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## Studies on the conversion of ketones of heterocyclic spiro compounds having barbituric acid moieties into oxime derivatives

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### Abstract

Five oxime derivatives 7, 11-bis-(4-chlorophenyl)-3-thioxo-2,4-diazaspiro[5,5]undecane-1,5,9-trione-9-oxime (2a), 7,11-bis-(4-methoxyphenyl)-2,4-diazaspiro[5,5]undecane-1,3,5,9-tetraone-9-oxime (2b), 7,11-diphenyl-2,4-diazaspiro[5,5]undecane-1,3,5,9-tetraone-9-oxime (2c), 7,11-bis-(4-methoxyphenyl)-3-thioxo-2,4-diazaspiro[5,5]undecane-1,5,9-trione-9-oxime (2d), 7,11-diphenyl-3-thioxo-2,4-diazaspiro[5,5]undecane-1,5,9-trione-9-oxime (2e) were synthesized from the corresponding 7,11-diaryl-2,4-diazaspiro[5,5]undecane-3-oxo (or thioxo)-1,5,9-triones (1a-e) with hydroxylaminehydrogenchloride in presence of pyrimidine in absolute alcohol. The structures of the compounds 2a-e were confirmed by their UV, IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectral data and elemental analyses.

**Keywords:** Spiro compounds; Oxime derivatives; Barbituric acid; 2-thiobarbituric acid

### Introduction

Conversion of carbonyl functionalities into oximes is an important reaction in organic chemistry. Classically, oximes are prepared (Sandier *et al.*, 1989) by refluxing an alcoholic solution of a carbonyl compound with hydroxylamine hydrochloride and pyridine. Oximes are highly crystalline compounds that find applications not only for protection, but also for purification and characterization of carbonyl compounds (Sandier *et al.*, 1989 and Greene *et al.*, 1999).

They are also useful for selective  $\alpha$ -activation (Whitesell *et al.*, 1983) and are extensively used as intermediates for the preparation of amides by the Beckmann rearrangement (Ramalingan *et al.*, 2007 and Furuya *et al.*, 2005) and fungicides and herbicides (Song *et al.*, 2005). In inorganic chemistry, oximes act as a versatile ligand.

On the other hand, spiro-pyrimidinetriones or pyrimidine-diones having barbituric acid or thiobarbituric acid moieties exhibit chemotherapeutic properties, and have also been found to possess antifungal activity (Bhasker *et al.*, 1992; Abdou *et al.*, 2007; Verma *et al.*, 2008; Birdar *et al.*, 2004 and Dandia *et al.*, 2006). Due to potential bioactivity of such nitrogen containing heterocyclic spiro compounds, research in this field (Levina *et al.* 1960, Bojarski *et al.* 1985) has been become more promising and attractive till todate.

Based on these facts, we decided to evaluate the conversion of ketones of nitrogen containing heterocyclic spiro compounds having barbituric acid and thiobarbituric acid moieties into oxime derivatives in the presence of NH<sub>2</sub>OH·HCl and pyridine under refluxing condition. Product formation was followed by TLC and the spectroscopic data of products were compared to those available in the literature.

### Materials and methods

The UV spectra were run in ethanol using SHIMADZU, UV-160A ultraviolet spectrophotometer. The IR spectra were recorded as KBr pellet using SHIMADZU IR-470 infra-red spectrophotometer in the range of 4000-400 cm<sup>-1</sup>. The <sup>1</sup>H NMR spectra were recorded on a Bruker 400 MHz NMR spectrophotometer. The solvent used was deuterated DMSO. The reactions described in the present paper were carried out primarily following a general procedure (Sandier *et al.*, 1989) and by changing the reaction conditions whenever necessary.

