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Imidazole Synthesis

One-Pot, Two-Step Metal and Acid-Free Synthesis of Trisubstituted Imidazole Derivatives via Oxidation of Internal Alkynes Using an Iodine/DMSO System

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Abstract: A one-pot, two-step, simple, efficient and eco-friendly oxidation of internal alkynes as a key step towards the synthesis of 2,4,5-trisubstituted imidazoles, using an inexpensive I_2/DMSO system, has been reported. This metal and acid-free synthesis proceeded smoothly to furnish a variety of synthetically useful trisubstituted imidazoles in moderate to excellent yields. In an effort to demonstrate the potential future applications of this system, a double oxidation study was undertaken and the desired trisubstituted imidazoles obtained in good to moderate yields.

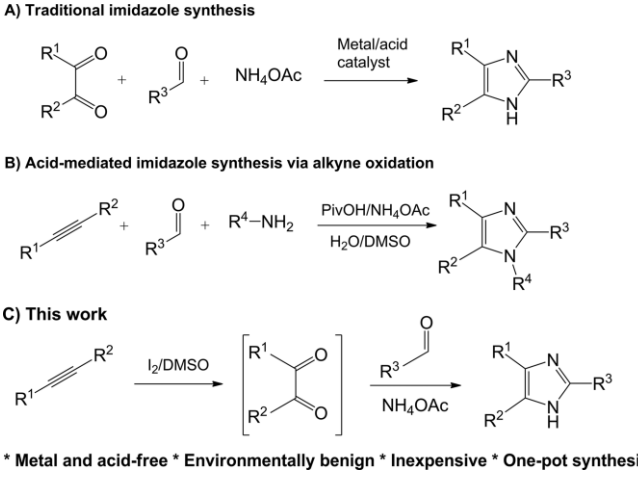
Introduction

Oxidation reactions form an area of paramount significance within the realm of synthetic organic chemistry.[1] These profound reactions allow chemists to design attractive methodologies that allow for the formation of carbon-carbon (C–C) bonds or the introduction of one or more electronegative atoms onto a molecule.[2] This has led to the steadily increasing development of novel, environmentally benign, inexpensive and high yielding oxidation protocols, thus allowing for the formation of complex molecules.[3]

There has been a long-standing interest in the development of internal alkyne oxidation to 1,2-diketones, as this is an important synthetic transformation that allows the generated diketones to be readily converted into various biologically active compounds.[4] Internal alkynes can be readily oxidized to 1,2-diketones by several methods[5] such as; the use of potassium permanganate,[6] ruthenium,[7] chromium[8] and cobalt oxidants[9] and a sulfur trioxide-dioxane complex[10] to name but a few. However, most of these methods suffer from several drawbacks such as harsh reaction conditions, displeasing product yields, tedious isolation procedures and the use of expensive and detrimental metal precursors.

These newly transformed diketones lead to the synthesis of valuable compounds such as N-heterocycles, which occupy an important place in the realm of synthetic organic chemistry and natural products research, as they are considered to be significant biological moieties and important chemical building blocks in the pharmaceutical and agrochemical industries.[11] Of those N-heterocyclic compounds, the trisubstituted imidazole motif is of utmost importance as it is an essential component in many natural products[12] and displays a vast range of biological activity such as inhibitors of p38 MAP kinase,[13] B-Raf kinase[14] and biosynthesis of interleukin **1** (IL-1).[15] Trisubstituted imidazoles, in particular, have rich medicinal applications and are known to act as good α-glucosidase inhibition agents.[16] These substituted imidazoles are also known to possess good photophysical properties such as organic light-emitting diodes (OLEDs)[17] and, in addition, can be used in photography as photosensitive compounds.[18]

Consequently, a plethora of routes have been devised for the synthesis of these valuable trisubstituted imidazole derivatives[19] and, traditionally, the cardinal synthesis towards trisubstituted imidazole derivatives involves the condensation of an α-diketone, aldehyde and ammonium acetate in the presence of a metal or acid catalyst (Scheme 1A).[20] An alternate strategy by Wang and co-workers utilized stoichiometric pivalic acid as an oxidant, together with a solvent mixture of DMSO/water to promote the synthesis of imidazole derivatives via alkyne oxidation (Scheme 1B).[21] However, most of the above methods



Scheme 1. Synthetic procedures towards 2,4,5-trisubstituted imidazoles.

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suffer from several drawbacks such as complex and laborious work-up procedures, use of toxic transition metal catalysts, produce a large amount of waste, strongly acidic conditions, the occurrence of side reactions, low yields and the use of expensive reagents. Thus, there is a dire need for an efficient and environmentally benign protocol for the synthesis of substituted imidazoles. Recently, molecular iodine has gained substantial interest due to its inexpensive, nontoxic and nonmetallic nature, and has thus become an important reagent for organic functional group transformations.[22] Dimethyl sulfoxide (DMSO) is an inexpensive, low-toxic solvent that has been used extensively as an oxidant[23] and synthon[24] in many renowned reactions such as the Swern oxidation,[25] Pfitzner-Moffatt oxidation[26] and the Corey-Chaykovsky epoxidation and cyclopropanation.[27] The combination of molecular iodine and DMSO has revolutionized synthetic methodology especially those related to oxidative processes.[28]

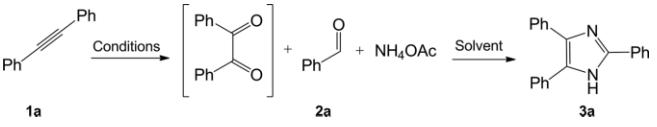
Herein we report an alternative method for the synthesis of imidazole derivatives using an internal alkyne, aldehyde, and ammonium acetate under metal and acid-free conditions (Scheme 1C).

