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Molecular iodine/DMSO mediated oxidation of internal alkynes and primary alcohols using a one-pot, two step approach towards 2,4,5-trisubstituted imidazoles: Substrate scope and mechanistic studies

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UNIVERSITY OF KWAZULU-NATAL
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03 February 2020

Subject: Molecular Iodine/DMSO Mediated Oxidation of Internal Alkynes and Primary Alcohols using a One-pot, Two Step Approach Towards 2,4,5-Trisubstituted Imidazoles: Substrate Scope and Mechanistic Studies

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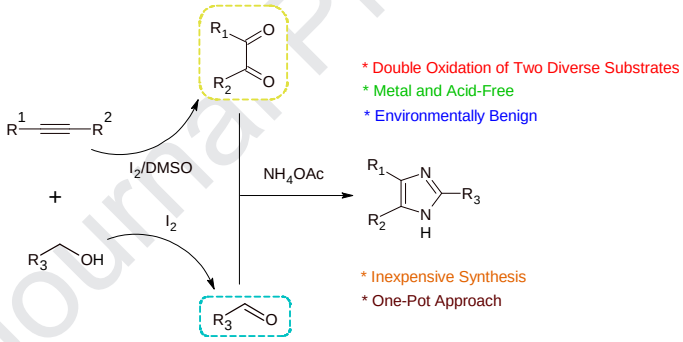

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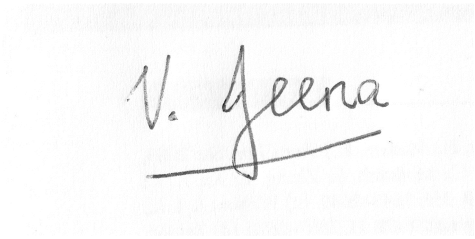

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Molecular Iodine/DMSO Mediated Oxidation of Internal Alkynes and Primary Alcohols using a One-pot, Two Step Approach Towards 2,4,5-Trisubstituted Imidazoles: Substrate Scope and Mechanistic Studies

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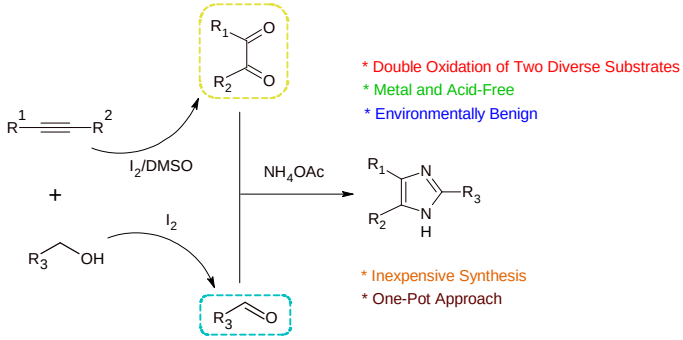

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Molecular Iodine/DMSO Mediated Oxidation of Internal Alkynes and Primary Alcohols using a One-pot, Two Step Approach Towards 2,4,5-Trisubstituted Imidazoles: Substrate Scope and Mechanistic Studies

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Keywords: alcohols, alkynes, imidazoles, iodine, oxidation.

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Abstract

An efficient, eco-friendly and practical oxidation of internal alkynes and primary alcohols as key steps towards the synthesis of 2,4,5-trisubstituted imidazoles is reported. This green synthetic methodology employed an acid and metal-free molecular iodine/DMSO system, to afford a variety of substituted imidazoles in moderate to good yields, with a range of functionalities tolerated. Mechanistic studies revealed two distinct oxidation pathways, which ultimately form the diketone and aldehyde that serve as key intermediates in the multicomponent domino synthesis.

1. Introduction

The preparation of complex molecules using simple substrates while maintaining economic and eco-friendly aspects constitutes a great challenge in modern, synthetic organic chemistry.[1] For many years, the general procedure for the synthesis of organic compounds

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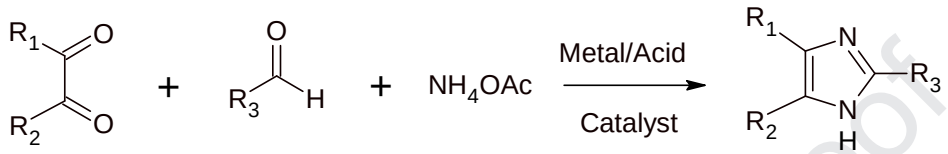
has been the stepwise formation of single bonds in the target molecule, with work-up procedures after each individual transformation.[2] However, a more advantageous approach would allow for the generation of multiple bonds, in the same reaction vessel, without the isolation of the intermediates to ultimately produce the target molecule.[3] With this objective in mind, there are two common approaches known as the Tandem Oxidation Process (TOP)[4] or the "Ireland" oxidative process,[5] which have significantly advanced this methodology. The tandem oxidation process involves mixing an alcohol, nucleophile and oxidant in a one-pot reaction where the alcohol is oxidized to the aldehyde and immediately trapped by the nucleophile to produce the target molecule. The "Ireland" oxidative process was reported by Robert Ireland, over 30 years ago, in which a series of alcohols were oxidized to their aldehyde derivatives, followed by the addition of the appropriate nucleophile, without isolation of the aldehyde, to produce an array of valuable compounds.[6] Both of these synthetic approaches, have a number of advantages such as a decrease in reaction time, cost effectiveness and produce the desired product in a higher yields when compared to traditional syntheses.

Multicomponent reactions (MCRs) represent one of the most important processes for the preparation of numerous compounds in synthetic organic chemistry. In a MCR, three or more substrates are combined to form a single product in a one-pot reaction.[7] These reactions offer an array of possibilities for the efficient formation of highly complex heterocyclic molecules in a single step, omitting the need for several work-up and purification steps, and aids in the minimization of waste, labour, time and cost, while maximizing the yield of the final product.[8]

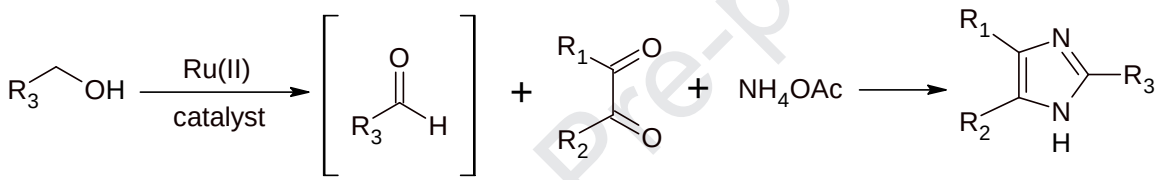
2,4,5-Trisubstituted imidazoles have been studied since the 19th century[9] and, remarkably, continue to find new applications, such as exciting biological activity against Alzheimer's

disease,[10] diabetes mellitus[11] and malaria[12] to name but a few. The classic approach to assemble these illustrious heterocycles occurs via the multicomponent reaction, between an α-diketone, aldehyde and ammonium acetate in the presence of transition metal catalysts or acidic media (Scheme 1a).[13]

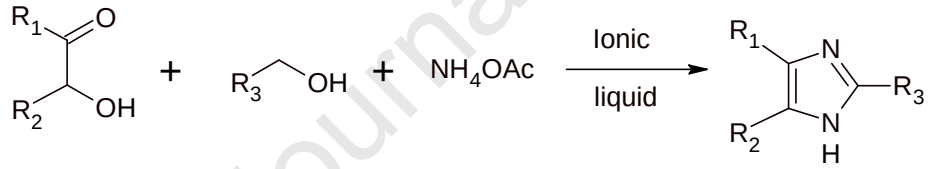
(a) Traditional Imidazole Synthesis



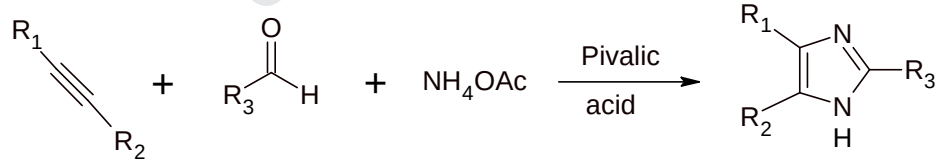
(b) Alcohol Oxidation Initiated Imidazole Synthesis

