THE DIRECT OXIDATION OF C_{SP}^3-H BENZYL ARYL KETONES TO 1,2-DIARYL DIKETONES AS A KEY STEP FOR THE MULTI-COMPONENT SYNTHESIS OF 2,4,5-TRISUBSTITUTED-1*H*-IMIDAZOLES

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By

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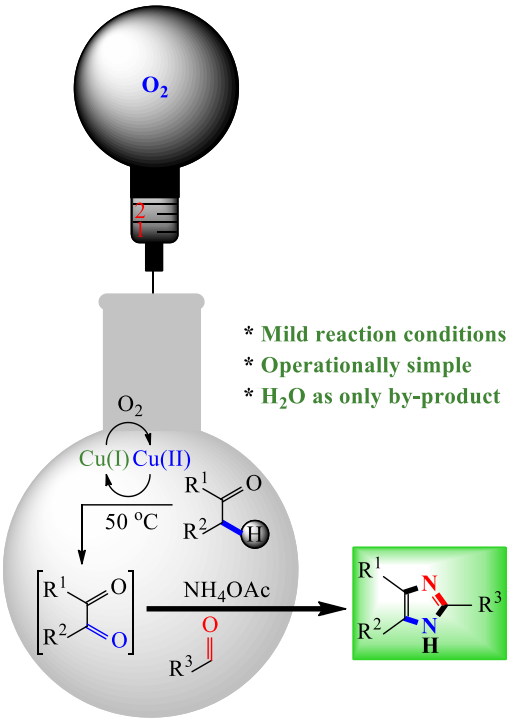
List of Publications

1. **Copper-Catalyzed Aerobic Benzylic sp^3 C-H Oxidation Mediated Synthesis of 2,4,5-Trisubstituted Imidazoles via a Domino Multi-component Reaction**

   Janeeka Jayram and Vineet Jeena

   Green Chem., 2017, **19**, 5841-5845



2. **An Iodine/DMSO-Catalyzed Sequential One-Pot Approach to 2,4,5-Trisubstituted-1*H*-imidazoles From α-Methylene Ketones**

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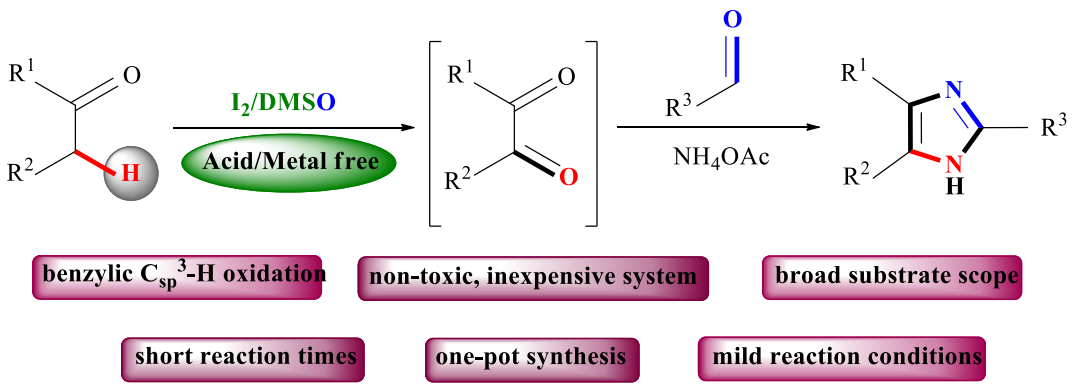
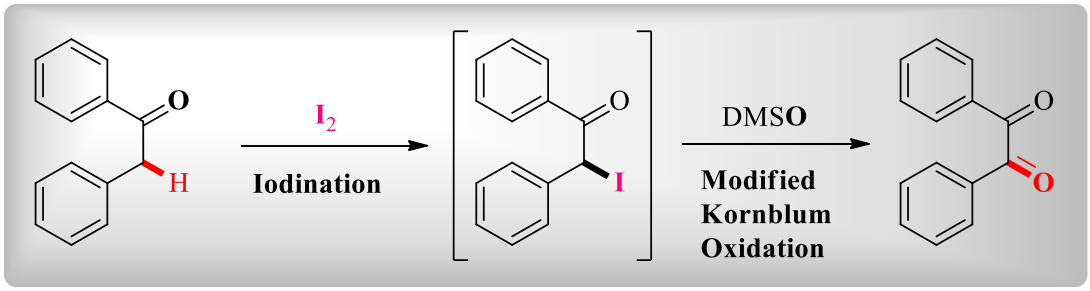
   RSC Adv., 2018, **8**, 37557-37563



3. **Iodine/DMSO promoted oxidation of benzylic Csp^3–H bonds to diketones - A mechanistic investigation**

Janeeka Jayram, Bheki A. Xulu and Vineet Jeena

Tetrahedron, 2019, **75**, 130617



Dedicated to

My

Parents

Minnesh and Sandiah Jayram

and

My

Beloved Grandmother

Dasodi Ramperthab

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Abbreviations

Abbreviation	Description
$(COCl)_2$	Oxalyl chloride
AA	Acrylic acid
Ac_2O	Acetic anhydride
ACC	Ammonium Chlorochromate
AMPS	2-Acrylamido-2-methyl-1-propane sulfonic acid
BDE	Bond Dissociation Energy
BHT	Butylated hydroxytoluene
BTPPC	Benzyltriphenyl phosphonium chloride
$CDCl_3$	Deuterated chloroform
CE	Carboxylesterase
COX	Cyclooxygenase
DCC	Dicyclohexylcarbodiimide
DCPFC	Dicarboxypyridinium fluorochromate
DG	Directing group
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DPS	Diphenyl sulfide
DPSO	Diphenyl sulfoxide
EPR	Electron paramagnetic resonance
ESI	Electron-spray ionization
EtOH	Ethanol
FTIR	Fourier-transform infrared spectroscopy
HAT	Hydrogen Atom Transfer
HRMS	High resolution mass spectroscopy
HX	Lewis acid
Hz	Hertz
IBX	2-Iodobenzoic acid
IR	Infrared

KPS	Potassium persulfate
LG	Leaving group
MAOS	Microwave assisted organic synthesis
MAPK	Mitogen activated protein kinase
MBA	Methyl bisacrylamide
MCR	Multi-component reaction
MW	Microwave
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NP	Nano particles
NSAID	Non-steroidal anti-inflammatory drug
O-DCB	*O*-Dichlorobenzene
P_2O_5	Phosphorous pentoxide
PCC	Pyridinium chlorochromate
PEG	Polyethylene glycol
Ph_3Sb	Triphenylstibane
PPh_3	Triphenyl phosphine
SET	Single Electron Transfer
SiO_2	Silicon dioxide
SSA	Silica sulfuric acid
TBA	Tetrabutyl ammonium
TEMPO	2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFAA	Trifluoroacetic anhydride
TM	Transition metal
TOF	Time-of-flight
TOP	Tandem oxidation process
WD	Wells-Dawson

Abstract

1,2-Diaryl diketones are significantly important structural motifs, in many fields of science, as well as important building blocks in synthetic organic chemistry, for the preparation of diverse *N*-heterocyclic compounds. Most unsymmetrical 1,2-diaryl diketones are, however, commercially unavailable and despite some constructive methods to furnish 1,2-diaryl diketones, there are many synthetic limitations to access these scaffolds. On the contrary, the direct oxidation of benzyl aryl ketones offers novel, innovative and improved transformations to access diverse 1,2-diaryl diketones for application in chemical syntheses. Accordingly, this thesis focuses on the direct oxidation of C_{sp}^3–H benzyl aryl ketones to the corresponding 1,2-diaryl diketones, *in situ*, for the preparation of 2,4,5-trisubstituted-1*H*-imidazoles. This methodology employs multi-bond forming procedures such as a domino sequence and a multi-component reaction (MCR) in an environmentally benign manner.

The first study describes an aerobic domino multi-component reaction to synthesize an array of 2,4,5-trisubstituted-1*H*-imidazoles from the direct oxidation of benzyl aryl ketones. This synthesis employs inexpensive copper as a catalyst in the presence of molecular oxygen as the terminal oxidant. An array of 2,4,5-trisubstituted-1*H*-imidazoles were furnished, from simple and commercially available benzyl aryl ketones coupled with aldehydes and ammonium acetate, in moderate to good yields (21-87%) under mild reaction conditions. 2,4,5-Trisubstituted-1*H*-imidazoles with substituents on the benzyl aryl ketone and benzaldehydes were isolated as a mixture of tautomers in moderate to good yields (52-72%). In an effort to improve the environmentally friendly nature of this synthetic protocol, a catalytic loading study was undertaken, whereby the catalyst loading was decreased from 5 mol% to 0.5 mol% to afford satisfactory yields of the desired imidazole product. Based on literary studies, a plausible reaction mechanism was proposed in order to rationalize the oxidation of benzyl aryl to diketones under the copper-O_2 oxidative system.

While the synthetic methodology, described in Chapter 2, proves its efficiency to make 2,4,5-trisubstituted-1*H*-imidazoles and, despite catalytic amounts of an inexpensive copper catalyst, the use of a transition metal detracts from the contemporary desire for green chemistry. Accordingly, Chapter 3 discloses the results of an improved methodology to synthesize 2,4,5-trisubstituted-1*H*-imidazoles from the direct oxidation of C_{sp}^3–H benzyl aryl ketones via

a sequential one-pot domino reaction. An air-moisture stable iodine/DMSO oxidative system was employed, affording a diverse range of 2,4,5-trisubstituted-1*H*-imidazoles in moderate to good yields (35-86%). With the aim of enhancing the diversity and possible biological relevance of the imidazole structural motif, a substrate scope, not known in literature, was established to furnish a series of novel 2,4,5-trisubstituted imidazoles in moderate to good yields (53-85%) as a mixture of tautomers. The iodine/DMSO system was extended to the domino convergent synthesis of two functionalized intermediates, benzil and benzaldehyde, prepared via the oxidation of benzyl phenyl ketone and benzyl alcohol, respectively, to produce the resulting 2,4,5-trisubstituted imidazole in a 48% isolated yield. A series of control experiments were undertaken to gain insight into the reaction mechanism, indicating a series of consecutive iodination/modified Kornblum oxidation/cyclization to afford the desired 2,4,5-trisubstituted imidazoles. As a result, a proposed reaction mechanism was provided in an effort to gain insight into the iodine/DMSO mediated oxidation of benzyl aryl ketones to afford, *in situ*, generated diketones for subsequent coupling with aldehydes and ammonium acetate to furnish 2,4,5-trisubstituted-1*H*-imidazoles.

The significant point of interest of Chapter Four is an in-depth mechanistic study into the iodine/DMSO mediated benzylic C_{sp}^3–H oxidation of a benzyl aryl ketone to a 1,2-diaryl diketone. An array of isolation and spectroscopic techniques (electron paramagnetic resonance [EPR], nuclear magnetic resonance [NMR]), radical traps and the judicious choice of experimental conditions was employed to support the proposed mechanism. The employment of EPR afforded a spectrum centred at g = 2.0011, characteristic of a phenolic radical of butylated hydroxytoluene (BHT) which subsequently inferred the presence of iodine radicals. This result proved the presence of benzylic radicals, positioned on the α-carbon of benzyl phenyl ketone, which were trapped *via* the radical inhibitor, 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO). A singlet at 5.92 ppm in the ^{1}H NMR spectrum is consistent with the C–O bond formation between the benzylic radical of benzyl phenyl ketone and the oxygen radical of TEMPO. These results indicated the involvement of an α-iodinated species, 2-iodo-1,2-diphenylethanone, as the key reactive intermediate in the oxidation reaction, which was subsequently isolated through a series of reaction conditions. The resulting characteristic signal at 6.65 ppm in the ^{1}H NMR spectrum corresponded to the α-proton of the α-iodoketone. The major source of oxygen in the diketone was proven via a sequence of experiments, proving dimethyl sulfoxide (DMSO) as the major source of oxygen.

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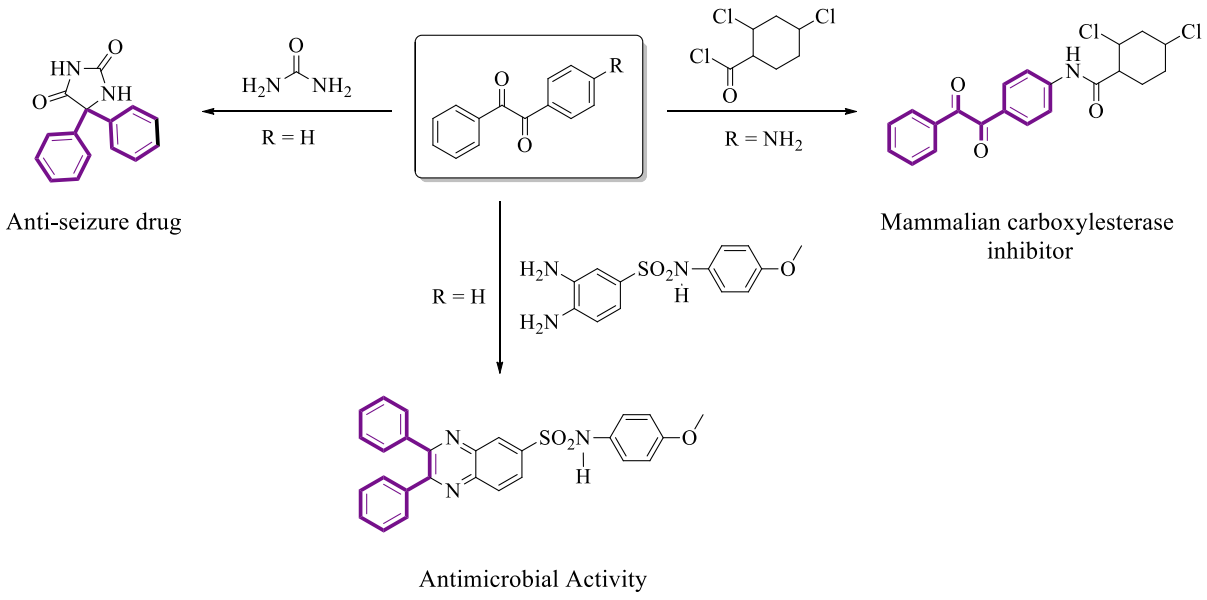
Chapter 1: Literature Review

1.1 The 1,2-Diaryl Diketone Structural Motif

1.1.1 Applications in Science

1,2-Diaryl diketones are a class of unique and versatile synthetic intermediates possessing high reactivity, owing to the presence of the characteristic vicinal electron-deficient carbonyl functional groups.[1] More notably, the 1,2-diaryl diketone motif displays rich applications across numerous fields of science[2] as these scaffolds are employed as key building blocks in synthetic organic chemistry to yield various biologically active carbohydrates[3] and *N*-heterocyclic compounds such as: quinoxalines, imidazoles, triazines, indolone-*N*-oxides and imidazolidines.[4] In addition, they are common photo-initiators in polymer chemistry and photosensitive agents in photocurable coatings.[5] Recently, 1,2-diaryldiketones have demonstrated potent inhibition of mammalian carboxylesterases (CE); enzymes involved in the hydrolysis of carboxylesters which form part of active biological species, application as an anti-seizure drug and antimicrobial activity (**Scheme 1**).[6]

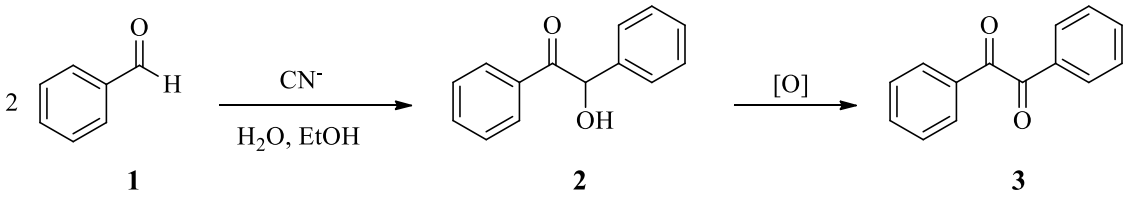


Scheme 1: Significance of 1,2-diaryl diketone structural motifs as precursors for important linear and *N*-heterocyclic compounds in the pharmaceutical industry.

1.1.2 Synthesis of 1,2-Diaryl Diketones

1.1.2.1 Classical Synthesis

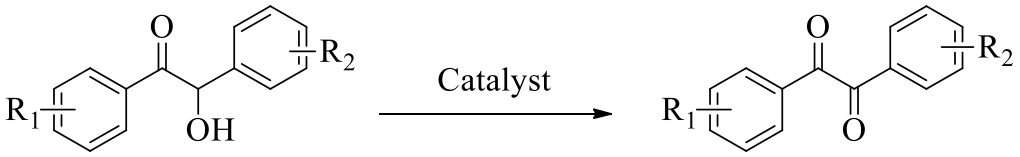
Classically, 1,2-diaryl diketones are prepared through the benzoin condensation of two aromatic aldehydes **1** to afford α-hydroxy ketones **2** which are subsequently oxidized ([O]) to yield the desired 1,2-diaryl diketone **3** (**Scheme 2**).[7] While this strategy shows high efficiency toward symmetrically substituted 1,2-diaryl diketones, its extension to the formation of unsymmetrically substituted 1,2-diaryl diketones is difficult due to the lack of regiochemical control in the cross-benzoin reaction of different aldehydes.[8]



Scheme 2: Classical synthesis of symmetric diphenylethanedione from the benzoin condensation of two aldehydes catalyzed by cyanide as the nucleophile.

1.1.2.2 Synthesis from Benzoin

Parallel to the classical synthesis, the most common synthetic route to access 1,2-diaryl diketones involves the direct oxidation of substituted benzoin derivatives. There are numerous catalysts employed to permit this transformation ranging from: the use of Burgess reagent (methyl *N*-(triethylammoniumsulfonyl)carbamate) under conventional heating, ammonium chlorochromate/silica gel (ACC/silica gel) *via* ultrasound irradiation, triphenylstibane (Ph_3Sb) under aerobic conditions to hydrophobic ionic liquid-supported 2-Iodoxybenzoic acid (IBX) and *N*-bromosuccinimide supported aluminium oxide (NBS-Al_2O_3) employing microwave irradiation (**Scheme 3**).[9]

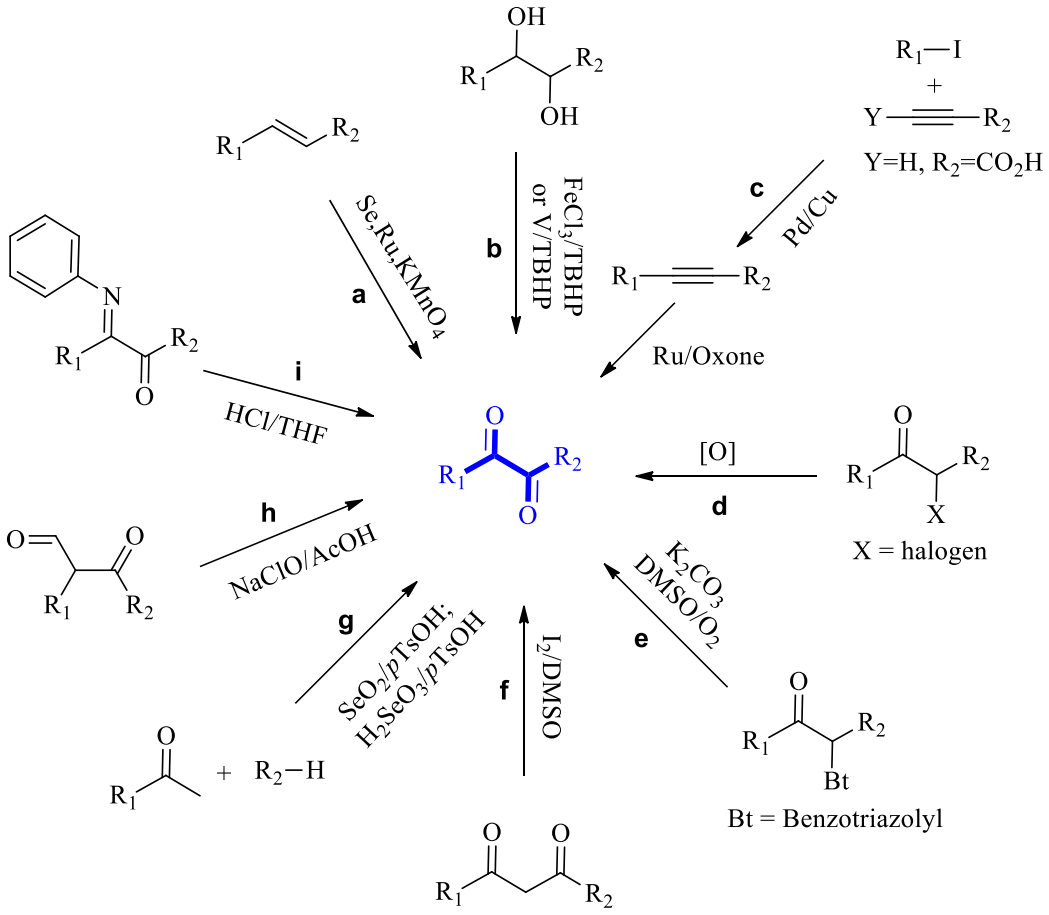


Scheme 3: Direct oxidation of benzoin to afford 1,2-diaryl diketones.

1.1.2.3 The Typical Synthetic Toolbox

Most unsymmetrical 1,2-diaryl diketones are not commercially available and thus, as a consequence of the burgeoning applications in natural, synthetic and medicinal chemistry, the typical synthetic toolbox encompasses several methodologies (**Scheme 4**) based on:

1. the oxidation of precursors such as olefins, vicinal diols, (internal) acetylenes, α-halo ketones and benzotriazolyl ketones (**a-e**);[10]
2. the oxidative C–C bond cleavage of 1,3-diketones (**f**);[11]
3. the oxidative coupling of acetophenones with unactivated arenes (**g**);[12]
4. non-oxidative protocols, commencing from β-ketoaldehydes (**h**) or iminoethanones (**i**).[8b, 13]



Scheme 4: Existing synthetic strategies to access unsymmetrical 1,2-diaryl diketones commencing from numerous substrates.

Despite some constructive synthetic methodologies, the access to diverse 1,2-diaryl diketone precursors employing methods from the typical synthetic toolbox (*vida supra*) has several disadvantages:

1. the discharge of bulk metal or organic waste;
2. the prior preparation of internal acetylenes (**Scheme 4**, **c**);
3. the utilization of toxic or expensive starting materials and/or transition metal catalysts;
4. the subsequent low yields and
5. the requirement for several non-trivial synthetic steps.

As a consequence of the increasing demand for sustainable and environmentally friendly oxidations, the development of a simple, straightforward and selective method to access

1,2-diaryl diketones is highly desired. Such a methodology should fulfill the following criteria (**Figure 1**):

Figure 1: Different efficiency considerations for the direct and selective oxidation of numerous substrates to furnish 1,2-diaryl diketones.

At this stage, it is necessary to point out that the direct oxidation of benzoin and the methods given in the synthetic toolbox is not the focus this PhD but rather information given in order to highlight the relevant literature. The central focus is, therefore, the direct functionalization of benzyl aryl ketones which will be discussed in the subsequent sections.

1.2 The Direct Functionalization of C_{sp}^3–H bonds

There are innumerable reports documented in literature for the direct functionalization of different substrates to furnish various substituted 1,2-diaryl diketones (*vida supra*). Conversely, the activation of diverse C_{sp}^3–H bonds, ubiquitous in natural and synthetic organic compounds,[14] is an established approach for the formation of carbon–carbon (C–C) and carbon-heteroatom (C–X, X = N, O, S) bonds in different *C*–, *N*–, *O*– and *S*–heterocycles – the essential link in all organic molecules.[15] This strategy introduces novel and innovative transformations, necessary, to prepare complex molecules displaying significant applications in the synthesis of pharmaceuticals, natural products, polymers and agrochemicals.[16] However, despite the various efficient ways that C_{sp}^3–H bonds are exploited in nature, as high value fragments in molecules by simple activation,[17] chemists have rarely paralleled such

general and convenient methodologies in synthetic compound assembly.[18] In view of this, two fundamental disadvantages have been identified and are therefore associated with C_{sp}^3–H functionalization in comparison with the easier and regio-selective activation of C_{sp}–H and C_{sp}^2–H bonds:[19]

(1) The chemically inert nature of C_{sp}^3–H bonds, which have inherently high thermodynamic stability, hinders achieving a complete regio-selectivity without requiring multiple synthetic steps. This general lack of reactivity derives from the fact that C_{sp}^3–H bonds are less acidic, non-polarizable, localized and lack proximal empty low-energy or high-energy filled orbitals.

(2) The similar bond dissociation energies (BDE) of diverse C_{sp}^3–H bonds (**Figure 2**), coupled with the energetic and spatial inaccessibility of the C–H bonding and anti-bonding orbitals, make site-selective functionalization difficult, particularly in complex molecules. Analysis of the BDE in **Figure 2** shows that the threshold for conversion of C–H bonds into a C=O group is approximately 90.0 kcal/mol. As the BDE increases above 90.0 kcal/mol, the ability to convert the unreactive C–H bonds to C=O becomes more challenging. This is further accentuated by the high reactivity of the enrolled reagents, capable of breaking these bonds, which is often incompatible with the functional groups in the molecule as well as chemo- and site-selective transformations.

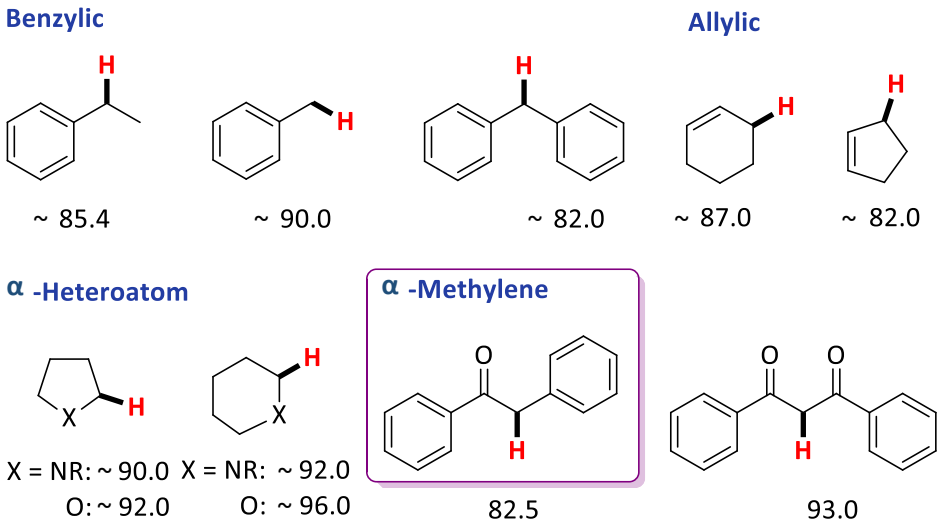
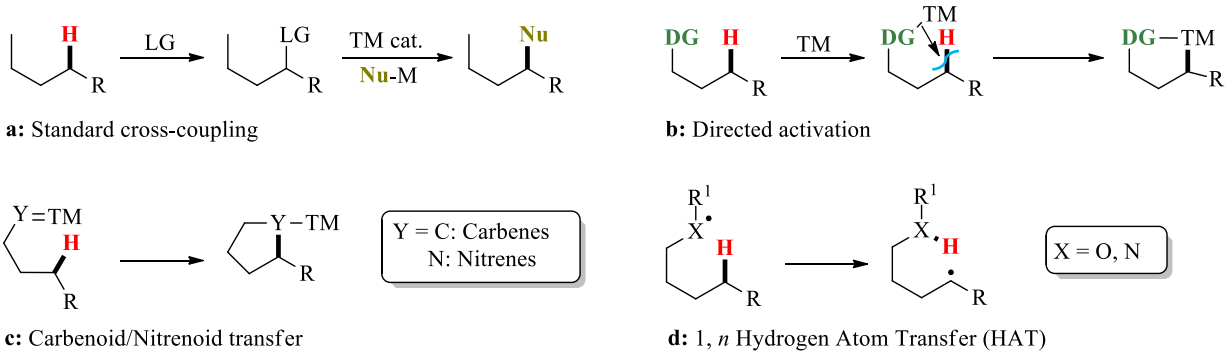


Figure 2: Bond dissociation energies (BDE in kcal/mol) of similar C_{sp}^3–H bonds present in different organic compounds.

Accordingly, different approaches[20] have been introduced over the past decade in order to address these challenges (**Scheme 5**): standard cross-coupling involving pre-insertion of a good leaving-group (LG), followed by nucleophilic (Nu) substitution or transition metal (TM) catalyzed coupling (**a**),[21] directed C–H metalation (via thermodynamically stable cyclic transition states) (**b**),[22] TM carbenoid or nitrenoid facilitated C–H insertion via concerted or single-electron transfer (SET) processes (**c**)[23] and 1, *n* hydrogen atom transfer (HAT) (**d**);[24] all of which enables $C_{sp}{}^3$–H functionalization in a chemo-, regio- and stereo-selective fashion. Among these, the use of auxiliary directing groups (DG), occasionally in the presence of mono or bidentate ligands not frequently part of the target molecule, which assist in TM catalyzed cross-coupling reactions, is the methodology of choice to control reactivity, regio-selectivity and site-selectivity in $C_{sp}{}^3$–H functionalization reactions so as to build structural patterns for synthetic chemistry.[19i, 25]



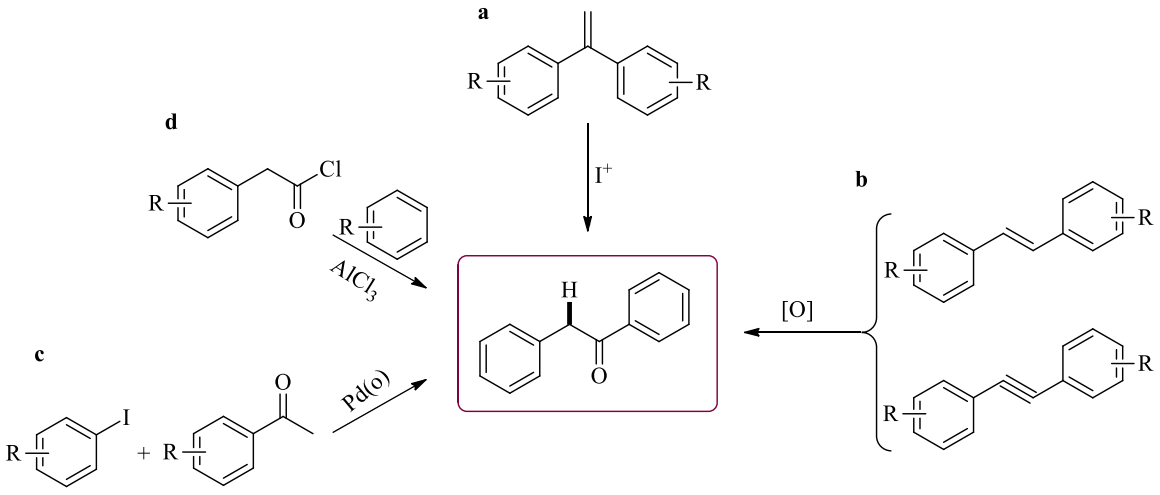
Scheme 5: Different strategies for $C_{sp}{}^3$–H functionalization of different substrates so as to allow controlled selectivity.

The direct and selective functionalization of $C_{sp}{}^3$–H bonds provides new and improved synthetic pathways to access valuable complex molecules, obviating the traditional requirement for pre-functionalization of starting materials, protecting groups and functional group manipulation/ exchange. Undoubtedly, there are fundamental benefits for integrating such a strategy in natural and synthetic chemistry, especially from the vantage point of environmental benignity and high atom/ step economy.[26] Thus, $C_{sp}{}^3$–H functionalization reactions, inspired by a rational design of experimental conditions, provide a complete regio-selectivity on substrates with numerous active sites and avenues for improvement in site-selectivity. This is an ongoing endeavour for researchers engaged in modern synthetic

chemistry, with a typical example involving the oxidative functionalization of benzylic methylene Csp^3–H bonds, as these are highly valuable feedstock materials in the pharmaceutical and industrial sectors.[27]

1.3 The Benzyl Aryl Ketone Structural Motif

Benzyl aryl ketones are a vital class of compounds found in several plants and marine sources.[28] While these compounds can be extracted, a literature survey search showed the following methodologies are available to access benzyl aryl ketones: I^+ rearrangement of 1,1-diaryl ethylenes (**Scheme 6, a**), oxidation of 1,2-stilbenes (**Scheme 6, b**), Pd(O) mediated alkylation of aryl halides with acetophenones (**Scheme 6, c**) and Friedel Crafts acylation of phenylacetyl chlorides (**Scheme 6, d**). Benzyl phenyl ketones are currently commercially available, and hence can be functionalized at the C_{sp}^3–H bond. Accordingly, this thesis focuses on the direct functionalization of commercially available benzyl aryl ketones for subsequent utilization in the synthesis of *N*-heterocyclic compounds.[29]



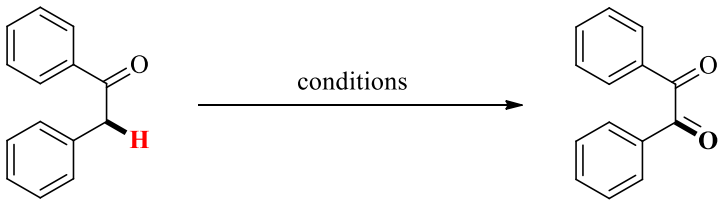
Scheme 6: Synthetic methods available to access benzyl aryl ketones

1.4 The Direct Oxidative Functionalization of C_{sp}^3–H Benzyl Aryl Ketones

1.4.1 The Synthesis of Benzil from the Oxidation of C_{sp}^3–H Benzyl Aryl Ketones

One of the most promising approaches is the direct oxidative functionalization of diverse benzyl aryl C_{sp}^3–H bonds into its respective carbonyl compound.[30] The introduction of an oxygen atom into an organic moiety, from simple methylene substrates, offers direct access to complex building blocks from readily available alkyl arenes.[31] Over the past 20 years, this methodology has been an area of profound interest for researchers in both academic and industrial settings, resulting in a plethora of outstanding syntheses to access substituted diketones.[32]

The direct oxidation of substituted benzyl aryl ketones, to 1,2-diaryl diketones, is a fundamental and indispensable transformation in synthetic organic chemistry (**Scheme 7**). Dating back to the 1900's, the widely employed methods to access these precursors from benzyl aryl ketones relied on the use of toxic selenium dioxide (SeO_2), hydrogen peroxide (H_2O_2) and unsustainable transition metal catalysts (thallium nitrate [$Tl(NO_3)_3$], pyridinium chlorochromate [PCC], Manganese dioxide [MnO_2], Manganese^{III}, Chromium^{VI} and Palladium^{II} complexes).[33] Accordingly, representative examples of the above mentioned catalysts will be discussed.



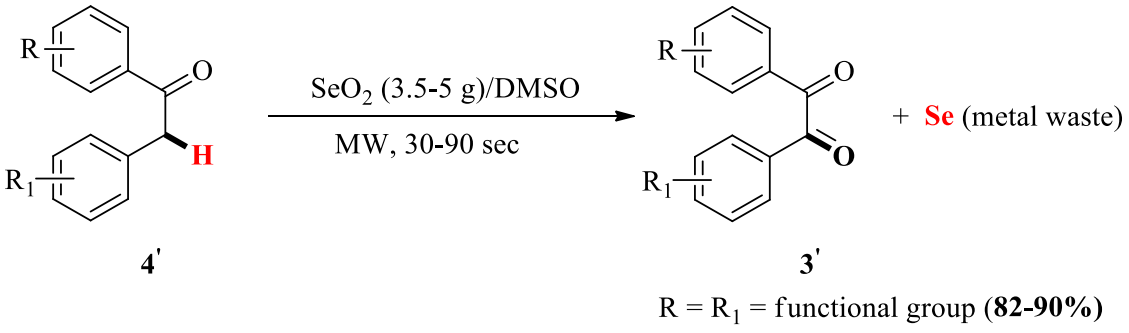
4 **3**

Scheme 7: Representative example for the conversion of benzyl aryl ketones to 1,2-diaryl diketones in the presence of different reaction conditions.

1.4.1.1 The Use of Selenium Dioxide (SeO_2)

Oxidation reactions with selenium dioxide (SeO_2) are generally performed in polar solvents such as: aqueous acetic acid, aqueous ethanol, aqueous dioxane and acetic anhydride-usually at high reaction temperatures (120-160 ^oC) for a minimum of eight hours. In the majority of cases, the reported yields are quantitative and some methods require two-step syntheses.[34] The addition of excess SeO_2 is necessary when acetic anhydride is used as a solvent, since the solvent consumes this reagent and gets oxidized to glyoxylic acid under prolonged refluxing. Moreover, the organic solid contains traces of selenium and organo-selenium compounds, some of which are bound in colloidal form when formed in the presence of the former-mentioned solvents. This, consequently, poses difficulty in processing the reaction media and, as a result, additional work-up procedures are necessary to extract pure diketone products in an effort to attain quality assurance of not contaminating the final product with heavy transition metals (TMs) [as defined previously].[35]

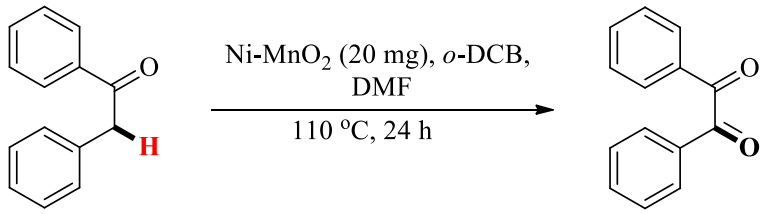
The oxidation of benzyl aryl ketones by SeO_2 was reported by Shirude *et al.* in 2006.[35] The reaction required an equivalent amount of selenium dioxide to aid in the oxidation of the benzyl functionality, affording the desired substituted benzil derivatives in 82-90%. Despite the use of microwave irradiation and short reaction times (30-90 seconds), significant amounts of selenium metal are produced as a by-product, which is detrimental to the environment (**Scheme 8**).



Scheme 8: Oxidation of benzyl aryl ketones by SeO_2 in the presence of DMSO, further exemplifying the endangerment of selenium metal by-product.

1.4.1.2 Different Manganese Oxides/Complexes as Oxidants

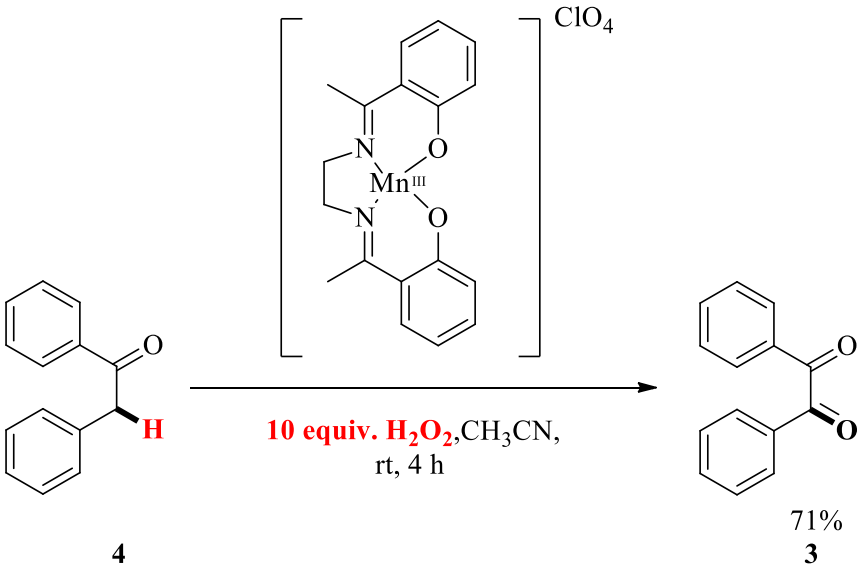
Nakai and co-workers reported the direct oxidation of diverse benzylic C_{sp}^3–H bonds, employing manganese-based oxides (M–MnO_2, M = Ni, Co, Fe, Cu); prepared by using tetra-*n*-butylammonium permanganate as the manganese source in the presence of *o*-dichlorobenzene (*o*-DCB) and dimethyl formamide (DMF). Among the various benzylic C_{sp}^3–H bonds employed, benzil **3** obtained an isolated yield of 60%, from benzyl phenyl ketone **4**, in a lengthy 24 hours oxidation reaction at 110 °C (**Scheme 9**).[36]



4 60% **3**

Scheme 9: Oxidation of benzyl phenyl ketone **4** using Ni-MnO_2 in the presence of *o*-dichlorobenzene (*o*-DCB) and dimethyl formamide (DMF).

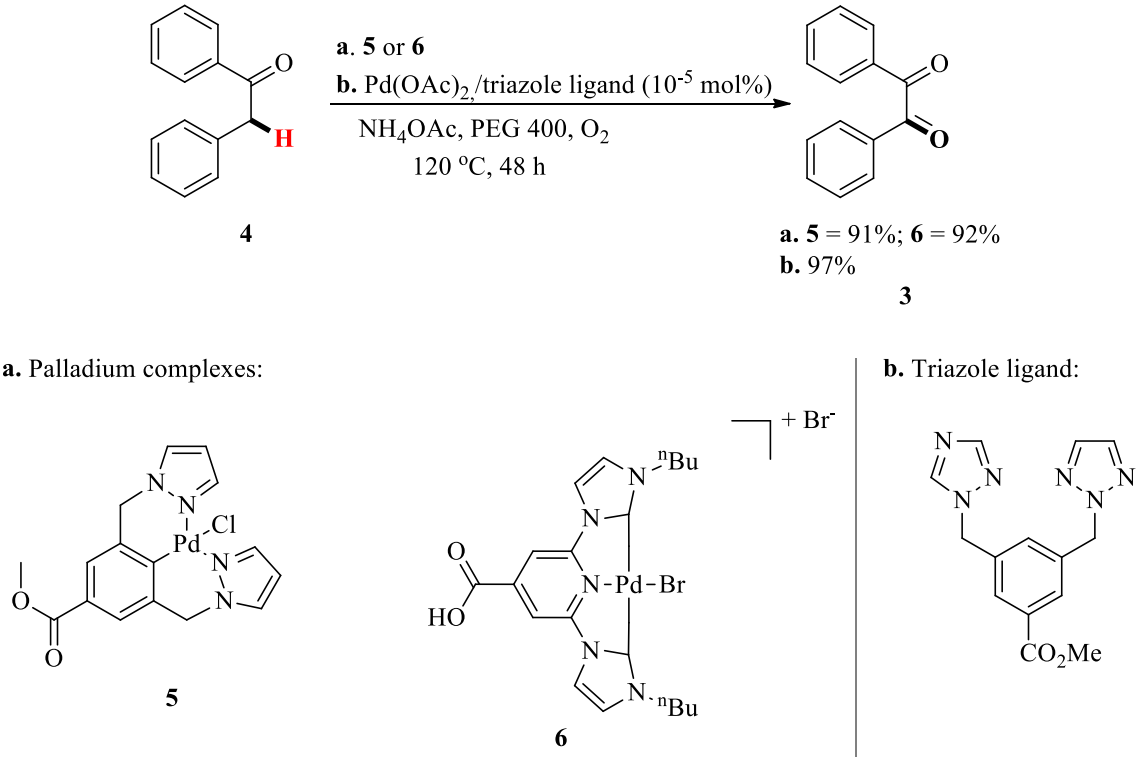
In a different study, Mardani and co-worker[37] prepared a complex manganese (III) catalyst (**Scheme 10**) and applied it to the oxidation of benzyl phenyl ketone, as one of the substrates, at room temperature. Despite the use of 0.1 mol% of the catalyst, ten equivalents of strong and acidic hydrogen peroxide (H_2O_2) was required to provide the source of oxygen in the desired benzil product which was obtained in an isolated yield of 61%. The large excess of hydrogen peroxide, required, was a result of its decomposition in the presence of the catalyst.



Scheme 10: Manganese (III) complex catalyzed oxidation of benzyl phenyl ketone in the presence of significant amounts of concentrated hydrogen peroxide (H_2O_2).

1.4.1.3 The Use of Palladium Metal

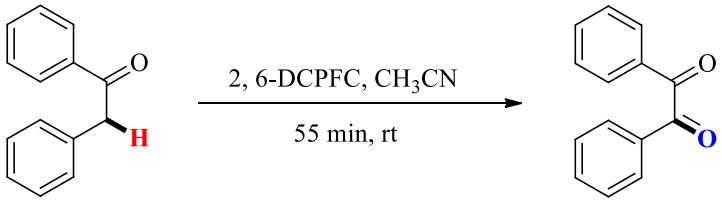
In 2011, the Urgoitia research group synthesized two palladium pincer complexes as active catalysts and applied it to the oxidation of benzyl phenyl ketone as one of the substrates. The reaction was conducted for 24 hours at 120 ºC under an oxygen atmosphere (**Scheme 11a**).[38] In 2015, the group reported a similar study using a palladium/triazole ligand catalytic system.[39] However, despite a quantitative yield for benzil **3**, the only advance in the methodology was the choice of catalysts. Moreover, the reaction media was acidified with hydrochloric acid (HCl) prior to extraction of the organic phase (**Scheme 11b**).



Scheme 11: Different palladium catalyzed direct oxidation of benzyl phenyl ketone **4** reported by the Urgoitia research group.

1.4.1.4 Chromium Derivatives as Oxidants

Chromium is another class of transition metal catalysts utilized in the oxidation of benzyl phenyl ketone. Sarrafi *et al.* employed an equivalent of, synthesized, 2,6-dicarboxypyridinium fluorochromate (2,6-DCPFC) from CrO_3 oxidized benzyl phenyl ketone to afford benzil in 95% (**Scheme 12**).[40] While Cr^{III} is present as a trace element in the body as an essential nutrient, Cr^{VI} is a known human carcinogen to cause numerous malignancies.[41]



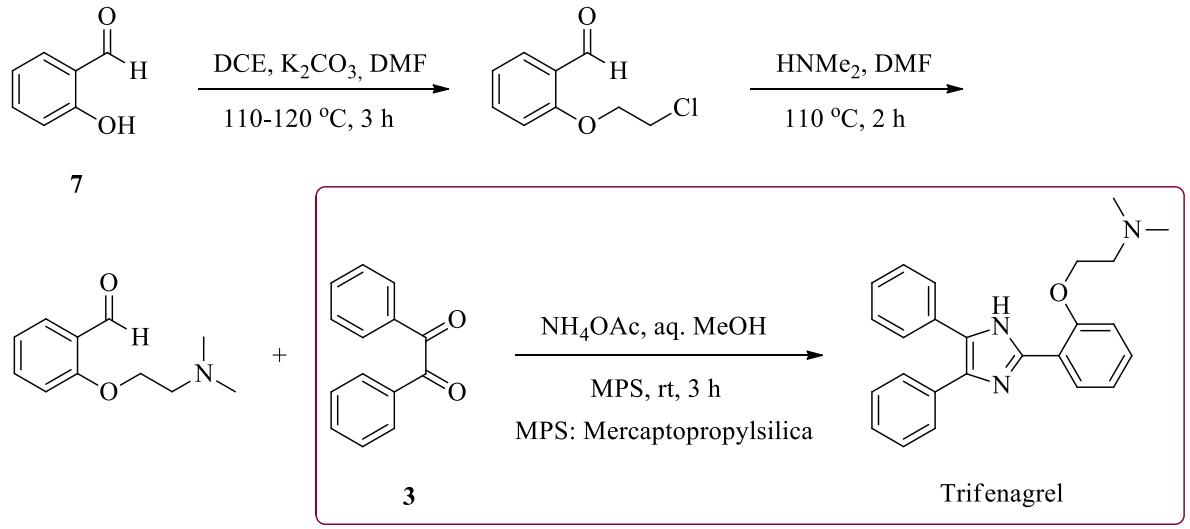
4 95% 3

Scheme 12: 2,6-Dicarboxypyridinium fluorochromate catalyzed direct oxidation of benzyl phenyl ketone **4** to afford benzil **3** by Sarrafi *et al*.

Inherent to the typical synthetic toolbox, with regard to the preparation of 1,2-diaryl ketones, these known methodologies encounter significant limitations, despite obtaining good to excellent yields, such as: the dependence on unsustainable and complex transition metals (Mn, Cr, Pd), employment of additives, stoichiometric amounts of toxic oxidants (SeO_2, H_2O_2) and harsh reaction conditions. As a result, the replacement of traditional oxidants, often used in stoichiometric amounts with more sustainable oxidants, is mandatory in order to improve the beneficial impact of selective oxidation for industrial chemical syntheses. Moreover, in light of ecological and economical demands, the nature of the oxidant is important and should be considered when scheduling a direct oxidative C_{sp}^3–H functionalization methodology.[42]

1.4.2 Oxidation of Benzyl Aryl Ketones to Substituted Benzils in Total Synthesis

Notwithstanding the shortcomings of the direct oxidation of benzyl aryl ketones to 1,2-diaryl diketones (*vida supra*), the two electrophilic centres of the vicinal diaryl motif of benzil **3a** was previously shown to have significant research interest in the pharmaceutical industry as a versatile and valuable substructure. In 2010, Mukhopadhyay synthesized the 2,4,5-trisubstituted-1*H*-imidazole drug, trifenagrel, which is a potent platelet aggregation inhibitor (**Scheme 13**).[43]



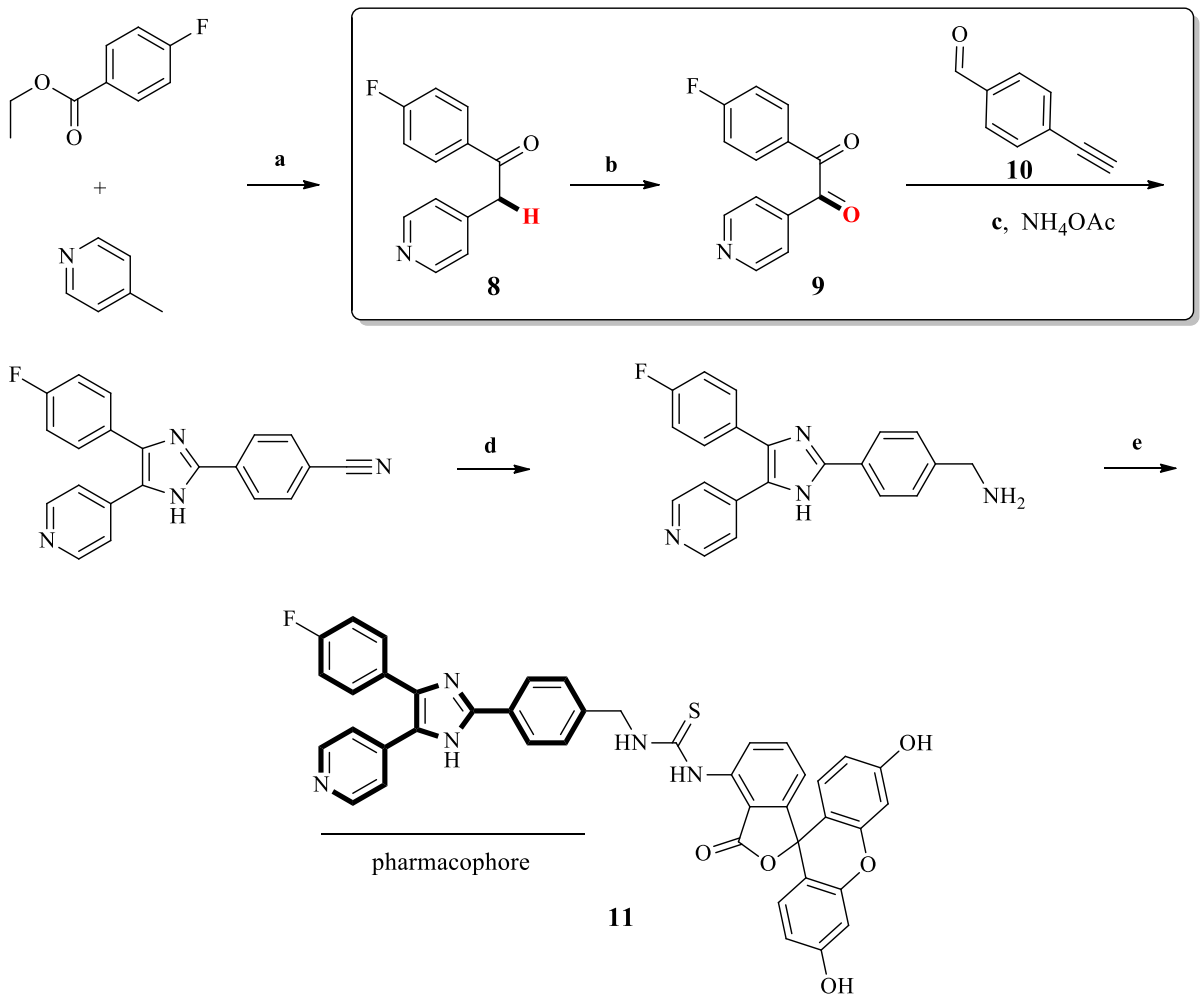
Scheme 13: Representative example to recall the importance of 1,2-diaryl diketones in the total synthesis of pharmaceutical drugs. Trifenagrel is a potent platelet aggregation inhibitor synthesized by the three-component coupling of benzil **3a**, 2-hydroxybenzaldehyde **7** and ammonium acetate.

