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A simple and convenient synthesis of α-cinnamic aryl-N-aryl nitrones [N-(3-phenylallylidene) aniline oxide] and their antibacterial activities

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Abstract

It is a popular two-step convenient method to prepare nitrones with distinctive phenylhydroxylamines and cinnamaldehydes. Nitrone is 1, 3-dipole and is one of the powerful substrate in 1,3-dipolar cycloadditions, it has drawn great attention because of its extensive tendency as a 1,3 dipole in Organic synthesis and its biological activities. Here the novel nitrones can be synthesized in exemplary yield (above 80%) and it has been confirmed by using ^{1}H and ^{13}C NMR techniques. The synthesized nitrone possess antibacterial activities in the bacterial strains of Pseudomonas aeruginosa, Bacillus marisflavi, Exiguobacterium Indicum and E.Coli.

Keywords: Nitrones, carbonyl condensation, recrystallization,1,3-dipole, antibacterial activities.

Introduction

The significance of nitrones in synthetic organic chemistry has been broadly illustrated. A huge number are isolable and stable mixtures, particularly those with C-aryl substituents that tend to dimerize or trimerize effectively and are in this way wagered produced in situ. The broad technique for framing nitrone is the build-up of N-alkylhydroxylamines with aldehydes or ketones[1]. In Organic chemistry, nitrone is a useful gathering comprising of an N-oxide of an imine. The general design is $R_2C=N+O-R'$, where R' isn't hydrogen. Nitrones are very flexible intermediates in regular union and are utilized, as a case, in the stereoselective arrangement of artificially valuable isoxazolidines through their 1, 3 dipolar cycloadditions with alkenes[2]. For the guidance of nitrones, the most well-known procedure is the build-up of aldehydes or ketones with N-monosubstituted hydroxylamines. Notwithstanding, this technique is difficult to be executed in the direction of non-formed cyclic nitrones and ketonitrones having unwieldy alkyl enterprises. Nitrones have many one-of-a-kind uses, along with 1, 3-dipolar cycloaddition to get entry to cyclic molecules and natural products, biological activity as spin-trapping dealers, bioorthogonal probes, a pharmacological pastime as remedies in precise cancers, and antioxidant interest in age-related illnesses[3]. Nitrones address a class of mixtures with flexible use as electron spin traps and cycloaddition responses. As nitrones go through 1, 3 dipolar cycloaddition under gentle circumstances with various unsaturated substances produce five-membered heterocycles[4-6]. Different problems include extremely long reaction times, tiresome chromatographic purifications, and the use of hazardous organic solvents. Therefore, it is a pleasure to look for unique and alternative approaches aimed at reducing the aforementioned constraints and improving many aspects of effectiveness and environmental reaction aspects. Here the nitrones are prepared by distinctive phenyl hydroxylamine and aldehydes within one hour. Cinnamaldehyde occurs evidently in the bark of cinnamon timber and different species of the genus Cinnamomum which possess various biological activities[7]. Hence the nitrone prepared from Cinnamaldehyde plays an important role in the synthesis of heterocyclic organic compounds. These nitrones can easily synthesize, exhibit high structural variety and potential range of applicability.

Methodology

Compound 2 is ready with 10g of ammonium chloride, 320ml of distilled water, and 16.6ml of nitrobenzene(1) in a 500ml conical flask. Then, at that point, the blend is mixed enthusiastically through a mechanical stirrer, and 23.6g of zinc dust of 90% purity is added for ten to fifteen minutes. As the reduction continues, the temperature climbs to 60–65°C. Blending goes on for fifteen minutes after all the zinc dust has been added, toward the end of which time the reaction is finished. While the solution is hot, it is filtered with suction to eliminate the zinc oxide, which is washed with boiling water. The filtrate is immersed in normal salt, around 60g being required, and cooled to 0°C by being set in an ice-salt combination. The compound (2) phenylhydroxylamine, which solidifies out in lengthy, light yellow needles, is filtered by suction (Scheme-I).

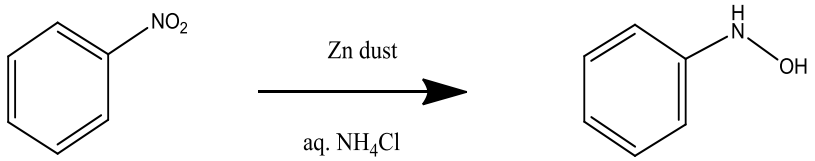
General procedure for the preparation of α-Cinnamic aryl-N-aryl nitrone: Phenyl hydroxylamine **2** (0.001mol), prepared by nitrobenzene, ammonium chloride, and Zn dust as a catalyst. After that **2** reacts with Cinnamaldehyde **3** in ethanol for 60 mins. to give a nitrone **4**. The completed reaction was monitored by TLC, and it was recrystallized with ethanol.

