

Mass spectrometry of some arylidene thioxobenzyl or thioxobiphenyloxyethyl thiazolidinone compounds

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Abstract. This paper reports the results of a comparative study of the electron impact mass spectrometry data for a series of previously synthesized 5-arylidene-3-(4-chloro-benzyl)-4-thioxo-thiazolidin-2-one, and 5-arylidene-3-(2-biphenyl-4-yl-2-oxo-ethyl)-4-thioxo-thiazolidin-2-one derivatives. Theoretical calculations of molecular mechanics, MOPAC-AM1, were used to explain the fragmentations observed.

Keywords: Mass spectra, thiazolidinones

1. Introduction

We recently reported the fragmentation routes of other chlorobenzyl imidazolidinedione and fluoro or chlorobenzyl thiazolidinedione compounds [1].

The mass spectrometry in positive- and negative-ion mode has also been reported for a series of 5-arylidene-3-chloro-benzyl-imidazolidine-2,4-dione and thiazolidine-2,4-dione derivatives [2].

Nonsteroidal antiinflammatory drugs (NSAIDs) are the most used in the treatment of inflammatory disease and are among the most widely used drugs. Thiazolidines appear in scientific papers as substances with great biological activity, including anti-inflammatory [3]. The thiazolidinediones (TDZs), also called glitazones or gitazones, are equally known to be insulin sensitizers and have been developed and used clinically as anti-diabetes agents [4]. It is now known that the molecular target of the thiazolidinediones is associated with a nuclear receptor called PPAR γ (peroxisome proliferator-activated receptor) [5,6].

Synthesis of some 5-benzylidene-thioxoimidazolidinones and thioxothiazolidinones substituted at the position 3 by benzyl or phenacyl group, were reported in previous papers [7–10].

This paper reports the results of a study of electron-impact mass spectrometry in positive-ion mode of a series of 5-arylidene-3-(4-chloro-benzyl)-4-thioxo-thiazolidin-2-one and 5-arylidene-3-(2-biphenyl-4-yl-2-oxo-ethyl)-4-thioxo-thiazolidin-2-one derivatives and possible fragmentation routes are outlined.

2. Experimental

The 5-arylidene-3-(4-chloro-benzyl)-4-thioxo-thiazolidin-2-one **1–9** were prepared by reacting thiazolidine-2,4-dione with 4-chloro-benzyl chloride in alkaline conditions. The action of the phosphorus pentasulphure allows 3-(4-chloro-benzyl)-4-thioxo-thiazolidin-2-one to be produced. The condensation of these 3-substituted compounds with benzaldehydes gave the corresponding thiazolidinones [11].

The 5-arylidene-3-(2-biphenyl-4-yl-2-oxo-ethyl)-4-thioxo-thiazolidin-2-one compounds **10–19** were prepared by reacting thiazolidine-2,4-dione with phosphorus pentasulphure followed by condensation with benzaldehydes. The alkylation in position-3 with 2-bromo-1-phenyl-ethanone in alkaline conditions produced the corresponding thiazolidinone compounds [12].

The electron-impact mass spectra are recorded on a R-1010C DELSI-NERMAG mass spectrometer by direct introduction at a nominal electron energy of 70 eV, a source temperature of 205°C and an emission current of 0.150 mA. The samples were volatilized in the source with temperature increasing from 30 to 300°C at the rate of 2°C per second.

