

SYNTHESIS, CHARACTERIZATION AND DPPH SCAVENGING ACTIVITY OF SOME BENZIMIDAZOLE DERIVATIVES

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ABSTRACT. A base-catalyzed conversion of aldehydes to benzimidazoles has been achieved. The compounds have been characterized by IR, NMR, microranalysis, and GC-MS. The reaction for the formation of benzimidazoles has been monitored with ¹H NMR and IR. The crystal structures of two derivatives, 2-(2-chlorophenyl)-1*H*-benzimidazole and 2-(1*H*-benzimidazol-2-yl)-4-nitrophenol, are presented. A study of the DPPH scavenging activity of these compounds showed that 2-(1*H*-benzimidazol-2-yl)phenol (**2**), 2-*p*-tolyl-1*H*-benzimidazole (**3**) and 2-(4-methoxyphenyl)-1*H*-benzimidazole (**7**) gave IC₅₀ values 1974, 773 and 800 μM.

KEY WORDS: Benzimidazole, *o*-Phenylenediamine, Aldehydes, Base catalysis, DPPH scavenging activity

INTRODUCTION

Benzimidazoles have been used in the synthesis of a variety of compounds and materials [1-2]. The common route for the synthesis of benzimidazoles from diamines is through a condensation reaction with carboxylic acids under acid catalysis at high temperatures [3]. Microwave irradiation has also been used to synthesize benzimidazoles by the reaction of anthranilic acid and *o*-phenylenediamine, however, *via* the base-catalyzed route (using potassium carbonate and ethanol) [4].

The aldehyde route has also been explored to achieve benzimidazoles from diamines despite the fact that monoimines or diimines should be the expected products. 2-Substituted benzimidazoles have been synthesized in the presence of alumina–methanesulfonic acid (AMA) by microwave irradiation [5]. Catalytic amounts of zinc acetate have been used to synthesize benzimidazoles from aldehydes and *o*-phenylenediamine at room temperature [6]. Boron trifluoride dietherate has also been used to catalyze the synthesis of benzimidazoles from *o*-phenylenediamine and aldehydes under solvent free conditions [7]. 1,3-Dibromo-5,5-dimethylhydantoin (DBH)–catalyzed solvent-free synthesis of 2-arylbenzimidazoles has been achieved *via* microwave irradiation of *o*-phenylenediamine and aryl aldehydes [8].

A wide variety of 2-substituted benzimidazoles and *bis*-benzimidazoles have been synthesized in high yields by PEG-mediated catalyst-free synthesis under solvent-free conditions [9]. The synthesis of benzimidazoles through the coupling of aldehydes with *o*-phenylenediamine by using highly acidic nanoporous aluminosilicate with 3D structure and cage-type pores as the catalyst has been achieved. The catalyst resulted in excellent yields in short reaction times presumably due to its high acidity, large pore diameter, high surface area, and cage-type 3D porous structure [10].

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Evaluation of the antioxidant activities of natural substances has been of interest in recent years. Antioxidants scavenge free radicals and reactive oxygen species and can be extremely important in inhibiting oxidative mechanisms that lead to degenerative diseases [11]. Free radicals have been implicated as playing a role in cardiovascular disease, cancer, Alzheimer's disease and Parkinson's disease. The antioxidant capacity of compounds sources is usually associated with their phenolic contents. Although plant polyphenols such as tannins and flavonoids have problems of astringency and protein binding which have grouped them under the category of anti-nutrients [12-13], they have been found useful as natural antioxidants in scavenging deleterious free radicals released in the body by fat metabolism [14]. Some phenolic compounds have also been tested for their antioxidant activity [15-17].

Herein, we report a base-catalyzed method for the synthesis of benzimidazoles from aldehydes and *o*-phenylenediamine, the characterization of the compounds with IR, NMR, microanalysis, GC-MS has been presented. The single crystal XRD of 2-(2-Chlorophenyl)-1*H*-benzimidazole (**4**) and 2-(1*H*-benzimidazol-2-yl)-4-nitrophenol (**8**) have been discussed. The DPPH scavenging activities of the compounds have also been discussed.

EXPERIMENTAL

Analytical grade reagents and solvents for synthesis and analysis which included; *o*-phenylenediamine, dimethyl sulfoxide, *m*-toluolaldehyde and 5-nitrosalicylaldehyde were obtained from Sigma Aldrich (USA) whilst tetrahydrofuran, salicylaldehyde, 2-bromosalicylaldehyde, 3-methoxybenzaldehyde, 4-methoxybenzaldehyde, 4-methylbenzaldehyde, 2-chlorobenzaldehyde, 4-nitrobenzaldehyde, toluene, ethyl acetate, ethanol, methanol and triethylamine (99%) were obtained from Merck Chemicals (SA). The chemicals were used as received (i.e. without further purification). ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance AV 400 MHz spectrometer operating at 400 MHz for ¹H and 100 MHz for ¹³C using DMSO-*d*₆ as solvent and tetramethylsilane as internal standard. Chemical shifts are expressed in ppm. FT-IR spectra were recorded on a Bruker Platinum ATR Spectrophotometer Tensor 27. Elemental analyses were performed using a Vario Elementar Microcube ELIII. Melting points were obtained using a Stuart Lasec SMP30 whilst the masses were determined using an Agilent 7890A GC System connected to a 5975C VL-MSD with electron impact as the ionization mode and detection by a triple-axis detector. The GC was fitted with a 30 m x 0.25 mm x 0.25 μm DB-5 capillary column. Helium was used as carrier gas at a flow rate of 1.6 mL.min⁻¹ with an average velocity of 30.2 cm s⁻¹ and a pressure of 63.7 kPa.

