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An Efficient Method for the Synthesis of α-Furfural Aryl-N-Aryl Nitrone and their Antimicrobial Activities

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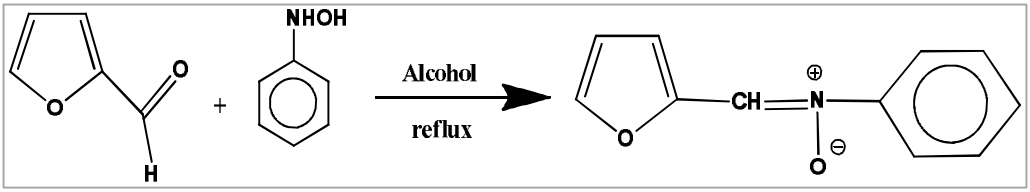
ABSTRACT

In organic chemistry, the synthesis of nitrone being a significant compound and highly useful in numerous applications of heterocyclic compounds via 1,3 dipolar cycloaddition reactions. The present research aims to synthesize the newly developed compound called α-Furfural aryl-N-aryl nitrone [N-(furan-2-ylmethylene) aniline oxide] under the simplest and eco-friendly method. The nitrone has been obtained from commercially available aldehyde and freshly prepared phenyl hydroxyl amine in presence of ethanol which gives an excellent yield. All of the synthesized compounds were characterized with the help of ^{1}H and ^{13}C NMR spectra. The synthesized nitrones were also found to get a good result in antimicrobial activities.

Graphical Abstract:



Synthesis of α-Furfural aryl-N-aryl nitrone.

Keywords: Nitrone, Furfuraldehyde, Phenyl hydroxyl amine, Anti-microbial activities.

INTRODUCTION

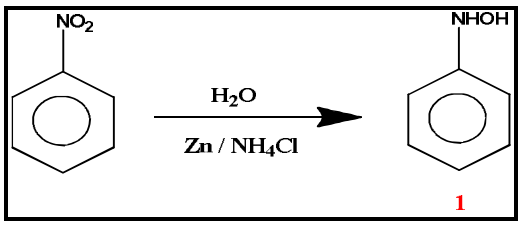
In organic field, the synthesis of novel nitrone was first developed by smith in the year of 1938. The word 'Nitrone' was originated from nitrogen ketone, a chemical relationship among nitrogen and carbonyl compounds [1]. The synthesized nitrone plays a vigorous role in synthesis of many heterocyclic compounds in organic chemistry. The universal method of synthesis of nitrone is the combination of hydroxyl amine and aldehyde in presence of non-toxic solvent by condensation method, eco-friendly methods and they are also synthesized with the help of several enzymes, it's all extremely useful for biological studies [2]. Most of the cases, including this paper, nitrone being a key intermediate of 1,3-dipolar cycloaddition reaction, that leads to get five-membered heterocyclic

compounds like isoxazolidine and isoxazolines [3]. The nitrone and its cycloaddition rection is mainly used in various pharmaceutical industries because of their ring opening system of isoxazolines and isoxazolidines [4, 5]. Many of the research paper says that nitrones can be easily produced, exhibit high structural variability and potential variety of applicability. The condensation reaction between carbonyls, hydroxylamines, imines is some methods for the synthesis of nitrones [6, 7]. The heterocyclic compounds such as azepanes, pyrrolidines, piperidones, indolizidines, and piperidines are prepared by the method of tandem reaction in presence of nitrones [9, 10]. In recent days two common methods are used to synthesize nitrones first is condensation reaction of hydroxyl amine with aldehyde and the second is oxidation of secondary amines or *N*, *N*-disubstituted amines [11]. One of the research papers proves the nitrone also synthesized by oxidation of pyrrolidines with HgO in presence of dichloromethane as a solvent to give the better yield [12]. In 1982, the nitrones plays a vital role in observation of biological active compounds and also used in therapeutic agents such as anti-cancer, anti-ageing, cardiac diseases and neuro degenerative diseases [13, 14]. One of the papers reviewed that the nitrone plays a major role in potential corrosion inhibitors using steel material in organic acidic medium. The results were moderate under the concentration between 50 to 150 ppm. The kind of paper proves the nitrone being an active corrosion inhibitor and good antibacterial activities [15]. Nitrones also have an many applications in supramolecular chemistry, in future many submissions are possible in synthesis of nitrone in this area of research [16, 17].