Similarly, the benzyl aryl ketone scaffold has an important influence in the synthesis of biologically relevant natural products[28, 44] and *N*-heterocycle compounds[45] such as 2,4,5-trisubstituted-1*H*-imidazoles.[46] Diverse pools of drug-like molecules that incorporate these unique scaffolds have demonstrated activity across numerous therapeutic categories, viz.: inflammation, central nervous system disorders, malignancies and extracellular cell stress, to name but a few.[29e, 47]

Mitogen Activated Protein Kinase p38 (MAPK) is an essential class of intracellular kinases activated by extracellular stress to the cell nucleus, resulting in several adaptive and physiological responses to extracellular environmental changes.[48] The p38α MAPK antagonist is the principal mediator of the inflammatory response to cell stress (arthritis, osmotic stress, heat shock), various malignancies and central nervous system disorders (cerebral ischemia, neuropathic pain and Alzheimer's).[49] Given the well-established role of p38α MAPK in various disease states, several inhibitors have been established to relieve these extracellular stresses.

With reference to the structural pharmacophore's ability to achieve potent inhibition of p38α MAPK, several studies indicate the 2,4,5-trisubstituted imidazole ring structure, substituted with vicinal pyridine and 4-fluorophenyl groups as a critical determinant for positioning and binding of the substituted *N*-heterocyclic groups to the binding site of p38α MAPK.[50]

Munoz and co-workers[51] synthesized a novel fluorescein-labelled ligand **11** that preferentially binds with high affinity to the inactive conformation of p38α MAPK (**Scheme 14**). Their synthetic procedure involved 1-(4-fluorophenyl)-2-(pyridine-4-yl)ethanone **8** as an essential precursor which was oxidized by SeO_2, to afford **9**. The formation of the pharmacophore scaffold involved the well-established Debus-Radziszewski imidazole synthesis, commonly known as the coupling of a 1,2-diaryl diketone **9**, an aldehyde **10** and ammonia.



Synthetic steps: a- LDA, THF, -78 °C; b- SeO_2, HOAc, 110 °C; c- HOAc, 180 °C, MW; d- LiAlH4, THF, 4 days; e- fluoroscein isothiocyanate, acetone, 80 °C, 24 h

Scheme 14: Synthesis of a fluorescein-labelled p38α MAPK inhibitor involving the direct SeO_2 oxidation of the benzyl aryl ketone as a key step to the corresponding imidazole *N*-heterocycle.

Despite the investment in, and growth of, modern synthetic organic chemistry within the pharmaceutical industry for the development of diverse compound libraries in drug discovery, interest within the academic labs has currently intensified towards the establishment of novel, chemical, methodologies as the basis for the synthesis of simple *N*-heterocyclic compounds with similar drug-related characteristics to those currently available.

1.4.3 Application of Benzyl Aryl Ketones in Simple *N*-Heterocyclic Syntheses

In recent years, diverse (un)symmetrical benzyl aryl ketones have been functionalized at the C_{sp}^3–H bond to furnish various substituted *N*-heterocyclic compounds with different carbon-heteroatom bonds:

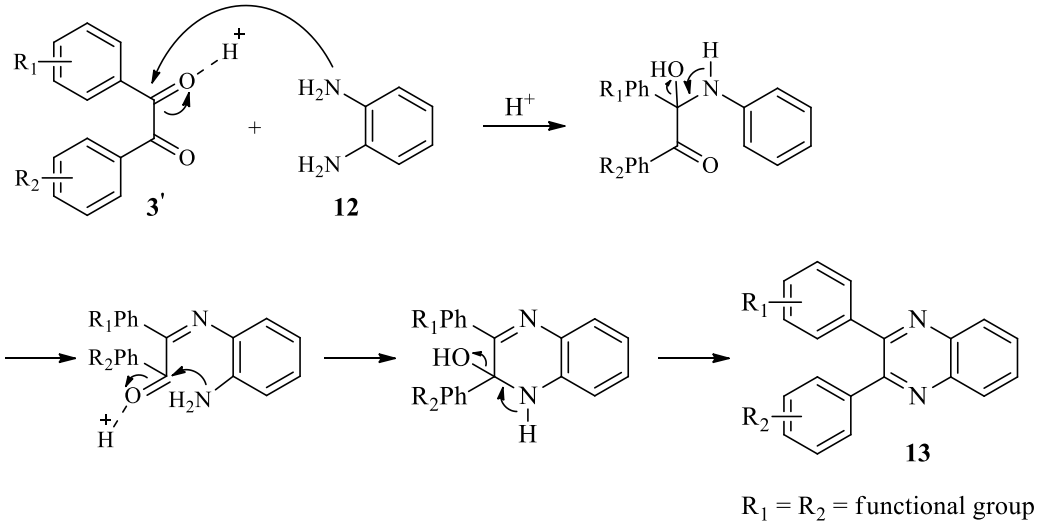
1. the linear coupling of benzyl aryl ketones with substituted 1,2-phenylenediamines to afford quinoxaline derivatives (*vida infra*, Chapter 1, 1.3.4.1);
2. the formation of 3-aroyl-2-aminoindoles;[52]
3. the cross-coupling of two benzyl aryl ketones to yield polysubstituted furans and thiophenes;[53]
4. the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles *via* azidation of C_{sp}^3–H bond;[54]
5. the coupling with nitriles to prepare oxazoles;[55]
6. the reaction of benzyl aryl ketones with vinyl azides affords 2,3,5-trisubstituted-1*H*-pyrroles.[56]

The significance of these methodologies is the direct functionalization of simple, commercially available benzyl aryl ketones. A representative example for the use of 1,2-diaryl diketones and subsequent benzyl aryl ketones will be discussed accordingly, focusing the synthesis of quinoxalines and imidazoles based on the starting materials and catalysts employed (*vida infra*). This, subsequently, highlights the choice of the catalyst/oxidative systems employed in this PhD.

1.4.3.1 The Two Component Synthesis of Quinoxalines

By far, the most common approach to utilize 1,2-diaryl diketones is nuceophilic two-component reaction for the synthesis of quinoxalines **13** which generally commences from the direct condensation of the two-carbon diketone, benzil **3**, and 1,2-phenylenediamines **12** by means of numerous catalysts to aid this transformation (**Scheme 15**).[57] Quinoxalines are important *N*-heterocycles, owing to their broad biological properties such as: antikinase,[58] anticonvulsant,[59] antiviral[60] and antimicrobial[61] agents. Various synthetic methodologies

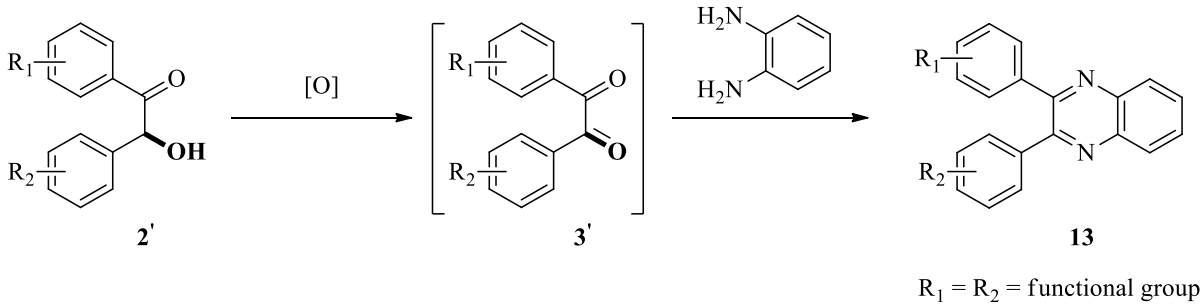
have been developed for the synthesis of these *N*-heterocycles wherein the substituted 1,2-diaryl diketone is replaced by epoxides,[62] alkynes,[63] α-bromo ketones[64] and vicinal diols.[65]



Scheme 15: Representative example of an acid-catalyzed quinoxaline synthesis commencing from the direct condensation of substituted benzil substrates with 1,2-phenylenediamines involving intramolecular cyclization and the removal of water.

Among these synthetic applications, an interesting approach was established which is based on the pioneering work of the Taylor research group which dubbed the oxidation of primary alcohols to aldehydes as the 'one-pot tandem oxidation process' (TOP).[66] The principle of this concept is the oxidation of the alcohol to the aldehyde which is trapped, *in situ*, by a nucleophile, leading to the one-pot preparation of synthetically useful compounds which are otherwise furnished *via* multi-step procedures. The advantage of such a method, obviates the necessity to isolate the often volatile aldehyde intermediate, resulting in shorter reaction times, minimal synthetic steps, improved yields and cost benefits.

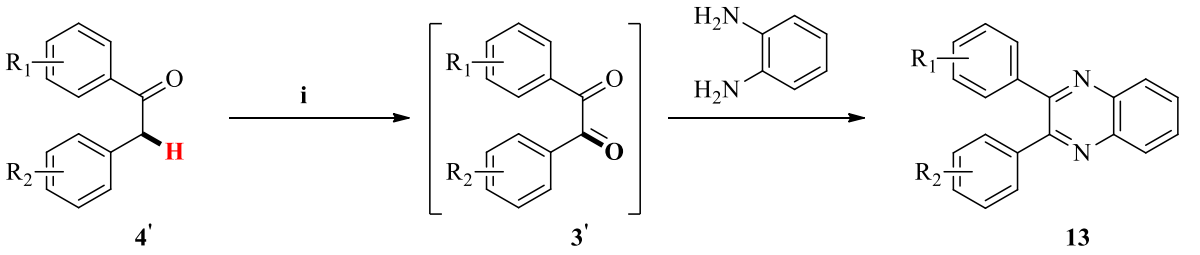
Several research groups have implemented the TOPs, since its proven success, to facilitate the oxidation of substituted secondary α-hydroxy ketones **2**, wherein the *in situ* prepared 1,2-diaryl diketones **3** are instantaneously condensed to the 1,2-phenylenediamine derivatives to afford the desired quinoxaline products **13** in good to excellent yields (62-100%) [**Scheme 16**].[67]



Scheme 16: Tandem oxidation of α-hydroxy ketones to afford quinoxaline derivatives in isolated yields ranging from 62-100%.

Recently, simple and diversely substituted benzyl aryl ketones avenued a more appealing approach to deliver quinoxalines. Inherent to α-hydroxy ketones, the 1,2-diaryl diketones are prepared *in situ*, followed by subsequent cyclization with 1,2-phenylenediamine substrates in a one-pot synthesis. This approach invoked the expansion of the substrate scope to afford diversely substituted quinoxaline *N*-heterocycles and the enhancement of the product yields.

Different research groups displayed the application of benzyl aryl ketones in the synthesis of quinoxaline compounds using various oxidants and reaction conditions. The scope of 1,2-diamines and benzyl aryl ketones was evaluated, affording the desired quinoxaline derivatives **13** in isolated yields ranging from 33-99% (**Scheme 17**).[68]

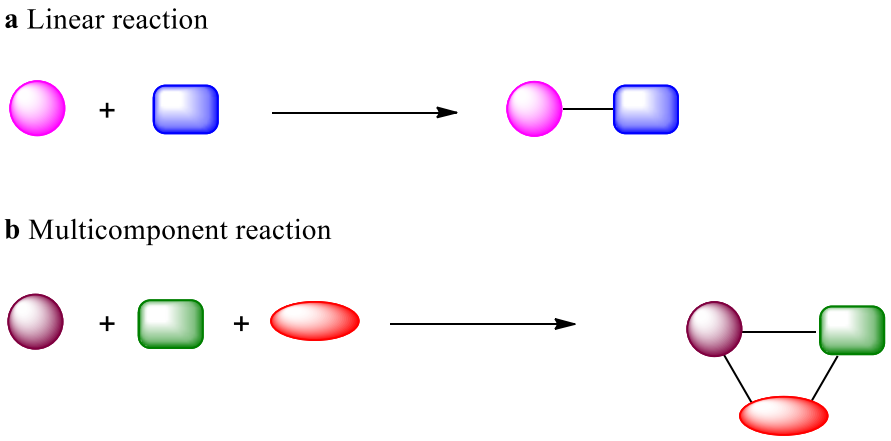


i. a) DABCO, DMF, air, 90 °C, 3-12 h, **73-99%**
b) Cu(II)/calex[4]arene complex, K_2CO_3, O_2, H_2O, 100 °C, 15 h, **33-88%**
c) CuO, I_2, DMSO, 100 °C, 5 h, **36-85%**
d) Et_3N, TEA, toluene, O_2, 90 °C, 12 h, **78-97%**

Scheme 17: The application of benzyl aryl ketones **2** in the synthesis of quinoxaline compounds employing various reaction conditions to afford isolated yields ranging from 36-99%.

1.5 Multi-component Reactions (MCR)

Contrary to the classical linear sequence of reactions between two components (**Scheme 18a**), as in the synthesis of quinoxaline compounds, the synergy of synthetic methods, reagents and catalysts (so as to form multiple bond forming processes between three or more substrates, in a single operation) has become the cornerstone of modern synthetic methodologies.[69] This concept, generally termed a multi-component reaction (MCR), involves one or more chemical transformations in which all reactants combine in a uniquely ordered way under the same or similar reaction conditions in a time-resolved manner. This subsequently affords end products that incorporate, in its scaffold, the majority of significant structural fragments of the added starting materials (**Scheme 18b**).



Scheme 18: Linear vs multi-component reactions: MCR advantageously generates uniquely synthesized and complex molecules that could not be prepared via traditional linear reaction schemes.

Understandably, these well-established convergent processes enable the features of an ideal chemical synthesis while fulfilling the principles of green chemistry in order to:[70]

1. furnish improved product yields, preventing the necessity to change the reaction media or purify reaction intermediates;
2. significantly reduce step count;
3. improve atom economy.

It is obvious that the adoption of such strategies minimizes waste production and enhances synthetic efficiencies.

Furthermore, multi-component reactions provide expedient diversity, variability and complexity[71] to create tailor-made compound libraries of simple organic molecules, viz. *N*-heterocycles[72] while requiring minimal time and effort as when compared to equivalent multistep procedures. Similarly, MCR's have also become an increasingly favoured tool in pharmaceutical and drug discovery research for the assembly of biomedical compounds in an eco-friendly way.[73] Accordingly, a combination of distinguished multi-component reactions, with post-reaction transformations, opens up avenues to facilitate molecular diversity-orientated syntheses. Inherent to their high-step economic reactions, simple experimental

conditions, and their one-pot character, the significance of multi-component reactions is reflected in the many publications reported in this field over the past decades.[74]

1.6 The Debus-Radziszewski Synthesis of 2,4,5-Trisubstituted-1*H*-Imidazoles

2,4,5-Trisubstituted-1*H*-imidazoles exist in many natural and pharmaceutical agents with an array of biological properties (**Figure 3**) ranging from stem cell fate regulators, cancer drugs and gasteroesophageal reflux regulators to anti-ulcerative agents and anti-inflammatories.[75] Therefore, much attention is focused on their synthesis by means of new and innovative ideas frequently developed to access this important moiety.

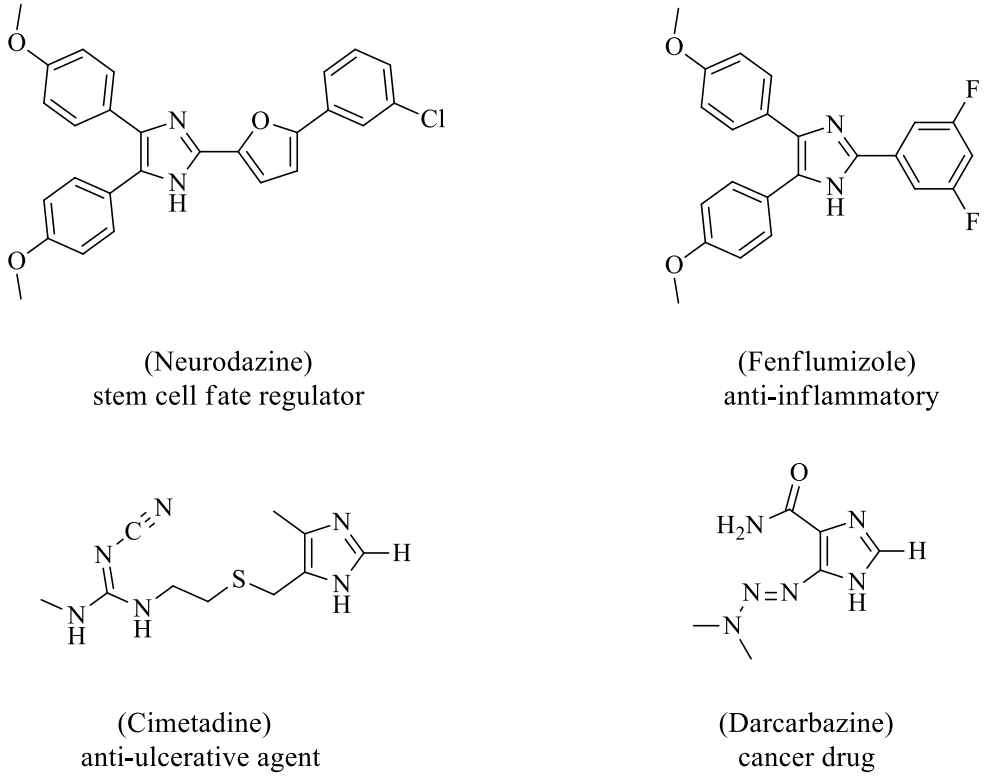
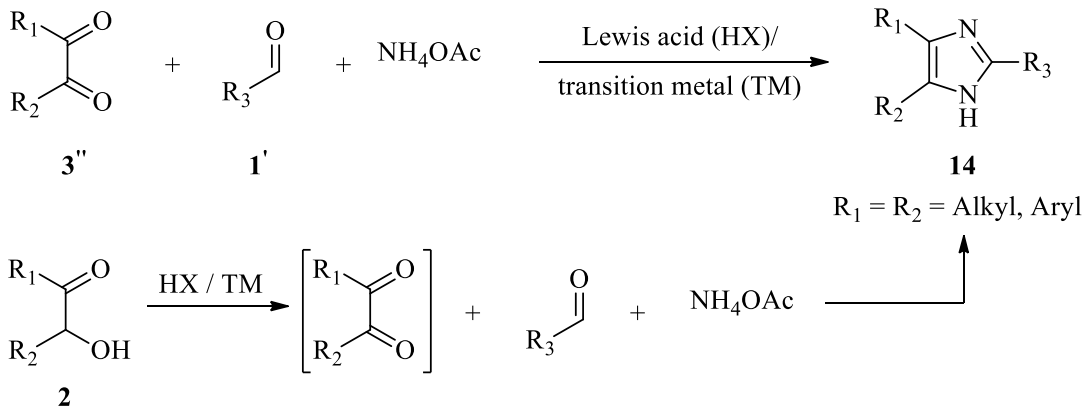


Figure 3: Structures of some important 2, 4, 5-trisubstituted-1*H*-imidazoles possessing different biological properties based on the substitutents present on the *N*-heterocyclic structural core.

1.6.1 General Method for 2,4,5-Trisubstituted-1*H*-imidazole Synthesis

There are a number of ways (acid-supported SiO_2, microwave assisted organic synthesis [MAOS], heterogeneous catalysts, rare earth metals) to generate 2, 4, 5-trisubstituted-1*H*-imidazoles **14** but generally, the predominant method involves the three-component condensation of an α-diketone **3**, aldehyde **1** and ammonium acetate; commonly known as the Debus-Radziszewski imidazole synthesis (**Scheme 19**).[76] In addition, the tandem oxidation of 1,2-diaryl α-hydroxy ketones **2** to *in situ* generated 1,2-diaryl diketones is a commonly applied methodology to access **14**.[77] Accordingly, the application of 1,2-diaryl α-hydroxy ketones and 1,2-diaryl diketones will, collectively, be discussed in the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles.



Scheme 19: General procedures for the Lewis acid (HX) and transition metal (TM) catalyzed synthesis of 2, 4, 5-trisubstituted-1*H*-imidazoles commencing from 1,2-diketones and 1,2-α-hydroxy ketones.

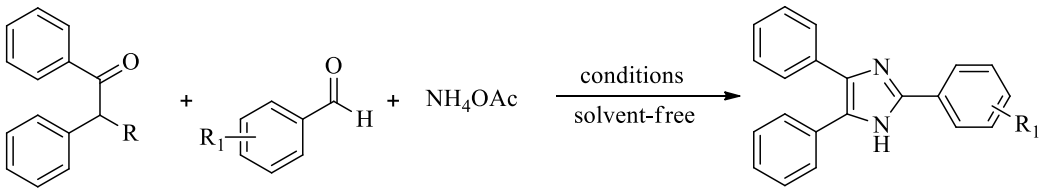
1.6.2 Acid-Supported Silicon Dioxide (SiO_2)

Silicon dioxide (SiO_2) has a high surface area (>800 m^2/g) and, as a result, easily absorbs moisture. Accordingly, researchers have utilized this characteristic to design catalysts with different types of acidity for application in synthetic organic chemistry. Concentrated and highly corrosive acids have been immobilized onto silica gel and applied to the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles.

In 2011, Maleki *et al.*[78] reported the use of concentrated sulfuric acid on silica gel for the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles from benzoin, or benzil, substituted benzaldehydes and ammonium acetate under solvent-free conditions. The reaction proceeded at 110 °C to afford the desired product in an isolated yield of 75-87% and 88-98%, respectively (**Table 1**, **entry 1**). A similar publication was issued by Nikoofar and co-workers[79] who reacted benzoin, or benzil, substituted benzaldehydes and ammonium acetate with concentrated nitric acid supported on nano silica (HNO_3@nano silica) at 100 °C for 2-8 hours. 2,4,5-trisubstituted-1*H*-imidazoles were afforded in lower isolated yields ranging from 67-91% and 61-92%, respectively (**Table 1**, **entry 2**). Inherent of the use of concentrated acid supported catalysts, Shaabani *et al.*[80] employed a high catalyst loading (0.5 g) of silica sulfuric acid (SSA) for the one-pot preparation of 2,4,5-trisubstituted-1*H*-imidazoles. Notably, in addition to the strong acid supported catalyst and reaction temperature, the desired *N*-heterocycles were obtained in lower isolated yields of 65-71% and 64-81%, respectively, using stoichiometric amounts of SSA, as when compared to the aforementioned methodologies (**Table 1**, **entry 3**).

There are numerous literary studies that utilize significantly high reaction temperatures to aid the transformations of the three-component synthesis of 2,4,5-trisubstituted-1*H*-imidazoles. In a publication reported by Karimi *et al*,[81] 2,4,5-trisubstituted-1*H*-imidazoles were furnished under solvent-free conditions at 140 °C within 3 hours. A further significant disadvantage of this methodology is the high catalyst loading: substrate ratio (0.3 g:0.5 mmol) and the use of Wells-Dawson heteropolyacid $H_6P_2W_{18}O_{64}{\cdot}24H_2O$ supported on silica (WD/SiO_2) as a catalyst (**Table 1**, **entry 4**).

Table 1: Acid supported SiO_2 catalyzed synthesis of substituted 2,4,5-trisubstituted-1*H*-imidazoles under various reaction conditions.



R = OH **2**
R = (=O) **3**

1''

14
R_1 = H, Me, OMe, OH, NO_2, Cl, Br, F, naphthyl, furyl

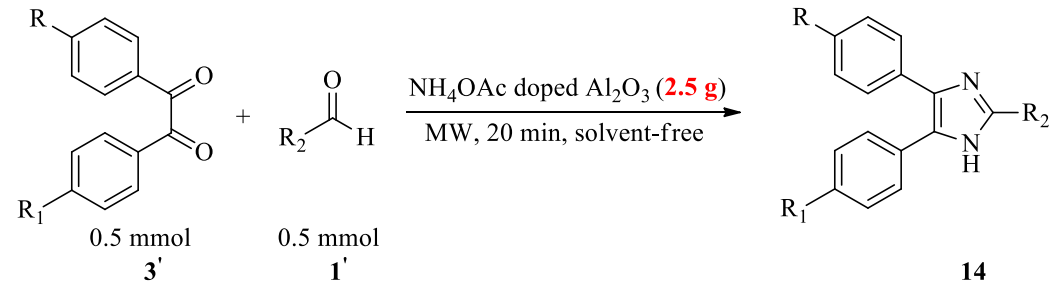
	2 or **3** (mmol)	**1** (mmol)	**NH_4OAc** (mmol)	**Catalyst** (g)	**T** (°C)	**Time** (h)	**Yield 14[a] (%)** b[b]	c[c]
1	1	1	5	H_2SO_4•SiO_2 (0.01)	110	0.45-1.15	75-87	88-98
2	1	1	2	HNO_3@nano SiO_2 (0.012)	100	2-9	67-91	61-92
3	1	1	6	SSA (**0.5**)	100	4-6.5	65-71	64-81
4	0.5	0.5	0.5	WD/SiO_2 (**0.3**)	**140**	3	-	85-90

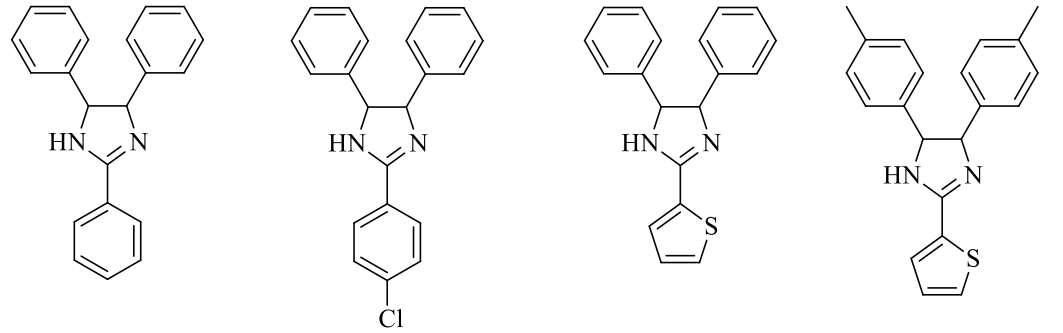
[a] Isolated yield, [b]benzoin, [c]benzil.

1.6.3 Microwave-Assisted Organic Synthesis (MAOS)

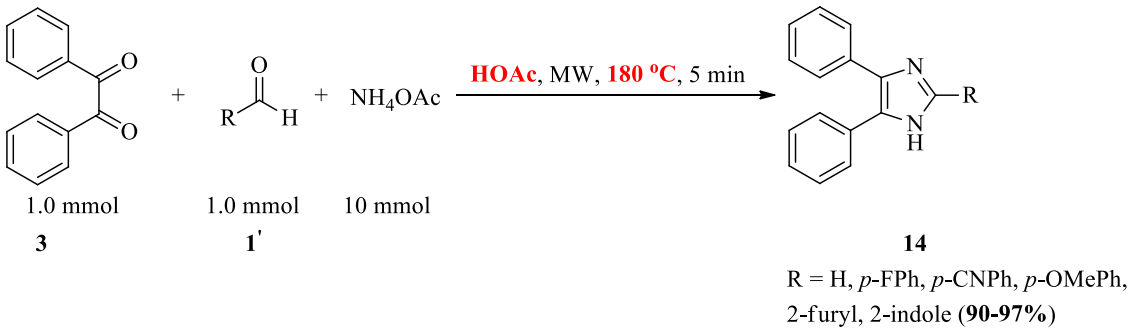
The synthetic technique of microwave-assisted organic synthesis (MAOS) is based on the observation that organic reactions progress faster and with higher yields under microwave irradiation when compared to conventional heating.[82] Usyatinsky and Khmelnitsky[83] reported a solvent-free microwave assisted one-pot synthesis of 2,4,5-trisubstituted-1*H*-imida zoles using acidic alumina saturated with ammonium acetate (**Table 2**). Although microwave irradiation afforded the products in 20 minutes, a significantly high catalyst loading: substrate ratio (2.5 g: 1.0 mmol) was utilized to afford the desired *N*-heterocyclic imidazoles in moderate yields (67-78%) with limited substrate scope (4 examples).

Table 2: Microwave-assisted synthesis of 2,4,5-trisubstituted-1*H*-imidazoles employing NH_4OAc doped Al_2O_3.





In an early example reported in 2002, Wolkenberg and co-workers[84] reported a high-yielding (80-99%) microwave-assisted synthesis of 2,4,5-trisubstituted-1*H*-imidazoles in the presence of concentrated acetic acid (HOAc), which has a boiling point of 118.1 °C. The resulting 2,4,5-trisubstituted-1*H*-imidazoles, however, were furnished in a pressurized environment at a significantly high reaction temperature of 180 °C (**Scheme 20**).

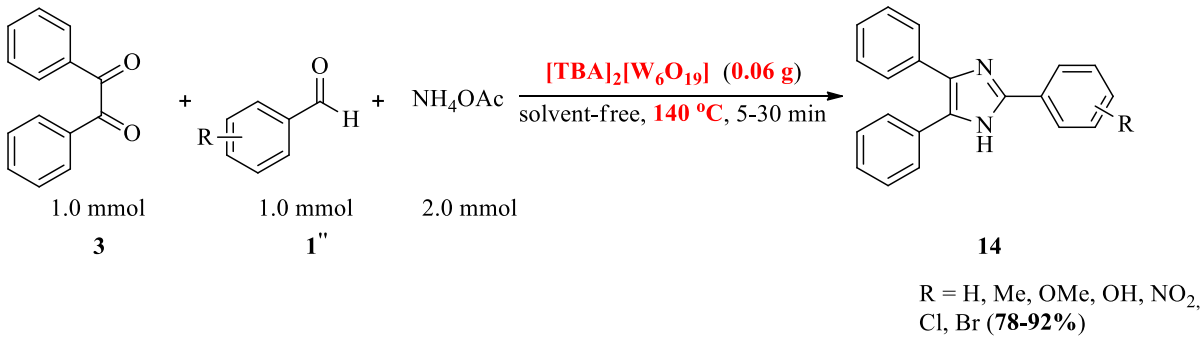


Scheme 20: Acetic acid promoted synthesis of substituted 2,4,5-trisubstituted-1*H*-imidazoles at 180 °C.

1.6.4 Heterogenous Catalysts

Many heterogenous catalysts were prepared and employed in the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles such as benzyltriphenylphosphonium chloride (BTPPC), a novel 1,3,5-Tris(2-hydroxyethyl)isocyanurate functionalized graphene oxide and ZrO_2-β-cyclodextrin, to name but a few.[85]

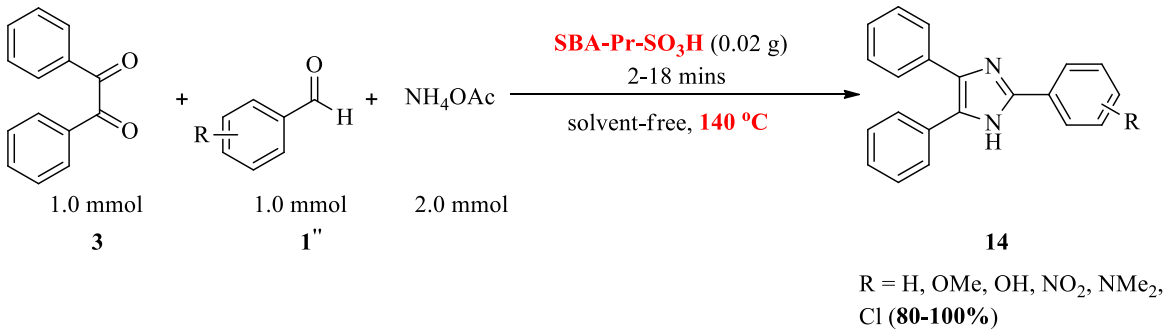
Substituted 2,4,5-trisubstituted-1*H*-imidazoles were prepared, in an isolated yield of 78-92%, by Ashrafi *et al.* (**Scheme 21**).[86] The reaction proceeded by heating benzil, substituted benzaldehydes and ammonium acetate at 140 °C under solvent-free conditions. Despite the good to excellent yields obtained, 30 mol% of a pre-formed tetrabutylammonium hexatungstate $[TBA]_2[W_6O_{19}]$ was utilized as a heterogenous catalyst to aid this transformation. A complex procedure was undertaken to prepare this catalyst, which required the use of: 60 mL combustible acetic anhydride, 18 mL corrosive HCl (12 mol/L) and 15.1 g tetrabutylammonium bromide (TBAB).



Scheme 21: Tetrabutylammonium hexatungstate $[TBA]_2[W_6O_{19}]$ catalyzed synthesis of substituted 2,4,5-trisubstituted-1*H*-imidazoles.

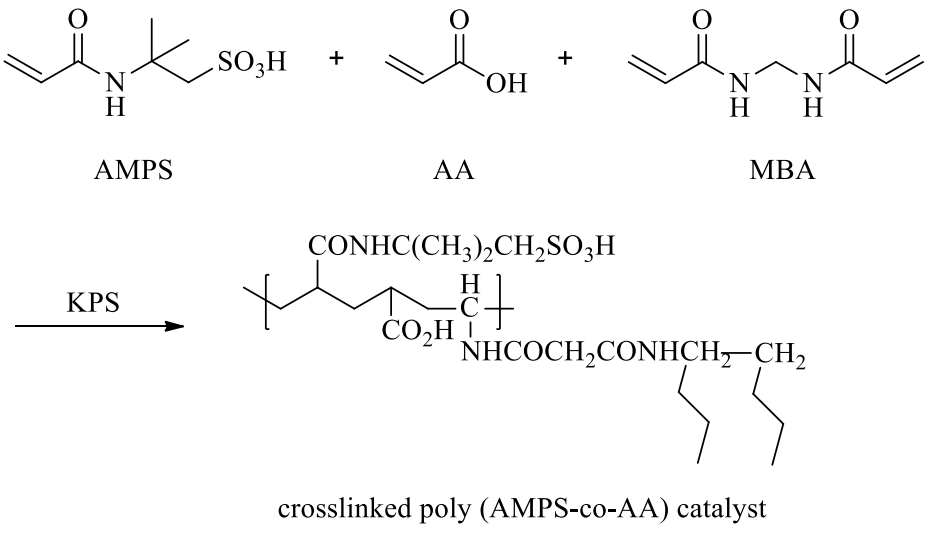
In a different publication, Ziarani and co-workers[87] prepared a sulfonic acid functionalized SBA-15 nanoporous material (SBA-Pr-SO_3H) and applied it to the one-pot three-component synthesis of 2,4,5-trisubstituted-1*H*-imidazoles from benzil, substituted benzaldehydes and ammonium acetate under solvent-free conditions (**Scheme 22**). Similarly, a significantly high reaction temperature (140 °C) was required to furnish the desired products. In addition, the

solid catalyst required activation in a vacuum at 100 °C and subsequent cooling to room temperature before commencing with the reaction.



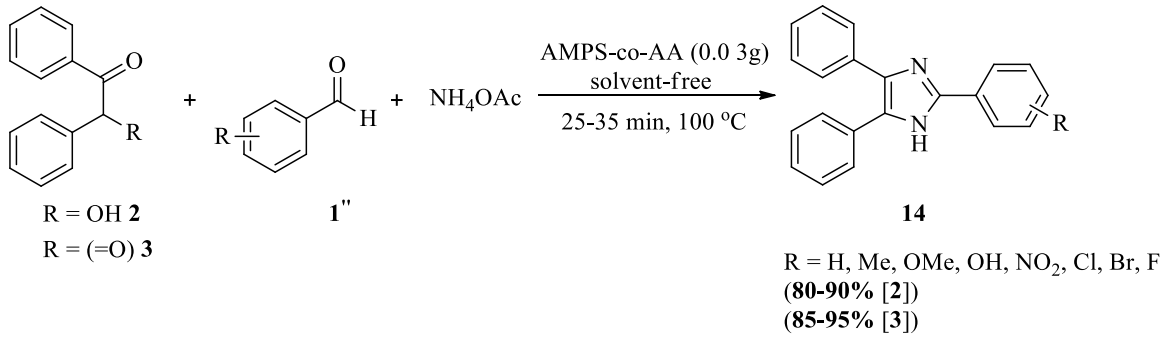
Scheme 22: Sulfonic acid functionalized SBA-15 nanoporous material as a catalyst for the preparation of 2,4,5-trisubstituted-1*H*-imidazoles at 140°C.

Mohammadi and co-workers[88] synthesized a novel crosslinked polymeric catalyst (AMPS-co-AA) through the polymerization of 2-acrylamido-2-methyl-1-propane sulphonic acid (AMPS) and acrylic acid (AA), in the presence of a crosslinking agent, N,N'-methylene bisacrylamide (MBA) and potassium persulphate (KPS) as a free radical initiator (**Scheme 23**).



Scheme 23: Synthesis of crosslinked poly (AMPS-co-AA) catalyst employed in the synthesis of substituted 2,4,5-trisubstituted-1*H*-imidazoles.

The synthesized polymeric catalyst was subsequently applied to the reaction of benzoin or benzil, substituted benzaldehydes and ammonium acetate under solvent-free conditions at 100 ^{o}C. The resulting 2,4,5-trisubstituted-1*H*-imidazoles were obtained in isolated yields of 80-90% and 85-95%, respectively (**Scheme 24**).

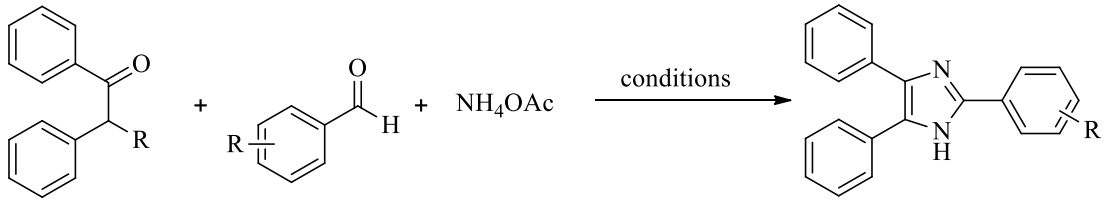


Scheme 24: Polymeric AMPS-co-AA catalyzed synthesis of 2,4,5-trisubstituted-1*H*-imidazoles from benzoin or benzil.

1.6.5 Rare Earth Metal Catalysts

Rare earth metals have been applied to a variety of organic reactions, including application in the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles as shown in **Table 3**. A sol-gel auto combustion technique in air, without the protection of inert gases, was employed by Pachpinde and co-workers[89] to prepare a holmium (Ho^{3+}) doped cobalt ferrite ($CoFe_2O_4$) nanoparticle for the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles (**Table 3**, **entry 1**). Triflates are known to act as strong Lewis acid catalysts in solution for the synthesis of numerous *N*-heterocyclic compounds. Wang *et al.*[90] reported the use of ytterbium trifluoromethanesulfonate [$Yb(OTf)_3$] in the presence of HOAc as catalyst (**Table 3**, **entry 2**). Similarly, Yu *et al.*[91] reported the use of europium-triflate ($Eu(OTf)_3$) catalyst for the preparation of 2,4,5-trisubstituted-1*H*-imidazoles (**Table 3**, **entry 3**). Despite the good to excellent yields and mild reaction temperatures, rare earth metals posit serious environmental consequences and the use of an acidic reaction media does not conform to an environmentally benign synthesis. (*vida supra*). Accordingly, even the use of catalytic amounts of these rare transition metals adds to environmental contamination.

Table 3: Rare earth metal catalyzed synthesis of substituted 2,4,5-trisubstituted-1*H*-imidazoles under different reaction conditions.



R = OH **2**
R = (=O) **3**

1''

14

R = H, Me, OMe, OH, NO_2, NMe_2, CN, Cl, F

	2 or **3** (mmol)	**1** (mmol)	**NH_4OAc** (mmol)	**Catalyst** (g)	**Solvent**	**T** (°C)	**Time** (h)	**Yield 14**[a] **(%)** **b**[b]	**c**[c]
1	1	1	4	**HO_3^+**/$CoFe_2O_4$ (20mol%)	EtOH	80	10-20[d]	84-95	88-98
2	1	1	10	**Yb**$(OTf)_3$ (0.03)	**HOAc**	70	2-6	-	17-97
3	5	5	12	**Eu**$(OTf)_3$ (5mol%)	EtOH	80	2	Trace-93	68-94

[a] Isolated yield, [b]benzoin, [c]benzil; [c]minutes.

Despite the plethora of chemical syntheses documented in literature for the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles, there are numerous notable drawbacks associated with these methodologies, such as the employment of:

1. harsh reaction conditions;
2. strong acidic media and/or acid-supported catalysts;
3. high catalyst loading:substrate ratio;
4. significantly high reaction temperatures;
5. pressurized environments;
6. preparation of complex heterogenous catalysts;
7. rare earth metal catalysts;
8. limited substrate scope

1.7 Aim of this Research Project

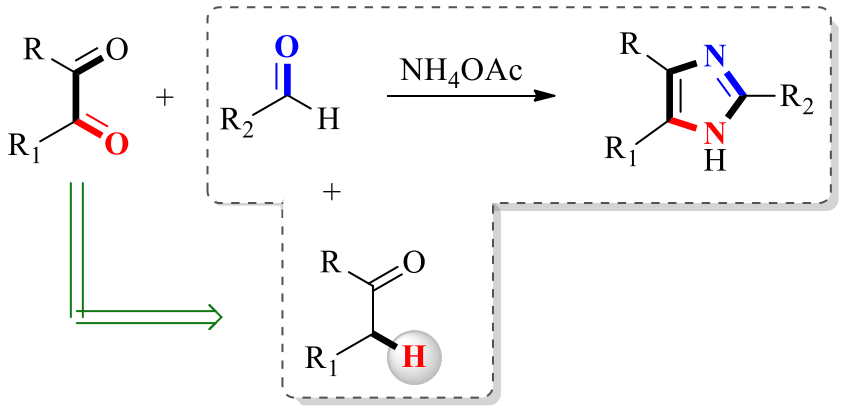
1,2-Diaryl diketones are established structural motifs in natural, synthetic and medicinal chemistry. Despite this significance, numerous challenges exist within the different synthetic routes to access these scaffolds. These include: harsh reaction conditions, the use of hazardous reagents, tedious isolation procedures and limited substrate scope (commencing from the diketone). Recent years have witnessed a surge in the functionalization of C_{sp}^3–H benzyl aryl ketones to the corresponding α-diketone. This type of transformation is translated in the improvement of previous methodologies and the development of new and innovative synthetic protocols. Ideally, the choice of the catalyst and reaction conditions are necessary, in order to achieve practical and unconventional transformations.

In context, the aim of this research project is to design and develop an environmentally benign synthetic methodology for application in the direct oxidation of simple and commercially available C_{sp}^3–H benzyl aryl ketones, *in situ*, to the corresponding diketones. This transformation is, subsequently, aimed at synthesizing diversely substituted 2,4,5-trisubstituted-1*H*-imidazoles *via* a one-pot domino multi-component reaction. The secondary aim of this project is to rationalize the proposed reaction mechanisms through a series of experimental conditions and spectroscopic techniques.

Chapter 2: Copper-Catalyzed Aerobic Benzylic sp^3 C-H Oxidation Mediated Synthesis of 2,4,5-Trisubstituted Imidazoles *via* a Domino Multi-component Reaction

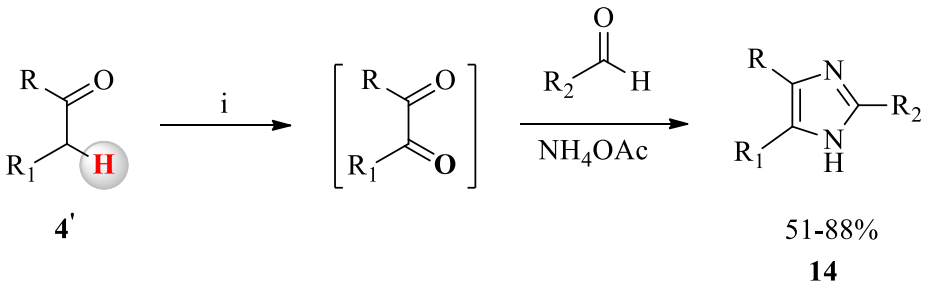
2.1 Retrosynthesis of 2,4,5-trisubstituted-1*H*-imidazoles

In 2017, a novel multi-component reaction was developed by this research group for the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles.[92] The reaction proceeds through the direct oxidation of the benzylic C_{sp}^3–H bond of simple and readily available benzyl aryl ketones, to furnish the *in situ* generated 1,2-diaryl diketones, which subsequently cyclize with substituted aldehydes to afford the desired 2,4,5-trisubstituted-1*H*-imidazoles (**Scheme 25**).



Scheme 25: Retrosynthesis of the multi-component 2,4,5-trisubstituted-1*H*-imidazole synthesis *via* the direct oxidation of benzyl aryl ketones to diketones which are subsequently coupled *in situ* to the corresponding *N*-heterocycle.

Selenium dioxide is a well-known oxidant in synthetic organic chemistry[93] and has been utilized in the direct oxidation of numerous benzyl aryl ketones to furnish diketones.[94] In addition, acetic acid is known to aid in the coupling of benzil, benzaldehyde and ammonium acetate, in the absence of a catalyst, to afford 2,4,5-trisubstiuted-1*H*-imidazoles.[95] Accordingly, substituted benzyl phenyl ketones **4**, substituted aldehydes **1** and excess ammonium acetate were reacted in the presence of 1 equivalent SeO_2 and 5 mL acetic acid at 180 ^oC. The resulting 2,4,5-trisubstituted-1*H*-imidazoles **14** were furnished in isolated yields ranging from 51-88% in 3 hours (**Scheme 26**).



i: SeO_2 (1.0 equiv), HOAc (5 ml), 180 ^oC, 3 h

Scheme 26: SeO_2/ HOAc catalyzed synthesis of 2,4,5-trisubstituted-1*H*-imidazoles at a significantly high temperature of 180 ^oC.

Despite the novelty, synthetic efficiency and high yields displayed in this methodology, it was afflicted with notable drawbacks such as: harsh reaction conditions, the use of stoichiometric amounts of toxic selenium dioxide, equivalent amount of selenium metal waste and significantly high reaction temperatures. Hence, there is growing concern in modern synthetic organic chemistry over sustainable development to employ environmentally benign processes. In this context, the concept of green chemistry assumes significance as it seeks to deliver a platform for sustainable chemical syntheses.

2.2 Green Chemistry for Sustainable Chemical Syntheses

Green chemistry[96] harnesses a vast body of chemical knowledge aimed at inventing novel and environmentally benign products and processes that:

1. can maximize the desired products and minimize by-products;
2. are highly efficient and non-polluting;
3. minimizes the generation or use of hazardous chemicals;
4. creates an environmentally friendly atmosphere;
5. displays low levels of waste production and
6. attains an intrinsically high atom economy (efficiency conversion of a chemical reaction).

Ideally, green chemistry seeks alternative and environmentally friendly reaction media while, simultaneously, striving to increase reaction rates, lower reaction temperatures and furnish products in high yields.[97]

The essential features of the concept of green chemistry are highlighted in the 12 principles outlined below. These key principles (listed below) can be collated into reducing the risk and minimizing the environmental/ ecological impact.[96]

1. **Waste prevention:** it is better to design chemical syntheses that minimizes the formation of waste than to remove it or reduce its toxicity when formed.
2. **Atom economy:** synthetic methods should be designed to maximize the incorporation of all reactants utilized in the process into the final products.
3. **Less hazardous chemical syntheses:** wherever practicable, use chemical reactants and form final products with minimized or no toxicity to mammalian health and the environment.
4. **Designing safer chemicals and products:** design chemicals and products to affect their desired function with reduced toxicity.
5. **Safer solvents and auxiliaries:** avoid the use of auxiliary substances (solvents, separation agents) wherever possible and should be innocuous when used.
6. **Design aimed at energy efficiency:** energy requirements for chemical processes should be recognized for their environmental and economic impact. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. **Renewable feedstock:** a raw material or feedstock should be renewable rather than depleting whenever possible.
8. **Reduction of derivatives:** minimize or avoid the use of derivatives as reactants (building blocks, protection/deprotection groups, temporary modified structures). These require additional synthetic steps, reagents and can generate waste.
9. **Catalytic Reagents:** catalytic reagents are superior to stoichiometric reagents. It enhances the extent of product formation under reduced temperature and pressure.
10. **Design aimed at degradation:** Chemical products should be designed so that at the end of their function they do not persist in the environment and breakdown into harmful degradation products.

11. **Real-time analysis for pollution prevention:** analytic methods should be designed to allow real-time, in-house monitoring and control prior to the formation of hazardous substances.
12. **Inherently safer chemistry for accident prevention:** substances used in a chemical process should be chosen so as to minimize the risk for chemical accidents, explosions and fires.

The above principles are used as a framework for cleaner and sustainable chemical processes. It is, however, unlikely to achieve all these goals simultaneously. In view of the principles of green chemistry, the previously reported SeO_2/ acetic acid synthesis of 2,4,5-trisubstituted-1*H*-imidazoles within this research group is in violation of these key principles. As a result, in an effort to address these disadvantages, the use of toxic selenium dioxide and concentrated acetic acid was replaced by choosing a more sustainable catalytic system.

2.3 Copper Catalysis with Molecular Oxygen

There exists the notion, central to Green Chemistry, that a catalytic amount of a reactant is sufficient to promote the rate, efficiency and selectivity of a chemical reaction. This is an overarching and recognizable aspect that offers significant energy, environmental and economic savings.

In context, earth-abundant copper exists in many metalloenzymes that catalyze aerobic oxidation reactions.[98] As a result, nature routinely employs enzymatic oxidizing systems based on the many advantages and unique features of copper, as a catalyst, to perform remarkable chemical transformations in a selective manner on simple and highly functionalized molecules. Independent of the biological applications, the use of copper as a catalyst[99] represents an appealing and viable alternative to the predominantly applied (noble) transition metal catalysts.[100] The economic and environmental advantages of copper catalysts for chemical transformations are, therefore, widely recognized.

Compared to other (noble) transition metal catalysts, copper catalysts are abundant, inexpensive, commercially and readily available, air tolerant and can be easily and safely handled. Accordingly, the development of copper catalysts in synthetic organic chemistry is incredibly rich because the Cu^0, Cu^+ and Cu^{2+} oxidation states are easily accessible, thereby allowing it to efficiently catalyze organic reactions through either one-electron or two-electron (radical or polar) mechanisms, or both.[101] Moreover, the different oxidation states of copper are known to coordinate well with different functional groups and heteroatoms, *via* Lewis acid interactions or pie-pie coordination.[102]

Copper in the +2 oxidation state is particularly interesting because it participates in one-electron redox reactions which are demonstrated in oxidation reactions of several electron-rich substrates, initiated *via* single electron transfer (SET) such as: phenols, tertiary amines, electron-rich arenes and heterocycles.[101c, 103] Copper (II) is perhaps more appealing as a one-electron oxidant because, under suitable reaction conditions, it can be regenerated by aerobic oxidation of the two-electron reductive by-product, copper(I), using ambient air or molecular oxygen as a stoichiometric oxidant.[104]

In this context, molecular oxygen has displaced most of the existing unsustainable oxidants, such as organic peroxides[105] and benzoquinones,[106] commonly employed in stoichiometric amounts. An advantage of using molecular oxygen, as a terminal oxidant, is that it has low molecular weight and is both atom-economical, inexpensive and environmentally benign, which makes it ideal. Oxygen can either transfer two electrons from a substrate to itself forming water (H_2O) or hydrogen peroxide as the only by-product (oxidase activity). Alternatively, it can act as a source of oxygen atoms that are incorporated into the end product (oxygenase activity), or both.[107]

The chemistry of copper catalysis, in combination with molecular oxygen, improves the beneficial impact of selective oxidation in chemical syntheses because it allows catalytic turnover in oxidative coupling reactions. This allows for the formation of new carbon-carbon (C–C) or carbon-heteroatom (C–X, X=N, O, S) bonds for diverse *N*–, *N*,*S*–, *N*,*O*– and *O*–heterocyclic syntheses.[108] Collectively, these features confer a remarkably broad range of

transformations in allowing the copper-O_2 system to catalyze the oxidation or oxidative coupling of many substrates such as: phenylacetylenes, stilbenes and α-hydroxyketones.[109]

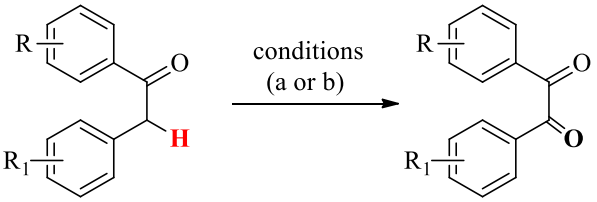
As a result, this became inherent to the interest within our research group to develop an improved methodology based on the copper catalysis with molecular oxygen in the context of the important attributes mentioned above.

