Tanzania Journal of Science 47(2): 745-753, 2021
ISSN 0856-1761, e-ISSN 2507-7961

Synthesis and Antimicrobial Activities of Some New Sulfonyl Phenoxides

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Received 30 Jan 2021, Revised 13 May 2021, Accepted 19 May 2021, Published May 2021
DOI: https://dx.doi.org/10.4314/tjs.v47i2.30

Abstract

Four new sulfonyl phenoxides were synthesized through *O*-sulfonylation reaction of phenolic compounds with 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl chloride in good yield. FT-IR, ^{1}H-NMR, ^{13}C-NMR, and DEPT 135 NMR were carried out to characterize and the thin layer chromatography (TLC) confirm the purity. Antimicrobial activities of the sulfonyl phenoxides against Gram-positive (methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, and *Bacillus subtilis*), Gram-negative (*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*), and *Candida albicans* were carried out using the standard microbiological method. The antimicrobial activities were referenced to ciprofloxacin and itraconazole, antibacterial and antifungal drug respectively. The *in vitro* antimicrobial studies of 5-chloro-1-ethyl-2-methyl-1*H*-imidazole-4-sulfonyl(4-chloro-3-methyl)phenoxide and 5-chloro-1-ethyl-2-methyl-1*H*-imidazole-4-sulfonyl-2-methylphenoxide showed moderate activity against *C. albicans*. The four sulfonyl phenoxides had weak activities against Gram-positive and Gram-negative bacteria.

Keywords: Sulfonyl phenoxides, Antimicrobial, Phenolic compounds, *O*-Sulfonylation reaction.

Introduction

Sulfonyl-functional group compounds are sulfones, sultones, sulfonamides, and sulfonyl phenoxides. Sulfonyl phenoxides are readily synthesized from alcohols and sulfonyl halides via nucleophilic substitution reaction. Sulfonyl chlorides are highly reactive electrophile but easily hydrolyzed. Sulfonyl phenoxides have broad applications in synthetic chemistry, pharmaceuticals, and agrochemicals. Some sulfonyl phenoxides are bioactive compounds (Fernandes et al. 2020). In pharmaceutical industries, sulfonyl phenoxides have anti-microbial (Aneja et al. 2018, Krishna 2018, Rendošová et al. 2018), anti-inflammatory (Arshia et al. 2019), anti-cancer activities (Rendošová et al. 2018, Du et al. 2019, Kanabar et al. 2020), etc.

Phenolic compounds are chemical component of flowers, fruits, vegetables, cereals, grains, and seeds. They have hydroxyl group and other substituents at different positions on the compounds. Phenolic compounds have been studied for their numerous properties, namely chemicals, biologicals, agricultural, and medical properties. Many phenolic compounds are used in food, pharmaceutical, and cosmetics production because of their organoleptic properties; color, aroma, taste, and astringency. In general, they are potent anti-oxidant (Zargoosh et al. 2019), anti-cancer (El-Ansari

et al. 2019), anti-atherosclerotic (Lutz et al. 2019), anti-inflammatory (Sato et al. 2020), anti-microbial (Bouarab-Chibane et al. 2019), anti-gout (Abu Bakar et al. 2018), anti-obesity (Yen et al. 2020), and anti-HIV (Krishna et al. 2020).

As part of our interest in developing *O*-sulfonylation reaction of phenolic compounds, this paper herein presents four sulfonyl phenoxides (5-Chloro-1-ethyl-2-methyl-1*H*-imidazole-4-sulfonyl(4-chloro-3-methyl)phenoxide, 5-Chloro-1-ethyl-2-methyl-1*H*-imidazole-4-sulfonyl-2-methylphenoxide, 5-Chloro-1-ethyl-2-methyl-1*H*-imidazole-4-sulfonyl-2,4,6-trinitrophenoxide, 5-Chloro-1-ethyl-2-methyl-1*H*-imidazole-4-sulfonyl-(*Z*)-4-(3-oxo-3-phenylprop-1-en-1-yl)phenoxide) synthesized from 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl chloride and phenolic compounds. The synthesized compounds were screened for antimicrobial activities against Gram-positive bacteria (methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), and *Bacillus subtilis)*, Gram-negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae)*, and *Candida albicans*.

