


Communication

# Convenient and Efficient Synthesis of Functionalized 2-Sulfenylindoles

Justyna Doroszuk, Mateusz Musiejuk, Bartosz Jędrzejewski,  
Juliusz Walczak and Dariusz Witt \* 

Department of Organic Chemistry, Faculty of Chemistry, Gdansk University of Technology, Narutowicza 11/12, 80-233 Gdansk, Poland; juswicz@student.pg.gda.pl (J.D.); mateusz.musiejuk@interia.eu (M.M.); barjedrz@student.pg.edu.pl (B.J.); pyrher@gmail.com (J.W.)

\* Correspondence: dariusz.witt@pg.edu.pl; Tel.: +48-(58)-3471851; Fax: +48-(58)-3472694

Received: 23 September 2020; Accepted: 1 October 2020; Published: 10 October 2020



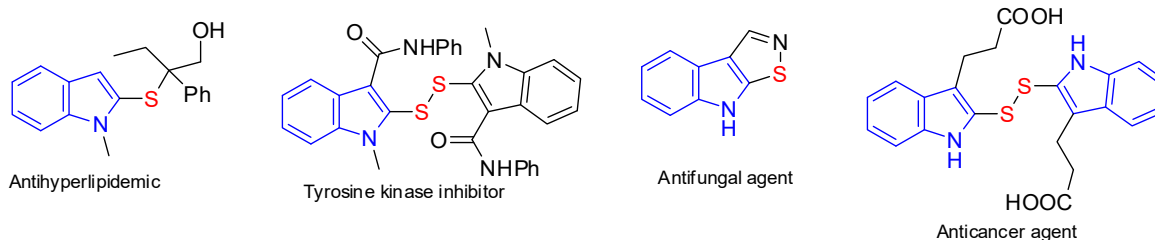
**Abstract:** A simple, efficient, and practical sulfenylation at the C2 position of *N*-tosylindoles under mild conditions was developed. The designed transformation is based on the reaction of *N*-tosylindoles with BuLi and *S*-alkyl, and *S*-aryl phosphorodithioates or thiotosylates to produce 2-sulfenylindoles in moderate to high yields. The presence of additional hydroxy, carboxy, or amino functionalities did not disturb the formation of products.

**Keywords:** indoles; sulfides; thiotosylates; sulfenylation; sulfenylindoles

## 1. Introduction

Indole is a structural functionality found in a diversity of biologically active molecules [1]. The functionalization of an indole ring by a variety of substituents and methods has been intensively studied [2–4]. These indole derivatives were used as blue-light emitting materials [5], materials for solar cells [6], potential prodrugs [7], and the dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) inhibitors [8].

Sulfenylindoles, as important derivatives of indoles, can be frequently found in medicinal and bioorganic chemistry. Selected examples are presented in Figure 1.

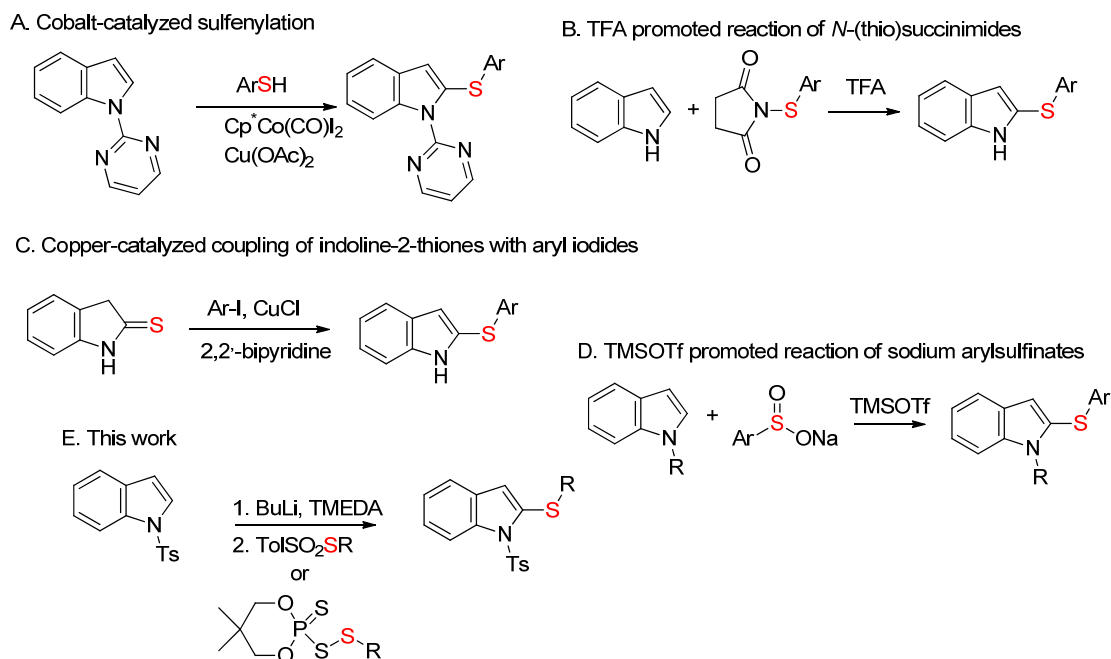


**Figure 1.** Selected examples of biologically active sulfenylindoles.

They were applied in drug discovery and development for the treatment of various diseases. Compounds for the treatment of cancer [9], HIV [10,11], vascular [12], heart disease [13], respiratory disorders [14], and allergies [15] were developed. These compounds were also applied as COX-2 inhibitors in medicinal chemistry [16,17] and potent inhibitors of tubulin polymerization [18,19].

There are many efficient methodologies for the synthesis of sulfenylindoles reported in the literature [20–25]. Among them, the direct sulfenylation of indoles is one of the most efficient and common strategies [26–33]. Due to the nucleophilic properties of an indole ring, it can be easily functionalized at the C3 position by using a variety of electrophiles. The formation of carbon–carbon

bonds and carbon–heteroatom bonds can be observed according to the structure of electrophiles. The 3-Sulfenylindoles are readily available by the reaction of indoles with a variety of sulfenylating reagents. The most commonly utilized reagents are sulfenyl halides [34], thiols [35], disulfides [36–38], arylsulfonyl hydrazides [39,40], arylsulfonyl chlorides [41,42], sulfinic acids [43], and sulfonium salts [44,45]. Usually, sulfenylation of indoles proceeds at the C3 position of an indole ring. In contrast, sulfenylation at the C2 position of indoles is difficult but has also been accomplished. The most common strategies involve introducing a directing group at the N1 position (Scheme 1A), [46] blocking the C3 position, [47] using a N-(thio)succinimide/trifluoroacetic acid (TFA) reaction system (Scheme 1B) [48], and removing the proton at the C2 position [49–52].



