

## 'Huisgen reaction' of aldonitrones with N-benzyl maleimide leading to synthesis of 2, 3-diaryl-5-benzyl-2*H*-3, 3a, 4, 5, 6, 6a-hexahydropyrrolo[3, 4-*d*]isoxazole-4, 6-diones

Jaspreet Kaur\*<sup>a</sup>, Baldev Singh<sup>b</sup> & Kewal Krishan Singal<sup>b</sup>

a) Department of Chemistry, G.H.G. Khalsa College, Gurusar Sadhar, Ludhiana 141 104

b) Department of Chemistry, Punjabi University, Patiala 147 002

E-mail: drjaspreet@hotmail.com

Received 20 April 2004; accepted (revised) 14 March 2005

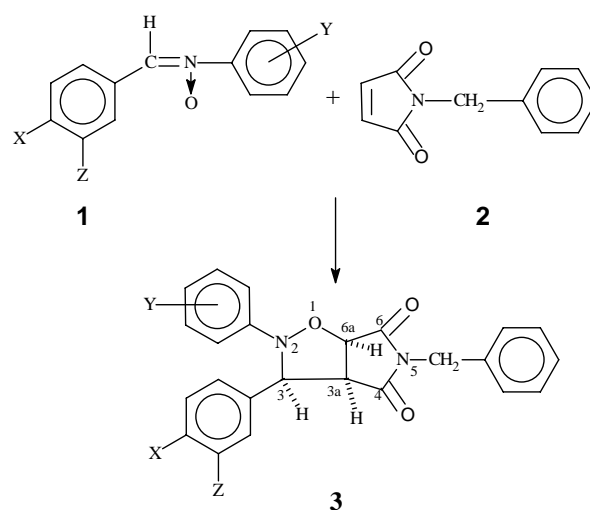
1,3-Dipolar cycloaddition reaction of variously substituted aldonitrones with N-benzyl maleimide leads to the synthesis of substituted 2, 3-diaryl-5-benzyl-2*H*-3, 3a, 4, 5, 6, 6a-hexahydropyrrolo[3, 4-*d*] isoxazole-4, 6-diones in good yield. Structures and stereochemistry of the products have been determined by detailed spectral studies.

**Keywords:** Huisgen reaction, aldonitrones, N-benzyl maleimide, isoxazole diones, stereochemistry

**IPC:** Int.Cl.<sup>7</sup> C 07 D

1, 3-Dipolar cycloaddition reaction provides an excellent method for the synthesis of heterocyclic compounds in good yields<sup>1-3</sup>. Among the plethora of 1, 3-dipoles, nitrones have eched an important place in organic chemistry. The 'Huisgen reaction' of nitrones with olefins has been extensively carried out to obtain isoxazoldines<sup>4</sup>. The cycloaddition reactions of nitrones with various activated double bonds like maleimides<sup>5,6</sup>, cinnamoyl piperidines<sup>7,8</sup> etc. and catalysed with various metals and chiral lewis acids have been reported<sup>10-12</sup>. We report herein our studies on 1, 3-dipolar cycloaddition reactions involving N-benzyl maleimide as the dipolarophile with different aldonitrones. The whole series of reactions gives a detailed study of effect of various substituents on the cycloadditions especially, when phenyl ring moves one atom away from nitrogen atom of imide moiety. For this purpose variously substituted nitrones have been prepared by using variously substituted aldehydes and variously substituted N-hydroxylamines<sup>13,14</sup>.

The cycloaddition reactions of variously substituted nitrones **1** with N-benzyl maleimide **2** have been carried out by refluxing equimolar amounts of both in sodium dried benzene (Ranbaxy). Work-up of the reaction mixture provided the crude product **3** as a single stereoisomer in good yield, which has been recrystallised from hexane-ethyl acetate (3: 1) mixture (**Scheme I**).



**Scheme I**

The cycloadducts **3** have been characterised as *cis*-2, 3-diaryl-5-benzyl-2*H*-3, 3a, 4, 5, 6, 6a-hexahydropyrrolo[3, 4-*d*]isoxazole-4, 6-diones on the basis of their melting points, elemental analysis and spectral (IR, <sup>1</sup>H NMR and mass) data. The physical data for the products **3** are reported in **Table I**.

