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RESEARCH ARTICLE

Synthesis and characterization of some new diisoxazolidine derivetives

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Abstract

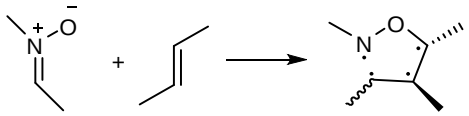
This research is concerned with the synthesis of diisoxazolidine compounds by 1,3-dipolarcycloaddition reactions of dianiline oxides with fumaric acid to yield one product, *anti*-cycloadduct.These compounds were characterized by using FT-IR, C.H.N. ,^{1}HNMR and Mass spectroscopy.

INTRODUCTION

1,3-dipolar cycloaddition reactions of nitrones offer one of the most versatile synthetic routes of hetrocyclic five-membered rings in organic chemistry. Concerted cycloaddition reactions are also among the most powerful tools for the stereospecific creation of new chiral centers in organic molecules. Nitrones are well-known to have 1,3-dipoles in thermal cycloaddition reactions[(1)] . 1,3-dipolar cycloaddition reactions of nitrone can be classified into the following classes:

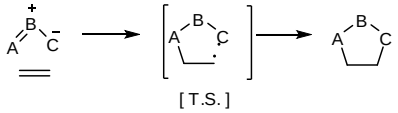
a- Nitrone-alkene cycloaddition reaction:

The nitrone-olefin 1,3-dipolar cycloaddition(1,3-DC) is a powerfull reaction in that it can create as many as three congruous stereogenic centers[(2-5)].The configuration of these centers could be influenced if the reaction system was designed[(6)].It is generally accepted that most 1,3-dipolar cycloaddition reactions are single-step concerted reactions,in which two new σ-bonds are formed simultaneously although not necessary at equal rates[(7,8)],as shown in equation (1).



...(1)

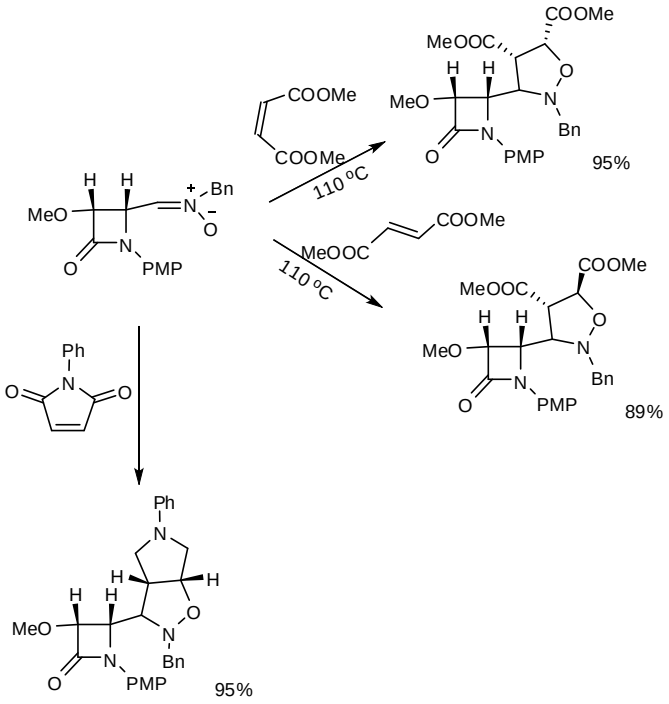
Two steps reaction involving a spin-paired diradical intermediate has been postulated[(7)], but not generally accepted, as shown in equation (2).



[T.S.]

...(2)

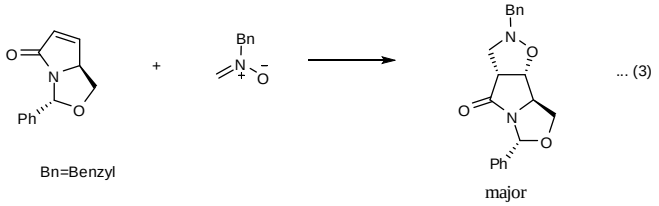
As an example, in 2002; Alcaide et al[(9)]. prepared isoxasolidine compounds from 1,3-dipolr cycloaddition reactions of optically active 2-azetidinone nitrones with electron-deficient alkenes, such as dimethyl fumarate, dimethyl malate or N-phenyl maleimide, as shown in scheme (1).



