Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2017, 9(8):80-84
(http://www.derpharmachemica.com/archive.html)

Synthesis and Characterization of Tetrasubstitued Imidazole by Using Silica Supported Catalysis

Sarnikar YP[1], Mane YD[2], Survarse SM[1], Khade BC[3*]

[1]Department of Chemistry, Dayanand Science College, Latur, Maharashtra, India
[2]Department of Chemistry, Shri Chhatrapati Shivaji College, Omerga, Maharashtra-413512, India
[3]Department of Chemistry, Dnyanopasak College, Parbhani, Maharashtra, India

---

ABSTRACT

A facile route for the synthesis of tetrasubstituted imidazole has been developed; the one pot synthetic protocol allows the efficient synthesis of biologically important scaffolds. By using alkyne as the key starting material, which was oxidized in situ to get active carbonyl species? The key reaction involved in this synthesis is formic acid catalyzed oxidation, I2 mediated oxidation and Silica supported cyclization to give tetrasubstituted imidazole.

Keywords: Oxidation, Imidazole, Cyclization, Biological scaffolds

---

INTRODUCTION

Heterocyclic compounds are organic compounds containing hetero atoms such as sulfur, oxygen and nitrogen etc. Heterocyclic compounds are natural products and play a vital role in biological processes. They are frequently occurs in nature particularly in nucleic acids, plant alkaloids and chlorophyll. Heterocyclic compounds are very important in human life because the basic skeleton of the genetic material DNA is made up of purine and pyrimidine heterocyclic like adenine, guanine, cytosine and thymine in hemoglobin, single globular protein subunit contains iron held in heterocyclic rings called porphyrin and imidazole. Vitamins, proteins, hormones containing aromatic heterocyclic systems and dyes, ink are also made up of heterocyclic compounds. Almost 90% of the medicines made up of with heterocyclic compounds. Synthetically produced heterocyclic are mainly used as agrochemicals and pharmaceuticals. Imidazole is one of ubiquitous structural units in numerous drug molecules and natural products [1,2]. Moreover, imidazole derivatives play important roles in synthetic chemistry: (a) As building blocks of naturally occurring products and complex meaningful molecules [3,4], (b) As efficient organic catalysts to promote facile reaction processes [5], (c) As ligands in metalloenzymes [6], (d) As precursors of carbene ligands [7,8] and environmentally friendly ionic solvents.

Due to its pharmaceutical importance there is a greater need to develop an efficient protocol for the synthesis of substituted imidazole. Here we tried to address the synthetic challenge by applying one pot synthetic protocol.

MATERIALS AND METHODS

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Analytical Thin Layer Chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} plates. Visualization on TLC was achieved by the use of UV light (254 nm). Column chromatography was undertaken on silica gel (100-200 mesh) using a proper eluent system. NMR spectra were recorded in chloroform-*d* and DMSO-d_6 at 300 or 400 or 500 MHz for ^{1}H NMR spectra and 75 MHz or 100 or 125 MHz for ^{13}C NMR spectra. Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: br=broad, s=singlet, d=doublet, t=triplet, q=quartet, sept=septet, dd=doublet of doublet, td=triplet of doublet, m=multiplet. Coupling constants, *J*, were reported in hertz unit (Hz). For ^{13}C NMR chemical shifts were reported in ppm referenced to the center of a triplet at 77.0 ppm of chloroform-*d* and 40.0 ppm center for DMSO-$d_{6.A.}$

RESULTS AND DISCUSSION

Our synthetic journey started with the commercially available diphenylacetylne (1a), substituted aldehydes (1b) and aromatic amines or aliphatic amines (1c). The first step was to oxidize alkyne by using formic acid in reflux condition by using neat solvent to give mono-oxidized phenyl ketone; in same pot was added Iodine in presence of DMSO as solvent, followed by subsequent addition of ammonium acetate and silica supported perchloric acid to give substituted imidazole (1d).

This reaction shows one pot protocol to synthesize different substituted imidazole; the silica gel supported catalyst was prepared in ether by addition of perchloric acid in silica at mild temperature to give catalyst and dried it on high vacuum to give good slid as powdered form.

The electron donating group tolerated well like trimethoxy benzaldehydes gave good yield (2a) 85%. Further we changed different aldehydes and by keeping diphenylacetylene and benzylamine as constant starting material. Electron withdrawing as well as neutral group tolerated well and gives excellent yields.

