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

Bruno Freitas Lira\textsuperscript{1,3}, Petrônio Filgueiras de Athayde Filho\textsuperscript{2,4}, Joseph Miller\textsuperscript{1,2,3,*}, Alfredo Mayall Simas\textsuperscript{3}, Aderson de Farias Dias\textsuperscript{1,†} and Maria Joaquina Vieira\textsuperscript{2}

\textsuperscript{1} Laboratório de Tecnologia Farmacêutica and \textsuperscript{2} Departamento de Química, Universidade Federal da Paraíba, 58.051-970, João Pessoa-PB, Brasil; \textsuperscript{†}e-mail: haderson@ltf.ufpb.br

\textsuperscript{3} Departamento de Química Fundamental, Universidade Federal de Pernambuco, 50.670-901, Recife-PE, Brasil.

\textsuperscript{4} Universidade Federal da Paraíba, Departamento de Ciências Básicas Sociais, 58.220-000, Bananeiras-PB, Brasil.

*Author to whom correspondence should be addressed; e-mail: millerjo@ltf.ufpb.br

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

\textbf{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-dicyclohexylcarbodiimide (DCC) at temperatures not exceeding 60°C. Trifluoroacetic 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.

\textbf{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.

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 munchrones 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 cyclodehydration 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
The 1,3-thiazolium-5-thiolates (4) are conveniently prepared via the munchrones (3) without isolating them using an *in situ* cycloaddition/cycloreversion sequence with CS$_2$ (Scheme 2).

**Scheme 2**

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$^2$ |
|-----------|---------------------|---|--------|--------|
| ![Structure](image) | ![Mesoionic](image) | CH$_3$ | Cl$_9$ | H$_3$C$_{15}$ |
| ![Structure](image) | ![Mesoionic](image) | CH$_3$ | F$_3$C$_{16}$ | H$_3$C$_{16}$ |
| ![Structure](image) | ![Mesoionic](image) | CH$_3$ | O$_2$N$_9$ | H$_3$C$_{16}$ |

(7)
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].

\[
\begin{align*}
\text{Ar}_2\text{CH}=\text{O} + \text{Na}^+\text{CN}^- + \text{CH}_3\text{NH}_3^+\text{Cl}^- & \rightarrow \text{Ar}_2\text{CH}\text{CH}_2\text{COOCH}_3 \\
\end{align*}
\]

(5)

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

\[
\begin{align*}
(5) + \text{Ar}^1\text{COCl} & \rightarrow \text{Ar}^1\text{NHAr}^2\text{COOH} \\
(6a)= \text{Ar}^1=p-\text{Cl-C}_6\text{H}_4; \text{R}=\text{CH}_3 \text{ and } \text{Ar}^2=p-\text{CH}_3\text{C}_6\text{H}_4 \\
(6b)= \text{Ar}^1=p-\text{CF}_3\text{C}_6\text{H}_4; \text{R}=\text{CH}_3 \text{ and } \text{Ar}^2=p-\text{CH}_3\text{C}_6\text{H}_4 \\
(6c)= \text{Ar}^1=p-\text{CF}_3\text{C}_6\text{H}_4; \text{R}=\text{CH}_3 \text{ and } \text{Ar}^2=p-(\text{CH}_3)_2\text{CH-C}_6\text{H}_4 \\
(6d)= \text{Ar}^1=p-\text{NO}_2\text{C}_6\text{H}_4; \text{R}=\text{CH}_3 \text{ and } \text{Ar}^2=p-(\text{CH}_3)_2\text{CH-C}_6\text{H}_4
\end{align*}
\]

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].
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) which 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.

Aknowledegements

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 chromatography 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.
Three different reagents were tested for the cyclodehydration step in the conversion of C-p-tolyl-N-p-chlorobenzoxy-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-dicyclohexylcarbodiimide - followed by reaction with CS₂ (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-chlorobenzoxy-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-chlorobenzoxy-N-methylglycine (6a) [13] (0.5g, 1.57 mmol) and trifluoroacetic 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-chlorobenzoxy-N-methylglycine (6a) (0.5g, 1.57 mmol) and 1,3-dicyclohexylcarbodiimide (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 C₁₇H₁₄ClN₂S₂: 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 (CAliph-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+-CH₃), 1294 (C-S’ str.), 1268, 1203 (C-H in plane and out-of plane def.), 1091,1018 (CAr–Cl str.), 831 (CAr -H, out-of plane def.); Mass spectrum m/z (%) - (see Figure 1): 331 (100), 316 (4.74), 181 (11.66), 179 (40.18); ¹H-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’); ¹³C-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.

