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Synthesis and antibacterial activity of new 2-Thiosubstituted-3-Nitro Imidazo [1,2-a] pyridine derivatives

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Abstract

To explore the antibacterial activity, a series of new 2-thioalkyl-3-nitroimidazo[1,2-a]pyridine derivatives (5a-k) were synthesized and characterized by ^{1}H, ^{13}C Nuclear Magnetic Resonance (NMR), and High-Resolution Mass Spectrometry (HRMS) analyses. These compounds were obtained by interaction of 2-(3-nitroimidazo[1,2-a]pyridin-2-yl)isothiouronium chloride salt 3 with functionalized alkyl chloride or bromide 4 in the presence of base. The synthesized compounds were evaluated *in vitro* on Gram-positive bacteria (*Staphylococcus aureus* ATCC 29213) and two others Gram-negative bacteria (*Pseudomonas aeruginosa* ATCC 27853 and *Pseudomonas aeruginosa* 933 C/21) by solid-state diffusion and liquid microdilution methods. None of the compounds showed any antibacterial activity on the bacteria tested.

Keywords: Antibacterial Activity; Imidazo[1,2-a]pyridine; Functionalized Halides; Analysis; *Staphylococcus aureus*; *Pseudomonas aeruginosa*

1. Introduction

The imidazo[1,2-a]pyridine scaffold is a major structural moiety found in many bioactive molecules [1]. The pharmacomodulations carried at the 3-position of this scaffold have led to the development of many drugs [2, 5]. The biological profile of these compounds mainly depends on the nature of the substituents. Heterocyclic thioester synthesis methods with interesting biological activities have been developed [6, 8]. Among them, the formation of a carbon-sulfur (C-S) bond on the imidazo[1,2-a]pyridine ring has given rise to considerable interest in organic synthesis. Indeed, these sulphenyl derivatives of imidazo[1,2-a]pyridine were usually obtained by substituting the 3-position of this ring. Most sulfenylation reactions have been carried out using sulfur reagents which are hazardous to handle, such as diphenyl disulfides [9], thiols [10], sulphonyl hydrazides [11], sodium benzenesulfinates [12], and p-tosylchlorides [13] with or without the use of catalysts. Despite the numerous sulfenylation methods of the imidazo[1,2-a]pyridine ring, the formation of the C-S bond in 2-position of this ring exists and remains difficult to achieve, in addition, it is still poorly elucidated. One such project was carried out by Rashmi Semwal et *al.* [14]. In their work, they realized disulfenylation on the imidazo[1,2-a]pyridine ring (in 2-and 3-position) using elemental sulfur and halides. These copper-catalyzed reactions were conducted in a single reaction step with good yields. In our earlier work, a 2-position monosulfenylation

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method using with benzyl groups from isothiouronium salts has been developed. In the framework of this study, we present this time the synthesis of new derivatives 2-alkylthioimidazo[1,2-a]pyridine and the evaluation of the antibacterial activity of these compounds.

2. Material and methods

2.1 Materials

2.1.1 Materials of Chemistry

All reagents and solvents were purchased from Sigma Aldrich and used without further purification unless otherwise noted. All anhydrous solvents, reagent grade solvents for chromatography and starting materials were purchased at the highest commercial quality from either Aldrich Chemical or Fisher Scientific. The reactions were monitored by TLC on precoated Merck 60 F254 silica gel plates and visualized using UV-Lamp (6 W, 254 nm and/or 365 nm) or KMnO4 solution followed by heating. Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded either on a Bruker Avance at 300, 400 and 75, 101 MHz. The spectra were internally referenced to the residual proton solvent signal. Residual solvent peaks were taken as reference ($CDCl_3$: 7.26 ppm, Acetone-d_6: 2.05 ppm, DMSO-d_6: 2.50 ppm) at room temperature. For ^{1}H NMR assignments, the chemical shifts are given in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet) and further qualified as app (apparent), br (broad signal) coupling constants, J are reported in Hz. HRMS were measured in the electrospray (ESI) mode on an LC-MSD TOF mass analyzer. Solid compound melting points were measured using a Köfler bench.

2.1.2 Biological Materials

Microbial strains

The antibacterial tests were carried out on three bacterial mice: *S. aureus* ATTC 29213, *P. aeruginosa* ATTC 27853 and *P. aeruginosa* 933C/21. These strains were provided by the Antibiotics, Natural Substances and Surveillance of Microorganisms to Antiinfectives Unit (ASSURMI) from the Department of Bacteriology and Virology at the Pasteur Institute of Cote d'Ivoire.