Materials and Methods

All chemicals were analytical grade. Thin layer chromatography (TLC) determinations were performed on aluminum plate silica gel coated with florescent indicator F_{254} (0.25 mm Kieselgel 60) in a solvent system (ethylacetate, hexane, petroleum ether, and methanol). FT-IR spectra were recorded using a CARY 630 instrument (Agilent Technologies, USA). Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a Bruker Avance 500 MHz spectrometer. DEPT 135 NMR spectra were recorded to determine the presence of CH_2. Chemical shifts for protons and carbons were reported in parts per million downfield from tetramethylsilane and were referenced to residual deuterated protium and the carbon resonance in the NMR solvent ($CDCl_3$ = δ 7.26 and 77.22 or CD_3OD = δ 4.70). Chemical shift data of multiplicity were presented as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants are reported in Hertz (Hz).

Methods

4-Hydroxychalcone: To a mixture of NaOH (1.00 g, 0.025 mol), water (10 mL), and ethanol (5 mL) at 0–5 °C was added distilled acetophenone (2.60 g, 0.022 mol) and then 4-hydroxybenzaldehyde (2.64 g, 0.022 mol) portion-wise with constant stirring. The reaction was maintained at 0–5 °C for 3 h, the mixture was kept in the refrigerator overnight and acidified with conc. HCl (3 mL, 12 M), washed with cold water until neutral to litmus and recrystallized from ethanol to afford pale yellow solid: 3.09 g, 62.71%; R_f, 0.40 (EtOAc: hex, 3:7), m.p. 182–183 °C (lit, 182-183 °C, Shubhalaxmi et al. 2013); FT-IR (ATR, neat, V_{max} cm^{-1}): 3300 (OH, brd), 3012 (Aromatic ring), 1655 (C=O), 1578, 1501 (C=C, str), 1460 (ring C-H), 1413, 1348, 1206, 1167, 1126, 999, 845, 712, 693; ^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 5.87 (s, OH), 7.32-7.33 (d, 2 H, *J* = 5 Hz, *m*-CH, O-phenyl), 7.47 (s, 2H, *o*-CH, O-phenyl), 7.52–7.54 (t, 2 H, CH, *J* = 5 and 5 Hz, *m*-CO-phenyl), 7.59-7.60 (d, CH, *J* = 5 Hz, *p*-CH-CO-phenyl), 7.72 (s, 2 H, *o*-CH, CO-phenyl), 7.74 -7.75 (d, H, *J* = 5 Hz, H-α), 8.00-8.01 (d, H, *J* = 5 Hz, H-β).

***N, N*^{1}–diethyloxamide (II):** Diethyl oxalate (I) (30 mL) was added drop-wise to a chilled 70% ethylamine (33 mL) with constant stirring. The white crystals formed were filtered, triturated in cold water, and air-dried to produce *N, N*^{1}-diethyloxamide (II): 26.04 g, 83%; R_f, 0.55 (EtOAc: hex, 3:7); m.p. 179-180 °C (lit, 180–181 °C, Trout 1966); FTIR: 3287, 2859, 1638, 1377, 1226, 1148, 821, and 770 cm^{-1}.

5-Chloro-1-ethyl-2-methylimidazole (III): A mixture of *N, N*^{1}-diethyloxamide (II) (24 g, 0.17 mol) and PCl_5 (72 g, 0.35 mol) in a 250-mL flat bottom flask equipped with a wide-open reflux condenser fitted to calcium chloride guard tube was stirred until a brownish solution was formed and then immersed in hot

