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Preparation and Charactrization of 1,3- dipolar cycloaddition of nitrones with but-2-ynedioic acid

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1.Abstract:

Some nitrones(1-3), derived from N-p-tolylhydroxylamine with substituted benzaldehyde such as(4-Chlorobenzaldehyde,4-Florobenzaldehyde, 4-Nitrobenzaldehyde) .Ther reaction with but-2-ynedioic acid include 1,3- dipolar cycloaddition reaction to give isoxazoles (4-6),They have been identified by ^{1}HNMR, IR and Mass spectra
keyword: nitrones, isoxazole, 1,3- dipolar cycloaddition, but-2-ynedioic acid

2. Introduction:

The reactions of nitrones dipoles play an important role in the history of cycloaddition reaction . The 1,3- dipolar cycloaddition also known as the Huisgen cycloaddition [1] is a classic reaction in organic chemistry consisting of the reaction of dipolarophile with a 1,3- dipolar compound [2] that allows the production of various five –membered heterocycles [3] . High specificity stereoselectivity associated with these reactions make them synthetically important [4-7] .It has been found that 1,3- dipolar cycloaddition reaction proceed through a concerted mechanism [8] .Most of dipolarophile are alkenes[9,10] ,alkynes[11] and molecules possessing related hetero atom functional groups (such as carbonyls [12-14] and nitriles[15-18]).Both inter and intra molecular nitrone and alkynes cycloaddition reaction have received attention of heterocycles of biological interest [19-22] .

3. Experimental

3.1 Apparatuses:

Melting points were determind using a Gallenkamp melting point apparatus .
Proton NMR spectra were recorded on a Bruker DRX 400 Advance spectrometer at 500 MHz and 125 MHz ,respectively,using deuterated solvents and TMS as an internal standard Chemical shifts are reported as δ values in ppm. Infrared spectra were obtained

by FT-IR-1600 Perkin-Elmer spectrophotometer. Thin layer chromatography (TLC) was performed on aluminum sheets silica gel from merk.Column chromatography was carried out using Merck silica gel (230-400 mesh). The TLC spots were visualized in UV and I_2. Mass spectra recorded on High-resolution mass spectra were recorded on an ESI-TOF Mariner Spectrometer (Perspective Biosystem)

3.2 Preparation Methods

3.2.1 Preparation of the nitrones(1-3)

The N-p-tolylhydroxylamine was prepared from nitro toluene according to ref [26] and α-aryl-N-phenyl nitrones (A1-3) from the substituted benzaldehyde and N-p-tolylhydroxylamine according to ref[27-34].

3.2.2 Preparation of the isoxazoles(4-6)

To A stirred solution of the nitrones (1-3) (5 mmole)[1.28 mg from comp.(1) and 1.145 mg from comp.(2) and 1.225 mg from comp.(3)] in dry toluene (50 ml) was added to but-2-ynedioic acid (5 mmole)[0.57 mg] and the solution was heated at refluxed for (48-72 h) .The resulting mixture was evaporated under reduced pressure.

The crude product was purified by column chromatography on silica gel eluting to give pure isoxazoles (4-6).

3.2.2.1 3-(4-nitrorophenyl)-2-p-tolyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid(4)

The product (4) was isolated by column chromatography on silica gel eluting with benzene\ methanol(8:2) as a brown solid product in 60 % yield ,m.p= 254-255C°.
IR: 1751 cm^{-1} (C=O), 3300 cm^{-1} s (OH), 1455 cm^{-1} (C=C),1300 cm^{-1} w (C-N); 1023 cm^{-1} m (NO_2 Asym), 1340 cm^{-1} w (NO_2 , sym);
^{1}HNMR : δ 11.58 ppm (s,2H) Carboxylic Acid O-H, 7.10- 8.52 ppm (m,8 H aromatic), 5.46 ppm (s,1H), 2.65 ppm (s,3H) Fig.(2); Mass: m\z = 370 $[M]^+$.Fig.(5)

3.2.2.2 3-(4-fluorophenyl)-2-p-tolyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid (5):

