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A novel and efficient 4-oxothiazolidine-1,2-dithiole rearrangement induced by Lawesson's reagent

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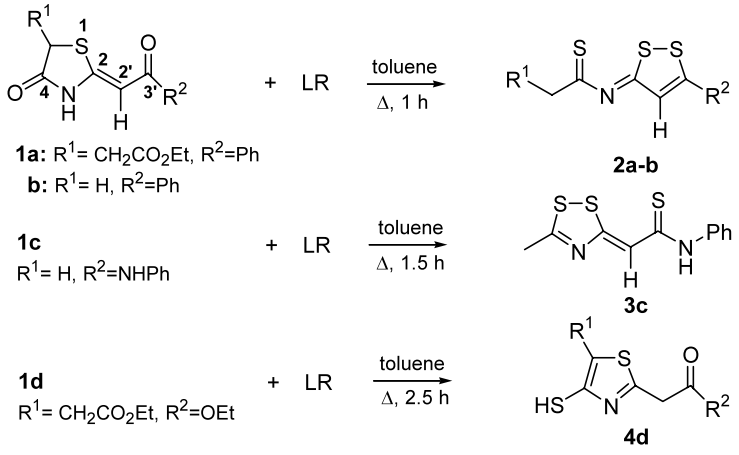
Abstract—Functionalized 1,2-dithioles have been synthesized by a ring opening–closing process of 5-substituted- and 5-unsubstituted-2-alkylidene-4-oxothiazolidines with Lawesson's reagent. The ^{13}C NMR data confirmed the *meso*-ionic structure of these aromatic-type 1,2-dithioles.

Over the past twenty years the thionation of different carbonyl compounds by Lawesson's reagent [LR: 2,4-bis(4-methoxyphenyl)-1,2,3,4-dithiadiphosphetane 2,4-disulfide][1] has been generally recognized as being superior versus P_4S_{10} and other thionation reagents. The application of this reagent has been extended in recent years to the synthesis of sulfur-containing heterocycles, such as benzothiazol-3-thiones,[2] tetrahydrothiophen-2-imines and benzothiazines.[3] New developments also include direct conversion of alcohols to thiols[4] and cyclization of unsubstituted and 2-monosubstituted 3-oxoesters or *N*-substituted 3-oxoamides affording 3*H*-1,2-dithiole-3-thiones.[5,6] Ángyán and coworkers[7] have reported that in a large number of the sulfur-containing acyclic and cyclic compounds, containing the fragment -S-X=Y-C=O with a *cis*-configuration of X=Y (X = C; Y = C or N), the 1,5-interaction of nonbonded S and O, may influence physicochemical properties and chemical reactivity of these compounds. In this context, the availability of the (*Z*)-2-alkylidene-4-oxothiazolidines of type **1**[8] (Scheme 1) and their configurational stability, attributed to a strong intramolecular oxygen–sulfur interaction of the 1,5-type, encouraged us to study their reactivity[9] and utility



Scheme 1.

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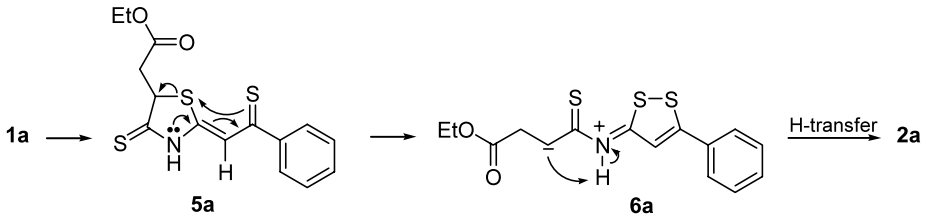


Scheme 2.

as precursors for synthetic purposes. Herein, we report the first, almost quantitative one-pot transformation of the (*Z*)-2-alkylidene-4-oxothiazolidines **1a**–**b** to 1,2-dithioles **2a**–**b** in the presence of an equimolar amount of Lawesson's reagent (Scheme 1).

Under identical conditions, the (*Z*)-4-oxothiazolidine **1c**, containing a β-enaminoamide structural unit, instead of the β-enaminone fragment in **1a**–**b**, afforded 1,2,4-dithiazole derivative **3c** in 40% yield. The analogous reaction of the β-enamino ester **1d** with LR led to the formation of the corresponding 4-mercaptothiazole **4d**. The reaction of precursors **1a**–**c** with LR proceeds in a highly regioselective fashion. The mechanism probably involves the formation of thione intermediates **5a**–**c** by an initial thionation of the C(2′) oxygen and ring oxygen of the thiazolidin-4-one derivatives **1a**–**c**, as outlined in Scheme 2 for substrate **1a**.[10] Thioxothiazolidine ring opening, occurring with a concomitant 1,2-dithiole closing process, followed by the H-transfer are subsequent steps.