Results and Discussion

Nitrones have been thoroughly proven as effective synthetic intermediates, and there are numerous techniques for synthesis of nitrones have been established.

To our best knowledge there has been no reports regarding the synthesis of α-Cinnamic aryl-N-aryl-nitrones with the handiest exception of some specific case. We present a generic approach for preparing title compounds in ethanol by condensation of Cinnamaldehyde, a flavonoid which exhibits biological activities like antibacterial, antifungal, anti-inflammatory and anticancer reacted with the pre-prepared phenylhydroxylamine. Finally, high yields of α-Cinnamic aryl-N-aryl-nitrones as crystals are achieved by starting with readily accessible Cinnamaldehydes and a compatible hydroxylamine, which can be easily synthesised using the technique described in the literature. Despite its well-documented usefulness, no technique for the general method of N-aryl-Cinnamic aryl-N-aryl nitrones has been reported.

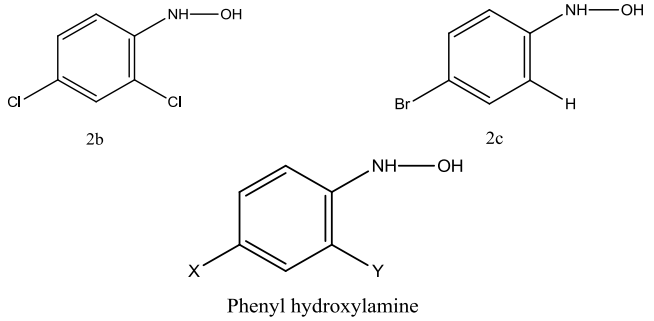
In the present investigation, the condensation was carried out with the addition of phenylhydroxylamine **2** with cinnamaldehyde **3** (Scheme-II). An equimolar combination of **2** with **3** was taken in a round bottom flask, around 30ml of Ethanol is utilized as a dissolvable and it was refluxed for 60 minutes. After it was cooled and recrystallized to give comparing nitrones[8,9]. The progress of all the reactions was monitored by TLC. The yield in all cases is good, more than 80 percent, giving only one product α-aryl-N-aryl nitrone. Pure α-Cinnamic aryl N-aryl nitrones (4) are especially interesting as 1,3-dipoles for 1,3-dipolar cycloaddition with a suitable dipolarophile, resulting in innovative synthesis of different substituted isoxazolidines. The spectral characterization for all the prepared compounds, 4a- 4e are below**.** A previous NMR spectrum of the representative case from the literature has been analyzed. From that, it has been noticed that the compound of C-(4-di-methylaminophenyl)-N-1-methyl-2-(4-chlorophenyl)-ethyl nitrone, the methylene hydrogens, appear at δ 2.79 and 3.37 as doublet of doublets, and the methine hydrogen at 0.8 ppm in the downfield region. The aldehyde chosen here (cinnamaldehyde) has a conjugated pi-bond system and reacts with pre-prepared phenylhydroxylamine (2) to give the product. And here, as the desired compound had no methylene protons, the methine proton near the nitrogen appears at 7.17 (d, J = 16.1 Hz, 1H). The ^{13}C NMR of the methine carbon appears at 140.2 ppm and the nearby conjugated pi system of carbons appears at 122.37 and 121.46 ppm respectively which confirms the formation of the novel nitrone **4a**. The spectrum of **4a** are below.



1 **2**

Scheme I

Scheme-1: The compound (2) phenylhydroxylamine, which solidifies out in lengthy, light yellow needles, is filtered by suction.