The IR spectra of **3** display two absorption bands, one is weak to medium in the region 1783-1742 cm<sup>-1</sup> and other is strong in the region 1740-1700 cm<sup>-1</sup> which have been assigned to the carbonyl stretching vibrations of imide moiety. The absorption bands in

**Table I** — Physical data for 2, 5-diaryl-5-benzyl-2*H*-3, 3a, 4, 5, 6, 6a-hexahydropyrrolo[3, 4-*d*]isoxazole-4, 6-diones **3**

Compd	X	Y	Z	Yield (%)	mp °C	Mol. formula	Calcd % (Found)			
							C	H	N	Cl
<b>a</b>	4-OH	H	3-OCH <sub>3</sub>	76	198-200	C <sub>25</sub> H <sub>22</sub> N <sub>2</sub> O <sub>5</sub>	69.56 (69.01)	5.11 (5.01)	6.51 (5.92)	— (—)
<b>b</b>	4-OCH <sub>3</sub>	H	H	78	170-72	C <sub>25</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	72.46 (71.90)	5.31 (5.28)	6.76 (6.51)	— (—)
<b>c</b>	H	H	H	74	160-63	C <sub>24</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>	75.0 (74.8)	5.20 (5.19)	7.29 (7.10)	— (—)
<b>d</b>	4-Cl	H	H	75	165-67	C <sub>24</sub> H <sub>19</sub> N <sub>2</sub> O <sub>3</sub> Cl	68.81 (68.40)	4.54 (4.42)	6.69 (6.58)	8.48 (8.20)
<b>e</b>	4-N(CH <sub>3</sub> ) <sub>2</sub>	H	H	70	196-98	C <sub>26</sub> H <sub>25</sub> N <sub>3</sub> O <sub>3</sub>	73.06 (72.01)	5.85 (5.53)	9.83 (9.41)	— (—)
<b>f</b>	4-OCH <sub>2</sub> -	H	3-OCH <sub>2</sub> -	72	208-10	C <sub>25</sub> H <sub>20</sub> N <sub>2</sub> O <sub>5</sub>	70.09 (69.01)	4.67 (4.51)	6.54 (6.41)	— (—)
<b>g</b>	4-OH	CH <sub>3</sub>	3-OCH <sub>3</sub>	74	206-08	C <sub>26</sub> H <sub>24</sub> N <sub>2</sub> O <sub>5</sub>	70.27 (69.80)	5.40 (5.31)	6.30 (6.27)	— (—)
<b>h</b>	4-OCH <sub>3</sub>	CH <sub>3</sub>	H	72	185-88	C <sub>26</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub>	72.89 (71.82)	5.60 (5.51)	6.54 (6.42)	— (—)
<b>i</b>	H	CH <sub>3</sub>	H	74	172-73	C <sub>25</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub>	75.3 (74.2)	5.52 (5.31)	7.03 (6.89)	8.20 (8.10)
<b>j</b>	4-Cl	CH <sub>3</sub>	H	79	215-17	C <sub>25</sub> H <sub>21</sub> N <sub>2</sub> O <sub>3</sub> Cl	69.36 (68.38)	4.85 (4.69)	6.47 (6.21)	— (—)
<b>k</b>	4-N(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>	H	78	208-10	C <sub>27</sub> H <sub>27</sub> N <sub>3</sub> O <sub>3</sub>	73.46 (72.21)	6.10 (5.89)	9.52 (9.41)	— (—)
<b>l</b>	4-OCH <sub>2</sub> -	CH <sub>3</sub>	3-OCH <sub>2</sub> -	76	205-07	C <sub>26</sub> H <sub>22</sub> N <sub>2</sub> O <sub>5</sub>	70.58 (69.42)	4.97 (4.83)	6.33 (6.21)	— (—)
<b>m</b>	4-OH	-Cl	3-OCH <sub>3</sub>	71	210-12	C <sub>25</sub> H <sub>21</sub> N <sub>2</sub> O <sub>3</sub> Cl	64.58 (63.44)	4.52 (4.41)	6.0 (5.92)	7.64 (7.41)
<b>n</b>	4-OCH <sub>3</sub>	-Cl	H	79	188-90	C <sub>25</sub> H <sub>21</sub> N <sub>2</sub> O <sub>4</sub> Cl	66.88 (66.46)	4.68 (4.54)	6.24 (6.10)	7.91 (7.82)
<b>o</b>	H	-Cl	H	78	180-81	C <sub>24</sub> H <sub>19</sub> N <sub>2</sub> O <sub>3</sub> Cl <sub>2</sub>	68.81 (68.42)	4.54 (4.21)	6.69 (6.48)	8.48 (8.24)
<b>p</b>	4-Cl	-Cl	H	75	196-98	C <sub>24</sub> H <sub>28</sub> N <sub>2</sub> O <sub>3</sub> Cl <sub>2</sub>	63.57 (62.41)	3.97 (3.46)	6.18 (6.02)	15.67 (5.41)
<b>q</b>	4-N(CH <sub>3</sub> ) <sub>2</sub>	-Cl	H	74	206-08	C <sub>24</sub> H <sub>24</sub> N <sub>3</sub> O <sub>3</sub> Cl	67.60 (66.50)	5.20 (8.92)	9.60 (9.11)	8.11 (7.96)
<b>r</b>	4-OCH <sub>2</sub> -	-Cl	3-OCH <sub>2</sub> -	79	212-14	C <sub>25</sub> H <sub>19</sub> N <sub>2</sub> O <sub>5</sub> Cl	64.86 (63.42)	5.20 (5.02)	9.10 (8.92)	7.69 (7.42)

