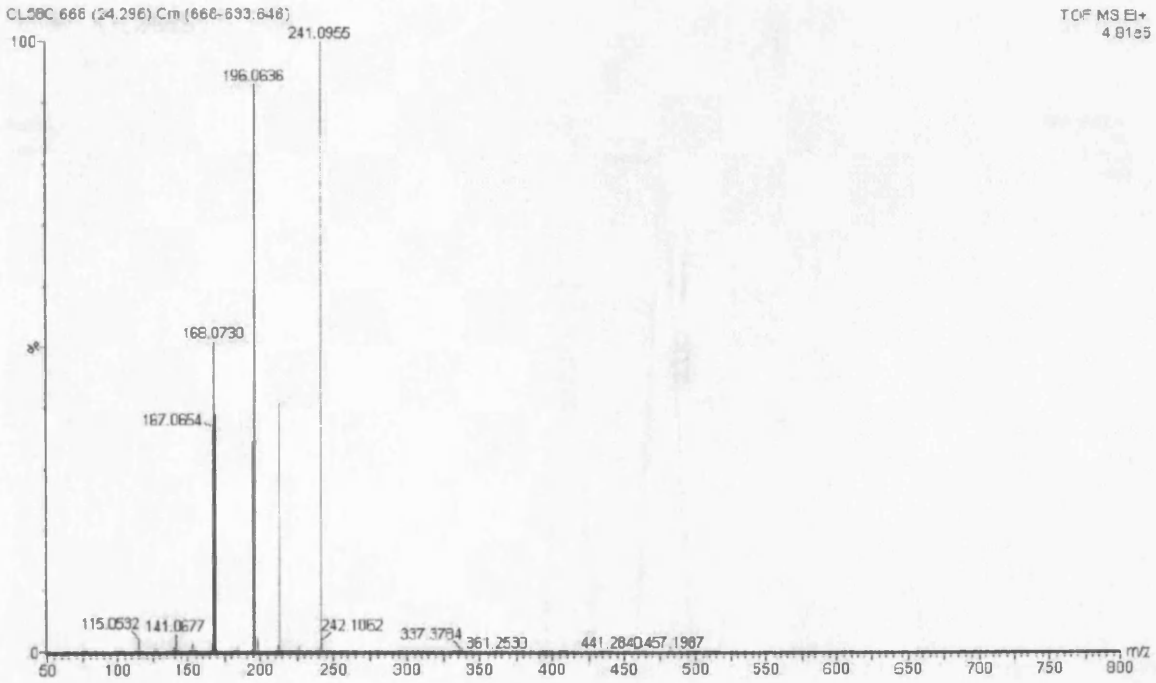
Pyridine 12a

- ^{1}H NMR



- GC-MS

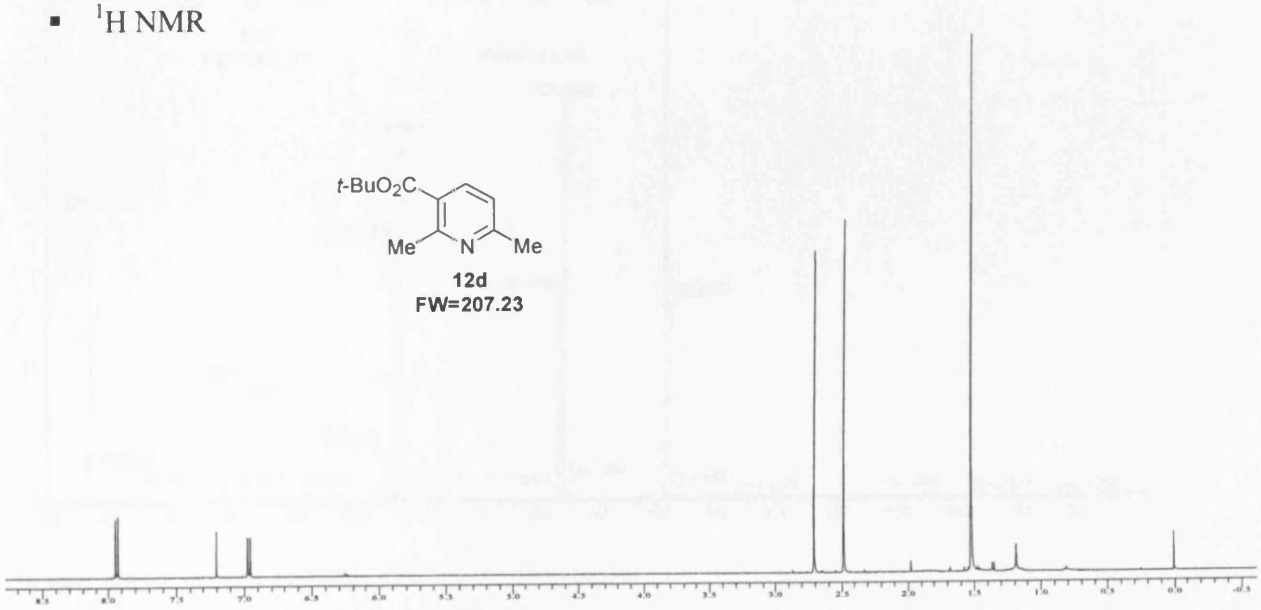




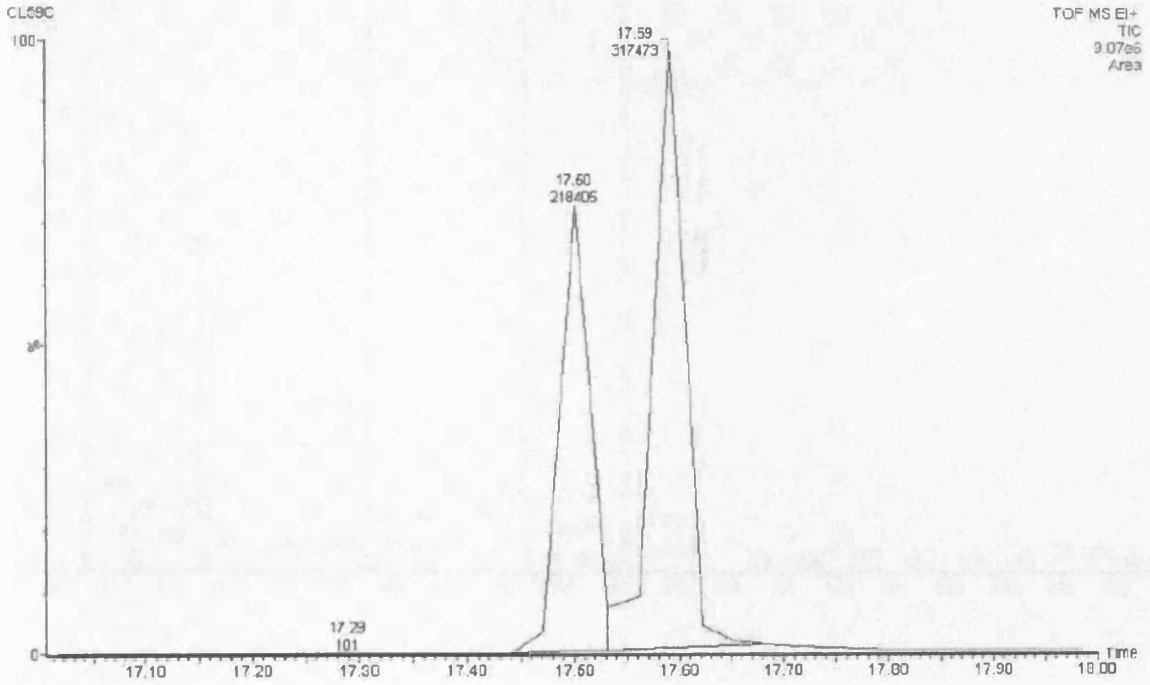
Pyridine 12b

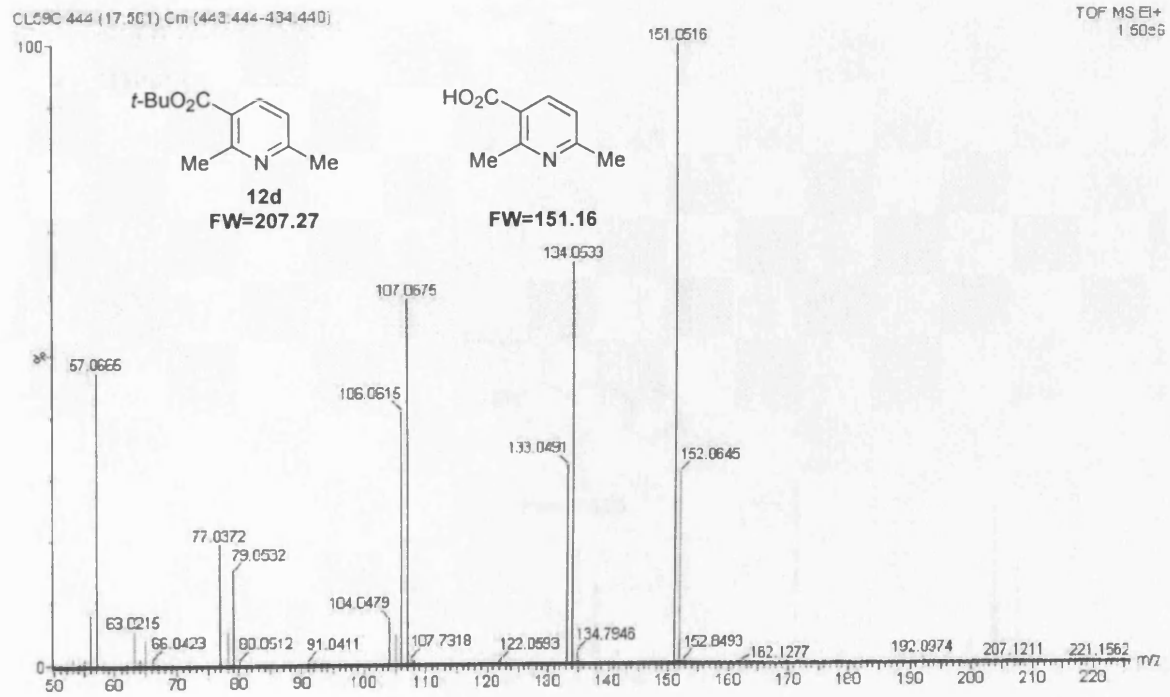
^{1}H NMR shows the target pyridine **12b** with traces of impurity, however the GC shows two picks. It seems that the *t*-butyl ester group hydrolyzed under the analyse conditions and only the corresponding carboxylic acid was detected

- ^{1}H NMR



- GC-MS


CL69C
100
%
0
17.59
317473
17.60
218405
17.29
101
TOF MS EI+
TIC
9.07e6
Area
Time
17.10
17.20
17.30
17.40
17.50
17.60
17.70
17.80
17.90
18.00


CL69C 444 (17.501) Cm (443:444-434:440)
TOF MS EI+
1.60e6
100
%
0
t-BuO2C
Me
N
Me
12d
FW=207.27
HO2C
Me
N
Me
FW=151.16
151.0516
134.0533
107.0675
57.0695
106.0615
133.0491
152.0645
77.0372
79.0532
104.0479
63.0215
66.0423
80.0512
91.0411
107.7318
122.0593
134.7946
152.8493
162.1277
192.0974
207.1211
221.1562
m/z
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70
80
90
100
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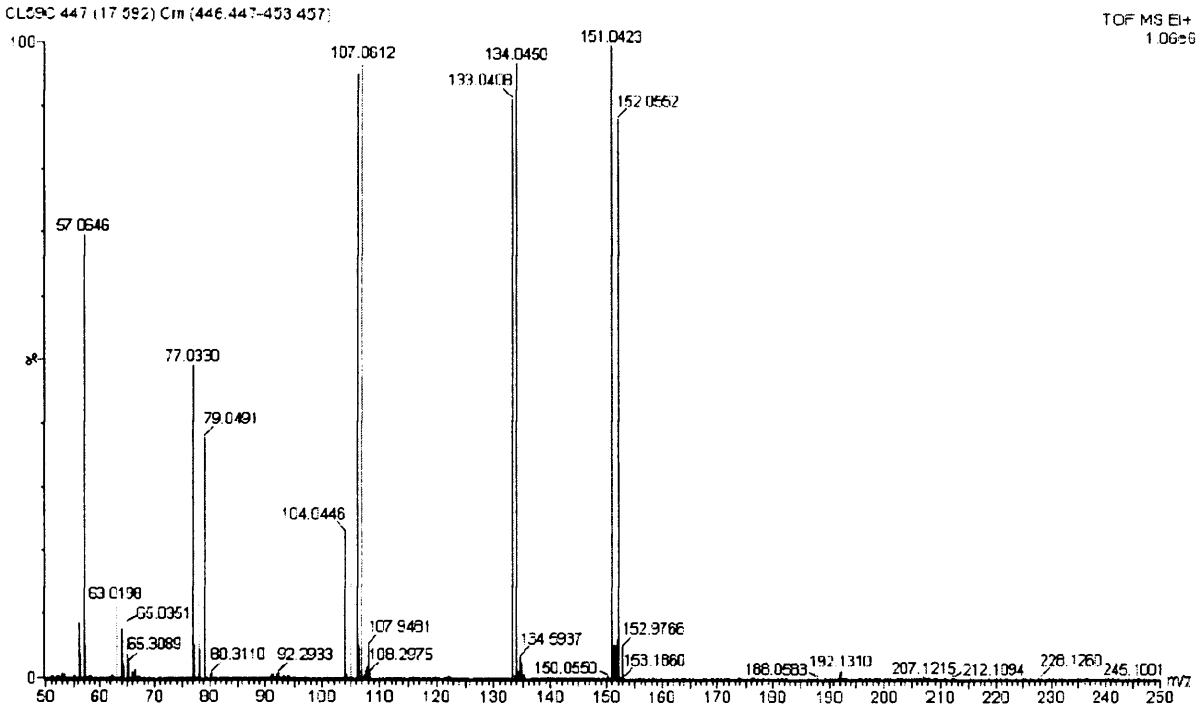
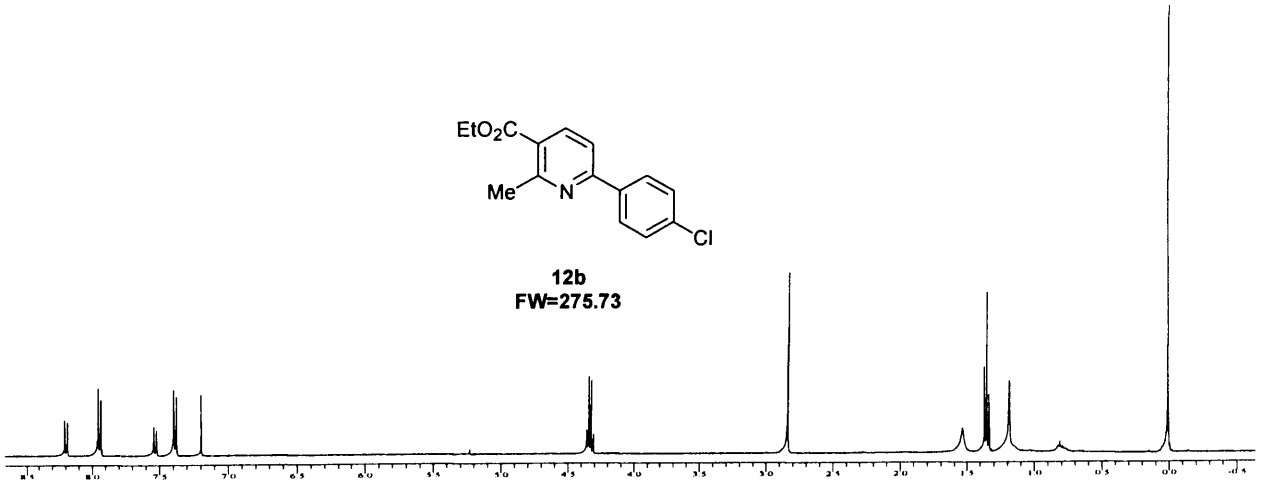
120
130
140
150
160
170
180
190
200
210
220

