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COMMUNICATION

Bromonitrothiolene-1,1-dioxides in a 'halogen dance' reaction

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The chemical behavior of 4-bromo-3-methyl-4-nitro-2- and 2-bromo-3-methyl-4-nitro-3-thiolene-1,1-dioxides in different solvents has been studied. These dioxides can undergo halo- and prototropic rearrangements, simultaneously in polar solvents, under very mild conditions. These transformations lead to another isomer, 2-bromo-3-methyl-4-nitro-2-thiolene-1,1-dioxide and products of disproportionation, such as 2,4-dibromo-3-methyl-4-nitro-2-thiolene-1,1-dioxide and Δ^2- and Δ^3-nitrothiolene dioxides.

Keywords: Heterocycles; Thiolene-1,1-dioxides (dihydrothiophene-1,1-dioxides); Mono- and dibromonitrothiolene-1,1-dioxides; Prototropic rearrangement; Bromotropic rearrangement; Halogen migration; Halogen dance

1. Introduction

Nitrothiolene-1,1-dioxides are important functionalized sulfur-containing heterocycles. They are very useful for the synthesis of difficult to obtain compounds and for theoretical studies such as oxime–nitronic tautomerism and allyl-vinyl isomerization [1–3]. The mutual influence of functional groups substantially activates the CH-acidic properties of nitrothiolene-1,1-dioxides in comparison with nitroalkenes and thiolene-1,1-dioxides. Nitrothiolene-1,1-dioxides undergo prototropic allyl-vinyl isomerization in the absence of base at room temperature in polar solvents [3]. To discern the influence of an additional electron-acceptor function on the lability of isomeric nitrothiolene-1,1-dioxides, we have now investigated the behavior of the bromo derivatives 4-bromo-3-methyl-4-nitro-2-, 2-bromo-3-methyl-4-nitro-3- and 2-bromo-3-methyl-4-nitro-2-thiolene-1,1-dioxides **1–3**, respectively, (figure 1) in solutions [4, 5].

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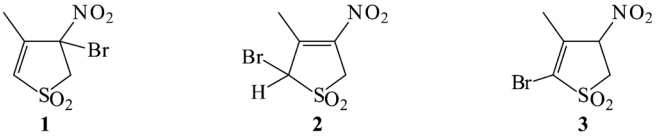
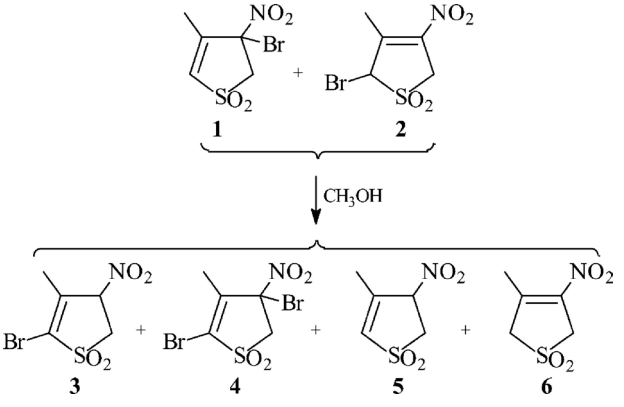


Figure 1.

2. Results and discussion

4-Bromo-3-methyl-4-nitro-2- and 2-bromo-3-methyl-4-nitro-3-thiolene-1,1-dioxides (**1** and **2**) were obtained by bromination of sodium 1,1-dioxo-3-methyl-2-thiolenyl-4-nitronate [4]. These isomers were formed as a mixture in a 1:3 ratio (total yield 98%) and were separated by fractional recrystallization from CCl_4 or $CHCl_3$. (The ratio of the products in the mixture was defined according to ^{1}H NMR spectroscopy data.) However, the use of more polar solvents (methanol, acetonitrile) in the reaction mixture promoted the chemical transformation of bromonitrothiolene-1,1-dioxides **1** and **2**. Thus, the brief (0.5 h) action of methanol on the mixture of compounds **1** and **2** at room temperature led to their complete conversion into 2-bromo-3-methyl-4-nitro-2-thiolene-1,1-dioxide (**3**), 2,4-dibromo-3-methyl-4-nitro-2-thiolene-1,1-dioxide (**4**), and isomeric Δ^2- and Δ^3-3-methyl-4-nitrothiolene-1,1-dioxides (**5** and **6**) in a 6:8:3:5 ratio (according to ^{1}H NMR spectroscopy data) (scheme 1). Analogous transformations were observed in acetonitrile-d_3, but products **3–6** were formed at a reduced rate under such conditions.