**Scheme 1.** General strategies for the synthesis of 2-sulfenylindoles (A–D) and our new approach (E).

Other practical procedures involve the reaction of copper-catalyzed coupling of indoline-2-thiones with aryl iodides (Scheme 1C) [53], acid-catalyzed rearrangement of 3-sulfenylindole [54,55], and multicomponent synthesis of thieno[2,3-*b*]indole derivatives [56–58]. Recently, regioselective sulfenylation at the C2 position of indoles with sodium arylsulfonates has been accomplished in the presence of TMSOTf as a promoter (Scheme 1D) [59].

Although the presented methods provided 2-sulfenylated indoles, the applied harsh conditions were incompatible with various functional groups. Moreover, in most cases, the arylsulfenyl group can be introduced in the C2 position. Thus, the development of an efficient and versatile strategy for the synthesis of 2-sulenyndoles possessing alkylsulfenyl and arylsulfenyl functionalities with additional functional groups is highly desirable. In this context, we report a regioselective sulfenylation at the C2 position of *N*-tosylindoles with sulfenylating reagents (Scheme 1E). Earlier studies demonstrated the application of readily available 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-disulfanyl derivatives for the preparation of functionalized unsymmetrical disulfides [60–64],  $\alpha$ -sulfenylated carbonyl compounds [65], and unsymmetrical alkynyl sulfides [66,67].

## 2. Materials and Methods

All 1-((4-methylphenyl)sulfonyl)indoles (**1a–d**) were obtained from indole, 5-methoxyindole, 5-bromoindole, and 5-aminoindole, respectively. Sodium hydride and *p*-toluenesulfonyl chloride were purchased from Merck (Darmstadt, Germany). All bromides required for preparation thiosylates **3** were purchased from ProChimia (Sopot, Poland). The 5,5-Dimethyl-2-thioxo-

1,3,2-dioxaphosphorinane-2-disulfanyl derivatives [60–65] **2** and thiotosylates [67] **3** were prepared by the literature methods. Sodium 4-methylbenzenesulfonothioate was obtained from sodium 4-methylbenzenesulfinate purchased from Merck (Darmstadt, Germany). *N,N,N',N'*-tetramethylethylenediamine (TMEDA) is available from Merck (Darmstadt, Germany). Tetrahydrofuran was pre-dried over KOH pellets and distilled. Subsequently, tetrahydrofurane (THF) was dried by heating under reflux over potassium in the presence of benzophenone as an indicator and distilled. Thin layer chromatography (TLC) was performed with silica gel Supelco UV254 (St. Louis, MI, USA). Column chromatography was performed using silica gel 60 (230–400 mesh, Merck, Darmstadt, Germany). NMR spectra were recorded on Bruker 400 MHz spectrometers. The residual solvent peak was used as the internal reference (CDCl<sub>3</sub>:  $\delta = 7.26$  ppm for <sup>1</sup>H,  $\delta = 77.0$  ppm for <sup>13</sup>C). IR spectra were recorded on Nicolet Is50 Fourier-transform infrared (FT-IR) spectrometer (Wien, Austria) by Attenuated Total Reflectance (ATR) method. Melting points were measured with Gallenkamp 7936B apparatus (Warwick, UK).

### 2.1. General Procedure for the Preparation of 2-sulfenyl-1-((4-methylphenyl)sulfonyl)-1H-indoles **8** from Phosphorodithioates **2**

To a stirred, cooled to 0 °C solution of indole **1a–d** (1 mmol) and *N,N,N',N'*-tetramethylethane-1,2-diamine (1 mmol) in dry THF (5 mL) was added dropwise *n*-BuLi (2.5 M in hexane; 1 mmol). The mixture was stirred at 0 °C for 5 min. Then the solution of phosphorodithioate disulfanyl derivative **2** (1 mmol) in dry THF (5 mL) was added. The reaction was warmed to room temperature and stirred for 15 min. The mixture was diluted with Et<sub>2</sub>O (30 mL) and washed with water (10 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. The products were purified by column chromatography.

### 2.2. General Procedure for the Preparation of 2-sulfenyl-1-((4-methylphenyl)sulfonyl)-1H-indoles **8** from Thiotosylates **3**

To a stirred, cooled to 0 °C solution of indole **1a–d** (1 mmol) and *N,N,N',N'*-tetramethylethane-1,2-diamine (1 mmol) in dry THF (5 mL) was added dropwise *n*-BuLi (2.5 M in hexane; 1 mmol). The mixture was stirred in 0 °C for 5 min. Then the solution of thiotosylates **3** (1 mmol) in dry THF (5 mL) was added. The reaction was warmed to room temperature and stirred for 15 min. The mixture was diluted with Et<sub>2</sub>O (30 mL) and washed with water (10 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The products were purified by column chromatography.

Synthesis of starting materials and 2-sulfenylindoles **8** with analytical data and copy of IR, and NMR spectra are in the Supplementary Materials.

## 3. Results and Discussion

The preliminary determination of the conditions was performed on *N*-tosylindole **1a** to obtain the required 2-sulfenylindole **8**. The sulfenylation at the C2 position of indoles was investigated, employing various electrophilic sulfenylating compounds **2–7** to determine the most efficient reagents. The results are summarized in Table 1.

By using didodecyl disulfide **4** and diphenyl disulfide **7**, expected products **8a** and **8b** were produced in 72% and 95% yields, respectively. It appeared that diaryl disulfides were more effective than dialkyl disulfides in this synthesis (Table 1; entries 3 and 6). Disulfide **7** is probably the better electrophile due to the better leaving group properties of the aryl thiolate anion. However, the main disadvantage of disulfides is the introduction of only half of a starting material into the product.

