One-Pot, Multicomponent Oxidative Synthesis of 2,4,5-Trisubstituted Imidazoles from Internal Alkenes Using an I_2/DMSO System

By

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Dissertation submitted in fulfillment for the degree of

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Thesis Declaration

The experimental work described in this dissertation was carried out in the School of Chemistry and Physics, University of KwaZulu-Natal, South Africa, under the supervision of Dr Vineet Jeena. The studies represent the original work by the author and have not been submitted in candidature for any other degree.

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Publication Declaration

The experimental work discussed in the publication as well as the writing of the publication was performed by myself and carried out in the School of Chemistry and Physics, University of KwaZulu-Natal, South Africa, under the supervision of Dr Vineet Jeena. I was the primary author and minor grammatical changes were performed by me under the supervision of Dr Vineet Jeena.

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Publication

ACID, METAL AND PEROXIDE-FREE SYNTHESIS OF 2,4,5-TRISUBSTITUTED IMIDAZOLES COMMENCING FROM INTERNAL ALKENES USING AN IODINE/DMSO SYSTEM.

Nonhlelo Majola and Vineet Jeena

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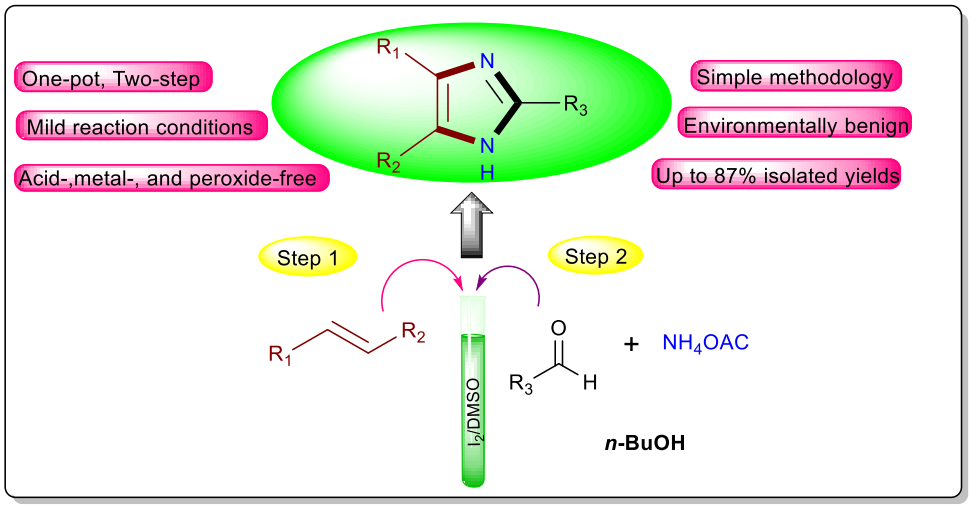

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Abbreviation List

Abbreviations	Descriptions
AChE	Acetylcholinesterase
Ac_2O	Acetic anhydride
AcOH	Acetic acid
AD	Alzheimer's Disease
Al_2O_3	Aluminium (III) Oxide
BnCl	Benzyl Chloride
BTPPC	Benzyltriphenylphosphonium Chloride
BSA	Benzeneseleninic Anhydride
CCl_4	Carbon tetrachloride
CF_3	Trifluoromethyl
Cl-Ph	Chlorobenzene
CSBP	Cytokinin Specific Binding Protein
$Cu(CH_3COO)_2$	Copper (II) acetate
$CuCl_2$	Copper (II) Chloride
dtbpy	4,4'-Di-t-butyl-2,2'-bipyridine
DCM	Dichloromethane
DM	Diabetes Mellitus

DME	Dimethoxy ethane
DMF	Dimethylformamide
Fe_3O_4	Iron (III) tetraoxide
H_2O_2	Hydrogen peroxide
HBr	Hydrobromic acid
HFIP	Hexafluoroisopropanol
HM	Hermaline
HSO_4	Hydrogen sulfate
IBA	Isobutyraldehyde
IBX	2-Iodoxybenzoic Acid
I_2O_5	Iodopentoxide
IC_{50}	Half maximal inhibitory concentration
KI	Potassium Iodide
K_2CO_3	Potassium Carbonate
$KMnO_4$	Potassium permanganate
KtBuO	Potassium *tert*-butoxide
LED	Light-emitting diode
LiOH	Lithium hydroxide
m	*meta*
µM	Micromolar

MAP	Mitogen-Activated Protein
MeOH	Methanol
*m*CPBA	*meta*-Chloroperoxybenzoic acid
MTO	Methyltrioxorhenium
MW	Microwave
NaBr	Sodium Bromide
Na_2CO_3	Sodium carbonate
$NaHSO_4$	Sodium Hydrogen Sulfate
NH_3	Ammonia
NH_4OAc	Ammonium Acetate
$(NH_4)_6Mo_7O_{24}•4H_2O$	Ammonium Heptamolybdate Tetrahydrate
$NiFe_2O_4$	Nickel Ferrite
NPC	Nanoparticle Crystal
o	o*rtho*
OsO_4	Osmium tetraoxide
p	*Para*
P-ELISA	Platelet Enzyme-Linked Immunosorbent Assay
$PdCl_2$	Palladium (II) Chloride
$Pd(OAc)_2$	Palladium (II) acetate
PF_6	hexafluorophopshate

P(*o*-tolyl)$_3$	Tri(*o*-tolyl) phosphine
ppy	polypyrrole
P-Selectin	Platelet Selectin
RAF	Rapidly Accelerated Fibrosarcoma
Rh_2O_3	Rhodium Oxide
[Ru(cymene)Cl_2]$_2$	(Cymene)ruthenium dichloride dimer
SiO_2	Silicon dioxide
$SnCl_4$	Tin (IV) Chloride
SO_3H	Sulfonic acid
TBAI	Tetra-*n*-butylammonium iodide
TBHP	*Tert*-butyl hydroperoxide
TEA	Triethanolamine
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TOF	Time-of-Flight
WHO	World Health Organization
Yb(OTf)$_3$	Ytterbium (III) Triflate
$ZnCr_2O_7$•3H_2O	Zinc dichromate trihydrate
$ZrCl_4$	Zirconium (IV) Chloride

ZrO_2	Zirconium dioxide

Abstract

Imidazoles are vital heterocyclic compounds usually incorporated in natural products such as biotin, vitamin B_{12}, histamine, and histidine. 2,4,5-Trisubstituted imidazoles, in particular, possess versatile biological and pharmaceutical activities such as antidiabetic, antimalarial, and analgesic properties. A traditional procedure for the synthesis of these elegant compounds involves the cyclocondensation reaction between a 1,2-diketone, an aldehyde, and ammonia in the presence of an acid or metal catalyst. However, this methodology suffers from various shortcomings such as the use of acid or metal catalysts, tedious work-up procedures, use of toxic reagents, and substrate scope limitations. Hence, the development of new methods to synthesize 2,4,5-trisubstituted imidazoles is of vital importance.

This study describes the preparation of 2,4,5-trisubstituted imidazoles from alkenes using an environmentally benign iodine/DMSO system. This novel methodology was applied to a broad substrate scope such as substituted benzaldehydes, heterocyclic aldehydes, bulkier aldehydes, and substituted stilbenes, and afforded the target compounds in moderate to high yields under mild reaction conditions. Preliminary mechanistic studies revealed that 1,2-diketone is a key intermediate and that the mechanism is not radical-mediated. It also revealed that the oxygen source is DMSO and that the coupling step is catalyzed by iodine coordination and hydrogen bonding from the solvent. Based on the results obtained from the preliminary mechanistic investigations, a reasonable mechanism is proposed.

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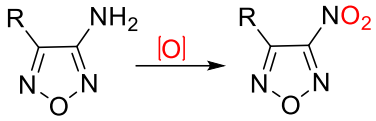
CHAPTER 1: INTRODUCTION

1.1. Oxidation reactions

In organic chemistry, oxidation refers to the introduction of oxygen in a molecule (**Scheme 1a**), whereas in inorganic chemistry, it refers to a loss of one or more electrons (**Scheme 1b**).[1] In academia and industry, oxidations are paramount as they play a vital role in the synthesis of new, complex compounds and the modification of existing ones.[2-5]



(a)

$$2Fe \rightarrow 2Fe^{2+} + 4e^{-}$$

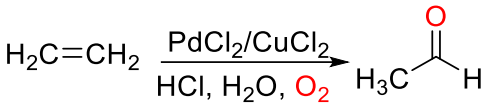
(b)

Scheme 1: **(a)** Oxidation of Aminofurazans to Nitrofurazans; **(b)** Oxidation of Iron (0) to Iron (II)

Oxidation reactions are widely employed in upgrading petrochemical feedstocks to more valuable chemicals, for example, unsaturated hydrocarbons are oxidized to value added products such as ketones, aldehydes, carboxylic acids, and alcohols.[6] These value-added products are usually the starting materials in the synthesis of complex molecules as well as numerous biologically active and pharmaceutical compounds.[7] Molecular oxygen,[8] hydrogen peroxide,[9] or oxygen-containing molecules are traditionally employed as oxidants, whilst transition metals[10, 11] and acids[12] generally catalyze these transformations.

1.2. Alkene Oxidation

Alkene oxidation has been an interesting field for researchers since the discovery of the Wacker Process by Philips more than a century ago.[13] About five decades later, Schmidt and co-workers reported the catalytic method where ethylene was converted to acetaldehyde in aqueous hydrochloric acid in the presence of $PdCl_2/CuCl_2$ catalyst using molecular oxygen as an oxidant (**Scheme 2**).[14] This process was extended to terminal alkenes, providing a simple route towards the preparation of methylene ketones and ketals.[15]

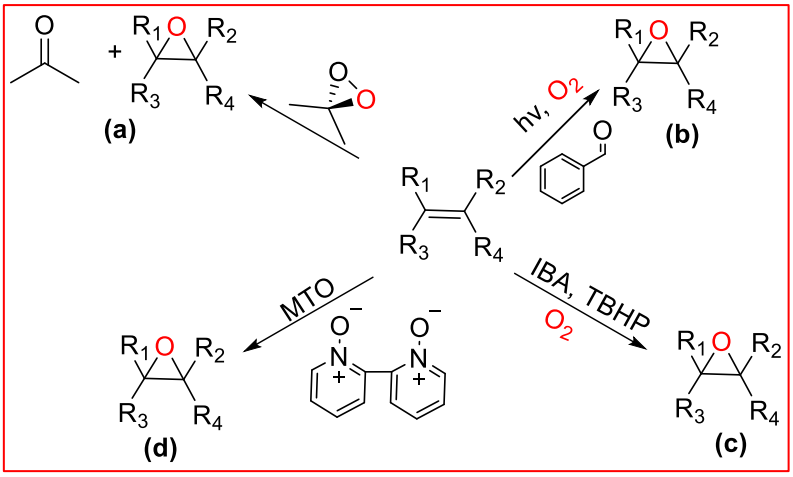


Scheme 2: The Wacker Process: Synthesis of acetaldehyde from ethylene

The C-H functionalization of internal alkenes is deemed challenging due to high thermodynamic stability; thus, transition-metal catalysts are usually employed.[16] However, these compounds can be employed as starting materials for the preparation of epoxides,[17-19] 1,2-diols,[20] and allylic compounds,[21] which will be discussed below.

1.2.1. Epoxidation of alkenes

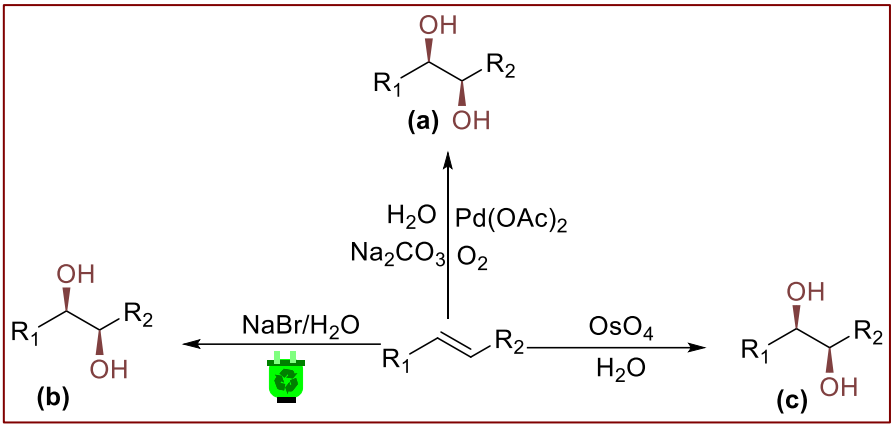
Epoxides are important in academia and industry as they are key intermediates in the production of various industrial and commercial products including epoxy resins, surfactants, and paints.[22-25] A classical approach toward epoxides synthesis is the direct alkene oxidation, leading to epoxidation on both micro-scale (laboratories) and macro-scale (industries).[26, 27] Different oxidants are employed in this synthesis such as molecular oxygen,[28] dioxiranes,[29, 30] peroxides[31], and methyl-trioxorhenium (MTO).[32] (**Scheme 3**).



Scheme 3: Epoxidation of alkenes using various oxidants and catalysts; **(a)** using dioxirane; **(b)** molecular oxygen and aldehyde in visible light; **(c)** isobutyraldehyde, *tert*-butyl hydroperoxide, and molecular oxygen system; **(d)** methyltrioxorhenium (MTO) and pyridine-based system

1.2.2. Dihydroxylation of alkenes

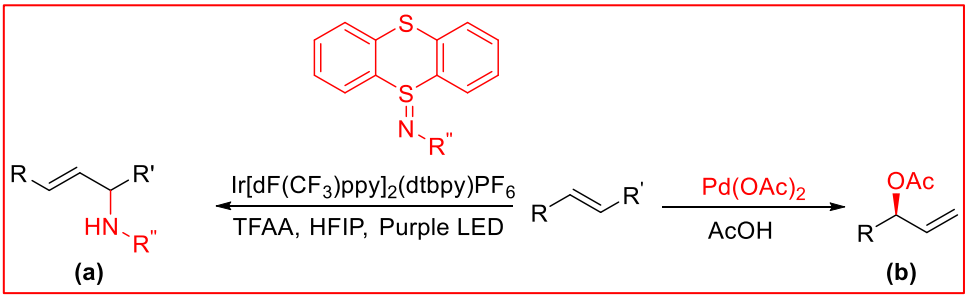
Vicinal diols (1,2-diols) are molecules where the two alcohol groups are on adjacent carbon atoms. These 1,2-diols are used in the preparation of key intermediates in fragrances, pharmaceuticals, and functional materials.[33, 34] Dihydroxylation of alkenes is the predominant method to access the vicinal diols[35] through different systems such as palladium-catalysis using molecular oxygen (**Scheme 4a**),[36] electrochemical modular-mediated (**Scheme 4b**),[37] and Osmium tetraoxide in water (**Scheme 4c**).[38, 39]



Scheme 4: Dihydroxylation of alkenes; **(a)** Palladium-catalyzed; **(b)** sodium bromide in water electrochemical modular system; **(c)** Osmium tetraoxide in water

1.2.3. Allylation of alkenes

The catalytic enantioselective allylic C-H functionalization of alkenes has been widely applied in the production of natural products, fine chemicals, pharmaceuticals, and functional materials.[40-42] This transformation is advantageous since it provides a direct route to chiral building blocks with a new stereocentre from petrochemical feedstocks whilst preserving the alkene functionality for further chemical elaboration.[43] Various metal-based catalysts have been discovered for allylic C-H oxidation of simple alkenes with cyclic or terminal double bonds[44-46] including an iridium-based complex (**Scheme 5a**)[47] and palladium acetate in acetic acid (**Scheme 5b**).[48]



Scheme 5: Allylation of alkenes; **(a)** Iridium-based complex, **(b)** Palladium acetate in acetic acid system

1.3. 1,2-Diaryl Diketones

1,2-Diaryl diketones are compounds where the carbonyl groups are on adjacent carbon atoms. These molecules possess high reactivity due to the presence of the two, adjacent electron-deficient carbonyl groups, hence, they are used as starting materials or intermediates in modern organic synthesis and organocatalytic transformations.[49-51] In addition, they are utilized as key building blocks in the preparation of biologically active compounds such as pyrazines,[52-55] dihydropyrazines,[56] quinoxalines,[57-60] oxazoles,[61] and imidazoles (*vide infra*).[62] Furthermore, 1,2-diketones have displayed unique applications as photo-initiators and photosensitive agents.[63] These compounds have also been reported to have vast biological activities including anticancer,[64, 65] antioxidant,[66, 67] antimicrobial,[68-70] and hypertensive properties (**Figure 1).**[71]

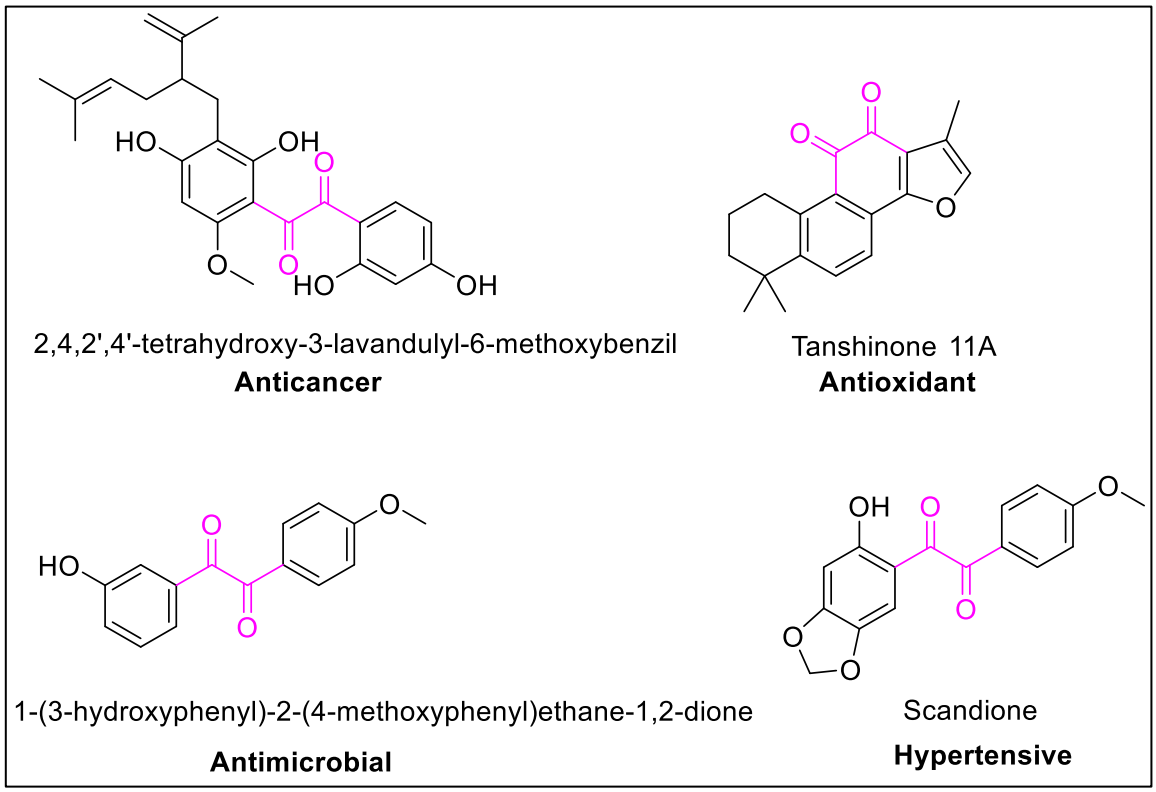
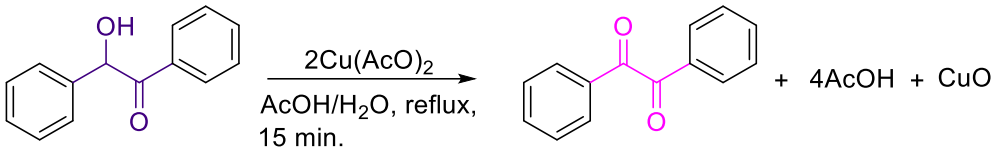


Figure 1: Biologically active 1,2-diketones

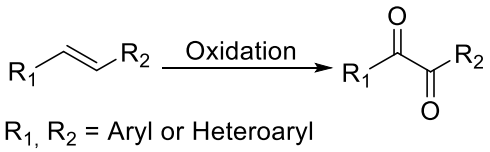
1.3.1. Accessible routes toward the preparation of 1,2-Diaryl Diketones

There are various methodologies utilized for the preparation of 1,2-diketones, mostly from the oxidation of suitable precursors such as α-hydroxyketones (benzoins),[72, 73] diarylalkynes,[74, 75] 1,3-diketones,[76, 77] 1,2-diols[78] and diarylalkenes (*vide infra*). In addition, these compounds can be prepared *via* oxidative-coupling pathways.[79] The classical preparation of 1,2-diketones (benzils) is the direct oxidation of benzoin using two equivalents of copper acetate in an acetic acid/water mixture for 15 minutes under reflux conditions which furnished benzil in 90% isolated yield (**Scheme 6**).[80]



Scheme 6: Classic synthesis of 1,2-diketones from benzoin oxidation

Among the reported methods in literature, alkene oxidation remains a direct route towards benzils, as they are cheaper and more easily accessible than other precursors.[81] Internal alkenes have been oxidized to form 1,2-diketones by utilizing various systems and catalysts including transition metals, anhydrides, and acidic media, which will be discussed in detail below (**Scheme 7**).

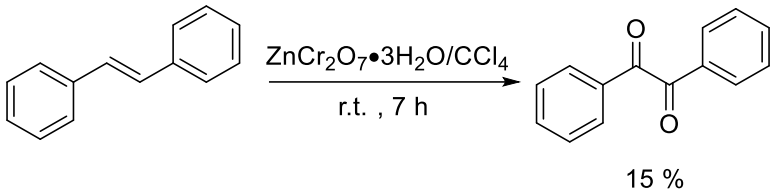


Scheme 7: Direct oxidation of alkenes to 1,2-diketones

1.3.1.1. Transition Metal-Based catalysts

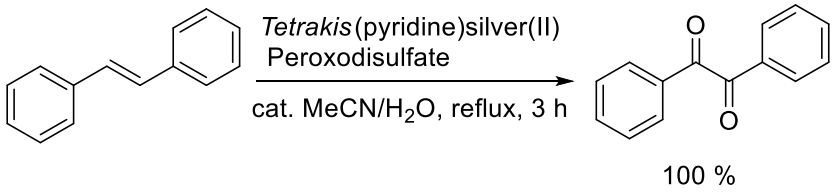
In 1986, Firouzabadi and co-workers reported the synthesis of benzil from *trans*–stilbene using zinc dichromate trihydrate as a catalyst. The reaction was conducted in

carbon tetrachloride for 7 hours and afforded the desired product in a low yield of 15% (**Scheme 8**).[82]



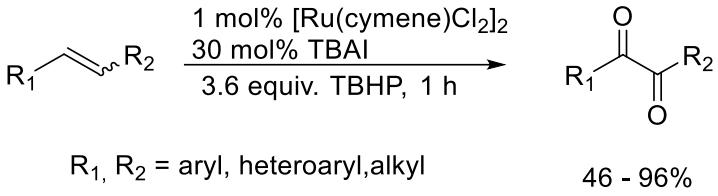
Scheme 8: Zinc dichromate trihydrate catalyzed oxidation of *trans*-stilbene

The shortcomings associated with this method include the use of an expensive transition metal catalyst ($ZnCr_2O_7•3H_2O$) and toxic solvent (carbon tetrachloride).[83] Six years later, these authors reported *tetrakis*(pyridine)silver(II) peroxodisulfate as an oxidative reagent in the synthesis of benzil from *trans*-stilbene (**Scheme 9**).[84] This system exhibited high efficiency as benzil was obtained in 100% isolated yield in 3 hours. Despite the excellent yield, the study was not extended to a range of stilbene derivatives to explore substrate and scope limitations.



Scheme 9: Oxidation of *trans*-stilbene to benzil using *tetrakis*(pyridine)silver(II) peroxodisulfate

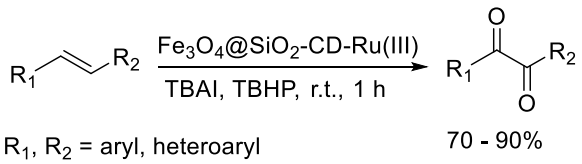
In 2011, Wan and co-workers designed the synthesis of 1,2-diketones from stilbenes using a ruthenium-based catalyst and *tert*-butyl hydroperoxide (TBHP) as an oxidant in a mixture of toluene/acetonitrile and water at room temperature (**Scheme 10**).[85] This system was applied to a broad substrate scope including aryl, heteroaryl, and alkyl-substituted alkenes furnishing the corresponding 1,2-diketones in 46 – 96% yields.



Scheme 10: Ruthenium-catalyzed 1,2-diketone synthesis from alkenes

Although this system exhibited high efficiency as up to 96% isolated yields were achieved, the use of a toxic peroxide (TBHP) in super stoichiometric amounts and the use of a transition-metal complex, $[Ru(cymene)Cl_2]_2$, which was not commercially available then and had to be prepared using expensive reagents (ruthenium trichloride and α-phellandrene)[86] detracts from this method.

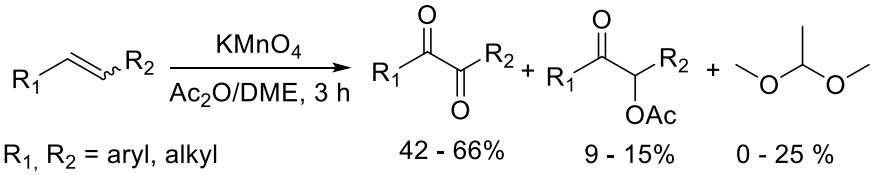
Motivated by the above system, Saberi and co-workers recently reported a ruthenium/dendrimer complex immobilized on silica-functionalized magnetite nanoparticles as a highly efficient and magnetically separable catalyst in the oxidation of stilbenes to benzil derivatives at room temperature (**Scheme 11**).[87] *Ortho-, meta-,* and *para*-substituted *trans*-stilbene derivatives bearing electron-donating and electron-withdrawing groups were converted to corresponding 1,2-diketones, where those with electron-donating substituents exhibited higher efficiency (up to 90% yields). Moreover, a polycyclic stilbene, 1-styryl naphthalene and 2-styryl-1*H*-pyrrole were oxidized to corresponding 1,2-diketones in good yields of 75 and 70% respectively.



Scheme 11: 1,2-Diketone synthesis from alkenes using silica-functionalized magnetite particles on ruthenium complex

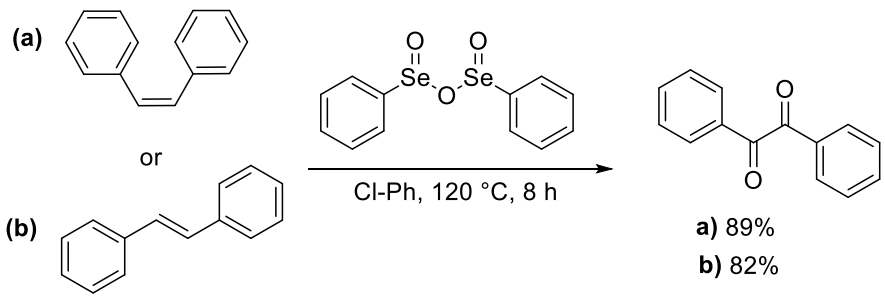
1.3.1.2. Use of Anhydride-Based Systems

In 1971, Sharpless and co-workers reported the preparation of 1,2-diketones from alkenes in the presence of potassium permanganate in acetic anhydride/ dimethoxyethane (**Scheme 12**).[88] The corresponding 1,2-diketones were obtained in 42 – 66% yields with ketoacetate and dimethoxyethane (DME) as by-products. This system was applicable to aryl- and alky-substituted stilbene derivatives; however, the occurrence of side-products makes this method less desirable.



Scheme 12: Preparation of 1,2-diketones from alkenes using potassium permanganate in acetic anhydride

In 1998, Rabideau and co-workers reported the benzeneseleninic anhydride promoted oxidative synthesis of 1,2-diketones from 1,2-diarylethanes and 1,2-diarylethenes. *Cis*- and *trans*-stilbenes were converted to benzil in the presence of benzeneseleninic anhydride (BSA) producing benzil in 89 and 82% yields, respectively (**Scheme 13**).[89]



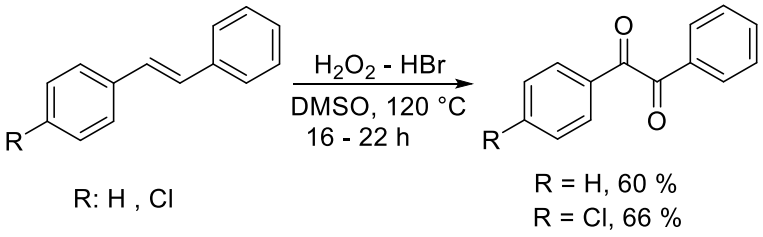
Scheme 13: Benzeneseleninic anhydride-assisted oxidation of stilbenes into benzil

The use of a toxic transition metal-based catalyst (BSA), and a chlorinated solvent which is non-green limits this method. Furthermore, the substrate and scope

limitations were not explored as stilbene derivatives and other alkenes were not examined.

1.3.1.3. Use of an acidic catalyst

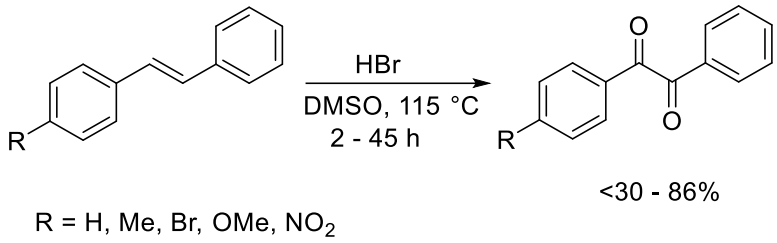
Yusubov and co-workers reported the synthesis of benzil from *trans*-stilbene in the presence of hydrobromic acid and hydrogen peroxide in dimethyl sulfoxide to afford benzil in a moderate 60% yield (**Scheme 14**).[90] A slight increase in yield was observed when 4-chlorostilbene was used and the corresponding benzil derivative was obtained in a 66% isolated yield.



Scheme 14: Benzil synthesis using HBr-H_2O_2/DMSO system

The role of hydrogen peroxide was to accelerate the formation of bromine ion from hydrobromic acid, however, it was reported that DMSO can also perform the same function,[91] hence the authors further developed this approach by omitting hydrogen peroxide.[92] *Trans*-stilbene derivatives were oxidized to corresponding 1,2-diketones in the presence of hydrobromic acid in DMSO affording corresponding benzils in <30 – 86% yields (**Scheme 15**).[92] It was observed that the volume of hydrobromic acid influenced the yield of the product as increasing the volume of the acid resulted in higher yields in shortened reaction times. Electron-donating substituents such as methyl- (Me) and methoxy (-OMe) groups were observed to accelerate the reaction whilst, electron-withdrawing substituents such as nitro group (-NO_2), slow down the

reaction. As a result, some nitro-substituted diketone derivatives could not be isolated and were obtained in trace amounts even after 45 hours.