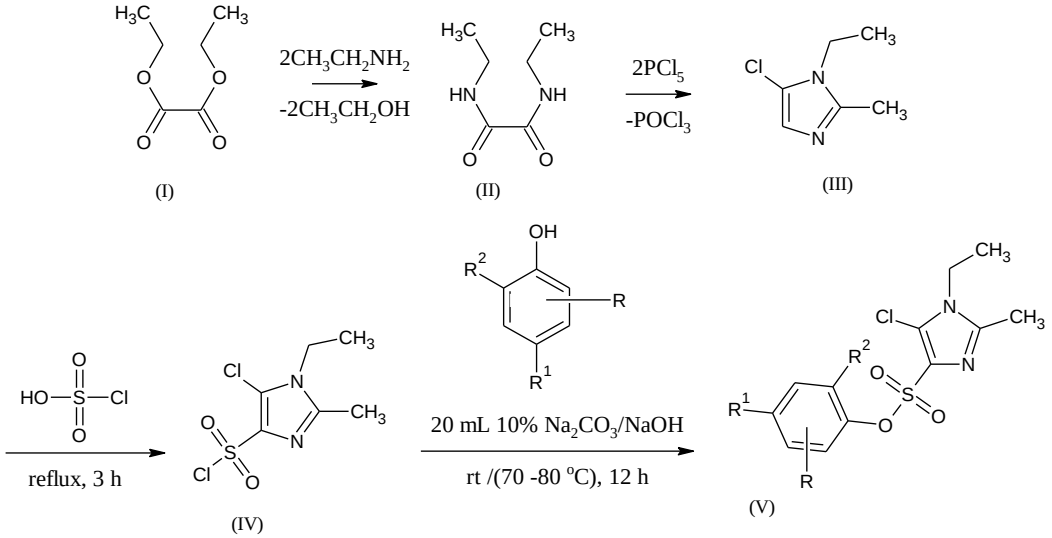
water for 30 min. The solution was left overnight at room temperature. And then, the solution was chilled and made alkaline with Na_2CO_3 (4.72 M, 45 mL) to afford dark brown organic layer (III) (18.30 g) which separated with the help of an *in situ* sodium chloride formed (salting-out liquid-liquid extraction) and was pipetted out without further work up.

$C_6H_9ClN_2S$: dark brown oil; yield 75.51%; $R_{f,}$ 0.83 ($CHCl_3$); FT-IR (ATR, neat, V_{max} cm^{-1}): 2981, 2859, 1638, 1508, 1495, 1430, 1383, 1260, 1148, 820 and 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, δ in ppm): 1.30-1.31 (t, J = 5 Hz, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 3.95-3.99 (q, 2 H, CH_2), 6.79-6.80 (s, H, NH).

5-Chloro-1-ethyl-2-methylimidazole-4-sulfonyl chloride (IV): In a 250 mL flat bottom flask equipped with reflux condenser, chilled distilled chlorosulphonic acid (67.5 mL, 1.02 mol) was carefully added to 5-chloro-1-ethyl-2-methylimidazole (III) (15 g, 0.10 mol), portion-wise. The mixture was fitted to a calcium chloride guard tube and then heated under reflux for 3 h. The solution was cooled, poured in crushed ice and filtered immediately to get the product (IV) (9 g) (Ovonramwen et al. 2020).

$C_6H_8Cl_2N_2O_2S$: brown powder; yield 53.52%; m.p. 116–117 °C; $R_{f,}$ 0.89 ($CHCl_3$); FTIR: 2981, 2853, 1638, 1508, 1498, 1437, 1377, 1351, 1263, 1226, 1187, 1142, 787, 722, 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, δ in ppm): 1.29–1.30 (t, 3 H, J = 10 Hz, CH_3), 2.39 (s, 3 H, CH_3), 3.95-4.01 (q, 2 H, CH_2).

Sulfonyl phenoxides: An equimolar mixture (0.005 mol) of 5-chloro-4-chlorosulfonyl-1-ethyl-2-methylimidazole (IV) (1.22 g) and phenolic compound were dissolved in 20 mL of 10% Na_2CO_3 (base, 10% NaOH; temperature, 70–80 °C). The mixture was stirred at 300 rpm, 25-28 °C for 12 h. The crude product was collected by filtration, washed with cold water, and recrystallized from ethanol to afford the respective sulfonyl phenoxides (V) (Scheme 1).



