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Heterocyclic Synthesis of Some New Isoxazolidine Derivatives *via* 1,3-Dipolar Cycloaddition of Nitrones to Styrene

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Abstract
A number of nitrones have been synthesized in three different procedures, starting with *N*-phenyl hydroxylamine, followed by the condensation reaction with some selected aldehydes. Furthermore, these nitrones were employed in the preparation of a number of new isoxazolidines. Cycloaddition reaction of nitrones to styrene produced the desired products.

Keywords: nitrones, reduction, condensation reaction, 1,3-dipolar cycloaddition reaction, novel isoxazolidine derivatives.

تحضير بعض مشتقات الأيزوكسازوليدين الجديدة عبر تفاعل الإضافة الحلقية للنيترونات إلى الستايرين

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الخلاصة
تم تحضير عدد من مشتقات النايترونات الجديدة باستخدام ثلاث طرائق مختلفة. مبتدئاً بتكثيف N- phenyl hydroxylamine مع بعض الألديهايدات المختارة. بعد الحصول على النايترونات المطلوبة تم استخدامها في تحضير عدد من الإيزوكسازوليدينات الجديدة من خلال تفاعل Cycloaddition للنايترونات الى الستايرين و التي انتجت المركبات المرغوبة.

1. Introduction

Both nitrones and isoxazilidine have received a great deal of interest and attracted much attention since their discovery. The chemistry of these species has been well developed because of their applications in synthetic [1-4] and pharmacological areas [5-11]. These medical and pharmacological applications have encouraged many researchers to investigate the synthesis of nitrones and their heterocyclic derivatives intensively. The synthesis of nitrones from aryl aldehydes and some nitro compounds using Zn as a catalyst was accomplished by Yannick Vallée and his co-workers [12]. Stanko in his thesis presented the

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synthesis of chiral nitrones from two different approaches [13]. Chakraborty and Sharma used the green method in synthesizing nitrones from chloral and hydroxylamine using water as a solvent [14]. Redcliffe in his thesis has reported the synthesis of some cyclic nitrones [15]. In 2013, a green synthesis methodology for nitrones synthesis was reported by Moghimi *et al*. This method involved the reaction of aldehyde and ketone derivatives with diaminoglyoxime [16]. Chen, Zhao, and Chen have prepared nitrones aryl aldehydes and hydroxylamine hydrochloride in a basic medium. These nitrones were found to have acidic and microbial corrosion inhibition effects [17]. Fluorinated nitrones have been synthesized by K. Marcin *et al.* from geminal diols and hydroxylamine using the Dean-Stark apparatus, leading to beta-lactam synthesis [18]. Another green synthesis strategy for the synthesis of a range of nitrone derivatives was reported by Shariatipour, Jadidinejad and Heydari, this process was efficient and eco-friendly by using glycerol as a recyclable solvent-catalyst [19]. Nitrones have a great role as intermediates in organic synthetic methodologies due to their 1,3-dipolar addition property Romeo *et al*. have reported a new strategy in the synthesis of isoxazilidine derivatives [20]. Yong Yea *et al*. have evolved an approach to the preparation of *β*-substituted vinylphosphonates and utilizing them in the synthesis of some novel isoxazilidines [21]. Yang, in 2012, reviewed the importance of nitrones and their novel transformations [2]. Microwave technology was used in the synthesis of novel isoxazolidine analogs by Gotkowska, Balzarini, and Piotrowska [8], and by Chakraborty *et al.* [12]. Maiuolo and De Nino have published a review on the preparation of isoxazolidine derivatives using a 1,3-dipolar cycloaddition strategy under different conditions [22]. Maiuolo *et al*. in 2020 also have reviewed many synthetic approaches for isoxazilidine synthesis [23].

According to these reports, we emphasize this protocol for the preparation of new nitrones using three different approaches for the synthesis of the titled compounds.