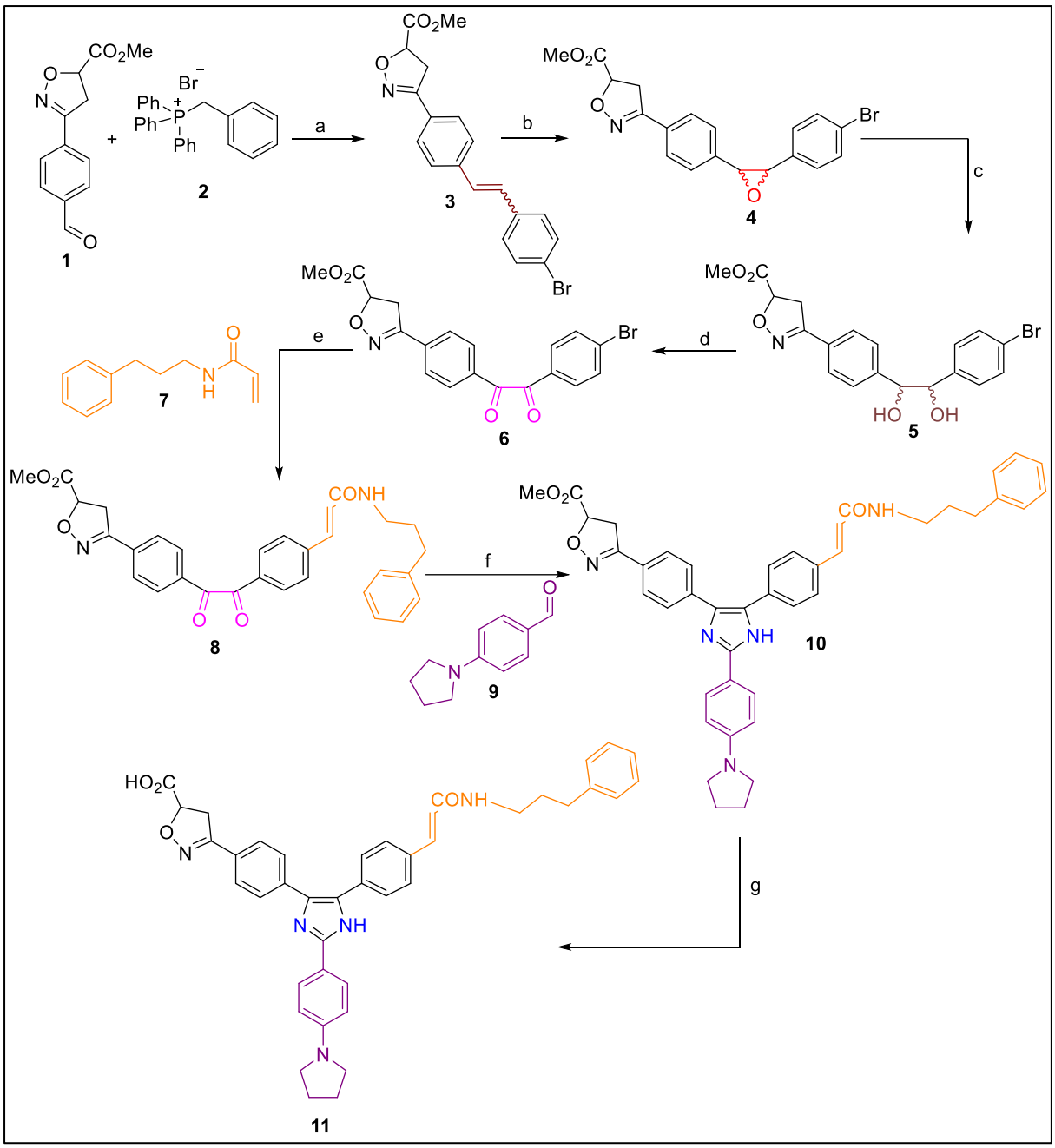


Scheme 15: Synthesis of benzils from stilbenes using HBr/DMSO system

There are also methodologies in which benzil is obtained as a side product, for example, Maurya and Kumar reported the synthesis of an oxovanadium-based coordination polymers and evaluated its catalytic potential on styrene, cyclohexene, and *trans*-stilbene oxidation where benzil was obtained in 6 – 7% yields.[93] Tabatabaeian and co-workers reported an ultrasonic-assisted ruthenium-catalyzed oxidation of aromatic and heteroatomic compounds, where benzil was obtained in 5% yield.[94] These methods are unlikely to be used in benzil synthesis as they produce the 1,2-diketones as a side product and in poor yields.

1.4. Alkene Oxidation in the Total Synthesis of 2,4,5-Trisubstituted Imidazoles

The oxidation of alkenes to 1,2-diketones has played an important role in organic synthesis as it has been shown to be one of the key steps in the total synthesis of biologically active 2,4,5-trisubstituted imidazoles. For example, Slee and co-workers[95] synthesized a series of 2,4,5-trisubstituted imidazoles to screen for anti-inflammatory activity. Their synthesis commenced from a Wittig olefination of aldehyde (**1**) with ylide (**2**) furnishing an alkene (**3**) in a 1:1 mixture of *cis* and *trans* isomers. Epoxidation of alkene (**3**) with *m*CPBA afforded intermediate (**4**) which was subsequently followed by the *in-situ* ring opening with formic acid to generate diol (**5**). The oxidation of diol (**5**) with TEMPO furnished the dione intermediate (**6)** which was reacted with acrylamide (**7**) under Heck reaction conditions to produce dione (**8**). The coupling reaction of ammonium acetate with dione (**8**) and an appropriate aldehyde (**9**) in acetic acid gives imidazole (1**0**). Final deprotection gave the imidazole (**11**) (**Scheme 16**),[95] which was found to inhibit P-Selectin and P-ELISA, which are cell adhesion molecules that work in a programmed manner to direct blood to the inflamed tissue, thus showing promising activity against inflammation.

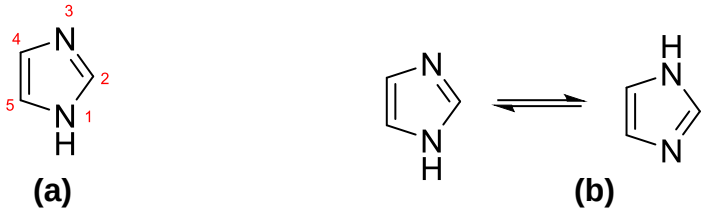


Synthetic steps: **a**-K*t*BuO, DMSO/THF, 2h; **b**-*m*CPBA, DCM, 40 °C; **c**-Formic acid, THF, 0 °C, **d**-TEMPO, DCM, 0.7 M NaBr, buffered bleach, quantitatve; **e**-$Pd(OAc)_2$, TEA, P(*o*-tolyl)$_3$; **f**-AcOH, NH_4OAc, 100 °C, 2 h; **g**- LiOH, dioxane, 18 h

Scheme 16: Application of alkene oxidation in total synthesis of biologically active 2,4,5-trisubstituted imidazoles

1.5. Imidazole Moiety

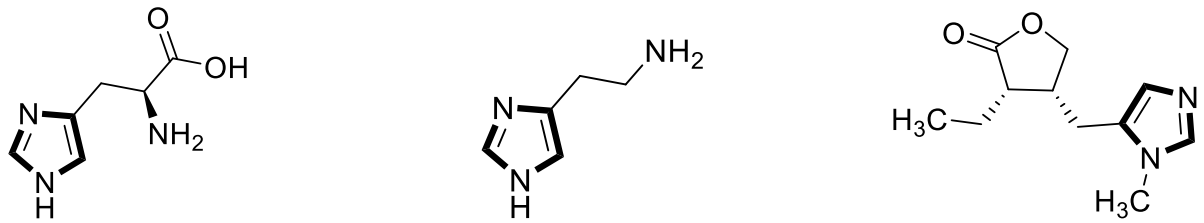
Imidazole (1,3-diaza-2,4-cyclopentadiene) is a planar five-membered ring with three carbon atoms and two nitrogen atoms situated in the first and third positions (**Figure 2a**). This compound has the molecular formula $C_3H_4N_2$ and is the simplest of the imidazole family. One of the nitrogen atoms is referred to as a pyrrole type since it is bonded to a proton. This compound exists in two equivalent tautomeric forms as hydrogen can be obtained in either of the nitrogen atoms (**Figure 2b**).[96]



(a) **(b)**

Figure 2: **(a)** Structure of the imidazole moiety; **(b)** Tautomeric forms of imidazoles

The imidazole moiety is found in several naturally occurring compounds such as vitamin B_{12},[97] histidine (**Figure 3a**),[98] histamine (**Figure 3b**),[99] biotin,[100] and pilocarpine alkaloids (**Figure 3c**),[101] to mention just a few. Histidine is a vital amino acid that is present in many proteins and enzymes, playing a huge role in the structure and binding of hemoglobin.[96]



(a) **(b)** **(c)**

Figure 3: Naturally occurring compounds containing the imidazole moiety; **(a)** histidine; **(b)** histamine; **(c)** pilorcapine alkaloid

1.6. 2,4,5-Trisubstituted Imidazoles

2,4,5-Trisubstituted-1*H*-imidazoles have been known for over a century[102] and possess numerous biological and pharmaceutical activities[96] which will be discussed below. In addition, these compounds possess good photophysical properties such as organic light-emitting diodes and thus can be used as photosensitizers.[103-105] Consequently, the synthesis of imidazoles has received a great deal of attention to unveil novel methodologies for the preparation of new derivatives.

1.6.1. Pharmacological applications of 2,4,5-trisubstituted imidazoles

1.6.1.1. Antidiabetic Activity

Diabetes Mellitus (DM) is a chronic disease caused by inadequate regulation of blood glucose levels which can be subdivided into type 1 and type 2.[106] Type 1 DM refers to a condition where insufficient insulin is produced in the body and therefore requires daily administration of insulin. Type 2 diabetes refers to the ineffective use of insulin in the body and this type is a result of prolonged hyperglycemia. Hyperglycemia refers to increased blood sugar levels, leading to damage nerves, blood vessels, and other body systems over time.[107] This disease can be treated by suppressing postprandial hyperglycemia and regulating postprandial glucose levels by inhibiting carbohydrate-hydrolyzing enzymes known as α-glucosidase.[108]

α-Glucosidase inhibitors are famous for their antiviral,[109] antitumor,[110] antidiabetic[111, 112], and immunoregulatory activities.[113] Currently used inhibitors in DM treatment include acarbose, miglitol and voglibose.[114] The latter inhibitors have been reported to induce the following side effects: flatulence, abdominal distention, and diarrhea. Hence, there is a dire need to find different α-glucosidase inhibiting agents that will minimize these disadvantages.[115]

In an effort to find a novel α-glucosidase inhibitor, Yar and co-workers prepared a series of 2,4,5-trialrylimidazoles. The α-glucosidase inhibiting activities for the synthesized compounds were tested where most of them presented good activity at low micromolar concentrations.[116] 2-(2-Hydroxyphenyl)-4,5-diphenyl-1*H*-imidazole (**Figure 4**) had an IC_{50} of 74.32 ± 0.39 µM, thus displaying the highest activity.

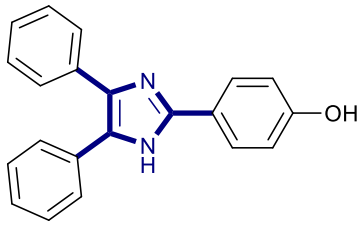


Figure 4: The chemical structure of 2-(2-hydroxyphenyl)-4,5-diphenyl-1*H*-imidazole

1.6.1.2. Antimalarial Activity

Malaria is a lethal disease caused by a *plasmodium* parasite, transmitted by the bite of infected mosquitoes.[117] The pathogens of this disease are the species of single-celled eukaryotic *Plasmodium* parasites including *P. malarae,*[118] *P. falciparum,*[119] *P. ovale wallikeri,*[120] *P. ovale curtisi,*[121] *P. vivax*[122] *and P. knowlesi.*[123] *Plasmodium falciparum* is the most noxious as it is responsible for ~90% of all infections.[124] In 2018, the World Health Organization (WHO) reported 228 million malaria cases across the world with 405 thousand deaths.[125] Treatment includes antimalarial drugs such as Quinine,[126] Quinidine[127] and Krintafel,[128] which typically leads to cross-resistance.

Researchers are continuously trying to find novel antimalarial compounds through pharmacophore hybridization.[129] Heterocyclic compounds such as imidazoles, quinolines, etc, have gained enormous attention as the substituted heterocycles play a paramount role in the development of compounds active against this disease.[130] Egan and co-workers screened a series of 2,4,5-trisubstituted imidazoles against

Plasmodium falciparum and 2-(3,5-dimethoxyphenyl)-4,5-bis(4-methoxyphenyl)-1*H*-imidazole (**Figure 5**) emerged as the most active.[131]

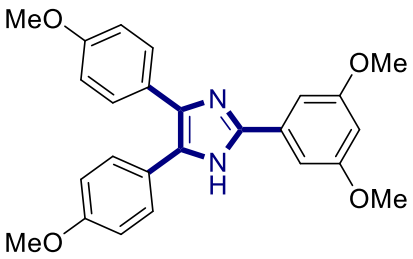


Figure 5: The chemical structure of 2-(3,5-dimethoxyphenyl)-4,5-bis(4-methoxyphenyl)-1*H*-imidazole

1.6.1.3. Acetylcholinesterase (AChE) Inhibition activity

The World Health Organization has declared Alzheimer's Disease (AD) as the global public health priority as there is no permanent cure for this disease.[132] According to WHO, in 2019, over 50 million people had dementia and AD was the primary cause of dementia as it accounted for 60 – 70% dementia cases.[133] AD is a neurodegenerative brain disorder associated with a low level of acetylcholine neurotransmitter either due to reduced synthesis or enzymatic activity of acetylcholinesterase on acetylcholine resulting in memory loss or cognitive impairment.[134] Acetylcholinesterase (AChE) is a hydrolase enzyme that hydrolyzes acetylcholine, which is a major part of central cholinergic pathways in the central nervous system.[135]

About 4 – 8% of elderly people in the world are affected by this disease and females are more prone to the disease.[136-139] Treatment approaches include restraining the acetylcholinesterase enzyme by increasing synaptic levels of acetylcholine. Clinical treatment of AD includes the use of drugs as AChE inhibitors, i.e., rivastigmine, galanthamine, donepezil and tacrine, to name but a few. [140-142] However, some of

these drugs has displayed health complications, for example, tacrine causes liver toxicity.[143]

The increase in mortality rate, complexities in disease and the limited drugs available to cure AD demand new and more effective pharmacological products. Thus, researchers are continuously aiming to find more potent drugs.[144, 145] The substituted imidazole nucleus is famous for a range of therapeutic effects as they have been reported as RAF kinase inhibitors,[146] CSBP kinase inhibitors[147] and orally active 5-lipoxygenase inhibitors,[148] to name but a few. Mutahir and co-workers synthesized a range of 2,4,5-trisubstituted imidazoles and screened them as potential acetylcholinesterase inhibitors.[135] 2-(3-Ethoxy-4-hydroxy)phenyl-4,5-diphenyl-1*H*-imidazole (**Figure 6**) was reported to be the most active in acetylcholinesterase inhibition with IC_{50} value of 102±0.12µM, making it a potential drug candidate for the treatment of AD.

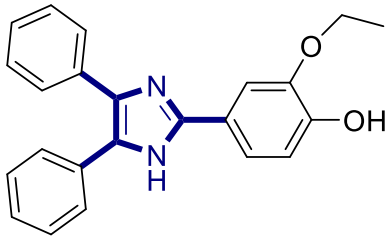
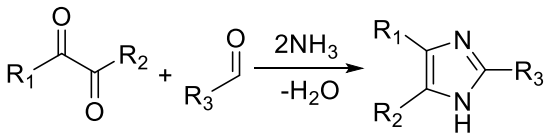


Figure 6: The chemical structure of 2-(3-ethoxy-4-hydroxy)phenyl-4,5-diphenyl-1*H*-imidazole

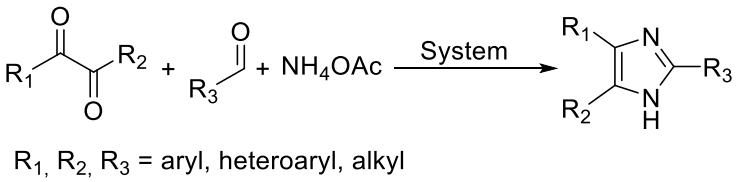
1.6.2. Synthetic routes toward the preparation of 2,4,5-trisubstituted imidazoles

In 1882, Radziszewski reported the first synthesis of 2,4,5-trisubstituted imidazole where a 1,2-diketone, an aldehyde, and ammonia, were coupled. This coupling reaction was a modification of the Debus reaction[149] that was reported back in 1858 by Henrich Debus hence it is known as Debus-Radziszewski reaction (**Scheme 17**).[102]



Scheme 17: The Debus-Radziszewski synthesis of 2,4,5-trisubstituted imidazole

Even though the Debus-Radziszewski reaction produces 2,4,5-trisubstituted imidazoles in quantitative yields, the use of ammonia, a toxic gas, has a detrimental effect to the environment.[150] In addition, handling and stoichiometric measurement of ammonia gas in the laboratory is difficult. However, it was reported that ammonium acetate can decompose to ammonia, and it was then used to replace ammonia in the Debus-Radziszewski imidazole synthesis as it is a solid and can be easily handled and measured. Various systems including transition-metal-based, microwave-assisted, and heterogeneous catalysts have been reported and will be discussed below.

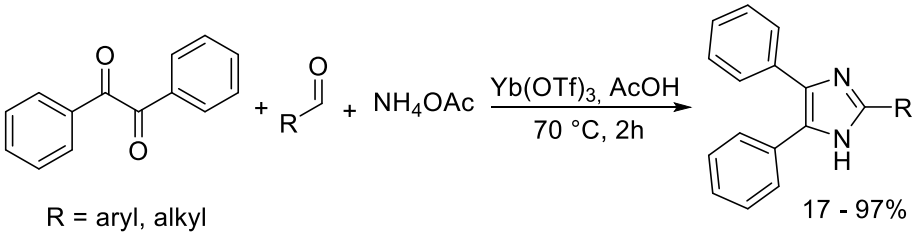


Scheme 18: Coupling reaction between a 1,2-diketone, an aldehyde and ammonium acetate as a modification to the Debus-Radziszewski reaction

1.6.2.1. Metal-Based catalysts

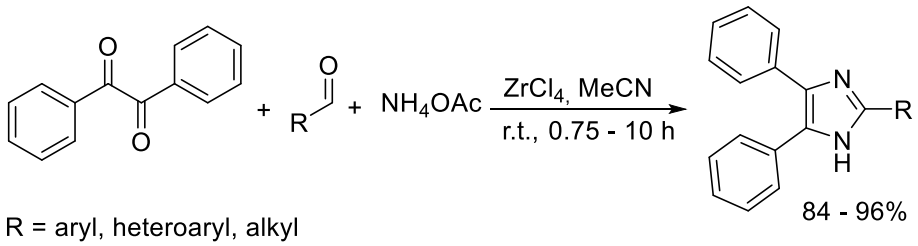
Various documented 2,4,5-trisubstituted imidazole syntheses employ the use of metal catalysts. Wang and co-workers reported the synthesis of 2,4,5-trisubstituted imidazoles from the coupling reaction between benzil, aldehydes and ammonium acetate in the presence of a rare-earth metal, ytterbium (III) triflate in acetic acid

(**Scheme 19**).[151] Both aryl-substituted and aliphatic aldehydes were explored and the corresponding imidazoles were obtained in 17 – 97% yields. This method, however, suffers from the use of rare-earth metal as well as acidic reaction conditions, which is a drawback for acid-sensitive substrates.



Scheme 19: Preparation of 2,4,5-trisubstituted imidazoles using ytterbium (III) triflate

In another study, Sharma and co-workers reported the synthesis of 2,4,5-trisubstituted imidazoles using zirconium (IV) chloride as a catalyst, producing target compounds in excellent yields (84 – 96%) (**Scheme 20**).[152] Although this system displayed efficiency, the use of an expensive metal-based catalyst limits this method.

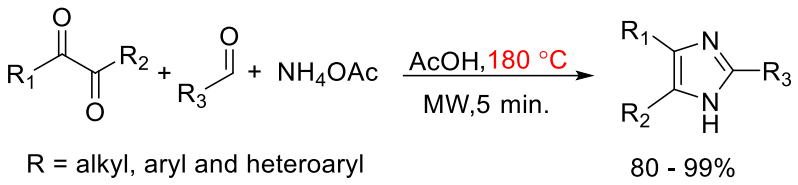


Scheme 20: Preparation of 2,4,5-trisubstituted imidazoles using zirconium (IV) chloride

1.6.2.2. Microwave-Assisted Imidazole Synthesis

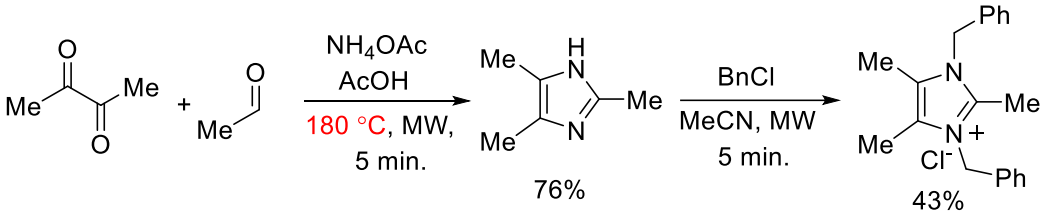
Microwave irradiation is generally applied in synthetic organic chemistry as it is efficient and significantly reduces reaction times compared to conventional heating.[153] Wolkenberg and co-workers reported the preparation of 2,4,5-trisubstituted imidazole from the cyclo-condensation of 1,2-diketone, an aldehyde, and ammonium acetate in

acetic acid at 180 °C under microwave irradiation conditions for 5 minutes.[154] Alkyl-, aryl- and heteroaryl- benzil and aldehyde derivatives were explored where the corresponding imidazoles were obtained in excellent isolated yields (80-99%) (**Scheme 21**).



Scheme 21: Imidazole synthesis in acetic acid under microwave-irradiation conditions

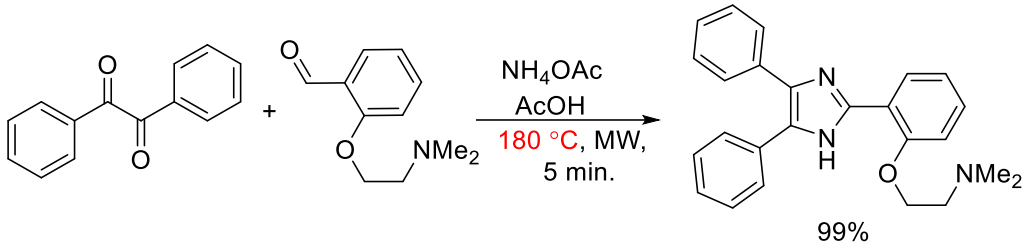
To highlight the utility of their optimized synthesis, the authors synthesized *Lepidiline B* which is an alkaloid that exhibits micromolar cytotoxicity against human cancer cell lines.[155] A cyclocondensation reaction between 2,3-butadione, acetaldehyde and ammonium acetate under optimal conditions was conducted where 2,4,5-trimethyl-1*H*-imidazole was obtained in 76% yield, and was further reacted with benzyl chloride (BnCl) in acetonitrile under MW irradiation resulting in *Lepidiline B* in 43% isolated yield (**Scheme 22**).



Scheme 22: Synthesis of *Lepidiline B* under microwave irradiation conditions

The authors further tested the robustness of their methodology by preparing Trifenagrel, a potent 2,4,5-trisubstituted imidazole arachidonate cyclooxygenase inhibitor that reduces platelet aggregation in various animal species and humans.[156] Its inhibition is 5-12 fold greater than that of aspirin and endomethacin without

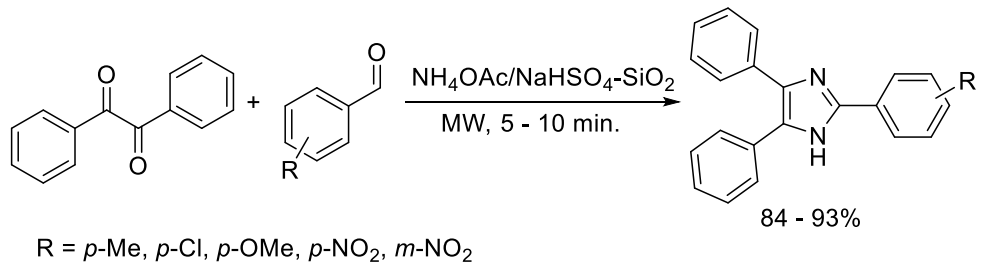
displaying gastric damage associated with typical cyclooxygenase inhibitors.[157] Benzil, 2-(2-dimethylaminoethoxy)benzaldehyde and ammonium acetate were coupled in acetic acid under optimized conditions and Trifenagrel was obtained in isolated yield of 99% (**Scheme 23**).



Scheme 23: Synthesis of Trifenagrel under microwave irradiation conditions

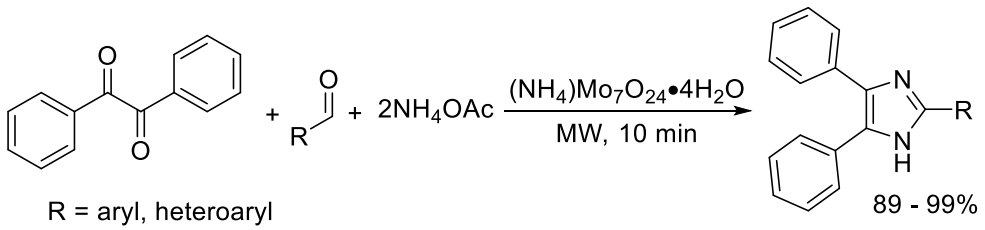
Despite the high yield of the compounds, this procedure utilized a high temperature of 180 °C, which is above the acetic acid boiling point, resulting in a pressurized system which possess a safety concern.

Two years later, Oskooie and co-workers reported the synthesis of 2,4,5-trisubstituted imidazoles where benzils, aldehydes, and ammonium acetate were coupled in the presence of $NaHSO_4$-SiO_2 under microwave irradiation conditions (**Scheme 24**).[158] *Para*-substituted benzaldehyde derivatives bearing electron-donating and electron withdrawing substituents were examined and corresponding imidazoles were obtained in good to excellent yields (84 – 93%). It was observed that the yields were influenced by the electronic effects as electron-donating substituents gave the corresponding imidazoles in higher yields compared to those bearing electron-withdrawing groups.



Scheme 24: Synthesis of 2,4,5-trisubstituted imidazole using of $NaHSO_4$-SiO_2

In 2010, Safari and co-workers explored and reported the molybdenum-based inorganic compound, $(NH_4)_6Mo_7O_{24}•4H_2O$, as a catalyst in the preparation of 2,4,5-trisubstituted imidazoles.[159] In this system, benzil, aldehydes, and ammonium acetate were coupled in the presence of $(NH_4)_6Mo_7O_{24}•4H_2O$ under microwave irradiation conditions (**Scheme 25**).[159] Aryl and heteroaryl aldehydes were explored and the corresponding imidazoles were furnished in excellent 89 – 99% yields. Although this method was highly efficient, some aromatic aldehydes bearing electron-withdrawing and steric groups such as 4-nitrobenzaldehyde and 2,6-dichlorobenzaldehyde were found to be incompatible with this system resulting in no product formation.



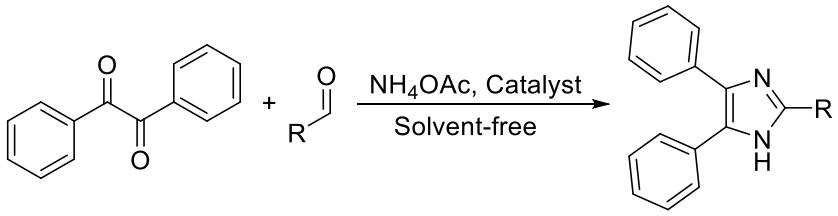
Scheme 25: Synthesis of 2,4,5-trisubstituted imidazoles using $(NH_4)_6Mo_7O_{24}•4H_2O$ under microwave irradiation conditions

1.6.2.3. Heterogeneous catalysts

Heterogeneous catalysis has become strategically vital for efficient and environmentally friendly organic transformation over the past few decades.[160-162] Various heterogeneous catalysts have been employed in 2,4,5-trisubstituted imidazole

synthesis, including benzyltriphenylphosphonium chloride (BTPPC)[163] and ZrO_2-Al_2O_3.[164] In 2013, Mirjalili and co-workers reported the preparation of 2,4,5-trisubstituted imidazoles from 1,2-diketones, substituted aldehydes, and ammonium acetate in the presence of nanosilica-supported tin chloride under neat conditions providing imidazoles in excellent 83 – 95% yields (**Table 1, entry 1**).[165] The use of highly volatile, corrosive Lewis acid (tin tetrachloride) which is difficult to handle[166] in the preparation of the catalyst limits the industrial application of this methodology.[166]

Table 1: Synthesis of 2,4,5-trisubstituted imidazoles using heterogeneous catalysts



Entry	NH_4OAc (mmol)	Catalyst	T (ºC)	Time (minutes)	Yield (%)
1[165]	1	Nano-$SnCl_4$ · SiO_2	130	120	93 – 95
2[167]	2	NanoZrO_2-βcyclodextrin	100	40-55	85 – 98
3[168]	2	Fe_3O_4@SiO_2.HM.SO_3H	110	10-15	82 – 95
4[169]	2	$NiFe_2O_4$@SiO_2 @aminoglucose	r.t.	8-15	90 – 98

Similar work was reported by Shashikanth and co-workers in 2015 where the coupling reaction was catalyzed by ZrO_2-supported β-cyclodextrin nanoparticles at 100 ˚C for

40 – 55 minutes, furnishing the desired imidazoles in excellent yields (85 – 98%) (**Table 1, entry 2**).[167]

Fe_3O_4@SiO_2.HM.SO_3H displayed high efficiency as a catalyst for the coupling of 1,2–diketone, substituted benzaldehydes and ammonium acetate at 110 °C under neat conditions, affording trisubstituted imidazoles in isolated yields in the range of 82 – 95% (**Table 1, entry 3**).[168] In 2018, Fekri and co-workers reported the preparation and characterization of amino-glucose functionalized silica-coated $NiFe_2O_4$ nanoparticles as a heterogeneous catalyst in the synthesis of 2,4,5-trisubstituted imidazole. Benzil, substituted benzaldehydes and ammonium acetate were coupled in the presence of $NiFe_2O_4$@SiO_2@aminoglucose under neat conditions at room temperature in 8-15 minutes providing substituted imidazoles in excellent yields (90 – 98%) (**Table 1, entry 4**).[169]

Despite the efficiency, excellent yields as well as mild reaction conditions displayed by using heterogenous catalytic methodologies, the utilization of commercially unavailable catalysts that has to be prepared under specialized conditions, detracts from this method.

The literature reports on the preparation of 2,4,5-trisubstituted imidazoles from the 1,2–diketones as the starting material are over saturated. While the documented methodologies (*vide supra*) are efficient, they also suffer from one or more of the following shortcomings:

1. Use of transition metals / rare earth metals
2. Acidic media
3. Harsh reaction conditions
4. Tedious work-up procedures

5. Substrate scope limitations

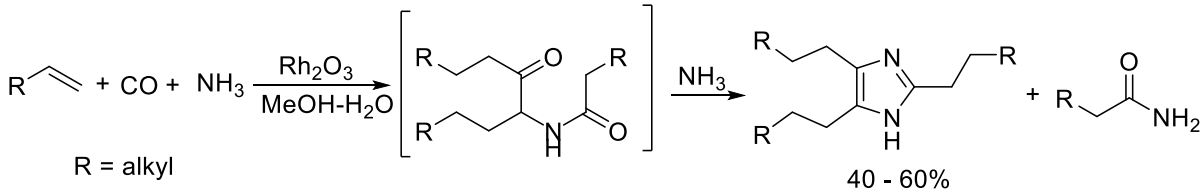
Moreover, some unsymmetrical 1,2-diketones are not commercially available and have to be prepared using harsh reaction conditions and excessive reagents. Consequently, there have been reports of 2,4,5-trisubstituted imidazole synthesis from various starting materials such as α-methylene ketones,[170] alkynes,[171] and alkenes (*vide infra*).

1.7. Synthesis of 2,4,5-trisubstituted imidazoles from alkenes

Few synthetic procedures for the preparation of 2,4,5-trisubstituted imidazoles have been documented commencing from alkenes, yet they are easily accessible and relatively cheap.[81] These methodologies utilize different catalysts such as rhodium oxide, 2-iodoxybenzoic acid (IBX)/iodine, and iron nanocomposite complex, which will be discussed below.

1.7.1. Use of rhodium oxide catalyst

In 1971, Iwashita and Sakuraba reported the preparation of 2,4,5-trisubstituted imidazoles from alkenes, carbon monoxide and ammonia in the presence of rhodium oxide to give 2,4,5-trialkyl imidazole as the major product and an amide as a minor product (**Scheme 26**).[172] The imidazoles synthesized by this method were obtained in fair to moderate yields (40 – 60%). However, this system was not applicable to internal alkenes as cyclohexene reaction only gave the amide and amines as products.[172]

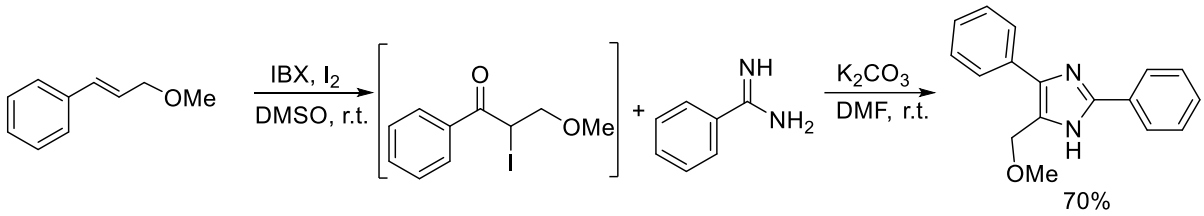


Scheme 26: Imidazole synthesis from alkenes using rhodium oxide

The shortcomings of this method include the occurrence of side-products, substrate scope limitations, the use of an expensive transition metal catalyst, and the use of toxic carbon monoxide.

