Asian Journal of Chemistry; Vol. 35, No. 8 (2023), 2001-2006

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2023.28074

Design, Synthesis of 5-(2-Methylbenzofuran)-2-aryl-2*H*-tetrazole Derivatives *via* Cross-Coupling of N-H Free Tetrazoles with Boronic Acids

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Received: 31 May 2023; *Accepted*: 20 July 2023; *Published online*: 31 July 2023; AJC-21337

Chemical intermediates derived from 1,3-dipolar cycloaddition reactions, such as 5-substituted 1*H*-tetrazole, are commonly utilized to synthesize 1,5-disubstituted tetrazoles. In this work, a highly effective and useful strategy for the synthesis of 5-(2-methylbenzofuran-3-yl)-2-phenyl-2*H*-tetrazoles using environmentally safe 1 atm. O_2 as oxidizer is reported. Moreover, the N-H unbound tetrazoles and low hazardous boronic acids are directly coupled with the catalytic amount (5 mol%) of Cu_2O to form C-N bond without any formation of the additives. The proposed method is simple for the Cu-catalyzed reactions, which require only mild conditions and green, atom-efficient chemistry for the regioselective synthesis of 2,5-disubstituted 2*H*-tetrazoles.

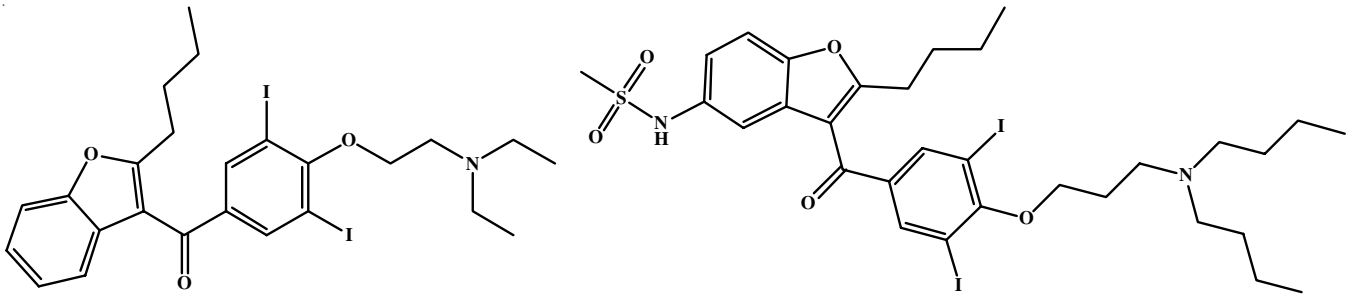
Keywords: Benzofuran, 2,5-Disubstituted 2*H*-tetrazoles, C-N bond, Low toxic, Regioselective.

INTRODUCTION

Heterocyclic compounds represent a privileged class of both natural origin and pharmaceutical significances [1,2]. Biological and pharmaceutical significance of benzofuran [3] (synthetic and natural isolated), its analogues are widely present as scaffolds in the complex molecules of natural products [4-6] showed high cytotoxicity [7] and showed variety of biological behaviours, includinganti-proliferative potential [8,9], anti-oxidant [10], potent antimicrobial [11], antibacterial [12,13], anticonvulsant and anti-inflammatory [14], Schiff bases as antidiabetic [15,16], antitumor [17] and antineophobic agents [18], amides [19], isoxazoles [20], sulphonamides [21], acts as anticancer agents. Benzofuran isatin conjugates inhibits potent VEGFR2 and cancer cell growth [22].

Recently, U.S. FDA approved several drugs, which contain benzofuran derivatives (Fig. 1) [23]. Tetrazoles are the important class of five-membered and nitrogen-rich heterocyclic compounds, scaffolds exhibit a several applications in the fields of organic synthesis, agriculture, coordination chemistry as surrogates for carboxylic acids [24,25] and especially in the field of medicinal chemistry [26-29]. Often utilized as lipophilic spacers and metabolically steady substitutes in pharmaceuticals, as antifog ants in photographic materials, explosives [30] and as high-density energy materials in materials science [31-34], information recording systems [35]. Tetrazoles and their derivatives have attracted considerable interest in the broad area of use and drawn much attention in designing drugs as bioactive compounds [36,37]. Tetrazoles found in various biologically and pharmacologically active moieties such as antibiotic, anti-inflammatory, antiallergic, antiviral, antifungal, antitubercular, antihypertensive, anti-HIV and antineoplastic agents [38-42], used as analgesic, herbicidal, antiproliferative, antimicrobial and anticancer agents [43-50]. Tetrazole ring-containing olmesartan medoxomil, valsartan, losartan and TAK-456 exhibit biological functions similar to those of medications from the antihypertensive family medicines [47,51] (Fig. 2). Demko & Sharpless [52] reported the synthesis of tetrazole [3 + 2] cycloaddition event of nitrile group and sodium azide, which is a conventional procedure for generating 5-substituted 1*H*-tetrazoles [53-55].