2.3.1 Direct Oxidation of Benzyl Aryl Ketones

The application of the Copper-O_2 oxidative system on the direct oxidation of diverse benzyl aryl $C_{sp}{}^3$–H bonds, to the corresponding ketone derivatives, is a topic of current research interest within synthetic organic chemistry fraternity.

Accordingly, in 2013, Goggiamani *et al.*[110] described a procedure for the oxidation of aromatic aryl ketones, providing the corresponding diketones in moderate to excellent yields (45-95%). A number of diketone compounds bearing chloro, bromo, iodo, methyl, methoxy, cyano, acetyl and methoxycarbonyl functionalitites were obtained using monohydrated copper acetate ($Cu(OAc)_2{\cdot}H_2O$) (15 mol%) and triphenylphosphine (PPh_3) (30 mol%) in 1,2,4-trimethylbenzene at 100 ^oC under 1 atm air (**Scheme 27**, **condition a**).

The method by Goggiamani *et al.* was appealing to the undertaken research study for its mild and green reaction conditions. An additional study, however, presented by Yu *et al.*[111] exemplified the possibility to further improve upon the desired approach of extending the green concept in this research (**Scheme 27**, **condition b**). This reaction is particularly appealing, owing to the mild reaction conditions employed, the use of 5 mol% of the copper catalyst and the excellent aerobic catalytic turnover.



R = H, Me, OMe, NO_2, Cl, Br, F
R_1 = H, Me, OMe, CO_2Me, CN, Br, F, I

a) $Cu(OAc)_2$ (15 mol%), PPh_3 (30 mol%), 1 atm O_2, 1,2,4-trimethylbenzene, 0.5-9 h, **45-95%**

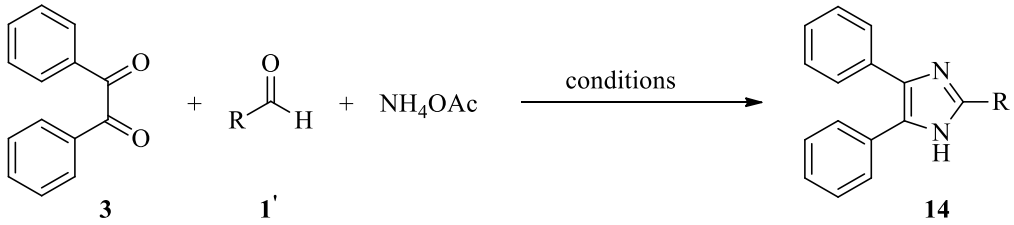
b) $Cu(OAc)_2$ (5 mol%), K_2CO_3 (5 mol%), 1 atm O_2, DMF, 50 ^oC, 0.5-10 h, **65-92%**

Scheme 27: Copper catalyzed aerobic oxidation of benzyl aryl ketones to afford 1,2-diaryl diketones in moderate to excellent yields (45-95%), as presented by Goggiamani and Yu, respectively.

2.3.2 Synthesis of 2,4,5-Trisubstituted-1*H*-imidazoles

Though the copper-O_2 oxidative system, reported by different research groups, has demonstrated a broad application in the synthesis of numerous heterocyclic compounds (*vida supra*), different types of copper containing catalysts[112] have been employed in the three-component coupling of benzil with aromatic aldehyde derivatives and ammonium acetate to furnish several 2,4,5-trisubstituted-1*H*-imidazoles. Different reaction conditions were employed to afford the desired products in moderate to excellent yields (**Table 4**, **entries 1-5**). A recycle-and-reuse study was undertaken by various research groups in order to study the recyclability of the heterogeneous catalysts. Good to excellent catalyst activity and productive yields (88-96%) were observed (**Table 4**, **entries 3-5**).

Table 4: Different copper catalyzed synthesis of 2,4,5-trisubstituted-1*H*-imidazoles under varying conditions.



3 **1'** **14**

R = Ph, MePh, OMePh, NO_2Ph, OHPh, NMe_2Ph, ClPh, BrPh, FPh, 2-furyl, 2-naphthyl

Entry	3:1 (mmol)	NH_4OAc (mmol)	Catalyst (mol%)	Temp (°C)	Time h	Yield-%[a]	R[b]	Reference
1	1:1	3	Cu NPs (10)	rt	5-9	76-94	88-94 (4)	Gandhare *et al.* (**110a**)
2	1:1	2.5	$CuCl_2 \cdot 2H_2O$ (10)	MW	12-14 min	85-92	-	Hangirgekar *et al.* (**110b**)
3	1:1	2	$Cu(NO_3)_2$-zeolite (300mg)	80	0.5	71-98	92-96 (5)	Sivakumar *et al.* (**110c**)
4	1:1	4.0	$Cu(TFA)_2$ (0.01mmol)	100	4	85-97	-	Song *et al.* (**110d**)
5	1:1	4	Fe_3O_4-PEG-Cu (10)	110	20-45min	88-98	92-96 (6)	Zarnegar *et al.* (**110e**)

[a]Isolated yield; [b]Recycles (cycles); NH_4OAc: ammonium acetate; $Cu(TFA)_2$: copper(II) trifluoroacetate; Cu NPs: copper nanoparticles; PEG: polyethylene glycol; MW: microwave

According to the literature review provided in sections 2.3.1 and 2.3.2, copper is capable of oxidizing benzyl aryl $C_{sp}{}^3$–H bonds to the corresponding diketones and enabling the coupling of benzil, aldehydes and ammonium acetate to afford 2,4,5-trisubstituted-1*H*-imidazoles. At this point, it was hypothesized that copper could function as a duel catalyst, whereby:

1. In the presence of molecular oxygen, it could oxidize the benzyl aryl ketones to 1,2-diketones *via* a single electron transfer (SET) catalytic cycle.

2. Copper could catalyze the coupling of the *in situ* generated 1,2-diaryl diketones, substituted aldehydes and ammonium acetate to furnish the desired 2,4,5-trisubstituted-1*H*-imidazoles.

To test this hypothesis, benzyl phenyl ketone, benzaldehyde and ammonium acetate were chosen as model substrates, in a test reaction, for the initial investigations to optimize the reaction conditions under varying conditions.

2.4 Results and Discussion

2.4.1 Optimization of Reaction Conditions

One of the fundamental objectives of green chemistry is to identify solvents that are inherently non-toxic, non-hazardous and non-polluting. Accordingly, our optimization studies commenced by reacting benzyl phenyl ketone **4a** with benzaldehyde **1a** and ammonium acetate with a catalytic amount of copper(II) acetate monohydrate ($Cu(OAc)_2.H_2O$) in the presence of molecular oxygen at 50 °C for 24 hours. This was conducted within a range of environmentally and ecologically friendly solvents. During the screening of the effect of more benign solvents, we found that acetonitrile (CH_3CN), ethanol (EtOH) and ethyl acetate (EtOAc) afforded satisfactory yields of 2,4,5-triphenyl-1*H*-imidazole **14a** (**Table 5**, **entries 1-3**). The reaction, however, failed in the presence of toluene and no product was isolated (**Table 5**, **entry 4**). These results suggest that the oxidation of benzyl aryl ketone to the corresponding 1,2-diaryl diketone does not proceed well in such solvents. The choice of solvent was therefore important in order to allow for maximum conversion of the substrates involved in the transformation of the benzyl aryl ketone, aldehyde, ammonium acetate and copper into 2,4,5-trisubstituted-1*H*-imidazoles.

Based on the work reported by Yu *et al.*[111] and other literary studies,[113] Copper-O_2 oxidation reactions proceed well in the presence of dimethyl formamide (DMF) as a reaction media. Consequently, DMF was chosen as the solvent for the optimization reactions (*vida infra*). In the presence of 5 mol% of $Cu(OAc)_2 \cdot H_2O$ and molecular oxygen, the reaction proceeded well to furnish the desired 2,4,5-triphenyl-1*H*-imidazole in an isolated yield of 77% (**Table 5**, **entry 5**). From this promising result, the same conversion was attempted by prolonging the reaction

time to 28 hours. This, however, only had a minimal influence on the reaction yield, wherein 80% of **13a** was isolated (**Table 5**, **entry 6**).

Subsequently, in order to understand the reaction system, control experiments were undertaken in the absence of the copper catalyst (**Table 5**, **entry 7**) or in the presence of atmospheric air (**Table 5**, **entry 8**). No product, however, was obtained from these reactions. The same result was obtained (**Table 5**, **entry 9**) when molecular oxygen was replaced with nitrogen (N_2). Owing to the low concentration of oxygen present in atmospheric air, molecular oxygen was necessary to permit the oxidation of benzyl phenyl ketone. Similarly, copper was essential to aid in the oxidation step of the reaction, along with the coupling of the *in situ* generated benzil intermediate with benzaldehyde and ammonium acetate. At this point, it was clear that the copper-O_2 system could effectively catalyze this transformation and, as a result, catalytic amounts of other copper catalysts, in the +1 and +2 oxidation states, were examined to further optimize the reaction conditions.

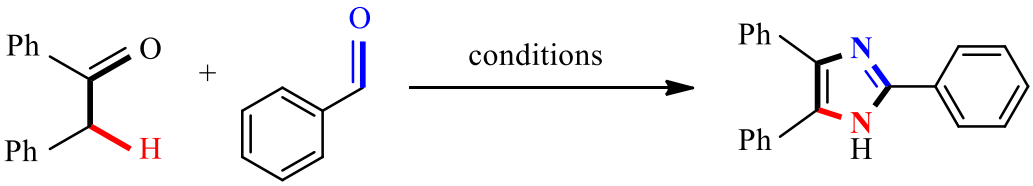
Different copper salts could affect the oxidation of benzyl phenyl ketone as well as the coupling step to afford the desired end product with comparable yields ranging from 82-87% (**Table 5**, **entries 10-13**). Among the copper catalysts screened, copper(II) chloride dihydrate ($CuCl_2.2H_2O$) afforded the desired 2,4,5-triphenyl-1*H*-imidazole **14a** in an isolated yield of 87% (**Table 5**, **entry 10**) and, as a result, it was chosen as the catalyst of choice for this study. At this stage, the use of DMF as a solvent with $CuCl_2.2H_2O$ was sub optimal, hence other solvents were not employed as an improved method was anticipated as a future study.

Depending on the reaction conditions, different synthetic procedures employ varying quantities of ammonium acetate to afford the desired product in maximum yield.[114] In order to complete the optimization study, the amount of ammonium acetate was therefore varied. When five and two equivalents were utilized, considerably lower yields of **14a** were obtained (**Table 5**, **entries 14-15**) and, as a result, the molar ratio of benzyl phenyl ketone: benzaldehyde: ammonium acetate was kept at 1:1:10. According to literary reports on the solubility of ammonium acetate in different solvents, the solubility in DMF is 0.1 g/100 g solvent, compared to other organic solvents (0.34-148 g/100 g solvent [such as ethanol, acetone, ethyl acetate and toluene]). The

lower yields obtained, when employing decreased quantities of ammonium acetate, may be as a result of its solubility in DMF.

Accordingly, the results displayed in **Table 5** showed that the reaction proceeded optimally with the mild reaction conditions described in **entry 10**, allowing maximum conversion into the desired product **14a** which produced spectroscopically pure 2,4,5-triphenyl-1*H*-imidazole upon recrystallization.

Table 5: Optimization of the experimental conditions for the formation of 2,4,5-triphenyl-1*H*-imidazole **13a** from benzyl phenyl ketone **1a** *via* a domino multi-component reaction[a]

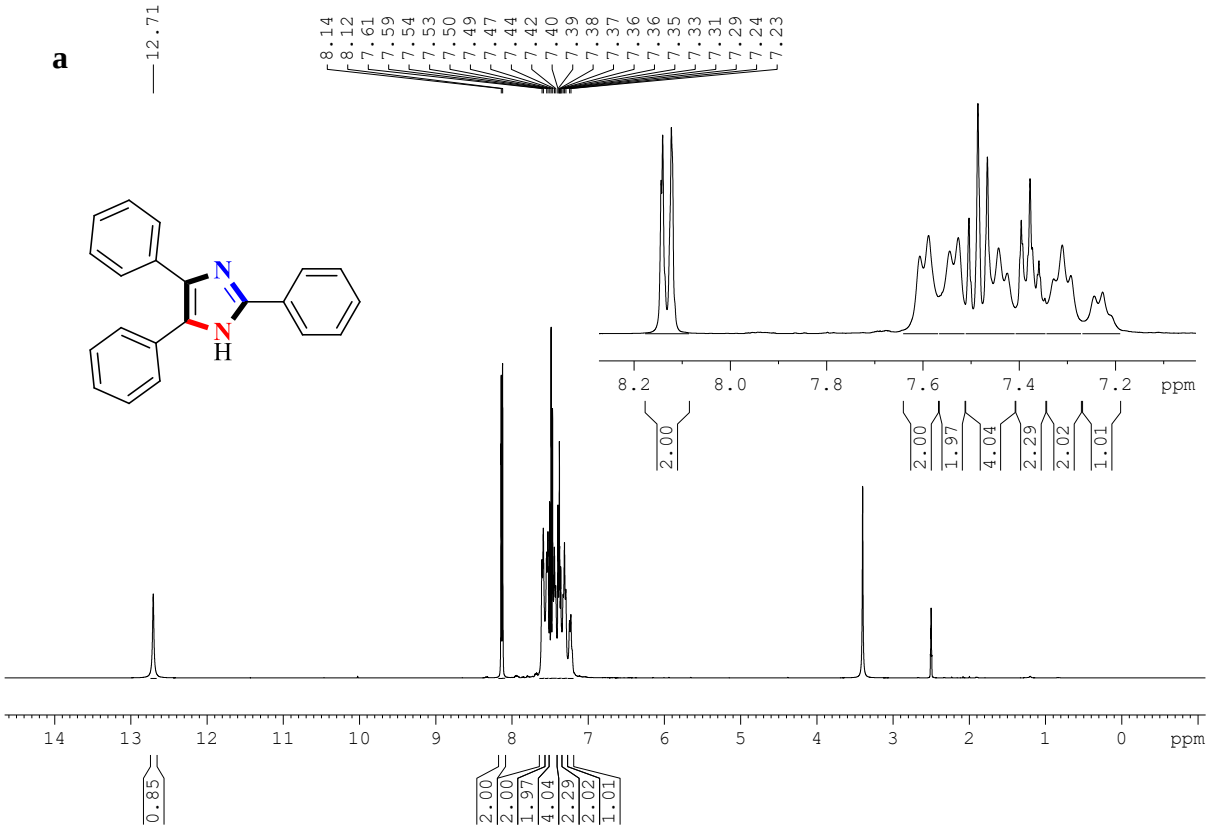


4a **1a** **14a**

Entry	Catalytic system	Solvent (1 mL)	Yield (%)[b]
1	$Cu(OAc)_2.H_2O/O_2$	CH_3CN	61
2	$Cu(OAc)_2.H_2O/O_2$	EtOH	65
3	$Cu(OAc)_2.H_2O/O_2$	EtOAc	63
4	$Cu(OAc)_2.H_2O/O_2$	PhMe	N. R.
5	$Cu(OAc)_2.H_2O/O_2$	DMF	77
6[c]	$Cu(OAc)_2.H_2O/O_2$	DMF	80
7	O_2	DMF	N. R.
8	$Cu(OAc)_2.H_2O$/air	DMF	N. R.
9	$Cu(OAc)_2.H_2O/N_2$	DMF	N. R.
10	**$CuCl_2.2H_2O/O_2$**	**DMF**	**87**
11	$CuCl/O_2$	DMF	83
12	$Cu(NO_3)_2.6H_2O/O_2$	DMF	85
13	CuI/O_2	DMF	82
14[d]	$CuCl_2.2H_2O/O_2$	DMF	43
15[e]	$CuCl_2.2H_2O/O_2$	DMF	21

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), ammonium acetate (5.0 mmol), [Cu] (5 mol%)/O_2 (balloon), 50 °C for 24 h. [b] Isolated yield. [c] 28 h. Ammonium acetate ([d] 2.5 mmol, [e] 1.0 mmol). N. R. = No reaction.

The optimized yield reported in Table for 4 structure **14a** was determined using nuclear magnetic resonance spectroscopy (NMR) and the collected data was compared to previous reports.[54, 115] A representative ^{1}H and ^{13}C NMR of **14a** has been illustrated in **Figure 4**. The characteristic signal at 12.71 ppm (**Figure 4a**) corresponds to the N–H proton of 2,4,5-triphenyl-1*H*-imidazole **14a**. Moreover, the ^{13}C NMR spectrum of this compound shows key signals corresponding to the carbon atoms of the imidazole ring: C_2 (145.5 ppm), C_4 (137.1 ppm) and C_5 (135.2 ppm) [**Figure 4b**]. Additionally, both spectrums are consistent with the formation of four new C–N bonds. All other protons were located at their respective positions, the carbon atoms, assigned accordingly, and in accordance with literature. The molecular mass for compound **14a** is 297.1313 g/mol. The mass spectroscopy (MS) results indicated a mass of 297.1388 indicative of $[M + H]^+$. This result is in agreement with the referenced literature. Melting points and infrared (IR) spectroscopy were conducted, referenced and were in agreement with the relevant literature reports.



† The spectrum continues on the next page

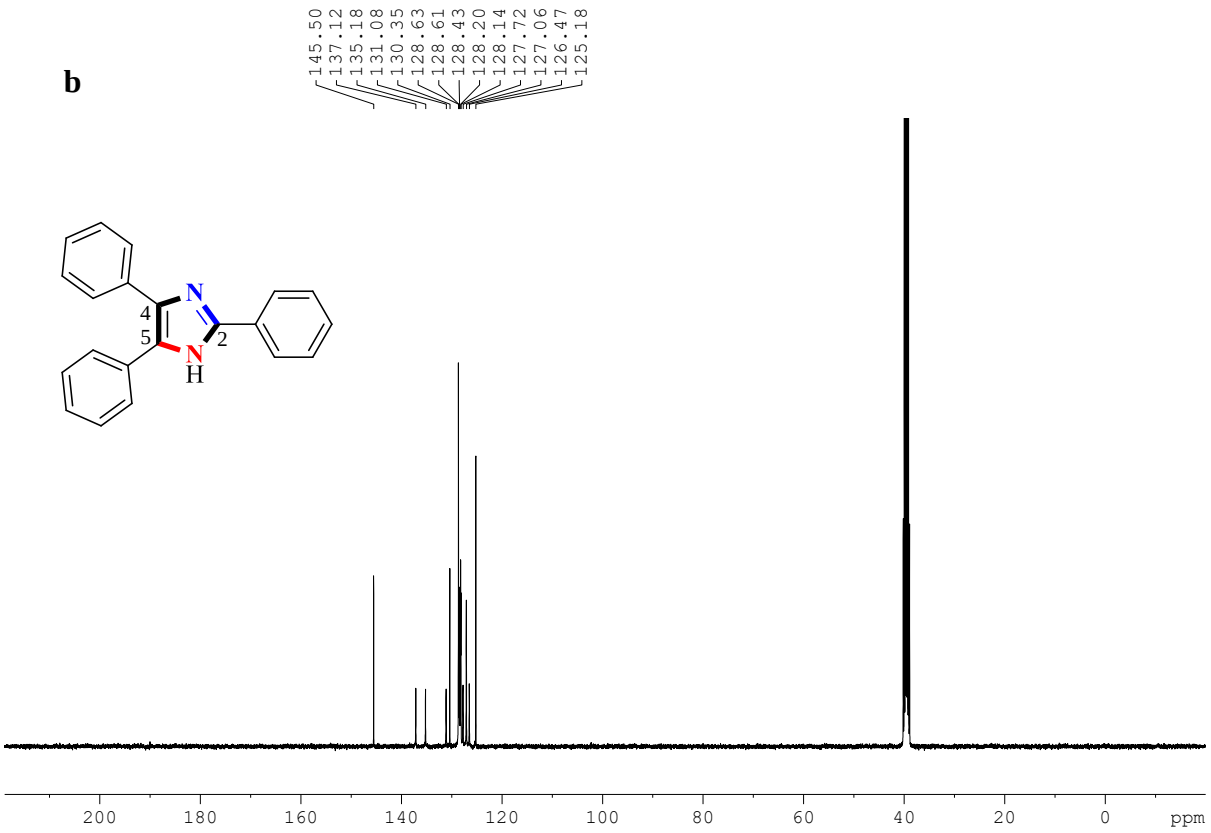


Figure 4: ^{1}H and ^{13}C NMR spectra in DMSO-d_6 of 2,4,5-triphenyl-1*H*-imidazole **14a**.

2.4.2 Library Synthesis of Diverse 2,4,5-Triaryl-1*H*-imidazoles

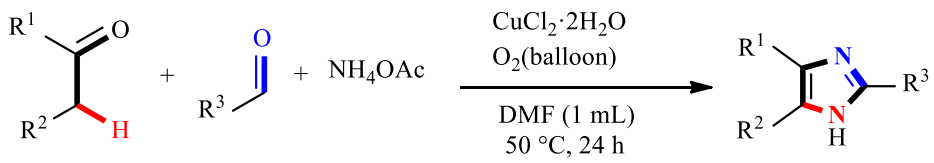
With the optimized reaction conditions in hand (**Table 6**, **entry 10**), the next avenue explored the scope and limitations of the devised system by varying the benzyl aryl ketones and aldehydes. The results are summarized in **Table 6**. Diversely substituted benzaldehydes, with either electron-donating (–OMe) or electron-withdrawing (–Cl, –Br, –F) functional groups in the *para* position, reacted smoothly with **4a** to afford the corresponding 2,4,5-triarylimidazoles **14b-14e** in good yields (60-87%). Similar results were obtained upon substitution at the *meta* position of **1a** providing good yields of 71-76% (**Table 6**, **14f-14g**). When *ortho*-substituted fluoro- and methoxybenzaldehyde were utilized as substrates, 2-(2-fluorophenyl)-4,5-diphenyl-1*H*-imidazole (**Table 6**, **14h**) and 2-(2-methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (**Table 6**, **14i**) were furnished in moderate yields (51% and 43%, respectively). The results demonstrated that a wide range of benzaldehydes, regardless of electron-rich or electron-deficient functional groups on the *para*-, *meta*-, *ortho*- position of the aryl group, was suitable substrates for the domino multi-component reaction.

Having applied numerous substituted aromatic aldehydes to the optimized reaction conditions, this study was subsequently extended to heterocyclic and aliphatic aldehydes, producing the corresponding imidazoles **14j-14l**, *albeit* in low isolated yields of 21-32%. The resulting yields demonstrated that these aldehydes do not couple particularly well under the given reaction conditions. These results are consistent with literature, as heterocyclic and specifically aliphatic aldehydes are not commonly examined in 2,4,5-trisubstituted-1*H*-imidazole synthesis, and, when they are, often result in low yields.[90, 116]

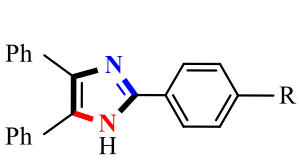
Next, reactions of benzaldehydes with substituted benzyl aryl ketones were evaluated. Unfortunately, 2-butanone and acetophenone were not compatible with this domino transformation despite employing varying reaction conditions in which only unreacted starting material was recovered (**Table 6**, **14m-14n**). This is probably due to the reduced nucleophilicity of these substrates.

Benzyl phenyl ketones, substituted with *para*-Cl or -Br functional groups, were well tolerated under the optimized reaction conditions and delivered **14o-14p** as mixtures of tautomers in good yields (67-72%). The formation of the tautomers is due to the presence of the fluid hydrogen on the nitrogen atom of the imidazole motif. Subsequently, coupling 4-chloro-2-phenylacetophenone with benzaldehydes, substituted with electron-withdrawing halogens in the *para* position, successfully afforded the corresponding 2,4,5-triaryl-1*H*-imidazoles **14q-14s** in moderate yields (52-68%). Compound **14q** were isolated as a mixture of tautomers, whereas compounds **14r-14s** were isolated as one of the tautomers of that compound.

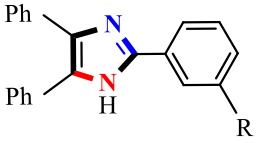
Table 6: Substrate scope for the Cu/O_2 catalyzed domino synthesis of 2,4,5-trisubstituted-1*H*-imidazoles under mild reaction conditions.



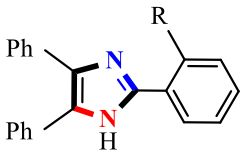
4 **1** **14**[a]



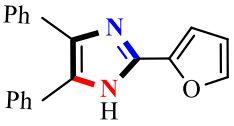
14a, R = H, 87%
14b, R = OMe, 60%
14c, R = Cl, 73%
14d, R = Br, 76%
14e, R = F, 80%



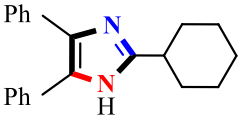
14f, R = NO_2, 76%
14g, R = F, 71%



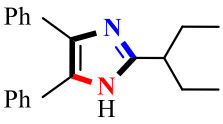
14h, R = F, 51%
14i, R = OMe, 43%[b]



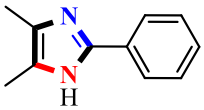
14j, 32%[b]



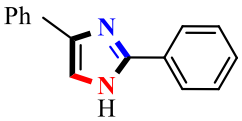
14k, 26%[b]



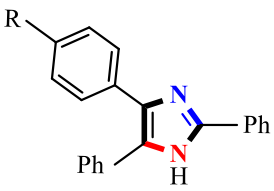
14l, 21%



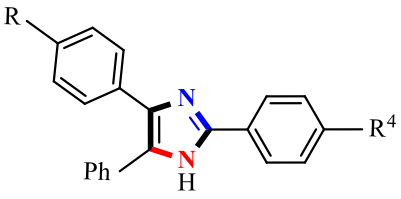
14m, 0%



14n, 0%[c]



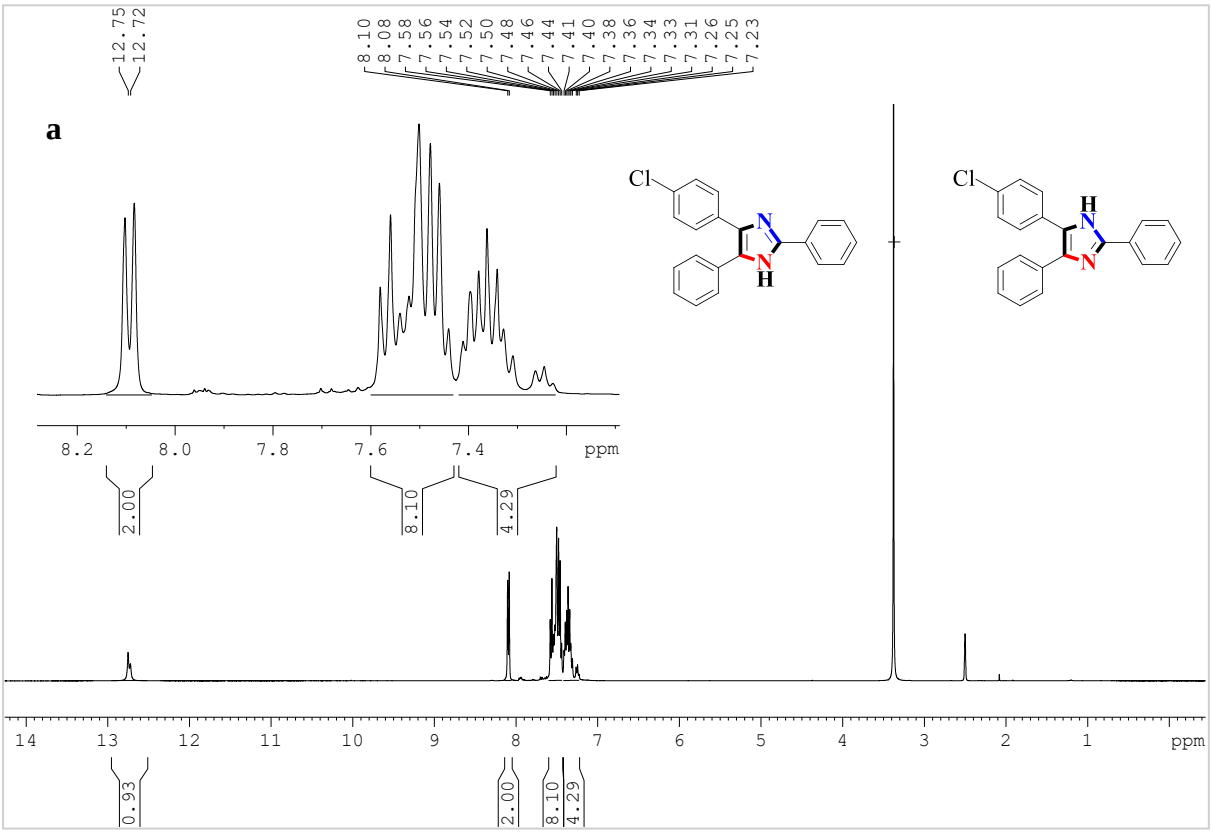
14o, R = Cl, 67%[d]
14p, R = Br, 72%[d]



14q, R = R^4 = Cl, 64%[d]
14r, R = Cl, R^4 = Br, 68%
14s, R = Cl, R^4 = F, 52%

Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), ammonium acetate (5.0 mmol), $CuCl_2 \cdot 2H_2O$ (5 mol%), O_2 (balloon), DMF (1 mL), 50 °C, 24 h. [a] Isolated yield. [b] 10 mol% $CuCl_2 \cdot 2H_2O$. [c] 24 h, 72 h, $CuCl_2 \cdot 2H_2O$ (0.5 mmol). [d] Mixture of tautomers.

A representative example of compound **14o** is displayed in **Figure 5**, characterized using ^{1}H and ^{13}C NMR. Upon analysis of the ^{1}H NMR spectrum, the signal for the –NH group on the imidazole motif is distinctly split at 12.72 ppm and 12.75 ppm (**Figure 5a**). This indicates that compound **14o** is a mixture of tautomers. Moreover, the ^{13}C NMR spectrum of this compound shows key signals corresponding to the carbon atoms of the imidazole ring: C_2 (145.6 ppm and 145.8ppm), C_4 (135.7 ppm and 137.7 ppm) and C_5 (133.9 ppm and 134.9 ppm) [**Figure 5b**]. Similar results were observed for compounds **14p-14q** which is given in the experimental section.



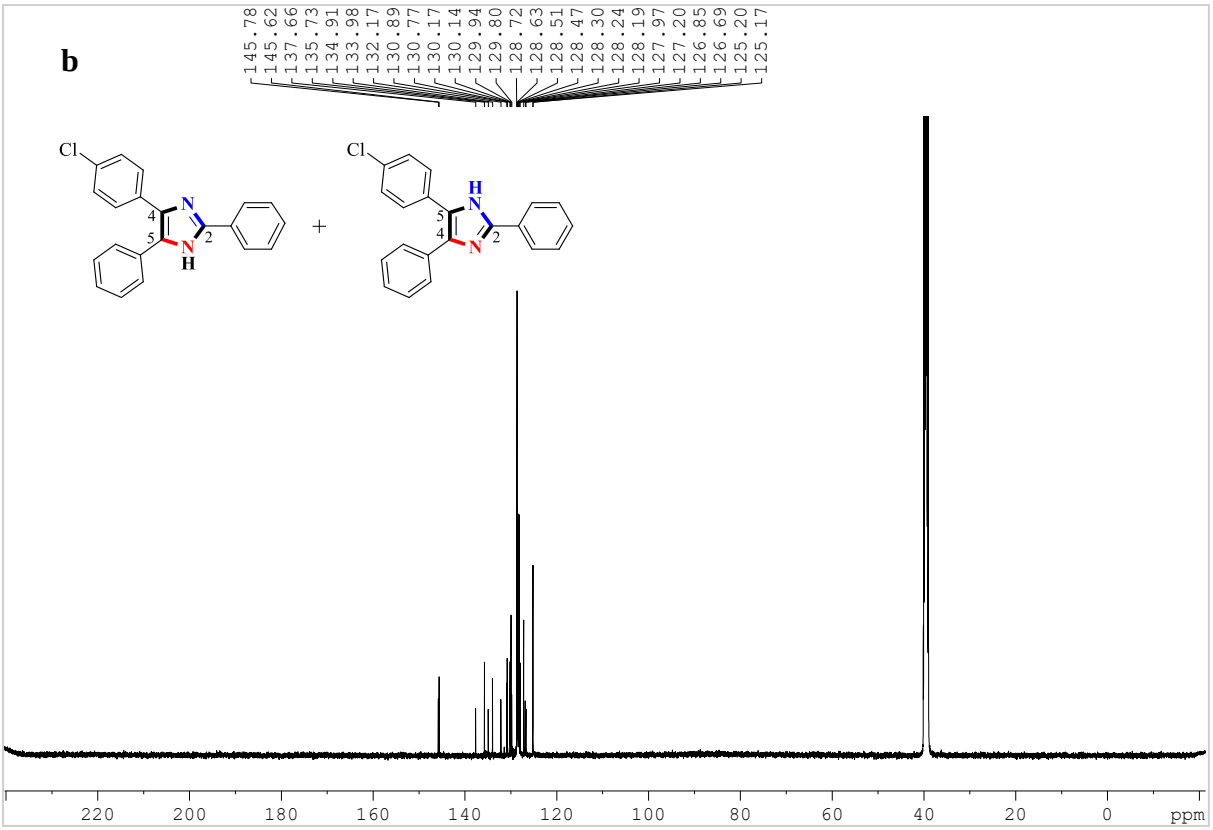


Figure 5: ^{1}H and ^{13}C NMR spectra in DMSO-d_6 of compound **14o** as a mixture of tautomers.

A temperature study was subsequently performed in an effort to understand its effect on the tautomers of compound **14o** (**Figure 6**). At 30 ^{o}C, compound **14o** exists as a mixture of tautomers. Upon increasing the temperature by 5 ^{o}C, the split in the NH signal at 12.72 ppm and 12.75 ppm converges, resulting in a dominant tautomer of **14o**. Similar results were obtained for the effect of temperature on the tautomeric forms of compounds **14p** and **14q** (**Figure 7** and **Figure 8**, respectively). The ^{1}H NMR spectra displays the split in –NH signal of these compounds.

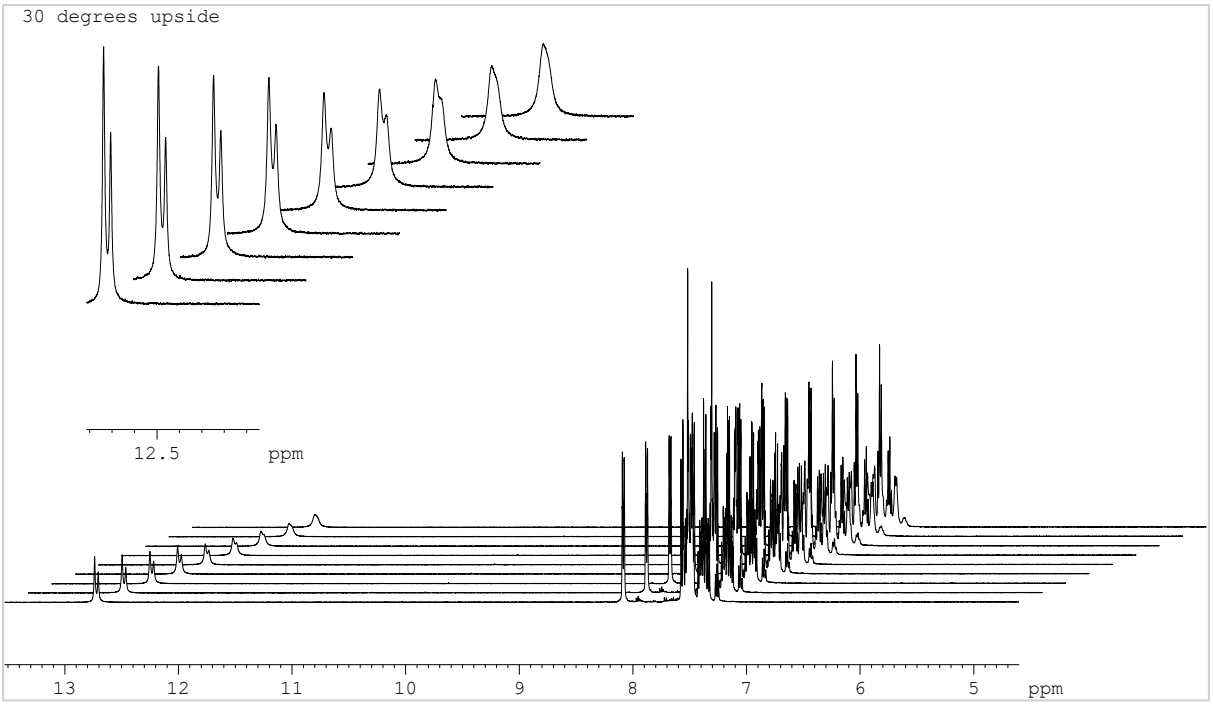


Figure 6: Effect of temperature on the tautomeric forms of compound **14o**.

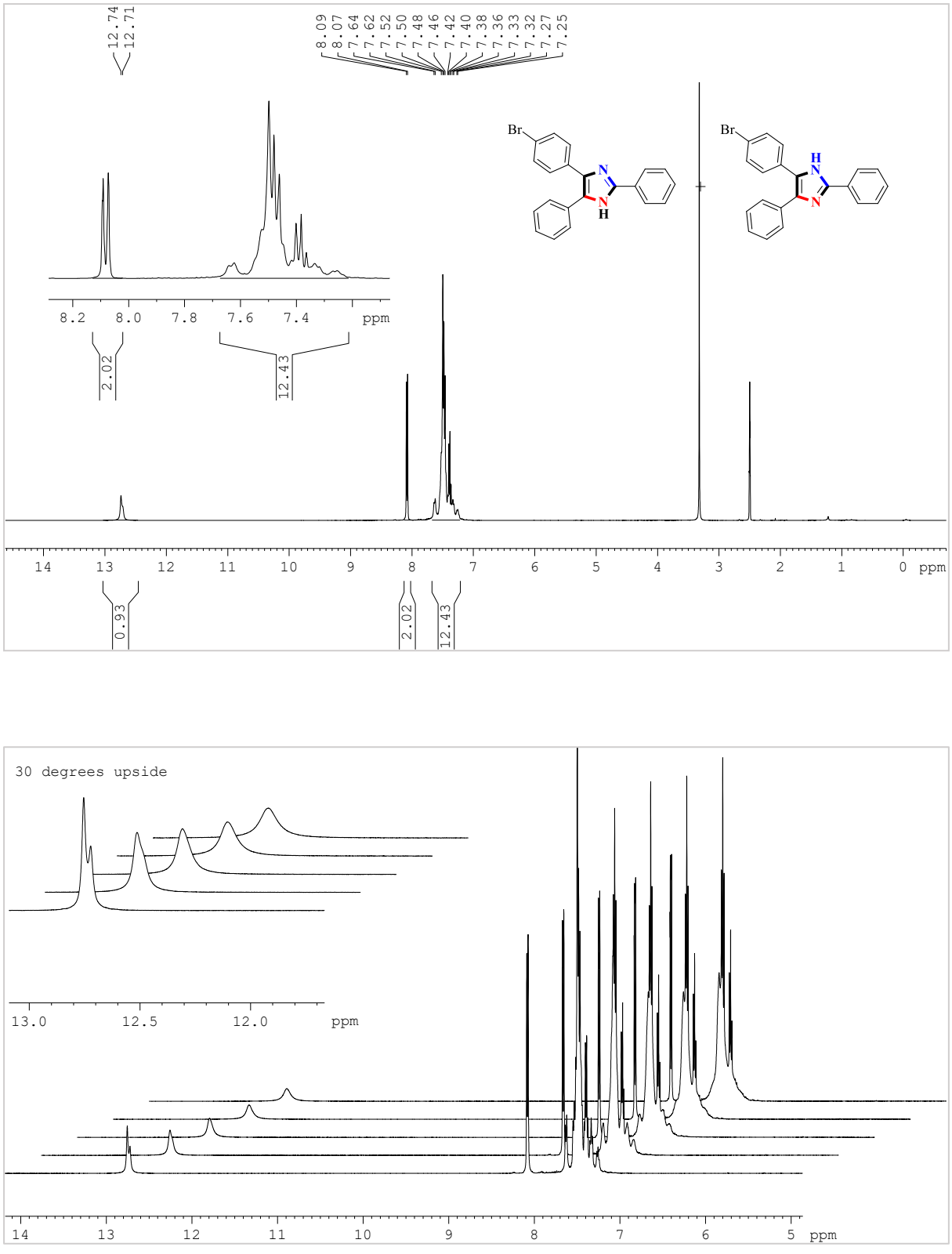


Figure 7: ^{1}H NMR spectrum and effect of temperature on the tautomeric forms of compound **14p**.

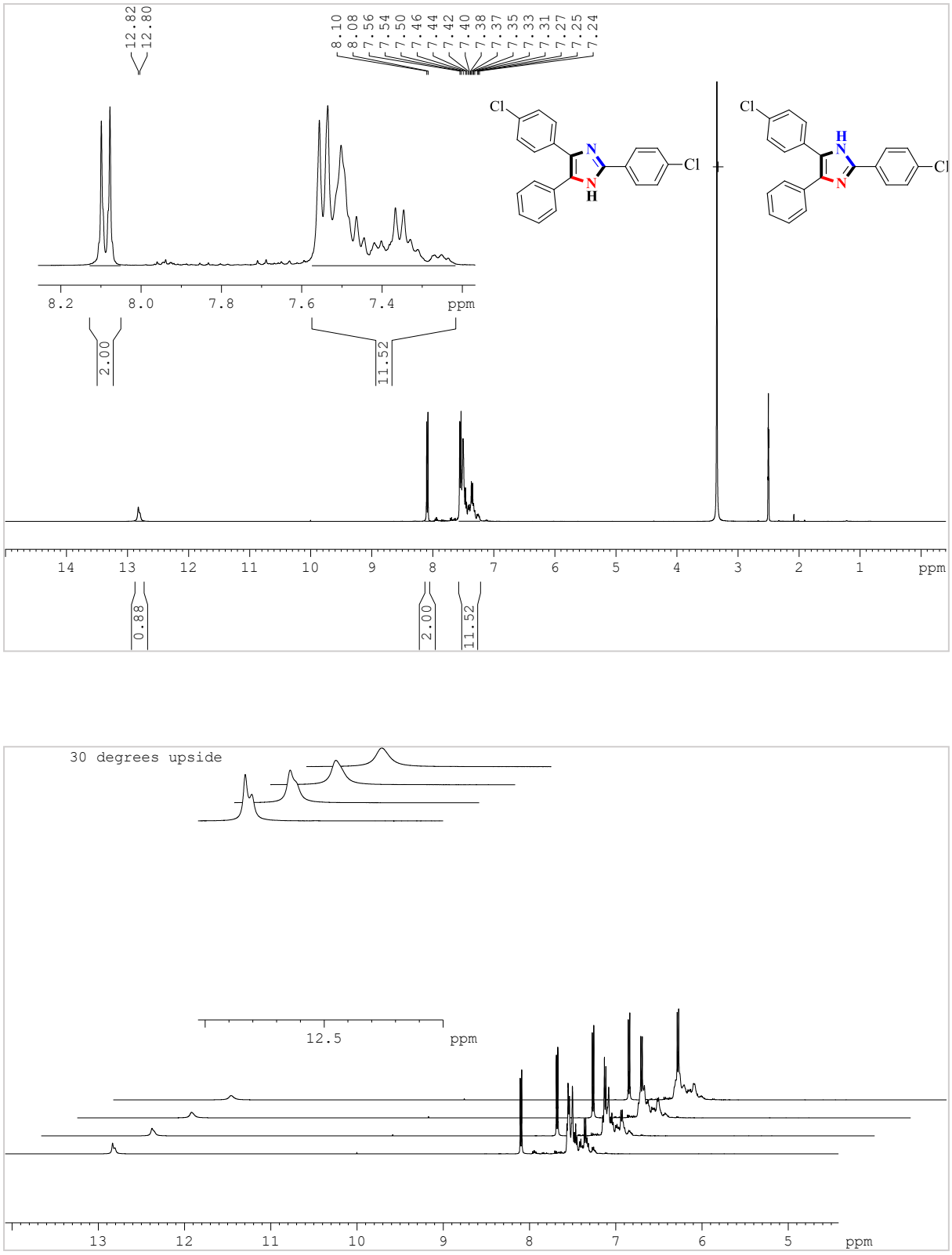
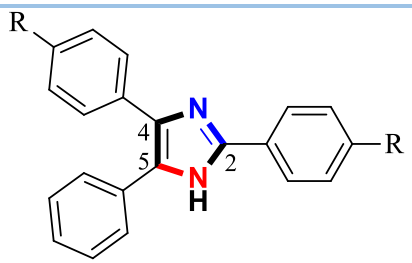


Figure 8: ^{1}H NMR spectrum and effect of temperature on the tautomeric forms of compound **14q**.

2.4.3 A Summary of the Experimental Data for Compounds **14a-14s**

The key signals in the ^{1}H and ^{13}C NMR spectra for the synthesis of compounds **14a-14s** is given in **Table 7**. Accordingly, signals characteristic to the NH functional group ranges from 11.87-13.09 ppm. The imidazole compounds **14o-14q** display split NH signals indicating a mixture of tautomers, whereas, **14r-14s** are the dominant tautomeric form. The ^{13}C signals for C-2, C-4, C-5 of the imidazole ring and the *m/z* value in the mass spectra are specified. Complete characterization of each compound is given in the experimental section and in agreement with the referenced literature report (*vida infra*).

Table 7: Experimental data for compounds **14a-14s**



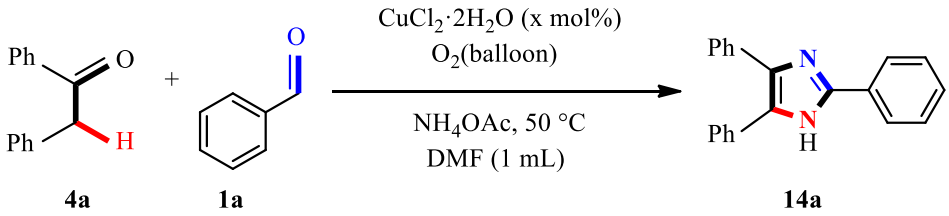
Compound	-NH (ppm)	C-2 (ppm)	C-4 (ppm)	C-5 (ppm)	MS (*m/z*)
14a	12.71	145.5	137.1	135.2	297.1388 $[M+H]^+$
14b	12.51	145.6	136.8	135.3	327.1494 $[M+H]^+$
14c	12.77	144.5	137.4	135.1	331.1009 $[M+H]^+$
14d	12.77	144.5	137.4	135.0	375.0500 $[M+H]^+$
14e	12.72	144.7	137.1	135.1	315.1307 $[M+H]^+$
14f	13.09	148.4	137.7	134.8	364.1071$[M+Na]^+$
14g	12.79	144.3	137.4	134.9	337.1122$[M+Na]^+$
14h	12.53	140.9	137.3	135.0	337.1114$[M+Na]^+$
14i	11.87	143.2	136.4	135.3	325.1345 $[M-H]^+$
14j	12.80	143.0	136.9	134.9	309.1007$[M+Na]^+$
14k	11.91	152.3	135.8	134.9	303.1869 $[M+H]^+$
14l	11.96	151.3	135.8	135.2	291.2007 $[M+H]^+$
14o	12.72, 12.75	145.6, 145.8	135.7, 137.7	133.9, 134.9	331.1006 $[M+H]^+$
14p	12.71, 12.74	145.8, 145.9	135.9, 137.8	134.4, 134.9	375.0492 $[M+H]^+$
14q	12.80, 12.82	144.6, 144.7	135.9, 137.9	132.3, 132.9	365.0616 $[M+H]^+$
14r	12.82	144.8	-	-	409.0110 $[M+H]^+$
14s	12.72	145.4	138.0	134.9	349.0907 $[M+H]^+$

2.4.4 Catalytic Loading Study

From a green chemistry perspective, it is more desirable to employ the minimum amount of catalyst for a chemical synthesis. Thus, in an effort to evaluate the developed system to improve the reaction greenness, a series of catalytic loading experiments were undertaken to investigate the effect of decreasing the quantity of the catalyst. (**Table** , **entries 1-6**). The metal catalyst

loading was decreased from 5-0.5 mol% and the product formation was evaluated. Under the optimized reaction conditions, the domino transformation was well tolerated, when as little as 0.5 mol% of $CuCl_2 \cdot 2H_2O$ was employed, affording **14a** in a moderate yield of 49%. In comparison to prolonging the reaction time to 5 days, the domino product **14a** could be furnished with comparable and improved yields ranging from 71-94%, commencing from the benzyl aryl ketone, aldehyde and ammonium acetate.

Table 8: Evaluation of the catalyst loading on the synthesis of 2,4,5-triphenyl-1*H*-imidazole **14a** employing the Cu/O_2 oxidative system.[a]



4a **1a** **14a**

Entry	Catalyst loading (x mol%)	Yield of 14a (%)[b]	
		24 h	5 days
1	5	87	94
2	4	84	90
3	3	79	88
4	2	68	85
5	1	57	78
6	0.5	49	71

Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), ammonium acetate (5.0 mmol), x mol% $CuCl_2.2H_2O/O_2$ (balloon). [b] Isolated yield.

Based on the optimization and catalytic loading study, the following improvements in the previously reported methodology on SeO_2/HOAc (see Chapter 2.1) within the group, are highlighted in **Table 9**.

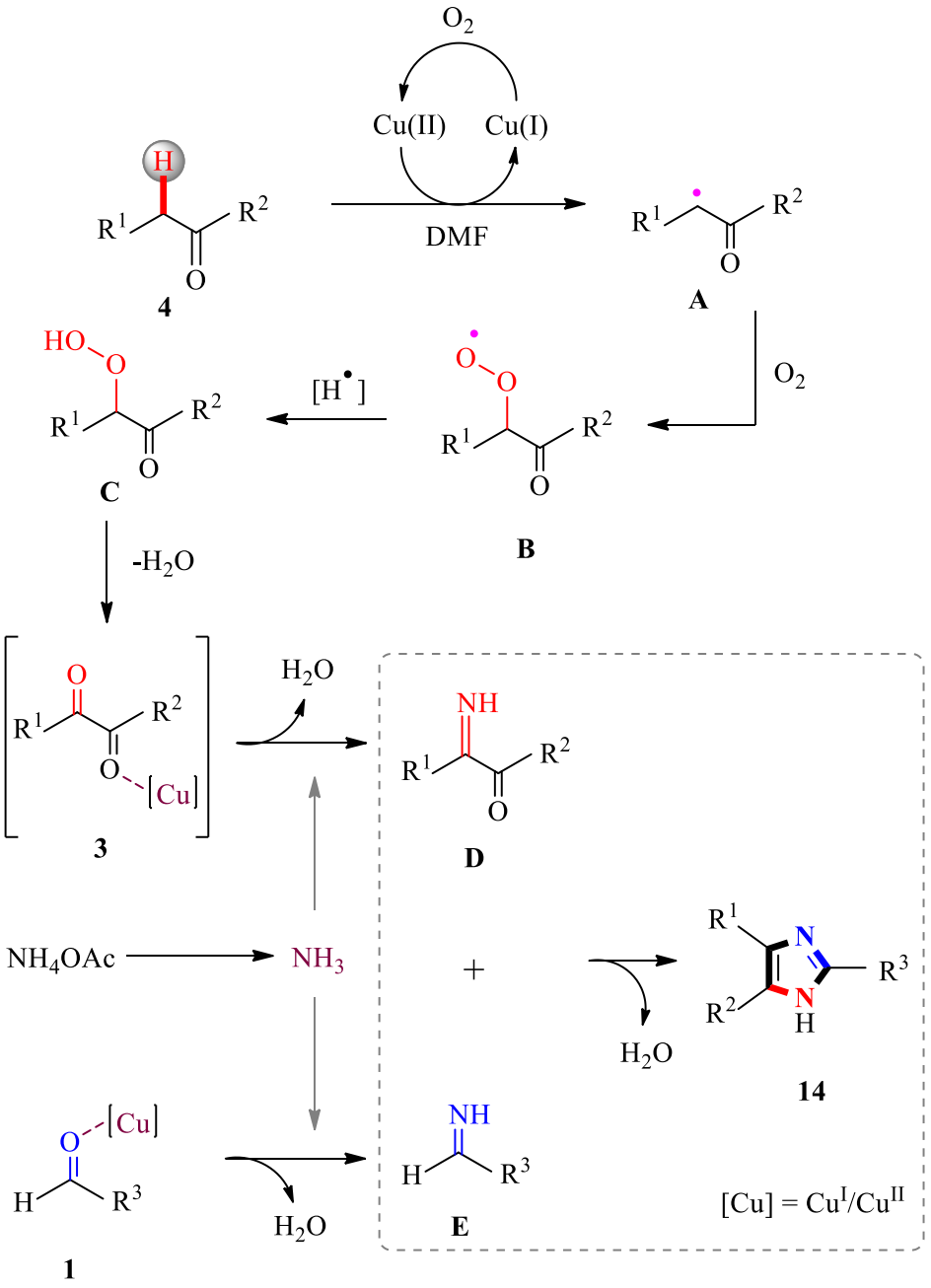
Table 9: Comparison of the reaction conditions employed within this research displaying an improved Cu/O_2 oxidative system compared to SeO_2/HOAc.