1.7.2. Use of IBX/iodine

In 2012, Donohoe and co-workers documented the direct preparation of imidazoles from alkenes using the ketoiodination / cyclization method.[173] *(E)*-(3-methoxyprop-1-en-yl)benzene was converted to a ketoiodide using IBX/I_2 in DMSO at room temperature, and the generated ketoiodide was further reacted with benzamidine in DMF in the presence of potassium carbonate for 12 hours giving 5-(methoxymethyl)-2,4-diphenyl-1*H*-imidazole in an isolated yield of 70% (**Scheme 27**).[173]



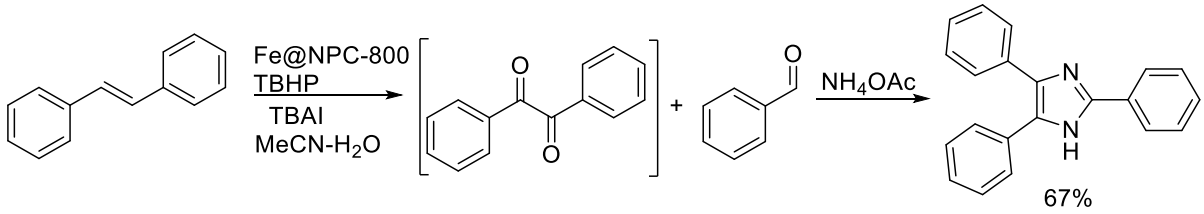
Scheme 27: Synthesis of 5-(methoxymethyl)-2,4-diphenyl-1*H*-imidazole using IBX-I_2/DMSO

There are several drawbacks associated with this system such as the use of a heat and shock-sensitive reagent (IBX), laborious work-up, and only a singular example was explored.

1.7.3. Using iron nanocomposite catalyst

In 2020, Yang and co-workers reported the synthesis of 1,2-diketones from 1,2-diarylethenes using iron nanocomposite catalyst, *tert*-butyl ammonium iodide and *tert*-butyl hydroperoxide in acetonitrile/water media.[174] They highlighted the application of their synthesis by extending their work toward the synthesis of 2,4,5-triphenyl-1*H*-

imidazole and was obtained in a moderate yield of 67% (**Scheme 28**).[174] The use of an iron nanocomposite complex as a catalyst, which is commercially unavailable and prepared under specialized conditions at high temperature, in combination with the use of toxic peroxide (TBHP) limits the widespread application of this method.



Scheme 28: Synthesis of 2,4,5-triphenyl-1*H*-imidazole using iron nanocomposite catalyst

The above-mentioned methodologies do not conform to green chemistry principles as they utilize toxic reagents, harsh reaction conditions, and tedious work-up procedures. Thus, there is still a need for the development of environmentally friendly methodologies towards the preparation of 2,4,5-trisubstituted imidazoles commencing from alkenes that use inexpensive reagents under mild reaction conditions.

1.8. Aims of this study

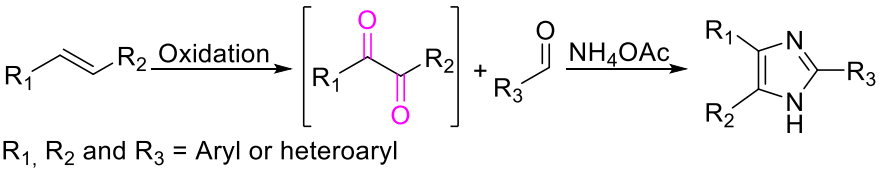
2,4,5-Trisubstituted imidazoles are vital heterocyclic compounds in organic chemistry because they possess versatile biological activities such as antidiabetic, antimalaria and enzyme inhibition (*vide supra)*. A multitude of documented synthetic methodologies toward the preparation of these compounds uses harsh reaction conditions, laborious work-up, expensive, and toxic reagents. In addition, they suffer from substrate and scope limitations.

The main aim of the project was to develop a novel, environmentally benign, simple procedure for the preparation of 2,4,5-trisubstituted imidazoles from internal alkenes using cheap reagents under mild reaction conditions *via* a one-pot multi-component reaction. This would be achieved by the oxidation of alkenes to 1,2-diketones using an environmentally friendly, acid- and metal-free system. The coupling of the *in situ* generated 1,2-diketone with aldehyde and ammonium acetate would furnish the desired 2,4,5-trisubstituted imidazoles. The secondary aim of this project was to conduct a series of control experiments to rationalize the mechanism of the reaction.

CHAPTER 2: RESULTS AND DISCUSSION

2.1. Proposed Synthesis

The preparation of 2,4,5-trisubstituted imidazoles commencing from alkenes has been explored using harsh reaction conditions, expensive catalysts, toxic reagents, and laborious work up.[172-174] Herein, we propose the synthesis of these compounds commencing from alkenes using a suitable system that is simple, metal- and acid-free, environmentally friendly and uses cheap reagents under mild reaction conditions. This study involves the oxidation of alkenes into 1,2-diketones which would then be coupled with aldehydes and ammonium acetate to furnish the desired imidazoles (**Scheme 29**).

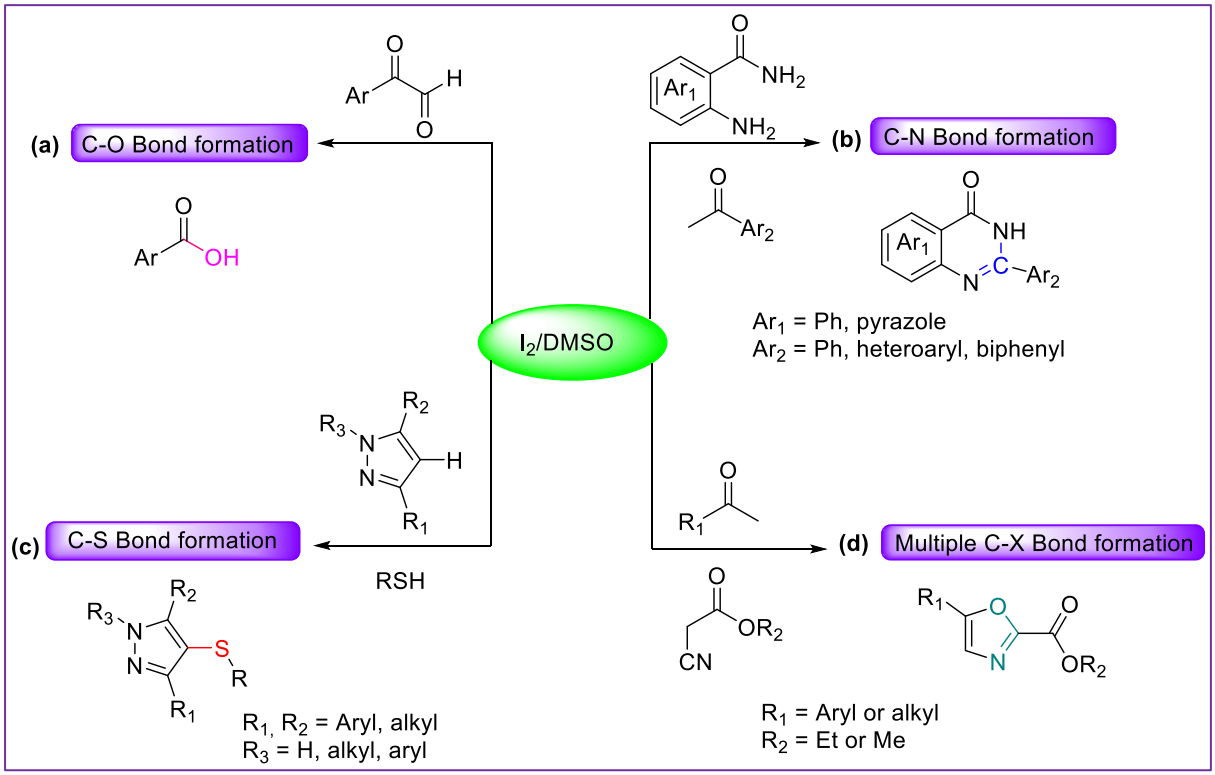


Scheme 29: Proposed 2,4,5-trisubstituted imidazole synthetic route

2.2. The Use of Molecular Iodine and DMSO

The use of molecular iodine has gained a considerable amount of interest in organic syntheses as it is a non-toxic, easy to handle, inexpensive reagent that is insensitive to air and moisture.[175, 176] On the other hand, DMSO is a highly polar, hygroscopic, water miscible solvent that is non-toxic and poses no threat to human health according to the USA Environmental Agency.[177] This reagent can act as a solvent, an oxidant, and an oxygen source in various organic transformations such as the Swern oxidation,[178] Pfitzner-Moffat oxidation,[179] Corey-Chaykovsky epoxidation,[180] to name but a few.

Iodine catalysis in combination with oxidants such as TBHP, H_2O_2, and DMSO has been explored of late owing to the environmental benign and as inexpensive reagents to replace traditionally used toxic metal oxidants.[181] I_2/DMSO, in particular, has emerged as a powerful, ecofriendly, metal-free effective system with diverse applications in synthetic organic chemistry including carbon-carbon and carbon-heteroatom bond formations (**Scheme 30**).[182]



Scheme 30: Applications of I_2/DMSO in organic chemistry; **a)** C-O Bond formation (carboxylic acid); **b)** C-N bond formation (quinazolin-4(3*H*)-one); **c)** C-S Bond formation (C-4 sulfenylated pyrazoles); **d)** Multiple C-X bond formation (oxazoles)

2.2.1. Alkene oxidation to 1,2-diketones

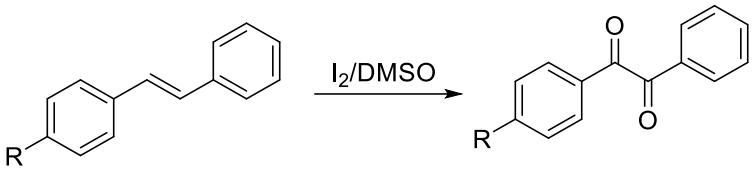
Filimonov and Yusubov reported the synthesis of benzil from *trans*-stilbene using the I_2/DMSO system at 155 °C for 10 hours obtaining benzil in 84% isolated yield (**Scheme**

31).[183] Although the substrate scope was not fully explored, it was clearly visible that I_2/DMSO catalyzes the alkene oxidation.

Scheme 31: *Trans*-stilbene oxidation using an I_2/DMSO system

Four years later, the authors followed up with supplementary studies where the substrate scope was explored. Methyl- (Me), methoxy- (OMe), and chloro- (Cl) substituted stilbenes were oxidized to the corresponding benzil derivatives and the results are displayed in **Table 2**.

Table 2: Oxidation of Stilbenes to benzils with I_2/DMSO[184]



R	Temperature / °C	Time / hr	Yield (%)
H	155	10	85
CH_3	145	25	62
OCH_3	145	9	80
Cl	145	30	83

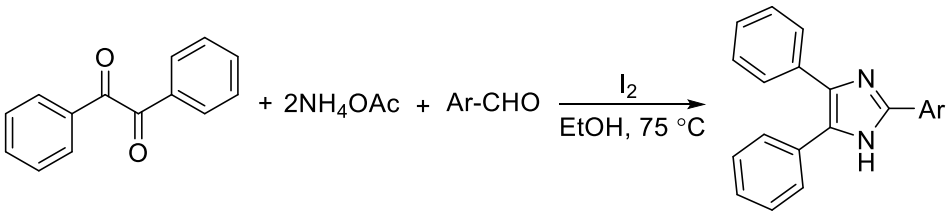
There has been a multitude of reports on the iodine-catalyzed oxidation of internal alkenes to 1,2-diketones including I_2/H_2O mediated[185] and KI-I_2/DMSO systems.[186]

Based on these observations, we hypothesized that 1,2-diketones could be prepared from internal alkenes as the work is well precedented in literature.

2.2.2. 2,4,5-Trisubstituted Imidazole synthesis

Kidwai and co-workers reported the preparation of 2,4,5-trisubstituted imidazoles from the condensation of benzils, aldehydes and ammonium acetate in ethanol in the presence of iodine catalyst at 75 °C for 15 – 25 minutes.[187] Various aldehydes were explored, and the results are summarized in **Table 3**.

Table 3: Synthesis of 2,4,5-trisubstituted imidazoles from benzils using I_2.[187]



Ar	Time/ min	Yield (%)
C_6H_5	15	99
***p*-MeO C_6H_4**	25	99
***o*-OH C_6H_4**	20	97
***p*-Cl C_4H_4**	25	98
***m*-NO_2 C_6H_4**	15	99
2-Thiophenyl	20	97
Piperonal	20	99

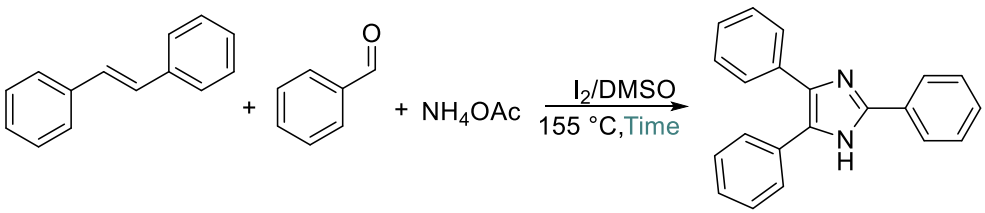
Encouraged by the results obtained by Kidwai and co-workers, we hypothesized that a coupling reaction between 1,2-diketone, an aldehyde and ammonium acetate in the presence of iodine will produce the 2,4,5-trisubstituted imidazoles.

Based on these observations, an optimization study was conducted by monitoring a reaction between *trans*-stilbene, benzaldehyde, and ammonium acetate under various reaction conditions to furnish 2,4,5-trisubstituted imidazoles.

2.3. Optimization Study

2.3.1. One-pot, One-step System

Our study commenced by examining a one-pot, one-step reaction between *trans*-stilbene, benzaldehyde, and ammonium acetate in the presence of iodine in DMSO for 1 hour. Unfortunately, the desired 2,4,5-triphenyl-1*H*-imidazole was not detected and only starting material was recovered (**Scheme 32, entry a**). Since the initial reaction was not successful, we speculated that giving the reactants more time to react would produce different results, hence, we repeated the experiment, except the reaction time was increased to 24 hours, however, the desired product was still not detected (**Scheme 32, entry b**).

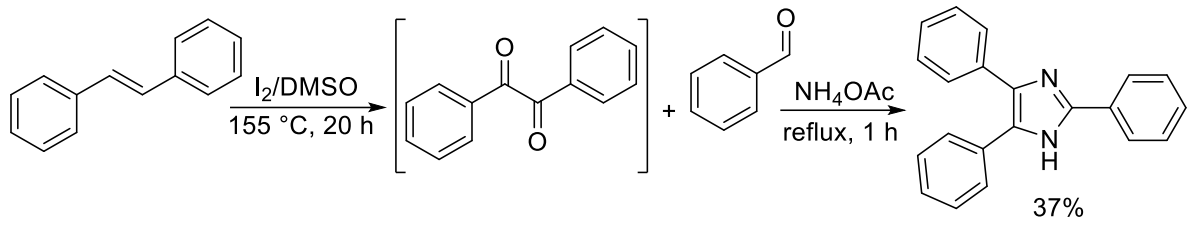


Scheme 32: Attempted one-pot, one-step synthesis of 2,4,5-triphenyl-1*H*-imidazole

2.3.2. One-pot, Two-step System

As the reaction was conducted using a one-pot, one-step process, the desired imidazole was not detected. With these results, we then turned our attention towards a two-step process whereby *trans*-stilbene was oxidized to benzil in the presence of iodine in DMSO at 155 °C for 20 hours. Thereafter, benzaldehyde and ammonium

acetate were added, and the mixture was refluxed for 1 hour, affording the desired product in a moderate but encouraging yield of 37% (**Scheme 33**).



Scheme 33: One-pot, two-step 2,4,5-triphenyl-1*H*-imidazole synthesis

The product was confirmed by ^{1}H NMR spectroscopy using deuterated DMSO as the solvent, in which a key singlet peak resonating around 12.68 ppm due to N-H peak was observed, proving that indeed the cyclization of the 2,4,5-triphenyl-1*H*-imidazole was successful as none of the starting materials have a similar peak. All other aromatic peaks were at the anticipated chemical shifts and integrated for the correct number of protons. (**Figure 7**).

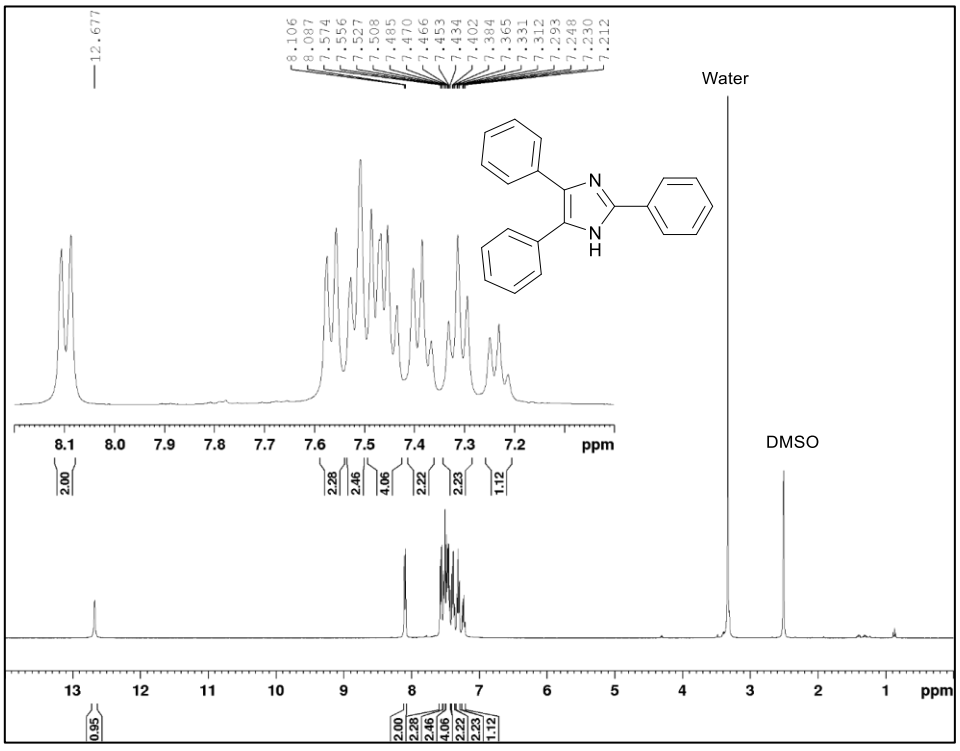


Figure 7: ^{1}H NMR spectrum of 2,4,5-triphenyl-1*H*-imidazole

In addition, the product was further confirmed by ^{13}C NMR spectroscopy which showed carbon atoms of the imidazole ring (C2, C4 and C5) at δ 146.0, 137.6 and 135.7, respectively. Also, other carbon atoms for the phenyl rings were observed in the aromatic region (**Figure 8**).

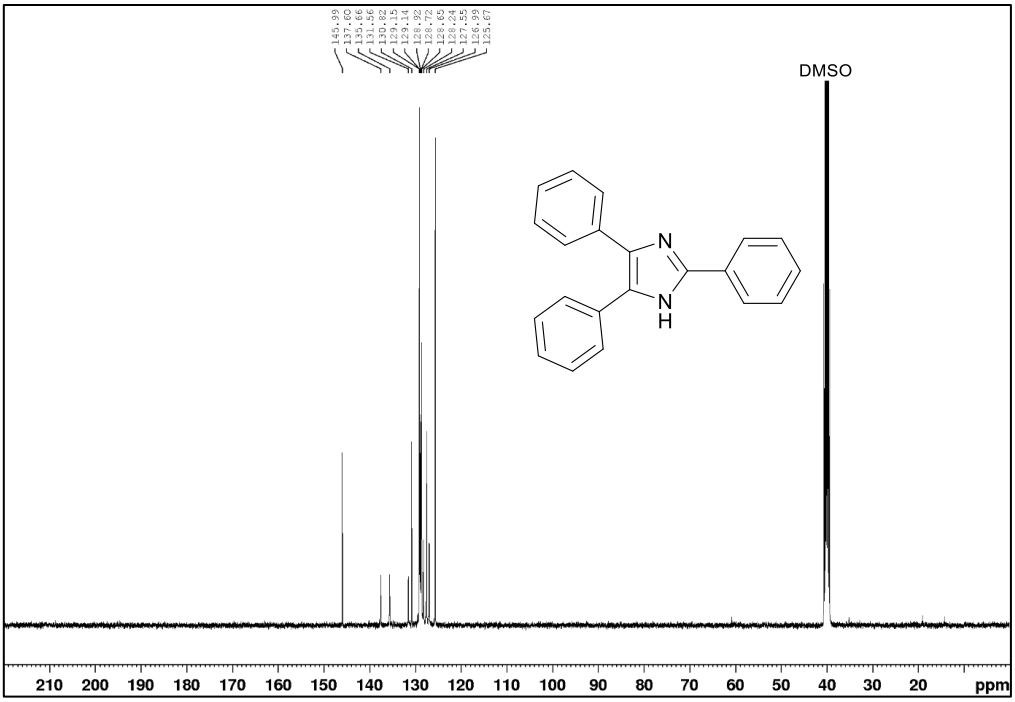


Figure 8: ^{13}C NMR spectrum of 2,4,5-triphenyl-1*H*-imidazole

Low-Resolution Mass Spectroscopy showed the base peak at *m/z* 295.1240 and *m/z* 296.1268 which are $[M-H]^+$ and $[M]^+$ peaks, respectively (**Figure 9**). Infrared spectroscopy confirmed the cyclization of the imidazole ring by showing the N-H bond, C=C, and C=N bond stretches at 3733.8 cm^{-1}, 1592.9 cm^{-1} and 1487.7 cm^{-1}, respectively (**Figure 10**).

In addition, the product had the uncorrected melting point of 269 – 271 °C which is in good agreement with the literature value of 270 – 272 °C.[171] All characterization data (^1H NMR, ^{13}C NMR, LRMS and IR) for the 2,4,5-triphenyl-1*H*-imidazole corresponded with literature.[171] Despite the success of the synthesis of 2,4,5-trisubstituted imidazole,

it was obtained in a moderate yield of 37% and we turned our attention towards improving the yield.

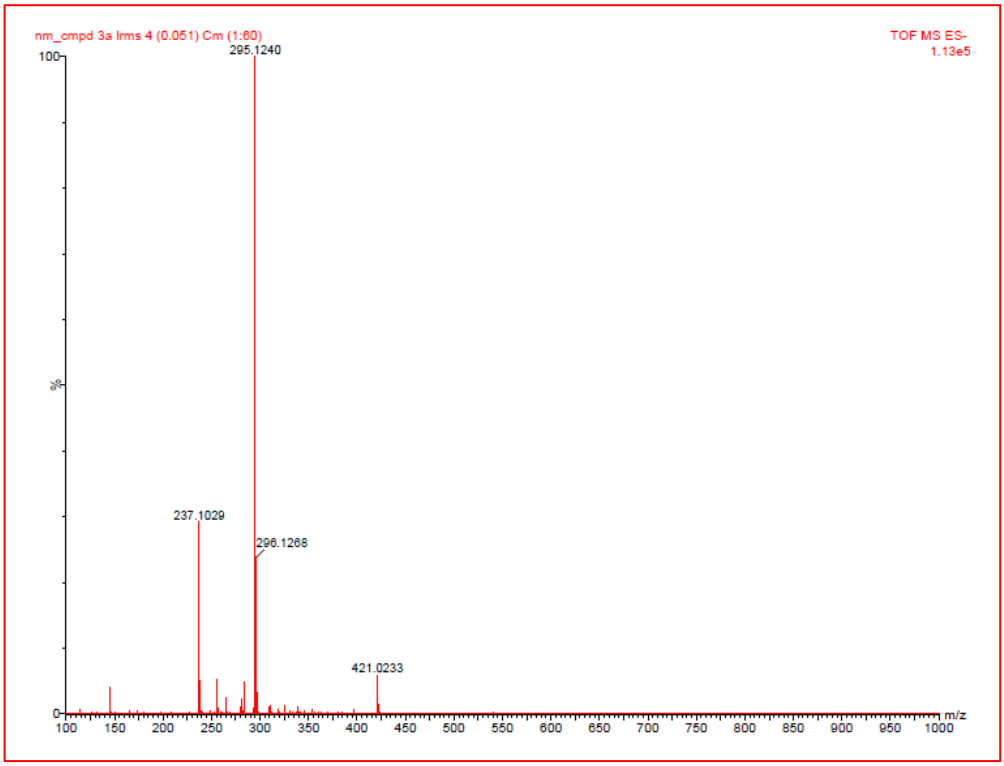


Figure 9: LRMS spectrum for 2,4,5-triphenyl-1*H*-imidazole

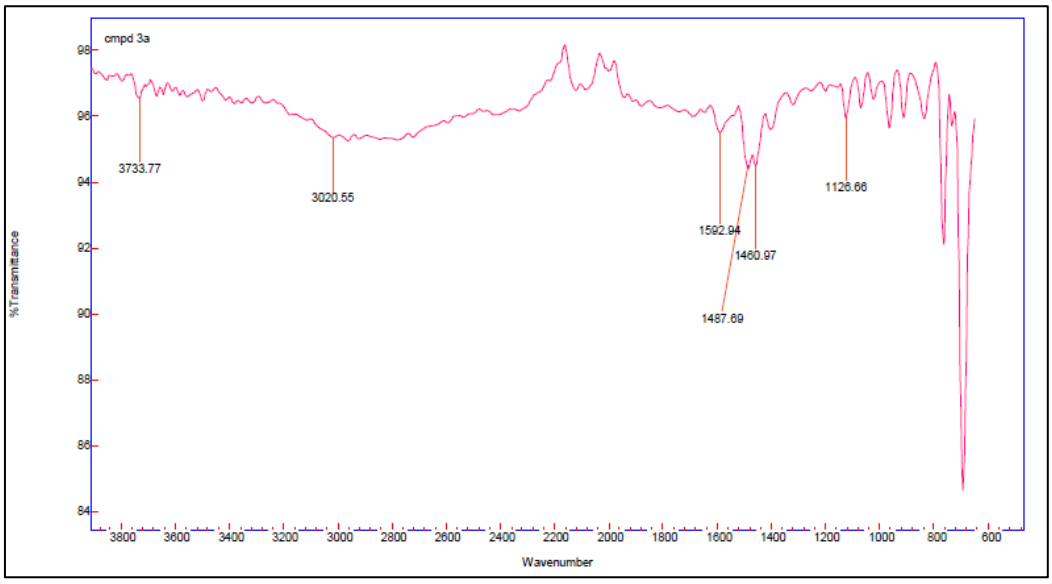
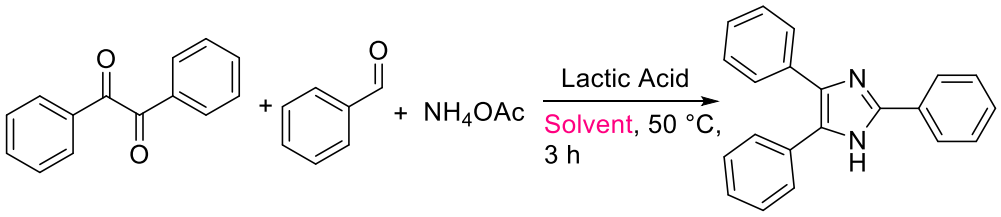


Figure 10: Infrared Spectroscopy for 2,4,5-triphenyl-1*H*-imidazole

2.3.3. Use of different coupling solvents

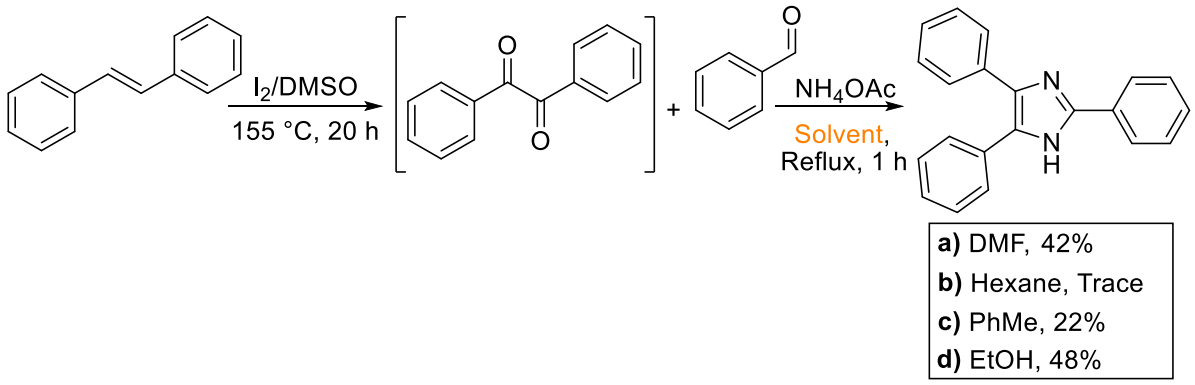
In an effort to improve the yield, we varied coupling solvents as 2,4,5-trisubtituted imidazoles syntheses are known to be solvent specific.[188, 189] This is evident by evaluating the work of Sonar and co-workers where they monitored the effect of solvent on imidazole preparation where a range of solvents (water, acetonitrile, methanol, DMF, DCM, dioxane and ethanol) were examined under the reaction conditions and the results are shown in **Table 4**. Ethanol emerged as the best solvent in their synthesis as the target imidazole was obtained in 55% yield **(Table 4, entry 7)**.

Table 4: Effect of solvent on 2,4,5-trisubstituted imidazole synthesis.[190]



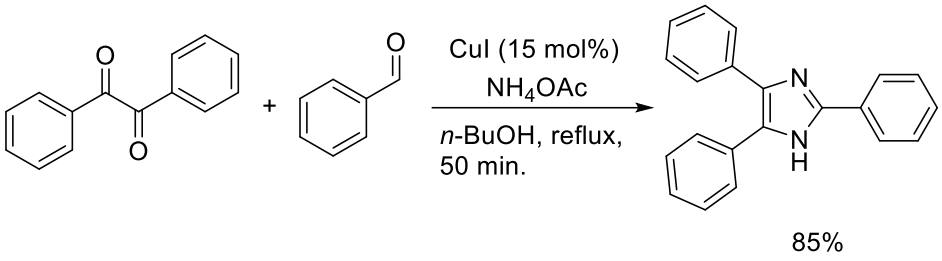
Entry	Solvent	Yield (%)
1	Water	37
2	Acetonitrile	30
3	Methanol	42
4	DMF	45
5	DCM	20
6	Dioxane	32
7	Ethanol	55

As seen above, the choice of solvent has a significant influence on imidazole synthesis, we then explored a range of polar and non-polar organic solvents in an attempt to increase the yield. The first solvent that was examined was the polar aprotic solvent, DMF, which produced the target compound in 42% (**Scheme 34, entry a**). The long chain solvent, hexane, was also explored under the same reaction conditions and the target compound was obtained in trace amounts as detected by ^{1}H NMR (**Scheme 34, entry b**). A high boiling solvent, toluene, was examined and the target compound was obtained in moderate yield of 22% (**Scheme 34, entry c**). Alcoholic solvents are known to favour the coupling of benzil, benzaldehyde and ammonium acetate,[191] and with this information in mind, we explored the use of ethanol as a solvent and under these conditions, 2,4,5-triphenyl-1*H*-imidazole was obtained in a 48% isolated yield (**Scheme 34, entry d**).



