HETEROCYCLES, Vol. 104, No. 9, 2022, pp. 1649 - 1660. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 17th June, 2022, Accepted, 6th July, 2022, Published online, 15th July, 2022
DOI: 10.3987/COM-22-14699

MOLECULAR IODINE MEDIATED SYNTHESIS OF 2,4,5-TRISUBSTITUTED IMIDAZOLES COMMENCING FROM α-METHYLENE KETONES AND BENZYLIC PRIMARY ALCOHOLS USING A ONE-POT, TWO-STEP APPROACH

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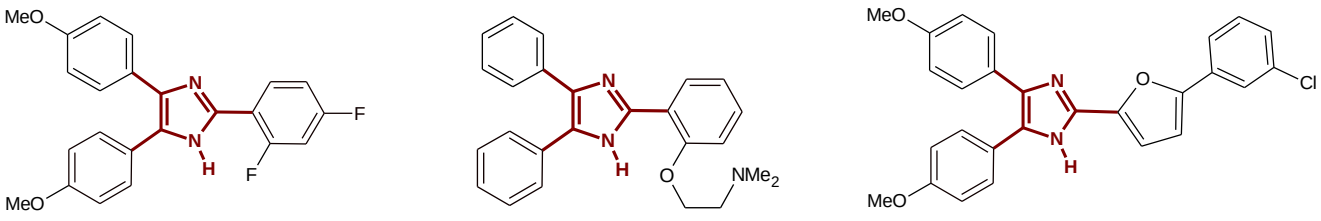
Abstract – A simple one-pot, two-step approach to 2,4,5-trisubstituted imidazoles has been developed commencing from α-methylene ketones and primary alcohols. Using an environmentally friendly, inexpensive, and readily available iodine-based system, a series of trisubstituted imidazoles were prepared in moderate to good yields under mild reaction conditions.

2,4,5-Trisubstituted imidazoles have been known for over 100 years[1] and are recognized for their anti-bacterial,[2] anti-inflammatory,[3] and anti-tubercular properties.[4] A smorgasbord of pharmacologically relevant 2,4,5-trisubstituted imidazoles is presented in Figure 1.



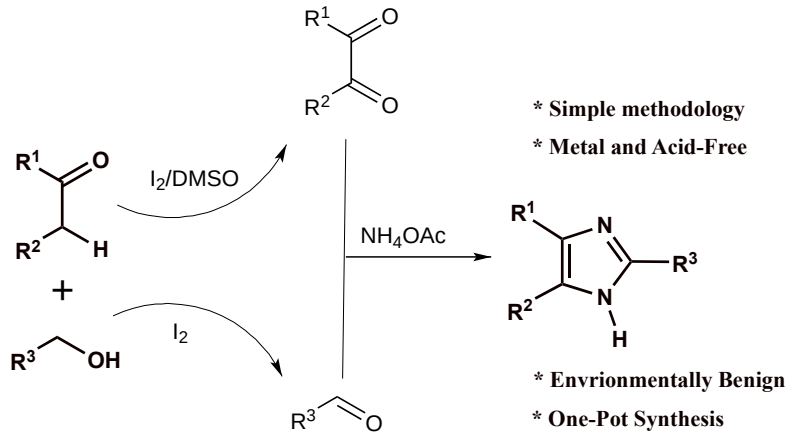
Fenflumizole **Trifenagrel** **Neurodazine**

Figure 1. Examples of pharmacologically relevant 2,4,5-trisubstituted imidazoles

Recently, studies on these fascinating trisubstituted molecules have shown they exhibit good activity against *Klebsiella pneumoniae*, a bacteria associated with the development of pneumonia.[5] 2,4,5-Trisubstituted imidazoles have also been shown to be active against *Plasmodium falciparum*[6,7] as well as inhibit α-glucosidase[8] suggesting their potential as lead compounds against malaria and diabetes mellitus

respectively.