	Previous Study	Current Study
Catalyst:	SeO_2	$CuCl_2 \cdot H_2O$
Loading:	1 equivalent: starting material	5 mol%: starting material
Solvent:	HOAc	DMF
Volume:	5 mL	1 mL
Temperature:	180 °C	50 °C

While the $Cu(II)/O_2$ oxidative system could affect the domino MCR to furnish diversely substituted 2,4,5-triaryl-1*H*-imidazoles, the scope of the research project was directed towards developing an in-depth understanding of the mechanism of the domino multi-component reaction in an effort to rationalize the formation of the imidazole compounds.

2.4.5 Proposed Reaction Mechanism

Based on literary studies, it was noted that copper, in the presence of molecular oxygen, catalyzed aerobic oxidation reactions *via* a radical mediated single electron transfer (SET) process (**Scheme 28**).[110-111, 117] Accordingly, the reaction initiates the Cu(II) oxidation of the benzyl aryl ketone **4** which is deprotonated at the α position to generate the benzylic radical **A**. This radical is subsequently trapped by molecular oxygen to afford the peroxide radical **B**. Upon capture of a hydrogen radical, intermediate **C** is furnished and followed by the successive elimination of one water molecule to afford the desired 1,2-diketone adduct **3**. Concurrently, the copper species in the solution activates substrate **4** and the 1,2-diaryl diketone **3** which, upon reaction with ammonia, affords the imine intermediates **D** and **E**. Subsequently, cyclocondensation of the imine intermediates furnishes the desired 2,4,5-triaryl-1*H*-imidazoles **14**.



Scheme 28: Plausible reaction mechanism for the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles **14** showing key reactive intermediates.

2.5 Concluding Remarks to Copper Catalysis for the Synthesis of 2,4,5-Trisubstituted-1*H*-imidazoles

In summary, a simple, environmentally benign and efficient method for the one-pot, multi-component synthesis of 2,4,5-triaryl-1*H*-imidazoles, a key structural motif in several important pharmacological drug molecules, was successfully developed from benzyl aryl ketones instead of the traditional 1,2-diaryl diketone. This methodology proceeds using catalytic copper(II) as a catalyst in the presence of molecular oxygen under mild reaction conditions without the use of additional Lewis acids or external additives. Since the developed system tolerates several functional groups, diversely substituted 2,4,5-triaryl-1*H*-imidazoles were furnished in moderate to good yields.

The results of the Cu(II)/O_2 oxidative system for the direct oxidation of benzyl aryl ketones to afford 2,4,5-triaryl-1*H*-imidazoles was drawn up for publication and subsequently accepted by the RSC journal *Green Chemistry*. The reference to this publication is given below and a copy of the article is available in appendix A.

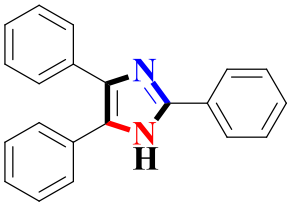
Reference:[118] J. Jayram and V. Jeena,*Green Chem.* **2017**, 19, 5841–5845

2.6 Experimental

2.6.1 General Information

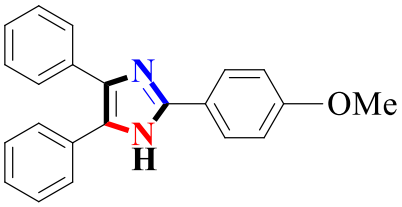
All reagents were purchased without further purification. All ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Advance III spectrometer operating at either 400 or 500 MHz. Chemical shifts (δ) were reported in ppm using the Dimethyl Sulfoxide-d_6 (DMSO-d_6) residual 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 unit (Hz). High-resolution electron-spray ionization (ESI) mass spectra were recorded on a time-of-flight (TOF) micromass spectrometer. Infra-Red (IR) spectra were recorded on Perkin Elmer FTIR Spectrometer. Absorption maxima are expressed in wavenumbers (cm^{-1}). Melting points were determined using Kofler hot-stage melting apparatus.

2.6.2 Typical Procedure for the Copper-O_2 Catalyzed Reaction of Benzyl Aryl Ketones, Aldehydes and Ammonium Acetate



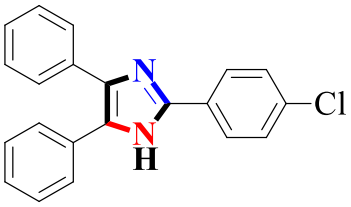
2-Phenylacetaphenone (0.5 mmol), benzaldehyde (0.5 mmol), ammonium acetate (5 mmol) and catalytic copper chloride dihydrate (5 mol%) were mixed in a round bottomed flask with 1 mL Dimethylformamide (DMF). An oxygen balloon was attached and the mixture was heated at 50 °C for 24 hours. After cooling, ice water was added to the reaction mixture to form a white precipitate which was filtered and dried in an oven at 50 °C for 2 hours. The crude product was recrystallized from 9:1 acetone: water to afford 2,4,5-triphenyl-1*H*-imidazole **14a**. The following compounds **14b-14s** were prepared by this method using the appropriate starting materials.

2,4,5-Triphenyl-1*H*-imidazole (14a, **$C_{21}H_{16}N_2$, 0.129g, 87%**):[54, 115] white solid. **Mp** 270-271 °C; **υ_{max} (neat, cm^{-1}):** 3419 (N-H), 3039 (C-H), 1600 (C=N), 1461 (C=C), 1488, 1128 (C-N); **^{1}H NMR (400 MHz, DMSO-D_6):** 12.71(s, 1H), 8.13 (d, *J* = 7.20 Hz, 2H,), 7.60 (d, *J* = 7.24 Hz, 2H), 7.53 (d, *J* = 7.12 Hz, 2H), 7.50-7.42 (m, 4H), 7.40-7.35 (m, 2H), 7.31 (t, *J* = 7.14 Hz, 2H), 7.24-7.23 (m, 1H); **^{13}C (100 MHz, DMSO-D_6):** 145.5, 137.1, 135.2, 131.1, 130.3, 128.6, 128.6, 128.4, 128.2, 128.1, 127.7, 127.1, 126.5, 125.2; **ESI-MS (*m/z*):** calcd for $C_{21}H_{17}N_2$ 297.1393, found 297.1388 $[M+H]^+$.

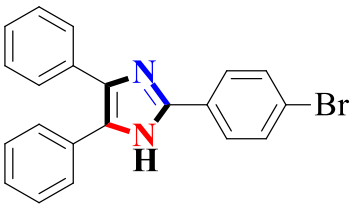


2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (14b, $C_{22}H_{18}N_2O$, 0.098g, 60%):[54] white solid. **Mp** 230-233 °C; **υ_{max} (neat, cm^{-1}):** 3415 (N-H), 3024 (C-H), 2959, 1613 (C=N), 1492 (C=C), 1245 (C-N), 1175 (C-O-C); **^{1}H NMR (400 MHz, DMSO-D_6):** 12.51 (s, 1H), 8.04

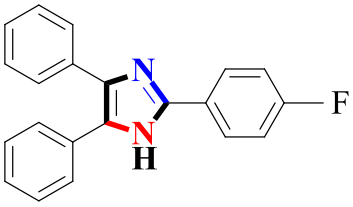
(d, *J* = 8.80 Hz, 2H), 7.57 (d, *J* = 7.40 Hz, 2H), 7.51 (d, *J* = 7.32 Hz, 2H), 7.43 (t, *J* = 7.46 Hz, 2H), 7.35 (t, *J* = 7.24 Hz, 1H), 7.30 (t, *J* = 7.50 Hz, 2H), 7.20 (t, *J* = 7.26 Hz, 1H), 7.05 (d, *J* = 8.84 Hz, 2H), 3.82 (s, 3H); **^{13}C (100 MHz, DMSO-D$_6$):** 159.4, 145.6, 136.8, 135.3, 131.2, 128.6, 128.3, 128.1, 127.6, 127.6, 127.1, 126.7, 126.4, 123.1, 114.1, 55.5; **ESI-MS (*m/z*):** calcd for $C_{22}H_{19}N_2O$ 327.1499, found 327.1494 $[M+H]^+$.



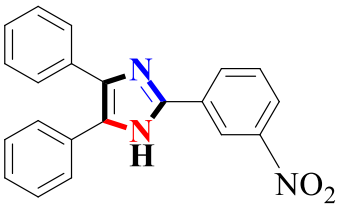
2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (14c, $C_{21}H_{15}ClN_2$, 0.121g, 73%):[119] white solid. **Mp** 263-264 °C; **υ_{max} (neat, cm^{-1}):** 3419 (N-H), 3059 (C-H), 3027, 1602 (C=N), 1485 (C=C), 1091 (C-N), 764 (C-Cl), 693; **^{1}H NMR (400 MHz, DMSO-D$_6$):** 12.77 (s, 1H), 8.12 (d, *J* = 8.56 Hz, 2H), 7.55-7.53 (m, 6H), 7.36 (m, 6H); **^{13}C (100 MHz, DMSO-D$_6$):** 144.5, 137.4, 135.1, 132.8, 131.0, 129.3, 128.8, 128.7, 128.5, 128.2, 127.9, 127.2, 126.9, 126.6; **ESI-MS (*m/z*):** calcd for $C_{21}H_{16}{}^{35}ClN_2$ 331.1004, found 331.1009 $[M+H]^+$.



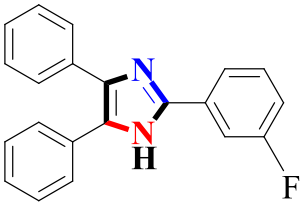
2-(4-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (14d, $C_{21}H_{15}BrN_2$, 0.142g, 76%): white solid. Mp 250-252 °C; **υ_{max} (neat, cm^{-1}):**[119] 3419 (N-H), 3057 (C-H), 2835, 1601 (C=N), 1482 (C=C), 1126 (C-N), 604 (C-Br); **^{1}H NMR (400 MHz, DMSO-D$_6$):** 12.77 (s, 1H), 8.05 (d, *J* = 8.60 Hz, 2H), 7.68 (d, *J* = 8.60 Hz, 2H), 7.54-7.52 (m, 4H), 7.36 (m, 6H); **^{13}C (100 MHz, DMSO-D$_6$):** 144.5, 137.4, 135.0, 131.7, 130.9, 129.6, 128.7, 128.4, 128.2, 127.9, 127.1, 126.6, 121.4; **ESI-MS (*m/z*):** calcd for $C_{21}H_{16}BrN_2$ 375.0499, found 375.0500 $[M+H]^+$.



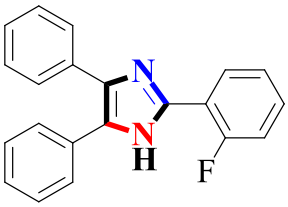
2-(4-Fluorophenyl)-4,5-diphenyl-1*H*-imidazole (14e, $C_{21}H_{15}FN_2$, 0.126g, 80%):[119a] white solid. **Mp** 189-190 °C; **υ_{max} (neat, cm^{-1}):** 3426 (N-H), 3028 (C-H), 2794, 1608 (C=N), 1492 (C=C), 1220 (C-N), 1159 (C-F); **^{1}H NMR (400 MHz, DMSO-D_6):** 12.72 (s, 1H), 8.14 (dd, *J* = 8.66 Hz, 5.50 Hz, 2H), 7.56 (d, *J* = 7.32 Hz, 2H), 7.51 (d, *J* = 7.24 Hz, 2H), 7.44 (t, *J* = 7.42 Hz, 2H), 7.38 (d, *J* = 7.16 Hz, 1H), 7.35-7.28 (m, 4H), 7.22 (t, *J* = 7.22 Hz, 1H); **^{13}C (100 MHz, DMSO-D_6):** 162.2 ($J_{C, F}$ = 246 Hz), 144.7, 137.1, 135.1, 131.1, 128.7, 128.4, 128.3, 128.2, 127.8, 127.4 ($J_{C, F}$ = 8.24 Hz), 127.1, 127.1 ($J_{C, F}$ = 2.90 Hz), 126.6, 115.7 ($J_{C, F}$ = 21.79 Hz) ; **ESI-MS (*m/z*):** calcd for $C_{21}H_{16}FN_2$ 315.1299, found 315.1307 $[M+H]^+$.



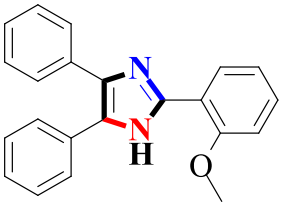
2-(3-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (14f, $C_{21}H_{15}N_3O_2$, 0.130g, 76%):[119] yellow solid. **Mp** 315-317 °C; **υ_{max} (neat, cm^{-1}):** 3397 (N-H), 3057 (C-H), 2860, 1601 (C=N), 1521 (N-O), 1347, 1480 (C=C), 1416, 1252 (C-N), 1071; **^{1}H NMR (400 MHz, DMSO-D_6):** 13.09 (s, 1H), 8.96 (s, 1H), 8.52 (d, *J* = 7.76 Hz, 1H), 8.21 (d, *J* = 8.08 Hz, 1H), 7.78 (t, *J* = 7.98 Hz, 1H), 7.55 (d, *J* = 7.20 Hz, 4H), 7.38 (m, 6H); **^{13}C (100 MHz, DMSO-D_6):** 148.4, 143.4, 137.7, 134.8, 131.8, 131.2, 130.7, 130.4, 129.2, 128.7, 128.4, 128.3, 128.1, 127.2, 126.8, 122.6, 119.4; **ESI-MS (*m/z*):** calcd for $C_{21}H_{15}N_2O_2Na$ 364.1064, found 364.1071 $[M+Na]^+$.



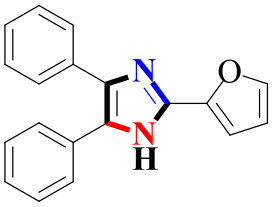
2-(3-Fluorophenyl)-4,5-diphenyl-1*H*-imidazole (14g, $C_{21}H_{15}FN_2$, 0.112g, 71%):[120] white solid. **Mp** 284-285 °C; **υ_{max} (neat, cm^{-1}):** 3435 (N-H), 3056 (C-H), 2970, 1618 (C=N), 1588 (C=C), 1483, 1220 (C-N), 1072 (C-F); **^{1}H NMR (400 MHz, DMSO-D_6):** 12.79 (s, 1H), 7.96 (d, *J* = 7.84 Hz, 1H), 7.91 (d, *J* = 10.23 Hz, 1H), 7.58-7.49 (m, 5H), 7.45 (m, 2H), 7.40-7.37 (m, 1H), 7.29-7.32 (m, 2H), 7.25-7.18 (m, 2H); **^{13}C (100 MHz, DMSO-D_6):** 162.5 ($J_{C, F}$ = 246 Hz), 144.3 ($J_{C, F}$ = 2.70 Hz), 137.4, 134.9, 132.7 ($J_{C, F}$ = 8.09 Hz), 130.9, 130.7 ($J_{C, F}$ = 8.99 Hz), 128.6, 128.4, 128.2, 127.9, 127.1, 126.6, 121.2 ($J_{C, F}$ = 2.70 Hz), 114.8 ($J_{C, F}$ = 21.57 Hz), 111.7 ($J_{C, F}$ = 21.57 Hz); **ESI-MS (*m/z*):** calcd for $C_{21}H_{15}FN_2Na$ 337.1119, found 337.1122 $[M+Na]^+$.



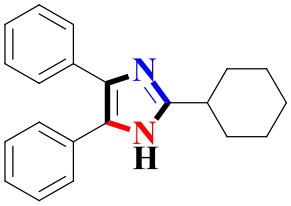
2-(2-Fluorophenyl)-4,5-diphenyl-1*H*-imidazole (14h, $C_{21}H_{15}FN_2$, 0.080g, 51%):[120] white solid. **Mp** 238-240 °C; **υ_{max} (neat, cm^{-1}):** 3457 (N-H), 3058 (C-H), 1602 (C=N), 1484 (C=C), 1470, 1441, 1253 (C-N), 1101; **^{1}H NMR (400 MHz, DMSO-D_6):** 12.53 (s, 1H), 8.01 (t, *J* = 7.70 Hz, 1H), 7.53-7.49 (m, 4H), 7.45 (t, *J* = 6.60 Hz, 1H), 7.38-7.32 (m, 8H); **^{13}C (100 MHz, DMSO-D_6):** 158.9 ($J_{C, F}$ = 252 Hz), 140.9 ($J_{C, F}$ = 1.39 Hz), 137.3, 135.0, 130.9, 130.5 ($J_{C, F}$ = 8.32 Hz), 129.7 ($J_{C, F}$ = 2.77 Hz), 128.6, 128.6, 128.2, 127.9, 127.2, 126.6, 124.7 ($J_{C, F}$ = 3.24 Hz), 118.7 ($J_{C, F}$ = 12.94 Hz), 116.3 ($J_{C, F}$ = 22.18 Hz); **ESI-MS (*m/z*):** calcd for $C_{21}H_{15}FN_2Na$ 337.1119, found 337.1114 $[M+Na]^+$.



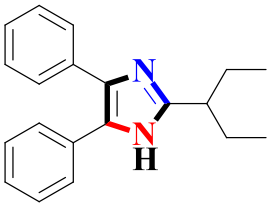
2-(2-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (14i, $C_{22}H_{18}N_2O$, 0.070g, 43%):[54] white solid. **Mp** 225-226 °C; **υ_{max} (neat, cm^{-1}):** 3428 (N-H), 3186 (C-H), 3065, 2840, 1601 (C=N), 1585, 1481 (C=C), 1470, 1251 (C-N), 1100 (C-O-C); **^{1}H NMR (400 MHz, DMSO-D_6):** 11.87 (s, 1H), 8.05 (dd, *J* = 7.72 Hz, 1.24 Hz, 1H), 7.53 (d, *J* = 7.52 Hz, 2H), 7.49-7.47 (m, 2H), 7.43 (t, *J* = 7.42 Hz, 2H), 7.38-7.35 (m, 2H), 7.29 (t, *J* = 7.27 Hz, 2H), 7.23-7.19 (m, 1H), 7.16 (d, *J* = 8.32 Hz, 1H), 7.07 (t, *J* = 7.46 Hz, 1H), 3.92 (s, 3H); **^{13}C (100 MHz, DMSO-D_6):** 156.0, 143.2, 136.4, 135.3, 131.2, 129.7, 128.8, 128.6, 128.5, 128.1, 127.6, 127.4, 127.1, 126.4, 120.6, 118.9, 111.6; **ESI-MS (*m/z*):** calcd for $C_{22}H_{17}N_2O$ 325.1339, found 325.1345 $[M-H]^+$.



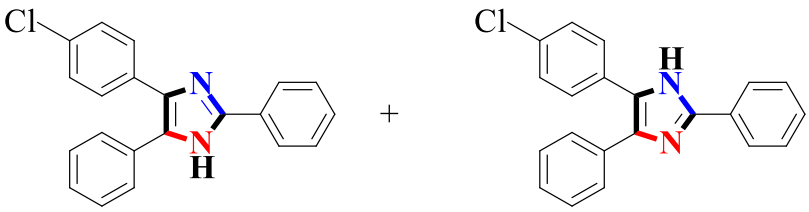
2-(2-Furan-2-yl)-4,5-diphenyl-1*H*-imidazole (14j, $C_{19}H_{14}N_2O$, 0.046g, 32%):[121] brown solid. Mp 228-230 °C; **υ_{max} (neat, cm^{-1}):** 3396 (N-H), 3025 (C-H), 1602 (C=N), 1445 (C=C), 1014 (C-N); **^{1}H NMR (400 MHz, DMSO-D_6):** 12.80 (s, 1H), 7.80 (d, *J* = 1.04 Hz, 1H), 7.53-7.47 (m, 4H), 7.42 (t, *J* = 7.36 Hz, 2H), 7.36 (t, *J* = 7.12 Hz, 1H), 7.30 (t, *J* = 7.44 Hz, 2H), 7.22 (t, *J* = 7.24 Hz, 1H), 6.98 (d, *J* = 3.08 Hz, 1H), 6.65 (dd, *J* = 3.36 Hz, 1.76 Hz, 1H); **^{13}C (100 MHz, DMSO-D_6):** 145.7, 143.0, 138.5, 136.9, 134.9, 130.8, 128.6, 128.3, 128.1, 127.8, 127.5, 127.1, 126.6, 111.8, 107.4; **ESI-MS (*m/z*):** calcd for $C_{19}H_{14}N_2ONa$ 309.1006, found 309.1007 $[M+Na]^+$.



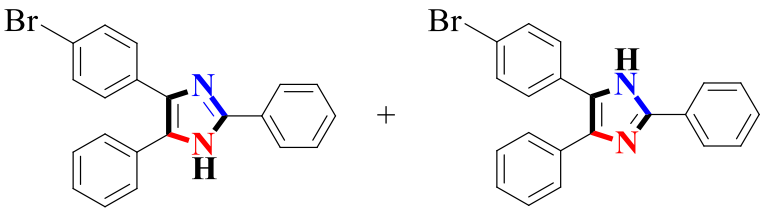
2-(Cyclohexyl)-4,5-diphenyl-1*H*-imidazole (14k, $C_{21}H_{22}N_2$, 0.040g, 26%):[54] brown solid. **Mp** 243-244 °C; **υ_{max} (neat, cm^{-1}):** 3389 (N-H), 3031, 2929, 2848 (C-H), 1603 (C=N), 1448 (C=C), 1426, 1182 (C-N); **^{1}H NMR (400 MHz, DMSO-D_6):** 11.91 (s, 1H), 7.48 (d, *J* = 7.40 Hz, 2H), 7.41-7.35 (m, 4H), 7.30-7.23 (m, 3H), 7.18-7.14 (m, 1H), 2.74-2.67 (m, 1H), 1.99-1.95 (m, 2H), 1.81-1.78 (m, 2H), 1.70-1.67 (m, 1H), 1.65-1.55 (m, 2H), 1.41-1.20 (m, 3H); **^{13}C (100 MHz, DMSO-D_6):** 152.3, 135.8, 134.9, 131.6, 128.5, 127.9, 127.8, 127.1, 126.9, 125.9, 125.7, 37.2, 31.5, 25.7, 25.6; **ESI-MS (*m/z*):** calcd for $C_{21}H_{23}N_2$ 303.1863, found 303.1869 $[M+H]^+$.



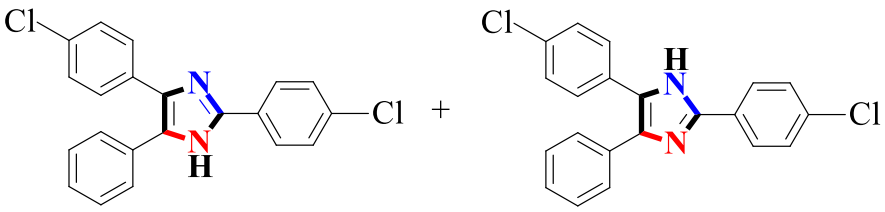
2-(pentyl-3-yl)-4,5-diphenyl-1*H*-imidazole (14l, $C_{20}H_{22}N_2$, 0.031g, 21%):[122] white solid. **Mp** 241-243 °C; **υ_{max} (neat, cm^{-1}):** 3142 (N-H), 3066, 3031, 2872, 2959, 2928 (C-H), 1062 (C=N), 1449 (C=C), 1428, 1188 (C-N); **^{1}H NMR (400 MHz, DMSO-D_6):** 11.96 (s, 1H), 7.49 (d, *J* = 7.48 Hz, 2H), 7.42-7.35 (m, 4H), 7.31-7.23 (m, 3H), 7.18-7.14 (m, 1H), 2.62-2.55 (m, 1H), 1.77-1.63 (m, 4H), 0.83 (t, *J* = 7.28, 6H); **^{13}C (100 MHz, DMSO-D_6):** 151.3, 135.8, 135.2, 131.7, 129.6, 129.5, 128.6, 128.1, 127.8, 127.1, 127.0, 126.1, 125.7, 42.3, 26.8, 12.1; **ESI-MS (*m/z*):** 291.2007 (100) $[M+H]^+$, 292.2039 (23).



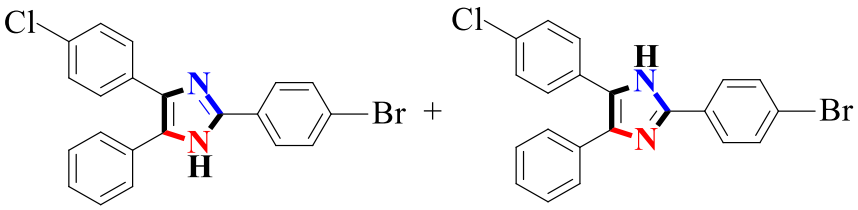
4-(4-Chlorophenyl)-2,5-diphenyl-1*H*-imidazole : 5-(4-Chlorophenyl)-2,4-diphenyl-1*H*-imidazole (14o, $C_{21}H_{15}ClN_2$, 0.111g, 67%):[54] white solid. **Mp** 241-243 °C; **υ_{max} (neat, cm^{-1}):** 3413 (N-H), 3054 (C-H), 1601 (C=N), 1501 (C=C), 1486, 1461, 1406, 1093 (C-N), 768 (C-Cl), 692; **^{1}H NMR (400 MHz, DMSO-D_6):** 12.75 (s, 1H), 12.72 (s, 1H), 8.09 (d, *J* = 7.56 Hz, 2H), 7.58-7.44 (m, 8H), 7.41-7.23 (m, 4H); **^{13}C (100 MHz, DMSO-D_6):** 145.8, 145.6, 137.7, 135.7, 134.9, 133.9, 132.2, 130.9, 130.8, 130.2, 130.1, 129.9, 129.8, 128.7, 128.6, 128.5, 128.5, 128.3, 128.2, 128.2, 127.9, 127.2, 126.9, 126.7, 125.2, 125.2; **ESI-MS (*m/z*):** calcd for $C_{21}H_{16}{}^{35}ClN_2$ 331.1004, found 331.1006 $[M+H]^+$.



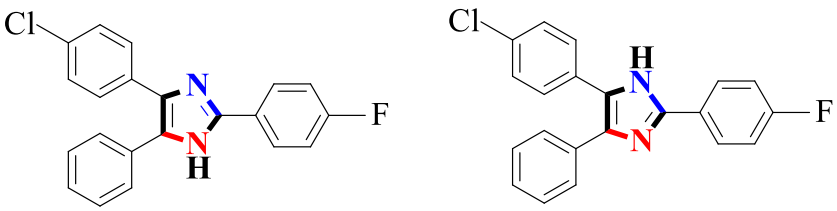
4-(4-Bromophenyl)-2,5-diphenyl-1*H*-imidazole : 5-(4-Bromophenyl)-2,4-diphenyl-1*H*-imidazole (14p, $C_{21}H_{15}BrN_2$, 0.135g, 72%):[54] white solid. **Mp** 253-255 °C; **υ_{max} (neat, cm^{-1}):** 3402 (N-H), 3054 (C-H), 2780, 1598 (C=N), 1539, 1483 (C=C), 1403, 1010 (C-N), 604 (C-Br), 542; **^{1}H NMR (400 MHz, DMSO-D_6):** 12.74 (s, 1H), 12.71 (s, 1H), 8.08 (d, 2H), 7.64-7.25 (m, 12H); **^{13}C (100 MHz, DMSO-D_6):** 145.9, 145.8, 137.8, 135.9, 134.9, 134.4, 131.6, 131.2, 130.8, 130.3, 130.2, 128.9, 128.8, 128.7, 128.6, 128.4, 128.4, 128.1, 127.3, 126.9, 126.8, 125.3, 120.8, 119.5; **ESI-MS (*m/z*):** calcd for $C_{21}H_{16}{}^{79}BrN_2$ 375.0499, found 375.0492 $[M+H]^+$.



2,4-Bis-(4-chlorophenyl)-5-phenyl-1*H*-imidazole : 2,5-Bis-(4-chlorophenyl)-4-phenyl-1*H*-imidazole (14q, $C_{21}H_{14}Cl_2N_2$, 0.117g, 64%):[92] white solid. **Mp** 250-252 °C; **υ_{max} (neat, cm^{-1}):** 3415 (N-H), 3062 (C-H), 2827, 1600 (C=N), 1500, 1479 (C=C), 1446, 1088 (C-N), 606 (C-Cl), 557, 480; **^{1}H NMR (400 MHz, DMSO-D_6):** 12.82 (s, 1H), 12.80 (s, 1H), 8.09 (d, *J* = 8.56 Hz, 2H), 7.56-7.24 (m, 11H); **^{13}C (100 MHz, DMSO-D_6):** 144.7, 144.6, 137.9, 135.9, 134.8, 133.8, 132.9, 132.3, 131.0, 130.6, 129.9, 129.7, 129.0, 128.9, 128.7, 128.7, 128.5, 128.5, 128.3, 128.2, 128.0, 127.2, 127.2, 126.9, 126.8; **ESI-MS (*m/z*):** calcd for $C_{21}H_{15}{}^{35}Cl_2N_2$ 365.0614, found 365.0616 $[M+H]^+$.



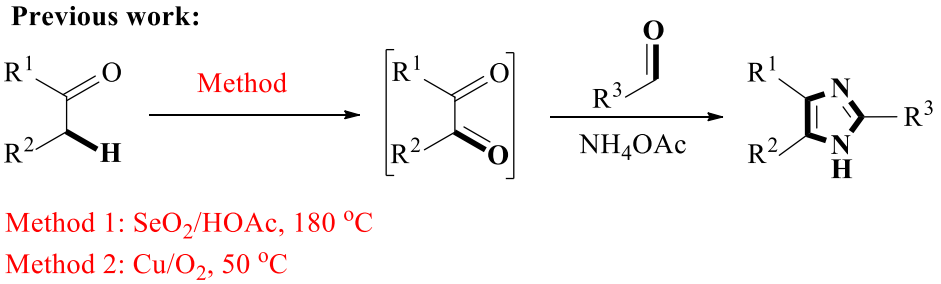
2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-phenyl-1*H*-imidazole (14r, $C_{21}H_{14}BrClN_2$, 138g, 68%): white solid. **Mp** 249-250 °C; **υ_{max} (neat, cm^{-1}):**[92] 3419 (N-H), 3064 (C-H), 2632, 1600 (C=N), 1500, 1479 (C=C), 1446, 1090 (C-N), 1068, 1008, 968, 773 (C-Cl), 728, 680, 526 (C-Br); **^{1}H NMR (400 MHz, DMSO-D_6):** 12.82 (s, 1H), 8.03 (d, *J* = 8.52 Hz, 2H), 7.68 (d, *J* = 8.52 Hz, 2H), 7.53 (t, *J* = 8.38 Hz, 4H), 7.41 (m, 5H); **^{13}C (100 MHz, DMSO-D_6):** 144.8, 131.7, 129.4, 128.9, 128.5, 128.2, 127.2, 125.3, 121.6; **ESI-MS (*m/z*):** calcd for $C_{21}H_{15}{}^{35}Cl^{79}BrN_2$ 409.0109, found 409.0110 $[M+H]^+$.



5-(4-Chlorophenyl)-2-(4-fluorophenyl)-4-phenyl-1*H*-imidazole (14s, $C_{21}H_{14}ClFN_2$, 0.090g, 52%): white solid. **Mp** 246-249 °C; **υ_{max} (neat, cm^{-1}):**[92] 3432 (N-H), 3067 (C-H), 2949, 2786, 1606 (C=N), 1503, 1488 (C=C), 1447, 1222 (C-F), 1091 (C-N), 774 (C-Cl), 698, 623; **^{1}H NMR (400 MHz, DMSO-D_6):** 12.77 (s, 1H), 8.13 (dd, 2H), 7.55 (t, 4H), 7.41-7.31 (m, 7H); **^{13}C (100 MHz, DMSO-D_6):** 162.6 ($J_{C,F}$ = 245 Hz), 145.4, 138.0, 136.2, 134.9, 134.1, 132.6, 131.5, 130.9, 130.2, 129.9, 129.0, 128.7, 128.5, 128.4, 127.8 ($J_{C,F}$ = 8.30 Hz), 127.6, 127.3, 127.2, 127.0 ($J_{C,F}$ = 2.96 Hz), 116.0 ($J_{C,F}$ = 22.52 Hz); **ESI-MS (*m/z*):** calcd for $C_{21}H_{15}{}^{35}ClFN_2$ 349.0910, found 349.0907 $[M+H]^+$.

Chapter 3: Preface

In an effort to improve the reaction conditions of the SeO_2/HOAc mediated direct oxidation of benzyl aryl ketones for the one-pot synthesis of 2,4,5-trisubstituted-1*H*-imidazoles,[92] a catalytic amount of earth abundant copper was employed, as cheap and non-toxic catalyst, in the presence of molecular oxygen as the terminal oxidant (**Scheme 29**).[118]



Scheme 29: Examples of the previous synthetic methodologies employed within this research group for the one-pot three-component synthesis of 2,4,5-trisubstituted-1*H*-imidazoles.

While this methodology was highly appealing and addressed the key drawbacks (*vida supra*) of the previously reported SeO_2/HOAc methodology, the shortcomings associated with the general use of a transition metal as a catalyst detracted from this methodology to access 2,4,5-trisubstituted-1*H*-imidazoles, and therefore serves as inspiration to establish completely metal-free chemical reactions as efficient alternatives. In addition, the choice of solvent is particularly important when improving a chemical synthesis based on the principles of Green Chemistry. Accordingly, owing to the environmentally damaging and toxic nature of DMF, this solvent is ranked number 9 for the health criteria, which makes it hazardous by default, and number 5 for environmental impact.[123] As a result, a high regulatory restriction is imposed on the employment of DMF based on the solvent selection guide for chemical synthesis (**Figure 9**). Consequently, the replacement of such solvents with less hazardous alternatives is recommended. Based on the toxic nature of DMF and the general use of a metal catalyst, an improved synthetic methodology for the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles was anticipated, involving the use on a non-metal catalyst (iodine) and a more environmentally friendly solvent (DMSO).

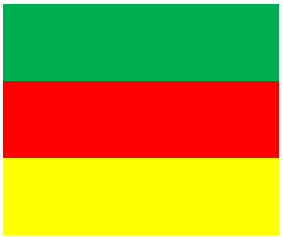
	Ranking	Color	Code
Safety score	3		Recommended
Health score	9		Hazardous
Environmental score	5		Problematic

Figure 9: Solvent guide for dimethyl formamide (DMF) according to the health, safety and environmental regulations published by the RSC journal, Green Chemistry.

Accordingly, the concept of transition-metal-free chemical syntheses has revolutionized synthetic methodologies, particularly those related to oxidative processes.[124] This interest, within the chemical community, driven mainly by the growing awareness from: atom economy, industrial interest, and environmental aspects, has witnessed a steep surge in recent years for the development of improved chemical processes.[125] Consequently, among the numerous non-metal catalyzed multi-component reactions documented in literature, it was crucial to select a highly reactive and versatile transition metal-free catalyst as well as the corresponding solvent media to permit the direct oxidation of the benzyl aryl ketones to the corresponding 1,2-diaryl diketones, *in situ*, to subsequently couple with substituted aldehydes and ammonium acetate for the formation of the desired 2,4,5-trisubstituted-1*H*-imidazoles. As a result, the project's focus was aimed towards the development of a non-toxic, acid- and metal-free procedure which utilized simple, inexpensive reagents and convenient procedures.

3.1 An Iodine/DMSO-Catalyzed Sequential One-Pot Approach to 2,4,5-Trisubstituted-1*H*-imidazoles From Benzyl Aryl Ketones

3.1.1 Dimethyl Sulfoxide (DMSO) as Terminal Oxidant

Dimethyl sulfoxide (DMSO) is an inexpensive and environmentally benign polar aprotic organo-sulfur compound with a proven safety and toxicity profile from the perspective of its biological utility.[126] In organic chemical syntheses, DMSO displays a versatile role as a solvent, oxidant and oxygen source.[127] In particular, there are well recognized literature reports where reaction procedures have incorporated DMSO as a mild oxidant, such as: the

Pfitzner-Moffatt oxidation,[128] the Swern oxidation,[129] the Corey-Chaykovsky reaction and the Kornblum Oxidation.[130]

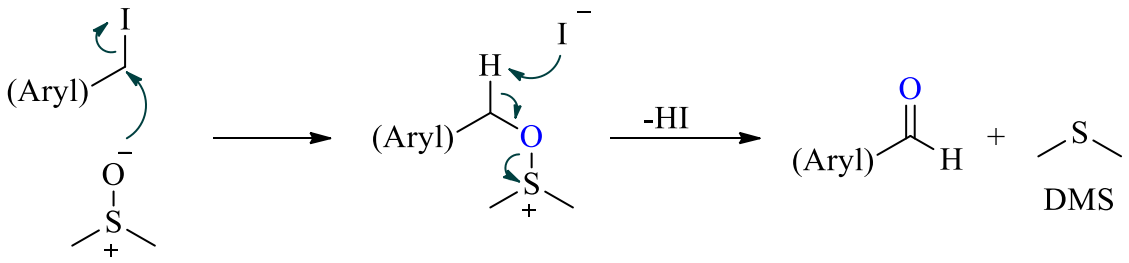
The choice to employ DMSO, as a solvent, derives from the solvent guide of classical solvents.[123] In comparison to the previous employment of DMF, a significant improvement is realized from the health and safety criteria of organic solvents. According to this guide, DMSO is ranked number 1 for both points and is problematic, rather than hazardous, as when compared to DMF (**Figure 10**). This essentially makes DMSO a safer choice of solvent to utilize. Based on the comparison above, DMSO is a suitable alternative to DMF; hence, attention was focused on DMSO to act as both a solvent and nucleophile in the oxidation of benzyl aryl ketones to diketones in the current study.

		Ranking	Color	Code
DMF	**Safety score**	3		Recommended
	Health score	**9**		Hazardous
	Environmental score	5		Problematic
DMSO	**Safety score**	1		Recommended
	Health score	**1**		Recomennded
	Environmental score	5		Problematic

Figure 10: Comparison of the health, safety and environmental regulations for DMF and DMSO, according to the solvent guide published by the RSC journal Green Chemistry.

There are numerous catalysts available (such as dicyclohexylcarbodiimide [DCC], acetic anhydride [Ac_2O], phosphorous pentoxide [P_2O_5], trifluoroacetic anhydride [TFAA] and oxalyl chloride [$(COCl)_2$]) which have been shown to activate DMSO as a valuable synthetic tool for the oxidation of primary alcohols to aldehydes and ketones.[131] Among the emergence of such catalysts, molecular iodine is known to be a more compatible, complimentary and

environmentally friendly non-metal catalyst in the presence of DMSO for the transformation of numerous chemical syntheses. In this context, an interesting feature of DMSO is its ability to oxidize organic iodides to the corresponding carbonyl compound, known as the Kornblum Oxidation. The Kornblum Oxidation is described as the direct oxidation of primary alkyl halides, affording an aldehyde by the action of DMSO with the simultaneous production of dimethyl sulfide (DMS) (**Scheme 30**).[132]



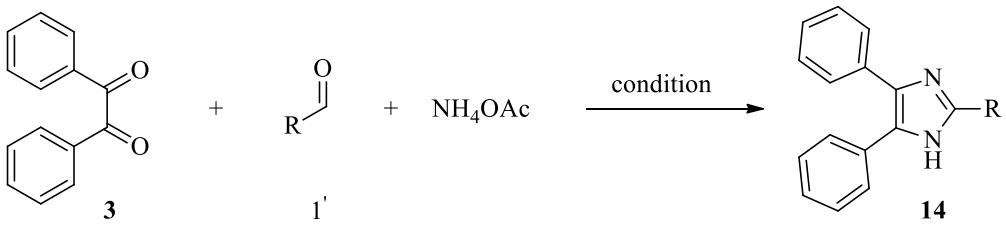
Scheme 30: Direct oxidation of a primary alkyl halide *via* the Kornblum Oxidation. The nucleophilic attack of the DMSO oxygen at the alpha carbon of the alkyl halide, with subsequent loss of HX, affords the oxidized alkyl product and dimethyl sulfide (DMS).

3.1.2 Molecular Iodine as a Catalyst

Molecular iodine (I_2) is an inexpensive and versatile catalyst, widely recognized as a safe and complementary replacement for transition metal catalysts. Consequently, this eco-friendly catalyst displays immense significance in various fields of science (such as biology, medicine and physics), due to its non-toxic properties, high stability and operational simplicity.[133] A particularly notable attribute of molecular iodine, in many cases, is its structural features and reactivity patterns that are similar to transition metals.[134] This would make molecular iodine the catalyst of choice. Moreover, the mild Lewis acidity, strong electrophilicity and valuable oxidizing properties are prime factors in its ability to function as a catalyst to effect, catalyze and promote a diverse range of chemical reactions.[135]

As a result, molecular iodine has been extensively explored as an effective and versatile catalyst in many multi-component reactions. Accordingly, in 2007 and 2012, three independent reports[136] were disclosed by Kidwai *et al.* (**Scheme 31**, **condition a**), Parveen *et al.* (**Scheme 31**, **condition b**) and Ren *et al.* (**Scheme 31**, **condition c**), respectively, employing molecular

iodine, as a sole catalyst, for the three component coupling of benzil, aromatic aldehydes and ammonium acetate to afford substituted 2,4,5-trisubstituted-1*H*-imidazoles in good to excellent yields.



3 **1'** **14**

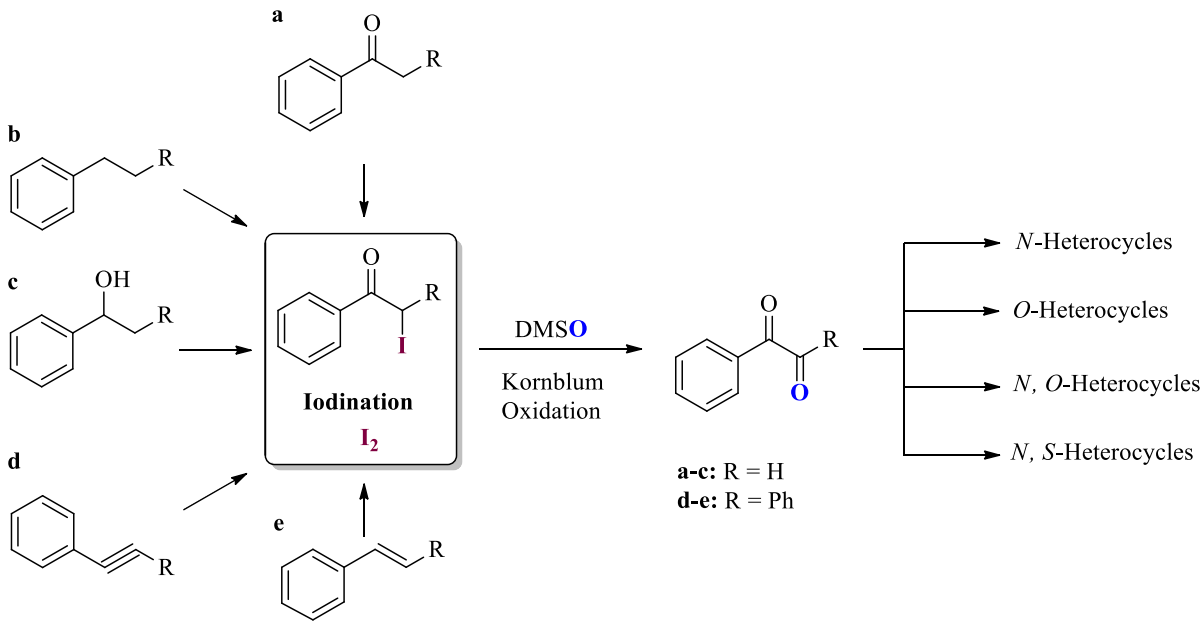
R = H, Me, OMe, OH, NO_2, Cl, 2-thiophenyl, piperonal

i. a. I_2 (5 mol%). EtOH, 75 ^oC, 15-25 min(s), **97-99%**
b. I_2 (15 mol%). solvent free, rt, 10-15 min(s), **85-90%**
c. I_2 (5 mol%). solvent free, 100 ^oC, 12-35 min(s), **90-98%**

Scheme 31: Various reaction conditions for the molecular iodine catalyzed synthesis of 2,4,5-trisubstituted-1*H*-imidazoles. In the absence of metal-catalysts, solvent free conditions, iodine has demonstrated its ability to effectively facilitate complex heterocyclic cyclizations in excellent 'green conditions (90-99% yields)'.

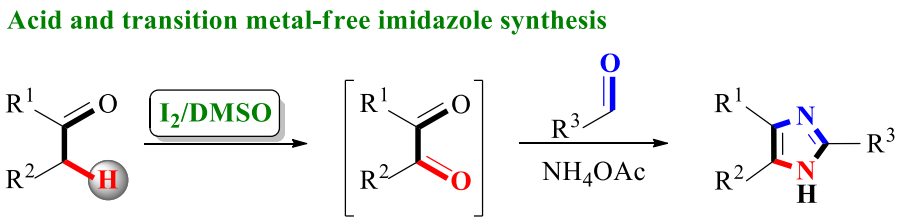
3.1.3 Iodine/DMSO Oxidative System

Collectively, the iodine/DMSO combination has established significance, in synthetic organic chemistry, as an environmentally benign and effective oxidative system, since it has realized numerous organic transformations. According to literary studies, the typical synthetic toolbox employing the iodine/DMSO oxidative system for the formation of 1,2-diketones, followed by subsequent heterocyclic syntheses, has been displayed in **Scheme 32**.[137] This oxidative system proceeds with iodination of the applied substrate, followed by a modified Korblum Oxidation (of substrates other than a primary alkyl halide) to afford the corresponding diketone for subsequent coupling into the desired heterocyclic compound.



Scheme 32: I_2/DMSO oxidation of diverse C–H bonds to afford 1,2-diketones which are subsequently coupled with other substrates to afford different heterocyclic compounds. The reaction proceeds with the formation of an iodinated intermediated, followed by a modified Kornblum Oxidation of the iodinated intermediate to furnish the corresponding diketone, *in situ*, for subsequent coupling into different heterocyclic compounds.

To the best of our knowledge, the literature has reported the I_2/DMSO oxidative system for different chemical transformations; hence, it was hypothesized that molecular iodine could effectively cleave the proton from the α-position of substituted benzyl phenyl ketones to afford an iodinated intermediate, permitting a modified Kornblum Oxidation by DMSO to yield the *in situ* generated 1,2-diaryl diketones to couple with aldehydes and ammonium acetate to furnish the desired imidazole end product (**Scheme 33**).



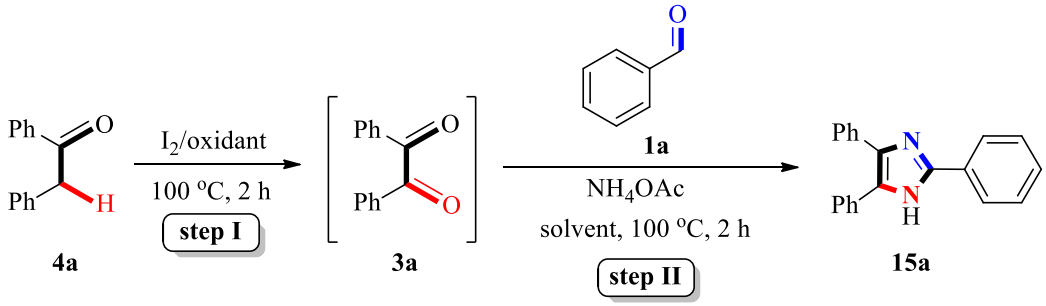
Scheme 33: Hypothesis for the iodine/DMSO mediated direct oxidation of benzyl aryl ketones, to *in situ* generated 1,2-diketones, for the one-pot multi-component synthesis of 2,4,5-trisubstituted-1*H*-imidazoles.

3.2 Optimization of Reaction Conditions

In search of the optimized experimental conditions, this study commenced with the one-pot reaction of benzaldehyde **1a**, benzyl phenyl ketone **4a** and ammonium acetate in DMSO for 4 hours at 100 °C in the presence of 0.5 equivalents of molecular iodine. The reaction failed to proceed and no product was detected (**Table 10a**, **entry 1**). On account of the failure of this reaction, a sequential one-pot reaction was attempted whereby benzyl phenyl ketone **4a** and iodine were heated in DMSO at for 2 hours at 100 °C. Thereafter, benzaldehyde **1a** and ammonium acetate were added and the mixture was left to react for a further 2 hours at 100 °C. Encouragingly, the desired product, 2,4,5-triphenyl-1*H*-imidazole **15a**, was obtained in an isolated yield of 54% (**Table 10a**, **entry 2**). Accordingly, this study focused on the sequential one-pot procedure to prepare these important scaffolds as it appeared to be the most viable synthetic route.

In general, the coupling reaction of benzil, aldehydes and ammonium acetate to afford 2,4,5-trisubstituted-1*H*-imidazoles is known to be solvent specific and proceeds particularly well in the presence of an alcohol solvent as it was recognized to promote the coupling of a diketone, aldehyde and ammonium acetate.[136a, 138] Thus, in an effort to encourage cyclization, the reaction was attempted in methanol and *iso*-propanol which afforded **15a** in isolated yields of 68% and 54%, respectively (**Table 10a**, **entries 3-4**). Having subsequently performed the reaction in ethanol, to our delight, the yield of the isolated product significantly increased to 82% (**Table 10a**, **entry 5**). It was, therefore, evident that ethanol was the most effective additive solvent to promote the multi-component reaction.

Table 10a: Optimization conditions for the formation of 2,4,5-triphenyl-1*H*-imidazole **15a** from benzyl phenyl ketone **1a** *via* a sequential one-pot multi-component reaction[a]



Entry	I_2 (equiv.)	Oxidant (1mL)	Solvent (2mL)	Yield[b] (%)
1[c]	0.5	DMSO	–	–
2	0.5	DMSO	–	54
3	0.5	DMSO	MeOH	68
4	0.5	DMSO	*i*-PrOH	54
5	**0.5**	**DMSO**	**EtOH**	**82**
6	0.25	DMSO	EtOH	74
7	0.10	DMSO	EtOH	32

[a] Reaction conditions: Step I: **4a** (1 mmol), I_2 (0.5 mmol), 100 °C for 2 h; Step II: **1a** (1 mmol), NH_4OAc (10 mmol), 100 °C for 2 h. [b] Isolated yield. [c] One-pot reaction.

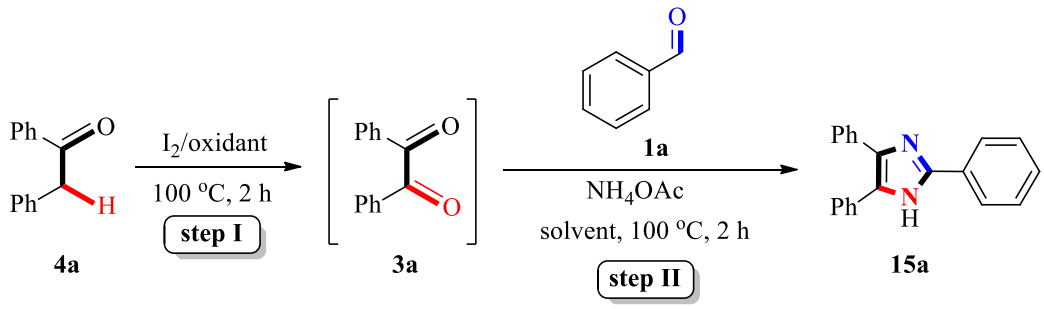
Following this, attempts were made to decrease the quantity of iodine in the reaction by employing 0.25 and 0.10 equivalents of the catalyst. The formation of **15a**, however, was substantially reduced to isolated yields of 74% and 32%, respectively (**Table 10a**, **entries 6-7**). Moreover, a reaction conducted without molecular iodine did not afford the end-product **15a** (**Table 10a**, **entry 8**). Therefore, it was confirmed that iodine was necessary to perform the transformations in this three-component reaction.

In an effort to analyze the role of DMSO in the reaction, the screening of alternative solvents such as: DMF, CH_3CN and toluene (PhMe) as oxidants was performed (**Table 10b**, **entries 9-11**). The results of these experiments revealed that only DMSO could furnish the desired imidazole, as no product was obtained in the presence of these solvents. This observation also

displayed that DMSO was the ideal coupling partner for molecular iodine which was further accentuated by the plethora of transformations effected by this oxidative system.