Bn = Benzyl
PMP = P-methoxy phenyl

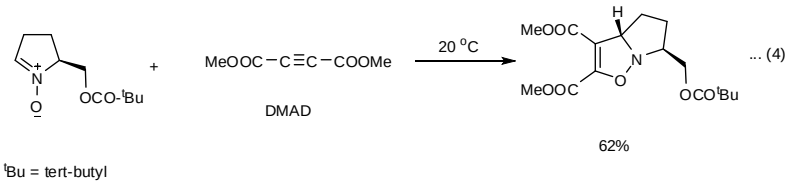
Scheme (1)

Deyine et al[10] have used (s)-pyroglutaminol derivative in 1,3-dipolar cycloaddition reactions with N-benzyl nitrone, leading to excellent yield, as shown in equation (3).



b- Nitrone-alkyne cycloaddition reaction:

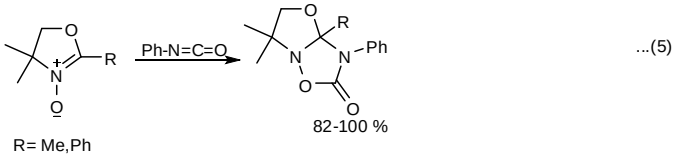
Nitrones react with alkynes, such as dimethyl acetylenedicarboxyate (DMAD), which undergo 1,3-dipolar cycloaddition reactions,as shown in equation (4)[11].



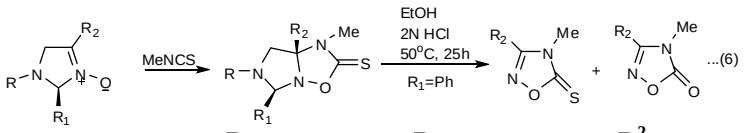
tBu = tert-butyl

c- Nitrone-isocyanate cycloaddition reaction:

Phenylisocyanate reacts with nitrone and undergoes 1,3-dipolar cycloaddition reactions, as shown in equation (5)[12].



Necdet and Fatma[13] reported that the 1,3-dipolar cycloaddition reactions of imidazole-3-oxide with methylisocyanate yielded cycloadducts in high yields which undergo ring opening to give oxadiazole-5-thione,as shown in equation (6).

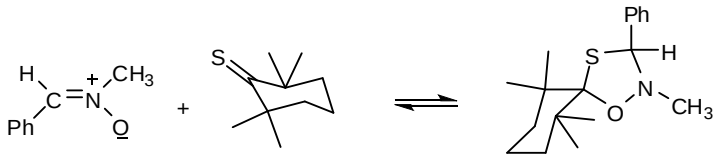


R	R_1	R^2
4-MeC_6H_4	H	Ph
4-$MeOC_6H_4$	H	4-$MeOC_6H_4$
4-$MeOC_6H_4$	H	Ph
4-$MeOC_6H_4$	Ph	Ph
4-MeC_6H_4	Ph	Ph

d- Nitrone-thio compound cycloaddition reaction :

Nitrone can be added to thio compounds, like thioketones, to give 1,4,2-oxathiozolidine.

Huisgen et al [14] studied the cycloaddition of nitrone with 2-methyl-3-phenyl-5-isoxathiozolidine,as shown in equation (7).



Synthesis of diisoxazolidine compounds

General Procedure

The appropriate dianiline oxides (1-7) (0.01 mole) were dissolved in dry toluene (15 ml) and the corresponding fumaric acid (2.32 g, 0.02mole) was added. The reaction mixture was refluxed for (20-30) hours. The solution was concentrated by rotary evaporator to give the crude product, which was then precipitated by chloroform, filtered and purified by column chromatography with eluent (chloroform: methanol) in a ratio of (8:2). Coloured crystals with different melting points were obtained. The purity of the synthesized compounds was determined by using Thin Layer Chromatography (T.L.C.) with the same above eluent, the results obtained are shown in table (1) .