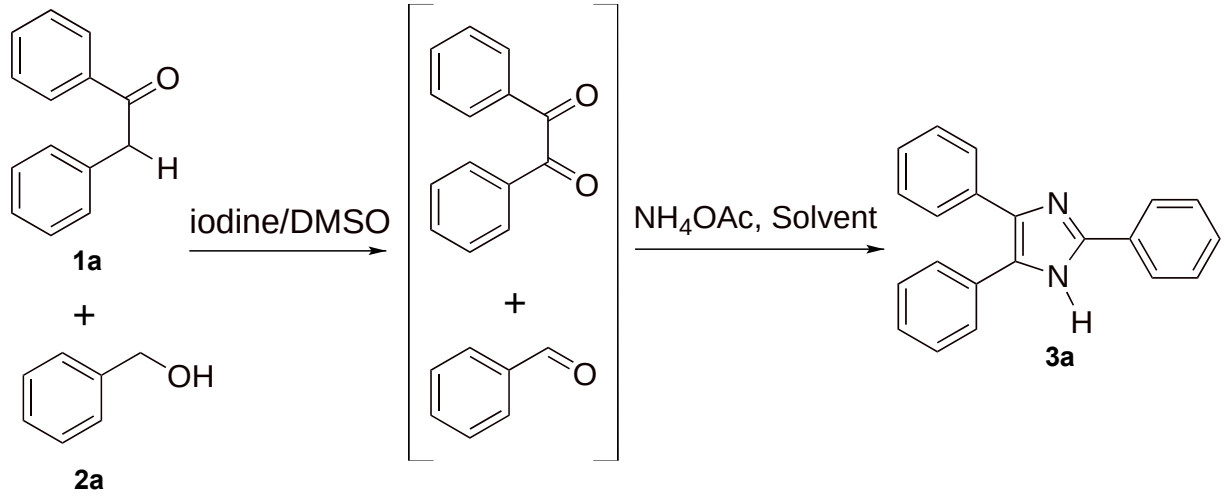
Given the importance of 2,4,5-trisubstituted imidazoles, several methods have been developed for the preparation of these valuable compounds.[9] 2,4,5-Trisubstituted imidazoles are generally synthesized by a three-component reaction using a 1,2-diketone, aldehyde, and ammonium acetate in the presence of transition metals or acidic media.[10,11] However, most of these synthetic methods suffer from serious drawbacks such as strongly acidic conditions, very high temperatures, and elaborate, multi-step procedures.[12,13] Hence, the development of new approaches that overcome these shortcomings is of vital importance. In recent years, the traditional approach to trisubstituted imidazoles has been modified to commence from an alcohol, which is oxidized to an aldehyde and, in the presence of the diketone and ammonium acetate, will ultimately produce the trisubstituted imidazole.[14] Our group has extended this methodology by reporting that α-methylene ketones can be oxidized to form the 1,2-diketone and, in the presence of an aldehyde and ammonium acetate, lead to the 2,4,5-trisubstituted imidazole.[15-17] Of late, iodine in combination with H_2O_2,[18,19] *tert*-butyl hydroperoxide (TBHP),[20,21] or *N*-bromosuccinimide (NBS)[22,23] has been extensively studied due to its environmentally friendly nature *in lieu* of rare or toxic, heavy metal systems.[24] In particular, the use of iodine, used either stoichiometrically or catalytically, in combination with dimethyl sulfoxide (DMSO) has received widespread attention from scientists the world over, to prepare a diverse range of synthetically useful compounds.[25] As part of our previous research, we have shown that α-methylene ketones can be oxidized to diketones using the iodine/DMSO system[26] and that primary alcohols could also be converted to aldehydes using an iodine-mediated system.[27] Based on these observations, we were intrigued by the possibility of combining these two synthetic approaches by commencing from an α-methylene ketone and primary alcohol, which could be used to prepare the intermediate diketone and aldehyde respectively, and in the presence of ammonium acetate, lead to the formation of 2,4,5-trisubstituted imidazoles. The proposed synthetic route is simple, metal and acid-free, environmentally benign, and involves a one-pot synthesis of 2,4,5-trisubstituted imidazoles *via* simultaneous C-H and O-H oxidation (Scheme 1).



