A SYNTHESIS AND STRUCTURAL CONFIRMATION OF 3,5-BIS(2-ALKYLIMIDAZOL-4-YL)-1,2,4-TRITHIOLANES

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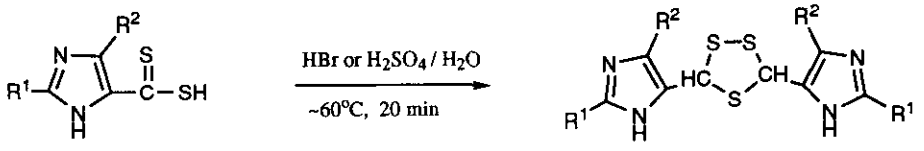
Abstract - The structures of the 4-formylimidazole equivalents which were prepared by heating 2-alkyl-4-dithiocarboxylimidazoles with 47% HBr or conc. H_2SO_4 have been revised to be 3,5-bis(2-alkylimidazol-4-yl)-1,2,4-trithiolanes by X-ray crystallographic analyses.

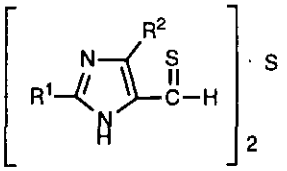
The chemistry of imidazoles having a variety of functional groups constitutes a rapidly expanding area of research, especially in the field of medicinal chemistry.[1]

As part of our studies of preparative routes to polysubstituted imidazoles, we have been examining reactivity of substituted 4-dithiocarboxylimidazoles (**1**).

Herein we describe revision of the structure of the product derived from the reaction of **1** on heating with 47% HBr or conc. H_2SO_4 in water. In earlier work,[2] the products have been proposed as thioformylimidazols (**3**).



1 **2**



3

In a typical synthesis, a suspension of free base of 2-methyl-4-dithiocarboxylimidazole[3] (**1a**: 15.8 g) in water (30 ml) was heated with 47% HBr (11.6 ml) around 60°C for 20 min. Heating the orange suspension resulted in the evolution of hydrogen sulfide with precipitation of sulfur and the formation of a red solution. After cooling and removing the sulfur, the solution was concentrated to precipitate the product, which was recrystallized from methanol to give air-sensitive colorless needles of dihydrobromide of 3,5-bis(2-methylimidazol-4-yl)-1,2,4-trithiolane (**2a**) in 71% yield (15.8 g): mp 176°C (decomp.), tlc: Rf 0.7 (EtOH), ^{1}H-nmr (270MHz, D_2O): δ 2.62 and 2.65 (6H in total, CH_3), 6.30 and 6.54 (1:5, 2H in total, CH), 7.34 and 7.51 (5:1, 2H in total, CH of the imidazole). Mass (FAB: m/z): 367 and 365$(M+H+HBr)^+$, 287 and 285$(M+H)^+$, 220, 159 and 127. Ir (KBr): 3160, 2935, 2895, 2840, 2800, 2700, 1620, 1545, 1500, 1430, 1405, 1380, 1295, 12650, 1240, 1210, 1105, 1075, 1040, 1020, 800, 695, 675, 660 cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_4S_3 \cdot 2HBr$: C, 26.91; H, 3.16; N, 12.56. Found: C, 26.95; H, 3.30; N,12.55. The ^{1}H nmr showed the presence of two isomers, *trans* and *cis* isomers, due to the C-3 and 5 asymmetric carbons.

The corresponding sulfate of **2a** was also prepared by heating with conc. H_2SO_4 in 66% yield: mp 145°C(decomp.).

Configuration of the *trans* isomer of **2a** was established by a single crystal X-ray study of the dihydrobromide as shown in Figure 1. The crystal data are as follows; $C_{10}H_{12}N_4S_3 \cdot 2HBr$, MW 446.25, monoclinic, $P2_1$, a=8.650(1), b=7.247(3), c=12.62(1)Å, β=99.70(1)°, V=783(1)Å^3, Z=2, Dx=1.89 gcm^{-3}, μ(CuKα)=10.801 mm^{-1}. The positions of Br atoms and all non-hydrogen atoms were revealed by the Patterson method and successive Fourier synthesis. Atomic parameters were refined by the blocked-diagonal least-squares calculations and the final R was 0.082.

This structure was reasonably supported by the ^{1}H-nmr and mass spectral data.

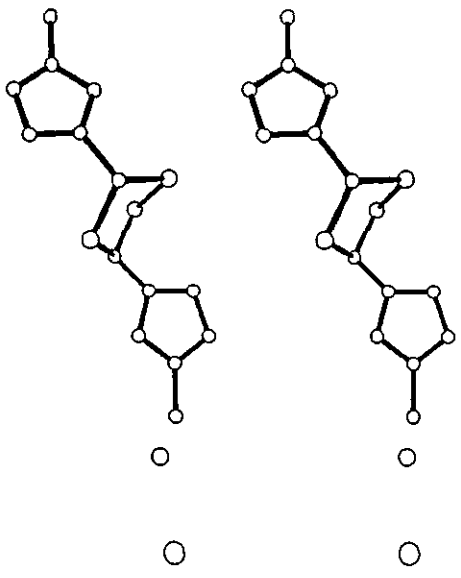


Figure 1. Stereoview of the *trans* isomer of 3,5-bis(2-methylimidazol-4-yl)-1,2,4-trithiolane·2HBr (**2a**·2HBr).

Accordingly, the proposed structure (**3**) was revised to the trithiolane structure (**2**).

