Solvent-Free Route for Microwave-Assisted Organic Synthesis

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Partial Fulfillment of the Requirements

for

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by

Toby Wai Shan CHOW

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Declaration

I hereby declare that the thesis summarizes my own work carried out since my registration for the Degree of Master of philosophy in August, 2004, and that it has not been previously included in a thesis, dissertation or report submitted to this or any other institution for a degree, diploma or other qualification

Toby Wai Shan CHOW

August, 2006

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Abstract

Microwaves offer a number of advantages over conventional heating such as non-contact heating, energy transfer instead of heat transfer and material selectivity. One particular advantage they can offer is efficiency in solventless reactions thus adding another green chemistry benefit. Ullmann type C-N couplings between N-heterocycles such as imidazole and pyrazole and aryl bromides with additive L-lysine or L-glutamine have been conducted in solvent free condition by microwave irradiation. Interestingly, this microwave assisted cross coupling can be promoted by different L-amino acids to different extents under solvent free conditions.

The functionalized N-arylimidazoles thus obtained were further used in the synthesis of the corresponding task-specific ionic liquids (TSILs) by quaternization with excess alkyl halide under solvent free condition. The reactions were also conducted by microwave heating and they proceeded cleanly with high yields. The conversion of the functionality of TSIL 1-butyl-3-(3-acetophenyl)imidazlium bromide was also studied.

Besides, we have demonstrated the application of our solvent free microwave-assisted Ullmann coupling system toward complex molecules. The C-N coupling system between imidazole and bromo-flavone was successfully developed and the same reaction between imidazole and a more complex flavone dimer was also investigated.

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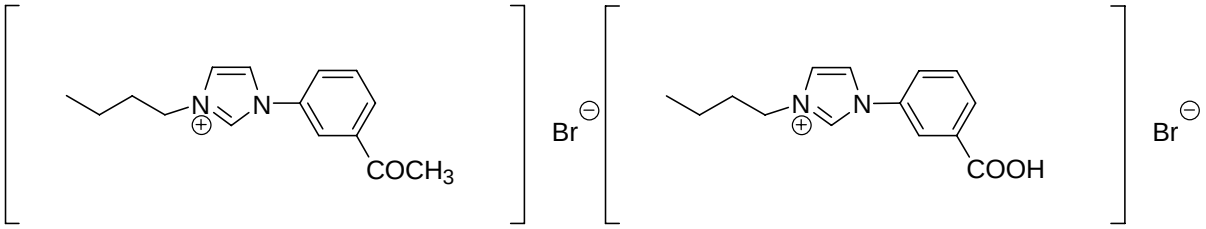
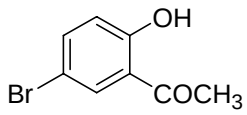
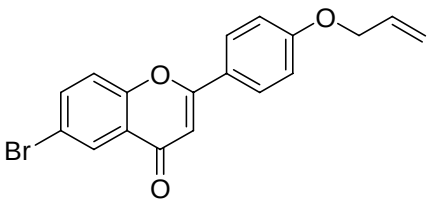
API	1-butyl-3-(3-aacetophenone)imidazolium bromide
CBI	3-butyl-1-(3-carboxyphenyl)-1H-imidazol-3-ium bromide
CMPS	Chloromethyl polystyrene
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EPA	US Environmental Protection Agency
GS	Ground state
MAOS	Microwave assisted organic synthesis
m-CBA	meta-chlorobenzoic acid
m-CPBA	meta-chloroperbenzoic acid
MFOs	Mixed-function oxidase
NHC	N-heterocyclic carbenes
NMP	N-methylpyrrolidone
Phen	1,10-phenanthroline
TS	Transition state
TSIL	Task specific ionic liquid



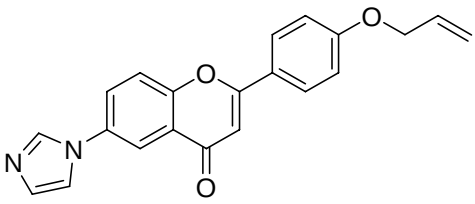
API **CBI**



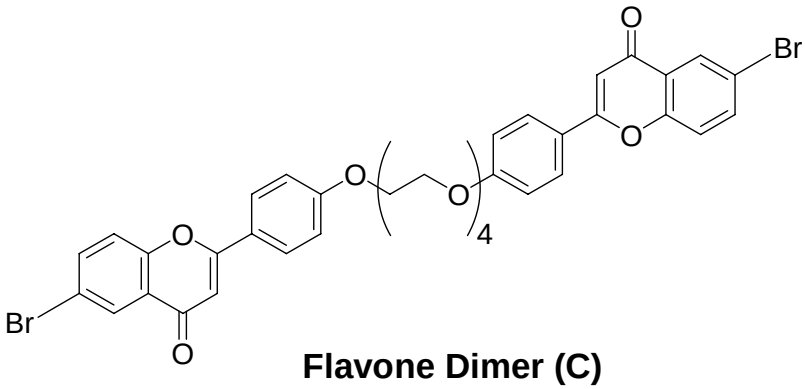
Flavone Precusor (A)



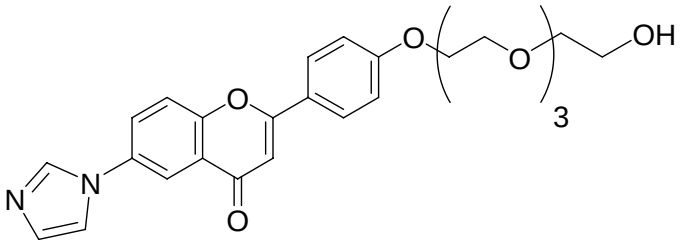
Flavone (B)



Flavone (D)



Flavone Dimer (C)



Side product (E)

Chapter 1 : Introduction

1.1 Principles of green chemistry

Green chemistry has recently drawn a lot of attention from the public and the scientific community thanks to their concerns for the environment and human health impact. Green chemistry includes such concepts as waste minimization, solvent selection, atom economy, intensive processing and alternative synthetic routes from sustainable resources. It was also defined by the US Environmental Protection Agency (EPA) [(1)]:

'To prompt innovative chemical technologies those reduce or eliminate the use or generation of hazardous substances in the design, manufacture and use of chemical products.'[(1)]

Over the last 10 years, green chemistry has gradually become recognized as both a culture and a methodology for achieving sustainability. The challenge for synthetic chemists is to develop products, processes and services in a sustainable manner to improve quality of life, the natural environment and industrial competitiveness. There are twelve principles of green chemistry that have been formulated by Paul Anastas and can serve as basic tenets of green chemistry and a direction for the future work of synthetic chemistry. These are highlighted as follows [(1,2)] :

1) **Prevention**

It is better to prevent waste than to treat or clean up waste after it has been created.

2) **Atom economy**

Synthetic methods should be designed to maximize the incorporation of all materials used into the final product.

3) **Less Hazardous chemical Synthesis**

Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to people or the environment.

4) **Designing safer chemicals**

Chemical products should be designed to effect their desired function while minimizing their toxicity.

5) **Safer Solvents and Auxiliaries**

The use of auxiliary substances (e.g. solvents) should be made unnecessary whenever possible and innocuous when used.

6) **Design for energy efficiency**

Energy requirements of chemical processes should be recognized for their environment and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7) Use of renewable feedstock

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8) Reduce derivatives

unnecessary derivatization (use of blocking groups, protection/de-protection process) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9) Catalysis

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents

10) Design for degradation

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products which do not persist in the environment.

11) Real-time analysis for pollution prevention

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12) Inherently safer chemistry for accident prevention

The kind and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including release, explosion and fire.

This thesis will deal with the subject of microwave-assisted Ullmann reaction in light of these principles of green chemistry.

1.2 Nature of Microwaves

Microwaves are electromagnetic radiations that have an electric component and a magnetic component (Figure 1.1). The microwave portion of the electromagnetic spectrum is between infrared radiation and radio frequencies, with a wavelength of 1mm to 1m, which corresponds to frequencies of between 300GHz and 300MHz (Figure 1.2) [3,4]. To avoid interference with telecommunication and cellular phone frequencies, all commercially available domestic microwave ovens and dedicated microwave reactors for chemical synthesis are operated at a frequency of 2.45 GHz.

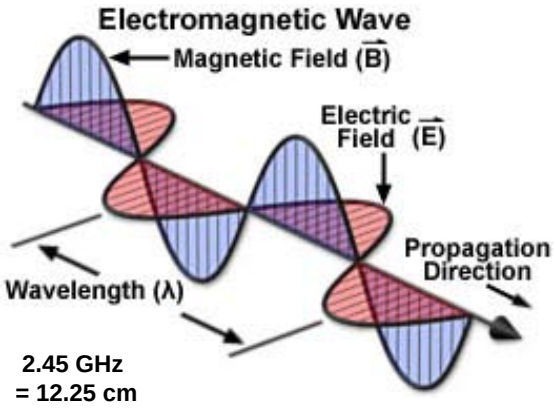


Figure 1.1 Electric and magnetic field component in microwave [5]

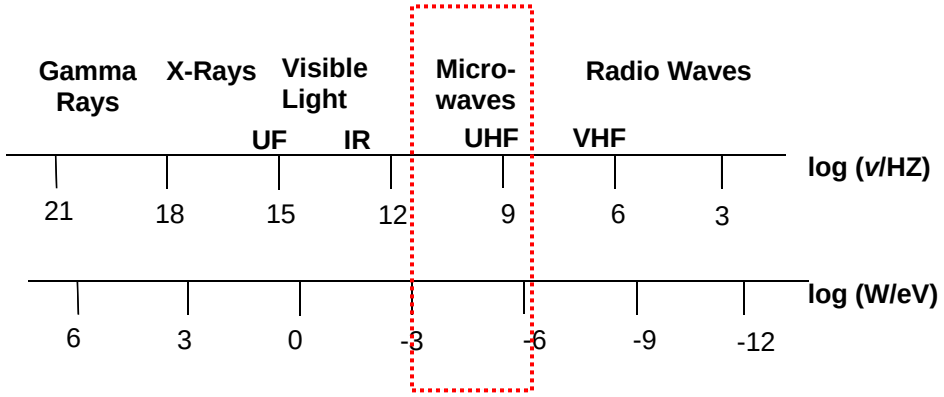


Figure 1.2 The electromagnetic spectrum [4]

It is important to recognize that the energy delivered by microwaves is insufficient for breaking down covalent chemical bonds. The energy of the microwave photon at a frequency of 2.45 GHz (0.0016 eV) is too low to cleave molecular bonds (Table 1.1) [3,6,7] and is also lower than Brownian motion. Direct absorption of electromagnetic energy in form of microwave cannot induce chemical reactions on the basis of such considerations.

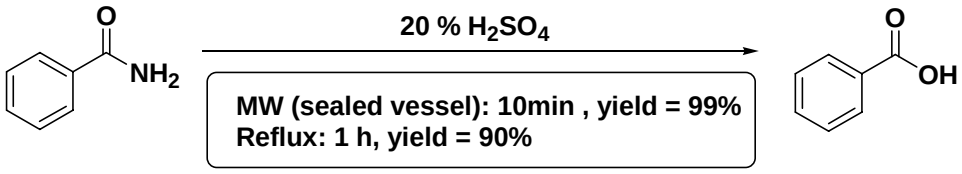
Radiation type	**Frequency (MHz)**	**Quantum energy (eV)**	**Bond type**	**Bond energy (eV)**
Gamma rays	3.0×10^{14}	1.24×10^{6}	C-C bond	3.61
X rays	3.0×10^{13}	1.24×10^{5}	C=C bond	6.35
Ultraviolet	1.0×10^{9}	4.1	C-O bond	3.74
Visible light	6.0×10^{8}	2.5	C=O bond	7.71
Infrared light	3.0×10^{6}	0.0012	C-H bond	4.28
Microwaves	2450	0.0016	O-H bond	4.80
Radio frequencies	1	4.0×10^{-9}	Hydrogen bond	0.04-0.44

Table 1.1 Comparison of radiation types and bond energies [3,6,7]

1.3 Microwave-Assisted Organic Synthesis (MAOS)

Microwave energy was firstly introduced in the application of heating foodstuff by Percy Spencer in the 1940s. After ten years of development, microwave technology has found a variety of technical applications in the chemical and related industries, such as food-processing, drying and polymer industries. Beside the commercial uses, it is also applied in analytical chemistry [8] (E.g. ashing, digestion and extraction), biochemistry [9] (E.g. protein hydrolysis, sterilization), pathology [10] (E.g. histoprocessing, tissue fixation) and medical treatments [11] (E.g. diathermy).

Until the late 1970s, microwave technology has been used in inorganic chemistry, while it has only been implemented in organic chemistry since the mid-1980s. The first report on the use of microwave heating to accelerate organic chemical transformations was published by the R. Gedye [3,11] in 1986. In this publication, the considerable rate increase in the hydrolysis of benzamide to benzoic acid under acidic condition [12] (Scheme 1.1) compared with classical thermal reflux conditions, heralded the utilization and advantages of microwave irradiation for organic synthesis.



Scheme 1.1 Hydrolysis of benzamide under microwave irradiation [12]

The slow development of microwave technology in chemical research is mainly attributed to its lack of controllability, reproducibility and safety aspects. In the early days, the experiments were carried out in sealed glass or Telfon vessels in a domestic household microwave oven without any temperature and pressure measurements. This occasionally led to violent explosions owing to the rapid uncontrolled heating of flammable organic solvents under closed systems.

Since 1990s, several groups successfully carried out organic transformations by microwave irradiation under solvent-free condition (dry-media), which eliminated the danger of explosions [13]. Although the safety aspects had improved and explosions reported were greatly reduced, the general technical difficulties of solvent free technique included non-uniform heating and mixing, and the precise determination of the reaction temperature remained unresolved. These problems were particularly difficult to be addressed in the scale up reactions.

Alternatively, standard organic solvent has been used in MAOS under open-vessel system, which can provide homogenousity, avoid the formations of hot spots and greatly improve safety. While the solvents are heated by microwave irradiations at atmospheric pressure, the boiling point of the solvent typically limits the reaction temperature of MASO. In order to achieve high reaction temperature, high boiling microwave-absorbing solvents such as DMSO, 1-methyl-2-pyrrolidone, 1,2-dichorobenzene and ethylene glycol have been frequently used in open-vessel microwave synthesis [14]. However, the problems in product isolation and recycle of solvent become serious challenges.

Since the 1990s, the number of publications using the microwave technology has increased exponentially (Figure 1.3) [3,15]. The main reasons for this include the development of solvent-free technique [3,13,15] and the availability of commercial microwave equipment intended for organic synthesis. The fast instrument innovations now allow for careful control of time, temperature, pressure and mixing by computer programs. This improvement removes most limitations by the solvent free technique and provide others benefits on reproducibility and safety aspects in addition.

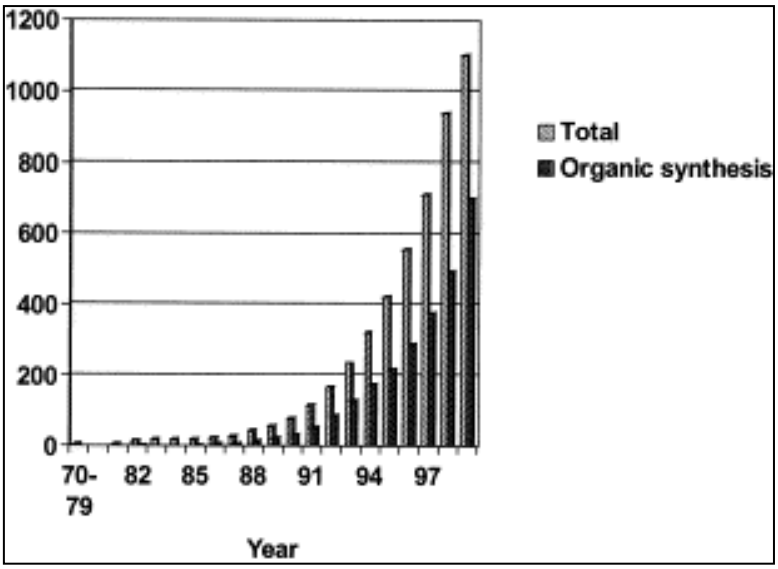


Figure 1.3
The accumulated number of published articles involving organic and inorganic microwave assisted synthesis 1970–1999 [13]

1.4 Heating mechanisms of microwave irradiation

1.4.1 Interaction between microwave and matters

Upon irradiation by microwaves, matters can absorb the energy, they can reflect the energy, or they can simply pass the energy (Figure 1.3). Only a few matters are pure absorbers (lossy dielectric), pure reflectors (electrical conductor), or completely transparent to microwaves (insulator). Besides, the chemical composition of materials, as well as the physical state, size and shape will also affect how the matters behave in a microwave field.

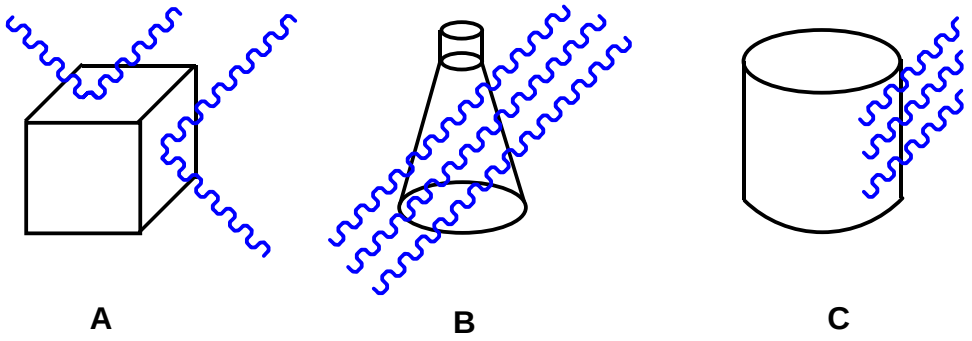


Figure 1.4 Interaction between microwaves and different materials: (a) electrical conductor, (b) insulator and (c) lossy dielectric [3]

1.4.2 Microwave dielectric heating

The materials are heated up by microwave irradiation based on 'microwave dielectric heating' effects [16,17]. This heating effect is dependent on the ability of a specific material (E.g. solvent or reagent) to absorb microwave energy (mentioned in section 1.4.1) and convert it into heat [3]. Dielectric heating effect arises from the interaction of the electric field component of the microwave with charged particles in the materials and it is mainly caused by two mechanisms in homogeneous systems: dipolar polarization and ionic conduction. If the charged particles are bound within the regions of the material, the electric field component will cause them to move until opposing forces balance the electric force, forming the basis of the dipolar polarization. If the charged particles are free to travel through the materials such as ions or electrons, a current will be induced which will travel in phase with the field, resulting in ionic conduction. If the system is heterogeneous, a third mechanism- interfacial polarization will apply.

1.4.2.1 Dipolar polarization

Dipolar polarization is the phenomenon responsible for the majority of microwave heating effects observed in 'solvent' systems [3,15]. For a substance able to be heated under microwave irradiation, it must possess a dipole moment, which is derived from the difference of electronegativity between individual atoms within the molecule. The dipole is sensitive to external electric fields. As the applied field oscillates, it will attempt to realign with the alternating electric field (Figure 1.4). In this process, energy is lost in the form of heat through molecular friction and dielectric loss.

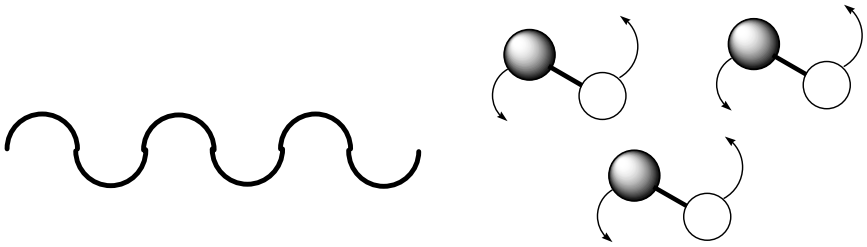


Figure 1.5 Dipolar molecules which try to align with an oscillating electric field [15]

This realignment is rapid for a free molecule, but in liquids, instantaneous alignment is prohibited by the intermolecular inertia with other molecules. Under a very high frequency electric field, the dipole will attempt to follow the field, but the intermolecular inertia stops any significant motion before the field has reversed. Since the dipole does not have enough time to realign, there is no net motion. If the frequency of field oscillation is very low, then the dipole will have sufficient time to aligning itself in phase with the electric field. Although some energy may be lost in collisions, the overall heating effect is small.

Between these two extremes, at frequencies in microwave regions which are low enough that the dipole has time to respond to the alternating field, and therefore to rotate, but high enough that the rotation does not precisely follow the field, this lagging behind of the dipole causes a phase difference between the orientation of the field and that of the dipole, which contributes to the energy lost in the form of heat from the dipole in random collisions and frictions, and finally gives rise to dielectric heating. Therefore, the heating characteristic of a particular material under microwave irradiation conditions is dependent on the dielectric properties of the material, which correlates to the

polarizability of the molecules in the electric field. The microwave absorbances for some common organic solvents are summarized in Table 1.2 [4].

Solvent	Tan δ	Boiling point (˚C)	Microwave absorbance
Ethylene glycol	1.350	197	very good
Ethanol	0.941	78	good
Dimethyl sulfoxide	0.825	189	good
Methanol	0.659	63	good
1,2-dichlorobenzene	0.280	180	medium
1-methyl-2-pyrrolidone	0.275	204	medium
N,N-dimethylfomamide	0.161	154	medium
Water	0.123	100	medium
Acetonitrile	0.062	81	medium
Tetrahydrofuran	0.047	66	low
Dichloromethane	0.042	40	low
Toluene	0.040	110	very low

Table 1.2 Dielectric properties of various solvents (2.45 GHz) [4]

It should be emphasized that although the frequency of the microwave approximately matches that of the rotational relaxation, the interaction between microwave irradiation and the polar molecules is not a quantum mechanical resonance phenomenon [3,16,17]. When the polar molecules couple with microwave irradiation, the microwave irradiation only increases the rotational velocity of the molecules and the transitions between the quantized rotational bands are not involved in the energy transfer. Therefore, the heat is generated by friction force between polar molecules, but not by the rotational relaxation.

For example, in the liquid form of water, for all practical purposes, the quantization of rotational levels is non-existent, only its gaseous form has quantized rotational energy levels in the microwave region. However, gases cannot be heated under microwave irradiation since the distance between the rotating molecules is long enough that not much inertia is given by the adjacent molecules. This allows them to follow the electric field perfectly and no phase difference will be generated [15]. Similarly, ice is also nearly microwave transparent since the water dipoles are constrained in a crystal lattice and cannot move as freely as in the liquid state. The presence of relatively high intermolecular inertia stops any significant motion of dipoles [3].

1.4.2.2 Conduction mechanism

For the ionic conduction mechanism [3,16,17], the dissolved charged particles in a sample (usually ions) oscillate back and forth under the influence of the electric field and induced currents will be generated (Figure 1.5). The heat will be created in sample owing to any electrical resistance, in terms of collision of moving ions with their neighboring molecules. The conductivity mechanism is a much stronger interaction than the dipolar mechanism with regard to the heat generating capacity [15].

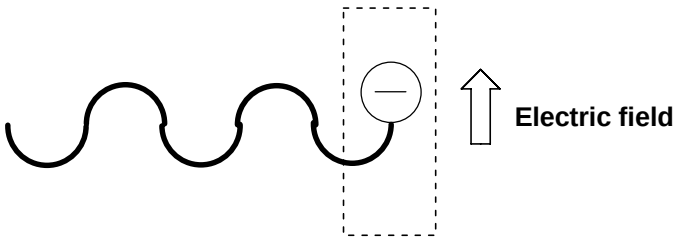


Figure 1.6 Ionic conduction mechanism [3]

Therefore, as an example, higher final temperature of the tap water is obtained when both distilled water and tap water are heated at a fixed time and fixed radiation power. This can be explained by the presence of ions in tap water to allow extra heating effect from the ionic conduction mechanism (Figure 1.6) [15].

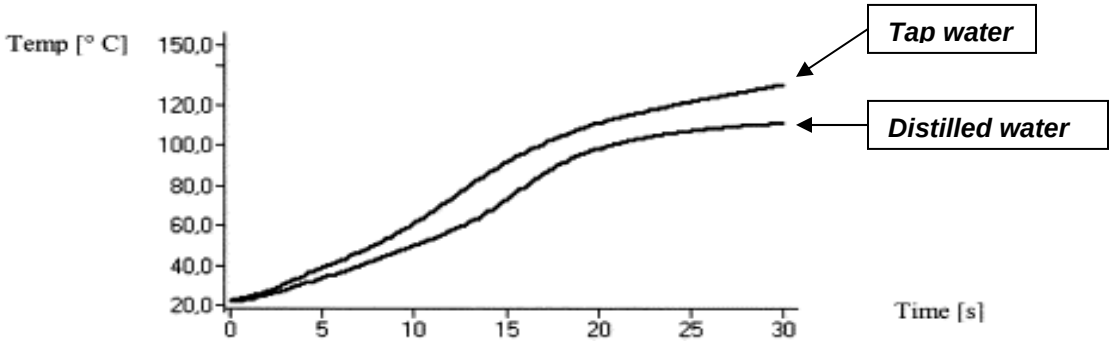


Figure 1.7 The temperatures increase of distilled water and tap water respectively at 150W microwave irradiation [15]

1.5 Acceleration of organic reactions by microwaves

From the very beginning, scientists already realized that a number of chemical processes can be carried out under microwave irradiation with a substantial reduction in the reaction time in comparison to conventional processes. Reactions that usually take many hours or days thermally can be run in considerably shorter time of just several minutes or even seconds under the influence of microwave irradiation. These phenomena are not fully understood. Two groups of theories have been proposed to explain for this rate enhancements: Thermal effect and specific microwave effect [(3)].

1.5.1 Thermal effect

Reviewing the present literature, many scientists suggest that in the majority of cases, the kinetics and the mechanism of the reactions under the microwave irradiation is still the same as that in conventional heating. The reduction in reaction time is due to purely thermal effect that follows common kinetic laws, which is the consequence of sudden and uncontrollable temperature growth of the reaction mixture under microwave irradiation. Four factors that can cause thermal effect are considered [(3,4)]:

(i) Superheating of the reaction mixture that in particular can be observed in the presence of a large quantity of electric carriers (i.e. ions);

(ii) 'Pressure cooking effect' caused by superheating of the reaction mixture with low boiling point solvent in sealed vessels;

(iii) Considerably faster heating rate of the reaction mixture means that the required temperature for a chemical reaction is achieved in a shorter time;

(iv) Increase of the diffusion rate on the phase boundaries leads to a better homogeneity of reaction mixture from the increasing temperature.

