J. prakt. Chem. 338 (1996) 420–423

Journal für praktische Chemie
Chemiker-Zeitung


# Regioselective Oxidation and Halogenation of 2-(Arylsulfenylimino)- and 2-(Arylsulfinylimino)-4-thiazolines [1]

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Received January 30th, 1996

*Dedicated to Professor R. Gompper (Munich) on the Occasion of his 70th Birthday*

**Abstract.** The synthesis of 4-thiazoline 2-iminium sulfinates (**3**) is described. From the salts **3** and NBS the 2-(arylsulfonylimino)-4-thiazolines (**4**) were formed, which have also been prepared by oxidation of 2-(arylsulfenylimino)-4-thiazolines (**5**) and by reaction of the arylsulfonyl chlorides (**6**) with 2-imino-4-thiazolines (**2**). The treatment of **5** with NBS (or NIS) in dry solvents results in 2-(arylsulfenylimino)-5-bromo (or iodo)-4-thiazolines (**7**); in the presence of $NaHCO_3$ 2-(arylsulfonylimino)-5-bromo-4-thiazolines (**8**) are formed. 2-(Arylsulfinylimino)-4-thiazolines (**10**) have also been halo- genated in the same manner with NBS or NIS to give the products (**11**).

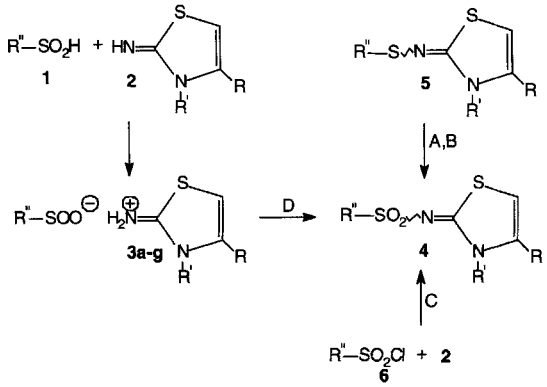
In connection with the aim to obtain 2-(arylsulfenylimino)-heterocycles we have recently reported the synthesis of 2-(arylsulfenylimino)-4-thiazolines **5** by the reaction of 2-imino-4-thiazoline-hydrochlorides **2**·HCl (existing as 4-thiazoline 2-iminium chlorides) with arylsulfenyl chlorides as well as by the reaction of *N*-arylsulfenylsuccinimides with 2-imino-4-thiazolines **2**. We have also shown that the treatment of 2-(arylsulfenylimino)-4-thiazolines **5** with *m*-chloroperbenzoic acid (m-CPBA) results in 2-(arylsulfinylimino)-4-thiazolines **10**. These substances were also synthesized by the reaction of sulfinyl chlorides with compounds **2** [1].

As previously discussed, both methods have disadvantages. The reaction with sulfinyl chlorides requires fairly strong conditions and often results in low yields and side reactions. The chemoselective oxidation with *m*-CPBA to the respective compounds **10** proved to be difficult. The result depends extremely on the reaction conditions and gives only moderate yields. On the other hand, the mixture $TiCl_3/H_2O_2$, which selectivily oxidizes sulfides to sulfoxides [2], gives only the corresponding sulfonyl compounds **4**.

*N*-Halogensuccinimides (NHS) are well known oxidizing reagents reported to convert sulfenamides into sulfinamides in high yields without formation of inconvenient by-products [3].

In this paper we report on the results of attempts to oxidize 2-(arylsulfenylimino)-4-thiazolines **5** with NHS to the corresponding 2-(arylsulfinylimino)-4-thiazolines **10**.

We have found that a cooled solution of *N*-chlorosuccinimide (NCS) as reported by Haake [3], affords the initial substances **5** only. However, the reaction of NCS with **5** over 4 days at 25 °C results in 2-(arylsulfonylimino)-4-thiazolines **4** (Scheme 1, Method A). These substances have also been prepared in yields of 16–48% by the reaction of salts **3** with 1 equiv. *N*-bromosuccinimide (NBS) (Scheme 1, Method D). The salts **3** were produced within 10 min by the reaction of the corresponding sulfinic acid **1** with 2-imino-4-thiazolines **2** in dioxane.The oxidation of **5** with *m*-CPBA in dichloromethane (Method B) or with $H_2O_2$ in acetic acid [4,5]




