A General Synthesis of Ring-Fused Mesoionic Thiazolines from 2,2-Dicyanooxiranes under Neutral Conditions

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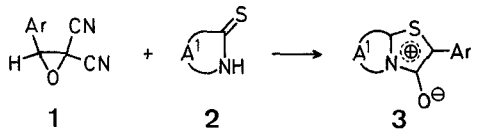
The particular structure of mesoionic derivatives gives these compounds interesting properties which have been investigated recently[1-4]. Among these properties, the ability to undergo [1,3]dipolar cycloadditions and, in the series of mesoionic thiazolones, the possibility to prepare β-lactams by desulphurisation[5,6] are worthy of notice.

In consequence, it seemed of interest to prepare some condensed mesoionic thiazolones (anhydro-4-hydroxythiazolium hydroxides) because their desulphurisation could be applicable in the total syntheses of penicillins, cephalosporins, or related compounds. We have already described a simple and general synthetic route to mesoionic thiazolones under neutral conditions[7,8]. We now show that this method can be extended to the synthesis of condensed mesoionic thiazolones. Several synthetic routes to such derivatives were unsuccessful[9], or the proposed methods are limited to particular cases[10-13]. However, an interesting synthetic route to various ring-fused mesoionic thiazolones has been described[14,15]. According to this method, an α-bromoacetyl chloride reacts with the appropriate cyclic thioamide in the presence of acetic anhydride/triethylamine to give the corresponding mesoionic thiazolone. In some cases, however, the acetyl chloride reacts with the mesoionic derivative or the thioamide can be oxidised[15].

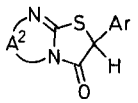
Good yields of the condensed mesoionic thiazolones **3** are obtained by simply reacting stoichiometric quantities of 2,2-dicyanooxiranes[8] **1** with the cyclic thioamides **2** (Scheme **A**, Table 1).



1 **2** **3**

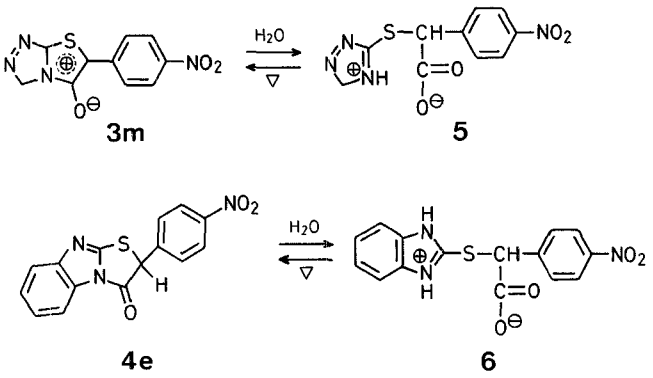
Scheme **A**

In contrast with other methods[9,15], this reaction can be applied to the synthesis of condensed mesoionic thiazolones with a second aromatic or heteroaromatic ring (compounds **3a-g**, Table 1). As expected[2,7,8], when the mesoionic thiazolones **3** have an acidic hydrogen atom α to the carbon located between the sulphur and the nitrogen, this hydrogen migrates onto the carbon bearing the aryl group to give the tautomeric imidazothiazoles **4** (Table 2).



4a-e

Some condensed mesoionic thiazolones have been shown to hydrolyse easily[15]. We have also observed a rapid hydrolysis of the mesoionic compound **3m** or the benzimidazothiazole **4e**, which are only obtained in good yields when the reaction is run in an anhydrous medium. When using wet solvents, we have only isolated and characterised the corresponding betaines **5** and **6**. It is of interest to note the reversibility of this reaction. We have shown that a simple thermolysis of the betaines **5** and **6** in anhydrous tetrahydrofuran gives back the compounds **3m** and **4e** (Scheme **B**).



