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## Regioselective Air Oxidation of Sulfides to O,S-Acetals in a Bubble Column

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In this paper the use of a bubble column for a metal-free, selective oxidation of  $\alpha$ -alkylthio-imines to *O*,*S*-acetals is presented. During the synthesis, which is straightforward to perform, the sulfides are oxidized to  $\alpha$ -alkoxy- or, respectively,  $\alpha$ hydroxysulfide by adding activated carbon in the presence of atmospheric oxygen only. We show that the use of the bubble column, which is unusual on laboratory scale, improves the efficiency of the reaction in comparison to common laboratory techniques. As atmospheric oxygen alone is used for oxidation, this method is cost saving, environmentally friendly, and safe.

Due to its unproblematic and environmentally friendly handling, the use of air as well as the use of molecular oxygen as oxidizing agents has steadily gained importance in preparative organic chemistry over the past years.<sup>[1]</sup> Often metals serve as catalysts during this process.<sup>[1a-e]</sup> An alternative method is, for example, the in situ generation of singlet oxygen from molecular oxygen by the addition of a photosensitizer (photo-oxidation).<sup>[1]</sup> The effectiveness of gas–fluid-reactions (or, respectively, of a three-phase reaction, if a heterogeneous catalyst is used) is usually highly dependent on the formation of the specific phase boundary and thus on the reaction conditions. On laboratory scale, the syntheses are usually performed under pressure in appliances that enforce these conditions such as an autoclave.<sup>[1a-g]</sup> Alternatively, the gas can be passed into the reaction solution in a reaction flask where the solution is blended using a magnetic stirrer.<sup>[1h-j]</sup> On the basis of these facts, an easy and effective metal-free oxidation using atmospheric oxygen was developed. The reaction was carried out in a heatable bubble column (Figure 1). Even though bubble columns are common in industrial usage,<sup>[2]</sup> they are rarely known on laboratory scale. As we demonstrated through the results of our work, the use of a bubble column, however, improves the effectiveness of multi-phase reactions compared with conventional methods considerably. As a model reaction for our analyses we chose the oxidation of  $\alpha$ -alkylthio-imines. The synthesis of O,S-acetals starting from sulfides has been an important part of research for many years.  $\alpha$ -Hydroxysulfides are accessible in a variation of the Pummerer reaction.<sup>[3]</sup> Following this

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Figure 1. Heatable bubble column to perform heterogeneous catalyzed gas-fluid-reactions.

strategy, sulfoxides, which are prepared from sulfides with the aid of common oxidizing agents, are treated with acids to obtain  $\alpha$ -hydroxysulfides. Alternatively, the use of singlet oxygen is possible. The peroxides formed during the oxidation can be converted to the  $\alpha$ -hydroxysulfides by using, for instance, triphenylphosphine.<sup>[1i-j]</sup> Through electrolysis and by also adding Et<sub>3</sub>N·HF,  $\alpha$ -alkoxylation is possible.<sup>[4]</sup> However, a halogenation (for example a chlorination with NCS) followed by a substitution is more common.<sup>[5]</sup> The use of a bubble column now provides an easy method for direct metal-free oxidation of  $\alpha$ -alkylthio-imines using atmospheric oxygen, where neither the use of toxic or expensive oxidizing agents nor light exposure requiring photosensitizers is needed.

2,5-Dihydrothiazoles (3-thiazolines) (1) were used as substrates for the exploration of the oxidation reaction. The synthesis of theses cyclic imines was first described by Asinger.<sup>[6]</sup> Based on this common synthesis,<sup>[7]</sup> a modified version<sup>[8]</sup> was established. Using this modified synthesis protocol a wider range of products was accessible. Both, the Asinger reaction itself and 3-thiazoline as the product of this reaction, form the basis for a large number of sequences of synthesis.  $^{[9]}$  They have already found industrial application.  $^{[10]}$ 

The 3-thiazolines used were synthesized following the classical (synthesis of 1 a-c, Scheme 1) and the modified (synthesis of 1 d-h, Scheme 1) synthesis protocol.