1.5.2 Specific microwave effect

When there are rate accelerations and sometimes altered product distributions in microwave heating rather than conventional heating, the observations have been explained not only due to the thermal effect but also by the 'specific microwave effect'. Historically, such effect was claimed when the outcome of a synthesis performed under microwave conditions was different from that of the conventionally heated counterpart at the same apparent temperature [4,15]. As mentioned in section 1.4.2, the microwave energy does not bring molecules to higher rotational or vibrational energy levels, however, the microwaves 'pump' the energy into the materials causing the accumulation of thermal energy within materials. This accumulation leads to the increase in the internal energy of materials and allows the materials to carry out a number of chemical reactions [3]. Four factors that can cause specific microwave effect are considered [3,4,18]:

(i) Formation of hot-spots with highly localized microscopic temperature owing to the selective heating of specific reaction components by direct interaction with microwave;

(ii) Increase in the transport of reagents by increasing the diffusion rate and molecular mobility within the reaction mixture especially for the reactions under solvent free condition;

(iii) Change of reaction selectivity owing to the increase in heating rate of the reaction mixture;

(iv) Increase in the polarity of the reacting molecules in the transition state compared to the ground state.

1.5.2.1 Rate acceleration of chemical reactions

The reaction rate of a temperature dependent chemical reaction can be described by the Arrhenius equation (Equation 4) [15]:

Equation 1: $\mathbf{K = A\, e^{-\Delta G/RT}}$ ***where*** **K= reaction rate constant**
A = pre-exponential factor
ΔG = activation energy
R = gas constant
T = absolute temperature at thermal equilibrium

According to the Arrhenius equation (Equation 1) [15], there are basically two ways to increase the reaction rate of a chemical reaction. First, the pre-exponential factor **A**, which describes the molecular mobility and depends on the frequency of vibrations of molecules at the reaction interface. As mentioned in the previous section, microwave can induce an increase in molecular vibrations, therefore factor **A** may be affected by microwave irradiation [3,15].

In another way, the reaction rate can also be altered by changing the activation energy **ΔG** of the reaction. Since the microwave effect resulted from the material and microwave interaction is based on the dipolar polarization phenomenon, the greater the polarity of a molecule the more pronounced will be the microwave effect when the rise in temperature is considered [3,8,19]. When the polarity increases during the reaction from the ground state towards the transition state, the transition state (TS) may gain relatively more effective stabilization from the dipole-dipole electrostatic interactions than that of the ground state (GS). This stabilization decreases the activation energy of the reaction and therefore enhances the reactivity of the reaction (Figure 1.7) [3,8,19]. However, the outcome from the microwave effect is essentially dependent on the reaction medium and the reaction mechanism, and can be masked or limited by either protic (e.g. alcohols) or aprotic solvents (e.g. DMF, DMSO, CH_3CN) [3,19].

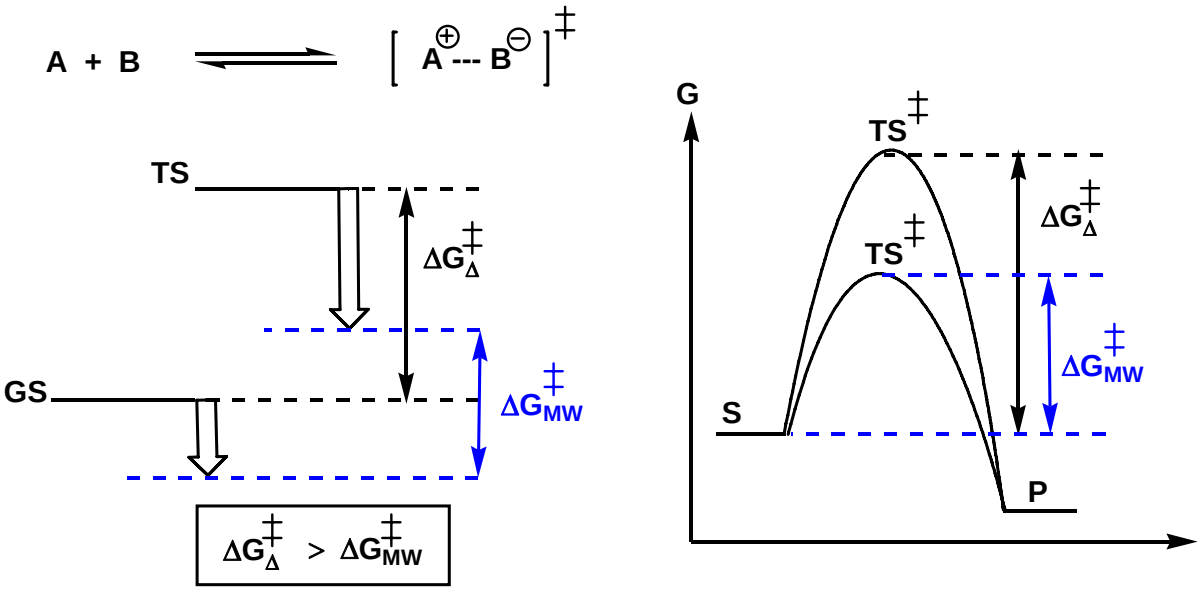


Figure 1.8 Relative stabilization of a more polar transition state (TS) compared with the ground state (GS) [3,19]

1.5.2.2 Selectivity of chemical reactions

As mentioned before, the alteration of polarity of the system during the reaction under microwave irradiation may result in the change in activation energy. When competitive reactions are involved, the GS is common for both processes; the pathway with more polar TS will be favored under microwave irradiation [20]. Therefore microwave irradiation possibly alters the chemo- or regioselectivity of reactions and gives different product distribution when compared with the conventional heating [3,19,21].

That microwaves are the source of volumetric heating of materials means that the temperature increase of the reaction mixture can be faster than for conventional heating methods. Based on the different heating mechanisms of microwave irradiation from conventional heating, the inversion of temperature pattern (i.e. higher internal than outer temperature) will also be obtained (Figure 1.8).

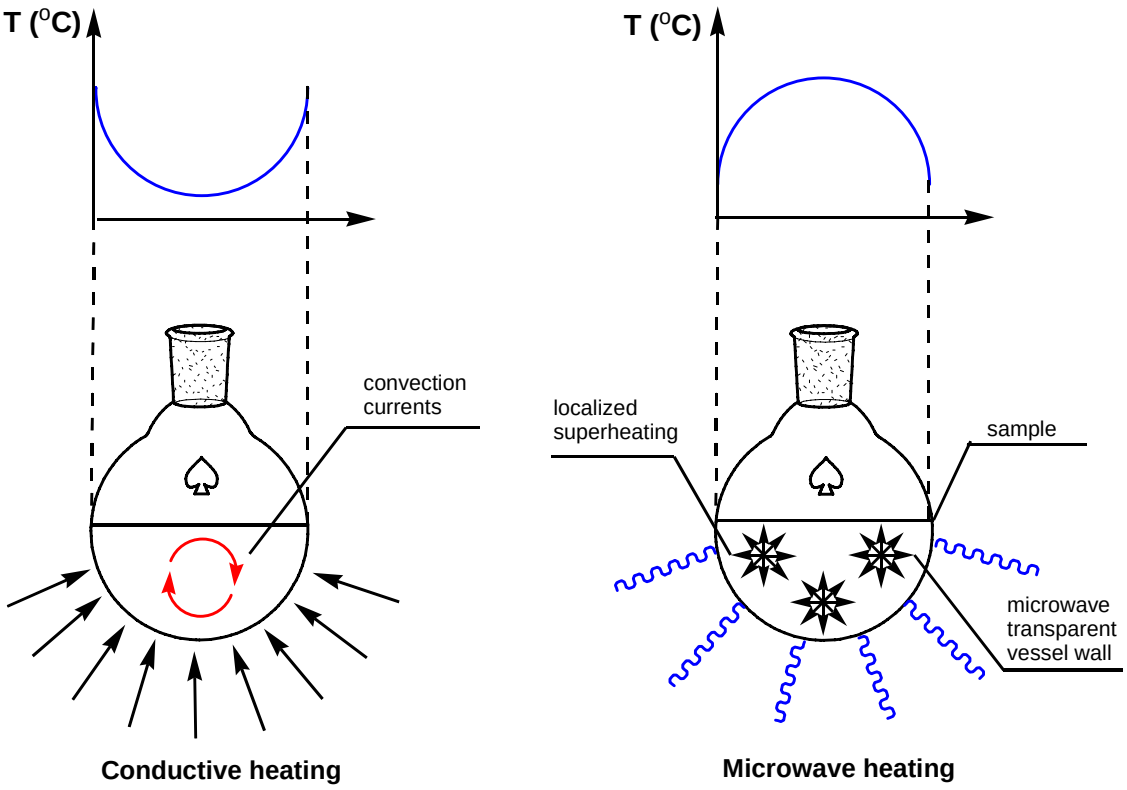
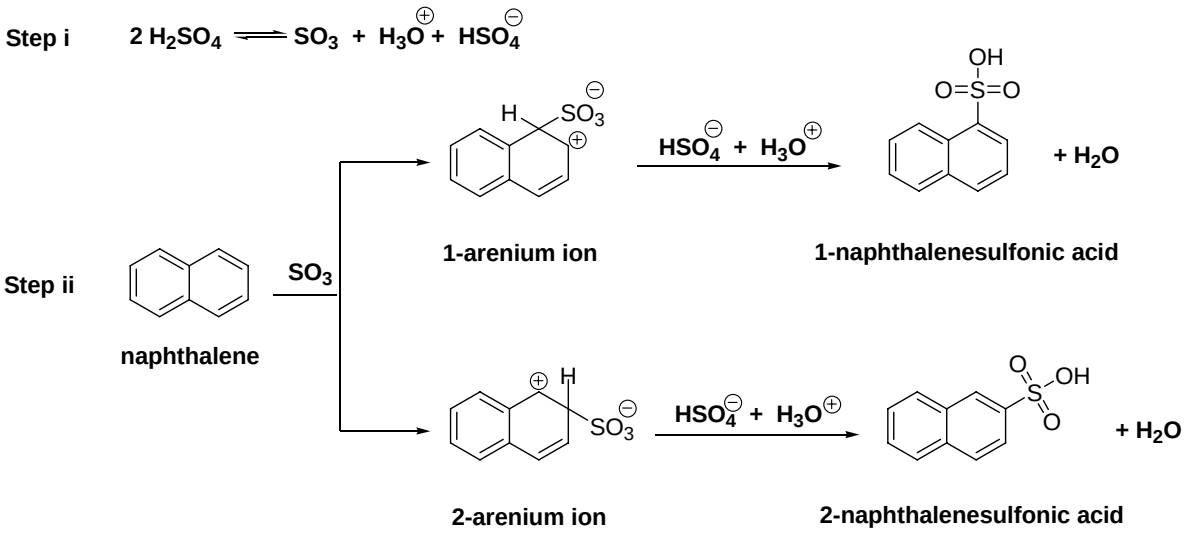


Figure 1.9 Different heating mechanisms and temperature gradients for material subjected to conventional and microwave heating [3]

These differences may have either kinetic or thermodynamic control of the reaction to give totally different products distribution with the mechanism and kinetics of the reaction unchanged. For example, for the sulfonation of naphthalene in the presence of sulfuric acid, the rate of temperature growth of the reaction mixture influenced the ratio of the isomers 1- and 2-napthalensulfonic acid (1- and 2-NSA) (Scheme 1.2) [3,21,22].



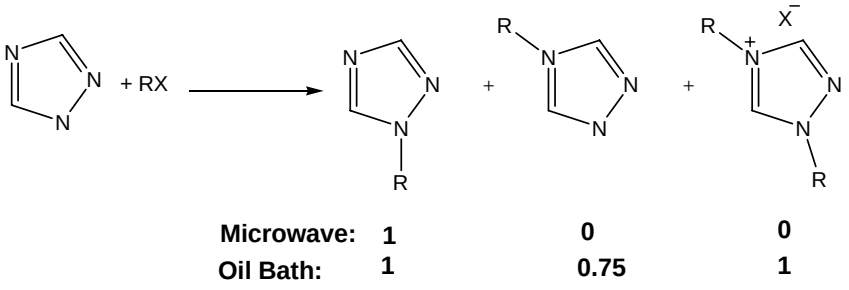
Scheme 1.2 Sulfonation of naphthalene [23]

1.6 Solvent-free condition under microwave irradiation

Microwave reactors have attracted considerable attention as alternatives to conventional reactors for carrying out synthetic reactions. One particular advantage they can offer is the efficiency in solventless reactions, thus adding another green chemistry benefit to that of the very short reaction times associated with microwave-assisted processes [(24)]. Apart from this reason, the use of solvent free conditions for microwave irradiation has many other benefits: simplicity, efficiency, easy workup, very often higher yields and enhanced reaction rates (due to high concentration of reactants). The absence of solvent is time and money saving and often leads to no waste treatment [(25)].

For solvent-free system, the energy conduction is not required. In the absence of solvent, the radiation is directly absorbed by the reactants, giving enhanced energy efficiency. In addition, microwave irradiation may benefit the synthetic reaction by means of many non-crystalline solid supports which can absorb microwave energy efficiently but are rather poor in conducting heat. This additional advantage allows the use of solid catalyst in certain reactions, giving a reaction rate enhancement [(25)].

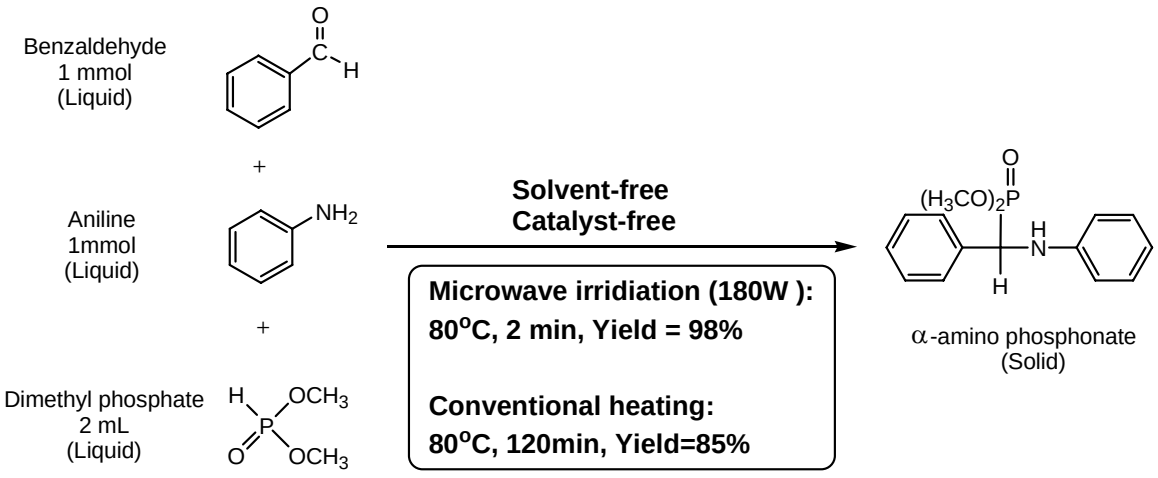
There are several examples of successful N-alkylation with a solid catalyst using a microwave irradiation as alternative energy source. When comparing to the conventional heating, the microwave-solvent free N-alkylation systems sometimes generate significantly different isomeric products ratio and product selectivity (Scheme 1.3) [(25)]:



Scheme 1.3 Microwave assisted N-alkylation [25]

1.6.1 Reaction in neat reagents

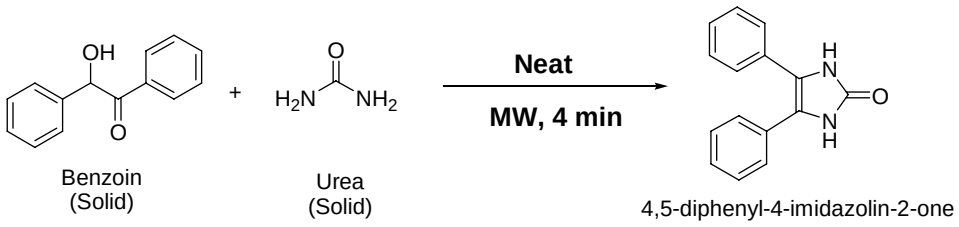
In early days, solvent-free approach was very popular in MAOS since it allowed the safe use of domestic household microwave ovens and standard open-vessel technology. One of the simplest methods involved the mixing of the neat reagents and subsequent irradiation with microwaves. For example, solvent-free and catalyst-free method for the α-amino phosphonate synthesis via Kabachnik-Fields reaction under microwave irradiation was developed by W. Zhang (Scheme 1.4) [26].



Scheme 1.4 Microwave-assisted solvent-free and catalyst-free Kabachnik-Fields reaction for α-amino phosphonate [26]

Since all the liquid reactants are in their liquid states under the reaction conditions, the reaction mixture can readily be heated up by microwave irradiation through dielectric heating mechanism even under solvent-free condition. However, the common drawback of such kind of liquid-phase solvent free condition is the non-uniform mixing thanks to the highly viscous reaction mixture.

In the case of pure solid organic reactants, since solid generally can not be heated by the microwave, small amounts of a polar solvent (E.g. water, N,N-dimethylformamide) are added into the reaction mixture to allow for a dielectric heating in practice [(4)]. Interestingly, in the reaction between benzoin and urea reported by A. Shaabani (Scheme 1.5) [(27)], direct mixing of two solid reactants without any addition of polar solvent, yielded 4,5-diphenyl-4-imidazolin-2-one within 4 min of microwave irradiation in a domestic oven.



Scheme 1.5 Synthesis of 4,5-diphenyl-4-imidazolin-2-one by reacting benzoin with urea [(27)]

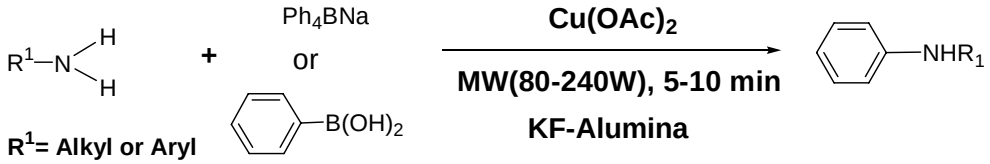
This was because the glass container and the glass rotary plate in a domestic oven were distinctly microwave-absorbing. When they were warmed to temperature of 120-140°C upon microwave irradiation, the benzoin melted through the convective heating. Once the

benzoin became liquefied, the microwave heating was initiated in the reaction mixture through dielectric heating mechanism [4,27].

1.6.2 Reaction using supporting materials

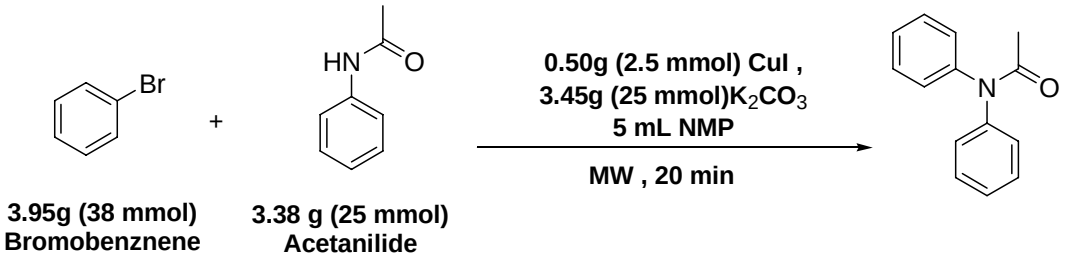
An alternative solvent-free technique utilizes microwave-transparent or weakly absorbing inorganic supports such as alumina, silica or clay materials [3,4]. The reagents are immobilized on the surface of porous solid support and then exposed to microwave irradiation. This method has advantages over the conventional solution-phase reactions because of their good dispersion of active reagent sites, associated selectivity and easier work up [4]. It is also regarded as friendly 'green' protocol because of its recyclability and avoidance of the use of solvent.

In the example shown in Scheme 1.6 [28], N-arylations of primary amines with sodium tetraphenylborate or arylboronic acids were performed on a strongly basic potassium fluoride/alumina support, doped with metal catalyst cupric acetate.



Scheme 1.6 N-arylation on $Cu(OAc)_2$-doped alumina [28]

Another example of C-N coupling between bromobenzene and acetanilide with catalyst copper iodide (Scheme 1.7) also demonstrated the use of potassium carbonate both as base and solid support in this reaction. In this example, small amount of 1-methylpyrrolidone (NMP) was also added to allow for a dielectric heating under microwave irradiation [29].



Scheme 1.7 C-N coupling on CuI-doped potassium carbonate with NMP [29]

1.7 Aims of this project

Waste prevention and environmental protection are major requirements in an overcrowded world of increasing demands. Synthetic chemistry continues to develop various techniques for obtaining better products with less environmental impact. One of the key aims in green chemistry is to replace or reduce the uses of the volatile organic solvents. Volatile organic solvents are at the top of the list of chemicals detrimental to the environment because of their huge consumption and their high volatility. On of the more promising approaches is solvent free organic synthesis. Solvent-free organic reactions make synthesis simpler, save energy and prevent solvent waste, hazards and toxicity.

In the recent 20 years, microwave irradiation is a rapid way of heating materials for domestic, industrial and medical purposes. Microwaves offer a number of advantages over conventional heating such as non-contact heating, energy transfer instead of heat transfer, material selectivity and volumetric heating, fast start-up and stopping. One particular advantage they can offer is efficiency in solventless reactions, thus providing promising safety standards and environmental friendlier alternative for performing chemical synthesis.

We are therefore interested in examining the following organic reactions under solvent free condition by microwave irradiation by taking advantages of their unique properties. These include:

(1) Ullmann type C-N coupling reactions between N-heterocycles with arylbromides

(2) Synthesis of functionalized ionic liquids

(3) Application of microwave-assisted C-N formations to complex molecules

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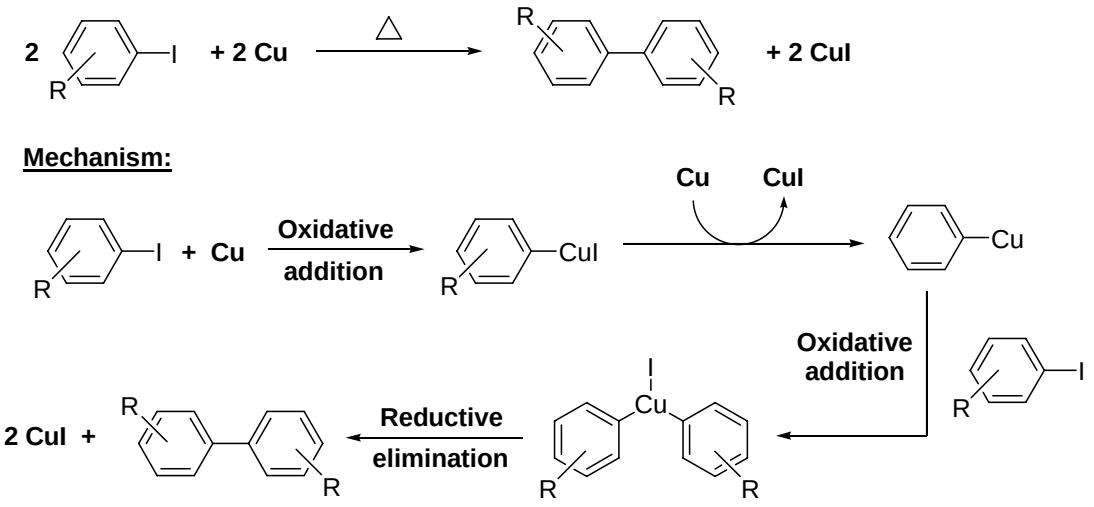
Chapter 2: Microwave-assisted Ullmann coupling reaction of N-hetercycles and aryl bromides under solvent free condition

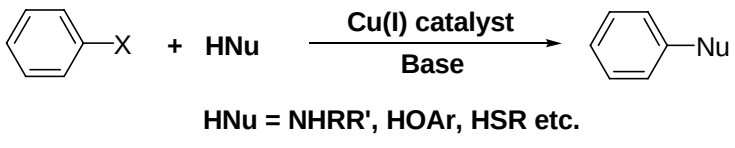
2.1 Introduction

2.1.1 The mechanism of Ullmann type C-N coupling

There are two different transformations referred to as the Ullmann reaction. The classical 'Ullmann reaction' is the synthesis of symmetric biaryls via copper-catalyzed coupling (Scheme 2.1) [(1)]. The other transformation also named as 'Ullmann reaction' includes copper-catalyzed nucleophilic aromatic substitution between various nucleophiles with aryl halides (Scheme 2.2) [(1)].



Scheme 2.1 Synthesis of symmetric biaryls via copper-catalyzed coupling [(1)]

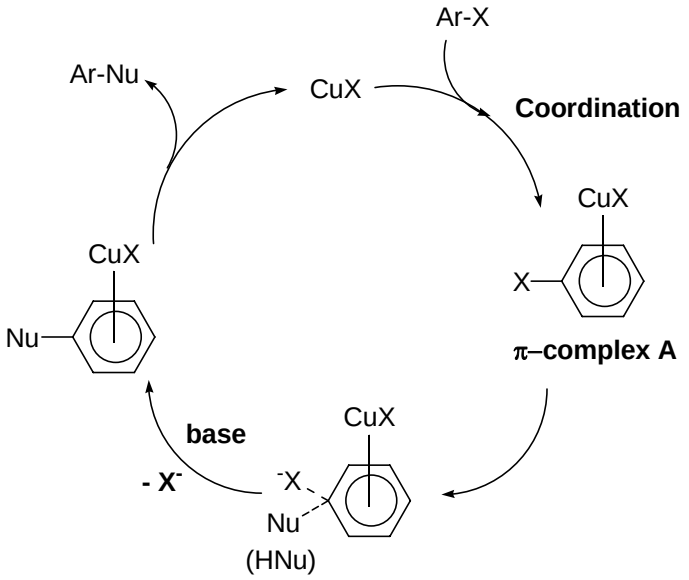


Scheme 2.2 Copper-catalyzed nucleophilic aromatic substitution between nucleophiles and aryl halides [(1)]

The nucleophilic aromatic substitution is different from the S_N1 and S_N2 mechanisms. It is accelerated by aryl halide with relatively more electronegative leaving group such as fluoro, or containing electron-withdrawing substituents in positions ortho and para to the leaving group [1,2,3]. For those aryl halide such as aryl iodide and aryl bromide, which have relatively less electronegative leaving group, they are relatively difficult to undergo aromatic nucleophilic substitution except when they are activated by the electron withdrawing group. [2,3]. If there is the presence of electron-donating substituents on aryl halide, aromatic nucleophilic substitution will be further hindered [1,2].

However, for those aryl halides which are inert to the aromatic nucleophilic substitution, they can readily proceed with substitution with the assistance from copper metal or copper complexes. Two mechanisms for Ullmann-type coupling reactions have been described in the literatures [4,5,6]: (1) π-complex mechanism proposed by Paine in 1987 [7,8] and (2) oxidative addition/reductive elimination mechanism proposed by Cohen in 1974 [8,9].