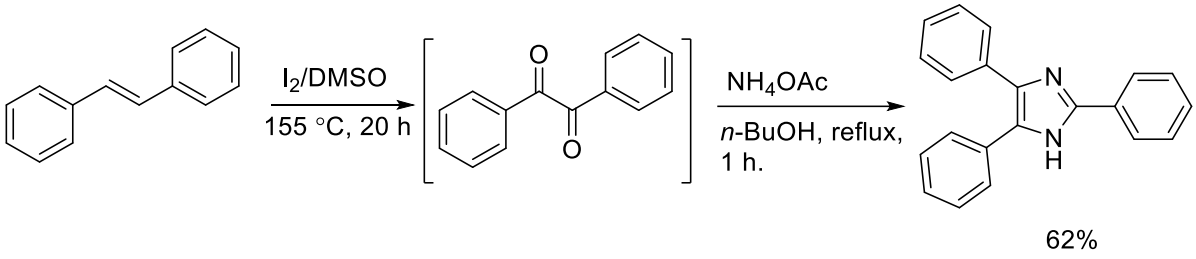
Scheme 34: Synthesis of 2,4,5-triphenyl-1*H*-imidazole in various organic solvents

Recently, Kadu and co-workers reported *n*-butanol as the best solvent for the similar cyclocondensation of benzil, benzaldehyde and ammonium acetate in the presence of a cuprous iodide catalyst affording 2,4,5-triphenyl-1*H*-imidazole in an isolated yield of 85% (**Scheme 35)**.[192]



Scheme 35: Synthesis of 2,4,5-triphenyl-1*H*-imidazole in butanol in the presence of cuprous iodide

With this information, we attempted to employ *n*-butanol as a solvent in the coupling of benzil, benzaldehyde and ammonium acetate and the desired product was obtained in 62% isolated yield (**Scheme 36**). As *n*-butanol provided a higher yield for the target compound compared to other solvents, it was then chosen as an ideal coupling solvent for subsequent reactions.

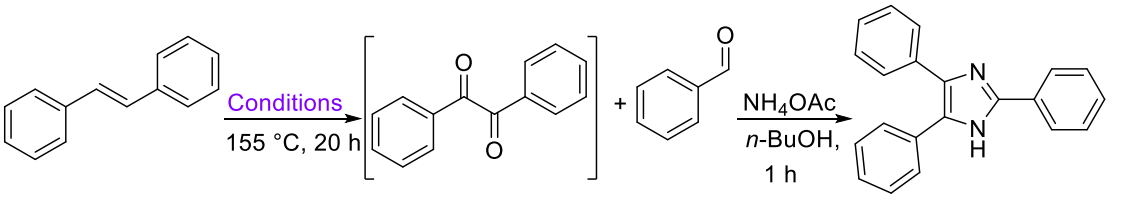


Scheme 36: Synthesis of 2,4,5-triphenyl-1*H*-imidazole using *n*-butanol as a solvent

2.3.4. Catalyst loading

To find the optimal catalyst loading, the reactions were conducted using various quantities of iodine and DMSO to monitor its effect on the reaction. The use of 1 equivalent of iodine in 1 mL of DMSO afforded the desired product in an isolated yield of 65% (**Scheme 37, entry a**). A slight increase to 1.25 equivalents of iodine in 0.5 mL DMSO afforded the desired product in an isolated yield of 85% (**Scheme 37, entry b**). A decrease in yield was observed when iodine quantity was increased to 1.5

equivalents, as well as when the DMSO volume was increased to 1.5 mL (**Scheme 37, entries c and d**). Further increase of both the iodine quantity (2 equivalents) and DMSO volume (2 mL) resulted in no reaction, as the 2,4,5-triphenyl-1*H*-imidazole was not obtained and only the starting material was recovered (**Scheme 37, entry e**). It was observed that the amounts of iodine and DMSO affects the reaction which is presumably due to DMSO playing multiple roles in the system as an oxygen source and reaction medium (*vide supra*).

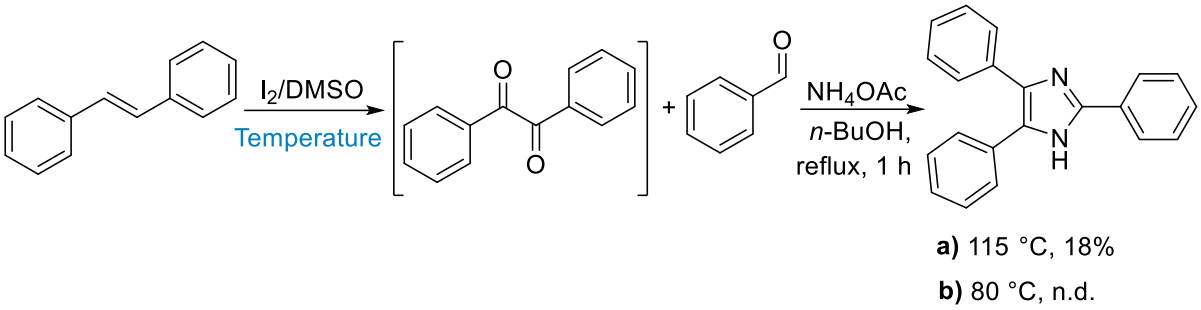


a) I_2 (1 equiv.)/DMSO (1 mL),65%
b) I_2 (1.25 equiv.)/DMSO (0.5 mL), 85%
c) I_2 (1.5 equiv.)/DMSO (0.5 mL), 58%
d) I_2 (1.5 equiv.)/DMSO (1.5 mL), 38%
e) I_2 (2 equiv.)/DMSO (2 mL), n.d.

Scheme 37: Synthesis of 2,4,5-triphenyl-1*H*-imidazole using varying quantities of iodine and DMSO volumes

2.3.5. Influence of Temperature

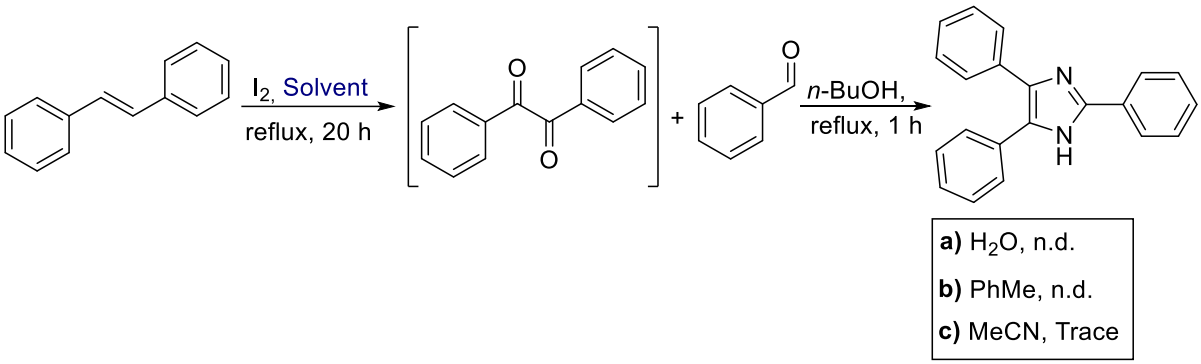
Next, we sought to probe the effect of temperature in the current system where we conducted the model reaction using lower temperatures. We attempted to decrease the step I temperature to 115 °C for 24 hours but the desired product was obtained in a diminished yield of 18% (**Scheme 38, entry a**). A further decrease in temperature to 80 °C for the same reaction time (24 hours) resulted in no reaction as the desired imidazole was not obtained and only the starting material was recovered (**Scheme 38, entry b**). This suggested that the temperature of 155 °C is essential for this system, thus, for subsequent reactions it was used as the optimal temperature.



Scheme 38: Attempted synthesis of imidazole in decreased reaction temperatures

2.3.6. Iodine coupling partner

Iodine catalysis in combination with various solvents has been reported,[193] and we sought to probe the effect of DMSO in the system where a non-polar solvent (PhMe), polar protic (H_2O) and polar aprotic (MeCN) were explored as iodine coupling partners. Unfortunately, no product was obtained when toluene and water were used (**Scheme 39, entries a and b**), and only trace amounts were obtained when acetonitrile was used (**Scheme 39, entry c**).



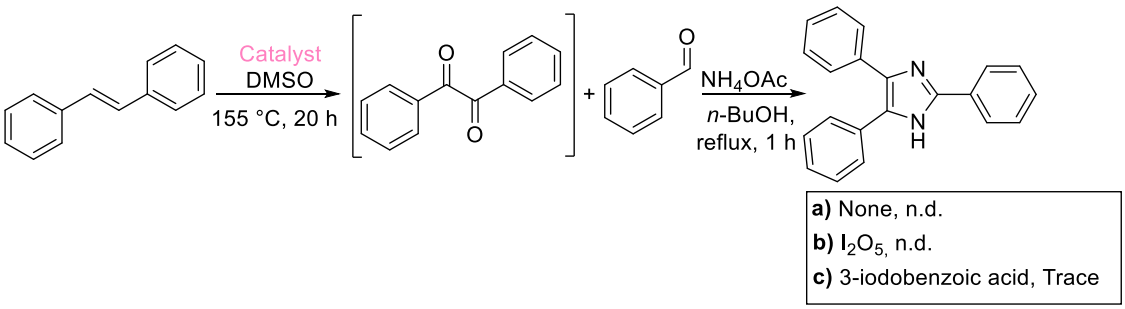
Scheme 39: Attempted imidazole synthesis using different solvents as iodine-coupling partners

This suggests that DMSO is an ideal coupling partner for iodine, and it is essential for this reaction as in its absence, the desired product was not detected. Thus, for subsequent reactions, DMSO was chosen as the iodine coupling partner.

2.3.7. Iodine Source

Our next step was to investigate the suitability of iodine in the developed reaction system. Our studies commenced by conducting the test reaction in the absence of iodine and no desired product was detected (**Scheme 40, entry a**). This implied that an iodine catalyst is essential for this system as in its absence, no product was formed.

We then turned our attention towards finding the best iodine source where other iodine-containing non-metals such as iodopentoxide (I_2O_5) and 3-iodobenzoic acid, were explored. No reaction occurred when I_2O_5 was used (**Scheme 40, entry b**), and only trace amounts of 2,4,5-triphenyl-1*H*-imidazole were obtained when 3-iodobenzoic acid was used (**Scheme 40, entry c**). This suggested that molecular iodine was the best source of iodine and essential for this synthesis as in its absence no product was obtained.



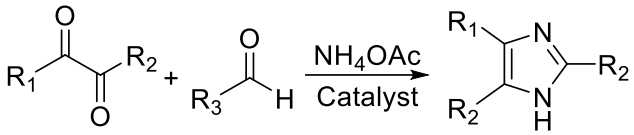
Scheme 40: Attempted synthesis of 2,4,5-triphenyl-1*H*-imidazole using different iodine sources

2.3.8. Amount of ammonium acetate

The documented 2,4,5-trisubstituted imidazole syntheses uses fluctuating amounts of ammonium acetate, for example, Ghogare and co-workers[194] reported the synthesis of imidazoles using two equivalents of ammonium acetate and the target compounds were obtained in 87 – 90% yields (**Table 5, entry 1**).

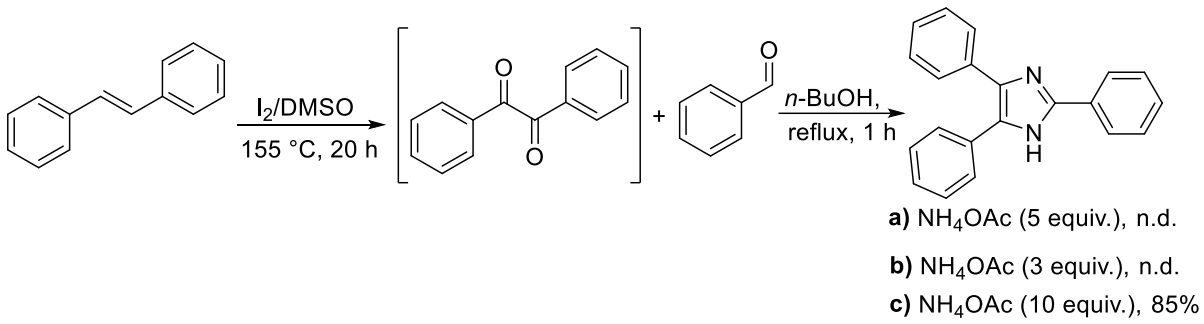
Ahmed and Hanoon[195] reported the imidazole preparation using three equivalents of ammonium acetate in which the products were obtained in 82 – 98% (**Table 5, entry 2**). On the other hand, Wang and co-workers[196] documented the synthetic methodology towards the preparation of imidazoles using six equivalents of ammonium acetate providing the target compounds in 78 – 98% yields (**Table 5, entries 3**).

Table 5: Use of various ammonium acetate equivalents in imidazole synthesis



Entry	Catalyst	Equivalents of NH_4OAc	Yields (%)
1	Mandelic acid	2	87 – 90
2	[{(IMC)-4-OMBH} BIM][HSO_4]$_3$	3	82 – 98
3	—	6	78 – 98

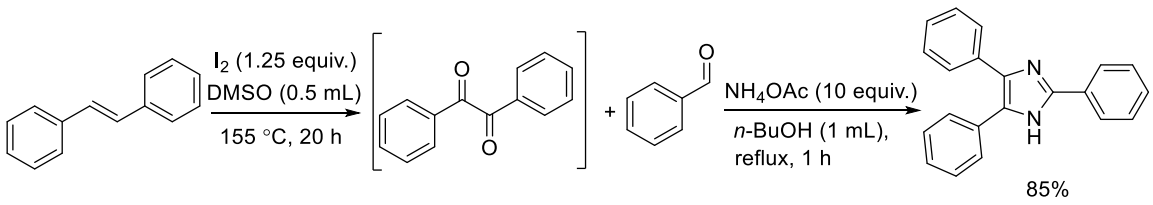
Thus, to complete this study we varied the amount of ammonium acetate, and no product was detected when five equivalents were used (**Scheme 41, entry a)**. A further decrease in ammonium acetate to three equivalents also resulted in no product formation (**Scheme 41, entry b**). Hence, ten equivalents were found to be optimal for imidazole preparation and used in our library synthesis.



Scheme 41: Attempted synthesis of triphenyl-1*H* imidazole using different amounts of ammonium acetate

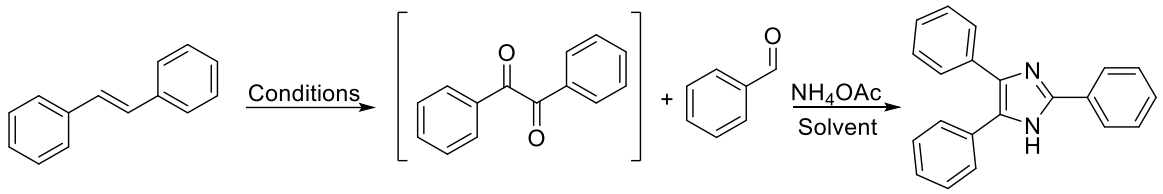
2.3.9. Optimized System

Upon completion of the optimization study, the influence of coupling solvents, catalyst loading, temperature, iodine coupling partner, iodine source and amount of ammonium acetate were investigated. The optimal conditions were found to be as per **Scheme 42**, with the target imidazole formed in 85% yield. The summary of the optimization study results is shown in **Table 6** and the optimized reaction conditions are highlighted in **entry 10**.



Scheme 42: Optimal reaction conditions.

Table 6: Optimization reaction conditions for the formation of 2,4,5 triphenylimidazole from *trans*-stilbene and benzaldehyde.[a]



Entry	Conditions	Solvent	Yield (%)[b]
1[c]	I_2/DMSO	–	N. R
2[d]	I_2/DMSO	–	N. R
3	I_2/DMSO	–	37
4	I_2/DMSO	DMF	42
5	I_2/DMSO	Hexane	Trace
6	I_2/DMSO	PhMe	22
7	I_2/DMSO	EtOH	48
8[e]	I_2/DMSO	*n*-BuOH	62
9[f]	I_2/DMSO	*n*-BuOH	65
10	I_2/DMSO	*n*-BuOH	85
11[g]	I_2/DMSO	*n*-BuOH	58
12[h]	I_2/DMSO	*n*-BuOH	38
13[i]	I_2/DMSO	*n*-BuOH	N. R
14[j]	I_2/DMSO	*n*-BuOH	18
15[k]	I_2/DMSO	*n*-BuOH	N. R
16[l]	I_2/PhMe	*n*-BuOH	N. R
17[m]	I_2/H_2O	*n*-BuOH	N. R
18[n]	I_2/MeCN	*n*-BuOH	Trace
19[o]	DMSO	*n*-BuOH	N. R
20	I_2O_5/DMSO	*n*-BuOH	N. R
21	3-Iodobenzoic Acid/DMSO	*n*-BuOH	Trace
22[p]	I_2/DMSO	*n*-BuOH	N. R
23[q]	I_2/DMSO	*n*-BuOH	N. R

[a] Reaction conditions: Step 1: **1a** (0.5 mmol), I_2/DMSO (0.5 mL), 20 h, 155 °C. Step 2: **2a** (0.5 mmol), NH_4OAc (10 equiv.), Solvent (2 mL), reflux, 1 h. [b] Isolated yield. [c] One pot, One step

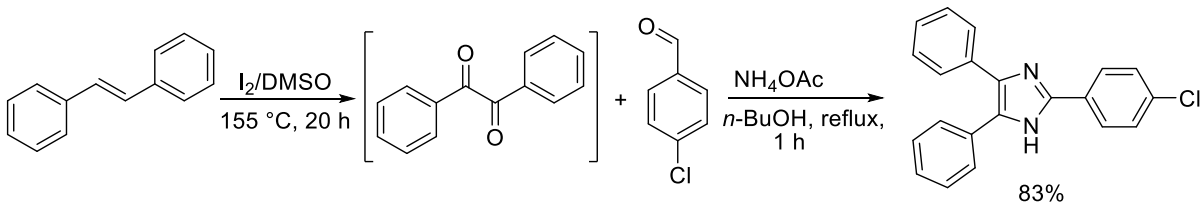
for 1 h. [d] One pot, one step for 24 h. [e] I_2 (1 equiv.)/DMSO (0.5 mL). [f] I_2 (1 equiv.)/DMSO (1 mL). [g] I_2 (1.5 equiv.)/DMSO (0.5 mL). [h] I_2 (1.5 equiv.)/DMSO (1.5 mL). [i] I_2 (2 equiv.)/DMSO (2 mL). [j] Step 1 for 24 h, 115 ˚C. [k] Step 1 at 80 ˚C. [l] Step 1 reflux. [m] Step 1 reflux. [n] Step1 reflux. [o] Absence of Molecular Iodine. [p] NH_4OAc (5 equiv.). [q] NH_4OAc (3 equiv.) N. R: No reaction.

2.4. Library Synthesis

With the optimized reaction conditions at hand, the substrate scope and limitations for this system was explored by varying substituted internal alkenes against various aromatic aldehydes to prepare 2,4,5-trisubstituted imidazoles. For discussion purposes, **only selected spectra** will be discussed, and full characterization of all the synthesized compounds has been provided in the experimental section, while copies of spectra are attached as an electronic copy.

2.4.1. Variation of *para*-substituted aldehydes

We began the library synthesis by varying benzaldehyde derivatives that were *para*-substituted bearing electron-withdrawing groups. When 4-chlorobenzaldehyde was used, the corresponding product, 2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole, was obtained in a good yield of 83% (**Scheme 43**).



Scheme 43: Synthesis of 2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole

This product was confirmed with ^{1}H NMR Spectroscopy (**Figure 11**) which displayed a singlet peak around 12.77 ppm due to the N-H signal confirming the formation of the imidazole ring. The aromatic protons in the region 8.12-7.22 ppm were also observed

which were in accordance with literature.[197] All the characterization data (^{13}C NMR, LRMS, IR and melting point) were also in good agreement with literature.[197]

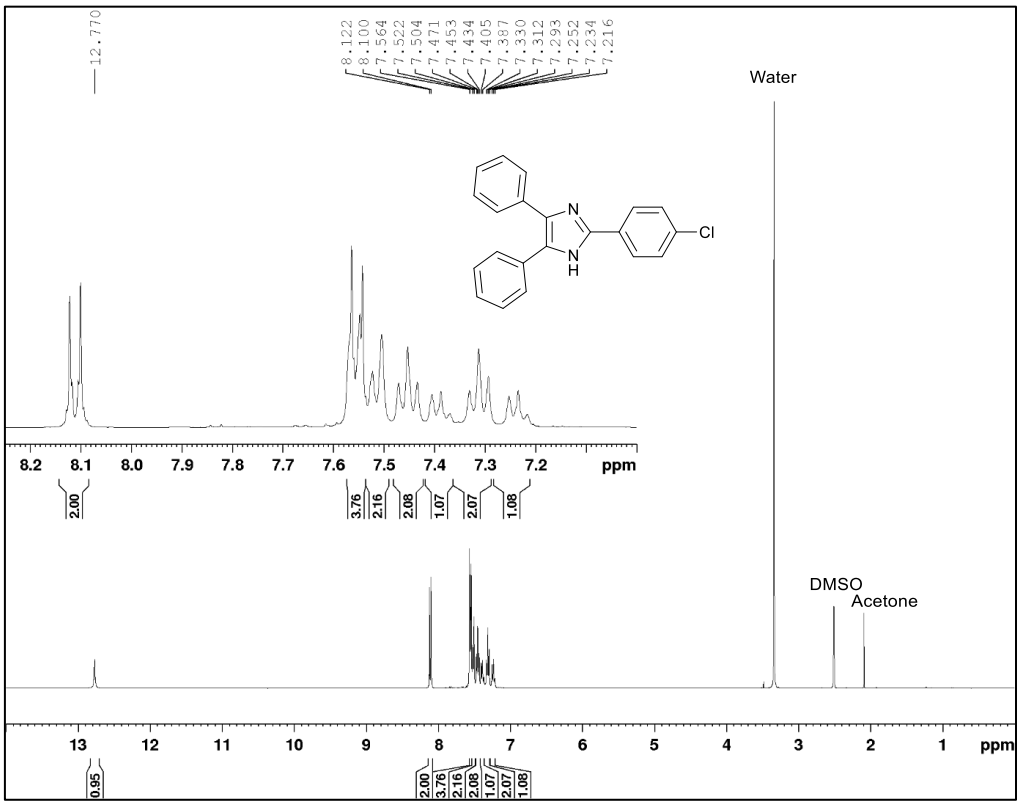
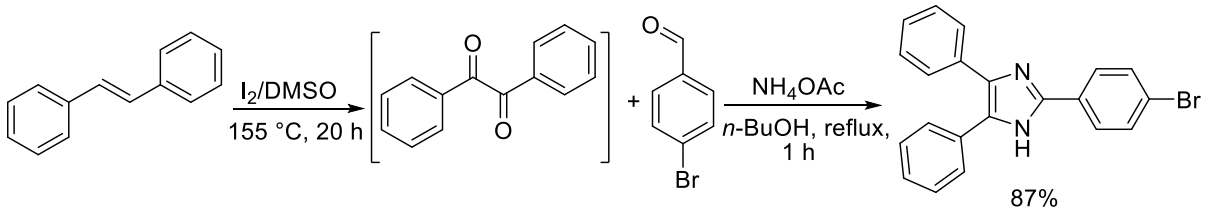


Figure 11: ^{1}H NMR spectrum of 2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole.

The study was extended to the use of 4-bromobenzaldehyde in which the product, 2-(4-bromophenyl)-4,5-diphenyl-1*H*-imidazole, was obtained in a good, isolated 87% yield (**Scheme 44**). The product was confirmed with Low-Resolution Mass Spectrometry (**Figure 12)** which showed the base peak at *m/z* 375.0323 $[M+H]^+$, which is in good agreement with literature.[198]



Scheme 44: Synthesis of 2-(4-bromophenyl)-4,5-diphenyl-1*H*-imidazole

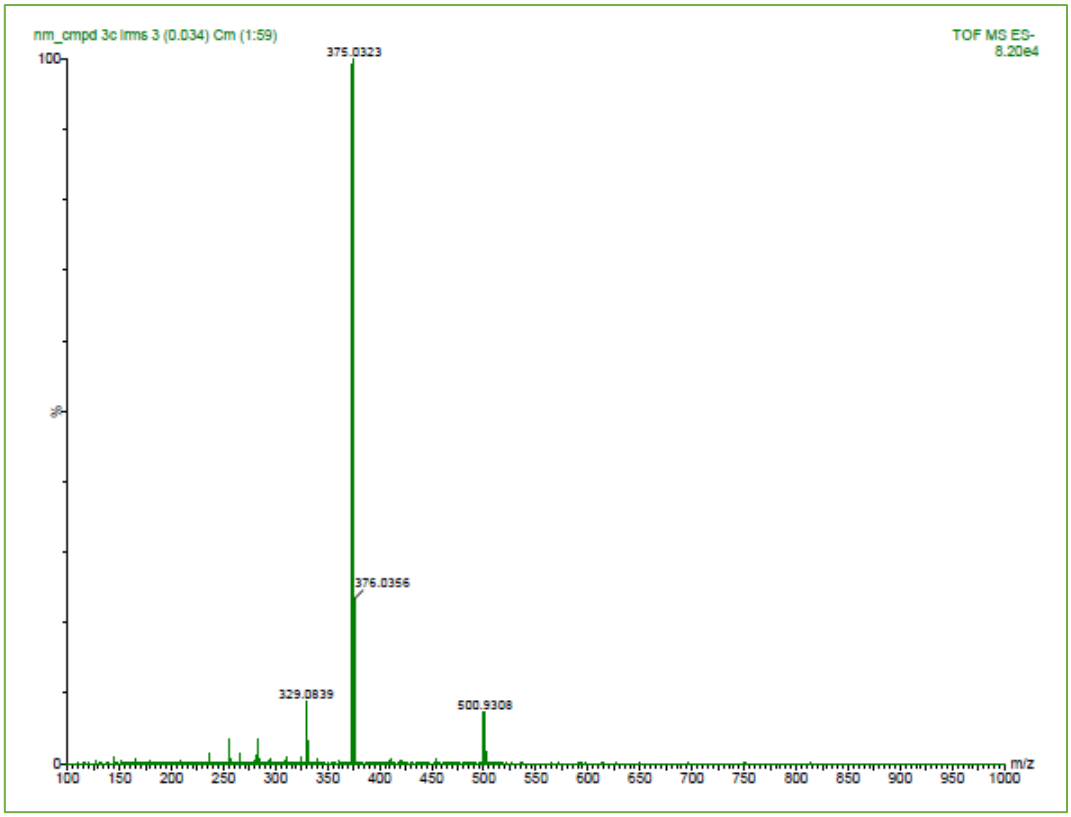
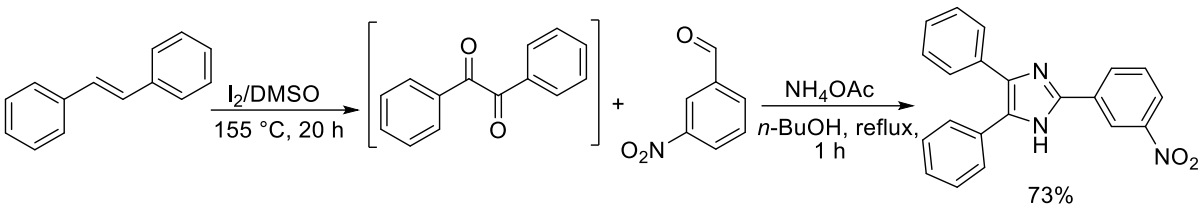


Figure 12: LRMS of 2-(4-bromophenyl)-4,5-diphenyl-1*H*-imidazole

The cross-coupling reaction of *para*-substituted 4-chloro and 4-bromobenzaldehyde appeared favourable producing the desired imidazoles in good 83% and 87% yields, respectively. Encouraged by these results, we extended the scope towards investigating the effect of *meta*-substituted benzaldehyde derivatives.

2.4.2. Variation of *meta*-substituted aldehydes

Next, benzaldehyde derivatives that are *meta*-substituted bearing electron withdrawing groups were explored. When 3-nitrobenzaldehyde was used, the corresponding product, 2-(3-nitrophenyl)-4,5-diphenyl-1*H*-imidazole was obtained in an isolated yield of 73% (**Scheme 45**).



Scheme 45: Synthesis of 2-(3-nitrophenyl)-4,5-diphenyl-1*H*-imidazole

The product was confirmed by the ^{1}H NMR spectroscopy (**Figure 13**) whereby a singlet key peak resonating at 13.08 ppm, is assigned to the N-H signal, indicating complete cyclization of the imidazole ring.[197]

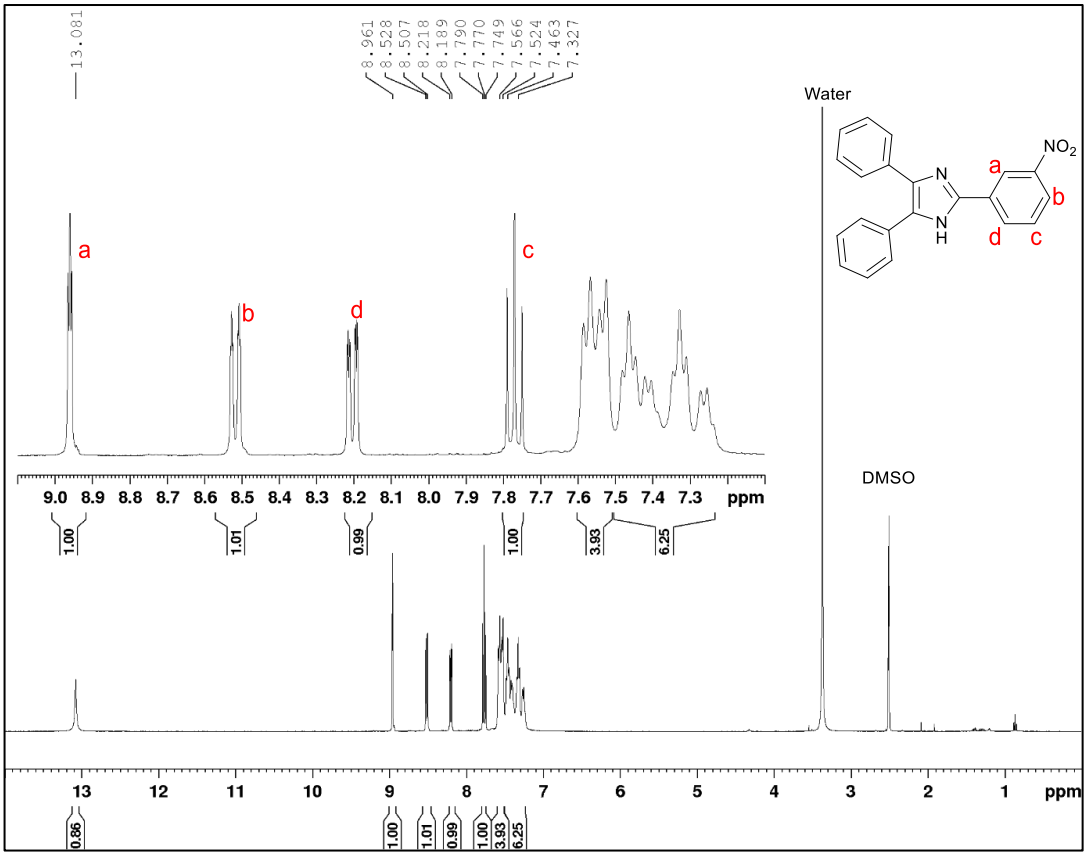
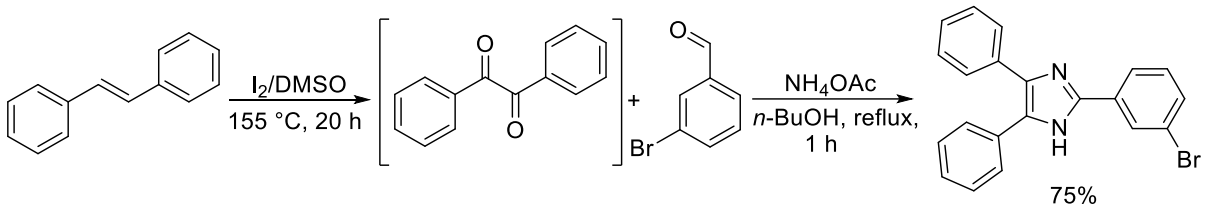


Figure 13: ^{1}H NMR spectrum of 2-(3-nitrophenyl)-4,5-diphenyl-1*H*-imidazole

When 3-bromobenzaldehdye was used, the corresponding product, 2-(3-bromophenyl)-4,5-diphenyl-1*H*-imidazole was obtained in an isolated yield of 75% (**Scheme 46**) where the molecular mass was confirmed by the High-Resolution-Mass

Spectrometry with the experimental mass *m/z* 375.0492 and the calculated mass *m/z* 375.0497 $[M+H]^+$. The spectrum displayed two base peaks *m/z* 375.0492 and *m/z* 377.0478 due to bromine having two isotopes (^{79}Br and ^{81}Br, respectively) (**Figure 14**).