the region 1610-1600 cm<sup>-1</sup> are due to skeletal vibrations of aromatic rings and in the region 1280-1150 cm<sup>-1</sup> have been assigned to nitrogen-oxygen (N-O) stretchings. Absorption band in the region 1485-1350 cm<sup>-1</sup> is of CH<sub>2</sub> bending vibrations of benzyl group. A sharp and medium absorption band in the region 1393-1376 cm<sup>-1</sup>, a weak absorption band at 1372-1349 cm<sup>-1</sup> and two weak absorption bands at

1183-1145 and 1094-1086 cm<sup>-1</sup> have been assigned to carbon-nitrogen (C-N) stretchings.

In the <sup>1</sup>H NMR spectra of *cis*-2-phenyl-3-(3'-methoxy-4'-hydroxyphenyl)-5-benzyl-2*H*-3, 3a, 4, 5, 6, 6a-hexahydropyrrolo[3, 4-*d*]isoxazole-4, 6-dione **3a** show a multiplet signal at δ 7.35-6.57 (equivalent to 13H, Ar-H), a singlet at δ 5.5 (1H, OH), doublet at

$\delta$  5.1 (1H, H<sub>3</sub>) due to coupling with proton H<sub>3a</sub> having coupling constant  $J_{H_3-H_{3a}}=7.89$  Hz. Another doublet at  $\delta$  5.07 (1H, H<sub>3</sub>) due to coupling with proton H<sub>3a</sub> having coupling constant  $J_{H_{6a}-H_{3a}}=8.84$  Hz. A singlet at  $\delta$  4.57 (2H, -CH<sub>2</sub>-) has been assigned to methylene protons of benzyl moiety. <sup>1</sup>H NMR spectra also show a triplet at  $\delta$  3.82 (1H, H<sub>3a</sub>) due to coupling with H<sub>3</sub> and H<sub>6a</sub> having coupling constants  $J_{H_{3a}-H_{6a}}=8.465$ Hz and  $J_{H_{3a}-H_3}=8.469$ Hz respectively. A singlet at  $\delta$  3.6 (3H, -OCH<sub>3</sub>) has been assigned to methoxy group.

The proton H<sub>3</sub> shows a downfield chemical shift as compared to protons H<sub>6a</sub> and H<sub>3a</sub>, because of presence of an electronegative nitrogen atom and aromatic ring adjacent to the carbon to which it is attached. The coupling constants of three protons H<sub>3</sub>, H<sub>3a</sub>, H<sub>6a</sub> are approximately equal (7.9-8.8 Hz) and is a typical of vicinally coupled *cis* protons. Therefore the three protons of isoxazolidinone ring are in *cis*-orientation with one another. From the NOESY – 2D experiment of this compound (**Figure 1**), it is clear that H<sub>3</sub>, H<sub>3a</sub> and H<sub>6a</sub> show coupling with each other and are in *cis*-orientation with each other.