### General Procedure

A mixture of 1g 7,11-diaryl-2, 4-diazaspiro[5,5]undecane-3-oxo (or thioxo)-1,5,9-triones, 1g of hydroxylaminehydrogenchloride, 10 mL of pyrimidine and 10 mL of absolute alcohol was heated under reflux for 8 hours on a oil bath at 110°-115°C. The solvents were removed by evaporation in a

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**Table I. Physical constants and analytical data of the compounds 2a-e**

Compound	m.p. (°C)	Yield %	R <sub>f</sub> value in tlc	Eluting Solvent	% C Found (Calcd)	% H Found (Calcd)	%N Found (Calcd)	Mol. formula	MS (m/z)
2a	244-245	86.0	0.82	CHCl <sub>3</sub> :EtOAc, 1:9	53.83 (54.55)	3.95 (3.71)	9.62 (9.09)	C <sub>21</sub> H <sub>17</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>3</sub> S	461.04
2b	229-230	78.0	0.86	„	62.76 (63.15)	5.32 (5.30)	9.47 (9.61)	C <sub>23</sub> H <sub>23</sub> N <sub>3</sub> O <sub>6</sub>	437.16
2c	246-247	79.0	0.79	„	66.57 (66.83)	5.17 (5.07)	10.87 (11.13)	C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sub>4</sub>	377.14
2d	275-276	68.0	0.64	„	60.91 (60.91)	5.38 (5.11)	9.98 (9.27)	C <sub>23</sub> H <sub>23</sub> N <sub>3</sub> O <sub>5</sub> S	453.14
2e	274-275	75.0	0.78	CHCl <sub>3</sub> :EtOAc, 9:1	63.38 (64.10)	5.13 (4.87)	10.69 (10.68)	C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub> S	393.11

rotatory vacuum evaporator. The mixture was cooled in an ice-bath and 10 mL of cold water was added to it. The mixture was stirred until the crystals appeared. The oxime was recrystallised by using absolute alcohol.

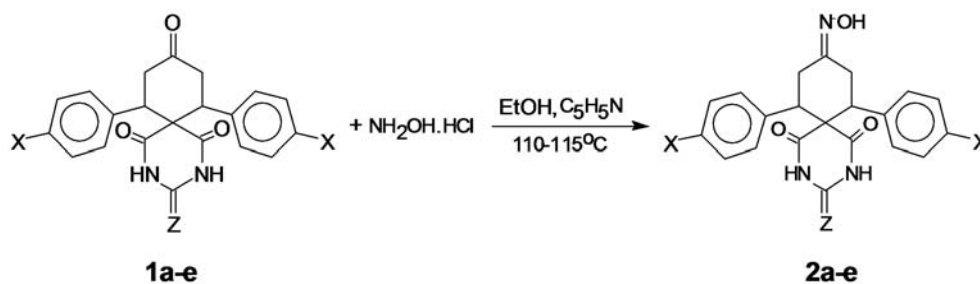
### Results and discussion

7,11-Diaryl-2, 4-diazaspiro[5,5]undecane-3-oxo (or thioxo)-1,5,9-trione-9-oxime 2a-e, were prepared by carrying out reactions of 7,11-diaryl-2,4-diazaspiro[5,5]undecane-3-oxo (or thioxo)-1,5,9-triones (Otto *et. al.*, 1976; Osman *et. al.*, 1996; Ahmed *et. al.*, 2005 and Ahmed *et. al.*, 2011) 1a-e with hydroxylaminehydrogenchloride in pyridine and absolute alcohol following a general experimental procedure based on a known method (Sandier *et. al.*, 1989 and Furniss *et. al.* 1980). The time and temperature of reaction were modified as required. The assignment to the structures of the com-

pounds 2a-e was made on the basis of their UV, IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectral data and elemental analyses.

Compounds 2a-e showed all expected λ<sub>max</sub> values in their UV spectra (Table II) in the range of 276-279 nm due to π→π\* and n→π\* transitions as reported (Bojarski *et. al.*, 1985; Osman *et. al.*, 1996 and Ahmed *et. al.*, 2005) previously. The IR data (Table II) of these compounds showed sharp and broad bands in the range (ν<sub>max</sub>) 3250-3500 cm<sup>-1</sup> for the N-H and N-OH groups. All other typical absorptions for 2a-e correspond well to expected ν<sub>max</sub> values (Bojarski *et. al.*, 1985; Osman *et. al.*, 1996 and Ahmed *et. al.*, 2005)

In their <sup>1</sup>H NMR spectra (Table III) the N-H protons of the compound 2a-e at position 2 and 4 are strongly deshielded (δ 10.47-11.26) since they are flanked by two C=O groups. The non-equivalence of these protons are caused by the