By very similar procedures, other analogs (**2b** - **2i**) were obtained as shown in Table 1.

The reaction mechanism from the 4-dithiocarboxylimidazole (for example, **1a**) to the trithiolane structure (**2a**) could be speculated according to Asinger *et al.*[4] by assuming oxidation and reduction of the produced hydrogen sulfide and sulfur in the process as shown in Scheme 1. The isolation and identification of the proposed intermediates are under study.

Although these labile trithiolanes (**2a** - **2i**) have been already utilized as convenient synthetic equivalents of the corresponding substituted 4-formylimidazoles,[5] these syntheses are now rationalized.

Scheme 1

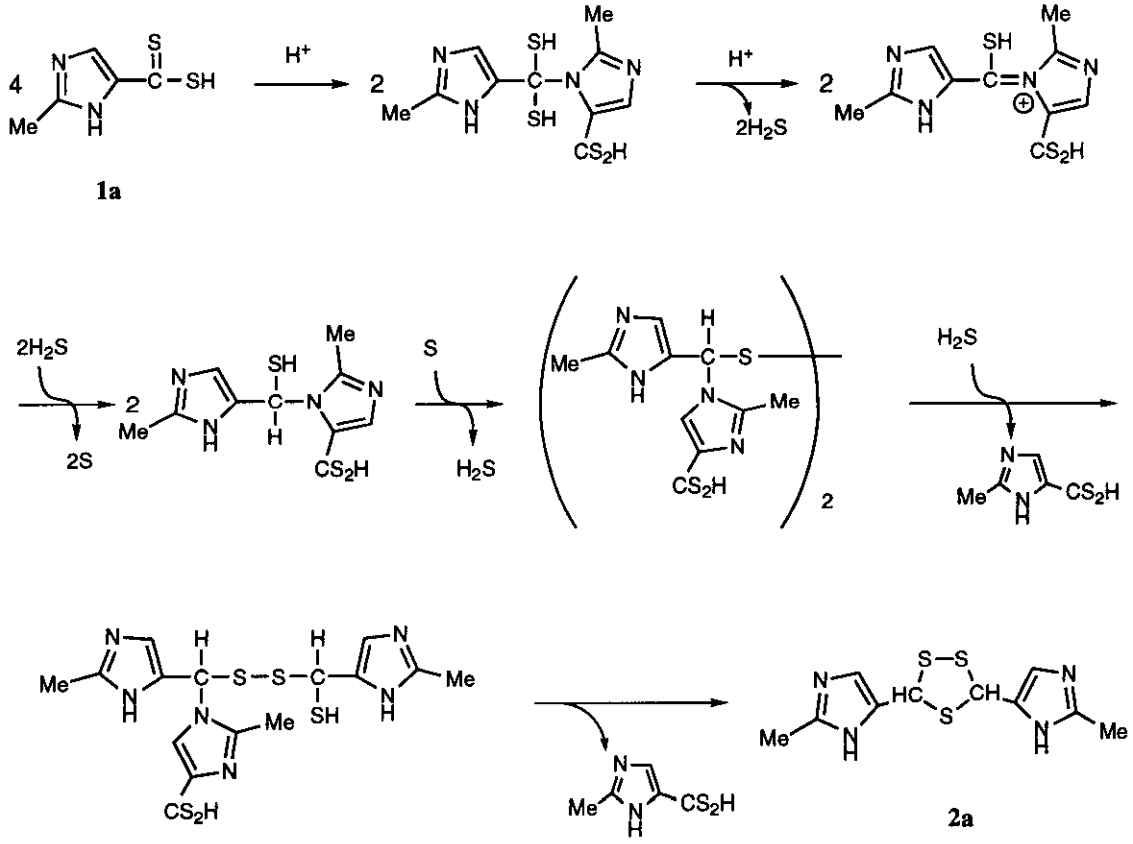
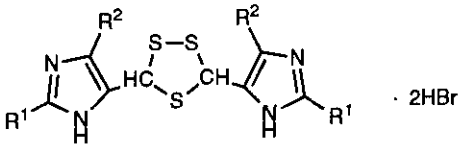


Table 1. Melting points and ^{1}H-nmr sprctral data of dihydrobromides of 3,5-Bis(2-alkylimidazol-4yl)-1,2,4-trithiolanes(**2a-2i**).



2

	R^1	R^2	yield(%)	mp(decomp.)	^{1}H-nmr (D_2O; δ)
2a	Me	H	71	176°C	2.62 and 2.65, 6.30 and 6.54, 7.34 and 7.51
2b	H	H	66	210°C	6.38 and 6.62, 7.55 and 7.70, 8.70 and 8.76
2c	Et	H	70	220°C	1.36 and 2.99, 6.30 and 6.54, 7.37 and 7.54
2d	n-$C_{11}H_{23}$	H	73	170°C	0.88, ~1.28, ~1.74, 2.96, 6.30 and 6.65, 7.43 and 7.75
2e	n-$C_{17}H_{35}$	H	88	165°C	0.89, ~1.26, 1.65, 2.94, 6.28 and 6.61, 7.41 and 7.72
2f	Ph	H	72	225°C	6.84, 7.79, 7.30~8.30
2g	H	Me	78	183°C	2.44 and 2.47, 6.42 and 6.74, 8.57 and 8.67
2h	Me	Me	72	230°C	2.62, 2.66, 9.74
2i	Et	Me	69	160°C	1.32 and 1.35, 2.33 and 2.37, 2.92 and 2.96, 6.31 and 6.61

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