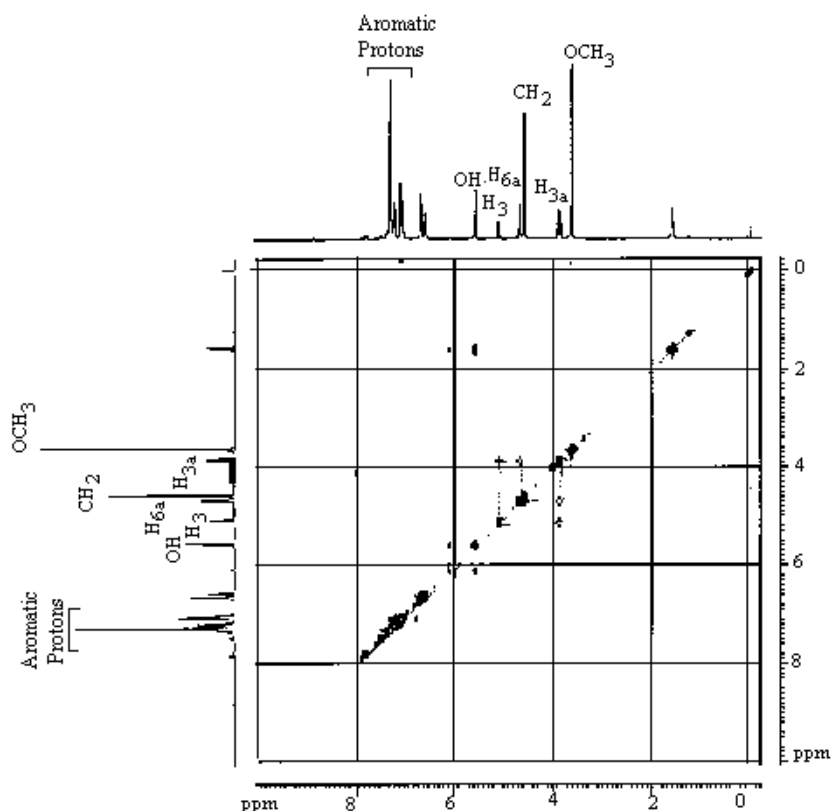
The mass spectrum (70 eV) of **3a** shows the presence of molecular ion peak as the base peak at

$m/z$  430(100). The major fragmentation of the molecular ion occurs through the retrocycloaddition leading to peaks at  $m/z$  243(13.6) and at  $m/z$  187(17.1) of C-(3-methoxy-4-hydroxy)-N-phenylazomethine-N-oxide and N-benzyl maleimide, respectively. On further fragmentation it gives  $m/z$  at 242(8.9), 227(25.7), 226(26.8), 211(6.2), 104(14.0), 151(9.7), 92(6.6), 91(66.9), 77(29.6). The probable mode of fragmentation is given in **Chart I**.

In these dipolar cycloaddition reactions, only single stereoisomer corresponding to *cis*-configuration has been obtained revealing the stereochemistry of the reaction.

At the transition state the preferred approach of dipole and dipolarophile is the one where the  $\pi$ - $\pi$  bonding and steric interactions are minimum between them. It seems that during these 1, 3-dipolar cycloadditions, in the transition state nitrene has the *trans*-orientation where the non-bonded steric interactions are minimum and secondary orbital interactions become dominant.

Therefore, N-aryl ring of nitrene and N-benzyl ring of maleimide become almost parallel to each other in final product. Thus “anti” orientation of nitrene formed predominantly and results in formation of *cis*-isomer as



