Molecules **2002**, *7*, 791-800

molecules

ISSN 1420-3049

http://www.mdpi.org

Synthesis and Characterization of some New Mesoionic 1,3-Thiazolium-5-thiolates via Cyclodehydration and *in situ* 1,3-Dipolar Cycloaddition/Cycloreversion

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Received: 25 February 2002; in revised form: 11 November 2002 / Accepted: 14 November 2002 / Published: 30 November 2002

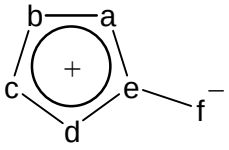
Abstract: The title compounds were synthesized from C-aryl-N-methylglycines by N-aroylation followed by a cyclodehydration to form the corresponding 1,3-oxazolium-5-olates. These were not isolated but converted to the title compounds by an *in situ* 1,3-dipolar cycloaddition/cycloreversion sequence using carbon disulphide. We have studied the cyclodehydration step using acetic anhydride, trifluoroacetic anhydride and 1,3-dicyclohexyl-carbodiimide (DCC) at temperatures not exceding 60°C. Trifluroacetic anhydride proved to be the best reagent, giving a better yield and more easily purified products, although yields were also acceptable with the other two reagents.

Keywords: Mesoionic 1,3-thiazolium-5-thiolates; Synthesis; Characterization.

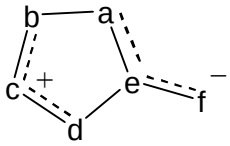
Introduction

Compounds now classified as mesoionic have been known for more than a century [1]. Since that time both the concept of mesoionic compounds and methods for synthesizing them have undergone extensive changes and modifications. Following an important paper by Schönberg [2], Baker and Ollis [3], Ollis and Ramsden [4] and Potts [5] put forward broadly similar definitions of mesoionic compounds. In particular, they stated or implied that they are aromatic. Structure (**1**) corresponds to these definitions.

However Miller, Simas [6] *et al*. indicated that mesoionic compounds are not aromatic although strongly stabilized by π-electron and charge delocalization. They proposed the following definition: "Mesoionic compounds are planar five-membered heterocyclic betaines with at least one side-chain whose α-atom is also in the ring plane and with dipole moments of the order of 5D. The electrons are delocalized over two regions separated by what are essentially single bonds. One region which includes the α-atom of the side-chain is associated with the HOMO and negative π-charge, while the other is associated with the LUMO and positive π-charge". Structure (**2**) corresponds to this definition, where it should be noted that a, b, c, d, e and f are commonly C, N, O, S or Se.



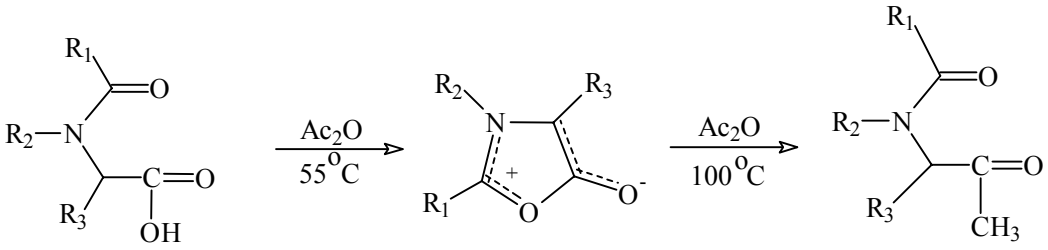
(1)



(2)

Mesoionic 1,3-oxazolium-5-olates [7] and 1,3-thiazolium-5-thiolates [8] are well-known, and there are extensive more recent references and reviews [9]. The munchnones have been conveniently prepared by cyclodehydration of α-acylaminoacids at about 55°C. They are however relatively unstable, especially when they possess a 3-H atom. Their lability is evident if , for example, the cyclo-dehydration reaction temperature is allowed to reach 100°C – ring opening then occurs (see Scheme 1, in which our representation (**3**) of mesoionic compounds is used)**.**

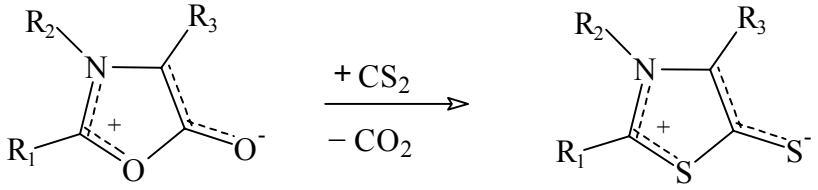
Scheme 1



(3)

The 1,3- thiazolium-5-thiolates (**4**) are conveniently prepared *via* the munchnones (**3**) without isolating them using an *in situ* cycloaddition/cycloreversion sequence with CS_2 (Scheme 2).