SCHEME 1

The behavior of individual bromonitrothiolene dioxides **1–4** in different solvents has been studied by means of ^{1}H NMR spectroscopy (table 1). The suitability of such an analytical method was confirmed by the observation of distinct, unencumbered signals of protons assignable to compounds **1–6** in the ^{1}H NMR spectra. The reactivity of individual isomers **1–3** towards the transformations was substantially dependent on the structure of the compounds.

Isomer **3** was stable for extended periods in $(CD_3)_2CO$, CD_3CN, CD_3OD and $(CD_3)_2SO$ (table 1). Isomer **2**, studied as the isolated compound, was the most labile compound among the monobromides **1–3**. It transformed easily into significant quantities of products **3–6** in methanol-d_4 and acetonitrile-d_3, and more slowly in the neat state (table 1, scheme 2).

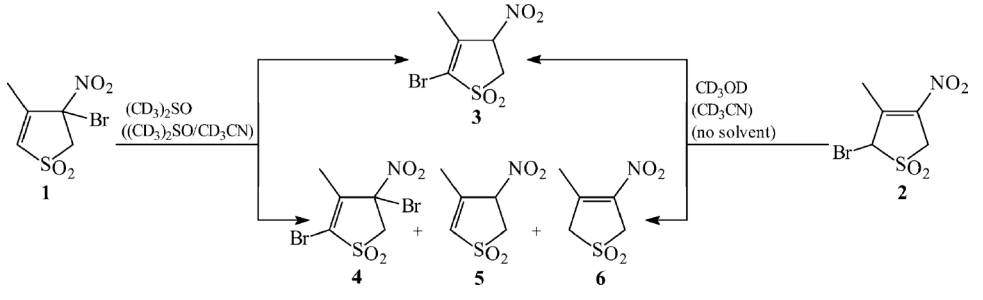
Isomer **1** rearranged into products **3–6** not only as a mixture with **2** but also as an individual substrate (table 1, scheme 2). However, the rearrangement of **1** alone proceeded slower than the mixture of **1** and **2** and required a more polar media of either $(CD_3)_2SO$ or mixtures of

Table 1. Transformations of bromonitrothiolene-1,1-dioxides **1–4**.

Exp. no.	Starting individual material (compd. %)	Solvent	Time	Mixtures of final materials (compd. %)			
1	**1** (100)	$CDCl_3$	48 h	**1** (100)			
2		CD_3CN					
3		CD_3OD					
4		$(CD_3)_2SO$	1 min	**3** (84)	**4** (8)	**6** (4)	**5** (4)
5		$(CD_3)_2SO$– CD_3CN (3:1)	2 h	**3** (78)	**4** (10)	**6** (8)	**5** (4)
6		$(CD_3)_2SO$–CD_3CN (1:1)	8 h	**3** (78)	**4** (9)	**6** (9)	**5** (4)
7		$CDCl_3$	48 h	**2** (100)			
8		CD_3CN	24 h	**3** (30)	**4** (45)	**6** (20)	**5** (5)
9	**2** (100)	CD_3OD	24 h	**3** (40)	**4** (28)	**6** (18)	**5** (14)
10		CH_3OH		**3** (40)	**4** (30)	**6** (20)	**5** (10)
11		No solvent	30 days	**3** (34)	**4** (40)	**6** (13)	**5** (13)
12	**3** (100)	$CDCl_3$	48 h				
13		CD_3CN		**3** (100)			
14		CD_3OD					
15		$(CD_3)_2SO$					
16	**4** (100)	$CDCl_3$					
17		CD_3CN		**4** (100)			
18		CD_3OD					
19		$(CD_3)_2SO$					

$(CD_3)_2SO$–CD_3CN. The rate of the transformations of **1** also exhibited solvent dependence. In DMSO-d_6, rearrangements proceeded almost instantly, whereas in a mixture of DMSO-d_6 and acetonitrile-d_3 the process became slower. Thus, among bromo derivatives **1–4**, compounds **1** and **2** as a mixture and/or individually can undergo rearrangements in polar solvents to give products **3–6**, with transformations of **2** proceeding more readily than those of **1**.