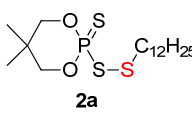
When **1a** was treated with *N*-(thiododecyl)phthalimide **5** or *N*-(thiododecyl)succinimide **6**, indole **8a** was obtained in 55% and 53% yield, respectively (Table 1; entries 4 and 5). Although *N*-(thiododecyl)phthalimide or *N*-(thiododecyl)succinimide are known as good electrophilic reagents, it looks like leaving groups, phthalimide or succinimide anions, are less efficient for examined transformation. The best yield was observed by using *S*-dodecyl toluenethiosulfonate **3a** or 1-((5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)disulfanyl) dodecane **2a** as the

sulfonylating reagent, with which **8a** was obtained in 83% and 72% yields, respectively (Table 1; entries 1 and 2). From a practical point of view, corresponding thiosulfonates and 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-disulfanyl derivatives are readily available from thiols or appropriate alkyl halides and were selected as sulfonylating reagents for further studies. In addition, THF was the best solvent to accomplish sulfonylation at the C2 position. *N,N,N',N'*-Tetramethylethane-1,2-diamine (TMEDA) was added to avoid the aggregation of regioselective [49] generated 2-lithium-*N*-tosylindoles and to improve their reactivity.


**Table 1.** Evaluation of the reaction conditions.

Entry <sup>1</sup>	R <sup>1</sup> -S-R <sup>2</sup>	<b>8</b>	Yield (%) <sup>2</sup>
1	<b>2a</b>	<b>8a</b>	72
2	<b>3a</b>	<b>8a</b>	83
3	<b>4</b>	<b>8a</b>	72
4	<b>5</b>	<b>8a</b>	55
5	<b>6</b>	<b>8a</b>	53
6	<b>7</b>	<b>8b</b>	95

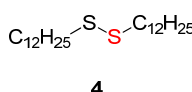
  



**2a**

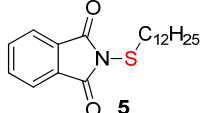


**3a**




**4**

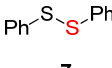
  



**5**



**6**



**7**

<sup>1</sup> Reaction conditions: **1a** (1 mmol), TMEDA (1 mmol), BuLi (1 mmol), 0 °C, THF, 5 min. Then, **2-7** (1 mmol) was added, rt, 15 min. <sup>2</sup> Isolated yields.

When the most efficient reagent and a useful set of conditions were determined, then we examined the scope of the reaction by subjecting indole derivatives **1a-d** to the sulfonylation at the C2 position by a variety of phosphorodithioate disulfanyl derivatives **2**. The results are summarized in Table 2.

As shown in Table 2, the formation of 2-sulfonylated indoles **8** was accomplished when the indole ring was not substituted (Table 2; entries 1–9) in 65–94% yields. The presence of an electron-donating or an electron-withdrawing group at the C5 position did not disturb the progress of the reaction, and appropriate indoles **8** were obtained in 69–91% yields (Table 2; entries 10–23). When the protected amino group was attached in the position C5 of an indole ring, then 2-sulfonylated indoles **8** were obtained in lower yields 65–78%. The formation of products **8** can be accomplished for alkyl and aryl derivatives **2**. Moreover, the presence of additional functional groups did not affect reactivity, and functionalized 2-sulfonyl indoles were produced in good yields.

Although the above reactions were successful, we were interested in that they improved the formation of 2-sulfonylated indoles **8** by using thiotosylates **3** as a sulfonylating reagent. We selected indoles **1a-d** and appropriate thiotosylates **3** with the same substitution pattern to clarify the effect of the sulfonylating reagent. The results are summarized in Table 3.

**Table 2.** Reaction of indoles **1** with phosphorodithioate disulfanyl derivatives **2**.

Entry <sup>1</sup>	R <sup>1</sup>	R <sup>2</sup>	<b>8</b>	Yield (%) <sup>2</sup>
1	H- <b>1a</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> -	<b>8a</b>	72
2		C <sub>6</sub> H <sub>5</sub> -	<b>8b</b>	94
3		CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>9</sub> -	<b>8c</b>	78
4		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> -	<b>8d</b>	78
5		4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	<b>8e</b>	86
6		CH <sub>3</sub> OOC(CH <sub>2</sub> ) <sub>10</sub> -	<b>8f</b>	75
7		HO(CH <sub>2</sub> ) <sub>11</sub> -	<b>8g</b>	67
8		4-CN-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	<b>8h</b>	65
9		C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	<b>8i</b>	87
10	CH <sub>3</sub> O- <b>1b</b>	CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>9</sub> -	<b>8j</b>	71
11		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> -	<b>8k</b>	81
12		4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	<b>8l</b>	86
13		CH <sub>3</sub> OOC(CH <sub>2</sub> ) <sub>10</sub> -	<b>8m</b>	72
14		HO(CH <sub>2</sub> ) <sub>11</sub> -	<b>8n</b>	78
15		4-CN-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	<b>8o</b>	72
16		C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	<b>8p</b>	82
17	Br- <b>1c</b>	CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>9</sub> -	<b>8r</b>	69
18		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> -	<b>8s</b>	84
19		4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	<b>8t</b>	91
20		CH <sub>3</sub> OOC(CH <sub>2</sub> ) <sub>10</sub> -	<b>8u</b>	79
21		HO(CH <sub>2</sub> ) <sub>11</sub> -	<b>8w</b>	76
22		4-CN-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	<b>8x</b>	69
23		C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	<b>8y</b>	85
24	BocNH- <b>1d</b>	CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>9</sub> -	<b>8z</b>	65
25		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> -	<b>8aa</b>	68
26		4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	<b>8ab</b>	72
27		CH <sub>3</sub> OOC(CH <sub>2</sub> ) <sub>10</sub> -	<b>8ac</b>	65
28		HO(CH <sub>2</sub> ) <sub>11</sub> -	<b>8ad</b>	71
29		4-CN-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	<b>8ae</b>	66
30		C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	<b>8af</b>	78

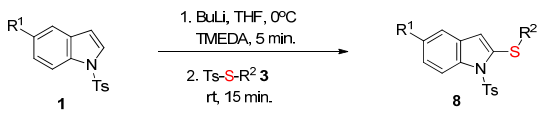
<sup>1</sup> Reaction conditions: **1** (1 mmol), TMEDA (1 mmol), BuLi (1 mmol or 2 mmol for **1d**), 0 °C, THF, 5 min. Then, **2** (1 mmol) was added, rt, 15 min. <sup>2</sup> Isolated yields.

