

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

### 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  $\delta$  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<sub>2</sub>. 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-tolyhydroxylamine was prepared from nitro toluene according to ref<sup>26</sup> and  $\alpha$ -aryl-N-phenyl nitrones (A1-3) from the substituted benzaldehyde and N-p-tolyhydroxylamine according to ref<sup>27-34</sup>.

#### 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-yndioic 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-nitrophenyl)-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<sup>-1</sup> (C=O), 3300 cm<sup>-1</sup> s (OH), 1455 cm<sup>-1</sup> (C=C), 1300 cm<sup>-1</sup> w (C-N); 1023 cm<sup>-1</sup> m (NO<sub>2</sub> Asym), 1340 cm<sup>-1</sup> w (NO<sub>2</sub>, sym);

<sup>1</sup>HNMR :  $\delta$  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]<sup>+</sup>.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);

<sup>1</sup>HNMR :  $\delta$  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]<sup>+</sup>. Fig.( 6 )

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

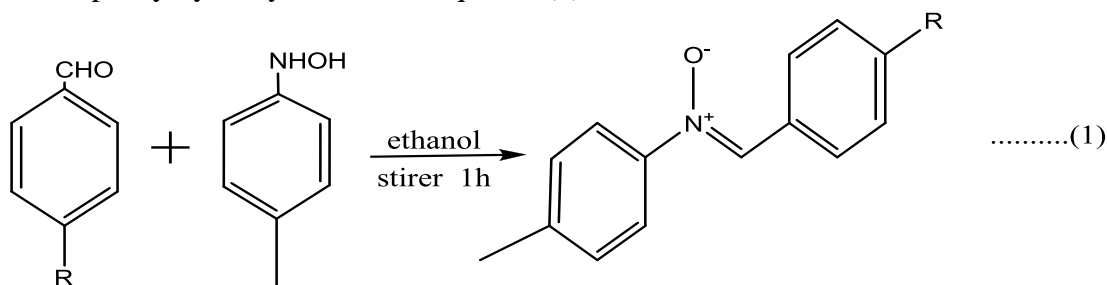
the product (6) was isolated by column chromatography on silica gel eluting with benzene\ methanol(8:2) as a yellow solid product in 55 % yield ,m.p= 210- 212 C°.

IR: 1747 cm<sup>-1</sup> (C=O), 3330 cm<sup>-1</sup> br (OH), 1492 cm<sup>-1</sup> (C=C), 1311 cm<sup>-1</sup> m (C-N),

<sup>1</sup>HNMR :  $\delta$  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]<sup>+</sup>. Fig.(7 )

#### 4. Results and Discussion

The nitrones(1-3) used in this study were prepared from the corresponding aldehyde with N-p-tolyhydroxylamine<sup>23,24</sup> Equation(1)



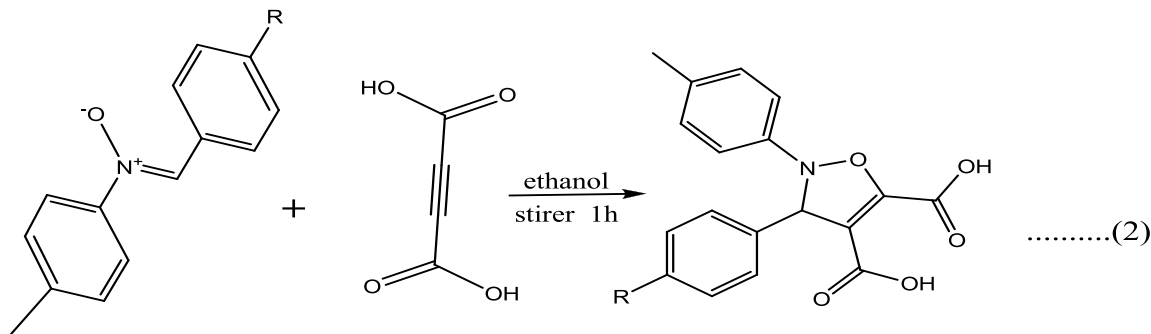
R= 4-NO<sub>2</sub>, 4-F , 4-Cl

(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<sup>25</sup> allowed the isolation of pure compounds. Equation(2)