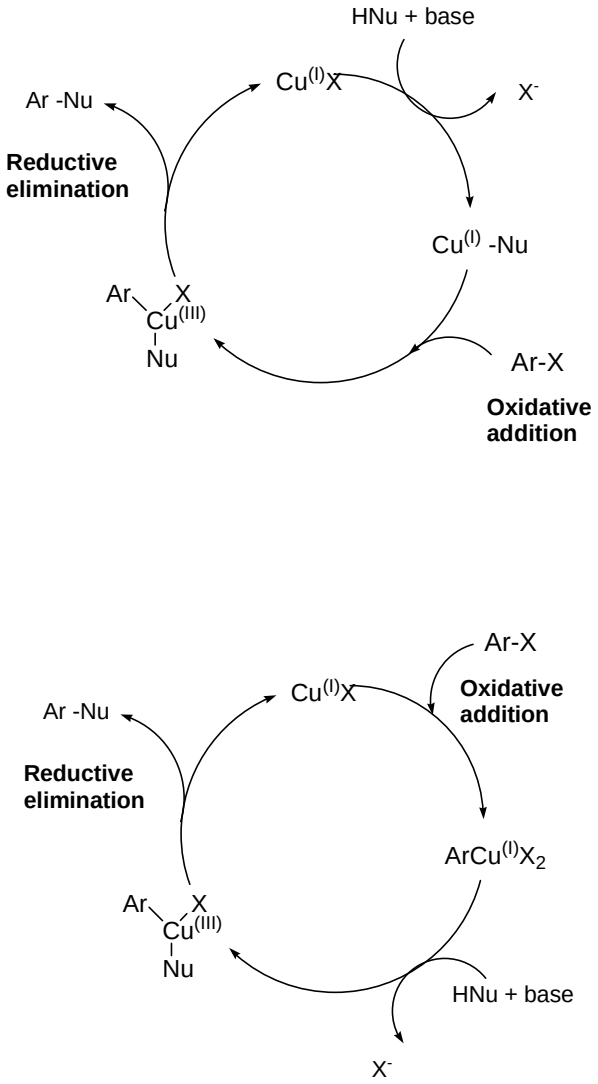
In the mechanism proposed by Paine [7,8], the Cu(I) complex binds to the π electron of aryl halide to give a π complex **A**. This coordination might make the aromatic ring on **A** more electron-deficient, thereby facilitating the nucleophilic attack of nucleophile (Scheme 2.3).



Scheme 2.3 π-Complex mechanism in Ullmann reaction proposed by Paine [7,8]

The intervention of the oxidative addition/reductive elimination mechanism in Ullmann reaction was first proposed by Cohen in 1974 [8,9]. The mechanism was next substantiated by several literature reports indicating Cu(I) and Cu(III) intermediates [10,11,12].

In this mechanism, Cu(I) complex may first undergo oxidative addition to the aryl halide generating a transient Cu(III) species , followed by nucleophilic substitution of copper-bound halide by the nucleophile, and then reductive elimination of the coupling product, regenerating the active catalyst [8,13,14]. However, it is still uncertain whether a nucleophilic substitution step preceeds or follows the oxidative addition step (Scheme 2.4). The ease of halogen displacement from the aromatic ring is opposite to that found in the un-catalyzed aromatic nucleophilic substitution. The trend is generally I > Br >> Cl >> F, which parallels the leaving ability of the halide ions [1,13].



Scheme 2.4 Two alternative oxidative addition/reductive elimination mechanistic pathways for copper-catalyzed nucleophilic aromatic substitution with aryl halides [14]

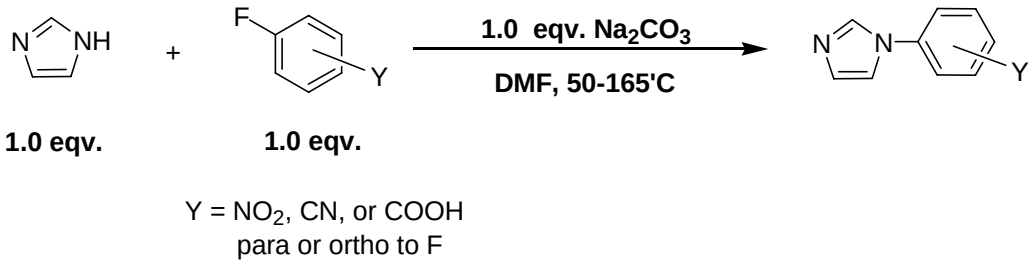
N-Arylimidazole and N-Arylpyrazoles are important compounds, particularly in pharmaceutical research [15,16,17,18]. A significant number of these structures are therapeutically useful, and many others are in the process of active study for biomedical applications. Targeted therapeutic areas for N-Arylimidazoles include thromboxane synthase inhibitors [17,19], AMPA receptor antagonists [17,20], AMP phosphodiesterase

inhibitors [17,21], cardiotonic agents [17,22] and topical anti-glaucoma agents [17,23]. N-Arylpyrazoles are a structural element in the non-steroidal anti-flammatory drug, Celecoxib, which is a potent and selective COX-2 inhibitor in pharmaceutical chemistry [18,24]. They are also structural elements of insecticides Pyraclofos and Fipronil in agrochemical chemistry [18]. As such, there is significant interest in developing efficient methods for their preparation.

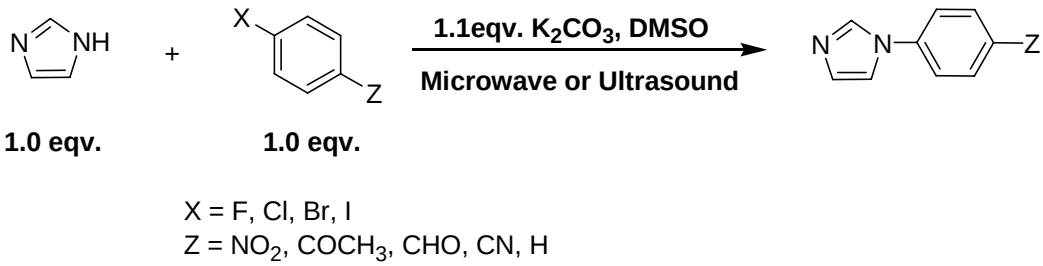
2.1.2 Limitations from previous reports

The synthesis of N-arylimidazoles and N-arylpyrazoles by direct formation of aryl-nitrogen bond has previously been reported. The methods commonly used for constructing the C-N bond between imidazole and pyrazole with aryl halide are: nucleophilic aromatic substitution [6,9,12] and Ullmann-type coupling [8,10,11,14].

The former method, which is only feasible for substrates which are activated by strongly electron withdrawing substituents and with fluoride as the leaving group, shows limited substrate diversity [2,3]. Besides it requires the use of environmental-unfriendly aryl fluorides as the starting reagents. The reactions also require to be performed in polar toxic solvent such as DMF or DMSO [25,26,27] and usually proceed at high temperature for prolonged reaction time (Scheme 2.5) [2,3,28]. Although the application of microwave irradiation and ultrasonic irradiation on this nucleophilic aromatic substitution has shortened the reaction time, the problem of using toxic solvent remains unsolved (Scheme 2.6) [29].

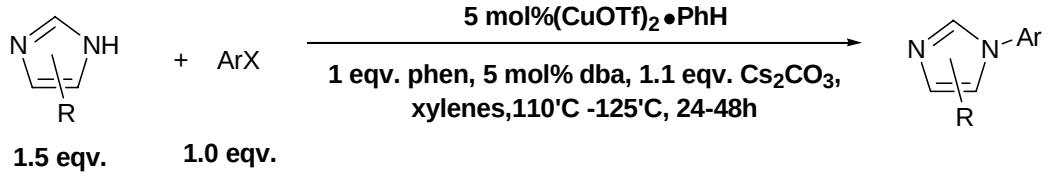


Scheme 2.5 A. L. Johnson's System [2]

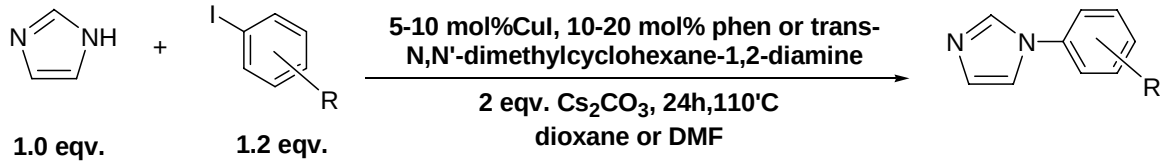


Scheme 2.6 S. Toma's System [29]

The Ullmann protocol shows a relatively broader substrate scope with respect to the aryl halide but still preferentially with those activated by electron withdrawing group [13,25,26,27]. However those copper-mediated or catalyzed reactions also need to be conducted in toxic polar solvents such as DMF, DMSO, nitrobenzene, N-methylpyrrolidone (NMP) or dioxane [25,26,27] .Besides the environmental unfriendly solvent problem, the transformation sometimes requires stoichiometric amount of expensive copper reagents such as $(CuOTf)_2$. benzene [25] or $Cu(OTf)_2$.toluene [28] and toxic additive such as 1, 10-phenanthroline (phen) [25,26,27] (Scheme 2.7 and 2.8).

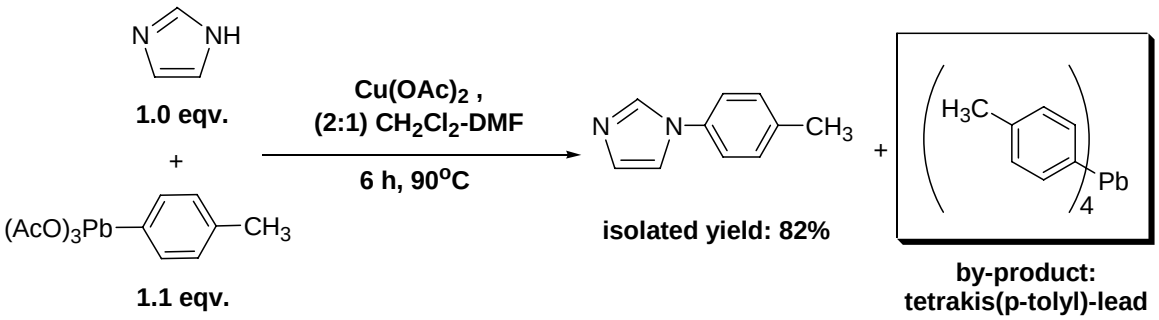


Scheme 2.7 S.L. Bachwald's System [25]



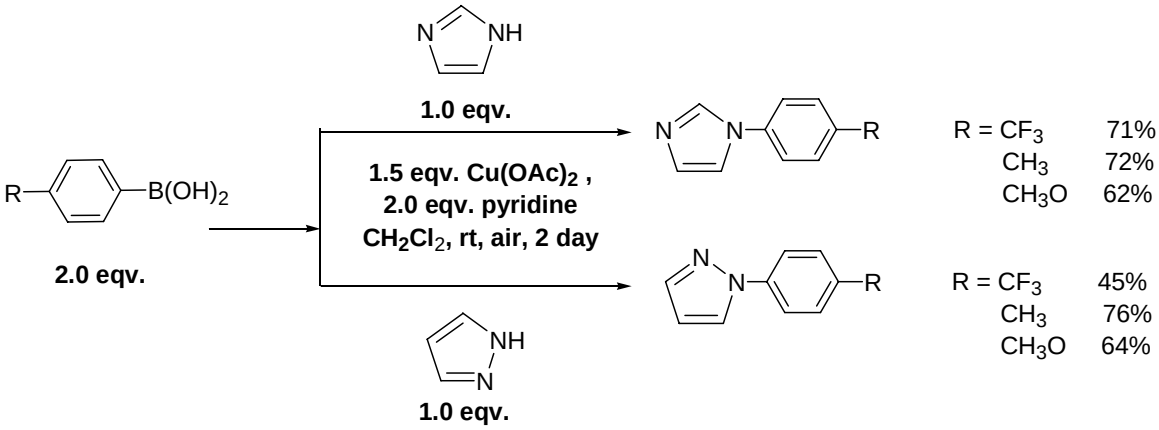
Scheme 2.8 J.C. Antilla and S.L. Bachwald's System [26]

Lopez-Alvarado has described N-arylation of imidazoles with *p*-tolyllead triacetate using a catalytic amount of $Cu(OAc)_2$ at 90°C (Scheme 2.9) [30,31]. Although there was improvement of N-arylimidazole yield and reduction in reaction time, the use of DMF as co-solvent still remains unavoidable. Besides, this method is limited to *p*-tolyllead and also it produces toxic organolead byproduct.

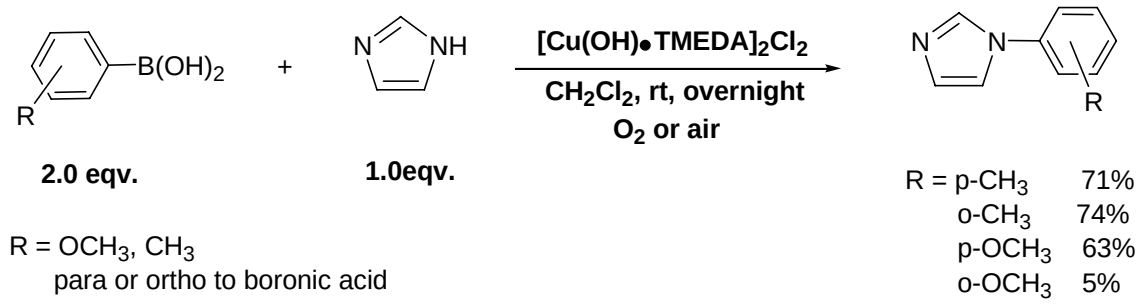


Scheme 2.9 Lopez-Alvarado's system [31]

In addition, synthesis of N-arylimidazoles by coupling imidazole and arylboronic acid with catalytic amount of copper salt has been described by several reports [32,33,34]. Those systems did not require copious quantities of toxic high boiling point toxic solvent; however, the drawback of those systems is the limited arylboronic acid diversity for the coupling reactions (Scheme 2.10, 2.11, 2.12).



Scheme 2.10 M. T. Chan's system [34]

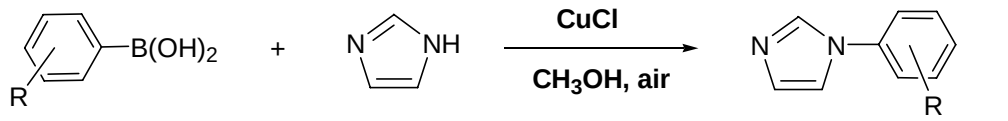


2.0 eqv. **1.0eqv.**

R = OCH_3, CH_3
para or ortho to boronic acid

R = p-CH_3 71%
o-CH_3 74%
p-OCH_3 63%
o-OCH_3 5%

Scheme 2.11 J. P. Collman's system [33]



1.0 eqv. **1.2eqv.**

R = OCH_3, CH_3

R = CH_3 97-98 %
OCH_3 92-93 %

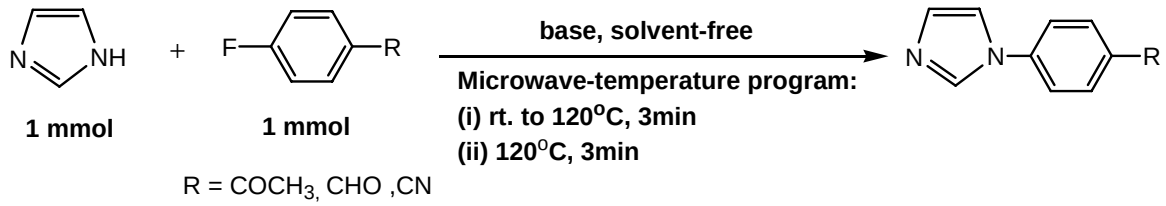
Scheme 2.12 R. G. Xie and X. Q. Yu's system [32]

2.2 Preliminary studies

As we mentioned in the Introduction section, there is a need to find improved synthesis of N-arylimidazoles and N-arylpyrazoles, especially methods which are compatible with the principles of green chemistry.

2.2.1 Microwave-assisted solvent free aromatic nucleophilic substitution

Although there is a previous report on the aromatic nucleophilic substitution of aryl halide and imidazole using microwave irradiation as the energy source rather than conventional heating [29], the reaction still required the use of toxic aprotic solvent such as DMSO or DMF. In this section, we examined the aromatic nucleophilic substitution between imidazole and aryl fluoride with electron withdrawing groups by microwave irradiation under solvent free condition. In solvent free conditions, we have to select an appropriate solid base. The base in aromatic nucleophilic substitution not only plays a role as catalysis, but also serves as a mineral solid support in the solvent free condition. In the preliminary studies, we have compared solid potassium carbonate with potassium phosphate tribasic (Scheme 2.13). Potassium carbonate had been previously used by others in DMSO [7,29], whereas several reports described the use of potassium phosphate tribasic as the base instead of sodium carbonate in C-N coupling reaction. [35,36] The results are summarized as in Table 2.1:



Scheme 2.13 Proposed solvent free-microwave aromatic nucleophilic substitution

Entry	*Substrates*	**^{1}H Nmr yield**		
		1 equiv. K_2CO_3	**1 equiv. K_3PO_4**	**2 equiv. K_3PO_4**
1	4-fluoroacetophenone	8%	45%	82%
2	4-fluorobenzaldehyde	33%	57%	74%
3	4-fluorobenzonitrile	44%	77%	84%

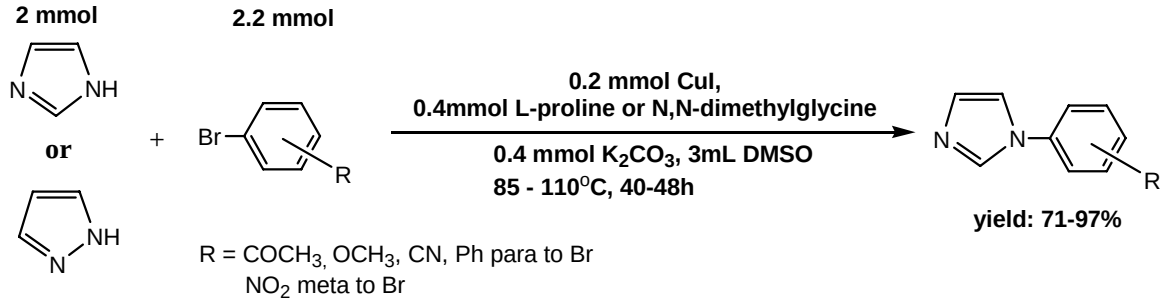
Table 2.1 Results of microwave assisted solvent free aromatic nucleophilic substitution with different bases and ratio

As we can see from Table 2.1, using 1 equiv. potassium phosphate tribasic gave 45 % yield of 4-(imidazol-1-yl)acetophenone (Entry 1), which was 5.5 times higher that from 1 equiv. potassium carbonate. Similar differences were also observed in other reactions: 1 equiv. potassium phosphate tribasic give 57 % yield of 4-(imidazol-1-yl)benzaldehyde (Entry 2) and 77 % yield of 4-(imidazol-1-yl)benzonitrile (Entry 3) which was 1.7 times and 1.8 times of 1 equiv. potassium carbonate respectively. From the above results, potassium phosphate tribasic does show superior catalytic effect on the reaction. This observation may be due to the larger surface area of the potassium phosphate tribasic (2mmol, 0.42g) than that of potassium carbonate (2mmol, 0.24g), thus improved the contact area between the base and the substrate and benefited in the heterogeneous reaction set up [37,38,39,40].

When comparing the product yields by using different base ratios of potassium phosphate tribasic under the same solvent free condition, 2 equiv. potassium phosphate tribasic gave 82 % yield of 4-(imidazol-1-yl)acetophenone (Entry 1) ,which was 1.8 times of that from 1 equiv. base. Similar improvement was also showed in other results, 2 equiv. potassium phosphate tribasic gave 74 % yield of 4-(imidazol-1-yl)benzaldehyde (Entry 2) and 84 % yield of 4-(imidazol-1-yl)benzonitrile (Entry 3) which was 1.3 times and 1.1 times of 1 equiv. base respectively. Double the amount of potassium phosphate tribasic used does show the improvement in product yields. This is believed also to be due to the increase in surface area.

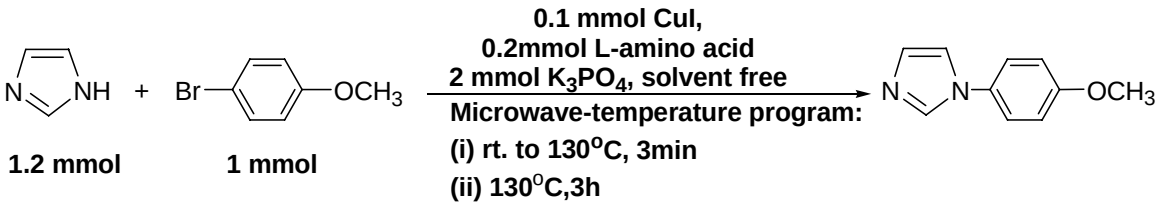
2.2.2 Screening of suitable additive for Ullmann type C-N coupling

Recently, Ma and Cai suggested an effective Ullmann-type coupling between aryl bromides with nitrogen hetercycles such as imidazoles and pyrazoles by using commercially available amino acid, L-proline or N,N-dimethylglycine and copper(I) iodide, together with potassium carbonate in DMSO (Scheme 2.14) [8]:



Scheme 2.14 D. Ma and Q. Cai's system [8]

We are interested to know if the reaction can be adapted for solvent-free conditions. Therefore, several amino acids (Figure 2.2) were investigated for the Ullmann coupling between imidazole and 4-bromoanisole together with copper(I) iodide, but using potassium phosphate tribasic as base and solid support and under solvent free condition with microwave irradiation (Scheme 2.15). The results are summarized in Table 2.2 and Figure 2.1.



Scheme 2.15 Proposed L-amino acid catalyzed Ullmann type C-N coupling system between imidazole and 4-bromoanisole

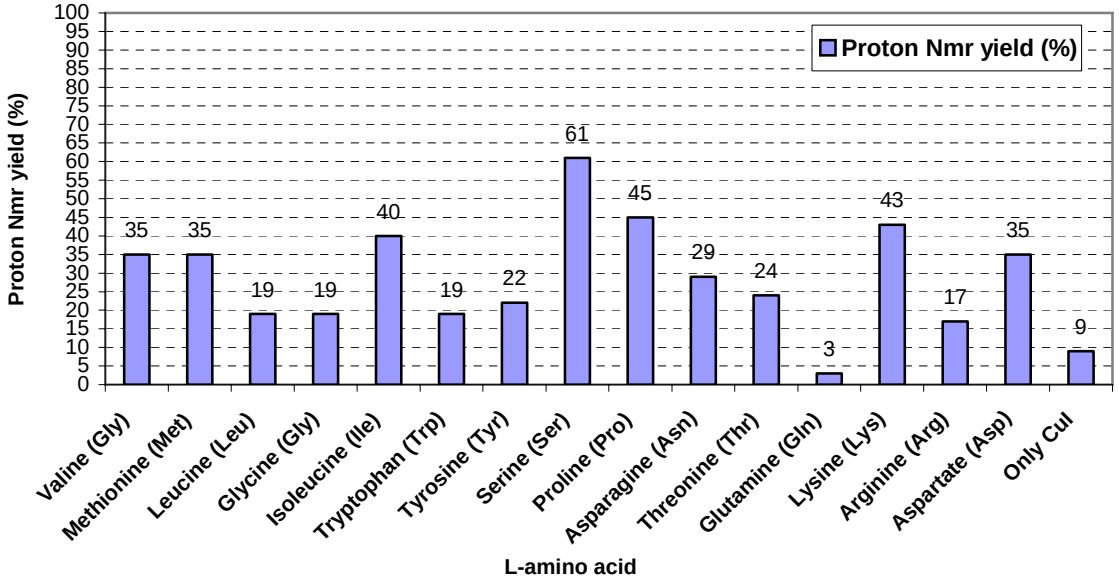
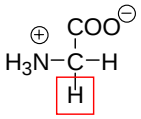


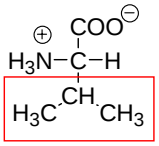
Figure 2.1 Ullmann type C-N coupling between 4-bromoanisole and imidazole with 15 standard L-amino acids

Nonpolar, aliphatic R groups

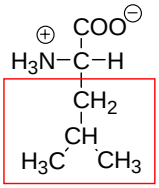
L-Glycine



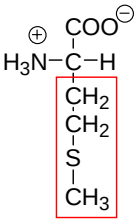
L-Valine



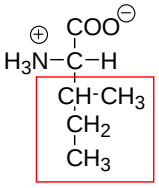
L-Leucine



L-Methionine

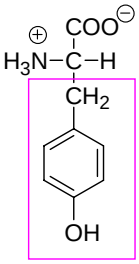


L-Isoleucine

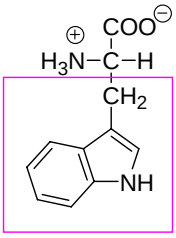


Aromatic R groups

L-Tyrosine

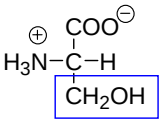


L-Tryptophan

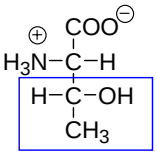


Polar, uncharged R groups

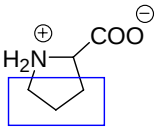
L-Serine



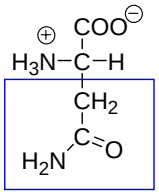
L-Threonine



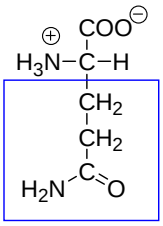
L-Proline



L-Asparagine

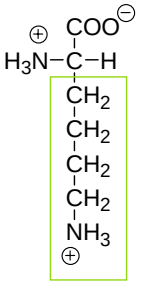


L-Glutamine

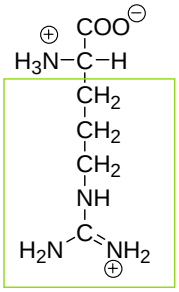


Positively charged R groups

L-Lysine



L-Arginine



Negatively charged R groups

L-Aspartate

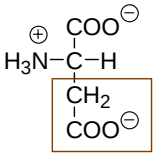


Figure 2.2 15 standard L-amino acids [38]

	L-amino acid	pK_1 (-COOH)	pK_2 ($-NH_3^+$)	pK_R (R group)	Hydropathy index [a]	^{1}H Nmr yield (%)
A	Proline (Pro)	1.99	10.96	---	1.60	45
	Methionine (Met)	2.28	9.21	---	1.90	35
	Valine (Val)	2.32	9.62	---	4.20	35
	Isoleucine (Ile)	2.36	9.68	---	4.50	40
	Leucine (Leu)	2.36	9.60	---	3.80	19
B	Threonine (Thr)	2.11	9.62	---	-0.70	24
	Tyrosine (Tyr)	2.20	9.11	10.07	-1.30	22
	Serine (Ser)	2.21	9.15	---	-0.80	61
	Glycine (Gly)	2.34	9.60	---	-0.40	19
	Tryptophan (Trp)	2.38	9.39	---	-0.90	19
C	Lysine (Lys)	2.18	8.95	10.53	-3.90	43
	Aspartate (Asp)	1.88	9.60	3.65	-3.50	35
	Asparagine (Asn)	2.02	8.80	---	-3.50	29
	Glutamine (Gln)	2.17	9.13	---	-3.50	3
	Arginine (Arg)	2.17	9.04	12.48	-4.50	17

Nonpolar, aliphatic R group
Aromatic R group
Polar, uncharged R group
Positively charged R group
Negatively charged R group

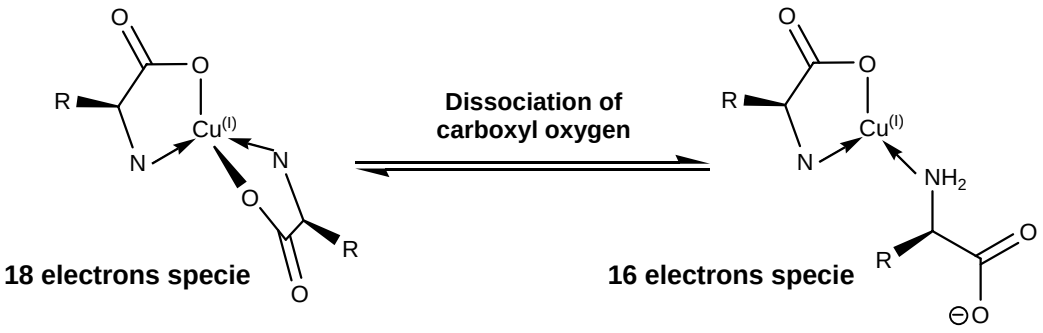
[a] *A scale combining hydrophobicity and hydrophilicity of r groups; it can be used to measure the tendency of an amino acid to seek an aqueous environment (-ve values) or a hydrophobic environment (+ve value)* [38,39]

Table 2.2 Ullmann type C-N coupling between 4-bromoanisole and imidazole with 15 standard L-amino acids

2.2.3 An interpretation of results

It is clear from the results in Figure 2.1 that different L-amino acids show different effect on the reaction. We offer the following interpretation. The Cu(I) has a d^{10} configuration , the symmetrical electron distribution means there are no ligand field effects and the ligand positions are sterically determined [37]. Also for the d^{10} system, d electrons are not considered but only the lone pairs of ligands [37]. Based on the oxidative addition/reductive elimination mechanism mentioned in action 2.1, copper(I) ions can chelate with amino acids through the carboxyl and amino groups [1,8]. One would expect that the basicity of both amino group and carboxyl group will play important roles in the complex formation and catalytic cycle.