![Fragmentation Diagram]

**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_{3}NS_{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 (v cm\(^{-1}\)) : 3030 (C\textsubscript{Ar}-H, str.), 2921, 2850 (C\textsubscript{Aliph}-H, str.), 1659, 1613, 1600, 1431 (C=C\textsubscript{Ar} str. and C=N mesoionic ring str.), 1407, 1323 (C-H, def. sym. and asym. of =N\textsuperscript{+}-CH\textsubscript{3}), 1295 (C-S’ str.), 1172, 1130 (C-F, str.), 1066, 1016 (C-H in plane and out-of plane def.), 844 (C\textsubscript{Ar} -H, out-of plane def.); Mass Spectrum m/z (%) - (see Figure 2): 365 (100), 350 (6.45), 233 (9.60), 179 (24.19); \textsuperscript{1}H-NMR \(\delta\) (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, H-14’); \textsuperscript{13}C-NMR \(\delta\) (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.

![Diagram](image)

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 C₁₉H₁₅F₃NS₂: 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=Ar str. and C=N mesoionic ring str.), 1434, 1390 (C-H, def. sym. and asym. of =N⁺-CH₃), 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.

![Diagram](image)
$^1$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$_2$O$_2$S$_2$: 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.

References

1. Fischer, E.; Besthorn, E. Über die Hydrazinverbindungen. Ann, 1882, 212, 316-339.
2. Schönberg, A. Constitution and isomerism of certain triazole derivatives of the nitrone type in the light of the Bredt rule and the theory of resonance. J. Chem. Soc. 1938, 824-5.
3. Baker, W.; Ollis, W.D. Mesoionic Compounds. *Quart. Rev.* **1957**, *11*, 15-29.

4. Ollis, W. D.; Ramsden, C. A. Mesoionic Compounds. *Adv. Hetero Cycl. Chem.* **1976**, *19*, 3-122

5. Potts, K. T. Mesoionic ring systems, heterocycles of theoretical interest and synthetic potential. *Lect. Hetero Cycl. Chem.* **1978**, *4*, 35-46.

6. Oliveira, M. B.; Miller, J.; Pereira, A. B.; Galembeck, S. E.; Moura G. L. C.; Simas, A. M. Mesoionic 2-N-cycloalkyl-1,3-dithiolium-4-thiolates. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1996**, *108*, 75-84.

7. Huisgen, R. Cycloaddition Reactions of Mesoionic Aromatic Compounds. *Chem. Soc. Spec. Publ.*, **1967**, *21*, 51-73.

8. Huisgen, R.; Funke, E.; Schaefer, F. C.; Gotthaerdt, H.; Brunn, E. Cycloadditions of mesoionic 5-oxazolone to some hetero-multiple bonds. *Tetrahedron Lett.* **1967**, *19*, 1809-1814.

9. (a) Newton, C. G.; Ramsden, C. A. Mesoionic heterocycles (1976–1980), *Tetrahedron* **1982**, *38* (20), 2964-3084; (b) Barrett, G. C. The chemistry of 1,3-thiazolinone hydroxy-1,3-thiazole systems, *Tetrahedron* **1980**, *36*, 2023-2058; (c) Ollis, W. D.; Stanforth, S. P. *Tetrahedron* **1985**, *41*, 2239-2329

10. Bayer, H. O.; Huisgen, R.; Knorr, R.; Schaefer, F.C. Preparation and properties of mesoionic oxazolones. *Chem Ber.* **1970**, *103*, 2581-2597

11. Edward, J. T.; Sheffler, R. H. Preparation of Mesoionic Dipyrido[1,2-a:b’1’,2’-c]imidazolium-11-thiolates from the Binz-Marx Reaction. *J. Org. Chem.* **1985**, *50*, 4855-4861

12. (a) Knorr, B.R.; Huisgen, R. Mechanism of the Dakin-West reaction. I. Reaction of secondary N-acylamino acids with acetic anhydride. *Chem Ber.* **1970**, *103*(8), 2598-2610; (b) Potts, K. T.; Choundhury, D. R. Mesoionic Compounds. 43. Ring Annalation Utilizing the Isomeric anhydro-2- and 3-Hydroxythiazolo[2,3-b]benzothiazolium Hydroxide Mesoionic Systems, *J. Org. Chem.* **1978**, *43*, 2697-2700

13. Clerin, D.; Meyer, B.; Fleury, J. P.; Fritz, H. Mesoionic trifluoroacetylated 5-imino oxazolines: a re-examination of the structure using $^{13}$C NMR spectroscopy and cycloaddition reactions, *Tetrahedron* **1976**, *32*, 1055-1059

14. (a) Potts, K. T., Chen, S. J.; Szmuszkovicz, J. Anhydro-2-Mercaptothiazolo[3,2-f]-phenanthridinium hydroxide, a mesoionic thiazole ring system containing exocyclic sulfur, *J. Org. Chem.* **1977**, *42*, 2525-2526; (b) see also ref. 8.

**Sample Availability:** Not available

© 2002 by MDPI (http://www.mdpi.org). Reproduction is permitted for noncommercial purposes.