As demonstrated, the expected 2-sulfenylindoles **8** were obtained in good yields independent of the substitution pattern of the indole ring. When the indole ring was not substituted at the C5 position, the yield of 2-sulfenylindoles **8a–8i** was in the range 68–92% (Table 3; entries 1–9). The presence of an electron-donating group at the C5 position did not disturb the reaction and 2-sulfenylindoles **8j–8p** were obtained in 67–82% yields (Table 3; entries 10–16). The substitution of the indole ring at the C5 position by an electron-withdrawing substituent did not affect the reactivity, and the corresponding 2-sulfenylindoles **8r–8y** were produced in good yields (68–86%) (Table 3; entries 17–23). However, when the protected amino group was present in the C5 position, a slightly lower yield (62–79%) of products **8z–8af** was observed (Table 3; entries 24–30).

Interestingly, the developed sulfenylation method can be applied to either *S*-alkyl thiosylates, or *S*-aryl thiosylates. The presence of additional functional groups, such as ester, cyano, hydroxy, and protected amino moieties or carbon–carbon double bonds, did not disturb the formation of 2-sulfenylindoles **8**. However, using thiosylates **3** instead of phosphorodithioate disulfanyl derivatives **2** as a sulfenyating reagent did not improve the yield of product **8**. Although both methods provided 2-sulfenylindoles **8** in comparable yields and tolerance of additional functional groups, the using of

thiotosylates **3** seems to be more convenient. These compounds are readily available from the reaction of appropriate alkyl halides and sodium thiotosylate or thiols and tosyl bromide.

**Table 3.** Reaction of indoles **1** with thiotosylates **3**.



Entry <sup>1</sup>	R <sup>1</sup>	R <sup>2</sup>	<b>8</b>	Yield (%) <sup>2</sup>
1	H- <b>1a</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> -	<b>8a</b>	83
2		C <sub>6</sub> H <sub>5</sub> -	<b>8b</b>	92
3		CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>9</sub> -	<b>8c</b>	81
4		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> -	<b>8d</b>	82
5		4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	<b>8e</b>	82
6		CH <sub>3</sub> OOC(CH <sub>2</sub> ) <sub>10</sub> -	<b>8f</b>	69
7		HO(CH <sub>2</sub> ) <sub>11</sub> -	<b>8g</b>	68
8		4-CN-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	<b>8h</b>	69
9		C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	<b>8i</b>	85
10	CH <sub>3</sub> O- <b>1b</b>	CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>9</sub> -	<b>8j</b>	78
11		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> -	<b>8k</b>	81
12		4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	<b>8l</b>	82
13		CH <sub>3</sub> OOC(CH <sub>2</sub> ) <sub>10</sub> -	<b>8m</b>	67
14		HO(CH <sub>2</sub> ) <sub>11</sub> -	<b>8n</b>	76
15		4-CN-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	<b>8o</b>	68
16		C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	<b>8p</b>	82
17	Br- <b>1c</b>	CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>9</sub> -	<b>8r</b>	74
18		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> -	<b>8s</b>	83
19		4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	<b>8t</b>	86
20		CH <sub>3</sub> OOC(CH <sub>2</sub> ) <sub>10</sub> -	<b>8u</b>	78
21		HO(CH <sub>2</sub> ) <sub>11</sub> -	<b>8w</b>	76
22		4-CN-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	<b>8x</b>	68
23		C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	<b>8y</b>	84
24	BocNH- <b>1d</b>	CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>9</sub> -	<b>8z</b>	70
25		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> -	<b>8aa</b>	79
26		4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	<b>8ab</b>	71
27		CH <sub>3</sub> OOC(CH <sub>2</sub> ) <sub>10</sub> -	<b>8ac</b>	62
28		HO(CH <sub>2</sub> ) <sub>11</sub> -	<b>8ad</b>	69
29		4-CN-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	<b>8ae</b>	63
30		C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	<b>8af</b>	78

<sup>1</sup> Reaction conditions: **1** (1 mmol), TMEDA (1 mmol), BuLi (1 mmol or 2 mmol for **1d**), 0 °C, THF, 5 min. Then, **3** (1 mmol) was added, rt, 15 min. <sup>2</sup> Isolated yields.

The suggested mechanism to explain the course of the reactions involves the initial regioselective formation of the 2-lithium-*N*-tosylindoles through the reaction of BuLi with *N*-tosylindoles **1**. The resulting lithium salt reacts with electrophilic phosphorodithioate disulfanyl derivatives **2** or thiotosylates **3** to yield 2-sulfenylindoles **8** (Figure 2).

The tosyl group protects the indole functionality and is also used as directing metalation group [68] to produce 2-lithium-*N*-tosylindoles. The regioselective proton removal is responsible for exclusive 2-sulfenylated *N*-tosylindole **8** formation. Although a variety of protected compounds **8** were obtained, we were interested in using them as starting materials for the preparation of nonprotected indoles. The standard basic conditions for tosyl group removal were applied [69]. Selected compounds **8c** and **8k** were treated with NaOH in MeOH/H<sub>2</sub>O, and the resulting mixture was refluxed overnight under nitrogen (Scheme 2).