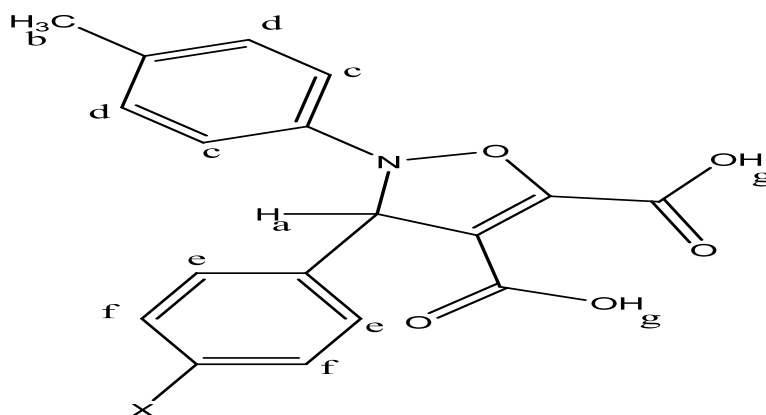
(1-3) R= 4-NO<sub>2</sub>, 4-F , 4-Cl

(4-6)

Equation(2)

The obtained isoxazoles were characterized spectroscopically. The formation of the cycloadducts was established by the FTIR, <sup>1</sup>HNMR and Mass spectroscopy. The <sup>1</sup>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<sub>3</sub>), 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  $\text{cm}^{-1}$  for the  $\text{NH}_2$  stretch and the sharp peak at 1647-1651  $\text{cm}^{-1}$  for  $\text{C}=\text{O}$  stretch



Fig(1) general structure of isoxazoles

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

Comp.	X	$\text{H}_a$	$\text{H}_b$	$\text{H}_c$	$\text{H}_d$	$\text{H}_e$	$\text{H}_f$	$\text{H}_g$
4	4- $\text{NO}_2$	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)

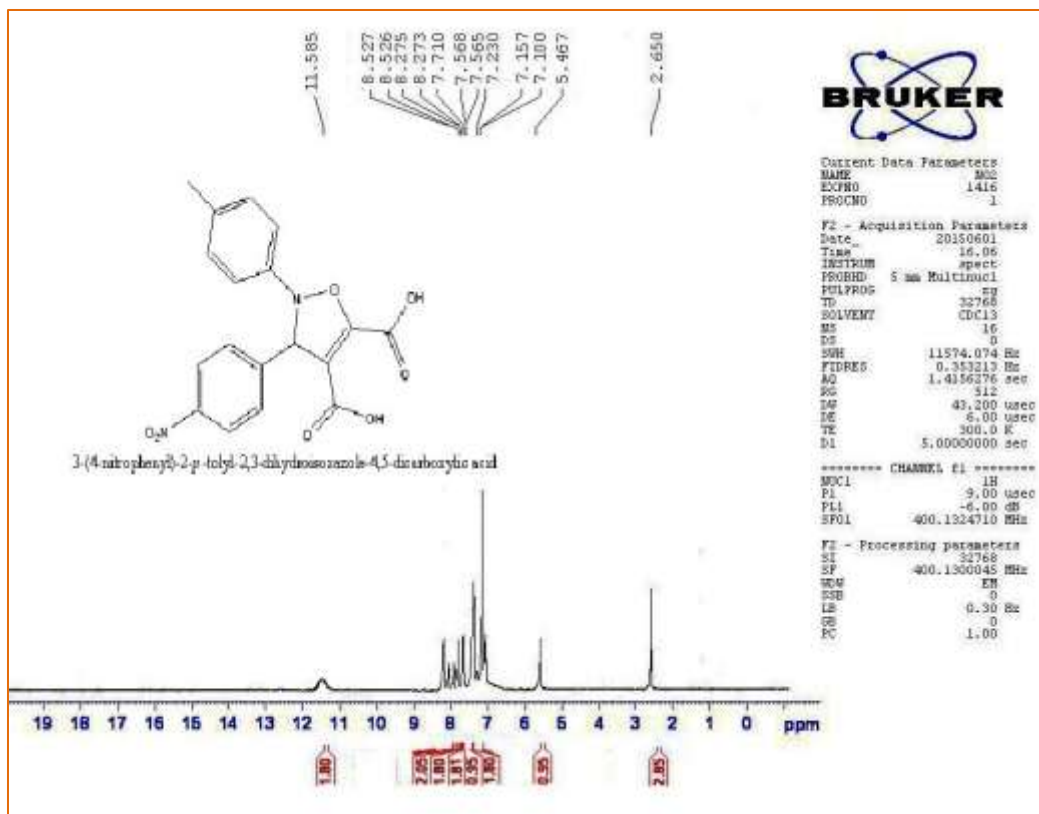


Fig (2) <sup>1</sup>HNMR for compound (4)