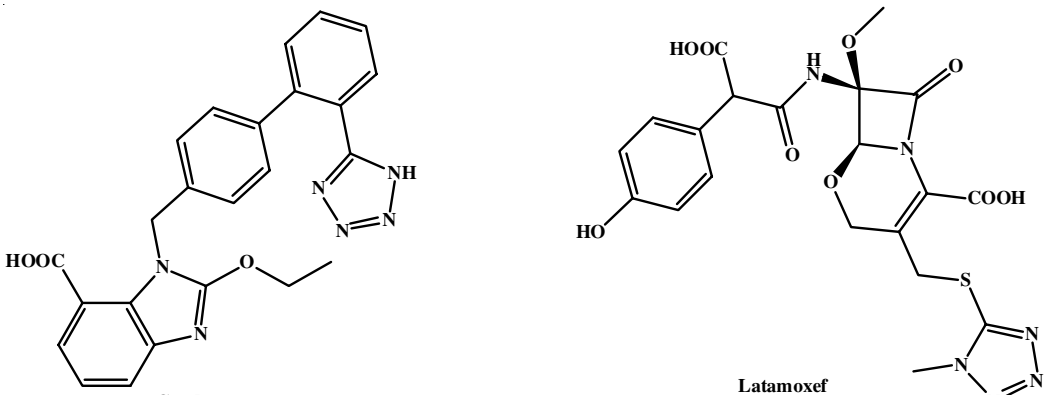
Hetero aryl C-N bond forming reactions are a notable example of popularly investigated contemporary organic synthetic reactions [56], because of the ubiquity of aromatic C-N bonds in a broad spectrum of areas including natural product, pharmaceutical, agrochemical, catalysis, coordination chemistry and polymer sciences [57]. Several approaches for synthesizing 5-substituted 2*H*-tetrazoles [58-60] includes Kakehi's synthesis



Amiodarone
(adrenergic channel blocker coronary vasodilator Ca channel blocker)

Dronedarone
(cardiovascular antiarrhythmic multi-channel blocker)

Fig. 1. U.S. FDA approved drugs contain benzofuran derivatives



Candesartan
(antihypertensive activity)

Latamoxef
(broad spectrum of β-lactam antibiotic)

Fig. 2. Drugs containing the tetrazole core

[61] (by employing phenylsulfonyl hydrazones and arene-diazonium salts), moreover, 5-substituted tetrazoles can also be synthesized directly where 2-arylation was mediated by Pd/Cu incorporating the substrates of Ar_2IBF_4 and tetrazoles of Na salts [62]. Han *et al*. [63,64] reported the synthesis of 2,5-disubstituted tetrazoles by combining N-H unbound 5-substituted tetrazoles and arylboronic acid by catalytic copper(II) oxide. The method presented herein would find extensive applications in a broad range of areas related to N-heterocycles.

Thus, the present work focused on the synthesis of 5-(2-methyl-benzofuran-3-yl)-2-phenyl-2*H*-tetrazoles derivatives by using copper(II) oxide and O_2 (1 atm) by aerobic oxidative direct cross-coupling to form new C-N bond.

EXPERIMENTAL

Unless otherwise specified, all the commercially available reagents and solvents were acquired respectively from Sigma-Aldrich, USA and S.D. Fine Chemicals, India. Reactions were conducted in the nitrogen atmosphere, otherwise mentioned. Silica gel 60-120 mesh was used for the column chromatography. On a Bruker spectrometer, ^{1}H NMR spectra were acquired using 500/400 MHz, while ^{13}C NMR spectra were obtained using of 126/101/100 MHz using tetramethyl silane used as internal standard. Electron spin ionization (ESI) methods were used to perform the mass spectral analysis. Aluminium sheets pre-coated with silica gel ($60F_{254}$, Merck) TLC were used during the progress of the chemical reactions in order to check the purity of compounds.

