Angewandte
International Edition Chemie

Synthetic Methods

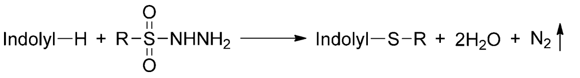
DOI: 10.1002/anie.201301437

Iodine-Catalyzed Regioselective Sulfenylation of Indoles with Sulfonyl Hydrazides**

*Fu-Lai Yang and Shi-Kai Tian**

The indole moiety is present in many biologically relevant molecules, and consequently, much attention has been paid to the synthesis of substituted indoles through either construction or modification of indole rings.[1] The electron-rich nature of indole rings enable them to undergo direct carbon–hydrogen bond functionalization with electrophiles to form carbon–carbon and carbon–heteroatom bonds. In this regard, the sulfenylation of indoles has been developed for the synthesis of indole thioethers, some of which serve as potent agents to treat cancer[2] and allergies,[3] from sulfenylating agents such as sulfenyl halides,[4] *N*-thioimides,[5] sulfonium salts,[6] thiols,[7] disulfides,[8] quinone mono-*O*,*S*-acetals,[9] and arylsulfonyl chlorides.[10] Nevertheless, many of these sulfenylating agents are unstable to air and moisture, are expensive, or possess unpleasant odors. Moreover, previously reported sulfenylation reactions of indoles frequently require excess sulfenylating agents, excess additives, or high temperature, suffer from a narrow substrate scope, or yield by-products unfriendly to the environment. To address such issues, it is highly desirable to explore new sulfenylating agents and reaction conditions for the sulfenylation of indoles.

Sulfonyl hydrazides are readily accessible and exist as stable solids, and they have been widely employed to form hydrazones and heterocycles which have versatile applications.[11] Moreover, sulfonyl hydrazides can be utilized as reductants[12] and sulfonyl sources[13] through the cleavage of their sulfur–nitrogen bonds, and very recently as aryl sources through the cleavage of their carbon–sulfur bonds.[14] In sharp contrast, little has been published on the cleavage of the sulfur–oxygen bonds of sulfonyl hydrazides for chemical synthesis. In this context, we envisioned that the reductive nature of the $NHNH_2$ group in the sulfonyl hydrazide might be utilized to remove the two oxygen atoms of the sulfonyl group under certain reaction conditions, and consequently, sulfonyl hydrazides could serve as effective sulfur electrophiles for the sulfenylation of indoles, wherein water and molecular nitrogen are expected to be generated as environmentally benign by-products [Eq. (1)].



$$\text{Indolyl—H} + \text{R—}\overset{\text{O}}{\underset{\text{O}}{\overset{\|}{\underset{\|}{\text{S}}}}}\text{—NHNH}_2 \longrightarrow \text{Indolyl—S—R} + 2\,\text{H}_2\text{O} + \text{N}_2\uparrow \qquad (1)$$

The sulfenylation of indole (**1a**) with *p*-toluenesulfonyl hydrazide (**2a**; 1.2 equiv) was selected as the model reaction to test our hypothesis. Initially, the reaction did not occur in ethanol in the presence of 10 mol% iodine and open to air at room temperature. To our delight, heating the mixture at 70 °C led to the formation of 3-(*p*-tolylthio)-1*H*-indole (**3a**) in 86% yield as a single regioisomer. For comparison, the reaction was performed under nitrogen and gave **3a** in a slightly lower yield (81%). Reducing the catalyst loading to 5 mol% resulted in a much lower yield (52%). A number of common solvents were examined, but no better yield was obtained.[15] Moreover, replacing iodine with *N*-iodosuccinimide (NIS) decreased the yield to 41%,[16] and even no desired product was obtained when replacing iodine with *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), or Bu_4NI.

In the presence of 10 mol% iodine, a range of aryl-, heteroaryl-, and alkylsulfonyl hydrazides smoothly underwent sulfenylation with indoles in ethanol to give structurally diverse thioethers in moderate to excellent yields with extremely high regioselectivity (Table 1).[17] In general, the sulfenylation reaction took place at the C3 position of the indole ring (Table 1, entries 1–25). However, the C2 position of the indole ring was the reaction site of choice when the C3 position was occupied by a substituent (Table 1, entries 26–28). Notably, the reaction tolerated a variety of functional groups such as alkoxy, fluoro, chloro, bromo, iodo, nitro, ester, and nitrile. In a few cases sulfonyl hydrazides decomposed significantly because of slow sulfenylation (see below), and to our delight, acceptable yields were obtained by increasing the amounts of sulfonyl hydrazides from 1.2 to 2 equivalents (Table 1, entries 18, 23, and 28).