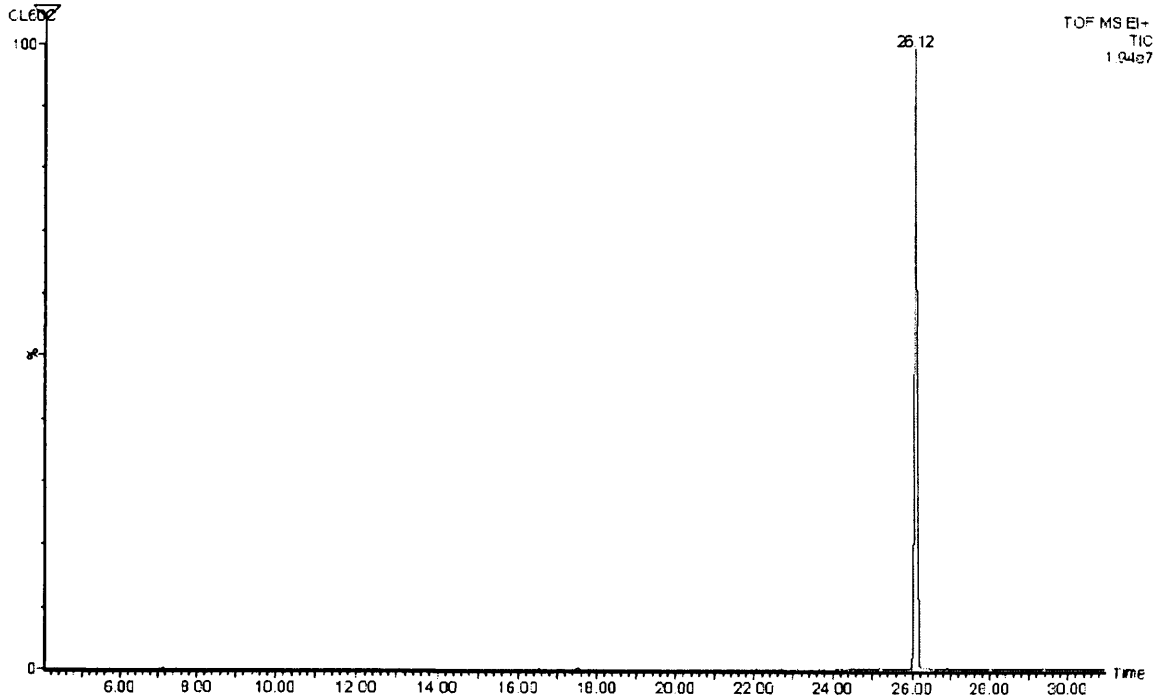


Pyridine 12c

- ^{1}H NMR



- GC-MS


CL60C
100
%
0
26.12
TOF MS EI+
TIC
1.94e7
6.00
8.00
10.00
12.00
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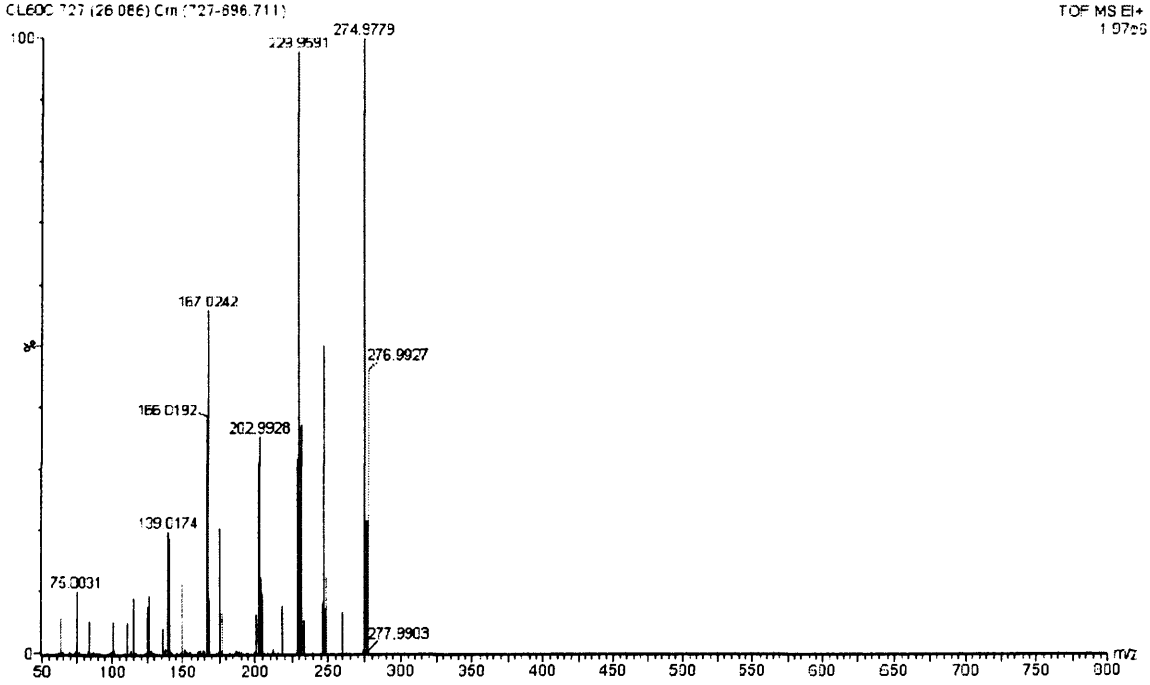
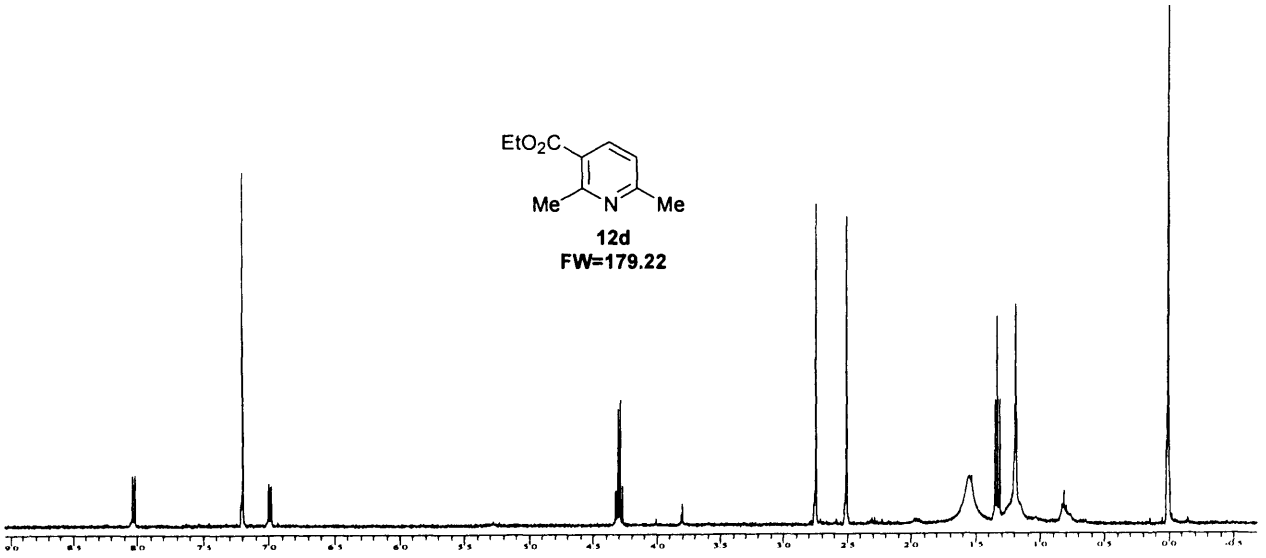
16.00
18.00
20.00
22.00
24.00
26.00
28.00
30.00
Time

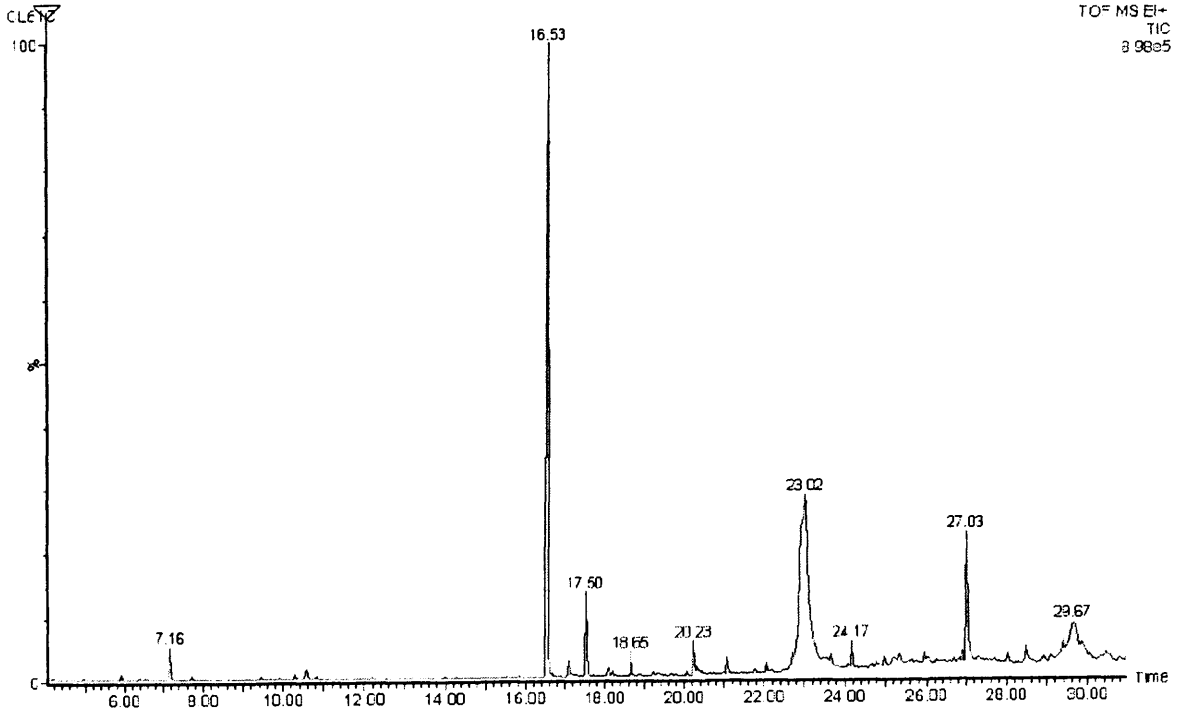

CL60C 727 (26.086) Cm (727-896.711)
TOF MS EI+
1.97e6
100
%
0
274.9779
229.9591
167.0242
276.9927
166.0192
202.9928
139.0174
75.0031
277.9903
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
m/z

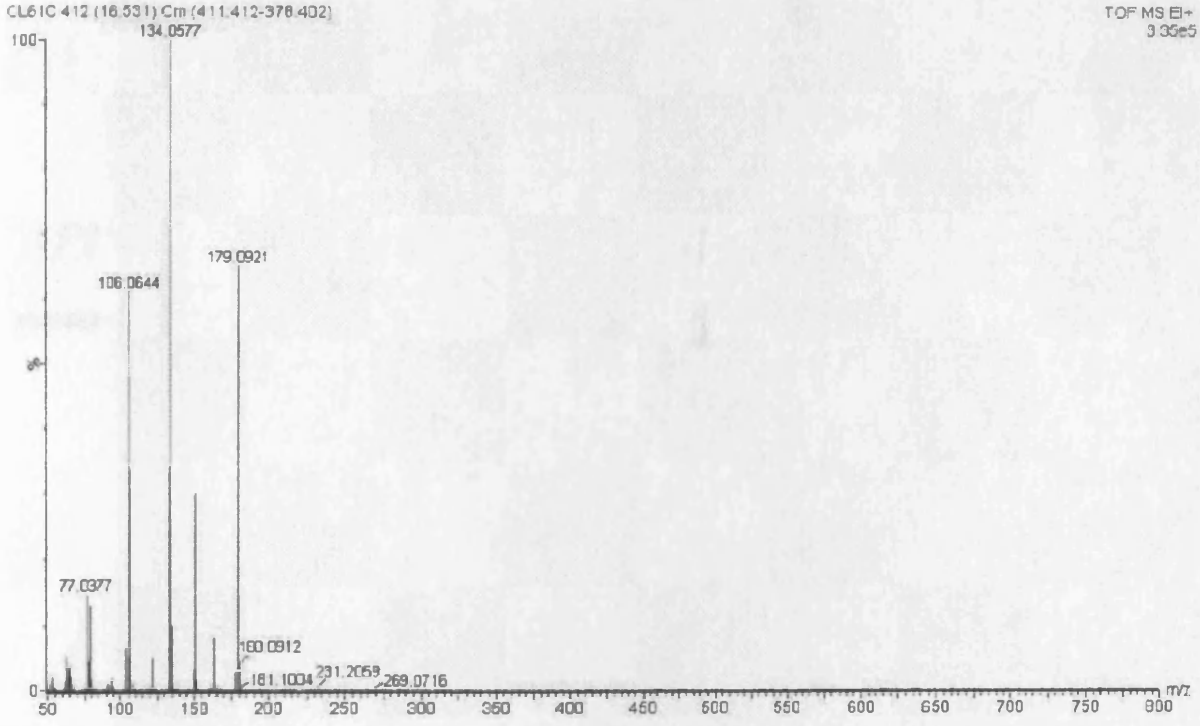
Pyridine 12d

- ^{1}H NMR



- GC-MS




CL61C 412 (16.531) Cm (411:412-378:402)
TOF MS EI+
3.39e5
100
%
0
134.0577
179.0921
106.0644
77.0377
180.0912
181.1004
231.2058
269.0716
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
m/z

APPENDIX B

JOC*Note*

A Simple Continuous Flow Microwave Reactor

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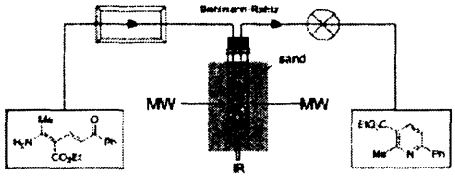
bagleymc@cf.ac.uk; robin.wood@astrazeneca.com

Received May 23, 2005



A new simple procedure for microwave-assisted organic synthesis under continuous flow processing has been developed for use in a monomodal microwave synthesizer with direct temperature control using the instrument's in-built IR sensor. This design makes optimum use of the standing wave cavity to improve the energy efficiency of microwave-assisted flow reactions.

Microwave-assisted organic synthesis (MAOS) has received increasing attention in recent years as a valuable alternative to the use of conductive heating for accelerating chemical reactions.[1] With no direct contact between the chemical reactants and the energy source, microwave-assisted chemistry is energy efficient, provides fast heating rates and enables rapid optimization of procedures. From the early experiments in domestic ovens[2] to the use of multimodal[3] or monomodal[4] instruments designed for organic synthesis, this technology has been implemented worldwide and continues to be developed.[5] However, although modern monomodal instruments dedicated for MAOS are very successful in small-scale operations, efforts to process this technology in continuous flow (CF) reactors are frustrated by the physical limitations of microwave heating, with a penetration depth of only a few centimeters and the limited dimensions of the standing wave cavity. Current technology has attempted to overcome these obstacles with conventional instruments by the use of CF reactors that pump the reagents through a small heated coil that winds in and out of the cavity,[6] with external temperature monitoring using a fiber optic sensor, although alternative methods, such as using a multimode batch[3,7] or CF reactor,[8] have also been described. We now wish to report our new method for carrying out MAOS under CF processing using a commercially available monomodal microwave synthesizer.

The principal design of our flow cell featured the need to make optimum use of the cavity and to be able to monitor the temperature of the flow cell directly using the instrument's in-built IR sensor. To this end, a standard pressure-rated glass tube (10 mL) fitted with a custom built steel head was filled with sand (~10 g) between two drilled frits (Figure 1) to minimize dispersion and effectively create a lattice of microchannels, charged with solvent (~5 mL volume), sealed using PTFE washers and connected to an HPLC flow system with a back-pressure regulator (Figure 2). The flow cell was inserted into the cavity of a self-tunable monomodal microwave synthesizer, irradiated, and stabilized at the required reaction temperature through moderation of microwave power before the introduction of reagents into the reactor. This system possessed a number of advantages over commercially available coils, including simple measurement of the flow cell temperature, no additional and expensive equipment required short of an HPLC pump, and the potential to carry out heterogeneous as well as homogeneous reactions simply by immobilizing a catalyst on the support in the glass tube.

The cell was first tested in two well-precedented microwave-assisted reactions operating under continuous flow (CF) processing, the hydrolysis of chloromethyl-

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‡ CEM Microwave Technology Ltd. Phone: +44-12-8062-2875. Fax +44-12-8062-2342.
§ AstraZeneca R&D.

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Published on Web 07/23/2005

JOC Note

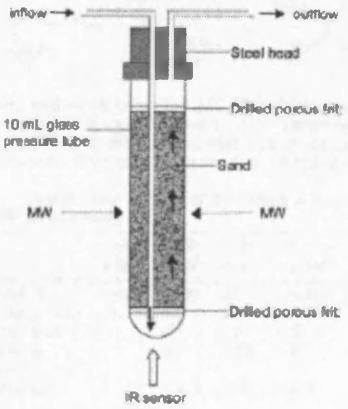


FIGURE 1. Flow cell schematic.

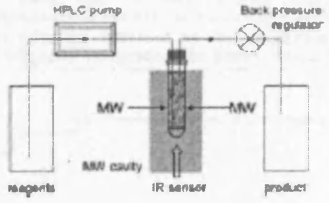
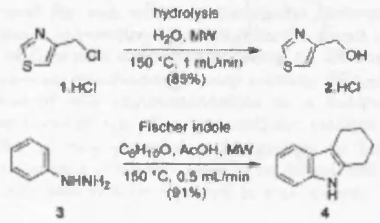


FIGURE 2. Schematic diagram of the CF reactor.

thiazole **1** to give hydrochloride **2**[9] and a Fischer indole synthesis[10] of **4** from hydrazine **3** and cyclohexanone in acetic acid, in both cases using sand as the packing agent. Under these conditions efficient conversions were achieved at 150 °C, processing 1 g in 15–30 min, to give alcohol **2** and indole **4** in 85% and 91% yield, respectively (Scheme 1).

Following the success of these flow reactions, efforts were made to develop a new microwave-assisted process

SCHEME 1. MW-Assisted CF Reactions



for the synthesis of pyridines based upon the Bohlmann–Rahtz (B-R)[11] reaction. The cyclodehydration of aminodienone **5** can be effected using conductive heating,[12] and with a Lewis[13] or Brønsted[14] acid catalyst, to give 2,3,6-trisubstituted pyridine **6** directly and with total regiocontrol, and this transformation has been applied in the synthesis of pyridine-containing thiopeptide antibiotics,[15] and their derivatives,[16] as well as pyrido[2,3-*d*]pyrimidines,[17] heterocyclic amino acids,[18] nonsteroidal antiinflammatory agents,[19] and combinatorial pyridine libraries.[20] Aminodienone **5** was prepared according to known procedures[12] and cyclodehydrated with CF processing under homogeneous conditions in toluene–acetic acid (5:1) over sand,[21] comparing the results to batch experiments carried out in a sealed tube and to the corresponding homogeneous CF process with a Teflon heating coil (Scheme 2). Under conditions that gave efficient conversion (>98%) to pyridine **6**, the processing rates of material using our glass tube reactor were considerably higher (Table 1). Additionally, CF reactions run at the same flow rate used less magnetron energy in a glass tube than in the heating coil (Table 1, Figures 3 and 4, and Supporting Information), demonstrating that a glass tube CF reactor

(9) For comparison, a solution of **1**·HCl (170 mg, 1.0 mmol) in H_2O (2 mL) was irradiated at 150 °C in a sealed glass tube (150 W) for 10 min and evaporated in vacuo to give **2**·HCl (151 mg, >98%). Comparable conductive heating procedures carried out at 150 °C in a sealed tube for 12 min, or at reflux for 30 min, gave thiazole **2**·HCl (90% or 85%, respectively, by HPLC). For related hydrolysis experiments using conductive heating, see: (a) Houssin, R.; Pommery, J.; Salauen, M.-C.; Deweer, S.; Goossens, J.-F.; Chavatte, P.; Henichart, J.-P. *J. Med. Chem.* **2002**, *45*, 533. (b) Hagen, S. E.; Domagala, J.; Gajda, C.; Lovdahl, M.; Tait, B. D.; Wise, E.; Holler, T.; Hupe, D.; Nouhan, C.; Urumov, A.; Zeikus, G.; Zeikus, E.; Lunney, E. A.; Pavlovsky, A.; Gracheck, S. J.; Saunders, J.; VanderRoest, S.; Brodfuehrer, J. *Med. Chem.* **2001**, *44*, 2319.

(10) For comparison, a solution of cyclohexanone (196 mg, 2 mmol) and **3** (220 mg, 2.2 mmol) in AcOH (4 mL) was irradiated at 150 °C in a sealed glass tube (150 W) for 10 min and then evaporated in vacuo. The residue was extracted with EtOAc, washed with H_2O, aqueous $NaHCO_3$ solution (2 N) and brine, dried ($MgSO_4$), and evaporated in vacuo to give **4** (212 mg, 62%), mp 113–115 °C. The comparable conductive heating procedure carried out at 150 °C in a sealed tube for 10 min gave **4** (94%), mp 115–117 °C, after purification by column chromatography on SiO_2 eluting with light petroleum–EtOAc (9:1). For related Fischer indole syntheses, see: (a) Am, J.; Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1997**, *62*, 2505. (b) Robinson, B. *Chem. Rev.* **1969**, *69*, 227. (c) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607. (d) Franco, L. H.; Palermo, J. A. *Chem. Pharm. Bull.* **2003**, *51*, 975. (e) Lipin'ska, T. *Chem. Heterocycl. Compd.* **2001**, *37*, 231. (f) Lipin'ska, T.; Guibe-Jampel, E.; Petit, A.; Loupy, A. *Synth. Commun.* **1999**, *29*, 1349.