3m **5**

4e **6**

Scheme **B**

In conclusion, all of the cyclic thiocarbamoyl compounds **2** that we have reacted with 2,2-dicyanooxiranes **1** have led to condensed mesoionic thiazolones **3** or their tautomeric forms **4** and the scope of this reaction seems to be only limited by the accessibility of oxiranes **1**. Studies on the synthesis of variously substituted 2,2-dicyanooxiranes are under way in our laboratory.

The 2,2-dicyanooxiranes **1** used were prepared according to Ref.[8] and 4-ethoxycarbonyl-5-methyl-2-thioxothiazoline according to Ref.[19]; the other cyclic thioamides **2** are commercial reagents.

Ring-Fused Mesoionic Thiazolines 3; General Procedures:

Method A: A mixture of the 2,2-dicyanooxirane **1** (10 mmol) and the cyclic thiocarbamoyl compound **2** (10 mmol) is dissolved in acetone (40 ml). After 24 h at room temperature, the intermediate oxathiole[8] is filtered, dried, and then heated at 180 °C for 20 min (oil bath) to give the mesoionic thiazolone **3**, which is washed with hot acetone (2 × 20 ml) or recrystallised from ethanol or acetone when it is sufficiently soluble.

Method B: The 2,2-dicyanooxirane **1** (10 mmol) and the thiocarbamoyl compound **2** (10 mmol) are heated at 150–180 °C for 10–30 min (oil bath). The mixture is then dissolved in acetone (10 ml) and the mesoionic compound **3** precipitates on addition of ether. It is then washed with hot acetone (2 × 20 ml) when it is not sufficiently soluble in various solvents.

Method C: A mixture of the 2,2-dicyanooxirane **1** (10 mmol) and the thiocarbamoyl compound **2** is dissolved in solvent (80 ml). After 20 h to 140 h (Tables 1 and 2) at room temperature, the precipitate is separated by filtration and recrystallised from ethanol or washed with hot acetone (2 × 20 ml) when it is not sufficiently soluble.

Betaine 5:

The mesoionic thiazolone **3m** (295 mg, 1 mmol) is heated under reflux for 1 h in a mixture of tetrahydrofuran (20 ml) and water (10 ml). The betaine **5** is obtained after evaporation of the solvent and recrystallisation from ethanol; yield: 0.250 g (80%); m.p. 172 °C.

$C_{10}H_8N_4O_4S$	calc.	C 42.86	H 2.86	N 20.00	S 11.43
(280.2)	found	42.95	2.80	19.83	11.42

I.R. (Nujol)[18]: ν = 3100–2000; 1604, 1595 cm^{-1}.

^{1}H-N.M.R. (CD_3COCD_3): δ = 4.47 (s, 2 H); 7.89 (m, 4 H); 8.31 ppm (s, 1 H).

Heating of betaine **5** (1 mmol) in anhydrous tetrahydrofuran (40 ml) for 20 h gives mesoionic thiazolone **3m** after evaporation of the solvent and recrystallisation from ethanol.

Betaine 6:

The benzimidazolo[1,2-*b*]thiazolone **4e** (329 mg, 1 mmol) is dissolved in a mixture of acetone (60 ml) and water (25 ml). After 48 h, the be-

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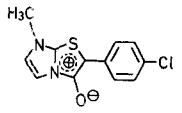
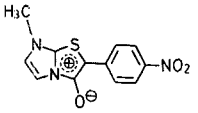
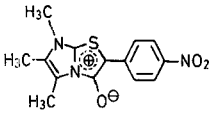
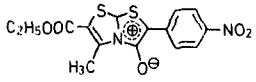
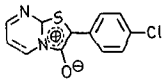
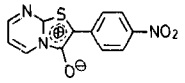
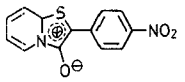
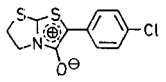
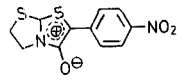
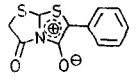
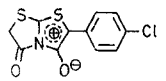
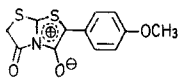
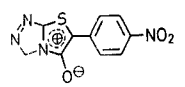
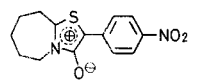
Table 1. Mesoionic Thiazolines **3**