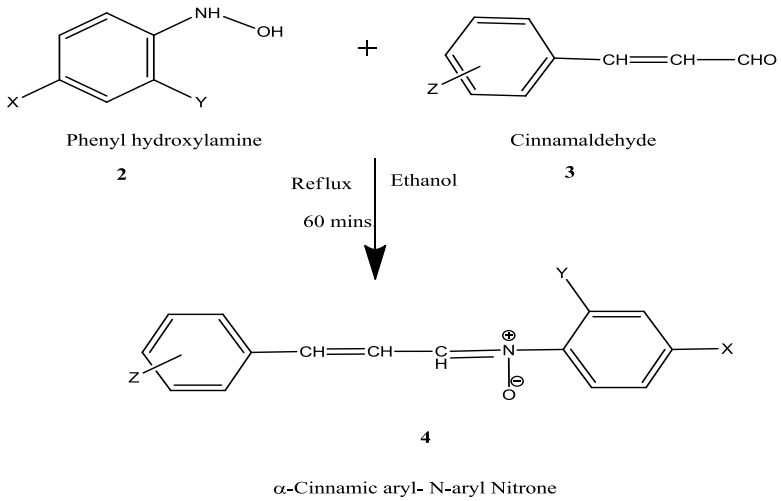


2b 2c

Phenyl hydroxylamine

2a

2d 2e



Scheme II

Scheme-2: the condensation was carried out with the addition of phenylhydroxylamine **2** with cinnamaldehyde **3.**

Table-1: Synthesized substituted novel nitrones.

Compound	X	Y	Z	Time (h)	Yield (%)
4a	H	H	H	1	85
4b	4-Cl	2-Cl	4-Cl	1	83
4c	4-Br	2-H	2-NO_2	1	85
4d	4-Cl	2-H	2-OH	1	82
4e	4-NO_2	2-H	α-CH_3	1	80

Spectral characterization of synthesized nitrones 4a- 4e: α-Cinnamic aryl-N-aryl Nitrone (N-(3-phenylallylidene)aniline oxide) (4a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.66 (m, 1H), 7.57 (t, *J* = 13.4 Hz, 1H), 7.90 – 7.13 (m, 1H), 7.44 (d, *J* = 19.3 Hz, 1H), 7.44 – 7.30 (m, 1H), 7.26 (s, 1H), 7.17 (d, *J* = 16.1 Hz, 1H), 2.17 (s, 1H), 1.63 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.77 (s), 152.87 (s), 147.40 (s), 140.20 (s), 136.48 (s), 136.12 (s), 134.01 (s), 131.32 (s), 130.35 – 129.43 (m), 129.29 – 128.35 (m), 127.91 (s), 127.57 (s), 127.05 – 125.34 (m), 122.37 (s), 121.46 (s), 119.08 (s), 77.47 (s), 77.15 (s), 76.83 (s).

2,4-dichloro-N-(3-(chlorophenyl)allylidene)aniline oxide(4b): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 – 8.10 (dd, *J* = 9.1, 1.4 Hz, 1H), 7.87 – 7.82 (d, *J* = 8.4 Hz, 1H), 7.54 – 7.50 (d, *J* = 2.2 Hz, 1H), 7.02(s),7.35 – 7.25 (m, 3H), 7.15 – 7.08 (dd, *J* = 15.6, 1.4 Hz, 1H).

^{13}C NMR (100 MHz) δ 145.75 – 145.63, 145.36 – 145.24, 138.55 – 138.43, 136.99 – 136.87, 136.50 – 136.38, 134.65 – 134.53, 130.04 – 129.92, 129.41 – 129.32, 129.37 – 129.25, 129.32 – 129.22, 127.92 – 127.80, 126.22 – 126.10, 125.64 – 125.52.

4-bromo-N-(3-(2-nitrophenyl)allylidene)aniline oxide (4c): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 – 8.04 (td, *J* = 8.9, 1.4 Hz, 1H), 7.93 – 7.87 (m, 1H), 7.86 – 7.74 (m, 1H), 7.66 – 7.51 (m, 2H), 7.23(s)7.43 – 7.37 (m, 0H).

^{13}C NMR (100 MHz) δ 147.35 – 147.25, 147.25 – 147.16, 145.92 – 145.80, 134.04 – 133.92, 133.66 – 133.54, 132.83 – 132.71, 132.40 – 132.28, 130.68 – 130.56, 129.42 – 129.30, 129.10 – 128.98, 124.98 – 124.86, 124.82 – 124.70, 124.42 – 124.30.

4-chloro-N-(3-(2-hydroxyphenyl)allylidene)aniline oxide (4d): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 – 8.24 (s, 1H), 8.09 – 8.04 (dd, *J* = 9.1, 1.4 Hz, 1H), 7.92 – 7.86 (m, 2H), 7.61 – 7.53 (dd, *J* = 15.9, 9.1 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.41 – 7.23 (m, 3H), 6.74 – 6.66 (m, 2H).