Different aromatic amines works well, even aliphatic amines gave good yield (2e), the aromatic aldehydes like parahydroxy aldehydes worked well to give good yield.

Figure 1 represents the common scheme of the reaction and prepared examples.

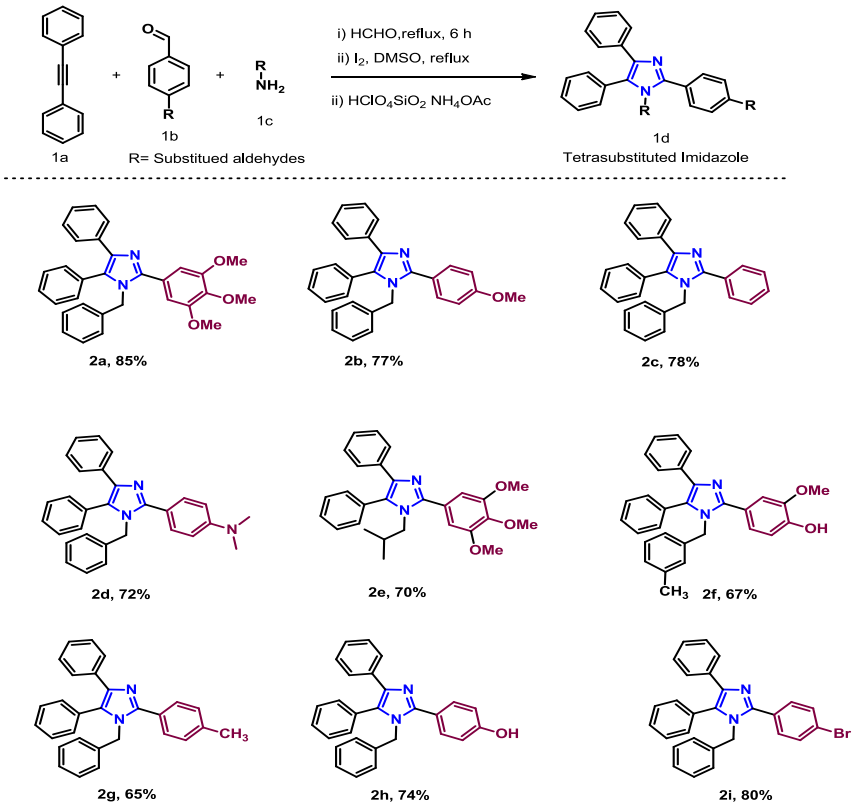


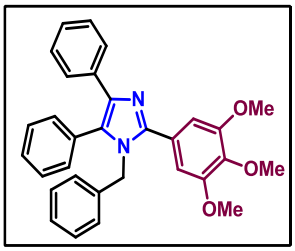
Figure 1: General representative scheme for saccharin derivatives

General procedure for the synthesis

To a stirred solution of diphenyl acetylene (1a, 1 mol), addition of formic acid (10 mL) refluxed it for 6 h, then subsequent addition of Iodine (0.5 mol) and DMSO (5 ml) refluxed 2 h, then was added aldehydes (1b, 1.2 mol), benzylamine (1c 1.5 mol) and ammonium acetate (1 mol); the reaction mixture stirred it for 12 h, after completion of the reaction by TLC, the resulting solution was quenched with water and extracted with ethyl acetate (50 × 2), the organic layer was washed with brine and dried it over Na_2SO_4. Solvent was removed on vacuo, and crude reaction mixture was prepared on column chromatography by using silica gel.

Spectral data

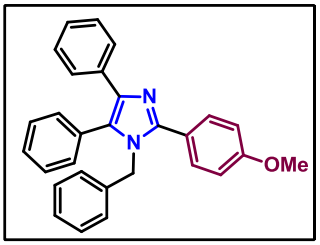
1-benzyl-4,5-diphenyl-2-(3,4,5-trimethoxyphenyl)-1H-imidazole (2a)