R = $C_6H_5$ ; R' = $R^1$-$C_6H_4$ ; R" = $R^2$-$C_6H_4$
A = $NCS/CH_2Cl_2$ ; B = m-CPBA/$CH_2Cl_2$ ; C = $Et_3N/CHCl_3$ ; D = $NBS/CH_2Cl_2$

**Scheme 1**

[1]) Lecture at the 2nd special conference on iminium salts, Stimpfach-Rechenberg, Germany, September 20–22, 1995

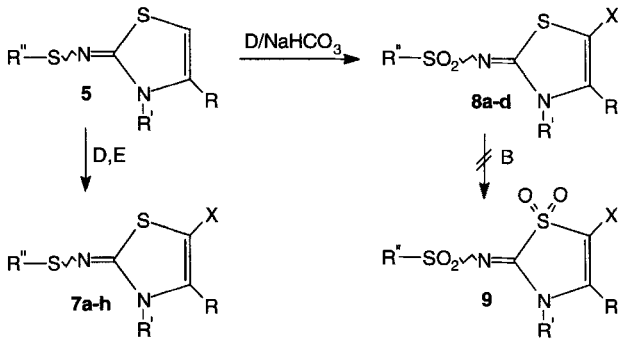
at 70–90 °C gives **4** in high purity. Undoubtedly, the less inexpensive and simplest method for the preparation of these compounds is the direct reaction of **2** with arylsulfonyl chlorides **6** (Scheme 1, Method C).

The structures of the compounds **3** and **4** are proved by microanalytical, $^{13}C$ NMR, $^{1}H$ NMR and mass spectral data. In the IR spectra of **3** the S=O frequency is found between $\nu$ = 1023–1007 $cm^{-1}$, the $NH_2^+$ stretching of the $C{=}NH_2^+$ group around $\nu$ =3104–3060 $cm^{-1}$. This is in accordance with the literature [6]. The respective mass spectra show the molecular ion peak of the 2-imino-4-thiazolines **2** as the base peak. In accordance with the investigation of similar compounds [7], we believe that the antisymmetric $SO_2$ stretching mode of **4** is located between $\nu_{as}$ = 1304–1276 $cm^{-1}$.Experimental data of the products **3** and **4** are given in table 1 and 2, respectively.

Some laboratories have introduced the use of catalysts in conjunction with NBS [8], and have applied these reagents to brominations of aromatic [9–14] and carbonyl substances [8, 15]. Additionally, NBS is a versatile synthetic reagent widely used to oxidize primary and secondary alcohols to aldehydes and ketones, respectively [16]. Nevertheless, the use of NBS as oxidizing agent for S,N-systems is unknown to our experience.

Using similar reaction conditions to those employed for NCS, compounds **5** were treated with NBS or NIS at room temperature during 2 days in dry dichloromethane without any catalytic agent. After evaporation of the solvent under reduced pressure pure regioselectively monohalogenated products **7** were isolated (Scheme 2, Methods D and E). When the reaction was run as above but with the addition of $NaHCO_3$ the products obtained were 2-(arylsulfonylimino)-5-bromo-4-thiazolines **8**, which have been also rapidly synthesized by the reaction of **4** with NBS. Oxidation of **8** with *m*-CPBA to form compounds **9** was impossible.

2-(Arylsulfinylimino)-4-thiazolines **10** have also been brominated in the same manner and gave 2-(arylsulfinylimino)-5-bromo-4-thiazolines **11** in yields of 51–63 %. We found this method applicable for the synthesis of 2-(arylsulfinylimino)-5-iodo-4-thiazolines **11a,b** when **10** was treated with *N*-iodosuccinimide (NIS) for 2 days at 25° C in dichloromethane (Scheme **3**, Table 5). The products **7** (Table 3), **8** (Table 4) and **11** (Table 5) were checked for purity by mass spectrometry. The $^{13}C$ NMR, $^{1}H$ NMR, IR spectra and elemental analysis are in agreement with these structures. Additional proof for the structures are given by X-ray crystallography of **4b**, **7b** and **11h** (for **7b** and **11h** see Fig.1 and Fig.2, resp.).The observed bond lengths and angles do not show any remarkable specialities. However, there is an intermolecular contact between a chlorine and a bromine atom of 3.5892(17) Å in the solid of **7b**, which is just below the sum of the van der Waals radii of 3.60 Å .