Scheme 2



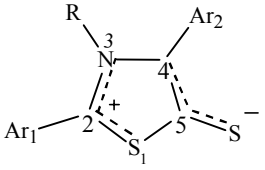
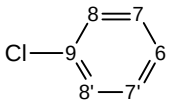
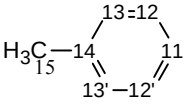
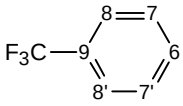
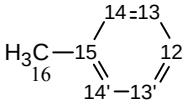
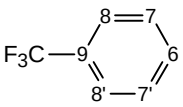
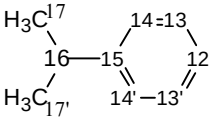
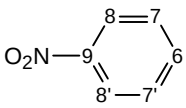
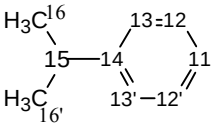
(**3**) (**4**)

Our principal interest in the title compounds relates to their potential for non-linear optics applications and as a source of useful biologically active compounds.

Results and Discussion

We have investigated the preparation of several 1,3-thiazolium-5-thiolates (Table 1), in particular the key cyclodehydration step to form intermediate (not isolated) 1,3-oxazolium-5-olates and have developed a convenient preparative sequence giving good yields of high purity final products.

Table 1: The four new mesoionic 1,3-thiazolium-5-thiolates synthesized

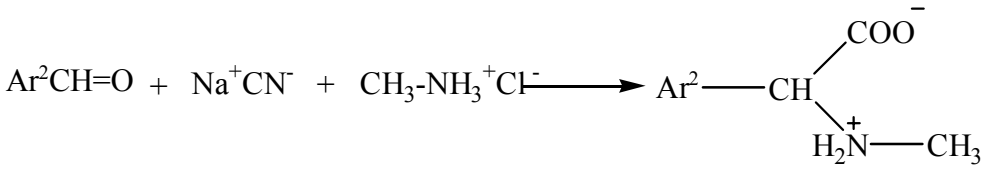
Structure	Mesoionic compounds	R	Ar^1	Ar^2
 (**7**)	**7a**	CH_3		
	7b	CH_3		
	7c	CH_3		
	7d	CH_3		

In the preparation of 2-(*p*-chlorophenyl)-3-methyl-4-(*p*-tolyl)-1,3-thiazolium-5-thiolate (**7a**) we tested three cyclodehydration reagents, *viz.* acetic anhydride, trifluoroacetic anhydride and 1,3-dicyclohexyl-carbodiimide (DCC), requiring a subsequent *in situ* cyclo-addition/cyclo-reversion reaction with CS_2. The yields were 26.1%, 59.7% and 48.0% respectively. In the preparation of the other mesoionic compounds we used only one method in each case (see Experimental Section).

The overall reaction sequence is as follows:

Stage 1 (Scheme 3): A Strecker reaction of aromatic aldehydes with sodium cyanide and methylammonium chloride and posterior hydrolysis gave C-aryl-N-methylglycines (**5**)[10].

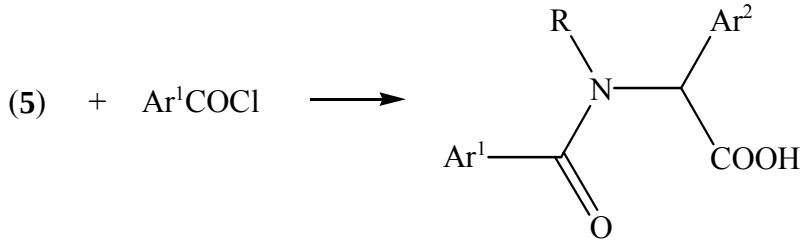
Scheme 3



(**5**)

Stage 2: N-aroylation of C-aryl-N-methylglycines (**5**) (Scheme 4) [11].