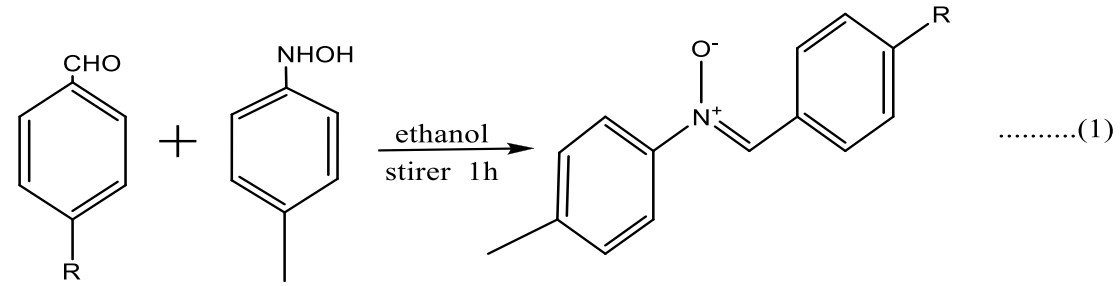
The product (5) was isolated by column chromatography on silica gel eluting with benzene\ methanol(8:2) as a brown solid product in 51 % yield ,m.p= 186 C°.
IR: 1747 (C=O), 3350 br (OH), 1423 (C=C),1307 w (C-N);
^{1}HNMR : δ 11.55 ppm (s,2H) Carboxylic Acid O-H, 6.91- 7.54 ppm (m,8 H aromatic), 5.66 ppm (s,1H), 2.51 ppm (s,3H) Fig.(3); Mass: m\z = 343 $[M]^+$. .Fig.(6)

3.2.2.3 3-(4-chlorophenyl)-2-p-tolyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid (6)

the product (6) was isolated by column chromatography on silica gel eluting with benzene\ methanol(8:2) as a yellow solid product in 55 % yield ,m.p= 210- 212 C°.
IR: 1747 cm^{-1} (C=O), 3330 cm^{-1} br (OH), 1492 cm^{-1} (C=C),1311 cm^{-1} m (C-N),
^{1}HNMR : δ 11.58 ppm (s,2H) Carboxylic Acid O-H, 7.17- 7.59 ppm (m,8 H aromatic), 5.46 ppm (s,1H), 2.65 ppm (s,3H) Fig.(4); Mass: m\z = 359 $[M]^+$. .Fig.(7)

4. Results and Discussion

The nitrones(1-3) used in this study were prepared from the corresponding aldehyde with N-p-tolylhydroxylamine[23,24] Equation(1)



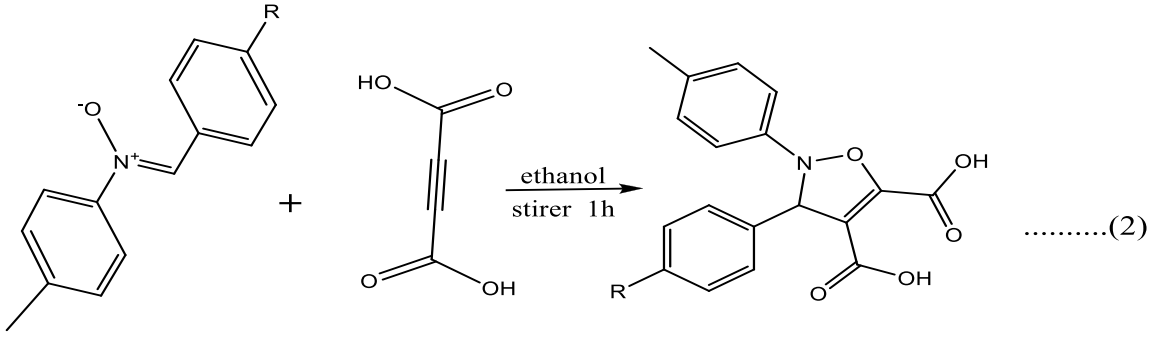
.....(1)

R= 4-NO_2 , 4-F , 4-Cl (1-3)

Equation(1)

Preparation of compound(4-6)