2. Experimental Part

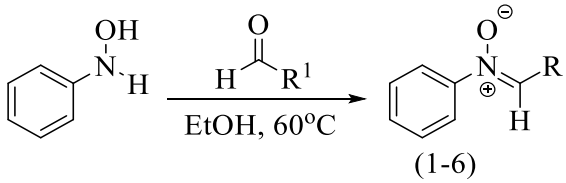
2.1. General: All solvents used were HPLC grade and were ordered from Fisher Scientific or Sigma-Aldrich. Pre-coated silica plates were used for thin-layer chromatography (0.2 mm, Merck DCalufolien Kieselgel 60 F254). At room temperature, spectra of nuclear magnetic resonance (NMR) were acquired using an Agilent 600 MHz spectrometer. Chemical shifts were recorded in parts per million (ppm) in relation to residual solvent. In Hertz, coupling constants (J) are given. A Shimadzu FTIR spectrophotometer was used to record infrared spectra. The uncorrected melting points were determined using electrothermal IA9200 digital melting point equipment. The compounds were named using Chemdraw software.

2.2. Synthesis of nitrones

General Procedure A: An aldehyde (10 mmol, 1.0 eq.) was added to a stirred solution of *N*-phenylhydroxylamine (10 mmol, 1.0 eq.) in methanol (10 ml). The reaction mixture was stirred at 60 ^{o}C until the starting material disappeared (monitored by TLC). Then, the solvent was extracted under reduced pressure to yield the crude product. The pure nitrone was obtained by recrystallization of the crude product from hot ethanol, which was stored in a dark and cold place.

General Procedure B: An aldehyde (10 mmol, 1.0 eq.) was added to a stirred solution of *N*-phenylhydroxylamine (10 mmol, 1.0 eq.) in ethanol (10 ml). The reaction mixture was stirred at room temperature. TLC was used to monitor the reaction until no starting material remained. The solvent was then extracted under reduced pressure, revealing the crude substance. The crude material was recrystallized from hot ethanol to yield pure nitrone, which was stored in a dark and cold place.

***General Procedure C*:** In a stirred solution of *N*-phenylhydroxylamine (10 mmol, 1.0 eq.) in ethanol (10 ml), an aldehyde (10 mmol, 1.0 eq.) was added. The reaction mixture was stirred at 60 °C until the precursor solution was consumed, which was monitored by TLC. To afford the crude product, the solvent was removed at reduced pressure. The precipitate formed was recrystallized from hot ethanol to produce pure nitrone, which was kept in a dark and cold place.



(1-6)

Scheme 1: Synthesis of nitrone.

Table 1: Optimization of the reaction conditions

Entry	Nitrone	Procedure A		Procedure B		Procedure C	
		Time hrs	**Yield %**	**Time hrs**	**Yield %**	**Time hrs**	**Yield %**
benzaldehyde	1	3.0	64	5.0	73	2.5	89
furfural	2	8.0	60	17.0	78	6.0	92
Piperonal	3	3.0	60	4.0	78	2.0	93
2-nitrobenzaldehyde	4	8.0	60	12.0	77	6.0	93
2,4-dichlorobenzaldehyde	5	8.0	63	44.0	75	4.0	92
vanillin	**6**	3.0	60	5.0	77	0.5	93

(*Z*)-*N*,1-diphenylmethanimine oxide (1)

Following the general procedure **C**. Yellow solid (1.75 g, 89%). : m.p.= 99-100 ^{o}C; IR (KBr) ν_{max} /cm^{-1}: 3103 (C-H imine), 3059 (C-H aromatic), 1546 (C=N), 1396 (C-N), 1068 (N-O^{-}); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm: 8.45–8.37 (2H, m, N-C-*o*-Ar*H*), 7.92 (1H, s, N=C*H*), 7.77 (2H, d, *J*=7.3 Hz, N-C-*o*-Ar*H*), 7.52–7.42 (6H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm: 149.0, 130.9, 129.9, 129.1, 129.0, 129.0, 128.9, 128.6, 121.7.