Scheme 46: Synthesis of 2-(3-bromophenyl)-4,5-diphenyl-1*H*-imidazole

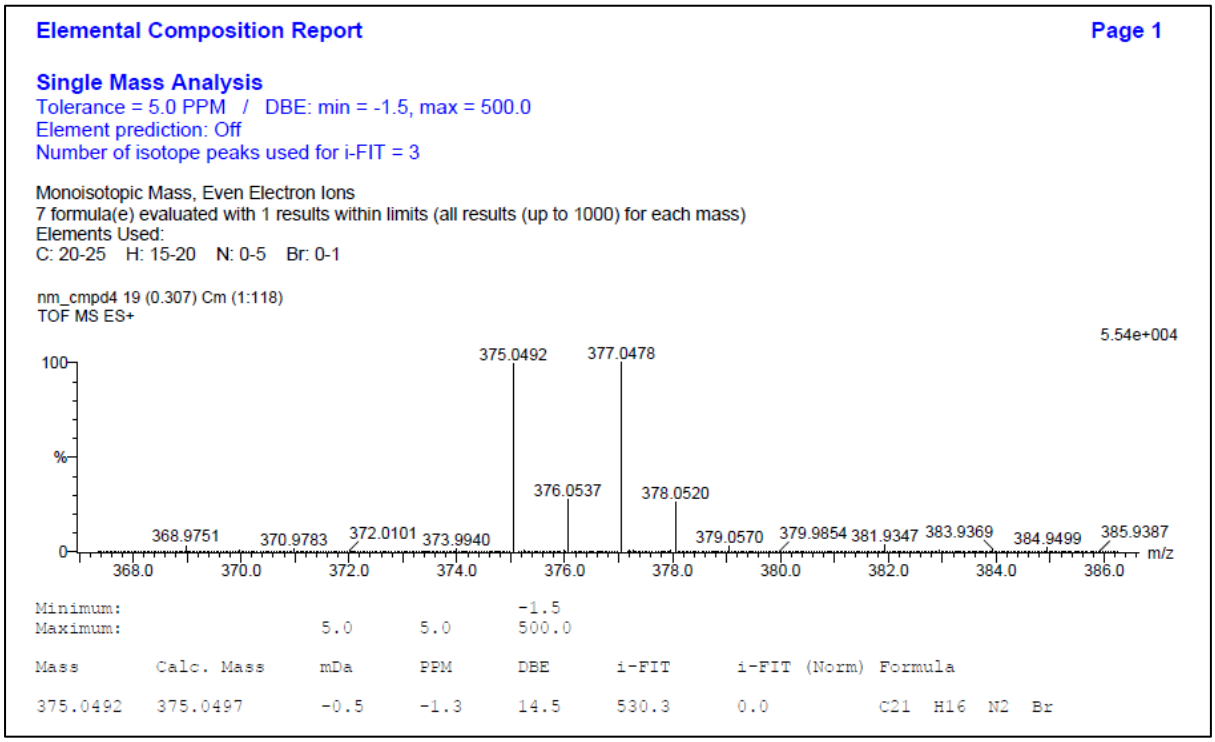
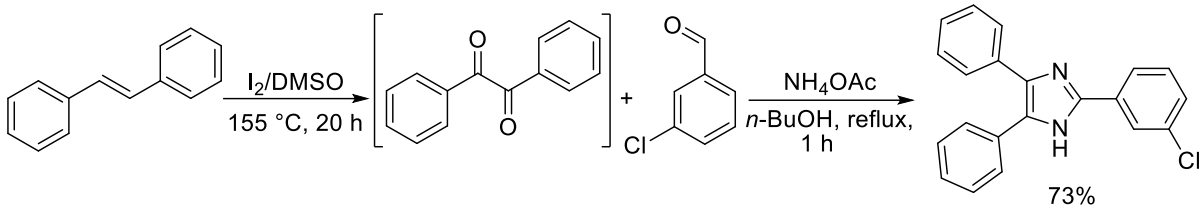


Figure 14: HRMS of 2-(3-bromophenyl)-4,5-diphenyl-1*H*-imidazole

The coupling reaction of 3-chlorobenzaldehyde afforded the corresponding 2-(3-chlorophenyl)-4,5-diphenyl-1*H*-imidazole product in 73% isolated yield (**Scheme 47**). This compound was confirmed using Infrared spectroscopy showing an N-H bond stretching frequency at 3376.7 cm^{-1} indicative of a successful cyclization of the

imidazole ring. The spectrum also showed stretching bands at 1579.6 and 1455.4 cm $^{-1}$ which was assigned to C=C. A stretching band appearing at 1129.3 cm^{-1} was assigned to C-Cl bond stretching (**Figure 15**), thus corresponding to the literature.[199]



Scheme 47: Synthesis of 2-(3-chlorophenyl)-4,5-diphenyl-1*H*-imidazole

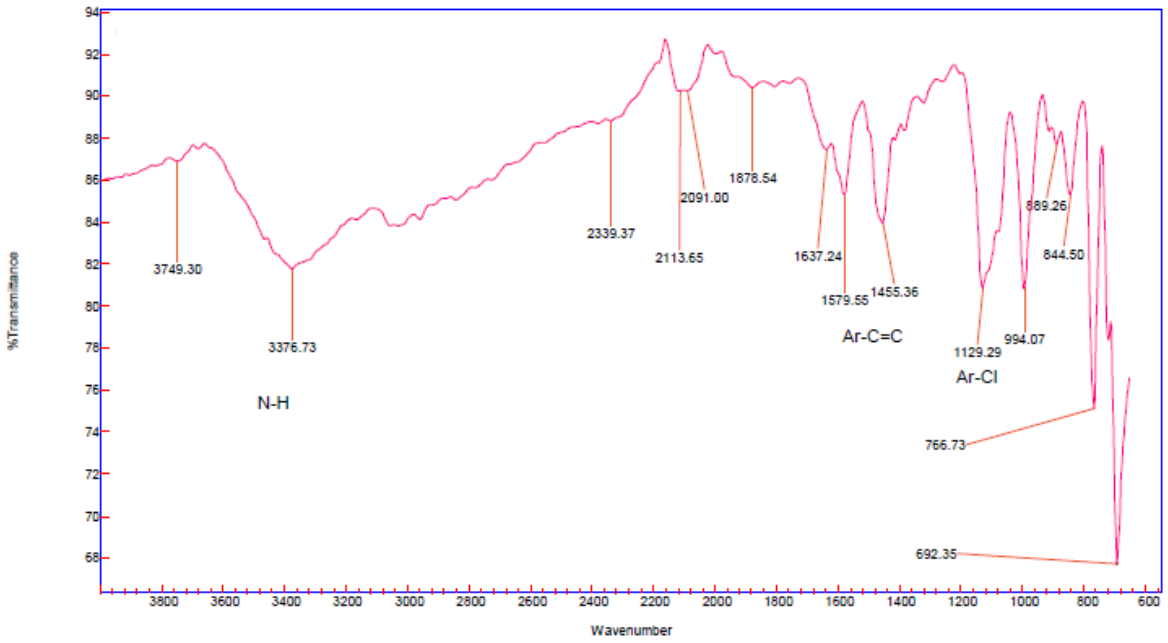
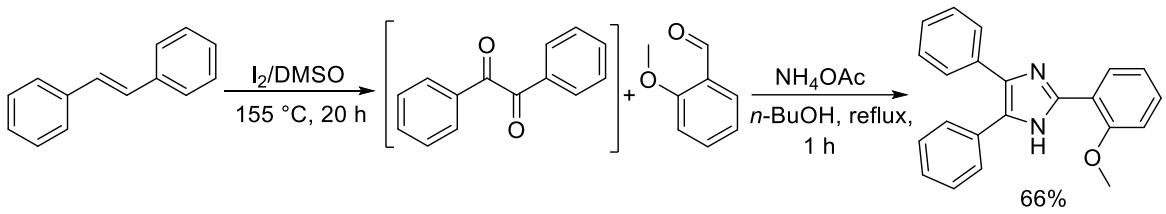


Figure 15: Infrared spectrum of 2-(3-chlorophenyl)-4,5-diphenyl-1*H*-imidazole

In summary, it was noted that the *meta*-substituted aldehyde derivatives bearing electron withdrawing groups produced the corresponding imidazoles in good yields of 73 – 75%. There was a slight decrease in yields when compared to those obtained when *para*-substituted derivatives were used. Next, the suitability of benzaldehyde derivatives bearing *ortho*-substituents was investigated in the current cross-coupling reaction.

2.4.3. Variation of *ortho*-substituted aldehydes

Next, *ortho*-substituted benzaldehyde derivatives bearing electron-donating groups were investigated. When 2-methoxybenzaldehyde was coupled, the corresponding product, 2-(2-methoxyphenyl)-4,5-diphenyl-1*H*-imidazole was obtained in a moderate yield of 66% (**Scheme 48**).



Scheme 48: Synthesis of 2-(2-methoxyphenyl)-4,5-diphenyl-1*H*-imidazole

The product was confirmed by ^{13}C NMR (**Figure 16**) where the methoxy carbon peak was observed at δ 56.0 and all the aromatic carbon atoms were observed in the region δ 156.5 – 112.1 which corresponds to the literature.[200]

Switching from 2-methoxybenzaldehyde to 2-methylbenzaldehyde did not bring about a huge change in the yield of the final product. For example, the coupling reaction of 2-methylbenzaldehyde afforded the corresponding imidazole in moderate 61% yield (**Scheme 49**) which is comparable to 66% yield obtained when 2-methoxybenzaldehyde was used.

The disappearance of a carbonyl peak at δ 195 – 210 associated with carbonyl peaks of aldehyde and benzil together with the appearance of a distinct methyl peak resonating at δ 21.6 in ^{13}C NMR spectrum of the product confirmed the formation of the desired 2-methyl substituted imidazole (**Figure 17**).

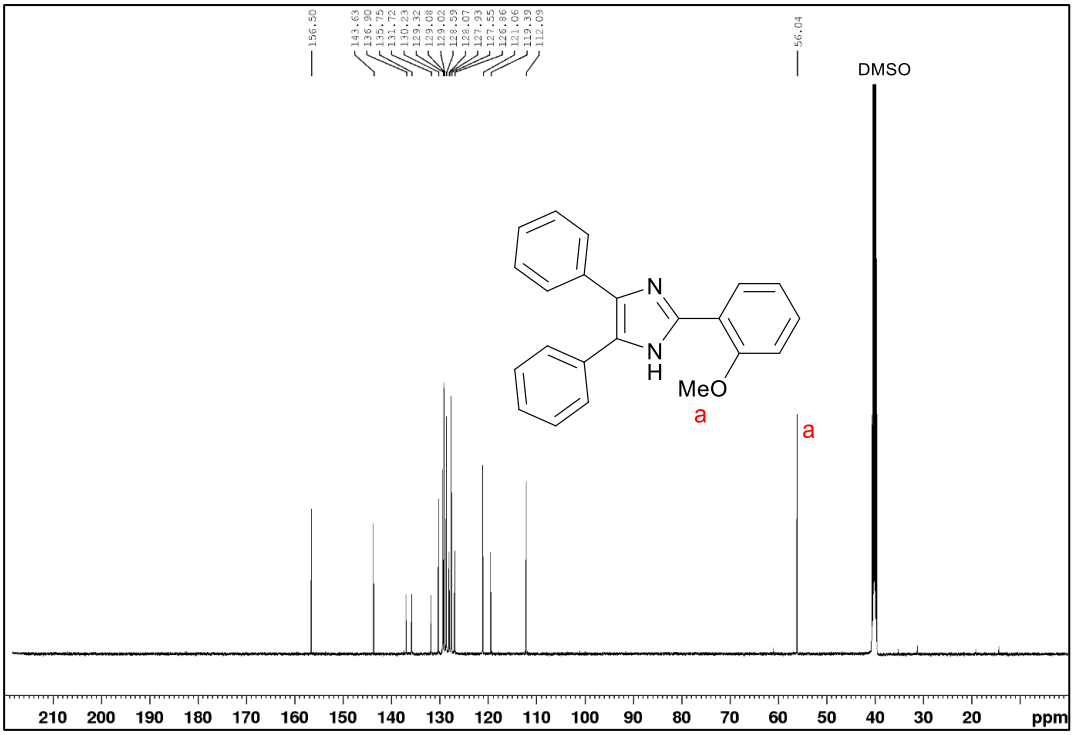
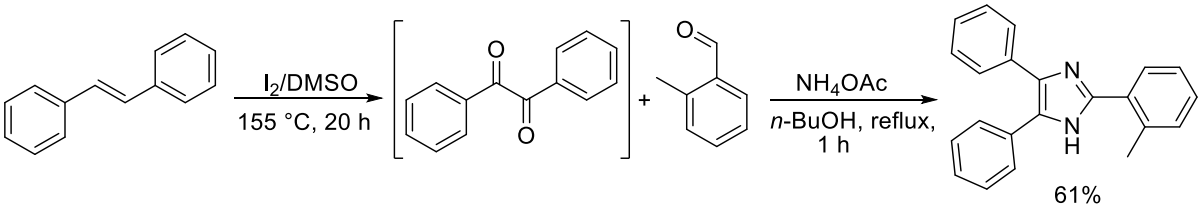


Figure 16: ^{13}C NMR spectrum of 2-(2-methoxyphenyl)-4,5-diphenyl-1*H*-imidazole



Scheme 49: Synthesis of 2-(2-methylphenyl)-4,5-diphenyl-1*H*-imidazole

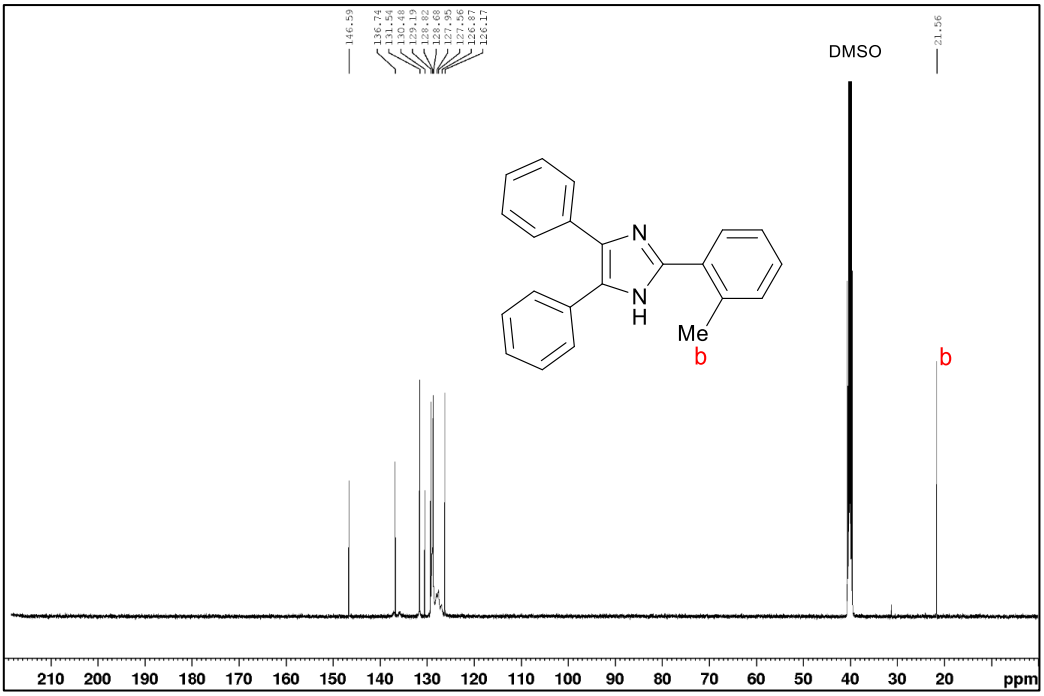


Figure 17: ^{13}C NMR spectrum of 2-(2-methylphenyl)-4,5-diphenyl-1*H*-imidazole

A comparison of ^{13}C NMR spectra of *ortho*-methoxy and *ortho*-methyl substituted imidazole revealed that the carbon atom from the methoxy group shifted downfield compared to the carbon atom of the methyl group given the electronegativity of the oxygen atom. To better illustrate this, we conducted an overlay of the NMR spectra, that involved overlaying **Figure 16** and **Figure 17** spectra. It is evident that these are two definitive peaks as they are both on either side of the DMSO-d_6 solvent (**Figure 18).**

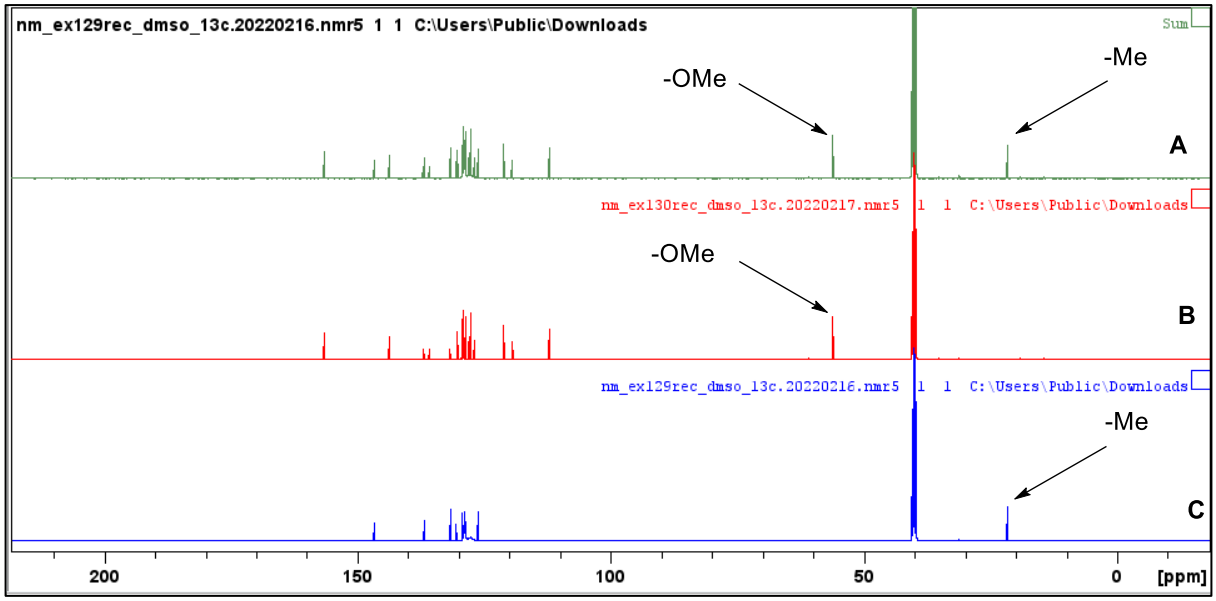


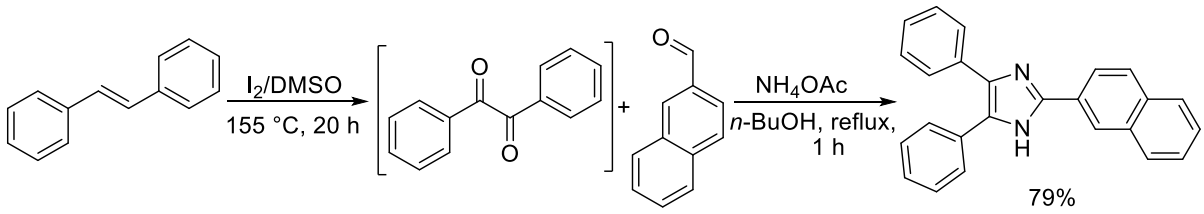
Figure 18: Comparison between CH_3 peaks (**A**) of the methoxy- (**B**) and methyl-substituted imidazole ^{13}C-NMR spectrum (**C**)

It is worth mentioning that the position of the substituent in an aldehyde has a great effect on the yield of the final imidazole product. For example, aldehydes with *para*-substituents afforded the corresponding imidazoles with higher yields than those with *ortho*-substituents. This observation is well documented in literature and is attributed to an increased steric hindrance for *ortho*-substituted aldehydes thus furnishing lower yields of the desired imidazoles compared to *para*-substituted aldehydes.[201]

2.4.4. Variation of different aldehydes other than benzaldehyde derivatives

The study was extended to other aldehydes with the aim of diversifying our scope. A bulky 2-naphthaldehyde was coupled with ammonium acetate and 1,2-diketone under optimal reaction conditions furnishing the corresponding product in 79% isolated yield (**Scheme 50**). The melting point of the product (274 – 276 °C) compares favourably to the melting point range of 273 – 276 °C reported by Safari and co-workers.[202] Even though a bulky 2-naphthaldehyde was used, it was interesting to note that the desired

product was obtained in good 74% yield irrespective of the size of an aldehyde. This observation indicates that our developed system accommodates bulky aldehydes as well.



Scheme 50: Synthesis of 2-(2-naphthyl)-4,5-diphenyl-1*H*-imidazole

The High-Resolution Mass Spectrum of the latter compound revealed an experimental molecular mass peak *m/z* 347.1555 $[M+H]^+$ with a calculated mass peak *m/z* 347.1548 (**Figure 19**).

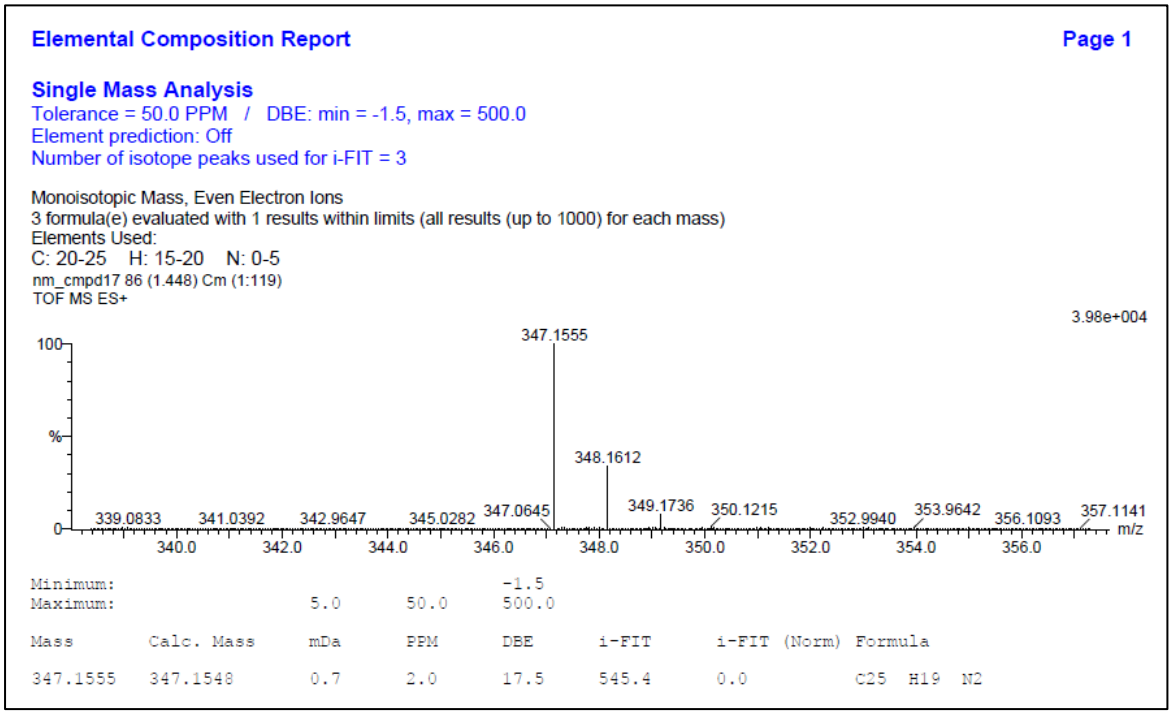
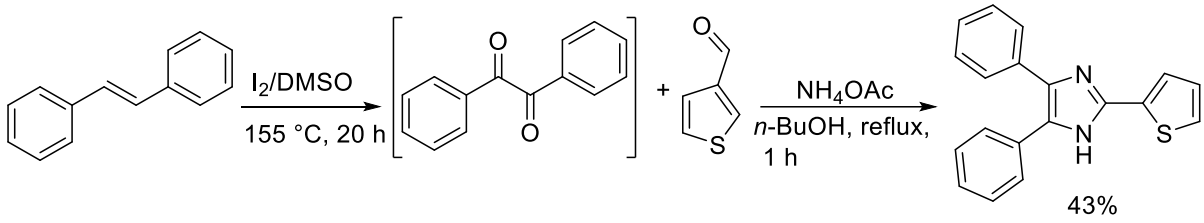


Figure 19: HRMS of 2-(2-naphthyl)-4,5-diphenyl-1*H*-imidazole

Extending our reaction scope to include heterocyclic aldehydes as coupling partners was favourable. For instance, the coupling reaction of 2-thiophene-carboxaldehyde,

benzil and ammonium acetate only afforded the corresponding 4,5-diphenyl-2-(thienyl)-1*H*-imidazole in moderate 43% yields (**Scheme 51**). The compound was confirmed by the melting point, where an experimental value of 258 – 260 °C compared favorably to the literature value of 259 – 261 °C.[203]



Scheme 51: Synthesis of 4,5-diphenyl-2-(thienyl)-1*H*-imidazole

Moreover, the functional groups present in this product were observed in infrared spectroscopy (**Figure 20**) which showed the N-H, C=C, and C=N bond stretches at 3382, 1591, and 1493 cm^{-1} confirming the successful cyclization of the imidazole ring.

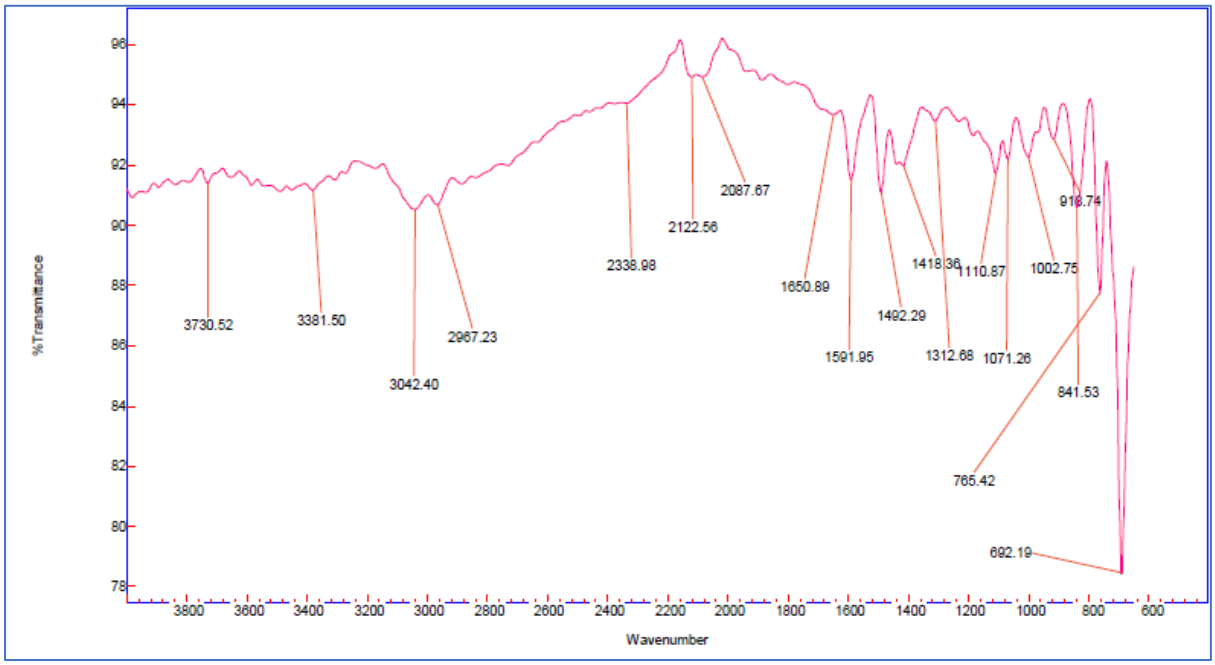
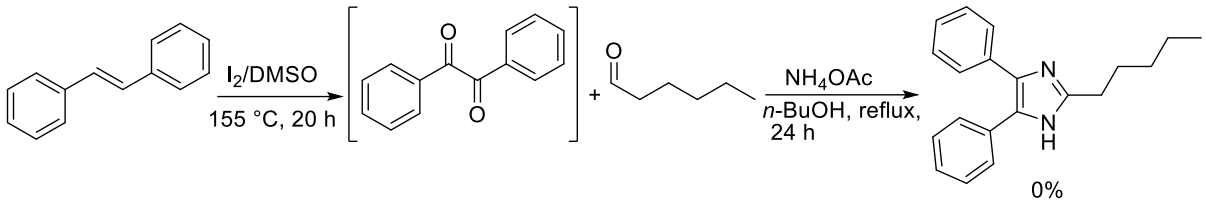


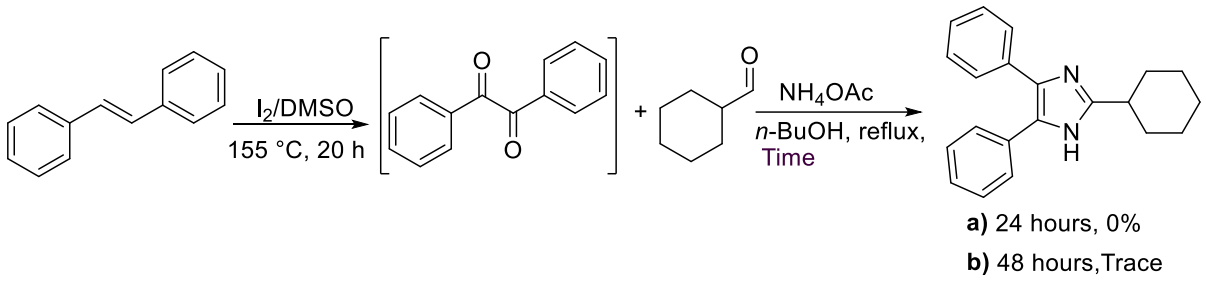
Figure 20: Infrared spectrum of 4,5-diphenyl-2-(thienyl)-1*H*-imidazole

However, the use of an aliphatic aldehyde, hexanal, was not successful as the corresponding imidazole was not obtained and only the starting material was recovered (**Scheme 52**).



Scheme 52: Attempted imidazole synthesis using hexanal

Next, a cyclic aliphatic aldehyde, cyclohexane-2-carboxaldehyde was explored under optimal reaction conditions and the target imidazole was not obtained (**Scheme 53, entry a**). We then hypothesized that increasing the coupling reaction time would allow reagents to interact more, thus, furnishing the desired product. Consequently, we conducted the reaction under the same reaction conditions except that step 2 was conducted for 48 hours, however, the corresponding imidazole was obtained in trace amounts (**Scheme 53, entry b)**.



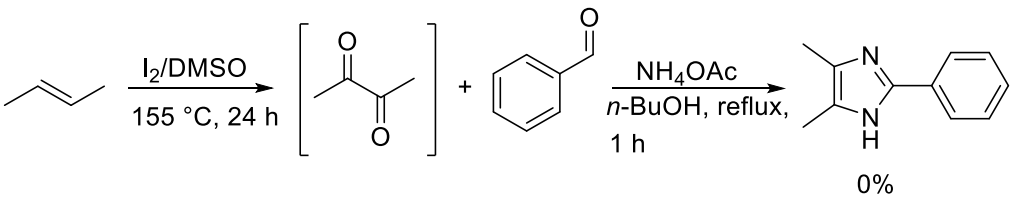
Scheme 53: Attempted synthesis of imidazole using cyclohexyl-2-carboxaldehyde

The aliphatic aldehydes explored (hexanal and cyclohexyl-2-carboxaldehyde) were incompatible with this system as the target compounds were not detected and only traces were observed even after prolonged reaction times. This is consistent with literature as aliphatic aldehydes are often problematic when employed in imidazole

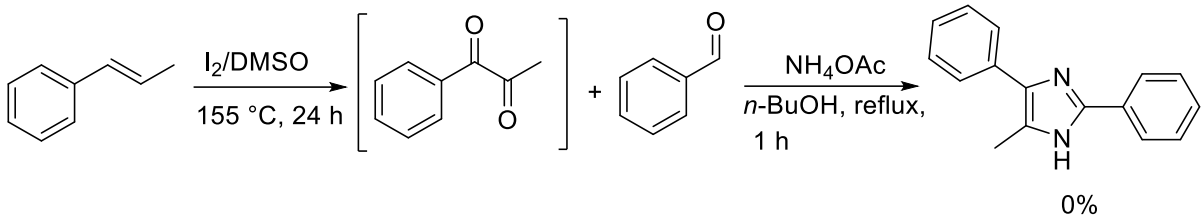
synthesis as they typically proceed to give corresponding imidazoles in very poor yields that cannot be isolated.[196] Literature reports suggest that imines are key intermediates in the coupling reactions between 1,2-diketones, aldehydes and ammonium acetate.[187, 204] However, formation of imines from aliphatic aldehydes is sluggish presumably because its formation is stabilized by conjugation with the aromatic ring and oftenly result in poor yields, thus slowing the formation of the desired imidazole.[205, 206]

2.4.5. Variation of internal alkenes

Internal alkenes were explored as starting materials to prepare corresponding 1,2-diketones which were then coupled with aldehyde and ammonium acetate to furnish the target 2,4,5-trisubstituted imidazoles. The use of *trans*-2-butene resulted in no product formation and the recovery of the starting material even after conducting the first step for 24 hours (**Scheme 54**) indicating that the coupling reaction to the desired product is not favourable. We speculated that a phenyl ring is vital for a 1,2-diketone formation as it provides stability to the intermediate towards the formation of the 1,2-diketone, and we explored the *trans*-*β*-methylstyrene as the starting material. Unfortunately, the desired product was not detected even after prolonged reaction times (**Scheme 55**).