Chemical substances

The synthesis products are composed of ten (10) 2-(thioalkyl)-3-nitro imidazo[1,2-a]pyridine (5a–k) derivatives.

2.2 Method

2.2.1 Chemical Method

Synthesis methods of 2-(3-nitroimidazo[1,2-a]pyridin-2-yl)isothiouronium chloride salt 3

To a solution of 2-chloro-3-nitroimidazo[1,2-a]pyridine 1 (57.2 mmol) in 50 mL of acetonitrile, thiourea 2 (1 eq., 57.2 mmol) was added. The mixture was brought to reflux for 2 hours. After cooling to room temperature, a precipitate was formed, filtered, washed several times with ethyl acetate and then dried in the open air to afford yellow crystals, yield = 96%, m.p = 192-194 °C.

General procedure for the synthesis of 2-alkylthio-3-nitroimidazo[1,2-a]pyridine derivatives (5a-k)

To a solution of 2-(3-nitroimidazo[1,2-a]pyridin-2-yl)isothiouronium chloride salt 3 (3.8 mmol) in 10 mL of absolute ethanol was added 10 mL of sodium hydroxide solution (2.5 eq, 9.5 mmol). The mixture was stirred under reflux, and then an appropriate alkylating agent (3 eq, 11.4 mmol) was added. The reaction was allowed to stir under reflux for one more hour. After cooling to room temperature, the mixture was diluted in dichloromethane and washed several times with water. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The residue obtained was purified by silica column chromatography (hexane/ethyl acetate: 6/4) to give compounds 5a-k.

Products characterizations

- 2-(methylthio)-3-nitroimidazo [1,2-a]pyridine 5a

Yellow powder, m.p = 218-220 °C, yield = 67%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.44 (d, *J* = 6.9 Hz, 1H, H_{Ar}), 7.77–7.55 (m, 2H, H_{Ar}), 7.20 (t, *J* = 6.3 Hz, 1H, HAr), 2.73 (s, 3H, S-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 131.57, 127.83; 116.61, 115.52, 13.77. HRMS (ESI) Calc. for $C_8H_8N_3O_2S$ [M + H^+] = 210.2120 Found = 210.2123.

- 2-(ethylthio)-3-nitroimidazo [1,2-a]pyridine 5b

Yellow powder, m.p = 138-140 °C, yield = 52%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.35 (dt, *J* = 6.9; 1.1 Hz, 1H, H_{Ar}), 7.55 (dtd, *J* = 8.9, 7.1, 1.2, 1H, H_{Ar}), 7.10 (dd, *J* = 6.8, 1.6 Hz, 1H, H_{Ar}), 3,24 (q, *J* = 7.4 Hz, 2H, S-CH_2), 1.39 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.69, 131.90, 128.25, 116.96, 115.79, 25.45, 14.70. HRMS (ESI) Calc. for $C_9H_{10}O_2N_3S$ [M + H^+] = 224.0375 Found = 224.0378.

- 2-(isobutylthio)-3-nitroimidazo [1,2-a]pyridine 5c

Yellow powder, m.p = 260-261 °C, yield = 54%. ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 9.45 (d, *J* = 6.9 Hz, 1H; H_{Ar}), 7.75 – 7.51 (m, 2H; H_{Ar}), 7.18 (t, *J* = 6.3 Hz, 1H; H_{Ar}), 3.26 (d, *J* = 6.8 Hz, 2H; S-CH_2), 2.18–2.01 (m, 1H; CH), 1.11 (d, *J* = 6.7 Hz, 6H, 2-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 131.49, 127.88, 116.55, 115.36, 39.03, 28.32, 22.09. HRMS (ESI) Calc. for $C_{11}H_{13}N_3NaO_2S$ [M + H^+] = 274.0312 Found = 274.0315.

- 2-(butylthio)-3-nitroimidazo [1,2-a]pyridine 5d

Yellow powder, m.p = 218-220 °C, yield = 68%. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm) 9.30 (dt, *J* = 6.9, 1.0 Hz, 1H. H_{Ar}), 7.86–7.73 (m, 2H; H_{Ar}), 7.42–7.33 (m, 1H; H_{Ar}), 3.25 (t, *J* = 7.3 Hz, 2H, S-CH_2), 1.73–1.64 (m, 2H, CH_2), 1.50–1.38 (m, 2H, CH_2), 0.89 (t, *J* = 7.4 Hz, 3H; CH_3). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ (ppm) 146.43, 133.33, 128.63, 116.72, 31.17 (S-CH_2), 29.98, 21.93 13.99. HRMS (ESI) Calc. for $C_{11}H_{13}N_3NaO_2S$ [M + H^+] = 274.0326 Found = 274.0332.

