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Original ring contraction of triazine derivatives to 1,2,4-thiadiazoles

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ABSTRACT

The oxidation of triazines **1** is described here. While treatment with *m*-CPBA or DMDO led to formation of a mixture of compounds, [TBA-OX] oxidation led exclusively to thiadiazoles **2** by ring contraction reaction.

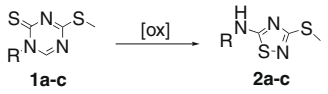
Compounds containing the 1,2,4-thiadiazole ring system have attracted considerable attention in recent years because of their promising biological properties.[1–5] Numerous methods have been published and reviewed several times for synthesizing this skeleton.[6–11] We report here the synthesis of 3,5-disubstituted-1,2,4-thiadiazoles (**2a–c**) by ring contraction of easily prepared triazinethiones (**1a–c**) in the presence of oxidizing agents (Scheme 1).

1,3,5-Triazinethiones **1a–c** were prepared in good yields from thiourea according to the standard procedures.[12,13] Inspired by previous work on oxidations of heterocycles we decided to investigate the behavior of triazinethione **1a** with *m*-chloroperoxybenzoic acid (*m*-CPBA) to convert C=S to C=O.[14] Unfortunately, under these conditions, a mixture of thiadiazole **2a** and triazinone **3a** was isolated (Scheme 2).

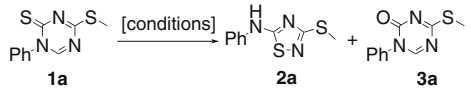
This result prompted us to study the reaction with other oxidizing agents such as dimethyldioxirane (DMDO) or Oxone® to obtain selectively thiadiazole **2a**. The results are summarized in Table 1.

Oxidation of the triazinethione **1a** using 1.2 equiv of *m*-CPBA in dichloromethane led to an equimolecular mixture of thiadiazole **2a** and triazinone **3a** (Table 1, entry 1). In contrast to literature data we did not observe oxidation of the sulfide (methyl sulfanyl group on triazine ring) into sulfoxide or sulfone. Triazinone **3a** results from oxidation of the thiocarbonyl group, while thiadiazole **2a** might arise from a ring contraction. For the formation of triazinone **3a**, *m*-CPBA reacts as an electrophilic oxygen-transfer agent; nucleophilic attack of the thiocarbonyl sulfur atom gives a sulfine which undergoes rearrangement into oxathiirane and finally provides the ketone by sulfur extrusion.[15] A possible mechanism for the formation of thiadiazole **2a** might involve the oxidation of the imine function of **1a** by the peroxy acid into oxaziridine. In this case the mechanism would involve a nucleophilic oxygen-transfer from the peroxy acid to the electrophilic carbon of C=N bond, followed by intramolecular displacement leading to the oxaziridine ring (Scheme 3).

Since *m*-CPBA can effectively be an electrophile as well as a nucleophile depending on the substrates, we studied the reaction with a more electrophilic oxidizing agent (DMDO) and a more nucleophilic one (Oxone®) in order to improve the regioselectivity of the oxidation step. Of course, our initial target **3a** can be easily obtained selectively by a non-oxidative method through conver-



Scheme 1. General strategy for the synthesis of 1,2,4-thiadiazoles by ring contraction of 1,3,5-triazinethiones.



Scheme 2. Synthesis of mixture of thiadiazole **2a** and triazinone **3a**.

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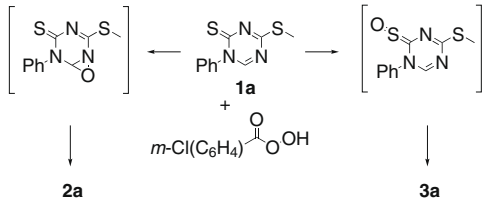
Table 1
Oxidation conditions

Entry	Conditions	Ratio **2a**	:	**3a**
1	*m*-CPBA	50	:	50
2	$(CF_3CO)_2O$	0	:	100
3	DMDO	32	:	68
4	Oxone®	57[a]	:	43
5	Oxone®/Al_2O_3	100	:	0
6	Oxone®/TFA	100	:	0
7	[TBA-OX]	100	:	0

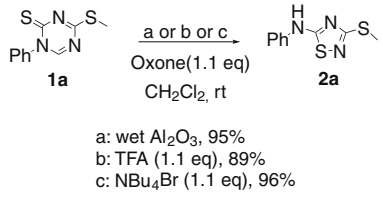
[a] Mixture of sulfide [SMe] and sulfoxide [S(O)Me].



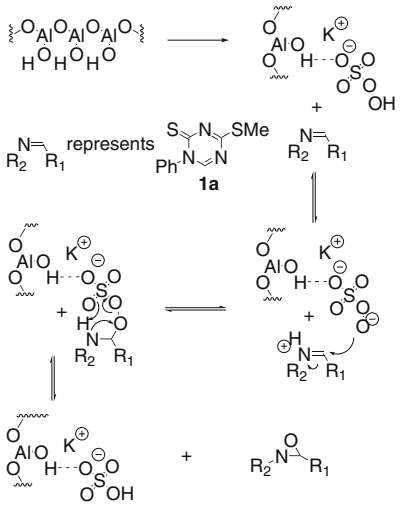
Scheme 3. Plausible intermediate for thiadiazole **2a** and triazinone **3a**.

sion of thiocarbonyl of **1a** to a carbonyl group using trifluoroacetic anhydride in 71% yield (Table 1, entry 2).[16] Dimethyl dioxirane is known to behave as an electrophilic oxidant and it led to triazinone **3a** as the major product rather than thiadiazole **2a** from triazinethione **1a** (Table 1, entry 3). Alternatively, potassium peroxomonosulfate triple salt ($2KHSO_5$, $KHSO_4$, and K_2SO_4) (Oxone® and caroate®) is known to behave as a nucleophilic oxidant. In the first experience using Oxone® in CH_3CN (heterogeneous system), the reaction of **1a** at room temperature for 24 h gave a mixture of 1,2,4-thiadiazole **2a** and triazinone **3a** (Table 1, entry 4). This preliminary result encouraged us to investigate further the reaction conditions for a more effective homogeneous system. We finally discovered three protocols leading selectively to compound **2a** (Scheme 4).