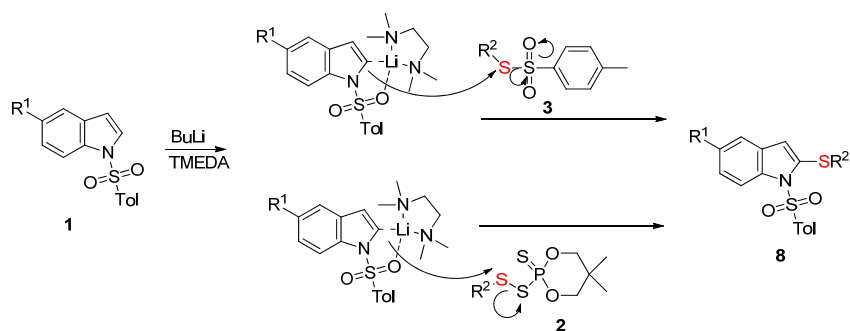
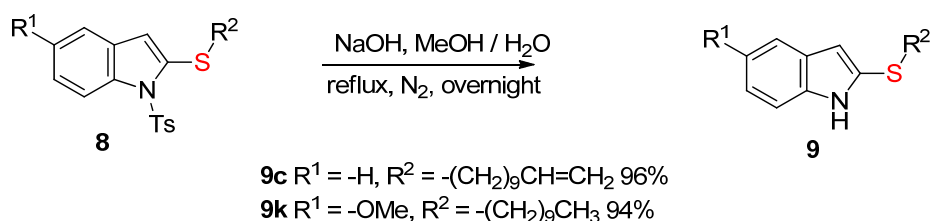


Figure 2. Plausible reaction mechanism.



Scheme 2. Formation of nonprotected indoles 9.

As demonstrated, the formation of nonprotected indole **9** was convenient and effective. When 2-sulfenylindoles **8c** and **8k** were treated with NaOH in methanol (conditions were not optimized), nonprotected products **9c** and **9k** were obtained in 96% and 94% yields, respectively. This deprotection method, together with the developed regioselective sulfenylation of *N*-tosylindoles **1** at the C2 position, gives an attractive alternative for the preparation of 3-unsubstituted nonprotected 2-sulfenylindoles.

#### 4. Conclusions

In summary, we developed a convenient, efficient, and versatile regioselective sulfenylation of 3-unsubstituted *N*-tosylindoles **1** to access a variety of new functionalized indole derivatives. These methods were accomplished with readily available phosphorodithioate disulfanyl derivatives **2** or thiotosylates **3** as the sulfenylating reagents, and regioselectively generated 2-lithium-*N*-tosylindoles. Moreover, developed methods can be applied to *S*-alkyl and *S*-aryl derivatives of **2** and **3**. The reactions were accomplished under mild conditions and the presence of various functional groups did not disturb the formation of 2-sulfenylindoles **8**.

**Supplementary Materials:** The following are available online at <http://www.mdpi.com/1996-1944/13/20/4492/s1>: Synthesis of starting materials and 2-sulfenylindoles **8** with analytical data and copy of IR, and NMR spectra.

**Author Contributions:** J.D., synthesis of starting materials and products, leading investigator; M.M., synthesis of starting materials and products, equal investigator; B.J., synthesis of starting materials and products, equal investigator; J.W., synthesis of starting materials, supporting investigator; D.W., project management, supervision, manuscript preparation. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the National Science Centre (NCN), grant number 2015/19/B/ST5/03359.

**Conflicts of Interest:** The authors declare no conflict of interest.

#### References

- Wan, Y.; Li, Y.; Yan, C.; Yan, M.; Tang, Z.I. A privileged scaffold for the design of anti-cancer agents. *Eur. J. Med. Chem.* **2019**, *183*, 111691–111709. [[CrossRef](#)] [[PubMed](#)]
- Poulsen, T.B.; Jørgensen, K.A. Catalytic Asymmetric Friedel–Crafts Alkylation Reactions—Copper Showed the Way. *Chem. Rev.* **2008**, *108*, 2903–2915. [[CrossRef](#)] [[PubMed](#)]
- Joucla, L.; Djakovitch, L. Transition Metal-Catalysed, Direct and Site-Selective N1-, C2- or C3-Arylation of the Indole Nucleus: 20 Years of Improvements. *Adv. Synth. Catal.* **2009**, *351*, 673–714. [[CrossRef](#)]