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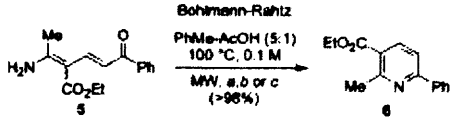
(21) The glass tube was filled with standard quartz sand, 40–100 mesh, suitable for use in chromatography. When aminodienone **5** was irradiated in toluene (without acetic acid) in the presence and absence of sand in a sealed tube, no appreciable difference was observed (13% versus 5% conversion, respectively), indicating that the sand has a negligible (if any) effect on the cyclodehydration.

SCHEME 2. Bohlmann–Rahtz Synthesis of 6[a]



[a] Reagents and conditions: (a) 150 W (initial power), sealed tube, 2 min; (b) 300 W (initial power), CF in Teflon heating coil, 1 mL/min; (c) 300 W (initial power) with simultaneous cooling.[22] CF in a glass tube charged with sand, 1 or 1.5 mL/min.

TABLE 1. Comparing MAOS of Pyridine 6 Using Sealed Tube or CF Processing

	sealed tube[a]	CF coil[b]	CF coil[b]	CF *glass* tube[c]	CF *glass* tube[c]
isolated yield, %	>98	>98	85[d]	>98	>98
residency time,[e] min	2	5[f]	3.3[f]	3	2
flow rate, mL min^{-1}		1	1.5	1	1.5
processing rate, mmol min^{-1}		0.1	0.15	0.1	0.15
total energy,[g] kJ		1411	762	850	735

[a] Batch experiment in a sealed glass tube. [b] CF processing in a Teflon heating coil. [c] CF processing in glass tube reactor charged with sand. [d] Based upon ^{1}H NMR analysis of crude reaction mixture. [e] Residency in the microwave cavity. [f] Residency in the heating coil. [g] Energy delivered by the magnetron in a flow reaction, obtained by integrating the power versus time profile.

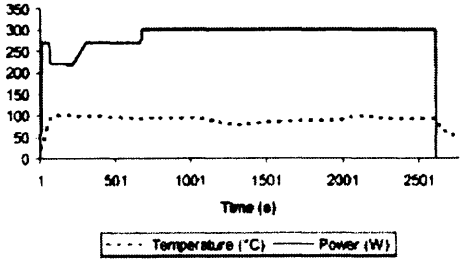


FIGURE 3. Reaction profile of the CF heating coil reactor at 1.5 mL min^{-1} flow rate.

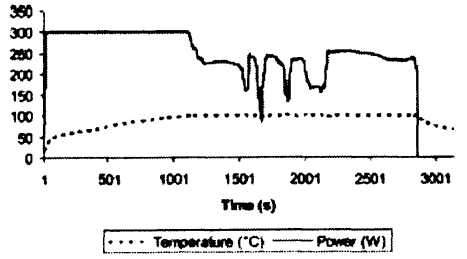


FIGURE 4. Reaction profile of the CF glass tube reactor at 1.5 mL min^{-1} flow rate.

offers (i) improved heating efficiency, (ii) the potential for operation on a large scale, (iii) successful transfer from batch to CF processing, and (iv) improved performance over commercial Teflon heating coils. A higher processing rate is possible with a glass tube reactor as a faster flow rate can be maintained without compromising the reaction temperature and yield. We have attributed this observation to be a direct consequence of the improved heating efficiency for reactions in the glass tube, as heating coils by design wind in and out of the optimum space.

In conclusion, a CF microwave reactor has been developed for use with a monomodal instrument for homogeneous reactions that enables the direct measurement of flow cell temperature using an IR sensor and possesses many advantages over existing CF technology. The use of this instrumentation in a heterogeneous process through use of an immobilized catalyst and the transfer of this processing technology to large-scale operations on a kilogram scale in an 80 mL cell are now underway and will be reported in due course.

Experimental Section

Microwave Reactions under CF Processing. The flow cell (see the Supporting Information for flow cell assembly) was primed with solvent at a given flow rate and stabilized at the reaction temperature. A flask was charged with the reaction mixture, which was then passed through the cavity at the given flow rate, washing with further batches of solvent.

4-Hydroxymethylthiazole (2) Hydrochloride. A solution of 4-chloromethylthiazole hydrochloride (2.0 g, 12 mmol) in H_2O (20 mL) was irradiated at 150 °C (150 W) in a pressure-rated glass tube (10 mL) filled with sand (~12 g) in a MW CF reactor at a flow rate of 1.0 mL min^{-1}. The cell was washed with H_2O (20 mL) at 150 °C and the combined solutions were evaporated in vacuo. Purification by recrystallization (Et_2O–EtOH) gave the title compound (1.5 g, 85%) as pale brown crystals, mp 112–114 °C (lit.[23] mp 115 °C) (found: $M^{+\cdot}$, 115.0093; C_4H_5NOS requires M 115.0092); ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.35 (1H, s), 8.20–7.70 (2H, br s), 7.60 (1H, s), 4.65 (2H, s).

2,3,4,9-Tetrahydro-1*H*-carbazole (4). A solution of cyclohexanone (1.96 g, 20 mmol) and phenylhydrazine (2.20 g, 22 mmol) in glacial AcOH (40 mL) was irradiated at 150 °C (150 W) in a pressure-rated glass tube (10 mL) filled with sand (~12 g) in a MW CF reactor at a flow rate of 0.5 mL min^{-1}. The cell was washed with AcOH (15 mL) at 150 °C and the combined solutions were evaporated in vacuo. The residue was extracted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and evaporated in vacuo. Purification by recrystallization (EtOAc–hexane) gave the title compound (3.1 g, 91%) as pale beige crystals, mp 114–116 °C (lit.[24] mp 115–116 °C) (found: $M^{+\cdot}$, 171.1057; $C_{12}H_{13}N$ requires M 171.1048); ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.56 (1H, s), 7.30 (1H, d, J = 7 Hz), 7.20 (1H, d, J = 8 Hz), 6.96 (app t, 1H, J = 7 Hz), 6.89 (1H, app t, J = 8 Hz), 2.68 (2H, t, J = 5.7 Hz), 2.60 (2H, t, J = 6.0 Hz), 1.86–1.74 (4H).

Ethyl 2-Methyl-6-phenylpyridine-3-carboxylate (6): Batch Synthesis in a Sealed Tube. A solution of aminodienone 5[11,12] (80 mg, 0.3 mmol) in PhMe–AcOH (5:1) (3 mL) was irradiated for 2 min at 100 °C (150 W) in a sealed pressure-rated glass tube. The reaction mixture was cooled by a flow of compressed air then partitioned between saturated aqueous $NaHCO_3$ and EtOAc, and the aqueous layer was further extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give the title compound (75 mg, >98%) as a yellow oil. **CF Synthesis in a Heating Coil Reactor.** A solution of aminodienone 5 (1.3 g, 5.1 mmol) in PhMe–AcOH (5:1) (50 mL) was irradiated at 100 °C (300 W) in a Teflon heating coil in a MW CF reactor at a flow rate of 1 mL min^{-1} and quenched in a

(22) With simultaneous cooling, IR temperature measurement may not record the accurate bulk temperature of the reaction mixture: see: Leadbeater, N. E.; Pillsbury, S. J.; Shanahan, E.; Williams, V. A. *Tetrahedron* **2005**, *61*, 3565.

(23) Houssin, R.; Pommery, J.; Salaün, M.-C.; Deweer, S.; Goossens, J.-F.; Chavatte, P.; Hénichart, J.-P. *J. Med. Chem.* **2002**, *45*, 533.

(24) Rogers, C. V.; Corson, B. B. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 884.

solution of saturated aqueous $NaHCO_3$. The mixture was extracted three times with EtOAc and the organic extracts were combined, dried ($MgSO_4$), and evaporated in vacuo to give the title compound (1.2 g, >98%) as a yellow solid. **CF Synthesis in a Glass Tube Reactor.** A solution of aminodienone **5** (80 mg, 0.3 mmol) in PhMe–AcOH (5:1) (3 mL) was irradiated at 100 °C (300 W) in a pressure-rated glass tube (10 mL) filled with sand (~12 g) in a MW CF reactor at a flow rate of 1.5 mL min^{-1}, while simultaneously cooling the tube in a flow of compressed air.[22] The mixture was quenched immediately in a solution of saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic extract was dried ($MgSO_4$) and evaporated in vacuo to give the title compound (75 mg, >98%) as a yellow solid, mp 44–45 °C (MeOH) (lit.[11] mp 44 °C) (found: C, 74.4; H, 6.5; N, 5.6l calcd for $C_{15}H_{15}NO_2$: C, 74.7; H, 6.3; N, 5.8) (found: MH^+, 242.1182; $C_{15}H_{15}NO_2$ requires *MH* 242.1182); IR (KBr) ν_{max} 2980, 2925, 2890, 1717, 1581, 1476, 1277, 1090, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H, d, J = 8.2 Hz), 8.00 (2H, m), 7.55 (1H, d, J = 8.2 Hz), 7.41 (3H), 4.33 (2H, q, J = 7.1 Hz), 2.85 (3H, s), 1.35 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 (C), 159.1 (C), 158.1 (C), 138.5 (CH), 137.6 (C), 128.7 (CH), 128.0 (CH), 126.5 (CH), 122.8 (C), 116.5 (CH), 60.3 (CH_2), 24.6 (Me), 13.5 (Me); MS (APcI) *m/z* (rel intensity) 241 (M^+, 91%), 240 (69), 212 (32), 196 (100), 195 (98), 168 (43), 167 (40).

Acknowledgment. We thank the EPSRC (award to M. C. Lubinu) and the Royal Society for their generous support.

Supporting Information Available: General experimental procedures, diagrams and photographs of apparatus, instructions for assembly, and all power/temperature versus time flow reaction profiles for the synthesis of pyridine **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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APPENDIX C

QSAR
& Combinatorial Science

Microwave-Assisted Synthesis of Pyrimidine Libraries**

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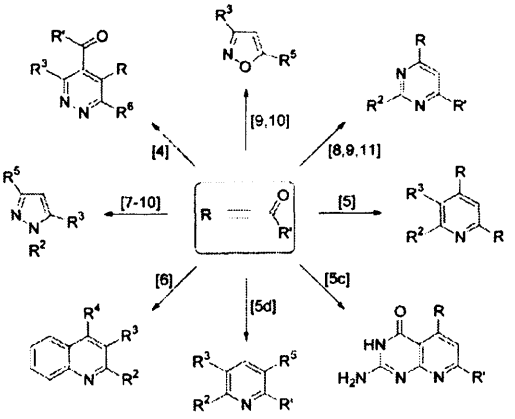
Full Paper

Di- or trisubstituted pyrimidine libraries are prepared in good yield by the microwave irradiation of an alkynone and either an amidine or guanidine at 120–150 °C in acetonitrile in the presence of sodium carbonate or at 100 °C after treatment with methanolic sodium methoxide in a sealed tube using a monomodal microwave synthesiser. These rapid and efficient methods often require no chromatographic purification and so are appropriate for automated combinatorial methodology and have been applied in the synthesis of a small library of potentially useful novel ligands for the estrogen receptor based on the pyrimidine template.

1. Introduction

The development of new methods for the rapid synthesis of heterocyclic compound libraries, both in solution and on solid-phase, continues to attract considerable attention in combinatorial chemistry [1] for the preparation of diverse structural motifs of biological and pharmaceutical importance [2]. Following our report on new methods for the solution-phase combinatorial synthesis of pyridine libraries by the Bohlmann-Rahtz reaction of alkynones as versatile synthetic intermediates [3], we set out to increase the heterocyclic diversity accessible by this methodology and thus develop a method for the rapid synthesis of pyrimidines from the same subset. Pyridazines [4], pyridines [5], pyrido[2,3-*d*]pyrimidines [5c], quinolines [6], pyrazoles [7–10], isoxazoles [9, 10], triazoles [10] and pyrimidines [8, 9, 11] have all been prepared from these intermediates (Scheme 1), the latter serving as valuable building blocks for the synthesis of biologically active targets and non-proteinogenic amino acids.[10] Although there is a wide range of methods available for the synthesis of pyrimidines, only a few of these procedures have been developed in combinatorial chemistry [12] and there is a great need for facile methodology that lends itself well to automation and that can incorporate a number of points of structural diversity in the target library, accessed from readily-available materials.



Scheme 1. Alkynones as versatile intermediates in heterocyclic synthesis.

The use of microwave dielectric heating [13] in synthetic chemistry has received increasing attention in recent years as a valuable alternative to conductive heating methodology. With no direct contact between the chemical reactants and the energy source, microwave-assisted chemistry is energy-efficient, provides fast heating rates and enables rapid optimisation of procedures and thus, with recent

* To receive all correspondence.

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Key words: Pyrimidines, microwave synthesis, heterocycles, library synthesis

advances in instrumentation and the introduction of automated focused synthesisers with a monomodal cavity, the development of new methodology for accelerating synthetic reactions has found considerable application [14]. We have shown that microwave-assisted conditions offer considerable advantages over traditional procedures in heteroannulation reactions for the synthesis of pyridines [15] and dihydropyrido[2,3-*d*]pyrimidines [16]. This study demonstrates that the synthesis of pyrimidines can also be accelerated dramatically by the use of microwave irradiation [17], and applies these findings to prepare a library template for potential application as ligands for the estrogen receptor.

2. Results and Discussion

Using two readily available ethynylcarbonyl compounds, we set out to test if existing procedures for the synthesis of a pyrimidine target library from this subset were suitable for high-throughput techniques. To this end, in two separate experiments, an excess of benzamidine hydrochloride salt (**1a**).HCl and sodium carbonate in acetonitrile and either phenylpropargyl aldehyde (**2**) or 1-phenyl-2-propyn-1-one (**4a**), the latter prepared from 1-phenyl-2-propyn-1-ol (**3a**) by oxidation with *o*-iodoxybenzoic acid (IBX) in dimethyl sulfoxide (DMSO) [5b], was heated at reflux for 2 hours (Scheme 2). Although the synthesis of 2,4-diphenylpyrimidine (**5a**) from ethynylketone (**4a**) proceeded in 95% yield after a simple filtration, the reaction of aldehyde (**2**) gave only a 78% yield of the same pyrimidine (**5a**) and required chromatographic purification and thus did not lend itself well to high-throughput methodology.

The same two experiments using benzamidine (**1a**) and an alkynal (**2**) or alkynone (**4a**) were repeated under microwave-assisted conditions in the presence of sodium carbonate. Each mixture was irradiated at 120 °C for 40 min in acetonitrile at an initial power of 90 W in a self-tunable microwave synthesiser, cooled and filtered to give pyrimidine (**5a**) in quantitative yield in both experiments. Although these results were very encouraging, in terms of reaction efficiency and facility, efforts were made to reduce the reaction time further by carrying out an homogeneous experiment in an alternative solvent, to establish a system that had potential for transfer to flow processing. A mixture of benzamidine hydrochloride (**1a**).HCl and sodium methoxide was stirred in methanol at room temperature and filtered. Phenylpropynone (**4a**) was added and the homogeneous solution was irradiated under different conditions in a sealed tube in a monomodal microwave synthesiser (Table 1). All of the microwave-assisted heteroannulation experiments proved to be very efficient, but the optimum conditions involved stirring a mixture of benzamidine (**1a**) and propynone (**4a**) at 100 °C in methanol for only 2 min to give a quatitative yield of pyrimidine (**5a**) (entry 4), thus providing an alternative homogeneous procedure for the rapid synthesis of pyrimidine heterocycles.

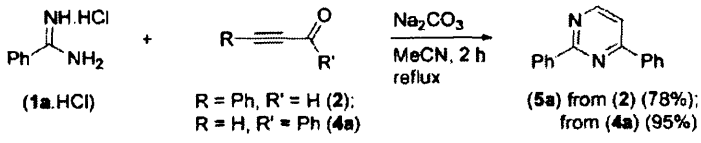
In order to examine the scope of our new microwave-assisted conditions, a mixture of benzamidine (**1a**) or acetamidine (**1b**) and a number of different readily-available ethynyl ketones (**4a–d**) or propargyl aldehyde (**2**) was irradiated either after treatment of the hydrochloride salt (**1**.HCl) with methanolic sodium methoxide or in acetonitrile in the presence of sodium carbonate and the results compared with studies conducted using more traditional heating methods (Table 2). Although the microwave-assisted procedure under homogeneous conditions (method B) did afford the pyrimidine product (**5**) in all cases, the efficiency of reaction was comparable (Table 2, entry 1 and 4) or lower (entry 5 and 6) than the corresponding thermal experiment carried out using conductive heating (method A). However, in all cases the microwave-assisted procedure conducted at 120 °C in acetonitrile in the presence of sodium carbonate (method C) was superior, generating the di- or trisubstituted pyrimidine (**5a–f**) rapidly and often in quantitative yield, in most cases without the need for chromatographic purification. Traditional experiments using conductive heating not only required much longer reaction times, but also gave a lower yield of product and often required purification by column chromatography.

Reagents & Conditions: thermal method A, Na_2CO_3, MeCN, reflux, 2 h; microwave method B, NaOMe, MeOH,

Table 1. Synthesis of pyrimidine (**5a**) using microwave irradiation after treatment with methanolic sodium methoxide.

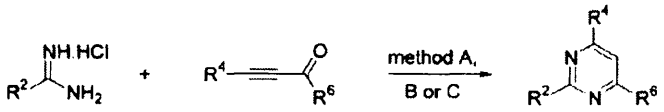
Entry	Microwave conditions	Yield [%] (**5a**)
1	120 °C (90 W), MeCN, Na_2CO_3	>98
2	70 °C (90 W), MeOH, NaOMe,[a] 10 min	92
3	70 °C (90 W), MeOH, NaOMe,[a] 20 min	97
4	100 °C (90 W), MeOH, NaOMe.[a]	>98

[a] Amidine (**1a**.HCl) was pretreated with NaOMe/MeOH



Scheme 2. Synthesis of pyrimidine (**5a**) from ethynylcarbonyl compounds.

Table 2. Synthesis of pyrimidines using conductive heating or microwave irradiation.



