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An α,α′-Dioxothione and Its [4 + 2] Cycloaddition with *trans*-Cyclooctene in the Reaction of Ninhydrin with Potassium Thiotosylate

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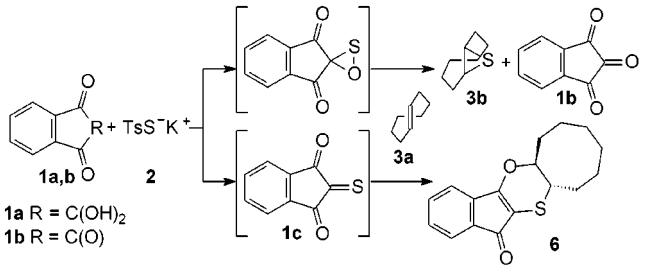
ABSTRACT



In the reaction of Ninhydrin (1a)/1,2,3-indantrione (1b) with potassium thiotosylate, 1,4-oxathiin 6 is formed in up to 63% yield as the trapping product of the intermediary α,α′-dioxothione 1c with *trans*-cyclooctene (3a). Additionally, up to 18% of the available sulfur is transferred to olefin 3a to thiirane 3b through the intermediary oxathiirane.

α,α′-Dioxothiones RC(O)C(S)C(O)R′ are elusive transients that may be prepared in situ and detected by trapping through [4 + 2] cycloaddition with dienes or electron-rich dienophiles. The first such diketothione was trapped in the reaction of dibromomalonate with potassium ethyl xanthogenate;[1] a more general method is to treat *β*-dicarbonyl compounds with phthalimide sulfenyl chloride, followed by base-catalyzed elimination of phthalimide.[2] A series of α,α′-dioxothiones has been prepared and trapped according to this method,[3] but to date no other sulfur-transferring agent appears to be available. A potentially attractive methodology for this purpose is to employ a sulfur nucleophile, which readily adds to the carbonyl group to form the corresponding thio hemiacetal[4] but is equipped with a good leaving group on the sulfur atom to afford the desired thione. Alternatively, 1,3 elimination would afford oxathiiranes, which have recently been established as effective sulfur-transfer agents to strained alkenes.[5]

We presently report that potassium thiotosylate (**2**) constitutes such a novel sulfur-atom donor in its reaction with the highly reactive triketone of Ninhydrin (**1a**), i.e., 1,2,3-indantrione (**1b**), to afford the intermediary α,α′-dioxothione **1c**. Evidence for the latter has been provided by trapping through [4 + 2] cycloaddition with *trans*-cyclooctene (**3a**) and 2,3-dimethyl-1,3-butadiene (**4**).

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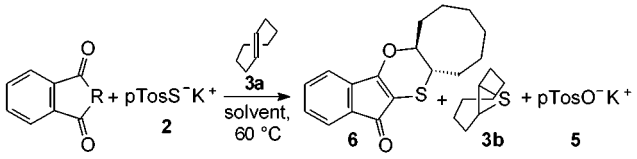
The thermal reaction (60 °C, 1−5 h) of Ninhydrin (**1a**) or its 1,2,3-indantrione (**1b**) with potassium thiotosylate (**2**) (Table 1) led in the presence of an excess of *trans*-cyclooctene (**3a**) to 1,4-oxathiin **6** (up to 63%) and tosylate **5** (90%) as the major products. Additionally, a small amount (11−18%) of *trans*-thiirane **3b** was formed. The product distribution remained the same, irrespective of whether the starting material was ninhydrin (**1a**) or its 1,2,3-indantrione (**1b**) (Table 1, entries 1 and 2). In acetonitrile (Table 1, entries 1−4), a colorless material precipitated. This was identified as potassium tosylate (**5**), which unlike potasssium thiotosylate (**2**) is insoluble in acetonitrile. The precipitation of tosylate **5** appears to be the driving force for this reaction, which will become evident later on (cf. Scheme 2). With 2 equiv (4 equiv) of thiotosylate **2** (entries 3 and 4), the yield of thiirane **3b** was slightly increased from 11 to 16% (18%) while the amount of 1,4-oxathiin **6** remained constant. A time profile of the reaction (entry 5) showed that trione **1b** was already 90% consumed after 1 h and completely after 3 h, with no significant change in the product distribution upon an additional 2 h of heating. Thiirane **3b** persisted under these reaction conditions; it was not ring-opened nor desulfurized by the nucleophilic thiotosylate **2** even on heating for 5 h, as confirmed by an independent control experiment. In d_6-acetone, the reaction was more sluggish (entry 6), while in d_6-DMSO (entries 7 and 8) no precipitation occurred, because the potassium tosylate (**5**) is soluble in DMSO. This solubility appears to be the reason that the reaction times were also considerably longer in DMSO than in acetonitrile and only traces of thiirane **3b** were detected. A mechanism consistent with the above experimental facts is shown in Scheme 1.