**Scheme 2**

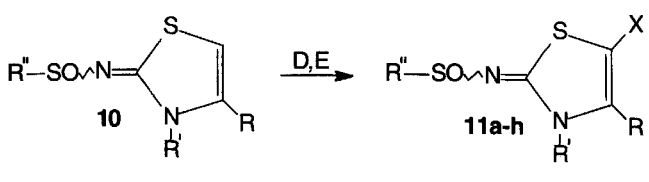
**Table 1** Yields of 4-Thiazoline-2-iminium sulfinates (**3a-g**)

| 3 | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|
| **a** | H | H | 91 |
| **b** | H | 4-$CH_3$ | 64 |
| **c** | 3-Cl | H | 61 |
| **d** | 4-Cl | H | 97 |
| **e** | 4-$OCH_3$ | H | 93 |
| **f** | 4-$NO_2$ | H | 79 |
| **g** | 4-$NO_2$ | 4-$CH_3$ | 95 |

**Table 2** Data of 2-(Arylsulfonylimino)-4-thiazolines (**4a-f**)

| 4 | $R^1$ | $R^2$ | Method Yield (%) A | B | C | D | m.p. (°C) |
|---|---|---|---|---|---|---|---|
| **a** | H | H | 17 | 82 | 73 | 16 | 205–206 |
| **b** | H | 4-$CH_3$ | – | – | – | 48 | 217–218 |
| **c** | 4-Cl | H | – | – | – | 36 | 249–250 |
| **d** | 4-Cl | 4-Cl | – | 63 | 75 | – | 270–272 |
| **e** | 4-F | 4-Cl | 29 | 67 | 58 | – | 253–256 |
| **f** | 4-$OCH_3$ | H | – | – | – | 18 | 250–251 |

We would like to thank the BASF AG, Ludwigshafen, for financial support.




**Scheme 3**

**Table 3** Data of 2-(Arylsulfenylimino)-5-bromo(or iodo)-4-thiazolines (**7a–h**)

| 7 | $R^1$ | $R^2$ | X | Yield (%) | m.p.°C |
|---|---|---|---|---|---|
| **a** | 3-Cl | 2-$NO_2$ | Br | 46 | 177–178 |
| **b** | 4-Cl | 2-$NO_2$ | Br | 63 | 186–187 |
| **c** | 4-F | H | Br | 51 | 163–165 |
| **d** | 4-F | 4-Cl | Br | 27 | 195–196 |
| **e** | 4-$OCH_3$ | 2-$NO_2$ | Br | 57 | 186–189 |
| **f** | 4-$NO_2$ | 4-Cl | Br | 47 | 153–155 |
| **g** | 4-$NO_2$ | 2-$NO_2$ | Br | 76 | 170–172 |
| **h** | 4-Cl | 2,4-$(NO_2)_2$ | I | 63 | 230–232 |

**Table 4** Data of 2-(Arylsulfonylimino)-5-bromo-4-thiazolines (**8a–d**)

| | $R^1$ | $R^2$ | X | Yield (%) | m.p. °C |
|---|---|---|---|---|---|
| **a** | H | H | Br | 60 | 194-195 |
| **b** | 3-Cl | H | Br | 93 | 235-236 |
| **c** | 4-Cl | H | Br | 79 | 230-233 |
| **d** | 4-$OCH_3$ | H | Br | 81 | 190-191 |

**Table 5** Data of 2-(Arylsulfinylimino)-5-bromo(or iodo)-4-thiazolines (**11a–h**)

| 11 | $R^1$ | $R^2$ | X | Yield (%) | m.p. °C |
|---|---|---|---|---|---|
| **a** | 4-Cl | H | I | 41 | 186-188 |
| **b** | 4-Cl | 4-$CH_3$ | I | 74 | 189-191 |
| **c** | 4-Cl | 4-$CH_3$ | Br | 51 | 160-162 |
| **d** | 4-F | H | Br | 58 | 175-176 |
| **e** | 4-F | 4-Cl | Br | 57 | 202-203 |
| **f** | 4-$OCH_3$ | 4-$CH_3$ | Br | 61 | 163-165 |
| **g** | 4-$NO_2$ | H | Br | 51 | 177-179 |
| **h** | 4-$NO_2$ | 4-$CH_3$ | Br | 63 | 210-211 |