Synthesis of 2*H*-chromene-3-carbonitrile (3a-c): Salicylaldehyde (**1a**, 10 g, 81.884 mmol) was treated with acrylonitrile (27.33 mL, 409.423 mmol) in the presence of DABCO (1.837 g, 16.377 mmol as catalyst at 80 ºC. The reaction mixture was allowed to stir for 12 h. Monitored the progress of the reaction with TLC and then concentrataed the solution at *vacuo*. Acidified the resultant crude by 5% dil. HCl and extract the reaction mass by using ethyl acetate as mobile phase and brain solution. Discard aqueous solvent and organic solvent was dried on anhydrous Na_2SO_4. The isolation of compound was performed through column chromatography using mesh size of 60-120 silica gel, eluted with EtOAc:hexane (0.5:10) to obtain yellow solid.

2*H*-Chromene-3-carbonitrile (3a): Yellow, yield: 71%, m.p.: 51-53 ºC, IR (KBr, ν_{max}, cm^{-1}): 2208 (C≡N), 1629 (C=C), 1213 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.30-7.24 (m, 1H), 7.16 (s, 1H), 7.10 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.80 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 154.33, 138.86, 132.77, 128.47, 122.47, 120.06, 116.61, 116.45, 103.35, 64.32. ESI-HRMS *m/z*: calcd. for $C_{10}H_7NO$: 158.0606 $[M + H]^+$; found: 158.0600.

8-Methoxy-2*H*-chromene-3-carbonitrile (3b): Yellow, yield: 73%, m.p.: 102-104 ºC. IR (KBr, ν_{max}, cm^{-1}): 2204 (C≡N), 1616 (C=C), 1087 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.16 (t, *J* = 1.3 Hz, 1H), 6.94 (d, *J* = 1.8 Hz, 1H), 6.92 (s, 1H), 6.74 (dd, *J* = 5.4, 3.7 Hz, 1H), 4.86 (s, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 148.07, 143.29,

138.87, 122.22, 120.72, 120.31, 116.36, 115.30, 103.49, 64.57, 56.16. ESI-HRMS *m/z*: calcd. for $C_{11}H_9NO_2$: 188.0711 $[M + H]^+$; found 188.0714.

6-Chloro-2*H*-chromene-3-carbonitrile (3c): Yellow, yield: 64%, m.p.: 90-91 ºC, IR (KBr, ν_{max}, cm^{-1}): 2213 (C≡N), 1629 (C=C), 1236 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.22 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.10 (d, *J* = 4.3 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 1H), 4.82 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 153.26, 137.42, 135.20, 130.65, 121.62, 118.41, 115.92, 114.49, 104.81, 64.45. EI-HRMS *m/z*: calcd. for $C_{10}H_6ClNO$: 192.0216 $[M + H]^+$; found: 192.0216.

Synthesis of 2-methylbenzofuran-3-carbonitrile (4a-c): Dissolved 2*H*-chromene-3-carbonitrile (**3a**, 8 g, 50.914 mmol) in 25 mL of DMSO solvent under cool condition followed by the addition of NaN_3 (3.9713 g, 61.097 mmol) at ambient temperature and then raise the temperature up to 130 ºC with 30 min continuous stirring resulting in the formation of a chocolate coloured solution formed. When the reaction was finished as confirmed by TLC, the reaction mass was poured into a freezing water (200 mL) in order to quench it. The resultant reaction was extracted by using ethyl acetate and brain solution and repeated the process by 2-3 times. Using anhydrous Na_2SO_4, the organic layer was dried and 60-120 mesh silica gel used as column chromatography 2-methylbenzofuran-3-carbonitrile (**4a**) was eluted with EtOAc:hexane (0.5:10) to obtain compound **4a** as white coloured solid.

2-Methylbenzofuran-3-carbonitriles (4a): White, yield: 81%, m.p.: 148-150 ºC, IR (KBr, ν_{max}, cm^{-1}): 2225 (C≡N), 1598 (C=C), 1002 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.62-7.57 (m, 1H), 7.48-7.45 (m, 1H), 7.36-7.31 (m, 2H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.83, 153.72, 125.56, 124.39, 119.50, 113.37, 111.49, 91.34, 13.88. ESI-HRMS *m/z*: calcd. for $C_{10}H_7NO$: 158.0606 $[M + H]^+$; found: 158.0600.