4. Cacchi, S.; Fabrizi, G. Update 1 of Synthesis and Functionalization of Indoles Through Palladium-Catalyzed Reactions. *Chem. Rev.* **2011**, *111*, 215–283. [[CrossRef](#)]
5. Hwu, J.R.; Hsu, Y.C.; Josephrajan, T.; Tsay, S.-C. Fine tuning of blue photoluminescence from indoles for device fabrication. *J. Mater. Chem.* **2009**, *19*, 3084–3090. [[CrossRef](#)]
6. Cho, I.; Jeon, N.J.; Kwon, O.K.; Kim, D.W.; Jung, E.H.; Noh, J.H.; Seo, J.; Seok, S.I.; Park, S.Y. Indolo[3,2-*b*]indole-based crystalline hole transporting material for highly efficient perovskite solar cells. *Chem. Sci.* **2017**, *8*, 734–741. [[CrossRef](#)]
7. Laube, M.; Gassner, C.; Kniess, T.; Pietzsch, J. Synthesis and Cyclooxygenase Inhibition of Sulfonamide-Substituted(Dihydro)Pyrrolo[3,2,1-*hi*]indoles and Their Potential Prodrugs. *Molecules* **2019**, *24*, 3807. [[CrossRef](#)]
8. Lechner, C.; Flaßhoff, M.; Falke, H.; Preu, L.; Loaëc, N.; Meijer, L.; Knapp, S.; Chaikuad, A.; Kunick, C. [*b*]-Annulated Halogen-Substituted Indoles as Potential DYRK1A Inhibitors. *Molecules* **2019**, *24*, 4090. [[CrossRef](#)]
9. Avis, I.; Martnez, A.; Tauler, J.; Zudaire, E.; Mayburd, A.; Abu-Ghazaleh, R.; Ondrey, F.; Mulshine, J.L. Inhibitors of the Arachidonic Acid Pathway and Peroxisome Proliferator-Activated Receptor Ligands Have Superadditive Effects on Lung Cancer Growth Inhibition. *Cancer Res.* **2005**, *65*, 4181–4190. [[CrossRef](#)]
10. Silvestri, R.; Artico, M.; Bruno, B.; Massa, S.; Novellino, E.; Greco, G.; Marongiu, M.E.; Pani, A.; De Montis, A.; La Colla, P. Synthesis and biological evaluation of 5H-indolo[3,2-*b*][1,5]benzothiazepine derivatives, designed as conformationally constrained analogues of the human immunodeficiency virus type 1 reverse transcriptase inhibitor L-737,126. *Antivir. Chem. Chemother.* **1998**, *9*, 139–148. [[CrossRef](#)]
11. Ragno, R.; Coluccia, A.; La Regina, G.; De Martino, G.; Piscitelli, F.; Lavecchia, A.; Novellino, E.; Bergamini, A.; Ciaprini, C.; Sinistro, A.; et al. Design, Molecular Modeling, Synthesis, and Anti-HIV-1 Activity of New Indolyl Aryl Sulfones. Novel Derivatives of the Indole-2-carboxamide. *J. Med. Chem.* **2006**, *49*, 3172–3184. [[CrossRef](#)] [[PubMed](#)]
12. Zhou, N.; Zeller, W.; Krohn, M.; Anderson, H.; Zhang, J.; Onua, E.; Kiselyov, A.S.; Ramirez, J.; Halldorsdottir, G.; Andresson, P.; et al. 3,4-Disubstituted indole acylsulfonamides: A novel series of potent and selective human EP3 receptor antagonists. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 123–126. [[CrossRef](#)] [[PubMed](#)]
13. Funk, C.D. Leukotriene modifiers as potential therapeutics for cardiovascular disease. *Nat. Rev. Drug Discov.* **2005**, *4*, 664–672. [[CrossRef](#)] [[PubMed](#)]
14. Ainge, D.; Butters, M.; Merifield, E.; Ramakrishnan, R.; Rayapati, R.N.; Sharma, P.R.; Thomson, C. Intermediates and processes for the preparation of 4-(acetylamino)-3-[(4-chlorophenyl)thio]-2-methyl-1H-indole acetic acid. PCT Int. Appl. WO Patent 2011004182 A1, 13 January 2011.
15. Unangst, P.C.; Connor, D.T.; Stabler, S.R.; Weikert, R.J.; Carethers, M.E.; Kennedy, J.A.; Thueson, D.O.; Chestnut, J.C.; Adolphson, R.L.; Conroy, M.C. Novel indolecarboxamidotetrazoles as potential antiallergy agents. *J. Med. Chem.* **1989**, *32*, 1360–1366. [[CrossRef](#)]
16. Maeda, Y.; Koyabu, M.; Nishimura, T.; Uemura, S. Vanadium-Catalyzed Sulfenylation of Indoles and 2-Naphthols with Thiols under Molecular Oxygen. *J. Org. Chem.* **2004**, *69*, 7688–7693. [[CrossRef](#)]
17. Campbell, J.A.; Broka, C.A.; Gong, L.; Walker, K.A.M.; Wang, J.-H. A new synthesis of 3-arylthioindoles as selective COX-2 inhibitors using PIFA. *Tetrahedron Lett.* **2004**, *45*, 4073–4075. [[CrossRef](#)]
18. De Martino, G.; La Regina, G.; Coluccia, A.; Edler, M.C.; Barbera, M.C.; Brancale, A.; Wilcox, E.; Hamel, E.; Artico, M.; Silvestri, R. Arylthioindoles, Potent Inhibitors of Tubulin Polymerization. *J. Med. Chem.* **2004**, *47*, 6120–6123. [[CrossRef](#)]
19. De Martino, G.; Edler, M.C.; La Regina, G.; Coluccia, A.; Barbera, M.C.; Barrow, D.; Nicholson, R.I.; Chiosis, G.; Brancale, A.; Hamel, E.; et al. New Arylthioindoles: Potent Inhibitors of Tubulin Polymerization. 2. Structure–Activity Relationships and Molecular Modeling Studies. *J. Med. Chem.* **2006**, *49*, 947–954. [[CrossRef](#)]
20. Chen, Y.; Cho, C.H.; Larock, R.C. A Novel Synthetic Route to 3-Sulfonyl- and 3-Selenylindoles by *n*-Bu<sub>4</sub>Ni-Induced Electrophilic Cyclization. *Org. Lett.* **2009**, *11*, 173–176. [[CrossRef](#)]
21. Guo, Y.J.; Tang, R.Y.; Li, J.H.; Zhong, P.; Zhang, X.G. Palladium-Catalyzed Annulation of 2-(1-Alkynyl)benzenamines with Disulfides: Synthesis of 3-Sulfonylindoles. *Adv. Synth. Catal.* **2009**, *351*, 2615–2618. [[CrossRef](#)]