**Figure 1** — 300 MHz NOESY-2D spectrum of **3a** in CDCl<sub>3</sub>

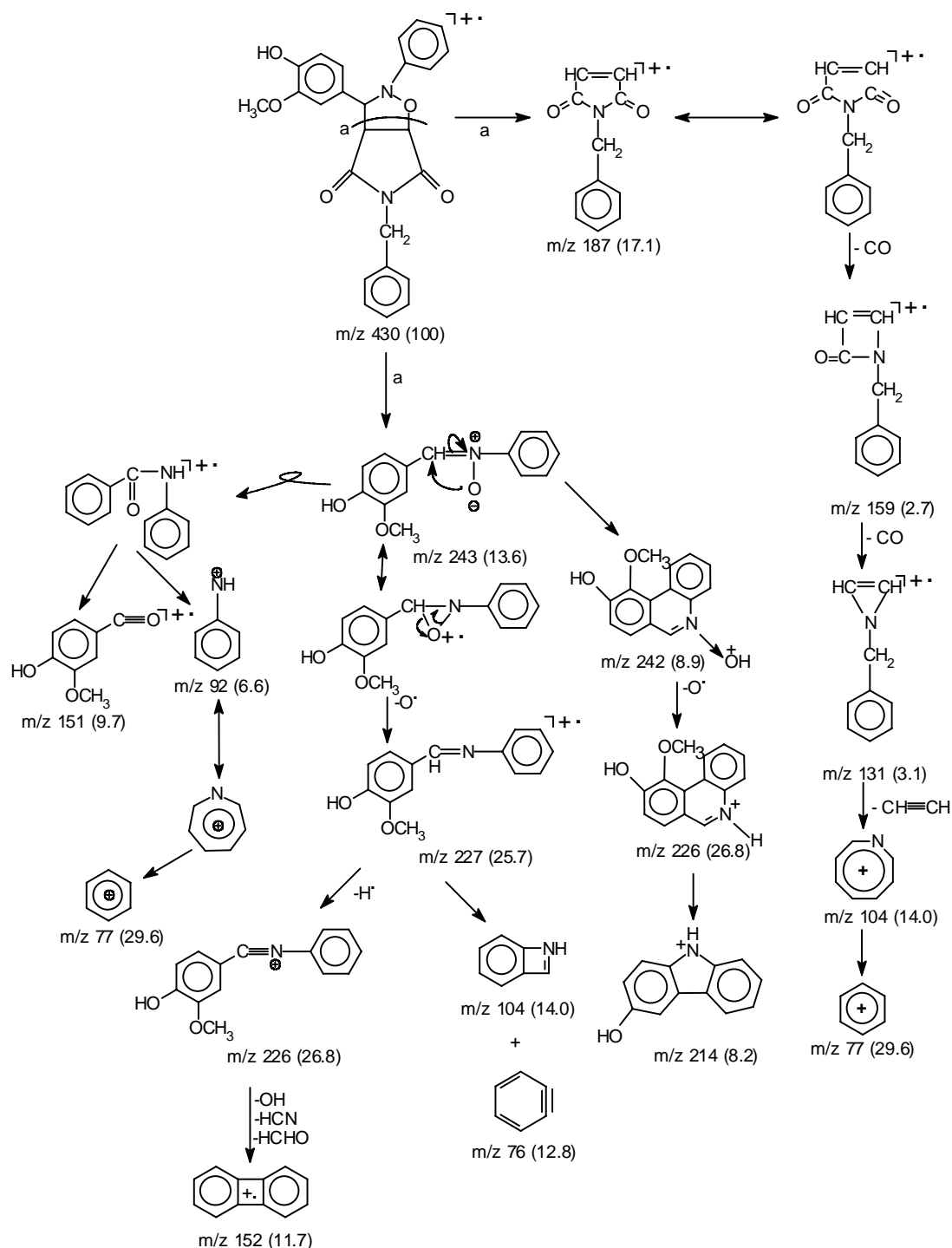


Chart 1

single product, because more secondary stabilisation and least bonding steric interaction occur in this form.

### Experimental Section

Melting points were determined by open-capillary method in paraffin bath and are uncorrected. IR

spectra were recorded in nujol on a Perkin-Elmer spectrum RX-I series FTIR spectrophotometer; and <sup>1</sup>H NMR spectra on a Bruker AC-300F (300MHz) spectrometer using TMS as internal standard (chemical shifts in δ, ppm). The mass spectra were recorded on VG-70-S mass spectrometer by SAIF,

Punjab University, Chandigarh. NOESY experiment have been got recorded from CIL, NIPER, Mohali.

**Synthesis of N-benzyl maleimide 2.** To the solution of maleic anhydride (0.2 mole, 19.6 g) in 75 mL dry chloroform, a solution of benzyl amine (21.4 g, 0.2 mole) in 20 mL of dry chloroform was added slowly, while stirring. The resulting thick paste was filtered to get a white powder of maleanilic acid. To this maleanilic acid was added acetic anhydride (67 ml) and anhydrous sodium acetate (6.5 g) and refluxed for 1 hr. The work-up of reaction mixture provided N-benzyl maleimide in 75% yield. It was recrystallised from pet. ether to get needle like crystals, m.p. 85-88°C (Found: C, 69.08; H, 4.69; N, 8.78. C<sub>11</sub>H<sub>9</sub>O<sub>2</sub>N requires C, 70.58; H, 4.812; N, 7.48%); IR (Nujol): 2946.7-2093.8, 1813.7, 1717.5, 1458.2, 1377.8, 722.8, 696.1, 452.4 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz): δ 7.25 (m, 5H, Ar-H), 6.7 (d, 2H, -CH=CH-), 4.6(s, 2H, -CH<sub>2</sub>-).