When considering the complex formation, since relatively soft Lewis acid Cu(I) tends to coordinate softer Lewis base, the amino acid with more basic amino group will be facilitated in the metal complex formation with Cu(I) ion according to the hard-soft acid-base concept (Scheme 2.16) [40,41]. However, focused on the catalytic cycle, the weakly coordinated oxygen on the carboxyl group is required to be dissociated from the 18 electrons complex to generate a vacant site before the oxidative addition of aryl halide. Therefore, the more acidic the carboxyl group owing to the weaker the conjugated base, the better it is dissociated from the metal complex which is the essential step for the catalytic cycles.



Scheme 2.16 Proposed structure for Cu(I) amino acid complex [1,8]

In addition, the reaction is conducted under solvent free condition and the system is heterogeneous, the solubility of that amino acid in the relatively non-polar aryl halide would be significant. The more hydrophobic amino acids are suggested to have better solubility in the reaction mixture and hence show better reactivity toward the C-N formation reaction.

Therefore, the capability of L-amino acids for promoting C-N formation reactions might be dependent on: (1) their reactivity as the coupling agents which relate to the basicity of the amino acids [8], (2) coordination ability as bidentate additives which depend on the structure of amino acids [8] and (3) solubility in non-polar reaction mixture which is associated with the hydrophobicity of amino acids.

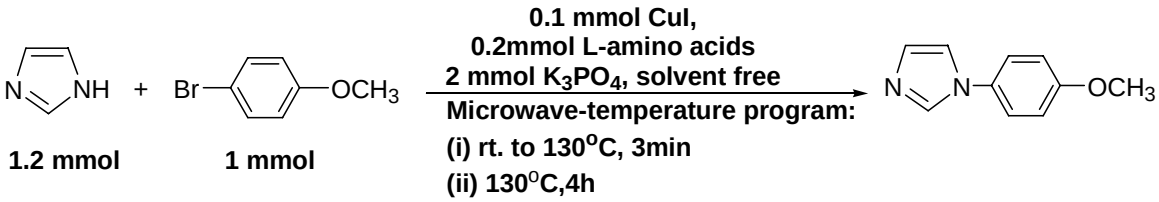
Based on the hydropathy index, 15 standard amino acids are classified into 3 groups, A to C (Table 2.2). For group A amino acids which have positive hydropathy index, decrease in the pK_1 of COOH group of amino acids generally provides improvement in reaction yields. Proline which has the relatively lower pK_1 (pK_1 = 1.99) (i.e. weaker the

conjugated base) and relatively higher pK_2 (pK_2 = 10.96) (i.e. stronger the conjugated base) showed the best result among group A. Although methionine has relatively less basic amino group (pK2 = 9.21) and is relatively hydrophilic among those amino acids in group A, it's relatively low pK_1 (pK_1 = 2.28) make it comparable to relatively hydrophobic valine and isoleucine with high pK_2 values (pK_2 = 9.62 and 9.68 respectively).

For group B which have negative hydropathy index, these amino acids give poor results toward the C-N formation reaction due to the solubility problem except serine. It is surprising that there are two amino acids lysine and aspartate in group C, which are supposed to be suffered seriously from solubility problem, can work comparably well in this reaction. This may be explained by one more amino group on lysine or one more carboxyl group on aspartate which provide extra opportunities for the coordination to copper ion. Also the secondary amino group of lysine is relatively basic (pK_R = 10.53), which makes it readily to form complex with copper(I) ion. Similarly, the more acidic carboxyl group on aspartate (pK_1 = 1.88) is suggested to contribute in the better reactivity in this reaction. However, arginine which also has one more amino group with high pK_2 (pK_2 = 12.48), did not show comparable result in this reaction. This may be due to the presence of three more basic amino groups which allowed the arginine to become polydentate ligand. The strong coordination between arginine and copper ion makes the ligand dissociation relatively difficult and not readily open a vacant site for the following oxidative addition of aryl halide.

2.3 The microwave assisted Ullmann type C-N coupling using L-lysine

Based on the results shown in section 2.2, six amino acids (L-valine, L-serine, L-proline, L-methionine, L-lysine and L-aspartate) were selected to undergo L-amino acid promoted Ullmann type coupling reaction between imidazole and 4-bromoanisole for longer reaction time (Scheme 2.17) and the results were shown as figure 2.3.



Scheme 2.17 Proposed L-amino acid catalyzed Ullmann type C-N coupling system between imidazole and 4-bromoanisole

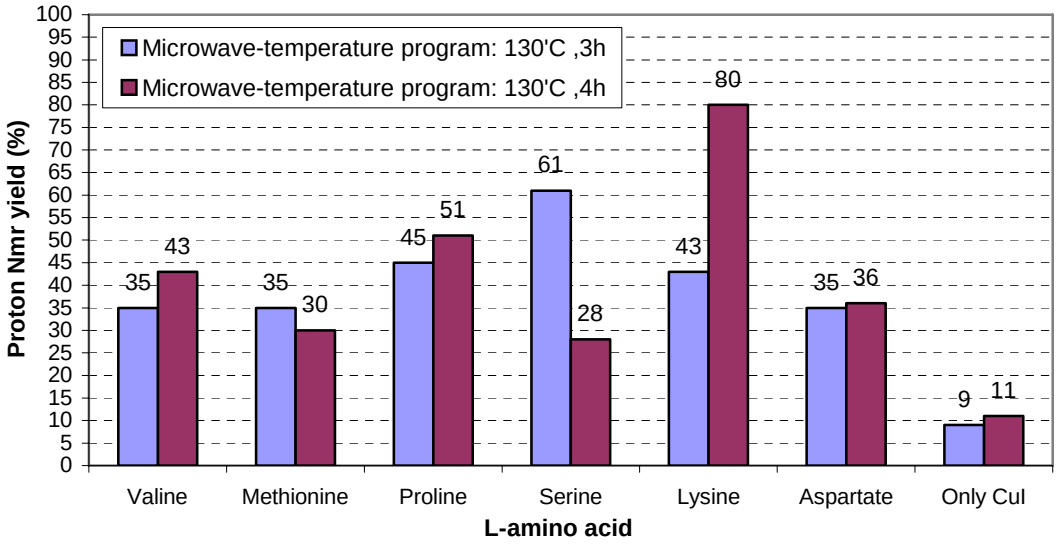
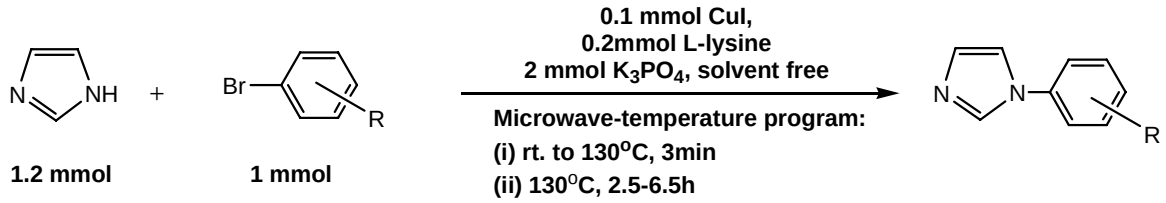


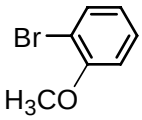
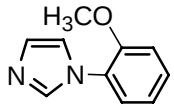
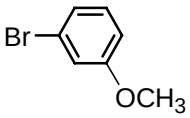
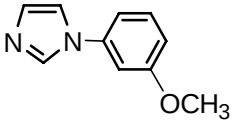
Figure 2.3 Ullmann type C-N coupling between 4-bromoanisole and imidazole with L-valine, L-serine, L-proline, L-methionine, L-lysine and L-aspartate

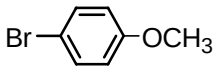
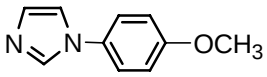
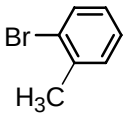
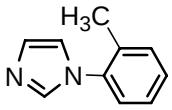
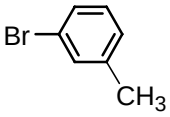
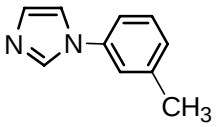
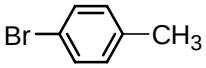
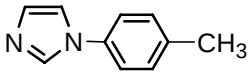
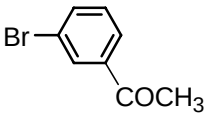
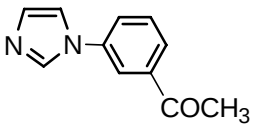
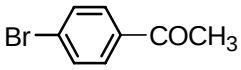
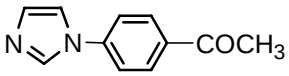
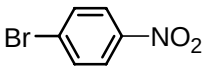
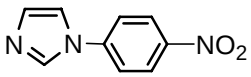
2.3.1 C-N coupling between imidazole and aryl bromides

Form the results obtained in Figure 2.2, no significant improvement in product yield in this reaction was obtained by prolonging the reaction time from 3 hours to 4 hours except the system using L-lysine as additive. Therefore, a microwave assisted Ullmann type C-N coupling between imidazole and aryl bromides under solvent free condition by using L-lysine as additive was developed (Scheme 2.18):



Scheme 2.18 Proposed L-lysine catalyzed Ullmann type C-N coupling between imidazole and aryl bromide

Entry	Substrate	Reaction condition [a]			Product	Isolated yield (%)
		Reaction temperature (°C)	Reaction time (h)	Microwave power (W)		
1		130	6.5	200		95
2		130	5.0	200		99

3		130	5.0	200		99
4		130	5.0	200		30
5		130	3.0	200		79
6		130	2.5	200		49
7		130	5.0	200		73
8		130	6.5	200		43
9		130	7.0	200		48

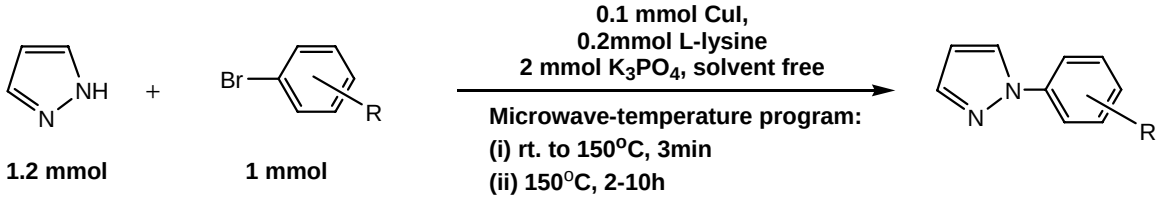
[a] *the reaction mixture was heated up from room temperature to 130°C by 500W microwave irradiation within 3 min*

Table 2.3 L-lysine promoted Ullmann type C-N coupling between aryl bromides and imidazole by microwave irradiation under solvent free condition

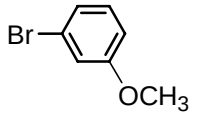
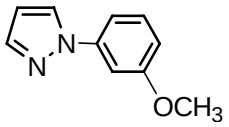
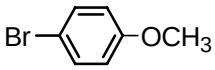
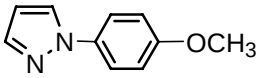
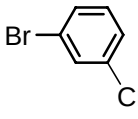
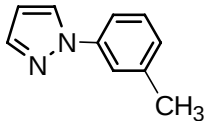
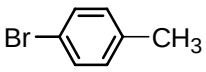
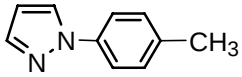
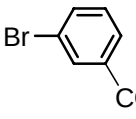
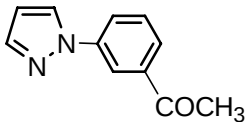
The cross coupling of a range aryl bromides with imidazole were investigated and the results are summarized in Table 2.3. The system worked well for both aryl bromides with electron donating substituents and electron withdrawing substituents at meta position (Entry 2, 5 and 7). And the system generally showed better results toward aryl bromides with electron donating substituents since the C-N forming of 3-bromoacetophenone yielded 73% after 5 hours while the 3-bromoanisole provided nearly completed conversion under the same condition (Entry 2 and 7).

The more significant observations were also obtained for those aryl bromides with substituents at ortho and para positions. In the case of electron rich bromoanisole, good yields were obtained for all positions (Entry 1, 2, 3). Even for the 2-bromoaniosle (Entry 1), which might be suggested to suffer from steric hindrance at ortho position, high yield still could be obtained by prolonged reaction times from 5 hours to 6.5 hours. However, the poor yield for the 2-bromotoluene not only suggested that ortho substituted aryl bromide may suffer from steric hindrance, the reactivity of system decreased with aryl bromides with less electron donating substituents at ortho and para positions (Entry 4, 6, 8 and 9). When comparing the reaction conditions of 4-bromotoluene, 4-bromoactophenone and 4-bromonitrobenzene, the C-N formations required longer reaction time to obtain similar yields (43-49%) when the substituents on aryl bromides become more electron withdrawing (Entry 6, 8 and 9).

2.3.2 C-N coupling between pyrazole and arylbromides



Scheme 2.19 Proposed L-lysine catalyzed Ullmann type C-N coupling between pyrazole and aryl bromide

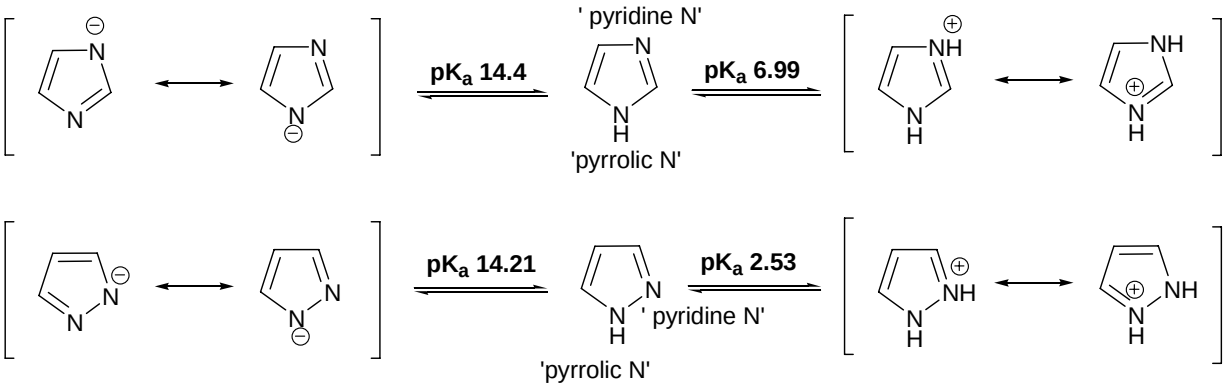
Entry	Substrate	Reaction condition [a]			Product	Isolated yield (%)
		Reaction temperature (°C)	Reaction time (h)	Microwave power (W)		
10		150	10	200		32
11		150	10	200		83
12		150	3.0	200		27
13		150	2.0	200		37
14		150	10.0	200		44

[a] *the reaction mixture was heated up from room temperature to 140°C by 500W microwave irradiation within 3 min*

Table 2.4 L-lysine promoted Ullmann type C-N coupling between aryl bromides and pyrazole by microwave irradiation under solvent free condition

A microwave assisted Ullmann type C-N coupling by L-lysine between pyrazole and aryl bromides was also investigated (Scheme 2.19) and the results are shown in Table 2.4. The system generally failed to work on C-N couplings between pyrazole and various aryl bromide either carrying the electron donating group or electron withdrawing group at different positions except 4-bromoanisole (Entry 11). For those meta substituted aryl bromides which worked well with imidazole, pyrazole also failed to give a satisfactory results toward the same C-N formations even when higher reaction temperature and longer reaction times were applied.

When comparing the two hetercycles imidazole and pyrazole (Scheme 2.20), the acidity of the two pyrrole-like nitrogens on the two heterocycles is very similar (pK_a 14.21 for pyrazole compared to pK_a 14.4 for imidazole) [42]. In contrast, the basicity of the two pyridine-like nitrogens on the two heterocycles is quite different, with pyrazole being considerably less basic than imidazole (pK_a 2.53 for pyrazole compared to pK_a 6.99 for imidazole) [42].



Scheme 2.20 Acidity and basicity of imidazole and pyrazole [42]

Therefore, the failure of pyrazole towards the Ullmann type C-N coupling in this system is suggested to be due to its reduced basicity of pyridine nitrogen of pyrazole. These results also demonstrate that the nucleophilicity of N-heterocycles is one of the key factors in the present coupling reaction; it especially plays an important role on the C-N formation for those meta substituted aryl bromides.

2.4 The microwave assisted Ullmann type C-N coupling using L-glutamine

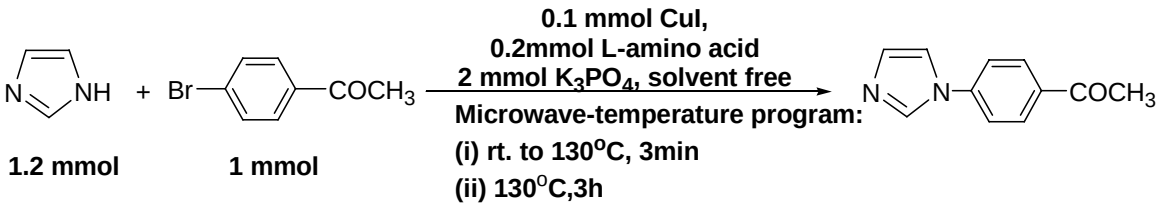
From the pervious section, the L-lysine only promoted the Ullmann type C-N coupling between imidazole and electron rich aryl bromides, showed a limited scope for this system. Therefore, several L-amino acids were investigated instead of L-lysine in the Ullmann type C-N formation reaction between imidazole and electron deficient 4-bromoacetophenone (Scheme 2.21). According to the Table 2.2, 5 standard amino acids with different properties were selected for the investigation (Table 2.5) and the results are shown in Figure 2.3:

	L-amino acid	pK_1 (-COOH)	pK_2 ($-NH_3^+$)	pK_R (R group)	Hydropathy index [a]	Description
A	Valine	2.32	9.62	---	4.20	Relatively hydrophobic
	Isoleucine	2.36	9.68	---	4.50	
	Leucine	2.36	9.60	---	3.80	
B	Aspartate	1.88	9.60	3.65	-3.50	One more COO^- group
C	Glutamine	2.17	9.13	---	-3.50	Relatively less basic amino group but more acidic carboxyl group

Nonpolar, aliphatic R group
Negatively charged R group
Polar, uncharged R group

[a] *A scale combining hydrophobicity and hydrophilicity of R groups; it can be used to measure the tendency of an amino acid to seek an aqueous environment (-ve values) or a hydrophobic environment (+ve value)* [38,39]

Table 2.5 5 Selected L-amino acids additives investigated in Ullmann C-N coupling reaction between imidazole and 4-bromoacetopheone



Scheme 2.21 Proposed L-amino acid catalyzed Ullmann type C-N coupling system between imidazole and 4-bromoacetopheone

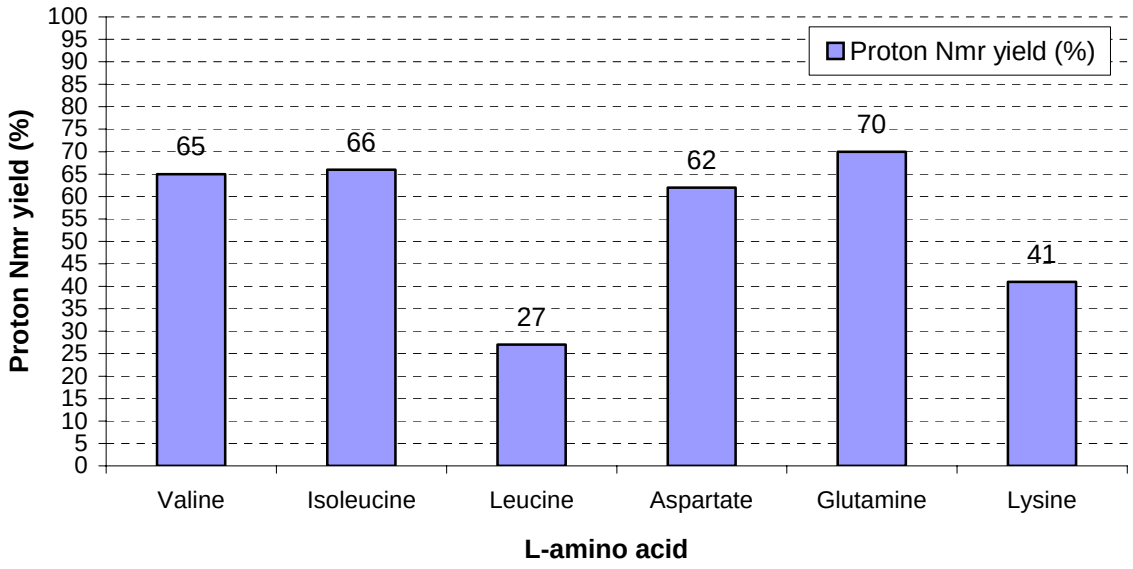
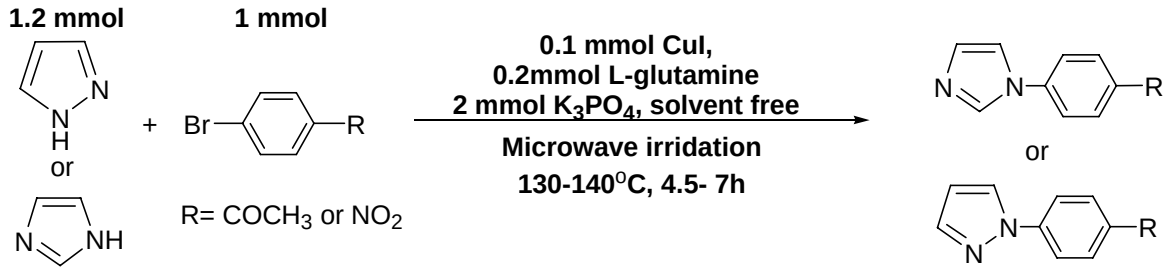
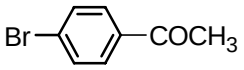
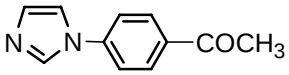
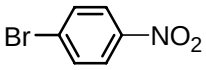
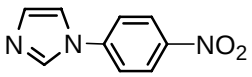
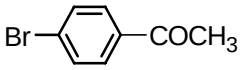
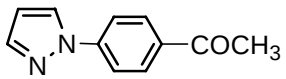


Figure 2.4 Ullmann type C-N coupling between 4-bromoacetopheone and imidazole with L-valine, L-isoleucine, L-leucine, L-aspartate and L-glutamine

Based on the above results shown in Figure 2.4, all selected amino acids led to improved results compared to L-lysine except L-leucine. Therefore, the microwave-assisted Ullmann type C-N coupling between imidazole and electron deficient aryl bromides was examined by using L-glutamine as additive under solvent free condition (Scheme 2.22 and Table 2.6):



Scheme 2.22 Proposed L-glutamine catalyzed Ullmann type C-N coupling system between imidazole and electron deficient arylbromides

Entry	Substrate	Reaction condition [a]			Product	Isolated yield (%)
		Reaction temperature (°C)	Reaction time (h)	Microwave power (W)		
1[b]		130	4.5	200		69
2[c]		130	6.5	200		43
3[b]		130	7.0	200		51
4[c]		130	7.0	200		48
5[b]		140	5.0	200		59

[a] *the reaction mixture was heated up from room temperature to desired reaction temperature by 500W microwave irradiation within 3 min*
[b] *L-glutamine was used as additive*
[c] *L-lysine was used as additive*

Table 2.6 L-glutamine promoted Ullmann type C-N coupling between electron deficient aryl bromides and N-heterocycles by microwave irradiation under solvent free condition

For the C-N coupling reaction between 4-bromoacetophenone and imidazole, L-glutamine provided a 1.6 time product to that of L-lysine system with reduced reaction time from 6.5 hours to 4.5 hours (Entry 1 and 2). In the case of 4-bromonitrobenznene (Entry 3 and 4), both systems gave similar results with product yield of 48-51%. This observations may be accounted for by the high melting point of 4-bromonitrobenzene (124-126°C) which limited the dielectric heating properties of the reaction mixture by microwave irradiation especially under solvent free condition.

When comparing the L-glutamine promoted C-N coupling between pyrazole and 4-bromoacetopheone to that of imidazole, similar observation was obtained as described in section 2.3.2. The pyrazole generally showed less reactive towards the cross coupling reaction than that of imidazole even applied with higher reaction temperature and prolonged reaction time.