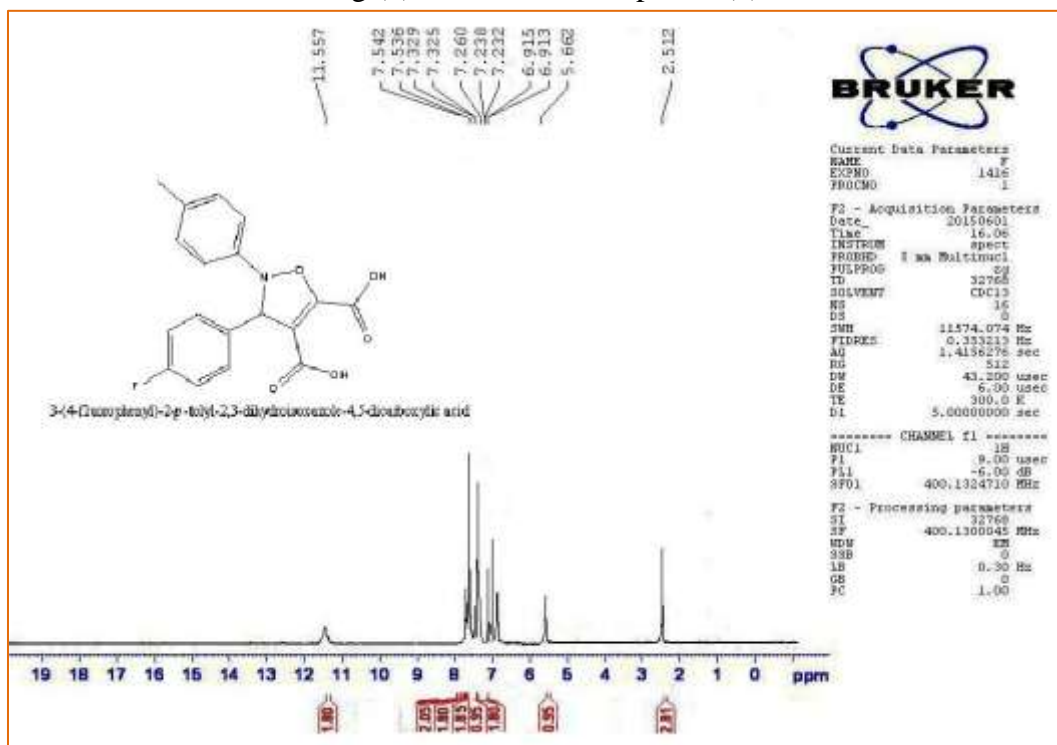


Fig (3) <sup>1</sup>HNMR for compound (5)

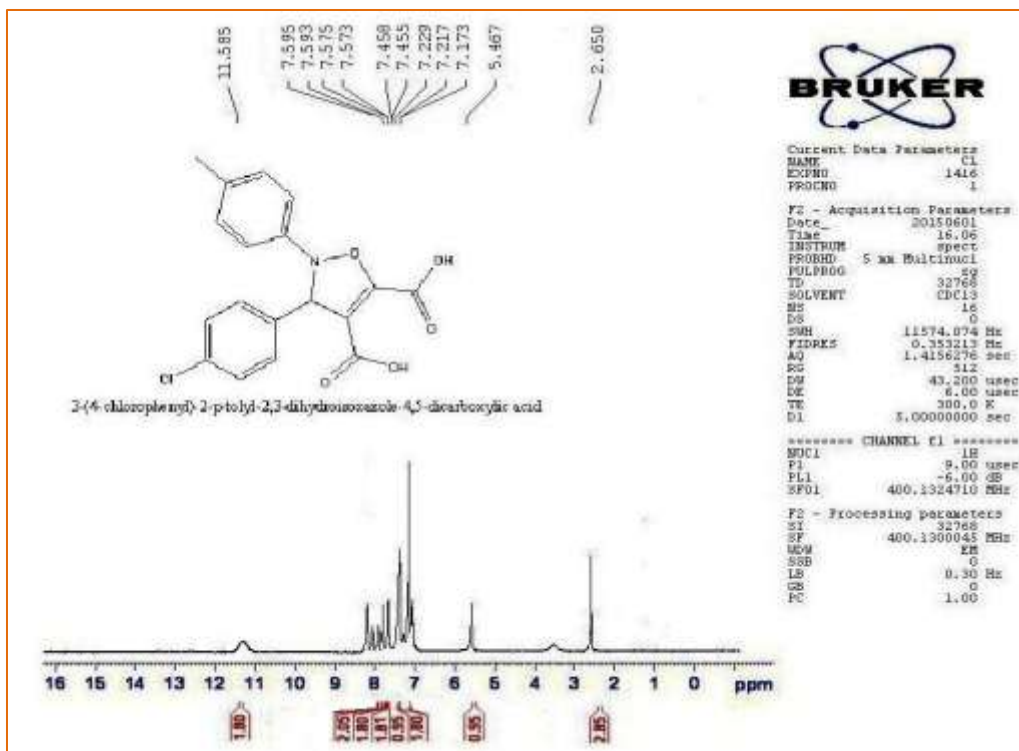


Fig (4) <sup>1</sup>H NMR for compound (6)