(*Z*)-1-(furan-2-yl)-*N*-phenylmethanimine oxide (2)

Following the general procedure C. Light brown solid (1.72 g, 92%). : m.p.= 88-90 ^{o}C; IR (KBr) ν_{max} /cm^{-1}: 3184 (C-H imine), 3099 (C-H aromatic), 3057 (C-H aromatic), 1593 (C=N), 1388 (C-N), 1068 (N-O^{-}); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm: 8.14 (1H, apparently s, *p*-Ar*H*), 7.99 (1H, d, *J*=7.6 Hz, O-C*H*), 7.77 (2H, apparently d, *J*=7.6 Hz, O-CC*H*+Ar*H*), 7.55 (1H, s, N=C*H*), 7.47–7.39 (3H, m, Ar*H*), 6.61 (1H, apparently s, O-C*H*CH); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm: 147.5, 147.2, 144.6, 129.9, 129.1, 124.3, 121.0, 116.5, 112.7.

(*Z*)-1-(benzo[d][1,3]dioxol-5-yl)-*N*-phenylmethanimine oxide (3)

Following the general procedure **C**. Light brown solid (2.24 g, 93%). : m.p.= 130-132 ^{o}C; IR (KBr) ν_{max} /cm^{-1}: 3190 (C-H imine), 3057 (C-H aromatic), 2895 (C-H aliphatic), 1618 (C=N), 1392 (C-N), 1056 (N-O^{-}); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm: 8.30 (1H, s, OCC*H*), 7.82 (1H, s, N=C*H*), 7.75 (2H, d, *J*=7.7 Hz, O-CC*H*CH +Ar*H*), 7.68 (1H, d, *J*=7.6 Hz, O-CCHC*H*), 7.51-7.41 (3H, m, Ar*H*), 6.90 (1H, d, *J*=8.2 Hz,), 6.04 (2H, s, OCH_2O); ^{13}C NMR

(151 MHz, $CDCl_3$) δ ppm: 190.3, 149.6, 148.8, 147.7, 134.3, 129.7, 129.1, 125.3, 121.6, 108.6, 108.5, 101.6.

(*Z*)-1-(2-nitrophenyl)-*N*-phenylmethanimine oxide (4)

Following the general procedure **C**. Yellow solid (2.25 g, 92%). : m.p.= 84-85 ^oC; IR (KBr) ν_{max} /cm^{-1}: 3180 (C-H imine), 3072 (C-H aromatic), 1589 (C=N), 1342 (C-N), 1091 (N-O^-); ^1H NMR (600 MHz, $CDCl_3$) δ ppm: 9.36 (1H, d, *J*=8.1 Hz), 8.58 (1H, s, 1H, s, N=C*H*), 8.08 (1H, d, *J*=8.2 Hz, O_2NCC*H*), 7.83-7.71 (3H, m, N-C-*o*-Ar*H*), 7.57 (1H, t, *J*=7.8 Hz, O_2NCCHC*H*), 7.52-7.48 (3H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm: 149.1, 147.5, 133.5, 130.6, 130.4, 129.4, 129.2, 128.4, 125.0, 124.5, 121.8.

(*Z*)-1-(2,4-dichlorophenyl)-*N*-phenylmethanimine oxide (5)