Scheme 4

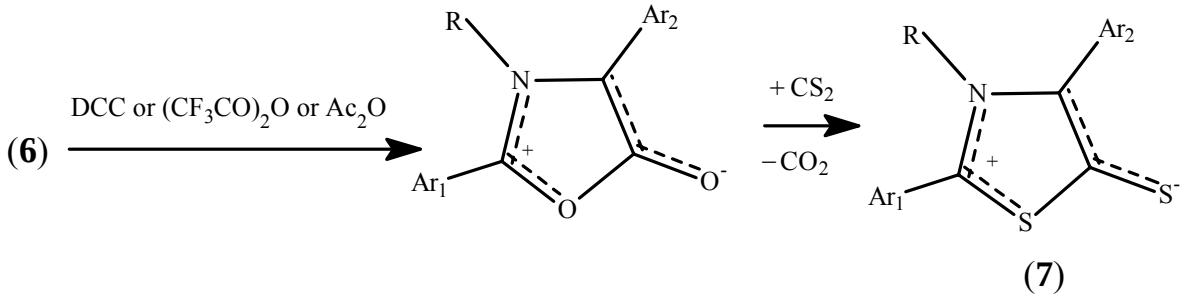


(**6**)

(**6a**)= Ar^1=*p*-Cl-C_6H_4; R= CH_3 and Ar^2=*p*-CH_3-C_6H_4
(**6b**)= Ar^1=*p*-CF_3-C_6H_4; R= CH_3 and Ar^2=*p*-CH_3-C_6H_4
(**6c**)= Ar^1=*p*-CF_3-C_6H_4; R= CH_3 and Ar^2=*p*-$(CH_3)_2CH$-C_6H_4
(**6d**)= Ar^1=*p*-NO_2-C_6H_4; R= CH_3 and Ar^2=*p*-$(CH_3)_2CH$-C_6H_4

Stage 3: Cyclodehydration of N-aroyl-C-aryl-N-methylglycines to form 1,3-oxazolium-5-olates and their *in situ* conversion to the title compounds in a 1,3-dipolar cycloaddition/cycloreversion sequence with carbon disulphide [9].

Scheme 5



Conclusions

We have synthesized four new mesoionic 1,3-thiazolium-5-thiolates (**7a-d**) containing different electron-donating and electron-withdrawing groups. They were obtained via 1,3-oxazolium-5-olates (not isolated) whìch were subjected to an *in situ* 1,3-cycloaddition/cycloreversion sequence with carbon disulphide. Their structures were confirmed by elemental analysis, infrared spectroscopy, mass spectrometry and ^{1}H- and ^{13}C-NMR spectrometry.

Aknowlegements

We are indebted to the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq) and the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES) for financial support.

Experimental

General

Solvents and reagents were purified and dried when necessary. The course of reactions forming mesoionic compounds was monitored by TLC using silica gel G. Hexane/chloroform mixtures were used as eluents. The final products were purified by column chromatograpy using neutral alumina (Merck) and the same eluents used for TLC. Mass spectra were obtained on a Finnigan GCQ Mat quadrupole Ion-Trap Spectrometer. IR spectra were obtained on a Bomen-Michelson IFS 66 spectrometer, using KBr discs. ^{1}H- and ^{13}C-NMR spectra were obtained on a Varian Unity Plus spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C), using TMS as internal reference and DMSO-d_6 or $CDCl_3$ as solvents. Elemental analyses were determined on a Perkin Elmer 240 instrument. Melting points were determined on a platinum plate in a Koffler apparatus coupled with a Carl-Zeiss microscope and are uncorrected.

Synthesis of mesoionic 1,3-thiazolium-5-thiolates (**4**)

Three different reagents were tested for the cyclodehydration step in the conversion of C-*p*-tolyl-N-*p*-chlorobenzoyl-N-methylglycine (**6a**) (see Scheme 4) to 2-(*p*-chlorophenyl)-3-methyl-4-(*p*-tolyl)-1,3-thiazolium-5-thiolate (**7a**) *viz.* acetic anhydride, trifluoroacetic anhydride and 1,3-dicyclohexyl-carbodiimide - followed by reaction with CS_2 (Scheme 5) [9].