Finally, numerous trisubstituted imidazole synthetic procedures employ varying amounts of ammonium acetate, depending on the reaction conditions, therefore an attempt to reduce the equivalence of ammonium acetate was therefore made.[112e, 114] Thus, to complete the optimization study, 5.0 and 2.5 equivalents of ammonium acetate were applied to the reaction conditions in Table 7a, entry 5. However, a notable decrease in isolated yields of 62% and 26%, respectively, was observed (**Table 10b**, **entries 12-13**). After screening various reaction conditions, the results described in **entry 5** were found to be optimal for maximum conversion to the desired 2,4,5-triphenyl-1*H*-imiddazole **15a**.

Table 10b: Optimization conditions for the formation of 2,4,5-triphenyl-1*H*-imidazole **15a** from benzyl phenyl ketone **1a** *via* a sequential one-pot multi-component reaction[a]



Entry	I_2 (equiv.)	Oxidant (1mL)	Solvent (2mL)	Yield[b] (%)
8	–	DMSO	EtOH	–
9	0.5	DMF	EtOH	–
10	0.5	CH_3CN	EtOH	–
11	0.5	PhMe	EtOH	–
12[c]	0.5	DMSO	EtOH	62
13[d]	0.5	DMSO	EtOH	26

[a] Reaction conditions: Step I: **4a** (1 mmol), I_2 (0.5 mmol), 100 °C for 2 h; Step II: **1a** (1 mmol), NH_4OAc (10 mmol), 100 °C for 2 h. [b] Isolated yield. [c] NH_4OAc (5.0 equiv.). [d] NH_4OAc (2.5 equivalents).

Having optimized the reaction conditions, the scope and limitations of the developed system were evaluated to access diverse 2,4,5-trisubstituted-1*H*-imidazoles by varying the benzyl aryl ketones and aldehydes. The ensuing results are displayed in **Table 11**.

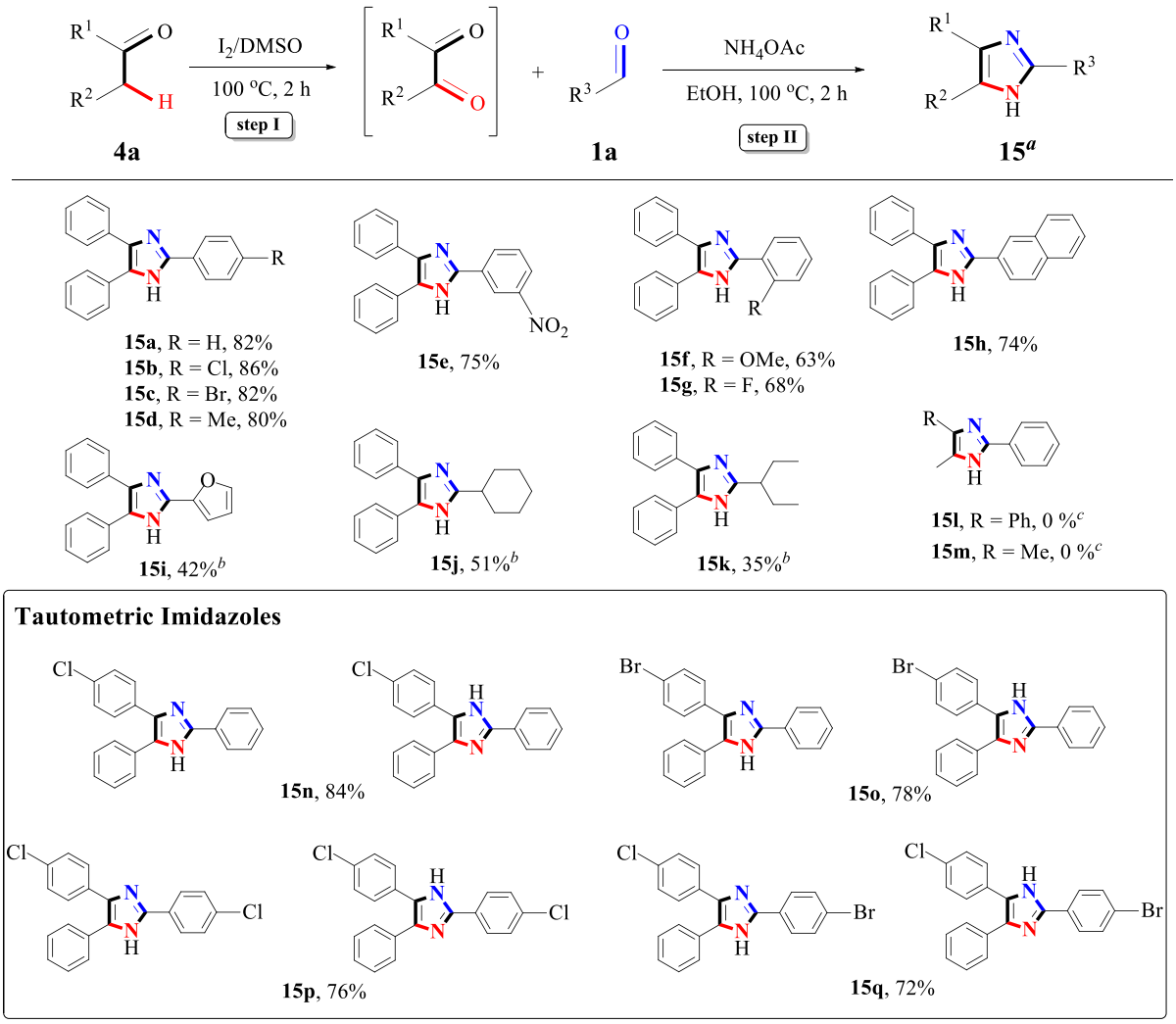
3.3 Library Synthesis of Diverse 2,4,5-Trisubstituted-1*H*-imidazoles

The coupling of benzaldehyde derivatives, bearing *para*-substituted electron-donating (–Me) or electron-withdrawing (–Cl, –Br), with benzyl phenyl ketone **4a** and ammonium acetate afforded 2,4,5-trisubstituted-1*H*-imidazoles (**Table 11**, **15a-15d**) in excellent isolated yields ranging from 80-86%. The substitution of a nitro functional group on the *meta* position of benzaldehyde participated smoothly in the domino multi-component reaction to afford 2-(3-nitrophenyl)-4,5-diphenyl-1*H*-imidazole (**Table 11**, **15e**) in a good yield of 75%. Similarly, *ortho*-substituted methoxy- and fluorobenzaldehyde, as substrates, coupled with **4a** and ammonium acetate to deliver 2-(2-methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (**Table 11**, **15f**) and 2-(2-fluorophenyl)-4,5-diphenyl-1*H*-imidazole (**Table 11**, **15g**) in acceptable isolated yields of 63% and 68%, respectively.

Encouraged by the results obtained from electron-donating and electron-withdrawing functional groups at the *ortho*, *meta* and *para* position of benzaldehyde, an attempt was made to diversify the type of aldehyde employed in this reaction. Accordingly, a bulkier aldehyde, such as 2-naphthaldehyde, was subject to the optimized reaction conditions which furnished the resulting 2-(naphthalene-2-yl)-4,5-diphenyl-1*H*-imidazole (**Table 11**, **15h**) in a satisfactory 74% yield.

In an effort to expand the scope of the developed methodology, heterocyclic and aliphatic aldehydes such as: furfural, cyclohexanecarboxaldehyde and 2-ethylbutyraldehyde reacted to afford imidazoles (**Table 11**, **15i-15k**) *albeit*, in moderate yields of 35-51% with prolonged reaction times. The results obtained were in accordance with the relevant literature as these substrates are not commonly applied to the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles, which, however, often result in low yields, when employed.[116]

Table 11: Substrate scope for the sequential one-pot multi-component synthesis of diverse 2,4,5-trisubstituted-1*H*-imidazoles **15** employing the I_2/DMSO oxidative system.



Reaction conditions: Step I: **1** (1 mmol), I_2 (0.5 mmol), DMSO (1 mL), 100 °C for 2 h; Step II: **2** (1 mmol), NH_4OAc (10 mmol), EtOH (2 mL), 100 °C for 2 h. [a] Isolated yield. [b] Step II: 24 h. [c] Step I: 24 h.

Having varied the aldehyde substrates, substituted benzyl aryl ketones were subsequently evaluated. Unfortunately, propiophenone and 2-butanone were not compatible with this domino multi-component reaction despite a prolonged reaction time (24 hours) as only the starting materials were recovered (**Table 11**, **15l-15m**). The effect of a reduced nucleophilicity of such substrates may have prevented this transformation from occurring. The substitution of *para*-Cl or -Br functional groups on benzyl phenyl ketone **4a** reacted smoothly to successfully

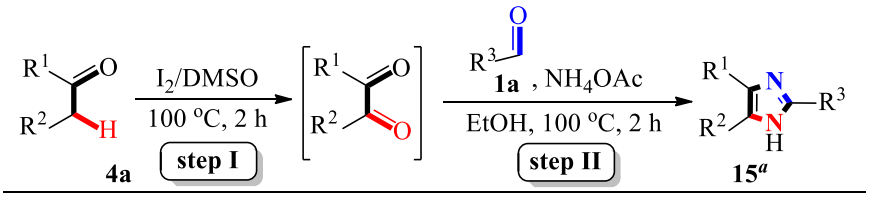
afford 2,4,5-trisubstituted-1*H*-imidazoles (**Table 11**, **15n-15o**) in good to high yields (78-84%). The coupling between 4-chloro-2-phenylacetophenone and *para*-substituted benzaldehydes, under the optimized reaction conditions, was well tolerated and subsequently furnished **15p-15q** (**Table 11**) in good isolated yields (66-76%). Owing to the presence of the fluid hydrogen on the nitrogen atom of the imidazole ring, compounds **15n-15q** are tautomers, however, were isolated as the dominant tautomeric form. Following the successful synthesis of diversely substituted 2,4,5-trisubstituted-1*H*-imidazoles, this project avenued the possibility of synthesizing a series of novel 2,4,5-trisubstituted-1*H*-imidazoles with possible biological significance.

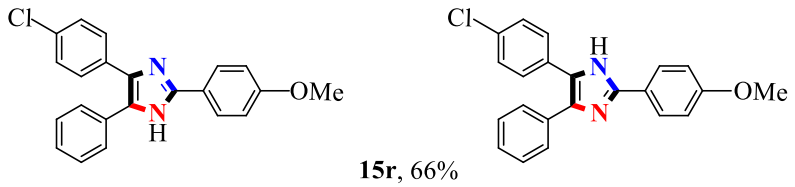
3.4 Synthesis of Novel 2,4,5-Trisubstituted-1*H*-imidazoles

Recently, the novelty of the chemotype of several 2,4,5-trisubstituted-1*H*-imidazoles display biological activity against different malarial strains.[139] As a result, in an effort to enhance the diversity, and hence the possible biological relevance of the imidazole structural motif, a substrate scope was established with this domino multi-component approach which could not be identified after an exhaustive review of the literature. The coupling of 4-Cl or -Br substituted benzyl phenyl ketones with *para*-substituted electron-donating or electron-withdrawing groups on benzaldehyde afforded the corresponding 2,4,5-trisubstituted-1*H*-imidazoles (**Table 12**, **15r-15u**) in acceptable yields (66-81%). Similarly, 4-chloro-2-phenylacetophenone coupled smoothly with *meta*-substituted nitrobenzaldehyde and *ortho*-substituted fluorobenzaldehyde to afford **15v-15w** (**Table 12**) in isolated yields of 85% and 53%, respectively. This series of novel 2,4,5-trisubstituted-1*H*-imidazoles (**15r-15w**) were synthesized and isolated as the dominant tautomeric form.

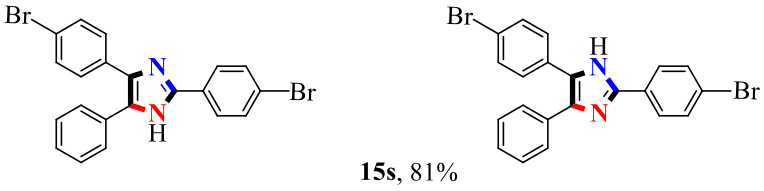
Consequently, the developed domino multi-component reaction for the synthesis of known and novel 2,4,5-trisubstituted-1*H*-imidazoles overcomes the inherent limitations of previous methodologies which are restricted to the accessibility of the starting materials. As a result, this creates a new avenue to prepare many novel imidazole derivatives with drug-like properties.

Table 12: Synthesis of novel 2, 4, 5-trisubstituted imidazoles *via* I_2/DMSO mediated sequential one-pot reaction of diverse benzyl aryl ketones and aldehydes.

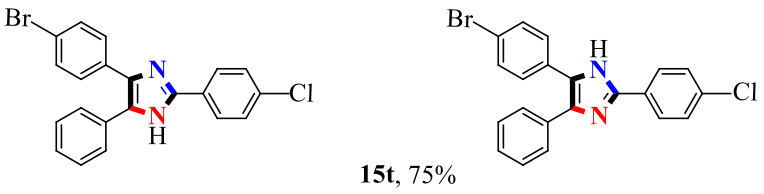




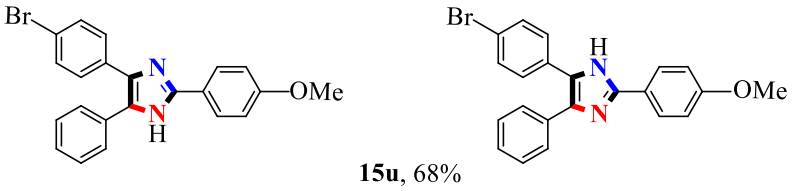
15r, 66%



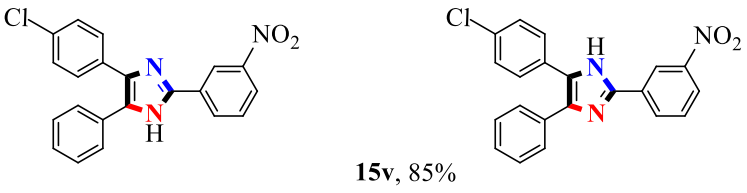
15s, 81%



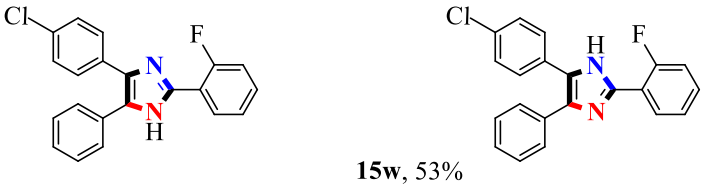
15t, 75%



15u, 68%



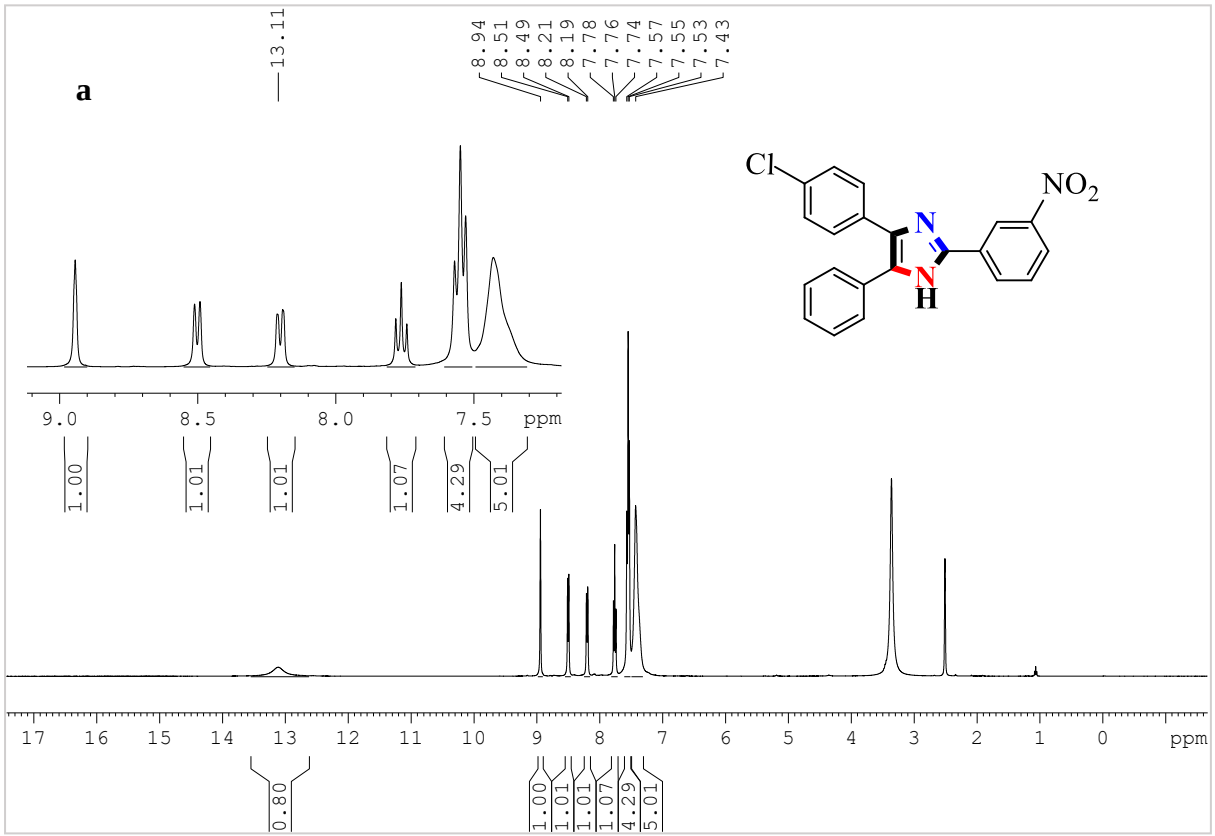
15v, 85%



15w, 53%

Reaction conditions: Step I: **1** (1 mmol), I_2 (0.5 mmol), DMSO (1 mL), 100 °C for 2 h; Step II: **2** (1 mmol), NH_4OAc (10 mmol), EtOH (2 mL), 100 °C for 2 h. [a] Isolated yield.

As a representative example, the isolated and novel 2,4,5-trisubstituted-1*H*-imidazole, 4-(4-chlorophenyl)-2-(2-nitrophenyl)-5-phenyl-1H-imidazole was characterized using ^{1}H and ^{13}C NMR, as depicted in **Figure 11**. The characteristic signal at 13.11 ppm (**Figure 11a**) corresponds to the NH proton of 4-(4-chlorophenyl)-2-(2-nitrohenyl)-5-phenyl-1*H*-imid azole **15v**. Owing to the presence of a single NH peak, this compound was isolated as a dominant tautomeric form of **15v**. Moreover, the ^{13}C NMR spectrum of this compound shows a key signal at 148.3 ppm corresponding to C_2 of the imidazole ring (**Figure 11b**). In addition, the fewer number of carbon signals in the spectrum is as a result of overlapping signals. All other protons were placed at their respective positions and the carbon atoms assigned accordingly. The molecular mass for compound **15v** is 375.0781 g/mol. The mass spectroscopy (MS) results indicated a mass of 374.0701 indicative of $[M - H]^{+}$ which compares favourably with literature. Melting points and infrared (IR) spectroscopy were conducted, referenced and were in agreement with the relevant literature reports.



† The spectrum continues on the next page

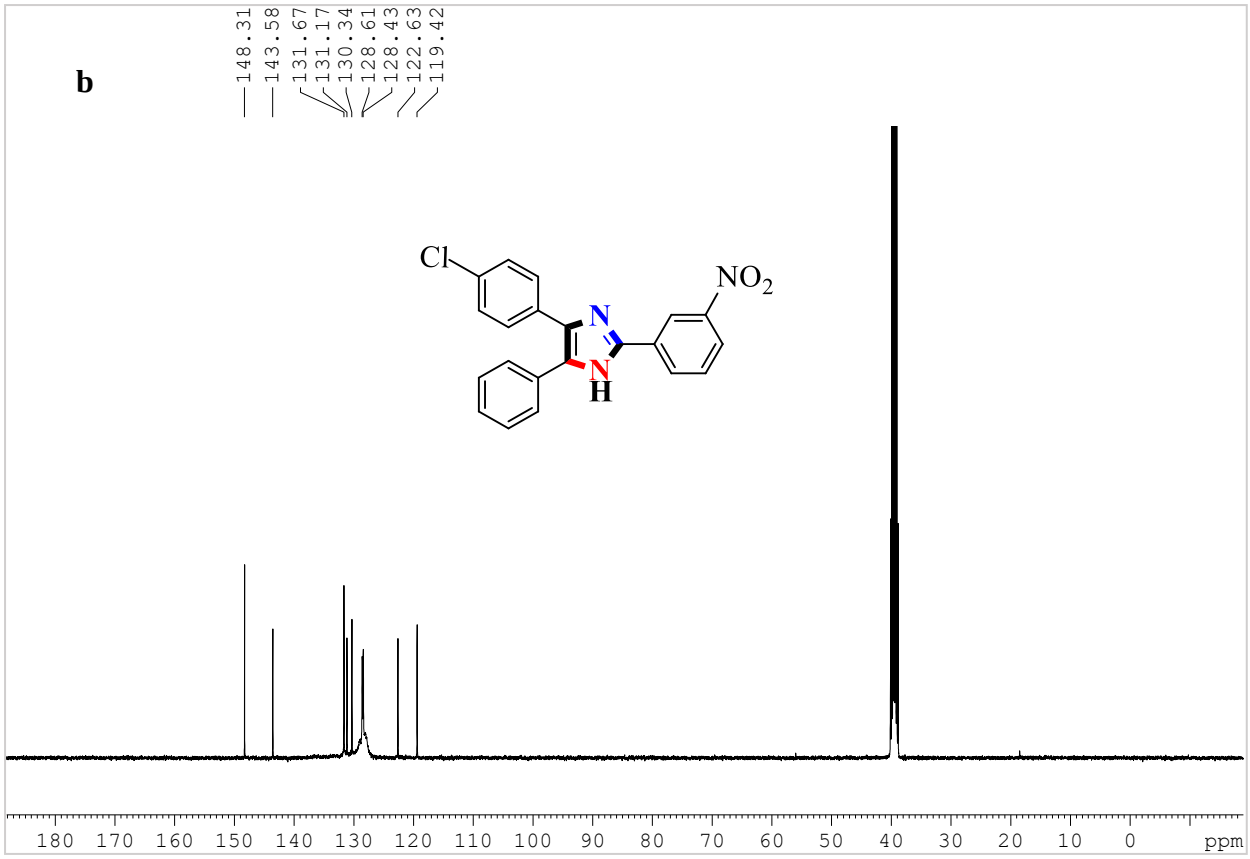
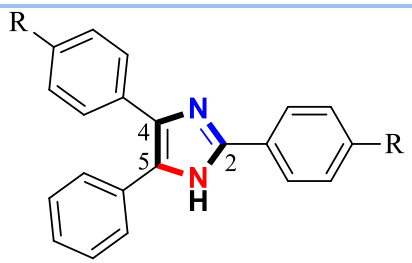


Figure 11: ^{1}H and ^{13}C NMR spectra in DMSO-d_6 of 4-(4-chlorophenyl)-2-(2-nitrophenyl)-5-phenyl-1H-imidazole (**15v**, **Table 11**).

3.5 A Summary of the Experimental Data for Compounds **15a-15w**

The key signals in the ^{1}H and ^{13}C NMR spectra for the synthesis of compounds **15a-15w** is given in **Table 13**. Accordingly, signals characteristic to the NH functional group ranges from 11.87-13.11 ppm. The imidazole compounds were isolated as a dominant tautomeric form owing to the single NH peak in the ^{1}H NMR spectra. The ^{13}C signals for C-2, C-4, C-5 of the imidazole ring and the *m/z* value in the mass spectra are also specified. Complete characterization of each compound is given in the experimental section and in agreement with the referenced literature report (*vida infra*).

Table 13: Experimental data for compounds **15a-15w**

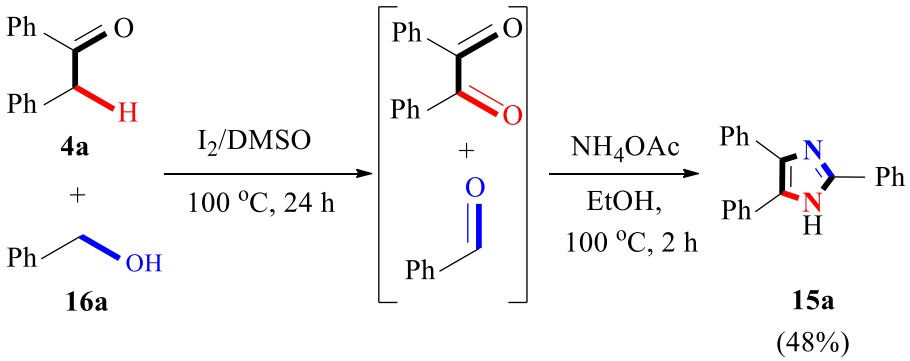


Compound	-NH (ppm)	C-2 (ppm)	C-4 (ppm)	C-5 (ppm)	MS (*m/z*)
15a	12.69	145.5	137.1	135.2	297.1396 $[M+H]^+$
15b	12.76	144.4	137.3	135.0	331.1011 $[M+H]^+$
15c	12.77	144.4	137.3	135.0	375.0503 $[M+H]^+$
15d	12.61	145.7	137.0	-	309.1393 $[M-H]^+$
15e	13.08	148.4	-	-	342.1248 $[M+H]^+$
15f	11.87	143.2	136.4	135.3	327.1503 $[M+H]^+$
15g	12.57	140.8	137.2	135.0	315.1305 $[M+H]^+$
15h	12.86	145.5	-	132.7	347.1553 $[M+H]^+$
15i	11.80	143.0	137.0	135.0	287.1189 $[M+H]^+$
15j	11.90	152.3	135.8	135.0	303.1862 $[M+H]^+$
15k	11.92	151.3	135.8	135.2	289.1707 $[M-H]^+$
15n	12.73	145.7, 145.9	135.8, 137.7	134.0, 135.0	331.1010 $[M+H]^+$
15o	12.77	145.7, 145.9	135.8, 137.7	134.4, 135.0	373.0344 $[M-H]^+$
15p	12.81	144.6	-	-	363.0455 $[M-H]^+$
15q	12.82	144.7	-	-	406.9953 $[M-H]^+$
15r	12.55	145.8	-	-	361.1116 $[M+H]^+$
15s	12.84	144.7	-	-	450.9443 $[M-H]^+$
15t	12.84	144.7, 144.8	136.0, 137.9	134.2, 134.8	406.9941 $[M-H]^+$
15u	12.56	145.9	-	-	403.0441 $[M-H]^+$
15v	13.11	148.3	-	-	374.0701 $[M-H]^+$
15w	12.60	141.1	137.8	134.7	347.0760 $[M-H]^+$

3.6 A Domino Convergent Synthesis

According to literary studies, the I_2/DMSO system is able to effect numerous organic transformations; hence, focus turned toward the convergent integration of two domino sequences commencing from the benzyl aryl ketone **4a** and benzyl alcohol **16a** to afford the desired imidazole end-product. The rationale behind this strategy was to commence from two different starting materials which could be oxidized simultaneously, in the same reaction vessel, to afford two suitably functionalized intermediates, benzil and benzaldehyde, to converge *en route* to the target imidazole.

To test this hypothesis, a preliminary experiment was attempted by reacting benzyl phenyl ketone **4a**, benzyl alcohol **16a** and I_2 in the same reaction vessel with the presence of DMSO at 100 °C for 24 hours. Thereafter, ammonium acetate and ethanol were added to the reaction mixture and heated at 100 °C for a further 2 hours to furnish **15a** in an un-optimized yield of 48% (**Scheme 34**). This result illustrated that the I_2/DMSO system could effect multiple chemical transformations (C–H and –OH oxidation), in the same reaction vessel, to converge into the desired product. Although this type of domino reaction was not a focal point of this thesis, it was anticipated that this reaction would inspire and avenue the design for more innovative, efficient and eco-friendly convergent integration syntheses, in the near future, for the preparation of valuable compounds from simple and commercially available starting materials.

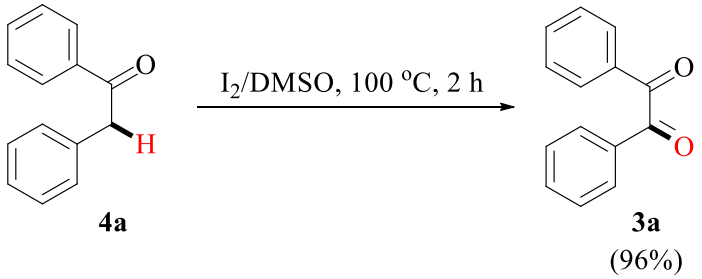


Scheme 34: Domino convergent synthesis of two different substrates, benzyl phenyl ketone and benzyl alcohol to afford 2,4,5-triphenyl-1*H*-imidazole **15a**.

The novel approach to synthesize **15a** was satisfactory and a proof-of-concept study validated the proposed domino convergent synthesis towards **15a**. However, to further understand the nature of the chemical processes involved, mechanistic studies were investigated.

3.7 Control Studies

In an effort to rationalize the reaction mechanism, a series of control experiments were performed. First, benzyl phenyl ketone **4a** was oxidized with I_2/DMSO at 100 °C for 2 hours to afford benzil **3a** in a 96% isolated yield, confirming that the diketone was an intermediate in the transformation (**Scheme 35**).



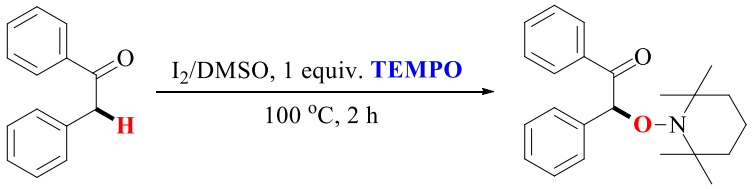
4a **3a** (96%)

Scheme 35: Direct I_2/DMSO facilitated oxidation of benzyl phenyl ketone **4a** to the corresponding 1,2-diketone **3a**.

Having successfully oxidized the benzyl aryl to the corresponding diketone, in an excellent yield, focus turned to rationalizing, detecting and isolating the key reactive intermediates in this sequential one-pot reaction.

3.7.1 Trapping *in-situ* radical adducts

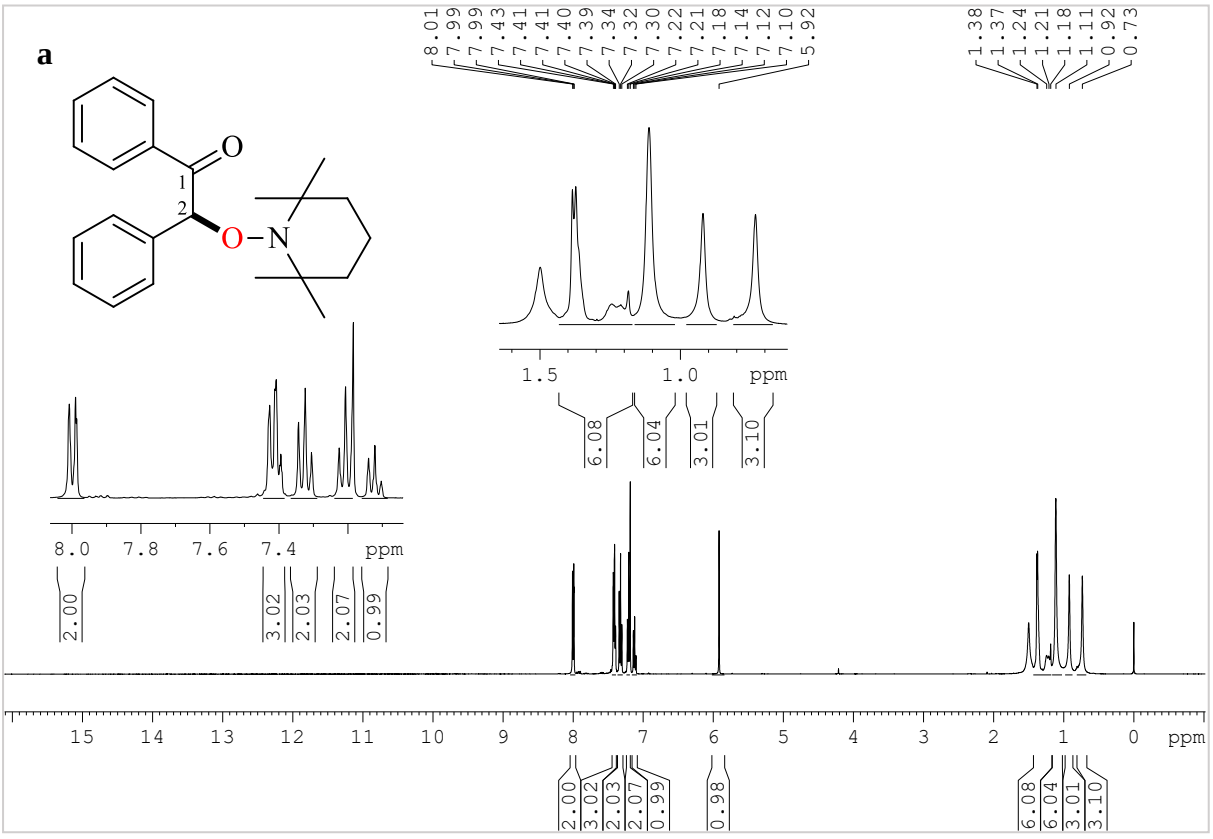
Under the standard iodine-catalysis conditions, the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) was added to **4a** and heated in the presence of DMSO to the capture product **17a** in an isolated yield of 46% (**Scheme 36**). This TEMPO-trapped reaction strongly supported the formation of a benzylic radical located on the α-position of benzyl phenyl ketone, therefore indicating a radical mediated mechanism.[111]



4a **17a**
(46%)

Scheme 36: Reaction of benzyl phenyl ketone **4a** with TEMPO to afford the capture product (S)-1,2-diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)ethanone **17a**.

The ^{1}H NMR spectrum displayed in **Figure 12a** depicts a singlet at 5.92 ppm[111] integrating for 1H (0.98), therefore, corresponding to the α-proton (C–2) of 1,2-diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)ethanone **17a**, indicating the formation of the C–O bond between the oxygen radical of TEMPO and the benzylic radical on **4a**. The ^{13}C spectrum of **17a** shows key signals at 198.3 ppm (C-1), consistant with a C=O group, and at 93.5 ppm (C-2) consistant with a –COR functional group (**Figure 12b**).



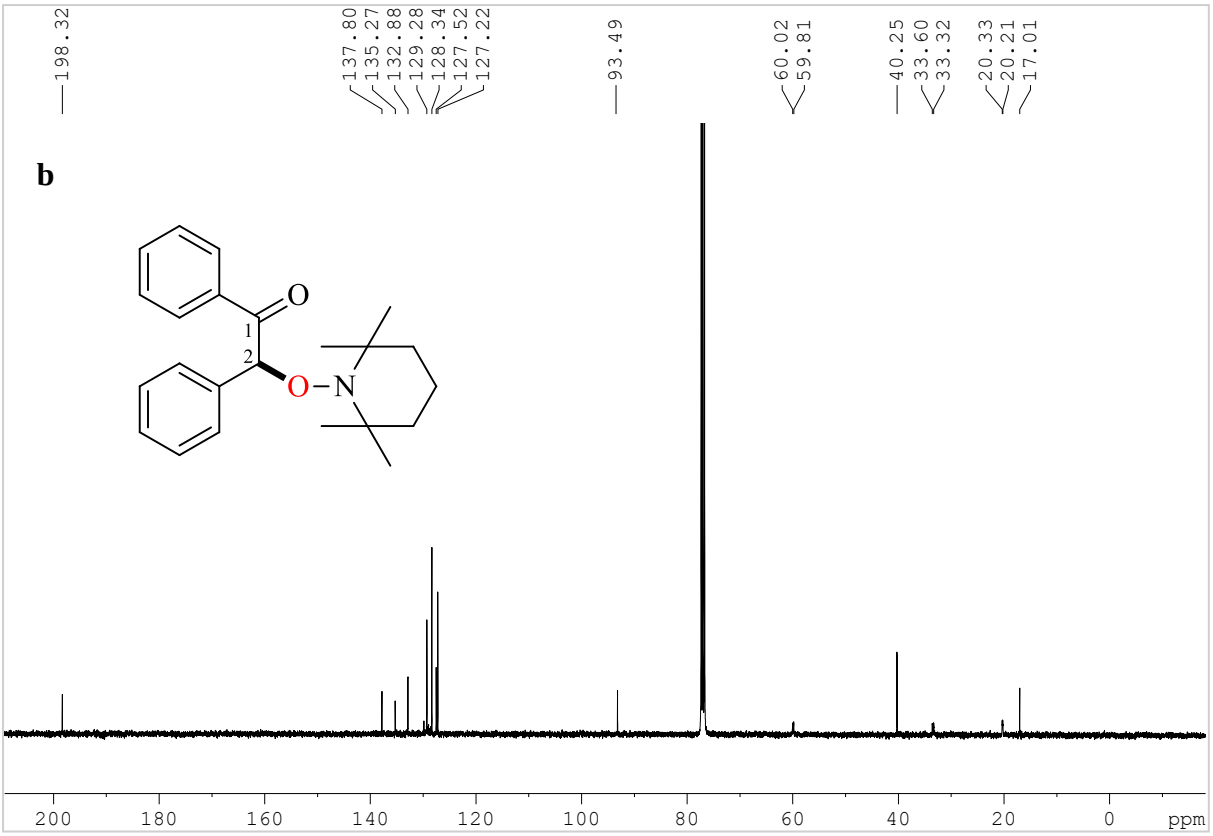
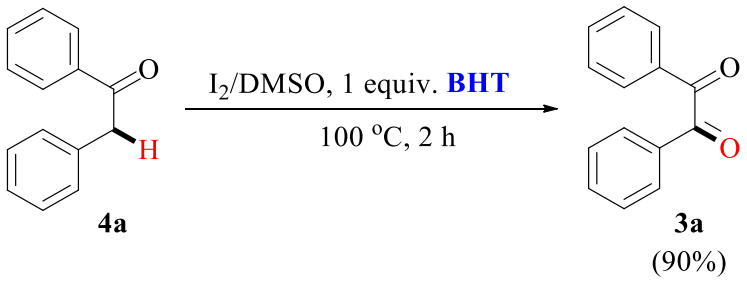


Figure 12: ^{1}H and ^{13}C NMR spectrum of the TEMPO-trapped adduct 1,2-diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)ethanone **17a** indicating a benzylic radical on the α-position of **4a**.

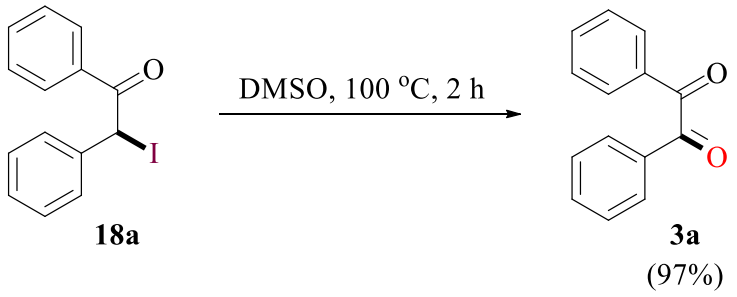
Next, in order to rule out the role of hydroxyl and peroxide radicals as intermediates in the reaction, benzyl phenyl ketone, iodine and butylated hydroxytoluene (BHT, known scavenger of hydroxyl and peroxide radicals)[140] were reacted under the standard reaction conditions (**Scheme 37**). The diketone **3a** was subsequently furnished in 90% yield, thereby proving non-participation of hydroxyl and peroxide radicals in the reaction.



Scheme 37: Reaction of benzyl phenyl ketone **4a** with BHT to afford benzil **3a**. The absence of BHT-OH/OOH species indicated that the mechanism did not proceed through hydroxyl or peroxide adducts.

3.7.2 Reactive Iodinated Species

Mechanistically, it was speculated that an α-iodinated species was the reactive intermediate in the oxidation of benzyl phenyl ketone to benzil. Accordingly, 2-iodo-1,2-diphenylethanone (**18a**) was synthesized, using a literature procedure[141] and subject to oxidation in the presence of DMSO affording **3a** in a 97% yield (**Scheme 38**). This result supported the notion that the α-iodoketone **18a** was an essential intermediate in the oxidation reaction.

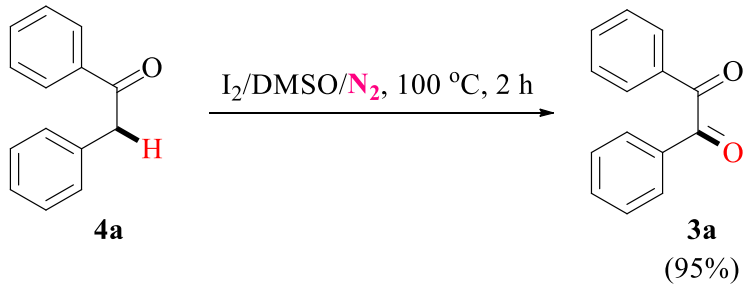


Scheme 38: Oxidation of 2-iodo-1,2-diphenylethanone **18a** with DMSO to furnish benzil **3a** in an isolated yield of 97%.

3.7.3 Determining the Source of Oxygen in the Diketone

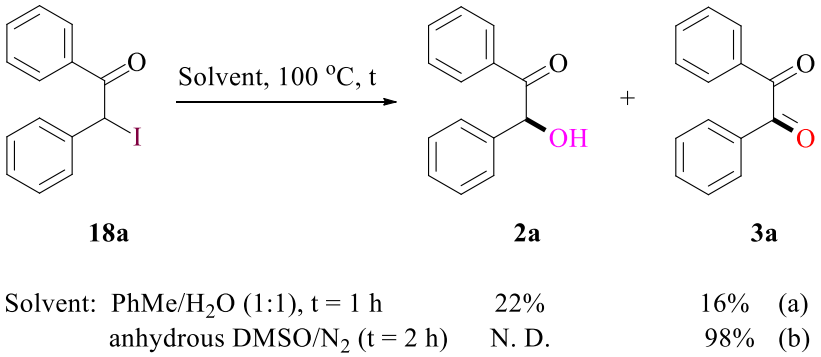
Having completed the iodination reaction, the next set of control experiments were undertaken to determine the source of oxygen in the diketone. Accordingly, there are three potential sources of oxygen in the reaction: molecular oxygen from the air, a trace amount of water in

DMSO and DMSO itself. In the presence of a nitrogen atmosphere, the reaction of benzyl phenyl ketone **4a** with iodine, in the presence of DMSO, proceeded well to provide benzil **3a** in a 95% yield indicating that oxygen from the air did not participate in the oxidation reaction (**Scheme 39**).



Scheme 39: Direct oxidation of **4a** with I_2/DMSO under a nitrogen atmosphere.

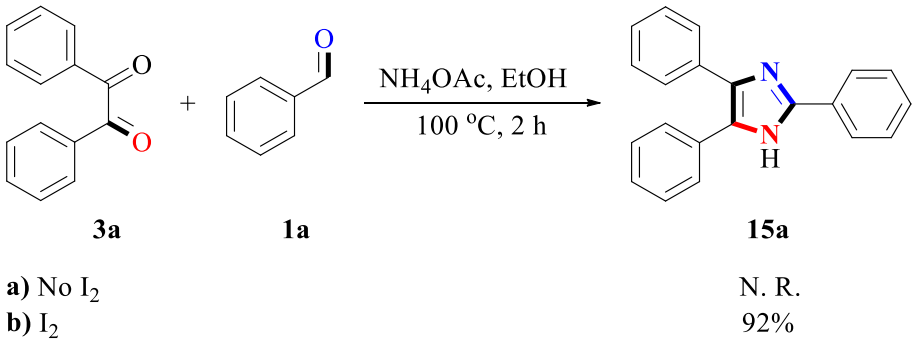
When the reaction was performed in a toluene/water biphasic mixture, the hydroxylation product benzoin **19a** and the diketone benzil **3a** were obtained in a 22% and 16% yield, respectively, **Scheme 40**, **a**). This indicated that the water present in DMSO played a minor role in the oxidation of benzyl phenyl ketone **4a** to afford **19a** which is further oxidized to provide **3a**. In the presence of anhydrous DMSO, under a nitrogen atmosphere, **3a** was furnished in a 98% yield. This preliminary result confirmed that the majority of oxygen in the diketone originated from DMSO (**Scheme 40**, **experiment b**).



Scheme 40: Oxidation of **18a** under different reaction conditions in order determine the source of oxygen in the 1,2-diketone product **3a**. The hydroxylation product was not determined (n. d.) when the reaction was performed under anhydrous conditions (condition b).

3.7.4 Effect of Molecular Iodine on the Coupling Reaction

Finally, in order to understand the role of iodine in the coupling reaction, a mixture of benzil **3a**, benzaldehyde **1a** and ammonium acetate was reacted in ethanol in the absence of iodine. The corresponding 2,4,5-triphenyl-1*H*-imidazole **15a** was, however, not obtained (**Scheme 41**, **a**). When the same reaction was replicated in the presence of iodine, **15a** was synthesized in a 92% yield, indicating that iodine facilitated a vital role in the coupling reaction leading to the desired imidazole obtained (**Scheme 41**, **b**).



Scheme 41: Effect of iodine on the coupling reaction of **4a**, **1a** and ammonium acetate to the corresponding 2,4,5-triphenyl-1*H*-imidazole **15a**. No reaction (N. R.) was observed when performed in the absence of molecular iodine (condition a).

The series of control experiments performed (*vida supra*) indicated that a benzylic radical and an α-iodinated species are the key reactive intermediates in this oxidation reaction. Furthermore, it was shown that DMSO is the major source of oxygen in the corresponding diketone product.

3.8 Plausible Reaction Mechanism

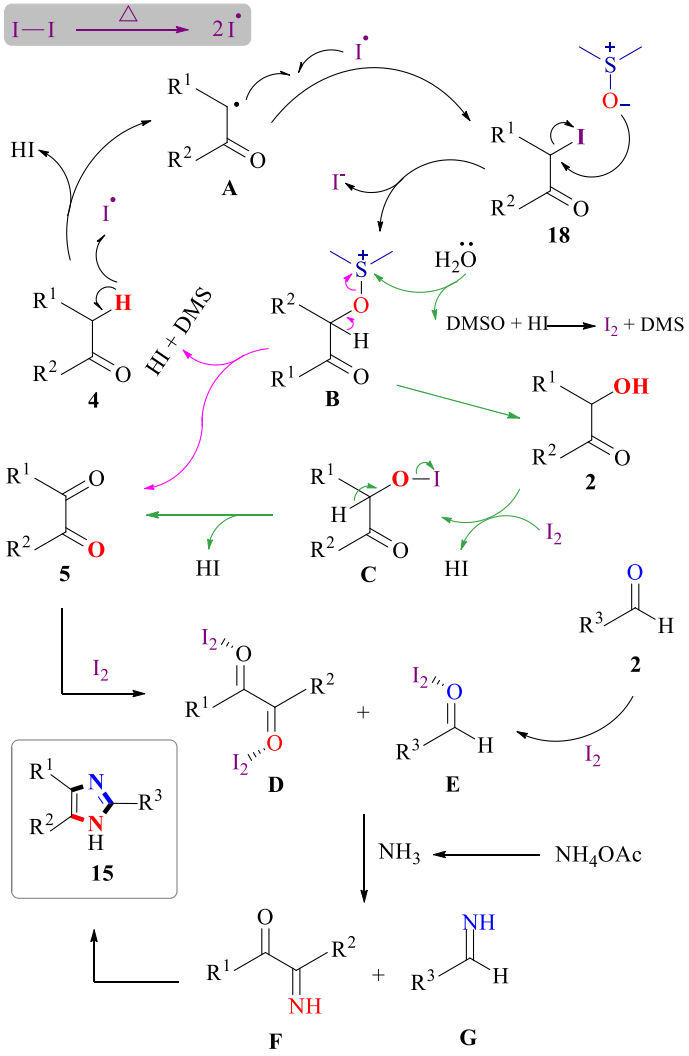
On the basis of the control results and literature reports, a plausible reaction mechanism of consecutive iodination/oxidation/cyclization has been outlined in **Scheme 42**. The reaction proceeds by an iodine assisted proton abstraction from the benzyl position of **4** to generate the benzylic radical **A**.[142] Subsequently, iodination affords the α-iodoketone intermediate, 2-iodo-

1,2-diphenylethanone **18** which reacts with DMSO to generate the corresponding active sulfoxide intermediate **B**.

There are two potential pathways proposed for the reaction of intermediate **B** to afford benzil **3**.[143] According to the control experiment in **Scheme 40**, the minor pathway (green)[144] involves the attack of a water molecule on the sulfur cation of **B** to afford the hydroxylation intermediate benzoin **2** which subsequently forms benzil **3** *via* intermediate **C**. In this step, DMSO and hydrogen iodide (HI) are regenerated for further cycle.

The major pathway (purple) proceeds with a proton abstraction from the α-carbon of **B**, followed by the removal of HI and dimethyl sulfide (DMS) which furnishes the desired diketone intermediate **3**. Accordingly, the oxidation of the α-iodinated intermediate **18** is not solely a DMSO catalyzed reaction, since some water is present, but primarily relies on the DMSO to react with **18** to afford **3**. Notably, 0.5 equivalents of iodine was employed in the reaction, since, as the mechanism proceeds, HI is released into solution which subsequently gets re-oxidized into I_2 to aid the coupling reaction (*vida infra*).

In terms of the coupling reaction,[145] the result of the control experiment in (**Scheme 41**, **condition b**) supports the fact that iodine is capable of binding to the carbonyl oxygen of the diketone and the aldehyde **1** owing to the mild Lewis acidity of iodine, thereby activating and increasing the reactivity of the substrates.[136a, 146] Moreover, iodine facilitates the formation of the imine intermediates **F** and **G** which undergo cyclocondensation to yield the desired 2,4,5-trisubstituted-1*H*-imidazole **15**.



Scheme 42: Plausible reaction mechanism for I_2/DMSO mediated synthesis of **15** indicating the key reactive intermediates to afford the 2,4,5-trisubstituted-1*H*-imidazoles.

3.9 Concluding Remarks to I_2/DMSO Facilitated Approach to 2,4,5-Trisubstituted-1*H*-imidazole Synthesis.

In summary, an improved, non-toxic, acid and transition metal-free, sequential one-pot approach to 2,4,5-trisubstituted-1*H*-imidazoles was developed by employing benzyl aryl ketones instead of the traditional diketone. This environmentally benign, convenient and practical route provides access to diversely substituted 2,4,5-trisubstituted-1*H*-imidazoles in moderate to good yields. In addition, mild experimental conditions and short reaction times are utilized, making this approach an alternative to conventional processes. Furthermore, a substrate scope was established by preparing a series of novel

2,4,5-trisubstituted-1*H*-imidazoles which could potentially have biological properties in good yields. In addition, this system was applicable to a domino convergent synthesis of benzyl phenyl ketone and benzyl alcohol to afford 2,4,5-triphenyl-1*H*-imidazole, *albeit* in moderate yields. A series of control experiments indicates a consecutive iodination/oxidation/cyclization mechanism to afford the desired imidazole. Having obtained minimal insight into the reaction mechanism, an in-depth mechanistic study was anticipated.

The results of the I_2/DMSO oxidative system for the direct oxidation of benzyl aryl ketones to afford 2,4,5-triaryl-1*H*-imidazoles was drawn up for publication and subsequently accepted by *RSC Advances*. The reference to this publication is given below and a copy of the article is available in Appendix A.

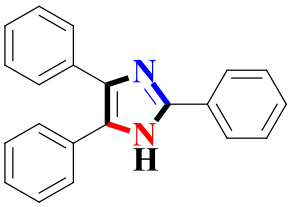
Reference:[147] J. Jayram and V. Jeena,*RSC Adv.* **2018**, 8, 37557-37563

3.10 Experimental

3.10.1 General Information

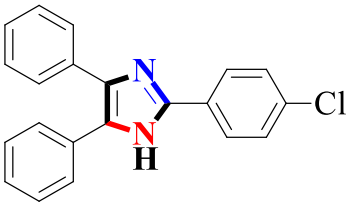
All reagents were purchased without further purification. All ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Advance III spectrometer operating at either 400 or 500 MHz. Chemical shifts (δ) were reported in ppm using the Dimethyl Sulfoxide-d_6 (DMSO-d_6) residual 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 unit (Hz). High-resolution electron-spray ionization (ESI) mass spectra were recorded on a time-of-flight (TOF) micromass spectrometer. Infra-Red (IR) spectra were recorded on Carey 630 FTIR. Absorption maxima are expressed in wavenumbers (cm^{-1}). Melting points were determined using Kofler hot-stage melting apparatus.