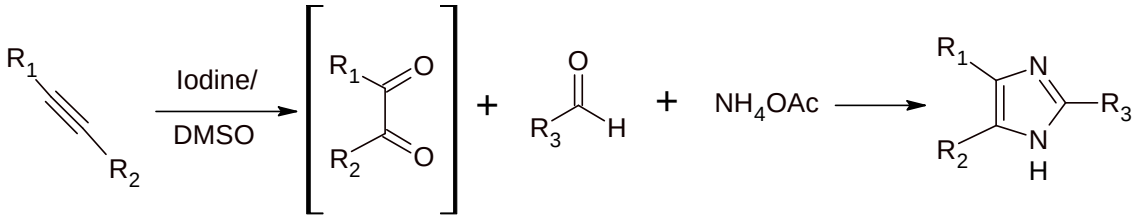


(c) Hydroxy Ketone and Alcohol Initiated Imidazole synthesis



(d) Alkyne Oxidation Initiated Imidazole Synthesis





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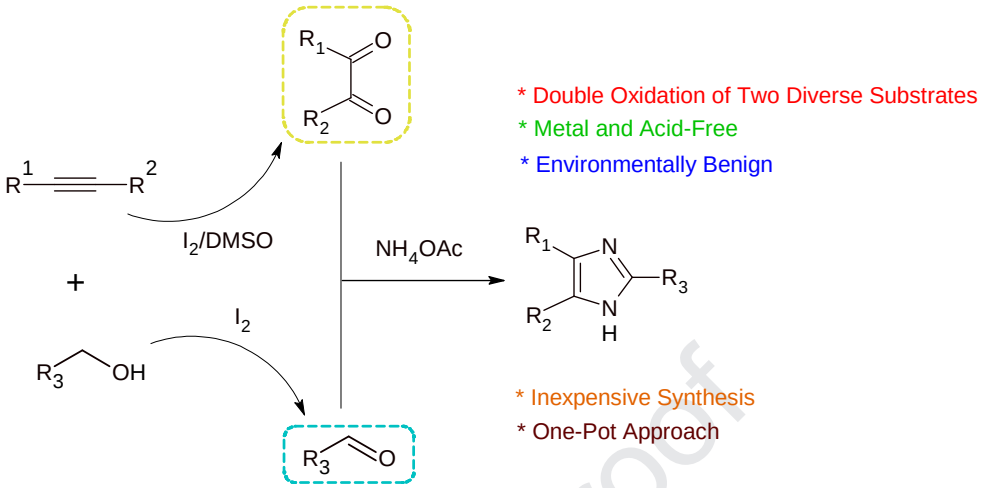
(e) This work



Scheme 1: Various synthetic approaches to 2,4,5-trisubstituted imidazoles.

Recently, this approach has evolved using a number of diverse substrates as reactants for one-pot imidazole synthesis. Rengan and co-worker extended the traditional imidazole synthesis by commencing from a primary alcohol which was oxidized to the aldehyde using a Ru(II) catalyst, followed by the addition of the diketone and ammonium acetate to produce a variety of 2,4,5-trisubstituted imidazole derivatives (Scheme 1b).[14] Mirjafari elaborated the standard approach by mixing α-hydroxyketones, primary alcohols and ammonium acetate simultaneously in a one-pot procedure, using the ionic liquid, 1-methyl-3*H*-imidazolium nitrate [Hmim][NO_3], as an oxidant and reaction medium under microwave irradiation that successfully formed a series of 2,4,5-trisubstituted imidazoles (Scheme 1c).[15] Wang and co-workers adjusted their strategy towards the synthesis of 2,4,5-trisubstituted imidazoles by commencing from an internal alkyne rather than the 1,2-diketone, to deliver 2,4,5-trisubstituted imidazoles. Various internal alkynes were oxidized to their subsequent 1,2-diketones, using a pivalic acid system in the presence of the aldehyde and ammonium acetate resulting in the formation of numerous trisubstituted imidazoles (Scheme 1d).[16] Our research group extended this methodology by using an I_2/DMSO oxidation system for transformation

of internal alkynes to 1,2-diketones, followed by the addition of numerous aldehydes and ammonium acetate to produce a variety of trisubstituted imidazoles (Scheme 1d).[17]

The combined use of molecular iodine and DMSO, has emerged as a valuable tool for the synthetic organic chemist and this system has been reported to perform in two ways: (i) reactions catalyzed via I_2 in a DMSO medium and (ii) I_2/DMSO mediated oxidative transformations.[18] Some transformations exhibited by this powerful system include, the oxidation of alkynes to glyoxals,[19] the selective sulfenylation of electron rich arenes and carbonyl compounds,[20] the synthesis of unsymmetrical organochalcogenides,[21] oxidative cross-coupling,[22] dehydrogenation[23] and oxidative cleavage[24] to name but a few. Using this information, we were intrigued by the possibility of an iodine mediated double oxidation of readily available starting materials (internal alkynes and primary alcohols) in the same reaction vessel, which would lead to their respective intermediates (diketones and aldehydes) that, in the presence of ammonium acetate, would ultimately converge to the desired 2,4,5-trisubstituted imidazoles (Scheme 1e).

2. Results and Discussion

We initiated our study by examining a one-pot reaction between diphenylacetylene (**1a**), benzyl alcohol (**2a**) and ammonium acetate (NH_4OAc) in DMSO for 2 h, in the presence of 2 equivalents of I_2, at 100 °C, however, the reaction failed to proceed, and no product was detected (Table 1, entry 1). A similar result was observed when the reaction was repeated for a longer duration (24 h) (Table 1, entry 2). Due to the failure of these two reactions, we then attempted a one-pot, two-step approach in which, **1a** and **2a** were reacted in DMSO for 24 h at 130 °C, in the presence of 2 equivalents of I_2. Subsequently, ammonium acetate was added, and the mixture was left to react for 2 h at 100 °C, however, only 12% of **3a** was produced (Table 1, entry 3). The synthesis of trisubstituted imidazoles are known to be solvent

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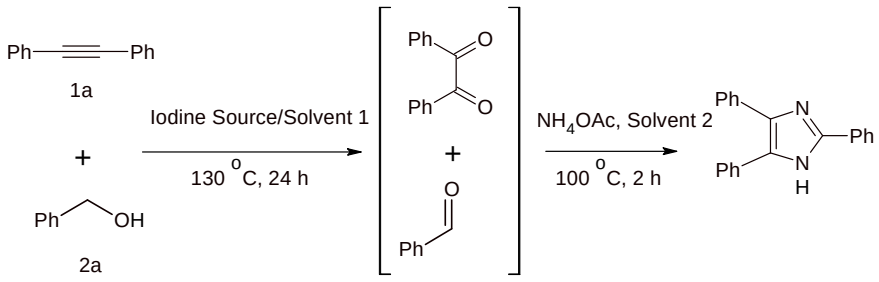
specific,[25] therefore, a range of solvents were added to encourage cyclization, however, no reaction to low yields were observed when dimethylformamide (DMF), dichloromethane (DCM), toluene (PhMe), acetonitrile (MeCN), water (H_2O) and tetrahydrofuran (THF) were added (Table 1, entries 4–9). Trisubstituted imidazole syntheses are known to proceed well in the presence of an alcohol solvent,[26] and encouragingly, when methanol (MeOH) was used, the desired product was formed in an isolated yield of 65% (Table 1, entry 10) and, to our delight, when ethanol (EtOH) was used as the solvent, 2,4,5-triphenyl imidazole was isolated in a yield of 86% (Table 1, entry 11). The reaction failed to produce the expected product when DMSO was replaced with THF, H_2O and MeCN (Table 1, entries 12-14), suggesting the crucial role of DMSO. Attempts were made to decrease the amount of iodine, however, varied amounts of 1.5 to 0.2 equivalents, resulted in a decrease in product yield (65%-21%) (Table 1, entries 15-18). Other iodine catalysts, such as iodine pentoxide (I_2O_5) and 2-iodobenzoic acid (IBX) were also evaluated and both catalysts resulted in no product formation (Table 1, entries 19-20). The reaction was attempted in the absence of I_2 (Table 1, entry 21) and DMSO (Table 1, entry 22), but failed to give **3a**. Attempts were made to lower the NH_4OAc loading to 5 and 2 equivalents, which resulted in decreased product yields of 33% and 10% respectively (Table 1, entries 23-24). To conclude, the conditions described in Table 1, entry 11, were found to be optimal and allowed for the maximum formation of the desired product **3a**.

