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Novel generation and ring closure of 1,3-thiaza-1,3-butadiene *S*-oxides through thermal cycloreversion of 6*H*-1,3,5-oxathiazine *S*-oxides

Kazuaki Shimada,* Islam Md. Rafiqul, Masanobu Sato, Shigenobu Aoyagi and Yuji Takikawa

Department of Chemical Engineering, Faculty of Engineering, Iwate University, Morioka, Iwate 020-8551, Japan

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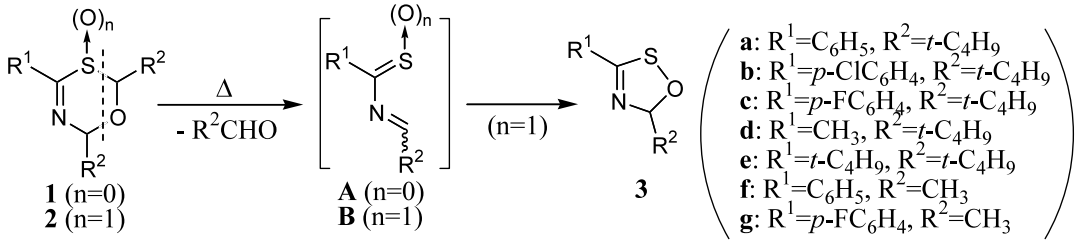
Abstract—Heating of 6*H*-1,3,5-oxathiazine *S*-oxides efficiently afforded 1,2,4-oxathiazoles through the mechanism involving thermal cycloreversion of the substrates and the subsequent ring closure of the intermediary 1,3-thiaza-1,3-butadiene *S*-oxides.

Immense interest has been focused on the preparation and synthetic use of thione *S*-oxides in the light of their heterocumulene-like structures and unique reactivities. However, in spite of high potentiality of new reactive intermediates toward various reagents, only limited studies concerning the generation of heterodienes cumulated with sulfine or sulfene substructures have been achieved due to the preparative difficulties of their precursors and the lack of suitable trapping methods of such reactive species.[1] In the course of the studies on chalcogenocarbonyl functionalities bearing π-conjugation systems, convenient routes for the generation of 1,3-thiaza-1,3-butadienes **A** only through thermal cycloreversion of 6*H*-1,3,5-oxathiazines **1** have been reported by several authors.[2] These findings just derived us to envisage the generation of the oxygenated variants **B** through an analogous route starting from 6*H*-1,3,5-oxathiazine *S*-oxides **2**. According to our expectation as mentioned above, we started our exploration for the preparation and thermal reactions of 6*H*-1,3,5-oxathiazine *S*-oxides **2**. In this paper, we report a generation of sulfine-type novel heterodienes **B** and the subsequent facile ring closure of **B** to give 5*H*-1,2,4-oxathiazoles **3**.

6*H*-1,3,5-Oxathiazines **1a–g** were prepared as single stereoisomers by treating an alkanethioamide or an arenethioamide with pivalaldehyde or 2,4,6-trimethyl-1,3,5-trioxane (paraldehyde) and $BF_3{\cdot}OEt_2$.[2,3] In contrast, all attempts for the synthesis of **1** bearing a bulky substituent were unsuccessful. Subsequent *m*CPBA oxidation of **1a–d** in CH_2Cl_2 at 0°C afforded the corresponding *S*-oxides **2a–d** as single epimers in quantitative yields. However, the relative stereochemistry of the newly-formed S–O bonds of **2a–d** was not determined through the ^1H NMR experiments using $Eu(fod)_3$ due to the instability of **2a–d** toward the contact with Lewis acids involving NMR shift reagents. In contrast, **2f** and **2g** were obtained as inseparable 3:1 epimeric mixtures and *m*CPBA oxidation of **1e** only gave a complex mixture.