22. Li, Z.; Hong, L.; Liu, R.; Shen, J.; Zhou, X. Copper-catalyzed chalcogenoamination of 2-alkynylanilines with dichalcogenides for one-step synthesis of 3-sulfenylindoles and 3-selenylindoles. *Tetrahedron Lett.* **2011**, *52*, 1343–1347. [[CrossRef](#)]
23. Liu, J.; Li, P.; Chen, W.; Wang, L. An efficient synthesis of 2-bromo(chloro)-3-selenyl(sulfenyl)indoles via tandem reactions of 2-(gem-dibromo(chloro)vinyl)anilines with diselenides(disulfides). *Chem. Commun.* **2012**, *48*, 10052–10054. [[CrossRef](#)] [[PubMed](#)]
24. Chitra, S.; Paul, N.; Muthusubramanian, S.; Manisankar, P. Solvent based selectivity in the synthesis of di(2-aryl-1H-3-indolyl) sulfides and 1-aryl-2-[(2-aryl-1H-3-indolyl)sulfonyl]-1-ethanones. *RSC Adv.* **2012**, *2*, 1432–1438. [[CrossRef](#)]
25. Han, D.; Li, Z.; Fan, R. Oxidative Nucleophilic Cyclization of 2-Alkynylanilines with Thiophenols under Metal-Free Conditions. *Org. Lett.* **2014**, *16*, 6508–6511. [[CrossRef](#)]
26. Tudge, M.; Tamiya, M.; Savarin, C.; Humphrey, G.R. Development of a Novel, Highly Efficient Halide-Catalyzed Sulfenylation of Indoles. *Org. Lett.* **2006**, *8*, 565–568. [[CrossRef](#)]
27. Yadav, J.S.; Subba Reddy, B.V.; Reddy, Y.J.; Praneeth, K. Iron(III) Chloride: A Versatile Catalyst for the Practical Synthesis of 3-Sulfenylindoles. *Synthesis* **2009**, 1520–1524. [[CrossRef](#)]
28. Fang, X.L.; Tang, R.Y.; Zhong, P.; Li, J.H. Iron-Catalyzed Sulfenylation of Indoles with Disulfides Promoted by a Catalytic Amount of Iodine. *Synthesis* **2009**, 4183–4189. [[CrossRef](#)]
29. Silveira, C.C.; Mendes, S.R.; Wolf, L.; Martins, G.M. The use of anhydrous CeCl<sub>3</sub> as a catalyst for the synthesis of 3-sulfenyl indoles. *Tetrahedron Lett.* **2010**, *51*, 2014–2016. [[CrossRef](#)]
30. Huang, D.; Chen, J.; Dan, W.; Ding, J.; Liu, M.; Wu, H. A Metal-Free Sulfenylation and Bromosulfenylation of Indoles: Controllable Synthesis of 3-Arylthioindoles and 2-Bromo-3-arylthioindoles. *Adv. Synth. Catal.* **2012**, *354*, 2123–2128. [[CrossRef](#)]
31. Marcantoni, E.; Cipolletti, R.; Marsili, L.; Menichetti, S.; Properzi, R.; Viglianisi, C. An Efficient Catalytic Method for Regioselective Sulfenylation of Electron-Rich Aza-Aromatics at Room Temperature. *Eur. J. Org. Chem.* **2013**, 132–140. [[CrossRef](#)]
32. Liu, Y.; Zhang, Y.; Hu, C.; Wan, J.P.; Wen, C. Synthesis of 3-sulfenylated indoles by a simple NaOH promoted sulfenylation reaction. *RSC Adv.* **2014**, *4*, 35528–35530. [[CrossRef](#)]
33. Zhang, H.; Bao, X.; Song, Y.; Qu, J.; Wang, B. Iodine-catalysed versatile sulfenylation of indoles with thiophenols: Controllable synthesis of mono- and bis-arylthioindoles. *Tetrahedron* **2015**, *71*, 8885–8891. [[CrossRef](#)]
34. Raban, M.; Chern, L.J. Reactions of arenesulfonyl chlorides with indole. Carbon-13 and proton nuclear magnetic resonance spectra of 3-(arylthio)indoles. *J. Org. Chem.* **1980**, *45*, 1688–1691. [[CrossRef](#)]
35. Schlosser, K.M.; Krasutsky, A.P.; Hamilton, H.W.; Reed, J.E.; Sexton, K. A Highly Efficient Procedure for 3-Sulfenylation of Indole-2-carboxylates. *Org. Lett.* **2004**, *6*, 819–821. [[CrossRef](#)]
36. Browder, C.C.; Mitchell, M.O.; Smith, R.L.; el-Sulayman, G. Thiomethylation of indole and haloindole zinc salts. *Tetrahedron Lett.* **1993**, *34*, 6245–6247. [[CrossRef](#)]
37. Li, Z.; Hong, J.; Zhou, X. An efficient and clean CuI-catalyzed chalcogenylation of aromatic azaheterocycles with dichalcogenides. *Tetrahedron* **2011**, *67*, 3690–3697. [[CrossRef](#)]
38. Ge, W.; Wei, Y. Iodine-catalyzed oxidative system for 3-sulfenylation of indoles with disulfides using DMSO as oxidant under ambient conditions in dimethyl carbonate. *Green Chem.* **2012**, *14*, 2066–2070. [[CrossRef](#)]
39. Yang, F.L.; Tian, S.K. Iodine-Catalyzed Regioselective Sulfenylation of Indoles with Sulfonyl Hydrazides. *Angew. Chem. Int. Ed.* **2013**, *52*, 4929–4932. [[CrossRef](#)]
40. Li, X.; Xu, Y.; Wu, W.; Jiang, C.; Qi, C.; Jiang, H. Copper-Catalyzed Aerobic Oxidative N-S Bond Functionalization for C-S Bond Formation: Regio- and Stereoselective Synthesis of Sulfones and Thioethers. *Chem. Eur. J.* **2014**, *20*, 7911–7915. [[CrossRef](#)]
41. Wu, Q.; Zhao, D.; Qin, X.; Lan, J.; You, J. Synthesis of di(hetero)aryl sulfides by directly using arylsulfonyl chlorides as a sulfur source. *Chem. Commun.* **2011**, *47*, 9188–9190. [[CrossRef](#)]
42. Chen, M.; Huang, Z.T.; Zhen, Q.Y. Visible light-induced 3-sulfenylation of N-methylindoles with arylsulfonyl chlorides. *Chem. Commun.* **2012**, *48*, 11686–11688. [[CrossRef](#)] [[PubMed](#)]
43. Liu, C.R.; Ding, L.H. Byproduct promoted regioselective sulfenylation of indoles with sulfinic acids. *Org. Biomol. Chem.* **2015**, *13*, 2251–2254. [[CrossRef](#)] [[PubMed](#)]