Mesoionic 2-(p-chlorophenyl)-3-methyl-4-(p-tolyl)-1,3-thiazolium-5-thiolate (**7a**)

Method 1: C-*p*-tolyl-N-*p*-chlorobenzoyl-N-methylglycine (**6a**) [12] (0.50g, 1.57 mmol) was dissolved in acetic anhydride (15 mL) and maintained at 60°C for one hour. After cooling to ambient temperature, carbon disulphide (10 mL) was added and the red reaction mixture heated under reflux at 60°C for another hour. After evaporation of the solvent, the residue was chromatographed using neutral alumina and eluted with chloroform/hexane. Slow evaporation gave red crystals of the title compound (29.1% yield), with m.p. 188-185°C.

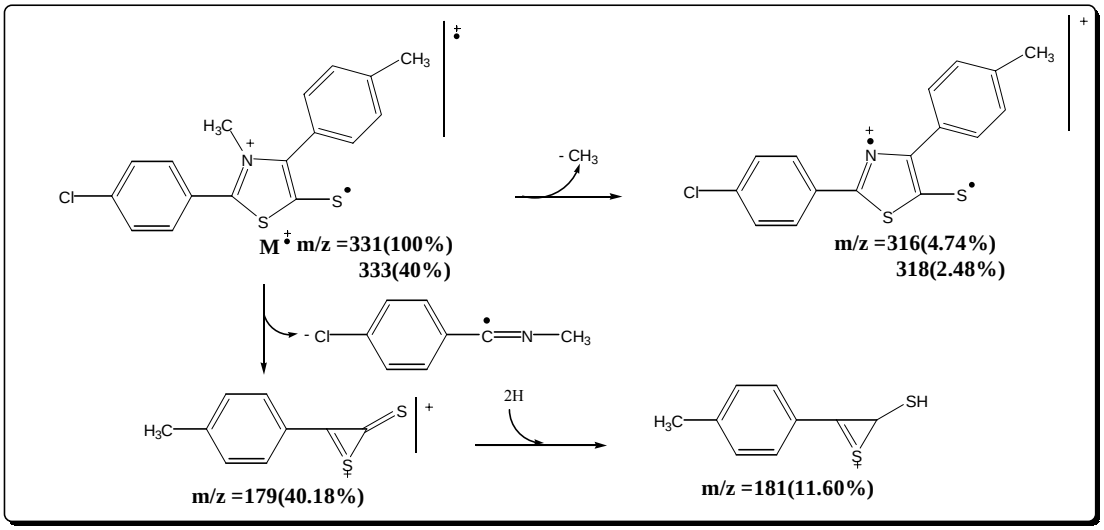
Method 2: C-*p*-tolyl-N-*p*-chlorobenzoyl-N-methylglycine (**6**a) [13] (0.5g, 1.57 mmol) and trifluoro-acetic anhydride (0.33g, 1.57 mmol) in chloroform (20 mL) were refluxed for one hour. After cooling to ambient temperature, carbon disulphide (10 mL) was added and the red reaction mixture refluxed for an additional hour. After evaporation of the solvent, the residue was chromatographed on neutral alumina and eluted with chloroform/hexane. Slow evaporation of the eluate gave the product as red crystals with m.p. 189-191°C (60% yield).

Method 3: C-*p*-tolyl-N-*p*-chlorobenzoyl-N-methylglycine (**6a**) (0.5g, 1.57 mmol) and 1,3-dicyclo-hexylcarbodiimide (DCC, 0.32g, 1.57 mmol) [14] were refluxed in chloroform (20 mL) for one hour. Carbon disulphide (5 mL) was then added forming a red solution which was refluxed for another hour. The solvent was then removed in the rotary evaporator at reduced pressure leaving a red solid. This was washed several times with ethanol in order to remove N,N'-dicyclohexylurea. The residue was chromatographed on neutral alumina and the product eluted with chloroform/hexane was allowed to evaporate slowly. The product was obtained as red crystals in 48% yield and had m.p. 188-190°C.