- Acid 2-(3-nitro-imidazo [1,2-a]pyridin-2-ylthio)acetic 5e

Yellow powder, m.p = 138-140 °C, yield = 60%. ^{1}H NMR (300 MHz, Acetone-*d*$_6$) δ (ppm) 9.44 (dt, *J* = 6.9, 1.0 Hz, 1H, H_{Ar}), 7.93–7.74 (m, 2H; H_{Ar}), 7.46 (td, *J* = 6.9, 1.4 Hz, 1H; H_{Ar}), 4.23 (s, 2H; S-CH_2), 4.21 (s, 1H; OH). ^{13}C NMR (75 MHz, Acetone-*d*$_6$) δ (ppm) 169.52, 132.29, 128.01, 116.45, 116.11, 32.42. HRMS (ESI) Calc. for $C_9H_7O_4N_3NaS$ [M + H^+] = 276.0148 Found = 276.0186.

- 2-(3-nitro-imidazo [1,2-a]pyridin-2-ylthio)acetonitrile (5f)

White powder, m.p = 198-200 °C, yield = 66%. ^{1}H NMR (300 MHz, Acetone-*d*$_6$) δ (ppm) 9.45 (dq, *J* = 2.2, 1.5 Hz, 1H, H_{Ar}), 7.98 – 7.85 (m, 2H; H_{Ar}), 7.59–7.47 (m, 1H, H_{Ar}), 4.37 (s, 2H, S-CH_2). ^{13}C NMR (75 MHz, Acetone-*d*$_6$) δ (ppm) 132.54, 128.05, 117.02, 116.78, 116.57, 15.50. HRMS (ESI) Calc. for $C_9H_6O_2N_4NaS$ [M + H^+] = 257.0191 Found = 257.0189.

- 2-(3-nitro-H-imidazo [1,2-a]pyridin-2-ylthio)ethyl acetate 5g

Yellow powder, m.p = 128-130 °C, yield = 73%. ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 9.44 – 9.37 (m, 1H; H_{Ar}), 7.66–7.59 (m, 2H; H_{Ar}), 7.24–7.15 (m, 1H; H_{Ar}), 4.24 (q, *J* = 7.1 Hz, 2H; CH_2), 4.12 (s, 2H; S-CH_2), 1.30 (t, *J* = 7.1 Hz, 3H; CH_3).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 168.75, 152.89, 145.97, 131.55, 127.68, 116.86, 115.75, 61.90, 33.04, 1417. HRMS (ESI) Calc. for $C_{11}H_{12}N_3O_4S$ [M + H^+] = 282.2935 Found = 282.2938.

- 3-(3-nitro-H-imidazo [1,2-a]pyridin-2-ylthio)ethyl propanoate 5h

Yellow powder, m.p = 128-130 °C, yield = 91%, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.42 (dt, *J* = 6.9, 1.1 Hz, 1H; H_{Ar}), 7.73–7.57 (m, 2H; H_{Ar}), 7.20 (td, *J* = 6.7, 1.8 Hz, 1H; H_{Ar}), 4.19 (q, *J* = 7.1 Hz, 2H; O-CH_2), 3.59–3.56 (m, 2H; S-CH_2), 2.94–2.87 (m, 2H, CH_2-C=O), 1.35–1.23 (t, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 171.74, 154.11, 146.23, 131.57, 127.80, 116.71, 115.57, 60.89, 34.32, 25.62, 14.23. HRMS (ESI) Calc. for $C_{12}H_{14}N_3O_4S$ [M + Na^+] = 296.3263 Found = 296.3259.

- 2-(3-nitro-imidazo [1,2-a]pyridin-2-ylthio)ethyl propanoate 5i

Yellow powder, m.p = 140-142 °C, yield = 54%, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.40 (d, *J* = 6.8 Hz, 1H; H_{Ar}), 7.62 (d, *J* = 14.1 Hz, 2H; H_{Ar}), 7.21 (dd, *J* = 8.3; 3.9 Hz, 1H; H_{Ar}), 4,75 (q, *J* = 7.3 Hz, 2H; CH_2), 4.30–4.14 (m, 1H; S-CH), 1.72 (d, *J* = 7.3 Hz, 3H, CH_3), 1.28 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.14, 152.99, 146.05, 131.55, 127.72, 116.78, 115.67, 61.73, 42.42, 17.83, 14.14. HRMS (ESI) Calc. for $C_{12}H_{14}O_4N_3S$ [M + H^+] = 296.0567 Found = 296.0526.