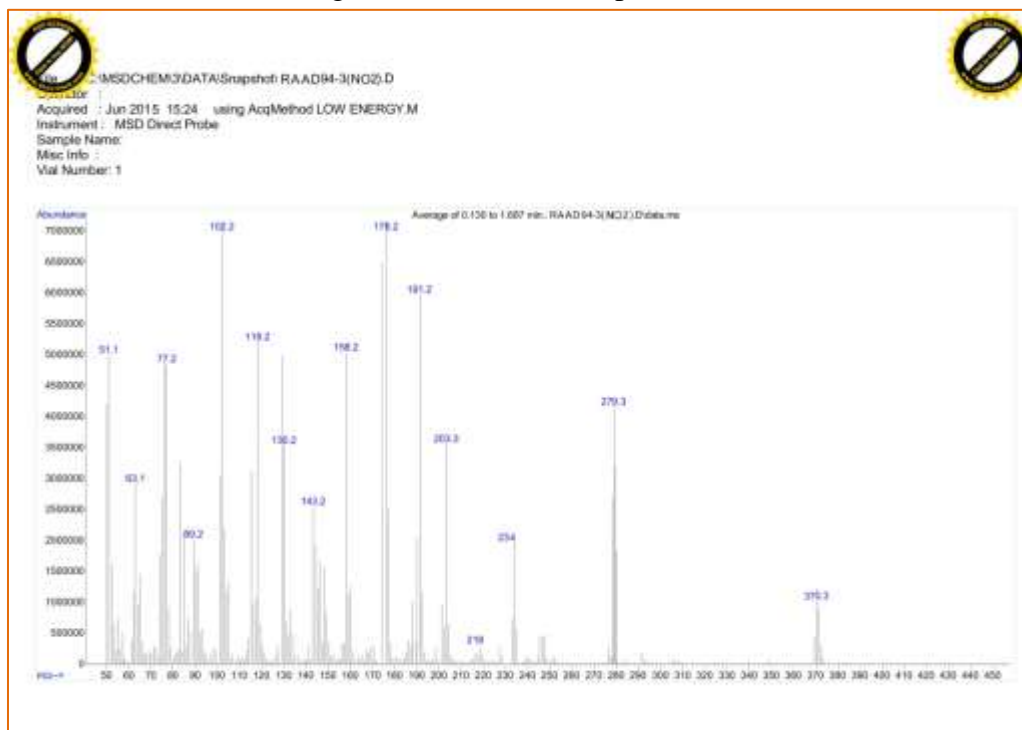


Fig (5) mass spectrum for compound (4)