Table (1) : reaction time melting point, yield and R_f of diisoxazolidine compounds

Symbole of diisoxazolidines	Reaction time (hours)	Melting point (°C)	yield (%)	R_f
C_1	22	156-158	73	0.94
C_2	24	164-166	74	0.95
C_3	28	172-174	68	0.97
C_4	20	174-176	89	0.93
C_5	20	156-158	88	0.83
C_6	20	152-154	78	0.90
C_7	27	162-164	64	0.86

2$^{\backslash}$,2$^{\backslash\backslash}$-diphenyl-dispiro[cyclohexa-2,5-diene-(1.3$^{\backslash}$),(4.3$^{\backslash\backslash}$)-diisoxazolidine]4$^{\backslash}$,5$^{\backslash}$,4$^{\backslash\backslash}$,5$^{\backslash\backslash}$-tetracarboxylic acid (C1):

From N,N'-(cyclohexa-2,5-diene-1,4-diylidene) dianiline oxide (1) yield 73%; m.p. (156-158)^{o}c; FT-IR υ (cm^{-1}) 1690cm^{-1} (C=O)stretching; 1226 cm^{-1} (N-O) stretching ; 3400 cm^{-1} (O-H) stretching ; 2872 cm^{-1} (C-H) stretching . δ_H(DMSO) 12.980 ppm (s,2H,5$^{\backslash}$a,5$^{\backslash\backslash}$a); 12.320 ppm (s,2H,4$^{\backslash}$a,4$^{\backslash\backslash}$a); (7.200-7.230) ppm (d,2H, c); (7.720-7.770) ppm (t,4H,b); (6.680-6.700) ppm (d,4H,a) ; 6.074 ppm (s,4H, cyclohexa-2,3,4,5-tetraene); 3.190 ppm (d,2H,4$^{\backslash}$,4$^{\backslash\backslash}$); 4.910 ppm (d,2H,5$^{\backslash}$,5$^{\backslash\backslash}$). m/z= 522 [M+]. Anal. Calc. for $C_{26}H_{22}N_2O_{10}$; C, 59.770; H, 4.214; N, 5.363 Found; C, 59.673; H, 4.212; N, 5.360.

2$^{\backslash}$,2$^{\backslash\backslash}$-diphenyl-dispiro[anthracene-(9.3$^{\backslash}$),(10.3$^{\backslash\backslash}$)-diisoxazolidine]4$^{\backslash}$,5$^{\backslash}$,4$^{\backslash\backslash}$,5$^{\backslash\backslash}$-tetracarboxylic acid (C2):

From N,N'-(anthracene-9,10-diylidene) dianiline oxide (2) yield 74%; m.p. (164-166)^{o}c; FT-IR υ (cm^{-1}) 1710cm^{-1} (C=O)stretching; 1219 cm^{-1} (N-O) stretching ; 3300 cm^{-1} (O-H) stretching ; 2892 cm^{-1} (C-H) stretching . δ_H(DMSO) 12.980 ppm (s,2H,5$^{\backslash}$a,5$^{\backslash\backslash}$a); 12.320 ppm (s,2H,4$^{\backslash}$a,4$^{\backslash\backslash}$a); (6.790-6.820) ppm (d,2H, c); (7.472-7.601) ppm (m,12H,b,d,e); (6.435-6.453) ppm (d,4H,a) ; 3.190 ppm (d,2H,4$^{\backslash}$,4$^{\backslash\backslash}$); 4.910 ppm (d,2H,5$^{\backslash}$,5$^{\backslash\backslash}$). m/z= 622 [M+]. Anal. Calc. for $C_{34}H_{26}N_2O_{10}$; C, 65.594; H, 4.180; N, 4.501 Found; C, 65.495; H, 4.178; N, 4.500.

2$^{\backslash}$,2$^{\backslash\backslash}$-diphenyl-dispiro[acenaphthalene-(1.3$^{\backslash}$),(2.3$^{\backslash\backslash}$)-diisoxazolidine]4$^{\backslash}$,5$^{\backslash}$,4$^{\backslash\backslash}$,5$^{\backslash\backslash}$-tetracarboxylic acid (C3):

From N,N'-(acenaphthalene-1,2-diylidene) dianiline oxide (3) yield 68%; m.p. (172-174)^{o}c; FT-IR υ (cm^{-1}) 1709 cm^{-1} (C=O)stretching; 1219 cm^{-1} (N-O) stretching ; 3500 cm^{-1} (O-H) stretching ; 2889 cm^{-1} (C-H) stretching . δ_H(DMSO) 12.800 ppm (s,2H,5$^{\backslash}$a,5$^{\backslash\backslash}$a); 12.000 ppm (s,2H,4$^{\backslash}$a,4$^{\backslash\backslash}$a); (6.784-6.824) ppm (d,2H, c); (7.472-7.601) ppm (m,10H,b,d,e); (6.435-6.453) ppm (d,4H,a) ; 3.590 ppm (d,2H,4$^{\backslash}$,4$^{\backslash\backslash}$); 4.810 ppm (d,2H,5$^{\backslash}$,5$^{\backslash\backslash}$). m/z= 596 [M+]. Anal. Calc. for $C_{32}H_{24}N_2O_{10}$; C, 64.429; H, 4.026; N, 4.697 Found; C, 64.329; H, 4.024; N, 4.696.