- 2-(2-chloroéthylthio)-3-nitro-H-imidazo [1,2-a]pyridine 5j

Red powder, m.p = 134-136 °C, yield = 93%, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.42 (d, *J* = 6.8 Hz, 1H; H_{Ar}), 7.73–7.62 (m, 2H, H_{Ar}), 7.25–7.18 (m, 1H; H_{Ar}), 3.90 (t, *J* = 5.8 Hz, 2H; CH_2-Cl), 3.66 (t, *J* = 9.7, 5.2 Hz, 2H, S-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 153.23, 131.69, 127.56, 116.84, 115.66, 42.21, 32.46. HRMS (ESI) Calc. for $C_9H_9ClN_3O_2S$ [M + H^+] = 258.7053 Found = 258.7057.

- 2-((3-nitroimidazo [1,2-a]pyridin-2-yl)thio)ethan-1-ol 5k

Yellow powder, m.p = 164-166 °C, yield = 84%, ^{1}H NMR (300 MHz, Acetone-d_6) δ (ppm) 10.29–10.17 (m, 1H; H_{Ar}), 8.75–8.52 (m, 2H; H_{Ar}), 8.25–8.19 (m, 1H; H_{Ar}), 4.97 (s, 1H, OH), 4.71 (t, *J* = 6.5 Hz, 2H; CH_2-OH), 4.30 (t, *J* = 6.5 Hz, 2H. S-CH_2). ^{13}C NMR (75 MHz, Acetone-d_6) δ (ppm) 132.16, 128.01, 116.36, 115.86, 60.75, 32.92. HRMS (ESI) Calc. for $C_9H_9O_3N_3NaS$ [M + Na^+] = 262.0374 Found = 262.0412.

2.2.2 Biological Methods

Preparation of inoculum for solid-state tests

The inoculum was prepared from a 24 h young colony. It was emulsified in 2 mL of NaCl solution. Then, the optical density was adjusted at 0.5 MC Farland using a densimat. The volume taken was 1000 µL for *S. aureus* and 10 µL for *P. aeruginosa*. This suspension was mixed in 10 mL of physiological water (0.9% NaCl), thus constituting the bacterial inoculum estimated at 10^6 bacteria/mL. The different preserved bacterial strains were subcultured by the streak method on Muller-Hinton Agar (MHA). They were incubated in an oven at 37 °C for 18 to 24 hours to obtain young and isolated colonies. These colonies were used to prepare the bacterial inoculum.

Preparation of the stock solution of chemicals

The substances were weighed and put in the test tubes to which a quantity of 70° alcohol was added. The different concentrations were obtained.

Sensitivity test

- Determination of inhibition zones

The agar diffusion technique in wells and the liquid microdilution method were used to perform the tests [15, 16]. A solution of 500 µg/mL concentration of the chemical was prepared. Petri dishes containing Muller-Hinton agar were swabbed with the prepared inoculum. Then, cups were made by pushing the large end of a Pasteur pipette into the agar and filled with 50 µL of the prepared chemical solution. The set was incubated at 37 °C for 24 hours. After this time, the inhibition diameter around each cup was measured with a caliper. The efficacy of the extracts was assessed according to the criteria of Ponce et *al.* [17]. Thus, a substance is said to be inactive if the inhibition diameter is less than 8 mm, whereas it is said to be active if the diameter is between 9 and 14 mm. It is considered very active when the diameter is between 15 and 19 mm and extremely active when the diameter is over 20 mm.

2.3 Statistical analysis

The results were analyzed using Excel 2013 software for descriptive analyses. The results of the antibacterial tests obtained were expressed as mean ± standard deviation.