m.p. 170-172ºC. IR (Neat)=ν_{max} 3445, 3059, 3025, 2934, 2836, 1706, 1609, 1542, 1542, 1487, 1452, 1391, 1338, 1296, 1255, 1175, 1113, 1024, 968, 843, 769, 695, 615, 525.1
H NMR (300 MHz, $CDCl_3$+DMSO) δ δ 7.54 (d, *J*=7.4, 2H), 7.10-7.40 (m, 11H), 6.94 (d, *J*=7.2, 2H), 6.80 (s, 3H), 5.12 (s, 2H) 3.80 (s, 3H), 3.65 (s,6H).
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) δ: 152.4, 147.1, 137.8, 137.3 136.9, 134.0, 133.8, 130.3, 130.1, 129.6, 128.3, 128.2, 128.1, 127.4, 126.8, 126.1, 125.7, 125.2, 105.6, 59.9, 55.2, 47.5. HRMS (ESI-MS): m/z calcd. For $C_{31}H_{28}N_2O_3$ $[M+H]^+$ 477.21597, found 477.21604.

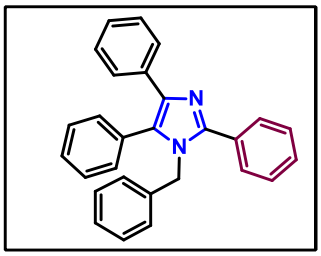
1-benzyl-2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole (2b)

White solid, m.p. 157-160ºC. IR (Neat)=ν_{max} 3445, 3059, 3025, 2934, 2836, 1706, 1609, 1542, 1542, 1487, 1452, 1391, 1338, 1296, 1255, 1175, 1113, 1024, 968, 843, 769, 695, 615, 525.
^{1}H NMR (300 MHz, $CDCl_3$+DMSO) δ 7.49-7.60 (m, 6H), 7.29-7.38 (m, 2H), 7.09-7.25 (m, 7H), 6.93(d, *J*=7.8, 2H), 6.79-6.82 (m, 2H), 5.10 (s, 2H), 3.82 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) δ**:** 159.5, 146.9, 137.8, 137.4 136.5, 136.0, 130.7**,** 130.6, 129.8,129.7, 128.8, 128.7, 128.5, 127.9, 127.1, 126.1, 126.0, 125.5, 122.9, 116.2, 114.0, 58.0, 47.5; HRMS (ESI-MS): m/z calcd. For *m/z* calc. $C_{29}H_{24}N_2O$ $[M+H]^+$ 417.19525, found. 417.19541.



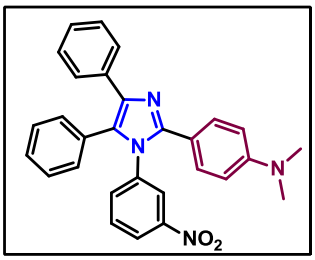
1,2,4,5-tetraphenyl-1H-imidazole (2c)

White solid, m.p. 2216-218ºC. IR (Neat)=ν_{max} 3445, 3059, 3025, 2934, 2836, 1706, 1609, 1542, 1440, 1394, 1312, 1134, 1072, 1024, 960, 918, 768.
^{1}H NMR (300 MHz, $CDCl_3$+DMSO) δ 7.55-7.62 (m, 2H), 7.38-7.45 (m, 2H), 7.18-7.32 (m, 12H), 7.10-7.16 (m, 2H), 7.02-7.08 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) δ: 145.8, 137.1, 136.3, 134.1,, 130.5, 130.0, 128.5,128.1,128.0,127.8,127.7,127.6,127.5,126.4,125.9; 125.0; HRMS (ESI-MS): m/z calcd. $C_{27}H_{20}N_2$ $[M+H]^+$ 373.16931, found: 373.16934.



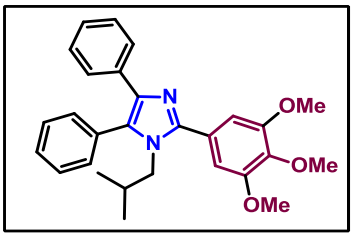
N,N-dimethyl-4-(1-(3-nitrophenyl)-4,5-diphenyl-1H-imidazol-2-yl)aniline (2d)

Yellowish solid, m.p. 170-172ºC. IR (Neat)=ν_{max} 3445, 3059, 3025, 2934, 2836, 1706, 1609, 1542, 1440, 1394, 1312, 1134, 1072, 1024, 960, 918, 768.
^{1}H NMR (300 MHz, $CDCl_{3+}$DMSO) δ 7.55-7.62 (m, 2H), 7.38-7.45 (m, 2H), 7.18-7.32 (m, 12H), 7.10-7.16 (m, 2H), 7.02-7.08 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_{3+}$DMSO) δ: 145.8, 137.1, 136.3, 134.1,, 130.5, 130.0, 128.5,128.1,128.0,127.8,127.7,127.6,127.5,126.4,125.9; 125.0; HRMS (ESI-MS): m/z calcd. $C_{27}H_{20}N_2$ $[M+H]$+373.16931, found: 373.16934.