2-(3-Methoxyphenyl)-1*H*-benzimidazole (**1**)

o-Phenylenediamine (3.24 g, 0.030 mol) was mixed with 3-methoxybenzaldehyde (4.08 g, 0.030 mol) in 20 mL of triethylamine and heated at 120 °C for 12 h. The reaction was followed by TLC to completion. The solvent was removed using the high vacuum pump and to obtain brown oil, which was washed with hot ethanol (150 mL) and the purified on a column using ethyl acetate:methanol (1:1). The product recrystallized as a light brown solid from ethanol. Melting point = 203–204 °C. Yield = (4.75 g) 70.62%. IR (ν_{max}, cm⁻¹) 3071 (N–H), 3002 (N–H), 2799 (C–H), 2685, 1602 (C=N), 1491 (C–N), 1434 (C–N). 784. ¹H NMR (ppm): 12.92 (s, 1H), 7.77 (m, 2H), 7.68 (m, 1H), 7.54 (m, 1H), 7.48 (m, 1H), 7.22 (m, 2H), 7.07 (m, 1H), 3.89 (s, 3H). ¹³C NMR (ppm): 159.6, 151.1, 143.6, 134.9, 131.4, 130.1, 122.6, 121.7, 118.8, 118.7, 115.9, 111.3, 55.3. LRMS (*m/z*, M⁺): Found for C₁₄H₁₂N₂O = 224.10, Expected mass = 224.26. Anal. calcd. for C₁₄H₁₂N₂O: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.60; H, 5.41; N, 12.22.

2-(1*H*-Benzimidazol-2-yl)phenol (**2**)

o-Phenylenediamine (3.24 g, 0.03 mol) was mixed with salicylaldehyde (3.66 g, 0.030 mol) in 20 mL of triethylamine and heated at 120 °C for 12 h. The reaction was followed by TLC to

completion. The solvent was removed at the pump and to obtain a brown solid which was washed with hot ethanol (150 mL) and purified on a column using ethyl acetate:methanol (1:1). The product recrystallized as a light brown solid from ethanol:THF (2:1). Melting point = 236–238 °C. Yield = (4.62 g) 73.29%, IR (ν_{\max} , cm^{-1}): 3238 (N–H), 3053 (N–H), 1630 (C=N), 1590 (C=C), 1488 (C–N), 1454 (C–N). ^1H NMR (ppm): 13.16 (br, 1H), 8.06 (d, J = Hz, 1H), 7.67 (m, 2H), 7.39 (m, 1H), 7.29 (m, 2H), 7.04 (m, 2H). ^{13}C NMR (ppm): 158.0, 151.6, 131.7, 126.2, 119.1, 117.2, 112.6. LRMS (m/z , M^+): Found for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}$ = 210.10, Expected mass = 210.23. Anal. calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.38; H, 4.64; N, 13.24.

2-*p*-Tolyl-1H-benzimidazole (3)

o-Phenylenediamine (3.24 g, 0.03 mol) was mixed with 4-methylbenzaldehyde (3.60 g, 0.03 mol) in 20 mL of triethylamine and heated at 120 °C for 12 h. The reaction was followed by TLC to completion. The mother liquor was allowed to stand overnight. The product was filtered, washed with hot ethanol (150 mL) and purified on a column with ethyl acetate:methanol (1:1). The product recrystallized as a light brown solid from ethanol:THF (1:1). Melting point = 270–271 °C. Yield = (4.72 g) 75.49%. IR (ν_{\max} , cm^{-1}): 3054 (N–H), 2915 (C–H), 1552 (C=C), 1500 (C=C), 1475 (C–N), 1452 (C–N). ^1H NMR (ppm): 12.86 (s, 1H), 8.11 (m, 2H), 7.57 (m, 1H), 7.46 (m, 1H), 7.38 (m, 2H), 7.15 (m, 2H), 2.44 (s, 3H). ^{13}C NMR (ppm): 151.37, 139.56, 129.31, 126.36, 125.96, 20.92. LRMS (m/z , M^+): Found for $\text{C}_{14}\text{H}_{12}\text{N}_2$ = 208.10, Expected mass = 208.26. Anal. calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.82; H, 5.68; N, 13.35.

2-(2-Chlorophenyl)-1H-benzimidazole (4)

o-Phenylenediamine (3.24 g, 0.03 mol) was mixed with 2-chlorobenzaldehyde (4.22 g, 0.03 mol) in 20 mL of triethylamine and heated at 120 °C for 12 h. The reaction was followed by TLC to completion. The solvent was removed at the pump and to obtain a brown oil. The dry product was washed with hot ethanol (150 mL) and the product recrystallized as a light brown solid from ethanol:THF (1:1). Melting point = 227–228 °C. Yield = (5.04 g) 73.64%. IR (ν_{\max} , cm^{-1}): 3061 (N–H), 3001 (N–H), 1590 (C=C), 1441 (C–N). ^1H NMR (ppm): 7.92 (d, J = Hz, 1H), 7.64 (m, 3H), 7.52 (m, 2H), 7.24 (m, 2H). ^{13}C NMR (ppm): 149.1, 132.0, 131.6, 131.2, 130.3, 129.9, 127.4, 122.2, 115.3. Found: C, 68.46; H, 3.89; N, 12.34. LRMS (m/z , M^+): Found for $\text{C}_{13}\text{H}_9\text{ClN}_2\text{O}$ = 228.80, Expected mass = 228.68. Anal. calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_4\text{S}\cdot\text{H}_2\text{O}$: C, 46.15; H, 4.61; N, 12.25. Found: C, 46.28; H, 3.97; N, 12.25.