Keywords: 6*H*-1,3,5-oxathiazine *S*-oxide; 1,3-thiaza-1,3-butadiene *S*-oxide; sulfine; 5*H*-1,2,4-oxathiazole; 1,2,4-thiadiazole.
* Corresponding author. Tel.: +81-19-621-6324; e-mail: shimada@iwate-u.ac.jp

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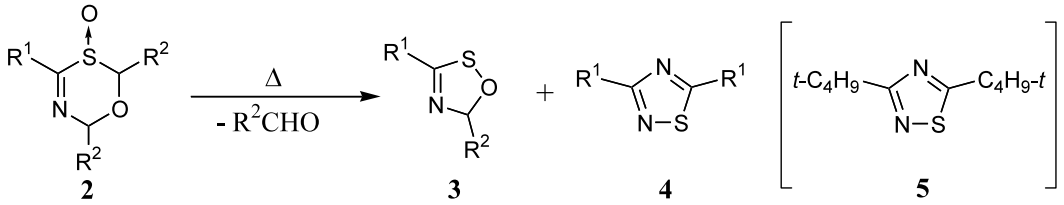
Heating a $CHCl_3$ or a benzene solution of *S*-oxides **2a–c** at refluxing temperature for several hours afforded the corresponding 5*H*-1,2,4-oxathiazoles **3a–c** in almost quantitative yields, and neither deoxygenation products **1a–c** nor nitriles **6a–c** were found in the crude products. However, **3** were relatively unstable toward the storage and the contact with silica gel and were quantitatively converted into 3,5-diaryl-1,2,4-thiadiazoles **4a–c** and elemental sulfur in both cases. Therefore, isolation of **3a–c** was carried out only through simple evacuation of volatile pivalaldehyde at rt. Treating a CH_2Cl_2 solution of **3a** with *p*-toluenesulfonic acid (1.1 mol amt.) gave a similar result to the reaction of **3a** with silica gel. It is noteworthy that 3,5-di-*t*-butyl-1,2,4-thiadiazole (**5**) was not found at all through these reactions. In contrast, heating of **2d** only gave a complex mixture. When a $CDCl_3$ solution of **2a** was kept standing in an NMR tube and was subjected to ^1H and ^{13}C NMR monitoring at 25°C, a gradual increasing in the intensities of the signals of **3a** and pivalaldehyde was observed along with decreasing of the signals of **2a** and almost 1:1 mixture of **3a** and pivalaldehyde with a small amount of **4a** was found after standing the solution for 300 h. Furthermore, standing of the resulting mixture for an additional 500 h resulted in conversion into a mixture of **4a** and pivalaldehyde in a 1:4 molar ratio along with precipitation of elemental sulfur. Contact of epimeric mixtures of **2f** or **2g** with silica gel in a similar manner also formed **4a** or **4c**, respectively. All results of the thermal reactions of **2** are summarized in Table 1. When an ethanolic solution of **2a** was heated at refluxing temperature for 26 h, thioamide **9a**[2c] was obtained in 12% yield along with **4a** (35%) and unidentified products. This result suggested that **9a** was afforded through the route involving the formation of heterodienes **B** followed by addition of ethanol to **B** and deoxygenation of the resulting thioamide *S*-oxides **8**.[4] However, all attempts for trapping of **B** using 2,3-dimethyl-1,3-butadiene, acetylenes, or allyltrimethylsilane were unsuccessful.

Heating of a $CDCl_3$ solution of **3a** at 100°C for 12 h in a sealed NMR tube gave a 1:1 mixture of nitrile **6a** and pivalaldehyde besides the formation of elemental sulfur, and when a $CHCl_3$ solution of **3b** was treated with PPh_3 (1.1 mol amt.) at rt, nitrile **6b** (89%) and $Ph_3P{=}S$ (86%) were exclusively obtained. Treatment of a $CHCl_3$ solution of **3b** with benzylamine (1.2 mol amt.) at rt for 12 h also afforded **6b** (93%). In these cases, neither 1,3-oxaza-1,3-butadiene, *p*-chlorobenzamide, pivalamide, nor their *N*-alkyl or *N*-aryl derivatives were found in the crude reaction mixtures. It is assumed that thiophilic attack of PPh_3 or benzylamine onto the sulfur atom of **3** causes S–O bond fission to accelerate retro [2+2+1]-type cycloreversion, and all these results indicated the 5*H*-1,2,4-oxathiazole ring structure in **3** rather than the alternative ring systems, such as 3*H*-1,2,4-oxathiazoles. It was assumed that the ring system of **3** was formed through the route involving thermal ring fission of **2** and the subsequent ring closure of 1,3-thiaza-1,3-butadiene *S*-oxides **B** as shown in Scheme 1. However, **3a–c** were oily matters, and *m*CPBA oxidation of **3a–c** only gave inseparable oily epimeric mixtures of the corresponding *S*-oxides **7** in approximate 3:1 ratios. Therefore, attempts for the final structural confirmation of compounds **3** or their derivatives **7** through X-ray crystallographic analysis were not possible at this time.