Results and Discussion

In search of optimal conditions, the one-pot reaction between diphenylacetylene (**1a**), benzaldehyde (**2a**) and ammonium acetate in DMSO for 2 h in the presence of 1.5 equivalents of molecular iodine (I_2) was examined, however, the desired product **3a** was not obtained (Table 1, entry 1). Thereafter, the reaction was attempted in a one-pot two-step manner, the diphenylacetylene was heated in DMSO for 1 h at 130 °C in the presence of 1.5 equivalents of molecular iodine (I_2). Thereafter, benzaldehyde and ammonium acetate were added, and the mixture was left to react for a further 2 h at 100 °C.

Encouragingly, the desired product, 2,4,5-triphenyl-1*H*-imidazole (**3a**) was obtained in a 39 % isolated yield (Table 1, entry 2). The coupling reaction of trisubstituted imidazoles is known to be solvent specific,[29] therefore, to promote this reaction, a range of organic solvents were added to encourage cyclization, however, no product was isolated in the presence of propan-2-ol, water and diethyl ether (Table 1, entries 3–5). When methanol was used, the desired product was formed in a 48 % isolated yield (Table 1, entry 6). We then turned our attention toward using ethanol, as many imidazole synthetic reactions are known to proceed well in the presence of this solvent[30] and, to our delight, the yield of the isolated product increased to 90 % (Table 1, entry 7).To determine if DMSO is the ideal coupling partner for I_2, we examined DMF, MeCN and THF (Table 1, entries 8–10), however, there was no product formation suggesting that DMSO is essential for this reaction. The loading of iodine was decreased, to 1, 0.5 and 0.1 equivalents, however, the formation of **3a** was substantially reduced to isolated yields of 77 %, 40 % and 31 %, respectively (Table 1, entries 11–13). Other iodine containing nonmetal catalysts such as; iodine pentoxide (I_2O_5) and 2-iodobenzoic acid (IBX) were screened (Table 1, entries 14–15) and both catalysts resulted in no product formation. There was no reaction in the absence of DMSO

Table 1. Optimization of reaction conditions for the synthesis of 2,4,5-triphenyl-1*H*-imidazole (**3a**).[a]



1a 2a 3a

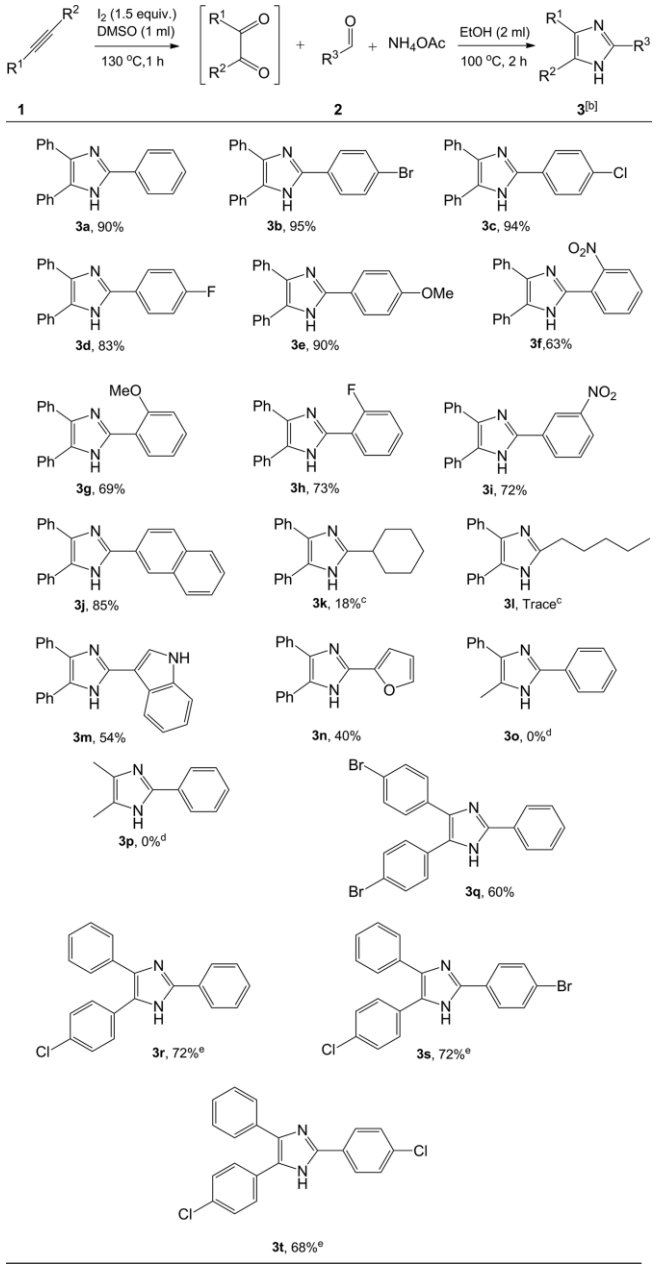
Entry	Conditions	Solvent (2 mL)	Yield (%)[b]
1[c]	I_2/DMSO	–	N.R
2	I_2/DMSO	–	39
3	I_2/DMSO	Propan-2-ol	N.R
4	I_2/DMSO	Water	N.R
5	I_2/DMSO	Diethyl ether	N.R
6	I_2/DMSO	Methanol	48
7	**I_2/DMSO**	**Ethanol**	**90**
8	I_2/DMF	Ethanol	N.R
9	I_2/MeCN	Ethanol	N.R
10	I_2/THF	Ethanol	N.R
11[d]	I_2/DMSO	Ethanol	77
12[e]	I_2/DMSO	Ethanol	40
13[f]	I_2/DMSO	Ethanol	31
14	I_2O_5/DMSO	Ethanol	N.R
15	IBX/DMSO	Ethanol	N.R
16	I_2	Ethanol	N.R
17	DMSO	Ethanol	N.R
18[g]	I_2/DMSO	Ethanol	14
19[h]	I_2/DMSO	Ethanol	11