^{13}C NMR (100 MHz) δ 156.48 – 156.36, 147.62 – 147.50, 145.52 – 145.40, 135.05 – 134.93, 134.69 – 134.57, 130.31 – 130.19, 129.58 – 129.48, 129.37, 127.76 – 127.64, 127.62 – 127.50, 124.70 – 124.58, 120.56 – 120.44, 116.60 – 116.48.

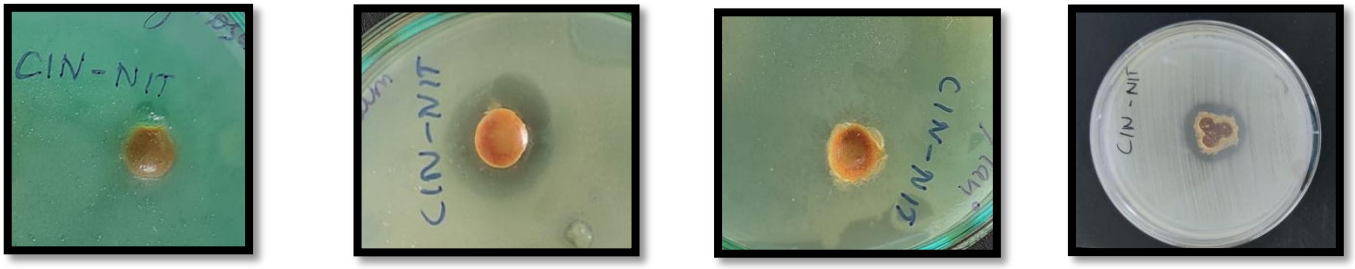
N-(2-methyl-3-phenylallylidene)-4-nitroaniline oxide (4e): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32 – 8.22 (m, 3H), 8.03 – 7.98 (p, *J* = 1.0 Hz, 1H), 7.46 – 7.40 (ddd, *J* = 8.6, 3.6, 1.6 Hz, 2H), 7.35 – 7.27 (m, 1H), 7.27 – 7.20 (m, 1H), 7.23(s), 6.96 – 6.92 (p, *J* = 1.5 Hz, 1H), 2.30 – 2.26 (d, *J* = 2.5 Hz, 1H).

^{13}C NMR (100 MHz) δ 152.80 – 152.68, 152.31 – 152.19, 142.29 – 142.17, 139.74 – 139.62, 139.18 – 139.06, 136.58 – 136.46, 129.54 – 129.42, 129.36 – 129.25, 129.25 – 129.13, 124.80 – 124.68, 123.72 – 123.60, 20.09 – 19.97.

Antibacterial activities of synthesized nitrones: To study the antibacterial activities, the disk diffusion method is used here. The method comprises setting paper circles soaked with antimicrobial specialists on a yard of microorganisms cultivated on the outer layer of an agar medium, hatching the plate for the time being, and estimating the presence or nonappearance of a zone of inhibition around the circles. Nitrones are found to exhibit antibacterial activity[10-12]. Hence, the antibacterial susceptibility testing on the synthesized nitrone 4 has been carried out at a concentration of 20mg/ml of DMSO in the inhibition zone diameter. All the nitrones had remarkable activity, no more distinctive property. Compound 4 is active against all four microorganisms tested. It is effective against Pseudomonas aeruginosa, Bacillus marisflavi, Exiguobacterium Indicum and *E.Coli* (Figure-1).