2.5 Conclusion

To conclude, we showed that Ullmann type C-N coupling of N-heterocycles with aryl bromides can be promoted by different L-amino acids to different extents under solvent free condition with microwave irradiation. Without using solvent, the L-lysine promoted cross couplings between imidazole and meta substituted aryl bromides or electron rich aryl bromides proceeded cleanly with satisfactory yields in relatively short reaction times. For those couplings between imidazole and electron deficient aryl bromides, which generally showed poor results in L-lysine system, the reaction was further improved by changing the additive from L-lysine to L-glutamine. The potential limitation of this catalytic system is that the less nucleophilic N-heterocycles (pyrazole) does not readily undergo C-N formations, generally giving unsatisfactory coupling product yield with various aryl bromides.

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Chapter 3: Microwave-assisted synthesis of functionalized ionic liquids

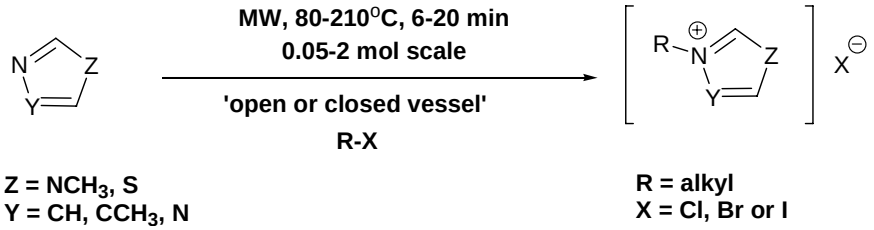
3.1 Introduction

3.1.1 Definition of ionic liquids

Ionic liquids are organic salts with melting points below 100°C, and are typically in their liquid state at room temperature [1]. Ionic liquids are different from conventional organic solvents because of their unique properties: non-volatility, non-flammability, thermal stability, high loading capacity, low toxicity and recyclability [1,2,3]. As these solvents are made up of a combination of anion and cation, the solvent can be designed for a particular use and for a particular set of properties by varying the combination of anion and cation [3]. Hence, ionic liquids are generally regarded as designer-solvents. The field of ionic liquids has been reviewed by several authors including Welton, Holbrey and Seddon [3].

Since the ionic liquids are entirely constituted of ions, their high polarity and boiling point render them a new class of reaction media that can be used in conjunction with microwave synthesis [4]. Ionic liquids interact very efficiently with microwaves through the ionic conduction mechanism and are rapidly heated at rates easily exceeding 10°C s^{-1} without any significant pressure build-up [4,5]. Therefore, safety problems arising from over-pressurization of heated sealed reaction vessels are minimized. It is worth noted that ionic liquids can also be very rapidly and efficiently prepared under solvent-free condition by microwave irradiation [6]. Comprehensive study on the microwave-assisted preparation of ionic liquids was published by Deetlefs and Seddon in 2003 [4,7]. These

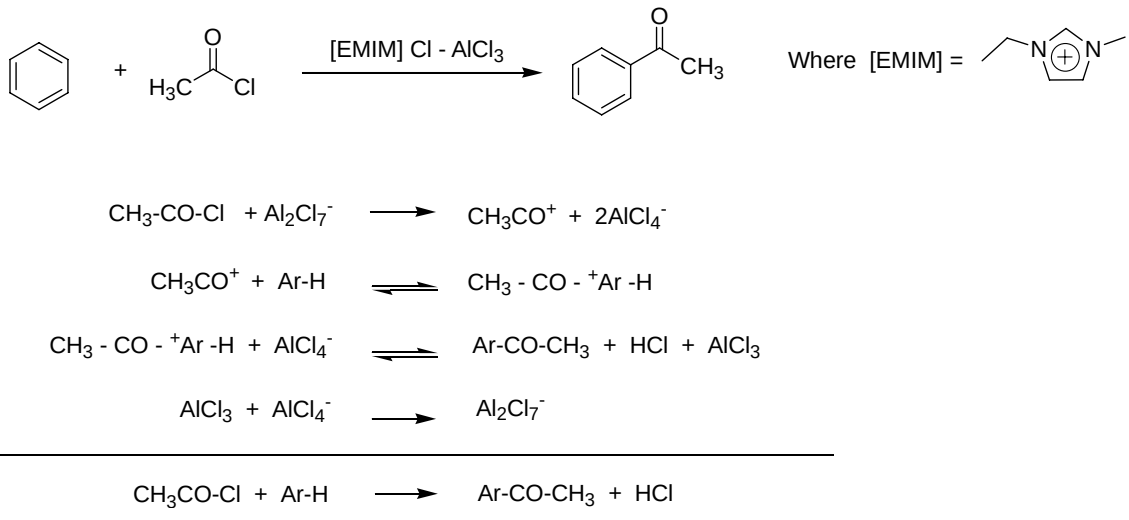
authors synthesized a large number of ionic liquids by solvent free alkylation of the corresponding basic heterocyclic core (Scheme 3.1).



Scheme 3.1 Preparation of ionic liquids under microwave condition by Deetlefts and Seddon [7]

3.1.2 Task specific ionic liquid (TSIL) concept

From the early studies probing the feasility of conducting electrophilic reactions in chloroaluminate ionic liquids (ILs), another page of history for the ionic liquid was opened.

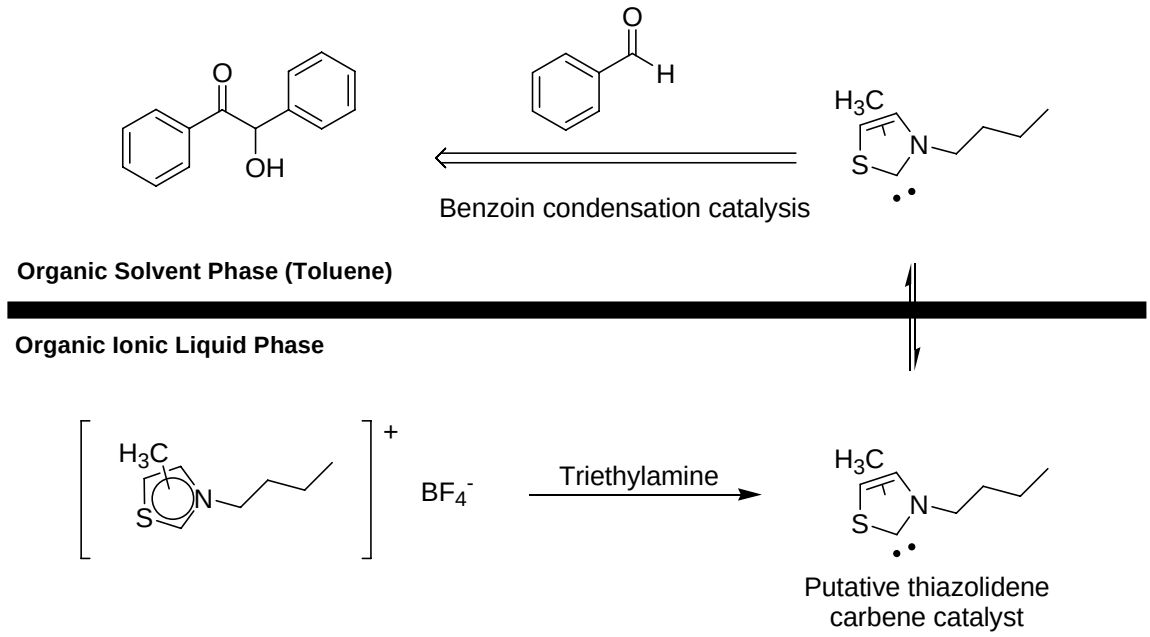


Scheme 3.2 John S. Wiles's proposed mechanism for the acylation of benzene employing [EMIM]Cl-$AlCl_3$ catalyst-solvent system [8]

The catalytic activity of the reaction was promoted by the capacity of the salt, and this capacity of the liquid was found to act like an electrophilic catalyst, which could be adjusted by varying the Cl^-/ $AlCl_3$ ratio of the complex anion [1]. Therefore, the acidic chloroaluminate ionic liquids which were rich in $AlCl_3$ catalyzed a variety of important electrophilic processes, including Friedel-Crafts chemistry (Scheme 3.2). This breakthrough further demonstrates that the ionic liquid can act not only as solvent but also as a catalyst for the reaction.

Despite the success of the chloroaluminate systems as combinations of solvent and catalysts in electrophilic reactions, the later development of new ionic liquid mainly focused on the creation of liquid salts that have high water stability [9]. While these new ionic liquids generally incorporated tetrafluoroborate, hexafluorophosphate and bis(trifluoromethyl)sulfonamide anions which imparted a high degree of water stability, the functional capacity inherent in the ionic liquid to the chloroaluminate anion was lost.

In 1999, K. J. Forrester and James H. Davis, Jr designed a thiazolium ionic liquid for the benzoin condensation (Scheme 3.3) and again demonstrated the possibility of ionic liquid acting as solvent-catalyst system [10].



Scheme 3.3 James H. Davis, Jr.s organic ionic liquid solvent-catalyst system for benzoin condensation [10]

A year later, Davis outlined their concept in a brief review, introducing the term 'task-specific ionic liquid' (TSIL) [11]. Task-specific ionic liquids (TSILs) may be defined as ionic liquids in which a functional group is covalently tethered to the cation or anion (or both) of the ionic liquid. This incorporation of the functionality aimed to impart the ionic liquid not only as a reaction medium but also as a reagent or catalyst in some reactions or processes.

3.1.3 TSIL as support for synthesis

The use of the solid supports is an enormous technology for many chemical applications such as solid acid catalysts, scavenging reagents for solution-phase synthesis, supports for solid-phase synthesis etc. [11,12]. It is mainly due to their lack of vapor pressure and

phase heterogeneity which facilitates product isolation. However, the common drawbacks of solid support were high reagent mass per volume ratio, serious heterogeneous kinetics and significant site deactivation [11,12].

TSILs can be thought of as liquid versions of solid-supported reagents. Like solid supported reagents, TSILs have feasibility of product separation owing to their absence of vapor pressure. Besides, TSILs gained the additional advantages of kinetic mobility of the grafted functionality and a relatively large operational surface area (Figure 3.1) [1]. Consequently, task-specific ionic liquid is drawing a significant attention from the chemical community to serve as an alternative of solid support in chemical industry thanks to this combination of features.

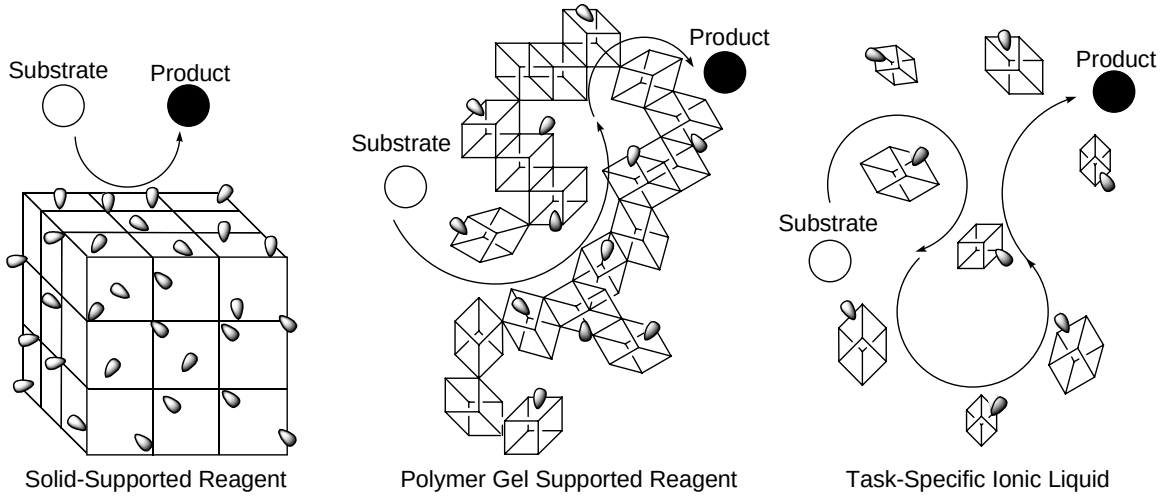


Figure 3.1 Operational surface area and kinetic mobility of solid supported reagent, polymer gel supported reagent and task specific ionic liquid [1]

3.1.4 Synthesis of functionalized ionic liquid

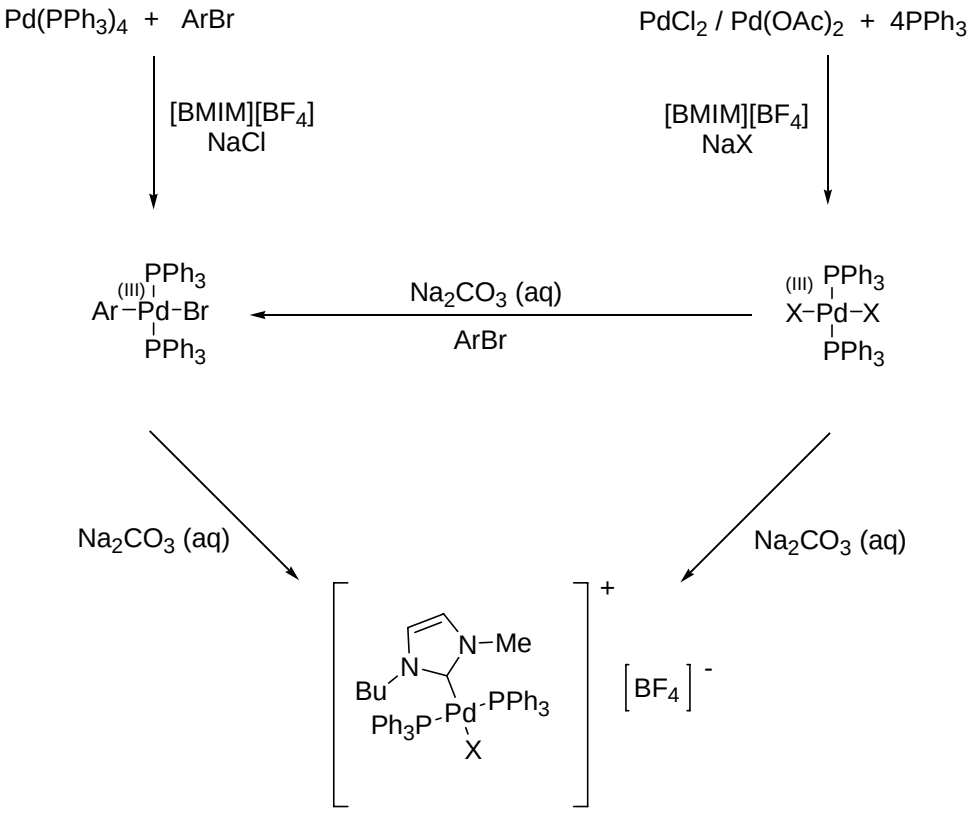
The incorporation of the functional group into an ion for the ionic liquid is usually a multi-step process. A number of areas should be taken into consideration in planning task-specific ionic liquid synthesis.

3.1.4.1 Selection of cationic core

Although the functional group can be anchored into cation or anion theoretically, the functionality is generally tethered into the cation in the TSILs development. The cationic core of a TSIL may be as simple as a single atom such as N, P or S in ammonium, phosphonium or sulfonium ions.

Alternatively, the cationic core can also be a relatively large heterocycles like imidazole, pyridine or pyrazole. The choice of the cation ion is important since it plays a determining role in both chemical and physical properties of ionic liquid. For example, while ionic liquids having a phosphonium cation generally exhibit better thermal stability, they possess a higher melting point which limited their use in room-temperature reactions [1,13].

On the other hand, if imidazolium-based ionic liquid was used in a metal-catalyzed reaction, there might be a possible interaction between the imidazolylidene carbenes and the transition metal ions [14] (Scheme 3.4).

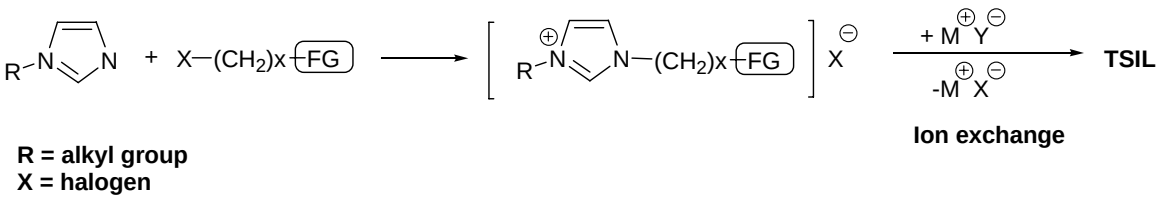


Scheme 3.4 Formation of mixed phosphine-imidazolylidene palladium complexes in ionic liquid [BMIM][BF_4] [12]

3.1.4.2 Source of functional group

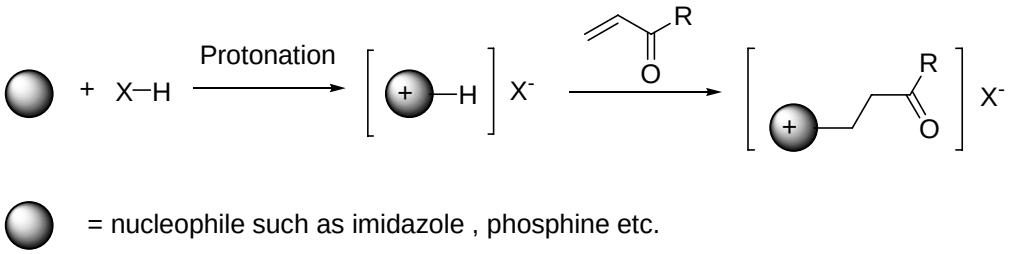
The incorporation of functional group into an ionic liquid is usually accomplished by grafting preexisting groups onto one of the ion structures [15,16]. Although the task-specific ionic liquid firstly featured the incorporation of the function within the cation core, subsequent research has focused on the incorporation of functionality into a branch appended to the cation [1,10].

The method used was almost always the same as that used to form conventional ionic liquid. For example, the displacement of halide from an organic functionalized alkyl halides is undergone by a parent imidazole, phosphine etc (Scheme 3.5).



Scheme 3.5 Formation of TSIL through the displacement of halide from functionalized alky halide by a nucleophile [1,11]

Recently, another effective method for TSIL synthesis was introduced by Wasserscheid and his co-workers. In this method, the imidazole or other nucleophile, which is first protonated by an acid such as HPF_6, will eventually be incorporated into the ionic liquid. Later the desired Michael acceptor is inserted into the N-H bond forming the TSIL (Scheme 3.6) [17]. Since this procedure does not need the anion metathesis step, the ionic liquid is free of halide and this may benefit the transition metal catalysis. However, the limitation is the relatively poor thermal stability of cation since it may undergo retro-Michael reaction at moderately elevated temperature.



Scheme 3.6 Wasserscheid's TSIL synthesis method by Michael reaction [11,18]

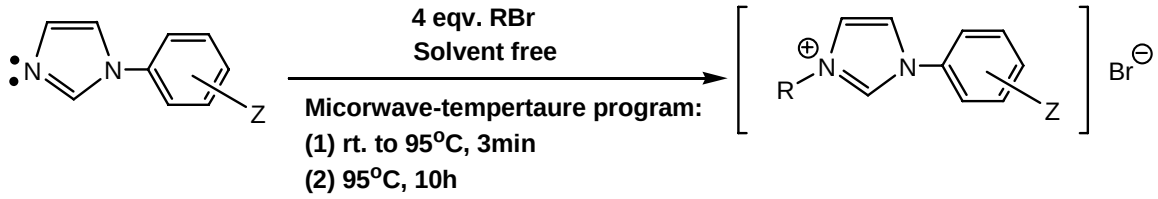
The key point for the TSIL synthesis is to select a substrate containing two functional groups with different reactivities: one is to allow for the attachment to the cationic core, the other is the interested functional group for the reaction or further modification [1].

3.1.4.3 Selection of anion

The anion of ionic liquid exercises a significant degree of control on the hydrophilicity and hydrophobicity of ionic liquid. The proper selection of anion can facilitate the product isolation and increase reaction homogeneity. For example, hexafluorophosphate salts which are usually not water miscible can be used in the extraction from aqueous solution [5,17,19], while those of the nitrate salts are readily mixed with water and can allow the ionic liquid homogenously mixed with aqueous reagent such as hydrogen peroxide [5]. Those of tetrafluoroborate may or may not be water miscible, depending on the nature of cation. Certain anions such as hexafluorophosphate are subject to hydrolysis at higher temperatures, while those such as bis(trifluoromethane)sulfonamide are not, but are extremely expensive [1].

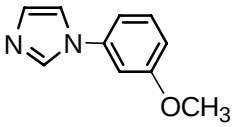
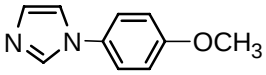
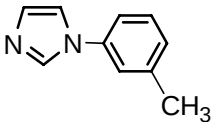
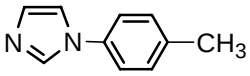
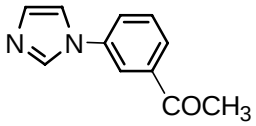
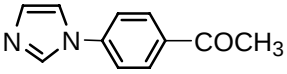
3.2 The microwave assisted synthesis of TSIL precursors under solvent free condition

Instead of using the functionalized alkyl halides to anchor the functional group into the ionic liquid, we tried to use the functionalized imidazoles as nucleophiles and displace the halide from the alkyl halides to give the corresponding desired TSILs (Scheme 3.7):



Scheme 3.7 Microwave assisted displacement reaction between N-arylimidazole and alkyl bromides under solvent free condition

Several N-arylimidazoles obtained in section 2.3.1 were transformed into their corresponding task-specific ionic liquids with 1-bromobuatne and 1-bromohexane by microwave irradiation under solvent free condition (Table 3.1).

Entry	N-arylimidazole	RBr	Reaction condition [a]			Isolated yield (%)
			Reaction temperature (°C)	Reaction time (h)	Microwave power (W)	
1		1-bromobutane	95	10	300	90
2		1-bromobutane	95	10	300	96
3		1-bromobutane	95	10	300	76
4		1-bromobutane	95	10	300	91
5		1-bromobutane	95	10	300	89
6		1-bromohexane	70	10	300	99
7		1-bromobutane	95	10	300	88

[a] the reaction mixture was heated up from room temperature to desired reaction temperature by 500W microwave irradiation within 3 min

Table 3.1 Microwave assisted synthesis of functionalized ionic liquids under solvent free condition

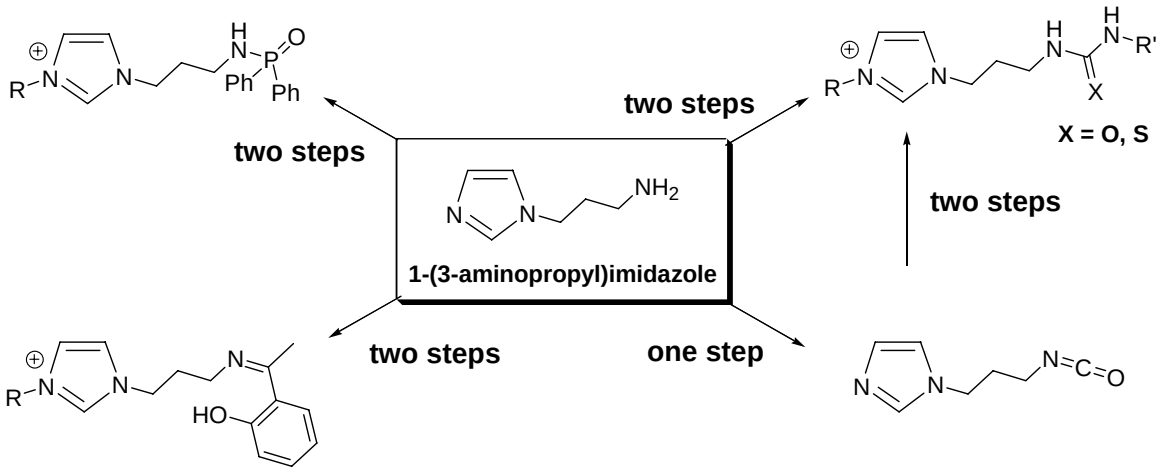
From table 3.1, the microwave assisted displacement reactions between N-arylimidazoles and alkyl halides give satisfactory results under solvent free condition. Excess alkyl halides were added due to its ease of vaporizations during the reaction process. For the reaction of 3-(imidazole-1-yl)acetophenone with alkyl bromides (Entry 5 and 6), entry 6 gives a better product yield even at a lower reaction temperature. This observation may be due to the better stabilization of the positive charge on the imidazlium N atom by the relatively more electron donating hexyl group.

Most TSILs synthesized are viscous oils at room temperature rendering the purifications difficult. Since the ionic liquids are only soluble in acetone and water, they can be emulsified out by acetone/diethyl ether solvent mixture. The emulsions are isolated by centrifuge to obtain pure ionic liquid.

3.3 Synthetic transformation of 1-(3-acetylphenyl)-3-butyl-1H-imidazol-3-ium bromide (API)

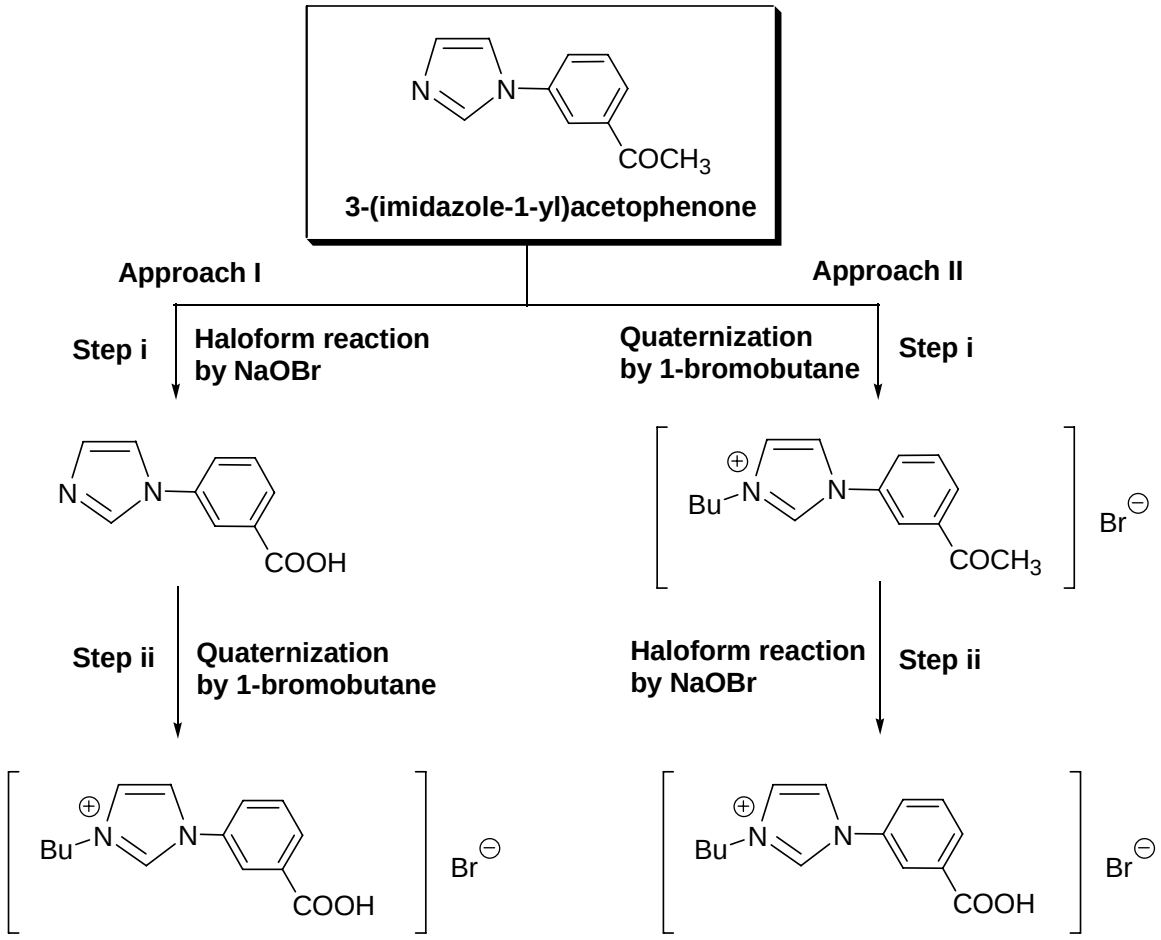
TSIL can directly be obtained by the displacement between the nucleophile and functionalized alkyl halide (Scheme 3.5), however, the electronic properties of the functional group will be affected by the adjacent alkyl group which limits their use to some organic synthesis. Another approach to synthesize the TSIL via displacement of alkyl halide by functionalized nucleophile, generally can add some extra electronic properties to the function groups, but the diversity of the functionality will limited by the availability of the desired nucleophiles.