The intermediacy of thione **5a**, though it was not detected under the experimental conditions employed, appears very likely. Similar thionation reactions have been reported previously,[3–5] including the formation of the 2-thioacylmethylene-3-aryl-5-phenyl-2*H*-1,3,4-thiadiazolenes **8** from the carbonyl analogues **7** and phosphorous pentasulphide.[11]

The regioselective character of the ring-closing process **5a**–**c**→**6a**–**c** can be rationalized in terms of the strongly directing interaction between the two sulfur atoms. Evidence for the very close contact of reactive sulfur atoms in **5a**–**c** is based on the X-ray analysis of a representative of the series, i.e. ethyl (*Z*)-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)ethanoate **1d**.[12] The O···S(1) nonbonded distance in **1d** (2.873(2) Å) is less than the sum of the van der Waal's radii (3.22 Å). The C(2) side chain is essentially coplanar with the ring which brings the carbonyl oxygen into close proximity to the sulfur atom. The directed π-delocalization of the typical push–pull unit in intermediates **5** (Scheme 2), consisting of an electron donor (NH), the intervening double bond and an electron acceptor (C=S), additionally enhances the **5**→**6** process.[13]

Characteristic spectroscopic data for the dithioles **2a**–**b** and 1,2,4-dithiazole **3c** are compiled in Table 1. In the ^{1}H NMR spectra the proton at C(4) of dithiole derivatives **2a** and **2b** absorbs at very low field, i.e. at 8.65 and 8.37 ppm, respectively, which is indicative of the aro-

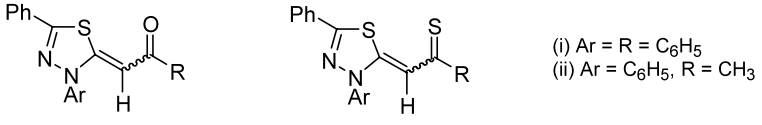
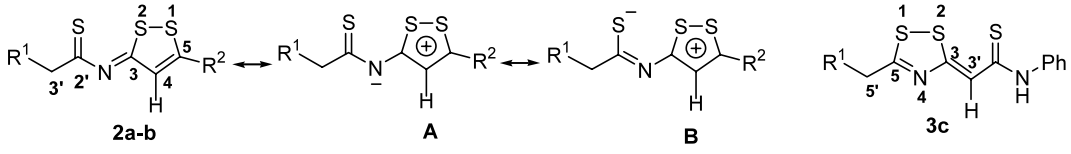
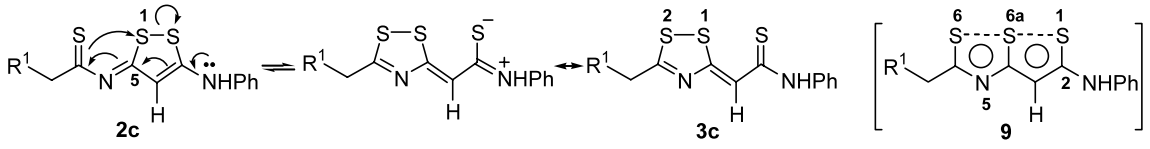


Table 1. Selected ^{13}C and ^{1}H NMR chemical shifts of 1,2-dithioles **2a**–**b** and 1,2,4-dithiazole **3c**



Entry	Product	C(2′)	C(3)	C(4)	C(5)	C(4)-H	C(3′)-H	
1	**2a**[a]	202.76	187.35	126.78	177.89	8.65	2.89	–
2	**2b**[b]	198.58	187.31	125.83	178.26	8.37	2.85	–
		C(5)[c]	C(3)[c]	C(3′)[c]	C=S[c]	C(3′)-H[c]	C(5′)-H[c]	NH
3	**3c**[a]	182.67	180.45	114.42	184.86	7.46	2.65	11.23

[a] DMSO-d_6.
[b] $CDCl_3$.
[c] C(5) atom in **3c** should be compared to C(2′) in **2a** and **2b**, [c] C(3) atom in **3c** should be compared to C(3) in **2a** and **2b**, etc.



Scheme 3.