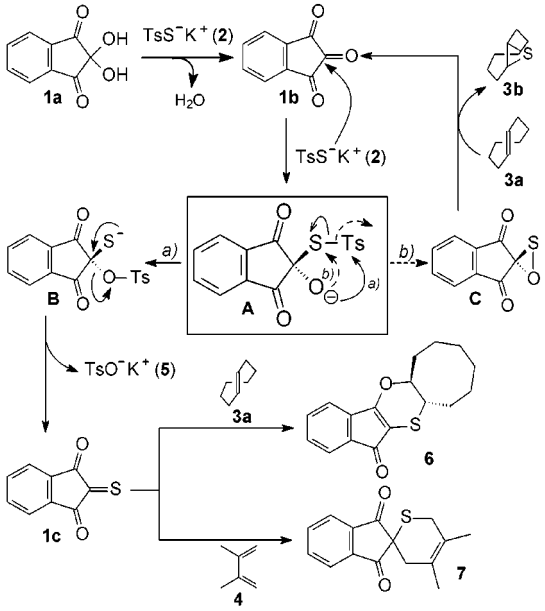
Table 1. Product Studies of the Reaction of Ninhydrin (**1a**)/Indantrione (**1b**) with Potassium Thiotosylate (**2**) and *trans*-Cyclooctene (**3a**)



entry		solvent	equiv 2	equiv 3a	t (h)	convn of 1 (%)[a]	products (%) 6[a]	3b[a]	5
1	**1a**	CD_3CN	1.0	2.6	5	>95	55	11	b
							43[c]		86[c]
2	**1b**	CD_3CN	1.0	2.6	5	>95	56	12	*b*
3	**1b**	CD_3CN	2.0	3.0	5	>95	56	16	*b*
4	**1b**	CD_3CN	4.0	4.0	5	>95	55	18	*b*
5	**1b**	CD_3CN	1.0	3.6	1	90	56	5	*b*
					3	>95	60	11	*b*
					5	>95	63	12	*b*
6	**1b**	d_6-acetone	1.0	2.6	4	89	36	9	*b*
7	**1a**	d_6-DMSO	1.0	3.0	7	9	11		*d*
					23	48	39	<5	89
8	**1b**	d_6-DMSO	1.0	3.0	5	31	23		*d*
					21	68	50	<5	90

[a] Determined from the ^{1}H NMR spectra of the crude reaction mixture after centrifugation to remove the precipitate of **5**; dimethyl isophthalate was employed as internal standard (error ± 5% of the stated values); conversion of **2** not determined because of severe overlap of NMR signals. [b] Not determinable by ^{1}H NMR spectroscopy because of precipitation. [c] Yield of isolated material. [d] Not determinable by ^{1}H NMR spectroscopy because of signal overlap with Ninhydrin (**1a**,**b**).