Scheme 1. Proposed synthetic route to 2,4,5-trisubstituted imidazoles

To test this hypothesis, we began our studies by evaluating the coupling of benzyl phenyl ketone **1a** and benzyl alcohol **2a** as part of an optimization study (Table 1). Before commencing with our experimental work, we identified two main challenges for the proposed synthesis. Firstly, we had to identify the correct conditions for our oxidation reaction, and secondly, determine the ideal conditions for the coupling reaction which would lead to our target imidazole. Our study commenced by mixing benzyl phenyl ketone **1a**, benzyl alcohol **2a,** and ammonium acetate, in the presence of iodine and DMSO for 24 hours. Unfortunately, the reaction was unsuccessful and only starting material was recovered (Table 1, entry 1). A literature review of trisubstituted imidazole synthesis revealed that the three-component coupling reaction is solvent specific and works best in the presence of ethanol.[28-30] Using this information, we attempted our next reaction step-wise, by mixing **1a** and **2a** in the presence of iodine and DMSO for 24 hours followed by the addition of ammonium acetate and ethanol, which produced the desired 2,4,5-triphenylimidazole in an isolated yield of 22% (Table 1, entry 2). Encouraged by this result, we attempted to reduce the reaction time through microwave irradiation but, under these conditions, no product was obtained (Table 1, entry 3). Based on this result, we focused on conventional heating and further explored this synthetic route by varying the amount of iodine, DMSO, ammonium acetate and reaction times (Table 1, entries 4 – 18). The variation in the quantity of iodine and DMSO had a profound effect on the yield (Table 1, entries 4 and 5). To rationalize this observation, we speculated that the amount of DMSO is crucial in the reaction since it acts as both the solvent and nucleophile (*vide infra*). An excessive amount of DMSO reduces the possibility of the iodine interacting with the methylene ketone, while lower quantities of DMSO affect the amount of nucleophile, resulting in a diminished product yield. We improved the yields by keeping the loading of iodine constant at 2.5 equivalent and reducing the amount of DMSO (Table 1, entries 5 – 7), which further confirms the importance of the quantity of DMSO in the reaction. When we varied the amount of iodine, a fluctuation in yield was also observed (Table 1, entries 8 and 9). During these studies, it was found that mixing benzyl phenyl ketone **1a** and benzyl alcohol **2a** with 2.5 equivalents iodine in 2.5 mL DMSO at 100 ^{o}C for 24 hours, followed by the addition of ammonium acetate and ethanol at 100 ^{o}C for a further 2 hours produced, to our delight, the target compound in a good yield of 84% (Table 1, entry 10). The varying of the coupling solvent (Table 1, entries 11 – 14) resulted in diminished yields which added credence to our hypothesis that ethanol is the most suitable solvent for trisubstituted imidazole formation. In the absence of iodine or DMSO, no product was observed highlighting their importance in the reaction (Table 1, entries 15 and 16). In an attempt to further improve synthetic efficiency, the reaction time of the first step was decreased from 24 hours to 12 hours using the optimal amount of iodine and DMSO, however, under these conditions, no product was observed (Table 1, entry 17). Finally, we attempted to decrease the amount of ammonium acetate, however, this change in reaction conditions also resulted in a lower yield (Table 1, entry 18).

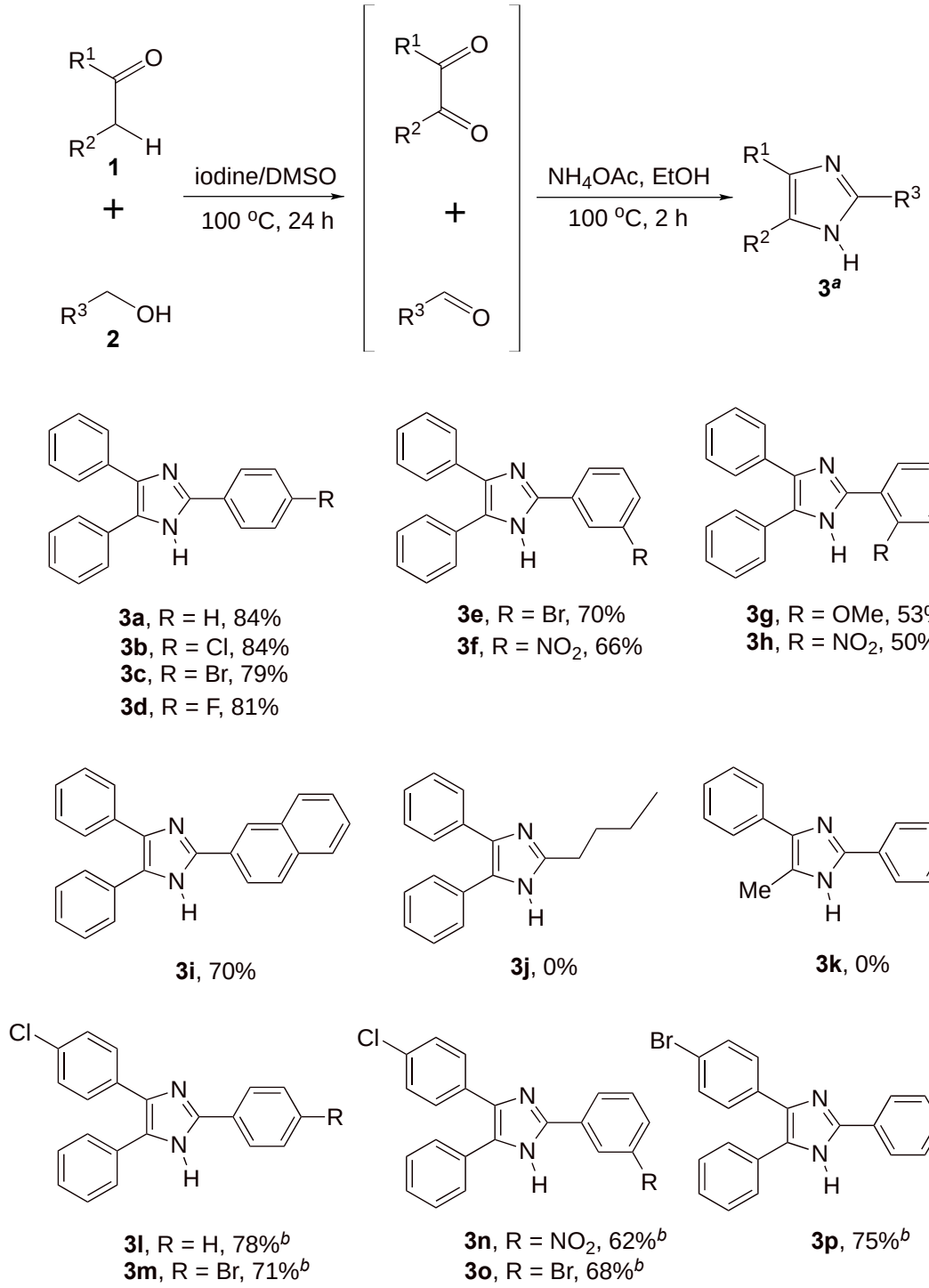
Table 1. Optimization of reaction conditions for the formation of 2,4,5-triphenylimidazole from benzyl phenyl ketone and benzyl alcohol[a]