2-methyl-2$^{\backslash}$,2$^{\backslash\backslash}$-diphenyl-dispiro[cyclopenta-(1.3$^{\backslash}$),(3.3$^{\backslash\backslash}$)-diisoxazolidine] 4$^{\backslash}$,5$^{\backslash}$,4$^{\backslash\backslash}$,5$^{\backslash\backslash}$-tetracarboxylic acid (C4):

From N,N'-(2-methyl cyclopentane-1,3-diylidene) dianiline oxide (4) yield 89%; m.p. (174-176)^{o}c; FT-IR υ (cm^{-1}) 1702 cm^{-1} (C=O)stretching; 1220 cm^{-1} (N-O) stretching ; 3425 cm^{-1} (O-H) stretching ; 2928 cm^{-1} (C-H) stretching . δ_H(DMSO) 12.982 ppm (s,2H,5$^{\backslash}$a,5$^{\backslash\backslash}$a); 12.323 ppm (s,2H,4$^{\backslash}$a,4$^{\backslash\backslash}$a); (7.198-7.222) ppm (d,2H, c); (7.720-7.766) ppm (t,4H,b); (6.435-6.453) ppm (d,4H,a) ; 1.010 ppm (d,3H, 2a); 1.750 ppm (s,4H,4,5) ; 2.220 ppm (quar.,1H,2) ; 3.190 ppm (d,2H,4$^{\backslash}$,4$^{\backslash\backslash}$); 4.912 ppm (d,2H,5$^{\backslash}$,5$^{\backslash\backslash}$). m/z= 526 [M+]. Anal. Calc. for $C_{26}H_{25}N_2O_{10}$; C, 59.315; H, 4.942; N, 5.323 Found; C, 59.284; H, 4.940; N, 5.321.

2-methyl-2$^{\backslash}$,2$^{\backslash\backslash}$-diphenyl-2H-dispiro[indane-(1.3$^{\backslash}$),(3.3$^{\backslash\backslash}$)-diisoxazolidine]4$^{\backslash}$,5$^{\backslash}$,4$^{\backslash\backslash}$,5$^{\backslash\backslash}$-tetracarboxylic acid (C5):

From N,N'-(indane-1,3(2H)- diylidene) dianiline oxide (5) yield 88%; m.p. (156-158)^{o}c; FT-IR υ (cm^{-1}) 1702 cm^{-1} (C=O)stretching; 1223 cm^{-1} (N-O) stretching ; 3500 cm^{-1} (O-H) stretching ; 2880 cm^{-1} (C-H) stretching . δ_H(DMSO) 12.800 ppm (s,2H,5$^{\backslash}$a,5$^{\backslash\backslash}$a); 12.000 ppm (s,2H,4$^{\backslash}$a,4$^{\backslash\backslash}$a); (6.788-6.820) ppm (d,2H, c); (7.517-7.600) ppm (m,8H,b,d,e); (6.430-6.450) ppm (d,4H,a) ; 2.105 ppm (s,2H,2) ; 3.193 ppm (d,2H,4$^{\backslash}$,4$^{\backslash\backslash}$); 4.914 ppm (d,2H,5$^{\backslash}$,5$^{\backslash\backslash}$). m/z= 560 [M+]. Anal. Calc. for $C_{29}H_{24}N_2O_{10}$; C, 62.142; H, 4.285; N, 5.000 Found; C, 62.140; H, 4.281; N, 4.996.