Scheme 1. Proposed Mechanism for the Formation of the Observed Products



Ninhydrin (**1a**) is dehydrated by thiotosylate **2** to the trione **1b**, of which the most reactive central carbonyl group is then nucleophilically attacked by thiotosylate **2** to form the tetrahedral intermediate **A**. For the latter, two possible reaction pathways may be considered: On one hand, the sulfinate group may undergo a 1,3 shift (path *a*) from the sulfur to the negatively charged oxygen atom to form the intermediate **B**. The incentive for this migration, despite the unfavored four-membered-ring transition state, is the preference of the "hard" sulfinate electrophile to reside on the "hard" oxygen nucleophile rather than on the "soft" sulfur site (HSAB principle).[6] Adduct **B** may then eliminate tosylate ion **5** under formation of α,α′-dioxothione **1c**. The overall process entails sulfur−oxygen exchange between trione **1b** and thiotosylate **2** to afford thione **1c** and tosylate **5**. On the other hand, the negatively charged oxygen atom may attack at the sulfur site (path *b*) and cyclize under 1,3 elimination of the sulfinate anion to oxathiirane **C**. In the presence of *trans*-cyclooctene (**3a**), α,α′-dioxothione **1c** cycloadds as a heterodiene to afford the novel 1,4-oxathiin **6** (deeply red colored) as a [4 + 2] cycloaddition product. Alternatively, since oxathiiranes are known for their sulfur-transferring propensity,[5] the intermediary oxathiirane **C** may transfer its sulfur atom to *trans*-cyclooctene (**3a**) under formation of thiirane **3b** and trione **1b**. The possibility that episulfide **3b**

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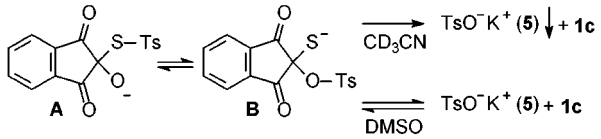
derives from extruded sulfur has been excluded by the following control experiment: A fully thermolyzed mixture of trione **1b** and thiotosylate **2**, to which *trans*-cyclooctene (**3a**) was added afterward, did not afford even traces of thiirane **3b**, although the latter persists under these conditions. Moreover, an additional control experiment confirmed that thiotosylate **2** alone did not transfer sulfur to *trans*-cyclooctene. Thus, sulfinate migration (path *a*) competes effectively with sulfinate elimination (path *b*) such that the formation of the α,α′-dioxothione **1c** intermediate dominates (Scheme 1). The yield of thiirane **3b** is not increased at the expense of the [4 + 2] cycloadduct **6** (Table 1, entries 1 and 4), because the oxathiirane **C** regenerates the trione **1b** in the sulfur transfer to the *trans*-cyclooctene (**3a**); finally, trione **1b** is converted to 1,4-oxathiin **6** (pathway *a*).

The longer reaction time in DMSO (Table 1, entries 7 and 8) may be rationalized if one supposes that the 1,3 migration of the sulfinate group is an equilibrium process (Scheme 2).

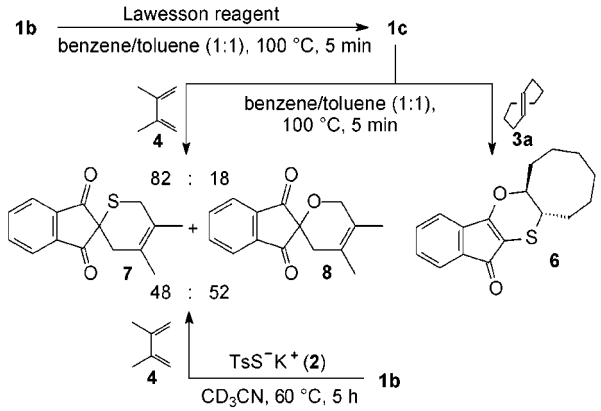
Scheme 2. Solvent-Dependent Equilibrium in the Migration of the Sulfinate Group



Thus, in acetonitrile (entries 1−5) this equilibrium is shifted to the right due to the fact that the eventually formed potassium tosylate is insoluble in acetonitrile. The intermediate **B**, thus, is irreversibly removed from the equilibrium, which accelerates the reaction rate. A control experiment confirmed the proposed equilibrium, since the addition of 2 equiv of tosylate **5**, right from the beginning, to the reaction mixture in DMSO as solvent (tosylate **5** soluble) inhibited the reaction; no cycloadduct **6** was detected.