Asinger already observed the oxidation of some of these 3thiazolines  $(1 a-g)^{[11]}$  but mistakenly postulated the structure of the corresponding sulfoxides 2 for the products of the oxidation reaction. We successfully reproduced this oxidation. Furthermore, we were able to verify that the products were not



Scheme 1. Synthesis of the 3-thiazolines 1.

the sulfoxides but rather the  $\alpha$ -alkoxy- or, respectively,  $\alpha$ -hydroxysulfides (**3**, **4**).<sup>[12]</sup> The proof of the structure was achieved by NMR, IR, and mass spectrometric analysis. In addition, we were able to obtain single crystals of one  $\alpha$ -alkoxy- and one  $\alpha$ hydroxysulfide to verify the structure by X-ray crystal structure analysis.<sup>[13]</sup>

As a first example, 3-thiazoline 1 a was oxidized in MeOH using atmospheric oxygen and a small amount of activated carbon (Darco, 12-20 mesh, granular; Sigma Aldrich) to the corresponding  $\alpha$ -methoxysulfide **3a**. Performing the oxidation in a round bottom flask and blending the suspension with the help of a conventional magnetic stirrer did not result in the formation of a product (Table 1, entry 1). However, the oxidation of 1 a was realized using a KPG stirrer and product 3 a was formed with a moderate yield of 47% (Table 1, entry 3). With a view to optimizing the reaction conditions, the model reaction was carried out in a bubble column as shown in Figure 1. In addition to a faster oxidation resulting in a shorter reaction time the use of the bubble column led to an increased yield of 75% (Table 1, entry 5). In the case of the oxidation of 3-thiazoline 3b, the same observations were made (Table 1, entries 2, 4, and 6).

The bubble column used consisted of an inner column (20 mm inner diameter), including a gas tube with a frit as a gas inlet, and an outer cladding filled with water to heat and maintain the temperature of the reaction mixture at  $55\,^{\circ}$ C (Figure 1). At this temperature, untreated compressed air was passed into the reaction mixture. A frit was used to break up the gas into tiny bubbles. The air pressure was adjusted with the help of a flow controller to ensure that the activated

Table 1. Investigations on the practical conduction of the oxidation of the 3-thiazolines 1.									
			F R <sup>21</sup>	$rac{1}{s}$ $rac{$	reaction path postulated by F. Asinger <sup>[11]</sup>	$\begin{array}{c} R^{1} \\ R^{2} \\ R^{2} \\ R^{2} \\ R^{3} \\$	₹4		
Entry	1	Method <sup>[a]</sup>	Solvent	Additive	Reaction time [h]	Product	$R^{1}-R^{2}=R^{3}-R^{4}$	R⁵	Yield <sup>[b]</sup> [%]
1	1 a	A	MeOH	activated carbon	40	3a		Me	-
2	1 b	А	MeOH	activated carbon	40	3 b	-(CH <sub>2</sub> ) <sub>6</sub> -	Me	-
3	1a	В	MeOH	activated carbon	50	3 a	$-CH_2C(CH_3)_2CH_2C(CH_3)_2-$	Me	47
4	1 b	В	MeOH	activated carbon	50	3 b	-(CH <sub>2</sub> ) <sub>6</sub>	Me	29
5	1 a	С	MeOH	activated carbon	20	3 a	$-CH_2C(CH_3)_2CH_2C(CH_3)_2-$	Me	75
6	1 b	С	MeOH	activated carbon	12	3 b	-(CH <sub>2</sub> ) <sub>6</sub>	Me	76
7	1a	С	MeOH	-	30	3 a	$-CH_2C(CH_3)_2CH_2C(CH_3)_2-$	Me	15
8 <sup>[c]</sup>	1a	С	MeOH	activated carbon	30	3 a	$-CH_2C(CH_3)_2CH_2C(CH_3)_2-$	Me	74
9	1 b	С	H <sub>2</sub> O	activated carbon	30	4a	-(CH <sub>2</sub> ) <sub>6</sub>	Н	-
10	1 b	С	EtOAc (wet)	activated carbon	20	4a	-(CH <sub>2</sub> ) <sub>6</sub> -	н	60
11	1 b	С	abs. EtOAc	activated carbon	20	4a	-(CH <sub>2</sub> ) <sub>6</sub>	Н	-

[a] In all cases the substrate will be dissolved in the solvent and compressed air is passed into the heated ( $55^{\circ}$ C) reaction mixture. Method A: The reaction mixture is blended using a magnetic stirrer (cylindrical, 25 mm, 900 rpm) in a 250 mL round bottom flask. Method B: The reaction mixture is blended using a KPG stirrer (crescent,, 100 mm, 900 rpm) in a 1000 mL round bottom flask. Method C: Heated bubble column (20 mm inner diameter, volume 170 mL, airflow 170–200 mL min<sup>-1</sup>) (Figure 1). [b] All yields are isolated yields. [c] The reaction took place under complete exclusion of light.