MATERIALS AND METHODS

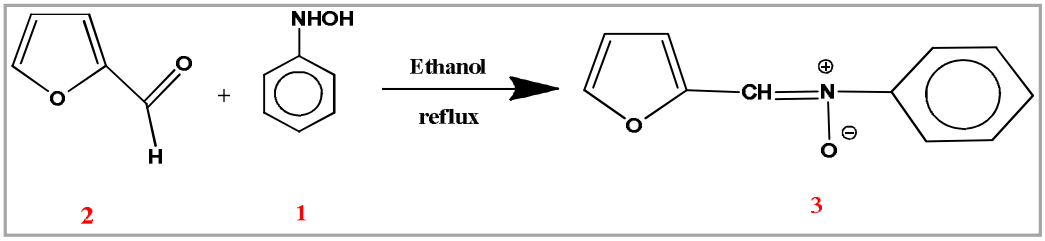
Materials and method: The Nitrobenzene and Ammonium chloride were purchased from Sigma-Aldrich. Zn powder, Furfuraldehyde from Nice brand used without any purification. The condensation method was used to synthesize nitrone they remains stable for a longer time and all the nitrone reactions were monitored by TLC using silica gel plates. Melting points were determined in open capillaries and are uncorrected. The Bruker nmr spectra was used to record ^{1}H NMR spectra using $CDCl_3$ as a solvent at 400 MHZ and TMS as internal standard. The same instrument is used to record ^{13}C NMR at 100 MHZ. The coupling constant (J) is shown in Hz. The synthesized nitrone was also tested under antimicrobial activities against bacterial strains, the compounds were dissolved in 100 µL of acetone solution. The agar plate was used in culture medium, it took 24 hrs for the growth of strain. The bacteria spreads uniformly in agar glass plates, the nitrone are active against specific microorganisms gram positive and gram negative bacteria. So, our study shows the synthesized nitrones has antibacterial activities [18].

Synthesis of phenyl hydroxyl amine: In a mechanical stirrer, place Ammonium chloride (5g) in 160 mL of water, and 8.3 mL of Nitrobenzene were mixed. To this mixture add 11.8g of Zn powder contains 90% purity about 15 min with the temperature increases to 60°-65°C. Then continue the stirring for further more 15 min until the temperature falls down. Filter the reaction mixture to remove the zinc oxide and wash it with 100 mL of hot water, again the filtered mixture was saturated with common salt (60g) and cool it with ice cold bath. The pale-yellow crystals of phenyl hydroxyl amine were filtered with suction and drain well. Finally, the phenyl hydroxyl amine **1** was synthesized as shown in scheme 1.