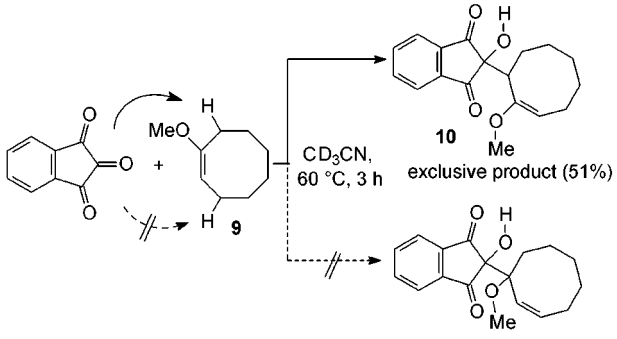
The *trans* configuration of cyclooctene **3a** is preserved in cycloadduct **6**, which is indicated by the NMR data. Therefore, the last step in the formation of 1,4-oxathiin **6** (Scheme 1) is clearly a concerted [4 + 2] cycloaddition with **3a**, and the α,α-dioxothione **1c** figures as a bona fide intermediate, since the carbon−sulfur double bond is essential for this compound to serve as a heterodiene partner. This is surprising, because electron-poor heterodienes such as **1c** have so far—in addition to their reactivity as dienophiles—only been trapped with electron-rich double bonds in inverse electron-demand Diels−Alder reactions. In the present case, the extraordinary reactivity of *trans*-configured cyclooctene **3a** derives from inherent pyramidalization,[7] which must prevail over electronic demand. To confirm unequivocally that cycloadduct **6** is the genuine trapping product of dioxothione **1c** with **3a**, thione **1c** was also prepared independently: Trione **1b** was treated with Lawesson reagent to yield **1c** in situ and then trapped with *trans*-cyclooctene (**3a**) to afford 1,4-oxathiin **6** as the major product, together with considerable amounts unidentified byproducts (Scheme 3). Similarly, the independently prepared

Scheme 3. Independent Synthesis of 1,4-Oxathiin **6** with Lawesson Reagent



dioxothione **1c** was also trapped with 2,3-dimethylbutadiene (**4**), to give the known[2c] dihydrothiopyran **7** and dihydropyran **8**, the trapping product of starting trione **1b**. The same products (nearly a 1:1 mixture) were also obtained in the reaction (Scheme 3) of trione **1b** with potassium thiotosylate (**2**) in the presence of 2,3-dimethylbutadiene (**4**). The mass balance of the trione in this case was >95%, whereas the corresponding mass balances in the reactions with *trans*-cyclooctene (**3a**) were only 55−63% (cf. Table 1, entries 1−8). Evidently, the dienophilic *trans*-cyclooctene (**3a**) is a moderately effective trapping agent, since as much as 45% (entries 1−5) of the intermediarily formed diketothione **1c** decomposes to unidentified products. Unfortunately, the use of the more reactive 2,3-dimethylbutadiene (**4**), but as diene partner and not as dienophile, is complicated by the fact that it reacts with the starting material, namely the 1,2,3-trione **1b**. Attempts to employ the 1-methoxycyclooctene (**9**) as the electron-rich dienophile disclosed another reactivity of the indantrione (**1b**), namely the formation of the carbonyl ene adduct **10** as the exclusive regioisomeric product (Scheme 4). It is noteworthy that this transformation constitutes the first example of a regioselective carbonyl ene reaction between a cyclic enol ether and a tricarbonyl compound.

Scheme 4. Carbonyl−Ene Reaction of Indantrione (**1b**) with 1-Methoxycyclooctene (**9**)



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In conclusion, the reaction between 1,2,3-indantrione (**1b**) and potassium thiotosylate (**2**) has provided a novel route (path *a* in Scheme 1) to its α,α′-dioxothione through the unprecedented sulfur-to-oxygen 1,3 migration of the sulfinate group in the tetrahedral adduct **A**. A promising feature of the latter adduct is its collapse through nucleophilic substitution on sulfur to the intermediary oxathiirane **C** (path b in Scheme 1), a class of highly reactive species which have so far only been accessible by photochemical or thermal cyclization of sulfines.[8] This opens up a new perspective in the in situ generation of the elusive oxathiiranes for sulfur-transfer purposes.

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Supporting Information Available: Experimental procedures and full characterization for products **6** and **10** with the pertinent NMR spectral data. This material is available free of charge in the Internet at http://pubs.acs.org.

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