(I) (II) (III) (IV) (V)

Compounds	R	R^1	R^2
1	*m*-CH_3	Cl	H
2	*o*-CH_3	H	H
3	2-NO_2	4-NO_2	6-NO_2
4	H	C=C-C(O)-Ph	H

Scheme 1: Synthesis of sulfonyl phenoxides.

5-Chloro-1-ethyl-2-methyl-1*H*-imidazole-4-sulfonyl(4-chloro-3-methyl)phenoxide (1): $C_{13}H_{14}Cl_2N_2O_3S$; off white solid; yield, 97.70%; m.p. 128–129 °C; R*f*, 0.71 (EtOAc: Pet, 3:1); FT-IR (ATR, neat, V_{max} cm^{-1}): 2982 (CH_3), 1651, 1603 (C=N, wk), 1528, 1506 (C=C, str), 1491 (ring C-H), 1372 (S=O, SO_2 as, str), 1260 (C–N bend, str), 1223, 1170 (S=O, SO_2 sy, str), 1122 (C–O str), 1058, 1003, 943, 872 (S=O, str), 824 (S–O, str), 798, 667 (C–Cl str); ^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 1.26–1.30 (t, *J* = 10 and 10 Hz, 3 H, CH_3, imidazole), 2.28 (s, 3 H, CH_3, phenyl), 2.43 (s, 3H, CH_3 imidazole), 3.92-3.98 (q, *J* = 10 Hz, 2 H, CH_2, imidazole), 6.86-6.87 (d, *J* = 5 Hz, H, *o*-phenyl), 7.04 (s, H, *o*-phenyl) 7.21-7.23 (d, *J* = 10 Hz, H, *m*-phenyl); ^{13}C NMR ($CDCl_3$, δ in ppm): 13.85 (CH_3, imidazole), 14.72 (CH_3 imidazole), 20.18 (CH_3 phenyl), 40.20 (CH_2 imidazole), 120.80 (*o*-CH, phenyl), 123.08 (C–Cl), 124.60 (*o*-C, phenyl), 128.04 (C-SO_2), 129.80 (*m*-C, phenyl), 132.78 (*p*-C, phenyl) 137.71 (*m*-CH, phenyl), 145.45 (C-2, imidazole), 147.70 (C-O-phenyl).

5-Chloro-1-ethyl-2-methyl-1*H*-imidazole-4-sulfonyl-2-methylphenoxide (2): $C_{13}H_{15}ClN_2O_3S$; white solid; yield, 95.60%; m.p. 96-97 ^oC; R*f*, 0.76 (EtOAc: Pet, 3:1); FT-IR (ATR, neat, V_{max} cm^{-1}): 3060 (Ar, imidazole C-H), 2986 (CH_3), 2937 (CH_2), 2762 (CH_2–N), 1654 (C=N), 1580, 1528 (C=C, str), 1502, 1439 (ring C-H), 1371 (S=O, SO_2 as, str), 1260 (C-N bend, str), 1178 (S=O, SO_2 sy, str), 1148, 1100 (C–O, str), 1025, 956, 861 (S=O, str), 816 (S–O, str), 787, 686 (C–Cl, str); ^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 1.26-1.29 (t, *J* = 10 and 5 Hz, 3 H, CH_3, imidazole), 2.22 (s, 3 H, CH_3, phenyl), 2.43 (s, 3 H, CH_3, imidazole), 3.92–3.97 (q, *J* = 10 Hz, 2 H, CH_2, imidazole), 7.08–7.16 (m, 4 H, phenyl); ^{13}C NMR ($CDCl_3$, δ in ppm): ^{13}C NMR ($CDCl_3$, δ in ppm): 13.83 (CH_3, imidazole), 14.74 (CH_3, imidazole), 16.33 (CH_3, phenyl), 40.16 (CH_2, imidazole), 122.21 (*o*-CH, phenyl), 122.81 (C-Cl), 126.86 (*p*-CH, phenyl), 126.99 (*o*-C, phenyl), 128.80 (C–SO_2), 131.49 (*m*-CH, phenyl) 131.55 (*m*-CH, phenyl), 145.28 (C-2, imidazole), 148.21 (C-O-phenyl).