3.10.2 Typical Procedure for the I_2/DMSO Catalyzed Reaction of Benzyl Aryl Ketones, Aldehydes and Ammonium Acetate



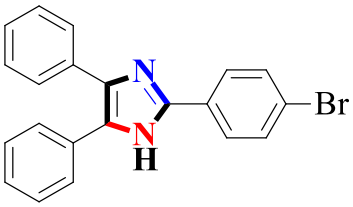
2-Phenylacetaphenone (1 mmol) and iodine (0.5 mmol) were mixed in a round bottomed flask with 1 mL DMSO and heated to 100 °C for 2 hours. Thereafter, benzaldehyde (1 mmol), ammonium acetate (10 mmol) and ethanol (2 mL) were sequentially added and the mixture heated to 100 °C for a further 2 hours. After cooling, a $Na_2S_2O_3$/ice water solution was added to the reaction mixture to yield the crude product which was filtered, air dried and recrystallized from ethanol to afford the desired 2,4,5-triphenyl-1*H*-imidazole **15a**. The following compounds **15b-15w** were prepared by this procedure using the appropriate starting materials.

2,4,5-Triphenyl-1*H*-imidazole (15a, $C_{21}H_{16}N_2$, 0.243g, 82%):[54, 115] white solid. **Mp** 271-273 °C; **υ_{max} (neat, cm^{-1})**: 3037, 2852, 1586, 1488, 1322; **^{1}H NMR (400 MHz, DMSO-D_6)**: 12.69(s, 1H), 8.11 (d, *J* = 7.64, 2H,), 7.58-7.56 (m, 2H), 7.53-7.50 (m, 2H), 7.48-7.43 (m, 4H), 7.39-7.36 (m, 2H), 7.32-7.29 (m, 2H), 7.24-7.22 (m, 1H); **^{13}C (100 MHz, DMSO-D_6)**: 145.5, 137.1, 135.2, 131.1, 130.3, 128.6, 128.4, 128.2, 128.1, 127.7, 127.1, 126.5, 125.2; **ESI-MS (*m/z*)**: calcd for $C_{21}H_{17}N_2$ 297.1393, found 297.1396 $[M+H]^+$.

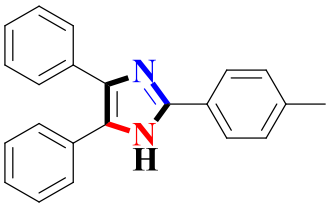


2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (15b, $C_{21}H_{15}ClN_2$, 0.284g, 86%):[119] white solid. **Mp** 262-263 °C; **υ_{max} (neat, cm^{-1})**: 3057, 2961, 1599, 1483, 1323, 764; **^{1}H NMR (400 MHz, DMSO-D_6)**: 12.76 (s, 1H), 8.10 (d, *J* = 6.47 Hz, 2H), 7.55-7.53 (m, 6H), 7.43-7.32 (m,

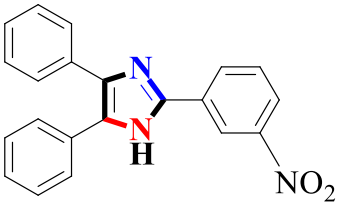
6H); **^{13}C (100 MHz, DMSO-D$_6$)**: 144.4, 137.3, 135.0, 132.7, 131.0, 129.2, 128.7, 128.6, 128.4, 127.1, 126.8; **ESI-MS (*m/z*)**: calcd for $C_{21}H_{16}{}^{35}ClN_2$ 331.1004, found 331.1011 $[M+H]^+$.



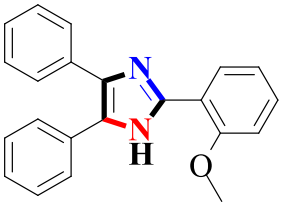
2-(4-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (15c, C$_{21}$H$_{15}$BrN$_2$, 0.307g, 82%):[119] white solid. **Mp** 250-251 °C; **υ_{max} (neat, cm^{-1})**: 3057, 1587, 1491, 1382, 724; **^{1}H NMR (400 MHz, DMSO-D$_6$)**: 12.77 (s, 1H), 8.04 (d, *J* = 6.18 Hz, 2H), 7.68 (d, *J* = 6.38 Hz, 2H), 7.53 (m, 4H), 7.44-7.24 (m, 6H); **^{13}C (100 MHz, DMSO-D$_6$)**: 144.4, 137.3, 135.0, 131.6, 130.9, 129.5, 128.6, 128.4, 128.2, 127.8, 127.1, 126.6, 121.4; **ESI-MS (*m/z*)**: calcd for $C_{21}H_{16}BrN_2$ 375.0499, found 375.0503 $[M+H]^+$.



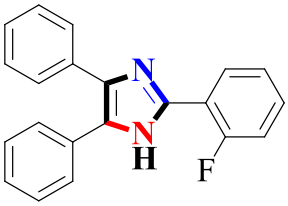
4,5-diphenyl-2-(*p*-tolyl)-1*H*-imidazole (15d, C$_{22}$H$_{18}$N$_2$, 0.248g, 80%):[148] white solid. **Mp** 231-233 °C; **υ_{max} (neat, cm^{-1})**: 3036, 2870, 1602, 1493, 1449; **^{1}H NMR (400 MHz, DMSO- D$_6$)**: 12.61 (s, 1H), 799-7.97 (m, 2H), 7.53-7.23 (m, 12H), 2.35 (s, 3H); **^{13}C (100 MHz, DMSO-D$_6$)**: 145.7, 137.7, 137.0, 135.3, 131.2, 129.3, 128.7, 128.5, 128.2, 128.0, 127.7, 127.1, 126.5, 125.2, 20.9; **ESI-MS (*m/z*)**: calcd for $C_{22}H_{17}N_2$ 309.1390, found 309.1393 $[M-H]^+$.



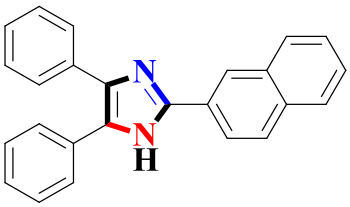
2-(3-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (15e, $C_{21}H_{15}N_3O_2$, 0.256g, 75%):[119] yellow solid. **Mp** 315-317 °C; **υ_{max} (neat, cm^{-1})**: 3059, 2861, 1584, 1522, 1480, 1347; **^{1}H NMR (400 MHz, DMSO-D_6)**: 13.08 (s, 1H), 8.95 (s, 1H), 8.51 (d, *J* = 6.31 Hz, 1H), 8.20 (d, *J* = 8.14 Hz, 1H), 7.77 (t, *J* = 8.00 Hz, 1H), 7.55 (d, *J* = 7.09 Hz, 4H), 7.39-7.37 (m, 6H); **^{13}C (100 MHz, DMSO-D_6)**: 148.4, 143.4, 131.8, 131.1, 130.4, 128.5, 127.6, 122.5, 119.4; **ESI-MS (*m/z*)**: calcd for $C_{21}H_{16}N_2O_2$ 342.1244, found 342.1248 $[M+H]^+$.



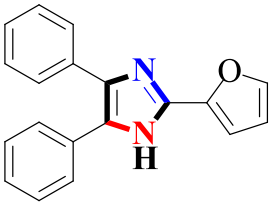
2-(2-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (15f, $C_{22}H_{18}N_2O$, 0.205g, 63%):[54] white solid. **Mp** 224-226 °C; **υ_{max} (neat, cm^{-1})**: 3059, 2834, 1583, 1468, 1249, 1016; **^{1}H NMR (400 MHz, DMSO-D_6)**: 11.87 (s, 1H), 8.06 (d, *J* = 6.35 Hz, 1H), 7.54 (d, *J* = 7.56 Hz, 2H), 7.49-7.47 (m, 2H), 7.43 (t, *J* = 7.50 Hz, 2H), 7.38-7.37 (m, 2H), 7.29 (t, *J* = 7.36 Hz, 2H), 7.23-7.19 (m, 1H), 7.17-7.15 (m, 1H), 7.07 (t, *J* = 7.40 Hz, 1H), 3.93 (s, 3H); **^{13}C (100 MHz, DMSO-D_6)**: 156.0, 143.1, 136.4, 135.3, 131.2, 129.7, 128.8, 128.6, 128.5, 128.1, 127.6, 127.4, 127.0, 126.4, 120.6, 118.9, 111.6, 55.5; **ESI-MS (*m/z*)**: calcd for $C_{22}H_{19}N_2O$ 327.1499, found 327.1503 $[M+H]^+$.



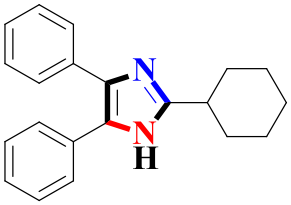
2-(2-Fluorophenyl)-4,5-diphenyl-1*H*-imidazole (15g, $C_{21}H_{15}FN_2$, 0.214g, 68%):[120] white solid. **Mp** 239-240 °C; **υ_{max} (neat, cm^{-1})**: 3028, 2777, 1577, 1483, 1252, 1100; **^{1}H NMR (400 MHz, DMSO-D_6)**: 12.57 (s, 1H), 8.03-7.99 (m, 1H), 7.55 (d, *J* = 7.32 Hz, 2H), 7.51-7.41 (m, 5H), 7.39-7.29 (m, 5H), 7.24-7.21 (m, 1H); **^{13}C (100 MHz, DMSO-D_6)**: 158.9 ($J_{C, F}$ = 247 Hz), 140.8 ($J_{C, F}$ = 1.42 Hz), 137.2, 135.0, 130.9, 130.4 ($J_{C, F}$ = 8.51 Hz), 129.6 ($J_{C, F}$ = 2.84 Hz), 128.5, 128.2, 127.8, 127.1, 126.6, 124.7 ($J_{C, F}$ = 2.84 Hz), 118.7 ($J_{C, F}$ = 12.29 Hz), 116.2 ($J_{C, F}$ = 20.80 Hz); **ESI-MS (*m/z*)**: calcd for $C_{21}H_{16}FN_2$ 3315.1299, found 315.1305 $[M+H]^+$.



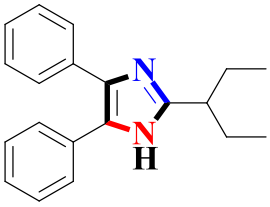
2-(naphthalen-2-yl)-4,5-diphenyl-1*H*-imidazole (15h, $C_{25}H_{18}N_2$, 0.256g, 74%):[149] white solid. **Mp** 274-275 °C; **υ_{max} (neat, cm^{-1})**: 3057, 2970, 1582, 1500, 1341; **^{1}H NMR (400 MHz, DMSO-D_6)**: 12.86 (s, 1H), 8.63 (s, 1H), 8.27 (d, *J* = 6.10 Hz, 1H), 8.02-7.93 (m, 3H), 7.59-7.51 (m, 6H), 7.39 (m, 6H); **^{13}C (100 MHz, DMSO-D_6)**: 145.5, 133.0, 132.7, 128.4, 128.2, 128.1, 127.8, 127.7, 126.7, 126.3, 123.7, 123.5; **ESI-MS (*m/z*)**: calcd for $C_{25}H_{19}N_2$ 347.1550, found 347.1553 $[M+H]^+$.



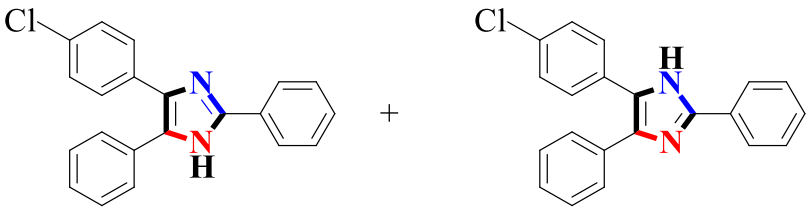
2-(2-Furan-2-yl)-4,5-diphenyl-1*H*-imidazole (15i, $C_{19}H_{14}N_2O$, 0.120g, 42%):[121] brown solid. **Mp** 229-231 °C; **υ_{max} (neat, cm^{-1})**: 3056, 2726, 1602, 1485, 1014; **^{1}H NMR (400 MHz, DMSO-D_6)**: 12.80 (s, 1H), 7.80 (m, 1H), 7.53-7.47 (m, 4H), 7.44-7.40 (m, 2H), 7.38-7.34 (m, 1H), 7.31-7.28 (m, 2H), 7.24-7.21 (m, 1H), 6.98 (d, *J* = 3.10 Hz, 1H), 6.64 (m, 1H); **^{13}C (100 MHz, DMSO-D_6)**: 145.7, 143.0, 138.5, 137.0, 135.0, 130.8, 128.6, 128.3, 128.2, 127.8, 127.5, 127.1, 126.6, 111.8, 107.4; **ESI-MS (*m/z*)**: calcd for $C_{19}H_{15}N_2O$ 287.1186, found 287.1189 $[M+H]^+$.



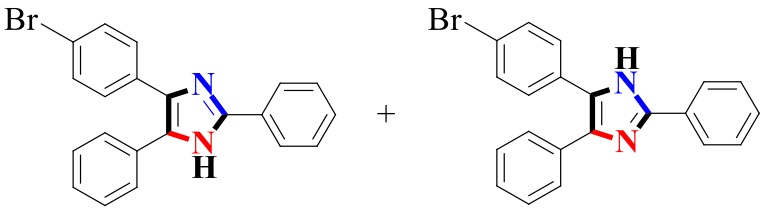
2-(Cyclohexyl)-4,5-diphenyl-1*H*-imidazole (15j, $C_{21}H_{22}N_2$, 0.154g, 51%):[54] pale brown solid. **Mp** 242-244 °C; **υ_{max} (neat, cm^{-1})**: 3032, 2926, 2848, 1602, 1534, 1499, 1447; **^{1}H NMR (400 MHz, DMSO-D_6)**: 11.90 (s, 1H), 7.48-7.46 (m, 2H), 7.39-7.35 (m, 4H), 7.31-7.23 (m, 3H), 7.18-7.14 (m, 1H), 2.73-2.66 (m, 1H), 1.98-1.95 (m, 2H), 1.81-1.78 (m, 2H), 1.70-1.67 (m, 1H), 1.64-1.54 (m, 2H), 1.40-1.20 (m, 3H); **^{13}C (100 MHz, DMSO-D_6)**: 152.3, 135.8, 135.0, 131.6, 128.5, 128.0, 127.8, 127.1, 127.0, 126.0, 125.7, 37.2, 31.5, 25.7, 25.6; **ESI-MS (*m/z*)**: calcd for $C_{21}H_{23}N_2$ 303.1863, found 303.1862 $[M+H]^+$.



2-(pentan-3-yl)-4,5-diphenyl-1*H*-imidazole (15k, $C_{20}H_{22}N_2$, 0.102g, 35%):[122] white solid. **Mp** 240-242 °C; **υ_{max} (neat, cm^{-1})**: 3064, 3030, 2957, 2925, 2869, 1601, 1498, 1333; **^{1}H NMR (400 MHz, DMSO-D_6)**: 11.92 (s, 1H), 7.51-7.49 (m, 2H), 7.42-7.36 (m, 4H), 7.31-7.23 (m, 3H), 7.18-7.16 (m, 1H), 2.62-2.55 (m, 1H), 1.79-1.62 (m, 4H), 0.86-0.82 (m, 6H); **^{13}C (100 MHz, DMSO-D_6)**: 151.2, 135.8, 135.2, 131.7, 129.5, 129.4, 128.5, 128.0, 127.8, 127.0, 126.9, 126.0, 125.6, 42.2, 26.6, 12.0; **ESI-MS (*m/z*)**: calcd for $C_{20}H_{21}N_2$ 289.1703, found 289.1707 $[M-H]^+$.

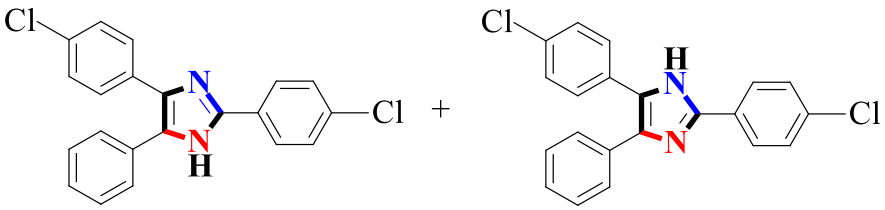


5-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (15n, $C_{21}H_{15}ClN_2$, 0.277g, 84%):[92] white solid. **Mp** 241-243 °C; **υ_{max} (neat, cm^{-1})**: 3038, 2969, 1541, 1485, 1091, 768; **^{1}H NMR (400 MHz, DMSO-D_6)**: 12.73 (s, 1H), 8.08 (d, *J* = 6.16 Hz, 2H), 7.57-7.25 (m, 12H); **^{13}C (100 MHz, DMSO-D_6)**: 145.9, 145.7, 137.7, 135.8, 135.0, 134.0, 132.3, 131.0, 130.8, 130.2, 130.2, 130.0, 129.9, 128.8, 128.7, 128.6, 128.6, 128.4, 128.4, 128.3, 128.1, 127.3, 127.0, 126.8, 125.3, 125.2; **ESI-MS (*m/z*)**: calcd for $C_{21}H_{16}{}^{35}ClN_2$ 331.1004, found 331.1010 $[M+H]^+$.

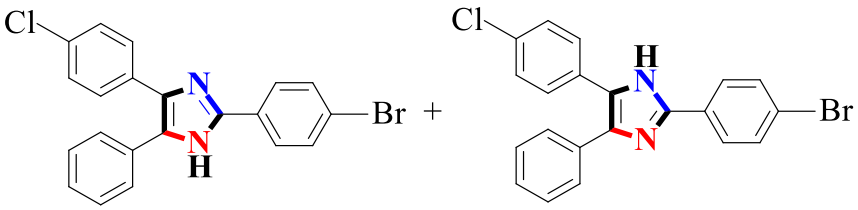


5-(4-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (15o, $C_{21}H_{15}BrN_2$, 0.292g, 78%):[92] white solid. **Mp** 253-255 °C; **υ_{max} (neat, cm^{-1})**: 3049, 2845, 1596, 1482, 1010, 767; **^{1}H NMR (400**

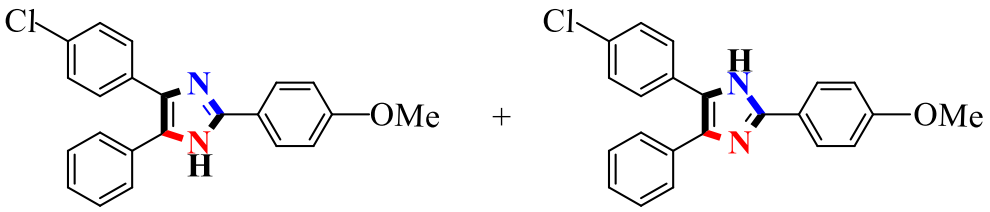
MHz, DMSO-D$_6$): 12.77 (s, 1H), 8.09 (d, *J* = 618 Hz, 2H), 7.62-7.27 (m, 12H); **^{13}C (100 MHz, DMSO-D$_6$)**: 145.9, 145.7, 137.8, 135.8, 135.0, 134.4, 131.6, 131.2, 130.8, 130.2, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1, 127.3, 127.0, 126.8, 125.3, 120.8, 119.5; **ESI-MS (*m/z*)**: calcd for $C_{21}H_{14}{}^{79}BrN_2$ 373.0339, found 373.0344 $[M-H]^+$.



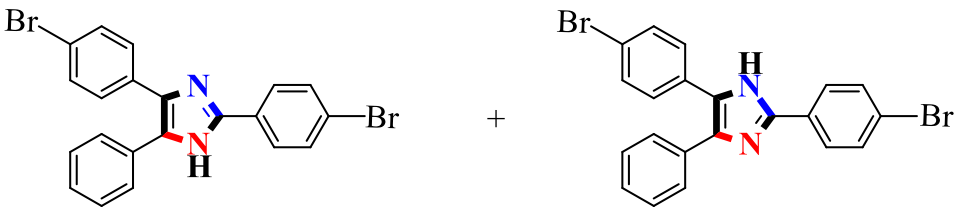
2,5-Bis-(4-chlorophenyl)-4-phenyl-1*H*-imidazole (15p, C$_{21}$H$_{14}$Cl$_2$N$_2$, 0.277g, 76%):[92] white solid. **Mp** 250-252 °C; **υ_{max} (neat, cm^{-1})**: 3060, 2835, 1599, 1500, 1478, 1445, 1087, 830; **^{1}H NMR (400 MHz, DMSO-D$_6$)**: 12.81 (s, 1H), 8.10 (d, *J* = 8.24 Hz, 2H), 7.55-7.41 (m, 11H); **^{13}C (100 MHz, DMSO-D$_6$)**: 144.6, 132.8, 129.0, 128.7, 128.6, 128.4, 126.9; **ESI-MS (*m/z*)**: calcd for $C_{21}H_{14}{}^{35}Cl_2N_2$ 363.0454, found 363.0455 $[M-H]^+$.



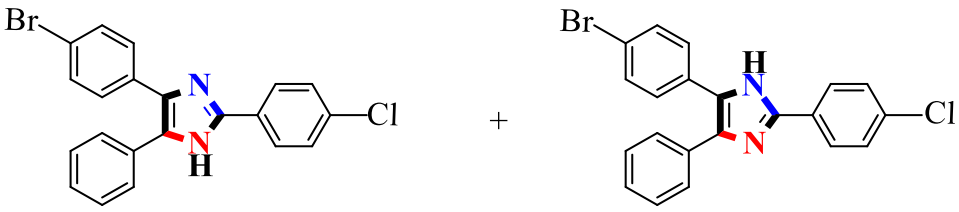
2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-phenyl-1*H*-imidazole (15q, C$_{21}$H$_{14}$BrClN$_2$, 0.294g, 72%):[92] white solid. **Mp** 251-253 °C; **υ_{max} (neat, cm^{-1})**: 3067, 2829, 1480, 1446, 1091, 830, 729; **^{1}H NMR (400 MHz, DMSO-D$_6$)**: 12.82 (s, 1H), 8.03-8.01 (m, 2H), 7.69-7.67 (m, 2H), 7.52-7.41 (m, 9H); **^{13}C (100 MHz, DMSO-D$_6$)**: 144.7, 131.8, 129.4, 129.0, 128.6, 128.2, 127.2, 125..4, 121.6; **ESI-MS (*m/z*)**: calcd for $C_{21}H_{13}{}^{35}Cl^{79}BrN_2$ 406.9949, found 406.9953 $[M-H]^+$.



5-(4-Chlorophenyl)-2-(4-methoxyphenyl)-4-phenyl-1*H*-imidazole (15r, $C_{22}H_{17}ClN_2O$, 0.238g, 66%): pale yellow solid. **Mp** 253-255 °C; **υ_{max} (neat, cm^{-1})**: 3067, 2829, 1480, 1446, 1091, 830, 729; **^{1}H NMR (400 MHz, DMSO-D_6)**: 12.55 (s, 1H), 8.02-8.00 (m, 2H), 7.52-7.38 (m, 9H), 7.05-7.03 (m, 2H), 3.82 (s, 3H); **^{13}C (100 MHz, DMSO-D_6)**:; **ESI-MS (*m/z*)**: 159.5, 145.8, 128.4, 126.7, 123.0, 114.1, 55.2; calcd for $C_{22}H_{18}{}^{35}ClN_2O$ 361.1109, found 361.1116 $[M+H]^+$.

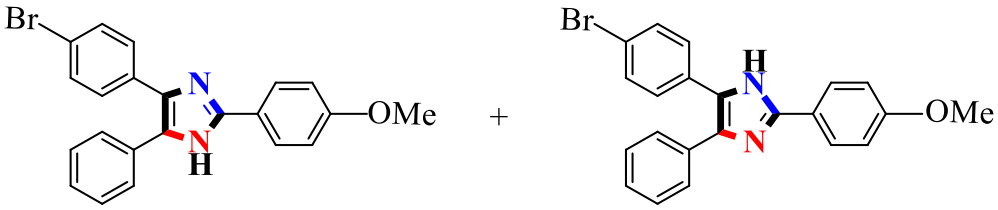


2,5-Bis-(4-bromophenyl)-4-phenyl-1*H*-imidazole (15s, $C_{21}H_{14}Br_2N_2$, 0.365g, 81%): white solid. **Mp** 252-255 °C; **υ_{max} (neat, cm^{-1})**: 3060, 2826, 1598, 1479, 1067, 826, 730; **^{1}H NMR (400 MHz, DMSO-D_6)**: 12.84 (s, 1H), 8.03 (d, *J* = 8.20 Hz, 2H), 7.69 (d, *J* = 8.20 Hz, 2H), 7.53-7.42 (m, 9H); **^{13}C (100 MHz, DMSO-D_6)**: 144.7, 131.7, 131.3, 129.4, 128.6, 127.1, 121.5; **ESI-MS (*m/z*)**: calcd for $C_{21}H_{13}{}^{79}Br_2N_2$ 450.9444, found 450.9443 $[M-H]^+$.

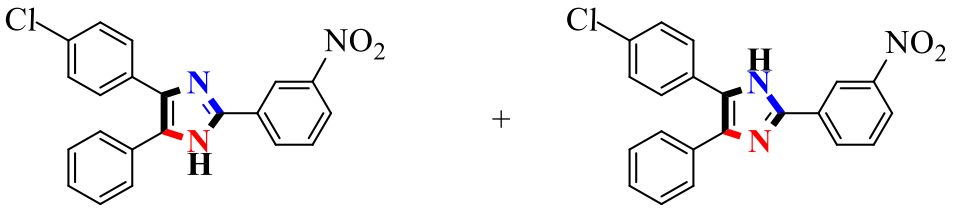


2-(4-Chlorophenyl)-5-(4-bromophenyl)-4-phenyl-1*H*-imidazole (15t, $C_{21}H_{14}BrClN_2$, 0.306g, 75%): white solid. **Mp** 249-251 °C; **υ_{max} (neat, cm^{-1})**: 3059, 2826, 1476, 1080, 823, 732; **^{1}H NMR (400 MHz, DMSO-D_6)**: 12.84 (s, 1H), 8.11 (d, *J* = 7.72 Hz, 2H), 7.56-7.50 (m,

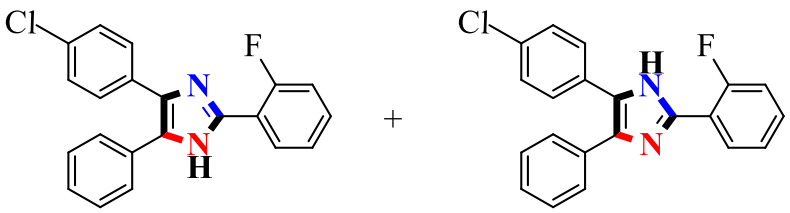
11H); **^{13}C (100 MHz, DMSO-D$_6$)**: 144.8, 144.7, 137.9, 136.0, 134.8, 134.2, 132.9, 131.6, 131.1, 130.6, 130.2, 130.0, 129.0, 128.9, 1288, 128.5, 128.3, 128.1, 127.3, 126.9, 120.9, 119.6; **ESI-MS (*m/z*)**: calcd for $C_{21}H_{13}{}^{35}Cl^{79}BrN_2$ 406.9949, found 406.9941 $[M-H]^+$.



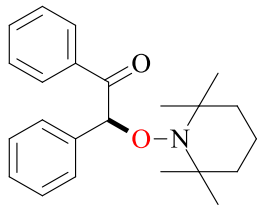
5-(4-Bromophenyl)-2-(4-methoxyphenyl)-4-phenyl-1*H*-imidazole (15u, $C_{22}H_{17}BrN_2O$, 0.275g, 68%): pale yellow solid. **Mp** 251-253 °C; **υ_{max} (neat, cm^{-1})**: 2960, 2832, 1607, 1481, 1246, 1173; **^{1}H NMR (400 MHz, DMSO-D$_6$)**: 12.56 (s, 1H), 8.03-8.01 (m, 2H), 7.53-7.38 (m, 9H), 7.06-7.04 (m, 2H), 3.83 (s, 3H); **^{13}C (100 MHz, DMSO-D$_6$)**: 159.5, 145.9, 131.2, 128.5, 128.4, 126.8, 123.0, 114.1, 55.2; **ESI-MS (*m/z*)**: calcd for $C_{22}H_{16}{}^{79}BrN_2O$ 403.0444, found 403.0441 $[M-H]^+$.



4-(4-Chlorophenyl)-2-(3-nitrophenyl)-5-phenyl-1*H*-imidazole (15v, $C_{21}H_{14}ClN_3O_2$, 0.319g, 85%): yellow solid. **Mp** 247-249 °C; **υ_{max} (neat, cm^{-1})**: 3070, 2858, 1518, 1476, 1345; **^{1}H NMR (400 MHz, DMSO-D$_6$)**: 13.11 (s, 1H), 8.94 (s, 1H), 8.50 (d, *J* = 7.76 Hz, 1H), 8.20 (d, *J* = 8.08 Hz, 1H), 7.76 (t, *J* = 8.00 Hz, 1H), 7.55 (t, *J* = 8.08 Hz, 4H), 7.43 (m, 5H); **^{13}C (100 MHz, DMSO-D$_6$)**: 148.3, 143.6, 131.7, 131.2, 130.3, 128.6, 128.4, 122.6, 119.4; **ESI-MS (*m/z*)**: calcd for $C_{21}H_{13}{}^{35}ClN_3O_2$ 374.0695, found 374.0701 $[M-H]^+$.



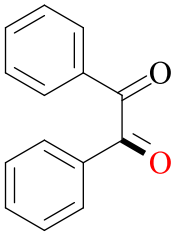
4-(4-Chlorophenyl)-2-(2-fluorophenyl)-5-phenyl-1*H*-imidazole (15w, $C_{21}H_{14}ClFN_2$, 0.184g, 53%): white solid. **Mp** 248-250 °C; **υ_{max} (neat, cm^{-1})**: 2963, 2728, 1500, 1483, 1223, 1090; **^{1}H NMR (400 MHz, DMSO-D_6)**: 12.60 (s, 1H), 8.00 (t, J = 7.48 Hz, 1H), 7.57-7.44 (m, 7H), 7.42-7.24 (m, 5H); **^{13}C (100 MHz, DMSO-D_6)**: 158.9 ($J_{C, F}$ = 250 Hz), 141.1 ($J_{C, F}$ = 1.46 Hz), 137.8, 135.9, 134.7, 133.8, 132.3, 131.1, 130.6, 130.5, 130.3 ($J_{C, F}$ = 7.84 Hz), 129.6 ($J_{C, F}$ = 1.81 Hz), 129.0, 128.7, 128.6, 128.3, 128.2, 128.1, 127.3, 126.8, 124.7 ($J_{C, F}$ = 3.62 Hz), 118.5 ($J_{C, F}$ = 12.06 Hz), 116.2 ($J_{C, F}$ = 21.70 Hz); **ESI-MS (*m/z*)**: calcd for $C_{21}H_{14}{}^{35}ClFN_2$ 347.0750, found 347.0760 $[M-H]^+$.



2-phenylacetophenone (1 mmol)), TEMPO (1 mmol) and iodine (0.5 mmol) were mixed in a round bottomed flask with 1 mL DMSO and heated to 100 °C for 2h. After cooling, a $Na_2S_2O_3$/water solution was added to the reaction mixture, extracted with dichloromethane, and dried over anhydrous $MgSO_4$. Removal of the solvent under vacuum, afforded the crude product which was purified by column chromatography using 9:1 hexane: ethyl acetate to afford **17a**.

1,2-diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)ethanone (17a, $C_{23}H_{29}NO_2$, 0.162g, 46%):[111] white solid. **Mp** 229-231 °C; **υ_{max} (neat, cm^{-1})**: 3068, 2922, 2852, 1667, 1596, 1446, 1262, 1042; **^{1}H NMR (400 MHz, DMSO-D_6)**: 8.01-7.99 (m, 2H), 7.43-7.39 (m, 3H), 7.34-7.30 (m, 2H), 7.22-7.18 (m, 2H), 7.14-7.10 (m, 1H), 5.92 (s, 1H), 1.38-1.37 (m, 6H), 1.24-1.11 (m, 6H), 0.92 (m, 3H), 0.73 (m, 3H); **^{13}C (100 MHz, DMSO-D_6)**: 198.3, 137.8, 135.3, 132.9, 129.3, 128.3, 127.5, 127.2, 93.5, 60.0, 59.8, 40.3, 33.6, 33.3, 20.3, 20.2, 17.0; **ESI-MS (*m/z*)**: calcd for $C_{23}H_{30}NO_2$ 352.2278, found 352.2277 $[M+H]^+$.

3.10.3 General Procedure for the Oxidation of Benzyl Phenyl Ketone with I_2/DMSO to Afford Benzil (**3a**).



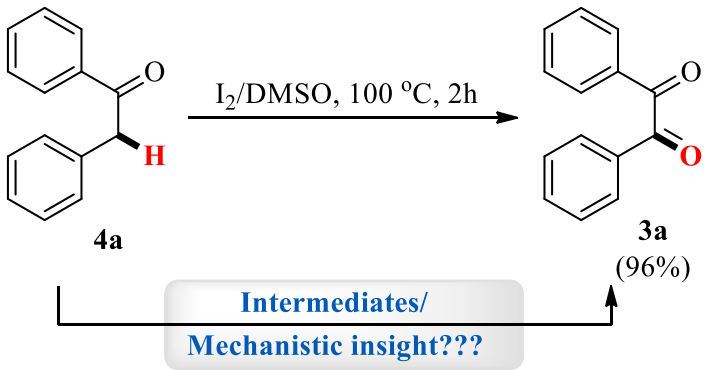
Benzyl phenyl ketone (1 mmol) and iodine (0.5 mmol) were mixed in a round bottomed flask with 1 mL DMSO and heated to 100 °C for 2h. After cooling, a $Na_2S_2O_3$/water solution was added to the reaction mixture, extracted with dichloromethane and dried over anhydrous $MgSO_4$. Removal of the solvent, under vacuum, afforded the crude product which was purified by column chromatography using 5:1 hexane: ethyl acetate.

Benzil **3a** (0.202 g, 96%) was obtained as a yellow solid:[150] **Mp** 94-96 °C; **υ_{maz} (neat, cm^{-1}):** 3064, 1655, 1590, 1449, 1208. **^{1}H NMR (400 MHz, $CDCl_3$):** 7.95-7.93 (m, 4H), 7.83-7.78 (m, 2H), 7.66-7.62 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$): 129.5, 129.5, 132.2, 135.5, 194.8. **GC-MS (*m/z*):** 210.0 (10), 105.0 (100).

Chapter 4: Iodine/DMSO Promoted Oxidation of Benzylic Csp^3–H Bonds to Diketones - A Mechanistic Investigation

4.1 Preface

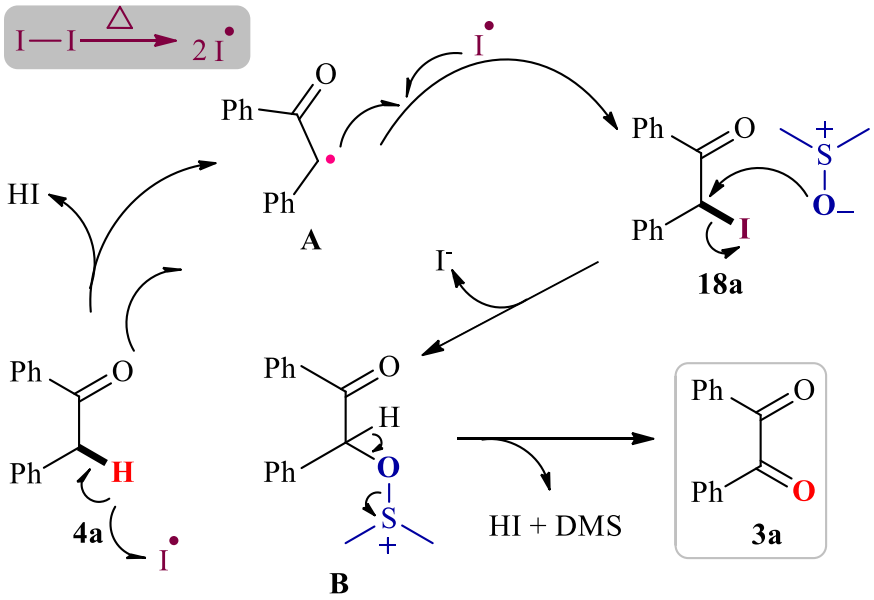
The I_2/DMSO mediated oxidation of benzyl aryl ketones to the corresponding *in situ* generated α-diketones, discussed in Chapter 3, was previously reported for the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles in moderate to good yields (35-86%). According to the research published within the group, the I_2/DMSO system successfully oxidized benzyl phenyl ketone **4a** to afford the 1,2-diketone in an isolated yield of 96% (**Scheme 43**). Although this oxidative system afforded the α-diketone in an excellent yield, the mechanistic insight into the reaction pathway was minimal. Hence, additional studies were required, in order to take the understanding of the reaction process forward and to provide definitive, mechanistic, proof for each step in the direct oxidation of the benzyl aryl ketone to the α-diketone employing the I_2/DMSO system; the significant point of interest in the current chapter.



Scheme 43: I_2/DMSO oxidation of benzyl phenyl ketone **4a** to benzil **3a**.

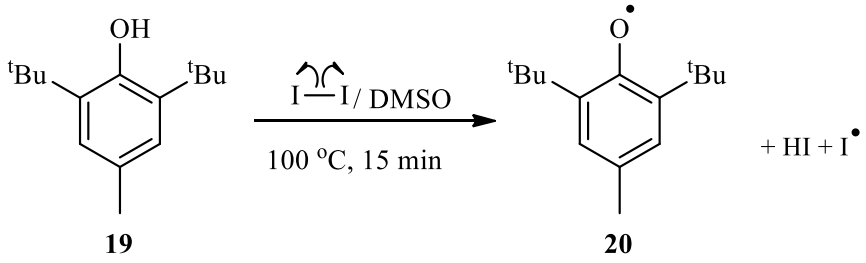
4.2 Results and Discussion

The theoretically proposed reaction mechanism was anticipated to proceed *via* initial iodination by I_2 employing 0.5 equivalents for maximum conversion into **18a**, followed by a modified Kornblum Oxidation in the presence of DMSO (**Scheme 44**). Accordingly, a series of experimental reactions and various spectroscopic techniques were undertaken to rationalize each step in the oxidation reaction of the proposed mechanistic pathway.



Scheme 44: Plausible mechanism for the I_2/DMSO oxidation of benzyl phenyl ketone **4a** to the corresponding diketone benzil **3a**, showing the key reactive intermediates in this transformation. The reaction proceeds with an I_2 cleavage, DMSO coupling and HI extraction, which all lead to the production of **3a**.

According to literature reports, it is known that the homolytic cleavage of molecular iodine occurs under thermal conditions to afford iodine radicals.[142] As a result, the mechanistic studies commenced by employing electron paramagnetic resonance spectroscopy (EPR) in order to explore the formation of iodine radicals in the reaction under thermal conditions. In general, free radicals are particularly unstable and a highly reactive species with a half-life of the order 10^{-9} s,[151] hence, BHT was employed as an anti-oxidant to detect the formation of iodine radicals in the reaction. BHT is a diamagnetic compound and, thus, no EPR signal was observed in the absence of iodine in the experiments undertaken. Next, molecular iodine and BHT were added to a reaction vessel with DMSO and the mixture heated to 100 °C for 15 minutes (**Scheme 45**).



19 **20**

Scheme 45: Formation of an oxygen radical from the reaction of I_2, BHT **19** and DMSO, resulting in the formation of hydrogen iodide (HI) and iodine radicals as a by-product.

After the 15 minute heating period, the reaction contents were transferred to a flat quartz EPR tube for analysis. An EPR signal, consistent with the presence of an organic radical, was observed (**Figure 13**). The resulting spectrum was characterized by four intense lines centred at g = 2.0011 which arose after BHT quenched iodine radicals *via H*-atom transfer, thereby generating a stable BHT radical species. The unpaired electrons located on the sterically hindered oxygen atom of BHT, and protected by the tertiary butyl groups, are stabilized by the π-system of the benzene ring. Moreover, the coupling of the electrons to the three equivalent protons of the 4-methyl groups afforded the recorded four-line EPR spectrum.[140b] The EPR signal and the g-value, calculated for the BHT radical obtained under the reaction conditions (I_2, BHT, DMSO, 100 °C, 15 minutes), were therefore comparable with the experimental data provided in the literature.[152] Consequently, these results correlate with the formation of a phenoxy radical (g = 2.0010-2.0091, $RPhO^{\cdot}$) which subsequently infers the presence of iodine radicals in the reaction.[153]

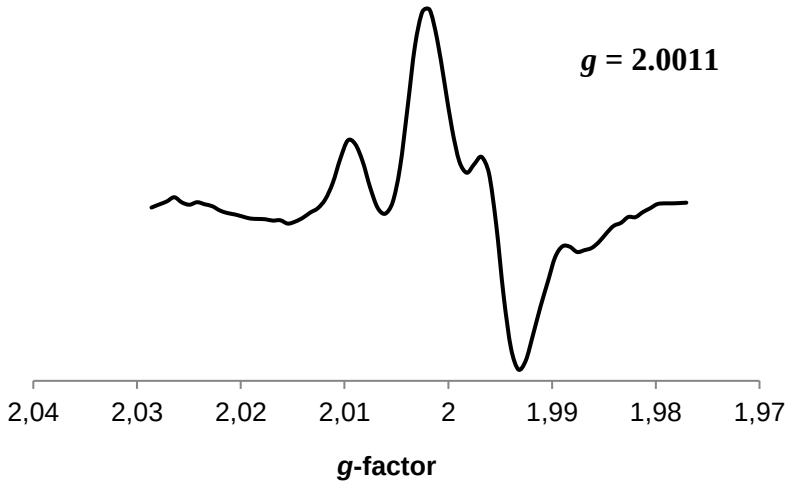
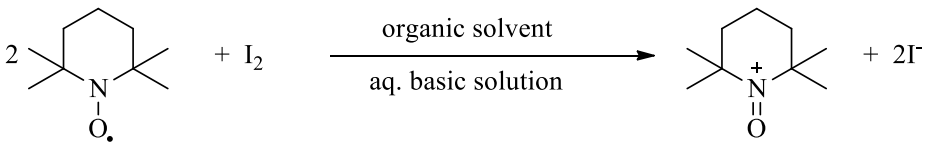


Figure 13: EPR spectrum of a heated I_2/BHT sample in DMSO characterized by four lines. The peak centralized at 2.0011 was indicative for the detection of the paramagnetic species $I^{\cdot}$ from BHT reacting with I_2.

Since the iodine radical was detected by EPR spectroscopy, this indicated that the oxidation reaction was initiated by the homolytic cleavage of molecular iodine under thermal conditions, thereby concluding a radical mediated mechanism. The presence of iodine radicals in the reaction, consequently, inferred the formation of a benzylic radical on benzyl phenyl ketone **4a**. In the previous study, the reaction of benzyl phenyl ketone, iodine and the radical inhibitor TEMPO in the presence DMSO was performed, under the standard reaction conditions, to afford the capture product **17a** in an isolated yield of 46% (**Chapter 3, Scheme 36**).

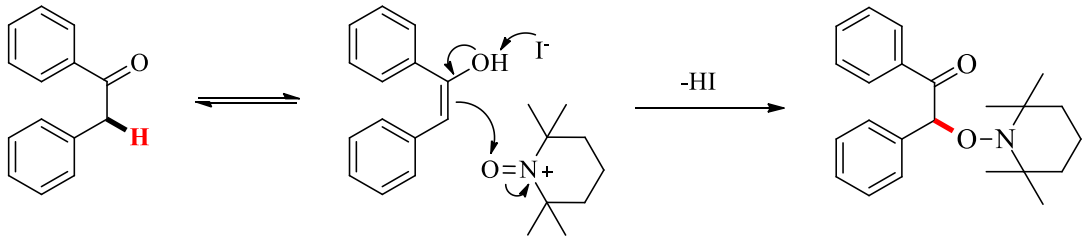
While the TEMPO-trapped reaction in **Scheme 36** theoretically supported the formation of intermediate **A** (**Scheme 44**), wherein the radical was located on the α-position of benzyl phenyl ketone **4a**, this experiment did not necessarily lead to this conclusion. It has been reported in the literature that the presence of a halogen co-catalyst,[154] TEMPO is readily oxidized to the corresponding *N*-oxoammonium cation **21** (**Scheme 46**).



21

Scheme 46: Iodine catalyzed *N*-oxoammonium cation **21** generation formed through the reaction of TEMPO with molecular iodine.

Moreover, *N*-oxoammonium cations are known to react with enolizable ketones, such as benzyl phenyl ketone **4a**, upon heating to generate the α-TEMPO ketone **17a** (**Scheme 47**). This is the *same* end product as though the α-benzylic radical intermediate **A** (**Scheme 44**) was hypothetically trapped by TEMPO itself. It is, however, notable that the formation of the *N*-oxoammonium cation is significantly influenced by the pH of the applied reaction media and the addition of an aqueous basic solution is essential to achieve the required conversion.[155]



4a **17a**

Scheme 47: *N*-oxoammonium catalyzed oxidation of the enolizable ketone **4a**.

Accordingly, in an effort to support the involvement of iodine radicals in the reaction, supplementary studies were undertaken so as to rule out the formation of the *N*-oxoammonium cation. This was achieved by monitoring the TEMPO radical using EPR spectroscopy. Initially, molecular iodine was treated with TEMPO in the presence of DMSO, under the optimized reaction conditions, to afford the EPR spectrum displayed in **Figure 14**. An intense triplet signal is ascribed to the stable free radical of TEMPO,[156] demonstrating that TEMPO was not oxidized by I_2, to the *N*-oxoammonium cation, upon heating within the elapsed time of the experiment (2 hours).

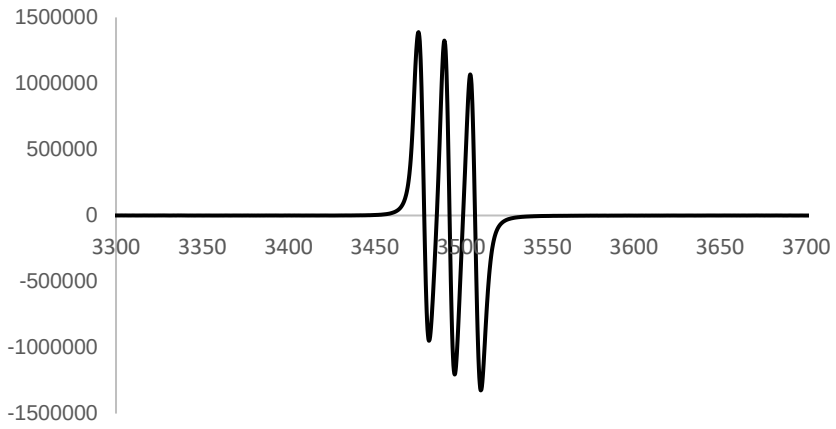


Figure 14: EPR spectrum for the reaction of iodine and TEMPO in DMSO showing three intense signals. The well-refined triplet of TEMPO demonstrated that the radical was not being oxidized under the utilized reaction conditions (I_2, TEMPO, DMSO and 100 ^oC for 2 hours).

The reaction was replicated with the addition of an aqueous solution of sodium bicarbonate ($NaHCO_3$), followed by heating at 100 °C for 2 hours and analyzed using EPR spectroscopy. This ensued the disappearance of the characteristic TEMPO signal, indicating the formation of the *N*-oxoammonium salt (**Figure 15**). Consequently, these results support the proposed reaction mechanism in **Scheme 44**, in which the reaction commenced *via* a radical mediated pathway and indicated that the capture adduct **17a** resulted from the formation of the benzylic intermediate **A** (**Scheme 44**), rather than by the reaction of the enolizable ketone **4a** with the *N*-oxoammoniun salt (**Scheme 47**).

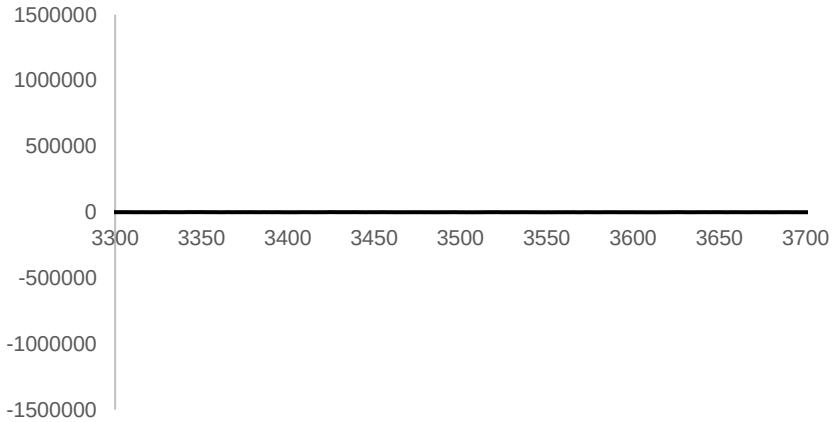


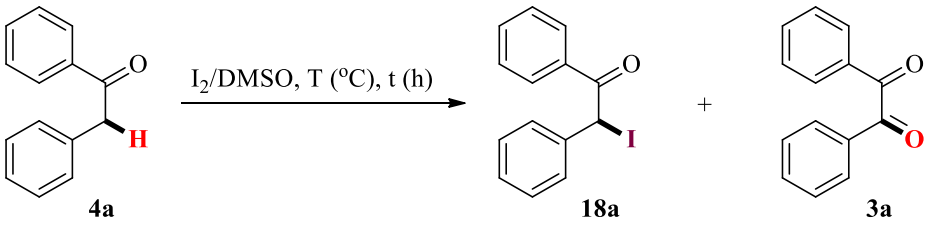
Figure 15: EPR spectrum for the reaction of iodine and TEMPO with aqueous $NaHCO_3$ showing the disappearance of the three characteristic signals. The absence of the characteristic

TEMPO triplet confirmed, under basic conditions and in the presence of I_2, that TEMPO was capable of being oxidized to the *N*-oxoammonium salt.

It was previously demonstrated in this research, owing to the involvement of benzylic and iodine radicals in the reaction, that the α-iodinated species 2--iodo--1,2-diphenylethanone **18a** was the reactive intermediate in the direct oxidation of benzyl phenyl ketone **4a** to afford benzyl **3a** (**Chapter 3**, **Scheme 38**). In this reaction, 2-iodo-1,2-diphenylethanone **18a** was synthesized and subjected to oxidation in the presence of DMSO to furnish benzil **3a** in an isolated yield of 97%.

Although the key reactive intermediate was prepared prior to oxidation by DMSO, an attempt was made in order to isolate the α-iodinated intermediate from the reaction by varying time and temperature, since the optimized reaction conditions result in complete oxidation of benzyl phenyl ketone **4a** to the α-diketone benzyl **3a** (**Table 14**, **entry 1**). Regardless of the numerous attempts to vary the reaction conditions, no success was achieved in isolating the reactive intermediate **18a**. On the contrary, the reaction proceeded to afford benzil **3a** in a 90% yield and unreacted benzyl phenyl ketone **4a** (**Table 14**, **entry 2**). Attempts were made to further decrease the reaction temperature in an effort to decrease the rate of oxidation. Only quantitative yields of **3a**, however, were obtained (**Table 14**, **entry 3-4**).

Table 14: Varying reaction conditions for the isolation of the α-iodinated intermediate **18a**.[a]



4a **18a** **3a**

Entry	Time (h)	Temp (°C)	Yield (%)		
			4a	**18a**	**3a**
1[b]	2	100	n. d.	n. d.	96
2	24	25	91	n. d.	<10
3	24	0	100	n. d.	n. d.
4	24	-78	100	n. d.	n. d.

[a] Determined by 1*H*-NMR. [b]Isolated yield.

As a result, the failure to isolate the α-iodoketone intermediate **18a** from the reaction was reasoned by solvation effects, along with the instability and reactivity of the C–I bond in dipolar aprotic solvents:[19c, 157]

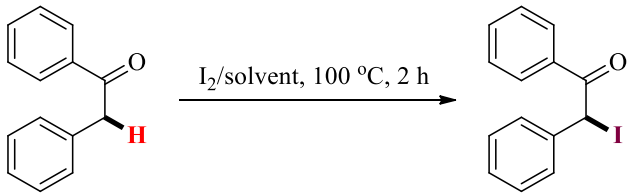
1. Carbon-iodine bonds are easily cleaved thermally, or photo-chemically, owing to the lower bond dissociation energy (BDE) [56.5 kcal mol^{-1}], as when compared to other carbon-halogen bonds and as a result are thermodynamically unstable in DMSO. This means that a slower reaction is required in order to make **18a** kinetically stable to be isolated;
2. Molecular iodine is least dependent upon *H*-bond stabilization with dipolar aprotic solvents, thus, it becomes highly electrophilic, allowing for immediate attack by DMSO on the α-carbon of the reactive intermediate **18a**;
3. The sulfoxide moiety of DMSO ($[CH_3]_2SO$) has an electronic charge, residing on both the oxygen and sulfur atoms which increases its nucleophilicity for interaction with an electrophile such as **18a**;

4. The corresponding iodide ion (I^-) distributes more effectively, the negative charge that it has acquired, making it a highly reactive leaving group in nucleophilic displacement reactions.

Accordingly, benzylic iodates are particularly difficult to observe and isolate if formed *in situ*, in the presence of a strong nucleophilic oxidant such as DMSO.