Entry	I_2 (equiv.)	DMSO (mL)	Solvent	Yield (%)[b]
1[c]	0.5	1	–	N. R
2	0.5	1	EtOH	22
3[d]	0.5	1	EtOH	N. R
4	1	2	EtOH	31
5	2.5	5	EtOH	19
6	2.5	3	EtOH	67
7	2.5	2	EtOH	71
8	1	2.5	EtOH	65
9	1.5	2.5	EtOH	68
10	**2.5**	**2.5**	**EtOH**	**84**
11	2.5	2.5	MeOH	63
12	2.5	2.5	H_2O	57
13	2.5	2.5	MeCN	N. R
14	2.5	2.5	–	55
15	–	2.5	EtOH	N. R
16[e]	2.5	–	EtOH	N. R
17[f]	2.5	2.5	EtOH	N. R
18[g]	2.5	2.5	EtOH	41

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), iodine, DMSO (2.5 mL), 100 °C for 24 h thereafter NH_4OAc (10 equiv.), solvent (2 mL) for 2 h. N. R = No reaction. [b] Isolated yield. [c] One-pot reaction. [d] Microwave reaction: Step 1 for 10 min + Step 2 for 10 min. [e] MeCN was used in place of DMSO. [f] First step reaction time: 12 h. [g] 5 equiv. of NH_4OAc.

With the optimized conditions in hand, we turned our attention towards the preparation of a series of diverse, trisubstituted imidazoles to explore the scope and limitations of this synthetic approach. To evaluate our devised system, a series of α-methylene ketones and alcohols were varied under the optimized conditions (Scheme 2).



Scheme 2. Reaction conditions: α-Methylene ketone (1 mmol), Alcohol (1 mmol), I_2 (2.5 mmol) in 2.5 mL DMSO at 100 °C for 24 h thereafter NH_4OAc (10 equiv.), EtOH (2 mL) at 100 °C for 2 h. [a] Isolated yield. [b] Mixture of tautomers.