The cycloaddition of nitrones (1-3) with but-2-ynedioic acid were carried out by refluxing (48-72 h) in dry toluene at 110 ˚C to give isoxazoles(4-6). In all cases ,The compounds were purified by column chromatography [25] allowed the isolation of pure compounds. Equation(2)



.....(2)

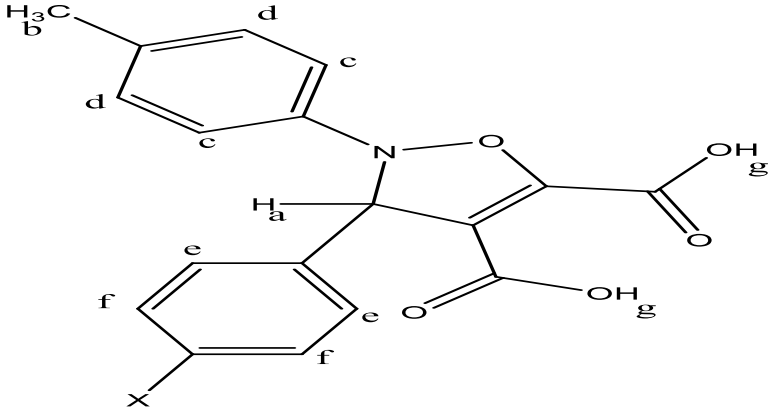
(1-3) R= 4-NO_2 , 4-F , 4-Cl (4-6)

Equation(2)

The obtained isoxazoles were characterized spectroscopically. The formation of the cycloadducts was established by the FTIR, ^{1}HNMR and Mass spectroscopy .The ^{1}HNMR spectrum of general structure isoxazoles (4-6)in Fig(1) list in table(1) spectrum showed a singlet at δ 2.51-2.65ppm for (C-CH_3)., a multiplet at δ 6.91-8.52 ppm for the

aromatic protons, a singlet at δ 5.46-5.66 ppm for proton(a) and a singlet at δ 11.55-11.58 ppm for acid proton,Fig.(2-4)

The IR spectrum included a peak at 3059-3150 cm^{-1} for the NH_2 stretch and the sharp peak at 1647-1651 cm^{-1} for C=O stretch



Fig(1) general structure of isoxazoles

Table (1): ^{1}HNMR spectral data (ppm) for isoxazoles(4-6)

Comp.	X	H_a	H_b	H_c	H_d	H_e	H_f	H_g
4	4-NO_2	5.47 (s,1H)	2.65 (s,3H)	7.1 (d,2H)	7.56 (d,2H)	8.27 (d,2H)	8.52 (d,2H)	11.58 (s,2H)
5	4-F	5.66 (s,1H)	2.51 (s,3H)	6.91 (d,2H)	7.23 (d,2H)	7.32 (d,2H)	7.5 (d,2H)	11.55 (s,2H)
6	4-Cl	5.46 (s,1H)	2.65 (s,3H)	7.17-7.21(d,2H)	7.45 (d,2H)	7.57 (d,2H)	7.59 (d,2H)	11.58 (s,2H)