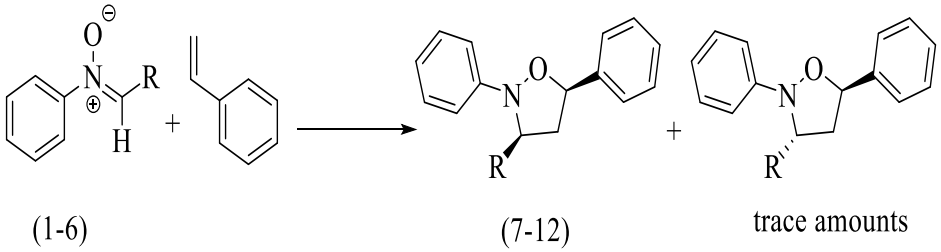
Following the general procedure **C**. Yellow solid (2.45 g, 92%). : m.p.= 79-80 ^oC; IR (KBr) ν_{max} /cm^{-1}: 3182 (C-H imine), 3072 (C-H aromatic), 1577 (C=N), 1384 (C-N), 1051(N-O^-); ^1H NMR (600 MHz, $CDCl_3$) δ ppm: 9.53 (1H, d, *J*=8.7 Hz, ClCC*H*CH), 8.37 (1H, s, N=C*H*), 7.50-7.21 (7H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm: 149.2, 136.2, 134.1, 130.3, 129.7, 129.2, 127.5, 127.5, 126.9, 126.6, 121.0.

(*Z*)-1-(3-hydroxy-4-methoxyphenyl)-*N*-phenylmethanimine oxide (6)

Following the general procedure C. Yellow solid (2.26 g, 93%). : m.p.= 198-199 ^oC; IR (KBr) ν_{max} /cm^{-1}: 3078 (C-H aromatic), 2943 (C-H aliphatic), 1571(C=N), 1390 (C-N), 1051 (N-O^-); ^1H NMR (600 MHz, DMSO) δ ppm: 9.79 (1H, s, O*H*), 8.38-8.32 (2H, m, N-C-*o*-Ar*H*), 7.85 (3H, m, HO-C*H*C + 2Ar*H*), 7.52-7.50 (2H, m, N=C*H*+CC*H*CHCOCH$_3$), 7.47-7.45 (1H, m, N-C-*m*-Ar*H*), 6.86 (1H, d, *J*=8.2 Hz, C*H*COCH$_3$), 3.79 (3H, s, OC*H*$_3$); ^{13}C NMR (151 MHz, DMSO) δ ppm: 144.0, 143.5, 141.3, 130.0, 124.9, 124.4, 120.2, 118.8, 116.8, 109.6, 105.8, 51.3.

2.3. Synthesis of isoxazolidines

***General Procedure D*:** At room temperature, styrene (1.04 g, 1.14 mL, 10 mmol, 1.0 eq.) was added to a vigorous stirring of nitrone (10 mmol, 1.0 eq.) in various solvents (25 mL). The reaction mixture was heated to reflux for the desired time until all of the starting components had been consumed (monitored by TLC 2:1, petroleum ether:ethyl acetate). The solvent was extracted under reduced pressure at ambient temperature, resulting in the crude product. To obtain pure isoxazolidine, the crude product was recrystallized from hot ethanol.



Scheme 2: General scheme of isoxazolidine synthesis.

Table 2: Synthesis of isoxazolidine

Nitrone	isoxazolidine	Time	Solvent	Yield %
1	**7**	3 days	Toluene and xylene	77
2	**8**	45 h	Benzene	69
3	**9**	5 days	Benzene	75
4	**10**	7 days	Benzene	68
5	**11**	5 days	Benzene	67
6	**12**	66 h	Ethanol (60%)	67

(*3S,5R*)-2,3,5-triphenylisoxazolidine (7)

Following the general procedure D. Pale yellow solid (2.31 g, 77%), m.p.= 115-117 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm: 7.59-6.95 (15H, m, aromatic protons), 5.19 (1H, dd, *J*=9.9, 5.7 Hz, OC*H*Ph), 4.94 (1H, t, *J*=7.8 Hz, NC*H*Ar), 3.23-3.17 (1H, m, NCHC*H*H), 2.49 (1H, dd, *J*=19.3, 10.8 Hz, NCHCH*H*); ^{13}C NMR (151 MHz, CDCl3) δ ppm: 152.5, 142.8, 137.7, 128.9, 128.8, 128.5, 128.3, 127.3, 126.8, 126.2, 121.3, 113.9, 80.6, 71.5, 48.7.