Recently, it has been reported that a heterogeneous mixture of wet alumina and Oxone® can react with ketones to give the corresponding esters or lactones in quantitative yields.[17] The reaction of compound **1a** with Oxone® in dichloromethane at room temperature for 24 h in presence of wet alumina gave only the desired ring contraction product **2a** in 95% yield without any trace of triazinone **3a** (Table 1, entry 5). Different parameters were investigated, including the amount of Oxone® used. The optimal molar ratio of $KHSO_5$/triazine was 2:1. Oxone® was mixed in CH_2Cl_2, dispersed and probably adsorbed on the surface of the alumina, catalyzing the oxidation in this way. Indeed, the reaction of triazinethione **1a** with non-supported Oxone® in dichloromethane at room temperature for 24 h gave only a 5% conversion of the substrate. Potassium peroxomonosulfate was probably adsorbed on the surface by hydrogen bonding, and acido-basic exchange may activate the imine by protonation into an iminium salt and thus induce the nucleophilic transfer of an oxygen atom (Scheme 5).[18]



Scheme 4. Different protocols for the synthesis of 1,2,4-thiadiazole **2a**.

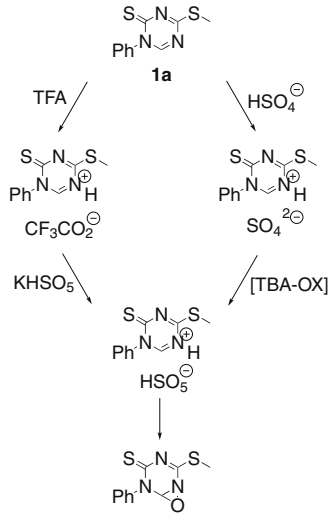


Scheme 5. Possible reaction pathway of the oxidation by Oxone/Alumina.

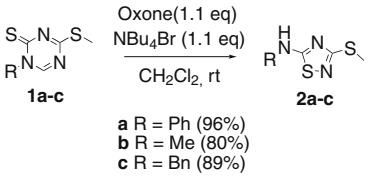
We obtained the same regioselectivity with trifluoroacetic acid in dichloromethane, and thiadiazole **2a** was isolated in 89% yield (Table 1, entry 6). It can be assumed that TFA ensures the protonation of the imine thus allowing, by anionic counter-ion exchange, the formation of the iminium peroxomonosulfate, which can lead to the oxaziridine through precedent way (Scheme 6).

We have also shown that the use of tetrabutylammonium Oxone® (TBA-OX) in dichloromethane was also efficient for the synthesis of thiadiazole **2a** from triazinethione **1a** in 96% yield (Table 1, entry 7). Very mild conditions and very simple work-up procedure were used. TBA-OX was prepared from potassium peroxomonosulfate triple salt by cationic exchange using NBu_4Br and gave a soluble version of the salts mixture, with the ammonium bromide acting as a phase transfer catalyst. We showed that buffering the reaction with $NaHCO_3$ inhibits the reaction and leads to a mixture of compounds. This result seems to confirm that the reaction is acid-catalyzed (protonation of the imine), with the hydrogen sulfate present in Oxone® playing the part of the Brönsted acid (Scheme 6).[19,20]

The ring contraction mechanism has yet to be elucidated. Activation of the oxaziridine by protonation, leading to the corre-



Scheme 6. Possible reaction pathway of the oxidation by TFA/Oxone and by [TBA-OX].



Scheme 7. Synthesis of 1,2,4-thiadiazoles **2a–c** by ring contraction of 1,3,5-triazinethiones **1a–c**.

sponding oxaziridinium salt, may induce a rearrangement resulting in the formation of thiadiazole **2a**. Unfortunately, all attempts to isolate the intermediate oxaziridine (or oxaziridinium salt) were unsuccessful and the mechanism of this unexpected ring contraction under oxidative conditions remains under investigation. Classically, imine function is oxidized to oxaziridine (with probably the formation of nitrone as a competing process in a relatively small proportion) but another mechanism could be envisaged by hydration at position 6 of triazine **1a**, followed by ring opening. Resulting acyclic moiety then cyclizes to give a thiadiazole derivative **2a**. Nevertheless, during our previous works we have never observed the hydration of the imine functions of heterocycles.

By applying the optimal conditions (Oxone®, NBu_4Br, and CH_2Cl_2) to substrates **1b** and **1c** (Scheme 7) thiadiazoles **2a–c** were isolated in good yields.

In conclusion, this report details an inexpensive and very simple method for the synthesis of thiadiazoles from triazinethiones under mild oxidative reaction conditions. It is suggested that compounds **1a–c** are first oxidized to the corresponding oxaziridines, followed by a subsequent ring contraction reaction to afford thiadiazoles **2a–c**. Further applications of this methodology and investigation of the ring contraction mechanism are now underway.

Acknowledgments

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