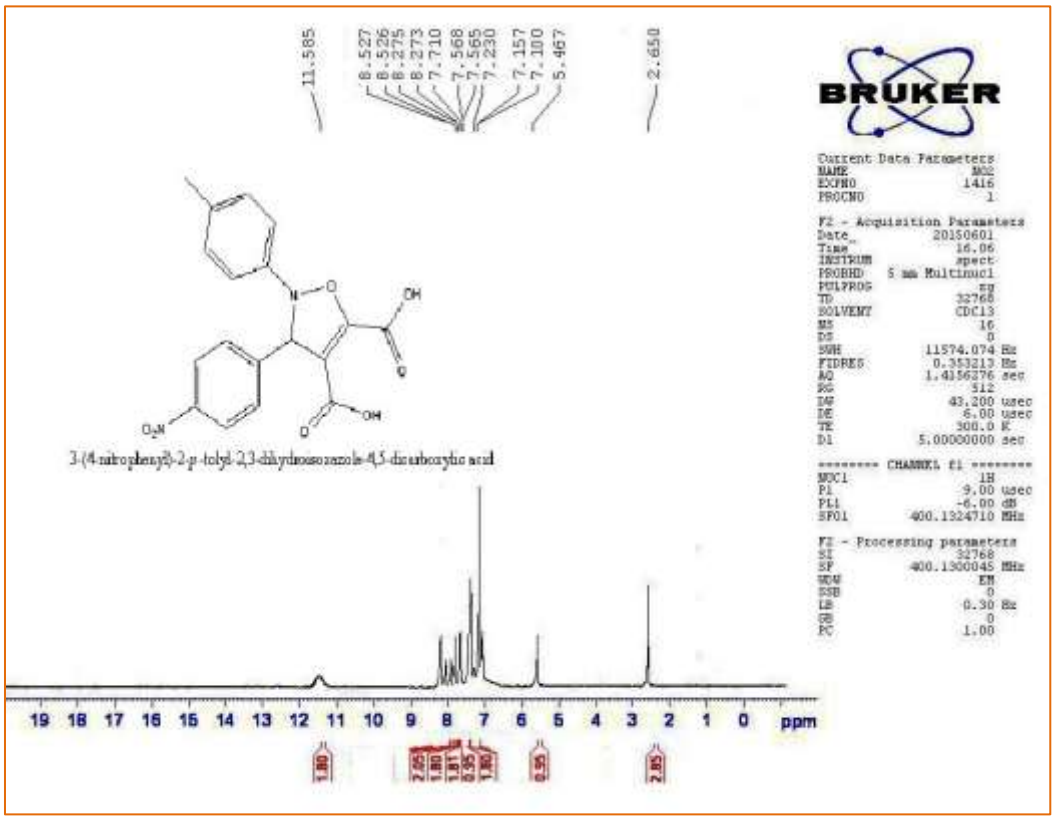


Fig (2) ^{1}HNMR for compound (4)

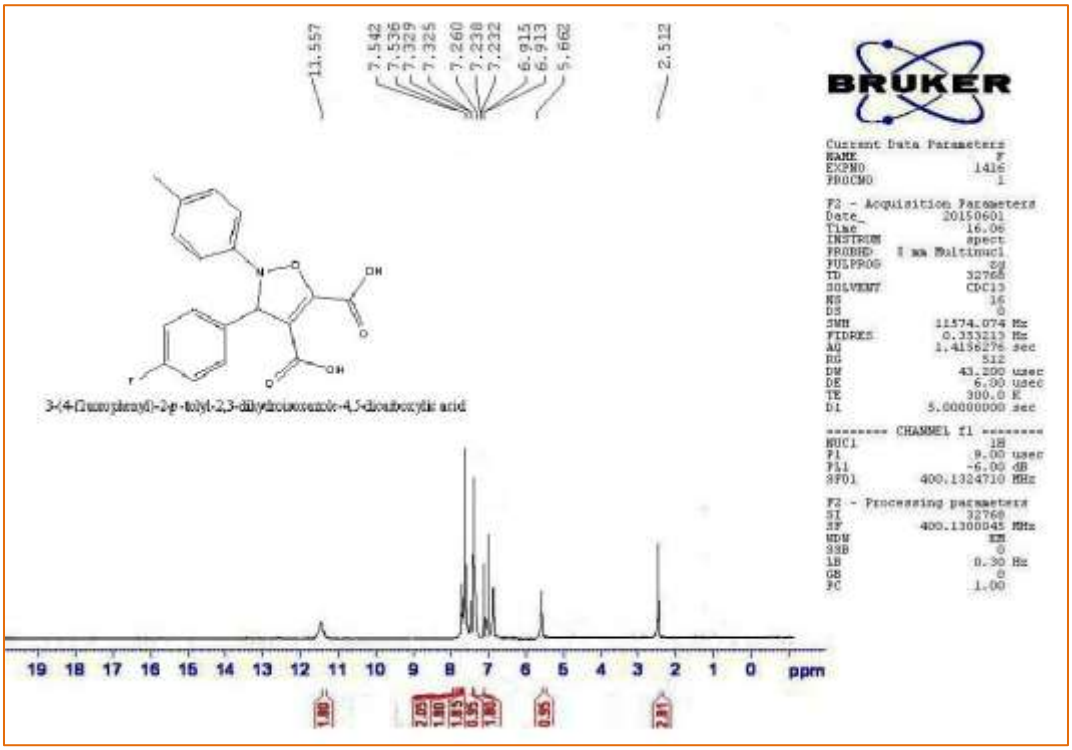


Fig (3) ^{1}HNMR for compound (5)