Therefore, transformation of the appended functional groups on the nucleophile or TSIL to another interested functionality becomes another synthetic route to obtain desired TSIL. In the example shown in scheme 3.8, the amine moiety of 1-(3-aminopropyl)imidazole was transformed into the functional group of interest [(1)]. The elaborated imidazoles can then quaternized at the ring nitrogen by treatment with alkyl halide to produce the corresponding N(3)-alkylimidazolium salts.



Scheme 3.8 Representative synthesis of task-specific ionic liquids beginning with 1-(3-aminopropyl)imidazole [1]

In chapter 2, we tried to prepare 3-(3-carboxyphenyl)-imidazole by the reaction imidazole with 3-bromobenzoic acid and it was unsuccessful. In this section, we tried to synthesize 3-butyl-1-(3-carboxyphenyl)-1H-imidazol-3-ium bromide (CBI) from the transformation of the methyl ketone group appended on the elaborated imidazole or ionic liquid 1-(3-acetylphenyl)-3-butyl-1H-imidazol-3-ium bromide (API) into corresponding carboxylic acid by the haloform reaction (Scheme 3.9).

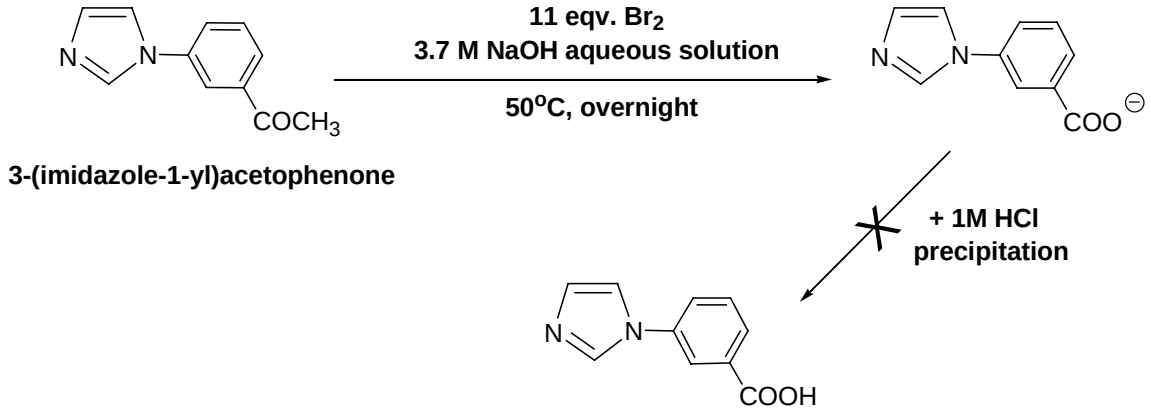


Scheme 3.9 The synthetic approach of 1-(3-carboxyphenyl)-3-butyl-1H-imidazol-3-ium bromide (CBI)

Formation of sodium hypohalite:

$Br_2 + 2\,NaOH \rightleftharpoons NaOBr + NaBr + H_2O$

Haloform reaction of 3-(imidazole-1-yl)acetophenone:



3-(imidazole-1-yl)acetophenone

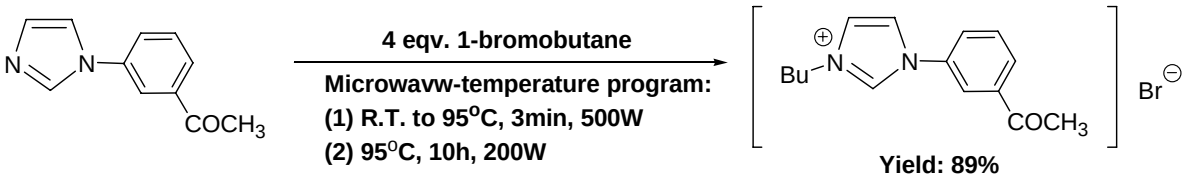
remain in aqueous reaction mixture

Scheme 3.10 Haloform reaction of 3-(imidazole-1-yl)acetophenone [20,21]

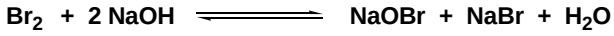
In method I, the methyl ketone of 3-(imidazole-1-yl)acetophenone was allowed to react with bromides in aqueous sodium hydroxide at 50°C overnight (Scheme 3.10). When TLC indicated the complete consumption of 3-(imidazole-1-yl)acetophenone, the reaction mixture was allowed to be acidified by 1M HCl in order to precipitate the corresponding acid. However, the corresponding benzoic acid exhibited 'zwitterion –like' property that made it very difficult to be precipitated. The corresponding acid remained in the aqueous reaction mixture, and the failure of isolation made the subsequent quaternization impossible.

Owing to the presence of hydrophobic butyl arm on the API, which may facilitate the product isolation from aqueous reaction mixture, method II was tried by using the 1-(3-acetylphenyl)-3-butyl-1H-imidazol-3-ium bromide (API) prepared from section 3.2 as the staring material in order to obtain the desired TSIL.

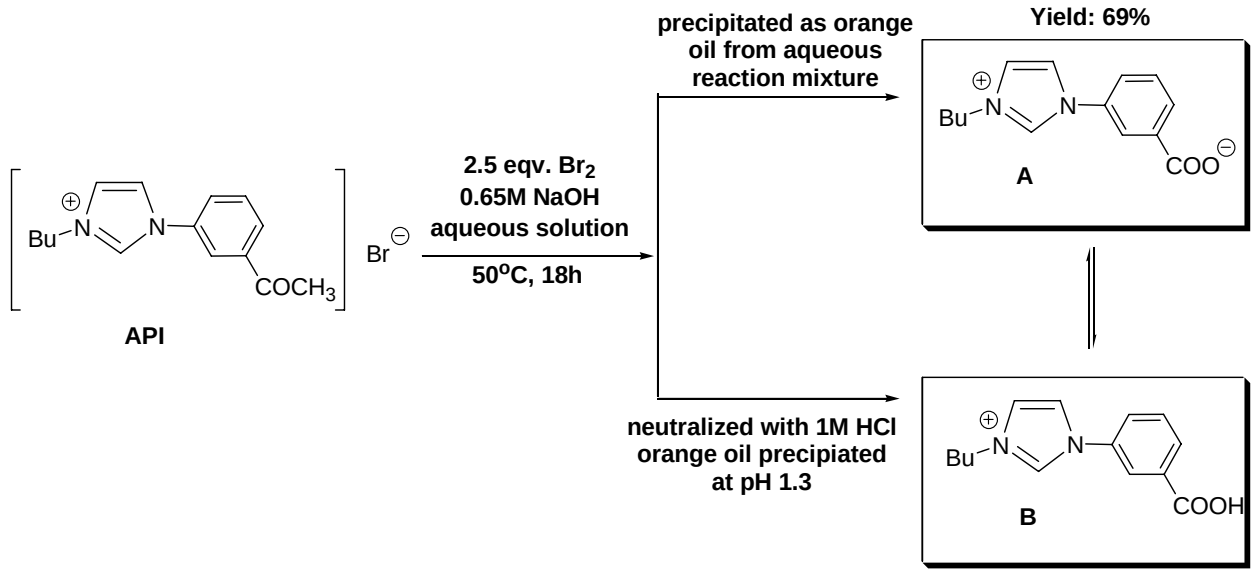
Formation of 1-(3-acetylphenyl)-3-butyl-1H-imidazol-3-ium bromide (API):



Formation of sodium hypohalite:

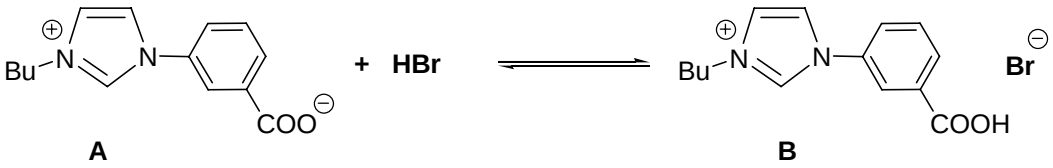


Haloform reaction of 1-(3-acetylphenyl)-3-butyl-1H-imidazol-3-ium bromide (API):



Scheme 3.11 Haloform reaction of 3-(3-acetylphenyl)-3-butyl-1H-imidazol-3-ium bromide (API) [20,21]

The API was also allowed to react with bromides in aqueous sodium hydroxide at 50°C for 18 hours (Scheme 3.11). When the reaction proceeded, some orange oil was precipitated out as the corresponding carboxylate ionic liquid (A). The remained reaction mixture was acidified by 1M HCl and the combination of corresponding carboxylate ionic liquid (A) and carboxylic acid ionic liquids (B) were precipitated out as orange oil at pH 1.3. The further addition of the 1M HCl caused the redissolution of the precipitate, giving a clear yellow solution. When the pure 3-(3-butyl-1H-imidazol-3-ium-1-yl)benzoate (A) was allowed to stand overnight, the presence of 3-butyl-1-(3-carboxyphenyl)-1H-imidazol-3-ium bromide (B) can be detected by proton Nmr, showing that the corresponding TSIL existed in an equilibrium with its conjugated base (Scheme 3.12).



Scheme 3.12 Equilibrium between the proton-donor ionic liquid (B) and proton acceptor ionic liquid (A)

The obtained TSIL exhibited 'amino acid –like' property (Table3.2). Different forms of the corresponding ionic liquid existed as in several equilibria. After the API reacted with sodium hypohalite, the product ionic liquid might exist as equimolar concentrations of the protonated ionic liquid (B) and the zwitterionic ionic liquid (A) at pH = 4.10. Some of the ionic liquid A was precipitated out as orange oil thanks to its dipolar property. When the pH of the aqueous reaction mixture was decreased to pH =1.3, the predominant ionic species was the protonated ionic liquid (B), and it was precipitated out with bromide ion.

If the pH of the aqueous reaction mixture was further decreased to pH < 1.3, the protonated ionic liquid (B) was redissolved in the reaction mixture giving yellow clear solution. At this stage, both nitrogens on imidazolium ion were charged and the ionic liquid was present largely as the fully protonated ionic species (C) which was very hydrophilic.

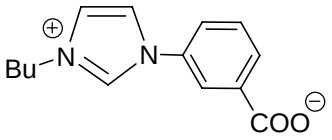
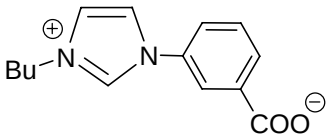
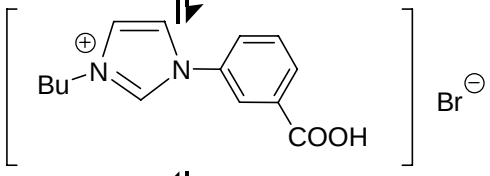
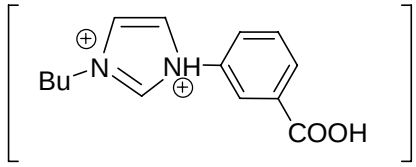
	pH of reaction mixture	**Observations**	**Possible forms of TSIL**
Before acidification	4.10	orange oil precipitated out	**A:** 
After acidification	>1.3	yellow clear solution	**A:** 
	1.3	orange emulsions precipitated out	**B:** 
	<1.3	orange emulsion redissolved giving clear yellow solution	**C:** 

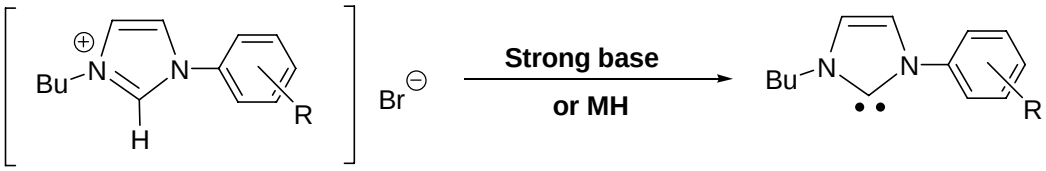
Table 3.2 Possible forms of the TSIL at different pHs

3.4 Discussion: Potential use of our TSILs

3.4.1 Catalyst appended TSIL

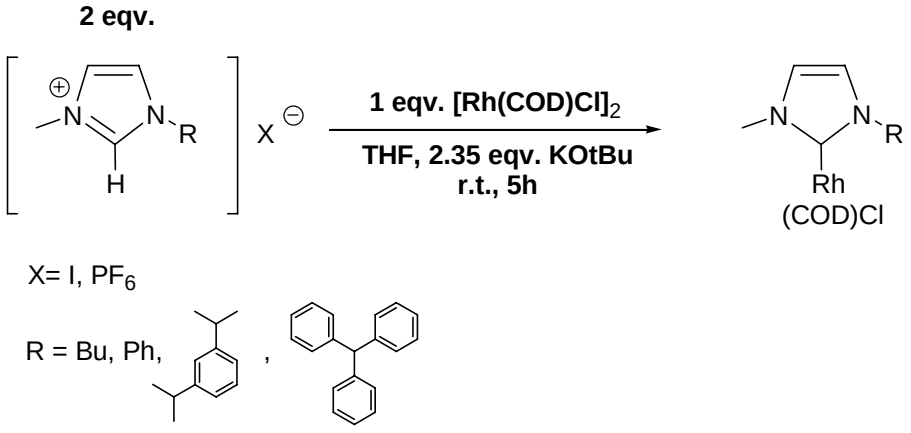
In the past few years, N-heterocyclic carbenes (NHC) were employed as ligands in organometallic and coordination chemistry [22]. The ligands show a high propensity to act as excellent σ-donors superior to those basic phosphanes and are able to form a stable carbon–metal bond with transition metals [23]. The substituent manipulations allow fine-tuning of the steric and electronic properties of the NHC ligand thus conferring special attributes to the metal complex [24]. Therefore, most NHCs have turned out to be quite efficient ligands in transition metal complexes and are widely used as highly active and rather selective catalysts in numerous fundamental chemical transformations such as hydrogenation [25], hydrosilylation [26] and isomerization [27].

The acidic proton at C_2 of the imidazolium ring of TSILs prepared from the section 3.2 can easily be deprotonated by a strong base such as K(Ot-Bu), Li(C_4H_9) or NaH to afford the persistent free carbenes (Scheme 3.13) [28,29].

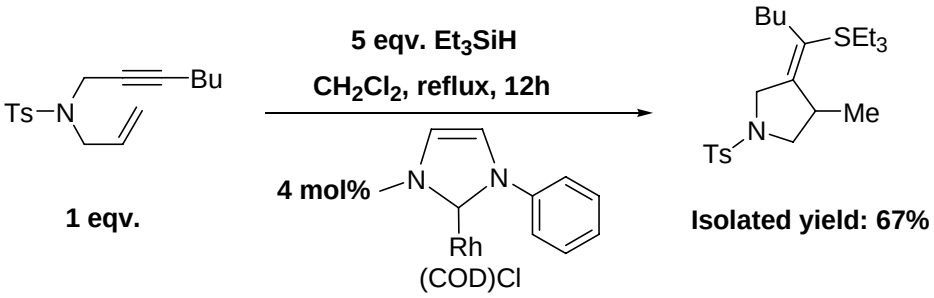


Scheme 3.13 Formation of imidazolium-based carbene from the deprotonation of TSIL [28,29]

These properties of TSILs showed their possibility to act as both catalyst source and solvent for certain NHC metal complex catalyzed reactions. Recently, transition metal catalyzed hydrosilylation/cyclization reaction of 1,6-enynes to 2-methyl-1-silylmethylidene-2-cyclopentane have been developed by Chung using rhodium N-heterocyclic carbene complexes (Scheme 3.14 and 3.15).



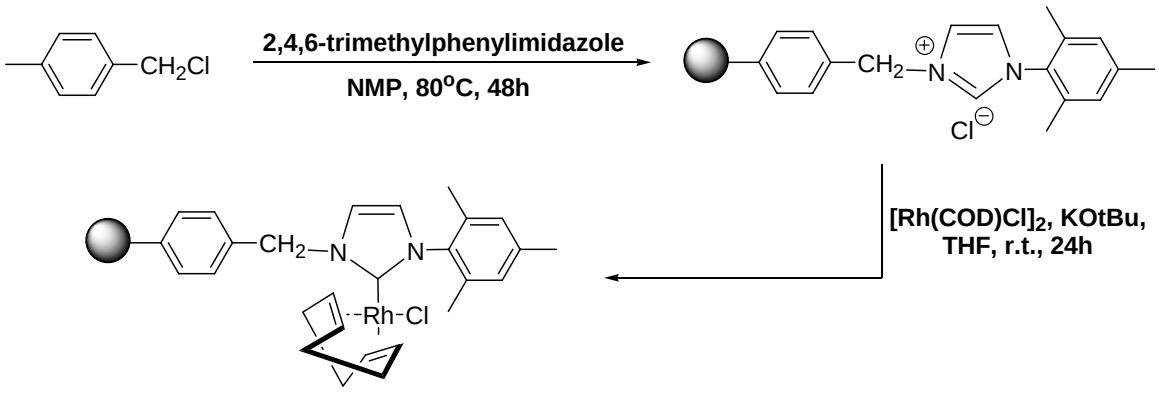
Scheme 3.14 Synthesis of Rhodium-HNC complex [30]



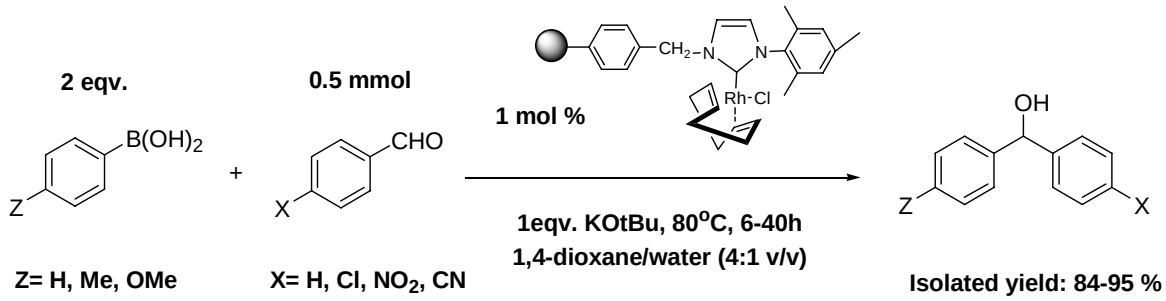
Scheme 3.15 Chung's hydrosilylation/cyclization system of 2-methyl-1-silylmethylidene-2-cyclopentane [30]

However, the use of dichloromethane as solvent not only limits the microwave application on this reaction due to its low boiling point, but also fails to allow the recycling of rhodium N-heterocyclic carbene complexes. By using the TSIL instead of organic solvent, the rhodium N-heterocyclic carbene complexes may be in situ formed within the TSIL and the hydrosilylation/cyclization reaction may also be carried out by microwave irradiation. The product may be simply isolated by ether or pentane from TSIL, and the remained TSIL-catalyst mixture may be recycled for the same reaction.

In 2006, Luo has prepared a polymer-supported N-heterocyclic (NHC)-rhodium complex from chloromethyl polystyrene (CMPS) resin for the addition of arylboronic acids to aldehydes (Scheme 3.16 and 3.17) [(31)].

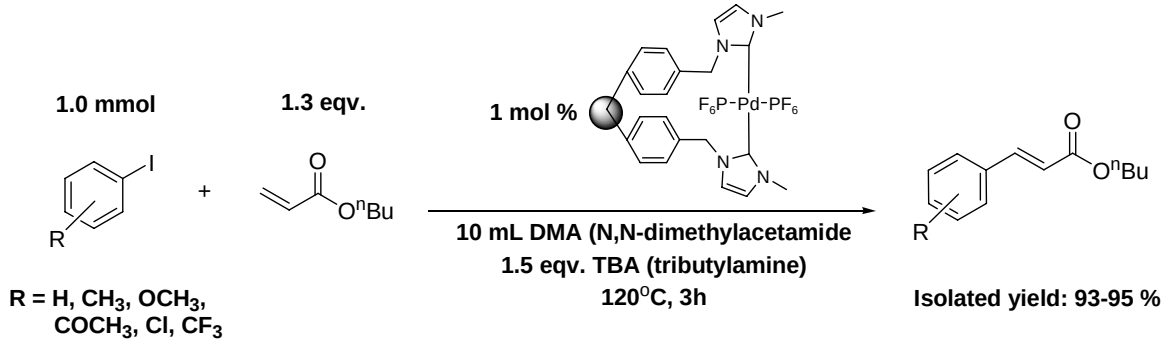


Scheme 3.16 Synthesis of polymer supported rhodium-HNC complex [(31)]



Scheme 3.17 Luo's system using polymer-supported N-heterocyclic carbene-rhodium complex catalyst [31]

Similar approach was also used in the heterogenous Heck reaction system using recyclable polymer-supported N-heterocyclic carbene-palladium complex developed by Lee (Scheme 3.18) [32].



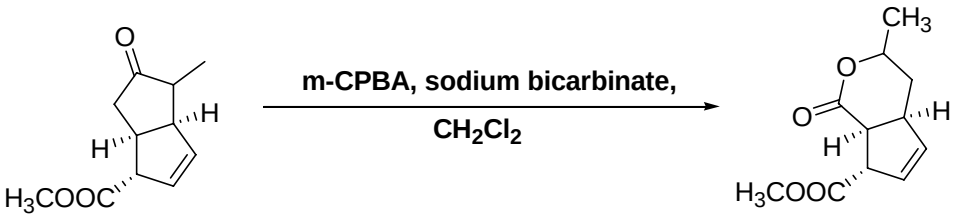
Scheme 3.18 Lee's system using polymer-supported N-heterocyclic carbene-palladium complex catalyst [32]

Although the polymer-supported catalyst can provide a simple product isolation and can be recycled for the same reaction, copious quantities of 1,4-dioxane are necessary to act as swelling solvent in Luo' system in order for the reaction to proceed. Similar solvent problem is also found in the Lee's heterogenous system that DMA must be used as solvent in this solvent dependent Heck-reaction.

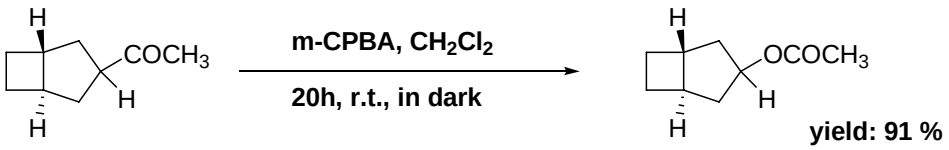
TSIL not only can provide carbene for the metal coordination to form the corresponding catalyst, the TSIL itself can also serve as a 'liquidified support' especially for those solvent dependent reactions. By changing the counter ions or the alkyl arms of imidazolium cation, the properties of the solvents can be designed for a particular reaction. The TSIL also allows the reaction to proceed with microwave application which can greatly improve the reaction efficiency.

3.4.2 Reagent appended TSIL

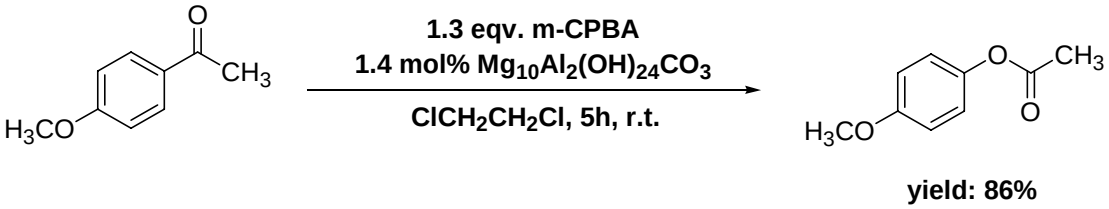
The most common peracid employed for Baeyer Villiger oxidation (BVO) is *m*-chloroperbenzoic acid (*m*-CPBA). Several successful BVO systems using *m*-CPBA were developed in organic solvent, examples include the Helbling's system (Scheme 3.19) [(33)], the Rampals system (Scheme 3.20) [(34)] and the Kaneda's system (Scheme 3.21) [(35)].



Scheme 3.19 Helbling's BVO system [(33)]

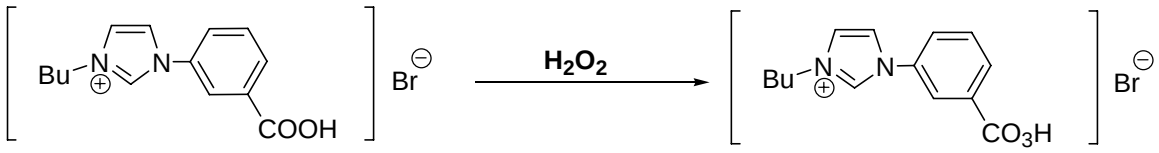


Scheme 3.20 Rampal's BVO system [34]



Scheme 3.21 Kanedas's BVO system [35]

Despite the success of Baeyer Villiger oxidation of ketones by using m-CPBA in those systems, the formation of stoichiometric amount of by-product meta–chlorobenzoic acid (m-CBA) becomes unavoidable. This not only generates the undesired waste from the reaction, but also makes the recovery of catalyst difficult. Therefore, the TSIL can be designed by anchoring the benzoic acid on the imidazolium moiety, and be converted into the perbenzoic acid by hydrogen peroxide (Scheme 3.22). Using this TSIL is green since only hydrogen peroxide will be added each time, and the oxidant and catalyst can be recycled in ionic liquid.