Table 1: Screening of optimal reaction conditions[a]



Entry	Iodine Source	Solvent 1	Solvent 2	Yield[b]
1[c]	I_2	DMSO	–	N.R
2[d]	I_2	DMSO	–	N.R
3	I_2	DMSO	–	12
4	I_2	DMSO	DMF	Trace
5	I_2	DMSO	DCM	N.R
6	I_2	DMSO	PhMe	18
7	I_2	DMSO	MeCN	N.R
8	I_2	DMSO	H_2O	N.R
9	I_2	DMSO	THF	N.R
10	I_2	DMSO	MeOH	65
11	**I_2**	**DMSO**	**EtOH**	**86**
12	I_2	THF	EtOH	N.R
13	I_2	H_2O	EtOH	N.R
14	I_2	MeCN	EtOH	N.R
15[e]	I_2	DMSO	EtOH	65
16[f]	I_2	DMSO	EtOH	62
17[g]	I_2	DMSO	EtOH	43
18[h]	I_2	DMSO	EtOH	21
19	I_2O_5	DMSO	EtOH	N.R
20	IBX	DMSO	EtOH	N.R
21	–	DMSO	EtOH	N.R
22	I_2	–	EtOH	N.R
23[i]	I_2	DMSO	EtOH	33
24[j]	I_2	DMSO	EtOH	10

[a] Reaction conditions: Step 1: **1a** (0.5 mmol), **2a** (0.5 mmol), I_2 (2 equiv.) solvent 1 (2 mL), 130 °C, 24 h. Step 2: NH_4OAc (10 equiv.), solvent 2 (2 mL), 100 °C, 2 h. [b] Isolated yield. [c] One-pot, one-step reaction, 100 °C, 2 h. [d] One-pot, one-step reaction, 100 °C, 24 h. [e] I_2 (1.5

equiv.)/DMSO (2 mL). [f] I_2 (1 equiv.)/DMSO (2 mL). [g] I_2 (0.5 equiv.)/DMSO (2 mL). [h] I_2 (0.2 equiv.)/DMSO (2 mL) [i] NH_4OAc (5 equiv.). [j] NH_4OAc (2 equiv.). N. R = No Reaction.

With the optimal reaction conditions in hand, we set out to explore the substrate generality of these transformations and the results are summarized in Scheme 2. Various electron-withdrawing and electron-donating para-substituted benzyl alcohol derivatives were reacted with **1a** and underwent smooth transformation, to afford the resulting 2,4,5- trisubstituted imidazoles, **3a-3f**, in good to excellent yields (70%-88%). Moderate to good imidazole yields, 53%-78%, were obtained with benzyl alcohol derivatives substituted at the *meta* and *ortho* positions (Scheme 2, **3g-3l**). Motivated by these results, we decided to expand our methodology, by assessing bulkier substrates such as, 2-naphthalenemethanol, which coupled well with **1a** to afford 2-(naphthalene-2-yl)-4,5-diphenyl-1*H*-imidazole in a 75% yield (Scheme 2, **3m**). The iodine/DMSO system was shown to be substrate dependent as steric and electronic factors influenced the yield. Based on the successful results obtained by substituted benzylic alcohols, we further explored heterocyclic and aliphatic substituted primary alcohols such as; 2-furanmethanol, cyclohexylmethanol and 1-hexanol, to produce **3n** and **3o** in yields of 16% and 22% respectively, however, no product was obtained when 1-hexanol was used, even with extended reaction times (Scheme 2, **3p**).

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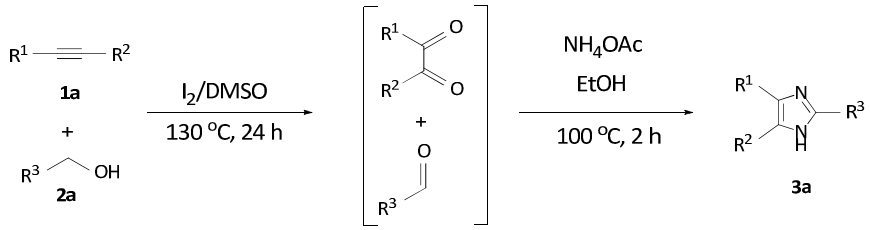
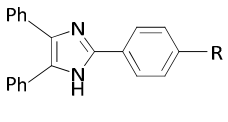
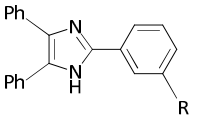
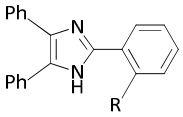




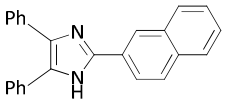
3a, R = H, 86%
3b, R = Cl, 85%
3c, R = Br, 83%
3d, R = F, 70%
3e, R = Me, 80%
3f, R = OMe, 88%



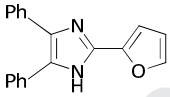
3g, R = Cl, 64%
3h, R = NO_2, 57%



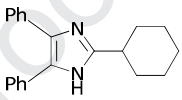
3i, R = OMe, 78%
3j, R = Me, 70%
3k, R = NO_2, 56%
3l, R = F, 53%



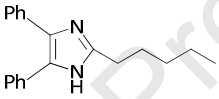
3m, 75%



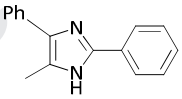
3n, 16%[c]



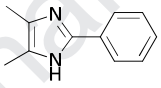
3o, 22%[c]



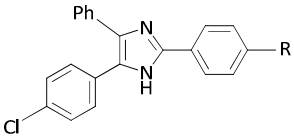
3p, 0%[c]



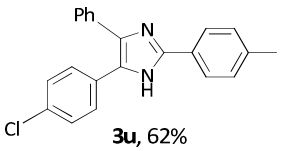
3q, 0%[c]



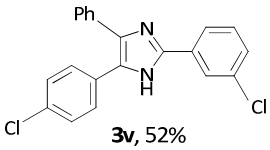
3r, 0%[c]