7-Methoxy-2-methylbenzofuran-3-carbonitrile (4b): White, yield: 75%, m.p.: 151-153 ºC. IR (KBr, ν_{max}, cm^{-1}): 2222 (C≡N), 1625 (C=C), 1205 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.29-7.25 (m, 1H), 7.18 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.86 (dd, *J* = 8.0, 0.9 Hz, 1H), 4.01 (s, 3H), 2.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.73, 145.19, 127.63, 125.26, 113.30, 111.55, 107.59, 91.77, 56.16, 13.86. ESI-HRMS *m/z*: calcd. for $C_{11}H_9NO_2$:188.0711 $[M + H]^+$; found: 188.0715.

5-Chloro-2-methylbenzofuran-3-carbonitrile (4c): Yellow, yield: 66%, m.p.: 100-101 ºC, IR (KBr, ν_{max}, cm^{-1}): 2230 (C≡N), 1615 (C=C), 1115 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.0 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.24 (dd, *J* = 8.8, 2.1 Hz, 1H), 2.59 (s, 3H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 152.75, 137.59, 132.31, 127.73, 127.38, 121.10, 118.01, 115.95, 104.85, 64.49. EI-HRMS *m/z*: calcd. for $C_{10}H_6ClNO$: 192.0216 $[M + H]^+$; found: 192.0216.

Synthesis of 5-(2-methylbenzofuran-3-yl)-1*H*-tetrazole (5a-c): Compound **4a** (3.5 g, 22.2749 mmol) dissolved in DMF, sodium azide (4.346 g, 66.8247 mmol) and NH_4Cl (5.903 g, 111.3745 mmol) were mixed followed by the addition of 2 mL of acetic acid and heated to 160 ºC for 8 h. Monitored the reaction progress by using TLC, the mass was extracted by ethyl acetate (200 mL) after being acidified with 5% HCl in water solution. Repeated the process by 2-3 times using anhydrous Na_2SO_4, organic layer dried and then concentrated the organic layer under *vacuo* to obtain a white solid.

5-(2-Methylbenzofuran-3-yl)-1*H*-tetrazole (5a): White, yield: 80%, m.p.: 202-204 ºC, IR (KBr, ν_{max}, cm^{-1}): 3417 (N-H), 1788 (C=N), 1641 (C=C), 1311 (N=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.97 (dd, *J* = 6.3, 2.8 Hz, 1H), 7.53-7.49 (m, 1H), 7.37-7.33 (m, 2H), 2.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 157.87, 152.20, 136.79, 124.72, 123.77, 120.00, 111.22, 14.22. ESI-HRMS *m/z*: calcd. for $C_{10}H_8N_4O$: 201.0776 $[M + H]^+$; found: 201.0808.

5-(7-Methoxy-2-methylbenzofuran-3-yl)-1*H*-tetrazole (5b): White, yield: 85%, m.p.: 205-207 ºC, IR (KBr, ν_{max}, cm^{-1}): 3411 (N-H), 1741 (C=N), 1645 (C=C), 1314 (N=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.28 (d, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.87 (dd, *J* = 11.0, 4.1 Hz, 1H), 4.01 (s, 3H), 2.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.61, 153.47, 149.67, 135.09, 125.27, 111.59, 107.60, 56.17, 13.88. ESI-HRMS *m/z*: calcd. for $C_{11}H_{10}N_4O_2$: 231.0882 $[M + H]^+$; found: 231.0922.

5-(5-Chloro-2-methylbenzofuran-3-yl)-1*H*-tetrazole (5c): Yellow, yield: 81%, m.p.: 163-164 ºC, IR (KBr, ν_{max}, cm^{-1}): 3531 (N-H), 1792 (C=N), 1645 (C=C), 1322 (N=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.87 (d, *J* = 8.7 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 161.03, 156.93, 155.50, 154.09, 129.13, 128.06, 127.13, 110.80, 14.30. ESI-HRMS *m/z*: calcd. for $C_{10}H_7ClN_4O$: 235.0386 $[M + H]^+$; found: 235.0385.