3. Results and discussion

3.1 Chemistry

The synthesis of compounds (5a-k) was performed in two steps starting from 2-chloro-3-nitro imidazo[1,2-a]pyridine 1 (Figure 1). The choice of this moiety is that we are considering substituting the chlorine atom for the sulfur atom in a nucleophilic substitution reaction. This substitution made it possible to change position-2 of the imidazo[1,2-a]pyridine scaffold with various functionalized alkyl substituents. Several attempts have been made to optimize the synthetic methodology for 2-chloro-imidazo[1,2-a]pyridine. Firstly, 2-chloro-imidazo[1,2-a]pyridine 1 reacted with 2-mercaptoacetic acid under reflux in a variety of solvents. In the presence of solvents such as dioxane, ethanol, dimethylsulfoxide, and the presence of multiple bases, no reaction was detected regardless of the reaction time. These different failures are due to the low electrophilic carbon at position-2. We opted for the attachment of an electron-

withdrawing group at the 3-position of the imidazo[1,2-a]pyridine ring intending to increase the electrophilicity of the carbon at the 2-position. Consequently, by an electrophilic substitution reaction in the aromatic series, the 3-position was substituted by a nitro group. For this series of compounds, the 3-position was substituted by a nitro group, a modulator of activity regularly found in compounds with anti-infectious activities [18]. Compound 1 was obtained by the nitration of the 3-position of 2-chloroimidazo[1,2-a]pyridine in sulfuric acid in the presence of nitric acid at room temperature with a 92% yield [19]. To obtain 2-(3-nitroimidazo[1,2-a]pyridin-2-yl)isothiouronium salt 3, we were inspired by the synthesis described Ibatullin et *al.* [20]. Compound 1 reacted with thiourea under reflux in acetonitrile for 48 hours. Upon completion of the reaction, the reaction medium was cooled to room temperature and the precipitate formed was filtered and washed several times with ethyl acetate yielding to compound 3 (96%). The ^{1}H NMR of compound 3 showed the presence of four signal groups (two doublets and two triplets) in the aromatic zone between 6.8 and 8.2 ppm corresponding to the pyridinic protons. We also observed the presence of two broad singletons. One at 10.01 ppm corresponds to the imine function proton of the salt (CH=NH) and another at 8.24 ppm corresponds to the two protons of the amine function (NH_2) of the isothiouronium salt.

The synthesis of new 2-thioalkyl-3-nitro imidazo[1,2-a] pyridine derivatives (5a-k) was carried out by substitution between compound 3 and various functionalized halides 4 in the presence of sodium hydroxide at the reflux of a water/ethanol mixture. Compounds (5a-k) were isolated in 56 to 92% yield. The ^{1}H NMR of compounds (5a-k) showed in addition to the disappearance of the two broad singletons at 10.01 ppm and 8.24 ppm corresponding to the NH and NH_2 protons of compound 3, the presence of a singlet or multiplet in the area of 2.73 to 3.66 ppm corresponding to the protons of the methylene linked to the sulfur ($S-CH_2$) for alkyl substituents. Signals from the methylene group directly bound to carbonyl and hydroxyl were observed at 4.12-4.37 ppm.

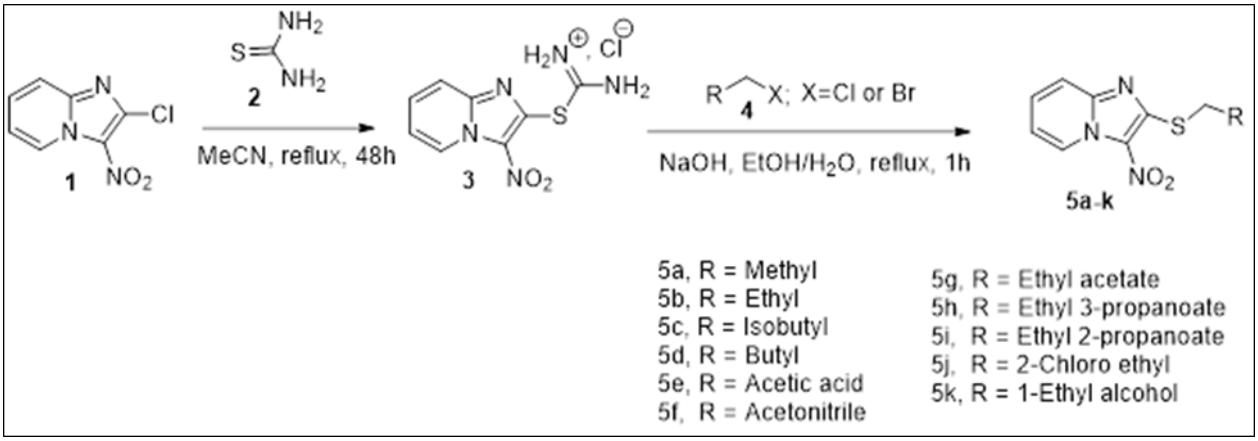

Figure 1 Synthesis of 2-thioalkyl-3-nitroimidazo [1,2-a] pyridine derivatives (5a-k)

Trials aimed at optimizing the method of synthesis of compounds 5 from compound 1 were studied. This method involved the direct substitution of the chlorine atom of compound 1 with 2-mercaptoacetic acid. As a result, compound 1 reacted with 2-mercaptoacetic acid in the presence of potassium carbonate under reflux in dioxane. After processing the reaction medium, a 96% yield was achieved for compound 5e. (Figure 2).