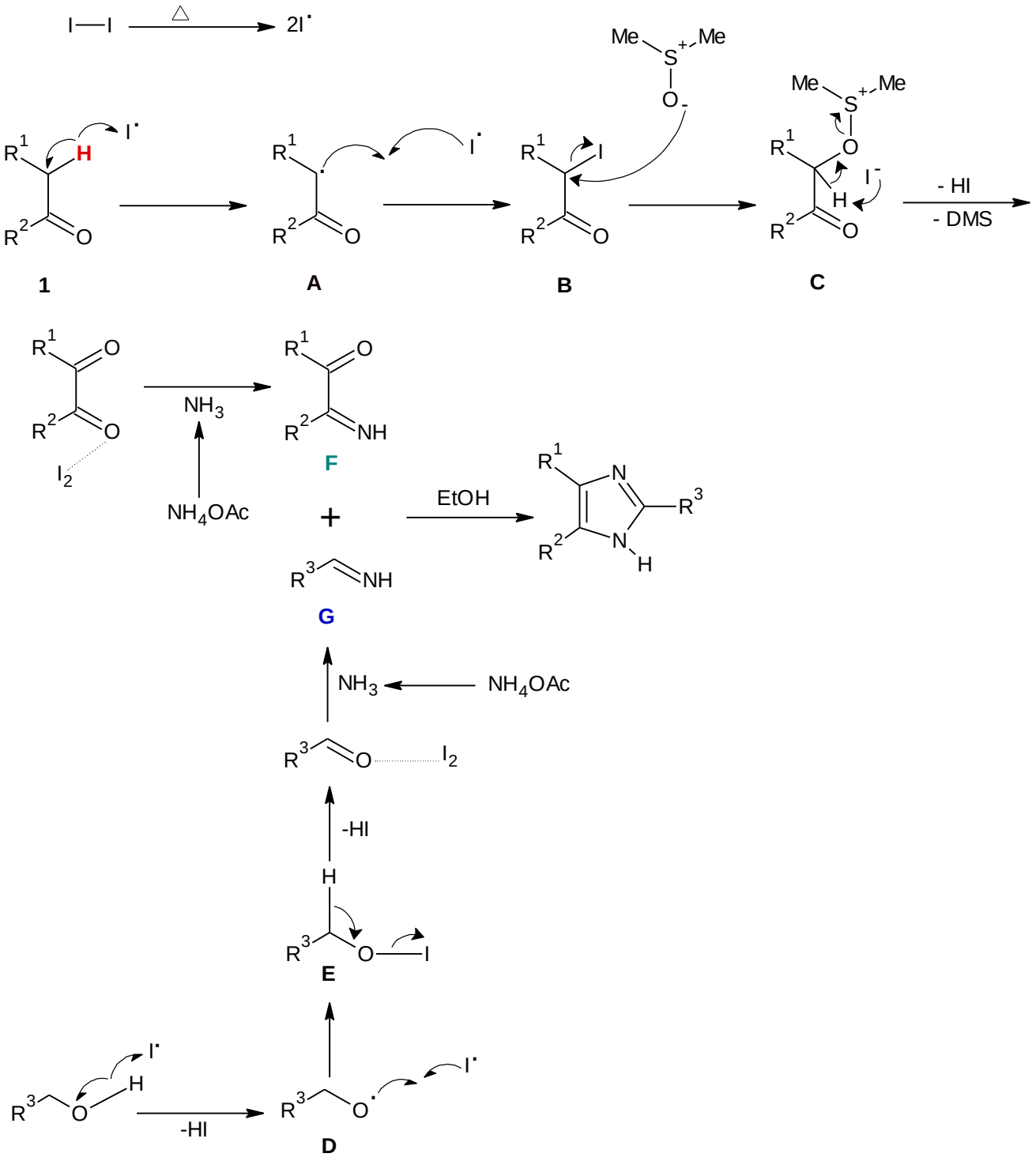
Benzyl alcohol substituted with a series of halogens at the *para*-position reacted smoothly to deliver the corresponding 2,4,5-trisubstituted imidazoles in good yields of 79-84% (Scheme 2, compounds **3b**-**3d**). This result showed that the presence of the halogen, at the *para*-postion, had little effect and, in all cases, good yields were obtained. Next, benzyl alcohols substituted at the *meta*-position were analyzed to produce the target imidazoles in moderate yields of 66-70% (Scheme 2, compounds **3e**,**f**), which were relatively consistent even when contrasting substitutents such as a halogen or nitro group were examined. However, substitution at the *ortho*-position using 2-methoxybenzyl alcohol and 2-nitrobenzyl alcohol as reactants produced the trisubstituted imidazoles diminished yet acceptable yields of 53% and 50% respectively (Scheme 2, compounds **3g**,**h**). It is predicted that the greater steric hindrance near the key aldehyde moiety may account for the decreased yields. The expansion of our methodology to a bulkier substrate, proceeded smoothly to afford the desired imidazole in a satisfactory yield of 70% (Scheme 2, compound **3i**).

Regrettably, attempts to prepare the corresponding imidazole using an aliphatic alcohol was unsuccessful and only starting material was recovered (Scheme 2, compound **3j**). This is consistent with literature as the iodine/DMSO system is ineffective on aliphatic alcohols resulting in no aldehyde formation.[31] Due to this, the coupling step is retarded by the low aldehyde concentration resulting in a break in the synthetic process. Next, we evaluated the effect of substituents on the α-methylene ketone. The presence of the benzene ring was found to be crucial as the use of propiophenone was not compatible with the transformation under several conditions and only the starting material was recovered (Scheme 2, compound **3k**). The use of chloro-substituted α-methylene ketones with various substituted alcohols produced the 2,4,5-trisubstituted imidazoles in good yields of 62-78% as a mixture of tautomers (Scheme 2, entries **3l**-**o**), due to the presence of the fluid hydrogen. Finally, to conclude this study, we monitored the reaction between a bromo-substituted α-methylene ketone and benzyl alcohol which produced the desired product in a yield of 75% as a mixture of tautomers (Scheme 2, compound **3p**).