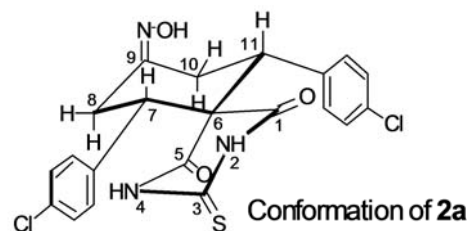
Substituents	2a	2b	2c	2d	2e
X	4-Cl	4-OCH <sub>3</sub>	H	4-OCH <sub>3</sub>	H
Z	S	O	O	S	S

**Table II. IR and UV spectral data of compounds 2a-e**

Compound	IR $\nu_{\max}$ in $\text{cm}^{-1}$					UV, $\lambda_{\max}$ (nm)( $\epsilon$ ) $\pi \rightarrow \pi^*$ & $n \rightarrow \pi^*$ of C=C-C=O
	N-OH, N-H	C=O,C=N	C=C in conj. with C=O	C=C aromatic	N-O	
2a	3300	1695,1660	1590, 1530	1485, 1380, 1180, 1085, 1440, 1360,	965	279 (19792)
2b	3500,3250	1690, 1640	1600, 1500	1180, 1115, 1075, 1485, 1440,	940	276 (1668)
2c	3450, 3250	1680, 1620	1575, 1520	1065, 1440, 1250, 1150, 1180, 1115,	945	279 (9328)
2d	3400,	1640, 1600	1500	1075, 1025, 1425, 1380	965	278 (2308)
2e	3250	1700, 1660	1510	1330, 1150, 1070;1030,	960	279 (1607)

anisotropy of the C-1 and C-5 carbonyl groups owing to the geometry of spiro structures as reported (Bojarski *et. al.*, 1985 and Ahmed *et. al.*, 2005) earlier.

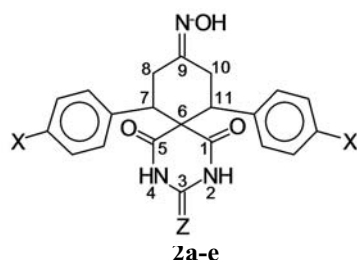
Although axial protons are shielded than equatorial protons the axial protons at positions 7, 8, 10 and 11 are considerably

**Table III.  $^1\text{H}$  NMR spectral data of the compounds 2a-e. [ $\delta$ ] in ppm and (J) in Hz]**

Protons	2a	2b	2c	2d	2e
2-H*	10.48	11.23	11.26	10.65	10.86
4-H*	10.47	11.11	11.10	10.59	10.67
N-OH	10.33	10.55	10.59	10.36	10.60
Aromatic	7.27-7.03	7.00-6.82	7.27-7.08	6.95-6.69	7.35-7.17
7-H <sub>ax</sub> , 11-H <sub>ax</sub>	3.95	3.88	3.89	3.88	4.01
<i>J</i> <sub>aa</sub>	17.60	14.65	14.46	14.31	13.73
<i>J</i> <sub>ae</sub>	4.75	4.88	4.70	4.45	4.41
8-H <sub>ax</sub> , 10-H <sub>ax</sub>	3.57	3.48	3.52	3.40	3.51
<i>J</i> <sub>aa</sub>	14.85	14.65	14.48	14.45	14.50
<i>J</i> <sub>gem</sub>	15.05	15.14	15.14	15.22	14.90
8-H <sub>eq</sub> , 10-H <sub>eq</sub>	2.51	2.40	2.45	2.40	2.50
<i>J</i> <sub>ae</sub>	4.89	4.88	4.78	4.40	4.74
<i>J</i> <sub>gem</sub>	13.45	15.44	15.13	15.40	14.91
X	---	3.68	---	3.70	---
	(4'-C1)	(4'-OCH <sub>3</sub> )	(H)	(4-OCH <sub>3</sub> )	(H)

\*  $\delta$  values of 2-H and 4-H are interchangeable.

deshielded and appeared at  $\delta$  3.40-4.01. The equatorial protons at positions 8 and 10 resonated at higher field ( $\delta$  2.40-2.51) than the axial protons of these positions. This may be explained by the proximity of the axial protons at 7, 8, 10 and 11 positions to the aromatic rings present at positions 7 and 11. The anisotropic effect of C=O on  $H_{eq}$  at C-8 and C-10 is also responsible for diamagnetic shift of these protons.



group by a thiocarbonyl group results in a downfield shift (Otto *et. al.*, 1976 and Ahmed *et. al.*, 2005).