[a] Reaction conditions: Step 1: **1a** (0.5 mmol), I_2 (1.5 equiv.)/DMSO (1 mL), 1 h, 130 °C. Step 2: **2a** (0.5 mmol), NH_4OAc (10 equiv.), solvent (2 mL), 2 h, 100 °C. [b] Isolated yield. [c] One-pot, one-step reaction, 100 °C, 2 h. [d] I_2 (1 equiv.)/DMSO (1 mL), 100 °C, 2 h. [e] I_2 (0.5 equiv.)/DMSO (1 mL), 100 °C, 2 h. [f] I_2 (0.1 equiv.)/DMSO (1 mL), 100 °C, 2 h. [g] NH_4OAc (5 equiv.). [h] NH_4OAc (2 equiv.). N. R = No reaction.

(Table 1, entry 16) or I_2 (Table 1, entry 17). Numerous trisubstituted imidazole synthetic procedures use fluctuating amounts of ammonium acetate,[31] therefore, an attempt to decrease the amount of ammonium acetate was made. When 5 and 2 equivalents were used, lower isolated yields of 14 % and 11 % were obtained (Table 1, entries 18–19). Therefore, the conditions described in (Table 1, entry 7), were found to be optimal and allowed for the maximum formation of the desired product **3a**. (See the Supporting Information for additional temperature, solvent volume and iodo source variation studies (S2-S3). Having optimized the reaction conditions, the scope of the developed system was assessed by varying the internal alkynes and aldehydes, the ensuing results of which are listed in Table 2.

The coupling of benzaldehyde derivatives, bearing *para*-substituted electron-withdrawing and electron-donating substituents, with **1a** afforded 2,4,5-trisubstituted imidazoles (Table 2, entries **3a–3e**) in high yields of 83 % to 95 %. Good imidazole yields of 63 % to 73 %, were obtained with benzaldehyde substituted at the *ortho* position (Table 2, entries **3f–3 h**). Similarly, *meta* substituted nitrobenzaldehyde resulted in 2-(3-nitrophenyl)-4,5-diphenyl-1*H*-imidazole (Table 2, entry **3i**) in a favorable yield of 72 %. Encouraged by these results, and to diversify our substrates, a bulkier aldehyde such as 2-naphthaldehyde was employed which delivered the resulting 2-(naphthalen-2-yl)-4,5-diphenyl-1*H*-imidazole in an excellent yield of 85 % (Table 2, entry **3j**). To expand the scope of our methodology, aliphatic aldehydes were employed, however, the correspond-

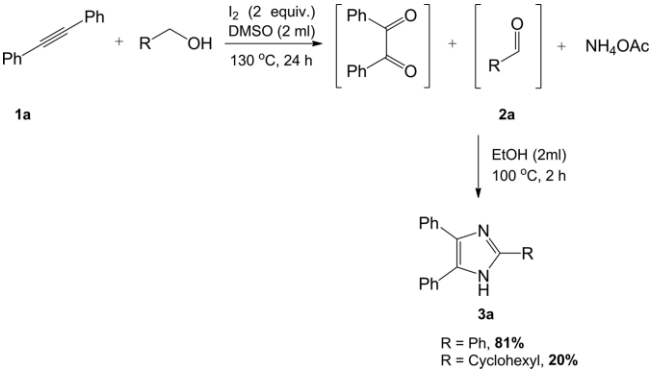
Table 2. Substrate scope of 2,4,5-trisubstituted-1*H*-imidazoles with various alkynes and aldehydes.[a]



[a] Reaction conditions: Step 1: **1** (0.5 mmol), I_2 (1.5 equiv.)/DMSO (1 mL), 1 h, 130 °C. Step 2: **2** (0.5 mmol), NH_4OAc (10 equiv.), EtOH (2 mL), 3 h, 100 °C. [b] Isolated yield. [c] Step 2: 24 h. [d] Step 1: 24 h. [e] Mixture of tautomers (see the Supporting Information for details).

ing alkylated imidazoles were synthesized in low yields of 18 % to trace amounts (Table 2, entry **3k** and **3l**). This result is consistent with literature, as aliphatic aldehydes are not commonly examined in trisubstituted imidazole synthesis,[32] and, when they are, often result in low yields. More encouraging, was the use of heterocyclic aldehydes, indole-3-carboxaldehyde and 2-furfural, which successfully proceeded to generate the desired products albeit in modest yields of 54 % and 40 %, respectively (Table 2, entries **3m** and **3n**). Next, the coupling reactions between benzaldehyde and various internal alkynes were examined. Unfortunately, 1-phenyl-1-propyne and 2-butyne resulted in no product formation, (Table 2, **3o-3p**), which is probably due to the reduced nucleophilicity of these substrates.[33] Thereafter, 1,2-bis(4-bromophenyl)acetylene reacted smoothly to successfully afford 4,5-bis(4-bromophenyl)-2-phenyl-1*H*-imidazole in a favorable yield of 60 % (**3q**). The coupling between 1-(4-chlorophenyl)-2-phenylacetylene with benzaldehyde derivatives also produced 2,4,5-triarylimidazoles, 3r–3t as a mixture of tautomers, due to the presence of the fluid hydrogen on the nitrogen atom, in satisfactory yields of 68 % to 72 %.