Method

A

В

A

В

Α

В

A

Yield

[%]

76

60

73

69

76

54

45

54

72



carbon was evenly dispersed throughout the entire volume of the reaction solution by the air  $(170-200 \text{ mL min}^{-1})$ . Discharge of the solvent was minimized by the use of a reflux condenser. The advantage of the bubble column in comparison to standard laboratory methods (round bottom flask combined with a magnetic or KPG stirrer) is the improved dispersion of the air and the activated carbon within the solution. As a consequence thereof the specific reaction interface is increased. Furthermore, the flow of the air results in a continuous thorough mixing of the solution. Thus, dependence of the reaction on the diffusion of reactants is decreased and the efficiency of the reaction is increased.

A control experiment (oxidation without activated carbon) revealed the influence of the ac-

tivated carbon on the reaction, even if a slight formation of the product **3a** was observed (15%, Table 1, entry 7). After the reaction, the used activated carbon can be filtered off and used repeatedly in further oxidation reactions. Light is, however, not a relevant factor for the feasibility of the oxidation process (Table 1, entry 8). This fact reveals that the reaction is not a function of the formation of singlet oxygen.

Oxidation product

3a. R = Me

3c, R = Me

4b. R = H

3e, R = Me

4d, R = H

3g, R = Me

**4f**, R = Me

yield shows the overall yield of both diastereomers.

A

В

In addition to the methoxylation to products **3a** and **b**, hydroxylation was targeted. Using water instead of MeOH did not lead to the desired product **4a** (Table 1, entry 9). However, the hydroxylation occurred when using wet EtOAc as solvent (Table 1, entry 10). Entry 11 shows that the presence of water is essential for the formation of the product.

Under the optimized conditions (Table 1, entries 5, 6, and 10) the other previously synthesized 3-thiazolines 1c-h were converted. Table 2 shows that the oxidation of 1c-h in the bubble column to the corresponding  $\alpha$ -alkoxysulfides (3a-h) occurred with satisfactory or even good yields in all cases. Accordingly, the synthesis of  $\alpha$ -hydroxysulfides is also possible. Here, aldiminic 3-thiazolines (1h) can be used alongside the ketiminic 3-thiazolines (1a-g). We could not detect any significant diastereoselectivity during the reaction process, for example, the conversion of 3-thiazoline 1d led to a diastereomeric mixture of 53:47 (3d) and 55:45 (4c), respectively.

The results demonstrate that the bubble column is a suitable device also on laboratory scale for performing reactions that utilize both a liquid and a gaseous phase. Thus, the use of a bubble column allowed the efficient and environmentally friendly oxidation of the sulfides **1**. Air as a means for oxidation is an enormous advantage of this synthesis method. The main advantageous aspects of air in this context are its low price



**3b**, R = Me

4a, R = H

 $3f_{B} = Me$ 

3i, R = Et

**3i**, R = *i*Pr

4e, R = H

3h, R = Me

 $3d^{(c)}$ , R = Me (dv = 53:47)

4c<sup>[c]</sup>, R=Me (dv=55:45)

A first step towards making this oxidation reaction a general method for the synthesis of  $\beta$ , $\gamma$ -unsaturated sulfides was accomplished by the oxidation of a  $\beta$ -ketosulfide to the corresponding *O*,*S*-acetal (12%; Scheme 2). We noticed that the formation of the product **5** only occurred when the reaction was performed in a bubble column and not in a solution blended using a KPG-stirrer.



Scheme 2. Oxidation of a  $\beta$ -keto sulfide.

Table 2. Oxidation of several 3-thiazolines using the bubble column (Figure 1).<sup>[a,b]</sup>

Method Yield Oxidation product

[%]

75

59

53

71

48

68

55

[a] Solvent: Method A: Respective alcohol. Method B: Wet EtOAc. [b] All yields are isolated yields. [c] The given

In conclusion, we synthesized new *O*,*S*-acetals starting from 3-thiazolines by introducing a hydroxyl or an alkoxy group. To achieve this, a synthesis protocol was used that made it possible to oxidize the substrates without using expensive metals, toxic oxidizing agents, or photosensitizer. With the aid of activated carbon the sulfides were oxidized to the *O*,*S*-acetals by atmospheric oxygen. Most noteworthy is the fact that the reactions were carried out in a bubble column, which is an unconventional apparatus for laboratory syntheses. The benefits of the bubble column in the reaction process lead to higher yields at decreased reaction times in comparison to the com-

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monly used laboratory techniques. Due to the large number of known syntheses in which gaseous reactants are involved and the easy handling of the bubble column, this apparatus has the potential to play a major role in laboratory organic syntheses in the immediate future.