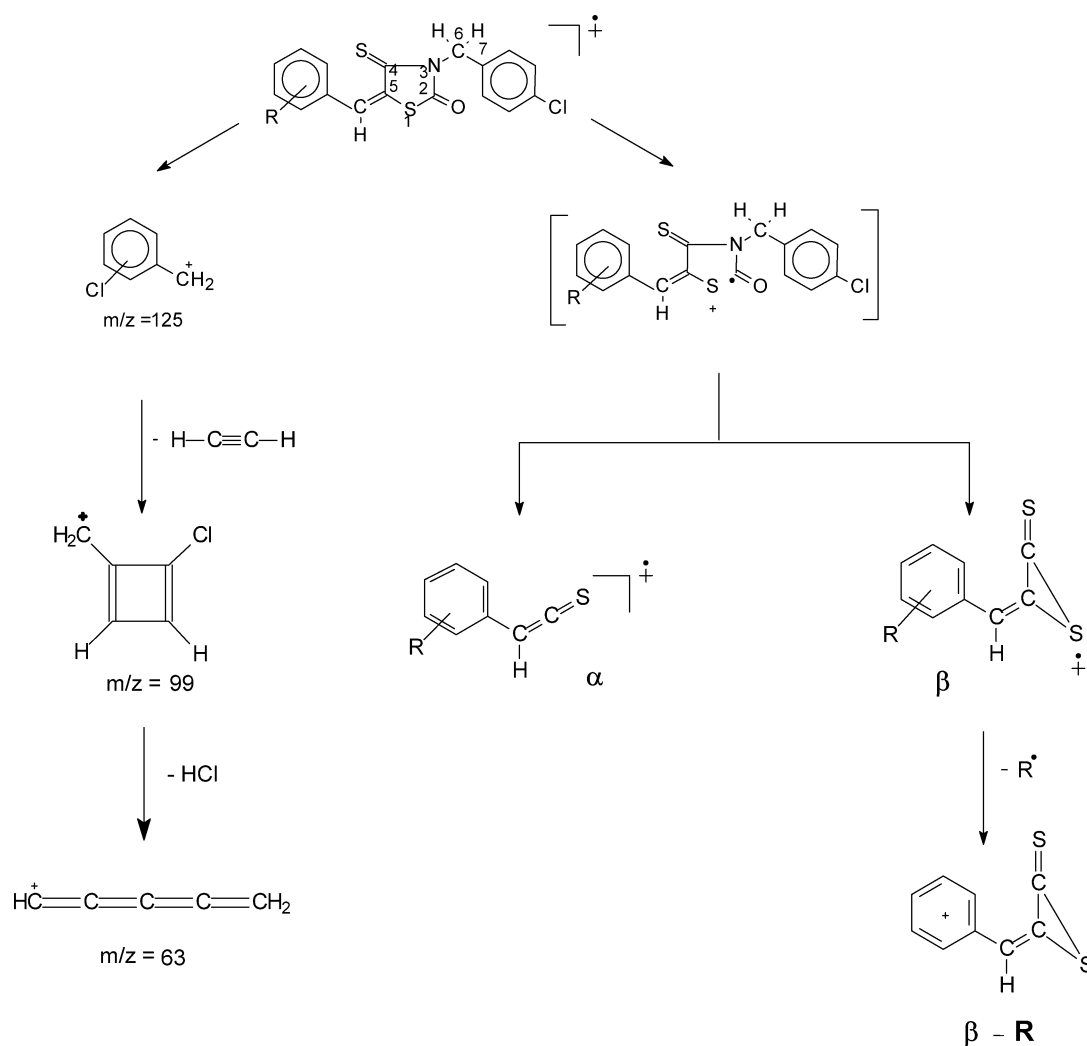
3. Results and discussion

The 5-arylidene-3-(4-chloro-benzyl)-4-thioxo-thiazolidin-2-one derivatives **1–9** show an intense molecular ion peak, with the exception of compounds **2** and **5** which are substituted by fluorine in position-2 M^+ 363 (7.4%) or by chlorine in positions-2,4 M^+ 413 (1.3%). When thiazolidinones have a biphenyloxyethyl radical in position-3 of the heterocyclic ring, the molecular ion peaks are lower than 1% for all the compounds studied.