The close qualitative composition of the mixtures of final products **3–6**, formed as a result of transformations of bromonitrothiolene dioxides **1** and **2**, suggests that both compounds

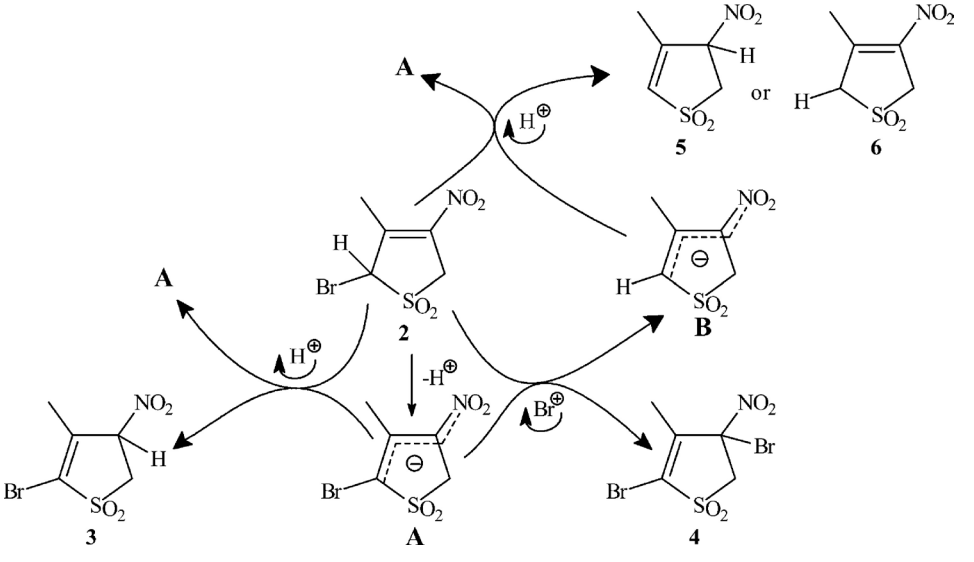


SCHEME 2

succumb to a similar fate. In both cases individual compounds, **1** and **2**, isomerize to a more stable monobromide **3** and disproportionate to give dibromide **4** and nitrothiolene-1,1-dioxides **5** and **6**; products **3–6** were identified using ^{1}H NMR spectral data of the individual compounds.

The results and literature data show that the isomerization of 2-bromo-4-nitro-3-thiolene-1,1-dioxide **2** into structure **3** is a prototropic rearrangement, typical for nitrothiolene-1,1-dioxides [3]. The mild conditions for this transformation are due to the influence of the additional acceptor, bromine atom. Rearrangement of **1** into **3** and disproportionation of **1** and **2** into **4–6**, which proceed under such mild conditions [$(CD_3)_2SO$, CD_3CN, CD_3OD at room temperature], cannot be explained by bromination–debromination reactions and most likely take place by halogen migration. Such rearrangements are recognized as a 'halogen dance' or 'halogen migration'. They have been reported for certain carbo- and heterocyclic aromatic halo derivatives [6], and for 3,4-dibromo-3-methoxycarbonylthiolane-1,1-dioxide [7]. However, the facile halotropic rearrangements of bromonitrothiolene-1,1-dioxides **1** and **2** presented herein differ substantially from literature examples, which only take place in the presence of strong bases (alkaline amides and acetylenides, lithium organic compounds) [6–9].

Literature examples of 'halogen dance' reactions for bromo containing thiophenes suggest the likelihood of proton and cationic migrations [10, 11]. Rearrangements of **2** can be viewed as a consecutive series of deprotonations and electropositive bromine transfers (scheme 3). The lability of compound **2** is due to the stability of resonance-stabilized anions **A** and **B**, which form as intermediates during the rearrangement. These intermediates can act as effective donors, reacting with H^+ and Br^+.



SCHEME 3

Such a scheme is not applicable to bromonitrothiolene dioxide **1**, which lacks labile hydrogens; this may explain the difference in reactivity between **1** and **2**. Moreover, the dependence of halotropic reactivity of **1** on the concentration of DMSO indicates the important role of this solvent in this reaction. Since DMSO is a solvent with strong cation affinity and can accelerate ionic reactions [12, 13], its interaction with bromide **1** may be as an acceptor of electropositive bromine, stimulating further transformations through resonance-stabilized thiolenyl-nitronate anions. This hypothesis is further supported by the fact that rearrangements of **1** proceed much easier in the presence of the easily deprotonated isomer **2**.

That 2-bromo-4-nitro-2-thiolene-1,1-dioxide **3** is more stable than isomer **1** was confirmed by calculations of heats of formation for these molecules conducted on the semi-empirical level, showing isomer **3** to be 12 kcal mol^{-1} more stable than bromonitrothiolene dioxide **1**.

3. Conclusions

Bromonitrothiolene dioxides were experimentally shown to be the first representatives of halo-containing organic substances that can undergo halo- and prototropic rearrangements, proceeding simultaneously, under very mild and neutral conditions (by the action of solvents). These processes are quite important, both theoretically and in applied aspects, since the 'halogen dance' reaction has found applications for the synthesis of difficult to obtain biologically active substances and analogs of natural compounds [9, 14].