2-Phenyl-1H-benzimidazole (5)

o-Phenylenediamine (3.24 g, 0.03 mol) was mixed with benzaldehyde (3.18 g, 0.03 mol) in 20 mL of triethylamine and heated at 120 °C for 12 h. The reaction was followed by TLC to completion. The solvent was removed at the pump and to obtain brown oil. The dry product was washed with hot ethanol (150 mL) and the product recrystallized as a light brown solid from ethanol:THF (1:1). Melting point = 291–292 °C. Yield = (4.54 g) 78.00 %. IR (ν_{\max} , cm^{-1}): 3048 (N–H), 1622 (C=N), 1591 (C=C), 1494 (C–N), 1462 (C–N). ^1H NMR (ppm): 12.90 (s, 1H), 7.56 (m, 2H), 7.48 (br, 1H), 7.35 (m, 4H), 7.01 (s, 2H). ^{13}C NMR (ppm): 151.2, 130.0, 129.8, 128.9, 126.4. LRMS (m/z , M^+): Found for $\text{C}_{13}\text{H}_{10}\text{N}_2$ = 194.10, Expected mass = 194.23. Anal. calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.43; H, 5.25; N, 14.30.

2-(4-Nitrophenyl)-1H-benzimidazole (6)

o-Phenylenediamine (3.24 g, 0.03 mol) was mixed with 4-nitrobenzaldehyde (4.53 g, 0.03 mol) in 20 mL of triethylamine and heated at 120 °C for 12 h. The reaction was followed by TLC to

completion. The solvent was removed at the pump and to obtain brown oil. The dry product was washed with hot ethanol (150 mL) and the product recrystallized as a light brown solid from ethanol:THF (1:1). Melting point = 320–321 °C. Yield = (5.52 g) 76.94%. IR (ν_{\max} , cm^{-1}): 3035 (N–H), 2952 (C–H), 1604 (C=N), 1512 (C=C), 1434 (C–N). ^1H NMR (ppm): 8.40 (m, 4H), 7.64 (m, 2H), 7.27 (m, 2H). ^{13}C NMR (ppm): 149.0, 147.8, 135.9, 127.3, 124.2, 122.9. LRMS (m/z , M^+): Found for $\text{C}_{13}\text{H}_9\text{N}_3\text{O}_2$ = 239.60, Expected mass = 239.23. Anal. calcd. for $\text{C}_{13}\text{H}_9\text{N}_3\text{O}_2$: C, 65.29; H, 3.79; N, 17.56. Found: C, 65.46; H, 3.85; N, 17.48.

2-(4-Methoxyphenyl)-1H-benzimidazole (7)

o-Phenylenediamine (3.24 g, 0.03 mol) was mixed with 4-methoxybenzaldehyde (4.08 g, 0.03 mol) in 20 mL of triethylamine and heated at 120 °C for 12 h. The reaction was followed by TLC to completion. The solvent was removed at the pump and to obtain brown oil. The dry product was washed with hot ethanol (150 mL) and the product recrystallized as a light brown solid from ethanol:THF (1:1). Melting point = 220–222 °C. Yield = (5.26 g) 78.16%. IR (ν_{\max} , cm^{-1}): 3054 (N–H), 2953 (C–H), 2835 (C–H), 1611 (C=N), 1500 (C=C), 1476 (C–N), 1454 (C–N). ^1H NMR (ppm): 12.78 (br, 1H), 8.18 (m, 2H), 7.50 (m, 2H), 7.22 (m, 2H), 7.16 (m, 2H). ^{13}C NMR (ppm): 160.6, 151.3, 128.0, 122.7, 114.3, 67.0, 55.3, 25.1. LRMS (m/z , M^+): Found for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$ = 224.10, Expected mass = 224.26. Anal. calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$: C, 74.98; H, 5.59; N, 12.49. Found: C, 74.72; H, 5.42; N, 12.63.

2-(1H-benzimidazol-2-yl)-4-nitrophenol (8)

o-Phenylenediamine (3.24 g, 0.03 mol) was mixed with 5-nitrosalicylaldehyde (5.01 g, 0.03 mol) in 20 mL of triethylamine and heated at 120 °C for 12 h. The reaction was followed by TLC to completion. The solvent was removed at the pump to obtain a yellow solid which was washed with hot ethanol (150 mL) and recrystallized as a yellow solid from DMSO:toluene (1:1). Melting point = 335–336 °C. Yield = (4.65 g) 60.69%. IR (ν_{\max} , cm^{-1}): 3274 (N–H), 3097 (N–H), 1628 (C=N), 1587 (C=C), 1407 (C–N). ^1H NMR (ppm): 9.12 (s, 1H), 8.26 (d, J = Hz, 1H), 7.73 (m, 2H), 7.35 (m, 2H), 7.20 (d, J = Hz, 1H). ^{13}C NMR (ppm): 164.1, 149.7, 139.3, 136.4, 127.0, 123.5, 122.9, 118.3, 115.0, 112.6. LRMS (m/z , M^+): Found for $\text{C}_{13}\text{H}_9\text{N}_3\text{O}_3$ = 255.80, Expected mass = 255.23. Anal. calcd. for $\text{C}_{13}\text{H}_9\text{N}_3\text{O}_3$: C, 61.18; H, 3.55; N, 16.46. Found: C, 61.29; H, 3.64; N, 16.56.

