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Synthesis, Characterization and 1, 3-Dipolar Cycloaddition of Novel Sugar-Derived Nitrones with *N*-Arylmaleimides

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Abstract

The chiral N-D-ribosylnitrones 5-10 have been synthesized in four steps respectively, in the fourth step, D-ribosyloxime (4) condensed with substituted benzaldehyde in cool condition. The heterocyclization of Z- nitrone 6 with substituted N-arylmaleimide by 1,3-dipolar cycloaddition were afforded new heterocyclic system of isoxazolidine derivatives 11-16 and 11'-16' as a mixture of diastereoisomers, the new isoxazolidines 11-16 have been separated purely and characterized by ^1H NMR, mass spectra and elemental analysis.

Keywords: *N*-sugar Nitrone, 1,3-dipolar cycloaddition, isoxazolidines.

Introduction

The utility of nitrones in synthetic organic chemistry has been widely illustrated[1-3]. Cycloadducts of nitrones are attractive intermediates for the synthesis of several classes of bioactive compounds as well as natural products[4–8]. The main reactions of nitrones involving such compounds are nucleophilic addition, and 1,3-dipolar cycloaddition to olefins and acetylenes. Both of these processes have been used as key steps in the preparation of diverse target molecules containing nitrogen. The 1,3-dipolar cycloaddition reaction between a nitrone and an olefin gives the isoxazolidine skeleton. Isoxazolidines containing two heteroatoms can be considered as masked forms of several functional group combinations. The introduction of a sugar moiety into nitrone can both improve the solubility of nitrone in water and reduce their toxicity towards living cell. Still the sugar moiety is a most useful chiral moiety in asymmetric chemistry, in view of their potential medicinal significance and pharmaceutical applications[9], the development of the synthetic procedures and utilities of glycosyl nitrone are of very importance. The stereochemistry of the 5-membered ring depends mainly on configuration of a nitrone and olefin since cycloadditions proceed regiospecifically and lead to the diastereoselective formation of products. The N, O bond of these adducts can be readily cleaved to produce acyclic molecules with stereocontrolled configuration at chirality centers. Here we present a very efficient and stereoselective synthesis of the new nitrones 5-10 and an overview 1,3-dipolar cycloaddition of nitrone 6 to substituted N-arylmaleimides.

Material and Methods

All the chemicals were purchased from Aldrich Chemical Co. and used without further purification. Melting points were determined on SMP1 melting point apparatus and are uncorrected. All reactions were monitored by thin layer chromatography, which was performed on aluminium-backed silica gel Merck 60 F_{254} plates, with detection by the exposure to iodine vapour. Column chromatography was performed on silica gel (lachema, 230-400 mesh). The ^1H and ^{13}C-NMR spectra were obtained using a Varian VXR 300 spectrometer at 300 MHz, the chemical shifts are reported in ppm scale. The coupling constants (*J*) are given in Hz. The elemental analysis of the compounds was performed on a Perkin Elmer 2400 Elemental Analyzer. Elemental data for C and H were measured within ±0.4% of the theoretical values.

General procedure for synthesis of sugar-derived-nitrones (5-10): The nitrones (**5-10**) were synthesized from D-ribose in four steps.

Preparation of D-ribosyloxime (2): Powdered hydroxylamine hydrochloride (20 g, 0.28 mol) in dry methanol 100 ml was neutralized with a sodium methoxide solution (prepared from 20 g sodium and 30 ml methanol). The solution was cooled in an ice-bath, the residue was filtered and washed with dry methanol (50 ml). The methanolic hydroxylamine solution was refluxed in a water-bath and powdered anhydrous D-ribose (30 g, 0.2 mol) was added slowly, the solution was evaporated, dried and recrystallisation from methanol.

Preparation of 2,3 -Di-O-isopropylidine-β-D-ribosyloxime (3): D-ribose oxime (10 g, 60 mmol) was added to a dry acetone 200 ml containing concentrated sulphuric acid 1ml and copper sulphate anhydrous 5 g was added to the solution. The reaction mixture was stirred overnight at RT. When TLC shows completion of the reaction the suspended copper sulphate was removed by filtration. The acetone solution was diluted with

chloroform (50ml), the chloroform layer was separated, washed with water (30 ml), dried over anhydrous $MgSO_4$, and evaporated to dryness.

Preparation of 5-O-Acetyl -2,3-di-O-isopropylidine-D-ribosyl oxime (4): 2,3–Di-O–isopropylidine-β–D–ribosyloxime (7 g, 34 mmol) was dissolved in dry pyridine 80 ml and cooled to 0 ^oC. A solution of acetic anhydride 1 ml in dry chloroform 70 ml was added at 0^oC. The reaction mixture was set a side overnight at room temperature. When TLC shows completion of the reaction, the reaction mixture was worked up as above to give pale yellow syrup.