Scheme 1. Synthesis of phenyl hydroxyl amine

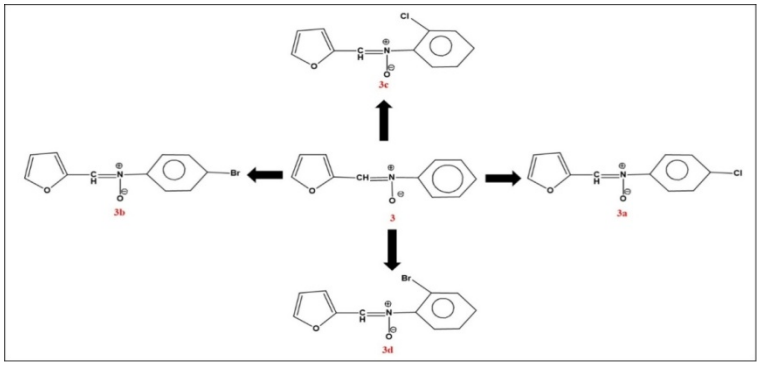
Synthesis of α-Furfural aryl-N-aryl nitrone: The synthesized phenyl hydroxyl amine (0.1 mol, 10.9 g) **1** was added to furfuraldehyde **2** (0.1 m, 9.6 g) in presence of alcohol and refluxed for one hour at room temperature, then it could be reduced to obtain α-Furfural aryl-N-aryl nitrone **3** (Scheme 2). The addition of substituted phenyl hydroxyl amine [1a-1d] with substituted furfuraldehyde [2a- 2d] to give different nitrones [3a-3d] as shown in scheme 3 and scheme 4. The yield of all the synthesized nitrones is good. Based on the good result of novel nitrone **3**, we synthesized nitrones [3a-3d] in presence of substituted phenyl hydroxyl amine [1a-1d] and substituted furfuraldehyde [2a- 2d] as shown in Scheme 3 and Scheme 4, spectral characterisation datas are shown in table 1. The yield of all the synthesized nitrones is quiet good.



Scheme 2. Synthesis of α-Furfural aryl-N-aryl nitrone.

RESULTS AND DISCUSSION

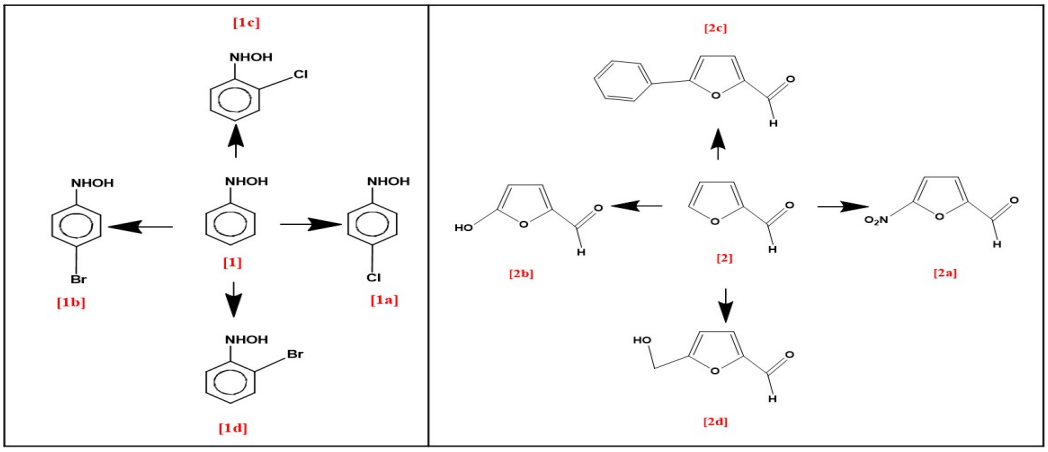
According to our proposed work, the reaction between furfuraldehyde **(2)** and phenyl hydroxyl amine **(1)** along with ethanol for the synthesis of α-Furfural aryl-N-aryl nitrone **(3)** scheme 1. The product obtained was evaporated off, and was confirmed by TLC. TLC indicated the formation of nitrone **(3)** as the major product in excellent yield. The ^{1}H NMR spectra of product **(3)** indicated the presence of expected product **(3)**. The synthesized nitrone was purified and further used to synthesis heterocyclic compound by 1,3-dipolar cycloaddition. The major starting material to synthesis α-Furfural aryl-N-aryl nitrone **(3)** is furfuraldehyde, it is a aldehyde with potent antimicrobial activity. Based on the good result of novel nitrone **3**, we synthesized nitrones [3a-3d] in presence of substituted phenyl hydroxyl amine [1a-1d] and substituted furfuraldehyde [2a- 2d] as shown in scheme 3 and scheme 4, spectral characterisation datas are shown in table 1. The yield of all the synthesized nitrones is quiet good



Scheme 3. Substituted Phenyl hydroxyl amine [1a-1d] and Substituted Furfuraldehyde [2a-2d].