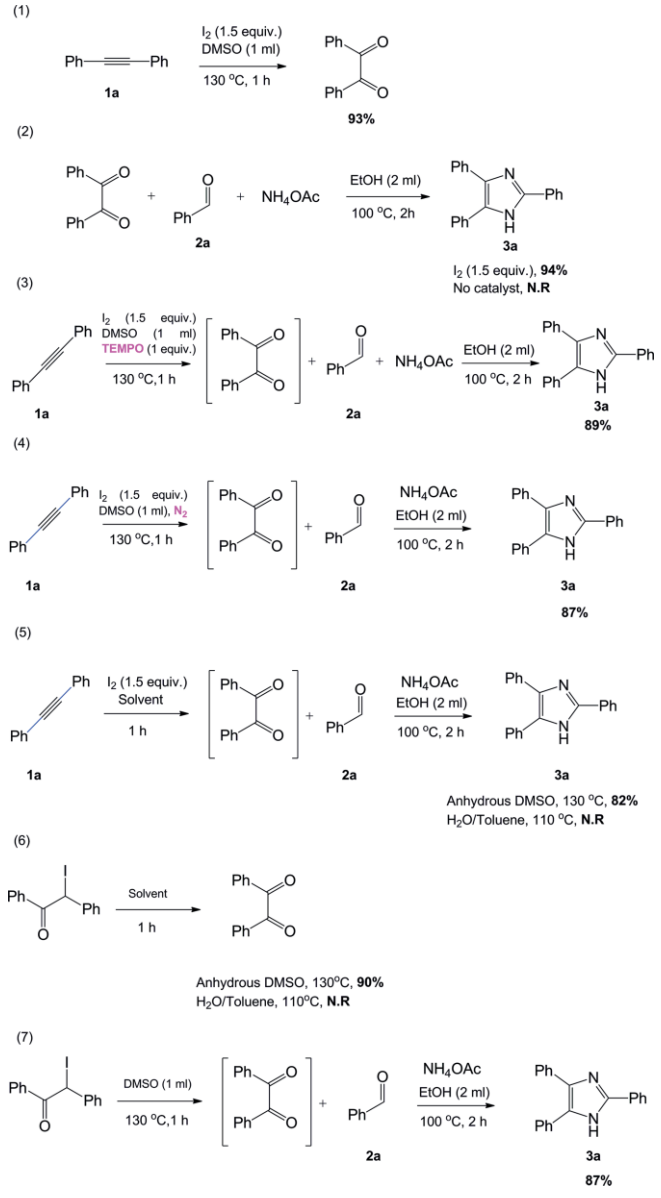
Next, we turned our attention towards the convergent integration of two domino sequences beginning from the internal alkyne and primary alcohols to produce trisubstituted imidazoles. The rationale behind this synthetic approach was to commence from two unusual starting materials (internal alkyne and primary alcohol) which could be converted into the diketone and aldehyde using the I_2/DMSO system, which would then serve as intermediates *en route* to the target imidazole. As a preliminary experiment, the oxidation of diphenylacetylene and benzyl alcohol was carried out, in the same reaction vessel, in the presence of 2 equivalents of I_2 in DMSO for 24 h, thereafter, ammonium acetate together with ethanol was added and the mixture was left to react for a further 2 h. To our absolute delight, this reaction proceeded smoothly and furnished the corresponding 2,4,5-triphenyl-1*H*-imidazole in an 81 % isolated yield (Scheme 2). With this exciting result in hand, we decided to test this double oxidation reaction with an aliphatic alcohol, which although successful, produced the target imidazole in a moderate 20 % isolated yield. These results illustrate that the I_2/DMSO system can effect multiple chemical transformations, in the same reaction vessel, and can become a key component of future convergent integration syntheses and may develop into a valuable synthetic strategy towards a range of fascinating compounds.



Scheme 2. Convergent synthesis of 2,4,5-trisubstituted imidazoles.

To gain insight into the reaction mechanism, a number of control experiments were carried out (Scheme 3). First, diphenylacetylene (**1a**) was oxidized with I_2/DMSO at 130 °C for 1 h, to afford benzil in a 93 % isolated yield, confirming that the diketone is indeed an intermediate in this transformation (Scheme 3, eqn. (1)). Next, a mixture of benzil, benzaldehyde and ammonium acetate, was treated with I_2 and ethanol and afforded **3a** in a yield of 94 %, while, in the absence of iodine, no product was detected, indicating that iodine plays a vital