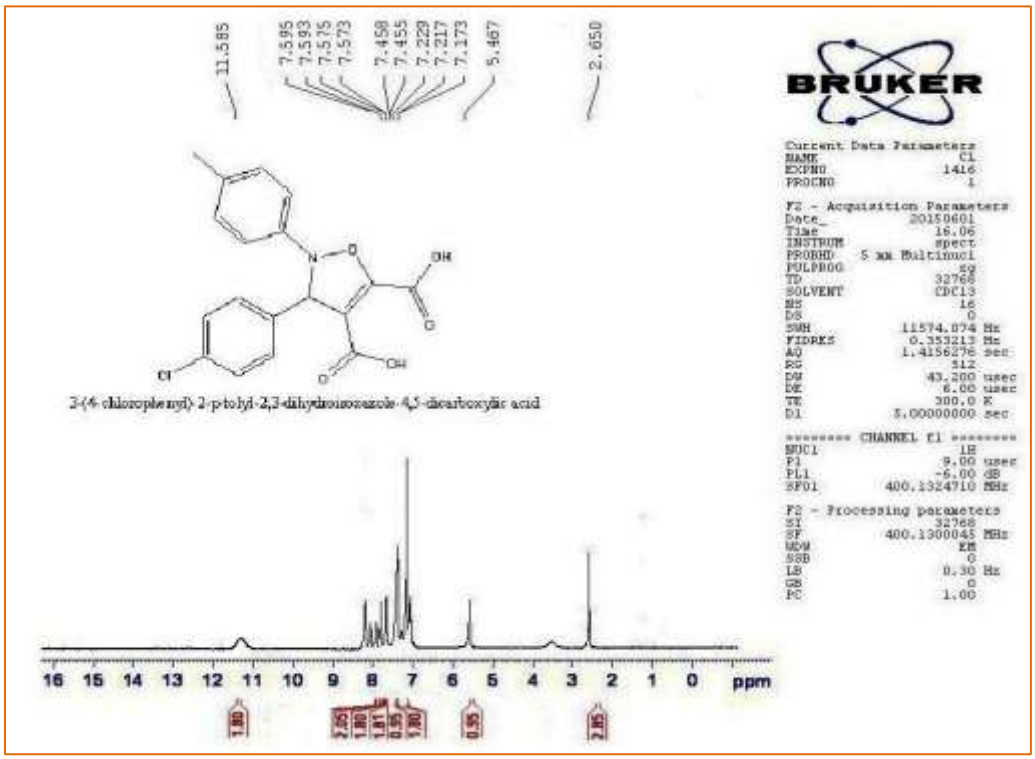


Fig (4) ^{1}HNMR for compound (6)