Table 2. Thionation of 2-alkylidene-4-oxothiazolidines **1a–d**

Entry	Thiazolidine	R^1	R^2	Reaction time (h)	Product	Mp (°C)	Yield (%)[a,b]
1	**1a**	CH_2CO_2Et	Ph	1	**2a**	64	92
2	**1b**	H	Ph	1	**2b**[16]	97	99
3	**1c**	H	NHPh	1.5	**3c**	217[c]	40
4	**1d**	CH_2CO_2Et	OEt	2.5	**4d**	Oil	50[d]

[a] Yields refer to isolated yields by column chromatography.
[b] All of the compounds gave satisfactory ^1H and ^{13}C NMR and MS spectra.
[c] Decomposition point.
[d] In addition to **4d** a large amount of polymeric material was isolated.

matic nature of the dithiole ring. This is confirmed by the ^{13}C shifts for C(3), C(4) and C(5) in the highly delocalized derivatives **2a–b** as indicated by the dipolar resonance structures **A** and **B**. These values matched those obtained in similar 1,2-dithiole-3-thiones.[5,14] The assignment of values above 195 ppm show undoubtedly the presence of a thioketone carbon C(2′).

Careful analysis of MS, ^1H and ^{13}C NMR spectroscopic data for **3c**, isolated by the thionation of β-enamino amide **1c**, under the same experimental conditions as for **1a–b**, revealed spectral features which correlated with the 1,2,4-dithiazole structure. The compound had an MS spectrum consistent with an elemental composition of $C_{11}H_{10}N_2S_3$ for either the expected 1,2-dithiole **2c**, or the actual 1,2,4-dithiazole derivative **3c**. However, the upfield shifts of the C(3′) and C(5′) protons observed in the ^1H NMR spectrum for 1,2,4-dithiazole **3c** (Table 1, entry 3) in comparison with the C(4) and C(3′) protons of 1,2-dithioles **2a** and **2b** (entries 1 and 2), suggest greater magnetic shielding by the surrounding moiety. The same effect was noted in the ^{13}C NMR spectrum of **3c**, which shows the upfield shifts for the C(5) and C(3) carbon nuclei versus the chemical shifts of the C(2′) and C(3) carbon nuclei, respectively, of either **2a** or **2b**.

Additionally, the chemical shift of the NH proton at 11.23 ppm, which is not in the expected range for structure **2c**, indicates the presence of the thioamide group.[15] 1,2-Dithioles **2a–b** exhibit two identical maxima in UV–vis spectra at 333 and 446 nm which are responsible for the orange color. The different ring system in 1,2,4-dithiazole **3c** was confirmed by the presence of two strong absorptions at λ_{max} 345 and 435 nm. Obviously, in situ generated dithiole **2c**, as the key intermediate en route to the 1,2,4-dithiazole **3c** (Scheme 3) readily participates in another opening–closing process, dictated by (i) the favorable positions of a pair of sulfur atoms and (ii) the electron donating ability of the nitrogen atom. It is tempting to propose the 1,6,6aλ^4-trithia-5-azapentalene structure **9** as a more adequate representation, implying the dominant contribution of 1,2,4-dithiazole **3c** to the ground-state of the system.

The results of thionation of precursors **1a–d** using LR are summarized in Table 2.

The typical procedure for the preparation of ethyl 3-(5-phenyl-[1,2]dithiol-3-ylidenethiocarbamoyl)propanoate **2a** is as follows: a colorless solution of (*Z*)-2-alkylidene-4-oxothiazolidine **1a** (0.164 mmol) and LR (0.164 mmol) in dry toluene (3 mL) was heated in an oil bath at 90–95°C. After a few minutes, the color of the reaction mixture turned dark reddish brown. The mixture was stirred at this temperature for an additional hour when TLC indicated the complete consumption of substrate **1a**. After cooling to room temperature, the solvent was evaporated in vacuo. The residue was chromatographed (toluene/ethyl acetate, 10:0→8:2, v/v) affording the dark orange crystalline 1,2-dithiole **2a** in 92% yield.

In conclusion, we have demonstrated that the one-pot, high yielding reaction of cyclic β-enamino ketones with LR can be applied as a rapid and new route to highly functionalized 1,2-dithiole derivatives in high yields. A pathway for the formation of these compounds and 1,2,4-dithiazole, obtained from the β-enamino amide precursor, is suggested. It is noteworthy that the thionation of the thiazolidine substrate having the β-enamino ester fragment, resulted in an aromatization reaction.

Acknowledgements

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