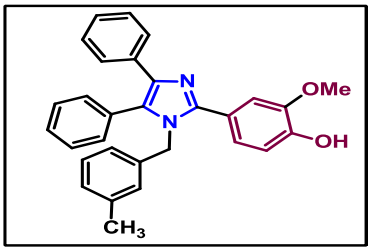
1-isobutyl-4,5-diphenyl-2-(3,4,5-trimethoxyphenyl)-1H-imidazole (2e)

White solid, m.p. 112-115ºC. IR (Neat)=ν_{max} 3054, 3023, 2954, 2925, 1950, 1588, 1522,1483, 1434, 1326, 1230, 1125, 1028, 881, 773,730,700,630 cm^{-1}
^{1}H NMR (300 MHz, $CDCl_3$+DMSO) δ 7.12-7.42 (m, 10H), 6.82 (d, *J*=7.2, 2H), 3.84 (s, 3H), 3.69 (s, 6H), 1.24 (m, 1H), 0.35 (d, *J*=6.8, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$+DMSO) δ: 152.4, 147.6, 142.2, 138.0, 136.6, 134.2, 133.8, 125.3, 122.8, 105.6, 60.1, 55.4, 47.6, 28.6, 21.3, 125.0; HRMS (ESI-MS): m/z calcd. $C_{28}H_{30}N_2O_3$ [M+H]+443.22654, found: 443.22662



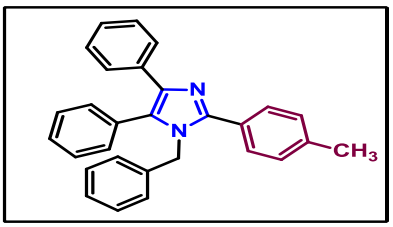
2-methoxy-4-(1-(3-methylbenzyl)-4,5-diphenyl-1H-imidazol-2-yl)phenol (2f)

White solid, m.p. 205-210ºC. IR (Neat)=ν_{max} 3054, 3023, 2954, 2925, 1950, 1588,1522,1481,434,1326, 1230, 1125, 1028, 881, 773,730,700,630 cm^{-1}
^{1}H NMR (300 MHz, $CDCl_3$+DMSO) δ 7.54 (d, *J*=7.4, 2H), 7.10-7.40 (m, 11H), 6.94 (d *J*=7.2, 2H), 6.80 (s, 3H), 5.12 (s, 2H) 3.80 (s 3H), 3.65 (s,6H).
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) δ: 158.2, 147.2, 141.2, 137.5 136.2, 134.0, 133.1, 130.0, 129.2, 128.7, 128.5, 128.2, 128.0, 127.5, 127.2, 126.2, 126.0, 124.9, 116.3, 114.2, 55.6, 47.5, 21.2; HRMS (ESI-MS): m/z calcd. $C_{30}H_{26}N_2O_2$ [M+H]+447.20592, found: 447.20604.



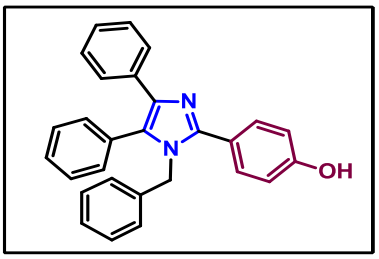
1-benzyl-2,4,5-triphenyl-1H-imidazole (2g)

White solid, m.p. 239-240ºC IR (Neat)=ν_{max} 3447, 3048, 1953, 1887, 1597, 1496, 1465, 3054, 3023, 1230, 1125, 1028, 881, 773,730,700,630 cm^{-1}
^{1}H NMR (300 MHz, $CDCl_3$+DMSO) δ 7.12-7.58 (m, 17H), 6.68-6.72 (m, 2H), 5.12 (s 2H)
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) δ: 146.4, 137.2, 139.9, 134.5, 131.1, 130.8, 130.2, 129.0, 128.9, 128.7, 128.5, 128.4, 128.0, 127.41, 26.8, 26.4, 25.8, 22.8; HRMS (ESI-MS): m/z calcd. $C_{28}H_{22}N_2$ [M+H]+387.18234, found: 387.18242 .