(1.HCl) (2) or (4) (5)

Entry	(1)	alkynone	product	R^2	R^4	R^5	Yield [%] (A)	Yield [%] (B)	Yield [%] (C)
1	(a)	(4a)	(5a)	Ph	H	Ph	95	>98	>98
2	(a)	(2)	(5a)	Ph	Ph	H	78[a]	–	>98
3	(b)	(2)	(5b)	Me	Ph	H	79[a]	–	91[a]
4	(b)	(4a)	(5b)	Me	H	Ph	91[a]	90	97[a]
5	(a)	(4b)	(5c)	Ph	Et	Me	91[a]	84	>98
6	(a)	(4c)	(5d)	Ph	Ph	Me	98[a]	75	>98
7	(a)	(4d)	(5e)	Ph	$SiMe_3$	Ne	88[a,b]	–	>98[b]
8	(b)	(4c)	(5f)	Me	Ph	Me	60[a,c]	–	82[a,c]

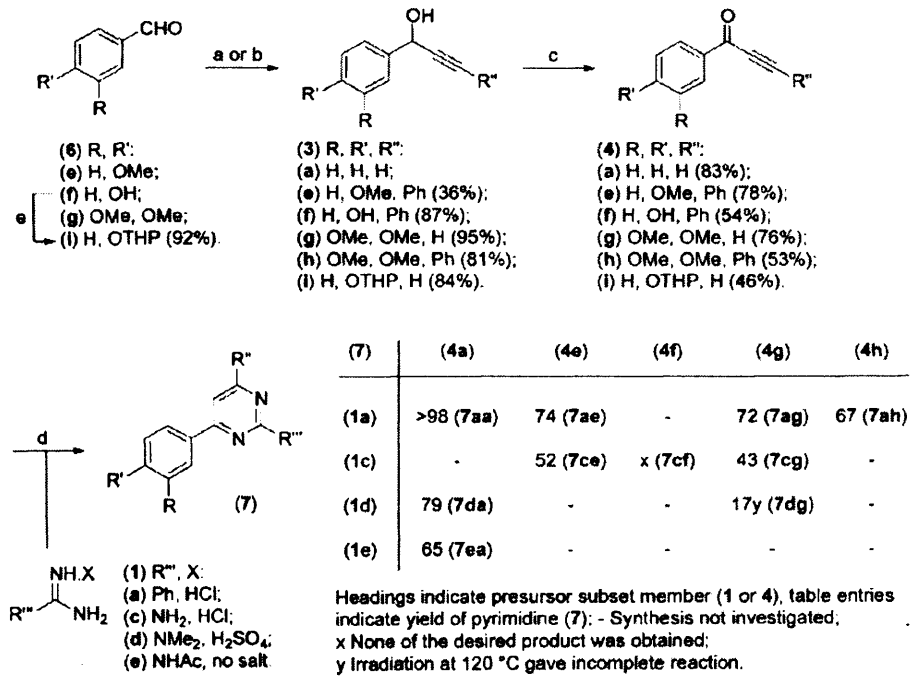
[a] Purification by columns chromatography was required;
[b] Protodesilylated product (R^4 = H) was obtained;
[c] Unreacted alkynone (4c) was present inat he crude reaction mixture

2 min; then 100 °C (90 W), 2 min; microwave method C, Na_2CO_3, MeCN, 120 °C (90 W), 40 min.

With successful microwave-assisted conditions established for the heteroannulation process, this methodology was applied to the synthesis of a heterocyclic library based on the pyrimidine template. 2-Aminopyrimidines have been shown to exhibit cardiotonic activity [18] and the analogous series of 2,4,6-trisubstituted pyridines bind to both estrogen receptor (ER) alpha and beta, with modest selectivity for the former [19], and so a combinatorial approach to the corresponding pyrimidines could provide rapid access to a novel non-steroidal library for potential application as selective estrogen receptor modulators or ligands for the nuclear receptor superfamily of ligand-regulated transcription factors [20]. To this end, a subset of 1-(4-alkoxyphenyl)prop-2-yn-1-ones (**4e–h**) was prepared by the addition of either ethynylmagnesium bromide or lithio phenylacetylide, generated from phenylacetylene by treatment with *n*-butyllithium, to the corresponding aldehydes (**6e–g**) in THF (36–95% yield) to give a subset of propargylic alcohols (**3a, e–h**), which was subsequently oxidised with IBX in DMSO (53–83% yield) to afford the heteroannulation precursors (Scheme 3) [3]. With a route to five different alkynones (**4a–e**) established, half of the reactions in a 4 × 5 combinatorial array were examined under microwave-assisted conditions with an amidine subset consisting of benzamidine (**1a**), guanidine (**1c**), 1,1-dimethylguanidine (**1d**) and *N*-acylguanidine (**1e**) salts to examine the scope of the procedure in a high-throughput run. In ten separate experiments run in series, microwave irradiation of one member of each subset (**1**) and (**4**), in acetonitrile in the presence of sodium carbonate gave rapid acess to a library of 2-amino-4-arylpyrimidines as well as a number of simpler analogues, (**7**), with four points of diversity. Although reactions with benzamidine (**1a**), guanidine (**1c**) and *N*-acetylguanidine (**1e**) performed well under the established microwave-assisted procedure at 120 °C, 1,1-dimethylguanidine (**1d**) needed more forcing conditions, requiring irradiation at 150 °C for 60 min at an initial power of 150 W. It was noteworthy that the irradiation experiment with (hydroxyphenyl)propynone (**4f**) failed to afford any of the corresponding pyrimidine (entry **1c** × **4f**) and so a modified method needed to be developed for the synthesis of 4-(4-hydroxyphenyl)pyrimidine targets that, on the basis of binding studies, contains the minimal pharmacophore for ER binding [19]. In spite of this set back, for the most part the target pyrimidines were obtained in moderate to good yield, with variations attributed to alkynone reactivity, and very high purity (usually >98%) after filtration and so a microwave-assisted heteroannulation approach does constitute a rapid method for the synthesis of pyrimidine libraries.

Reagents & Conditions: (a) for (**3g**), HCCMgBr, THF, 0 °C, 2 h; RT, 16 h; NH_4Cl, (aq); (b) for (**3e, f, h**), PhCCH, *n*BuLi, THF, −78 °C, 35 min; then (**6**); 16 h; NH_4Cl, (aq); (c) IBX, DMSO, RT, 5 h; H_2O; (d) (**1a, c,e**), Na_2CO_3, MeCN, 120 °C (90 W), 40 min; (**1d**), Na_2CO_3, MeCN, 150 °C (150 W), 60 min; (e) LiOTf, , dihydropyran, $ClCH_2CH_2Cl$, reflux, 18 h. RT = room temperature.

Finally, in an effort to apply this methodology to the synthesis of potential ligands for the estrogen receptor containing a phenolic pharmacophore, 4-hydroxybenzaldehyde (**6f**) was protected as its tetrahydropyranyl (THP) ether (**6i**) by treatment with dihydropyran and lithium trifluoromethanesulfonate (LiOTf) in 1,2-dichloroethane [21] and elaborated according to our established procedure, by reaction with ethynylmagnesium bromide followed by oxidation with IBX, to give the THP ether derivative of (4-hydroxyphenyl)propynone (**4i**) (Scheme 3). Microwave irradiation with guanidine (**1c**) at 120 °C or *N,N*-dimethylguanidine (**1d**) at 150 °C gave pyrimidine (**7ci**) or (**7di**) in 90 or 82% yield, respectively (Scheme 4). Deprotection by



(7)	(4a)	(4e)	(4f)	(4g)	(4h)
(1a)	>98 (7aa)	74 (7ae)	-	72 (7ag)	67 (7ah)
(1c)	-	52 (7ce)	x (7cf)	43 (7cg)	-
(1d)	79 (7da)	-	-	17y (7dg)	-
(1e)	65 (7ea)	-	-	-	-

Headings indicate presursor subset member (1 or 4), table entries indicate yield of pyrimidine (7): - Synthesis not investigated; x None of the desired product was obtained; y Irradiation at 120 °C gave incomplete reaction.

Scheme 3. Rapid synthesis of members of a 4 × 5 arylpyrimidine library (7) from an alkynone subset (4).

treatment with hydrochloric acid (4 N) and extraction provided a five step route to pyrimidines (**7cf**) and (**7df**) containing a phenolic pharmacophore as a novel ligand template for potential application in binding to the estrogen receptor.

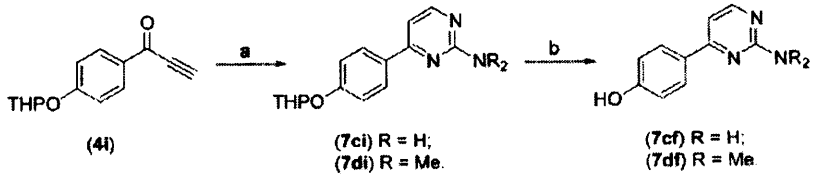
Reagents & Conditions: (a) (**1c**), Na_2CO_3, MeCN, 120 °C (90 W), 40 min (90%); or (**1d**), Na_2CO_3, MeCN, 150 °C (150 W), 60 min (82%); (b) 4N HCl, THF, RT, 30 min.

3. Conclusions

In summary, we have described new microwave-assisted methods for the rapid synthesis of di- or trisubstituted pyrimidines from ethynylcarbonyl compounds and shown their use in the preparation of pyrimidine libraries using methodology that can be transferred readily to either flow processing or automated synthesis for high-throughput application.

4. Experimental Section

Commercially available reagents were used without further purification: solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40–60 °C and ether refers to diethyl ether. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex



Scheme 4. Synthesis of pyrimidines containing a phenolic pharmacophore.

silica 60. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF_{254} that were visualised under UV light (at 254 and/or 360 nm). Microwave irradiation experiments were performed using a self-tunable CEM Discover™ focused monomodal microwave synthesiser at the given temperature by varying the irradiation power (initial power given in parentheses).

Melting points (m.p.) were determined on a Kofler hot stage apparatus. Infra-red (IR) spectra were recorded in the range 4000 – 600 cm^{-1} on a Perkin-Elmer 1600 series FTIR spectrometer using KBr disks for solid samples and thin films between NaCl plates for liquid samples or as a nujol mull and are reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ at 25 °C unless stated otherwise using a Bruker DPX 400 instrument operating at 400 MHz for ^1H spectra and 100 MHz for ^{13}C spectra and were reported in ppm; J values were recorded in Hz and multiplicities were expressed by the usual conventions (s = singlet, d = doublet, t = triplet, app = apparent, m = multiplet). Low-resolution mass spectra (MS) were determined using a Fisons VG Platform II Quadrupole instrument using atmospheric pressure chemical ionization (ApcI) unless otherwise stated. ES refers to electrospray ionization, CI refers to chemical ionization (ammonia) and EI refers to electron ionization. High-resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at University College of Wales, Swansea, UK using the ionization methods specified. Microanalyses were recorded using a Perkin-Elmer 240C Elemental Analyzer.

4.1. General procedure for the synthesis of propargylic alcohols (3) from aldehydes (6) using ethynylmagnesium bromide

To a stirred solution of ethynylmagnesium bromide in THF (0.5 M; 15 ml, 7.5 mmol) at 0 °C under an atmosphere of nitrogen, a solution of aldehyde (6) (5.0 mmol) in dry THF (10 ml) was added. The solution was stirred for 2 h, warmed to room temperature and stirred overnight. Saturated aqueous ammonium chloride solution (2 ml) was added and the solvent removed *in vacuo*. The residue was partitioned between ether (30 ml) and saturated aqueous ammonium chloride solution (30 ml) and the ethereal extract was washed with brine (30 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the *propargylic alcohol* (3).

4.2. General procedure for the synthesis of propargylic alcohols (3) from aldehydes (6) using lithio phenylacetylide

A solution of *n*-butyllithium (2.5 M; 5.0 ml, 12.4 mmol) was added dropwise over 10 min to a stirred solution of phenylacetylene (1.4 ml, 12.4 mmol) in dry THF (15 ml) at – 78 °C under an atmosphere of nitrogen. The solution was stirred for 35 min and added dropwise to a solution of the aldehyde (6) (6.2 mmol) in dry THF (30 ml) at – 78 °C under an atmosphere of nitrogen. The mixture was stirred overnight, poured over ice (10 g) and partitioned between saturated aqueous ammonium chloride solution (30 ml) and ether (30 ml). The aqueous layer was further extracted with ether (2 × 25 ml) and the combined ethereal extracts were washed sequentially with water (25 ml) and brine (25 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the *propargylic alcohol* (3).

4.3. General procedure for the oxidation of propargylic alcohols (3) to alkynones (4) using IBX[22]

A solution of IBX (3.50 g, 12.5 mmol) in DMSO (90 ml) was stirred at room temperature until homogeneous. A solution of the propargylic alcohol (3) (5 mmol) in DMSO (10 ml) was added dropwise and the mixture was stirred for 5 h. Water (15 ml) was added and the solution was stirred at room temperature for 10 min, cooled in ice, partitioned between water (50 ml) and ether (50 ml) and filtered through Celite®. The aqueous layer was further extracted with ether (2 × 25 ml) and the combined organic extracts were washed sequentially with water (3 × 50 ml), saturated aqueous sodium hydrogencarbonate solution (50 ml) and brine (50 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the *alkynone* (4).

4.4. General procedure for the synthesis of pyrimidines (5) using conductive heating (method A)

A mixture of the ethynylcarbonyl compound (2 or 4) (1.0 mmol), amidine hydrochloride salt (1).HCl (1.2 mmol) and sodium carbonate (2.4 mmol) in acetonitrile (10 ml) was heated at reflux for 2 h and then allowed to cool. The solution was filtered and evaporated *in vacuo* to give the *pyrimidine* (5).

4.5. General procedure for the synthesis of pyrimidines (5) using microwave irradiation (method B)

A mixture of the amidine hydrochloride salt (1).HCl (1.2 mmol) and sodium methoxide in methanol (25 wt%; 0.3 ml, 1.3 mmol) was stirred for 5 min, filtered and diluted with methanol (5 ml). Ethynylcarbonyl compound (4) (1.0 mmol) was added and the mixture was irradiated for 2 min at 100 °C (initial power 150 W) in a sealed tube using a self-tunable CEM microwave synthesizer and then allowed to cool using a flow of compressed air. The solution was partitioned between water and ethyl acetate and the aqueous layer was further extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give the *pyrimidine* (5).

4.6. General procedure for the synthesis of pyrimidines (5 or 7) using microwave irradiation (method C)

A mixture of the ethynylcarbonyl compound (**2** or **4**) (1.0 mmol), amidine hydrochloride salt (**1**).HCl (1.2 mmol) and sodium carbonate (0.25 g, 2.4 mmol) in acetonitrile (5 or 10 ml) was irradiated at 120 °C (initial power 90 W) for 40 min, or at 150 °C (initial power 150 W) for 120 min for reactions with 1,1-dimethylguanidine sulfate (**1d**.H_2SO_4), in a sealed tube using a self-tunable CEM microwave synthesizer and then allowed to cool using a flow of compressed air. The solution was filtered and evaporated *in vacuo* to give the *pyrimidine* (**5** or **7**).

4.7. General procedure for the deprotection of tetrahydropyranyl ethers[23]

Hydrochloric acid (4 M; 10 ml, 40 mmol) was added to a stirred solution of the THP ether (0.3 mmol) in THF (3 ml) at room temperature. After stirring for 30 min, brine (15 ml) was added and the mixture was extracted with chloroform (15 ml). The organic extract was washed with brine (15 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give the phenol (**7df**) or the aqueous layer was treated with saturated aqueous sodium hydrogencarbonate solution to pH 6 and extracted with ethyl acetate to give the phenol (**7cf**).

2,4-Diphenylpyrimidine (5a)

Using general procedure 4.6 (method C) with benzamidine hydrochloride salt (**1a**.HCl) (0.19 g, 1.2 mmol) and either phenylpropargyl aldehyde (**2**) (0.13 g, 1.0 mmol) or 1-phenylprop-2-yn-1-one (**4a**) (0.13 g, 1.0 mmol) gave the *title compound* (**5a**) (0.23 g, > 98%) as a yellow solid, mp 72–73 °C (lit. m.p.[34] 71 °C); (Found: MH^+, 233.1070. $C_{16}H_{12}N_2$ requires MH^+ 233.1073); ^1H NMR: δ = 8.73 (d, ^3J(H,H) = 4.0, 1 H; 6-H), 8.50 (m, 2 H; *o*-Ph*H*), 8.13 (m, 2 H; *o*-Ph*H*), 7.49 (d, ^3J(H,H) = 4.0, 1 H; 5-H), 7.43 (6 H; *m,p*-Ph*H*); ^{13}C NMR: δ = 164.6 (C), 164.0 (C), 157.8 (CH), 137.8 (C), 136.9 (C), 131.1 (CH), 130.8 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 127.3 (CH), 114.6 (CH); IR (Nujol): 1563; MS: *m/z* (%) 233 (100) [MH^+].

2-Methyl-4-phenylpyrimidine (5b)

Using general procedure 4.6 (method C) with acetamidine hydrochloride salt (**1b**.HCl) (0.11 g, 1.2 mmol) and either phenylpropargyl aldehyde (**2**) (0.14 g, 1.0 mmol) or 1-phenylprop-2-yn-1-one (**4a**) (0.14 g, 1.0 mmol) gave the *title compound* (**5b**) (0.15 g, 91% or 0.16 g, 97%, respectively) as an orange solid, m.p. 50–51 °C (lit. m.p. [25] 50–51 °C) after purification by column chromatography on silica, eluting with light petroleum-ether (1:1); (Found: MH^+, 171.0918 $C_{11}H_{10}N_2$ requires MH^+ 171.0917); ^1H NMR: δ = 8.57 (d, ^3J(H,H) = 5, 1 H; 6-H), 7.97 (m, 2 H; *o*-Ph*H*), 7.41 (4 H; *m, p*-Ph*H* and 5-H), 2.73 (s, 3 H; Me); ^{13}C NMR: δ = 168.4 (C), 164.1 (C), 157.4 (CH), 136.9 (C), 130.8 (CH), 128.9 (CH), 128.9 (CH), 127.2 (CH), 127.2 (CH), 114.0 (CH), 26.3 (Me); IR (Nujol): 1550; MS: *m/z* (%) 171 (100) [MH^+].

4-Ethyl-6-methyl-2-phenylpyrimidine (5c)

Using general procedure 4.6 (method C) with benzamidine hydrochloride salt (**1a**.HCl) (0.19 g, 1.2 mmol) and hex-3-yn-2-one (**4b**) (0.10 g, 1.0 mmol) gave the *title compound* (**5c**) (0.19 g, > 98%) as a yellow oil; (Found: MH^+, 199.1237. $C_{13}H_{14}N_2$ requires MH^+ 199.1235); ^1H NMR: δ = 8.35 (m, 2 H; *o*-Ph*H*), 7.39 (3 H; *m,p*-PhH), 6.80 (s, 1 H; 5-H), 2.64 (q, ^3J(H,H) = 8, 2 H; CH_2), 2.44 (s, 3 H; 6-Me), 1.22 (t, ^3J(H,H) = 8, 3 H; Me); ^{13}C NMR: δ = 171.6 (C), 166.9 (C), 164.0 (C), 138.3 (C), 132.0 (CH), 128.7 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 116.7 (CH), 30.9 (Me), 24.3 (CH_2), 12.8 (Me); IR (Nujol): 1556; MS: *m/z* (%) 199 (100) [MH^+].