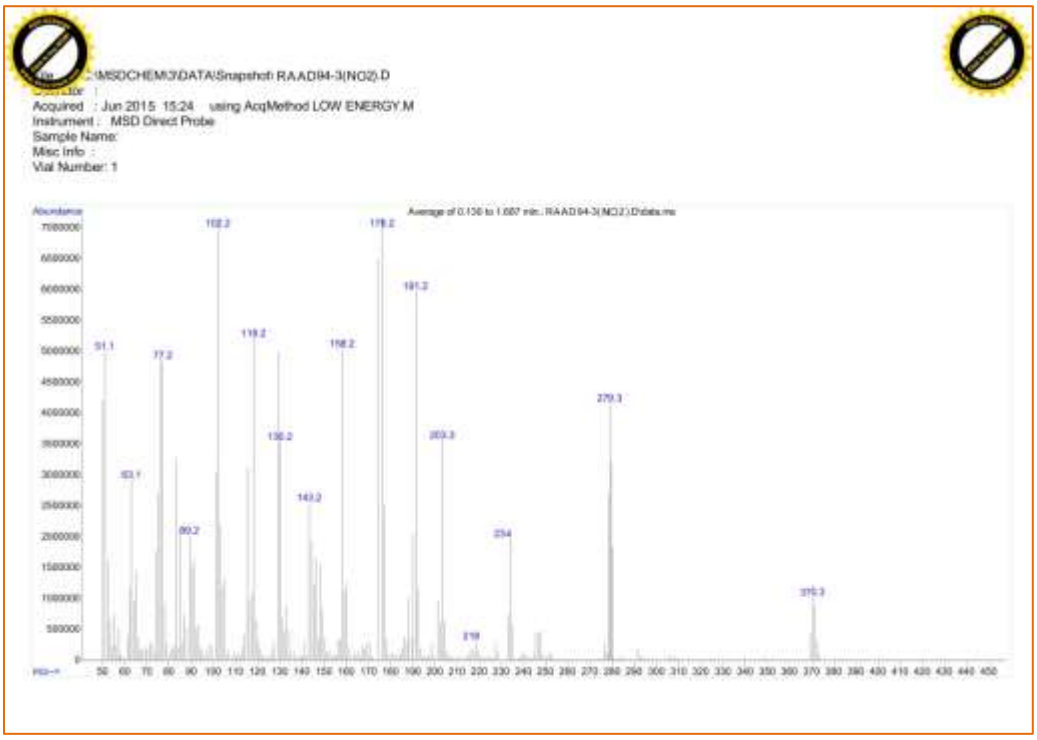


Fig (5) mass spectrum for compound (4)

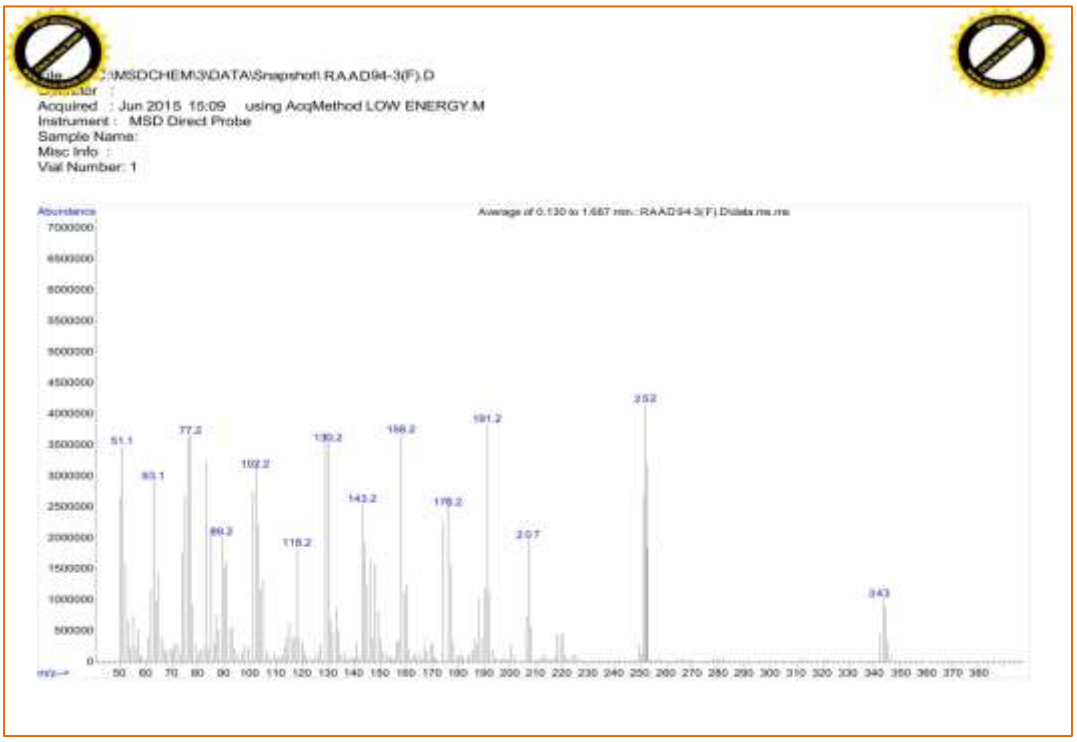


Fig (6) mass spectrum for compound (5)