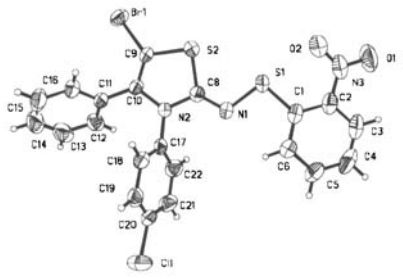



*Fig. 1* Molecular structure of **7b** (ORTEP-plot with 50% probability)
Selected bond distances [Å] and angles [°]: C(1)-S(1) 1.754(5), S(1)-N(1) 1.705(4), N(1)-C(8) 1.274(6), C(8)-S(2) 1.774(5), C(8)-N(2) 1.390(6), S(2)-C(9) 1.749(5), C(1)-S(1)-N(1) 99.90(22), S(1)-N(1)-C(8) 112.69(33)

## Experimental

Melting points were determined with a micro heating stage of Boëtius (Carl Zeiss Jena) without correction. $^1$H NMR and

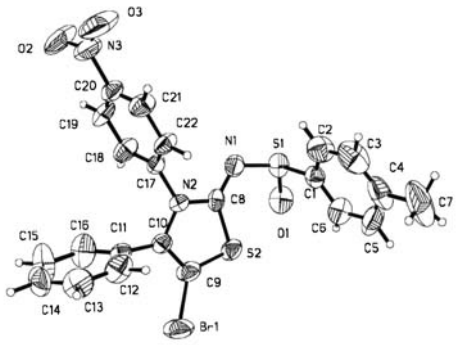



*Fig. 2* Molecular structure of **11h** (ORTEP-plot with 50% probability)
Selected bond distances [Å] and angles [°]: C(1)-S(1) 1.814(8), S(1)-O(1) 1.497(6), S(1)-N(1) 1.665(7), N(1)-C(8) 1.292(9), C(8)-S(2) 1.768(8), C(8)-N(2) 1.362(9), C(1)-S(1)-N(1) 99.99(35), S(1)-N(1)-C(8) 120.07(59)

$^{13}$C NMR spectra were taken with an AC 250 spectrometer (Bruker) using TMS as an internal reference and mass spectra on a AMD 402-3 spectrometer (Intectra GmbH). IR spectra were recorded on a 205FT-IR spectrophotometer. Elementary analyses were performed by a CHNS-932 LECO analyzer.

### Crystal Structure Determination

Crystals of **7b** and **11h** were measured on a Siemens P4 four circle diffractometer after taking rotational photos and determining the unit cells in automatic mode. The unit cell measures found are: a=10.007(1)Å, b=9.158(1)Å, c=23.158(1)Å, β= 90.10(1)° for **7b**, that crystallizes in $P2_1/n$ and a= 25.934(4)Å, b=8.043(2)Å, c=21.970(4)Å, β=104.83(1)° for **11h**, crystallizing in C2/c. The data were collected in routine ω-scan. The structures were solved by direct methods (Siemens SHELXTL, 1990, Siemens Analytical X-ray Inst. Inc.) and refined by the full-matrix least squares method of SHELXL-93 [17]. All non-hydrogen atoms were refined anisotropically. Although some hydrogen positions could be seen from the difference Fourier map, all hydrogens were put into their theoretical positions and refined using the „riding model". The weighting scheme was calculated according to $w=1/[\sigma^2(Fo^2)+(0.0562P)^2+0.0000P]$ for **7b** and $w=1/[\sigma^2(Fo^2)+(0.0848P)^2+0.0000P]$ for **11h** with $P=(Fo^2+2Fc^2)/3$ in both cases. Since the absorption coefficient μ was above 20 cm$^{-1}$ for both data sets an empirical absorption correction was performed using the XEMP part of Siemens SHELXTL.
The reflection to parameter ratio was 2575/271 for **7b** and 2848/281 for **11h**. The weighted R2 (wR2, based on $F^2$) was 0.1116 and 0.1927, respectively, while the conventional R1 were calculated to be 0.0414 for 2126 observed reflections of **7b** and 0.069 for 1707 observed reflections of **11h** (observation criterion: $I > 2\sigma(I)$ ).
Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, on quoting the depository number CSD-405120 (**7b**) and CSD-405121 (**11h**),

the names of the authors, and the journal citation. Data for **4b** may be obtained on quoting the depository number CSD-405122.