Synthesis of 5-(2-methylbenzofuran-3-yl)-2-phenyl-2*H*-tetrazole (7a-i): In Schlenk tube, compound 5-(2-methylbenzofuran-3-yl)-1*H*-tetrazole (**5a**, 0.100 g, 0.499 mmol), dissolved in DMSO (5 mL), pyridine (0.121 mL, 1.499 mmol) in presence of O_2 (1 atm) were added to the required amount of simple boronic acid (0.121 g, 0.999 mmol) and then the mixture was allowed to heat at 100 ºC about 8 h. Monitored the reaction progress by using TLC, mass mixture was diluted with saturated aq. NH_4Cl (25 mL) and then extracted with DCM (150 mL). Repeated the process 2-3 times using anhydrous Na_2SO_4, the organic layer was dried, reduce the organic layer under *vacuo*, by using chromatography to obtain pure product 5-(2-methylbenzofuran-3-yl)-2-phenyl-2*H*-tetrazole (**7a**) as a white solid.

5-(2-Methylbenzofuran-3-yl)-2-phenyl-2*H*-tetrazole (7a): White, yield: 73%, m.p.: 110-112 ºC, IR (KBr, ν_{max}, cm^{-1}): 1639 (C=C), 1313 (N=N), 1245 (C-N), 1109 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.44 (dt, *J* = 6.5, 2.9 Hz, 1H), 7.35-7.26 (m, 5H), 7.15-7.07 (m, 3H), 2.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 160.94, 157.99, 154.12, 130.40, 129.91, 126.57, 124.21, 123.36, 122.87, 121.39, 118.93, 118.50, 110.71, 14.29. ESI-HRMS *m/z*: calcd. for $C_{16}H_{12}N_4O$: 277.1089, $[M+2H]^+$; found: 279.0543.

2-(4-Bromophenyl)-5-(2-methylbenzofuran-3-yl)-2*H*-tetrazole (7b): White, yield: 75%, m.p.: 121-123 ºC, IR (KBr, ν_{max}, cm^{-1}): 1649 (C=C), 1318 (N=N), 1311 (C-N), 1187 (C-O-C); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.88-8.08 (m, 1H), 7.57 (dd, *J* = 24.8, 8.8 Hz, 4H), 7.46-7.35 (m, 1H), 7.32-7.20 (m, 2H), 2.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 161.05, 156.96, 154.16, 135.12, 129.99, 126.52, 128.27, 126.19, 126.07,

124.38, 123.35, 121.66, 121.57, 14.30. ESI-HRMS *m/z*: calcd. for $C_{16}H_{11}BrN_4O$ 355.0194 $[M + H]^+$; found: 355.0192.

5-(2-Methylbenzofuran-3-yl)-2-(*p*-tolyl)-2*H*-tetrazole (7c): White, yield: 77%, m.p.: 109-110 ºC, IR (KBr, ν_{max}, cm^{-1}): 1651 (C=C), 1312 (N=N), 1241 (C-N), 1184 (C-O-C); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 8.08 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.49-7.44 (m, 1H), 7.34-7.28 (m, 4H), 2.88 (s, 3H), 2.41 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 161.05, 156.88, 154.09, 139.43, 134.41, 130.39, 130.35, 124.26, 123.40, 121.58, 121.32, 120.60, 111.58, 111.01, 21.13, 14.33. ESI-HRMS *m/z*: calcd. for $C_{17}H_{14}N_4O$ 291.1246 $[M + H]^+$; found: 291.1235.

5-(7-Methoxy-2-methylbenzofuran-3-yl)-2-phenyl-2*H*-tetrazole (7d): White, yield: 74%, m.p.: 110.5-113 ºC, IR (KBr, ν_{max}, cm^{-1}): 1648 (C=C), 1317 (N=N), 1253 (C-N), 1130 (C-O-C); ^1H NMR (500 MHz, $CDCl_3$) δ pm: 7.74 (dd, *J* = 22.5, 7.5 Hz, 3H), 7.57-7.40 (m, 3H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.05-6.97 (m, 1H), 4.03 (s, 3H), 2.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 160.19, 156.91, 145.54, 144.80, 144.13, 143.27, 136.68, 130.22, 128.64, 128.11, 127.78, 119.66, 119.15, 56.79, 15.19. ESI-HRMS *m/z*: calcd. for $C_{17}H_{14}N_4O_2$: 307.1248 $[M + H]^+$; found: 307.1231.