Based on literature reports[32-34] as well as our earlier studies,[26,27] the predicted mechanism for this synthetic methodology is outlined below (Scheme 3). To begin the process, molecular iodine is cleaved by heat to form iodine radicals. These iodine radicals abstract a proton from the methylene ketone **1** to form the radical **A**. This radical reacts with another iodine radical to form the α-iodinated intermediate **B**, which reacts with DMSO to form intermediate **C**, which undergoes deprotonation with the removal of HI and dimethyl sulfide (DMS), to produce the diketone.

Concurrently, the oxidation of alcohol is predicted to commence with proton abstraction from the –OH group to form the phenoxy radical **D**. This newly formed radical is quenched by an iodine radical to produce intermediate **E**, which undergoes deprotonation, accompanied by the release of HI, to generate the key intermediate aldehyde. Molecular iodine is known to display mild Lewis acid properties and is predicted to coordinate to the carbonyl compounds to increase their reactivity.[35]

Finally, ammonium acetate decomposes to ammonia, which attacks the reactive carbonyl compounds resulting in the formation of crucial imine intermediates **F** and **G** which cyclocondense to form the target imidazole.



Scheme 3. Proposed route to 2,4,5-trisubstituted imidazoles commencing from α-methylene ketones and primary alcohol

In summary, we have developed a simple, environmentally friendly, and efficient procedure for the synthesis of 2,4,5-trisubstituted imidazoles from α-methylene ketones and primary alcohols. This unique synthetic approach produces a series of trisubstituted imidazoles in good yields under mild reaction conditions.

EXPERIMENTAL

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 either 400 or 100 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 residual peak (δ 39.51). High-resolution electron-spray ionization (ESI) mass spectra were recorded on a time-of-flight (TOF) micromass spectrometer. Infrared (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.

Typical procedure for the preparation of 2,4,5-trisubsituted imidazoles (3). **2,4,5-Triphenyl-1*H*-imidazole (3a).** A solution of benzyl phenyl ketone (196 mg, 1 mmol), benzyl alcohol (104 µL, 1 mmol), iodine (2.5 mmol) in 2.5 mL DMSO was heated at 100 ºC for 24 h. Thereafter, NH_4OAc (10 mmol) and 2 mL EtOH were added, and the mixture heated for a further 2 h. The reaction mixture was then cooled and a solution of cold 1% aq. $Na_2S_2O_3$ was added dropwise to the reaction mixture to form a precipitate which was filtered and dried. The crude precipitate was recrystallized with EtOH to afford **3a**[27] as a white solid (248 mg, 84%); mp 270-273 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 12.69 (s, 1H), 8.15-8.06 (d, J = 7.34 Hz, 2H), 7.61-7.39 (m, 8H), 7.39-7.21 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6): 146.0, 137.6, 135.6, 131.8, 130.9, 129.2, 129.9, 128.8, 128.7, 128.2, 127.70, 127.10, 125.69; IR: ῦ = 3393 (N-H), 2964 (C-H), 1462 (C=C); ESI-MS (*m*/*z*): 297.1236 (100) $[M+H]^+$, 298.1268 (25).

2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (3b):[16] a white solid (278 mg, 84%); mp 262-265 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 12.73 (s,1H), 8.14-8.08 (d, J = 8.62 Hz, 2H), 7.58-7.49 (m, 6H), 7.48-7.17 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): 145.0, 137.9, 135.8, 133.2, 131.6, 129.9, 129.3, 129.1 129.0, 128.9, 128.4, 127.7, 127.3, 127.2; IR: ῦ = 3203 (N-H), 1481 (C=C), 1126 (C-N); ESI-MS (*m*/*z*): 329.1065 (100) $[M-H]^+$, 331.1049 (36).

2-(4-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (**3c**)**:**[16] a white solid (297 mg, 79%); mp 256-258 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 12.80 (s,1H), 8.09-8.01 (d, *J* = 8.56 Hz, 2H), 7.71-7.65 (d, *J* = 8.55 Hz, 2H), 7.57-7.50 (m, 4H), 7.44-7.21 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): 145.1, 137.7, 135.5, 132.3, 131.7, 130.7, 130.2, 129.6, 129.0, 128.3, 127.2, 126.6, 121.9.; IR: ṽ = : 3305 (N-H), 2643 (C-H), 1601 (C=C); ESI-MS (*m*/*z*): 375.0461 (100)) $[M]^+$, 376.0492 (24).