Preparation of D-ribose derived nitrones (5-10)[10]: 5-O-Acetyl-2,3–di-O-isopropylidine-β-D-ribosyloxime (0.5 g, 2 mmol) was dissolved in absolute ethanol 20 ml and cooled to 10 ^oC with stirring, substituted benzaldehyde (2mmol) dissolved in ethanol and added drop wise during 10-15 min. stirring for (2-4 hr) at room temperature, when TLC shows completion of the reaction, the crude nitrone product was filtered, the solvent was evaporated and the combined crude solids were dried and then crystallized by ethanol. Compound (**6)** is taken as a representative example to explain characterization data.

C-(4-Chlorophenyl)-N-(5′-Acetyl-2′,3′-di-O-isopropylidine-β-D-ribosyl)-nitrone (6): Yield 60%; mp 114-116 ^oC; R_f 0.55;^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 1.32 (3H, s, CH_3), 1.54 (3H, s, CH_3), 2.20 (3H, s, $COCH_3$), 3.73 (2H, m, $ACOCH_2$,), 4.25 (1H, m, ribosyl), 4.55 (1H, d, ribosyl), 4.60 (1H, d, ribosyl), 5.30 (1H, d, ribosyl), 6.90 (1H, s, N=CH), 7.17-7.28 (m, 4H, Ar-H). Anal. Cal. For $C_{17}H_{20}ClNO_5$: C, 57.71; H, 5.70; Found C, 57.73; H 5.90%.

General procedure for synthesis of N-sugar isoxazolidines (11-16)[11]: Nitrone (**6)** (50 mg, 0.13 mmol) was dissolved in dry toluene 25 ml, and the corresponding maleimides (0.13 mmol) were heated at 110^oC under reflux for 4-7 hr, the reaction mixture, which followed by TLC ($CHCl_3$: MeOH, 8:2) to indicate the completion of reaction, was concentrated under vacuum. The resulting syrup residue was purified by column chromatography (chloroform) and then crystallized from chloroform-petroleum ether. Yellow solid crystals were obtained.

2-(5′-Acetyl-2′,3′-di-O-isopropylidine-β-D-ribosyl)-3-(4-chlorophenyl)-5-phenyl-4,6-dioxo-2,3,3a,4,6,6a-hexahydro-pyrrolo[3,4-d] isoxazole (11): Yield 30%; mp 170-172 ^oC; R_f 0.60; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm) 1.32 (3H, s, CH_3), 1.57 (3H, s, CH_3), 2.11 (3H, s, $COCH_3$), 3.46 (1H, s, isoxazolidine), 3.69 (2H, m, $AcOCH_2$), 3.89 (1H, d, isoxazolidine), 4.38 (1H, m, ribosyl), 4.57 (1H, d, ribosyl), 4.63 (1H, d, ribosyl), 4.98 (1H, d, $J_{3a\text{-}6a}$ = 7.4Hz, isoxazolidine), 5.32 (1H, d, ribosyl), 7.27-7.88 (9H, m, Ar-H); Anal. Cal. For $C_{27}H_{27}ClN_2O_7$: C, 61.54; H, 5.16; Found C, 61.44; H, 5.08%. ^{13}C-NMR (300 MHz, $CDCl_3$): 26.16 (CH_3), 26.71 (CH_3), 50.00 (C-3a), 67.54 (C-3), 75.01 (C-6a), 76.35 (C-3′), 77.68 (C-2′), 82.50 (C-4′), 83.39 (C-5′), 105.30 (C-1′), 112.44 (C-Me), 122.922, 125.25, 127.37, 127.70, 127.77, 127.81, 128.04, 128.20, 129.01, 129.97, 132.28, 132.35, 132.45, 132.50, 134.29 (aromat.C), 170.00 (C=O), 170.48 (C=O), 174.10 (C=O).

2-(5′-Acetyl-2′,3′-di-O-isopropylidine-β-D-ribosyl)-3,5-di-(4-chlorphenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydro-pyrrolo[3,4-d]isoxazole (12): Yield 35%; mp 125-127 ^oC; R_f 0.65; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 1.33 (3H, s, CH_3), 1.55 (3H, s, CH_3), 2.22 (3H, s, $COCH_3$), 3.52 (1H, s, isoxazolidine), 3.70 (2H, m, $ACOCH_2$), 3.92 (1H, d, isoxazolidine), 4.25 (1H, m, ribosyl), 4.52 (1H, d, ribosyl), 4.54 (1H , d, ribosyl), 4.90 (1H, d, $J_{3a\text{-}6a}$ = 9Hz, isoxazolidine), 5.32 (1H, d, ribosyl), 7.17-7.64 (8H, m, Ar-H); Anal. Cal. For $C_{27}H_{26}Cl_2N_2O_7$: C, 57.76.; H, 4.67; Found C, 57.72; H, 4.63%.