**Synthesis of 2-phenyl-3-(3'-methoxy-4'-hydroxyphenyl)-5-benzyl-2H-3,3a,4,5,6,6a-hexahydropyrrolo[3,4-d]isoxazole-4,6-dione 3a.** In a 250 mL round-bottomed flask fitted with a reflux condenser, a mixture of C-(3-methoxy-4-hydroxyphenyl)-N-phenylazomethine N-oxide (2.43 g, 0.01 mole) and N-benzyl maleimide (1.87 g, 0.01 mole) in sodium dried benzene (Ranbaxy) (50 mL) was heated to reflux for 12-18 hr and then cooled under the tap. The crude product that separated out, was filtered and recrystallised from hexane-ethyl acetate (3:1) mixture to get white amorphous powder, m.p. 198-200°C (Found: C, 69.56; H, 5.11; N, 6.51. C<sub>25</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub> requires C, 69.01; H, 5.01; N, 8.95%); IR (Nujol): 3289.2, 2949.5, 2936.2, 1708.8, 1598.5, 1515.3, 1491.9, 1463.7, 1377.8, 1340.1, 1263, 1093.7, 1036.0, 730.0, 693.7, 476.3, 465.7 cm<sup>-1</sup>; <sup>1</sup>H NMR (300MHz): δ 6.57-7.35(13H, Ar-H), 5.5(s, 1H, OH), 5.07(d, 1H,

H-6a,  $J_{H_3-H_{3a}} = 7.95\text{Hz}$ ), 4.66 (d, 1H, H<sub>3</sub>,  $J_{H_{6a}-H_{3a}} = 8.84\text{Hz}$ ), 4.57(s, 2H, -CH<sub>2</sub>-), 3.82(t, 1H, H<sub>3a</sub>,  $J_{H_{3a}-H_{6a}} = 8.465\text{Hz}$  and  $J_{H_{3a}-H_3} = 8.277\text{Hz}$ ), 3.6(s, 3H, -OCH<sub>3</sub>); MS m/z (Relative Intensity): M<sup>+</sup> 430 (100), other prominent ions are at m/z 243 (13.6), 227 (25.7), 226 (26.8), 187 (17.1), 104 (14.0), 77 (29.6).

Compounds **3b-3r** were prepared similarly and their physical data are given in **Table I**.

### Acknowledgement

The authors are grateful to the Head, Department of Chemistry, Punjabi University, Patiala for providing research facilities.

### References

- 1 Torsell K B G, *Nitrile oxides, Nitrones and Nitronates in organic synthesis*, (VCH, New York), **1988**.
- 2 Curran D P, *Advances in cycloadditions*, (Jai Press Inc, Greenwich) Vol.I, **1988** and Vol.II, **1990**.
- 3 Padwa A, *1,3-Dipolar cycloadditions chemistry*, (Wiley-Interscience, New York), Vol.I and Vol.II, **1984**.
- 4 Grunanger P & Vita-Finzi P, *Isoxazoles, Part I-In the Chemistry of heterocyclic compounds*, edited by Tayler E C and Weissberger, (Wiley, New York), **1991**.
- 5 Hamer T & Macaluso A, *Chem Rev*, **64**, **1974**, 473.
- 6 Singal K K, *Synth Commun*, **26** (19), **1996**, 3571.
- 7 Banerji A, Banerji J, Haldar S, Maiti K, Basu S, Prange T & Neumann A, *Indian J Chem*, **37B**, **1998**, 105.
- 8 Jensen K B & Roberson M, *J Org Chem*, **65**, **2000**, 9080.
- 9 Ian S Y & Michael A K, *Org Lett*, **6** (7), **2004**, 139.
- 10 Seiji I, Hiroyusi M & Hisao N, *Tetrahedron*, **58** (41), **2002**, 8281.
- 11 Sibi M P, Ma Z & Jasperde C P, *J Am Chem Soc*, **126**, **2004**, 718.
- 12 Carmona D, Lamata M P, Viguri F, Rodriguez R, Oro L A & Balana A I, *J Am Chem Soc*, **126**, **2004**, 2716.
- 13 Singal K K & Kaur J, *J Indian Council of Chemists*, **17**(3), **2001**, 16.
- 14 Singh N & Krishan K, *J Indian Chem Soc*, **11**(9), **1973**, 884.