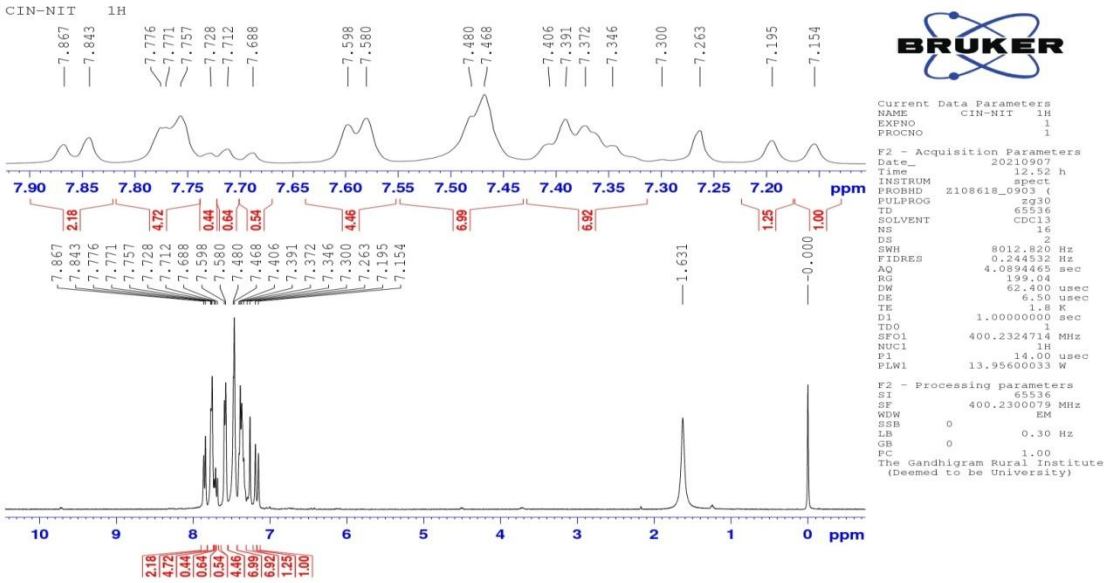
Table-2: Concentration: 20mg/ml of DMSO.

Bacterial Strain	Synthesized nitrones
Pseudomonas aeruginosa	10mm
Bacillus marisflavi	9 mm
Exignobacterium indicum	20mm
E. coli	8 mm



Pseudomonas aeruginosa ***Bacillus marisflavi*** ***Exignobacterium indicum*** ***E. coli***

Figure-1: Antibacterial activities of synthesized nitrones.



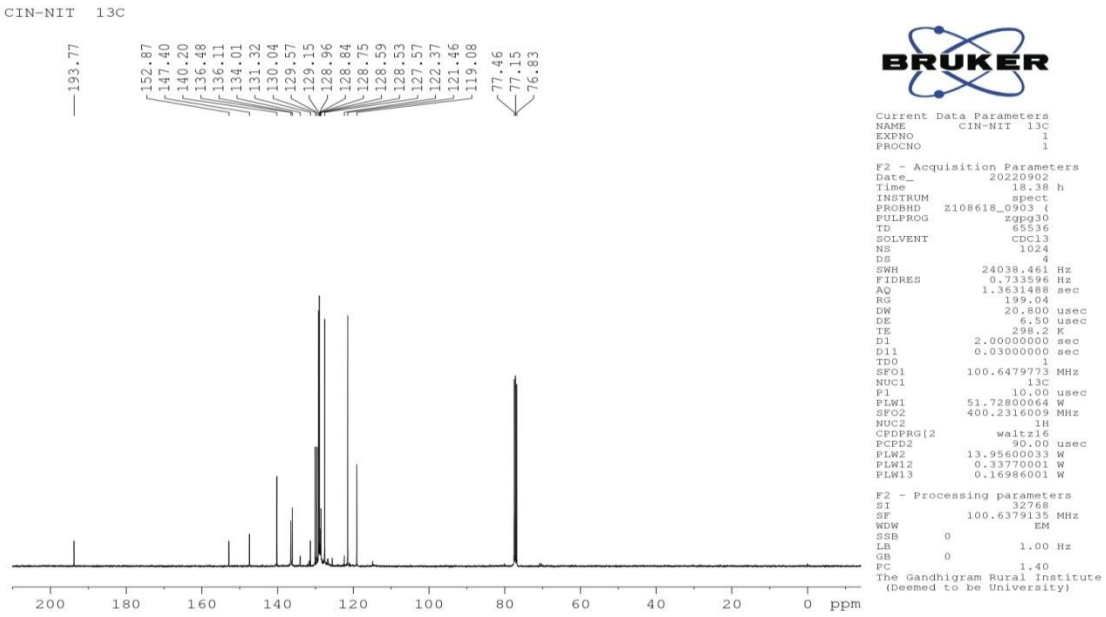


Figure-2: (a) ^{1}H NMR and (b) ^{13}C NMR of synthesized nitrones.

Conclusion

The synthesized nitrones were confirmed by ^{1}H and ^{13}C techniques. The novel nitrones were stable for a long period of time and it can be furtherly used to synthesize various heterocyclic systems with suitable dipolarophiles. The perceptions made in 4a- 4e models tried show that nitrone and its firmly related compounds do have powerful antibacterial activities.

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