2-methyl-2,4,5,6-tetrahydro2$^{\backslash}$,2$^{\backslash\backslash}$-diphenyl-dispiro[cyclohexa-(1.3$^{\backslash}$),(3.3$^{\backslash\backslash}$)-diisoxazolidine]4$^{\backslash}$,5$^{\backslash}$,4$^{\backslash\backslash}$,5$^{\backslash\backslash}$-tetracarboxylic acid (C6):

From N,N'-(1-methyl cyclohexane-1,3-diylidene) dianiline oxide (6) yield 78%; m.p. (152-154)^{o}c; FT-IR υ (cm^{-1}) 1710 cm^{-1} (C=O)stretching; 1217 cm^{-1} (N-O) stretching ; 3300 cm^{-1} (O-H) stretching ; 2887 cm^{-1} (C-H) stretching . δ_H(DMSO) 12.980 ppm (s,2H,5$^{\backslash}$a,5$^{\backslash\backslash}$a); 12.320 ppm (s,2H,4$^{\backslash}$a,4$^{\backslash\backslash}$a); (7.198-7.220) ppm (d,2H, c); (7.720-7.766) ppm (t,4H,b); (6.682-6.704) ppm (d,4H,a) ; 0.290 ppm (d,3H, 2a); 1.060 ppm (quin.,2H,5) ; 1.600 ppm (t,4H,4,6) ;2.220 ppm (quar.,1H,2); 3.190 ppm (d,2H,4$^{\backslash}$,4$^{\backslash\backslash}$); 4.912 ppm (d,2H,5$^{\backslash}$,5$^{\backslash\backslash}$). m/z= 540 [M+]. Anal. Calc. for $C_{27}H_{27}N_2O_{10}$; C, 60.000; H, 5.185; N, 5.185 Found; C, 59.980; H, 5.183; N, 5.181.

2-methyl-2$^{\backslash}$,2$^{\backslash\backslash}$-diphenyl-dispiro[naphthalene-(1.3$^{\backslash}$),(2.3$^{\backslash\backslash}$)-diisoxazolidine] 4$^{\backslash}$,5$^{\backslash}$,4$^{\backslash\backslash}$,5$^{\backslash\backslash}$-tetracarboxylic acid (C7):

From N,N'-(naphthalene-1,2-diylidene) dianiline oxide (7) yield 64%; m.p. (162-164)^{o}c; FT-IR υ (cm^{-1}) 1710 cm^{-1} (C=O)stretching; 1217 cm^{-1} (N-O) stretching ; 3450 cm^{-1} (O-H) stretching ; 2920 cm^{-1} (C-H) stretching . δ_H(DMSO) 12.980 ppm (s,2H,5\a,5\\a); 12.000 ppm (s,2H,4\a,4\\a); (6.788-6.820) ppm (d,2H, c); (7.517-7.600) ppm (m,10H,b,d,e,f,g,h); (6.430-6.450) ppm (d,4H,a) ; (6.070-6.090) ppm (d,1H, 4); (5.410-5.430) ppm (d,1H,3) ; 3.193 ppm (d,2H,4\,4\\); 4.914 ppm (d,2H,5\,5\\). m/z= 572 [M+]. Anal. Calc. for $C_{30}H_{24}N_2O_{10}$; C, 62.937; H, 4.195; N, 4.895 Found; C, 62.887; H, 4.193; N, 4.892.

Result and Discussion [15-17]

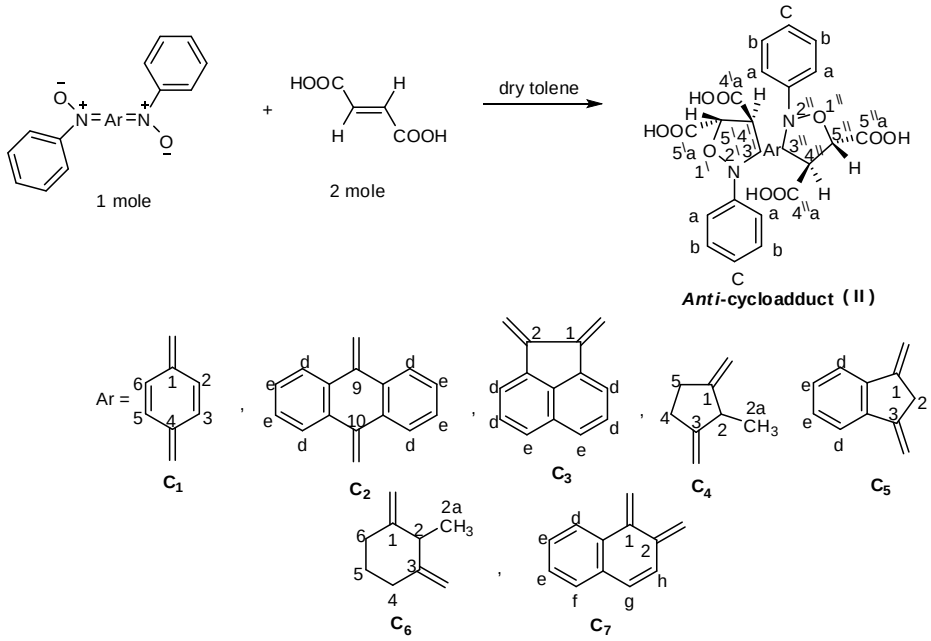
Treatment of the dianiline oxides(1-7) with fumaric acid in boiling dry toluene gave, after purification from recrystallization or short column of silica gel, the pure anticyclo adduct diisoxazolidines derivatives (C1-C7) in 64-89% yield,as crystalline compounds (scheme 2).The structures of these products were established from their elemental analysis, FT-IR,^{1}H NMR and Mass spectra.