2-(4-Bromophenyl)-5-(7-methoxy-2-methylbenzofuran-3-yl)-2*H*-tetrazole (7e): Yellow, yield: 71.3%, m.p.: 118.3-190.5 ºC, IR (KBr, ν_{max}, cm^{-1}): 1658 (C=C), 1322 (N=N), 1272 (C-N), 1180 (C-O-C); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.61 (d, *J* = 8.9 Hz, 2H), 7.52-7.46 (m, 1H), 7.47-7.42 (m, 2H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 3.85 (s, 3H), 2.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 160.12, 158.29, 152.44, 145.54, 140.91, 130.34, 130.06, 128.11, 127.78, 125.03, 122.86, 118.82, 114.85, 48.5, 14.37. ESI-HRMS *m/z*: calcd. for $C_{17}H_{13}BrN_4O_2$: 385.0300 $[M + H]^+$; found: 385.0311.

5-(7-Methoxy-2-methylbenzofuran-3-yl)-2-(*p*-tolyl)-2*H*-tetrazole (7f): Off-white, yield: 80%, m.p.: 114.4-116 ºC, IR (KBr, ν_{max}, cm^{-1}): 1649 (C=C), 1319 (N=N), 1263 (C-N), 1131 (C-O-C); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.73-7.61 (m, 3H), 7.47-7.37 (m, 2H), 7.20-7.14 (m, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 2.82 (s, 2H), 1.18 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 160.19, 156.93, 145.54, 144.13, 136.70, 129.85, 129.20, 128.10, 124.14, 120.69, 121.60, 114.08, 111.88, 48.44, 14.30. ESI-HRMS *m/z*: calcd. for $C_{18}H_{16}N_4O_2$: 321.1351 $[M + H]^+$; found: 321.1352.

5-(5-Chloro-2-methylbenzofuran-3-yl)-2-phenyl-2*H*-tetrazole (7g): Brown, yield: 65%, m.p.: 117-119.3 ºC, IR (KBr, ν_{max}, cm^{-1}): 1658 (C=C), 1327 (N=N), 1332 (C-N), 1116 (C-O-C); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 8.07 (d, *J* = 0.7 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.51-7.46 (m, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.33-7.28 (m, 1H), 2.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 160.47, 158.32, 150.45, 141.15, 136.67, 129.88, 127.80, 124.47, 121.72, 121.00, 120.71, 111.74, 14.39. ESI-HRMS *m/z*: calcd. for $C_{16}H_{11}ClN_4O$: 311.0699 $[M + H]^+$; found 311.0692.