Scheme 54: Attempted synthesis of imidazole from *trans*-2-butene

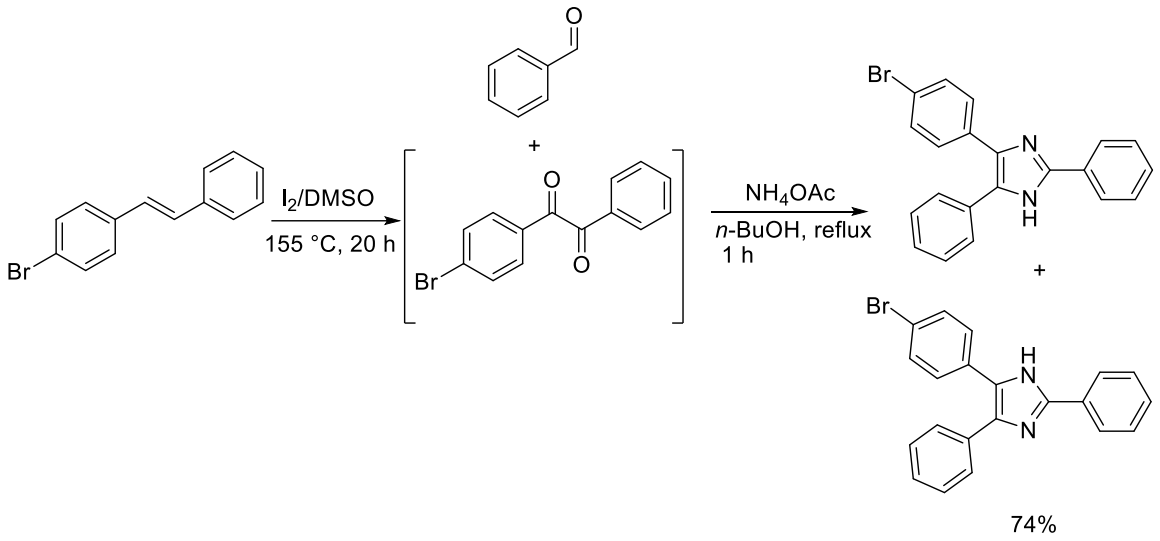


Scheme 55: Attempted synthesis of imidazole using *trans-β*-methylstyrene

Both *trans*-2-butene and *trans-β*-methylstyrene resulted in no product formation, only unreacted starting materials were recovered. This is in agreement with literature as aliphatic substrates are typically incompatible with internal alkene oxidation to 1,2-diketone formation and oftenly does not yield the desired product,[207] presumably due to reduced nucleophilicity of these substrates. Our next step was to investigate the suitability of substituted stilbenes under optimal reaction conditions.

Para-substituted stilbene, 4-bromostilbene, was employed as the starting material to form the corresponding 1,2-diketone in DMSO in the presence of molecular iodine at 155 °C for 20 hours. The *in-situ* generated 4-bromosubstituted 1,2-diketone was then coupled with benzaldehyde and ammonium acetate in *n*-butanol under reflux conditions to furnish the corresponding imidazole in a good, isolated yield of 74% (**Scheme 56**).

The product was confirmed by ^{1}H NMR spectroscopy where a broad peak around 12.75 ppm was observed which resonates for N-H, presumably due to the presence of tautomers. In addition, all the expected aromatic peaks were observed in the anticipated chemical shifts (aromatic region) of 8.10 – 7.31 ppm and integrated for the correct number of protons (**Figure 21**).



Scheme 56: Synthesis of 4-(4-bromobephyl)-2,5-diphenyl-1*H* imidazole

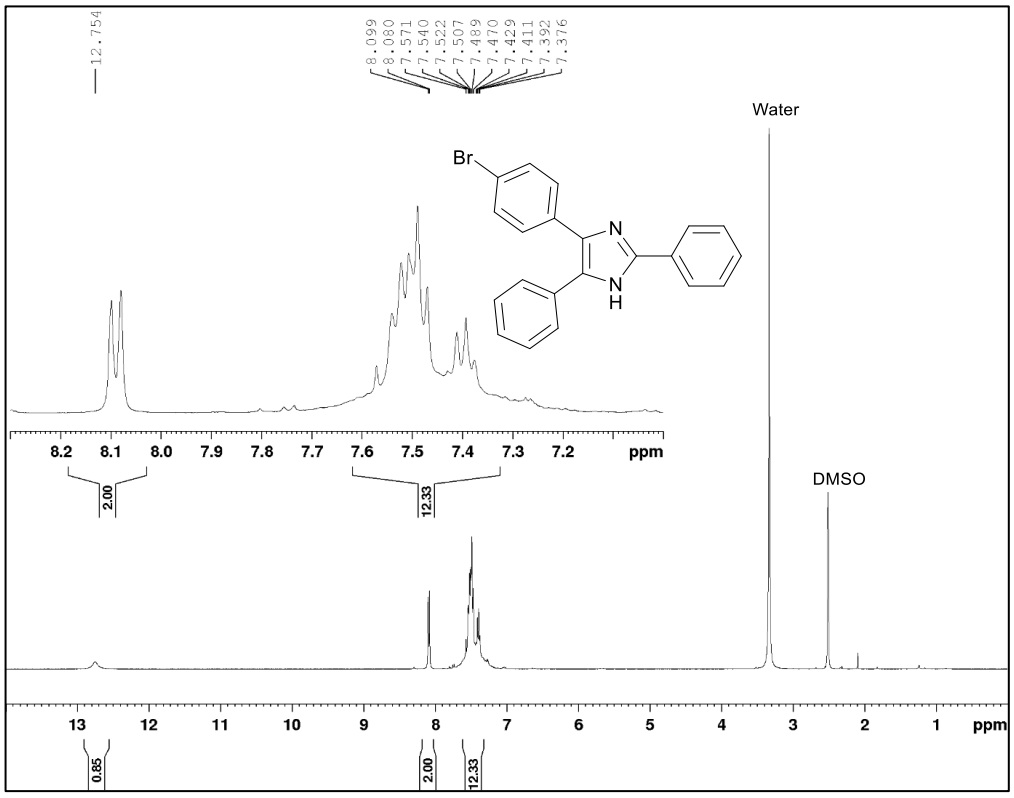
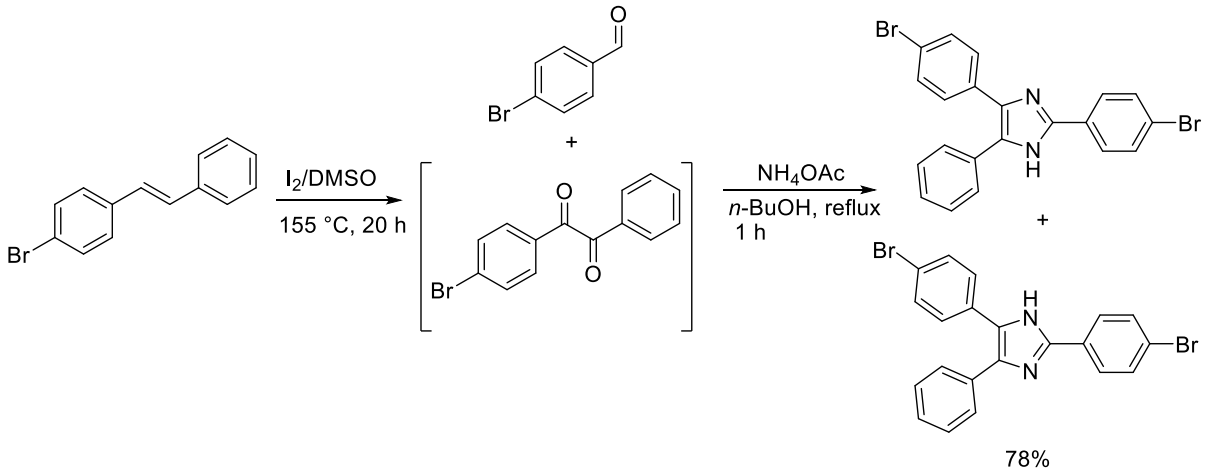


Figure 21: ^{1}H-NMR spectrum of 4-(4-bromophenyl)-2,5-diphenyl-1*H*-imidazole

In addition, this product had an uncorrected melting point of 254 – 256 °C which compares favourably to the literature value of 253 – 255 °C.[208] All the characterization data (^{13}C NMR and IR) for this compound corresponds to the literature.[208]

Encouraged by these results, we were intrigued to vary both the *para*-substituted alkene and *para*-substituted benzaldehyde derivative simultaneously. 4-Bromostilbene was oxidized to 4-bromobenzil in DMSO in the presence of molecular iodine at 155 °C for 20 hours. Thereafter, it was coupled with 4-bromobenzaldehyde and ammonium acetate in *n*-butanol under reflux conditions for 1 hour and the corresponding imidazole was obtained in a good yield of 78%, as a mixture of tautomers (**Scheme 57**). This was due to the proton bonded to the nitrogen being fluid, as it can move around to the other nitrogen due to the starting material (stilbene derivative) being unsymmetrical.[208]



Scheme 57: Synthesis of 2,5-Bis-(4-bromophenyl)-4-phenyl-1*H* imidazole

This product was confirmed by ^{1}H NMR spectroscopy where all the expected aromatic peaks were observed in the anticipated chemical shifts (8.05 – 7.37 ppm) (**Figure 22**). However, it was noted that a key singlet peak around 12.86 ppm was not clearly visible, presumably due to the proton exchange with trace water in deuterated DMSO.[209] The product was further confirmed by Low-Resolution Mass Spectrometry as this is a known compound, which showed a base peak at *m/z* 452.9750 $[M+H]^+$ and a peak at *m/z* 450.9771 $[M-H]^+$ (**Figure 23**).

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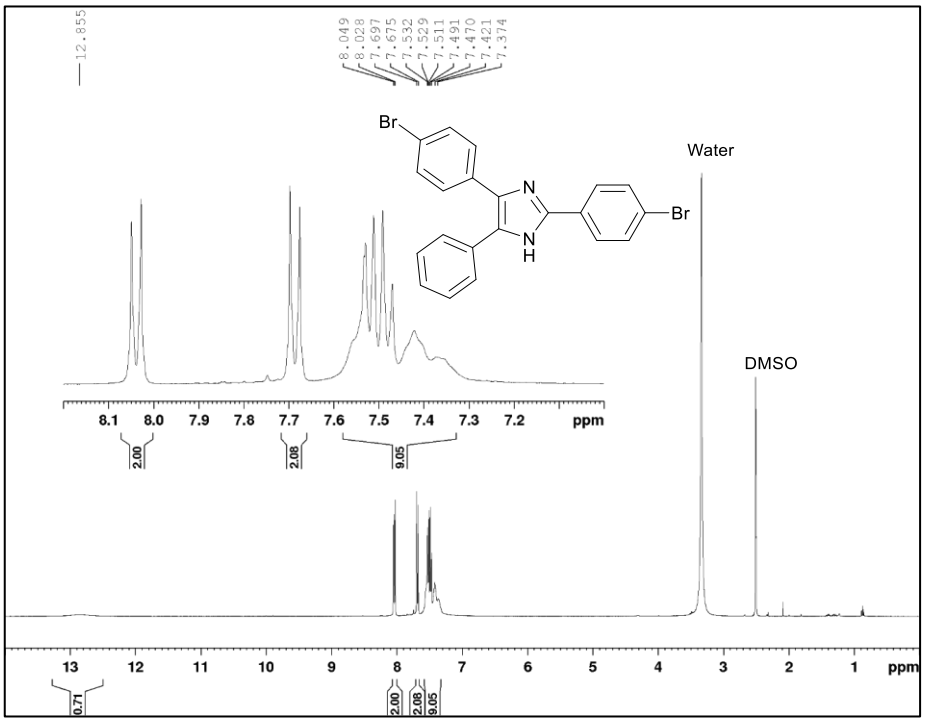
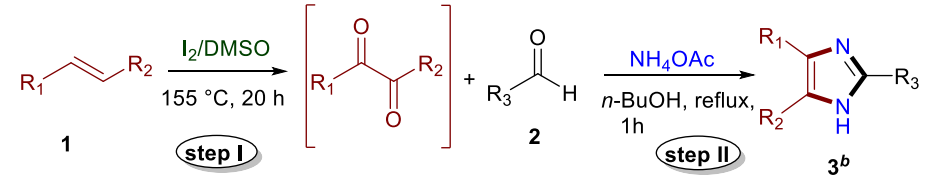


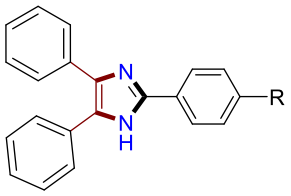
Figure 22: ^{1}H-NMR spectrum of 2,5-Bis-(4-bromophenyl)-4-phenyl-1*H*-imidazole

Figure 23: LRMS of 2,5-Bis-(4-bromophenyl)-4-phenyl-1*H*-imidazole

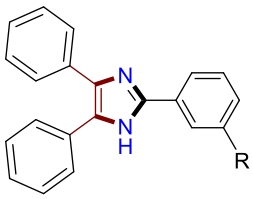
On completion of our library synthesis, we had synthesized twelve 2,4,5-trisubstituted derivatives and the results are summarized in **Table 7.**

Table 7: Substrate scope for the one pot, multicomponent oxidative synthesis of 2,4,5-trisubstituted imidazoles commencing from internal alkenes using I_2/DMSO system.

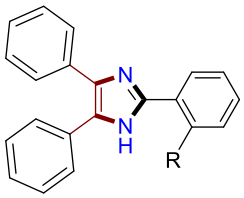




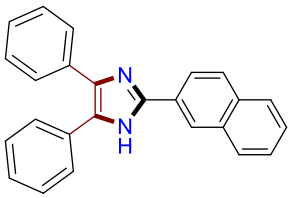
3a, R = H, 85%
3b, R = Cl, 83%
3c, R = Br, 87%



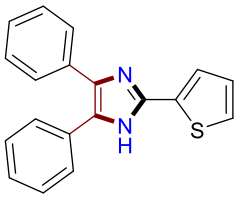
3d, R = NO_2, 73%
3e, R = Br, 75%
3f, R = Cl, 73%



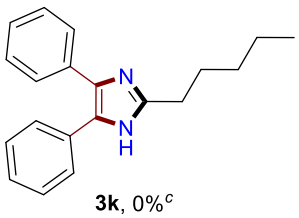
3g, R = OMe, 66%
3h, R = Me, 61%



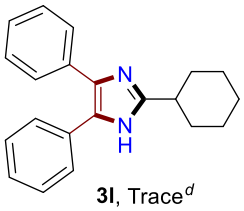
3i, 79%



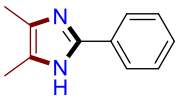
3j, 43%



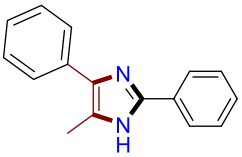
3k, 0%[c]



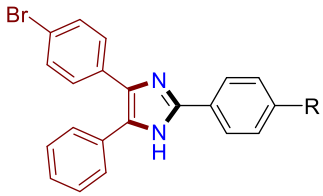
3l, Trace[d]



3m, 0%[e]



3n, 0%[e]

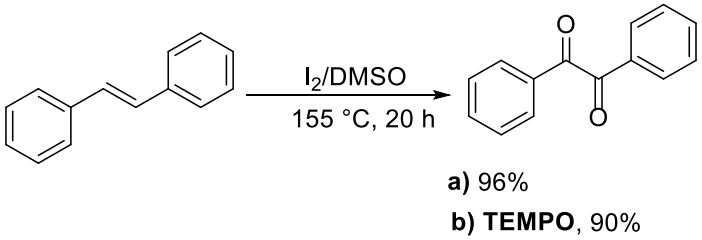


3o, R = H, 74%[f]
3p, R = Br, 78%[f]

[a] Reaction conditions: Step I: 1 (0.5 mmol), I_2 (1.25 equiv.) in DMSO (0.5 mL) at 155 °C for 20 hours. Step II: 2 (0.5 mmol), NH_4OAc (10 mmol) in *n*-BuOH (1 mL) reflux for 1 hour. [b] isolated yields. Step II for 24 h. [d] Step II for 48 h. [e] Step I for 24 h. [f] Mixture of tautomers.

2.5. Preliminary Mechanistic Investigations

To gain insight into the reaction mechanism, a series of control experiments were conducted. Firstly, *trans*-stilbene was reacted with I_2/DMSO at 155 °C for 20 hours to afford benzil in an isolated yield of 96% (**Scheme 58, entry a)**. This product was confirmed by ^{1}H NMR spectroscopy which showed all the aromatic peaks at the anticipated aromatic region (7.52-8.01 ppm) (**Figure 24**). In addition, this product was also confirmed by ^{13}C NMR spectrum which showed a key carbonyl peak around 195 ppm, due to the presence of two carbonyl carbon atoms which corresponds to the literature (**Figure 25)**. This suggested that the 1,2-diketone is indeed a key intermediate in the synthesis of trisubstituted imidazoles. Next, we turned our attention towards determining the mechanistic pathway as the 1,2 diketone formation has been shown to proceed via a radical pathway.[200] A radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction mixture under the same conditions which resulted in the formation of benzil in 90% isolated yield, suggesting that 1,2-diketone formation does not proceed *via* a radical pathway (**Scheme 58, entry b)**. On completion of this study, it was evident that a 1,2-diketone is a key intermediate and its formation from the alkene does not proceed *via* radical pathway.



Scheme 58: Control experiments into the formation of 1,2-diketone

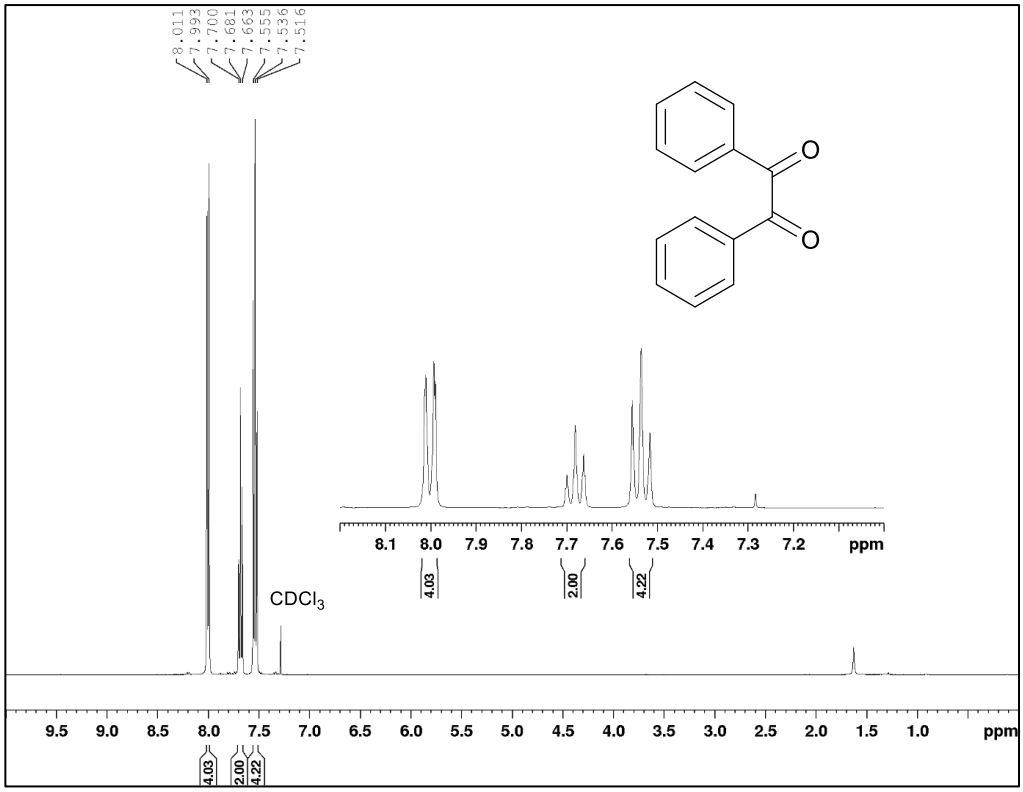


Figure 24: ^{1}H NMR spectrum of benzil

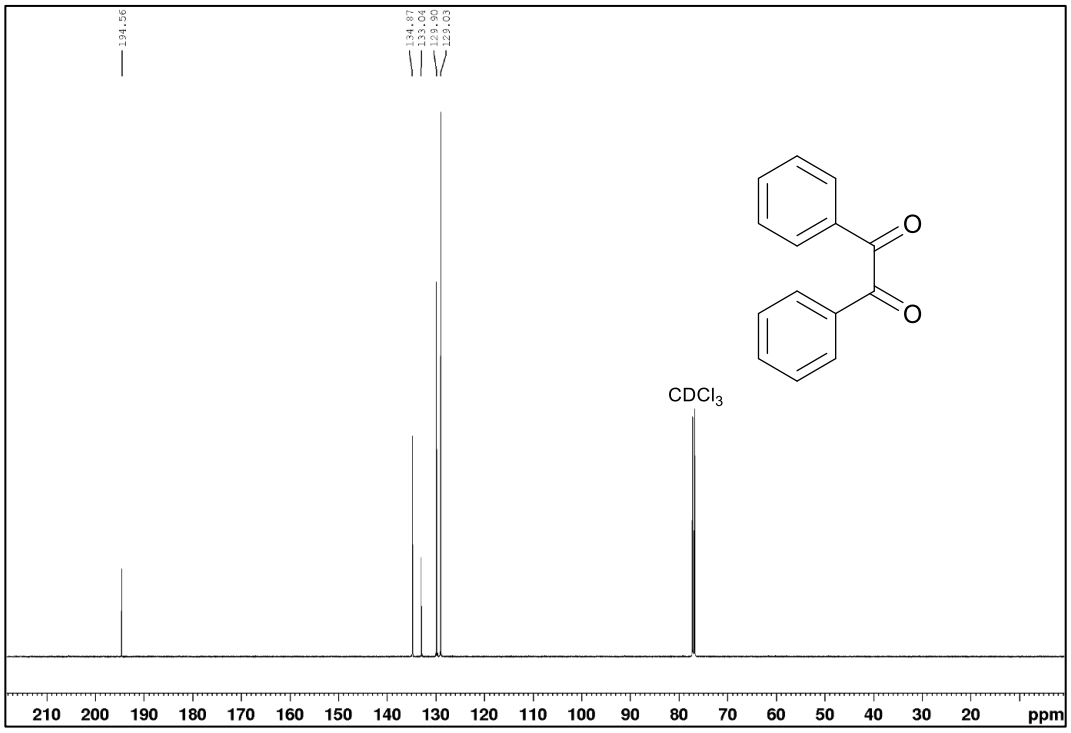
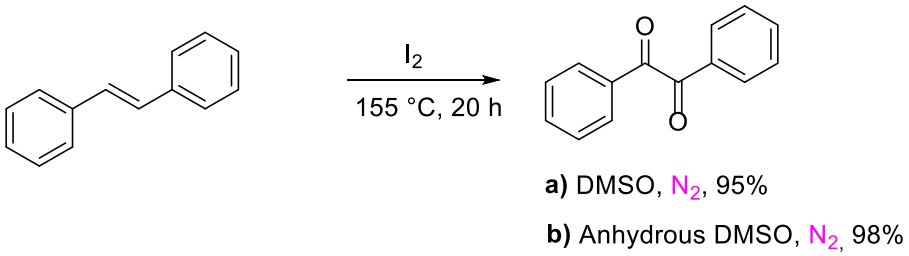


Figure 25: ^{13}C NMR spectrum of benzil

Next, we sought to determine the oxygen source in the formation of a 1,2-diketone. Hypothetically, there are three potential oxygen sources for the preparation of 1,2-diketone from internal alkenes, namely, molecular oxygen from the air, trace water in DMSO, and DMSO itself. To determine the oxygen source, *trans*-stilbene was first oxidized to benzil under inert conditions, and it was obtained in an isolated yield of 95%, indicating that molecular oxygen is not part of the system (**Scheme 59, entry a)**. Next, this oxidation reaction was conducted under inert conditions using anhydrous DMSO, which afforded benzil in an isolated 98% yield, suggesting that trace water in DMSO is not the oxidant in this case (**Scheme 59, entry b)**. The results from this study indicated that DMSO itself is the source of oxygen in this transformation.

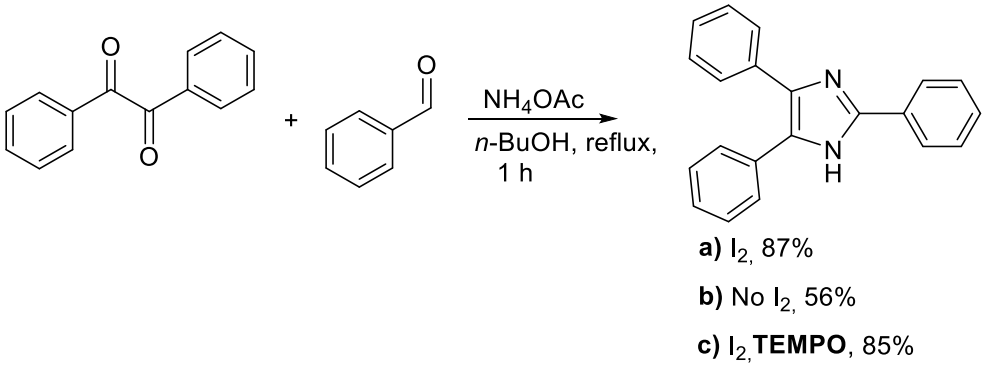


Scheme 59: Control experiments for the determination of oxygen source

We then sought to determine the catalyst for the coupling step whereby benzil, benzaldehyde and ammonium acetate was refluxed in *n*-butanol for 1 hour to form 2,4,5-triphenyl-1*H*-imidazole. In the presence of molecular iodine, the target imidazole was obtained in an isolated 87% yield (**Scheme 60, entry a)**, suggesting that molecular iodine is part of the coupling step and assists in imidazole formation.

Trisubstituted imidazole syntheses are known to proceed in the absence of a catalyst in alcoholic solvents.[196] In light of this, we conducted the coupling reaction in the absence of molecular iodine and the triphenyl imidazole was obtained in an isolated 56% yield (**Scheme 60, entry b)**. This result is presumably due the reaction being

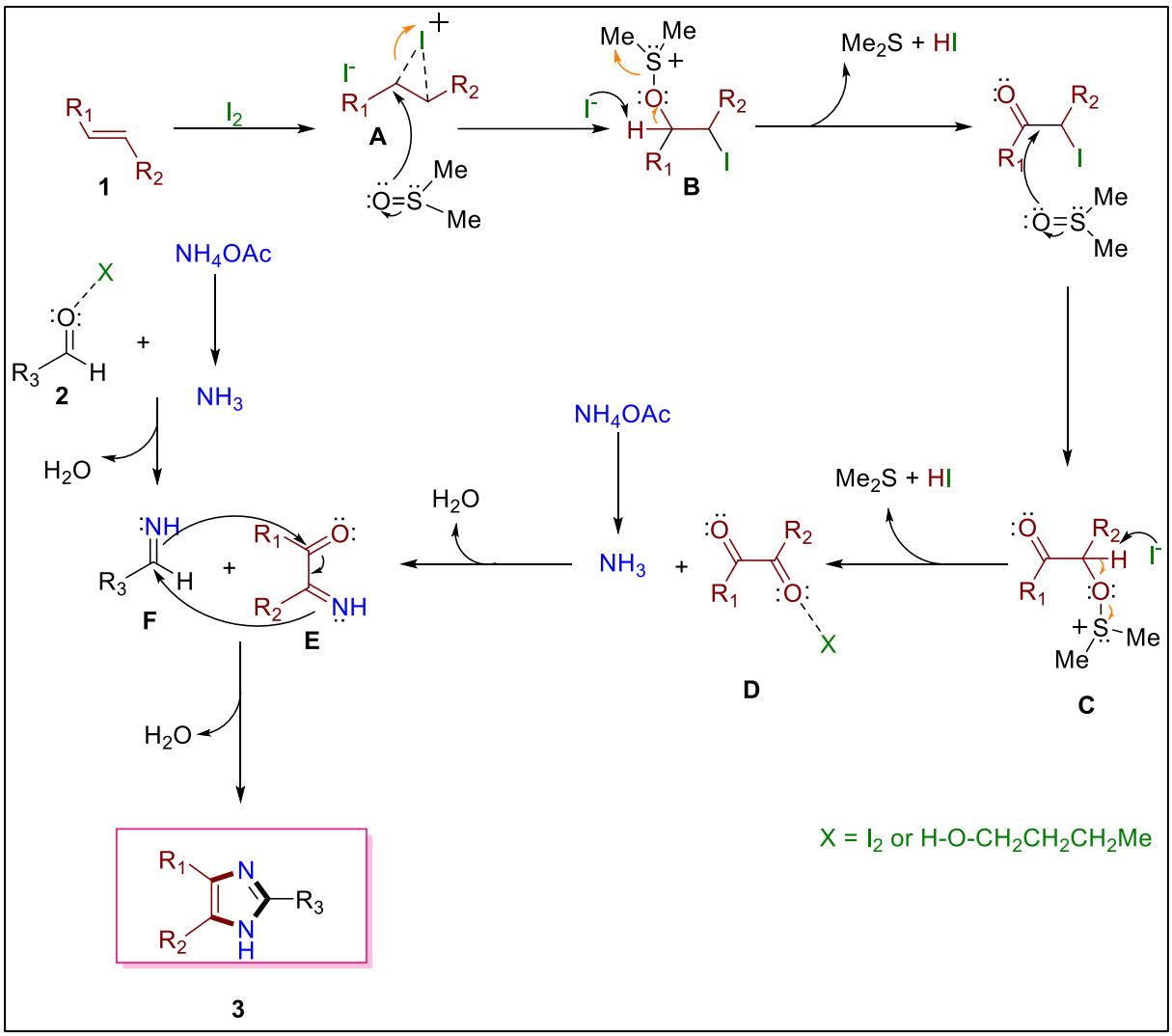
catalyzed by the solvent, *n*-butanol, *via* hydrogen bonding. In the presence of both molecular iodine and TEMPO, the target compound was obtained in a good 85% yield, indicating that the coupling step does not proceed *via* a radical pathway (**Scheme 60, entry c**).



Scheme 60: Control reactions for the coupling step

2.6. Proposed Reaction Mechanism

Based on the results obtained from the control experiments and literature reports,[171, 186, 210-212] a plausible mechanism is outlined in **Scheme 61**. This reaction commences with the activation of the alkene double bond to form the iodonium intermediate **A**. This intermediate is attacked by a molecule of DMSO to form intermediate **B** which releases dimethyl sulfide to generate an iodoketone. This iodoketone is trapped by a molecule of DMSO to form intermediate **C**, which proceeds to form a 1,2-diketone **D**, whilst releasing another molecule of dimethyl sulfide. Simultaneously, the 1,2-diketone **D** and an aldehyde **2** are activated by either molecular iodine or hydrogen bonding from *n*–butanol and upon reaction with ammonia generates imine intermediates **E** and **F** which then undergo the cyclocondensation to furnish the desired 2,4,5-trisubstituted imidazole.



Scheme 61: Plausible mechanism for the synthesis of 2,4,5-trisubstituted imidazoles

The results of this study were drawn up for publication and accepted by the journal, Heterocycles. A copy of the published paper is attached in the Appendix.

Majola N and Jeena V, *Heterocycles* **2022**, *106* (1), 186-200.