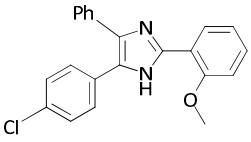
3s, R = 4-H, 66%
3t, R = 4-F, 56%



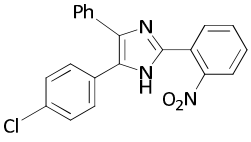
3u, 62%



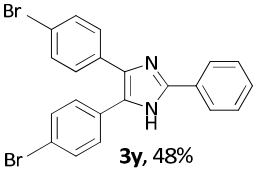
3v, 52%



3w, 60%



3x, 62%



3y, 48%

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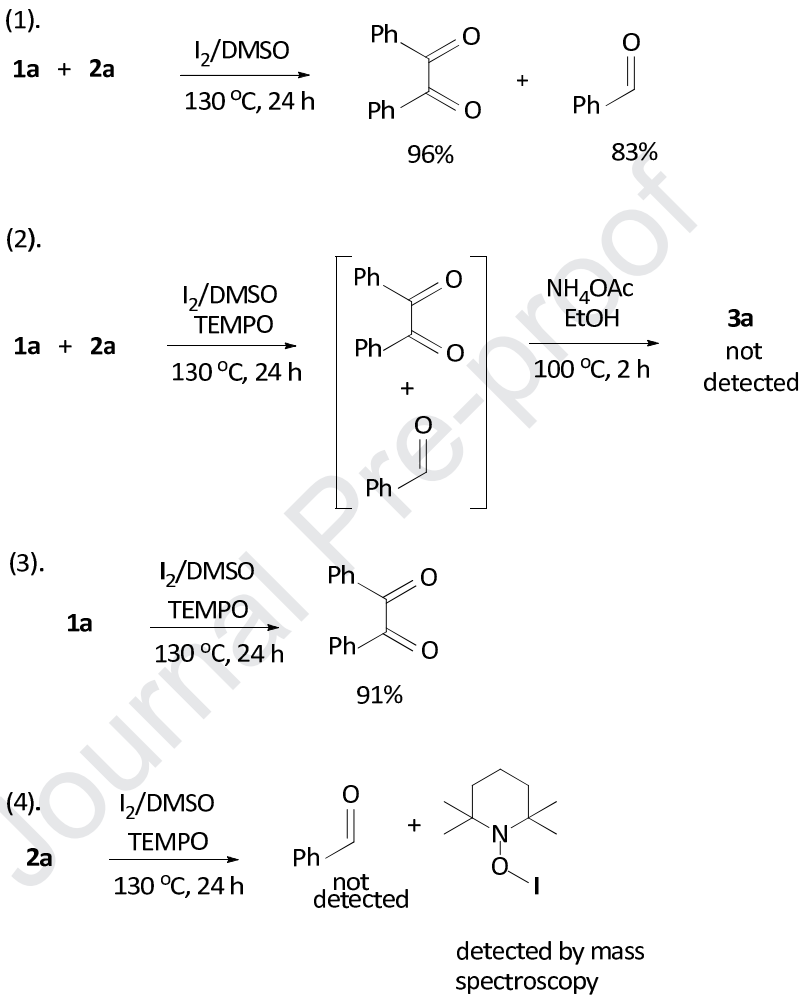
Scheme 2: Substrate scope of 2,4,5-trisubstituted-1*H*-imidazoles with various internal alkynes and primary alcohols. Reaction conditions: Step 1: 1 (0.5 mmol), 2 (0.5 mmol), I_2 (2 equiv.)/DMSO (2 mL), 130 °C, 24 h. Step 2: NH_4OAC (10 equiv.), EtOH (2 mL), 100 °C, 2 h. [b] Isolated yield. [c] Step 2: 24 h.

This result is consistent with literature, as aliphatic aldehydes do not couple well in trisubstituted imidazole synthesis and, when they do, often result in low yields.[27] Next, the coupling reactions between benzyl alcohol and various internal alkynes were examined. Unfortunately, 1-phenyl-1-propyne and 2-butyne resulted in no product formation, which is probably due to the reduced nucleophilicity of the reagents (Scheme 2, **3q**-**3r**).[28] The coupling of 1-chloro-4-(phenylethynyl)benzene with benzyl alcohol and 4-fluorobenzyl alcohol under the optimized reaction conditions, successfully afforded the trisubstituted imidazoles, **3s** and **3t** in good yields of 66% and 56% respectively. Given the promising biological activity of 2,4,5-trisubstituted imidazoles highlighted earlier in this manuscript, the synthesis of novel imidazoles would be welcome addition to medicinal chemistry. As a result, this methodology was used to prepare new 2,4,5-trisubstituted imidazoles, **3u** to **3x**, in yields of 52% - 62%. Encouraged by the above results, we were curious to investigate the reaction of 1,2-bis(4-bromophenyl)acetylene with **2a**, which reacted smoothly to afford 4,5-bis(4-bromophenyl)-2-phenyl-1*H*-imidazole in a modest yield of 48% (Scheme 2, **3y**).

To gain insight into the reaction mechanism, several control experiments were conducted (Scheme 3). In experiment 1, **1a** and **2a** were oxidized under standard conditions, to afford benzil and benzaldehyde in isolated yields of 96% and 83%, respectively (Scheme 3, eqn. (1)). This indicates that the diketone and the aldehyde are intermediates in this domino synthesis. Next, the radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) was

added to the reaction mixture under standard conditions, however, **3a** was not formed, indicating that one (or both) of the substrates undergoes oxidation via a radical mediated pathway (Scheme 3, eqn. (2)). To further, rationalize this observation, the oxidation of the alkyne and alcohol was carried out individually.



Scheme 3: Control experiments for the I_2/DMSO catalyzed trisubstituted imidazole synthesis.

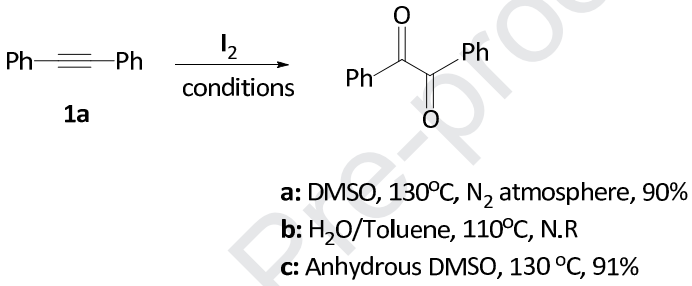
Firstly, TEMPO was added to **1a** in the I_2/DMSO system resulting in the formation of benzil in a 91% isolated yield, suggesting that the oxidation of the alkyne does not proceed via a radical mediated pathway (Scheme 3, eqn. (3)). Under similar conditions, TEMPO was added

in the oxidation of **2a** however, benzaldehyde was not detected but the TEMPO-iodine adduct was identified (determined by mass spectroscopy). This result indicates that this transformation may proceed *via* a radical mediated pathway (Scheme 3, eqn. (4)). On completion of reactions 3 and 4, it was concluded that the synthesis of the trisubstituted imidazoles, proceeds via two different oxidation methods *viz*. a non-radical oxidative pathway for the internal alkyne and a radical mediated pathway for the primary alcohol.

To understand the mechanistic pathway of this double oxidation, multicomponent reaction, a series of additional experimental reactions and spectroscopic analyses were performed. Our initial studies focused on the synthesis of the diketone as we attempted to gain insight into its formation. We had previously shown that the iodo-ketone may be a key intermediate in the alkyne oxidation[17] and we set about attempting to isolate this intermediate to prove its existence in this reaction. However, despite various reaction conditions only the diketone was observed with trace amounts of the iodo-ketone. Consequently, it was postulated that it is difficult to isolate the iodoketone, if generated in the presence of a strong nucleophilic solvent such as DMSO. This prompted us to alter the optimized reaction conditions to allow for isolation of the iodinated intermediate using a variety of solvents (ESI, Table 1). Weak nucleophilic solvents such as MeCN, THF, dichloroethane (DCE) and iso-propanol, unfortunately resulted in no or minimal product formation. However, when EtOH was employed; the iodoketone intermediate was obtained in an isolated yield of 28%, which proved that the iodoketone is a key intermediate in the alkyne oxidation.

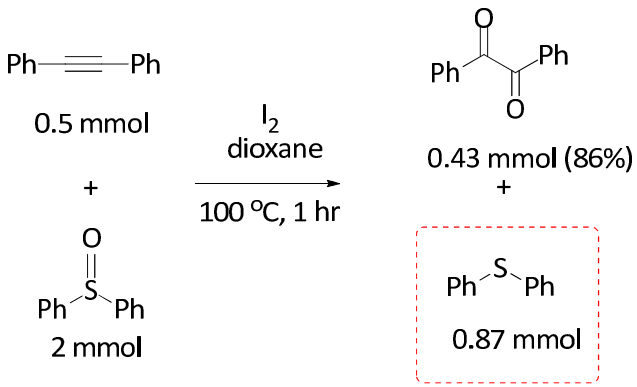
Secondly, we decided to probe the source of oxygen atoms in the final diketone and it was evident that there were three sources of oxygen namely, (i) oxygen from the air, (ii) oxygen from the trace water in the DMSO and (iii) DMSO itself (Scheme 4). **1a** was reacted with I_2

and DMSO under an N_2 atmosphere, affording the 1,2-diketone in a 90% isolated yield, thus indicating that the reaction is not dependent on O_2 from the atmosphere. Next, a water and toluene biphasic solvent mixture was used, however the reaction did not proceed and only starting material was obtained, suggesting that the trace amount of H_2O found in DMSO does not play a role in the alkyne oxidation. Finally, the test reaction was carried out in freshly distilled, anhydrous DMSO, which resulted in the formation of the 1,2-diketone in a 91% isolated yield, implying that DMSO is the source of oxygen in the isolated diketone.