44. Rao, H.; Wang, P.; Wang, J.; Li, Z.; Sun, X.; Cao, S.  $K_2S_2O_8$ /arenesulfinate: An unprecedented thiolating system enabling selective sulfenylation of indoles under metal-free conditions. *RSC Adv.* **2014**, *4*, 49165–49169. [[CrossRef](#)]
45. Xiao, F.; Xie, H.; Liu, S.; Deng, G.J. Iodine-Catalyzed Regioselective Sulfenylation of Indoles with Sodium Sulfates. *Adv. Synth. Catal.* **2014**, *356*, 364–368. [[CrossRef](#)]
46. Gensch, T.; Klauk, F.J.R.; Glorius, F. Cobalt-Catalyzed C–H Thiolation through Dehydrogenative Cross-Coupling. *Angew. Chem. Int. Ed.* **2016**, *55*, 11287–11291. [[CrossRef](#)]
47. Nalbandian, C.J.; Miller, E.M.; Toenjes, S.T.; Gustafson, J.L. A conjugate Lewis base–Brønsted acid catalyst for the sulfenylation of nitrogen containing heterocycles under mild conditions. *Chem. Commun.* **2017**, *53*, 1494–1497. [[CrossRef](#)]
48. Hostier, T.; Ferey, V.; Ricci, G.; Pardo, D.G.; Cossy, J. TFA-promoted direct C–H sulfenylation at the C2 position of non-protected indoles. *Chem. Commun.* **2015**, *51*, 13898–13901. [[CrossRef](#)]
49. Saulnier, M.G.; Gribble, G.W. Generation and reactions of 3-lithio-1-(phenylsulfonyl)indole. *J. Org. Chem.* **1982**, *47*, 757–761. [[CrossRef](#)]
50. Katritzky, A.R.; Lue, P.; Chen, Y.X. An alternative route to 2-substituted indoles via N-aminal-directed lithiation. *J. Org. Chem.* **1990**, *55*, 3688–3691. [[CrossRef](#)]
51. Fukuda, T.; Mine, Y.; Iwao, M. Selective C-3 and C-2 lithiation of 1-(2,2-diethylbutanoyl)indole. *Tetrahedron* **2001**, *57*, 975–979. [[CrossRef](#)]
52. Qian, D.C.; Alford, P.E.; Kishbaugh, T.L.S.; Jones, S.T.; Gribble, G.W. 1,2-Bis(phenylsulfonyl)indole as an acceptor of organocuprate nucleophiles. *Arkivoc* **2010**, 66–73.
53. Zhou, S.; Xiao, G.; Liang, Y. Copper-catalyzed synthesis of 2-sulfenylindoles from indoline-2-thiones and aryl iodides. *Tetrahedron Lett.* **2017**, *58*, 338–341. [[CrossRef](#)]
54. Hamel, P.; Girard, Y.; Atkinson, J.G. Acid-catalysed isomerization of indol-3-yl sulphides to indol-2-yl sulphides: Unexpected intermolecular nature of the rearrangement. *J. Chem. Soc. Chem. Commun.* **1989**, 63–65. [[CrossRef](#)]
55. Hamel, P.; Girard, Y.; Atkinson, J.G. Acid-catalyzed isomerization of 3-indolyl sulfides to 2-indolyl sulfides: First synthesis of 3-unsubstituted 2-arylthioindoles. Evidence for a complex intermolecular process. *J. Org. Chem.* **1992**, *57*, 2694–2699. [[CrossRef](#)]
56. Li, B.; Ni, P.; Huang, H.; Xiao, F.; Deng, G.-J. Three-Component Thieno[2,3-*b*]indole Synthesis from Indoles, Alkenes or Alkynes and Sulfur Powder under Metal-Free Conditions. *Adv. Synth. Catal.* **2017**, *359*, 4300–4304. [[CrossRef](#)]
57. Prochnow, T.; Maroneze, A.; Back, D.F.; Zeni, G. Synthesis of 3-(Organochalcogen) Chalcogenazolo Indoles via Cascade Cyclization of *N*-Alkynylindoles. *J. Org. Chem.* **2019**, *84*, 2891–2900. [[CrossRef](#)]
58. Nguyenab, T.T.; Tran, P.H. One-pot multicomponent synthesis of thieno[2-*C-b*]indoles catalyzed by a magnetic nanoparticle-supported [Urea]<sub>4</sub>[ZnCl<sub>2</sub>] deep eutectic solvent. *RSC Adv.* **2020**, *10*, 9663–9671. [[CrossRef](#)]
59. Ji, Y.-Z.; Li, H.-J.; Zhang, J.-Y.; Wu, Y.-C. Switchable regioselection of C–H thiolation of indoles using different TMS counterions. *Chem. Commun.* **2019**, *55*, 11864–11867. [[CrossRef](#)]
60. Antoniow, S.; Witt, D. A Novel and Efficient Synthesis of Unsymmetrical Disulfides. *Synthesis* **2007**, 363–366. [[CrossRef](#)]
61. Lach, S.; Demkowicz, S.; Witt, D. An efficient and convenient synthesis of unsymmetrical disulfides from thioacetates. *Tetrahedron Lett.* **2013**, *54*, 7021–7023. [[CrossRef](#)]
62. Szymelfejnik, M.; Demkowicz, S.; Rachon, J.; Witt, D. Functionalization of Cysteine Derivatives by Unsymmetrical Disulfide Bond Formation. *Synthesis* **2007**, 3528–3534. [[CrossRef](#)]
63. Kowalczyk, J.; Barski, P.; Witt, D.; Grzybowski, B.A. Versatile and Efficient. Synthesis of  $\omega$ -Functionalized Asymmetric Disulfides via Sulfenyl Bromide Adducts. *Langmuir* **2007**, *23*, 2318–2321. [[CrossRef](#)] [[PubMed](#)]
64. Demkowicz, S.; Rachon, J.; Witt, D. A Versatile and Convenient Preparation of Unsymmetrical Diaryl Disulfides. *Synthesis* **2008**, 2033–2038. [[CrossRef](#)]
65. Okragla, E.; Demkowicz, S.; Rachon, J.; Witt, D. A Convenient and Efficient  $\alpha$ -Sulfenylation of Carbonyl Compounds. *Synthesis* **2009**, 1720–1724. [[CrossRef](#)]
66. Doroszuk, J.; Musiejuk, M.; Demkowicz, S.; Rachon, J.; Witt, D. Convenient and efficient synthesis of functionalized unsymmetrical alkynyl sulfides. *RSC Adv.* **2016**, *6*, 105449–105453. [[CrossRef](#)]

67. Dorozuk, J.; Musiejuk, M.; Ponikiewski, Ł.; Witt, D. Convenient and Efficient Diastereoselective Preparation of Functionalized Z-Alkenyl Sulfides. *Eur. J. Org. Chem.* **2018**, *2018*, 6333–6337. [[CrossRef](#)]
68. Desarbre, E.; Coudret, S.; Meheust, C.; Merour, J.-V. Synthesis of 2-Substituted-1H-Pyrrolo[2,3-b]Pyridines: Preparation of 7-Azaolivacine Analogue and 7-Azaindolopyridopyrimidine Derivatives. *Tetrahedron* **1997**, *53*, 3637–3648. [[CrossRef](#)]
69. Kozikowski, A.P.; Chen, Y.-Y. Intramolecular nitrile oxide cycloaddition (INOC) reactions in the indole series. 2. Total synthesis of racemic and optically active paliclavine and 5-epi-paliclavine. *J. Org. Chem.* **1981**, *46*, 5248–5250. [[CrossRef](#)]



© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).