For the compounds 2a-e, the chemical shift values of the carbonyl carbon at position C-9 were found at  $\delta$  154.57-158.85. This value is in good agreement with the literature values (Levy *et. al.*, 1972). The chemical shift values for carbonyl carbon at positions C-1 and C-5 were  $\delta$  167.20-172.53. The non-equivalences of these carbons are caused by the anisotropy of the C-1 and C-5 carbonyl groups owing to the geometry of spiro structures (Bojarski *et. al.*, 1985).

In the compounds 2a-e, the  $\delta$  values (interchangeable) of C-7 and C-11 were observed at 48.06-50.33. The chemical shift values (interchangeable) of C-8 and C-10 of these compounds were found at  $\delta$  32.97-33.67 and 25.86-26.53 respec-

**Table IV.**  $^{13}\text{C}$  NMR spectral data of the compounds 2a-e. [ $\delta$  in ppm]

Compound	9-C	1-C*	5-C	3-C	Aromatic	6-C	7-C*	11-C	8-C*	10-C	X
2a	156.21	168.24	168.31	170.12	138.15, 138.10 133.18, 133.20, 127.15, 126.90	60.18	50.09	48.37	33.17	26.45	---
2b	158.85	172.53	171.05	149.21	154.80, 130.40 129.09, 129.04 114.16	60.29	49.53	48.25	33.24	26.10	55.19
2c	154.57	172.24	170.87	149.04	138.46, 138.40 128.91, 128.17 128.02, 127.98	59.85	50.33	49.05	32.97	25.86	---
2d	158.66	167.20	167.81	169.24	155.44, 131.11 129.21, 113.99 139.15, 139.10	60.15	49.50	48.06	33.20	26.50	55.14
2e	155.21	167.64	167.41	168.93	128.71, 128.15 127.90	59.78	50.19	48.87	33.67	26.53	---

\*  $\delta$  values of 1-C, 7-C and 8-C are interchangeable with 5-C, 11-C and 10-C respectively.

The structures of the compounds 2a-e were further confirmed by their  $^{13}\text{C}$  NMR spectra (Table III). The chemical shift values are in good agreement with those of reported earlier (Ahmed *et. al.*, 2005) for similar compounds. In the compounds 2a-e, chemical shifts of carbonyl carbons at C-3 were found to be at  $\delta$  149.04-170.12 and are deshielded due to the resonance of amide functional group. In the compounds 2a, 2d and 2e, the chemical shifts of thioxo carbon at C-3 were found to be at  $\delta$  168.93-170.12. From the above values it is clear that the replacement of a carbonyl

tively, slightly lower than those of C-7 and C-11. This is due to the effect of =N-OH group which is present next to them.

The  $^{13}\text{C}$  shifts of carbons of aromatic rings are assigned on the basis of the correlation chart of  $^{13}\text{C}$  NMR spectral data available in the literature (Ahmed *et. al.*, 1998). The spiro carbon C-6 of the compounds 2a-e showed chemical shift values at  $\delta$  59.78-60.29 which are similar to the literature values (Levy *et. al.*, 1972). The value for chloro-carbon in the aromatic ring for the compound 2a was observed at  $\delta$  133.18.

The high resolution mass spectra of the compounds 2a-e showed peaks for their respective molecular ions ( $M^+$ ) at m/z 461.04, 437.16, 377.14, 453.14 and 393.11 respectively. The isotopic pattern for dichloro compound 2a was observed in the ratio of 9:6:1. In 2a the peak for  $M^+$  was 461.04 (27%), for  $M^+2$  was 463.02 (17%) and that for  $M^+4$  was 465.01 (3%). From the fragmentation pattern in these spectra it is observed that most of the prominent peaks were formed due to loss of CO, CONH/CSNH, substituted phenyl, tropylium, styryl, methyl, and keten fragments. This is in conformity with the mass spectral fragmentation pattern of those as reported before for 7,11-diphenyl-2,4-diazaspiro[5,5]undecane-1,3,5,9-tetraones (Otto *et. al.*, 1976; Osman *et. al.*, 1996 and Ahmed *et. al.*, 2005).

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