2-(3-Methylphenyl)-1H-benzimidazole (9)

o-Phenylenediamine (3.24 g, 0.03 mol) was mixed with *m*-methylbenzaldehyde (3.60, 0.03 mol) in 20 mL of triethylamine and heated at 120 °C for 12 h. The reaction was followed by TLC to completion. The solvent was removed at the pump and to obtain brown solid, which was washed with ethanol and purified on a column using ethyl acetate:methanol (1:1). The product was recrystallized from methanol:THF (1:1) and obtained as a white solid. Melting point = 213–215 °C. Yield = (4.87 g) 78.00%. IR (ν_{\max} , cm^{-1}): 3052 (N–H), 2986 (C–H), 2879 (C–H), 1661 (C=N), 1590 (C=C), 1487 (C–N). ^1H NMR (ppm): 12.88 (s, 1H), 8.04 (d, J = Hz, 1H), 7.99 (d, J = Hz, 1H), 7.66 (m, 1H), 7.54 (s, 1H), 7.41 (m, 1H), 7.31 (m, 1H), 7.20 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (ppm): 151.5, 138.1, 130.4, 130.2, 128.77, 127.0, 123.6, 121.9, 115.0, 21.0. LRMS (m/z , M^+): Found for $\text{C}_{14}\text{H}_{12}\text{N}_2$ = 194.10. Expected mass = 194.23. Anal. calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_3$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.67; H, 6.42; N, 11.95.

X-ray crystallography

X-ray diffraction analyses of **4** and **8** were performed at 200 K using a Bruker Kappa Apex II diffractometer with monochromated Mo $\text{K}\alpha$ radiation (λ = 0.71073 Å). APEXII [18] was used

for data collection and SAINT [18], for cell refinement and data reduction. The structures were solved by direct methods using SHELXS-2013 [19], and refined by least-squares procedures using SHELXL-2013 [20], with SHELXLE [20], as a graphical interface. All non-hydrogen atoms were refined anisotropically. Carbon-bound H atoms were placed in calculated positions (C–H 0.95 Å for aromatic carbon atoms and C–H 0.99 Å for methylene groups) and were included in the refinement in the riding model approximation, with Uiso (H) set to 1.2Ueq (C). The H atoms of the methyl groups were allowed to rotate with a fixed angle around the C–C bond to best fit the experimental electron density (HFIX 137 in the SHELX program suite [19], with Uiso (H) set to 1.5Ueq (C). Nitrogen-bound H atoms were located on a difference Fourier map and refined freely. Data were corrected for absorption effects using the numerical method implemented in SADABS [19].

DPPH assay

1,1-Diphenyl-2-picryl-hydrazyl (DPPH) and ascorbic acid were purchased from Sigma–Aldrich (South Africa). A stock solution of DPPH (0.2 mM) was prepared in methanol. The solvents and other chemicals were of analytical grade. Compounds **1** to **9** (64 to 30×10^{-6} mM) were tested for DPPH scavenging activity. Ascorbic acid (500 to 23×10^{-8} μ M) was used as a positive control. Briefly, 100 μ L of each compound was added to a 96 well microtitre plate followed by addition of 100 μ L DPPH (0.2 mM). Microtitre plates were wrapped in aluminium foil and kept in the dark at room temperature for 30 min. Spectrophotometric measurements were done at 517 nm using a BioTek Epoch 2 microtitre plate reader. The data was expressed as mean \pm SD. The experiment was carried out in triplicate. An average was obtained from the triplicate values for sample and blank, the blank was subtracted from all samples. The % DPPH scavenging = ((Abs DPPH-Abs Sample)/(Abs DPPH))*100. The result was then plotted against the log of concentration.

RESULTS AND DISCUSSION

General studies

The disappearance of the carbonyl of the aldehydes and ketones were confirmed by both the IR and the ^{13}C NMR spectra for all the compounds. The ^1H NMR spectrum of compound **1** gave a singlet peak at 12.92 ppm for the proton of the benzimidazole and another singlet at 3.89 ppm for a methyl group. The ^{13}C NMR and DEPT spectra confirmed the formation of a benzimidazole by the carbon at the 2-position appearing at 159.6 ppm as well as the presence of the methyl group at 55.3 ppm. A broad signal at 13.16 ppm in the ^1H NMR spectrum of compound **2** confirmed the hydroxyl proton. The signal at 158.0 ppm in the ^{13}C NMR spectrum confirmed the formation of benzimidazole of compound **2**.

A singlet peak at 12.92 ppm in the ^1H NMR spectrum of compound **3** confirmed the proton of the benzimidazole. Another singlet signal at 2.44 ppm for three protons confirmed the presence of the methyl group. The signal at 151.37 ppm in the ^{13}C NMR spectrum confirmed the formation of the benzimidazole in compound **3**. The signal at 149.1 ppm in the ^{13}C NMR spectrum of compound **4** was attributed to the benzimidazole carbon.

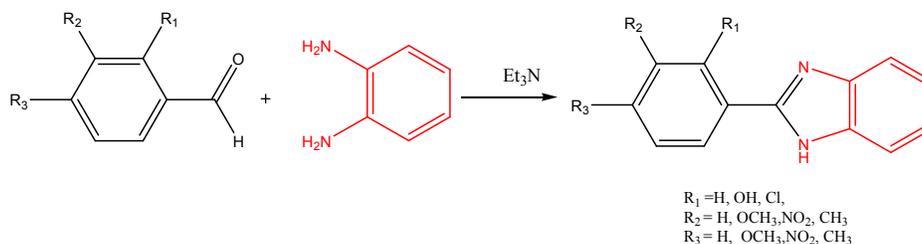
The proton of the benzimidazole occurred as a singlet signal at 12.90 ppm in the ^1H NMR spectrum of compound **5**, the signal at 151.2 ppm in the ^{13}C NMR spectrum also confirmed the formation of benzimidazole. In the ^{13}C NMR spectrum of compound **6** the signal at 149.0 ppm is attributable to the benzimidazole carbon. In the ^1H NMR spectrum of compound **7**, the benzimidazole proton occurred as a broad signal at 12.78 ppm whilst the ^{13}C NMR spectrum confirmed the benzimidazole carbon at 160.6 ppm.