Scheme 4: Control experiment determining the source of oxygen for benzil formation.

To further substantiate this result, we carried out an additional study. During the oxidation of internal alkynes, DMSO is, predicted to be reduced to dimethyl sulfide (DMS) however, DMS is a volatile species and attempts at its isolation would be challenging. This prompted us to use diphenyl sulfoxide (DPSO) as a surrogate nucleophile, as its reductive product, diphenyl sulfide (DPS) can easily be isolated and analyzed spectroscopically.[29] The reaction of **1a** with I_2 and DPSO in dioxane, rendered benzil in an isolated yield of 86% and 0.87 mmol of DPS was obtained. The mole ratio of DPS: benzil (0.87: 0.43), is approximately 2: 1, which suggests that two molecules of DMSO are required to oxidize one molecule of the internal alkyne and that both oxygen atoms on the diketone arise from the DMSO (Scheme 5).



Scheme 5: Oxidation of alkyne with DPSO under optimized conditions.

We then turned our attention to the alcohol oxidation and, as proposed from the control studies, the primary alcohol oxidation is expected to proceed *via* a radical mediated pathway consequently, Electron Paramagnetic Resonance (EPR) was used to detect any radical species. The addition of benzyl alcohol, I_2/DMSO and 5,5-dimethylpyrroline-N-oxide (DMPO) resulted in the appearance of a 1:2:2:1 quartet with a coupling constant of 14.09 Gauss, characteristic of a phenoxyl radical (Figure 1)[30] which implies homolytic cleavage of the O–H bond.

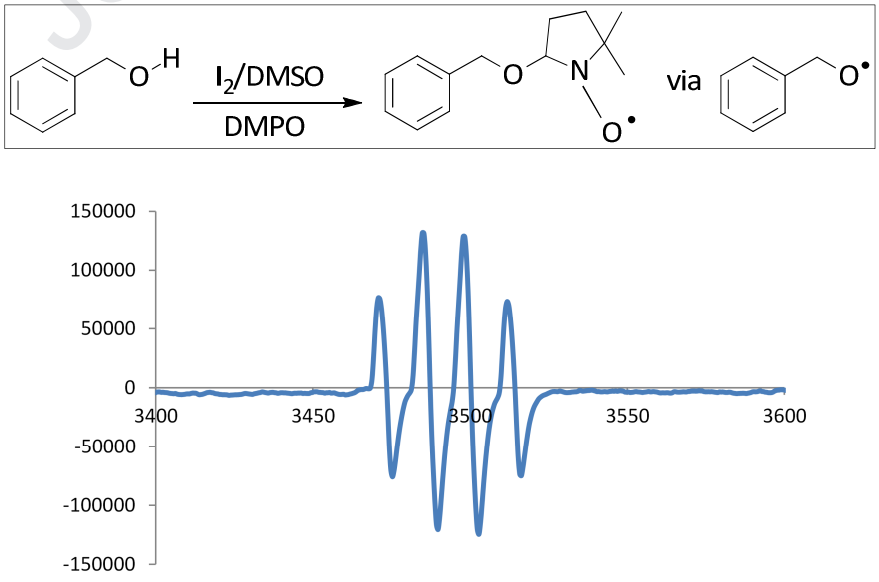


Figure 1: EPR spectrum showing the DMPO-trapped phenoxyl radical.

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This observation suggests that upon heating, the I–I bond is cleaved homolytically to produce iodine radicals, which initiate the homolytic cleavage of the O–H bond to generate a phenoxyl radical.

Based on our experimental observations and previous literature reports,[31] we propose a mechanistic pathway to rationalize the trisubstituted imidazole formation via a double oxidation (Scheme 6). The reaction begins with the activation of the triple bond of the alkyne **1** by iodine to furnish the iodonium intermediate A. The addition of DMSO on **A** allows for the formation of iodide intermediate **B**, followed by the removal of weakly basic DMS. The newly formed iodoketone **C**, is immediately trapped by a molecule of DMSO, to produce intermediate **D**, which further proceeds to form the diketone **E** through the expulsion of a second molecule DMS. Concurrently, a proton is abstracted from the hydroxy of the primary alcohol **2** by an iodine radical to afford the corresponding phenoxyl radical intermediate **F**. Thereafter, iodination affords the corresponding iodo intermediate **G**, followed by deprotonation which delivers the aldehyde **H**, while expelling a molecule of HI. Finally, intermediates **E** and **H** are activated by iodine and upon reaction with ammonium acetate, form imine intermediates **I** and **J** which undergo cyclocondensation to afford the desired 2,4,5-trisubstituted imidazole **3**.

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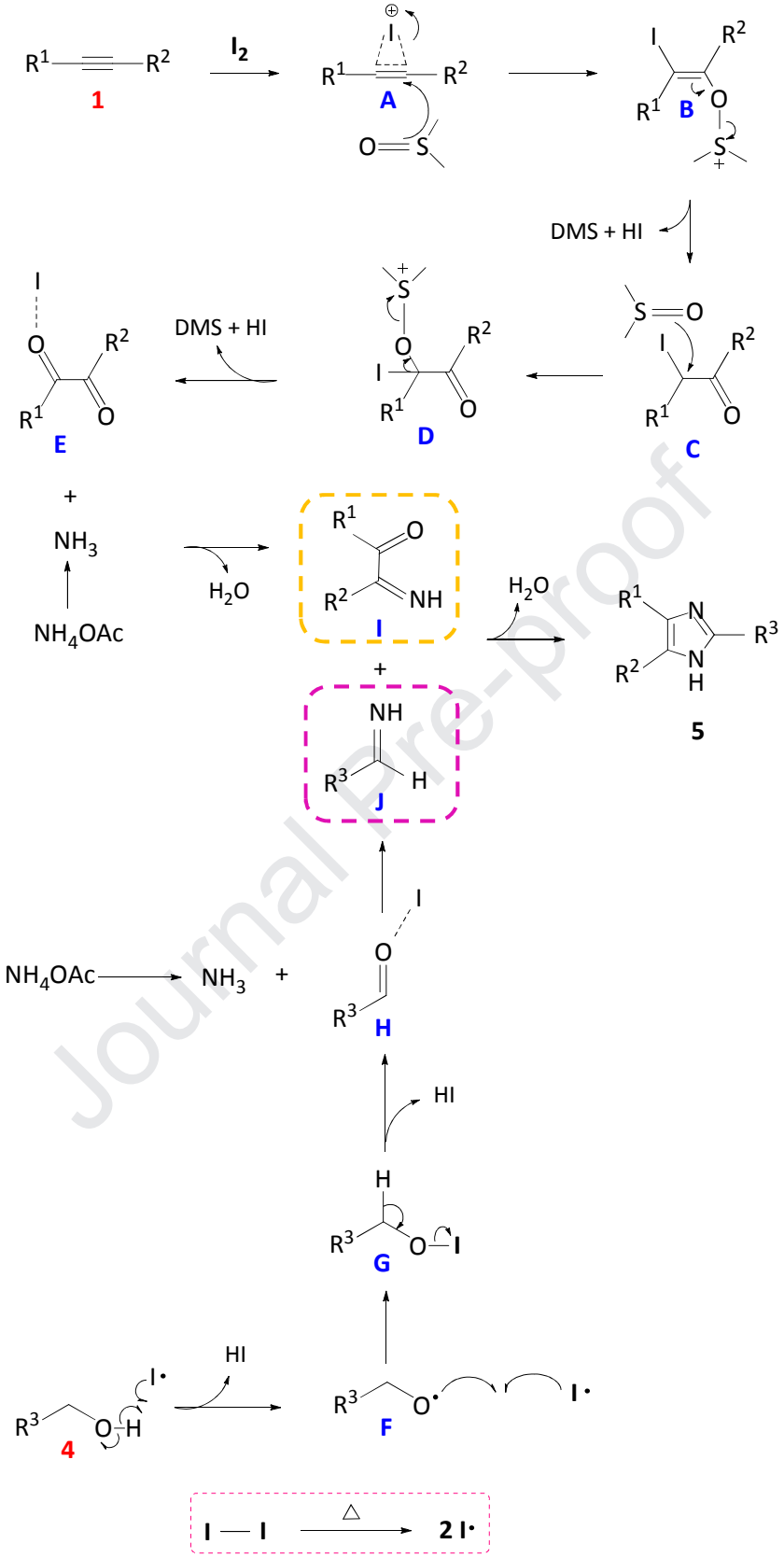

Scheme 6: Plausible mechanism for the double oxidation, multicomponent domino synthesis of trisubstituted imidazoles.