2-(5′-Acetyl-2′,3′-di-O-isopropylidine-β-D-ribosyl)-3-(4-chlorphenyl)-5-(2,6-dichlorophenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydro-pyrrolo[3,4-d]isoxazole (13): Yield 27%; mp 130-132 ^oC; R_f 0.70; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 1.37 (3H, s, CH_3), 1.58 (3H, s, CH_3), 2.19 (3H, s, $COCH_3$), 3.56 (1H, s, isoxazolidine), 3.87 (2H, m, $ACOCH_2$), 3.97 (1H, d, isoxazolidine), 4.25 (1H, m, ribosyl), 4.54 (1H, d, ribosyl), 4.61 (1H , d, ribosyl), 4.90 (1H, d, $J_{3a\text{-}6a}$ = 8.7 Hz, isoxazolidine), 5.34 (1H, d, ribosyl), 7.35-7.86 (7H, m, Ar-H); Anal. Cal. For $C_{27}H_{25}Cl_3N_2O_7$: C, 54.42; H, 4.23; Found C, 54.30; H, 4.20%.

2-(5′-Acetyl-2′,3′-di-O-isopropylidine-β-D-ribosyl)-3-(4-chlorphenyl)-5-(4-nitrophenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydro-pyrrolo[3,4-d]isoxazole (14): Yield 35%; mp 140-143 ^oC; R_f 0.75; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 1.29 (3H, s, CH_3), 1.51 (3H, s, CH_3), 2.32 (3H, s, $COCH_3$), 3.51 (1H, s, isoxazolidine), 3.66 (2H, m, $ACOCH_2$), 3.90 (1H, d, isoxazolidine), 4.23 (1H, m, ribosyl), 4.48 (1H, d, ribosyl), 4.61 (1H , d, ribosyl), 5.07 (1H, d, $J_{3a\text{-}6a}$ = 8.3, Hz isoxazolidine), 5.34 (1H, d, ribosyl), 7.10-7.57 (8H, m, Ar-H); Anal. Cal. For $C_{27}H_{26}ClN_3O_9$: C, 56.70; H, 4.58; Found C, 56.57; H, 4.55%.

2-(5′-Acetyl-2′,3′-di-O-isopropylidine-β-D-ribosyl)-3-(4-chlorphenyl)-5-(4-bromophenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydro-pyrrolo[3,4-d]isoxazole (15) : Yield 40%; mp 165-167 ^oC; R_f 0.65; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 1.34 (3H, s, CH_3), 1.49 (3H, s, CH_3), 2.23 (3H, s, $COCH_3$), 3.52 (1H, s, isoxazolidine), 3.65 (2H, m, $ACOCH_2$), 3.89 (1H, d, isoxazolidine), 4.36 (1H, m, ribosyl), 4.50 (1H, d, ribosyl), 4.76 (1H , d, ribosyl), 4.76 (1H, d, $J_{3a\text{-}6a}$ = 7.8 Hz, isoxazolidine), 5.42 (1H, d, ribosyl), 7.12-7.87 (8H, m, Ar-H); Anal. Cal. For $C_{27}H_{26}BrClN_2O_7$: C, 53.53; H, 4.33; Found C, 53.57; H, 4.34%.