The conventional method of compound **(3)** was confirmed by spectral analysis of NMR (^{1}H & ^{13}C). The ^{1}H NMR spectra of product **(3)** revealed the δ8.33 (t, J = 15.0 Hz, 6H), 8.16 (d, J = 7.8 Hz, 35H), 8.01 (d, J = 3.5 Hz, 30H), 7.79 (dd, J = 7.9, 1.7 Hz, 67H), 7.65 (dd, J = 19.4, 11.5 Hz, 10H), 7.62 – 6.87 (m, 310H), 6.74 (d, J = 7.1 Hz, 6H), 6.70 – 3.97 (m, 94H), 6.25 (d, J = 6.9 Hz, 4H), 6.29 – 3.97

(m, 40H) these signals confirm the compound **(3)** is obtained well. For ^{13}C NMR spectra (100 MHz,$CDCl_3$): δ 147.56, 147.32, 144.68, 129.97, 129.21, 128.82, 124.35, 121.08, 116.55, 112.73, 77.37, 77.06, 76.74 signals are appeared. All the nitrone compounds **(3-3d)** were confirmed by spectral data. This suggested that the nitrone derivative of compound **(3-3d)** formed well.



Scheme 4. Substituted α-Furfural aryl-N-aryl nitrone [3a-3d].

Table 1. Melting point, analytical and spectral characterization data of nitrones [3-3d]

Product	Observed % (Calcd)	m.p. (°C)	^1H NMR	^{13}C NMR
3	$C_{11}H_9NO_2$: C, 70.58; H, 4.85; N,7.48;O,17.09Found: C, 70.47; H, 4.81; N,7.35;O,17.02	180	δ8.33 (t, J = 15.0 Hz, 6H), 8.16 (d, J = 7.8 Hz, 35H), 8.01 (d, J = 3.5 Hz, 30H), 7.79 (dd, J = 7.9, 1.7 Hz, 67H), 7.65 (dd, J = 19.4, 11.5 Hz, 10H), 7.62 – 6.87 (m, 310H), 6.74 (d, J = 7.1 Hz, 6H), 6.70 – 3.97 (m, 94H), 6.25 (d, J = 6.9 Hz, 4H), 6.29 – 3.97 (m, 40H).	δ 147.56, 147.32, 144.68, 129.97, 129.21, 128.82, 124.35, 121.08, 116.55, 112.73, 77.37, 77.06, 76.74
3a	$C_{11}H_{14}ClNO_2$ C, 58.03; H, 6.20; Cl, 15.57; N, 6.15; O, 14.05 Found: C, 58.01; H, 6.11; Cl, 15.44; N, 6.07; O, 14.02	175	δ 7.86 (s, 1H), 7.62 (d, *J* = 5.1 Hz, 1H), 7.50 (s, 0H), 3.72 (m, 2H), 3.11 (m, 2H)	δ 28.28, 34.36, 59.82, 74.09, 116.66, 116.91, 119.46, 154.03, 154.37
3b	$C_{11}H_{15}BrNO_2$ C, 48.37; H, 5.54; Br, 29.25; N, 5.13; O, 11.71 C, 48.23; H, 5.48; Br, 29.21; N, 5.06; O, 11.62	172	δ 7.56 (s, 1H), 7.20 (s, 0H), 6.33 (d, *J* = 6.4 Hz, 1H), 5.98 (s, 1H), 3.70 (m, 2H), 3.20 (m, 2H)	δ 28.21, 33.80, 50.29, 74.47, 103.09, 114.40, 120.11, 151.56, 169.29
3c	$C_{11}H_8ClNO_2$ C, 59.61; H, 3.64; Cl, 16.00; N, 6.32; O, 14.44 C, 59.54; H, 3.58; Cl, 15.93; N, 6.28; O, 14.31	180	δ 7.57 (s, 1H), 7.18 (s, 0H), 6.59 (dt, *J* = 6.0, 0.9 Hz, 1H), 4.56 (dd, *J* = 5.9, 0.9 Hz, 2H), 3.74 (t, *J* = 5.9 Hz, 1H), 3.67 (dd, *J* = 6.7, 1.5 Hz, 1H), 3.20 (dd, *J* = 5.6, 1.5 Hz, 1H), 2.63 (ddd, *J* = 6.6, 4.8, 1.6 Hz, 1H), 1.85 (m, 1H)	δ 23.84, 24.07, 30.38, 32.49, 53.18, 57.57, 77.61, 112.13, 116.72, 118.74, 151.89, 161.36.
3d	$C_{11}H_8BrNO_2$ C, 49.65; H, 3.03; Br, 30.03; N, 5.26; O, 12.03; C, 49.55; H, 3.00; Br, 29.94; N, 5.19; O, 12.02	190	δ 7.76 (m, 2H), 7.58 (s, 1H), 7.19 (s, 0H), 6.93 (tt, *J* = 4.6, 1.5 Hz, 1H), 6.65 (d, *J* = 6.0 Hz, 1H), 3.66 (dd, *J* = 6.8, 1.5 Hz, 1H), 3.11 (dd, *J* = 5.5, 1.5 Hz, 1H), 2.87 (m, 2H), 2.57 (ddd, *J* = 6.6, 4.9, 1.5 Hz, 1H), 2.42 (ddd, *J* = 5.7, 4.9, 1.6 Hz, 1H)	δ 23.59, 24.40, 25.80, 26.32, 30.28, 30.40, 31.69, 33.66, 61.77, 77.46, 112.85, 116.49, 120.22, 154.43, 161.20