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3. Conclusions

In conclusion, we have developed an innovative method for the synthesis of 2,4,5-trisubstituted imidazoles from internal alkynes and primary alcohols, *via* a simple, efficient, eco-friendly and inexpensive double oxidation, domino sequence. The developed system is applicable to a wide variety of substrates, making this an alternate synthetic approach that could replace conventional trisubstituted imidazole synthesis. Control and mechanistic studies predict that the internal alkyne undergoes oxidation to the diketone *via* the iodoketone intermediate while the primary alcohol undergoes oxidation *via* a radical mediated pathway. Further insight into the mechanism was provided through the judicious use of spectroscopy and the isolation of key intermediates to provide valuable information into this sophisticated synthetic procedure.

4. Experimental Details

All reagents were purchased and used without further purification. All ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer operating at 400 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/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.

General Procedure for the Synthesis 2,4,5-Trisubstituted Imidazoles (3).

Alkyne (0.5 mmol, 1 equiv.), primary alcohol (0.5 mmol, 1 equiv.), I_2 (1 mmol, 253.8 mg, 2 equiv.) and DMSO (2 mL) were mixed in a round bottom flask and heated at 130 °C for 24 h. Thereafter, ammonium acetate (5 mmol, 385.4 mg, 10 equiv.) and EtOH (2 mL) was added to the mixture and heated at 100 °C for 2 h. After cooling, a solution of 1% $Na_2S_2O_3$ was added dropwise to the mixture to form a precipitate which was filtered and dried. The crude product was recrystallized from EtOH to afford spectroscopically pure imidazole **3**.

2,4,5-Triphenyl-1*H*-imidazole (3a).[16,32]

This compound was prepared as described in the general procedure to produce the target compound as a white solid. Yield 86% (127.4 mg).

mp: 271 – 272 °C.

IR (cm^{-1}) 3757, 3037, 1586, 1461, 1484, 1126.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.69 (s, 1H), 8.12-8.10 (d, J = 7.58 Hz, 2H), 7.65-7.41 (m, 8H), 7.39-7.25 (m, 5H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 146.0, 137.6, 135.7, 131.6, 130.9, 129.1, 128.9, 128.7, 128.65, 128.2, 127.6, 127.0, 125.7.

HRMS (ESI) calculated for $C_{21}H_{16}N_2$: 297.1392, found 297.1398.

2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (3b).[33, 34]

This compound was prepared as described in the general procedure. White solid. Yield 85% (140.6 mg).

mp: 261-263 °C.

IR (cm^{-1}) 2841, 1483, 1127, 766.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.78 (s, 1H), 8.13 – 8.11 (d, J = 8.25 Hz, 2H), 7.57 – 7.55 (m, 6H), 7.46 – 7.41 (m, 3H), 7.32 – 7.26 (m, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 144.9, 137.8, 135.5, 133.2, 131.4, 129.7, 129.2, 129.1, 128.9, 128.7, 128.3, 127.6, 127.3, 127.1.

HRMS (ESI) calculated for $C_{21}H_{15}N_2Cl$: 329.0846, found 329.0846.

2-(4-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (3c).[33,34]

This compound was prepared as described in the general procedure. White solid. Yield 83% (155.7 mg).

mp: 254-256 °C.

IR (cm^{-1}) 2965, 2085, 1597, 1481, 1125, 766.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.78 (s, 1H), 8.06-8.04 (d, J = 9.08 Hz, 2H), 7.71-7.69 (d, J = 8.64 Hz, 2H), 7.57-7.51 (m, 4H), 7.48-7.44 (m, 2H), 7.42-7.40 (m, 1H), 7.34-7.30 (m, 2H), 7.26-7.24 (s, 1H);

^{13}C NMR (100 MHz, DMSO-d_6): δ 145.0, 137.8, 135.5, 132.1, 131.4, 130.0, 129.13, 129.1, 128.9, 128.7, 128.3, 127.6, 127.1, 121.9.

HRMS (ESI) calculated for $C_{21}H_{15}N_2Br$: 373.0340, found 373.0344.

2-(4-Fluorophenyl)-4,5-diphenyl-1*H*-imidazole (3d).[33,34]

This compound was prepared as described in the general procedure. White solid. Yield 70% (110.0 mg).

mp: 262-264 °C.

IR (cm^{-1}) 2647, 1655, 1499, 1225, 1160.

1H NMR (400 MHz, DMSO-d_6): δ 12.69 (s, 1H), 8.16 – 8.12 (m, 2H), 7.55 – 7.53 (m, 4H), 7.36 – 7.31 (m, 8H).

^{13}C NMR (100 MHz, DMSO-d6): δ 163.8, 161.4, 145.2, 137.6, 135.6, 131.5, 129.1, 128.9, 128.7, 128.2, 127.8 (d, $J_{c,f}$ = 8.2 Hz), 127.5 (d, $J_{c,f}$ = 3.4 Hz), 127.0, 116.2 (d, $J_{c,f}$ = 21.6 Hz).

HRMS (ESI) calculated for $C_{21}H_{15}N_2F$: 313.1141, found 313.1135.

2-(4-Methylphenyl)-4,5-diphenyl-1*H*-imidazole (3e).[34,35]

This compound was prepared as described in the general procedure. White solid. Yield 80% (124.1 mg).

mp: 230-232 °C.

IR (cm^{-1}) 3755, 2840, 1585, 1487, 1437.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.59 (s, 1H), 8.00 – 7.98 (d, J = 8.57 Hz, 2H), 7.58 – 7.53 (m, 4H), 7.45 – 7.44 (m, 4H), 7.31 – 7.29 (m, 4H), 2.37 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.3, 138.3, 136.1, 135.5, 134.6, 132.6, 131.4, 130.4, 129.7, 129.6, 129.2, 129.0, 128.7, 128.4, 128.2, 128.0, 127.7, 127.2, 125.7, 21.4.

HRMS (ESI) calculated for $C_{22}H_{18}N_2$: 309.1392, found 309.1398.

2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (3f).[32]

This compound was prepared as described in the general procedure. White solid. Yield 88% (143.6 mg).

mp: 230-233 °C.

IR (cm^{-1}) 2645, 2104, 1609, 1492, 1243, 1175.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.51 (s, 1H), 8.04 – 8.02 (d, J =8.60 Hz, 2H), 7.53 – 7.31 (m, 10H), 7.07 – 7.05 (d, J = 8.10 Hz, 2H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 159.4, 145.6, 136.8, 135.3, 131.2, 128.6, 128.3, 128.1, 127.6, 127.57, 127.0, 126.7, 126.4, 123.1, 114.1, 55.2.

HRMS (ESI) calculated for $C_{22}H_{18}N_2O$: 325.1341, found 325.1349.

2-(3-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (3g).[34,36]

This compound was prepared as described in the general experiment procedure. White crystalline solid. Yield 64% (105.9 mg).

mp: 231-233 °C.