(*3S,5R*)-3-(furan-2-yl)-2,5-diphenylisoxazolidine (8)

Following the general procedure D. Pale brown oil (2.00 g, 69%). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm: 7.80 (1H, d, *J*=7.8 Hz, OC*H*CH), 7.51-7.20 (10H, m, aromatic protons), 7.20 (1H, d, *J*=8.0 Hz, OCHCHC*H*), 7.00 (1H, t, *J*=7.3 Hz, OCHC*H*CH), 5.18 (1H, t, *J*=7.1 Hz, OC*H*Ph), 5.02 (1H, t, *J*=7.7 Hz, NC*H*Ar), 3.10-3.01 (1H, m, NCHC*H*H), 2.71-2.63 (1H, m, NCHCH*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm: 154.5, 151.8, 142.4, 137.8, 129.0, 128.6, 128.4, 126.9, 121.8, 114.3, 110.4, 106.6, 80.2, 65.31, 43.5.

(*3S,5R*)-3-(benzo[d][1,3]dioxol-5-yl)-2,5-diphenylisoxazolidine (9)

Following the general procedure D. Yellow solid (2.59 g, 75%), m.p.= 103-105 oC; 1H NMR (600 MHz, CDCl3) δ ppm: 7.79-6.48 (13H, m, aromatic protons), 5.98 (2H, d, *J*=2.5 Hz, OCH_2O), 5.16 (1H, t, *J*=7.1 Hz, OC*H*Ph), 4.84 (1H, t, *J*=7.7 Hz, NC*H*Ar), 3.20-3.09 (1H, m, NCHC*H*H), 2.45 (1H, dd, *J*=20.2, 10.0 Hz, NCHCH*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm: 152.4, 148.1, 146.8, 137.7, 136.8, 128.9, 128.6, 128.4, 126.8, 121.4, 119.3, 113.9, 108.3, 106.8, 101.0, 80.5, 71.4, 48.9.

(*3S,5R*)-3-(2-nitrophenyl)-2,5-diphenylisoxazolidine (10)

Following the general procedure D. Yellow crystal (2.35 g, 68%), m.p.= 109-110 oC; 1H NMR (600 MHz, CDCl3) δ ppm: 8.29 (1H, d, J=7.9 Hz, O2NCCH), 8.09 (1H, d, J=8.1 Hz, O2NCCCH), 7.72 (1H, t, J=7.5 Hz, O2NCCHCH), 7.48 (1H, t, J=7.7 Hz, O2NCCCH), 7.40-7.23 (7H, m, aromatic protons), 7.09-6.91 (3H, m, aromatic protons), 5.72 (1H, t, J=7.1 Hz, OCHPh), 5.23 (1H, t, J=7.8 Hz, NCHAr), 3.56-3.46 (1H, m, NCHCHH), 2.31-2.25 (1H, m, NCHCHH); 13C NMR (151 MHz, CDCl3) δ ppm: 154.5, 151.8, 142.4, 137.8, 129.0, 128.6, 128.4, 126.9, 122.35, 121.8, 116.1, 114.3, 110.4, 106.6, 80.2, 65.3, 43.5.

(*3S,5R*)-3-(3,5-dichlorophenyl)-2,5-diphenylisoxazolidine (11)

Following the general procedure D. Dark black oil (2.47 g, 67%). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm: 7.91 (1H, d, *J*=8.3 Hz, ClC*H*Cl), 7.60-7.26 (9H, m, aromatic protons), 7.08-6.93 (3H, m, aromatic protons), 5.29 (1H, t, *J*=7.1 Hz, OC*H*Ph), 5.21 (1H, t, *J*=7.8 Hz,

NC*H*Ar), 3.44-3.33 (1H, m, NCHCH*H*), 2.30-2.20 (1H, m, NCHC*H*H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm: 151.6, 139.3, 129.2, 129.1, 128.9, 128.5, 127.8, 126.9, 122.3, 121.6, 115.3, 113.7, 80.6, 68.2, 46.8.