Product	Reaction conditions Method/time/solvent	Yield [%]	m.p. [°C][a]	Molecular formula[b]	I.R. (nujol)[c] $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (DMSO)[d] δ [ppm]
3a 	A/—	80	240°	$C_{12}H_9ClN_2OS$ (264.0)	1616 (m)	3.49 (s, 3H); 7.00 (d, 1H, J=2 Hz); 7.22 (d, 1H, J=2 Hz); 6.7–7.4 (m, 4H)
3b 	A/—	100	>350°	$C_{12}H_9N_3O_3S$ (275.0)	1630 (m)	3.30 (s, 3H); 7.56 (d, 1H, J=2 Hz); 7.78 (d, 1H, J=2 Hz); 8.2 (m, 4H)
3c 	A/—	100	290°	$C_{14}H_{13}N_3O_3S$ (303.0)	1643 (m)	1.87 (s, 3H); 1.93 (s, 3H); 3.57 (s, 3H); 8.2 (m, 4H)[e]
3d 	B/20 min	60	275°	$C_{15}H_{12}N_2O_5S_2$ (364.0)	1704 (s) 1640 (m)	1.22 (t, 3H, J=8 Hz); 2.74 (s, 3H); 4.24 (q, 2H, J=8 Hz); 8.0 (m, 4H)[e]
3e 	C/24 h/THF (N_2)	50	278°	$C_{12}H_7ClN_2OS$ (262.0)	1629 (m)	7.0–9.1 (m)[f]
3f 	C/20 h/THF (N_2)	80	>350°	$C_{12}H_7N_3O_3S$ (273.0)	1630 (m)	7.2–8.7 (m)
3g 	C/24 h/acetone	100	298° (C_2H_5OH)	$C_{13}H_8N_2O_3S$ (272.0)	1638 (m)	7.6–9.0 (m)
3h 	C/48 h/acetone	100	262°	$C_{11}H_8ClNOS_2$ (269.0)	1588 (m)	4.20 (t, 2H, J=8 Hz); 4.72 (t, 2H, J=8 Hz); 7.5 (m, 4H)[f]
3i 	C/48 h/acetone	99	>350°	$C_{11}H_8N_2O_3S_2$ (280.0)	1600 (m)	4.22 (t, 2H, J=8 Hz); 4.76 (t, 2H, J=8 Hz); 8.0 (m, 4H)[f]
3j 	B/30 min	53	257° (acetone)	$C_{11}H_7NO_2S_2$ (249.0)	1790 (s); 1716 (m)[g]	4.52 (s, 2H); 7.6 (m, 5H)[f]
3k 	B/30 min	60	219° (acetone)	$C_{11}H_6ClNO_2S_2$ (283.0)	1791 (s); 1716 (m)[g]	4.25 (s, 2H); 7.2 (m, 4H)[f]
3l 	B/30 min	32	253° (acetone)	$C_{12}H_9NO_3S_2$ (279.0)	1784 (s); 1711 (m)[g]	3.94 (s, 3H); 4.44 (s, 2H); 7.2 (m, 4H)[f]
3m 	C/48 h/THF (N_2)	100	212° (C_2H_5OH)	$C_{10}H_6N_4O_3S$ (262.0)	1584 (m)	5.67 (s, 2H); 8.0 (m, 4H)
3n 	C/24 h/acetone	40	252° (C_2H_5OH)	$C_{14}H_{14}N_2O_3S$ (290.0)	1621 (m)	1.8 (m, 6H); 3.2 (m, 2H); 4.2 (m, 2H); 8.0 (m, 4H)

[a] Product washed with hot acetone unless otherwise stated.