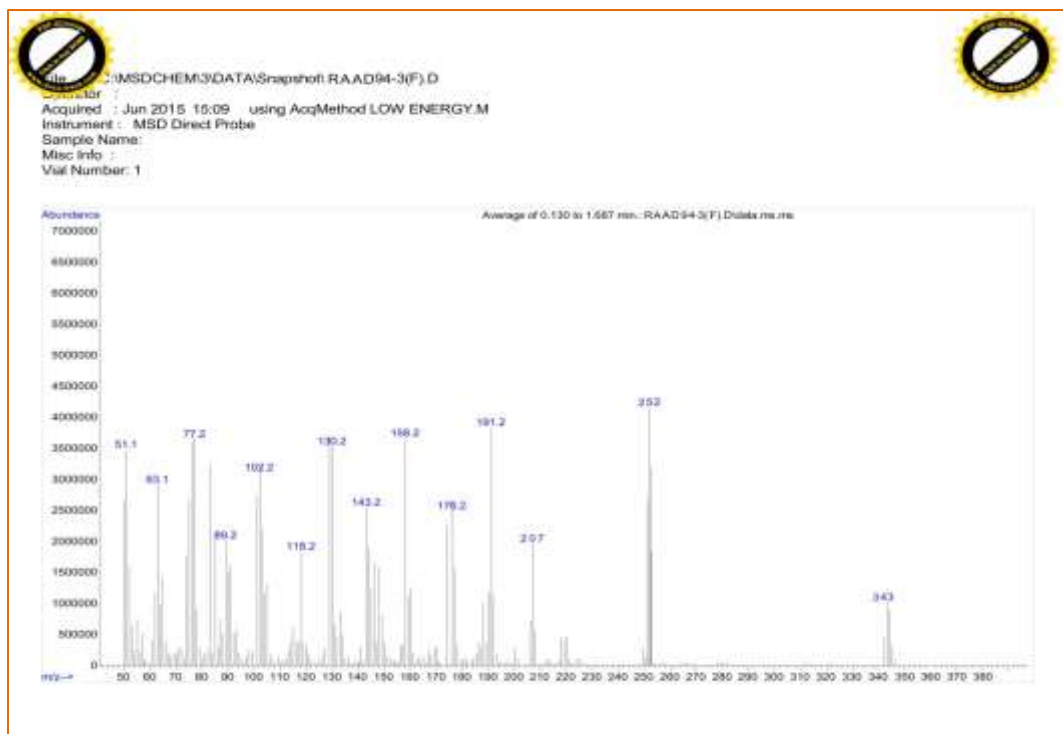


Fig (6) mass spectrum for compound (5)

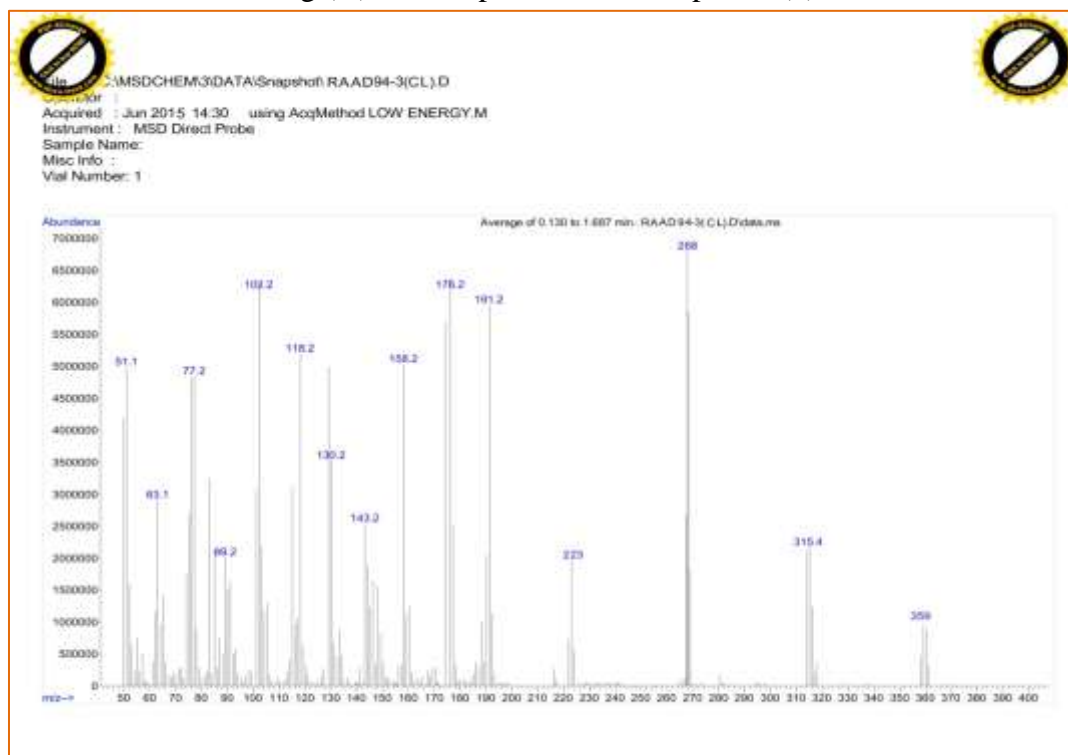


Fig (7) mass spectrum for compound (6)

## 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).

## 6.References

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تحضير وتشخيص ودراسة الاضافة  
الحلقية ١,٣-ثنائية القطب للنايترونات مع حامض بيوتانين ثنائي كربوكسيل  
رائد جميل علي.  
المديرية العامة للتربية في ذي قار  
(قسم الناصرية)

الملخص:

حضرت بعض مركبات النايترونات مشتقة من تفاعل ن- بارا توليل هيدروكسيل امين مع معوضات البنز الدهايد(٤-كلوروبنز الدهايد، ٤-فلوروبنز الدهايد، ٤-نايتروبنز الدهايد)، ثم تفاعل مع حامض بيوتانين ثنائي الكربوكسيل ضمن تفاعلات الاضافة الحلقية ١,٣- ثنائية القطب للنايترونات ليعطي مركبات الازوكسازول وتم تشخيصها باستخدام طيف الاشعة تحت الحمراء وطيف بروتون للرنين النووي المغناطيسي وكذلك طيف الكتلة