5-((*3S*,*5R*)-2,5-diphenylisoxazolidin-3-yl)-2-methoxyphenol (12)

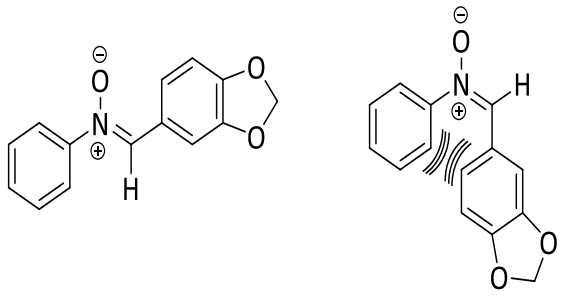
Following the general procedure D. (2.32 g, 67%) Yellow solid. M.p.= 121-123 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm: 7.47-6.92 (13H, m, aromatic protons), 5.61 (1H, s, O*H*), 5.19 (1H, t, *J*=7.1 Hz, OC*H*Ph), 4.86 (1H, t, *J*=7.8 Hz, NC*H*Ar), 3.88 (3H, s, OCH_3), 3.19-3.12 (1H, m, NCHCH*H*), 2.48 (1H, dd, *J*=20.2, 10.0 Hz, NCHCH*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm: 152.5, 146.9, 144.8, 138.0, 134.8, 128.9, 128.5, 126.8, 121.3, 119.0, 115.9, 114.2, 113.9, 108.5, 80.3, 71.3 , 55.9, 48.6.

3. Results and discussion

The aim of this project is to synthesize a series of new nitrones involving the condensation strategy of *N*-phenylhydroxylamine with a range of different aldehydes. Toward the synthesis of isoxazolidine derivatives. Different conditions were investigated for the purpose of improving this reaction. The first procedure (A), included the synthesis of nitrones as indicated in the abstract from its precursors *N*-phenylhydroxylamine with different aldehydes. (Scheme 1, Table 1). The second procedure (B), as stated above, uses ethanol as a solvent. In this procedure, the formation of the corresponding nitrones took a long time but with a better yield (Scheme 1, Table 1). The optimization conditions revealed that procedure C is the best one. (Scheme 1, Table 1). We found that the best optimum yield of nitrone was achieved at 60 ^{o}C and shorter time as indicated below. All the FT-IR spectra for the synthesized nitrones illustrated showed the evanescence of (C=O) of aldehyde's carbonyl stretching band within the region (1740-1720) cm^{-1} and the appearance of (C=N), (C-N), and (N-O) bands within the regions (1618-1546) cm^{-1}, (1396-1342) cm^{-1}, and (1091-1051) cm^{-1}, respectively.

Configurational determination of compounds 2 and 3:

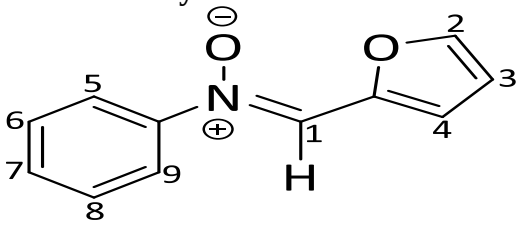
Inouye has concluded that a solvent effect directly on the configuration of the nitrones This study has surprisingly explained that the *E*-nitrones will be the major product in non-polar solvents, whilst in polar solvents, *Z*-nitrones are the major product. Additionally, the steric hindrance effect in the *Z*-isomer nitrones will be less than in the *E*-isomer, which leads to the *Z*-isomer being more stable [24]. This study strongly agreed with our findings (Figure 1).