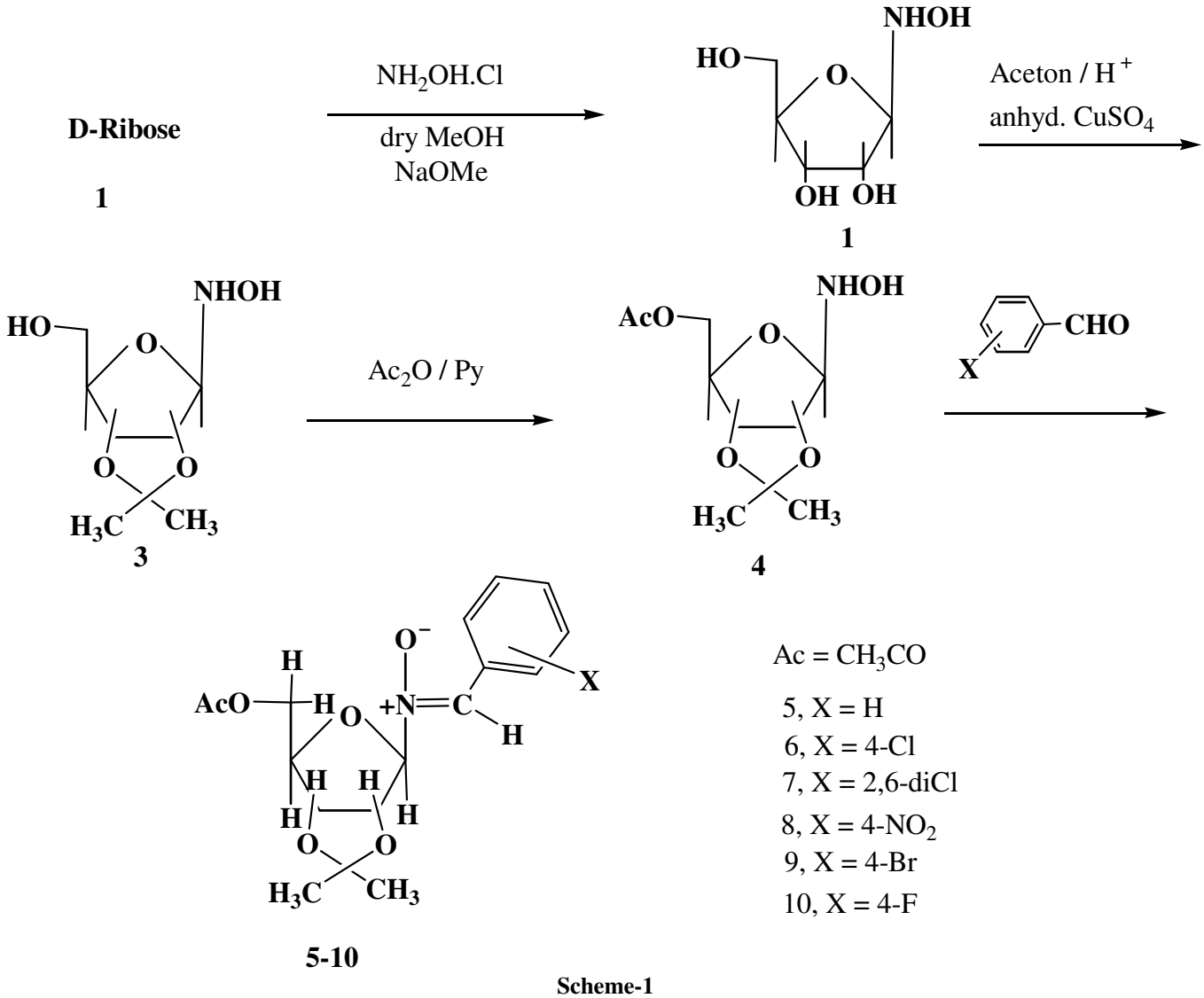
2-(5′-Acetyl-2′,3′-di-O-isopropylidine-β-D-ribosyl)–3-(4-chlorphenyl)-5-(4-fluorophenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydro-pyrrolo[3,4-d]isoxazole (16): Yield 30%; mp 190-193; R_f 0.55; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 1.32 (3H, s, CH_3), 1.55 (3H, s, CH_3), 2.25 (3H, s, $COCH_3$), 3.54 (1H, s, isoxazolidine), 3.56 (2H, m, $ACOCH_2$), 3.90 (1H, d, isoxazolidine), 4.26 (1H, m, ribosyl), 4.52 (1H, d, ribosyl), 4.58

(1H , d, $J_{3a\text{-}6a}$ = 8.2 Hz, isoxazolidine), 4.73 (1H, d, ribosyl), 5.37 (1H, d, ribosyl), 7.24-7.68 (8H, m, Ar-H); Anal. Cal. For $C_{27}H_{26}ClFN_2O_7$: C, 59.51; H, 4.81; Found C, 59.55; H, 4.99 %.