In every case the principal fragmentation for arylidene thioxobenzyl thiazolidinones **1–9** is the cleavage of the side chain in position-3 producing the ion m/z 125 ($4\text{-ClC}_6\text{H}_4\text{CH}_2^+$) accompanied by the expulsion of HCl and acetylene and leading to the formation of the ions m/z 89, m/z 99 and m/z 63 [2,13]. The other fragmentations of these compounds involve the degradation in heterocyclic ring by way of two important cleavage processes. The first route of the degradation pattern, previously reported by Pitta et al. [2] for some analogous compounds, leads to the α -ion. The second route is formed by the double cleavage of the $N_3\text{--}C_4$ and $S_1\text{--}C_2$ single bonds leading to the β -ion. For these compounds the β -ion loses the substituent of the phenyl ring giving the ions $\beta\text{-R}$. The relative abundance of these fragments are reported in Table 1 and the degradation pattern are summarized in Fig. 1.

In the arylidene thioxobiphenyloxyethyl thiazolidinone compounds **10–19**, reported in Table 2, fragmentations probably leading to the ions α m/z 152 and β m/z 196 (9.8% and 13.3%) were observed for the **17** and **18** compounds, substituted by a fluorine atom in positions *ortho* or *para* in the radical arylidene. These thiazolidinone compounds substituted by thioxobiphenyloxyethyl group in the 3-position of heterocyclic ring, show the ion m/z 181 ($4\text{-C}_6\text{H}_5\text{C}_6\text{H}_4\text{CO}^+$), formed by the cleavage of the $C_6\text{--}C_7$ single bond, as the preferred fragmentation route. The biphenylacylium ion base peak of these compounds loses carbon monoxide to give the ion m/z 153. This fragment follows two specific degradation routes leading to the formation of ions m/z 77 (C_6H_5^+) and ion m/z 127 respectively through loss of an acetylene molecule. The degradation pattern of these compounds are summarized in Fig. 2.

The biphenylacylium ion formed by the rupture of the lateral chain is the base peak for the thiazolidinones **10–19** with the exception of the 3-(2-biphenyl-4-yl-2-oxo-ethyl)-5-(4-fluorobenzylidene)-4-thioxo-thiazolidin-2-one **18** compound which showed a similar base peak, the fragment m/z 152 being formed by the degradation of the side chain or by type α degradation of the thiazolidine ring.

Fig. 1. Schematic representation of the route for the thioxobenzyl arylidene thiazolidinones compounds **1-9**.Table 1
Characteristic peaks for compounds **1-9**

N ^o	R	Ions m/z (I %)				
		M ⁺	m/z 125	α	β	β -R
1	H	345 (100)	83.6	134 (34.3)	178 (38.6)	177 (28.9)
2	2-F	363 (7.4)	100	152 (13.2)	196 (2)	177 (1.1)
3	4-F	363 (90.1)	100	152 (52.3)	196 (25.8)	177 (3.7)
4	4-Cl	379 (65)	100	168 (16.3)	212 (6.6)	177 (40.7)
5	2,4-Cl ₂	413 (1.3)	100	202 (1.8)	246 (0.2)	211 (4.3)
6	4-OCH ₃	375 (100)	64	164 (24.1)	208 (14.9)	177 (33.2)
7	2,4-OCH ₃	405 (20)	100	194 (11.7)	238 (0.6)	207 (7.2)
8	3,4,5-OCH ₃	435 (36)	100	224 (10.6)	268 (2.6)	237 (20.3)
9	2-CH ₃	359 (25.8)	99.7	148 (10.6)	192 (7.5)	177 (20.5)