2-(4-Flourophenyl)-4,5-diphenyl-1*H*-imidazole (3d):[27] a white solid (254 mg, 81%); mp 251-253 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 12.73 (s,1H), 8.17- 8.10 (m, 2H), 7.59-7.50 (m, 4H), 7.43-7.25 (m, 8H); ^{13}C NMR (100 MHz, DMSO-d_6): 163.9, 161.4, 145.2, 138.0, 135.7, 131.5, 129.2, 128.9, 128.8, 127.2, 127.9, 127.7, 127.4, 116.2; IR: ṽ = 3464 (N-H), 2646 (C-H), 1605 (C=C); ESI-MS (*m*/*z*): 315.1307 (100)) $[M+H]^+$, 316.1342 (25).

2-(3-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (3e):[36] a white solid (263 mg, 70%); ^{1}H NMR (400 MHz, DMSO-d_6: 12.81 (s, 1H), 8.36-8.27 (s, 1H), 8.15-8.05 (d, *J* = 7.78, 1H), 7.61-7.25 (m, 12H); ^{13}C NMR (100 MHz, DMSO-d_6): 144.3, 137.7, 134.6, 132.9, 131.4, 131.3, 128.9, 128.4, 128.2, 128.0, 127.7, 127.1, 126.8, 124.5, 122.6; IR: ṽ = 3382 (N-H), 3050 (C-H), 1620 (C=C); ESI-MS (*m*/*z*): 375.1045 (100) $[M]^+$, 378.1064 (25).

2-(3-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (3f):[17] a yellow solid (225 mg, 66%); mp 310-312 ºC; ^{1}H NMR (400 MHz, DMSO-d_6: 13.08 (s, 1H), 8.96 (s, 1H), 8.54-8.50 (d, *J* = 7.84 Hz, 1H), 8.23-8.18 (d, *J* = 8.10 Hz, 1H), 7.80-7.74 (t, *J* = 7.94 Hz, 1H), 7.61-7.50 (m, 4H), 7.50-7.21 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): 148.8, 143.8, 132.3, 131.6, 131.7, 130.9, 128.9, 123.0, 119.9; IR: ṽ = 3320 (N-H), 2859 (C-H), 1581 (C=C); ESI-MS (*m*/*z*): 342.1702 (100)) $[M+H]^+$, 343.1734 (25).

2-(2-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (3g):[27] a white solid (173 mg, 53%); mp 206-208 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 11.94 (s, 1H), 8.09-8.05 (d, *J* = 7.70 Hz, 1H), 7.54-7.52 (m, 2H), 7.52-7.49 (m, 2H), 7.42-7.38 (m, 2H), 7.38-7.36 (m, 2H), 7.36-7.31 (m, 2H), 7.30-7.27 (m, 1H), 7.19-7.14 (m, 1H), 7.11-7.05 (m, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 156.5, 143.6, 136.5, 135.5, 130.3, 129.4, 128.8, 128.7, 128.4, 128.2, 127.6, 127.5, 126.9, 126.6, 121.2, 119.4, 112.1, 56.2; IR: ṽ = 3050 (N-H), 2836 (C-H), 1584 (C=C); ESI-MS (*m*/*z*): 327.1894 (100)) $[M+H]^+$, 328.1933 (25).

2-(2-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (3h):[27] a yellow solid (170 mg, 50%); mp 226-228 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 12.97 (s, 1H), 8.03-7.99 (d, *J* = 7.89 Hz, 1H), 7.95-7.91 (d, *J* = 8.07 Hz, 1H), 7.81-7.76 (t, *J* = 7.68Hz, 1H), 7.66-7.61 (t, *J* = 7.81 Hz, 1H), 7.54-7.48 (m, 4H), 7.43-7.25 (m, 6H); ^{13}C

NMR (100 MHz, DMSO-d_6): 148.8, 141.6, 132.6, 130.3, 130.0, 128.9, 124.5, 123.9; IR: ṽ = 3349 (N-H), 2963 (C-H), 1581 (C=C); ESI-MS (*m*/*z*): 340.1046 (100) $[M-H]^+$, 341.1070 (25).

2-(2-Naphthalenyl)-4,5-diphenyl-1*H*-imidazole (3i):[27] a white solid (243 mg, 70%); mp 272-276 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 12.86 (s, 1H), 8.64 (s, 1H), 8.31-8.25 (d, *J* = 8.57, 1H), 8.04-7.92 (m, 3H), 7.63-7.51 (m, 6H), 7.51-7.19 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): 146.0, 133.5, 133.2, 128.9, 128.7, 128.6, 128.3, 128.2, 127.2, 126.8, 124.2, 123.9; IR: ṽ = 3395 (N-H), 2969 (C-H), 1599 (C=C); ESI-MS (*m*/*z*): 347.1567 (100)) $[M+H]^+$, 348.1597 (29).