2,4-Diphenyl-6-methylpyrimidine (5d)

Using general procedure 4.6 (method C) with benzamidine hydrochloride salt (**1a**.HCl) (0.19 g, 1.2 mmol) and 4-phenylbut-3-yn-2-one (**4c**) (0.14 g, 1.0 mmol) gave the *title compound* (**5d**) (0.25 g, > 98%) as a colorless solid, m.p. 86–87 °C; (Found: MH^+, 247.3110. $C_{17}H_{14}N_2$ requires MH^+ 247.3110); ^1H NMR: δ = 8.49 (m, 2 H; *o*-Ph*H*), 8.08 (m, 2 H; *o*-Ph*H*), 7.36 (7 H; *m,p*-Ph*H* and 5-H), 2.44 (s, 3 H; Me); ^{13}C NMR: δ = 167.1 (C), 164.3 (C), 163.7 (C), 138.2 (C), 137.3 (C), 130.7 (CH), 130.5 (CH), 128.9 (CH), 128.9 (CH), 128.5 (CH), 128.5 (CH), 127.5 (CH), 127.5 (CH), 127.2 (CH), 127.2 (CH), 114.0 (CH), 24.7 (Me); IR (Nujol): 1548; MS: *m/z* (%) 247 (100) [MH^+].

4-Methyl-2-phenylpyrimidine (5e)

Using general procedure 4.6 (method C) with benzamidine hydrochloride salt (**1a**.HCl) (0.19 g, 1.2 mmol) and 4-(trimethylsilyl)but-3-yn-2-one (**4d**) (0.14 g, 1.0 mmol) gave the *title compound* (**5d**) [26] (0.17 g, > 98%) as an orange oil; (Found: MH^+, 171.0918. $C_{11}H_{10}N_2$ requires MH^+ 171.0917); ^1H NMR: δ = 8.50 (d, ^3J(H,H) = 4.0, 1 H; 6-H), 8.33 (m, 2 H; *o*-Ph*H*), 7.34 (3 H; *m,p*-PhH), 6.90 (d, ^3J(H,H) = 4.0, 1 H; 5-H), 2.45 (s, 3 H; Me); ^{13}C NMR: δ = 167.4 (C), 164.4 (C), 156.4 (CH), 134.5 (C), 128.0 (CH), 128.0 (CH), 127.4 (CH), 127.4 (CH), 116.5 (CH), 26.7 (Me); IR (Nujol): 1560; MS: *m/z* (%) 171 (100) [MH^+].

2,4-Dimethyl-6-phenylpyrimidine (5f)

Using general procedure 4.6 (method C) with acetamidine hydrochloride salt (**1b**.HCl) (0.11 g, 1.2 mmol) and 4-phenylbut-3-yn-2-one (**4c**) (0.14 g, 1.0 mmol) gave the *title compound* (**5f**) [26] (0.15 g, 82%) as yellow oil after purification by column chromatography on silica, eluting with light petroleum-ether (1:1); (Found: MH^+, 185.2402. $C_{12}H_{12}N_2$ requires MH^+ 185.2402); ^1H NMR: δ = 7.96 (m, 2 H; *o*-Ph*H*), 7.40 (3 H; *m, p*-Ph*H*), 7.29 (s, 1 H; 5-H), 2.68 (s,

3 H; 2-Me), 2.42 (s, 3 H; 4-Me); ^{13}C NMR: δ = 167.8 (C), 167.2 (C), 164.1 (C), 137.1 (C), 130.7 (CH), 128.9 (CH), 128.9 (CH), 127.2 (CH), 127.2 (CH), 113.5 (CH), 26.1 (Me), 24.2 (Me); IR (Nujol): 1558; MS: *m/z* (%) 185 (100) [MH$^+$].

(4-Tetrahydropyranyloxy)benzaldehyde (6i) [21]

Lithium trifluoromethanesulfonate (0.94 g, 6 mmol) was added to a stirred solution of 4-hydroxybenzaldehyde (**6f**) (1.22 g, 10 mmol) and dihydropyran (1.43 g, 17 mmol) in 1,2-dichloromethane (50 ml) and the mixture was heated at reflux overnight and then allowed to cool. Chloroform (100 ml) was added and the mixture was washed successively with aqueous sodium hydroxide solution (10%; 2 × 25 ml), brine (15 ml) and water (15 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound* (**6i**) (1.89 g, 92%), used directly in the synthesis of propargylic alcohol (**3i**), as a yellow oil; ^{1}H NMR: δ = 9.82 (s, 1 H; CHO), 7.76 (d, ^3J(H,H) = 9, 2 H; 2,6-H), 7.09 (d, ^3J(H,H) = 9, 2 H; 3,5-H), 5.47 (app t, ^3J(H,H) = 3, 1 H; CH), 3.80 (m, 1 H; OC*H*H), 3.55 (m, 1 H; OCH*H*), 2.02 – 1.40 (6 H; $(CH_2)_3$); IR: ν_{max} = 2930, 1699 (C=O), 1597, 1461, 1378.

Preparation of propargylic alcohol subset members (3e–i) [3]

Using general procedures 4.1 and 4.2 gave the following: *1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol* (**3e**) [27] (0.9 g, 36%) after purification by column chromatography on silica, eluting with ethyl acetate-light petroleum (1:3), as a pale orange solid, m.p. 59 °C; ^{1}H NMR: δ = 7.48 (d, ^3J(H,H) = 9, 2 H; 2′,6′-H), 7.42 (m, 2 H), 7.25 (m, 3 H), 6.86 (d, ^3J(H,H) = 9, 2 H; 3′,5′-H), 5.58 (s, 1 H; 1-H), 3.75 (s, 3 H; OMe); IR: ν_{max} = 3359 (O–H), 2922, 2194, 1461, 1377; *1-(4-hydroxyphenyl)-3-phenylprop-2-yn-1-ol* (**3f**) (1.2 g, 87%) which was used impure without further purification; *1-(3,4-dimethoxyphenyl)prop-2-yn-1-ol* (**3g**) (0.91 g, 95%) as a pale yellow solid, m.p. 98 – 99 °C; ^{1}H NMR: δ = 7.02 (2 H; 2′,5′-H), 6.79 (d, ^3J(H,H) = 9, 1 H; 6′-H), 5.35 (app s, 1 H; 1-H), 3.84 (s, 3 H; OMe), 3.82 (s, 3 H; OMe), 2.61 (d, ^4J(H,H) = 2, 1 H; 3-H), 2.50 (br d, ^3J(H,H) = 2, 1 H; OH); IR: ν_{max} = 3237 (O-H), 2917, 2107, 1524, 1406; *1-(3,4-dimethoxyphenyl)-3-phenylprop-2-yn-1-ol* (**3h**) (1.3 g, 81%) which could be purified by column chromatography on silica, eluting with ethyl acetate-light petroleum (1:3), to give an off-white solid (0.4 g, 22%), m.p. 87 °C; ^{1}H NMR: δ = 7.41 (m, 2 H), 7.30 (3 H), 7.10 (m, 2 H), 6.82 (d, ^3J(H,H) = 9, 1 H; 6′-H), 5.58 (s, 1 H; 1-H), 3.85 (s, 3 H; OMe), 3.82 (s, 3 H; OMe), 2.30 (br s, 1 H; OH); ^{13}C NMR: δ = 149.1 (C), 149.0 (C), 133.3 (C), 131.7 (CH), 128.6 (CH), 128.4 (CH), 122.4 (C), 119.2 (CH), 110.9 (CH), 109.9 (CH), 88.8 (C), 86.6 (C), 65.0 (CH), 56.0 (Me), 55.9 (Me); IR: ν_{max} = 3282 (O-H), 2922, 1612, 1592, 1466, 1379, 1136; *1-(4-tetrahydropyranyloxyphenyl)prop-2-yn-1-ol* (**3i**) (0.78 g, 84%) as a yellow oil from (4-tetrahydropyranyloxy)benzaldehyde (**6i**) (0.82 g, 4 mmol) after purification by column chromatography on silica, eluting with methanol (1%) in chloroform; ^{1}H NMR: δ = 7.39 (d, ^3J(H,H) = 9, 2 H; 2′,6′-H), 6.98 (d, ^3J(H,H) = 9, 2 H; 3′,5′-H), 5.33 (2 H; 2CH), 3.81 (m, 1 H; OC*H*H), 3.52 (m, 1 H; OCH*H*), 2.58 (d, ^4J(H,H) = 2, 1 H; 3-H), 2.00 – 1.40 (6 H; $(CH_2)_3$); IR: ν_{max} = 3400 (O–H), 3251, 2927, 2120, 1463, 1377.

o-Iodoxybenzoic acid (IBX) [22]

Potassium bromate (26.4 g, 0.16 mol) was added to a stirred solution of 2-iodobenzoic acid (30.4 g, 0.12 mol) in sulfuric acid (0.73 M, 400 ml) at 55 °C and the solution was stirred at 68 °C overnight. The mixture was cooled in ice and the resulting colorless precipitate filtered, washed sequentially with water (15 ml), ethanol (15 ml), water (15 ml) and ethanol (15 ml) and sucked dry to give the *title compound* as a colorless solid.

Preparation of alkynone subset members (4a, e–i) [3]

Using general procedure 4.3 gave the following: *1-phenylprop-2-yn-1-one* (**4a**) (0.54 g, 83%) as a yellow solid, m.p. 48 – 49 °C (lit. m.p. [5b] 49 – 50 °C); ^{1}H NMR: δ = 8.10 (d, ^3J(H,H) = 7.5, 2 H; *o*-PhH), 7.57 (t, ^3J(H,H) = 7.5, 1 H; *p*-PhH), 7.44 (t, ^3J(H,H) = 7.5, 2 H; *m*-PhH), 3.38 (s, 1 H; 3-H); IR: ν_{max} = 3233, 2097, 1665, 1451, 1379; *1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one* (**4e**) (0.39 g, 78%) from 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol (**3e**) (0.48 g, 2 mmol) after stirring for 18 h as a yellow solid, m.p. 91 – 94 °C (lit. m.p. [28] 90 – 92 °C); ^{1}H NMR: δ = 8.13 (d, ^3J(H,H) = 7, 2 H; 2′,6′-H), 7.61 (d, ^3J(H,H) = 8, 2 H; *o*-PhH), 7.37 (3 H; *m*, *p*-PhH), 6.92 (d, ^3J(H,H) = 7, 2 H; 3′,5′-H), 3.83 (s, 3 H; OMe); IR: ν_{max} = 2922, 2194, 1709 (C=O), 1461, 1379; *1-(4-hydroxyphenyl)-3-phenylprop-2-yn-1-one* (**4f**) (0.42 g, 54%) from 1-(4-hydroxyphenyl)-3-phenylprop-2-yn-1-ol (**3f**) (0.78 g, 3.5 mmol) as a brown solid, m.p. 122 – 123 °C (lit. m.p. [29] 124 – 125 °C); ^{1}H NMR: δ = 8.08 (d, ^3J(H,H) = 9, 2 H; 2′,6′-H), 7.62 (dd, ^3J(H,H) = 8, 1, 2 H; *o*-PhH), 7.44 (m, 1 H; *p*-PhH), 7.35 (m, 2 H; *m*-PhH), 6.90 (d, ^3J(H,H) = 9, 2 H; 3′,5′-H); IR: ν_{max} = 3175 (O-H), 3019, 2204, 1675 (C=O), 1602, 1460, 1376, 1320; *1-(3,4-dimethoxyphenyl)prop-2-yn-1-one* (**4g**) (0.58 g, 76%) from 1-(3,4-dimethoxyphenyl)prop-2-yn-1-ol (**3g**) (0.77 g, 4 mmol) as a yellow solid, m.p. 117 °C; ^{1}H NMR: δ = 7.82 (dd, ^3J(H,H) = 8, ^4J(H,H) = 1, 1 H; 6′-H), 7.55 (app s, 1 H; 2′-H), 6.87 (d, ^3J(H,H) = 8, 1 H; 5′-H), 3.91 (s, 3 H; OMe), 3.88 (s, 3 H; OMe), 3.33 (s, 1 H; 3-H); IR: ν_{max} = 3233 2097, 1631 (C=O), 1597, 1582, 1466, 1377; *1-(3,4-dimethoxyphenyl)-3-phenylprop-2-yn-1-one* (**4h**) (0.14 g, 53%) from 1-(3,4-dimethoxyphenyl)-3-phenylprop-2-yn-1-ol (**3h**) (0.27 g, 1 mmol) as a yellow solid, m.p. 93 – 94 °C (lit. m.p. [30] 95 – 96 °C); ^{1}H NMR: δ = 7.89 (dd, ^3J(H,H) = 8, ^4J(H,H) = 2, 1 H; 6′-H), 7.62 (app s, 1 H; 2′-H), 7.60 (m, 2 H; *o*-PhH), 7.40 (3 H; *m*, *p*-PhH), 6.82 (d, ^3J(H,H) = 8, 1 H; 5′-H), 3.92 (s, 3 H; OMe), 3.90 (s, 3 H; OMe); IR (KBr): ν_{max} = 2922, 2204, 1631 (C=O), 1456; *1-(4-tetrahydropyranyloxyphenyl)prop-2-yn-1-one* (**4i**) (0.31 g, 46%) from 1-(4-tetrahydropyranyl-

oxyphenyl)prop-2-yn-1-ol (**3i**) (0.70 g, 3 mmol) as a yellow solid, m.p. 60–62 °C; ^{1}H NMR: δ = 8.21 (d, ^3J(H,H) = 9.2 H; 2′,6′-H), 7.05 (d, ^3J(H,H) = 9, 2 H; 3′,5′-H), 5.48 (app t, ^3J(H,H) = 3, 1 H; CH), 3.80 (m, 1 H; OC*H*H), 3.60 (m, 1 H; OCH*H*), 3.31 (s, 1 H; 3-H), 2.00–1.40 (6 H; $(CH_2)_3$); IR (KBr): ν_{max} = 3278, 2929, 2072, 1686 (C=O), 1462, 1372.

Synthesis of pyrimidine library (7)