The benzimidazole proton occurred as a singlet at 9.12 ppm in the ^1H NMR spectrum of compound **8** and the occurrence of a benzimidazole carbon was noticed at 151.5 ppm in the ^{13}C

NMR spectrum. The ^1H NMR spectrum of compound **9** gave a signal at 12.88 ppm attributable to the benzimidazole proton whilst the signal at 151.5 ppm in the ^{13}C NMR spectrum confirmed the formation of the benzimidazole. Table 1 gives the scope and yields of the different derivatives of the synthesized benzimidazoles. The base, triethylamine, was used as a solvent.

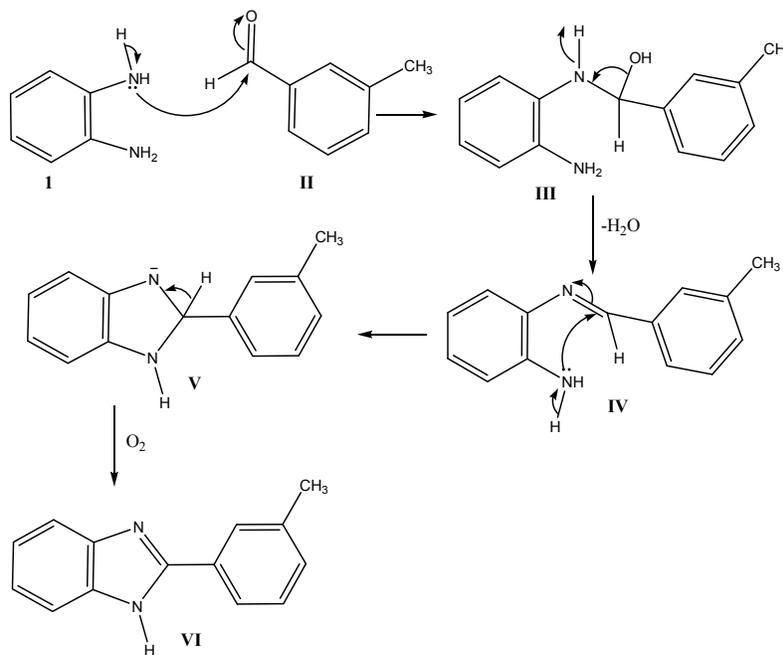
Table 1. Scope and yields of substituted benzimidazoles

Entry	Aldehyde	Product	Reaction Time (h)	%Yields
1	3-OCH ₃ C ₆ H ₄ CHO		12	71
2	2-OHC ₆ H ₄ CHO		12	73
3	4-CH ₃ C ₆ H ₄ CHO		12	75
4	2-ClC ₆ H ₄ CHO		12	74
5	C ₆ H ₅ CHO		12	78
6	4-NO ₂ C ₆ H ₄ CHO		12	77
7	4-OCH ₃ C ₆ H ₄ CHO		12	78
8	2-OH-5-NO ₂ C ₆ H ₃ CHO		12	61
9	3-CH ₃ C ₆ H ₄ CHO		12	78



Scheme 1. Synthesis scheme of benzimidazoles from aldehydes and *o*-phenylenediamine

Scheme 1 gives the synthesis route for the base-catalyzed formation of benzimidazoles from aldehydes and *o*-phenylenediamine. The reaction is proposed to proceed by the abstraction of a proton from an amine of *o*-phenylenediamine by triethylamine (I), which allows for the attack of the carbonyl of the aldehyde (II) by the amine forming a hydroxylamine (III) (Scheme 2). The loss of water from (III) gives an imine (IV) which loses a proton to yield (V), and a further proton loss and rearrangement leads to the formation of (VI). The proton loss stages are proposed to be activated by triethylamine, of which the last step is facilitated by the presence of oxygen hence the base-catalysis.



Scheme 2. Proposed mechanism for the synthesis of compound 2 from an aldehyde.

The ^1H NMR of the reaction for the first hour was done at ten minutes intervals. The formation of the aldehyde (IV in Scheme 2) is evidenced by the peak at 9.96 ppm (Figure 1).

The aldehydic proton begins to disappear after 40 min, which is consistent with the formation of **V** in the mechanism in Scheme 2. Also the protons at 7.80 and 7.43 ppm also disappear from the spectrum within the first hour. Upon attachment of the carbon atom from the aldehyde the four protons from the *o*-phenylene diamine molecule become non-equivalent this makes the protons appear as four signals in the spectrum. The signal at 7.80 ppm merges with that at 7.82 ppm which is a signal for two protons with integration for two protons, whilst the signal at 7.43 ppm also merges with signal at 7.33 ppm which also gives integration for two protons. There is no direct experimental evidence for the oxidation step it is postulated to happen *via* oxidation in literature.