## **Experimental Section**

**General:** All reactions were performed in standard glassware with no special precautions taken for the exclusion of moisture or air or in a heated bubble column (Figure 1). MeOH was refluxed with Mg and freshly distilled prior to use. Activated carbon was purchased from Sigma Aldrich (Darco, 12–20 mesh, granular). Preparative column chromatography was carried out using Grace SiO<sub>2</sub> (0.035– 0.070 mm, type KG 60). Yields refer to analytically pure samples. Isomer ratios were determined by means of <sup>1</sup>H NMR integrals of cleanly separated signals.

Characterization: TLC was performed on Machery-Nagel SiO<sub>2</sub> F254 plates on aluminum sheets. Melting points were obtained on a melting point apparatus (Laboratory Devices) and were uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded using a Bruker AM 300 (measuring frequency: <sup>1</sup>H NMR—300.1 MHz), a Bruker AMX R 500 (measuring frequency: <sup>1</sup>H NMR—500.1 MHz, <sup>13</sup>C NMR— 125.8 MHz) or a Bruker Avance III 500 (measuring frequency:  $^1\mathrm{H}$  NMR—499.9 MHz,  $^{13}\mathrm{C}$  NMR—125.7 MHz) spectrometer in  $\mathrm{CDCI}_3$ or  $C_6 D_6$  solution. All chemical shifts are quoted on the  $\delta$  scale in ppm. As an internal standard, the signal of residual non-deuterated solvent was used [CDCl<sub>3</sub>]: 7.26 (<sup>1</sup>H NMR) and 77.16 ppm (<sup>13</sup>C NMR);  $C_6 D_6 :$  7.16 (^1H NMR) and 128.06 ppm (^13C NMR)].  $^{[14]}$  Assignments of the signals were supported by measurements applying DEPT and COSY techniques. Mass spectra were obtained on a Waters Q-TOF Premier (electrospray ionization) and a Finnigan-MAT 212 mass spectrometer with isobutane as reagent gas (chemical ionization). The IR spectra were recorded using a Bruker Tensor 27 spectrometer equipped with a "Golden Gate" diamond-ATR (attenuated total reflection) unit.

**Synthesis**: (*RS*)-2-Chlorocyclooctanone,<sup>[15]</sup> 2-chloro-2-phenylacetaldehyde,<sup>[16]</sup> 1,2-diphenyl-2-(*p*-tolylthio)ethan-1-one,<sup>[17]</sup> and 2,2,5,5tetramethyl-2,5-dihydro-thiazol<sup>[18]</sup> were prepared according to published procedures. 3-Thiazolines **1a**, **1b**, **1d–1g**<sup>[11]</sup> and **1c**<sup>[19]</sup> were prepared analogous to reported syntheses. Due to the hitherto incomplete characterization, all these 3-thiazolines were fully characterized (see the Supporting Information for further details). Compounds **3a** and **4a–4f** were previously reported by Asinger and co-workers, but an incorrect structure was assigned by them.<sup>[11]</sup>

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- [12] Comparison of IR spectra and melting points reveals that Asinger and co-workers also synthesized the  $\alpha$ -alkoxy- and  $\alpha$ -hydroxysulfide (**3** and **4**). Melting points [°C] (F. Asinger<sup>[11]</sup>/this work): **3a** 124.5/123; **4a** 145–146/139; **4b** 180–181/174; **4c** (diastereomeric mixture) 133–135/135; **4d** 112–115/117; **4e** 165/160; **4f** 165–170/167. A targeted synthesis of a sulfoxide was realized by oxidation with *m*CPBA starting from 2,2,5,5-tetramethyl-3-thiazoline<sup>[19]</sup> (product: 2,2,5,5-tetramethyl-2,5-dihydro-thiazol-1-oxid **6**). The IR spectrum of this product exhibits a characteristic IR band at 1034 cm<sup>-1</sup>. The oxidation of the 3-thiazolines **1** used in this work to the sulfoxides **2** is not possible with the aid of the common methods.
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