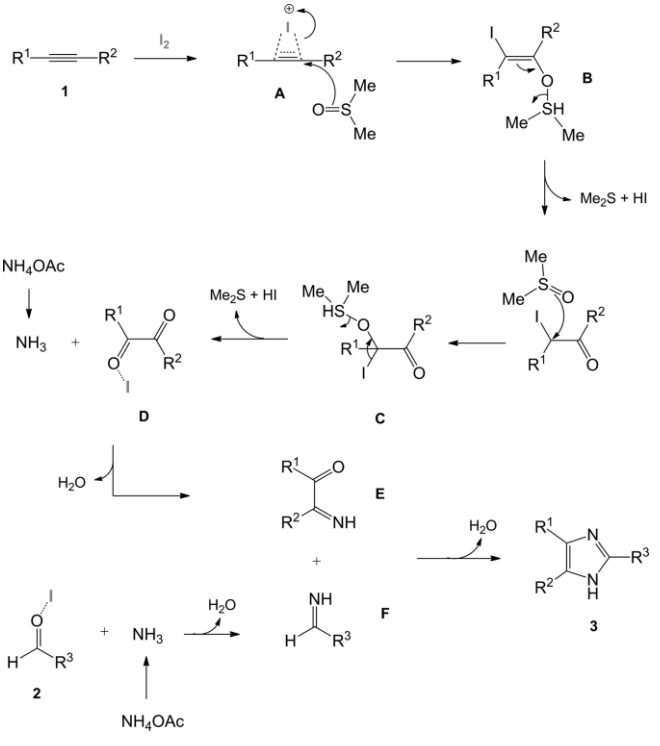
role in the coupling reaction leading to the trisubstituted imidazole[34] (Scheme 3, eqn. (2)). The radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction mixture under the standard conditions and **3a** was formed in an 89 % isolated yield, suggesting that the reaction does not proceed via a radical pathway (Scheme 3, eqn. (3)). The test reaction was also carried out under an N_2 atmosphere, which resulted in **3a** being formed in an 87 % isolated yield, indicating that the oxidation is not dependent on O_2 from the atmosphere (Scheme 3, eqn. (4)).



Scheme 3. Control experiments for I_2/DMSO catalysed trisubstituted imidazole synthesis.

The next set of control experiments was conducted to determine the source of oxygen in the diketone, which could originate from either the DMSO or trace H_2O present in DMSO. In the presence of, freshly distilled, anhydrous DMSO, **3a** was synthesized in an 82 % isolated yield, suggesting that DMSO is the dominant source of oxygen. When the same reaction was replicated, with H_2O and toluene as a solvent mixture, the reaction did not proceed as only starting material was observed, suggesting that trace H_2O in DMSO does not play a role in the oxidation of the internal alkyne (Scheme 3, eq. (5)). Finally, we speculated that the iodoketone was an intermediate in this synthetic route as we could rationalize its formation mechanistically, and proceeded to synthesize this compound using a literature process[35] and test its reactivity. Firstly, the iodoketone was heated in anhydrous DMSO, which resulted in the formation of benzil in an excellent yield of 90 % (Scheme 3, eqn. (6)). However, when the same reaction was attempted in a solvent mixture of H_2O and toluene, no product was obtained (Scheme 3, eqn. (6)). Lastly, we reacted the iodoketone to form benzil, and upon the addition of benzaldehyde and ammonium acetate, led to the formation of **3a** in an 87 % isolated yield (Scheme 3, eqn. (7)). These results suggest that the iodoketone is an important intermediate in the alkyne oxidation and it reacts with DMSO to generate the diketone, which upon addition of the aldehyde and ammonium acetate leads to the observed imidazole.

Based on the results of our control experiments and previous literature reports,[36] a likely mechanism is outlined in Scheme 4. It is feasible that the reaction begins with the activation of the triple bond of the alkyne by iodine to furnish the iodonium intermediate **A**. The addition of DMSO on **A** allows for the formation of the iodide intermediate **B**, simultaneously dispelling the weakly basic dimethyl sulfide (Me_2S).[37] The generated iodoketone is immediately trapped by a molecule of DMSO, to form intermediate **C**, which progresses to form the expected 1,2-diketone while expelling a second molecule of Me_2S. Thereafter, **A** and the aldehyde (**2**) are concurrently activated by



Scheme 4. Plausible mechanism for the synthesis of trisubstituted imidazoles.

iodine and upon reaction with ammonium acetate, form imine intermediates **E** and **F**. Both imine intermediates undergo cyclocondensation to afford the desired 2,4,5-trisubstituted imidazole **3** (Scheme 4).

Conclusions

In summary, we have described a simple, efficient, eco-friendly and inexpensive methodology for the synthesis of 2,4,5-trisubstituted imidazoles from various internal alkynes, aldehydes, and ammonium acetate via an I_2/DMSO oxidation system. The developed system provides a convenient and practical route that can be applied to a range of substrates, making this imidazole synthetic technique an alternative approach that could replace conventional processes. Furthermore, this system was applicable to a convergent integration domino sequence of an internal alkyne and primary alcohol, resulting in the formation of trisubstituted imidazoles. Supplementary studies expanding the scope of this methodology as well as in-depth mechanistic studies are underway in our laboratories and will be reported in due course.