Using general procedure 4.6 (method C) gave the following: 2,4-diphenylpyrimidine (**7aa**) (0.23 g, > 98%) as reported earlier (**5a**); *2,4-diphenyl-6-(4-methoxyphenyl)pyrimidine* (**7ae**) (62 mg, 74%), from benzamidine hydrochloride salt (**1a**.HCl) (39 mg, 0.25 mmol), 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one (**4e**) (59 mg, 0.25 mmol) and sodium carbonate (53 mg, 0.5 mmol), as a colorless solid, m.p. 137 °C (lit. m.p. [31] 132–136 °C); ^{1}H NMR: δ = 8.65 (dd, ^3J(H,H) = 7, 2, 2 H; *o*-Ph*H*), 8.22 (d, ^3J(H,H) = 9, 4 H; 2′,6′-H and *o*-Ph*H*), 7.90 (s, 1 H; 5-H), 7.50 (6 H; 2 × *m*, *p*-Ph*H*), 7.01 (d, ^3J(H,H) = 8.8, 2 H; 3′,5′-H), 3.85 (s, 3 H; Me); IR (KBr): ν_{max} = 2923, 1597, 1463, 1377; *2-phenyl-4-(3,4-dimethoxyphenyl)pyrimidine* (**7ag**) (0.21 g, 72%) as a yellow solid, m.p. 114–116 °C; ^{1}H NMR: δ = 8.73 (d, ^3J(H,H) = 5, 1 H; 6-H), 8.49 (m, 2 H; *o*-Ph*H*), 7.84 (d, ^4J(H,H) = 1.8, 1 H; 2′-H), 7.72 (dd, ^3J(H,H) = 8.4, ^4J(H,H) = 1.8, 1 H; 5′-H), 7.50 (d, ^3J(H,H) = 5, 1 H; 5-H), 7.56–7.37 (3 H, *m*,*p*-Ph*H*), 6.94 (d, ^3J(H,H) = 8.4, 1 H; 6′-H), 3.98 (s, 3 H; Me), 3.92 (s, 3 H; Me); ^{13}C NMR: δ = 164.4 (C), 163.4 (C), 157.6 (CH), 151.6 (C), 149.3 (C), 137.9 (C), 130.7 (CH), 129.7 (C), 128.6 (CH), 128.2 (CH), 120.4 (CH), 113.9 (CH), 111.0 (CH), 109.8 (CH), 2 × 56.1 (Me); IR (KBr): ν_{max} = 2928, 1458, 1379; *2,4-diphenyl-6-(3,4-dimethoxyphenyl)pyrimidine* (**7ah**) (0.12 g, 67%), from benzamidine hydrochloride salt (**1a**.HCl) (94 mg, 0.6 mmol), 1-(3,4-dimethoxyphenyl)-3-phenylprop-2-yn-1-one (**4h**) (0.13 g, 0.5 mmol) and sodium carbonate (0.13 g, 1.2 mmol), as a yellow solid, m.p. 107 °C; ^{1}H NMR: δ = 8.64 (dd, ^3J(H,H) = 7.6, ^4J(H,H) = 1.8, 2 H; *o*-Ph*H*), 8.22 (dd, ^3J(H,H) = 7.6, ^4J(H,H) = 1.8, 2 H; *o*-Ph*H*), 7.89 (2 H; 5-H and 2′-H), 7.77 (dd, ^3J(H,H) = 8.4, ^4J(H,H) = 2, 1 H; 5′-H), 7.48 (6 H; 2 × *m*,*p*-Ph*H*), 6.96 (d, ^3J(H,H) = 8.4, 1 H; 6′-H), 4.00 (s, 3 H; Me), 3.94 (s, 3 H; Me); ^{13}C NMR: δ = 164.5 (C), 164.3 (C), 164.2 (C), 151.5 (C), 149.3 (C), 138.2 (C), 137.6 (C), 130.7 (CH), 130.6 (CH), 130.2 (C), 128.9 (CH), 128.5 (CH), 128.4 (CH), 127.3 (CH), 120.3 (CH), 110.9 (CH), 110.0 (CH), 109.7 (CH), 56.1 (Me), 56.0 (Me); IR (KBr): ν_{max} = 2922, 1573, 1524, 1456, 1359; *2-amino-4-phenyl-6-(4-methoxyphenyl)pyrimidine* (**7ce**) (0.12 g, 52%) as an off-white solid, m.p. 159–161 °C (lit. m.p. [32] 160–162 °C), after purification by column chromatography on silica, eluting with ethanol (5%) in chloroform; ^{1}H NMR: δ = 8.03 (4 H; 2′,6′-H and *o*-Ph*H*), 7.42 (3 H; *m*, *p*-Ph*H*), 7.35 (s, 1 H; 5-H), 6.93 (d, ^3J(H,H) = 8.8, 2 H; 3′,5′-H), 5.09 (br s, 2 H; NH_2), 3.81 (s, 3 H; Me); IR: ν_{max} = 3330 (N–H), 3194 (N–H), 2922, 1646, 1563, 1401, 1379, 1180; *2-amino-4-(3,4-dimethoxyphenyl)pyrimidine* (**7cg**) (0.10 g, 43%) as a yellow solid, m.p. 138–139 °C, after purification by column chromatography on silica, eluting with ethyl acetate-light petroleum (3:1); ^{1}H NMR: δ = 8.23 (d, ^3J(H,H) = 5.4, 1 H; 6-H), 7.59 (d, ^4J(H,H) = 1.8, 1 H; 2′-H), 7.50 (dd, ^3J(H,H) = 8.4, ^4J(H,H) = 1.8, 1 H; 5′-H), 6.95 (d, ^3J(H,H) = 5.4, 1 H; 5-H), 6.88 (d, ^3J(H,H) = 8.4, 1 H; 6′-H), 5.05 (br s, 2 H; NH_2), 3.93 (s, 3 H; Me), 3.88 (s, 3 H; Me); ^{13}C NMR: δ = 165.0 (C), 163.1 (C), 158.3 (CH), 151.3 (C), 149.2 (C), 129.7 (C), 120.2 (CH), 110.8 (CH), 109.7 (CH), 107.1 (CH), 56.0 (Me); IR (KBr): ν_{max} = 3392 (N–H), 2932, 1626, 1517, 1464; *2-(dimethylamino)-4-phenylpyrimidine* (**7da**) [18] (79 mg, 79%), from 1,1-dimethylguanidine sulfate (**1d**.H_2SO_4) (0.163 g, 0.6 mmol), 1-phenylprop-2-yn-1-one (**4a**) (65 mg, 0.5 mmol) and sodium carbonate (0.13 g, 1.2 mmol), as a pale brown solid, m.p. 43–44 °C; ^{1}H NMR: δ = 8.31 (d, ^3J(H,H) = 5.2, 1 H; 6-H), 8.00 (m, 2 H; *o*-Ph*H*), 7.40 (3 H; *m*, *p*-Ph*H*), 6.85 (d, ^3J(H,H) = 5.2, 1 H; 5-H), 3.21 (s, 6 H; NMe_2); IR (KBr): ν_{max} = 2929, 1592, 1573, 1466, 1407, 1377; *2-(dimethylamino)-4-(3,4-dimethoxyphenyl)pyrimidine* (**7dg**) (17%), from 1,1-dimethylguanidine sulfate (**1d**.H_2SO_4) (0.163 g, 0.6 mmol), 1-(3,4-dimethoxyphenyl)-prop-2-yn-1-one (**4g**) (95 mg, 0.5 mmol) and sodium carbonate (0.13 g, 1.2 mmol) at 120 °C, as a pale brown solid, m.p. 110–112 °C after purification by column chromatography on silica, eluting with methanol (1%) in chloroform; ^{1}H NMR: δ = 8.27 (d, ^3J(H,H) = 5.2, 1 H; 6-H), 7.66 (d, ^4J(H,H) = 2, 1 H; 2′-H), 7.57 (dd, ^3J(H,H) = 8.3, ^4J(H,H) = 2, 1 H; 6′-H), 6.87 (d, ^3J(H,H) = 8.3, 1 H; 5′-H), 6.80 (d, ^3J(H,H) = 5.2, 1 H; 5-H), 3.20 (s, 6 H; NMe_2); IR (KBr): ν_{max} = 1573, 1408; *N-acetyl-2-amino-4-phenylpyrimidine* (**7ea**) (70 mg, 65%), from *N*-acetylguanidine (**1e**) (61 mg, 0.6 mmol), 1-phenylprop-2-yn-1-one (**4a**) (65 mg, 0.5 mmol) and sodium carbonate (0.13 g, 1.2 mmol), as a yellow solid, m.p. 213–217 °C (lit. m.p. [33] 220–221 °C) after washing the filtered solid with further portions of acetonitrile and evaporating *in vacuo*; ^{1}H NMR: δ = 8.56 (d, ^3J(H,H) = 5.3, 1 H; 6-H), 8.18 (s, 1 H; NH), 8.03 (m, 2 H; *o*-Ph*H*), 7.45 (3 H; *m*, *p*-Ph*H*), 7.35 (d, ^3J(H,H) = 5.3, 1 H; 5-H), 2.56 (s, 3 H; Me); IR: ν_{max} = 3330, 2922, 1662 (C=O), 1587; *2-amino-4-(4-tetrahydropyranyloxyphenyl)pyrimidine* (**7ci**) (98 mg, 90%), from guanidine hydrochloride (**1c**.HCl) (46 mg, 0.48 mmol), 1-(4-tetrahydropyranyloxyphenyl)prop-2-yn-1-one (**4i**) (92 mg, 0.4 mmol) and sodium carbonate (0.10 g, 1.0 mmol), as a yellow solid, m.p. 192–195 °C; ^{1}H NMR: δ = 8.23 (d, ^3J(H,H) = 5.4, 1 H; 6-H), 7.89 (d, ^3J(H,H) = 8.7, 2 H; 2′,6′-H), 7.06 (d, ^3J(H,H) = 8.7, 2 H; 3′,5′-H), 6.93 (d, ^3J(H,H) = 5.4, 1 H; 5-H), 5.44 (app t, ^3J(H,H) = 3, 1 H; CH), 4.90 (s, 2 H; NH_2), 3.80 (m, 1 H; OC*H*H), 3.60 (m, 1 H; OCH*H*), 2.00–1.40 (6 H; $(CH_2)_3$); IR: ν_{max} = 3746 (N–H), 3320 (N–H), 3320, 2951, 1626, 1466; *2-(dimethylamino)-4-(4-tetrahydropyranyloxyphenyl)pyrimidine* (**7di**) (0.11 g, 82%), from 1,1-dimethylguanidine sulfate (**1d**.H_2SO_4) (0.13 g, 0.48 mmol), 1-(4-tetrahydropyranyloxyphenyl)prop-2-yn-1-one (**4i**) (92 mg, 0.4 mmol) and sodium carbonate (0.10 g, 1.0 mmol), as a brown oil; ^{1}H NMR: δ = 8.25 (d, ^3J(H,H) = 5.2, 1 H; 6-H), 7.96 (d, ^3J(H,H) = 9, 2 H; 2′,6′-H), 7.06 (d, ^3J(H,H) = 9, 2 H; 3′,5′-

H), 6.78 (d, ^3J(H,H) = 5.2, 1 H; 5-H), 5.43 (app t, ^3J(H,H) = 3, 1 H; CH), 3.19 (s, 3 H; NMe2), 3.83 (m, 1 H; OC*H*H), 3.55 (m, 1 H; OCH*H*), 2.00–1.40 (6 H; $(CH_2)_3$); IR: ν_{max} = 3019, 2951, 1573.

Synthesis of phenolic pyrimidines (7cf and 7df)

Using general procedure 4.7 gave *2-amino-4-(4-hydroxyphenyl)pyrimidine* (**7cf**); ^{1}H NMR: δ 8.21 (d, ^3J(H,H) = 5.4, 1 H; 6-H), 7.84 (d, ^3J(H,H) = 8.6, 2 H; 2′,6′-H), 6.91 (d, ^3J(H,H) = 5.4, 1 H; 5-H), 6.85 (d, ^3J(H,H) = 8.6, 2 H; 3′,5′-H), 5.15 (s, 2 H; NH_2); *2-(dimethylamino)-4-(4-hydroxyphenyl)pyrimidine* (**7df**) as a yellow solid, m.p. 192–194 °C; ^{1}H NMR: δ = 8.25 (d, ^3J(H,H) = 5.2, 1 H; 6-H), 7.94 (d, ^3J(H,H) = 8.6, 2 H; 2′,6′-H), 6.85 (d, ^3J(H,H) = 8.6, 2 H; 3′,5′-H), 6.78 (d, ^3J(H,H) = 5.2, 1 H; 5-H), 3.20 (s, 6 H; NMe_2); IR: ν_{max} = 3437 (O-H), 2932, 1578, 1510, 1408.

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APPENDIX D

Regioselective Microwave-Assisted Synthesis of Substituted Pyrazoles from Ethynyl Ketones

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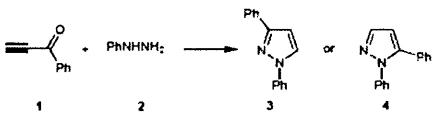
Abstract: Reaction of α,β-ethynyl ketones and hydrazine derivatives gives 1,3- and 1,5-disubstituted pyrazoles in good yield. Microwave irradiation in concentrated hydrochloric acid–methanol (1.5% v/v), with concurrent cooling at sub-ambient temperatures or at 120 °C, for 30 or 2 minutes, respectively, facilitates rapid heterocyclization and preferentially gives the 1,3-disubstituted regioisomer.

Key words: ethynyl ketones, pyrazoles, heterocycles, microwave synthesis, concurrent heating and cooling

The cyclocondensation of ethynyl ketones and a number of different binucleophilic species provides a versatile approach for the synthesis of diverse nitrogen-containing heteroaromatic building blocks from simple precursors. Pyridines,[1] pyrazoles,[2–5] isoxazoles,[2,5] triazoles[5] and pyrimidines[2,4,6] have all been prepared from these intermediates, with applications in the synthesis of non-proteinogenic amino acids,[6] complex thiopeptide natural products,[7] terpyridine α-helix mimetics,[8] non-steroidal anti-inflammatory agents,[9] and heterocyclic combinatorial libraries.[10–12] Following our own studies on the development of more efficient and expedient procedures for the synthesis of pyridines,[13–21] pyrimidines,[12,22] and pyrido[2,3-*d*]pyrimidines[14,23,24] from ethynyl ketones, we investigated methods for the preparation of pyrazoles from these versatile precursors. Although the cyclocondensation of hydrazine and ethynyl ketones proceeds efficiently under well-established conditions,[2] the regioselectivity of reactions involving substituted hydrazines can be poor[2–5] and is often contradictory in the literature.[3,25,26] We set out to discover a way to control the regioselectivity of this heteroannulation process, using either traditional methods or microwave irradiation, and to effect the transformation simply and rapidly, resolving any literature ambiguities.

The heterocyclization of phenylpropynone (**1**) and phenylhydrazine (**2**) was chosen as the reaction of study. This pyrazole synthesis can give rise to two different regioisomeric products, 1,3-diphenylpyrazole (**3**) or 1,5-diphenylpyrazole (**4**), respectively (Scheme 1). According to Kirmse, the 1,3-disubstituted product **3** is obtained as a single regioisomer, albeit in only 15% yield, by stirring a solution of **1** and the hydrazine hydrochloride (**2**·HCl) in methanol overnight (Scheme 2, a), and is reported to proceed through conjugate addition of the anilino amine followed by cyclodehydration under the reaction conditions.[25] The related cyclocondensation of ethynyl ketone **5** and phenylhydrazine (**2**), studied by Baldwin as a route to non-proteinogenic pyrazole amino acids, liberated the free base of the hydrazine by the addition of Na_2CO_3 and gave an inseparable mixture of 1,3- and 1,5-regioisomers, **6** and **7** respectively, in a ratio of 1:1 and 67% yield when stirred at reflux in ethanol (Scheme 2, b).[5] These reports can be contrasted with the findings of Miller and Reiser who observed that when a solution of an electron-rich arylpropynone, such as **8**, and hydrazine derivative **9** was heated at reflux in methanolic hydrochloric acid for 12 hours, both pyrazole regioisomers were obtained in equal amounts in high yield and a different mechanism was suggested.[3] Conversely, when a solution of **8** and **9** was stirred in methanol at room temperature for 15 hours, then heated at reflux on addition of concentrated hydrochloric acid, only the 1,5-disubstituted pyrazole **11** was formed in 74% yield (Scheme 2, c and d).



1 2 3 4

Scheme 1 Heterocyclization of propynone **1** and phenylhydrazine **2**.

In order to compare and contrast the reported literature conditions for transformation of a given set of precursors, an alcoholic solution of phenylpropynone (**1**)[18] and phenylhydrazine (**2**), used as either the free base or hydrochloride salt, was submitted to the four alternative procedures. The regioisomeric products, 1,3-pyrazole **3** and 1,5-pyrazole **4** were separated by column chromatography and the yields compared (Table 1). In all cases, both regioisomers were obtained with the 1,3-regioisomer **3** formed preferentially for cases where any appreciable selectivity was observed (entries 1, 3 and 4).

Cursory examination of these results indicated that acid-mediated cyclization conditions were necessary to facilitate regioselective reaction. In order to test this hypothesis a number of modified procedures, some with microwave dielectric heating which has been employed to good effect in related heteroannulation reactions,[12,15,22] were investi-

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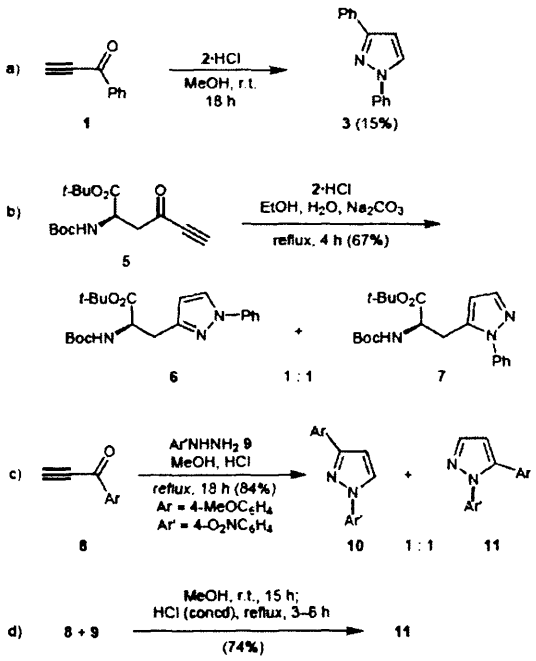


Scheme 2 Regioselectivity in pyrazole syntheses reported by: (a) Kirmse et al.;[25] (b) Baldwin et al.;[5] (c) and (d) Miller et al.[3]

Table 1 Reinvestigating the Cyclocondensation of Propynone 1

Entry	Reagents and conditions	Yield (%)[a]	
		3	4
1[25]	2·HCl, MeOH, r.t., 18 h	53	10
2[5]	2·HCl, EtOH, H_2O, Na_2CO_3, reflux, 4 h	39	41
3[3]	2, MeOH, r.t., 15 h; then concd HCl, reflux, 2 h	81	14
4[3]	2, MeOH, concd HCl, reflux, 15 h	76	15

[a] Isolated yield of pyrazoles 3 and 4 after chromatographic purification on silica.

gated for the reaction of propynone 1 and the free-base phenylhydrazine 2 (Table 2). The regioselectivity of each experiment was examined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. It was observed that microwave irradiation in toluene (entry 1) or toluene–acetic acid (entry 2) at 120 °C gave both pyrazoles with no regioselectivity after 40 minutes. A two-step process, with initial condensation in toluene followed by heating at reflux on addition of acetic acid (entry 3) or montmorillonite K 10 (entry 4) did improve the regioselectivity but not above and beyond the two-step process using a stronger Brønsted acid (entry 5). Without the acidification step (entry 6) the presence of intermediates was observed in the crude ^{1}H NMR spectrum and both pyrazole regioisomers were present in equal amounts. Concurrent dielectric heating and cooling[27,28] gave similar levels of regioselectivity to their 'microwave-free' counterparts but in a very short time (entries 8 and 9). One-step processes (entries 10–14) carried out in concentrated HCl–methanol (1.5% v/v) all proceeded with similar levels of regiocontrol, the concurrent heating and cooling procedure (entry 13) being comparable in its outcome to a prolonged experiment at sub-ambient temperature (entry 12). Of greatest interest was the reaction carried out under microwave dielectric heating at 120 °C (entry 14), which demonstrated that a 5:1 ratio of pyrazoles 3 and 4 could be obtained under acidic conditions in only two minutes.

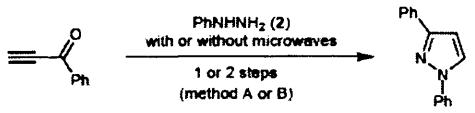
It was apparent from our observations that the process was probably much more facile than was originally believed and this could account for the short reaction times of concurrent heating and cooling experiments (Table 2, entry 13 vs. 12, for example). Thus in order to properly quantify the advantages of this methodology, a solution of 1 and 2 was submitted to reaction at 0 °C either in concentrated HCl–methanol (1.5% v/v) for 30 minutes (method A) or in a two-step process in methanol with addition of concentrated HCl after 15 minutes (method B). The isolated yields of pyrazoles 3 and 4 after purification on silica were

Table 2 Modified Conditions for the Synthesis of Pyrazoles 3 and 4

Entry	Reagents and conditions[a]	Ratio of 3:4[b]
1	MW, PhMe, 120 °C (150 W), 40 min	1:1
2	MW, PhMe–AcOH (5:1), 120 °C (150 W), 40 min	1:1
3	PhMe, r.t., 15 h; then AcOH, reflux, 4 h	3:1
4	MeOH, r.t., 15 h; then montmorillonite K 10, reflux, 4 h	5:1
5	MeOH, r.t., 15 h; then concd HCl, reflux, 2 h	*6:1*
6	MeOH, r.t., 15 h	1:1
7	MeOH, –20 °C, 15 h; then concd HCl, reflux, 4 h	6:1
8[c]	MW, MeOH, 0 °C (170 W), 30 min; then concd HCl, reflux, 4 h	5:1
9[c]	MW, MeOH, 0 °C (90 W), 20 min	1:1
10	Concd HCl–MeOH (1.5% v/v), reflux, 15 h	*6:1*
11	HCl (4 M) in dioxane, reflux, 8 h	5:1
12	Concd HCl–MeOH (1.5% v/v), 0 °C, 15 h	7:1
13[c]	MW, concd HCl–MeOH (1.5% v/v), 0 °C (50 W), 20 min	7:1
14	MW, concd HCl–MeOH (1.5% v/v), 120 °C (120 W), 2 min	5:1

[a] Two-step processes were carried out in one pot by the direct addition of further reagents without work-up. MW indicates microwave irradiation at the specified temperature through moderation of initial magnetron power (which is given in parentheses).
[b] The ratio of 3:4 is taken from ^{1}H NMR spectroscopic analysis of the crude reaction mixture unless given in italics in which case it is from the isolated yields of pyrazoles 3 and 4 after chromatographic purification on silica (as reported in Table 1).
[c] Reaction carried out using the CEM Discover® Coolmate apparatus, with concurrent irradiation and cooling.

Table 3 Comparing the Isolated Yields[a] of Pyrazole 3 (4) with and without Concurrent Heating and Cooling



1 3

Method[b]	No irradiation (yield, %)	Concurrent heating and cooling (yield, %)[c]
A	75 (13)	84 (15)
B	83 (13)	82 (11)

[a] Isolated yields of pyrazole 3 after chromatographic purification on silica. Yields in parentheses are of the minor regioisomer 4.
[b] Method A: concd HCl–MeOH (1.5% v/v), 0 °C, 30 min. Method B: MeOH, 0 °C, 15 min; then concd HCl, 0 °C, 15 min.
[c] Concurrent heating and cooling was carried out using the CEM Discover® Coolmate apparatus by irradiating at 60 W power whilst circulating a coolant through the microwave cavity.