IR (cm^{-1}) 3028, 2103, 1682, 1578, 1458, 1023, 846, 769.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.82 (s, 1H), 8.17 – 8.16 (t, J = 1.71 Hz, 1H), 8.07 – 8.05 (m, 1H), 7.55 – 7.50 (m, 5H), 7.45 – 7.39 (m, 7H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.1, 138.4, 136.5, 134.3, 133.4, 132.8, 131.6, 131.2, 130.4, 129.5, 129.3, 129.0, 128.8, 127.7, 127.4.

HRMS (ESI) calculated for $C_{21}H_{15}N_2Cl$: 329.0846, found 329.0847.

2-(3-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (3h).[33,34]

This compound was prepared as described in the general procedure. Yellow solid. Yield 57% (97.3 mg).

mp: 301-302 °C.

IR (cm^{-1}) 2858, 1585, 1522, 1476, 1418, 1346, 1252, 1072.

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^{1}H NMR (400 MHz, DMSO-d_6): δ 13.14 (s, 1H), 8.97 (s, 1H), 8.55 – 8.51 (d, J = 8.01 Hz, 1H), 8.25 – 8.20 (d, J = 7.61 Hz, 1H), 7.82 – 7.76 (t, J = 7.62 Hz, 1H), 7.59- 7.54 (m, 4H), 7.41 – 7.36 (m, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.9, 143.9, 132.4, 131.7, 130.9, 129.0, 128.2, 123.0, 119.9.

HRMS (ESI) calculated for $C_{21}H_{15}N_3O_2$: 340.1086, found 340.1076.

2-(2-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (3i).[32]

This compound was prepared as described in the general procedure. White solid. Yield 78% (127.3 mg).

mp: 210-211 °C.

IR (cm^{-1}) 3067, 2841, 1588, 1528, 1473, 1392.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.89 (s, 1H), 8.09-8.07 (d, J = 7.20 Hz, 1H), 7.56 (m, 2H), 7.50 (m, 2H), 7.45-7.42 (m, 2H), 7.40-7.38 (m, 2H), 7.32-7.29 (m, 2H), 7.24-7.21 (m, 1H), 7.19-7.17 (m, 1H), 7.10-7.07 (m, 1H), 3.94 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 156.5, 143.6, 136.9, 135.8, 131.7, 130.2, 129.3, 129.1, 128.6, 128.1, 127.9, 127.6, 126.9, 121.1, 119.4, 112.1, 56.1.

HRMS (ESI) calculated for $C_{22}H_{18}N_2O$: 325.1341, found 325.1344.

2-(2-Methylphenyl)-4,5-diphenyl-1*H*-imidazole (3j).[37]

This compound was prepared as described in the general procedure. White solid. Yield 70% (108.6 mg).

mp: 201-204 °C.

IR (cm^{-1}) 3101, 2987, 2101, 1660, 1400, 1315.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.47 (s, 1H), 7.74-7.72 (m, 1H), 7.54 (m, 4H), 7.36-7.31 (m, 9H), 2.50 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 146.6, 136.8, 131.6, 130.5, 129.2, 129.1, 128.7, 128.0, 127.5, 126.9, 126.2, 21.6.

HRMS (ESI) calculated for $C_{22}H_{18}N_2$: 309.1392, found 309.1389.

2-(2-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (3k).[38]

This compound was prepared as described in the general procedure. Yellow solid. Yield 56% (95.6 mg).

mp: 268-272 °C.

IR (cm^{-1}) 2959, 1583, 1523, 1479, 1410, 1301, 1071.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.95 (s, 1H), 8.02-8.00 (d, J = 6.4 Hz, 1H), 7.95-7.92 (d, J = 7.0 Hz, 1H), 7.82-7.78 (t, J = 7.0 Hz, 1H), 7.67-7.63 (t, J = 6.55 Hz, 1H), 7.51-7.49 (m, 4H), 7.39 (m, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 148.8, 141.5, 132.6, 130.3, 130.0, 129.0, 124.5, 124.0.

HRMS (ESI) calculated for $C_{21}H_{15}N_3O_2$: 340.1086, found 340.1080.

2-(2-Fluorophenyl)-4,5-diphenyl-1*H*-imidazole (3l).[39]

This compound was prepared as described in the general procedure. White solid. Yield 53% (83.3 mg).

mp: 239-240 °C.

IR (cm^{-1}) 3047, 1580, 1473, 1218, 1097, 759.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.54 (s, 1H), 8.03-8.00 (t, J = 15.30, 5.9 Hz, 1H), 7.54-7.52 (m, 4H), 7.50-7.45 (m, 2H), 7.40-7.33 (m, 7H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 160.6, 158.1, 141 (d, $J_{C,F}$ = 1.75 Hz), 137.7, 135.5, 131.4, 130.8 (d, $J_{C,F}$ = 8.26 Hz), 130.1 (d, $J_{C,F}$ = 2.59 Hz), 129.0, 128.7, 128.3, 127.6, 127.0, 125.2 (d, $J_{C,F}$ = 3.28 Hz), 119.2 (d, $J_{C,F}$ = 12.56 Hz), 116.8 (d, $J_{C,F}$ = 21.60 Hz).

HRMS (ESI) calculated for $C_{21}H_{15}N_2F$: 313.1141, found 313.1135.

2-(2-Naphthyl)-4,5-diphenyl-1*H*-imidazole (3m).[40]

This compound was prepared as described in the general procedure. White solid. Yield 75% (129.9 mg).

mp: 274-275 °C.

IR (cm^{-1}) 3050, 1586, 1445, 1407, 1340, 1262, 1069.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.88 (s, 1H), 8.65 (s, 1H), 8.31-8.29 (d, J = 8.29 Hz, 1H), 8.04-7.95 (m, 3H), 7.59-7.56 (m, 6H), 7.41 (m, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 146.0, 133.5, 133.2, 128.9, 128.7, 128.6, 128.3, 128.2, 127.2, 126.8, 124.2, 124.0.

HRMS (ESI) calculated for $C_{25}H_{18}N_2$: 345.1392, found 345.1393.

2-(2-Furanyl)-4,5-diphenyl-1*H*-imidazole (3n).[16]

This compound was prepared as described in the general procedure. White solid. Yield 16% (22.9 mg).

mp: 225-230 °C.

IR (cm^{-1}) 2818, 2721, 1599, 1442, 1071.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.82 (s, 1H), 7.81 (m, 1H), 7.54-7.51 (m, 4H), 7.45-7.42 (m, 2H), 7.39-7.37 (m, 1H), 7.33-7.29 (m, 2H), 7.25-7.24 (m, 1H), 6.99-6.98 (d, J = 3.25 Hz, 1H), 6.66 – 6.65 (m, 1H).

13C NMR (100 MHz, DMSO-d6): δ = 146.6, 143.9, 139.5, 137.9, 135.8, 131.7, 129.5, 129.3, 129.1, 128.7, 128.4, 128.0, 127.5, 112.8, 108.3.

HRMS (ESI) calculated for $C_{25}H_{18}N_2$: 286.3272, found 285.0739.

2-Cyclohexyl-4,5-diphenyl-1*H*-imidazole (3o).[32]

This compound was prepared as described in the general procedure. White solid. Yield 22% (33.3 mg).

mp: 240-243 °C.

IR (cm^{-1}) 3050, 1586, 1445, 1407, 1340, 1262, 1108.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.91 (s, 1H), 7.49-7.47 (d, J = 7.56 Hz, 2H), 7.42-7.36 (m, 4H), 7.32-7.24 (m, 3H), 7.19-7.16 (m, 1H), 2.74-2.68 (m, 1H), 2.00-1.97 (m, 2H), 1.82-1.79 (m, 2H), 1.72-1.69 (m, 1H), 1.65-1.56 (m, 2H), 1.41-1.24 (m, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 153.3, 136.7, 135.9, 132.6, 129.5, 128.9, 128.7, 128.1, 127.8, 127.0, 126.7, 38.1, 32.3, 26.6, 26.4, 21.6.