Experimental Section

General Remarks: All reagents were purchased and used without further purification. All ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on the Bruker Avance III spectrometer operating at 400 MHz. Chemical shifts (δ) were reported in ppm using the dimethyl sulfoxide-d_6 ([D_6]DMSO) residual peak (δ 2.50) for ^{1}H NMR spectroscopy. Chemical shifts for ^{13}C NMR were reported relative to [D_6]DMSO (δ 39.51). The following abbreviations were used to describe peak splitting patterns: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants, *J*, were reported in Hertz (Hz). High-resolution electron-spray ionization (ESI) mass spectra were recorded in a time of flight (TOF) micromass spectrometer. Infra-red (IR) spectra were recorded on the Carey 630 FTIR. Absorption maxima are expressed in wavenumbers (cm^{-1}). Melting points were determined using a Kofler hot-stage melting apparatus.

General Procedure for the Synthesis of 2,4,5-Trisubstituted Imidazoles: A mixture of internal alkyne (0.5 mmol), I_2 (1.5 equiv.) and DMSO (1 mL) was reacted for 1 h at 130 °C. Thereafter, aldehyde (0.5 mmol), ammonium acetate (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 reaction mixture to form a precipitate which was filtered and dried. The crude product was recrystallized with ethanol to afford the desired product **3**.

2,4,5-Triphenyl-1*H*-imidazole (3a):[21,38] Yield 134.84 mg (90 %); white solid; m.p. 270–272 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.66 (s, 1 H), 8.09–8.07 (d, *J* = 7.6 Hz, 2 H), 7.53–7.52 (m, 4 H), 7.49–7–45 (m, 3 H), 7.38–7.35 (m, 6 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 146.0, 137.6, 135.7, 131.6, 130.9, 129.14, 129.1, 128.9, 128.71, 128.7, 128.2, 127.6, 127.0, 125.7 ppm. IR: ṽ = 3757, 3037, 1586, 1461, 1484, 1126 cm^{-1}. ESI-MS (*m*/*z*) 297 [M + H]$^+$.

2-(4-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (3b):[39,40] Yield 178.25 mg (95 %); white solid; m.p. 254–256 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.78 (s, 1 H), 8.07–8.03 (d, *J* = 8.5 Hz, 2 H), 7.71–7.68 (d, *J* = 8.7 Hz, 2 H), 7.57–7–51 (m, 4 H), 7.48–7.44 (m, 2 H), 7.41–7.40 (m, 1 H), 7.34–7.30 (m, 2 H), 7.26–7.23 (m, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 145.0, 137.9, 135.5, 132.1, 131.4, 130.1, 129.13, 129.1, 128.9, 128.7, 128.3, 127.6, 127.1, 121.9 ppm. IR: ṽ = 3594, 2640, 2195, 1599, 1478, 1125, 765 cm^{-1}. ESI-MS (*m*/*z*) 375 [M + H]$^+$.

2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (3c):[39,40] Yield 155.48 mg (94 %); white solid; m.p. 262–264 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.77 (s, 1 H), 8.13–8.10 (d, *J* = 8.5 Hz, 2 H), 7.57–7.55 (d, *J* = 8.96 Hz, 4 H), 8.53–8.51 (m, 2 H), 7.48–7.44 (m, 2 H), 7.41–7.38 (m, 1 H), 7.34–7.30 (m, 2 H), 7.26–7.22 (m, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 145.3, 138.2, 135.9, 133.6, 131.8, 130.1, 129.6, 129.5, 129.3, 128.7, 128.0, 127.7, 127.5 ppm. IR: ṽ = 2837, 1480, 1127, 763 cm^{-1}. ESI-MS (*m*/*z*) 375 [M + H]$^+$.

2-(4-Fluorophenyl)-4,5-diphenyl-1*H*-imidazole (3d):[39,40] Yield 130.46 mg (83 %); white solid; m.p. 262–264 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.69 (s, 1 H), 8.16–8.12 (m, 2 H), 7.54 (m, 4 H), 7.49–7.23 (m, 8 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 163.8, 161.4, 145.2, 128.9, 128.2, 127.9 (d, $J_{C,F}$ = 6.57 Hz), 127.5 (d, $J_{C,F}$ = 2.7 Hz), 116.1 (d, $J_{C,F}$ = 21.3 Hz) ppm. IR: ṽ = 2639, 1607, 1491, 1223, 1159 cm^{-1}. ESI-MS (*m*/*z*) 315 [M + H]$^+$.

2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (3e):[38] Yield 146.9 mg (90 %); white solid; m.p. 230–233 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.51 (s, 1 H), 8.05–8.03 (d, *J* = 8.84 Hz, 2 H), 7.54–7.25 (m, 10 H), 7.07–7.05 (d, *J* = 8.83 Hz, 2 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 159.9, 146.1, 137.1, 135.9, 131.7, 128.8, 127.6, 127.2, 123.6, 114.6, 55.7 ppm. IR: ṽ = 2960, 2095, 1609, 1490, 1241, 1174 cm^{-1}. ESI-MS (*m*/*z*) 327 [M + H]$^+$.

2-(2-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (3f):[41] Yield 107.53 mg (63 %); yellow solid; m.p. 268–272 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.96 (s, 1 H), 8.03–8.00 (dd, *J* = 1.15 Hz, 7.77 Hz, 1 H), 7.95–7.93 (d, *J* = 7.8 Hz, 1 H), 7.82–7.78 (t, *J* = 7.44 Hz, 1 H), 7.67–7.63 (t, J = 7.80 Hz, 1 H), 7.53–7.51 (m, 4 H), 7.47–7.26 (m, 8 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 148.8, 141.5, 132.6, 130.3, 130.0, 129.0, 128.0, 124.5, 124.0 ppm. IR: ṽ = 2964, 1583, 1523, 1480, 1415, 1302, 1071 cm^{-1}. ESI-MS (*m*/*z*) 364 [M + Na]$^+$.