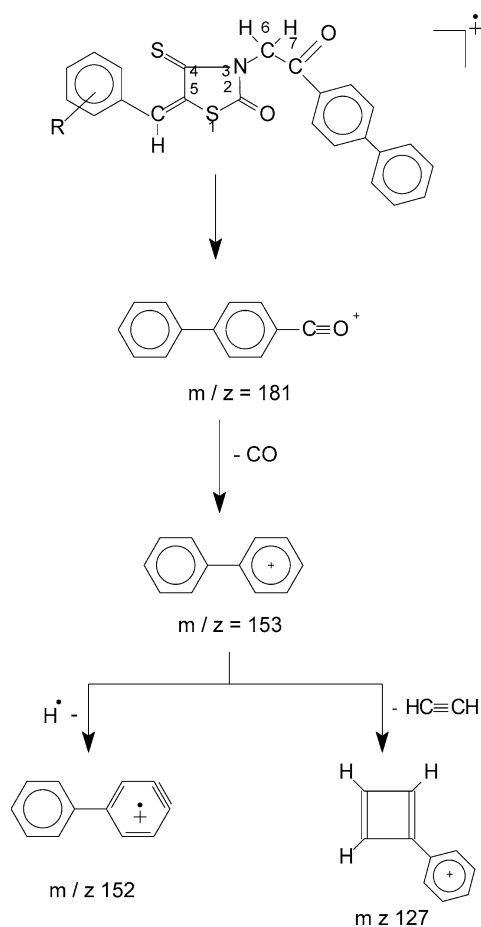


Fig. 2. Schematic representation of the route for the thioxophenylphenacyl arylidene thiazolidinones compounds **10–19**.

Table 2
Characteristic peaks for compounds **10–19**

N°	R	Ions m/z (I %)				
		M^+	m/z 181	m/z 152	m/z 153	m/z 127
10*	H	415 (1.51)	71.9	73.1	79.2	13.5
11**	4-Cl	449 (1)	100	15.9	9.5	2.5
12	2-Cl	449 (0.1)	100	47.4	24	5.9
13	3-Cl	449 (0.11)	100	53.9	28.4	7.4
14	3,4-Cl ₂	483 (0.03)	100	49.4	24	5.7
15	2-Br	493 (0.64)	100	62.2	27.9	10.8
16**	3-Br	493 (0.61)	100	16.8	9.3	1.8
17	2-F	433 (0.55)	100	82.2	35.9	8.8
18	4-F	433 (0.9)	94.7	100	31.1	8.6
19	4-OCH ₃	445 (0.03)	100	54.1	26.6	7.9

* m/z 182 (100%), m/z 153 (79.2%).

**ci NH₃ + isobutane.

Table 3
Charge densities in doublet state of the atoms N₃, C₆ and C₇ for compounds **1–19**

N ^o	N ₃	C ₆	C ₇	N ^o	N ₃	C ₆	C ₇	N ^o	N ₃	C ₆	C ₇
1	-0.260	0.011	-0.174	7	-0.262	0.013	-0.183	13	-0.255	-0.082	0.251
2	-0.260	0.010	-0.173	8	-0.264	0.014	-0.173	14	-0.255	-0.084	0.261
3	-0.260	0.010	-0.173	9	-0.260	0.011	-0.175	15	-0.255	-0.084	0.251
4	-0.260	0.010	-0.173	10	-0.257	-0.082	0.263	16	-0.255	-0.084	0.262
5	-0.260	0.011	-0.172	11	-0.257	-0.082	0.263	17	-0.255	-0.084	0.25
6	-0.261	0.010	-0.177	12	-0.256	-0.083	0.263	18	-0.255	-0.084	0.251
								19	-0.255	-0.084	0.254

A survey using theoretical calculations of molecular mechanics was conducted with the aim of demonstrating the importance of using a combination of experimental and theoretical studies in order to understand and identify the structural characteristics that enable the explanation of the fragmentation mechanism observed in the mass spectrometry.

When fragmentation occurs as a result of electron impact the probability of a bond breaking is related to the strength of the bond, the possibility of low energy transfer and the stability of the neutral and charged fragments formed by the process.

Molecular mechanics was used in this work, with the aid of the Chemoffice (Version 5.0) computer program and ChemDraw Ultra to generate the structures of the compounds and Chem3D Pro for preliminary geometrical optimization. The compounds were optimized using method AM1 of the MOPAC program.