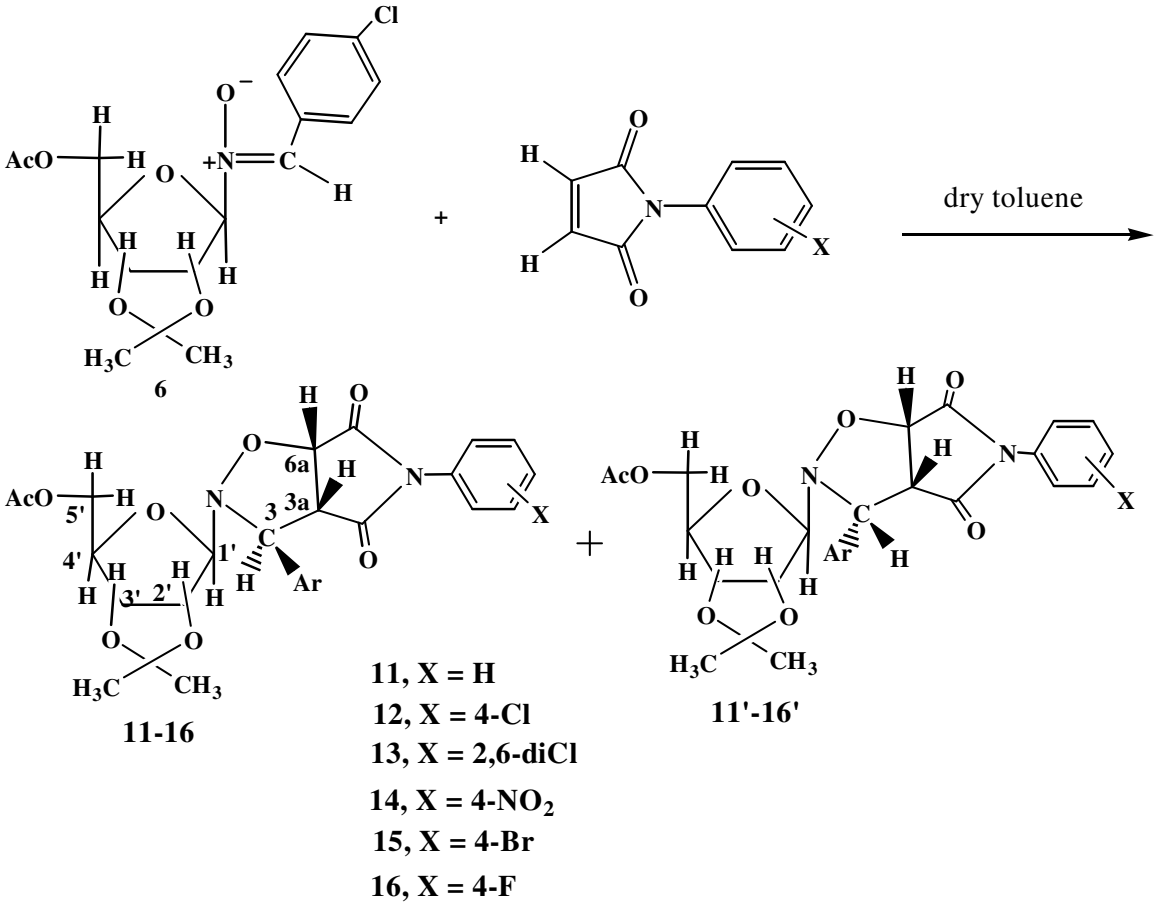
Results and Discussion

The chiral *N*- sugar derived nitrones **5-10** have been synthesized from protected D-ribosyloxime **4** and substituted benzaldehyde (scheme 1). All nitrones **5-10** have stable crystalline compounds and diastereomerically pure. The structure and configuration of nitrone **6** was determined by the analyses of their spectral data. It has been reported that nitrone **6** has pure product in the Z-configuration, This consideration is in accord with Vasella's results that the N-glycosylaldehydonitrones possess a Z-configuration[12-13].

The structure of nitrone **6** was confirmed by ^{1}H NMR and mass spectroscopy. The phenyl ring protons are observed as a multiple and (N=CH) proton as singlet with chemical shifts of 7.17-7.28 and 6.90 ppm, respectively. The 1,3-dipolar cycloadditions of *N*-D-ribosylnitrone **6** with *N*-aryl maleimides by refluxing a toluene solution to provide the corresponding cycloadducts, isoxazolidines **11-16** and **11'-16'** as a mixture of diastereoisomers have shown in (scheme 2) and the obtained results are presented in (table 1). The structures of isoxazolidines **11-16** were confirmed by ^{1}H NMR and mass spectroscopy. For example in **11**, the isoxazolidine ring protons are observed as singlet, doublet and doublet with chemical shifts of 3.46, 3.89 and 4.98 ppm, $J_{3a\text{-}6a}$ = 7.4Hz, respectively. Analysis of **11** by elemental analysis also conformed.



Scheme-1
Synthesis of nitrones 5-10



Scheme-2
Reaction of nitone 6 with *N*-aryl maleamides

The diastereomeric **11'-16'** were inability of separating by column chromatography because of extremely unstable and unsuitable for isolation in appreciable chemical purity and yield, which only the preponderant isomers **11-16** were isolated in a pure state. Induction of three asymmetric centers at C_3, C_{3a} and C_{6a} positions of the newly developed isoxazolidine derivatives have made this synthesis highly attractive. The development of diastereomers can be rationalized by an *exo* approach of nitrone **6** which has *Z* configuration for the formation of major cycloadducts **11-16** (*exo* transition state). The minor cycloadducts **11'-16'** has also *endo* approach of *Z*-nitrone (*endo* transition state) (figure 1). The distinction between the arrangements of H-3, H-3a and H-6a atoms is based on spectroscopic data using the $J_{3\text{-}3a}$ and $J_{3a\text{-}6a}$ coupling constants. The bridgehead protons H-3a and H-6a, which have always *cis*-arrangement, is indicated by coupling constant $J_{3a\text{-}6a}$ = 9Hz.