2-(2-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (3g):[38] Yield 112.60 mg (69 %); white solid; m.p. 223–225 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 11.90 (s, 1 H), 8.10–8.08 (dd, *J* = 1.57 Hz, 7.42 Hz, 1 H), 7.58–7.56 (d, *J* = 7.65 Hz, 2 H), 7.49–7.47 (m, 2 H), 7.42–7.41 (t, J = 7.20 Hz, 2 H), 7.39–7.36 (m, 2 H), 7.31–7.28 (t, J = 7.20 Hz, 2 H), 7.23–7.20 (m, 1 H), 7.18–7.16 (d, *J* = 8.10 Hz, 1 H), 7.09–7.06 (t, *J* = 7.42 Hz, 1 H), 3.93 (s, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 156.9,144.1, 137.3, 136.2, 132.2, 130.7, 129.7, 129.5, 129.4, 129.0, 128.5,128.4, 128.0, 127.3,121.5, 119.8, 112.5, 56.5 ppm. IR: ṽ = 3196, 3061, 2836, 1582, 1466, 1246, 1097 cm^{-1}. ESI-MS (*m*/*z*) 327 [M + H]$^+$.

2-(2-Fluorophenyl)-4,5-diphenyl-1*H*-imidazole (3h):[42] Yield 114.74 mg (73 %); white solid; m.p. 268–272 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.55 (s, 1 H), 8.04–8.01 (td, *J* = 1.70 Hz, 1.40 Hz, 2.26 Hz, 1 H), 7.58–7.49 (m, 4 H), 7.49–7.45 (m, 1 H), 7.44–7.18 (m, 8 H), 7.53–7.51 (m, 4 H), 7.47–7.26 (m, 8 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 160.6, 158.1, 141.3 (d, $J_{C,F}$ = 2 Hz), 137.8, 135.5, 131.4, 130.8 (d, $J_{C,F}$ = 8.1 Hz), 130.10 (d, $J_{C,F}$ = 2.9 Hz), 128.9, 125.1 (d, $J_{C,F}$ = 4.6 Hz), 119.1 (d, $J_{C,F}$ = 11.5 Hz), 116.6 (d, $J_{C,F}$ = 20.6 Hz) ppm. IR: ṽ = 3036, 1578, 1480, 1221, 1099, 701 cm^{-1}. ESI-MS (*m*/*z*) 315 [M + H]$^+$.

2-(3-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (3i):[39,40] Yield 122.89 mg (72 %); yellow solid; m.p. 268–272 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 13.10 (s, 1 H), 8.97 (s, 1 H), 8.54–8.52 (d, *J* = 7.70 Hz, 1 H), 8.24–8.22 (d, *J* = 7.87 Hz, 1 H), 7.82–7.78 (t, J = 8.04 Hz, 16.0 Hz, 1 H), 7.57–7.56 (m, 4 H), 7.41 (m, 6 H) ppm. ^{13}C NMR (100 MHz,

[D_6]DMSO): δ = 148.8, 143.8, 132.3, 131.6, 130.8, 128.9, 128.3, 127.9, 123.0, 119.9 ppm. IR: ṽ = 2738, 1580, 1518, 1476, 1415, 1344, 1248, 1069 cm^{-1}. ESI-MS (*m/z*) 342 $[M + H]^+$.

2-(2-Naphthyl)-4,5-diphenyl-1*H*-imidazole (3j):[43] Yield 147.22 mg (85 %); white solid; m.p. 274–276 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.87 (s, 1 H), 8.64 (s, 1 H), 8.29–8.27 (d, *J* = 8.84 Hz, 1 H), 8.04–7.95 (m, 3 H), 7.60–7.53 (m, 6 H), 7.43–7.39 (m, 6 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): 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 ppm. IR: ṽ = 2738, 1580, 1518, 1476, 1415, 1344, 1248, 1069 cm^{-1}. ESI-MS (*m/z*) 347 $[M + H]^+$.

2-Cyclohexyl-4,5-diphenyl-1*H*-imidazole (3k):[38] Yield 27.2 mg (18 %); white solid; recrystallization solvent: ethyl acetate; m.p. 240–241 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 11.91 (s, 1 H), 7.49–7.47 (d, *J* = 7.62 Hz, 2 H), 7.42–7.37 (m, 4 H), 7.32–7.24 (m, 3 H), 7.19–7.16 (m, 1 H), 2.74–2.69 (m, 1 H), 2.00–1.97 (m, 2 H), 1.82–1.80 (m, 2 H), 1.71–1.56 (m, 3 H), 1.42–1.17 (m, 3 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 152.9, 136.3, 135.5, 132.1, 129.0, 128.5, 128.3, 127.6, 127.5, 126.5, 126.2, 37.7, 32.0, 26.2, 26.1, 21.2 ppm. IR: ṽ = 3031, 2925, 2850, 1593, 1446, 1366, 1183 cm^{-1}. ESI-MS (*m/z*) 303.