5-Chloro-1-ethyl-2-methyl-1*H*-imidazole-4-sulfonyl-2,4,6-trinitrophenoxide (3): $C_{12}H_{10}ClN_5O_9S$; orange solid; yield, 83.43%; m.p. 283–284 °C; R*f*, 0.63 (MeOH: Pet, 1:1); FT-IR (ATR, neat, V_{max} cm^{-1}): 3090 (Ar, imidazole C–H), 2982 (CH_3), 2822 (CH_2), 1633 (C=N, str), 1558 (C=C, str), 1491 (ring C-H, NO_2 as, str), 1428, 1379 (S=O, SO_2 as, str), 1331 (NO_2 sy, str), 1264 (C-N bend, str), 1200, 1159 (S=O, SO_2 sy, str), 1066 (C-NO, str), 932, 906, 850 (C–NO), 820 (S–O, str), 753, 708 (C–Cl str); ^{1}H NMR (500 MHz, CD_3OD, δ in ppm): 1.20-1.23 (t, 3 H, *J* = 5 and 10 Hz, CH_3, imidazole), 2.31 (s, 3 H), 3.91–3.97 (q, *J* = 10 Hz, 2 H, CH_2, imidazole), 8.80 (s, 2 H, phenyl): ^{13}C NMR (CD_3OD, δ in ppm) 12.46 (CH_3, imidazole), 13.83 (CH_3, imidazole), 39.62 (CH_2, imidazole), 116.39 (C–Cl), 127.27 (*m*-2CH-phenyl), 128.10 (C–SO_2), 134.26 (*o*-2C-phenyl), 141.20 (*p*-C-phenyl), 144.92 (C-2, imidazole), 162.65(C-O-phenyl).

5-Chloro-1-ethyl-2-methyl-1*H*-imidazole-4-sulfonyl-(*Z*)-4-(3-oxo-3-phenylprop-1-en-1-yl)phenoxide (4): $C_{21}H_{19}ClN_2O_4S$; yellow solid; yield, 20.93%; m.p. 283–284 °C; R*f*, 0.52 (EtOAc: hex); FT-IR (ATR, neat, V_{max} cm^{-1}): 2924 (CH_3), 2854 (CH_2), 1648 (C=O), 1595 (C=N), 1578, 1501 (C=C, str), 1460 (ring C-H), 1413, 1379 (S=O, SO_2 as, str), 1348, 1256 (C-N bend, str), 1206, 1195 (S=O, SO_2 sy, str), 1167, 1145, 1126, 962 (S=O, str), 845 (S–O, str), 712, 693 (C–Cl, str); ^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 1.30–1.34 (t, *J* = 5 and 10 Hz, 3 H, CH_3, imidazole), 2.48 (s, 3 H, CH_3, imidazole), 3.95–4.00 (q, *J* = 10 Hz, 2 H, CH_2, imidazole), 7.23–7.24 (d, *J* = 5 Hz, 2 H, *o*-CH, O-phenyl), 7.47 (s, 2 H, *m*-CH, O-phenyl), 7.50–7.52 (t, CH, *J* = 5 and 5 Hz, 2 H, *m*-CO-phenyl), 7.60-7.61 (d, *J* = 5 Hz, H, *p*-CH-CO-phenyl), 7.72 (s, 2 H, *o*-CH, CO-phenyl), 7.75–7.76 (d, *J* = 5 Hz, H, H-α), 8.00-8.01 (d, *J* = 5 Hz, H, H-β); ^{13}C NMR ($CDCl_3$, δ in ppm) 13.92 (CH_3, imidazole), 14.77 (CH_3, imidazole), 40.21 (CH_2, imidazole), 122.80 (*m*-2CH, O-phenyl), 122.89 (C-α, chalcone), 123.16 (C–Cl), 122H8.27 (*p*-C, O-phenyl), 128.49 (2CH, *o*-CO-phenyl), 128.70 (C–SO_2), 129.68 (2CH, *m*-CO-phenyl), 133.01 (2CH, *m*-