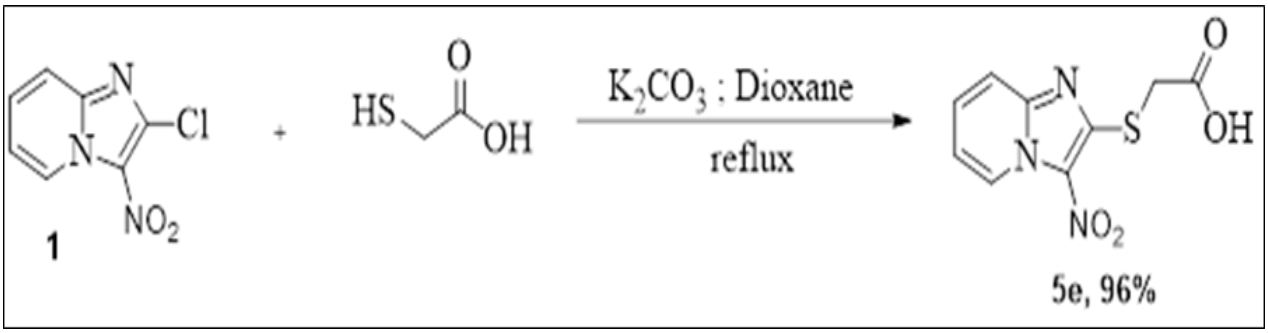

Figure 2 Synthesis of compound 5e from 2-mercaptoacetic acid

This synthesis route gave a better yield compared to the first 96% to 60 %. In the future, it will be applied to other halides to verify the effectiveness of this synthesis methodology.

3.2 Biology

The antibacterial activity of the synthesized compounds (5a-k) was evaluated *in vitro* by the agar diffusion and liquid microdilution method on gram positive and negative bacteria. Table 1 summarizes the results of the agar diffusion tests. A zone of inhibition threshold of 12 mm diameter was used to define appreciable antibacterial activity.

Table 1 Diameter of the inhibition zones of compounds (5a-k)

	Inhibition zones diameter (mm)*		
	Gram Negative		**Positive Gram**
Compounds	***P. aeruginosa***	***P. aeruginosa***	***S. aureus***
	ATTC 27853	**933C/21**	**ATTC 29213**
5a	6±0.00	6±0.04	7±0.00
5b	7±0.00	6±0.00	6±0.00
5c	6±0.00	8±0.00	7±0.00
5d	6±0.01	7±0.02	6±0.00
5e	8±0.02	6±0.01	7±0.00
5f	6±0.01	7±0.04	6±0.00
5g	7±0.00	6±0.00	8±0.00
5h	6±0.00	6±0.00	6±0.00

The diameters of the inhibition zones (mm), including the diameter of the well (6 mm), are expressed as ±SD of the tests performed in triplicate. The results obtained showed that the agar diffusion tests revealed that all the derivatives tested had no activity on the three strains of *S. aureus* ATTC 29213, *P. aeruginosa* ATTC 27853, and *P. aeruginosa* 933C/21 at the concentration of 1000 mg/mL.

4. Conclusion

This work made it possible to develop a synthetic route to form a carbon-sulfur bond at the 2-position of the imidazo[1,2-a]pyridine ring through a nucleophilic substitution reaction. The 2-position of imidazo[1,2-a]pyridine was substituted with various thioalkyl groups using isothiouronium salts as an intermediate. Thus, ten (10) compounds derived from the 2-(thio-substituted) imidazo[1,2-a]pyridine were synthesized. All the compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy and HRMS. The study of the antibacterial activity of the compounds was performed on gram positive and gram negative batteries. None of the compounds were found to be antibacterial.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflicts of interest regarding the publication of this paper.

Author contributions

E.A. performed the syntheses, T.E.C. and D.Z. participated in the design and direction of the project, P-A.A. participated in the purification of the compounds, B.C. and A.A conceptualized the biological study and methodology. S.C., write the paper and supervised the project. All authors have read and agreed to the published version of the manuscript.

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