2.7. Conclusion

In summation, a novel method using an acid-, metal-free, and environmentally benign I_2/DMSO system to synthesize 2,4,5-trisubstituted imidazoles commencing from internal alkenes and aldehydes has been developed. This methodology was applied to broad range of substrates and the target imidazoles were prepared in moderate to good yields. Preliminary mechanistic studies suggested that a 1,2-diketone is indeed a key intermediate, the oxidation is not radical-mediated, DMSO is the source of oxygen, and that the coupling reaction is catalyzed by molecular iodine and *n*-butanol.

2.8. Future Work

- Aliphatic substrates were found to be incompatible with the system and it would be interesting to expand the scope towards aliphatic substrates by tempering with the optimal conditions to find target compounds from aliphatic alkenes and aldehydes.
- In this study, preliminary mechanistic studies were conducted, it would be interesting to conduct in-depth mechanistic investigations.
- It would be interesting to conduct a domino convergent synthesis of 2,4,5-trisubstituted imidazoles commencing from internal alkenes and alcohols.

CHAPTER 3

I. GENERAL INFORMATION

All reagents were purchased on Sigma-Aldrich and used without further purification. All ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker Avance III Spectrometer operating at 400 MHz. Chemical shifts (δ) were reported in ppm using deuterated dimethyl sulfoxide (DMSO-d_6) residual peak (δ 2.50) for ^{1}H NMR. Chemical shifts of ^{13}C NMR were reported relative to DMSO-d_6 (δ 39.51). The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants, *J*, were reported in Hertz units (Hz). Low- and High-Resolution electron-spray ionization (ESI) mass spectra were recorded on a time-of-flight (TOF) micromass spectrometer. Infrared (IR) spectra were recorded on Agilent Carey 630 Spectrometer. Melting points were determined using the Kofler-hot stage melting point apparatus and are uncorrected.

Experimental procedure for the optimization of reaction conditions

One-Pot, One-Step for 1 hour (Table 6, entry 1)

Trans-stilbene (90.1 mg, 0.5 mmol), molecular iodine (126.91 mg, 0.5 mmol), benzaldehyde (52 µL, 0.5 mmol) and ammonium acetate (385.41 mg, 10 mmol) were mixed in a 10 mL test tube with DMSO (0.5 mL) and heated to 130 °C for 1 hour. After cooling, 10 mL of sodium thiosulfate/ice-cold water were added. Unfortunately, no precipitate was obtained and only the starting material was recovered.

One-Pot, One-Step for 24 hours (Table 6, entry 2)

The reaction was conducted under the same conditions as **Table 6, entry 1** except the time was increased to 24 hours. No precipitate was obtained, only the starting material was detected by ^{1}H NMR.

One-Pot, Two-Step (Table 6, entry 3)

Trans-stilbene (90.1 mg, 0.5 mmol) and iodine (126.91 mg, 0.5 mmol) were added in a 10 mL test tube with 0.5 mL and the mixture was heated at 155 °C for 20 hours. Thereafter, benzaldehyde (52 µL, 0.5 mmol) and ammonium acetate (385.91 mg, 5 mmol) was added, and the mixture was further refluxed for 1 hour. Thereafter, 10 mL of sodium thiosulfate/ice-cold water solution was added where the crude product was precipitated, filtered, and dried in an oven. The precipitate was recrystallized in an acetone: water (9:1) solution to afford the desired product in 37% yield.

In the presence of different organic solvents (Table 6, entries 4 – 8)

i. Reaction was conducted under the same reactions conditions as **Table 6, entry 3** except DMF was added as a solvent in step 2 (**Table 6, entry 4)** and the targeted imidazole was obtained in 42% yield.
ii. Reaction was conducted the same as **Table 6, entry 3** except hexane was used as a solvent in step 2 and imidazole was obtained in trace amounts (**Table 6, entry 5**).
iii. Reaction conducted under the same reactions conditions as **Table 6, entry 3** except toluene was used as a solvent in step 2 and the triphenyl imidazole was obtained in 22% yield **(Table 6, entry 6**).

iv. Reaction conducted under the same conditions as **Table 6, entry 3** except ethanol was used as a solvent for step 2 and the triphenyl imidazole was obtained in 48% yield **(Table 6, entry 7)**.

v. Reaction conducted under the same conditions as **Table 6, entry 3** except *n*-butanol was used as a solvent in step 2 and the triphenyl imidazole was obtained in 62% yield (**Table 6, entry 8**).

Catalyst Loading (Table 6, entries 9 – 13)

These reactions were conducted under the same reaction conditions as **Table 6, entry 8** except varying quantities of molecular iodine and DMSO volumes were used.

i. Using 1 mL of DMSO gave the desired product in 65% yield (**Table 6, entry 9**).

ii. Using 0.625 mmol of molecular iodine have the triphenyl imidazole in a good, isolated yield of 85% (**Table 6, entry 10**).

iii. Using 0.75 mmol of molecular iodine gave the triphenyl imidazole in 58% yield (**Table 6, entry 11**).

iv. Using 0.75 mmol of molecular iodine in 1.5 mL DMSO gave the desired imidazole in 38% yield (**Table 6, entry 12**).

v. When 1 mmol iodine and 2 mL DMSO was used, the desired product was not detected by 1H NMR and only the starting material was recovered (**Table 6, entry 13**).

The influence of temperature (Table 6, entries 14 and 15)

i. The reaction was conducted under the same conditions as **Table 6, entry 8** except in the first step the mixture was heated at 115 °C and the desired product was obtained in 18% yield (**Table 6, entry 14**).

ii. The reaction under the same conditions as **Table 6, entry 8** except in step 1, the mixture was heated to 80 °C and the desired product was not detected (**Table 6, entry 15**).

Iodine Coupling Partner (Table 6, entries 16 – 18)

i. The reaction was conducted under the same conditions as **Table 6, entry 8** except toluene was used as a solvent in step 1, and the desired product was not detected (**Table 6, entry 16**).

ii. The reaction was conducted under the same conditions as **Table 6, entry 8** except water was used as a solvent in step 1, and the desired product was not detected (**Table 6, entry 17**).

iii. The reaction was conducted under the same conditions as **Table 6, entry 8** except acetonitrile was used as a solvent in step 1, and the desired product was obtained in trace amounts (**Table 6, entry 18**).

Iodine Source (Table 6, entries 19 – 21)

i. The reaction was conducted under the same reaction conditions as **Table 6, entry 8** except in the absence of iodine, and the desired product was not detected as only the starting materials was recovered (**Table 6, entry 19**).

ii. The reaction was conducted under the same reaction conditions as **Table 6, entry 8** except iodopentoxide was used as the iodine source and the desired product was not detected (**Table 6, entry 20**).

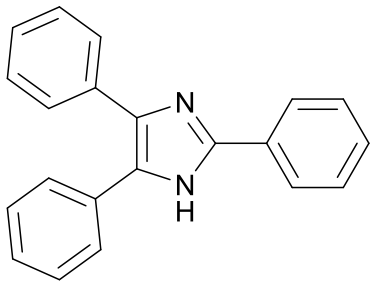
iii. The reaction was conducted under the same reaction conditions as **Table 6, entry 8** except 3-iodobenzoic acid was used as the iodine source and the desired product was obtained in trace amounts (**Table 6, entry 21**).

Amount of Ammonium Acetate (Table 6, entries 22 and 23)

i. The reaction was conducted under the same reaction conditions as **Table 6, entry 8** except 2.5 mmol of ammonium acetate was used and the desired product was not detected (**Table 6, entry 22**).

ii. The reaction was conducted under the same reaction conditions as **Table 6, entry 8** except 1.5 mmol of ammonium acetate was used in step 2 and the desired product was not detected (**Table 6, entry 23**).

2,4,5-Triphenyl-1*H*-imidazole (3a)[171]



Typical Procedure for the preparation of 2,4,5-trisubsituted imidazoles (3).

Trans-stilbene (0.5 mmol) and iodine (0.625 mmol) were mixed in a 10 mL test tube with 0.5 mL DMSO and heated at 155 °C for 20 hours. Thereafter, aldehyde (0.5 mmol), ammonium acetate (5 mmol), and *n*-butanol (1 mL) were added, and the mixture was refluxed for 1 hour. After cooling, 10 mL of sodium thiosulfate/ice-cold water was added to the mixture where the crude product was precipitated, filtered and dried in an oven. The crude precipitate was recrystallized from acetone: water (9:1) solution to yield the desired product as a white solid (252 mg, 85%)

Mp 269 – 271 °C; (Reported 270 – 272 °C)[171]

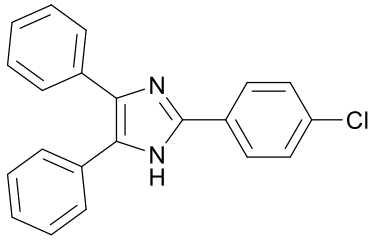
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.68 (s, 1H), 8.11-8.09 (d, J = 7.45 Hz, 2H), 7.57-7.56 (m, 2H), 7.53- 7.51 (m, 2H), 7.49-7.43 (m, 4H), 7.40-7.37 (m, 2H), 7.33 – 7.29 (m, 2H), 7.25 – 7.21 (m, 1H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 146.0, 137.6, 135.7, 131.6, 130.8, 129.2, 129.1, 128.9, 128.7, 128.65, 128.2, 127.6, 127.0, 125.7;

ν_{max} (neat, cm^{-1}): 3734, 3021, 1592, 1488, 1461, 1127;

ESI-MS (*m/z*): 295.1240(100) [M-H$^+$], 296.1268 (25) [M$^+$]

2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (3b)[197, 213]



Following the general procedure for **3a**, except now that 4-chlorobenzaldehyde (70.28 mg, 0.5 mmol) was used instead of benzaldehyde and afforded the desired product as a creamy white solid (83%).

Mp 261 – 263 °C; (Reported 261 – 263 °C)[214]

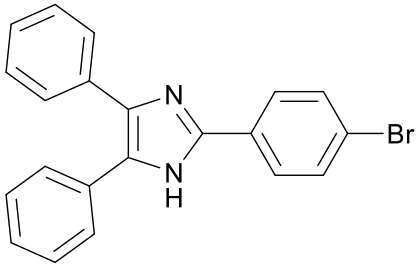
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 ppm (s, 1H), 8.12-8.10 ppm (d, J = 8.41 Hz, 2H), 7.57 – 7.54 (m, 2H), 7.52 – 7.50 (m, 2H), 7.48 – 7.43 (m, 2H), 7.40 -7.39 (m, 2H), 7.33 – 7.29 (m, 2H), 7.25 – 7.22 (m, 1H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 144.9, 137.8, 135.5, 133.2, 131.4, 129.7, 129.2, 129.1, 129, 128.9, 128.7, 128.3, 127.6, 127.3, 127;

ν_{max} (neat, cm^{-1}) = 2638.7, 1482, 1126, 766;

ESI-MS (*m/z*) = 329.0857 (100) $[M-H]^+$, 331.0836 $[M+H]^+$

2-(4-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (3c)[215, 216]



Following the procedure for **3a**, except now that 4-bromobenzaldehyde (82.51 mg, 0.5 mmol) was used instead of benzaldehyde and afforded the desired product as a creamy white solid (87%)

Mp 256 – 258 ºC; (Reported 255 – 258 °C)[216]

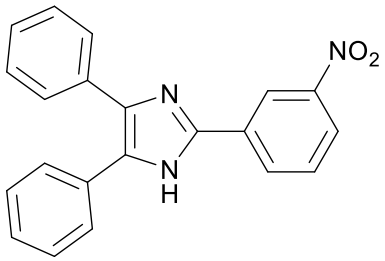
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 8.06 – 8.03 (d, J = 8.57 Hz, 2H), 7.70 – 7.68 (d, J = 8.52 Hz, 2H), 7.53 (m, 4H), 7.48 – 7.22 (m, 6H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 145, 137.9, 135.5, 132.1, 131.06, 130, 129.5, 129.1, 128.9, 127.6, 121.9;

ν_{max} (neat, cm^{-1}) : 3430, 2648, 2109, 1596, 1478, 1124, 764;

ESI-MS (*m/z*): 375.03 (100) $[M+H]^+$, 376.04 (25) $[M+2H]^+$

2-(3-nitrophenyl)-4,5-diphenyl-1*H*-imidazole (3d)[197, 213]



Following the procedure for **3a**, except now that 3-nitrobenzaldehyde (76.56 mg , 0.5 mmol) was used instead of benzaldehyde, afforded the desired product as a yellow solid (73%)

Mp 315 – 317 °C; (Reported 315 – 317 °C)[200]

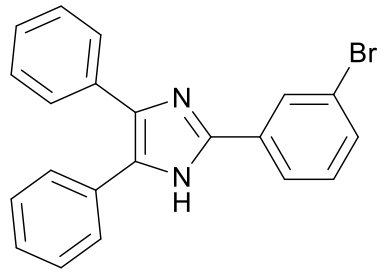
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 8.96 (s, 1H), 8.52 (d, J =8.01 Hz, 1H), 8.21 (d, J =8.23 Hz, 1H), 7.78 (t, J = 8.00 Hz, 1H), 7.57 – 7.52 (m, 4H), 7.46 – 7.33 (m, 6H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 148.8, 143.9, 138.2, 135.2, 132.3, 131.6, 131.1, 130.8, 130, 129.2, 128.9, 128.7, 127.6, 127.3, 123, 119.9;

ν_{max} (neat, cm^{-1}) : 2853, 1584, 1524, 1471, 1346, 1418, 1252, 1073;

ESI-MS (*m/z*): 343.1117 (15) $[M+2H]^+$, 342.1087 $[M+H]^+$

2-(3-bromophenyl)-4,5-diphenyl-1*H*-imidazole (3e)[217]



Following the procedure for **3a**, except now that 3-bromobenzaldehyde (59 µL, 0.5 mmol) was used instead of benzaldehyde, afforded the desired product as a yellow solid (75%)

Mp 300 – 301 °C; (Reported 292 – 294 °C)[218]

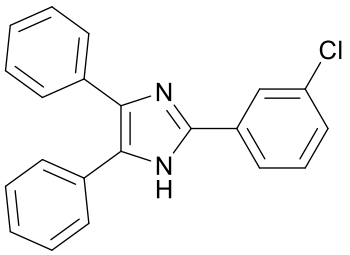
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 8.32- 8.11 (m, 1H), 8.09 (d, J = 8.11 Hz, 1H), 7.58 – 7.22 (m, 12H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 144.35, 137.92, 135.4, 133, 131.3, 131.25, 129.3, 129.1, 128.9, 128.7,128.4, 128, 127.6, 127.1, 124.5, 122.6;

ν_{max} (neat, cm^{-1}) : 3025.1, 1687, 1578, 1458, 1070, 846, 695;

HRMS (*m/z*): calcd mass for $C_{21}H_{16}N_2Br$ $[M+H]^+$ 375.0497, found 375.0492 (ppm error = -1.3)

2-(3-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (3f)[199]



Following the procedure for 3a, except now that 3-chlorobenzaldehyde (56.67 µL , 0.5 mmol) was used instead of benzaldehyde, afforded the desired product as a white solid (73%)

Mp 297-299 °C; (Reported 304°C)[219]

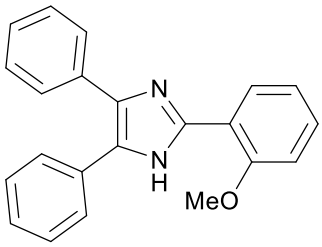
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.16 (s, 1H), 8.08- 8.05 (d, J = 7.89 Hz, 1H), 7.56 – 7.29 (m, 12H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 144.5, 134.1, 132.8, 131.1, 128.9, 128.4, 128.2, 127.8, 125.1, 124.2**;**

ν_{max} (neat, cm^{-1}) : 3377,1580,1455,1129, 767;

ESI-MS (*m/z*): 329.1046 (100) $[M-H]^+$, 331.1026 $[M+H]^+$, 332.1050 $[M+2H]^+$

2-(2-methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (3g)[200, 220]



Following the procedure for **3a**, except now that 2-methoxybenzaldehyde (68.08 mg , 0.5 mmol) was used instead of benzaldehyde, afforded the desired product as a white solid (66%)

Mp 207 – 209 °C; (Reported 208 – 210 °C)[218]

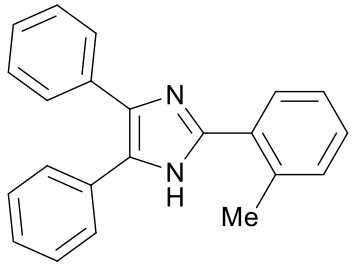
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.08 - 8.05 (m, 1H), 7.54 (d, J = 7.45 Hz, 2H), 7.49 – 7.48 (m, 2H), 7.35 (t, J = 7.55 Hz, 2H), 7.39 – 7.35 (m, 2H), 7.30 (t, J = 7.51 Hz, 2H), 7.23 – 7.20 (m, 1H), 7.17 (d, J =8.12 Hz, 1H), 7.08 (t, J = 7.51 Hz, 1H), 3.93 (s, 1H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 156.5, 143.6, 136.9, 135.8, 131.7, 130.2, 129.3, 129.08, 129.02, 128.6, 128.1, 127.9, 127.6, 126.9, 121, 119.4, 112.1, 56.04;

ν_{max} (neat, cm^{-1}) : 3064, 2839, 1590, 1527, 1472, 1391.4;

ESI-MS (*m/z*): 327.1439 (100) $[M+H]^+$, 349.1248 (30)

2-(2-methylphenyl)-4,5-diphenyl-1*H*-imidazole (3h)[221, 222]



Following the procedure for **3a**, except now that *o*-tolualdehyde (57.8 µL, 0.5 mmol) was used instead of benzaldehyde, afforded the desired product as a yellow solid (61%)

Mp 228-230 °C; (Reported 230 – 232 °C)[222]

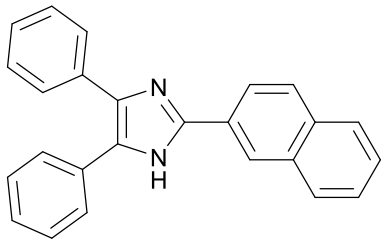
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 7.74 - 7.72 (m,1H), 7.55 (m, 4H), 7.34 -7.30 (m, 9H), 2.65 (s, 3H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 146.6, 136.7, 131.5, 130.5, 129.2, 128.8, 128.7, 127.9, 127.6, 126.9, 126.2, 21.6;

ν_{max} (neat, cm^{-1}): 3151.9, 2961.19, 2102.49, 1646.6, 1398.4, 1316 ;

LRMS (*m/z***)**: 311.1480 $[M+H]^+$, 312.1516 (10) $[M+2H]^+$

2-(2-naphthyl)-4,5-diphenyl-1*H*-imidazole (3i)[202]



Following the procedure for **3a**, except now that 2-naphthaldehyde (78.09 mg , 0.5 mmol) was used instead of benzaldehyde, afforded the desired product as a yellow solid (79%)

Mp 274 – 276 °C; (Reported 273 – 276 °C)[202]

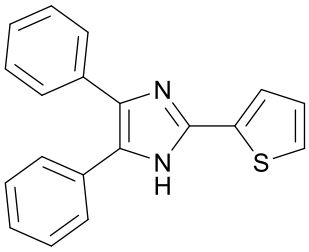
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.64 (s, 1H), 8.30 – 8.27 (m, 1H), 8.03 – 7.94 (m, 3H), 7.60 – 7.52 (m, 6H), 7.47 – 7.25 (m, 6H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 146, 136, 133.5, 133.2, 128.9, 128.7,128.6, 128.3, 128.2, 127.7, 127.2, 126.8, 124.2, 124;

ν_{max} (neat, cm^{-1}) :2761.3, 1589.3, 1498, 1447, 1409, 1343, 1264, 1072;

HRMS (*m/z*): Calcd mass for $C_{25}H_{19}N_2$ $[M+H]^+$ 347.1548, found 347.1555 (ppm error = 2.0)

4,5-diphenyl- 2-(thienyl)-1*H*-imidazole (3j)[192]



Following the procedure for **3a**, except now that 2-thiophene-carboxaldehyde (47.73 µL, 0.5 mmol) was used instead of benzaldehyde, afforded the desired product as a brown solid (43%)

Mp 258-260 °C; (Reported 259 – 261 °C)[203]

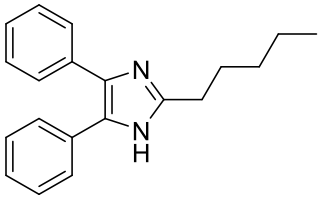
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 7.70 (d, J = 3.68 Hz, 1H), 7.56 – 7.40 (m, 8H), 7.31 (m, 2H), 7.25 – 7.16 (m, 2H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 142.1, 137.3, 135.3, 134.4, 131.3, 129.6, 129.2, 128.8, 128.6, 128.4, 128.3, 127.6, 127.1, 126.7, 124.2;

ν_{max} (neat, cm^{-1}): 3381.50, 1650, 1002.8;

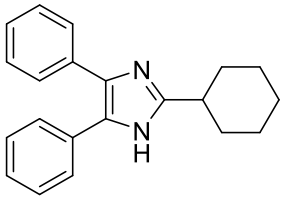
LRMS (*m/z*): 301.0802 (100) $[M-H]^+$, 302.0837 (25) $[M^+]$, 303.0798 $[M+2H]^+$

2-pentyl-4,5-diphenyl-1*H*-imidazole (3k)



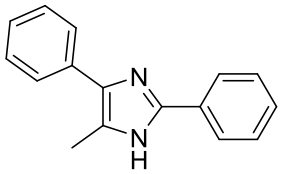
Following the procedure for **3a**, except that hexanal (61.45 µL ,0.5 mmol) was used instead of benzaldehyde and the reaction was coupled for 24 hours. The target product was not detected.

2-cyclohexyl-4,5-diphenyl-1*H*-imidazole (3l)



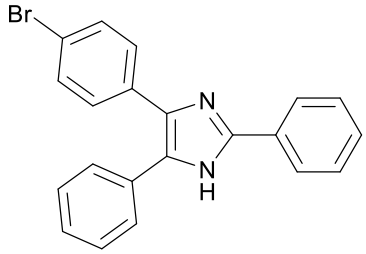
Following the procedure for **3a**, except that cyclohexane-2-carboxaldehyde (51.93 µL ,0.5 mmol) was used instead of benzaldehyde and the reaction was coupled for 24 hours. The target product was not detected. Repeating this experiment and coupling the reaction for 48 hours afforded the target imidazole in trace amounts as observed in the ^{1}H NMR spectroscopy.

5-methyl-2,4-diphenyl-1*H*-imidazole (3n)



Following the procedure for **3a**, except that *trans*-β-methylstyrene (64.86 µL ,0.5 mmol) was used instead of *trans*-stilbene and the first step was conducted for 24 hours. However, the target product was not detected.

5-(4-bromophenyl)-2,4-diphenyl-1*H*-imidazole (3o)[208]



Following the procedure for **3a**, except now that 4-bromostilbene (129.57 mg, 0.5 mmol) was used instead of stilbene, afforded the desired product as a white solid (74%)

Mp 254 – 256 °C; (Reported 253 – 255 °C)[208]

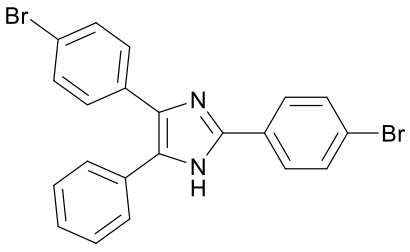
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (s, 1H), 8.09 (d, J = 7.44 Hz, 2H), 7.57- 7.38 (m, 12H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 146.3, 131.8, 130.7, 129.9, 129.2, 129.1, 128.8, 128.6, 128, 125.7;

ν_{max} (neat, cm^{-1}) : 3046.52, 2825.86, 1562.05, 1461.67, 979.40, 767**;**

LRMS (*m/z*): 375.0597 (100) $[M+H]^+$, 376.0633 (24)

2,5-Bis-(4-bromophenyl)-4-phenyl-1*H*-imidazole (3p)[208]



Following the procedure for **3a**, except now that 4-bromostilbene (129.57 mg, 0.5 mmol) and 4-bromobenzaldehyde (82.51 mg, 0.5 mmol) were used, afforded the desired product as a white solid (78%)

Mp 253 – 256 °C; (Reported 252 – 255)[208]

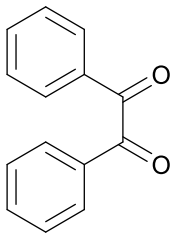
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.04 (d, J = 8.53 Hz, 2H), 7.70 – 7.68 (d, J = 8.67 Hz, 2H), 7.53 – 7.37 (m, 9H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 145.4, 132.1, 131.8, 130, 129.9, 129.1, 128.5, 128.1, 127.6, 121.9, 120.5;

ν_{max} (neat, cm^{-1}): 3063, 2828, 1601, 1477, 1069, 825, 722;

LRMS (m/z): 452.9750 (100) $[M+H]^+$, 450.9771 (50) $[M-H]^+$, 455.9761 (15)

Benzil (4a, $C_{14}H_{10}O_2$, 96%)[85, 185]



Trans-stilbene (90.1 mg, 0.5 mmol) and iodine (159 mg, 0.625 mmol) were mixed in a 10 mL test tube with 0.5 mL of DMSO and the mixture was heated at 155 °C for 20 hours. After cooling, 10 mL of sodium thiosulfate/ice-cold water was added to the mixture where the crude product was precipitated, filtered, and dried. It was then recrystallized in ethanol to afford benzil as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, J = 8.27 Hz, 4H), 7.68 (t, J = 7.43 Hz, 2H), 7.45 (t, J = 7.78 Hz, 4H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 194.6, 134.9, 133, 129.9, 129.

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APPENDIX

HETEROCYCLES, Vol. 106, No. 1, 2023, pp. 186 - 200. © 2023 The Japan Institute of Heterocyclic Chemistry
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ACID, METAL AND PEROXIDE-FREE SYNTHESIS OF 2,4,5-TRISUBSTITUTED IMIDAZOLES COMMENCING FROM INTERNAL ALKENES USING AN IODINE/DMSO SYSTEM

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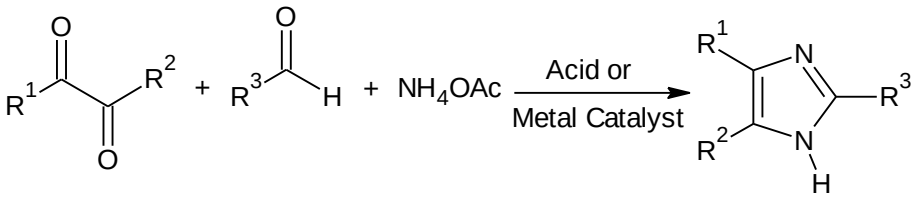
Abstract – An efficient acid, metal and peroxide-free synthesis of 2,4,5-trisubstituted imidazoles commencing from internal alkenes and aldehydes using an inexpensive and eco-friendly iodine/DMSO system has been reported. This simple methodology affords a plethora of 2,4,5-trisubstituted imidazoles in moderate to good yields under mild reaction conditions. Based on preliminary control studies, a reasonable mechanism to the target imidazole is proposed.

Oxidations play a vital role in academia and industry as it assists in the creation of new, complex molecules or the modification of existing ones.[1] Given the importance of this transformation, the demand for novel, environmentally benign, and cost-effective oxidation methods have steadily increased.[2] Within this context, the oxidation of alkenes, in particular, continues to be of importance as it is used to prepare epoxides,[3] carbonyls,[4] and 1,2-diols.[5] Additionally, the conversion of internal alkenes to α-diketones is of interest to organic chemists as it allows for the generation of synthetically useful compounds such as quinoxalines and spirocycles.[6] Hence, a multitude of synthetic routes have been devised for the conversion of internal alkenes to α-diketones and selected examples include the use of potassium permanganate in acetic anhydride[7] and ruthenium-catalyzed hydrogen abstraction.[8]

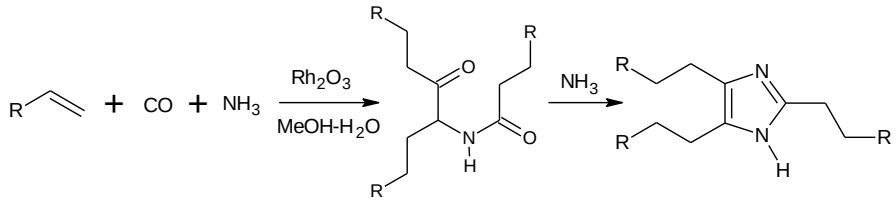
2,4,5-Trisubstituted imidazoles are important heterocyclic compounds as they display interesting biological[9,10] and synthetic applications.[11] The traditional route towards these fascinating molecules involves the multicomponent reaction of a α-diketone, aldehyde and ammonium acetate in the presence of a metal or acid catalyst (Scheme 1a) such as acetic acid,[12] ytterbium triflate,[13] and $(NH_4)_6Mo_7O_{24}•4H_2O$,[14] to name but a few. Surprisingly, there are limited synthetic routes towards 2,4,5-trisubstituted imidazoles commencing from alkenes and one of the earliest reports involves the use of a rhodium oxide catalyst and ammonia in a methanol-water mixture in the presence of carbon monoxide (Scheme 1b).[15] The challenges associated with this approach include the use of an expensive rhodium catalyst, employment of toxic carbon

monoxide, formation of side-products, substrate scope limitations as well as poor yields. Approximately four decades later, a singular example of a 2,4,5-trisubstituted imidazole synthesis using a ketoiodination/cyclization methodology from internal alkenes was reported (Scheme 1c).[16] The limitations of this method include the use of a laborious work-up procedure and the use of heat and shock-sensitive 2-iodoxybenzoic acid (IBX). More recently, Yang and co-workers reported the synthesis of α-diketones using an internal alkene *via* a bifunctional iron nanocomposite catalyst, *tert*-butyl hydroperoxide (TBHP) and tetrabutylammonium iodide (TBAI) in an acetonitrile-water medium (Scheme 1d).[17] The authors highlighted the utility of the synthesized α-diketone by extending their study to the preparation of 2,4,5-triphenyl-1*H*-imidazole. Despite the novelty of this approach, the use of a transition-metal complex which is not commercially available and has to be prepared by a tedious approach as well as the use of potentially dangerous hydroperoxides detracts from this methodology.

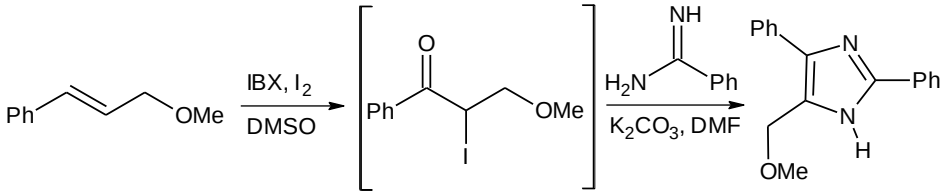
a.] Traditional Synthesis



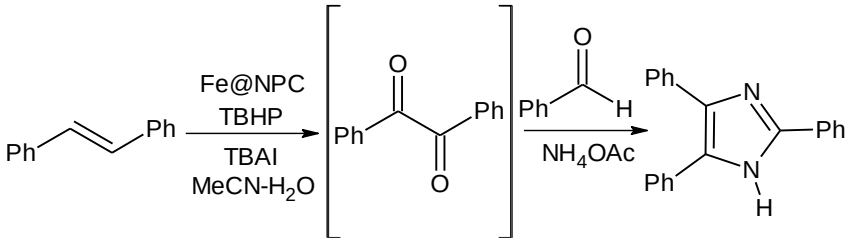
b.] *J. Org. Chem.*, 1971, 36, 3927.



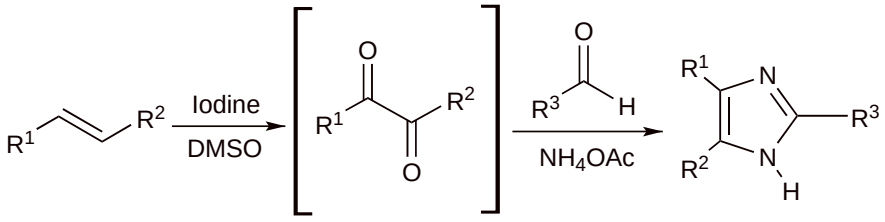
c.] *Org. Biomol. Chem.*, 2012, 10, 1093.



d.] ***ACS Catal.*****, 2020, 10, 4617.**



e.] This work (acid, metal and peroxide free synthesis)

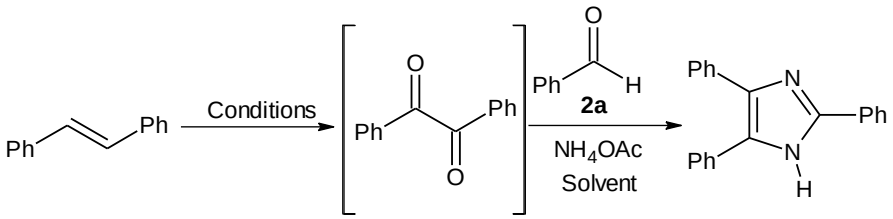


Scheme 1. Different synthetic routes towards 2,4,5-trisubstituted imidazoles

Recently, the iodine/DMSO system has emerged as a powerful tool in chemistry as it exhibits diverse applications in organic synthesis[18] and previously, we have reported the efficient synthesis of 2,4,5-trisubstituted imidazoles from α-methylene ketones,[19] and internal alkynes[20,21] using this system. Given the challenges highlighted above for imidazole synthesis commencing from alkenes, herein we report a simple route towards the construction of these fascinating molecules using an acid, metal and peroxide-free approach (Scheme 1e).