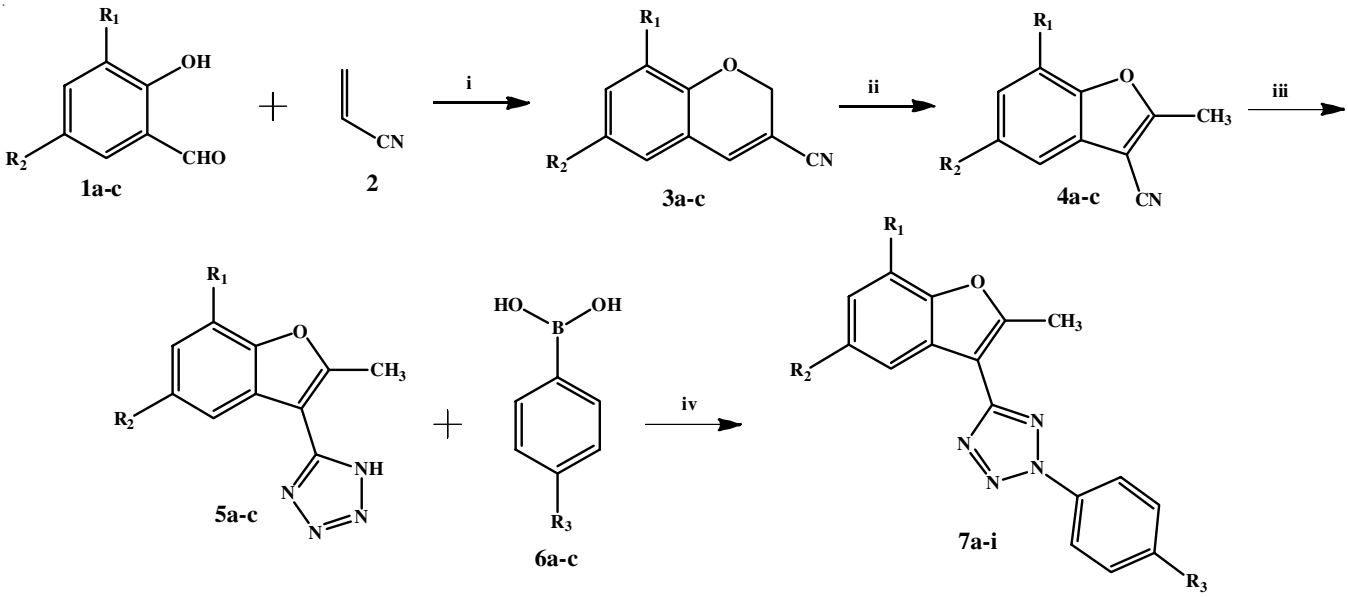
2-(4-Bromophenyl)-5-(5-chloro-2-methylbenzofuran-3-yl)-2*H*-tetrazole (7h): Off-white, yield: 72%, m.p.: 122.5-126.7 ºC, IR (KBr, ν_{max}, cm^{-1}): 1663 (C=C), 1336 (N=N), 1343 (C-N), 1112 (C-O-C); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 8.12 (d, *J* = 2.1 Hz, 1H), 7.45-7.41 (m, 1H), 7.41-7.36 (m, 1H), 7.67-7.59 (m, 4H), 2.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 160.50, 158.35, 152.46, 141.43, 135.12, 133.03, 127.78, 127.70, 128.82, 124.49, 122.98, 112.83, 110.97, 14.37. ESI-HRMS *m/z*: calcd. for $C_{16}H_{10}BrClN_4O$: 388.9805 $[M + H]^+$; found 388.9812.

5-(5-Chloro-2-methylbenzofuran-3-yl)-2-(*p*-tolyl)-2*H*-tetrazole (7i): White, yield: 74%, m.p.: 119-121.5 ºC, IR (KBr, ν_{max}, cm^{-1}): 1648 (C=C), 1322 (N=N), 1326 (C-N), 1188 (C-O-C); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.59 (d, *J* = 8.1 Hz, 2H), 7.47-7.41 (m, 1H), 7.35-7.27 (m, 1H), 7.28-7.22 (m, 1H), 7.14-7.08 (m, 2H), 2.86 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 160.44, 158.29, 152.45, 140.98, 139.95, 136.25, 128.82, 129.03, 124.45, 121.69, 120.59, 112.83, 110.97, 21.13, 14.38. ESI-HRMS *m/z*: calcd. for $C_{17}H_{13}ClN_4O$: 325.0856 $[M + H]^+$; found 325.0853.

RESULTS AND DISCUSSION

A facile novel synthetic approach of 5-(2-methylbenzofuran-3-yl)-2-phenyl-2*H*-tetrazole hybrids (**7a-i**) is presented in **Scheme-I**. Different substituted salicylaldehydes (**1a-c**) were cyclized in presence of acrylonitrile (**2**) and DABCO as catalyst at 120 ºC by using Baylis-Hillman reaction, azaenolate formed by Michael addition reaction, which further reacts with carbonyl of salicylaldehyde to form an intermediate. The intermolecular nucleophilic substitution of hydroxyl group in salicylaldehyde leads to the elimination of DABCO and formation of pyran ring by removing water molecule to obtain corresponding 2*H*-chromene-3-carbonitriles (**3a-c**). Subsequently, substances endured ring contraction and rearrangement when compounds (**3a-c**) reacted by sodium azide in the presence of DMSO at 160 ºC to form intermediate 2-methylbenzofuran-3-carbonitriles (**4a-c**). Additionally, **4a-c** performed the 1,3-dipolar cycloaddition in presence of sodium azide in DMF with ammonium chloride, acetic acid to produce appropriate benzofuran-tetrazoles (**5a-c**). These precursors **5a-c** treated with phenyl boronic acids in presence of environmental benign O_2 (1 atm), pyridine as base, DMSO as solvent, heated to 100 ºC for about 8 h leads to the formation of target compounds (**7a-i**), which contains new C-N bond where boronic acids and the N-H of tetrazole directly coupled. Catalytic copper activated by DMSO in the reaction process is crucial step, by means of oxidative copper amination reaction, formation of tetrazole anion complex with DMSO by oxygen oxidizes Cu^I catalyst to Cu^{II}. In presence of boronic acid, complex Cu^{II} disproportionates to Cu^I and aryl Cu^{III} and finally the hetero-aryl C-N coupled product obtained by facile elimination of the Cu^{III} species.