Elemental analysis, calc. for $C_{17}H_{14}ClNS_2$: C = 61.52; H = 4.25; N = 4.22; S = 19.32%; Found: C = 61.48; H = 4.50; N = 4.15; S = 18.67%; IR (ν cm^{-1}): 3081, 3042 (C_{Ar}-H, str.), 2990, 2920 (C_{Aliph}-H, str.), 1600, 1550, 1483 (C=C_{Ar} str. and C=N mesoionic ring str.), 1433, 1398 (C-H, def. sym. and asym. of $=N^+$-CH_3), 1294 (C-S^- str.), 1268, 1203 (C-H in plane and out-of plane def.), 1091,1018 (C_{Ar}–Cl str.), 831 (C_{Ar}-H, out-of plane def.); Mass spectrum m/z (%) - (see Figure 1): 331 (100), 316 (4.74), 181 (11.66), 179 (40.18); ^{1}H-NMR δ (ppm): 2.35 (s, 3H, H-15), 3.62 (s, 3H, H-10), 7.20-7.58 (m, 8H aromatic: H-7, H-7', H-8, H-8', H-12, H-12', H-13 and H-13'); ^{13}C-NMR δ (ppm): 162.21 (C-5),

152.63 (C-2), 139.45 (C-4), 137.97 (C-6), 130.99 (C-13, C-13'), 130.82 (C-8, C-8'), 129.83 (C-7, C-7'), 129.54 (C-12, C-12'), 126.59 (C-9), 126.15 (C-11), 40.53 (C-10) and 21.40 (C-15).

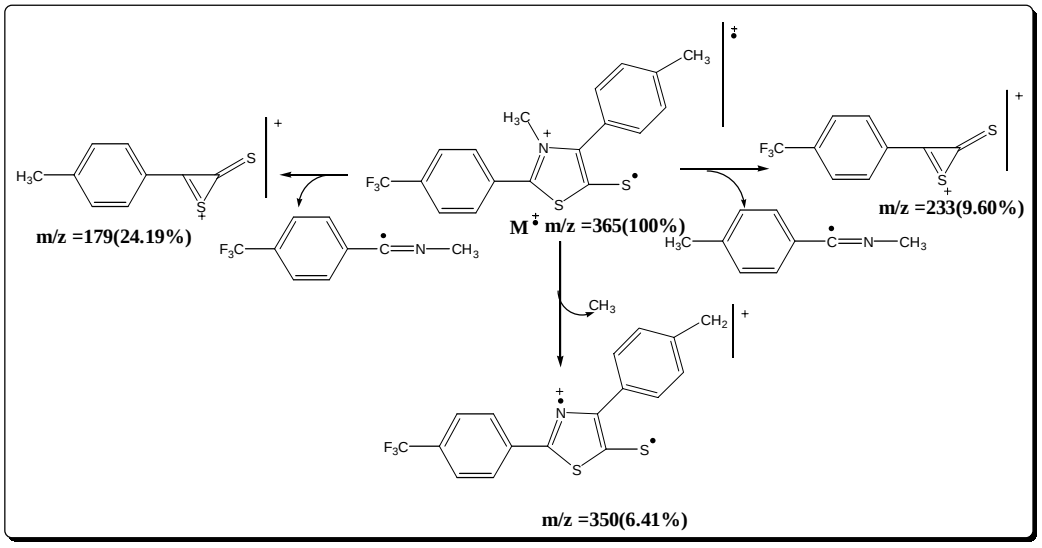
Figure 1 - Fragmentation of **7a**.



Mesoionic 2-(p-trifluorophenyl)-3-methyl-4-(p-tolyl)-1,3-thiazolium-5-thiolate (**7b**)

Prepared from C-*p*-tolyl-N-*p*-trifluorophenyl-N-methylglycine (**6b**) using 1,3-dicyclohexyl-carbodiimide (DCC) as the dehydration agent (Method 3). The reaction furnished 0.360g of the desired product (58.0% yield) with m.p. 203-205°C; Elemental analysis, calc. for $C_{18}H_{14}F_3NS_2$: C = 59.16; H = 3.86; N = 3.83; S = 17.55%; Found: C = 58.78; H = 3.78; N = 4.07; S = 18.01%; IR (ν cm^{-1}): 3030 (C_{Ar}-H, str), 2921, 2850 (C_{Aliph} -H, str.), 1659, 1613, 1600, 1431 (C=C_{Ar} str. and C=N mesoionic ring str.), 1407, 1323 (C-H, def. sym. and asym. of $=N^+$-CH_3), 1295 (C-S^- str.), 1172, 1130 (C-F, str.), 1066, 1016 (C-H in plane and out-of plane def.), 844 (C_{Ar} -H, out-of plane def.); Mass Spectrum m/z (%) - (see Figure 2): 365 (100), 350 (6.45), 233 (9.60), 179 (24.19); ^{1}H-NMR δ (ppm): 2.34 (s, 3H, H-16), 3.65 (s, 3H, H-11), 7.20-7.86 (m, 8H aromatic; H-7, H-7', H-8, H-8', H-13, H-13', H-14 and H-14'); ^{13}C-NMR δ (ppm): 161.70 (C-5), 148.5 (C-2), 142.07 (C-4), 139.50 (C-6), 133.3 (C-9), 131.0 (C-14, C-14'), 130.13 (C-7, C-7'), 129.5 (C-13, C-13'), 126.45 (C-8, C-8'), 120.23 (C-10), 40.57 (C-11) and 21.29 (C-16).