4. Experimental

IR spectra were recorded on a Specord IR-75 spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker AC-200 spectrometer at 200 MHz in $CDCl_3$ with HMDS as an internal standard. Starting bromonitrothiolene-1,1-dioxides **1** and **2** were prepared according to ref. [4].

4.1 *Transformation of 2-bromo-3-methyl-4-nitro-3-thiolene-1,1-dioxide (2) in the absence of solvent. Synthesis of 2-bromo-3-methyl-4-nitro-2-thiolene-1,1-dioxide (3) and 2,4-dibromo-3-methyl-4-nitro-2-thiolene-1,1-dioxide (4)*

Compound **2**, a colorless oil, (0.5 g, 2 mmol) was exposed at room temperature for one month to give 0.41 g of colorless crystals (mp 60 °C), containing a mixture of **3** and **4** and 3-methyl-4-nitro-3- and 2-thiolene-1,1-dioxides (**5** and **6**) in a 3:3:1:1 ratio (according to ^{1}H NMR data). Fractional recrystallization from chloroform yielded 0.13 g (25%) of **3** (mp 160-161 °C), 0.15 g (22%) of **4** (mp 99–100 °C) and 0.05 g (7%) of **6** (a mixture of **6** and a sample, prepared according to ref. [16], gave no depression of mp).

^{1}H NMR δ ($CDCl_3$) for **3** (ppm): 2.12 (3H, s, CH_3), 4.05 and 3.86 (2H, m, CH_2, $^2J = 15$ Hz), 5.63 (1H, dd, CH, $^3J = 3, 7$ Hz). Anal. calcd. (%) for **3**: C, 23.40; H, 2.34; N, 5.47. Found: C, 23.47; H, 2.52; N, 5.50.

^{1}H NMR δ ($CDCl_3$) for **4** (ppm): 2.21 (3H, s, CH_3), 4.63 and 4.22 (2H, m, CH_2, $^2J = 15$ Hz); Anal. calcd. (%) for **4**: C, 17.91; H, 1.49; N, 4.18. Found: C, 18.28; H, 1.85; N, 4.32.

4.2 *Transformation of 2-bromo-3-methyl-4-nitro-3-thiolene-1,1-dioxide (2) in methanol*

Compound **2** (0.1 g, 0.4 mmol) was dissolved in methanol (10 mL) and stirred for 24 h at room temperature, after which the solvent was evaporated to give 0.09 g of an oily deposit (mp 60°C) containing a mixture of **3**–**6** (4:3:1:2 ratio) (according to ^{1}H NMR data).

4.3 *Transformations of mixture of 4-bromo-3-methyl-4-nitro-2-thiolene-1,1-dioxide (1) and 2-bromo-3-methyl-4-nitro-3-thiolene-1,1-dioxide (2) in methanol. Synthesis of 2-bromo-3-methyl-4-nitro-2-thiolene-1,1-dioxide (3) and 2, 4-dibromo-3-methyl-4-nitro-2-thiolene-1,1-dioxide (4)*

A colorless oil of a mixture of **1** and **2** (0.63 g, 2.5 mmol) in a 1:3 ratio (according to ^{1}H NMR data), obtained by the bromination of sodium 1,1-dioxo-3-methyl-2-thiolenyl-4-nitronate [4], was crystallized in methanol (3 mL) in a Petri dish for 30 min to give a colorless paste, which was then dried in vacuum evaporator containing calcium chloride. This preparation produced 0.62 g of oily deposit containing a mixture of **3** and **4** and 3-methyl-4-nitro-3- and 2-thiolene-1,1-dioxides (**5** and **6**) in a 6:8:1:5 ratio (according to ^{1}H NMR data).

Fractional recrystallization from chloroform yielded 0.17 g (27%) of **3** and 0.23 g (28%) of **4**; mp and spectral data of products **3** and **4** were the same as those for samples produced by the previous method.

4.4 *Transformations of compounds 1 (2, 3 and 4) in solutions studied by means of ^{1}H NMR spectroscopy*

General procedure. Compound **1** (**2**–**4**) (1 mmol) was dissolved in deuterated solvent (0.5 mL). The dynamics of transformations of initial products was monitored by ^{1}H NMR spectra. Solvents used, reaction time and qualitative composition of initial and final reaction solutions are presented in table I. For correct identification of the signals of the mixtures' components, the spectral data of individual bromonitrothiolene-1,1-dioxides **1–4** and nitrothiolene-1,1-dioxides **5** and **6** were used [4, 15]. Relative amounts of starting substances **1** and **2** and reaction products **3–6** were defined by comparison of integral curves for signals of methylene protons of these compounds and solvent signals.

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