The IR spectrum of compound **7a** absorption at olefin (C=C) 1639 cm^{-1} and N=N observed at 1313 cm^{-1}, C-O-C appears at 1109 cm^{-1} and absorption at 1245 cm^{-1} indicates new C-N bond formation. The ^1H NMR the characteristic protons of compound **7a**, $-CH_3$ protons observed as singlet at δ 2.85 ppm, indicates the contraction of pyran ring converted to furan ring, remaining protons appeared in aromatic region as fallows δ 7.44 ppm as doublet of triplet, δ 7.35-7.26 ppm appeared as multiplet and δ 7.15-7.07 ppm observed as multiplet. ^{13}C NMR C-2 methyl carbon signal appeared at δ 14.29 ppm, characteristic new C-N bond carbon appears at δ 130.40 ppm, 5′-tetrazole carbon



6a; R_3 = H; 6b; R_3 = Br; 6c; R_3 = CH_3;

1a, 3a, 4a, 5a; R_1 = H	**1a, 3a, 4a, 5a, 7a; R_1 = H, R_3 = H**	**1a, 3a, 4a, 5a, 7d; R_1 = OCH_3, R_3 = H**	**1a, 3a, 4a, 5a, 7g; R_2 = Cl, R_3 = H**
1b, 3b, 4b, 5b; R_1 = OCH_3	**1a, 3a, 4a, 5a, 7b; R_1 = H, R_3 = Br**	**1a, 3a, 4a, 5a, 7e; R_1 = OCH_3, R_3 = Br**	**1a, 3a, 4a, 5a, 7h; R_2 = Cl, R_3 = Br**
1c, 3c, 4c, 5c; R_2 = Cl	**1a, 3a, 4a, 5a, 7c; R_1 = H, R_3 = CH_3**	**1a, 3a, 4a, 5a, 7f; R_1 = OCH_3, R_3 = CH_3**	**1a, 3a, 4a, 5a, 7i; R_2 = Cl, R_3 = CH_3**

Scheme-I: Synthesis of 5-(2-methylbenzofuran-3-yl)-2-phenyl-2*H*-tetrazoles derivatives [**Reagents and conditions:** (i) DABCO, 80 °C, 12 h; (ii) NaN_3, DMSO, 160 °C, 30 min; (iii) NaN_3, NH_4Cl, AcOH, DMF, 120 °C, 8 h; (iv) Substituted phenyl boronic acids, Cu_2O (5 mol%), pyridine, O_2 (1 atm), DMSO, 100 °C, 8 h]

signal resonates at δ 160.94 ppm, C-2 carbon attached to oxygen of furan ring signalling at δ 157.99 ppm and C-7a carbon appeared at δ 154.12 ppm, while C-3 signals at δ 122.87 ppm and C-3a observed at δ 129.91 ppm.

Conclusion

In summary, a direct coupling of benzofuran N–H unbound tetrazoles with low hazardous boronic acids for the synthesis of 5-(2-methylbenzofuran-3-yl)-2-phenyl-2*H*-tetrazole derivatives (**7a-i**) *via* Cu_2O (5 mol%) catalyzed aerobic benign O_2 (1 atm) oxidative reaction is successfully achieved. In addition, the protocol also exhibits excellent functional group compatibility. Consequently, this protocol represents a facile, atom-efficient, universally applicable, clean synthesis of benzofuran 2,5-disubstituted 2*H*-tetrazoles. It has some advantages over previous methods in terms of simple procedure, mild reaction conditions and good yields.

ACKNOWLEDGEMENTS

One of the authors, Govu Ramana, thanks to the DST-INSPIRE (IF 160114), India, for providing the fellowship. Thanks are also due to The Head, Department of Chemistry and Central Facilities for Research & Development (CFRD), Osmania University, Hyderabad, India for providing the research labratory and spectral analysis facilities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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