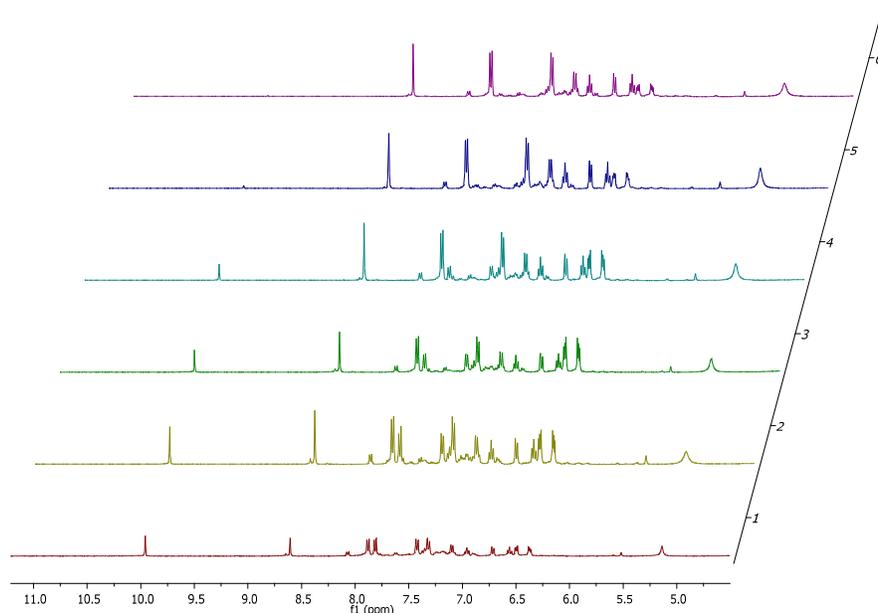


Figure 1. The ^1H NMR spectrum of the progress of the reaction of *o*-phenylene diamine with 3-methylbenzaldehyde was again measured at 1 hour intervals but no significant changes were observed.

The IR spectrum (Figure 2) measured at 10 min intervals for the first hour confirms formation of a hydroxyl group as shown in **III** in the mechanism in Scheme 2. The hydroxyl group disappears in the course of the reaction which is consistent with the loss of hydroxyl group as water in **IV** of Scheme 2. The increase in the intensity of the signals at 1456 and 1492 cm^{-1} in the IR spectrum confirms the formation of benzimidazole.

Characterization of crystal structures

Compound **4** recrystallized as a light brown solid from ethanol:THF(1:1), whilst compound **8** recrystallized as a yellow solid from DMSO:toluene (1:1). The computed and crystallographic data and selected bond lengths and bond angles for all the crystal structures are provided in Tables 2 and 3. The ORTEP diagrams for compounds **4** and **8** at 50% ellipsoid are presented in Figures 3 and 4. Compound **4** crystallized in the orthorhombic space group *Pbca*, while compound **8** crystallized in the triclinic space group *P-1*.

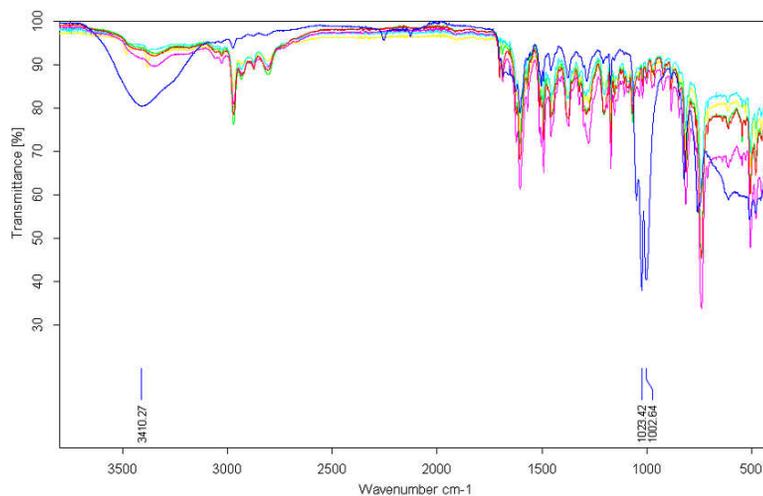


Figure 2. IR spectrum of the progress of reaction, measurement done at 10 min intervals.

Table 2. Crystallographic data and structure refinement summary for compounds **4** and **8**

Property	Compound 4	Compound 8
Formula	C ₁₃ H ₉ ClN ₂	C ₁₃ H ₉ N ₃ O ₃
CCDC Number	1062232	1062215
Formula Weight	228.67	255.23
Crystal System	Orthorhombic	Triclinic
Space group	<i>Pbca</i>	<i>P-1</i>
a(Å)	7.0310(4)	6.4211(5)
b(Å)	9.9397(7)	8.2150(6)
c(Å)	32.1093(18)	10.7976(9)
α(°)	90	100.794(3)
β(°)	90	99.810(3)
γ(°)	90	94.002(3)
V [Å ³]	2244.0(2)	548.26(7)
Z	8	2
D(calc) [g/cm ³]	1.354	1.546
Mu(MoKa) [/mm]	0.311	0.114
F(000)	944	264
Crystal Size [mm]	0.11 x 0.25 x 0.41	0.04 x 0.16 x 0.31
Temperature (K)	200	200
Radiation [Å]	0.71073	0.71073
θ Min-Max [°]	2.5, 28.3	2.0, 28.3
Dataset	-9: 8 ; -11: 13 ; -42: 42	8: 8 ; -10: 10 ; -14: 14
Tot., Uniq. Data, R(int)	19671, 2793, 0.023	9939, 2718, 0.023
Observed Data [I > 2.0 sigma(I)]	2321	2052
Nref	2793	2718
Npar	149	177
R ₁	0.0523	0.0478
wR2	0.1293	0.1324
S	1.08	1.11
Max. and Av. Shift/Error	0.00, 0.00	0.00, 0.00
Min. Residual. Dens. [e/Å ³]	-0.37	-0.27
Max. Residual Dens. [e/Å ³]	0.31	0.29

The bond distances of N1–C1, and N2–C1, which were 1.323(2), and 1.355(2) Å, respectively, were consistent with the C–N bond of the amide of compound **4** whilst N2–C22 bond length was 1.376(2). The bond angles of C1–N1–C21 and C1–N2–C22 are 105.1(1) and 107.1(1)°, respectively around the nitrogen atoms.