The series of arylidene thioxobenzyl thiazolidinones **1–9** and arylidene thioxobiphenyloxyethyl thiazolidinone compounds **10–19**, were submitted to two types of calculation. Firstly the AM1 method was used, with the keywords: AM1 PRECISE, VECTOR, FORCE, MMOK, Gnorm = 0.5 and the values of the formation heat, bond length and the density of charge of the atoms were recorded for each compound. Shortly afterwards, each of the compounds was submitted to a new calculation using the same procedure mentioned above and the additional keyword: DOUBLET, CHARGE = +1, since, under electron impact, the compounds lose an electron generating the ion cation or the ion-radical.

To solve the problem of configuration around the double bond ethylenic, the two possible Z and S diastereoisomers were treated by the MOPAC program/AM1. For all compounds it was observed that the Z isomer exhibits a formation heat lower than that of the E isomer. These results show that the Z isomer is thermodynamically the stabler. The potential for ionization shows that the Z isomer has a greater capacity to free its electrons, thereby endowing it with greater stability.

With regard to the formation of ions and their fragmentation mechanisms, on electron impact, the values for the charge densities of the atoms (Table 3) and for bond lengths (Table 4) may indicate their mode of formation.

The analysis of the charge density of the atoms N₃, C₆ and C₇ in the side chain situated in position-3 for (Z) arylidene thioxobenzyl thiazolidinones **1–9** compounds shows that cleavage of this side chain giving the ion *m/z* 125 (4-ClC₆H₄CH₂⁺), is justified by the largest concentration of negative charge in the nitrogen atom. In the **1** compound the difference in density of charge between N₃ and C₆ is 0.271 while for C₆ and C₇ it is 0.185. For (Z) arylidene thioxobiphenyloxyethyl thiazolidinone compounds **10–19** observation of the charge density of the atoms N₃, C₆ and C₇ shows that the difference in charge between atoms of the bond N₃C₆ is smaller than that of C₆ C₇ which justifies the rupture around C₆C₇ giving rise to the conjugated system, the ion *m/z* 181 (4-C₆H₅C₆H₄CO⁺). In the **10** compound the difference in density of charge between N₃ and C₆ is 0.175 while for C₆ and C₇ it is 0.345.

Table 4
Bond lengths in doublet state for heterocyclic ring for compounds **1–9**

N°	S ₁ –C ₂	C ₂ –N ₃	N ₃ –C ₄	C ₄ –C ₅	C ₅ –S ₁
1	1.926	1.378	1.399	1.399	1.795
2	1.926	1.378	1.399	1.400	1.795
3	1.926	1.378	1.399	1.400	1.795
4	1.927	1.378	1.399	1.400	1.795
5	1.929	1.379	1.396	1.398	1.801
6	1.927	1.378	1.398	1.398	1.795
7	1.928	1.379	1.397	1.397	1.799
8	1.925	1.378	1.398	1.401	1.798
9	1.927	1.378	1.398	1.400	1.798

The mechanism of the degradation pattern of the heterocyclic ring S₁C₂N₃C₄C₅S₁ for (Z) arylidene thioxobenzyl thiazolidinones **1–9** compounds leading to the formation of either the α - or the β -ion is explained by initial formation of the intermediary by the rupture of the bond S₁C₂ having a greater bond length than S₁C₅ (see Fig. 1). The other bonds form part of a conjugated system. For compounds **10–19** the degradation pattern of the heterocyclic ring does not produce strong intensity fragments.

4. Conclusion

The following generalizations can be drawn from the study of electron impact mass spectra: the degradation process shows the formation of stabilized ion benzylum for arylidene benzylthio thiazolidinones compounds and stabilized ion biphenylacylium for arylidene thioxobiphenyloxyethyl thiazolidinone compounds. The degradation pattern is in concordance of molecular mechanic studies.

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