### 4-Thiazoline-2-iminium sulfinates (3a–g) (General procedures)

A solution of 0.01mol 2-imino-4-thiazoline (**2**) in 20mL anhydrous dioxane is added to a solution of 0.01mol sulfinic acid (**1**) in 10mL anhydrous dioxane. The reaction mixture is stirred for 10min. The precipitated salt **3** is filtered off, washed with dry ether, dried one day on the air and used in the next step (Method D) without purification.

### 2-(Arylsulfonylimino)-4-thiazolines (4a–f)

*Method A:*
A solution of 0.01mol *N*-chlorosuccinimide in 50mL anhydrous dichloromethane is added dropwise at 25 °C to a solution of 0.01mol 2-(arylsulfenylimino)-4-thiazolines (**5**) in 50mL anhydrous dichloromethane. The reaction mixture is shaked (shaking maschine) for 4d. The solvent is evaporated under reduced pressure, and the residue is recrystallized from ethanol/water.

*Method B:*
A solution of 0.01mol (85%) *m*-chloroperbenzoic acid in 80mL dry dichloromethane is added dropwise at 80°C to a stirred solution of 0.01mol 2-(arylsulfenylimino)-4-thiazoline (**5**) in 100mL dry dichloromethane. Stirring is continued for 1h, then the solution is evaporated to dryness under reduced pressure. The residue is purified by recrystallization from ethanol.

*Method C:*
A solution of 0.01mol sulfonyl chloride (**6**) in 50mL anhydrous chloroform is added dropwise at room temperature to a mixture of 0.01mol 2-imino-4-thiazoline (**2**) and 0.01mol triethylamine stirred in 50mL anhydrous chloroform. After addition, the mixture is stirred 3h, the solvent is evaporated under reduced pressure, and the residue is recrystallized from ethanol/water.

*Method D:*
A solution of 0.01mol *N*-bromosuccinimide in 20mL anhydrous dichloromethane is added to a slurry of 50mL dichloromethane and the corresponding 4-thiazoline-2-iminium sulfinate **3** (0.01mol). The reaction mixture is stirred at room temperature for 2h and then filtered to remove the precipitated succinimide. The solution is evaporated to dryness under reduced pressure. The residue is purified by recrystallization from ethanol.

### 2-(Arylsulfenylimino)-5-bromo-4-thiazolines (7a–g) and 2-(Aryllsulfenylimino)-5-iodo-4-thiazoline (7h)

*Methods D and E:*
A solution of 0.01mol *N*-bromosuccinimide or *N*-iodosuccinimide in 50mL anhydrous dichloromethane is added at room temperature to a solution of 0.01mol 2-(arylsulfenylimino)-4-thiazoline (**5**) in 50mL dichloromethane. The mixture is stirred for 2d, the solvent is evaporated under reduced pressure, and the residue is recrystallized from dry ethanol.

### 2-(Arylsulfonylimino)-5-bromo-4-thiazolines (8a–d)

A solution of 0.01mol 2-(arylsulfenylimino)-4-thiazoline (**5**) in 50mL dry dichloromethane is added at room temperature to a mixture of a 10mL solution of $NaHCO_3$ and a solution of 0.01mol *N*-bromosuccinimide in 50mL dichloromethane stirred at room temperature. After addition, the reaction mixture is stirred 3h. The organic phase is dried with magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue is purified by recrystallization from ethanol.

### 2-(Arylsulfinylimino)-5-bromo(or iodo)-4-thiazolines (11a–h)

*Methods D and E:*
A solution of 0.01mol *N*-bromosuccinimide or *N*-iodosuccinimide in 50mL anhydrous dichloromethane is added at room temperature to a solution of a 0.01mol 2-(arylsulfinylimino)-4-thiazoline (**10**) in 50mL dichoromethane. The mixture is stirred for 2d, the solvent is evaporated under reduced pressure, and the residue is recrystallized from dry ethanol.

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