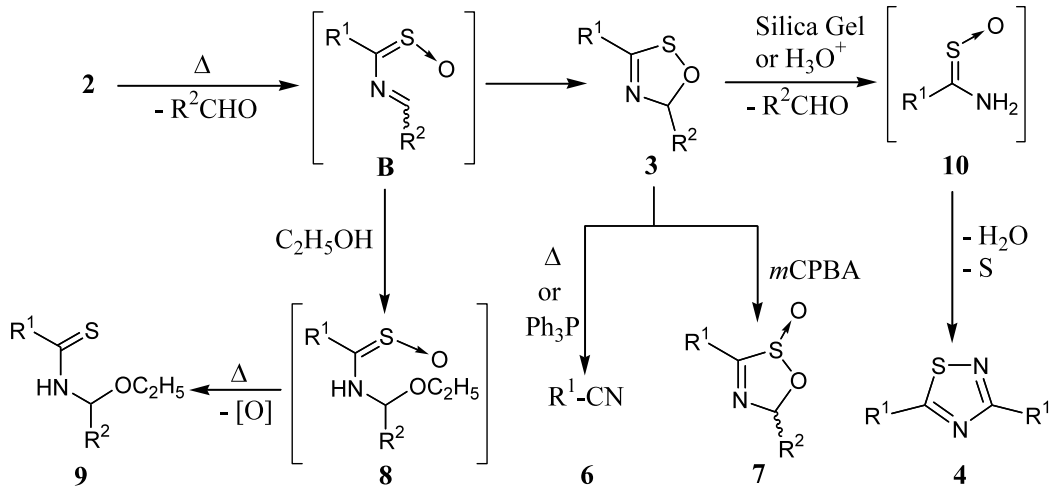
Table 1. Formation of 5*H*-1,2,4-oxathiazoles **3** through thermal cycloreversion of **2**



2 **3** **4** **5**

Substrate			Solvent	Temp. (°C)	Time (h)	Yield (%)		
R^1	R^2	**2**				**3**	**4**	R^2CHO
C_6H_5	*t*-C_4H_9	**2a**[a]	Benzene	Reflux	5	92 (**3a**)	0	0[b]
C_6H_5	*t*-C_4H_9	**2a**[a]	$CDCl_3$	rt	300	85 (**3a**)[c]	15 (**4a**)[c]	Quant.
C_6H_5	*t*-C_4H_9	**2a**[a]	$CDCl_3$	rt	800	0 (**3a**)	Quant. (**4a**)[c]	Quant.
p-ClC_6H_4	*t*-C_4H_9	**2b**[a]	Benzene	Reflux	6	93 (**3b**)	0	0[b]
p-FC_6H_4	*t*-C_4H_9	**2c**[a]	Benzene	Reflux	8	91 (**3c**)	0	0[b]
C_6H_5	CH_3	**2f**[d]	Benzene	Reflux	5	0[e]	50 (**4a**)[f]	0[b]
p-FC_6H_4	CH_3	**2g**[d]	Benzene	Reflux	5	0[e]	53 (**4c**)[f]	0[b]

[a] A single stereoisomer.
[b] Aldehydes were assumed to get away during the heating.
[c] Estimated yields based on the integration of the ^1H NMR spectrum of the reaction mixture.
[d] Epimeric mixture.
[e] Not isolated.
[f] An epimeric mixture of **2f** or **2g** was heated, and the resulting mixtures were taken in contact with silica gel. The yields of **4** were based on the starting **1f** and **1g**.



Scheme 1. Plausible pathway for the formation of **3**, **4**, **6**, **7**, and **9**.

It is noteworthy that 1,2,4-thiadiazoles **4** were efficiently obtained through the contact of **3** with silica gel or a Lewis acid. Several authors reported the formation of **4** through oxidative dimerization of primary thioamides,[5] and now we can propose a plausible pathway of conversion of **3** into **4** involving the formation of thioamide *S*-oxides **10** through acid-induced hydrolytic fragmentation of **3** and the subsequent condensation of **10**.

In conclusion, we have found a generation of novel sulfine-type intermediates **B** through thermal cycloreversion of 6*H*-1,3,5-oxathiazine *S*-oxides **2** and a facile ring closure of **B** into 5*H*-1,2,4-oxathiazoles **3**. Further attempts for the expansion of the generation method to other oxidized variants of 1,3-thiaza-1,3-butadienes through a similar route starting from **1** are in progress in our laboratory.

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