(*Z*)-isomer (*E*)-isomer

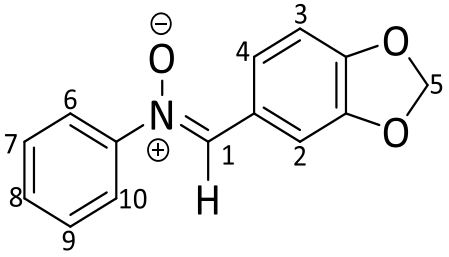
Figure 1: *Z*-isomer and *E*-isomer nitrones

Determination of configuration of 2 by ^{1}H NMR:



The structure of 2 was determined by the use of ^{1}H and COSY NMR spectroscopy. It was found that H at C-1 appears as a singlet at 7.55 ppm, H at C-2 appears as a doublet with one coupling constant J = 7.6 Hz at 7.99 ppm, and H at C-4 appears as a doublet with one coupling constant J = 7.6 Hz at 7.77 ppm, which overlapped with one of the phenyl group's aromatic protons. Moreover, HSQC NMR spectroscopy was used in the determination of the structure of 2. ^{13}C NMR of this compound showed the following results measured by ppm: 147.50 (N=*C*H), 147.22 (N-*C*), 144.69 (N=CH-*C*), 129.95 (Ar quat.C), 129.18 (ArCH), 124.36 (ArCH), 121.02 (ArCH), 116.52 (O-*C*H), 112.72 (O-CH*C*H). From the HSQC NMR spectrum, we can strongly confirm the right structure of nitrone 2.

Determination of the configuration of 3 by ^{1}H NMR:



Using ^{1}H and HSQC NMR spectroscopy, the structure of 3 was determined. It was found that H at C-1 appears as a singlet at 7.82 ppm, H at C-2 appears as a singlet at 8.30 ppm, and two protons at C-5 appear as a singlet at 6.04 ppm. ^{13}C NMR of this compound illustrated these results measured by ppm: 190.3 (O-*C*), 149.6 (O-*C*), 148.8 (N-*C*), 147.7 (N=CH-*C*), 134.3 (N=*C*H), 129.7 (Ar quat.C), 129.1 (ArCH), 125.3 (ArCH), 121.6 (ArCH), 108.6 (OC*C*H), 108.5 (OC*C*H), 101.6 (O-*C*H_2). The configuration of compounds 2 and 3 was confirmed. Therefore, this would be considered essential for determining the configuration of the rest of the nitrones using ^{1}H NMR alone.

To achieve success in the synthesis of nitrones, we considered that the protocol could be extended to the synthesis of isoxazolidine using a 1,3-dipolar cycloaddition reaction. The cyclization strategy involved heating at reflux for nitron with styrene in the different solvents. Each product was obtained at the indicated (Table 2).

In order to establish the stereochemistry of the isoxazolidine, compound 10a produced X-ray quality crystals from hexane/EtOAc. The structure of 10a was proven obviously by single-crystal X-ray diffraction, which showed this compound is a ***cis***-diastereoisomer. The substituents at C-3 and C-5 were on the same face (Figure 2).