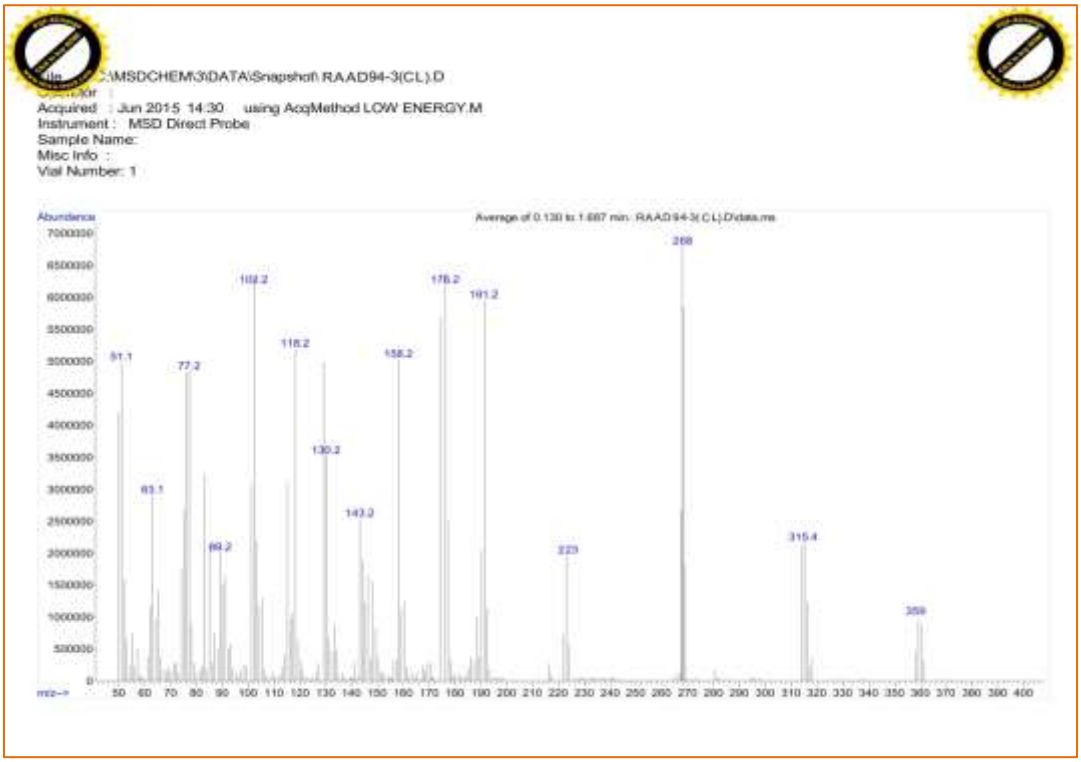


Fig (7) mass spectrum for compound (6)

5. Conclusion:

In conclusion, 1,3- dipolar cycloaddition reaction of some nitrones (1-3) with but-2-ynedioic acid to give new isoxazoles (4-6).

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تحضير وتشخيص ودراسة الاضافة
الحلقية 3,1-ثنائية القطب للنايترونات مع حامض بيوتاين ثنائي كربوكسيل

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الملخص:
حضرت بعض مركبات النايترونات مشتقة من تفاعل ن- بارا توليل هيدروكسيل امين مع معوضات البنزالدهايد(4-كلوروبنزالدهايد,4-فلوروبنزالدهايد,4-نايتروبنزالدهايد,) .ثم تفاعل مع حامض بيوتاين ثنائي الكربوكسيل ضمن تفاعلات الاضافة الحلقية 3,1- ثنائية القطب للنايترونات ليعطي مركبات الازوكسازول وتم تشخيصها باستخدام طيف الاشعة تحت الحمراء وطيف بروتون للرنين النووي المغناطيسي وكذلك طيف الكتلة