The IR spectra of all diisoxazolidine compounds were characterized by the disappearance of the absorption band that was attributed to the (C=N) stretching which appeared at (1583-1602) cm^{-1} due to dinitrone compounds. This fact confirmed the correct expected chemical structures of these compounds.

The IR spectra of diisoxazolidine compounds showed strong absorption bands in the range of (1690-1710) cm^{-1} due to (C=O) stretching of carboxylic acid group. Broad absorption bands appeared in the region (3300-3500) cm^{-1} which were characteristic of all diisoxazolidine compounds and were due to (OH) stretching. Also, strong absorption bands appeared between the range (1219-1226) cm^{-1} due to the stretching of the (N-O) groups. Moreover, all these spectra showed that the weak absorption bands,which appeard in the range (3056-3083) cm^{-1}, were due to the stretching of aromatic (C-H). In addition to these absorption bands, all the IR spectra of diisoxazolidine compounds showed weak bands between the region (2872-2920) cm^{-1} which were attributed to the (C-H), (CH_2) and (CH_3) groups.

These results are in accordance with the information in the literature and references.

Most of the synthesized diisoxazolidine compounds **(II)** were characterized by ^{1}H NMR spectroscopy.



The ^{1}H NMR spectra of (C_1, C_2, C_3, C_4, C_5, C_6 and C_7) diisoxazolidine compounds showed doublet signal within the region (3.190-3.590) ppm due to the fact that $H_{4\,4\\}$ in isoxazolidine rings coupled with $H_{5\,5\\}$. The $H_{5\,5\\}$, in the same rings, showed doublet signal within the region(4.810-4.914)ppm, which coupled with the $H_{4\,4\\}$ in the rings.The protons of aromatic rings system showed multiplet signal within the region (7.475-7.622)ppm.The protons of N-phenyl groups showed doublet signal within the region (6.430-6.704) ppm due to the protons at a position, while the protons at c position for this group showed doublet signal within the region (6.784-7.230) ppm. The other protons in b position for this group showed triplet signal at chemical shift (7.720-7.230) ppm .

The proton of carboxylic acid on 4\a,4\\a in isoxazolidine rings showed singlet signal within the region (12.000-12.323) ppm, while the other protons of carboxylic acid on 5\a,5\\a also showed a singlet signal but in a low field,as compared with the above protons,within the region (12.800-12.982) ppm because of the high electronegativity of the oxygen atom at position 1\,1\\ of the rings.

In addition, the ^{1}H NMR spectrum of C_1 compound showed singlet signal at chemical shift (6.074)ppm due to the four protons equivalent at positions 2,3,5 and 6.

The ^{1}H NMR spectrum of C_4 compound showed doublet signal at chemical shift (1.010)ppm,which attributed to the protons 2a, and a quartet signal at chemical shift (2.220)ppm due to the proton 2.In addition, a singlet signal appeared at chemical shift (1.750)ppm,which attributed to the four protons equivalent at positions 4 and 5.

The ^{1}H NMR spectrum of C_5 compound showed singlet signal at chemical shift (2.105)ppm due to the protons 2.

The ^{1}H NMR spectrum of C_6 compound showed doublet signal at chemical shift (0.290)ppm due to the protons 2a, ,a quartet signal at chemical shift (2.220)ppm,which attributed to the proton 2, and a triplet signal at chemical shift (1.600)ppm which assigned to the four protons equivalent at positions 4and 6.In addition, quantet signal appeared at chemical shift (1.060) ppm due to the protons 5.

The mass spectra of diisoxazolidine [18-20] showed the peaks at (m/z=522,622,596,526,560,540 and 572) which represented the molecular ion [M+] of (C1-C7) compounds, respectively.

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