HRMS (ESI) calculated for $C_{25}H_{18}N_2$: 301.1705, found 301.1700.

5-(4-Chlorophenyl)-2,4-diphenyl-1*H*-imidazole (3s).[41]

This compound was prepared as described in the general procedure. White solid. Yield 66% (109.2 mg).

mp: 242-245 °C.

IR (cm^{-1}) 3043, 1583, 1483, 1462, 1404, 1092.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.81 (s, 1H), 8.11-8.09 (d, J = 9.11 Hz, 2H), 7.57-7.50 (m, 6H), 7.42-7.38 (m, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.9, 145.7, 137.7, 135.8, 134.9, 134.0, 132.3, 131.0, 130.8, 130.3, 130.0, 129.8, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.3, 126.9, 126.8, 125.2.

HRMS (ESI) calculated for $C_{21}H_{15}N_2Cl$: 331.1002, found 331.1002.

5-(4-Chlorophenyl)-2-(4-fluorophenyl)-4-phenyl-1*H*-imidazole (3t).[42]

This compound was prepared as described in the general procedure. White solid. Yield 56% (97.7 mg).

mp: 247-249 °C.

IR (cm^{-1}) 2967, 2786, 1601, 1538, 1484, 1442, 1221, 1089, 770.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.76-12.73 (m, 1H), 8.15-8.12 (m, 2H), 7.58-7.47 (m, 6H), 7.37-7.31 (m, 5H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 163.9, 161.5, 145 (d, $J_{C,F}$ = 15.09 Hz), 138.2, 136.3, 135.4, 134.4, 132.7, 131.0 (d, $J_{C,F}$ = 23.5 Hz), 130.4 (d, $J_{C,F}$ = 12.8 Hz), 130.1, 129.3 (d, $J_{C,F}$ = 7.4 Hz), 129.0 (d, $J_{C,F}$ = 4.1 Hz), 128.7, 128.5, 127.9 (d, $J_{C,F}$ = 8.23 Hz), 127.7, 127.4 (d, $J_{C,F}$ = 2.88 Hz), 127.3, 116.2 (d, $J_{C,F}$ = 22.6 Hz).

HRMS (ESI) calculated for $C_{21}H_{15}N_2F$: 347.0751, found 347.0743.

5-(4-Chlorophenyl)-4-phenyl-2-(p-tolyl)-1*H*-imidazole (3u).

This compound was prepared as described in the general procedure. White solid. Yield 62% (106.9 mg).

mp: 240-241 °C.

IR (cm^{-1}) 3026, 2917, 2107, 1988, 1650, 1485, 1315, 1088, 966, 823, 768.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.66 (s, 1H), 8.00 (d, J = 7.77 Hz, 2H), 7.54-7.52 (m, 4H), 7.49-7.38 (m, 5H), 7.31-7.29 (d, J = 8.36 Hz, 2H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 138.0, 136.1, 135.5, 134.6, 132.6, 131.4, 130.4, 129.7, 129.6, 129.2, 129.0, 128.7, 128.4, 128.2, 128.0, 127.7, 127.2, 125.7, 21.4.

HRMS (ESI) calculated for $C_{22}H_{17}N_2Cl$: 343.1002, found 343.1001.

2-(3-Chlorophenyl)-5-(4-chlorophenyl)-4-phenyl-1*H*-imidazole (3v).

This compound was prepared as described in the general procedure. White solid. Yield 52% (95 mg).

mp: 251-253 °C.

IR (cm^{-1}) 3049, 2960, 2077, 1576, 1468, 1089, 967, 829.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.88 (s, 1H), 8.17-8.16 (m, 1H), 8.07-8.05 (d, J = 8.00 Hz, 1H), 7.55-7.51 (m, 5H), 7.46-7.40 (m, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 144.7, 136.6, 134.1, 132.6, 131.6, 131.2, 130.4, 129.7, 129.0, 128.5, 127.9, 125.2, 124.2.

HRMS (ESI) calculated for $C_{21}H_{14}N_2Cl_2$: 363.0456 found 363.0462.

5-(4-Chlorophenyl)-2-(2-methoxyphenyl)-4-phenyl-1*H*-imidazole (3w).

This compound was prepared as described in the general procedure. White solid. Yield 60% (108.3 mg).

mp: 250-252 °C.

IR (cm^{-1}) 3197, 2107, 2083, 1588, 1472, 1015, 830, 742.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.96 (s, 1H), 8.07-8.04 (dd, J = 1.81 Hz, 7.68 Hz, 1 H), 7.56-7.33 (m, 10H), 7.19-7.06 (m, 2H), 3.93 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 156.5, 144.0, 143.8, 131.5, 131.3, 130.8, 130.5, 130.4, 129.4, 129.21, 129.16, 129.0, 128.7, 128.66, 128.4, 128.3, 127.7, 127.1, 126.7, 121.1, 119.3, 112.1, 56.1.

HRMS (ESI) calculated for $C_{22}H_{17}N_2OCl$: 359.0951 found 359.0955.

5-(4-Chlorophenyl)-2-(2-nitrophenyl)-4-phenyl-1*H*-imidazole (3x).

This compound was prepared as described in the general procedure. Yellow solid. Yield 62% (116.5 mg).

mp: 249-250 °C.

IR (cm^{-1}) 3053, 2106, 2081, 1663, 1522, 1349, 1091, 1012, 833, 768.

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.02 (s, 1H), 8.01-7.94 (dd, J = 7.86 Hz, 22.66 Hz, 2 H), 7.82-7.78 (t, J = 7.86 Hz, 1H), 7.68-7.64 (t, J = 7.40 Hz, 1H), 7.52-7.44 (m, 8H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 148.8, 141.8, 132.6, 131.9, 130.4, 130.2, 130.13 130.1, 130.0, 129.3, 129.2, 129.0, 128.9, 128.5, 124.5, 123.9.

HRMS (ESI) calculated for $C_{21}H_{14}N_3O_2Cl$: 374.0696, found 374.0701.

4,5-Bis(4-bromophenyl)-2-phneyl-1*H*-imidazole (3y).[17]

This compound was prepared as described in the general procedure. White solid. Yield 48% (32.5 mg).

mp: 209-212 °C.

IR (cm^{-1}) 2322, 2094, 1639, 1482, 1073, 965, 828.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.86 (s, 1H), 8.10-8.07 (d, J = 8.81 Hz, 2H), 7.61-7.57 (m, 5H), 7.52-7.46 (m, 6H), 7.43-7.39 (m, 1H);

^{13}C NMR (100 MHz, DMSO-d_6): δ 146.6, 137.0, 132.3, 131.9, 130.7, 130.4, 129.2, 129.0, 128.5, 126.2, 121.8, 120.8.

HRMS (ESI) calculated for $C_{21}H_{14}N_2Br_2$ 452.9602, found 452.9608.

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03 February 2020

Subject: Highlights for Molecular Iodine/DMSO Mediated Oxidation of Internal Alkynes and Primary Alcohols using a One-pot, Two Step Approach Towards 2,4,5-Trisubstituted Imidazoles: Substrate Scope and Mechanistic Studies

- 2,4,5-trisubstituted imidazoles were synthesized, using an innovative Iodine mediated double oxidation, from internal alkynes and primary alcohols.
- A plethora of imidazoles was prepared in modest to good yields.
- Mechanistic studies involved the use of radical traps, surrogate nucleophiles and Electron Paramagnetic Resonance (EPR) spectroscopy.
- The iodine mediated alkyne and alcohol oxidation was shown to proceed via two distinct oxidative pathways.

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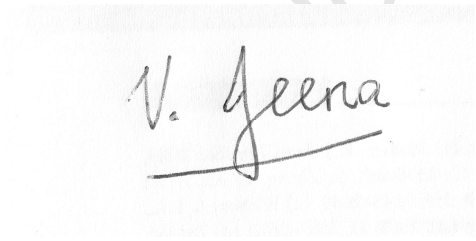

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