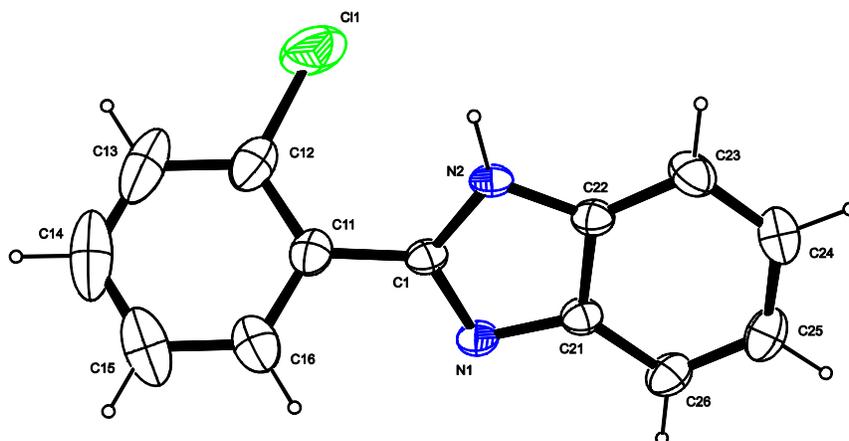


Figure 3. An ORTEP diagram of compound **4** at 50% ellipsoid.

The bond distances of O1–C22 and O2–N3 which were 1.339(2) and 1.236(2) Å, respectively, in compound **8** are slightly longer than the average bond length of C=O bonds on the CCDC database which is 1.228 Å [21]. The torsion angles of C22–N2–C3–O2 and C21–N1–C2–O2 in compound **1** were 5.3(3)° and 180.0(3)° respectively.

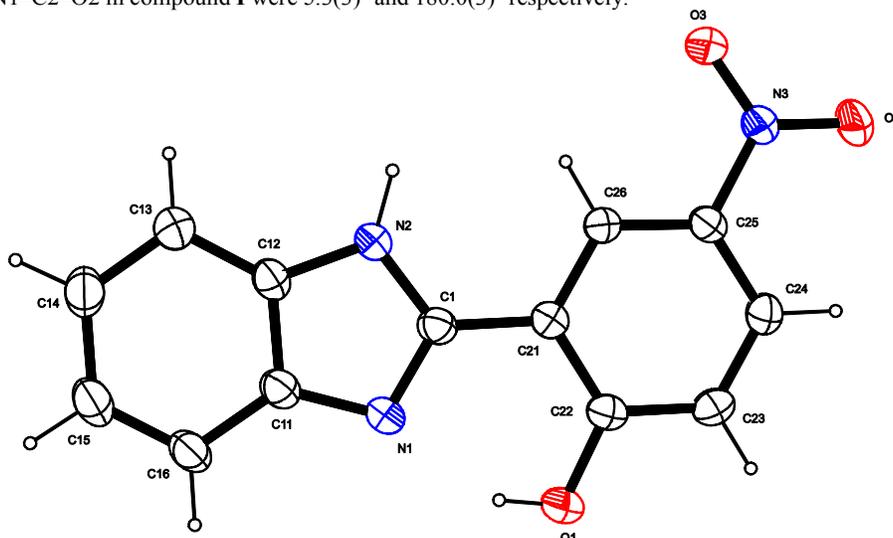


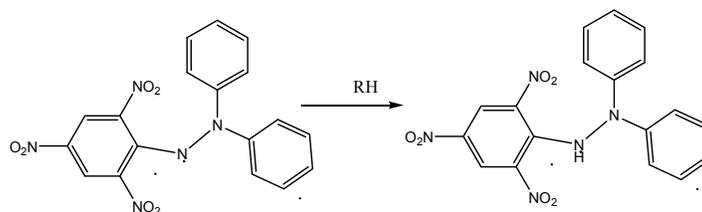
Figure 4. An ORTEP diagram of compound **8**.

Table 2. Selected bond lengths (Å) and bond angles (°) of compounds **4** and **8**

Bond lengths			
Compound 4		Compound 8	
C11–C12	1.733(2)	O1–C22	1.339(2)
C21–C22	1.401(2)	N3–C25	1.451(2)
N1–C1	1.323(2)	O2–N3	1.224(2)
C23–C24	1.379(3)	O3–N3	1.236(2)
N2–C1	1.355(2)	N1–C1	1.327(2)
N2–C22	1.376(2)	C21–C22	1.414(3)
C25–C26	1.374(3)	N1–C11	1.390(2)
C12–C13	1.389(4)	N2–C1	1.359(2)
C14–C15	1.386(4)	N2–C12	1.381(2)
Bond angles			
Compound 4		Compound 8	
C1–N1–C21	105.1(1)	C1–N1–C11	105.3(2)
N2–C22–C23	132.1(2)	C1–N2–C12	107.2(1)
C1–N2–C22	107.1(1)	O2–N3–C25	119.3(1)
N1–C1–N2	112.8(1)	O3–N3–C25	117.8(1)
N1–C1–C11	122.8(2)	O2–N3–O3	122.9(1)
N2–C1–C11	124.2(2)	N1–C1–C21	122.8(2)
N1–C21–C22	109.5(1)	N1–C1–N2	112.5(2)
N1–C21–C26	130.3(2)	N1–C11–C12	109.4(2)
N2–C22–C21	105.5(1)	N2–C1–C21	124.6(2)

DPPH scavenging activity

Antioxidant activity is a commonly studied area of research [22, 23]. DPPH is a stable free radical that can accept an electron or hydrogen radical to become a stable diamagnetic molecule. Due to its odd electron, the methanolic solution of DPPH shows a strong absorption band at 517 nm. DPPH radical reacts with various electron donating molecules (reducing agents or antioxidants). When electrons become paired off, bleaching of DPPH solution is the outcome, this results in the formation of the colourless 2,2'-diphenyl-1-picryl hydrazine. Reduction of the DPPH radicals can be estimated quantitatively by the decrease in absorbance 517 nm [24]. Scheme 3 gives the formation of the DPPH radical. The activity of the compounds being tested is determined by their ability to easily contribute a proton to the DPPH radical. The data was expressed as mean \pm SD. The data is given in Table 2. Plots of percentage scavenging activity against log of concentrations of compounds **1-9** and ascorbic acid are shown in Figure 5.