[b] Satisfactory microanalyses (C ±0.34, H ±0.33, N ±0.32, S ±0.35; exceptions: **3a, g,** C ±0.54; **3c, m,** N ±0.70; **3m,** S ±0.56) and high resolution mass spectra (±0.002 mass units) obtained.

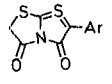
[c] Perkin-Elmer 225 spectrometer.

[d] JEOL JNM MH 100 or Bruker WP 80 DS spectrometers.

[e] Pyridine solution.

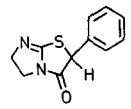
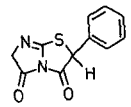
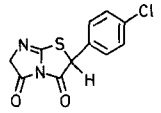
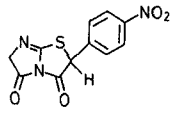
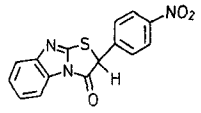
[f] $CDCl_3/CF_3COOH$ solution.

[g] The presence of two carbonyl bands at ~1790 (s) and ~1715 (m) cm^{-1} could be explained by a "non-classical mesoionic thiazolone structure **3'**:



3'

Table 2. Imidazothiazoles **4**

Product	Reaction conditions Method/time/solvent	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (nujol)[b] $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$)[c] δ [ppm]
4a 	C/50 h/acetone	56	140° (C_2H_5OH)	$C_{11}H_{10}N_2OS$ (218.0)	1723 (s)	3.73 (t, 2H, J=8 Hz); 4.35 (t, 2H, J=8 Hz); 5.50 (s, 1H); 7.4 (m, 4H)
4b 	C/140 h/acetone	70	208° (C_2H_5OH)	$C_{11}H_8N_2O_2S$ (232.0)	1772 (m); 1744 (s)[d]	4.62 (s, 2H); 5.78 (s, 1H); 7.5 (m, 5H)[e]
4c 	C/140 h/acetone	76	207° (C_2H_5OH)	$C_{11}H_7ClN_2O_2S$ (266.0)	1771 (m); 1744 (s); 1720 (m)[d]	4.62 (s, 2H); 5.80 (s, 1H); 7.4 (m, 4H)[e]
4d 	C/140 h/acetone	80	245° (C_2H_5OH)	$C_{11}H_7N_3O_4S$ (277.0)	1750 (m); 1717 (s)	4.38 (s, 2H); 5.63 (s, 1H); 8.0 (m, 4H)
4e 	C/48 h/anhydrous acetone (N_2)	99	204° (C_2H_5OH)	$C_{15}H_9N_3O_3S$ (311.0)	1728 (s)	5.68 (s, 1H); 7.3–8.2 (m, 8H)

[a] Satisfactory microanalyses (C ±0.38, H ±0.12, N ±0.48, S ±0.35) and high resolution mass spectra (±0.001 mass units) obtained.
[b] Perkin-Elmer 225 spectrometer.
[c] JEOL JNM MH 100 spectrometer.
[d] CCl_4 solution.
[e] $CDCl_3/CF_3COOH$ solution.

taine **6** is filtered and recrystallised from ethanol; yield: 0.295 g (85%); m.p. 228°C.

$C_{15}H_{11}N_3O_4S$ (329.3)	calc.	C 54.71	H 3.34	N 12.77	S 9.73
	found	54.64	3.35	12.87	9.66

I.R. (Nujol)[18]: ν=3100–2000; 1613, 1597, 1588 cm^{-1}.

^{1}H-N.M.R. (CD_3SOCD_3): δ=6.54 (s, 1H); 7.2–8.4 ppm (m, 8H).

Heating of betaine **6** (1 mmol) in anhydrous toluene (40 ml) for 18 h, gives the pure benzimidazolo[1,2-*b*]thiazolone **4e** after evaporation of the solvent and recrystallisation from ethanol.

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