Antimicrobial study of N-(furan-2-ylmethylene)aniline oxide: The synthesized nitrone **3** were screened for antimicrobial activities against gram positive and gram negative bacteria shown in table 2. The N-(furan-2-ylmethylene)aniline oxide were dissolved in 100 µL of acetone solution, it is suffiicent to grow the bacteria in agar plates. The amikacin is used in standard disc. The nitrone spreads well in agar plates after the 24 h of incubation. The values are observed with the specific organisms like *Escherichia coli*, *Klebsiella oxytoca*, *Pseudomonas aeruginosa*, *Staphylococcus*

aureus and *Staphylococcus epidermidis*. Figure 1 represents the organisms of α-Furfural aryl-N-aryl nitrone [**18**].

Figure 1. Gram positive and gram negative bacterial strain of α-Furfural aryl-N-aryl nitrone

Table 2. Gram positive and gram negative bacteria, organisms and their values of α-Furfural aryl-N-aryl nitrone

Standard disc	Gram positive or negative bacteria	Organisms	α-Furfural aryl-N-aryl nitrone
AK-18 mm	Gram positive bacteria	*Staphylococcus aureus*	15 mm
AK-24 mm		*Staphylococcus epidermidis*	18 mm
AK-17 mm	Gram negative bacteria	*Escherichia coli*	25 mm
AK-18 mm		*Klebsiella oxytoca*	15 mm
AK-24 mm		*Pseudomonas aeruginosa*	26 mm

CONCLUSION

In this work, a series of synthesized phenyl hydroxyl amine was added with different substituted furfuraldehyde to get a novel nitrone compounds under condensation reaction with excellent yield. The method used to synthesize these nitrones is very simple, cost efficient, lesser time and environmentally friendly. All the nitrones are formed well by confirming the results of ^{1}H NMR, ^{13}C NMR spectra and antimicrobial studies. In future work, this nitrone protocol aims to synthesize many five membered heterocyclic compounds such as isoxazolines and isoxazolidines.

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