Scheme 3.22 Proposed generation of perbenzoic acid on the TSIL

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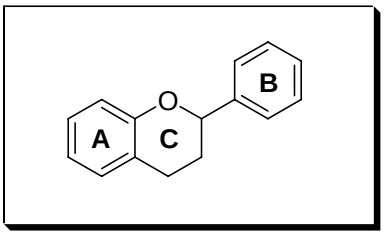
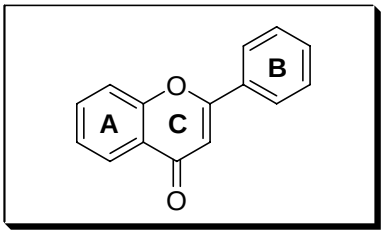
Chapter 4: Applied to complex molecules

4.1 Introduction

The term flavonoid refers to a class of plant secondary metabolites based around a phenylbenzopyrane structure. The structural components common to these molecules include two benzene rings on either side of a 3-carbon ring (Scheme 4.1) [1,2]. Multiple combinations of hydroxyl groups, sugars, oxygen and methyl group attached to these structures create the various classes of flavonoids: flavanols, flavanones, flavones, flavan-3-ols (catechins), anthocyanins and isoflavones [1,2]. Flavones are ketone derivatives of flavonoids (Scheme 4.1).



Basic stucture of flavonoid



Basic stucture of flavone

Scheme 4.1 Basic structures of flavonoid and flavone [1,2]

Flavonoids have been referred to as 'nature's biological response modifiers' because of strong experimental evidence for their ability to modify the body's reaction to allergens, viruses and carcinogens [1,2,3]. Flavonoids are very powerful antioxidants, protecting cell from oxidative and free radical damage, and hence show anti-allergic, anti-inflammatory, anti-microbial and anti-cancer activity. Therefore, both natural and synthetic flavonoids have been tested as potential medicinal agents against human diseases [2,3].

Flavonoids have been intensively studied for their potential as anti-inflammatory agents. One of the more interesting findings in studies of human immune response and inflammatory reactions involved identifying nitric oxide (NO) as a major participant. In 1995, Krol has demonstrated that certain flavonoids have a significant inhibitory effect on the production of NO [2,4].

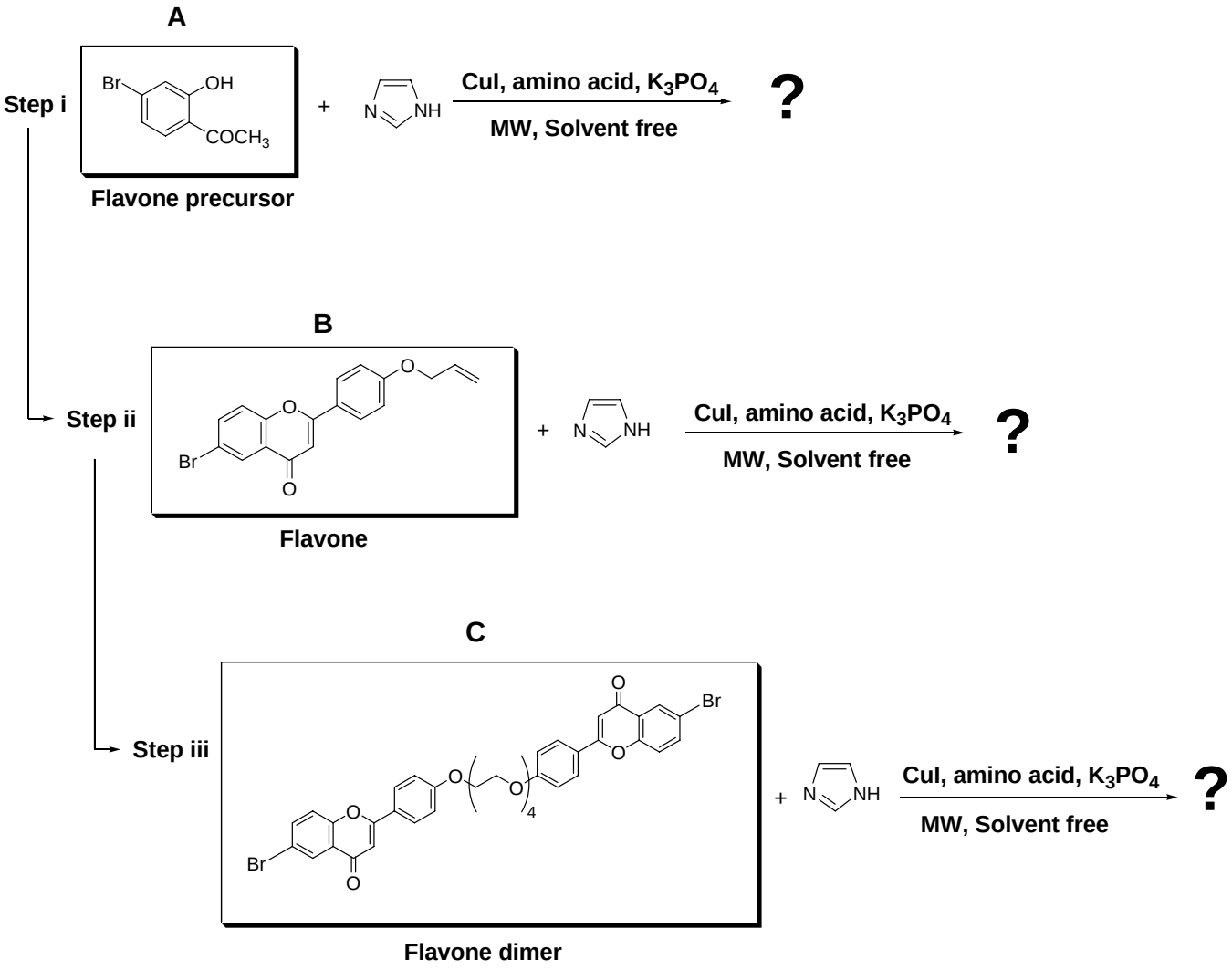
Besides, several workers have shown that certain flavonoids are active against HIV at one stage or another of infection. In 1992, Baylor and colleagues has shown that baicalin, which is extracted from *Scutellaria baicalensis*, can inhibit human T-cell leukemia virus type 1 (HTLV-1) [2,5].

One important application of flavonoids is their anti-carcinogenic effects. Most of the chemical carcinogens such as PAHs seem to require metabolic activation to DNA-reactive intermediates by cytochrome-P450-mediated mixed-function oxidase (MFOs) in order to exert their carcinogenic action [1,3]. The covalent binding of these reactive intermediates to cellular DNA, leading to adduct formation, is considered to be a critical event in the initiation of carcinogenesis [1,3]. Flavonoids may inhibit carcinogenesis by acting as ‘blocking agents’ towards the carcinogenic reactive intermediates which inhibit carcinogenesis by one or more possible mechanisms [1,3].

4.2 Synthetic approach

Recently, based on the ‘blocking properties’ of flavonoids, our group has successfully synthesized a series of flavonoid dimers to act as the modulators of multidrug resistance P-glycoprotein. Generally, different functionalities on the modulators showed different extents of modulating activities toward the P-glycoprotein. Therefore, the present research project aims to further couple an imidazole moiety onto the flavonoid dimer to serve as a possible derivative for the study.

Based on the microwave assisted Ullmann type C-N coupling system between imidazole and arylbromides developed in chapter 2, we tried to apply this system to bromo substituted flavone and bromo substituted flavone dimer. The investigation was first started with the microwave assisted C-N formation between flavone precursor 2-hydroxy-4-bromoacetopheone (**A**) and imidazole (Step i). Then the same Ullmann C-N coupling was proceeded to the more complex 2-(4-(allyloxy)phenyl)-6-bromo-4H-chromen-4-one, bromo substituted flavone (**B**), (Step ii) and finally to the target flavone dimer (**C**) (Step iii) (Scheme 4.2).

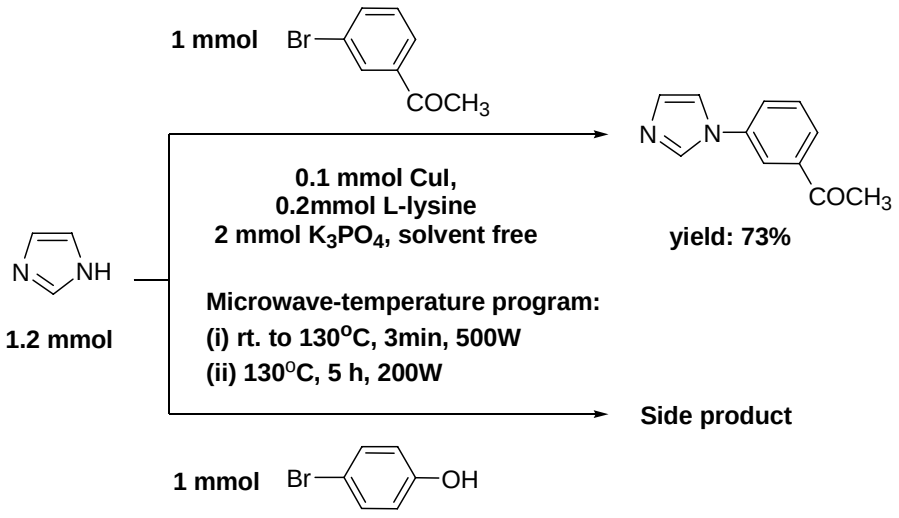


Scheme 4.2 Synthetic approach for the microwave assisted Ullmann type C-N coupling between imidazole and flavones

4.3 Result and discussions

4.3.1 Microwave assisted Ullmann type coupling of imidazole with flavone precursor 2-hydroxy-4-bromoacetopheone (A)

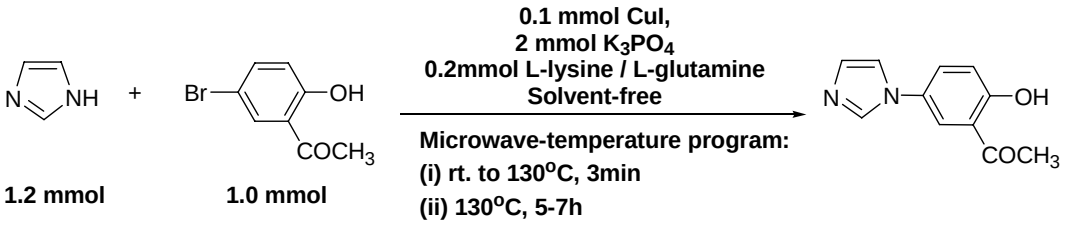
Based on our microwave assisted Ullmann type C-N coupling system described in chapter 2, without using any solvent, L-lysine generally promoted cross couplings between imidazole and *meta* substituted aryl bromide cleanly with satisfactory yields. However, for those couplings between imidazoles and electron deficient aryl bromides, the system showed poor results. From the preliminary studies of L-lysine promoted C-N coupling of imidazole with 3-bromoacetophenone (Scheme 4.3), our microwave assisted Ullmann type C-N coupling system worked well to give good yield of the *meta* substituted acetophenone. However, in the case of 4-bromophenol, a side reaction occurred and the reaction gave a 'polymer-like' gum as the predominant product [6,7,8].



Scheme 4.3 Microwave assisted Ullmann type C-N couplings of imidazole with 3-bromoacetopheone and 4-bromophenol by using l-lysine as additive

For the flavone precursor, 2-hydroxy-4-bromoacetopheone, on the one hand possessing a *meta* substituted carbonyl group, was suggested as being favored in this system, but also containing a hydroxyl group in the *para* position which may hinder the precursor towards the same reaction.

The 2-hydroxy-4-bromoacetophenone was allowed to undergo microwave assisted Ullmann type C-N coupling with imidazole according to our solvent free system described in chapter 2 (Scheme 4.4) and the results were shown in table 4.1.



Scheme 4.4 Proposed L-amino acid promoted Ullmann type C-N coupling between imidazole and 2-hydroxy-4-bromoacetopheone

Entry	L-amino Acid Additive	Solvent [a]	Reaction Condition [b]			^{1}H Nmr Yield (%)
			Reaction Temperature (°C)	Reaction Time (h)	Microwave power (W)	
1	L-lysine	---	130	5	200	31 (18) [c]
2	L-lysine	---	130	7	200	37
3	L-glutamine	---	130	7	200	28
4	L-lysine	H_2O	85	5	200	no reaction
5	L-lysine	DMF	85	5	200	no reaction
6	L-lysine	DMF	130	5	200	trace

[a] *1 mL solvent was used for entry 4-6*
[b] *the reaction mixture was heated up from room temperature to desired reaction temperature by 500W microwave irradiation within 3 min*
[c] *Isolated yield*

Table 4.1 L-amino acid promoted Ullmann type C-N coupling between imidazole and the flavone precursor 2-hydroxy-4-bromoacetophenone by microwave irradiation under solvent free condition

From table 4.1, the coupling reaction between 2-hydroxy-4-bromoacetophenone and imidazole by using L-lysine as additive provided a slightly better result to that of L-glutamine (Entry 2 and 3). When the L-lysine promoted C-N coupling reaction was allowed to work for prolonged reaction time from 5 hours to 7 hour, no significant improvement of the N-arylimidazole yield was shown (Entry 1 and 2).

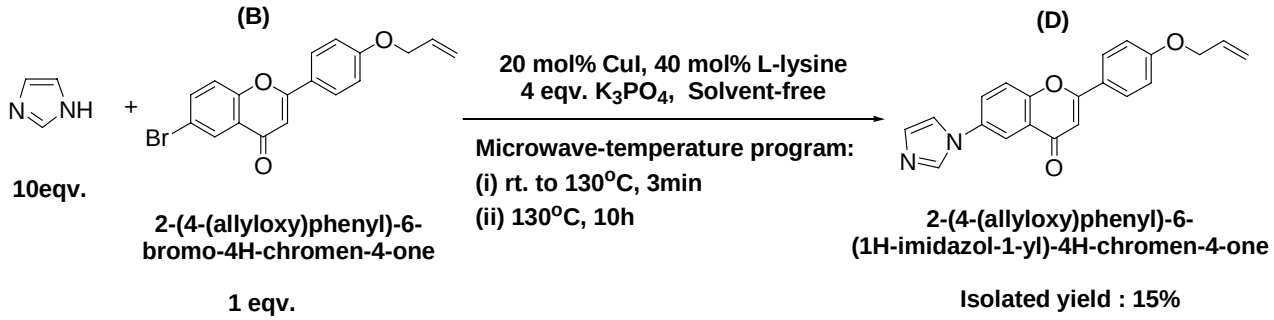
The same coupling reactions were also examined in two solvent systems. Due to the presence of the polar hydroxyl group on 2-hydroxy-4-bromoacetophenone, water and DMF were chosen as solvents to provide better homogeneity in this reaction.

When water was used as the solvent, the L-lysine promoted C-N formation reaction was conducted at a temperature below its boiling point (85°C), no desired N-arylimidazole was obtained (Entry 4). The same result was obtained for the C-N formation of 2-hydroxy-4-bromoacetophenone with imidazole at 85°C by using DMF as solvent (Entry 5).

When the C-N formation was allowed to proceed under the same condition as Entry 1 (130°C , 5 h) ,but with the use of high boiling point DMF as solvent, only a trace amount of N-arylimidazole was obtained (Entry 6). This observation showed the enhanced reaction rate was obtained by using solvent free procedure for this microwave assisted reaction, and the reason was the higher concentration of reactants in solvent free condition [9,10,11].

4.3.2 Microwave assisted Ullmann type coupling of imidazole with 2-(4-(allyloxy)phenyl)-6-bromo-4H-chromen-4-one (B)

Given the successful application of our microwave assisted Ullmann type C-N coupling to flavone precursor (A) in the previous section, the more complex flavone (B) was also tried in the same system to afford the desired imidazole substituted flavone (Scheme 4.5). Because of its more complex structure, the flavone (B) has a relatively high melting point (170-172°C) than that of its flavone precursor (A) (58-61°C). Therefore, excess imidazole which has relatively low melting point (89°C) was used in this reaction in order to provide the dielectric heating under microwave irradiation. Several reaction conditions were tested for this C-N coupling of flavone (B) as shown in table 4.2.



Scheme 4.5 Proposed L-lysine promoted Ullmann type C-N coupling between imidazole and flavone (B)

Entry	Catalyst Loading		K_3PO_4 (eqv.)	Imidazole (eqv.)	Solvent [c]	Reaction Condition [d]			^{1}H Nmr Yield (%)
	CuI (mol %)	L-lysine (mol %)				Reaction Temp. (°C)	Reaction Time (h)	MW Power (W)	
1	**10**	**20**	**2**	**10**	**---**	**140**	**7**	**200**	**31**
2 [a]	**10**	**20**	**2**	**10**	**---**	**140**	**7**	**---**	**15**
3	**20**	**40**	**4**	**10**	**---**	**140**	**7**	**200**	**58**
4 [b]	**20**	**40**	**4**	**10**	**---**	**140**	**10**	**200**	**64 (15)** [e]
5	**10**	**20**	**2**	**10**	**DMF**	**140**	**7**	**200**	**No reaction**

[a] *Reaction was performed under solvent free condition by conventional method*
[b] *0.5 mmol flavone (B) was used for entry 4*
[c] *1 mL solvent was used for entry 5*
[d] *the reaction mixture was heated up from room temperature to 140°C by 500W microwave irradiation within 3 min*
[e] *Isolated yield*

Table 4.2 L-lysine promoted Ullmann type C-N coupling between imidazole and the flavone (B) precursor with microwave irradiation under solvent free condition

Based on the results obtained in Table 4.2, when the flavone (B) was allowed to react with imidazole using the L-lysine promoted C-N formation at 140°C for 7 hours both by microwave irradiation and conventional heating under solvent free conditions, the microwave heating (Entry 1) generally showed enhanced reaction rate than that of conventional heating (Entry 2). The reason may be that the non-crystalline solid support

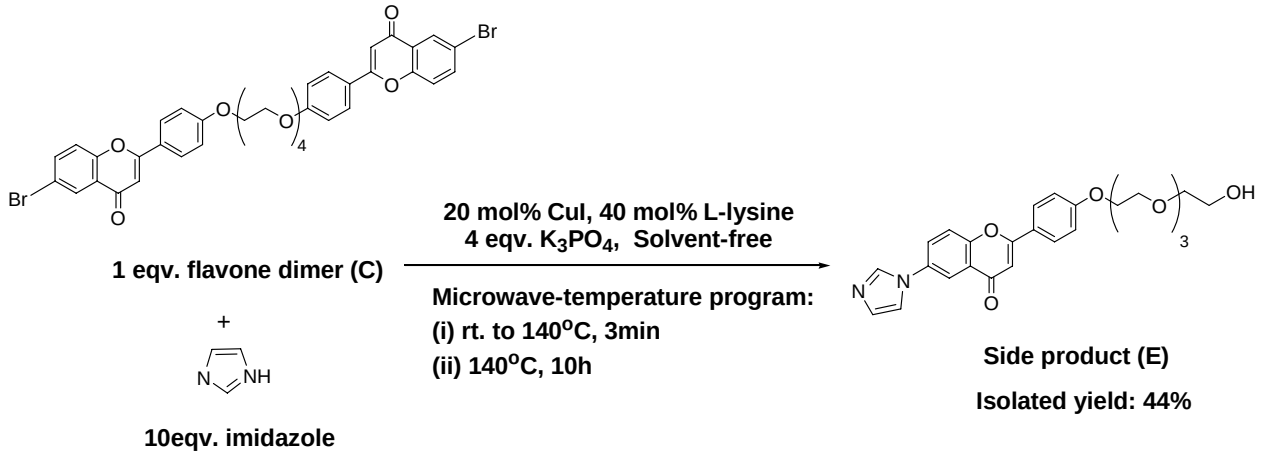
can absorb microwave energy more efficiently than conduction heating [9,10,11]. Without the heat transfer from solvent by dielectric heating, the catalyst support can be directly heated up by microwave irradiation and transfer the heat to the bulk reaction mixture by conduction under solvent free condition. This superheating of the catalyst cannot be duplicated by conventional heating [9,10,11].

When the C-N formations was allowed to proceed under the same condition as Entry 1 (140°C , 7 h) ,but with the use of high boiling point DMF as solvent, no reaction product was obtained (Entry 5). This observation suggests significant reaction rate enhancement from solvent free condition for this microwave assisted reaction, which may also be explained by the higher concentration of reactants provided by solvent free procedure [9,10,11].

In the C-N coupling reaction using double catalyst loading (Entry 3), 1.8 times product yield was obtained from this reaction condition compared to that of Entry 1. The further prolonged reaction time for the same reaction using double catalyst loading (Entry 4), did not show significant product yield improvement in this reaction, and gave the isolated yield of product flavone in 15%.

4.3.3 Microwave assisted Ullmann type coupling of imidazole with flavone dimer (C)

Based on the possible coupling of imidazole to the flavone (B) under our microwave assisted Ullmann type coupling by L-lysine under solvent free condition, we tried to apply our system towards the more complex flavone dimer (C). The L-lysine promoted C-N coupling of flavone dimer (C) with excess imidazole was allowed to work at 140°C for 10 hours by microwave irradiation under solvent free condition (Scheme 4.6). However, the flavone dimer suffered from the decomposition in this Ullmann type C-N coupling reaction, giving the predominant side product (E).



Scheme 4.6 Proposed L-lysine promoted Ullmann type C-N coupling between imidazole and flavone dimer (C)

4.4 Conclusion

In conclusion, we have investigated the microwave assisted Ullmann type C-N coupling reaction of imidazole towards flavone precursor (A), flavone (B) and flavone dimer (C) under solvent free condition. The system can be successfully applied to complex flavone (B) and its precursor (C), giving the desired imidazolyl-substituted flavone and N-aryl imidazole as final products respectively. In this section, the solvent free procedure showed the essential and important role for this microwave assisted C-N formations. However, this system failed in the coupling reaction of flavone dimer to imidazole, giving the undesired side product (E) as major product which was resulted from the cleavage of one flavone moiety from the flavone dimer.

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Chapter 5 : Experimental section

5.1 General protocols

Materials

All chemicals were purchased from Aldrich or Sigma and used as received.

Instrumentations

- Proton (^{1}H) and carbon (^{13}C) NMR spectral measurements were carried out on a Bruker DPX-400MHz NMR spectrometer.

- Milestone MicroSYNTH microwave organic synthesis labstation (Temperature range 0-300°C, microwave frequency 0-1000W) was used for the microwave irradiation

Figure 5.1
The Milestone MicroSYNTH microwave organic synthesis labstation

Figure 5.2
The MicroSYNTH controller

5.2 Experimental-Chapter 2

5.2.1 Microwave assisted solvent free S_NAr reactions of aryl fluorides with imidazole

Aryl fluorides (1 mmol), imidazole (1 eqv.) and potassium phosphate tribase (2 eqv.) were added into the reaction vessel (Figure 5.3). The reaction mixture was irradiated for 3 minutes to allow for the temperature rise from room temperature to 120°C and then further irradiated for 3-4 minutes at 120°C (Figure 5.4). The reaction mixture was cooled to room temperature and the product was extracted by dichloromethane. Dichloromethane was evaporated in vacuo to afford the crude product.

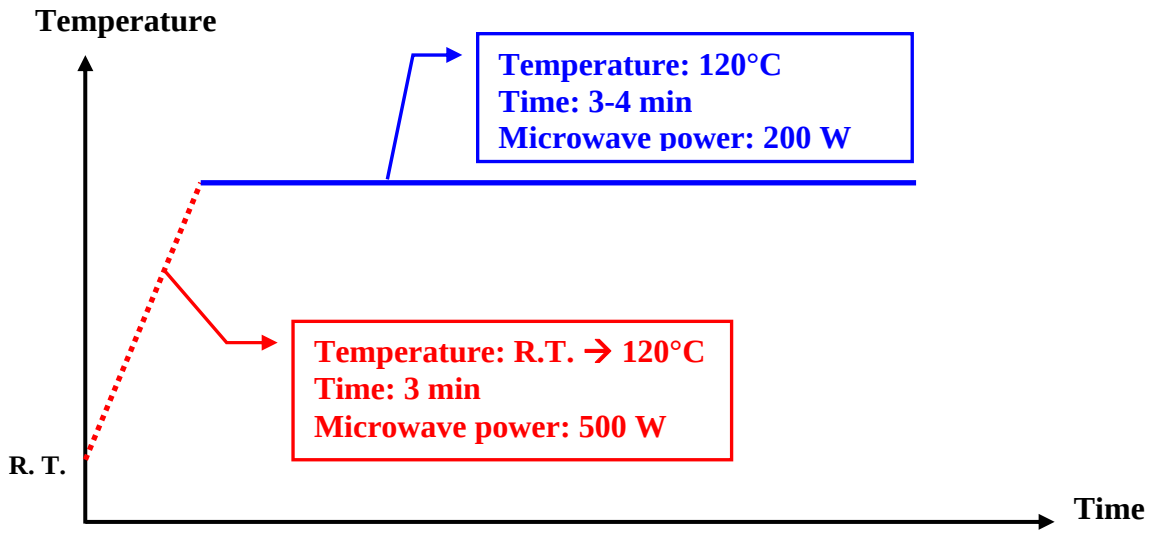

Figure 5.3 Microwave-temperature program for solvent free S_NAr reactions of aryl fluorides with imidazole

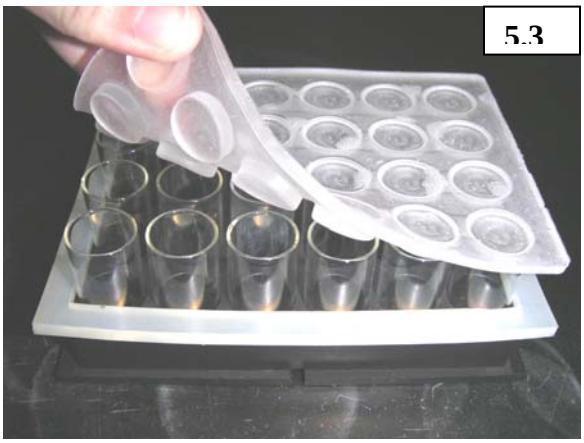

Figure 5.4 24-positions Microwell plates

Figure 5.5 The CombiChem rotor fits neatly into the MicroSYNTH cavity

5.2.2 Microwave assisted L-amino acid promoted Ullmann type coupling between imidazole and aryl bromide under solvent free condition

(1) Purification of cuprous iodide

The CuI was purified by dissolving an appropriate quantity of CuI in boiling saturated aqueous potassium iodide over 45min. Pure CuI was obtained by cooling and diluting the solution with water, followed by filtering and washing sequentially with water, ethanol, ethyl acetate, diethyl ether and *n*-hexane. The white precipitate was dried in vacuum for 24 hours.