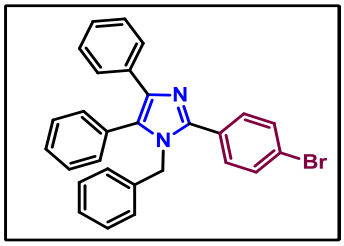
4-(1-benzyl-4,5-diphenyl-1H-imidazol-2-yl)phenol (2h)

White solid, m.p. 134-135ºC IR (Neat)=ν_{max} 3447, 3056, 3027, 2931, 2658, 2583, 1892, 1708, 1606, 1542, 1485, 1446, 1396, 1355, 1277, 1232, 1163, 1100, 1072, 1022, 973, 838, 767, 724, 695, 529 cm^{-1}
^{1}H NMR (300 MHz, $CDCl_3$+DMSO) δ 9.30 (s, 1H), 7.04-7.62 (m, 15H), 7.09-7.25 (m, 7H), 6.93(d, *J*=7.8, 2H), 6.84 (d, *J*=8.5 2H), 6.74-6.84 (m, 2H), 5.08 (S, 2H).
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) δ: 157.8, 147.5, 137.2, 136.5, 134.4, 130.6**,** 130.5, 129.8, 129.2, 128.4, 128.2, 128.1, 127.6, 126.8, 126.0, 125.7, 125.4, 121.2, 115.5, 47.5. HRMS (ESI-MS): m/z calcd. $C_{29}H_{24}N_2O$ [M+H]+403.18006 found: 403.18013.



1-benzyl-2-(4-bromophenyl)-4,5-diphenyl-1H-imidazole (2i)

White solid, m.p. 170-172ºC IR (Neat)=ν_{max}, 3059, 1951, 1708, 1598, 1498, 1478, 1446, 1442, 1357, 1324, 1181, 1069, 1006, 972, 830, 722, 693, 665, 517 cm^{-1}
^{1}H NMR (300 MHz, $CDCl_{3+}$DMSO) δ 7.10-7.62 (m, 17H), 6.76-6.82 (m, 2H), 5.12 (s, 2H).
^{13}C NMR (75 MHz, $CDCl_{3+}$DMSO) δ: 146.1, 137.5, 136.6, 133.8, 131.1, 130.3, 130.0, 129.9, 129.8, 129.3, 128.3, 128.1, 127.5, 126.8, 126.1, 125.8, 125.5, 47.5.HRMS (ESI-MS): m/z calcd. $C_{28}H_{21}BrN_2$ $[M+H]^+$ 465.09517 found: 465.09517.



CONCLUSION

In summary we have developed a simple and efficient protocol for the synthesis of tetrasubstitued imidazole in single pot. This protocol allows simple operation of the reaction condition and can be extended to diverse multisubstituted imidazole. The scope of the reaction was shown with the respect of the amines as well as aldehydes. The biological evaluation of the compound is currently under progress in our laboratory.

REFERENCES

[1] Z. Jin, *Nat. Prod. Rep*., **2009**, 26, 382.
[2] K.A. Alvi, P. Crews, D.G. Loughhead, *J. Nat. Prod*., **1991**, 54, 1509.
[3] G.J. Atwell, J.Y., Fan, K. Tan, W.A. Denny, *J. Med. Chem*., **1998**, 41, 4744.
[4] R.E. Looper, M.T.C. Runnegar, R.M. Williams, *Angew. Chem*., **2005**, 117, 3947.
[5] B.A. Trofimov, L.V. Andriyankova, K.V. Belyaeva, A.G. Mal'kina, L.P. Nikitina, A.V. Afonin, I.A. Ushakov, *J. Org. Chem*., **2008**, 73, 9155.
[6] G.A. Burley, D.L. Davies, G.A. Griffith, M. Lee, K. Singh, *J. Org. Chem*., **2010**, 75, 980.
[7] D. Orain, H. Mattes, *Tetrahedron Lett.*, **2006**, 47, 1253.
[8] O.A. Attanasi, P. Davoli, G. Favi, P. Filippone, A. Forni, G. Moscatelli, F. Prati, *Org. Lett*., **2007**, 9, 3461.