3-(4,5-Diphenyl-1*H*-imidazol-2-yl)-1*H*-indole (3m):[44] Yield 91.0 mg (54 %); white solid; recrystallization solvent: ethanol; m.p. 215–220 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.28 (s, 1 H), 11.38 (s, 1 H), 8.52–8.50 (d, *J* = 6.89 Hz, 1 H), 8.02 (s, 1 H), 7.68–7.66 (m, 2 H), 7.56–7.54 (m, 2 H), 7.46–7.44 (m, 3 H), 7.38–1.32 (m, 3 H), 7.25–7.16 (m, 3 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 144.2, 136.8, 136.5, 136.2, 132.1, 129.1, 128.6, 127.8, 127.4, 126.6, 126.2, 125.6, 124.3, 122.3, 122.0, 120.1, 112.1, 107.3 ppm. IR: ṽ = 3418, 2072, 1600, 1493, 1452 cm^{-1}. ESI-MS (*m/z*) 336 $[M + H]^+$.

2-(2-Furanyl)-4,5-diphenyl-1*H*-imidzole (3n):[21] Yield 57.0 mg (40 %); brown solid; m.p. 228–230 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.81 (s, 1 H), 7.81 (d, *J* = 1.06 Hz, 1 H), 7.54–7.51 (m, 4 H), 7.49–7.42 (m, 2 H), 7.39–7.37 (m, 1 H), 7.33–7.29 (m, 2 H), 7.25–7.24 (m, 1 H), 6.99–6.98 (d, *J* = 3.16, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 146.2, 143.5, 139.1, 137.5, 135.4, 131.3, 129.1, 128.8, 128.7, 128.3, 128.0, 127.6, 127.1, 112.3, 107.9 ppm. IR: ṽ = 2819, 2722, 1600, 1483, 1071 cm^{-1}. ESI-MS (*m/z*) 286 $[M + H]^+$.

4,5-Bis(4-bromophenyl)-2-phenyl-1*H*-imidazole (3q): Yield 54.50 mg (60 %) (based on a 0.15 mmol scale); white solid; m.p. 210–214 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.80 (s, 1 H), 8.09–8.07 (d, *J* = 7.23 Hz, 2 H), 7.66–7.55 (m, 5 H), 7.53–7.46 (m, 6 H), 7.42–7.39 (m, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 146.6, 136.6, 132.1, 132.0, 130.5, 130.2, 129.2, 129.0, 128.6, 125.8, 121.3 ppm. IR: ṽ = 2322, 2094, 1639, 1482, 1073, 965, 828 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{14}Br_2N_2$ 452.9602 found 452.9608.

5-(4-Chlorophenyl)-2,4-diphenyl-1*H*-imidazole (3r):[45] Yield 117.40 mg (72 %); white solid; m.p. 242–245 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.75 (s, 1 H), 8.11–8.09 (d, J = 7.72 Hz, 2 H), 7.57–7.50 (m, 6 H), 7.48–7.38 (m, 6 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 146.8, 146.6, 138.7, 136.7, 135.9, 135.0, 133.2, 131.9, 131.8, 131.2, 131.1,131.0, 130.8, 129.8, 129.7, 129.52, 129.50, 129.3, 129.28, 129.23, 129.0, 128.2, 127.9, 127.7, 126.2, 126.18 ppm. IR: ṽ = 3043, 1583, 1483, 1462, 1404, 1092, 767 cm^{-1}. HRMS (ESI): cald. for $C_{21}H_{15}N_2Cl$ $[M + H]^+$ 331.1002, found 331.1009.

2-(4-Bromophenyl)-5-(4-Chlorophenyl)-4-phenyl-1*H*-imidazole (3s):[46] Yield 147.50 mg (72 %); white solid; m.p. 252–254 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.84 (s, 1 H), 8.05–8.03 (d, *J* = 8.65 Hz, 2 H), 7.71–7.68 (d, *J* = 8.68 Hz, 2 H), 7.56–7.52 (t, *J* = 8.55 Hz, 4 H), 7.42 (m, 5 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 145.7, 132.7, 130.3, 129.9, 129.5, 129.2, 128.1, 126.3, 122.5 ppm. IR: ṽ = 2641, 1599, 1478, 1442, 1070 cm^{-1}. HRMS (ESI): cald. for $C_{21}H_{14}N_2ClBr$ 409.0107, found 409.0114.

2,5-Bis(4-chlorophenyl)-4-phenyl-4-phenyl-1*H*-imidazole (3t) (See the Supporting Information):[46] Yield 124.19 mg (68 %); white solid; m.p. 245–249 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.83 (s, 1 H), 8.12–8.10 (d, *J* = 8.47 Hz, 2 H), 7.57–7.38 (m, 11 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): 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 ppm. IR: ṽ = 2114, 1602, 1577, 1443, 1391, 1323, 773 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{15}N_2Cl_2$ 365.0612, found 365.0619.

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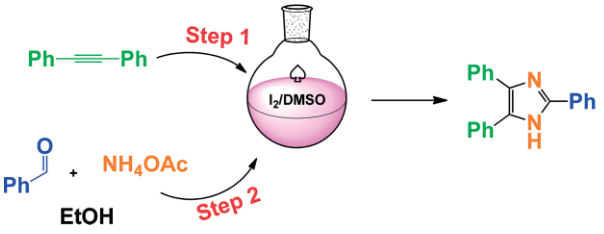
Imidazole Synthesis

Metal and acid-free, environmentally benign, inexpensive



A one-pot, two-step, simple, efficient and eco-friendly oxidation of internal alkynes as a key step towards the synthesis of 2,4,5-trisubstituted imidazoles, using an inexpensive I_2/DMSO system, has been reported. This metal and acid-free reaction proceeded smoothly to furnish a variety of substituted imidazoles in moderate to excellent yields.

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