O-phenyl), 133.79 (CH, *p*-CO-phenyl), 137.92 (C, CO-phenyl), 143.08 (C-2, imidazole), 145.41 (C-β, chalcone), 150.87 (C-O-phenyl), 190.17 (C=O).

Antimicrobial activities

Determination of zone of inhibition

The microbial growth inhibitory activities of the synthesized sulfonyl phenoxides were determined by the agar well plate method where the compounds were initially dissolved in dichloromethane and distilled water (1:1). Those compounds with activities were later tested at concentrations of 10, 15, 20, 60 mg/mL against clinical isolated Gram-positive bacteria (methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), and *B. subtilis)*, Gram-negative bacteria (*P. aeruginosa*, *E. coli*, *K. pneumoniae)*, and *C. albicans* cultured and subcultured using the standard microbiological method. Sterile nutrient and Sabouraud dextrose agar plates were prepared for bacteria and fungi respectively and standardized inoculum of test organisms was spread uniformly.

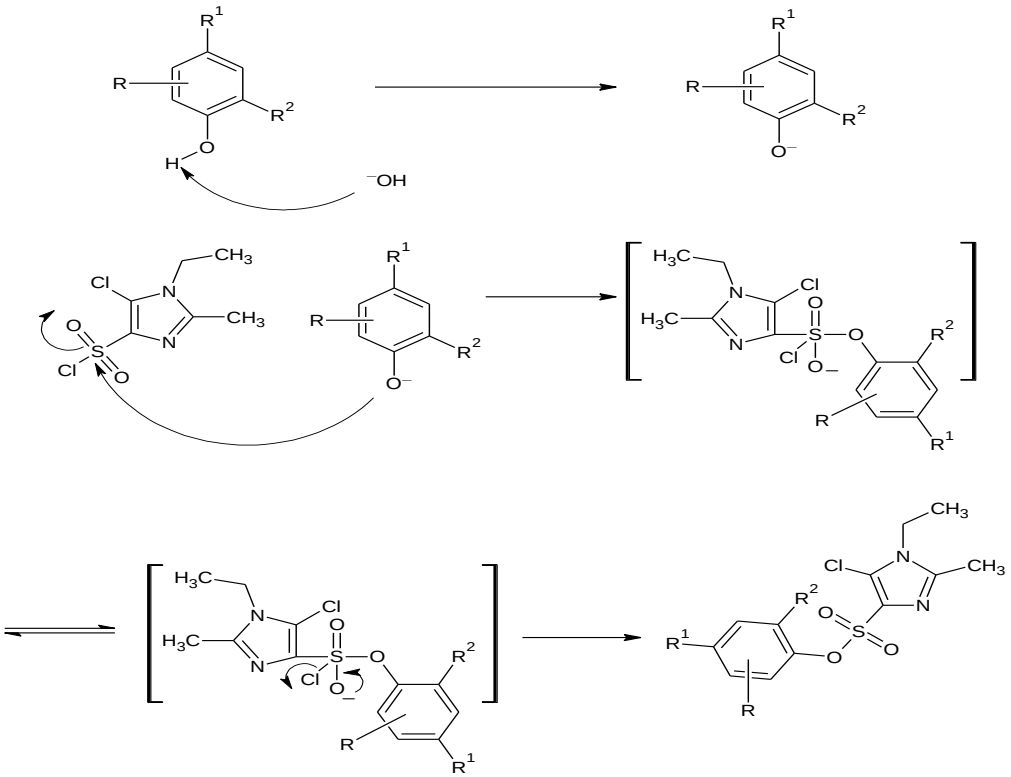
Six wells were bored using a sterile borer (8 mm) and 100 µL of the test concentrations, standard antibiotic, and the solvent control were added to each well. The plates were left on the table for 1 h for the test solution to diffuse into the medium and then incubated at 37 °C for 18–24 h. The resultant zone of inhibitions of microbial growth around the well was measured in mm. The test was performed in triplicate. Standard antibiotics ciprofloxacin (30 mg/mL), and itraconazole (50 mg/mL) were tested against bacteria and fungi respectively as the positive control (Ovonramwen et al. 2020).