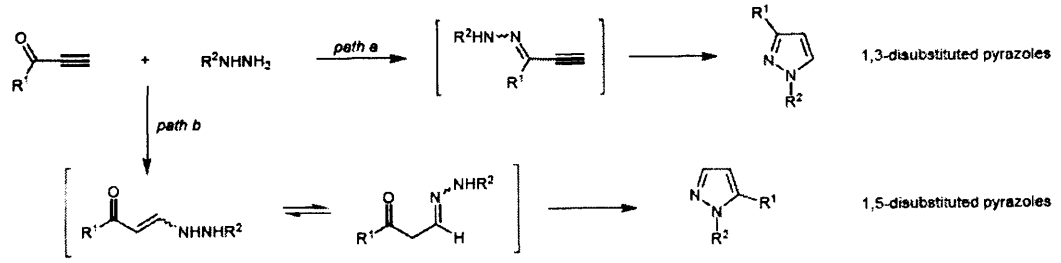
compared for experiments with and without concurrent heating (Table 3). It was found that the two-step process (method B) showed no benefits through concurrent heating and cooling, whereas the yield of pyrazole **3** was slightly but significantly improved by microwave irradiation at 0 °C in concentrated HCl–methanol (method A).

Concurrent heating and cooling using a cold finger has been shown to improve the synthesis of compounds that are inherently thermally unstable.[27,28] We believe that the differences in chemical yield that we have observed could be attributed to the supply of extra energy by the oscillating field, which under acidic conditions has led to an increase in the reaction rate.

With conditions established for the microwave-assisted synthesis of pyrazoles in only two minutes, efforts were made to establish the scope of this new methodology. To this end, a number of hydrazine derivatives were reacted with either an ethynyl ketone[10,12] or phenylpropargyl aldehyde by microwave irradiation at 120 °C (initial power 120 W) for two minutes in concentrated HCl–MeOH (1.5% v/v) and the pyrazole products[31] separated by column chromatography (Table 4). It was apparent that reasonable overall yields were obtained but the regioselectivity of reaction varied considerably with substrate. The dominant 1,3-regioisomers were identified with a downfield shift in the resonance of the pyrazole ring protons[3] by ^{1}H NMR spectroscopic analysis, by NOESY experiments,[32] and by a red shift in their long-wavelength absorption maxima,[33] relative to the corresponding 1,5-isomers,[34] presumably as a consequence of unfavorable steric interactions in the latter.[3]

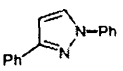
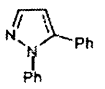
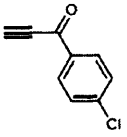
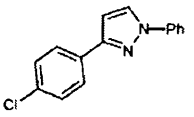
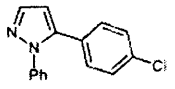
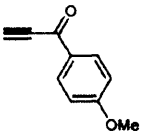
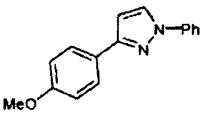
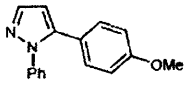
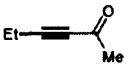
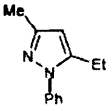
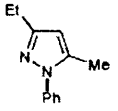
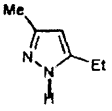
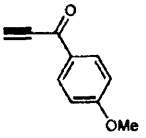
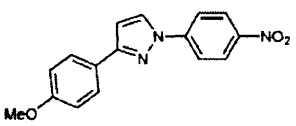
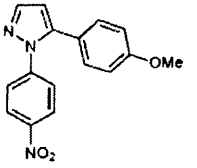
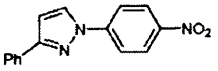
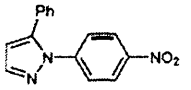
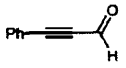
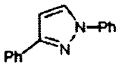
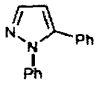
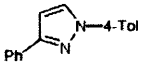
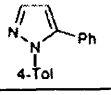
The variation in regioisomer composition observed in our experiments can be rationalized in accordance with the mechanistic findings of Miller and Reiser[3] and Coispeau and Elguero,[26] and involves increased competition under acidic conditions of hydrazone formation by 1,2-addition of the more basic terminal nitrogen of the hydrazine derivative (path a), as opposed to Michael addition/enamine–hydrazone tautomerization (path b), which on heterocyclization leads preferentially to the 1,3-disubstituted products (Scheme 3). This preference would appear to be less pronounced for the cyclocondensation of electron-rich ethynyl ketones at high temperature or in the absence of a strong acid, both of which promote the Michael addition–heterocyclization pathway (path b). This mechanistic interplay is supported by earlier observations (Scheme 2, b–d) and would appear to be highly substrate-dependent, although it can be controlled to give reasonable regioselectivities through the use of a strong Brønsted acid under microwave irradiation.

In conclusion, we have demonstrated that microwave irradiation of hydrazine derivatives and ethynyl ketones gives the corresponding pyrazoles in good yield with the major regioisomer generated according to the mechanistic rationale of Miller and Reiser.[3] The process can be effected in one or two steps using concurrent heating and cooling and is complete in only two minutes in concentrated HCl–methanol at 120 °C. With such short reaction times, this procedure offers an opportunity for facile transfer to a microwave flow reactor[28–30] with continuous processing. These studies are now underway and will be reported in due course.



Scheme 3 Mechanistic rationale for the regioselective synthesis of 1,3-disubstituted pyrazoles from ethynyl ketones.

Table 4 Microwave Irradiation of Hydrazine Derivatives and Ethynyl Carbonyl Compounds in Concd HCl–MeOH (1.5% v/v) at 120 °C for Two Minutes

Entry	Hydrazine derivative	Ethynyl carbonyl compound	Isolated yield (%) of product(s)			
1	$PhNHNH_2$			76		15
2	$PhNHNH_2$			64		22
3	$PhNHNH_2$			50		30
4	$PhNHNH_2$			61		9
5	NH_2NH_2			83		
6[a]	$4\text{-}O_2NC_6H_4NHNH_2$			58		23
7[a]	$4\text{-}O_2NC_6H_4NHNH_2$			52		31
8	$PhNHNH_2$			58		28
9	$4\text{-}MeC_6H_4NHNH_2$			47		40

[a] Irradiation at 120 °C for 5 min.

1,3-Diphenylpyrazole (3)

A solution of phenylhydrazine (1, 50 mg, 0.46 mmol) and phenylpropynone (2a,[18] 60 mg, 0.46 mmol) in concd HCl–MeOH (1.5% v/v, 3 mL) was irradiated (without concurrent cooling in an air stream) in a sealed tube at 120 °C for 2 min using a CEM Discover® single-mode microwave synthesizer, by moderating the initial microwave power (120 W). After cooling in a stream of compressed air, the solution was evaporated in vacuo. Purification by column chromatography on silica, eluting with CH_2Cl_2, gave the title compound[33] (77 mg, 76%) as a colorless solid and 1,5-diphenylpyrazole (4)[34] (155 mg, 15%) as a pale yellow solid.

In an alternative procedure, the same solution was irradiated at 0 °C for 30 min, using the CEM Discover® CoolMate apparatus at a microwave power of 60 W, by circulating a coolant through the cavity. After evaporating in vacuo, purification by column chromatography on silica, as described above, gave the title compound[33] (85 mg, 84%) and 1,5-diphenylpyrazole[34] (15 mg, 15%), with identical physical properties.

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(31) All pyrazoles exhibited satisfactory characterization data, including ^{1}H NMR, ^{13}C NMR, IR, MS and HRMS.
(32) Qualitative NOESY effects were seen for 1,3-disubstituted pyrazoles (Table 4, entries 1, 6 and 8) between the aryl *ortho*-methine resonances and the pyrazole methine signals, the latter of which were well separated (see ref. 3) in chemical shift in the ^{1}H NMR spectrum of both pyrazole regioisomers. The 5-ethyl-trisubstituted pyrazole (entry 4) showed NOESY effects between the aryl *ortho*-methine resonances and the methylene protons.
(33) 1,3-Diphenylpyrazole (**3**): mp 81–83 °C (lit.[35] mp 84–85 °C); R_f = 0.61 (CH_2Cl_2). HRMS: *m/z* [MH$^+$] calcd for $C_{15}H_{13}N_2$: 221.1073; found: 221.1074 [MH$^+$]. IR (nujol): ν_{max} = 1598, 1526, 1504, 1360, 1264, 1114, 1061, 1046, 954, 755, 686 cm^{-1}. UV (CH_2Cl_2): λ_{max} (ε) = 284 (17959), 224 (6189) nm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (1 H, d, J = 2.5 Hz, 5-H), 7.85 (2 H, m, PhH), 7.71 (2 H, m, PhH), 7.38 (4 H, PhH), 7.24 (2 H, m, PhH), 6.71 (1 H, d, J = 2.5 Hz, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3 (C), 140.6 (C), 133.5 (C), 129.8 (CH), 129.1 (CH), 128.5 (CH), 128.4 (CH), 126.7 (CH), 126.2 (CH), 119.5 (CH), 105.4 (CH) ppm. MS (APCI): *m/z* (%) = 221 (100) [MH$^+$], 194 (5), 118 (10).
(34) 1,5-Diphenylpyrazole (**4**): mp 52–55 °C (lit.[35] mp 55–56 °C); R_f = 0.18 (CH_2Cl_2). HRMS: *m/z* [MH$^+$] calcd for $C_{15}H_{13}N_2$: 221.1073; found: 221.1072 [MH$^+$]. IR (nujol): ν_{max} = 1596, 1541, 1502, 1450, 1385, 1224, 1158, 1130, 1068, 960, 761, 695 cm^{-1}. UV (CH_2Cl_2): λ_{max} (ε) = 252 (14493). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (1 H, d, J = 1.5 Hz, 3-H), 7.28–7.22 (8 H, PhH), 7.19–7.15 (2 H, m, PhH), 6.45 (1 H, d, J = 1.5 Hz, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0 (C), 140.3 (CH), 140.1 (C), 130.6 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 127.4 (CH), 125.2 (CH), 107.9 (CH) ppm. MS (APCI): *m/z* (%) = 221 (100) [MH$^+$], 194 (10), 152 (5), 103 (5).
(35) Auwers, K. v.; Schmidt, W. *Ber. Dtsch. Chem. Ges.* **1925**, *58*, 528.

APPENDIX E

Microwave-Assisted Oxidative Aromatization of Hantzsch 1,4-Dihydropyridines using Manganese Dioxide

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Abstract: 4-Aryl- and 4-alkyl-1,4-dihydropyridines, prepared by microwave-assisted Hantzsch reaction, are readily and efficiently aromatized in only one minute using commercial manganese dioxide in the absence of an inorganic support at 100 °C under microwave irradiation. This rapid procedure is more efficient than microwave-assisted aromatization using Pd/C, iodine or o-iodoxybenzoic acid (IBX) and gives the dehydrogenated or 4-dealkylated product in 91–100% yield (13 examples).

Key words: aromatization, Hantzsch dihydropyridines, heterocycles, microwave synthesis, oxidation

Since its discovery by Hantzsch in 1881,[1] the preparation of 1,4-dihydropyridine-3,5-dicarboxylate (1,4-DHP) derivatives by condensation of an aldehyde, β-keto ester and ammonia has attracted substantial interest as a multicomponent condensation reaction that provides heterocycles of pharmacological importance.[2] The 1,4-DHP motif is found in a number of chemotherapeutic agents for the treatment of cardiovascular disease such as hypertension and angina pectoris,[3] including the 4-(2-chlorophenyl) derivatives amlodipine (**1**) and felodipine (**2**), 4-(2-nitrophenyl)DHP derivative nifedipine (**3**) and 4-(3-nitrophenyl) derivatives nicardipine (**4**), nimodipine (**5**) and nitrendipine (**6**), amongst others[2] (Figure 1). This important class of calcium channel antagonists relaxes the cardiac muscle by decreasing the transmembrane calcium current on binding[4] and so considerable effort has been devoted to establish efficient methods for their synthesis.

The metabolism of these drugs is catalyzed in the liver by cytochrome P-450[5] and commences by oxidative aromatization to give the corresponding 1,4-dehydro derivatives, which are largely devoid of pharmacological activity. Notably, the 1,4-DHP motif also features in hydride transfer biotransformations from the reduced nicotinamide adenine dinucleotide (NADH and NADPH) coenzymes, and analogues thereof, that mediate hydrogen transfer reactions in biological systems.[6] In order to understand and model these biological processes, and as a useful synthetic approach to polysubstituted pyridines, the oxidative aromatization of 1,4-DHP derivatives has received considerable attention from synthetic chemists. A wide variety of oxidants have been studied in the reaction, including urea nitrate,[7] peroxydisulfate-Co(II),[7] clay-supported ferric

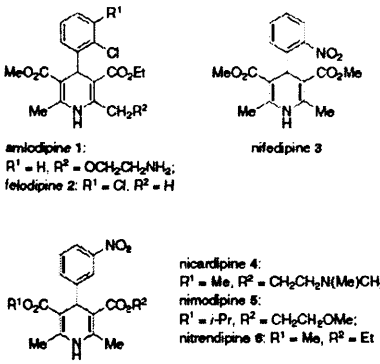

Figure 1 Some chemotherapeutic agents based upon 1,4-DHP derivatives for the treatment of cardiovascular disease.

and cupric nitrate,[8] ceric ammonium nitrate,[9] pyridinium chlorochromate (PCC),[10] $BrCCl_3$/hv,[11] nitric acid,[12] nitric oxide,[13,14] *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide,[14] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[15] $Bi(NO_3)_3$,[16] $Zr(NO_3)_4$,[17] $Mn(OAc)_3$,[18] Pd/C,[19] I_2/MeOH,[20] $KMnO_4$,[10b,21] *tert*-butyl hydroperoxide,[22] Co(II)-catalyzed auto oxidation,[23] CrO_3,[24] and nitrous acid,[25] amongst others,[24,26] all with varying degrees of success.

Despite a plethora of methods for this transformation, prolonged reaction times, poor yields and the competing oxidative dealkylation of 4-benzyl- and *sec*-alkyl-substituted DHP substrates[25] has led to the investigation of many alternative procedures,[2,27] such as solvent free conditions,[12,16,26b] the use of sonication[8,15] and microwave (MW) heating,[2,7,12,15,16,26e,26h,28] in particular with MnO_2 as oxidant.[29,30] The first microwave-assisted method utilized MnO_2 supported on Mexican bentonite clay in a domestic oven, giving the corresponding pyridines in a very short time (10 min) and reasonable yield (47–100%).[29] A recent modification gave further improvements by immobilizing the MnO_2 on HZSM-5 zeolite,[30] but found that in the absence of an inorganic solid support incomplete reactions and alternative products were obtained. We now wish to report our own findings on new methods for the oxidative aromatization of 1,4-DHP derivatives that overcame these difficulties and prioritized the need for excellent yields using cheap, commercially available reagents coupled with

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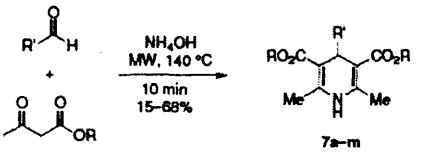
microwave irradiation, to dramatically reduce reaction times.[31]

The 1,4-DHP derivatives required for this study were obtained by microwave-assisted Hantzsch synthesis,[2,32] in a single-mode microwave cavity synthesizer according to the conditions of Öhberg.[32d] A mixture of the aldehyde, β-keto ester and aqueous ammonia was irradiated at 140 °C to give the pure 1,4-DHP derivatives **7a–m** in poor to average yields following recrystallization (Scheme 1, Table 1). Although the yields for these transformations were disappointing (15–68%) next to Öhberg's report,[32d] they did compare reasonably with those obtained using equivalent conductive heating procedures and gave the product in high purity, on the basis of a comparison of physical and spectroscopic properties with literature data. Interestingly, the irradiation of ethyl acetoacetate, formaldehyde and aqueous ammonia (entry 9) gave a mixture of 1,4-DHP **7i** and the corresponding pyridine **8i**, in a ratio of 3.5:1, respectively, indicating that for this substrate spontaneous oxidative aromatization occurs at least in part under the reaction conditions.



Scheme 1 Microwave-assisted Hantzsch 1,4-DHP synthesis using a monomodal microwave synthesizer.

In the search for a rapid procedure for oxidative aromatization, 1,4-DHP **7a** was submitted to a range of conditions with a number of different oxidants, coupled with microwave irradiation (Table 2). Irradiating **7a** in a methanolic solution of iodine at 100 °C for 20 minutes failed to generate the product (entry 1), whereas the use of conductive heating at reflux for 24 hours gave pyridine **8a**.[20] Similarly irradiation over Pd/C in acetic acid at 120 °C for 10 minutes gave only a trace of product (entry 2), in contrast to conductive heating methods.[19] Conversion to the pyridine **8a** under microwave-assisted conditions was however facilitated using Pd/C by increasing the temperature to 180 °C (entry 3) but at these high temperatures a small amount of oxidative dealkylation also occurred, giving a mixture of products. The irradiation of a mixture of *o*-iodoxybenzoic acid (IBX) and **7a** in DMSO was also investigated, but at 180 °C a mixture of products was obtained (entry 4). Carrying out the reaction at a lower temperature in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4) did overcome some of these difficulties (entry 5), but failed to effect complete conversion to pyridine **8a**. However, either heating a mixture of **7a** and manganese dioxide in dichloromethane at reflux overnight with conductive heating (entry 6) or at 100 °C for 1 minute in a monomodal microwave synthesizer (entry 7), gave pyridine **8a** in quantitative yield without the need for further purification. The facility and rapidity of the microwave-assisted procedure compares very favorably to traditional heating methods and demonstrates that no inorganic support is required for efficient conversion, despite previous reports.[29,30]

The scope of this rapid microwave-assisted oxidative aromatization was explored using 1,4-DHP derivatives **7a–m**

Table 1 Microwave-Assisted Synthesis of 1,4-DHP Derivatives **7a–m**

Entry	Product	R	R′	Yield (%)[a]
1	**7a**	Me	Ph	47
2	**7b**	Me	4-$NO_2C_6H_4$	15
3	**7c**	Me	4-ClC_6H_4	45
4	**7d**	Me	4-$MeOC_6H_4$	27
5	**7e**	Et	Ph	39
6	**7f**	Et	4-$NO_2C_6H_4$	36
7	**7g**	Et	4-ClC_6H_4	45
8	**7h**	Et	4-$MeOC_6H_4$	23
9	**7i**	Et	H	54[b]
10	**7j**	Et	Me	21
11	**7k**	Et	Et	68
12	**7l**	Et	*i*-Pr	21
13	**7m**	Et	$PhCH_2$	25

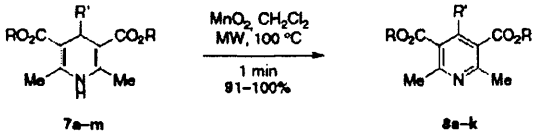
[a] Isolated yield of pure **7** after recrystallization.
[b] A 3.5:1 crude mixture of 1,4-DHP **7i** (42%) and pyridine **8i** (12%) was obtained by ^1H NMR spectroscopic analysis, which was used directly without purification.