(2) Typical procedure for the Ullmann type coupling between imidazole and arylbromide

CuI (10 mol%), L-amino acid (20 mol %), imidazole (1.2 eqv.), potassium phosphate tribasic (2 eqv.) and aryl bromide (1 mmol) were added to the reaction vessel (Figure 5.3 and 5.4). The reaction mixture was irradiated for 3 min to allow the temperature rise from room temperature to 130°C, and then further irradiated for 3 - 6.5 hours at 130°C (Figure 5.5). The reaction mixture was cooled to room temperature and the product was extracted by ethyl acetate. Ethyl acetate was evaporated in vacuum and the product was purified by column chromatography on silica gel using *n*-hexane and ethyl acetate mixture as the eluent.

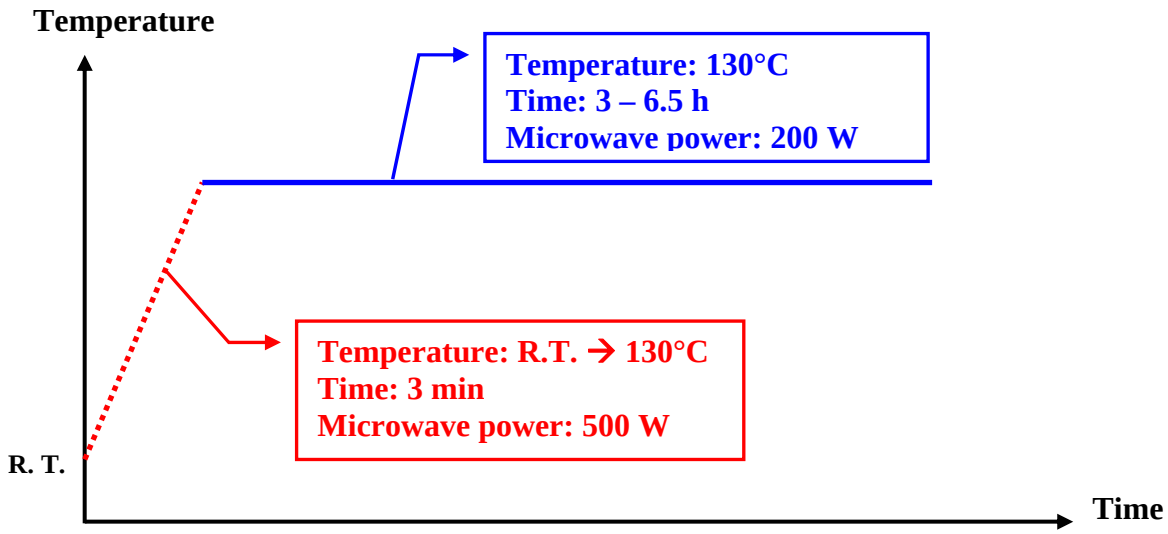

Figure 5.6 Microwave-temperature program for solvent free Ullmann type coupling between aryl bromides and imidazole

(3) Typical procedure for the Ullmann type coupling between pyrazole and aryl bromide

CuI (10 mol%), L-amino acid (20 mol %), pyrazole (1.2 eqv.), potassium phosphate tribasic (2 eqv.) and aryl bromide (1 mmol) were added to the reaction vessel. The reaction mixture was irradiated for 3 min to allow for the temperature rise from room temperature to 150°C, and then further irradiated for 2 - 10 hours at 150°C (Figure 5.6). The reaction mixture was cooled to room temperature and the product was extracted by ethyl acetate. Ethyl acetate was evaporated in vacuum and the product was purified by column chromatography on silica gel using *n*-hexane and ethyl acetate mixture as the eluent.

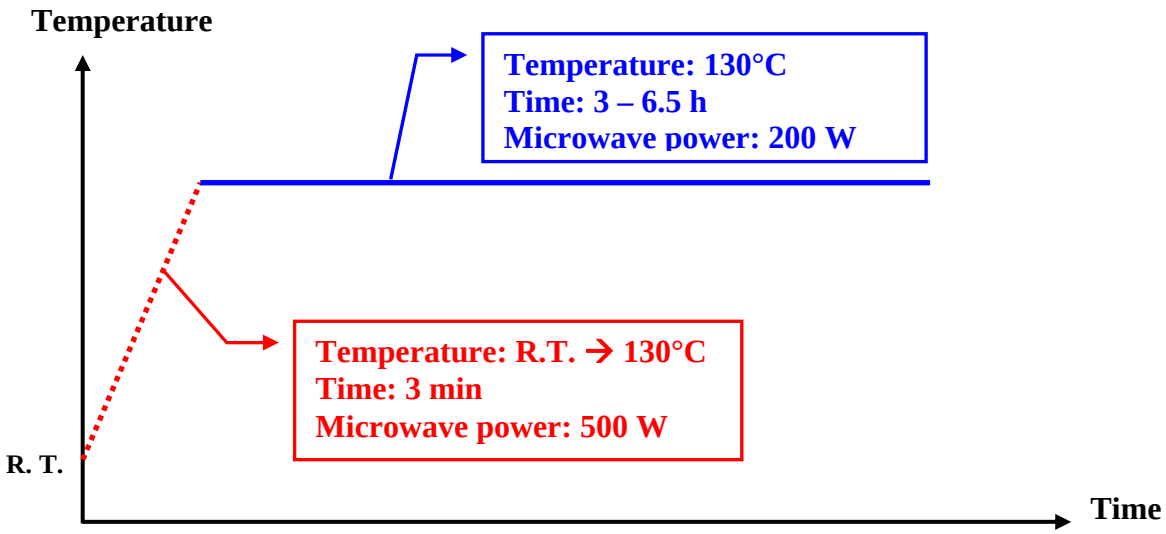

Figure 5.7 Microwave-temperature program for solvent free Ullmann type coupling between aryl bromides and pyrazole

3-(Imidazol-1-yl)anisole

^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 6.83 (s, 2H), 6.89 (d, J=8.0 Hz, 1H), 7.11 (s, 1H), 7.19 (s, 1H), 7.29 (t, J=8.0 Hz, 1H), 7.77 (s, 1H)

^{13} C NMR ($CDCl_3$) δ 55.5, 107.6, 112.6, 113.6, 118.2, 130.2, 130.7, 135.5, 138.4, 160.6

LRMS m/z ($M + H^+$) 175; HRMS Calcd for $C_{10}H_{11}N_2O$ ($M + H^+$) 175.0871, found 175.0879

3-(Imidazol-1-yl)acetophenone

^{1}H NMR ($CDCl_3$) δ 2.67 (s, 3H), 7.24 (s, 1H), 7.35 (s, 1H), 7.60 (d, J=12.3, 2H), 7.92-7.97 (m, 2H), 8.0 (s, 1H)

^{13} C NMR ($CDCl_3$) δ 26.7, 118.1, 120.7, 125.6, 127.3, 130.3, 130.8, 135.5, 137.8, 138.7, 196.8

LRMS m/z 186; HRMS Calcd for $C_{11}H_{10}N_2O$ 186.0793, found 186.0792

3-(Pyrazol-1-yl)anisole

^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 6.39 (s, 1H), 6.77 (d, J=10.2 Hz, 1H), 7.15-7.19 (m, 1H), 7.24-7.29 (m, 2H), 7.65 (s, 1H), 7.85 (s, 1H)

^{13} C NMR ($CDCl_3$) δ 55.5, 105.0, 107.6, 111.1, 112.4, 126.9, 130.1, 141.0, 141.3, 160.5

LRMS m/z 174; HRMS Calcd for $C_{10}H_{10}N_2O$ 174.0793, found 174.0794

3-(Pyrazol-1-yl)acetophenone

^{1}H NMR ($CDCl_3$) δ 2.67 (s, 3H), 6.52 (s, 1H), 7.57 (t, J=8, 1H), 7.75 (s, 1H), 7.87 (d, J=8Hz, 1H), 7.96 (d, J= 8Hz, 1H), 8.02 (d, J=2.32, 1H), 8.27 (s, 1H)

^{13} C NMR ($CDCl_3$) δ 26.8, 108.1, 118.4, 123.5, 126.1, 126.8, 129.8, 138.2, 140.5, 141.5, 197.3

LRMS m/z 186; HRMS Calcd for $C_{11}H_{10}N_2O$186.0793, found 186.0789

5.3 Experimental-Chapter 3

5.3.1 Typical procedure for the microwave assisted synthesis of TSIL precursors under solvent free condition

N-arylimidazole (0.25 mmol) and alkyl bromide (4 eqv.) were added to the reaction vessel. The reaction mixture was irradiated for 3 min to allow for the temperature rise from room temperature to 95°C, and then further irradiated for 10 hours at 95°C (Figure 5.7). The reaction mixture was cooled to room temperature. The resulted oil was redissolved in acetone, and emulsified out by addition of diethyl ether. The emulsion was isolated by centrifuge (40 x 100 rmp, 10 minutes) 3 times to obtain pure TSIL.

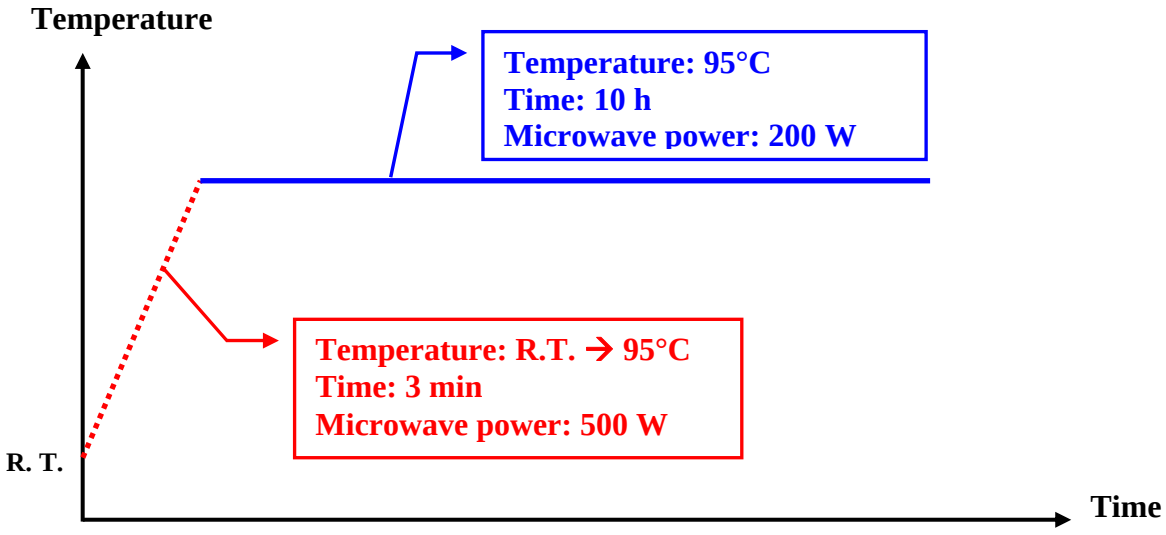

Figure 5.7 Microwave-temperature program for microwave assisted synthesis of TSIL precursors under solvent free condition

5.3.2 Typical procedure for the haloform reaction of 1-(3-acetylphenyl)-3-butyl-1-H-imidazol-3-ium bromide (API)

Bromine (0.10g, 0.625 mmol, 2.5 eqv.) was added into a solution of sodium hydroxide (1.25 mmol, 5 eqv.) in 1mL water. The orange reaction mixture was allowed to be stirred at 0°C in closed system for 2 hours. 1-(3-acetylphenyl)-3-butyl-1-H-imidazol-3-ium bromide (API) (0.082g, 0.25mmol) was dissolved into 2 mL water and then introduced into the reaction mixture. After the solution was changed from orange to yellow milky mixture, the whole reaction mixture was allowed to heat at 45-50°C for 18 hour. When the reaction was completed, the reaction mixture was cooled down to room temperature. The yellow aqueous layer was descanted, and crude orange oil was left. The resulted oil was redissolved in acetone, and emulsified out by addition of diethyl ether. The emulsion was isolated by centrifuge (40 x 100 rmp, 10 minutes) 3 times to obtain pure 1-butyl-3(3-carboxylphenyl)imidazolium bromide.

1-(3-Methoxyphenyl)-3-butyl-1H-imidazol-3-ium bromide

^{1}H NMR ($CDCl_3$) δ 0.97 (t, J=7.3, 3H), 1.38-1.47 (m, 2H), 1.92-2.00 (m, 2H), 3.95 (s, 3H), 4.55 (t, J=7.3, 2H), 7.01 (d, J=8.2, 1H), 7.20 (d, J=7.8, 1H), 7.39-7.43 (m, 2H), 7.50 (s, 1H), 11.21 (s, 1H)

^{13}C NMR ($CDCl_3$) δ 13.5, 19.5, 32.2, 50.3, 56.6, 107.1, 112.9, 117.0, 120.1, 122.2, 131.2, 135.4, 136.7, 161.3

LRMS m/z (M^+) 231; HRMS Calcd for $C_{14}H_{19}N_2O$ (M^+) 231.1497, found 231.1487

1-(4-Methoxyphenyl)-3-butyl-1H-imidazol-3-ium bromide

^{1}H NMR ($CDCl_3$) δ 0.96 (t, J=7.3, 3H), 1.47-1.37 (m, 2H), 1.98-1.91 (m, 2H), 3.83 (s, 3H), 4.55 (t, J=7.4, 2H), 7.03 (d, J=8.9, 2H), 7.45 (s, 1H), 7.55 (s, 1H), 7.68 (d, J=8.8, 2H), 10.94 (s, 1H)

^{13}C NMR ($CDCl_3$) δ 13.5, 19.5, 32.2, 50.2, 55.7, 115.5, 120.6, 122.3, 123.4, 127.4, 136.1, 160.8

LRMS m/z (M^+) 231; HRMS Calcd for $C_{14}H_{19}N_2O$ (M^+) 231.1497, found 231.1508

3-Butyl-1-*m*-toly-1-H-imidiazol-3-ium bromide

^{1}H NMR ($CDCl_3$) δ 0.94 (t, J=7.3, 3H), 1.36-1.46 (m, 2H), 1.99-1.87 (m, 2H), 2.42 (s, 3H), 4.63-4.55 (m, 2H), 7.28 (d, J=8.4, 2H), 7.38 (t, J-5.2, 1H), 7.55 (d, J=8.0, 1H), 7.58 (s, 1H), 7.69 (s, 1H), 10.88 (s,1H)

^{13}C NMR ($CDCl_3$) δ 13.5, 19.5, 21.3, 32.2, 50.2, 118.8, 120.7, 122.3, 123.0, 130.3, 121.0, 134.3, 135.7, 141.1

LRMS m/z (M^+) 215; HRMS Calcd for $C_{14}H_{19}N_2$ (M^+) 215.1548, found 215.1547

3-Butyl-1-*p*-toly-1-H-imidiazol-3-ium bromide

^{1}H NMR ($CDCl_3$) δ 0.91 (t, J=7.4, 3H), 1.33-1.42 (m, 2H), 1.89-1.96 (m, 2H), 2.34 (s, 3H), 4.52 (t, J=8.0, 2H), 7.28 (d, J=8.4, 2H), 7.62 (d, J=10.6, 2H), 7.74 (s, 1H), 7.78 (s, 1H), 10.73 (s, 1H)

^{13}C NMR ($CDCl_3$) δ 13.4, 19.4, 21.0, 32.2, 50.1, 120.8, 121.5, 123.1, 131.0, 132.0, 135.4, 140.5

LRMS m/z (M^+) 215; HRMS Calcd for $C_{14}H_{19}N_2$ (M^+) 215.1548, found 215.1545

1-(3-Acetylphenyl)-3-butyl-1H-imidazol-3-ium bromide

^{1}H NMR ($CDCl_3$) δ 0.95 (t, J=7.3, 3H), 1.37-1.46 (m, 2H), 2.02-1.94 (m, 2H), 2.72 (s, 3H), 4.55 (t, d=7.3, 2H), 7.66-7.69 (m, 2H0, 7.98 (s, 1H), 8.05 (d, J=7.8, 1H), 8.15 (d, J=8.6, 1H), 8.41 (s, 1H), 11.23 (s, 1H)

^{13}C NMR ($CDCl_3$) δ 13.5, 19.5, 27.4, 32.1, 50.3, 120.7, 121.4, 123.1, 126.1, 129.6, 131.1, 134.8, 136.4, 138.9, 196.7

LRMS m/z (M^+) 243; HRMS Calcd for $C_{15}H_{19}N_2O$ (M^+) 243.1497, found 243.1502

1-(4-Acetylphenyl)-3-butyl-1H-imidazol-3-ium bromide

^{1}H NMR ($CDCl_3$) δ 0.82 (t, J=7.4, 3H), 1.33-1.24 (m, 2H), 1.91-1.83 (m, 2H), 2.51 (s, 3H), 4.44 (d, J=7.3, 2H), 7.79 (s, 1H), 7.97 (s, 1H), 7.97 (s, 1H), 8.16 (s, 1H), 10.81 (s, 1H)

^{13}C NMR ($CDCl_3$) δ 13.3, 19.3, 26.8, 32.0, 50.2, 121.0, 121.8, 123.7, 130.4, 135.5, 137.4, 137.6, 196.5

LRMS m/z (M^+) 243; HRMS Calcd for $C_{15}H_{19}N_2O$ (M^+) 243.1497, found 243.1503

1-(3-Acetylphenyl)-3-hexyl-1H-imidazol-3-ium bromide

^{1}H NMR ($CDCl_3$) δ 0.87 (t, J=6.8, 3H), 1.28-1.43 (m, 6H), 2.00-2.16 (m, 2H), 4.58 (t, J=7.4, 2H), 7.48 (s, 1H), 7.7-7.8 (m, 2H), 8.09 (d, J=7.8, 1H), 8.20 (d, J=9.7, 1H), 8.41 (s, 1H), 11.41 (s, 1H)

^{13}C NMR ($CDCl_3$) δ 13.9, 22.3, 25.9, 27.4, 30.2, 31.1, 50.6, 120.7, 121.4, 123.0, 126.1, 129.6, 131.1, 134.9, 136.3, 138.9, 196.7

LRMS m/z (M^+) 271; HRMS Calcd for $C_{17}H_{23}N_2O$ (M^+) 271. 1810, found 271.1818

3-(3-Butyl-1H-imidazol-3-ium-1-yl)benzoate

^{1}H NMR ($(CD_3)_2CO$) δ 0.98 (t, J=8.0, 3H), 1.44-1.49 (m, 2H), 4.58 (t, J-4.5, 2H), 7.81 (t, J=8.5, 1H), 8.13 (s, 1H), 8.16 (d, J=8.5, 1H), 8.26 (d, J=8.0, 1H), 8.43 (s, 1H), 8.56 (s, 1H), 10.72 (s, 1H)

^{13}C NMR ($(CD_3)_2CO$) δ 13.0, 19.2, 31.8, 49.8, 121.3, 122.0, 123.7, 135.3, 136.1, 138.6, 196.6

5.4 Experimental-Chapter 4

5.4.1 Typical procedure for the Ullmann type coupling between imidazole and the flavone precursor 2-hydroxy-4-bromoacetophenone (A)

CuI (10 mol%), L-amino acid (20 mol %), imidazole (1.2 eqv.), potassium phosphate tribasic (2 eqv.) and 2-hydroxy-4-bromoacetophenone (0.215g, 1 mmol) were added to the reaction vessel. The reaction mixture was irradiated for 3 min to allow for the temperature rise from room temperature to 130°C, and then further irradiated for 5-7 hours at 130°C (Figure 5.8). The reaction mixture was cooled to room temperature and the product was extracted by ethyl acetate. Ethyl acetate was evaporated in vacuum and the product was purified by column chromatography on silica gel using *n*-hexane and ethyl acetate mixture as the eluent.

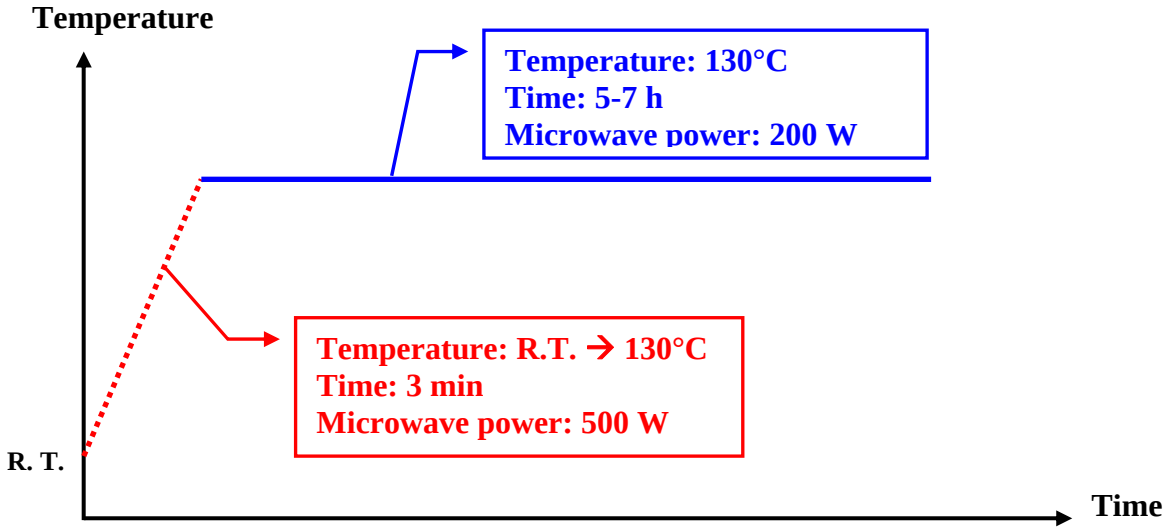

Figure 5.8 Microwave-temperature program for solvent free Ullmann type coupling between flavone precursor 2-hydroxy-4-bromoacetophenone with imidazole

5.4.2 Typical procedure for the Ullmann type coupling between imidazole and 2-(4-(allyloxy)phenyl)-6-bromo-4H-chromen-4-one (B)

CuI (20 mol%), L-amino acid (40 mol %), imidazole (10 eqv.), potassium phosphate tribasic (4 eqv.) and flavone (B) (0.179g, 0.5 mmol) were added to the reaction vessel. The reaction mixture was irradiated for 3 min to allow for the temperature rise from room temperature to 140°C, and then further irradiated for 10 hours at 140°C (Figure 5.9). The reaction mixture was cooled to room temperature and the product was extracted by dichloromethane. Dichloromethane was evaporated in vacuum and the product was purified by column chromatography on silica gel using dichloromethane and acetone mixture as the eluent.

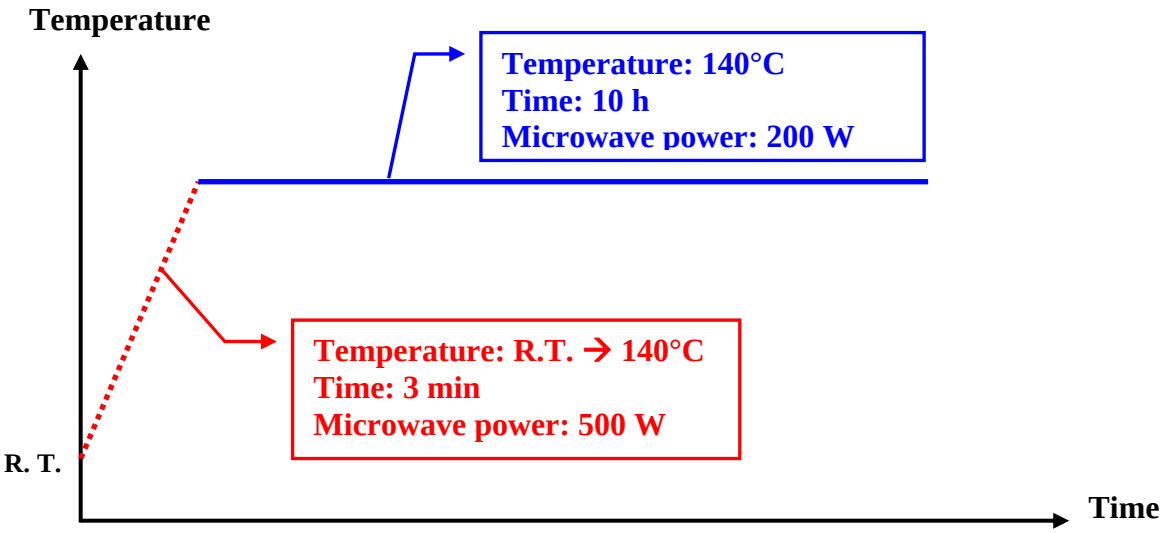

Figure 5.9 Microwave-temperature program for solvent free Ullmann type coupling between flavone (B) with imidazole

5-(Imidazol-1-yl)-2-hydroxyacetophenone

^{1}H NMR ($CDCl_3$) δ 2.68 (s, 3H), 7.11 (d, J=8.8, 1H), 7.21 (s, 2H), 7.50 (d, J=8.8, 1H), 7.71 (s, 1H), 7.76 (s, 1H), 12.38 (s, 1H)

^{13}C NMR ($CDCl_3$) δ 26.7, 118.9, 119.6, 120.1, 124.1, 128.9, 130.4, 130.7, 136.0, 161.7, 203.7

LRMS m/z ($M + H^+$) 203; HRMS Calcd for $C_{11}H_{10}N_2O_2$ ($M + H^+$) 203.0821, found 231.0815

2-(4-(allyloxy)phenyl)-6-(1H-imidazol-1-yl)-4H-chromen-4-one (Flavone D)

^{1}H NMR ($CDCl_3$) δ 4.64 (d, J=5.0, 2H), 5.35 (d, J=10.0, 1H), 5.46 (d, J=17.0, 1H), 6.05-6.08 (m, 1H), 6.79 (s, 1H), 7.06 (d, J=10.0, 2H), 7.27 (s, 1H), 7.41 (s, 1H), 7.69-7.75 (m ,2H), 7.90 (d, J=9.0, 2H), 7.98 (s, 1H), 8.23 (s, 1H)

^{13}C NMR ($CDCl_3$) δ 67.0, 106.0, 115.3, 117.4, 118.3, 120.0, 123.6, 124.9, 126.4, 128.1, 130.9, 132.4, 134.4, 154.7, 161.7, 163.9., 177.3

LRMS m/z ($M + H^+$) 345; HRMS Calcd for $C_{21}H_{16}N_2O_3$ ($M + H^+$) 345.1239, found 345.1232

2-[4-(2-{2-[2-(2-Hydroxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-phenyl]-6-imidazol-1-yl-chromen-4-one (Side Product E)

^{1}H NMR ($CDCl_3$) δ 3.70-3.77 (m, 8H), 3.87-3.91 (m, 4H), 4.16-4.22 (m, 4H), 6.80 (s, 1H), 6.93 (d, J=8.8, 2H), 7.05 (d, J=8.6, 1H), 7.70-7.74 (m, 2H), 7.89 (t, J=8.0, 4H), 8.24 (s, 1H)

^{13}C NMR ($CDCl_3$) δ 26.3, 29.2, 67.6, 67.7, 69.5, 70.6, 70.8, 105.9, 114.2, 115.1, 120.2, 123.4, 124.8, 128.1, 130.4, 130.5, 154.9, 161.9, 162.6, 164.0, 177.3, 196.8