Therefore, alternate experimental conditions were explored and literature reports disclosed that benzylic iodates have successfully been synthesized and isolated *via* oxidation in weak, nucleophilic solvents (such as ethanol, methanol, dichloroethane, acetonitrile), in good to excellent yields.[158] Using this approach, the oxidation reaction was implemented in a series of weak nucleophilic solvents (**Table 15**), rather than DMSO, under the optimized reaction conditions to furnish the α-iodoketone intermediate, 2-iodo-1,2-diphenylethanone **18a**. Initially, benzyl phenyl ketone **4a** and iodine were heated at 100°C for 2 hours in tetrahydrofuran (THF) or dichloroethane (DCE). The reaction, however, failed to produce the desired intermediate **18a** (**Table 15**, **entries 1-2**). The solvent was, subsequently, changed to acetonitrile (CH_3CN) and *iso*-propanol (*i*-PrOH). Only a minor quantity of the α-iodinated intermediate, however, was detected in both solvents (**Table 15**, **entries 3-4**). Finally, when **4a** and iodine were treated in ethanol, under the optimal reaction conditions, the target α-iodinated intermediate **18a** was isolated in a yield of 26% which allowed for spectroscopic analysis of the product (**Table 15**, **entry 5**).

Table 15: Oxidation of benzyl phenyl ketone **1** in various weak nucleophilic solvents in order to isolate **18a**.[a]



4a **18a**

Entry	Solvent	Yield (%)	
		4a	**18a**
1	Tetrahydrofuran (THF)	100	n. d.
2	Dichloroethane (DCE)	100	n. d.
3	Acetonitrile (CH_3CN)	91	<10
4	Iso-propanol (i-PrOH)	90	<10
5[b]	**Ethanol (EtOH)**	**74**	**26**

[a] Determined by 1H-NMR. [b]Isolated yield.

The ^{1}H NMR spectrum, displayed in **Figure 16**, has depicted a singlet at 6.647 ppm[141] corresponding to the α-proton of 2-iodo-1,2-diphenylethanone, identifying **18a** as the key reactive intermediate in the oxidation of benzyl phenyl ketone. This, therefore, further supported the proposed reaction mechanism, in **Scheme 44**, for the I_2/DMSO mediated oxidation process.

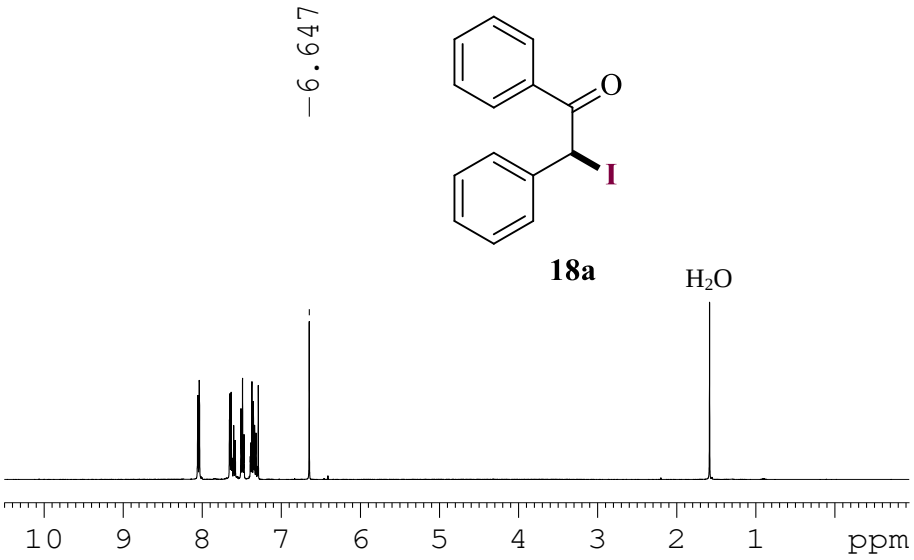
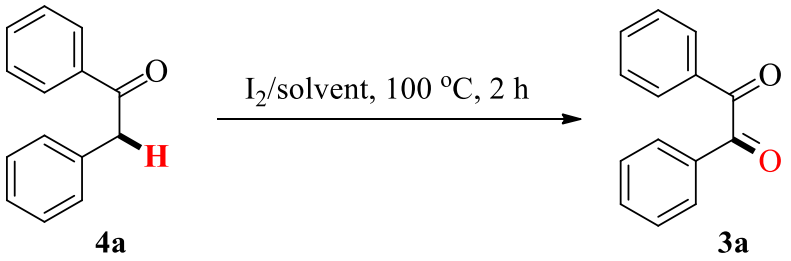


Figure 16: ^{1}H NMR spectrum of the α-iodinated intermediate 2-iodo-1, 2-diphenylethanone **18a** displaying the characteristic peak at 6.647 ppm corresponding to the α-proton of **18a**.

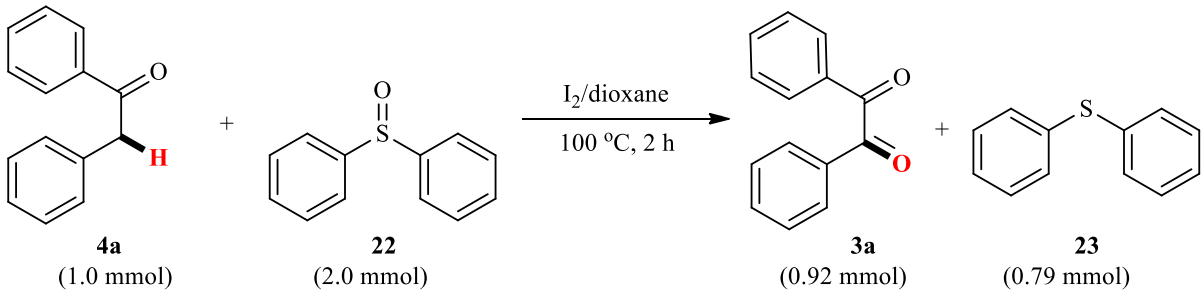
The results attained for the α-iodinated intermediate supported the effect of solvent (solvation) on the reaction pathway in terms of the nucleophilicity of the oxidant (solvent), as well as the isolation of the highly reactive key intermediate **18a**, in the direct I_2/DMSO oxidation of the benzyl group of benzyl phenyl ketone.

Finally, supplementary studies were previously reported for determining the source of oxygen in the reaction (**Scheme 48**). There were three noted sources of oxygen in the reaction system: oxygen from the atmosphere, a trace amount of water in DMSO and DMSO itself. When the reaction was performed under a nitrogen atmosphere, benzil **3a** was obtained in an isolated yield of 95% indicating that O_2 from the atmosphere does not participate in the reaction (**Scheme 48a**). The oxidation product, benzil **3a**, was subsequently afforded in a yield of 16% when the solvent was changed to a 1:1 toluene/water biphasic media hence; water plays a minor role as the source of oxygen in the diketone (**Scheme 48b**). The results of the final experiment (**Scheme 48c**) revealed that the major source of oxygen in the α-diketone originated from DMSO when the reaction was replicated the presence of anhydrous DMSO under a nitrogen atmosphere. While the results of this study are only an observation, effort was made to isolate the reductive product of the sulfoxide moiety in order to spectroscopically prove the source of oxygen in the diketone benzil.



Scheme 48: Control experiments in order to determine the source of oxygen in benzil **3a**. The proposed sources were identified as either DMSO, water or atmospheric O_2.

The reductive product of DMSO is dimethyl sulfide (DMS) which is challenging to isolate and spectroscopically analyze; hence diphenyl sulfoxide (DPSO)[159] was employed as the souce of oxygen in the reaction, since its reductive product, diphenyl sulfide (DPS), can be isolated and analyzed using NMR spectroscopy. Thus, benzyl phenyl ketone **4a** and diphenyl sulfoxide **22** were reacted in dioxane to afford benzil **3a** and DPS **23** in 92% and 79%, respectively. (**Scheme 49**). The reaction afforded a molar ratio (0.86:1) of **3a: 23** which substantiated the proposed mechanism of oxygen in **3a** arising from the DMSO/DPS.



23:**3a** = 0.79 mmol:0.92 mmol = 0.85:1 ≈

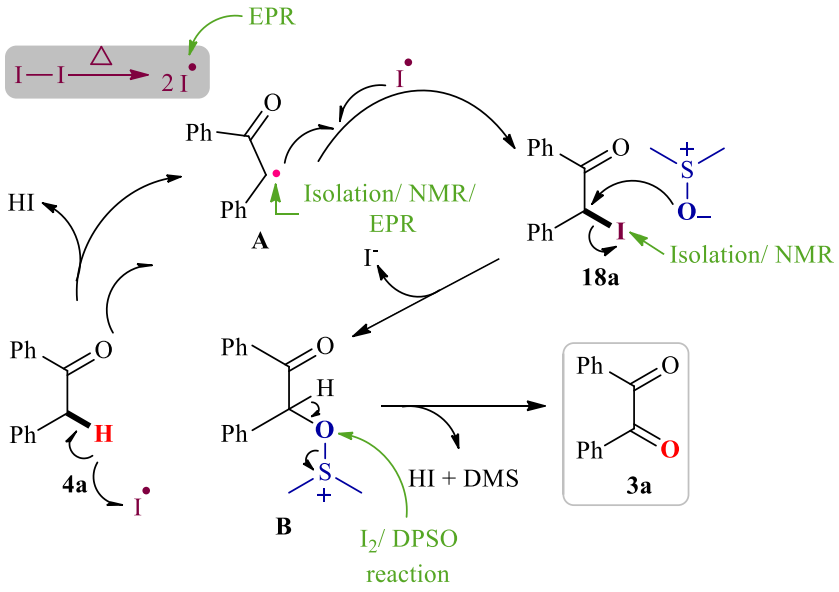
Scheme 49: Oxidation of benzyl phenyl ketone with DPSO under the optimized reaction conditions. The spectroscopic analysis of the reaction media identified the production of diphenyl sulfide **23**, substantiating the proposal of DMSO being the oxygen source in **3a**.

The results of this experiment indicated that one molecule of DMSO reacted with one molecule of benzyl phenyl ketone **4a** and the second oxygen atom in benzil **3a** originated from the dimethyl sulfoxide. Hence, the oxidation of **4a** is not solely a DMSO promoted reaction, since

a catalytic amount of water exists (as observed in **Scheme 48 –** toluene/water, 16% yield of **3a**), but relies, primarily, on DMSO to react with the α-iodoketone **18a** to furnish benzil **3a**.

4.3 Concluding Remarks to the In-depth Mechanistic Insight of the Iodine/DMSO Promoted Oxidation of Benzylic C_{sp}^3–H Bonds to Diketones

In summary, this research study has provided definitive insight into the mechanism of the direct benzyl C_{sp}^3–H oxidation of a benzyl aryl ketone, employing the I_2/DMSO system. The plausible reaction mechanism was proven to proceed through: iodine and benzylic radicals, an α-iodoketone, and 2-iodo-1,2-diphenylethanone as the key reactive intermediate, and oxidation *via* DMSO (the major source of oxygen in the α-diketone). Each reaction step and key intermediate was proven by means of isolation and spectroscopic techniques: EPR spectroscopy, NMR analysis, the judicious choice of radical spin traps and experimental conditions in order to support the proposed oxidation mechanism (**Scheme 50**). This study has, therefore, provided much needed insight into the direct oxidation of benzyl aryl ketones to afford synthetically useful α-diketones.



Scheme 50: Proposed reaction mechanism depicting the various techniques employed in order to detect and isolate the key reactive intermediates in the I_2/DMSO mediated oxidation of benzyl phenyl ketone **4a** to the corresponding diketone **3a**.

The results of the in-depth mechanistic insight into the iodine/DMSO oxidative system for the direct oxidation of the benzyl aryl ketone, benzyl phenyl ketone, to afford the diketone, benzil, was drawn up for publication and subsequently accepted by the journal *Tetrahedron*. The reference to this publication is given below and a copy of the article is available in Appendix A.

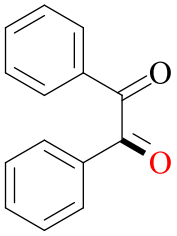
Reference:[160] J. Jayram, Bheki A. Xulu and V. Jeena, *Tetrahedron* **2019**, 75, 130617

4.4 Experimental

4.4.1 General Information

All reagents were purchased without further purification. All ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Advance III spectrometer operating at 400 MHz. Chemical shifts (δ) were reported in ppm using the Dimethyl Sulfoxide-d6 (DMSO-d6) residual peak (δ 2.50) or Chloroform ($CDCl_3$) residual peak (δ 7.26) for ^{1}H NMR. Chemical shifts of ^{13}C NMR were reported, relative to DMSO-d6 (δ 39.51) or $CDCl_3$ (δ 77.0). 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 unit (Hz). High-resolution/Low-resolution electron-spray ionization (ESI) mass spectra were recorded on a time-of-flight (TOF) micromass spectrometer. Infra-Red (IR) spectra were recorded on Carey 630 FTIR. Absorption maxima are expressed in wavenumbers (cm^{-1}). Melting points were determined using Kofler hot-stage melting apparatus. EPR measurements were conducted using a Bruker EMX Ultra X spectrometer.

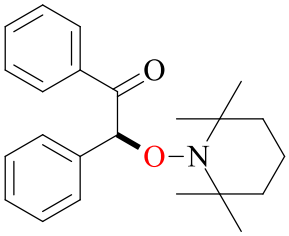
4.4.2 General Procedure for the Oxidation of Benzyl Phenyl Ketone with I_2/DMSO to Afford Benzil (**3a**).



Benzyl phenyl ketone (1 mmol) and iodine (0.5 mmol) were mixed in a round bottomed flask with 1 mL DMSO and heated to 100 °C for 2h. After cooling, a $Na_2S_2O_3$/water solution was added to the reaction mixture, extracted with dichloromethane and dried over anhydrous $MgSO_4$. Removal of the solvent, under vacuum, afforded the crude product which was purified by column chromatography using 5:1 hexane: ethyl acetate.

Benzil **3a** (0.202 g, 96%) was obtained as a yellow solid:[150] **Mp** 94-96 °C; **υ_{maz} (neat, cm^{-1}):** 3064, 1655, 1590, 1449, 1208. **^{1}H NMR (400 MHz, $CDCl_3$):** 7.95-7.93 (m, 4H), 7.83-7.78 (m, 2H), 7.66-7.62 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$): 129.5, 129.5, 132.2, 135.5, 194.8. **GC-MS (*m/z*):** 210.0 (10), 105.0 (100).

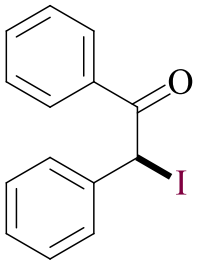
4.4.3 General Procedure for the Synthesis of 1, 2-Diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)ethanone (**17a**).



Benzyl phenyl ketone (1 mmol), TEMPO (1 mmol) and iodine (0.5 mmol) were mixed in a round bottomed flask with 1 mL DMSO and heated to 100 °C for 2h. After cooling, a $Na_2S_2O_3$/water solution was added to the reaction mixture, extracted with dichloromethane and dried over anhydrous $MgSO_4$. Removal of the solvent under vacuum, afforded the crude product which was purified by column chromatography using 9:1 hexane: ethyl acetate.

1, 2-Diphenyl-2-((2, 2, 6, 6-tetramethylpiperidin-1-yl)oxy)ethanone 17a (0.163 g, 46%) was obtained as a white solid:[111] **Mp** 229-231 °C; **υ_{maz} (neat, cm^{-1}):** 3068, 2922, 2852, 1667, 1596, 1446, 1262, 1042; **^{1}H NMR (400 MHz, $CDCl_3$):** 8.01-7.99 (m, 2H), 7.43-7.39 (m, 3H), 7.34-7.30 (m, 2H), 7.22-7.18 (m, 2H), 7.14-7.10 (m, 1H), 5.92 (s, 1H), 1.38-1.37 (m, 6H), 1.24-1.11 (m, 6H), 0.92 (m, 3H), 0.73 (m, 3H); **^{13}C NMR (400 MHz, $CDCl_3$):** 198.3, 137.8, 135.3, 132.9, 129.3, 128.3, 127.5, 127.2, 93.5, 60.0, 59.8, 40.3, 33.6, 33.3, 20.3, 20.2, 17.0; **HRMS (ESI-TOF) *m/z*:** calcd for $C_{23}H_{30}NO_2$ 352.2278, found 352.2277 $[M+H]^+$.

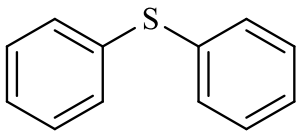
4.4.4 General Procedure for the Synthesis of α-Iodinated Intermediate 2-Iodo-1,2-diphenylethanone (**18a**).



Benzyl phenyl ketone (1 mmol) and iodine (0.5 mmol) were mixed in a round bottomed flask with 1 mL ethanol and heated to 100 °C for 2h. After cooling, the solvent was removed under vacuum, affording the crude product which was purified by column chromatography using 9:1 hexane: ethyl acetate.

2-Iodo-1, 2-diphenylethanone 18a (0.085 g, 26%) was obtained as a yellow solid:[141] **Mp** 92-93 °C; **υ_{maz} (neat, cm^{-1}):** 3056, 1670, 1210, 746; **^{1}H NMR (400 MHz, $CDCl_3$):** 8.06-8.04 (m, 2H), 7.66-7.58 (m, 3H), 7.51-7.47 (m, 2H), 7.39-7.30 (m, 3H), 6.65 (s, 1H); **^{13}C NMR (400 MHz, $CDCl_3$):** 27.8, 128.7, 128.8, 128.9, 129.0, 129.5, 133.6, 133.7, 137.4, 192.3; **HRMS (ESI-TOF) *m/z*:** $[M + Na]^+$ Calcd for $C_{14}H_{11}IONa^+$ 344.9755; found 344.9745.

4.4.5 General Procedure for the Oxidation of Benzyl Aryl Ketones by Diphenyl Sulfoxide (DPSO) to Afford Diphenyl Sulfide (DPS) (**23**).



Benzyl phenyl ketone (1 mmol), diphenyl sulfoxide (2 mmol) and iodine (0.5 mmol) were mixed in a round bottomed flask with 1 mL dioxane and heated to 100 °C for 2h. After cooling, a $Na_2S_2O_3$/water solution was added to the reaction mixture, extracted with dichloromethane and dried over anhydrous $MgSO_4$. Removal of the solvent, under vacuum, afforded the crude product which was purified by column chromatography using 9:1 hexane: ethyl acetate to afford benzil **2** (0.194 g, 92%) as a yellow solid and diphenyl sulfide **7**.

Diphenyl sulfide 23 (0.147 g, 79%) was obtained as a clear liquid:[161] **Mp** 60-62 °C; **υ_{maz} (neat, cm^{-1}):** 3056, 1578, 1474, 1438, 1023; **^{1}H NMR (400 MHz, DMSO-d6):** 7.2-7.41 (m, 10H); **^{13}C NMR (400 MHz, DMSO-d6):** 127.4, 129.5, 130.7, 134.8; **HRMS (ESI-TOF) *m/z*:** $[M]^+$ Calcd for $C_{12}H_{10}S$ 186.0503; found 186.0507.

5 Conclusion

The current thesis, entitled: “the direct oxidation of C_{sp}^3-H benzyl aryl ketones to 1,2-diaryl diketones as a key step for the multi-component synthesis of 2,4,5-trisubstituted-1*H*-imidazoles”, is centred around the development of environmentally benign multi-step syntheses in a single step, employing multi-bond forming methodologies such as: one-pot domino sequences, multi-component reactions and one-pot sequential reactions for the preparation of substituted 2,4,5-trisubstituted-1*H*-imidazoles.

This research project commenced with the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles *via* a simple and efficient one-pot multicomponent reaction. A catalytic copper(II) catalyzed aerobic oxidation of benzyl aryl ketones, instead of the traditional diketone, was employed under mild reaction conditions and without the necessity of additional Lewis acids or external additives. The optimized reaction tolerated several functional groups (X, [X= halogen], -nitro, -furyl, -ethyl, -cyclohexyl) to afford an array of diversely substituted 2,4,5-trisubstituted-1*H*-imidazoles in moderate to good yields (21-87%).

The subsequent study describes an improved, non-toxic, acid and transition metal-free approach to access 2,4,5-trisubstituted-1*H*-imidazoles *via* a sequential one-pot reaction. The developed protocol commenced from an iodine/DMSO mediated oxidation of benzyl aryl ketones to the corresponding 1,2-diaryl diketone, *in situ*, to couple with aldehydes and ammonium acetate to afford the desired *N*-heterocyclic compounds. Various diversely substituted 2,4,5-trisubstituted-1*H*-imidazoles were furnished in acceptable yields (35-86%) under mild reaction conditions and improved reaction times. A series of novel 2,4,5-trisubstituted-1*H*-imidazoles, with possible drug-like properties, were synthesized in good yields in an effort to establish a substrate scope. A domino convergent oxidation of two different substrates, benzyl phenyl ketone and benzyl alcohol, was simulateously attempted, which, subsequently, afforded the imidazole end-product in an isolated yield of 48%. Finally, a series of control experiments was undertaken in order to gain insight into the reaction mechanism to yield the desired imidazole.

The final chapter provides an in-depth mechanistic study in order to provide definitive proof for the direct oxidation of a benzyl aryl ketone, to the corresponding diketone, under the iodine/DMSO oxidative system. The series of experiments undertaken proved that the reaction proceeds *via* consecutive iodination/ oxidation/ cyclization involving iodine and benzylic radicals, an α-iodinated ketone, 2-iodo-1,2-diphenylethanone (as the reactive intermediates) and DMSO as the major source of oxygen in the product. Various isolation and spectroscopic techniques (EPR, NMR), radical spin traps and experimental conditions were carefully chosen so as to lend support to the proposed oxidation mechanism.

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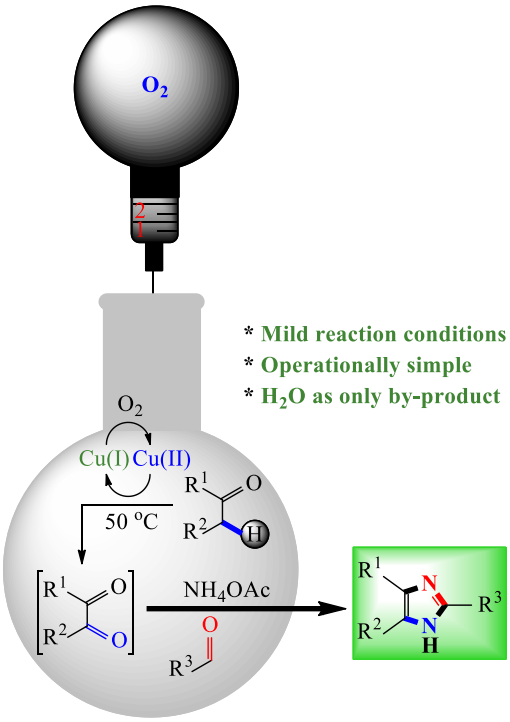
Appendix

Publication 1

Copper-Catalyzed Aerobic Benzylic sp^3 C-H Oxidation Mediated Synthesis of 2,4,5-Trisubstituted Imidazoles via a Domino Multi-component Reaction

Janeeka Jayram and Vineet Jeena

Green Chem., 2017, **19**, 5841-5845



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ARTICLE

Copper-catalyzed aerobic benzylic sp^3 C-H oxidation mediated synthesis of 2,4,5-trisubstituted imidazoles via a domino multi-component reaction

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An efficient and practical aerobic benzylic sp^3 C-H oxidation as a key step towards the domino multi-component synthesis of 2,4,5-trisubstituted imidazoles has been reported. This green methodology employs an inexpensive catalytic copper/oxygen system and proceeds under mild reaction conditions. A variety of substituted imidazoles are prepared in moderate to excellent yields from α-methylene ketones using this innovative methodology.

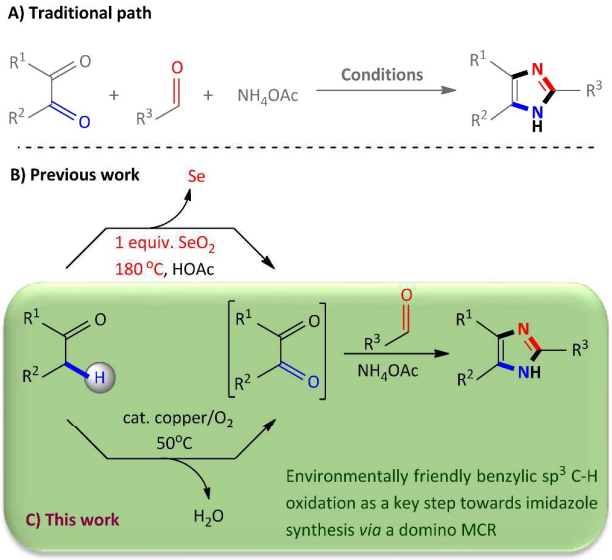
Introduction

Oxidation reactions are one of the most attractive methodologies for the formation of carbon-carbon (C–C) and carbon-heteroatom (C–X, X = N, O, S, etc.) bonds,[1] and their synthetic scope and utility have significantly advanced over the past decade.[2] More recently, there have been steadily growing demands for novel environmentally benign and cost-effective oxidation methods for the formation of complex molecules.[3] Accordingly, the well renowned tandem oxidation process (TOP) was developed as an effective method in the synthesis of a wide array of useful compounds.[4] This famous domino reaction, pioneered by the Taylor research group, involves an oxidation reaction, specific to the alcohol functional group, in which the carbonyl compound is trapped *in situ* leading to a range of efficient protocols for the one-pot preparation of synthetic targets, which are otherwise prepared *via* multi-step procedures.[5]

Apart from the commonly used alcohol functional group, hydrocarbons (R-H) provide the ideal reactant in terms of atom-economical synthesis of organic compounds.[6] Indeed, the synthetic scope and utility of direct sp^3 C-H oxidations have encouraged research in this area with numerous sp^3 C-H oxidation methods recently reported.[7] Given the popularity of the TOP, a new approach was developed which involved the trapping of a diketone from a sp^3 C-H oxidation and this methodology has been used to synthesize quinoxalines[8] and pyrazines[9] by trapping the generated 1, 2-diaryldiketone with *o*-phenylenediamine and ethylenediamine, respectively, as part of a simple, one-pot two component synthesis.

Imidazoles are a vital class of nitrogen-containing heterocycles that are present in numerous bioactive molecules and possess known biological and pharmacological activity.[10] Traditionally, the condensation of an α-diketone, aldehyde and ammonium acetate is the predominant method for the construction of imidazoles (Scheme 1, A).[11] However, most α-diketones are often not commercially available and their preparation process, suffer from several drawbacks such as (1) high catalyst loading; (2) harsh reaction conditions and (3) low product yields and tedious work-up procedures.[12] Therefore, if simple α-methylene ketones could be applied instead of α-diketones in this synthesis, it would be a more efficient methodology to access imidazoles.

Consequently, a selenium dioxide mediated sp^3 C-H oxidation strategy[13] was applied, within our research group,



Scheme 1 Different routes towards the synthesis of 2,4,5-trisubstituted imidazoles

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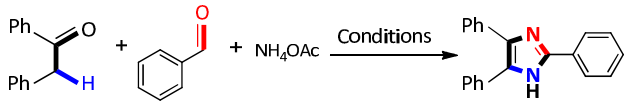
for the synthesis of substituted imidazoles (Scheme 1, B); since this reagent is well known in the synthetic organic chemistry community[14] and has been used to generate diketones in high yields *via* the oxidation of α-methylene ketones.[15] Unfortunately, although this methodology proves its efficiency, the synthetic procedure does not conform to all standards of a ''green'' chemical synthesis owing to the use of stoichiometric, toxic selenium dioxide, production of selenium waste and high reaction temperatures (180 °C).

Thus, in an effort to address the key challenges of the above approach, a more environmentally friendly and sustainable copper/molecular oxygen (Cu/O_2) catalytic system[16] was chosen for the synthesis of 2,4,5-trisubstituted imidazoles (Scheme 1, C). To test this hypothesis, we decided to monitor a test reaction between benzyl phenyl ketone, benzaldehyde and ammonium acetate under various reaction conditions.

Results and Discussion

Initially, our studies commenced by reacting benzyl phenyl ketone **1a** with benzaldehyde **2a** and ammonium acetate in the presence of molecular oxygen and a catalytic amount of copper(II) acetate monohydrate ($Cu(OAc)_2.H_2O$) in a range of environmentally friendly solvents at 50 °C for 24 hours. Encouragingly, the desired product 2,4,5-triphenylimidazole **3a** was obtained in satisfactory yields (Table 1, entries 1-3), however, no product was isolated in the presence of toluene as a solvent (Table 1, entry 4). As the reaction was affected by solvent choice, we decided to probe this approach further by utilizing dimethylformamide (DMF) as the reaction media, as many Cu/O_2 oxidation reactions proceed well in the presence of this solvent.[17] Using DMF as a solvent, the yield of the desired product increased to 77% (Table 1, entry 5). From this promising result, the prolonging of the reaction time to 28 hours only had a slight influence on the yield, with 80% of **3a** obtained (Table 1, entry 6). To gain further insight into the reaction system, control experiments were conducted in the absence of the copper catalyst (Table 1, entry 7) and in the presence of air (Table 1, entry 8), however, no product was detected. Replacing molecular O_2 with nitrogen (N_2) also resulted in no reaction (Table 1, entry 9). At this point, we were confident that the Cu/O_2 catalytic system was ideal for this transformation and we sought to further evaluate the reaction system. Next, various copper catalytic systems (Table 1, entries 10-13) were screened to further optimize the reaction conditions which resulted, to our delight, in copper (II) chloride dihydrate ($CuCl_2.2H_2O$) furnishing the desired product **3a** in an excellent isolated yield of 87%. Various synthetic procedures use fluctuating amounts of ammonium acetate depending on the reaction conditions employed to produce the desired product in maximum yield.[18] Thus, to complete our optimization study, the amount of ammonium acetate was varied, however, considerably lower yields were obtained when 5 and 2 equivalents were used (Table 1, entries 14-15) and as a result the molar ratio of benzyl phenyl ketone: aldehyde: ammonium acetate was kept at 1:1:10.

Table 1 Optimization of the reaction conditions for the formation of 2,4,5-triphenylimidazole from benzyl phenyl ketone **1a** *via* a domino multicomponent reaction[a]



1a **2a** **3a**

Entry	Catalytic system	Solvent (1 mL)	Yield (%)[b]
1	$Cu(OAc)_2.H_2O/O_2$	CH_3CN	61
2	$Cu(OAc)_2.H_2O/O_2$	EtOH	65
3	$Cu(OAc)_2.H_2O/O_2$	EtOAc	63
4	$Cu(OAc)_2.H_2O/O_2$	PhMe	N. R.
5	$Cu(OAc)_2.H_2O/O_2$	DMF	77
6[c]	$Cu(OAc)_2.H_2O/O_2$	DMF	80
7	O_2	DMF	N. R.
8	$Cu(OAc)_2.H_2O$/air	DMF	N. R.
9	$Cu(OAc)_2.H_2O/N_2$	DMF	N. R.
10	**$CuCl_2.2H_2O/O_2$**	**DMF**	**87**
11	$CuCl/O_2$	DMF	83
12	$Cu(NO_3)_2.6H_2O/O_2$	DMF	85
13	CuI/O_2	DMF	82
14[d]	$CuCl_2.2H_2O/O_2$	DMF	43
15[e]	$CuCl_2.2H_2O/O_2$	DMF	21

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), ammonium acetate (5.0 mmol), [Cu] (5 mol%)/O_2 (balloon), 50 °C for 24 h. [b] Isolated yield. [c] 28 h. Ammonium acetate ([d] 2.5 mmol, [e] 1.0 mmol). N. R. = No reaction.

Consequently, the conditions described in entry 10 were found to be optimal, allowing for maximum conversion into the desired product **3a**. This methodology proceeds well under mild reaction conditions (50°C) and produces spectroscopically pure imidazole upon recrystallization.

With the optimal reaction conditions in hand, the scope of the devised system was evaluated by varying the α-methylene ketone and aldehydes (Scheme 2). Benzaldehydes substituted with either electron-donating or electron-withdrawing functional groups in the *para* position reacted smoothly with **1a** to provide the corresponding 2,4,5-triarylimidazoles **3b-3e** in good to excellent yields (60-87%). Similar results were obtained upon substitution at the *meta* position of benzaldehyde (Scheme 2, **3f-3g**). In addition, *ortho*-substituted fluoro- and methoxybenzaldehyde delivered 2-(2-Fluorophenyl)-4,5-diphenyl-1H-imidazole **3h** and 2-(2-Methoxyphenyl)-4,5-diphenyl-1H-imidazole **3i** in a moderate yields (51% and 43%, respectively). In order to expand the scope of our methodology, heterocyclic and aliphatic aldehydes were evaluated and also furnished the desired imidazoles **3j-3l**, albeit in moderate yields. Next, reactions of benzaldehyde with substituted α-methylene ketones were investigated. Unfortunately, 2-butanone and acetophenone were not compatible with this transformation, even though various reaction conditions were attempted and only starting

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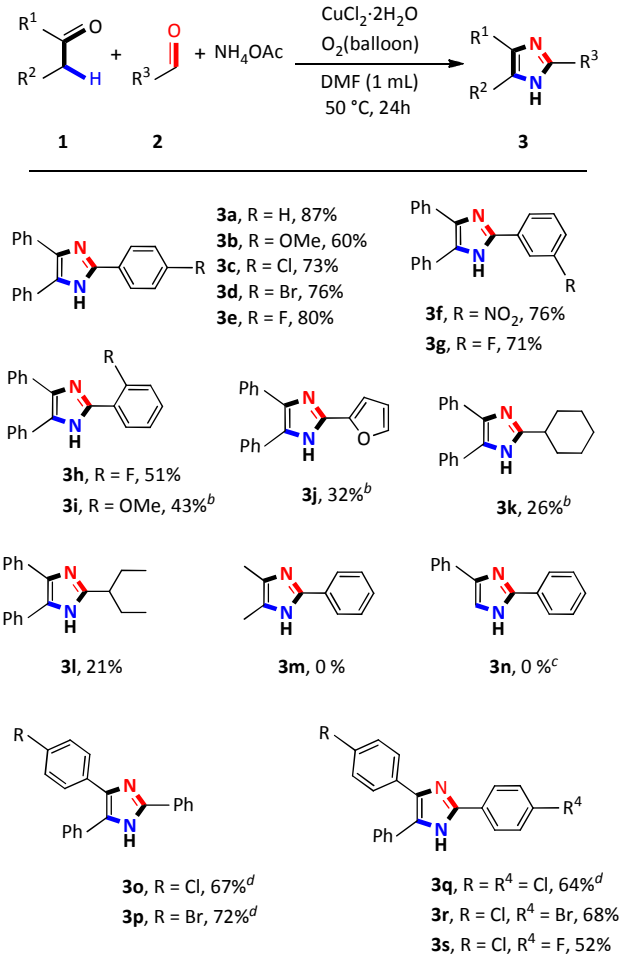
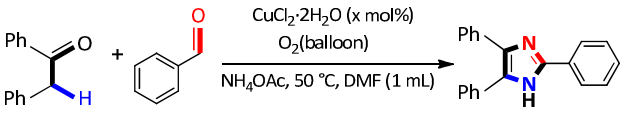
material was recovered (**3m-3n**).[19] 2-Phenylacetophenone substituted with *para*-Cl or Br groups reacted smoothly to furnish 2,4,5-triarylimidazoles **3o-3p** as mixtures of tautomers in good yields (see ESI). Subsequently, coupling 4-chloro-2-phenylacetophenone with *para*-halogen substituted benzaldehydes under the optimized reaction conditions successfully afforded the corresponding novel heterocyclic imidazoles **3q-3s** in moderate yields (52-68%). In particular, 2,4,5-triarylimidazoles **3r-3s** were isolated as indistinguishable tautomers (see ESI).



Scheme 2 Substrate scope. Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), ammonium acetate (5.0 mmol), $CuCl_2 \cdot 2H_2O$ (5 mol%), O_2 (balloon), DMF (1 mL), 50 °C, 24 h. [a] Isolated yield. [b] 10 mol% $CuCl_2 \cdot 2H_2O$. [c] 24 h, 72 h, $CuCl_2 \cdot 2H_2O$ (0.5 mmol). [d] Mixture of tautomers, (see ESI for details).

In order to further evaluate the developed system and improve reaction greenness, a catalytic loading study was conducted (Table 2, entries 1 – 6). The metal catalyst loading was decreased from 5 – 0.5 mol% and the product formation evaluated. As can be seen, the desired product can be obtained in satisfactory yields albeit with longer reaction times. Impressively, the reaction was effective when as little as 0.5 mol% of catalyst was used.

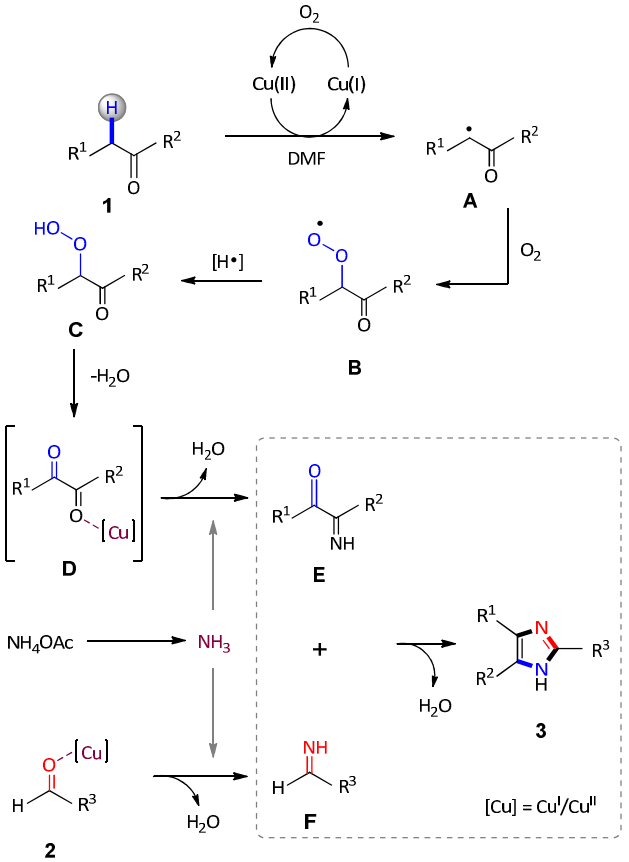
Table 2 Investigation of the catalyst loading[a]



Entry	Catalyst loading (x mol%)	Yield of **3a** (%)[b] 24 h	5 days
1	5	87	94
2	4	84	90
3	3	79	88
4	2	68	85
5	1	57	78
6	0.5	49	71

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), ammonium acetate (5.0 mmol) $CuCl_2.2H_2O/O_2$ (balloon). [b] Isolated yield.

Based on previous literature,[7a,8c,20] our proposed mechanism to rationalize product formation is presented in Scheme 3. The α-methylene ketone **1** undergoes oxidation with Cu(II) and deprotonation to generate benzyl radical **A**, which is trapped by molecular oxygen to afford the peroxide radical **B**.



Scheme 3 Plausible reaction mechanism for imidazole formation

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Upon capture of a hydrogen radical, to produce intermediate **C**, and elimination of water, the diketone **D** is produced. Concurrently, substrate **2** and the 1,2-diaryldiketone are activated by the Cu species and upon reaction with ammonia, produce imine intermediates **E** and **F**. Subsequently, the imine intermediates undergo cyclocondensation to afford the desired 2,4,5-trisubstituted imidazole **3**.

Conclusion

In summary, we have developed a simple, environmentally friendly and efficient procedure for the one-pot, multi-component synthesis of 2,4,5-triarylimidazoles using α-methylene ketones instead of the traditional diketone. This environmentally friendly approach provides access to substituted 2,4,5-triarylimidazoles in moderate to excellent yields using a catalytic amount of readily available and inexpensive copper catalyst in the presence of molecular oxygen under mild reaction conditions. The developed system was found to be applicable to a wide range of substrates and the catalyst loading could be further decreased with satisfactory yields obtained. Supplementary studies expanding the scope of this methodology as well as in-depth mechanistic studies are currently underway in our laboratories and will be reported in due course.

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Copper-catalyzed aerobic benzylic sp^3 C-H oxidation mediated synthesis of 2,4,5-trisubstituted imidazoles via a domino multi-component reaction

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Subject: Graphical abstract for Copper-catalyzed aerobic benzylic sp^3 C-H oxidation mediated synthesis of 2,4,5-trisubstituted imidazoles via a domino multi-component reaction

Dear Professor Li

Please find attached the graphical abstract.

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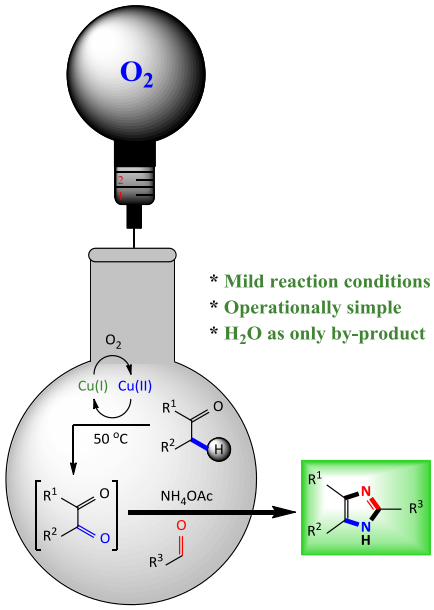

Kind Regards

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Publication 2

An Iodine/DMSO-Catalyzed Sequential One-Pot Approach to 2,4,5-Trisubstituted-1*H*-imidazoles From α-Methylene Ketones

Janeeka Jayram and Vineet Jeena

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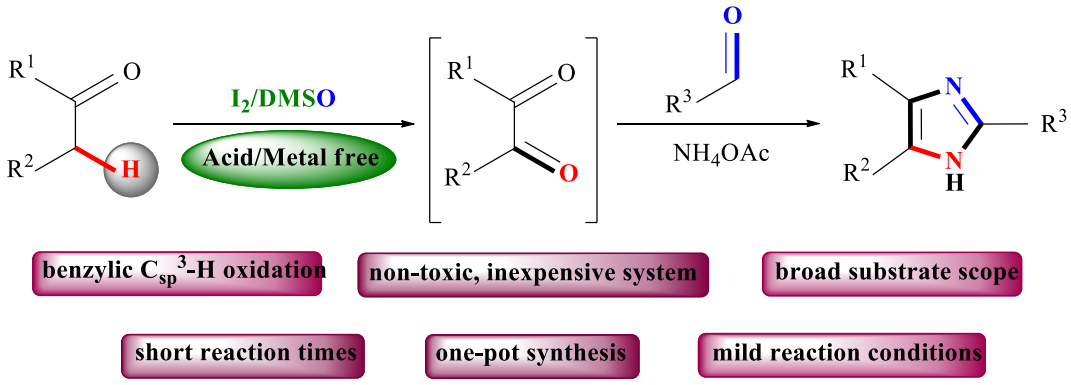

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An iodine/DMSO-catalyzed sequential one-pot approach to 2,4,5-trisubstituted-1*H*-imidazoles from α-methylene ketones†

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A sequential one-pot approach to 2,4,5-trisubstituted imidazoles has been developed from α-methylene ketones and aldehydes. This methodology employs air-moisture stable reaction conditions and an inexpensive iodine/DMSO system affording a diverse range of known and novel (substrate scope) 2,4,5-trisubstituted imidazoles in moderate to excellent yields. The iodine/DMSO system was extended to the domino convergent synthesis of two functionalized intermediates, benzil and benzaldehyde, to produce the final product.

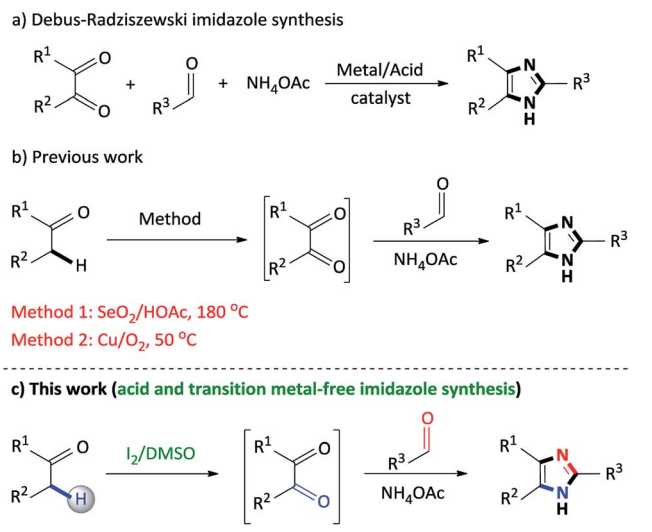
Introduction

2,4,5-Trisubstituted imidazoles occupy a special place in the realm of natural, pharmaceutical and synthetic organic chemistry, as this moiety exhibits numerous biological and pharmacological properties.[1] This particular *N*-heterocyclic family has expanded its applications in various fields such as cosmetics,[2] polymer chemistry,[3] agro chemicals,[4] materials chemistry (OLEDS, optical electronics, dye sensitized solar cells),[5] photography as photosensitive compounds[6] and industry as a corrosion inhibitor of certain transition metals.[7] Accordingly, synthetic routes to access 2,4,5-trisubstituted imidazoles are of vital importance and thus, develop on a daily basis.

The classical approach to assemble trisubstituted imidazoles involves the cyclocondensation of an α-diketone, aldehyde and ammonium acetate using transition metal catalysts or acidic media (Scheme 1a).[8] However, several of these transformations involve harsh reaction conditions, multistep synthetic operations, tedious isolation procedures and low yields. In particular, while synthetically useful, such methodologies are limited to accessibility of starting materials which in turn restrict product diversity.[9]

Recently, the selective oxidation of non-activated carbon–hydrogen (C–H) bonds has become an area of profound interest in contemporary organic synthesis toward the formation of new carbon–carbon (C–C) and carbon–heteroatom (C–X, X = N, O, S, *etc.*) bonds.[10] Specifically, the direct oxidation of unreactive benzylic C_{sp^3}–H bonds has received significant research interest to assemble C–N bonds, since it represents an atom-economical strategy.[11] Within this context, numerous innovative systems for the oxidation of α-methylene ketones to diketones have been reported such as $Cu(OAc)_2/Ph_3P$,[12] $Cu(OAc)_2 \cdot H_2O/K_2CO_3$,[13] DMSO/$KHCO_3$ (ref. 14) KO^{t}Bu/18-Crown-6/O_2,[15] $Pd(OAc)_2$/triazole ligand[16] and CuO/I_2/DMSO.[17]

Our research group has recently developed a new type of one-pot domino process to synthesize 2,4,5-trisubstituted imidazoles through a SeO_2/HOAc (Scheme 1b, Method 1) mediated oxidative cyclization from readily available α-methylene ketones and aldehydes.[18] However, the notable disadvantages of this protocol is the stoichiometric use of toxic selenium dioxide, selenium waste, acidic media and high reaction temperatures. Thus, in an effort to address the factors above, a copper/O_2 (Scheme 1b, Method 2)[19] methodology was developed, however, while this approach proves its efficiency, the use of a transition



Scheme 1 Synthetic routes toward the preparation of 2,4,5-trisubstituted imidazoles.

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metal catalyst detracts from this synthetic procedure. As a result, there is scope for further improvements toward the development of non-toxic, acid and metal-free syntheses using simple, inexpensive reagents and convenient procedures, in which the above mentioned drawbacks can be addressed.

In this context, the concept of transition metal-free C–H oxidation reactions is currently an active area of research and swiftly growing field in synthetic organic chemistry.[20] Notably, in recent years, molecular iodine (I_2) has proven to be an excellent catalyst for various organic transformations owing to its inexpensive, non-toxic properties and mild Lewis acidity.[21] Additionally, dimethylsulfoxide (DMSO) is an inexpensive and environmentally friendly polar aprotic compound that performs a versatile role as a solvent, oxidant and oxygen source in various organic syntheses.[22] In recent times, the iodine/DMSO combination has received considerable attention, in synthetic organic chemistry, as an effective and eco-friendly oxidative system as it has effected numerous organic transformations.[23]

In continuation of our studies on nitrogen heterocyclic synthesis,[24] we herein report an improved, non-toxic, acid and transition metal free, I_2/DMSO promoted coupling of benzylic C_{sp^3}–H α-methylene ketones with aldehydes to synthesize 2,4,5-trisubstituted imidazoles (Scheme 1c).

Experimental

Typical procedure for the I_2/DMSO-catalyzed reaction of α-methylene ketones, aldehydes and ammonium acetate

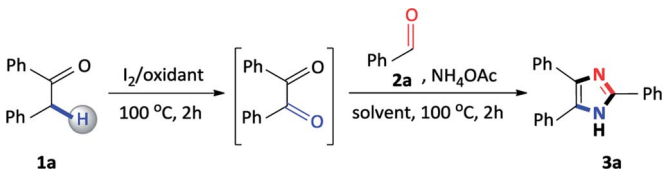
2-Phenylacetophenone (196 mg, 1.0 mmol) and iodine (126 mg, 0.5 mmol) were mixed in a round bottomed flask with 1 mL DMSO and heated to 100 °C for 2 hours. Thereafter, benzaldehyde (102 μL, 1.0 mmol), ammonium acetate (770 mg, 10 mmol) and ethanol (2 mL) were sequentially added and the mixture heated to 100 °C for a further 2 hours. After cooling, a $Na_2S_2O_3$/ice water solution was added to the reaction mixture to yield the crude product which was filtered, air dried and recrystallized from ethanol to afford the desired product.