Our study commenced by examining a one-pot reaction between *trans*-stilbene **1a**, benzaldehyde **2a**, and ammonium acetate in DMSO for 1 hour in the presence of 1 equivalent molecular iodine. Unfortunately, the desired product **3a** was not detected and only starting material was recovered (Table 1, entry 1). Next, we repeated the experiment except the reaction time was increased to 24 hours, however, the desired product was still not detected (Table 1, entry 2). Based on these observations, we turned our attention towards a one-pot, two-step process where *trans*-stilbene **1a** was reacted with molecular iodine in DMSO for 24 hours at 155 ^{o}C, thereafter, benzaldehyde **2a** and ammonium acetate were added, and the mixture was further refluxed for 1 hour. Under these conditions, the desired product was obtained in a moderate but encouraging isolated yield of 37% (Table 1, entry 3). The syntheses of 2,4,5-trisubstituted imidazoles are

Table 1. Optimization of reaction conditions for the formation of 2,4,5-triphenylimidazole from *trans*-stilbene[a]



1a **3a**

Entry	Conditions	Solvent	Yield (%)[b]
1[c]	I_2/DMSO	–	N. R
2[d]	I_2/DMSO	–	N. R
3	I_2/DMSO	–	37
4	I_2/DMSO	DMF	42
5	I_2/DMSO	hexane	Trace
6	I_2/DMSO	PhMe	22
7	I_2/DMSO	EtOH	48
8[e]	I_2/DMSO	*n*-BuOH	62
9[f]	I_2/DMSO	*n*-BuOH	65
10	I_2/DMSO	*n*-BuOH	85
11[g]	I_2/DMSO	*n*-BuOH	58
12[h]	I_2/DMSO	*n*-BuOH	38
13[i]	I_2/DMSO	*n*-BuOH	N. R
14[j]	I_2/DMSO	*n*-BuOH	18
15[k]	I_2/DMSO	*n*-BuOH	N. R
16[l]	I_2/PhMe	*n*-BuOH	N. R
17[m]	I_2/H_2O	*n*-BuOH	N. R
18[n]	I_2/MeCN	*n*-BuOH	Trace
19[o]	DMSO	*n*-BuOH	N. R
20	I_2O_5/DMSO	*n*-BuOH	N. R
21	3-iodobenzoic acid/ DMSO	*n*-BuOH	Trace
22[p]	I_2/DMSO	*n*-BuOH	N. R
23[q]	I_2/DMSO	*n*-BuOH	N. R

[a] Reaction conditions: Step 1: **1a** (0.5 mmol), I_2 (1 equiv.) / DMSO (0.5 mL), 20 h, 155 °C. Step 2: **2a** (0.5 mmol), NH_4OAc (10 equiv.), Solvent (2 mL), reflux, 1 h. [b] Isolated yield. [c] One pot, one step for 1 h. [d] One pot, one step for 24 h. [e] I_2 (1 equiv.) / DMSO (0.5 mL). [f] I_2 (1 equiv.)/DMSO (1 mL). [g] I_2 (1.5 equiv.) / DMSO (0.5 mL). [h] I_2 (1.5 equiv.) /DMSO (1.5 mL). [i] I_2 (2 equiv.)/DMSO (2 mL). [j] Step 1 for 24 h, 115 °C.

[k] Step 1 at 80 °C. [l] Step 1 reflux. [m] Step 1 reflux. [n] Step1 reflux. [o] Absence of Molecular Iodine. [p] NH_4OAc (5 equiv.). [q] NH_4OAc (3 equiv.) N. R: No reaction.

known to be solvent-specific,[22,23] and a range of organic solvents were examined (DMF, hexane and toluene), however, in all cases, trace to moderate yields were observed (Table 1, entries 4 – 6). Ethanol is known to favour the three-component imidazole reaction,[24,25] however, in this case, (Table 1, entry 7) the target imidazole was formed in a moderate yield of 48%. Recently, *n*-butanol has been reported as the best solvent for a multicomponent coupling reaction between an α-diketone, aldehyde and ammonia which produced 2,4,5-trisubstituted imidazoles in excellent yields.[26] Inspired by this result, the use of *n*-butanol as a solvent, in the current synthesis, produced the desired imidazole in an improved yield of 62% (Table 1, entry 8).

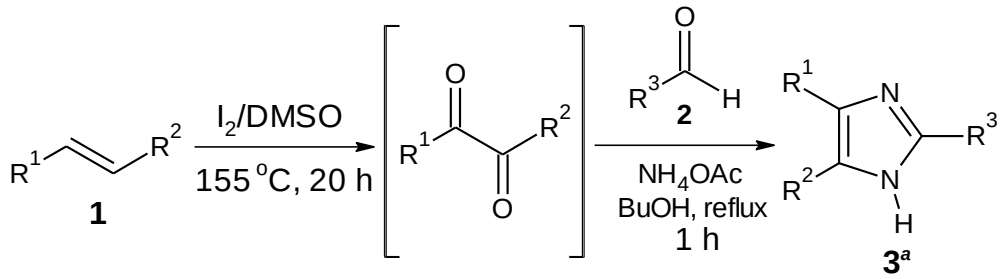
To find the optimal catalyst loading for this reaction, the iodine quantity and DMSO volumes were varied. When the volume of DMSO was increased to 1 mL, it afforded the 2,4,5-trisubstituted imidazole in an isolated yield of 65% (Table 1, entry 9). Increasing the molecular iodine quantity to 1.25 equivalents and decreasing the DMSO volume to 0.5 mL resulted in the formation of the desired product **3a** in a good, isolated yield of 85% (Table 1, entry 10). Using 1.5 equivalents of molecular iodine in 0.5 mL DMSO decreased the amount of the desired product to 58% (Table 1, entry 11) while increasing the volume of DMSO to 1.5 mL decreased the desired product even further to 38% (Table 1, entry 12). Increasing both the iodine quantity to 2 equivalents and DMSO volume to 2 mL resulted in no product formation and the recovery of the starting materials (Table 1, entry 13). It was clear that the amount of iodine and DMSO affects the reaction and may be due to DMSO playing multiple roles in the system.

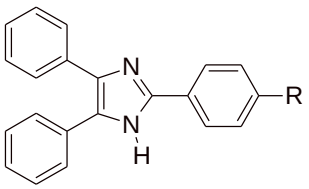
We then attempted to decrease the temperature to 115 °C for the first step but this change resulted in a diminished isolated yield of 18% (Table 1, entry 14). Further decrease in temperature to 80 °C resulted in no product formation and only the starting material was recovered (Table 1, entry 15). To determine if DMSO is the ideal coupling partner for iodine, we examined toluene (PhMe), acetonitrile (MeCN), and water as potential iodine coupling partners. No product was obtained in toluene and water (Table 1, entries 16 and 17), whereas only trace amounts were obtained in acetonitrile (Table 1, entry 18) signifying the critical role of DMSO.

When molecular iodine was omitted, no reaction occurred (Table 1, entry 19) implying that iodine is essential for this reaction. Other non-metal, iodine-containing catalysts were also examined to determine if indeed molecular iodine is the best iodine source. When iodopentoxide (I_2O_5) was used, no product was obtained (Table 1, entry 20) while the use of 3-iodobenzoic acid afforded the desired product in trace amounts (Table 1, entry 21) suggesting that molecular iodine is the best iodine source for this system. In

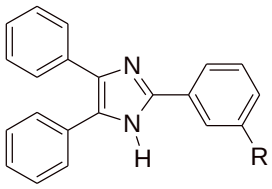
previous imidazole syntheses, fluctuating amounts of ammonium acetate have been used[27,28] and we varied its amount by using 5 and 3 equivalents, however, under these conditions, no product was obtained (Table 1, entries 22 and 23). Therefore**,** the conditions described in Table 1, entry 10, were found to be the optimal as it allowed for maximum formation of the desired product.

With the optimized conditions in hand, the substrate scope for substituted internal alkenes against various aromatic aldehydes was explored and the results are depicted in Scheme 2. The varying of benzaldehyde derivatives substituted at the *para*-position afforded 2,4,5-trisubstituted imidazoles in good yields of 83 and 87% (Scheme 2, entries 3b and 3c). Varying the benzaldehyde derivatives that are *meta*-substituted with electron-withdrawing groups afforded the imidazoles in good yields of 73% – 75% (Scheme 2, entries 3d – 3f). Moderate yields of 61% – 66% were obtained when *ortho*-substituted benzaldehyde derivatives bearing electron-donating groups were used (Scheme 2, entries 3g and 3h). Encouraged by these results, a bulky aldehyde, 2-naphthaldehyde, was employed which afforded the 2-(naphthalen-2-yl)-4,5-diphenyl-1*H*-imidazole in a good yield of 79% (Scheme 2, entry 3i). To diversify our scope, a five-membered ring aldehyde bearing a heteroatom (2-thiophenecarboxaldehyde) was employed which afforded the corresponding imidazole in 43% isolated yield (Scheme 2, entry 3j). The use of an aliphatic aldehyde such as hexanal was not successful and only starting material was recovered (Scheme 2, entry 3k) while cyclohexane-2-carboxaldehyde afforded the desired product in trace amounts (Table 2, entry 3l). This is in accordance with the literature, as aliphatic aldehydes are often problematic in imidazole synthesis and normally result in poor yields of corresponding imidazoles.[29] The use of diverse alkenes, but-2-ene, and *trans*-β-methylstyrene were found to be incompatible with this system as they resulted in no product formation and the recovery of the starting materials. (Scheme 2, entries 3m and 3n respectively). To expand this scope, the use of 4-bromostilbene as a starting material and benzaldehyde afforded the corresponding imidazole as a mixture of tautomers in a good yield of 74% (Scheme 2, entry 3o) while the use of a *para*-substituted bromobenzaldehyde afforded the corresponding imidazole in a good yield of 78%, also as a mixture of tautomers (Table 2, entry 3p).

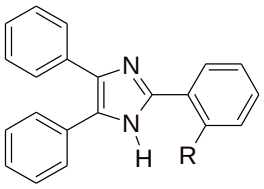




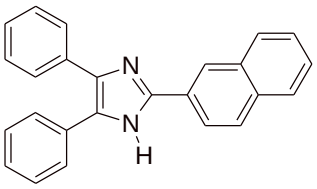
3a, R = H, 85%
3b, R = Cl, 83%
3c, R = Br, 87%



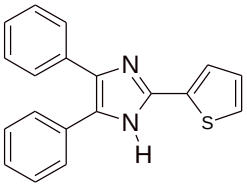
3d, R = NO_2, 73%
3e, R = Br, 75%
3f, R = Cl, 73%



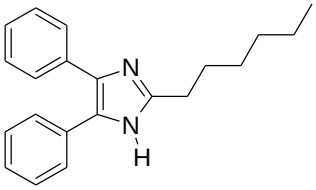
3g, R = OMe, 66%
3h, R = Me, 61%



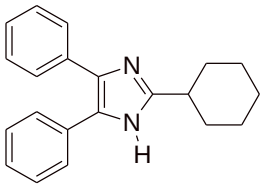
3i, 79%



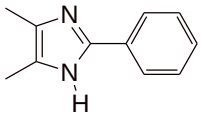
3j, 43%



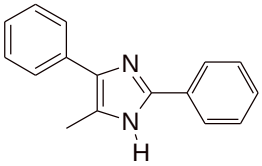
3k, 0%[b]



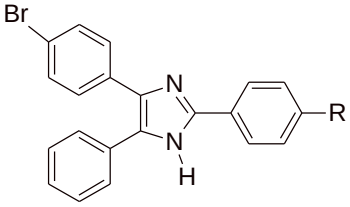
3l, Trace[c]



3m, 0%[d]



3n, 0%[d]



3o, R = H, 74%[e]
3p, R = Br, 78%[e]

Scheme 2. Reaction conditions: Step 1: **1** (0.5 mmol), I_2 (1.25 equiv.) in DMSO (0.5 mL) at 155 °C for 20 h. Step 2: **2** (0.5 mmol), NH_4OAc (5 mmol) in *n*-BuOH (1 mL) reflux for 1 h. [a] Isolated yield. [b] Step 2 for 24 h. [c] Step 2 for 48 h. [d] Step 1 for 24 h. [e] Mixture of tautomers.

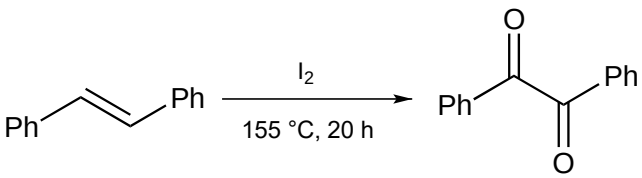
To gain insight into the reaction mechanism, various control experiments were carried out and firstly, *trans*-stilbene **1a** was reacted with I_2/DMSO at 155 °C for 20 hours to afford benzil **4a** an isolated yield of 96% (Scheme 3, reaction i). This result indicates that the α-diketone is indeed a key intermediate in the trisubstituted imidazole synthesis. To provide more information on the α-diketone formation, a radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO) was added to the reaction mixture under the same conditions and benzil was still formed in an isolated yield of 90% (Scheme 3, reaction ii). This suggests that the α-diketone formation does not proceed via a radical pathway.

1a (i) **4a** (96%)

(ii) TEMPO: **4a** (90%)

Scheme 3. Control experiments into the formation of the α-diketone

Next, we focused our attention on determining the oxygen source in the formation of the key α-diketone. Hypothetically, there are three possible sources of oxygen for the preparation of benzil from *trans*-stilbene, namely, molecular oxygen from the air, trace water in DMSO, and DMSO itself. To determine the oxygen source for this transformation, the benzil synthesis was first conducted under inert conditions and **4a** was obtained at an isolated yield of 95% (Scheme 4, reaction i), suggesting that oxygen from the air is not part of this system. Next, this oxidation reaction was then conducted under inert conditions using anhydrous DMSO, and **4a** was still obtained at an isolated yield of 98% (Scheme 4, reaction ii). This indicates trace water from the DMSO is not the source of oxygen and that DMSO is the source of oxygen in the formation of α-diketone.



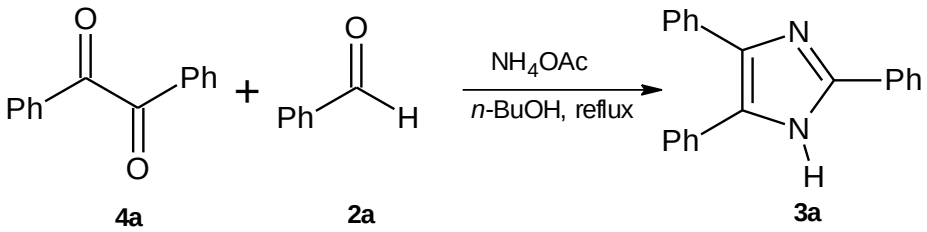
1a **4a**

(i) DMSO, N_2 (95%)

(ii) anhydrous DMSO, N_2 (98%)

Scheme 4. Control experiments into the source of the oxygen atoms in the formation of benzil

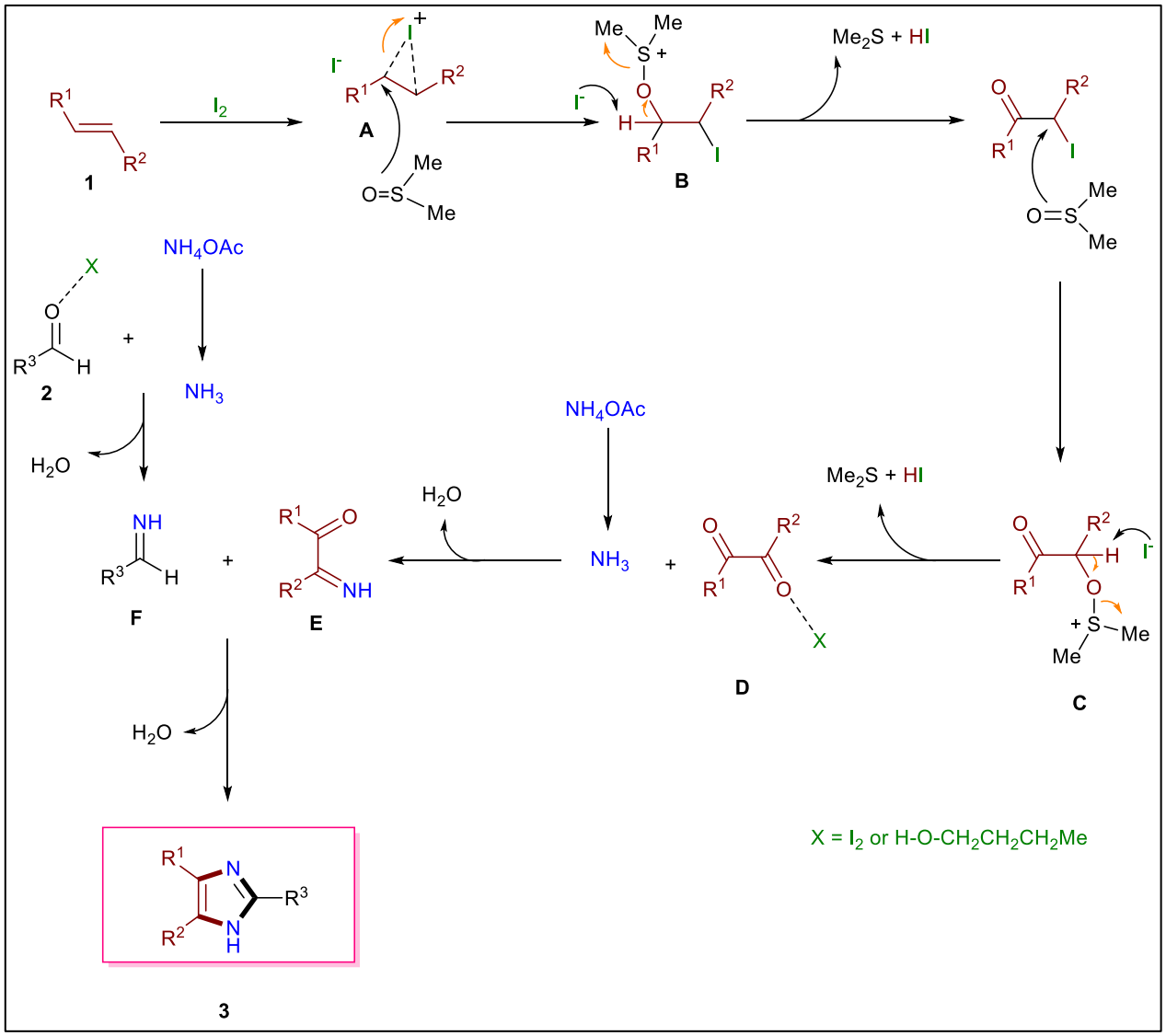
Thereafter, the coupling step was examined whereby benzil **4a**, benzaldehyde **2a**, and ammonium acetate were refluxed in *n*-butanol to form the 2,4,5-triphenylimidazole. In the presence of molecular iodine, the imidazole was formed in an isolated yield of 87% (Scheme 5, reaction i). This suggests that iodine is part of coupling process and assists in imidazole formation. Interestingly, in the absence of molecular iodine, the imidazole was still obtained in an isolated yield of 56% (Scheme 2, reaction ii). We speculate this observation is due to the reaction being catalyzed by the solvent (*n*-butanol) via hydrogen bonding as trisubstituted imidazole synthesis is known to proceed in the absence of catalyst in polar, protic solvents.[30] Finally, the addition of TEMPO had little impact on the reaction as the target imidazole was still formed in a yield of 85% suggesting that the coupling step does not proceed by a radical pathway.



(i) I_2 (87%)
(ii) No I_2 (56%)
(iii) I_2, TEMPO (85%)

Scheme 5. Analysis of the coupling step for the formation of 2,4,5-triphenylimidazole

Based on the results from the control experiments as well as literature reports,[31-35] a plausible mechanism is outlined in Scheme 6. The reaction commences with the activation of the double bond of the alkene by iodine to form iodonium intermediate **A**. Next, a molecule of DMSO attacks **A** to form intermediate **B**, whilst releasing dimethyl sulfide to generate an iodoketone. The generated iodoketone is then trapped by a molecule of DMSO to form intermediate **C**, which proceeds to form a α-diketone, while simultaneously releasing another molecule of dimethyl sulfide. Concurrently, α-diketone **D** and an aldehyde **2** are activated by either iodine or hydrogen bonding from *n*-butanol and upon reaction with ammonia forms imine intermediate **E** and **F** which undergo cyclocondensation to afford the desired 2,4,5-trisubstituted imidazole.



Scheme 6. Proposed route to 2,4,5-trisubstituted imidazoles commencing from internal alkenes

In conclusion, an innovative method using I_2/DMSO system to prepare 2,4,5-trisubstituted imidazoles commencing from internal alkenes and aldehydes has been developed. This methodology was applied to a variety of substrates and the target imidazole derivatives were prepared in moderate to good yields. Preliminary mechanistic investigations suggested that an α-diketone is indeed a key intermediate and that the reaction is catalyzed by molecular iodine and *n*-butanol.

EXPERIMENTAL

All reagents were purchased and used without further purification. All ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker Avance III Spectrometer operating at either 400 or 500 MHz. Chemical shifts (δ) were reported in ppm using deuterated dimethyl sulfoxide (DMSO-d_6) residual

peak (δ 2.50) for ^{1}H-NMR. Chemical shifts of ^{13}C-NMR were reported relative to DMSO-*d*$_6$ (δ 39.51). The following abbreviations were used to describe peak splitting patterns where appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants, *J*, were reported in Hertz units (Hz). Low-Resolution electron-spray ionization (ESI) mass spectra were recorded on a time-of-flight (TOF) micromass spectrometer. Infrared (IR) spectra were recorded on Agilent Carey 630 Spectrometer. Melting points were determined using the Kofler-hot stage melting point apparatus and are uncorrected.

Typical Procedure for the preparation of 2,4,5-trisubstituted imidazoles (3): Alkene (0.5 mmol) and iodine (0.625 mmol) were mixed in a 10 mL test tube with 0.5 mL DMSO and heated at 155 °C for 20 h. Thereafter, aldehyde (0.5 mmol), ammonium acetate (5 mmol), and *n*-butanol (1 mL) were added, and the mixture was refluxed for 1 h. After cooling, 10 mL of sodium thiosulfate/ice-cold water was added to the mixture where the crude product was precipitated, filtered, and dried in an oven. The crude precipitate was recrystallized from acetone: water (9:1) solution to yield the desired product.

2,4,5-Triphenyl-1*H*-imidazole (3a, $C_{21}H_{16}N_2$, 85%):[36] as a white solid; mp 269-271 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12,69 (s, 1H), 8.11-8.09 (d, *J* = 7.45 Hz, 2H), 7.55 – 7.51 (m, 4H), 7.47 – 7.40 (m, 3H), 7.38 – 7.26 (m, 6H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 146.0, 137.6, 135.7, 131.6, 129.2, 129.1, 128.9, 128.7, 128.65, 128.2, 127.6, 127.0, 126.7; ṽ (neat, cm^{-1}): 3734, 3021, 1592, 1488, 1461, 1127; ESI-MS (*m/z*): 295.1240 (100) [M-H$^+$], 296.1268 (25) [M$^+$].

2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (3b, $C_{21}H_{15}N_2Cl$, 83%):[37,38] Creamy white solid; mp 261-263 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.77 ppm (s, 1H), 8.12-8.10 ppm (d, *J* = 8.41 Hz, 2H), 7.57 – 7.54 (d, *J* = 8.67 Hz, 2H), 7.53 – 7.51 (m, 2H), 7.48 – 7.43 (m, 2H), 7.41 – 7.38 (m, 2H), 7.26 – 7.22 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) *δ* 144.9, 137.8, 135.5, 133.2, 129.7, 129.2, 129.1, 129, 128.9, 128.7, 128.3, 127.6, 127; ṽ (neat, cm^{-1}) = 2638.7, 1482, 1126, 766; ESI-MS (*m/z*) = 329.0857 (100) [M-H]$^+$, 331.0836 [M+H]$^+$.

2-(4-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (3c, $C_{21}H_{15}BrN_2$, 87%):[39,40] mp 256-258 °C ^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 12.78 (s, 1H), 8.06 – 8.03 (d, *J* = 8.57 Hz, 2H), 7.70 – 7.68 (d, *J* = 8.52 Hz, 2H), 7.53 (m, 4H), 7.48 – 7.22 (m, 6H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) *δ* 145, 137.9, 135.5, 132.1, 131.06, 130, 129.5, 129.1, 128.9, 127.6, 121.9; ṽ (neat, cm^{-1}) : 3430, 2648, 2109, 1596, 1478, 1124, 764; ESI-MS (*m/z*): 375.03 (100) [M+H]$^+$, 376.04 (25) [M+2H]$^+$.

2-(3-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (3d, $C_{21}H_{15}O_2N_3$, 73%):[37,38] yellow solid; mp 315-317 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 13.08 (s, 1H), 8.96 (s, 1H), 8.53 – 8.51 (d, *J* =8.01 Hz, 1H), 8.22

– 8.19 (d, *J* = 8.23 Hz, 1H), 7.80 – 7.75 (t, *J* = 8.00 Hz, 1H), 7.57 – 7.52 (m, 4H), 7.46 – 7.33 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.8, 143.9, 138.2, 135.2, 132.3, 131.6, 131.1, 130.8, 130, 129.2, 128.9, 128.7, 127.6, 127.3, 123, 119.9; ṽ (neat, cm^{-1}) : 2853, 1584, 1524, 1471, 1346, 1418, 1252, 1073; ESI-MS (*m/z*): 343.1117 (15) $[M+2H]^+$, 342.1087 $[M+H]^+$.

2-(3-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (3e, $C_{21}H_{15}BrN_2$, 75%):[41] Yellow solid; mp 300-301 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 8.32 (m, 1H), 8.10 – 8.09 (d, *J* = 8.11 Hz, 1H), 7.56 – 7.22 (m, 12H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.35, 137.92, 135.4, 133, 131.3, 131.2, 129.3, 129.1, 128.9, 128.7,128.4, 128, 127.6, 127.1, 124.5, 122.6; ṽ (neat, cm^{-1}) : 3025, 1687, 1578, 1458, 1070, 846, 695; ESI-MS (*m/z*): 375.0492 (100) $[M+H]^+$, 377.0478 (100), 376.0537 (30) $[M+2H]^+$.

2-(3-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (3f, $C_{21}H_{15}ClN_2$, 73%):[42] white solid; mp 297-299 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.16 (s, 1H), 8.08 – 8.05 (d, *J* = 7.89 Hz, 1H), 7.56 – 7.29 (m, 12H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.5, 134.1, 132.8, 131.1, 128.9, 128.4, 128.2, 127.8, 125.1, 124.2; ṽ (neat, cm^{-1}): 3377, 1580, 1455, 1129, 767; ESI-MS (*m/z*): 329.1046 (100) $[M-H]^+$, 331.1026 $[M+H]^+$, 332.1050 $[M+2H]^+$.

2-(2-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (3g, $C_{22}H_{18}ON_2$, 66%):[43,44] White solid; mp 207-209 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.08-8.05 (d, *J* = 7.66 Hz, 1H), 7.55- 7.53 (d, *J* = 7.45 Hz, 2H), 7.49 – 7.47 (m, 2H), 7.45 – 7.42 (t, *J* = 7.55 Hz, 2H), 7.39 – 7.37 (m, 2H), 7.32 – 7.28 (t, *J* = 7.51 Hz, 2H), 7.23 – 7.20 (m, 1H), 7.18 – 7.16 (d, *J* = 8.12 Hz, 1H), 7.10 – 7.06 (t, *J* = 7.51 Hz, 1H), 3.93 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.5, 143.6, 136.9, 135.8, 131.7, 130.2, 129.3, 129.08, 129.02, 128.6, 127.9, 127.6, 126.9, 121, 119.4, 112.1, 56.04; ṽ (neat, cm^{-1}) : 3064, 2839, 1590, 1527, 1472, 1391; ESI-MS (*m/z*): 327.1439 (100) $[M+H]^+$, 349.1248 (30).

2-(2-Methylphenyl)-4,5-diphenyl-1*H*-imidazole (3h, $C_{22}H_{18}N_2$, 61%):[21,45] White solid; mp 228-230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 7.73 (m,1H), 7.55 (m, 4H), 7.34 – 7.30 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.6, 136.7, 131.5, 130.5, 129.2, 128.8, 128.7, 127.9, 127.6, 126.9, 126.2, 21.6; ṽ (neat, cm^{-1}): 3151, 2961, 2102, 1646, 1398, 1316; ESI-MS (*m/z*): 311.1480 $[M+H]^+$, 312.1516 (10) $[M+2H]^+$.

2-(2-Naphthyl)-4,5-diphenyl-1*H*-imidazole (3i, $C_{25}H_{18}N_2$, 79%):[46] White solid; mp 274-276 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 8.64 (s, 1H), 8.30 – 8.27 (d, *J* = 8.60 Hz, 1H), 8.03 – 7.94 (m, 3H), 7.60 – 7.51 (m, 6H), 7.41 – 7.30 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146, 136, 133.5, 133.2, 128.9, 128.7, 128.6, 128.3, 128.2, 127.7, 127.2, 126.8, 124.2, 124; ṽ (neat, cm^{-1}): 2761.3, 1589.3, 1498, 1447, 1409, 1343, 1264, 1072; ESI-MS (*m/z*): 347.1555 (100), 348.1612 (30).

4,5-Diphenyl-2-(thienyl)-1*H*-imidazole (3j, $C_{19}H_{14}N_2S$, 43%):[26] Brown solid; mp 258-260 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 7.70 – 7.69 (d, J = 3.68 Hz, 1H), 7.56 – 7.40 (m, 8H), 7.31 (m, 2H), 7.25 – 7.16 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.1, 137.3, 135.3, 134.4, 131.3, 129.6, 129.2, 128.8, 128.6, 128.4, 128.3, 127.6, 127.1, 126.7, 124.2; ṽ (neat, cm^{-1}): 3381, 1650, 1002; ESI-MS (*m/z*): 301.0802 (100) $[M-H]^+$, 302.0837 (25) $[M^+]$, 303.0798 $[M+2H]^+$.

5-(4-Bromophenyl)-2,4-diphenyl-1*H*-imidazole (3o, $C_{21}H_{15}BrN_2$, 74%):[19] White solid; mp 254-256 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (s, 1H), 8.10 – 8.08 (d, J = 7.44 Hz, 2H), 7.57 – 7.37 (m, 12H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.3, 131.8, 130.7, 129.9, 129.2, 129.1, 128.8, 128.6, 128, 125.7; ṽ (neat, cm^{-1}): 3046, 2825, 1562, 1461, 979, 767; ESI-MS (*m/z*): 375.0597 (100) $[M+H]^+$, 376.0633 (24).

2,5-Bis-(4-bromophenyl)-4-phenyl-1*H*-imidazole (3p, $C_{21}H_{14}Br_2N_2$, 78%):[19] Creamy white solid; mp 253-256 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 8.05 – 8.03 (d, J = 8.62 Hz, 2H), 7.70 – 7.68 (d, J = 8.67 Hz, 2H), 7.53 – 7.34 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.3, 132.1, 131.8, 129.9, 129.1, 128.5, 128.1, 127.6, 122; ṽ (neat, cm^{-1}): 3063, 2828, 1601, 1477, 1069, 825, 722; ESI-MS (*m/z*): 452.9750 (100) $[M+H]^+$, 450.9771 (50) $[M-H]^+$, 455.9761 (15).

Benzil (4a, $C_{14}H_{10}O_2$, 96%):[47,48] Yellow solid, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.01 – 7.99 (d, J = 8.27 Hz, 4H), 7.7 – 7.66 (t, J = 7.43 Hz, 2H), 7.56 – 7.51 (t, J = 7.78 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.6, 134.9, 133, 129.9, 129.

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