Scheme 3. The formation of the DPPH radical.

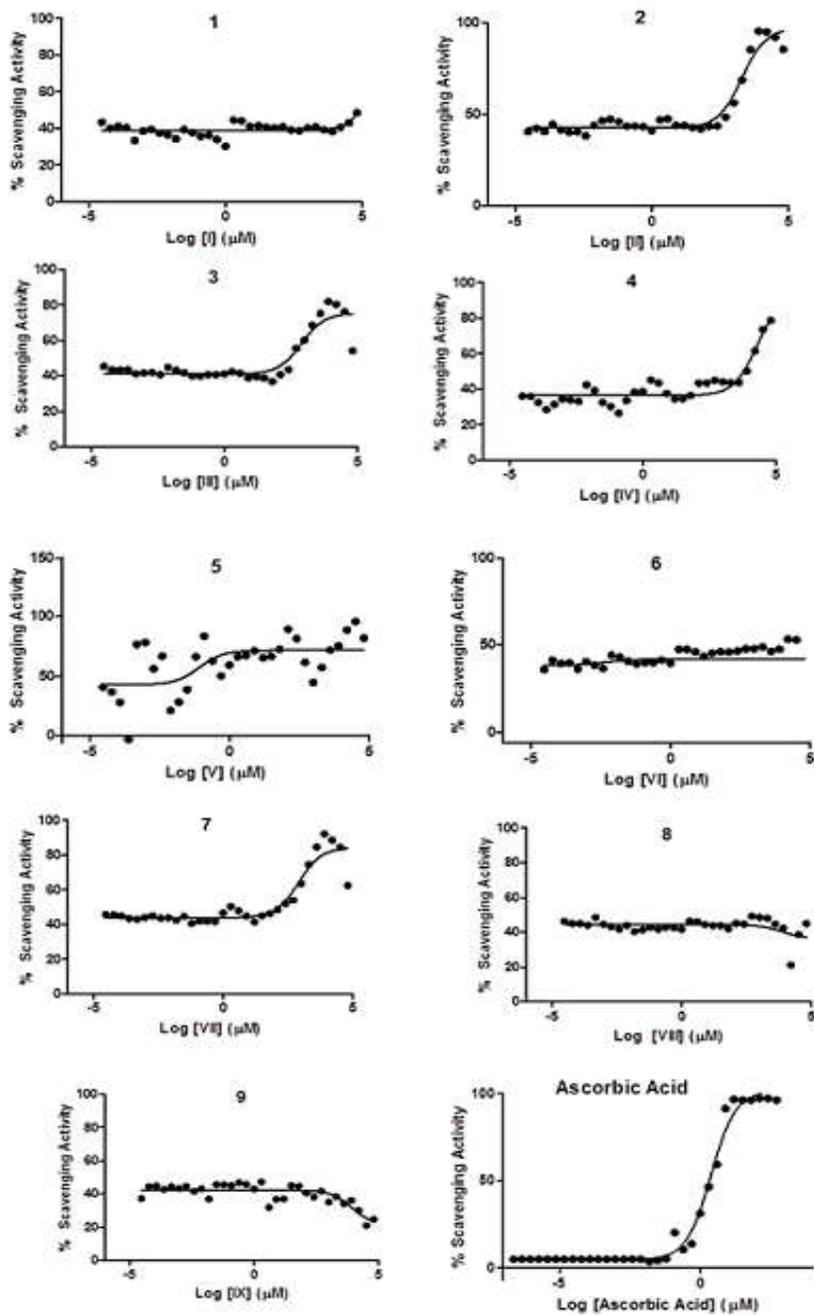


Figure 5. Plots of percentage scavenging activity against log of concentrations of compounds 1-9 and ascorbic acid.

Table 2. DPPH scavenging activity of compounds 1-9.

Compound	IC-50 (μM)
1	NC
2	1974
3	773
4	18843
5	0.0828
6	0.005078
7	800
8	7601
9	8909
Ascorbic acid	2.37

In these set of compounds their scavenging activity is greatly influenced by the ease of loss of a proton. Of all the compounds tested only compounds **2**, **3** and **7** exhibited DPPH activity. In the case of compounds **3** and **7** their activity could be due to their symmetrical nature allowing them to easily occupy the binding site of the DPPH. The very low activities of these compounds could be because they do not have readily available proton for scavenging but might interact *via* association with the radical to form a stable complex. Compound **2** on the other hand could donate the proton on the hydroxyl group in it DPPH scavenging activity.

CONCLUSION

A base-catalyzed synthesis method for the formation of benzimidazoles from aldehydes and diaminobenzene has been developed, and the derivatives that represent the scope of the reaction are presented and have been fully characterized using IR, NMR, microanalysis and GC-MS. The single crystal XRD of 2-(2-chlorophenyl)-1*H*-benzimidazole (**4**) and 2-(1*H*-benzimidazol-2-yl)-4-nitrophenol (**8**) have been discussed. The DPPH scavenging activities of the compounds have also been presented.

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Supplementary material. Supplementary data associated with this article can be found in the online version. CCDC numbers 1062232 and 1062215 contain the crystal structures associated with this article.

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