^{1}H-NMR analysis of the major isoxazolidines **11-16** indicate that each diastereomer has H-3, H-3a are characteristic for the *exo*-addition, For example in **12** the signals for the H-6a and H-3a appear as doublets at δ= 4.90 and 3.92 ppm respectively, with coupling constant at $J_{3a\text{-}6a}$ = 9 Hz. In the H-3, H-3a, the proton H-3 and H-3a fails to display coupling since ϕ = 90°C. This feature of the NMR spectrum is indicating for the formation of major cycloadducts *exo*-addition[14-15]

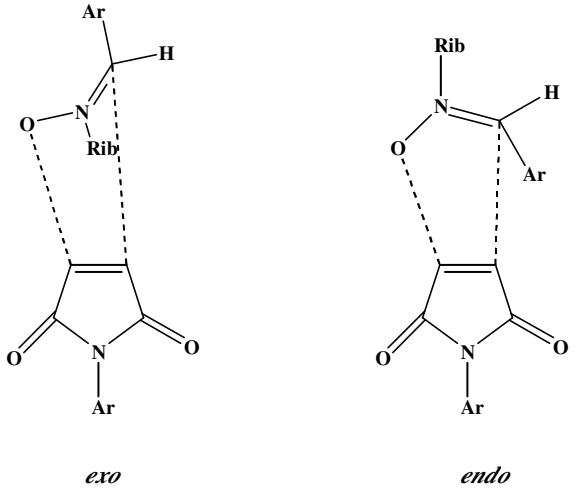


Figure-1
Two possible N-arylmaleimides approaches to nitrone 6

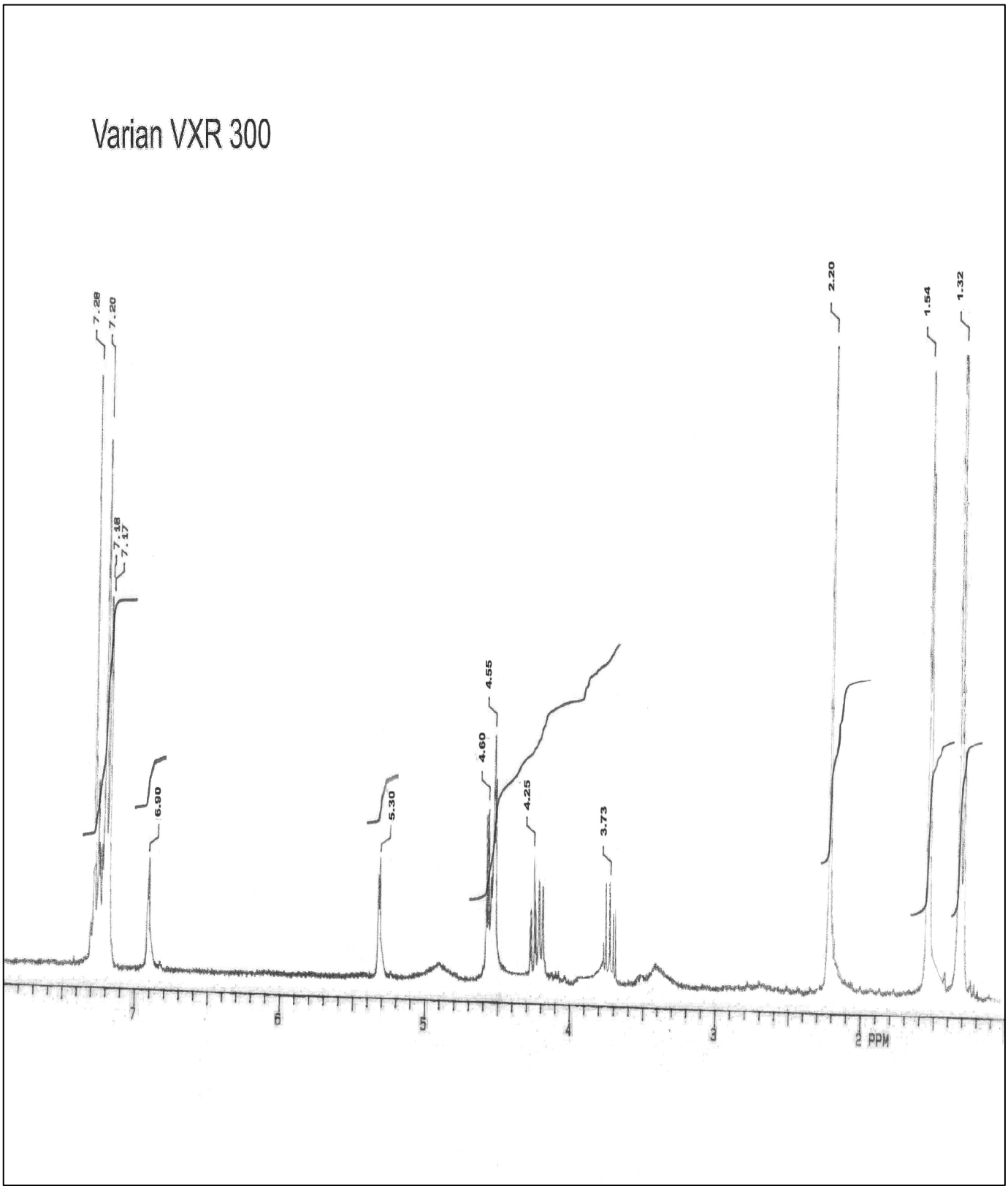


Figure-2
^{1}H-NMR spectra of compound 6

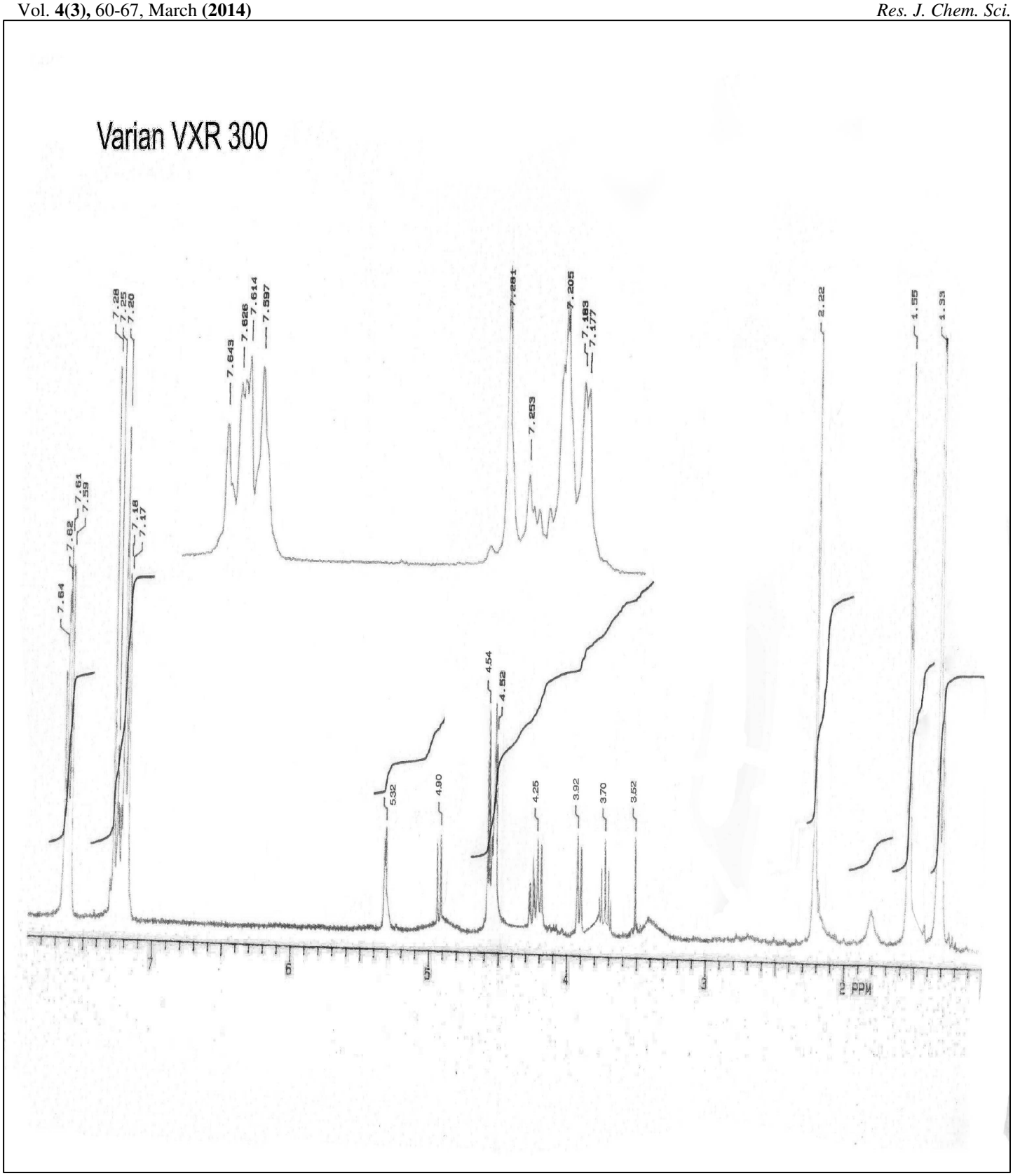


Figure-3
^{1}H-NMR Spectra of compound 11

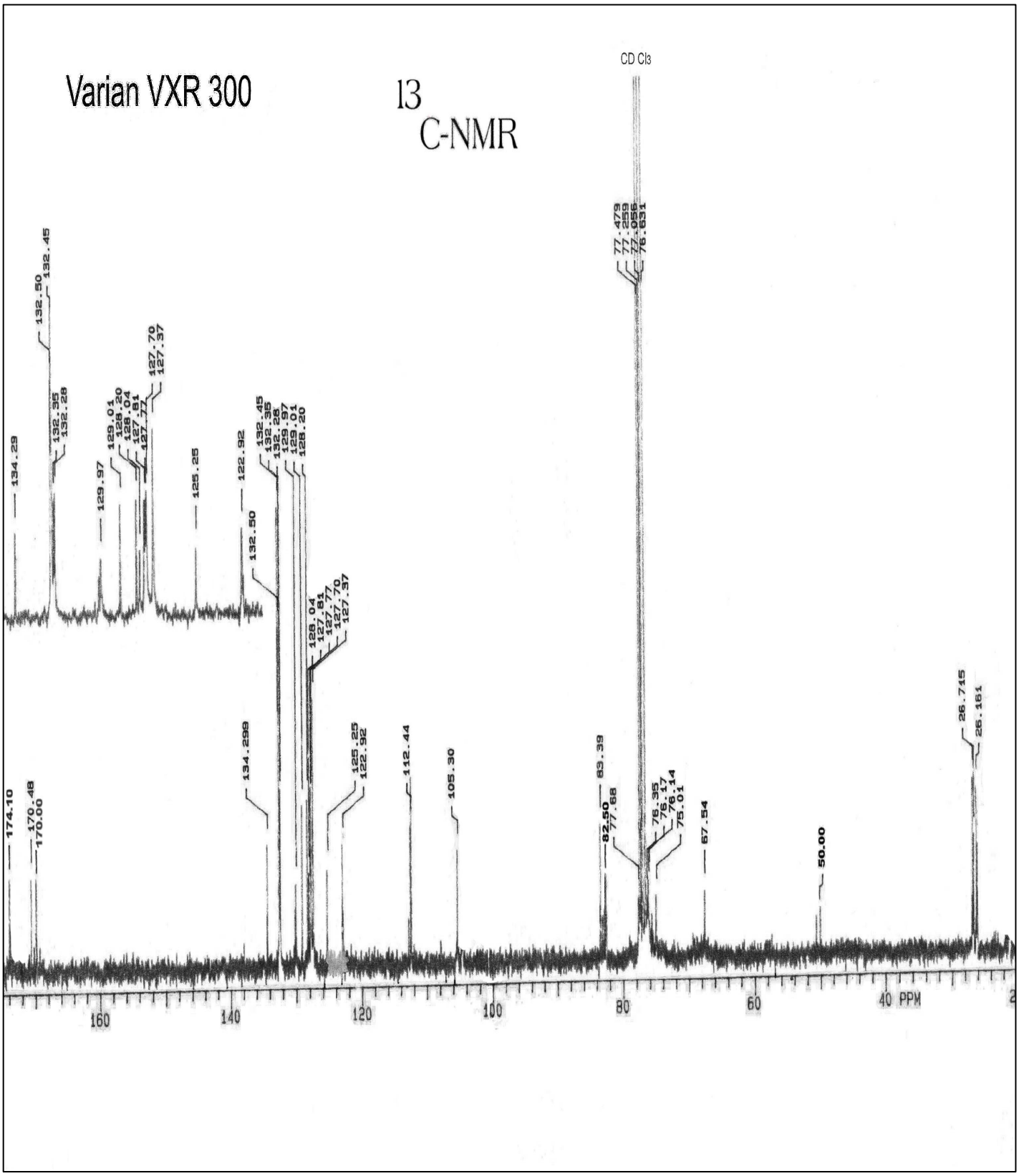


Figure-4
^{13}CNMR spectra of compound 11

Conclusion

A series of novel isoxazolidine derivatives **11-16** were synthesized by 1,3- dipolar cycloaddition of nitrone 6 with N-arylmaleimide substituted and characterized by ^{1}H NMR, mass spectroscopy and elemental analysis. The development of diastereomers can be rationalized by an *exo* approach of nitrone 6 which has *Z*-configuration for the formation of *exo* addition as a pure major cycloadducts **11-16**.

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