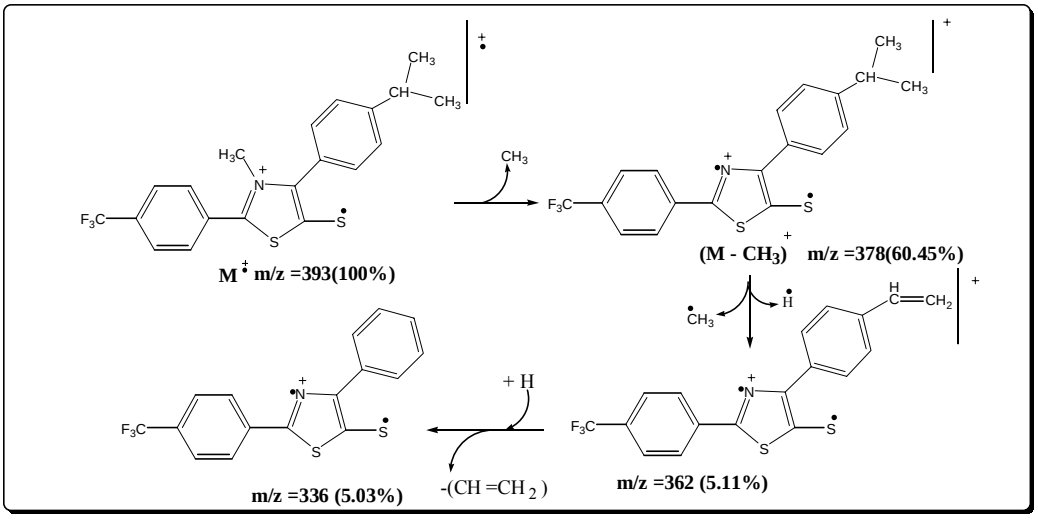
Figure 2 - Fragmentation of **7b**.



Mesoionic 2-(p-trifluorophenyl)-3-methyl-4-(p-isopropylphenyl)-1,3-thiazolium-5-thiolate (**7c**)

Prepared from C-*p*-isopropylphenyl-N-*p*-trifluorophenyl-N-methylglycine (**6c**) with trifluoroacetic anhydride as the dehydrating agent (Method 2). The desired product was obtained in 59.0% yield (0.410g) and had m.p. 199-201°C; Elemental Analysis, calc. for $C_{19}H_{15}F_3NS_2$: C =61.05; H=4.61; N =3.56; S = 16.30%; Found: C = 61.26; H = 4.94; N=3.57; S = 15.99%; IR (ν cm^{-1}): 3100, 3050 (C_{Ar}-H, str), 2963, 2873 (C_{Aliph} -H, str.), 1612-1550 (C=C_{Ar} str. and C=N mesoionic ring str.), 1434, 1390 (C-H, def. sym. and asym. of $=N^{+}$-CH_3), 1291 (C-S^{-} str), 1170, 1132 (C-F, str.), 1039, 1018 (C-H in plane and out-of plane def.) and 839 (C_{Ar} -H, out-of plane def.); Mass spectrum m/z (%) - (see Figure 3): 393 (100), 378 (60.45), 362 (5.11), 336 (5.03);

Figure 3 - Fragmentation of **7c**.