Determination of minimum inhibitory concentration (MIC)

The minimum inhibitory concentration (MIC) values of the sulfonyl phenoxides were determined using the agar dilution method. Four different concentrations range of 100 µL of the synthesized compounds were incorporated into their respective molten agar and allowed to set. This was also repeated for ciprofloxacin and itraconazole as positive control and the diluent as a negative control. Each of the standardized test microorganisms was radially streaked onto the prepared plates. The plate was left to stand for 1 h at room temperature, incubated at 37 °C for 18-24 h. The MIC was recorded as the lowest concentrations that inhibited the growth of each of the test organisms (Ovonramwen et al. 2020).

Results and Discussion

5-Chloro-1-ethyl-2-methylimidazole was synthesized from *N, N*^{1}-diethyloxamide *via* Wallach synthesis. A neat chlorosulfonylation reaction produced 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl chloride. This was reacted with phenolic compounds in the 10% sodium carbonate or sodium hydroxide in an S_N2 reaction mechanism to afford sulfonyl phenoxides (**1-4).** The lone pair sp^2 electrons of the phenolic compound O (nucleophile) attacked the electrophilic sulfur atom in 5-chloro-1-ethyl-2-methylimidazole-4-sulfonyl chloride (electrophile) and pushed charge out onto its electronegative O atom. This produced the first intermediate. Then proton on the O of the protonated phenoxide-group was transferred to the negatively charged O of sulfonyl-group. HCl was eliminated from the second intermediate to produce sulfonyl phenoxides (Scheme 2).



Scheme 2: Proposed mechanism for the sulfonyl phenoxides.

The synthesized compounds were assigned their structure by detailed analysis of FTIR, ^{1}H, ^{13}C NMR, and DEPT (Figures S1–S16). Compound **4** was the only sulfonyl phenoxide prepared in the presence of 10% sodium hydroxide at 70-80 ^{o}C. The compound's low yield (20.93%) might be from the reaction conditions (Tingare et al. 2018, Álvarez et al. 2019).

In FTIR, the appearance of 1126-1066 cm^{-1} of C-O vibrational stretching confirmed the formation of the sulfonyl phenoxides (Oliveira et al. 2016, Ovonramwen et al. 2020). The presence of C=O group in compound **4** and aromatic C=C group gave the absorption band at 1648 cm^{-1} and 1580-1528 cm^{-1}, respectively. The FTIR were consistent with the published data (Rosa et al. 2019).

^{1}H NMR of the alkyl groups on imidazole ring appeared upfield as triplet, singlet and quartet in these orders with a coupling constant J ~ 10 and 5 Hz for the triplet signal. The ethylenic protons of compound **4** appeared as doublets at 7.75–7.76 ppm and 8.00-8.01 ppm for H-α and H-β, respectively with a coupling constants J ~ 5 Hz. This confirmed *cis* configuration of vinylic protons. The aromatic protons appeared between 6.86 to 8.80 ppm. The protons on the C-O-phenyl of compounds **1** and **2** appeared upfield at 6.85–7.23 because of the electron-donating effect (+I effect) of methyl group. The C-O-phenyl of compound **3** signal appeared as a singlet with a downfield shift at 8.80 ppm as result of electron-withdrawing effect (–I effect) of the nitro groups at positions C-2, C-4, and C-6. The C-O-phenyl protons of compound **4** at δ 7.23–7.47 ppm lied between those of compound **3** and compounds **1** and **2** because of enone group and extra phenyl of chalcone were less electronegative than the three nitro groups.