Table 2 Exploring Microwave-Assisted Methods for the Oxidative Aromatization of 1,4-DHP **7a**

Entry	Conditions[a]	Results
1	I_2, MeOH, MW, 100 °C, 20 min	**7a**, **8a** (trace)
2	Pd/C, AcOH, MW, 120 °C, 10 min	**7a**, **8a** (trace)
3	Pd/C, AcOH, MW, 180 °C, 10 min	**8a**[b]
4	IBX, DMSO, MW, 180 °C, 1 min	**8a**[c]
5	IBX, [Bmim]BF_4, MW, 120 °C, 1 min	**7a**:**8a** (1:17)
6	MnO_2, CH_2Cl_2, reflux, 18 h	**8a** (ca. 100%)
7	MnO_2, CH_2Cl_2, MW, 100 °C, 1 min	**8a** (ca. 100%)

[a] Initial MW irradiation power of 150 W was moderated throughout the course of the reaction in order to maintain the required temperature.
[b] Compound **8a** was contaminated with 4-dealkylated pyridine (R = Me, R′ = H), as shown by ^1H NMR spectroscopic analysis.
[c] Compound **8a** was contaminated with unidentified side products, as shown by ^1H NMR spectroscopic analysis.

(Scheme 2, Table 3) under the same reaction conditions. In all cases excellent yields of pyridines **8** were obtained. 4-Aryl substrates **7a–h** (entries 1–8) and 4-alkyl-1,4-DHP derivatives, where R′ = H, Me or Et, **7i–k** respectively (entries 9–11), gave the products of oxidative aromatization **8a–k**, whereas 4-*i*-Pr and 4-benzyl derivatives, **7l** and **7m** respectively, gave the product of oxidative dealkylation **8i** (entries 12 and 13). This observation is in accord with the reported behavior of these derivatives under oxidative conditions.[2] In the case of DHP derivative **7i**, which was generated in the Hantzsch reaction along with the corresponding pyridine **8i**, irradiating the crude mixture in the presence of MnO_2 completed conversion to tetrasubstituted pyridine **8i**, which was isolated in 51% overall yield over the two steps.



Scheme 2 Oxidative aromatization of 1,4-DHP derivatives **7a–m** using MnO_2.

Table 3 Synthesis of Pyridines **8a–k** by Oxidative Aromatization or Oxidative Dealkylation of 1,4-DHP Derivatives **7a–m**

Entry	Substrate	Product	R	R′	Yield (%)[a]
1	**7a**	**8a**	Me	Ph	ca. 100
2	**7b**	**8b**	Me	4-$NO_2C_6H_4$	99
3	**7c**	**8c**	Me	4-ClC_6H_4	97
4	**7d**	**8d**	Me	4-$MeOC_6H_4$	96
5	**7e**	**8e**	Et	Ph	99
6	**7f**	**8f**	Et	4-$NO_2C_6H_4$	93
7	**7g**	**8g**	Et	4-ClC_6H_4	94
8	**7h**	**8h**	Et	4-$MeOC_6H_4$	99
9	**7l**[b]	**8i**	Et	H	94[b]
10	**7j**	**8j**	Et	Me	97
11	**7k**	**8k**	Et	Et	98
12	**7l**	**8i**	Et	H	91
13	**7m**	**8i**	Et	H	98

[a] Isolated yield of pure **8**.
[b] A mixture of **7l** and **8i** was used (51% overall yield over 2 steps).

In conclusion, microwave irradiation of 1,4-DHP derivatives at 100 °C in CH_2Cl_2 provides tetra- or pentasubstituted pyridines in only one minute without the use of an inorganic solid support. The reaction proceeds by either oxidative aromatization, for 4-aryl or linear primary 4-alkyl substrates, or oxidative dealkylation for 4-*sec*-alkyl or 4-benzyl substrates. This extremely facile and rapid process provides the target pyridines without the need for further purification and in excellent yield.

Commercially available reagents were used without further purification; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40–60 °C. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Analytical TLC was carried out using aluminum-backed plates coated with Merck Kieselgel 60 GF_{254} that were visualized under UV light (at 254 and/or 360 nm). Melting points were determined on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded, as a Nujol mull for solid samples or as a thin film between NaCl plates for liquid samples, in the range 4000–600 cm^{-1} on a Perkin-Elmer 1600 series FTIR spectrometer and peaks are reported in cm^{-1}. ^1H NMR spectra were recorded at 400 MHz in $CDCl_3$ at 25 °C using a Bruker DPX 400 instrument and were reported in ppm. In vacuo refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump.

Microwave-Assisted Hantzsch 1,4-DHP Synthesis; Diethyl 2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (7e); Typical Procedure

According to the method of Öhberg,[32d] a mixture of benzaldehyde (0.27 g, 2.5 mmol), ethyl acetoacetate (1.63 g, 12.5 mmol), and 35% aq NH_4OH (0.17 g, 10.0 mmol) was irradiated for 10 min at 140 °C in a CEM Discover monomodal microwave synthesizer at an initial power of 150 W. The mixture was allowed to cool and concentrated in vacuo. Purification by column chromatography on silica, eluting with light petroleum–EtOAc (7:3), followed by recrystallization (aq EtOH) gave 1,4-DHP **7e** (0.294 g, 39%) as a pale-yellow solid; mp 158–160 °C (Lit.[33] mp 156–157 °C).

IR (Nujol): 3340, 1688, 1650, 1298, 1212, 1124, 1090, 1018, 827 cm^{-1}.

^1H NMR: δ = 7.20–7.02 (5 H), 5.74 (br s, 1 H), 4.92 (s, 1 H), 4.03 (m, 4 H), 2.25 (s, 6 H), 1.18 (t, 6 H, *J* = 7.1 Hz).

Dimethyl 2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (7a)

Pale-yellow solid; mp 199–200 °C (Lit.[34] mp 198–199 °C).

IR (Nujol): 3341, 1700, 1648, 1433, 1344, 1300, 1222, 1121, 1101, 1053, 1018, 764, 700 cm^{-1}.

^1H NMR: δ = 7.26 (m, 2 H), 7.22 (m, 2 H), 7.13 (m, 1 H), 5.74 (br s, 1 H), 5.04 (s, 1 H), 3.67 (s, 6 H), 2.35 (s, 6 H).

Dimethyl 2,6-Dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (7b)

Yellow solid; mp 198–200 °C (Lit.[34] mp 198–199 °C).

IR (Nujol): 3341, 1704, 1650, 1519, 1345, 1216, 1123, 1097, 1016, 830 cm^{-1}.

^1H NMR: δ = 8.03 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 5.68 (br s, 1 H), 5.03 (s, 1 H), 3.58 (s, 6 H), 2.29 (s, 6 H).

Dimethyl 4-(4-Chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7c)

Pale-yellow solid; mp 198 °C (Lit.[34] mp 194–196 °C).

IR (Nujol): 3333, 1697, 1650, 1345, 1306, 1210, 1121, 1020, 842 cm^{-1}.

^1H NMR: δ = 7.23 (m, 4 H), 5.70 (br s, 1 H), 5.00 (s, 1 H), 3.68 (s, 6 H), 2.37 (s, 6 H).

Dimethyl 4-(4-Methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7d)
Pale-yellow solid; mp 184–185 °C (Lit.[35] mp 181–183 °C).

IR (Nujol): 3345, 1694, 1650, 1303, 1271, 1212, 1174, 1121, 1094, 1049, 1026, 820 cm^{-1}.

^1H NMR: δ = 7.11 (d, *J* = 8.7 Hz, 2 H), 6.69 (d, *J* = 8.7 Hz, 2 H), 5.61 (br s, 1 H), 4.88 (s, 1 H), 3.69 (s, 3 H), 3.58 (s, 6 H), 2.27 (s, 6 H).

Diethyl 2,6-Dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (7f)
Yellow solid; mp 131–132 °C (Lit.[36] mp 129–130 °C).

IR (Nujol): 3315, 1702, 1646, 1517, 1348, 1302, 1212, 1119, 1094, 1019, 824 cm^{-1}.

^1H NMR: δ = 8.01 (d, *J* = 8.8 Hz, 2 H), 7.38 (d, *J* = 8.8 Hz, 2 H), 5.65 (br s, 1 H), 5.04 (s, 1 H), 4.03 (m, 4 H), 2.30 (s, 6 H), 1.17 (t, *J* = 7.1 Hz, 6 H).

Diethyl 4-(4-Chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7g)
Pale-yellow solid; mp 147–148 °C (Lit.[15] mp 144–146 °C).

IR (Nujol): 3354, 1695, 1650, 1334, 1298, 1213, 1169, 1086, 1015, 830 cm^{-1}.

^1H NMR: δ = 7.16 (d, *J* = 8.6 Hz, 2 H), 7.11 (d, *J* = 8.6 Hz, 2 H), 5.55 (br s, 1 H), 4.89 (s, 1 H), 4.03 (m, 4 H), 2.26 (s, 6 H), 1.15 (t, *J* = 7.1 Hz, 6 H).

Diethyl 4-(4-Methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7h)
Pale-yellow solid; mp 159–161 °C (Lit.[37] mp 159 °C).

IR (Nujol): 3339, 1690, 1649, 1301, 1253, 1213, 1121, 1088, 1030, 834 cm^{-1}.

^1H NMR: δ = 7.12 (d, *J* = 8.7 Hz, 2 H), 6.68 (d, *J* = 8.7 Hz, 2 H), 5.48 (br s, 1 H), 4.87 (s, 1 H), 4.03 (m, 4 H), 3.69 (s, 3 H), 2.26 (s, 6 H), 1.15 (t, *J* = 7.1 Hz, 6 H).

Diethyl 2,6-Dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7i)[38]
Pale-yellow solid, as a mixture of **7i** and **8i** (3.5:1), which was used without separation.

^1H NMR: δ= 5.18 (br s, 1 H), 4.24 (q, *J* = 7.1 Hz, 4 H), 3.35 (s, 2 H), 2.27 (s, 6 H), 1.37 (t, *J* = 7.1 Hz, 6 H).

Diethyl 4-Methyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7j)
Colorless solid; mp 130–131 °C (Lit.[38] mp 131 °C).

IR (Nujol): 3343, 1697, 1641, 1493, 1299, 1224, 1099, 1061 cm^{-1}.

^1H NMR: δ = 5.41 (br s, 1 H), 4.13 (m, 4 H), 3.75 (q, *J* = 6.5 Hz, 1 H), 2.21 (s, 6 H), 1.24 (t, *J* = 6.9 Hz, 6 H), 0.90 (d, *J* = 6.5 Hz, 3 H).

Diethyl 4-Ethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7k)
Pale-yellow solid; mp 111–112 °C (Lit.[39] mp 110 °C).

IR (Nujol): 3312, 1699, 1651, 1302, 1211, 1133, 1072, 999 cm^{-1}.

^1H NMR: δ = 5.48 (br s, 1 H), 4.11 (m, 4 H), 3.86 (t, *J* = 5.5 Hz, 1 H), 2.10 (s, 6 H), 1.29 (m, 2 H), 1.22 (t, *J* = 7.2 Hz, 6 H), 0.67 (d, *J* = 7.5 Hz, 3 H).

Diethyl 4-Isopropyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7l)
Yellow solid; mp 95–97 °C (Lit.[39] mp 97 °C).

IR (Nujol): 3342, 1694, 1650, 1298, 1216, 1089, 1049 cm^{-1}.

^1H NMR: δ = 5.42 (br s, 1 H), 4.12 (m, 4 H), 3.85 (d, *J* = 5.4 Hz, 1 H), 2.24 (s, 6 H), 1.53 (m, 1 H), 1.24 (t, *J* = 7.2 Hz, 6 H), 0.67 (d, *J* = 6.8 Hz, 6 H).

Diethyl 4-Benzyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7m)
Pale-yellow solid; mp 112–114 °C (Lit.[15] mp 114–116 °C).

IR (Nujol): 3330, 1694, 1656, 1299, 1241, 1214, 1099, 1054, 750, 699 cm^{-1}.

^1H NMR: δ = 7.07 (3 H), 6.93 (m, 2 H), 5.15 (br s, 1 H), 4.12 (d, *J* = 5.5 Hz, 1 H), 3.99 (m, 4 H), 2.51 (d, *J* = 5.5 Hz, 2 H), 2.11 (s, 6 H), 1.18 (t, *J* = 7.2 Hz, 6 H).

Microwave-Assisted Synthesis of Pyridines Using MnO_2; Diethyl 2,6-Dimethyl-4-phenylpyridine-3,5-dicarboxylate (8e); Typical Procedure
A mixture of **7e** (0.12 g, 0.36 mmol) and MnO_2 (0.32 g, 3.6 mmol) in CH_2Cl_2 (2 mL) was irradiated for 1 min at 100 °C in a CEM Discover monomodal microwave synthesizer at an initial power of 150 W. The mixture was allowed to cool, filtered though Celite and concentrated in vacuo to give pyridine **8e** (0.118 g, 99%) as a colorless solid; mp 63 °C (Lit.[25] mp 63–64 °C).

IR (Nujol): 1730, 1556, 1289, 1229, 1098, 1041, 754, 704 cm^{-1}.

^1H NMR: δ = 7.30–7.18 (m, 5 H), 3.94 (q, *J* = 7.1 Hz, 4 H), 2.53 (s, 6 H), 0.82 (t, *J* = 7.1 Hz, 6 H).

Dimethyl 2,6-Dimethyl-4-phenylpyridine-3,5-dicarboxylate (8a)
Colorless solid; mp 137 °C (Lit.[5] mp 135–136 °C).

IR (Nujol): 1732, 1556, 1288, 1113, 1036, 825 cm^{-1}.

^1H NMR: δ = 7.30 (3 H), 7.18 (m, 2 H), 3.46 (s, 6 H), 2.52 (s, 6 H).

Dimethyl 2,6-Dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate (8b)
Pale-yellow solid; mp 150–152 °C (Lit.[23] mp 148 °C).

IR (Nujol): 1721, 1602, 1558, 1516, 1346, 1303, 1231, 1099, 1048, 834 cm^{-1}.

^1H NMR: δ = 8.19 (d, *J* = 8.8 Hz, 2 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 3.50 (s, 6 H), 2.56 (s, 6 H).

Dimethyl 4-(4-Chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (8c)
Colorless solid; mp 138–140 °C (Lit.[23] 137–139 °C).

IR (Nujol): 1731, 1556, 1241, 1211, 1098, 1039, 1019, 832 cm^{-1}.

^1H NMR: δ = 7.28 (d, *J* = 8.9 Hz, 2 H), 7.12 (d, *J* = 8.9 Hz, 2 H), 3.50 (s, 6 H), 2.53 (s, 6 H).

Dimethyl 4-(4-Methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (8d)
Pale-yellow solid; mp 115–117 °C (Lit.[23] mp 115 °C).

IR (Nujol): 1731, 1609, 1562, 1513, 1292, 1245, 1180, 1111, 1030, 829 cm^{-1}.

^1H NMR: δ = 7.09 (d, *J* = 8.7 Hz, 2 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 3.77 (s, 3 H), 3.51 (s, 6 H), 2.51 (s, 6 H).

Diethyl 2,6-Dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate (8f)
Pale-yellow solid; mp 115–117 °C (Lit.[15] mp 114–116 °C).

IR (Nujol): 1723, 1601, 1556, 1518, 1349, 1295, 1230, 1105, 1045, 842 cm^{-1}.

^1H NMR: δ = 8.18 (d, *J* = 8.7 Hz, 2 H), 7.38 (d, *J* = 8.7 Hz, 2 H), 3.97 (q, *J* = 7.2 Hz, 4 H), 2.57 (s, 6 H), 0.92 (t, *J* = 7.2 Hz, 6 H).

Diethyl 4-(4-Chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (8g)
Pale-yellow solid; mp 64–65 °C (Lit.[15] mp 65–67 °C).

IR (Nujol): 1731, 1556, 1231, 1103, 1044, 835 cm^{-1}.

^1H NMR: δ = 7.28 (d, *J* = 8.9 Hz, 2 H), 7.12 (d, *J* = 8.9 Hz, 2 H), 3.99 (q, *J* = 7.1 Hz, 4 H), 2.54 (s, 6 H), 0.91 (t, *J* = 7.1 Hz, 6 H).

Diethyl 4-(4-Methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (8h)
Colorless solid; mp 49 °C (Lit.[37] mp 51–53 °C).

IR (Nujol): 1730, 1610, 1556, 1515, 1292, 1250, 1180, 1106, 1028, 832 cm^{-1}.

^1H NMR: δ = 7.13 (d, *J* = 8.7 Hz, 2 H), 6.82 (d, *J* = 8.7 Hz, 2 H), 3.97 (q, *J* = 7.1 Hz, 4 H), 3.75 (s, 3 H), 2.52 (s, 6 H), 0.93 (t, *J* = 7.1 Hz, 6 H).

Diethyl 2,6-Dimethylpyridine-3,5-dicarboxylate (8i)
Colorless solid; mp 72–73 °C (Lit.[18] mp 70–71 °C).

IR (Nujol): 1721, 1591, 1555, 1298, 1254, 1223, 1107, 1045, 772 cm^{-1}.

^1H NMR: δ = 8.60 (s, 1 H), 4.33 (q, *J* = 7.2 Hz, 4 H), 2.78 (s, 6 H), 1.34 (t, *J* = 7.2 Hz, 6 H).

Diethyl 2,6-Dimethyl-4-methylpyridine-3,5-dicarboxylate (8j)
Colorless oil.[25]

IR (film): 2981, 1727, 1567, 1446, 1285, 1220, 1106, 1042 cm^{-1}.

^1H NMR: δ = 4.34 (q, *J* = 7.1 Hz, 4 H), 2.46 (s, 6 H), 2.19 (s, 3 H), 1.32 (t, *J* = 7.1 Hz, 6 H).

Diethyl 4-Ethyl-2,6-dimethylpyridine-3,5-dicarboxylate (8k)
Colorless oil.[39]

IR (film): 2979, 1729, 1568, 1447, 1414, 1384, 1278, 1236, 1208, 1106, 1040, 860 cm^{-1}.

^1H NMR: δ = 4.34 (q, *J* = 7.1 Hz, 4 H), 2.52 (q, *J* = 7.6 Hz, 2 H), 2.45 (s, 6 H), 1.32 (t, *J* = 7.1 Hz, 6 H), 1.11 (t, *J* = 7.6 Hz, 3 H).

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