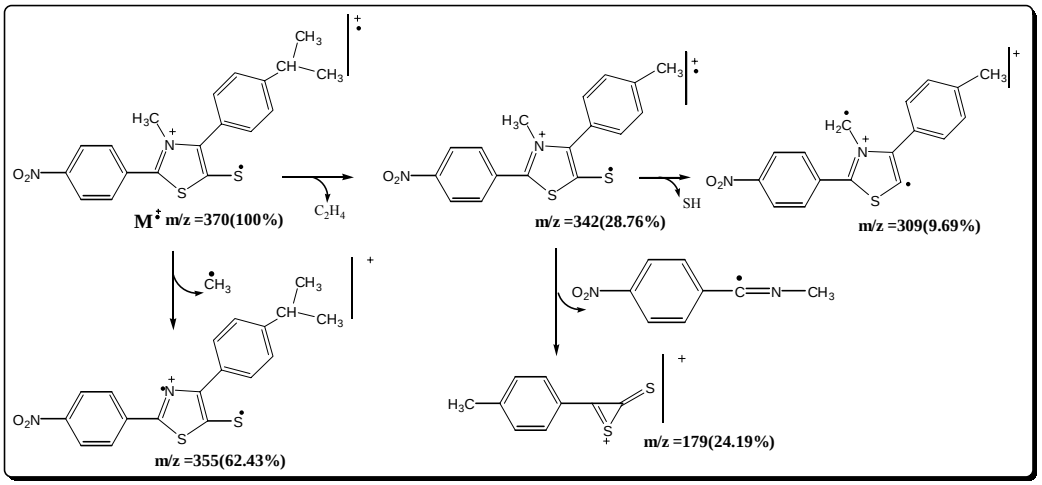


^{1}H-NMR δ (ppm): 1.20-1.39 (d, 6H, H-17, H-17'), 2.81-2.95 (m, 1H, H-16), 3.63 (s, 3H, H-11), 7.23-7.76 (m, 8H aromatic, H-7, H-7', H-8, H-8', H-13, H-13', H-14 and H-14'); ^{13}C-NMR δ (ppm): 162 (C-5); 151.42 (C-2); 150.06 (C-15); 142.17(C-4); 132.50 (C-6); 131.06 (C-7, C-7'); 130.29 (C-12); 130.10(C-14, C-14'); 126.89 (C-13, C-13'); 126.79 (C-9); 126.34 (C-8, C-8'); 120.52 (C-10); 40.66 (C-11); 33.90 (C-16) and 23.66 (C-17, C-17').

Mesoionic 2-(p-nitrophenyl)-3-methyl-4-(p-isopropylphenyl)-1,3-thiazolium-5-thiolate (**7d**)

Prepared from C-*p*-isopropylphenyl-N-*p*-nitrobenzoyl-N-methylglycine (**6d**) using acetic anhydride as the dehydrating agent (Method 1). The desired product was obtained as violet crystals in 38.6% yield (0.410g) and had m.p. 211-214°C; Elemental analysis, calc. for $C_{19}H_{18}N_2O_2S_2$: C = 61.59; H = 4.90; N = 7.56, S = 17.31%; Found: C = 61.33; H = 4.71; N = 7.77; S = 16.98%; IR (ν cm^{-1}): 3016 (C_{Ar}-H, str), 2961, 2925 (C_{Aliph} -H, str.), 1600-1597 (C=C_{Ar} str. and C=N mesoionic ring str.), 1518, 1342 (N-O, NO_2 group sym. and asym str.), 1401, 1433 (C-H, =N^+-CH_3 sym. and asym. def.), 1282 (C-S^- str.) and 1102, 1058, 751 (C_{Ar} -H, in plane and out-of plane def.); Mass spectrum m/z (%) - (see Figure 4): 370 (100), 355 (62.43), 342 (28.76), 309 (9.69), 179 (5.34); ^{1}H-NMR δ (ppm): 1.19-1.22 (d, 6H, H-16, H-16'), 2.85-2.97 (m, 1H, H-15), 3.71 (s, 3H, H-10), 7.24-8.35 (m, 8H aromatic: H-7, H-7', H-8, H-8', H-12, H-12', H-13, H-13'); ^{13}C-NMR δ (ppm): 164.8 (C-5), 152.48 (C-2), 150.81 (C-14), 149.0 (C-9), 148.99 (C-6), 132.51 (C-11), 131.13 (C-12, C-12'), 130.95 (C-13, C- 13'), 127.04 (C-8, C-8'), 124.56 (C-7, C-7'), 41.09 (C-10), 33.94 (C-15) and 23.67 (C-16, C-16').

Figure 4 - Fragmentation of **7d**.



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Sample Availability: Not available

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