In ^{13}C NMR spectra, C–Cl, C-SO_2, C-2, and aromatic carbons appeared in these range; 116.39–123.16, 128.08–128.80, 143.08–145.45, and aromatic ring 120.80–162.65 ppm, respectively. These were in line with literature values (Ovonramwen et al. 2020, Sigma-Aldrich 2021). The C=O of compound **4** resonated at 190.17 ppm. This compared favorably with the literature data (Grosso et al. 2019, Rosa et al. 2019). The α- and β- carbon atoms of the carbonyl appeared at 122.89 and 145.41 ppm respectively. The C-O-phenyl of compound **3** appeared as most deshielded at 162.65 ppm because of the electron-withdrawing effect of the nitro groups. The C-O-phenyl signal of compound **1** and **2** resonated between 147.70–148.21 as a result of electron-donating effect of methyl group. The C-O-phenyl signal of compound **4** lied at 150.87 ppm between the signal of compound **3**, and compounds **1** and **2**.

The four newly synthesized compounds were tested for their antibacterial and anticandidal activities (Figure S17). The zone of inhibition for *C. albicans* using the cup-plate method on compound **1** and **2** gave 13.50 ± 0.21 mm and 19.00 ± 0.25 mm respectively and the standard itraconazole gave 21.50 ± 0.37 mm (Table 1). However, these activities might be because of the methyl group at *ortho* or *meta* position of the phenyl rings respectively. The MIC of the compounds **1** and **2** using the agar dilution method were 61.00 ± 0.14 mg/L and 31.00 ± 0.10 mg/L respectively. Compounds **3** and **4** had no antifungal activity against tested fungi as reported in previous studies (Shakhatreh et al. 2016, Ovonramwen et al. 2020). All the sulfonyl phenoxides showed no *in vitro* antibacterial activity against Gram-positive bacteria (MSSA, MRSA, and *B. subtilis)*, Gram-negative bacteria (*P. aeruginosa*, *E. coli*, *K. pneumoniae*) as reported in literature (Shakhatreh et al. 2016, Alhameed et al. 2020, Ovonramwen et al. 2020). Therefore, the sulfonyl phenoxides had no effect on the thickness of peptidoglycan layer of the bacterial cell wall and on the presence or absence of the outer lipid membrane.

Table 1: Zones of inhibition of sulfonylphenoxides and standard drugs in mm

	Average inhibition zone							
Compounds	*P aeruginosa*	MRSA	MSSA	*E. coli*	*K. pneumoniae*	*B. subtilis(T)*	*B. subtilis*	*C. albicans*
1	–	–	–	–	–	–	–	13.50
2	–	–	–	–	–	–	–	19.00
3	–	–	–	–	–	–	–	–
4	–	–	–	–	–	–	–	–
Ciprofloxacin	27.00	27.00	31.00	27.00	26.00	25.00	28.00	
Itraconazole	–	–	–	–	–	–	–	21.50

Conclusions

The four sulfonylphenoxides were synthesized under mild reaction conditions. 5-Chloro-1-ethyl-2-methyl-1*H*-imidazole-4-sulfonyl-(*Z*)-4-(3-oxo-3-phenylprop-1-en-1-yl)phenoxide had low yield as a result of its *cis*-configuration and reaction conditions. The *in vitro* antimicrobial studies on 5-chloro-1-ethyl-2-methyl-1*H*-imidazole-4-sulfonyl(4-chloro-3-methyl)phenoxide and 5-chloro-1-ethyl-2-methyl-1*H*-imidazole-4-sulfonyl-2-methylphenoxide showed moderate activities against *C. albicans*. All the sulfonyl phenoxides had weak activities against Gram-positive and Gram-negative bacteria.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

Authors appreciate Dr. Zulfiqar Ali of University of Mississippi, USA for NMR

characterization. And also, appreciate Dr. V. Imieje and Dr. O. Erharuyi who guided in sending the samples for characterization, while Dr. (Mrs) U. F. Babaiwa exposed to microbial analysis.

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