5-(4-Chlorophenyl)-2,4-diphenyl-1*H*-imidazole (3l):[17] a white solid (258 mg, 78%); mp 240-243 ºC; ^{1}H NMR (400 MHz, DMSO-d_6: 12.75-12.73 (s, 1H), 8.13-8.08 (d, *J* = 7.55 Hz, 2H), 7.61-7.43 (m, 8H), 7.42-7.30 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): 146.3, 146.2, 138.2, 136.3, 135.5, 135.5, 132.7, 131.5, 131.3, 131.07, 130.7, 130.5, 130.3, 129.9, 129.2, 129.03, 128.8 128.8, 128.7, 128.5, 128.2, 127.8, 127.4, 127.2, 126.8, 125.7; IR: ṽ = 3386 (N-H), 3052 (C-H), 1582 (C=C); ESI-MS (*m*/*z*): 331.0876 (100) $[M+H]^+$, 333.0864 (38).

2-(4-Bromophenyl)-5-(4-chlorophenyl)-4-phenyl-1*H*-imidazole (3m):[17] a white solid (291 mg, 71%); mp 249-251 ºC; ^{1}H NMR (400 MHz, DMSO-d_6: 12.83 (s, 1H), 8.07-8.00 (d, *J* = 8.60 Hz, 2H) 7.72-7.65 (d, *J* = 8.48 Hz, 2H), 7.58-7.29 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): 145.2, 132.2, 129.9, 129.1, 128.9, 128.2, 127.7, 125.7, 122.0; IR: ṽ = 3404 (N-H), 3058 (C-H), 1476 (C=C); ESI-MS (*m*/*z*): 411.0114 (100), 409.0136 (74) $[M]^+$.

5-(4-Chlorophenyl)-2-(3-nitrophenyl)-4-phenyl-1*H*-imidazole (3n):[17] a yellow solid (233 mg, 62%); mp 274-276 ºC; ^{1}H NMR (400 MHz, DMSO-d_6: 13.11 (s, 1H), 8.94 (s, 1H), 8.53-8.46 (d, *J* = 7.94 Hz, 1H), 8.22-8.15 (d, *J* = 8.16 Hz, 1H), 7.78-7.70 (t, *J* = 7.99 Hz, 1H), 7.62-7.49 (m, 4H), 7.49-7.19 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6): 148.8, 144.1, 132.2, 131.7, 130.8, 129.2, 128.8, 123.1, 119.9; IR: ṽ = 3291 (N-H), 3068 (C-H), 1520 (C=C); ESI-MS (*m*/*z*): 376.0744 (100)) $[M+H]^+$, 378.0723 (36).

2-(3-Bromophenyl)-5-(4-chlorophenyl)-4-phenyl-1*H*-imidazole (3o): a white solid (279 mg, 68%); mp 262-264 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 12.86 (s,1H), 8.31 (s, 1H), 8.14-8.05 (d, *J* = 7.88Hz, 1H), 7.61-7.49 (m, 5H), 7.49-7.21 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): 144.6, 138.5, 136.6, 135.2, 134.23, 132.9, 132.2, 131.6, 131.4, 131.4, 131.1, 130.4, 130.1, 129.6, 129.2, 129.1, 128.9, 128.7, 128.6, 128.1, 127.8, 127.4, 124.6, 122.6; IR: ṽ = 3325 (N-H), 3056 (C-H), 1476 (C=C); ESI-MS (*m*/*z*): calcd for $C_{21}H_{15}N_2BrCl$ 409.0107, found 408.9968.

5-(4-Bromophenyl)-2,4-diphenyl-1*H*-imidazole (3p):[16] a white solid (281 mg, 75%); mp 250-252 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 12.78-12.69 (s,1H), 8.13-8.06 (d, J = 7.57 Hz, 2H), 7.67-7.22 (m,12H); ^{13}C NMR (100 MHz, DMSO-d_6): 146.4, 146.2, 138.2, 136.3, 135.4, 134.9, 132.1, 131.6, 131.3, 130.7, 130.6, 129.4, 129.3, 129.2, 129.03, 128.84, 128.8, 128.5, 127.8, 127.4, 127.2, 125.7, 121.2, 119.9; IR: ṽ = 3321 (N-H), 3075 (C-H), 1596 (C=C); ESI-MS (*m*/*z*): 377.0502 (100) $[M+2H]^+$, 378.0539 (24).

ACKNOWLEDGEMENTS

L. P. M. is grateful to the University of KwaZulu-Natal (Dean's Discretionary Fund) for a postgraduate bursary. We are grateful to the National Research Foundation of South Africa for a Thuthuka research grant (TTK180410319052).

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