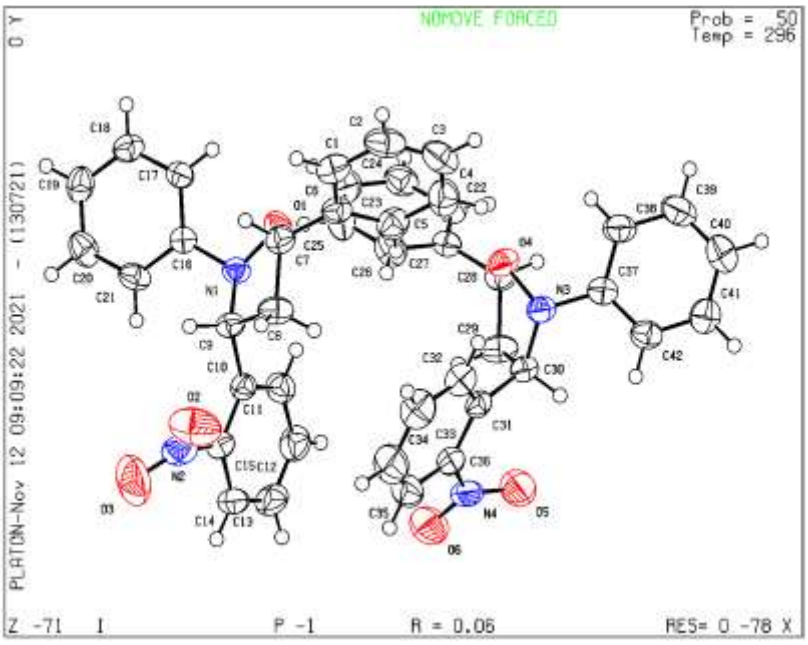


Figure 2: The crystal structure of the main product 10a confirms the *cis*-configuration

Moreover, the proton at C-3 (5.23 ppm) displays a triplet with a coupling constant of 7.8 Hz in the ^{1}H NMR spectrum for compound 10a, while the proton at C-5 shows a triplet (5.72) with a coupling constant of 7.8 Hz (7.1 Hz). Furthermore, the protons at C-4 showed two multiplet signals at 3.56-3.46 and 2.31-2.25. The spectroscopic data for the remaining products is identical and closely matched to compound 10a, allowing us to determine the stereochemistry (Figure 3).

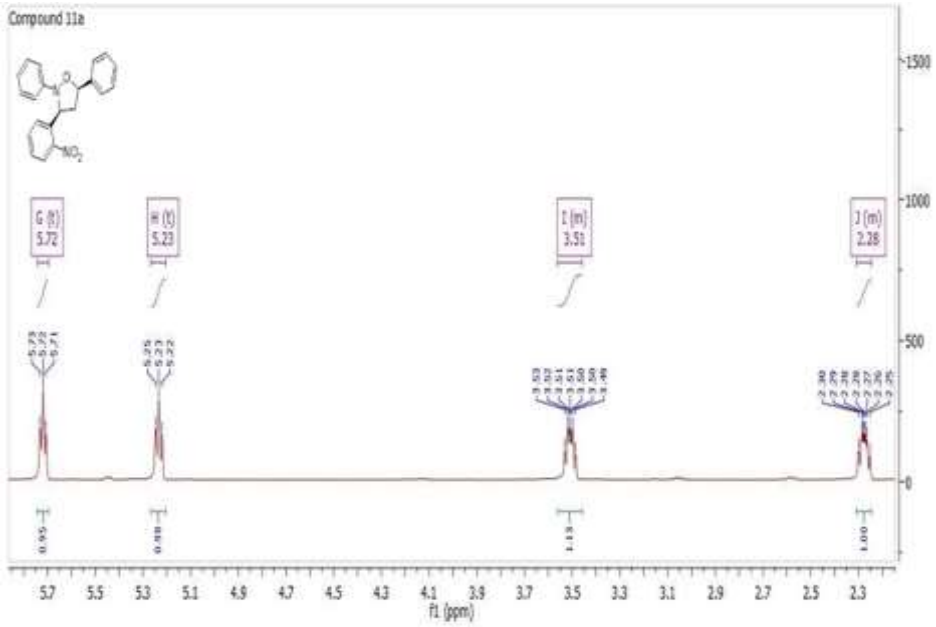


Figure 3: ^{1}H NMR signals of the protons at C-3, C-5 and C-4 for compound 10a

4. Conclusions

In summary, we have successfully evolved a new and effective methodology for the production of nitrones using commercially available starting materials. We have extended the application of the 1,3-dipolar cycloaddition methodology in the preparation of novel isoxazolidine derivatives, *via* adding nitrones to styrene under catalyst-free conditions.

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