The detailed characterization data for **3a–3w** are provided in the ESI.†

Results and discussion

Initially, our studies commenced using benzyl phenyl ketone **1a** and benzaldehyde **2a** as a model substrate and the results are presented in Table 1. Firstly, **1a**, **2a**, ammonium acetate and I_2 were added to DMSO and the mixture was heated at 100 °C for 4 hours, however, the reaction failed to proceed and no product was detected (Table 1, entry 1). Due to the failure of this reaction, we focused on sequential additions and accordingly, we attempted a reaction with **1a** and I_2 in DMSO, and heated at 100 °C for 2 hours, followed by the addition of **2a** and ammonium acetate at 100 °C for a further 2 hours. Encouragingly, the expected 2,4,5-triphenylimidazole **3a** was obtained in an isolated yield of 54% (Table 1, entry 2). Accordingly, we focused our studies on a sequential one-pot approach to prepare these scaffolds as this seemed to be the most viable synthetic route. In general, 2,4,5-trisubstituted imidazole syntheses proceed well

Table 1 Reaction optimization for the formation of 2,4,5-triphenylimidazole[a]



1a 3a

Entry	I_2 (equiv.)	Oxidant (1 mL)	Solvent (2 mL)	Yield[b] (%)
1[c]	0.5	DMSO	—	—
2	0.5	DMSO	—	54
3	0.5	DMSO	MeOH	68
4	0.5	DMSO	i-PrOH	54
5	**0.5**	**DMSO**	**EtOH**	**82**
6	0.25	DMSO	EtOH	74
7	0.10	DMSO	EtOH	32
8	—	DMSO	EtOH	—
9	0.5	DMF	EtOH	—
10	0.5	CH_3CN	EtOH	—
11	0.5	PhMe	EtOH	—
12[d]	0.5	DMSO	EtOH	62
13[e]	0.5	DMSO	EtOH	26

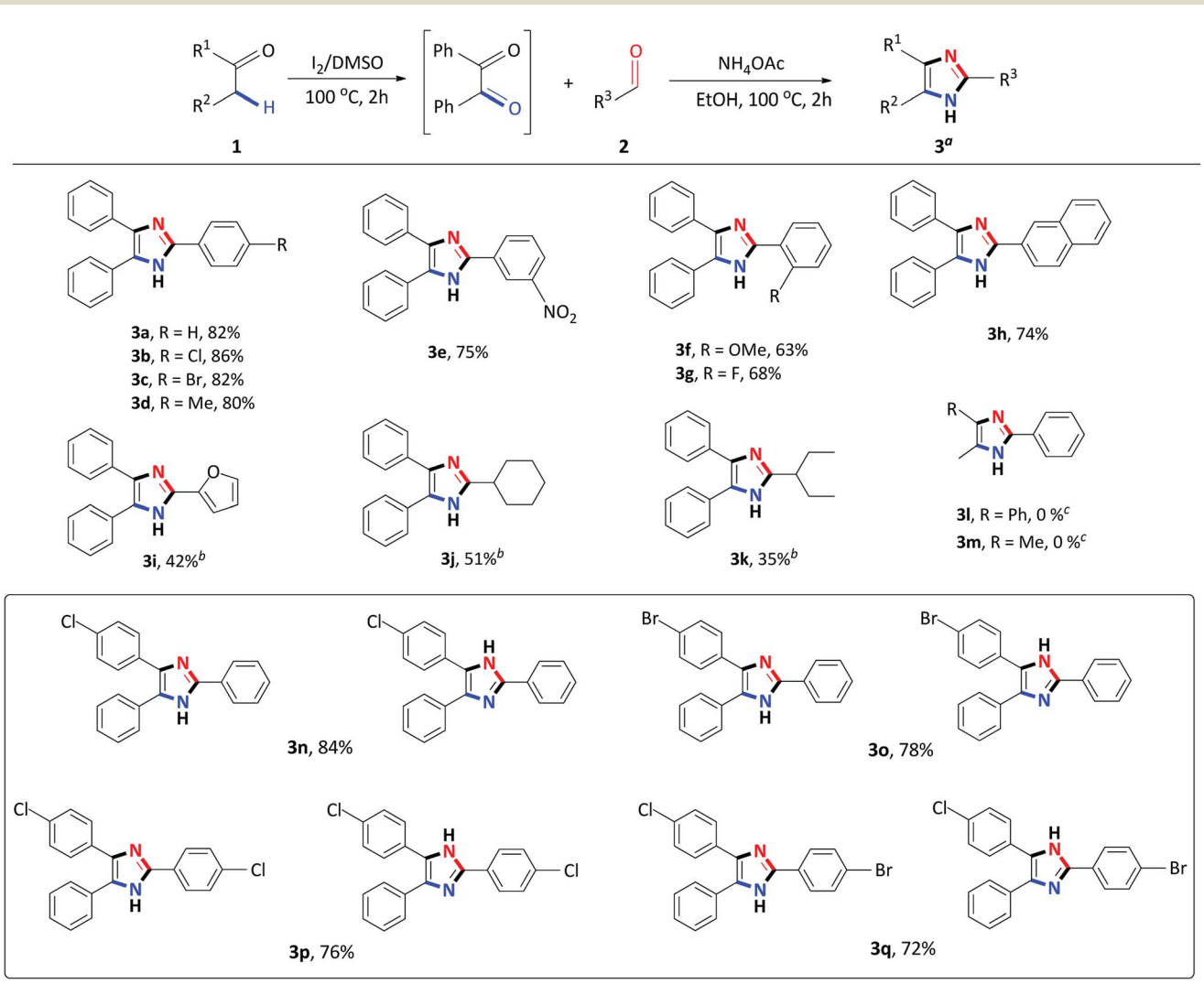
[a] Reaction conditions: Step I: **1a** (1 mmol), I_2 (0.5 mmol), 100 °C for 2 h; Step II: **2a** (1 mmol), NH_4OAc (10 mmol), 100 °C for 2 h. [b] Isolated yield. [c] One-pot reaction. [d] NH_4OAc (5.0 equiv.). [e] NH_4OAc (2.5 equiv.).

in the presence of an alcohol solvent as it is known to favour the coupling of a diketone, aldehyde and ammonium acetate.[25] Thus, in order to improve the yield, the reaction was attempted with methanol and iso-propanol affording **3a** in 68% and 54% yield respectively (Table 1, entries 3 and 4). Finally, ethanol was shown to be the best performing additive solvent as the yield significantly increased to 82% (Table 1, entry 5). Attempts were made to decrease the amount of iodine, however, 0.25 and 0.10 equivalents lowered the yield of the desired product to 74% and 32% respectively (Table 1, entries 6 and 7). Furthermore, performing the reaction in the absence of iodine resulted in no product formation thus, confirming its importance in this multicomponent reaction (Table 1, entry 8). The reaction also failed to produce the expected 2,4,5-triphenylimidazole **3a** when DMSO was replaced with alternative oxidants such as dimethylformamide (DMF), acetonitrile (CH_3CN) and toluene (PhMe) confirming its vital importance in the reaction (Table 1, entries 9–11). Many synthetic procedures use varying amounts of ammonium acetate depending on the reaction conditions employed to produce the desired product in maximum yield.[26] Thus, to complete the study, the amount of ammonium acetate was reduced to 5.0 and 2.5 equivalents, however, the yield of **3a** considerably decreased to 62% and 26% (Table 1, entries 12 and 13). To conclude, the conditions described in entry 5 were found to be optimal, allowing for maximum conversion to the desired product **3a**.

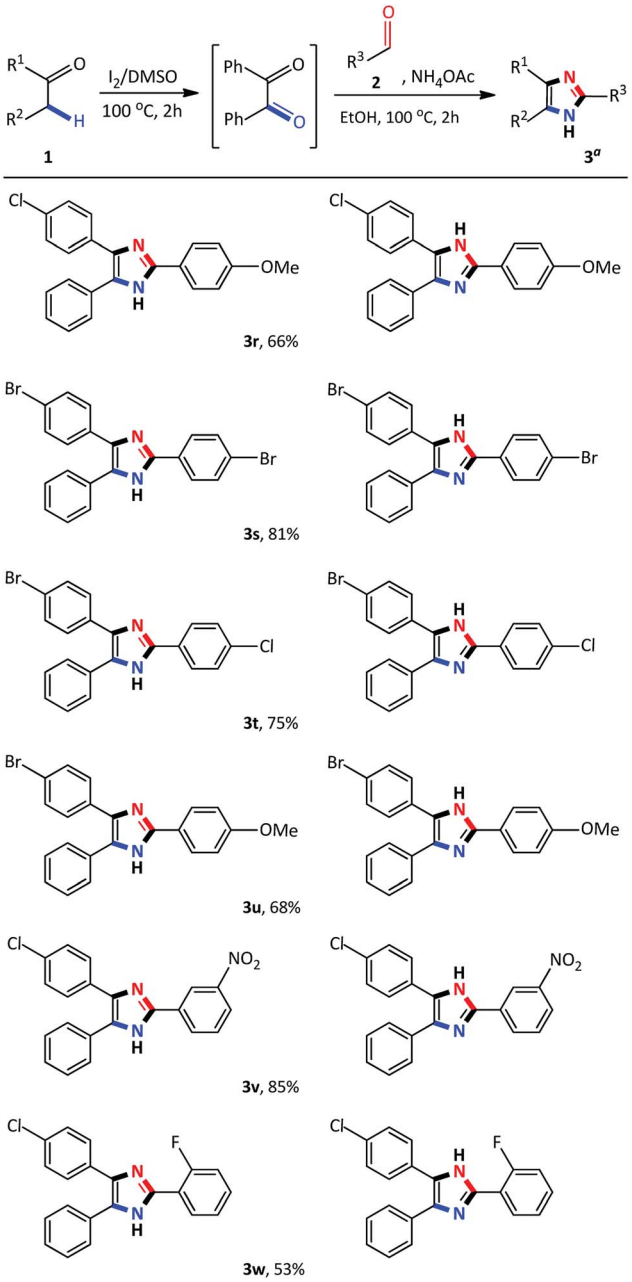
Having identified the optimized reaction conditions, the applicability of the devised system was evaluated by varying the α-methylene ketone and aldehyde (Scheme 2). The various

electron-withdrawing and electron-donating *para*-substituted benzaldehydes all underwent a smooth transformation with **1a** to provide the corresponding 2,4,5-trisubstituted imidazoles **3b–3d** in good to excellent yields (80–86%). Similar results were obtained upon substitution at the *meta* and *ortho* position of benzaldehyde producing good yields of 63–75% (Schemes 2 and **3e–3g**). In order to expand the scope of our methodology, a bulkier substrate, 2-naphthaldehyde was evaluated and also coupled smoothly with **1a** to afford 2-(naphthalene-2-yl)-4,5-diphenyl-1*H*-imidazole **3h** in a 74% yield. We further extended our methodology to heterocyclic and aliphatic aldehydes such as furfural, cyclohexanecarboxaldehyde and 2-ethylbutyraldehyde to produce the desired imidazoles **3i–3k** albeit, in moderate yields with prolonged reaction time. Next, reactions of benzaldehyde with substituted α-methylene ketones were investigated. Unfortunately, propiophenone and 2-butanone were not compatible with this system, and only starting material was recovered. Benzyl phenyl ketone **1a** substituted with *para*-Cl or Br-groups reacted smoothly to furnish 2,4,5-trisubstituted imidazoles **3n–3o** in good to excellent yields (78–84%). Similarly, coupling 4-chloro-2-phenylacetophenone with *para* substituted benzaldehydes, under the optimized reaction conditions, successfully afforded the corresponding heterocyclic imidazoles **3p–3r** in good yields (66–76%). Compounds **3n–3r** were isolated as a mixture of tautomers due to the presence of the fluid hydrogen on the nitrogen atom.

Recently, several 2,4,5-trisubstituted imidazoles were shown to have activity against malarial strains owing to the novelty of the chemotype.[27] As a result, in order to enhance the diversity and thus the possible biological relevance of the imidazole scaffold, we decided to establish substrate scope with this strategy which is not known in literature. As a result, a series of novel 2,4,5-trisubstituted imidazoles **3r–3w** were synthesized as a mixture of tautomers in good to excellent yields (53–85%) (Scheme 3). Consequently, this atom-economical synthetic procedure overcomes the limitations of previous methodologies which are restricted to the accessibility of starting materials, thus creating a new avenue to synthesize numerous novel imidazole derivatives yielding drug like properties. Next, we turned our attention to the domino convergent synthesis of two

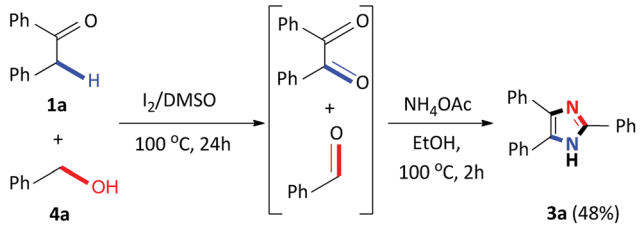


Scheme 2 Step I: **1** (1 mmol), I_2 (0.5 mmol), DMSO (1 mL), 100 °C for 2 h; Step II: **2** (1 mmol), NH_4OAc (10 mmol), EtOH (2 mL), 100 °C for 2 h. [a]Isolated yield. [b]Step II: 24 h. [c]Step I: 24 h.



Scheme 3 Synthesis of novel 2,4,5-trisubstituted imidazoles. Step I: **1** (1 mmol), I_2 (0.5 mmol), DMSO (1 mL), 100 °C for 2 h; Step II: **2** (1 mmol), NH_4OAc (10 mmol), EtOH (2 mL), 100 °C for 2 h. [a]Isolated yield.

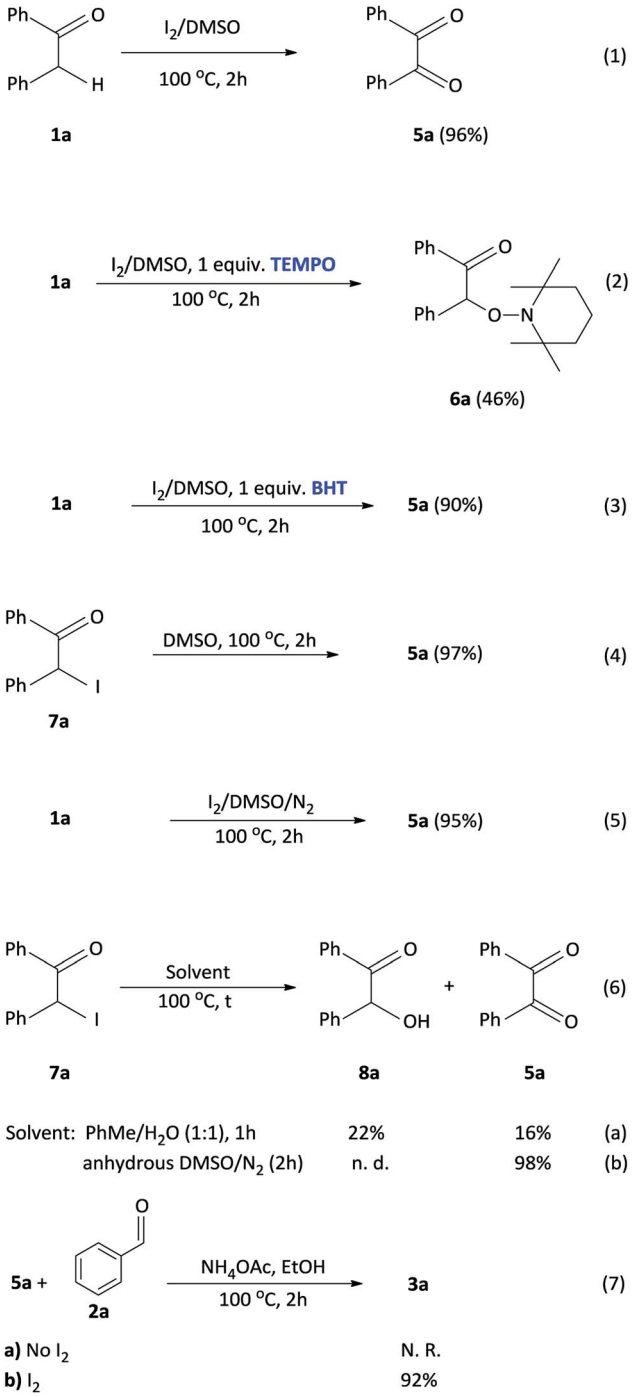
suitably functionalized intermediates, benzil and benzaldehyde, to converge onto the final product **3a**. As previously mentioned, the I_2/DMSO system is able to effect numerous organic transformations, hence, we rationalized that this system could simultaneously oxidize the benzyl phenyl ketone **1a** and benzyl alcohol **4a**, in the same reaction vessel, to produce the diketone and aldehyde which will subsequently form the desired imidazole using our devised system. To test this hypothesis we mixed benzyl phenyl ketone **1a** and benzyl alcohol **4a** in the presence of I_2/DMSO and heated the mixture at 100 °C for 24 hours to form the corresponding diketone and aldehyde. Thereafter, ammonium acetate and ethanol were



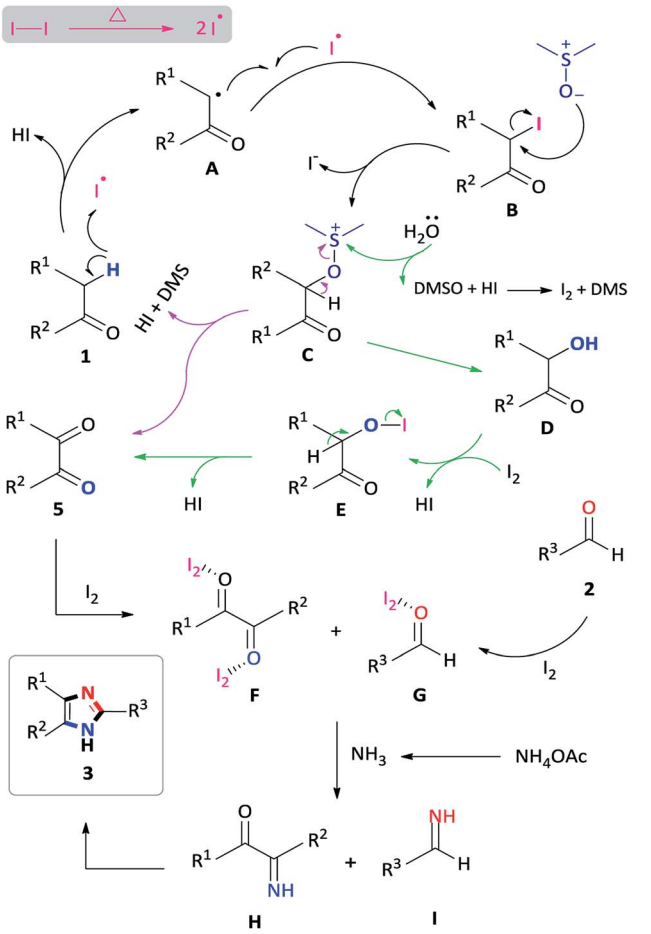
Scheme 4 Domino convergent synthesis of 2,4,5-triphenyl imidazole **3a**.

added to the reaction and heated at 100 °C for a further 2 hours to afford **3a** in an isolated yield of 48% (Scheme 4). This result illustrates that the I_2/DMSO system can successfully oxidize two different substrates simultaneously, in the same reaction vessel, for convergent synthesis into the desired product. We further anticipate that this result would inspire the design for more efficient and eco-friendly domino convergent syntheses for the preparation of complex products from simple materials *via* this innovative synthetic strategy.

To investigate a plausible reaction mechanism, a series of control experiments were performed (Scheme 5). In experiment 1, benzyl phenyl ketone **1a** was oxidized, in the presence of I_2/DMSO to benzil **5a** (96%) which indicates that the diketone is an intermediate in the reaction. Under the iodine-catalysis conditions, the addition of the radical inhibitor (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) afforded the capture adduct **6a** in 46% (experiment 2). The TEMPO-trapped reaction strongly supports the formation of **6a**, in which the radical is located at the α-position of benzyl phenyl ketone. In order to rule out the role of hydroxyl and peroxide radicals as an intermediate, a reaction of benzyl phenyl ketone **1a** with butylated hydroxytoluene (BHT)[28] in the presence of I_2 in DMSO was performed (experiment 3). In this reaction, the diketone was obtained in 90% yield, thereby proving non participation of peroxide radicals in our reaction. Mechanistically, we proposed that an α-iodinated species is the reactive intermediate in the oxidation of **1a** to afford the benzil intermediate **5a**. Accordingly, 2-iodo-1,2-diphenylethanone **7a** was synthesized[29] and subject to oxidation in DMSO affording benzil in 97% yield (experiment 4). Having completed the iodination reaction, we sought to determine the source of oxygen in the oxidation reaction. Accordingly, there are three potential oxygen sources in the reaction system: molecular oxygen in air, a trace amount of water in the solvent DMSO and, DMSO itself. The reaction proceeded well under a nitrogen atmosphere affording **5a** in 95% yield indicating that oxygen from the air does not participate in the reaction (experiment 5). When the reaction was performed in a toluene/water biphasic mixture, the hydroxylation product **8a** and benzil intermediate **5a** was obtained in 22% and 16% yield respectively, indicating that water plays a minor role in the oxidation reaction to afford **8a** which is further oxidized to provide **5a** (experiment 6). Furthermore, the reaction of **7a** in anhydrous DMSO under a nitrogen atmosphere afforded the diketone intermediate in 98% yield (experiment 6b). This preliminary result confirms that majority of the incorporated oxygen in the benzil intermediate is indeed



Scheme 5 Control experiments.



Scheme 6 Plausible mechanism for imidazole synthesis.

coming from DMSO. Finally, in order to understand the effect of iodine in the coupling reaction, **1a**, **2a** and ammonium acetate was reacted in ethanol to afford the corresponding 2,4,5-triphenylimidazole **3a**, however, no product was obtained (experiment 7a). Moreover, the addition of iodine resulted in 92% formation of **3a** indicating that iodine plays a role in the coupling reaction (experiment 7b). On the basis of the above observations, we propose a plausible mechanism of consecutive iodination/oxidation/cyclization for the synthesis of 2,4,5-trisubstituted imidazoles (Scheme 6). The reaction proceeds with an iodine assisted proton abstraction from the methylene position of **1** to generate the benzyl radical **A**.[30] Subsequently, iodination affords the corresponding α-iodinated intermediate, 2-iodo-1,2-diphenylethanone **B**, which reacts with DMSO to generate the active intermediate **C**. Two possible pathways could be proposed for the reaction of **C** to form the benzil intermediate **5**.[31] Based on control experiment 6, the minor pathway (green) involves a water attack on the sulfur cation of **C** to form the hydroxylation intermediate **D**, regenerating DMSO and HI for further cycle, which subsequently forms **5** through intermediate **E**.[32] On the other hand, the major pathway (purple) involves proton abstraction from the α-carbon of **C**, followed by the removal of HI and DMS, affording the desired benzil intermediate **5**. Accordingly, the oxidation of **B** is not solely a DMSO catalyzed reaction, since the catalytic water still exists, but majorly relies on the DMSO to react with the α-iodinated intermediate to afford the diketone intermediate **5**. In terms of the coupling reaction,[33] iodine is capable of binding to the carbonyl oxygen of the diketone intermediate **5** and aldehyde **2**, owing to its mild Lewis acidity, thus increasing the reactivity of the substrates,[34] which is supported by control experiment 7b. Moreover, iodine facilitates the formation of the imine intermediates **H** and **I** which condense to form the desired imidazole **3**.

Conclusion

In summary, an improved, non-toxic, acid and transition metal free, sequential one-pot approach to 2,4,5-trisubstituted imidazoles was developed using α-methylene ketones instead of the traditional diketone. This environmentally friendly I_2/DMSO system provides access to various substituted 2,4,5-trisubstituted imidazoles in moderate to excellent yields, under mild conditions and short reaction times. Moreover, a substrate scope was established by synthesizing novel 2,4,5-trisubstituted imidazoles, in good to excellent yields, which could potentially have biological properties. In addition, this approach could effect a domino convergent synthesis of the desired imidazole albeit in a moderate yield, through the simultaneous oxidation of benzyl phenyl ketone and benzyl alcohol. Supplementary studies expanding the scope of this methodology as well as in-depth mechanistic experiments are currently underway in our laboratories and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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Publication 3

Iodine/DMSO promoted oxidation of benzylic Csp^3–H bonds to diketones - A mechanistic investigation

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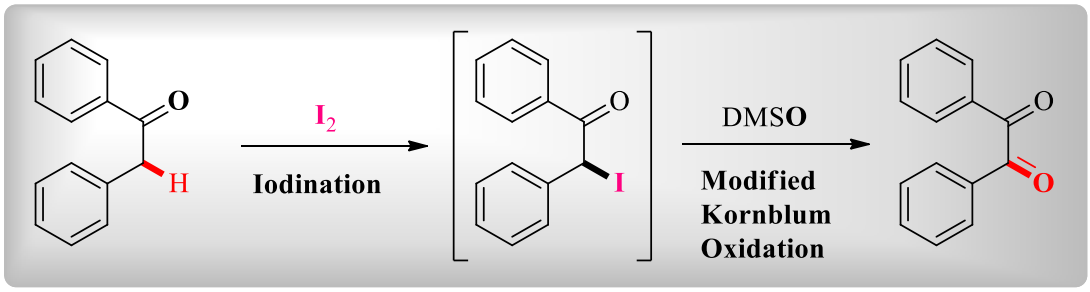

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Iodine/DMSO promoted oxidation of benzylic C^3_{sp}—H bonds to diketones – A mechanistic investigation

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ABSTRACT

This article describes a mechanistic investigation into the I_2/DMSO mediated benzylic C^3_{sp}—H oxidation of an α-methylene ketone. The electron paramagnetic resonance (EPR) spectrum centred at $g = 2.0011$ supports the involvement of iodine and benzylic radicals, as the α-iodinated compound 2-iodo-1,2-diphenylethanone was isolated as a key reactive intermediate. The oxidation reaction relies, primarily, on DMSO as a source of oxygen in benzil, proven by the reaction of benzyl phenyl ketone with diphenyl sulfoxide (DPSO).

1. Introduction

Conceptually, the direct transformation of C^3_{sp}—H bonds into carbon—carbon (C—C) and carbon—heteroatom (C—X, X = N, O, S) bonds offers new methodologies to prepare synthetically valuable molecules, as these approaches reduce pre-functionalization of starting materials while improving atom/step economy [1]. The chemically inert nature of C^3_{sp}—H bonds, however, due to: poor acidity, a high bond dissociation energy (BDE), thermodynamic stability and an unreactive molecular orbital profile, hinder the achievement of a complete regio-selectivity without requiring multiple synthetic steps [2]. Despite selectivity issues in recent decades, direct C^3_{sp}—H functionalization methods have developed substantially [3]. This, however, often necessitates the use of expensive transition metal catalysts, toxic reagents, high energy throughput and harsh reaction conditions which result in functional group incompatibility and limited substrate scope [4].

Accordingly, C^3_{sp}—H functionalization reactions, inspired by a rational design of experimental conditions, leading to significant improvement in both selectivity and applicability, present an ongoing challenge to researchers engaged in modern synthetic organic chemistry [5]. In context the highly appealing, direct and selective, oxidation of benzylic C^3_{sp}—H bonds is currently an active area of research, owing to its relevant approach to synthetically useful arylcarbonyl compounds such as α-diketones which often serve as important precursors for heterocyclic syntheses, with various attractive methodologies documented in literature [6].

In particular, molecular iodine (I_2) is now the most frequently used catalyst for many organic transformations and, is widely recognized as a replacement for environmentally unfriendly reagents, owing to its low toxicity, operational simplicity, high stability and various other user-friendly characteristics [7]. Moreover, dimethyl sulfoxide (DMSO) is an inexpensive and environmentally friendly dipolar aprotic solvent, oxidant and oxygen source in many organic syntheses [8]. Collectively, the I_2/DMSO combination is currently a distinct and complimentary alternative to unsustainable oxidation methodologies, since it has realized numerous organic transformations [9].

Accordingly, we have recently reported an I_2/DMSO oxidation of the benzylic C^3_{sp}—H bonds of benzyl phenyl ketone **1** to afford the corresponding α-diketone **2** in an isolated yield of 96% (Scheme 1) [10]. While we were satisfied with the excellent yield, our mechanistic insight into the reaction pathway was minimal. Thus, a significant point of interest, in the current study, was to provide definitive, mechanistic proof for the oxidation of the α-methylene ketone to the α-diketone using the I_2/DMSO system.

2. Results and discussion

Our theoretically proposed mechanism was anticipated to

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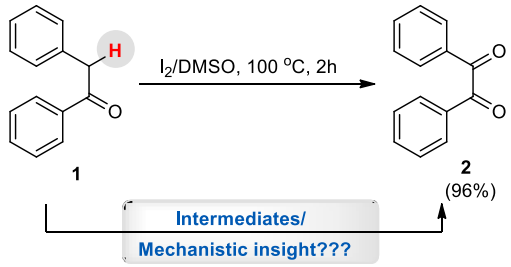


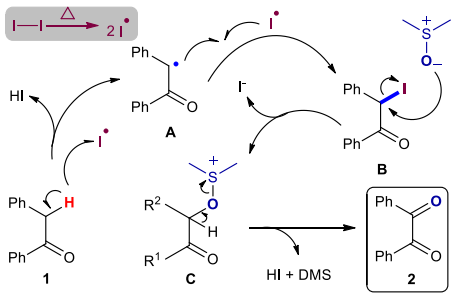
Scheme 1. I_2/DMSO oxidation of benzyl phenyl ketone **1** to benzil **2**.

proceed *via* initial iodination by molecular iodine (I_2), followed by a modified Kornblum oxidation in the presence of dimethyl sulfoxide (DMSO) as presented in Scheme 2. Consequently, a series of experimental reactions and spectroscopic techniques were undertaken to rationalize each step in the proposed reaction pathway for the formation of the α-diketone, benzil **2**.

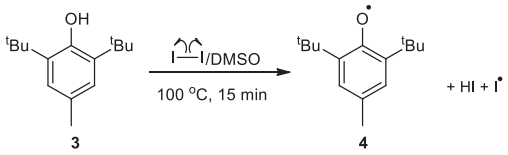
Based on literary studies, the homolytic cleavage of molecular iodine is known to occur under thermal conditions so as to afford iodine radicals [11]. Our mechanistic studies, therefore, commenced by exploring the formation of iodine radicals in our reaction, under thermal conditions, using Electron Paramagnetic Resonance (EPR) spectroscopy. Generally, free radicals are extremely unstable and a highly reactive species with a half-life of the order 10^{-9} s [12] hence butylated hydroxytoluene (BHT) was used as an anti-oxidant to detect the formation of iodine radicals in our reaction. BHT is a diamagnetic molecule and, accordingly, no EPR signal was observed in the absence of iodine in our experiments. Subsequently, molecular iodine and BHT were reacted in DMSO and the mixture heated to 100 °C (Scheme 3).

Following transfer into a flat quartz tube, an EPR signal, consistent with the presence of an organic radical, was observed (Fig. 1). The spectrum is characterized by four intense lines centred at $g = 2.0011$ which arises, as BHT quenches iodine radicals through *H*-atom transfer and generates a stable BHT radical species. The unpaired electron which is located on the sterically hindered oxygen atom, and protected by the tertiary butyl groups, is stabilized by the π-system of the benzene ring. The coupling of the electron to the three equivalent protons of the 4-methyl group gives rise to the recorded four-line EPR spectrum [13]. The EPR spectrum and the *g*-value for the BHT radical, obtained under our reaction conditions, are comparable with the experimental data provided in literature [14,15]. This result therefore correlates with the formation of a phenoxy radical ($g = 2.0010–2.0091$, RPhO·) [16], which subsequently implies the presence of iodine radicals in our reaction.

Since the iodine radical was detected using EPR spectroscopy, this indicates that the oxidation reaction is initiated by the thermal homolytic cleavage of molecular iodine supporting a radical



Scheme 2. Plausible mechanism for the I_2/DMSO oxidation of benzyl phenyl ketone **1**.



Scheme 3. Formation of oxygen radical from the reaction of I_2 and BHT in DMSO.

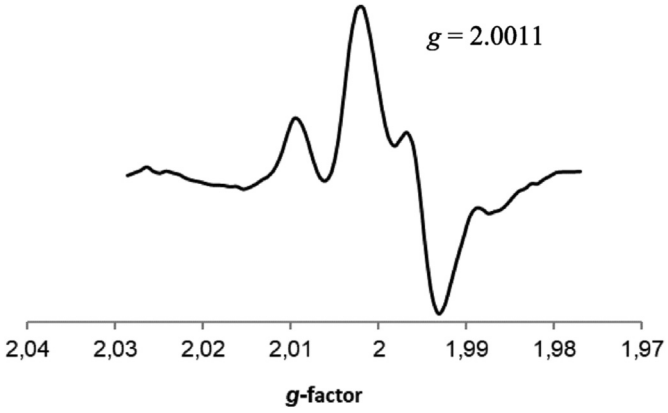


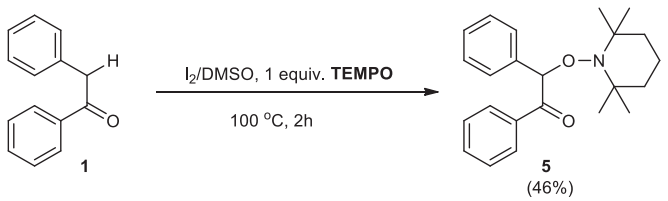
Fig. 1. EPR spectrum of a heated I_2/BHT sample in DMSO.

mediated mechanism. The presence of iodine radicals in the reaction infers the formation of a benzylic radical on benzyl phenyl ketone **1**. Consequently, an iodine radical assisted proton abstraction from the α-methylene position of **1** was proposed to generate benzylic radical **A**. As a result, we aimed to trap the benzylic radical using the spin trap (2, 2, 6, 6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and, under the standard reaction conditions, benzyl phenyl ketone, iodine and the radical inhibitor TEMPO were added to DMSO and heated to 100 °C for 2 h, affording the capture product **5** in 46% yield (Scheme 4).

The singlet at 5.92 ppm [17] in the NMR spectrum corresponds to the α-proton (C–H) of 1, 2-diphenyl-2-((2, 2, 6, 6-tetramethylpiperidin-1-yl)oxy)ethanone **5** (Fig. 2), indicating the formation of the C–O bond between the benzylic radical of intermediate **A** and the oxygen radical of TEMPO.

While the TEMPO trapped reaction in Scheme 4 theoretically supports the formation of **A**, in which the radical is located on the α-position of **1**, this experiment does not necessarily lead to this conclusion. It has been reported that in the presence of a halogen co-catalyst [18], TEMPO is readily oxidized to the corresponding *N*-oxoammonium cation as shown in Scheme 5.

Additionally, it is known that *N*-oxoammonium cations, upon heating, react with enolizable ketones to generate the α-TEMPO ketone **5** (Scheme 6). This is the *same* end product as though the α-benzylic radical **A** was hypothetically trapped by TEMPO itself. It was, however, noted that the conversion to the *N*-oxoammonium



Scheme 4. Reaction of benzyl phenyl ketone **1** with TEMPO to afford 1,2-diphenyl-2-((2, 2, 6, 6-tetramethylpiperidin-1-yl)oxy)ethanone **5**.

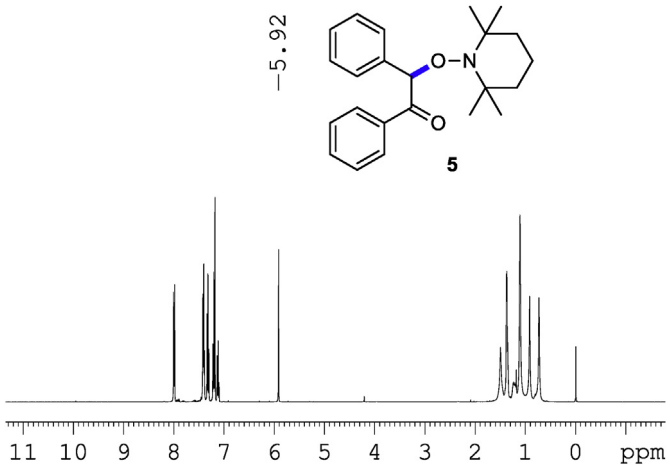
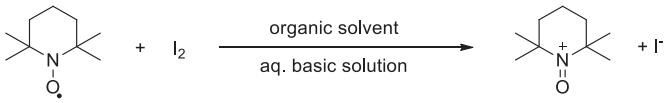
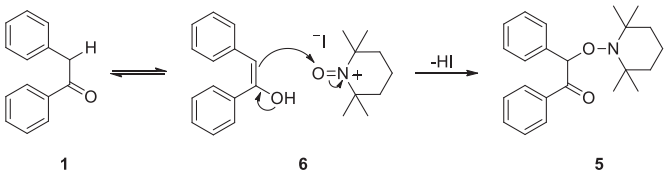


Fig. 2. NMR spectrum of 1,2-diphenyl-2-((2, 2, 6, 6-tetramethylpiperidin-1-yl)oxy) ethanone **5**.



Scheme 5. Iodine catalyzed *N*-oxoammonium cation generation.



Scheme 6. *N*-oxoammonium catalyzed oxidation of enolizable **6**.

salt is significantly influenced by the pH of the applied reaction media and the addition of an aqueous solution of base is necessary to achieve the required conversion [19].

Thus, in order to support the involvement of iodine and benzylic radicals in our reaction, supplementary studies were undertaken to rule out the formation of the *N*-oxoammonium salt. This was achieved by monitoring the TEMPO radical using EPR spectroscopy. Initially, molecular iodine and TEMPO were reacted in DMSO under the optimized reaction conditions to afford the EPR spectrum, displayed in Fig. 3. An intense triplet signature is ascribed to the stable free radical of TEMPO [20], indicating that TEMPO was not

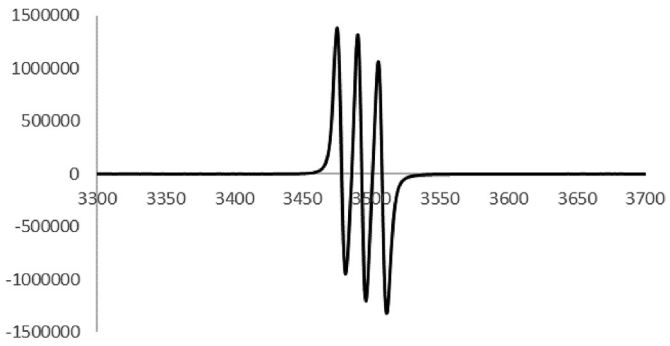


Fig. 3. EPR spectrum for the reaction of iodine and TEMPO in DMSO.

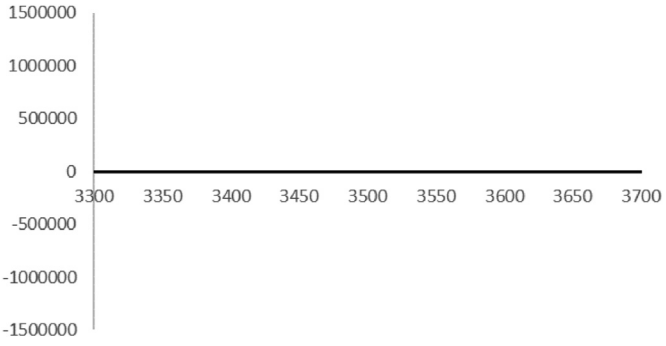


Fig. 4. EPR spectrum for the reaction of iodine and TEMPO with aqueous $NaHCO_3$.

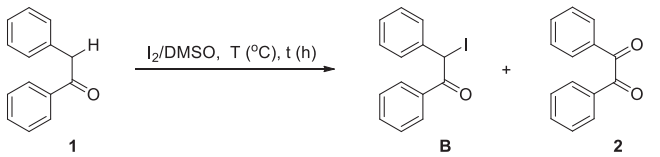
oxidized by molecular iodine upon heating within the elapsed time of the experiment.

The reaction was repeated with the addition of an aqueous solution of sodium bicarbonate ($NaHCO_3$), followed by heating for 2 h and analyzed using EPR spectroscopy. This resulted in the disappearance of the characteristic TEMPO signal, indicating the formation of the *N*-oxoammonium cation (Fig. 4). Consequently, these experiments support the proposed reaction mechanism presented in Scheme 2 in which the reaction proceeds *via* a radical pathway and indicates that the capture product **5** originates from the formation of **A,** rather than by reaction of the enolizable ketone and *N*-oxoammonium salt.

Next, owing to the involvement of iodine and benzylic radicals in our reaction, an α-iodinated species **B** was predicted to be the reactive intermediate in the oxidation of **1** to afford benzil **2**. As a result, we sought to isolate the α-iodinated intermediate from the reaction by varying time and temperature (Table 1), since the optimized reaction conditions afford complete oxidation of benzyl phenyl ketone **1** to benzil **2** (Table 1, entry 1). Despite numerous attempts of varying reaction conditions, we did not achieve any success in isolating the target α-iodinated intermediate. On the contrary, the reaction proceeded to deliver the α-diketone **2** or unreacted benzyl phenyl ketone **1** (Table 1, entry 2). We attempted to further decrease the reaction temperature so as to decrease the rate of oxidation, however, only quantitative yields of benzyl phenyl ketone **1** was obtained (Table 1, entries 3–4).

As a result, the failure to isolate the α-iodinated reactive intermediate from the reaction is reasoned by solvation effects, as well as the instability and reactivity of the C–I bond in dipolar aprotic solvents [21]: (i) Carbon–iodine (C–I) bonds are easily cleaved

Table 1
Varying reaction conditions for isolation of the α-iodinated intermediate.[a]



Entry	Time (h)	Temp (°C)	Yield (%)		
			1	B	2
1[b]	2	100	n. d.	n. d.	96
2	24	25	90	n. d.	10
3	24	0	100	n. d.	n. d.
4	24	− 78	100	n. d.	n. d.

[a] Determined by ^{1}H NMR.
[b] Isolated yield.

thermally, or photo-chemically, due to the lower bond dissociation energy (BDE), 56.5 kcal mol^{-1}, as compared to other carbon–halogen bonds. (ii) Molecular iodine is least dependent upon hydrogen bond stabilization with dipolar aprotic solvents. Its nucleophilicity thus decreases, allowing for immediate attack by DMSO on the α–carbon of **B**. (iii) The sulfoxide moiety of DMSO has an electronic charge, residing on both the oxygen and sulfur atoms, which increases its nucleophilicity for interaction with an electrophile such as **B**. (iv) The corresponding iodide ion (I^-) distributes, more effectively, the negative charge that it has obtained, making it a highly reactive leaving group in nucleophilic displacements. Benzylic iodates are therefore difficult to observe and isolate, if formed *in situ*, in the presence of a strong nucleophilic solvent such as DMSO.

As a result, the utility of alternate reaction conditions were explored and literary studies disclosed that benzylic iodates have successfully been synthesized and isolated *via* oxidation in weak, nucleophilic protic solvents, in good to excellent yields [22]. Using this approach, the oxidation was performed in a series of weak nucleophilic solvents (Table 2), rather than DMSO, under the optimized reaction conditions to provide the α-iodinated intermediate, 2-iodo-1, 2-diphenylethanone **B**. Initially, benzyl phenyl ketone **1** was heated to 100 °C in tetrahydrofuran (THF) or dichloroethane (DCE) for 2 h, however, the reaction failed to produce the α-iodinated intermediate **B** (Table 1, entries 1–2). We, subsequently, changed the solvent to acetonitrile (CH_3CN) and *iso*-propanol (*i*-PrOH), however, only a minor amount of iodo-intermediate was detected (Table 1, entries 3–4). However, when benzyl phenyl ketone **1** and iodine were reacted in ethanol, under the optimized reaction conditions, the target α-iodinated intermediate **B** was isolated in a yield of 26% (Table 2, entry 5).

Analysis of the NMR spectra, provided in Fig. 5, shows the singlet at 6.65 ppm [23] corresponding to the α-proton of **B**, identifying the iodo-ketone as a key intermediate in the oxidation process, thus further supporting the mechanism proposed in Scheme 2.

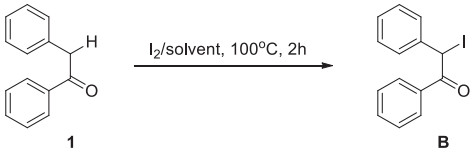
A supplementary study was performed in which the α-iodinated intermediate was heated in DMSO, under the optimized reaction conditions, to afford benzil in 97% yield thus adding further credence that **B** is the key intermediate in our reaction (Scheme 7).

This result supports the effect of solvent (solvation) on the reaction pathway in terms of the nucleophilicity of the oxidant (solvent) and isolation of the highly reactive intermediate, **B**, in the I_2/DMSO oxidation of the α-methylene group of benzyl phenyl ketone.

Having completed the isolation of the reactive intermediate 2-iodo-1,2-diphenylethanone from the reaction, we turned our attention to determining the source of oxygen in the reaction. Accordingly, there are three potential oxygen sources in the reaction system: molecular oxygen in the air, a trace amount of water in the solvent DMSO and DMSO itself. The reaction proceeded well under a nitrogen atmosphere, affording **2** in 95% yield and indicating that oxygen from the air does not participate in the reaction (Scheme 8, a). When the reaction was performed in a 1:1 toluene/water biphasic media, the oxidation product **2** was isolated in 16% yield, indicating that water plays a minor role in the oxidation reaction to afford **2** (Scheme 8, b). Finally, the reaction of benzyl phenyl ketone **1** in anhydrous DMSO, under a nitrogen atmosphere, afforded the diketone in 98% yield (Scheme 8, c).

This result suggests that the major source of oxygen in the diketone originates from DMSO and, in order to support this result, we aimed to isolate the reductive product of the sulfoxide moiety. The reductive product of DMSO is dimethyl sulfide (DMS) which is difficult to isolate and spectroscopically analyze; hence we turned our attention to the use of diphenyl sulfoxide (DPSO) [24] as the source of oxygen, since its reductive product, diphenyl sulfide (DPS), can be isolated and analyzed using NMR spectroscopy. Thus, the reaction of benzyl phenyl ketone and diphenyl sulfoxide (DPSO) in dioxane afforded benzil **2** and DPS **8** in 92% and 79% yield,

Table 2
Oxidation of benzyl phenyl ketone 1 in weak nucleophilic solvents.[a]



1 B

Entry	Solvent	Yield (%)	
		1	B
1	Tetrahydrofuran (THF)	100	n. d.
2	Dichloroethane (DCE)	100	n. d.
3	Acetonitrile (CH_3CN)	91	9
4	*Iso*-propanol (*i*-PrOH)	90	10
5[b]	**Ethanol (EtOH)**	**74**	**26**

[a] Determined by ^{1}H-NMR.
[b] Isolated yield.

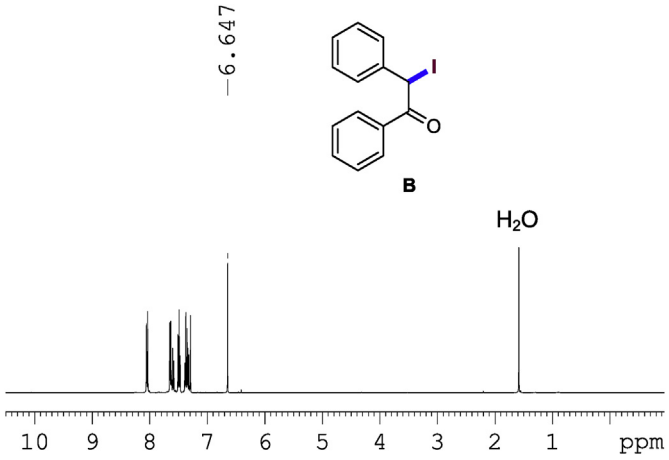
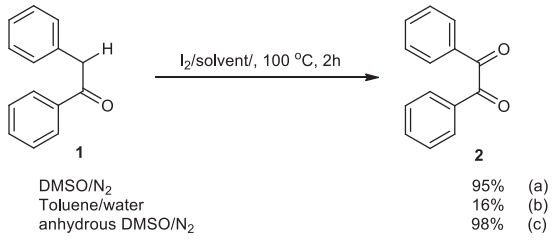
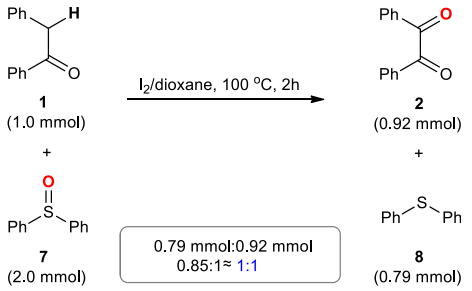


Fig. 5. NMR spectrum of α-iodinated intermediate 2-iodo-1, 2-diphenylethanone **B**.

Scheme 7. Oxidation of α-iodinated intermediate B to afford benzil **2**.



Scheme 8. Control experiments determining oxygen source in benzil **2**.



Scheme 9. Oxidation of benzyl phenyl ketone with DPSO under the optimized reaction conditions.

respectively, with a mole ratio of approximately 1:1 (Scheme 9).

This indicates that one molecule of DMSO reacts with one molecule of benzyl phenyl ketone and the second oxygen atom in benzil originates from the sulfoxide. Accordingly, the oxidation of **1** is not solely a DMSO catalyzed reaction, since the catalytic water still exists but relies, primarily, on DMSO to react with the α-iodinated intermediate to afford the diketone benzil **2**.

3. Conclusions

In conclusion, this research provides insight into the mechanism of the benzylic C^3_{sp}—H oxidation of an α-methylene ketone using an I_2/DMSO system. The proposed reaction mechanism was proven to proceed through: iodine and benzylic radicals, an α-iodinated intermediate, 2-iodo-1,2-diphenylethanone, and oxidation *via* DMSO (the major source of oxygen in benzil). Each key intermediate and reaction step was proven using isolation and spectroscopic techniques: EPR spectroscopy, NMR analysis, the judicious choice of radical spin traps and experimental conditions to support our proposed oxidation reaction. This study, therefore, provides much needed insight into the benzylic C^3_{sp}—H oxidation of an α-methylene bond to afford synthetically useful α-diketones.

4. Experimental details

All reagents were purchased without further purification. All ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Advance III spectrometer operating at 400 MHz. Chemical shifts (δ) were reported in ppm using the Dimethyl Sulfoxide-d6 (DMSO-d_6) residual peak (δ 2.50) or Chloroform ($CDCl_3$) residual peak (δ 7.26) for ^{1}H NMR. Chemical shifts of ^{13}C NMR were reported, relative to DMSO-d_6 (δ 39.51) or $CDCl_3$ (δ 77.0). 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 unit (Hz). High-resolution/Low-resolution electron-spray ionization (ESI) mass spectra were recorded on a time-of-flight (TOF) micromass spectrometer. Infra-Red (IR) spectra were recorded on Carey 630 FTIR. Absorption maxima are expressed in wavenumbers (cm^{-1}). Melting points were determined using Kofler hot-stage melting apparatus. EPR measurements were conducted using a Bruker EMX Ultra X spectrometer.

4.1. General procedure for α-methylene oxidation with I_2/DMSO to afford benzil (2)

Benzyl phenyl ketone (1.0 mmol, 0.196 g)) and iodine (0.5 mmol, 0.126 g) were mixed in a round bottomed flask with 1 mL DMSO and heated to 100 °C for 2 h. After cooling, a $Na_2S_2O_3$/water solution was added to the reaction mixture, extracted with dichloromethane and dried over anhydrous $MgSO_4$. Removal of the solvent, under vacuum, afforded the crude product which was purified by column chromatography using 5:1 hexane:ethyl acetate.

Benzil **2** (0.202 g, 96%) was obtained as a yellow solid: Mp 94–96 °C; υ_{maz} (neat, cm^{-1}): 3064, 1655, 1590, 1449, 1208. ^{1}H NMR (400 MHz, $CDCl_3$): 7.95–7.93 (m, 4H), 7.83–7.78 (m, 2H), 7.66–7.62 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$): 129.5, 129.5, 132.2, 135.5, 194.8. GC-MS (*m/z*): 210.0 (10), 105.0 (100) [25].

4.2. General procedure for synthesis of 1, 2-diphenyl-2-((2, 2, 6, 6-tetramethylpiperidin-1-yl)oxy)ethanone (5)

Benzyl phenyl ketone (1.0 mmol, 0.196 g), TEMPO (1.0 mmol, 0.156 g) and iodine (0.5 mmol, 0.126 g) were mixed in a round bottomed flask with 1 mL DMSO and heated to 100 °C for 2 h. After cooling, a $Na_2S_2O_3$/water solution was added to the reaction mixture, extracted with dichloromethane, and dried over anhydrous $MgSO_4$. Removal of the solvent under vacuum, afforded the crude product which was purified by column chromatography using 9:1 hexane:ethyl acetate.

1, 2-Diphenyl-2-((2, 2, 6, 6-tetramethylpiperidin-1-yl)oxy) ethanone **5** (0.163 g, 46%) was obtained as a white solid: Mp 229–231 °C; υ_{maz} (neat, cm^{-1}): 3068, 2922, 2852, 1667, 1596, 1446, 1262, 1042; ^{1}H NMR (400 MHz, $CDCl_3$): 8.01–7.99 (m, 2H), 7.43–7.39 (m, 3H), 7.34–7.30 (m, 2H), 7.22–7.18 (m, 2H), 7.14–7.10 (m, 1H), 5.92 (s, 1H), 1.38–1.37 (m, 6H), 1.24–1.11 (m, 6H), 0.92 (m, 3H), 0.73 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 198.3, 137.8, 135.3, 132.9, 129.3, 128.3, 127.5, 127.2, 93.5, 60.0, 59.8, 40.3, 33.6, 33.3, 20.3, 20.2, 17.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{30}NO_2$ 352.2276; found 352.2277 [17].

4.3. General procedure for synthesis of α-iodinated intermediate 2-iodo-1, 2-diphenylethanone (B)

Benzyl phenyl ketone (1.0 mmol, 0.196 g) and iodine (0.5 mmol, 0.126 g) were mixed in a round bottomed flask with 1 mL ethanol and heated to 100 °C for 2 h. After cooling, the solvent was removed under vacuum, affording the crude product which was purified by column chromatography using 9:1 hexane:ethyl acetate.

2-Iodo-1,2-diphenylethanone **B** (0.085 g, 26%) was obtained as a yellow solid: Mp 92–93 °C; υ_{maz} (neat, cm^{-1}): 3056, 1670, 1210, 746; ^{1}H NMR (400 MHz, $CDCl_3$): 8.06–8.04 (m, 2H), 7.66–7.58 (m, 3H), 7.51–7.47 (m, 2H), 7.39–7.30 (m, 3H), 6.65 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): 27.8, 128.7, 128.8, 128.9, 129.0, 129.5, 133.6, 133.7, 137.4, 192.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{11}IONa^+$ 344.9752; found 344.9745 [23].

4.4. General procedure for α-methylene oxidation by diphenyl sulfoxide (DPSO) to afford diphenyl sulfide (DPS) (8)

Benzyl phenyl ketone (1.0 mmol, 0.196 g), diphenyl sulfoxide (2.0 mmol, 0.404 g) and iodine (0.5 mmol, 0.126 g) were mixed in a round bottomed flask with 1 mL dioxane and heated to 100 °C for 2 h. After cooling, a $Na_2S_2O_3$/water solution was added to the reaction mixture, extracted with dichloromethane and dried over anhydrous $MgSO_4$. Removal of the solvent, under vacuum, afforded the crude product which was purified by column chromatography using 9:1 hexane:ethyl acetate to afford benzil **2** (0.194 g, 92%) as a yellow solid and diphenyl sulfide **7**.

Diphenyl sulfide **8** (0.147 g, 79%) was obtained as a clear liquid: Mp 60–62 °C; υ_{maz} (neat, cm^{-1}): 3056, 1578, 1474, 1438, 1023; ^{1}H NMR (400 MHz, DMSO-d_6): 7.2–7.41 (m, 10H); ^{13}C NMR (400 MHz, DMSO-d_6): 127.4, 129.5, 130.7, 134.8; HRMS (ESI-TOF) *m/z*: $[M]^+$

Calcd for $C_{12}H_{10}S$ 186.0503; found 186.0507 [26].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.130617.

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