While the decomposition of sulfonyl hydrazides proceeded very slowly in ethanol at 70 °C,[13f] it was dramatically accelerated by iodine. Treatment of **2a** with 10 mol% iodine gave the sulfonothioate **5a** and disulfide **6a** in 44 and 33% yields, respectively (Scheme 1). Moreover, **5a** could be reduced to give **6a** under the same reaction conditions but in only 15% yield, which suggested that there was at least one more intermediate leading to **6a**. To gain more insights, we carried out electron-spray ionization (ESI) mass spectrometric analysis of the iodine-catalyzed reaction mixture of **1a** and

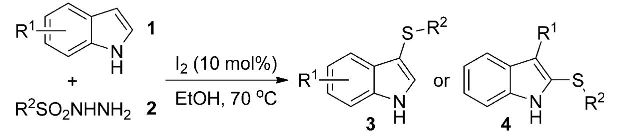
---

[*] F.-L. Yang, Prof. Dr. S.-K. Tian
Department of Chemistry
University of Science and Technology of China
Hefei, Anhui 230026 (China)
E-mail: tiansk@ustc.edu.cn
Prof. Dr. S.-K. Tian
Key Laboratory of Synthetic Chemistry of Natural Substances,
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032 (China)

[**] We are grateful for the financial support from the National Natural Science Foundation of China (21232007 and 21172206), the National Basic Research Program of China (973 Program 2010CB833300), and the Program for Changjiang Scholars and Innovative Research Team in University (IRT1189).

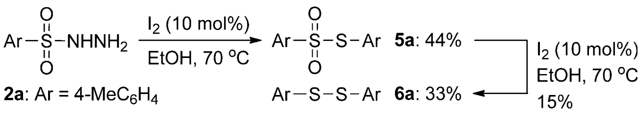
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201301437.

Table 1: Iodine-catalyzed regioselective sulfenylation of indoles with sulfonyl hydrazides.[a,b]



Entry	**1** (R^1)	**2** (R^2)	**3** or **4**	Yield [%][c]
1	**1a** (H)	**2a** (4-MeC$_6$H$_4$)	**3a**	84
2	**1a** (H)	**2b** (Ph)	**3b**	79
3	**1a** (H)	**2c** (4-MeOC$_6$H$_4$)	**3c**	75
4	**1a** (H)	**2d** (4-FC$_6$H$_4$)	**3d**	72
5	**1a** (H)	**2e** (4-ClC$_6$H$_4$)	**3e**	88
6	**1a** (H)	**2f** (4-BrC$_6$H$_4$)	**3f**	82
7	**1a** (H)	**2g** (4-IC$_6$H$_4$)	**3g**	81
8	**1a** (H)	**2h** (4-O$_2$NC$_6$H$_4$)	**3h**	89
9	**1a** (H)	**2i** (3-O$_2$NC$_6$H$_4$)	**3i**	90
10	**1a** (H)	**2j** (2,5-Cl$_2$C$_6$H$_3$)	**3j**	85
11	**1a** (H)	**2k** (2,4,6-Me$_3$C$_6$H$_2$)	**3k**	63
12	**1a** (H)	**2l** (2-naphthyl)	**3l**	90
13	**1a** (H)	**2m** (2-thienyl)	**3m**	66
14	**1a** (H)	**2n** (Me)	**3n**	69
15	**1a** (H)	**2o** [(CH$_2$)$_7$Me]	**3o**	58
16	**1a** (H)	**2p** (CH$_2$Ph)	**3p**	67
17	**1b** (1-Me)	**2b** (Ph)	**3q**	88
18[d]	**1c** (2-Me)	**2b** (Ph)	**3r**	67
19	**1d** (2-Ph)	**2b** (Ph)	**3s**	87
20	**1e** (4-Br)	**2b** (Ph)	**3t**	82
21	**1f** (5-OMe)	**2b** (Ph)	**3u**	80
22	**1g** (5-Br)	**2b** (Ph)	**3v**	89
23[d]	**1h** (5-NO$_2$)	**2b** (Ph)	**3w**	59
24	**1i** (5-CO$_2$Me)	**2b** (Ph)	**3x**	70
25	**1j** (6-Cl)	**2b** (Ph)	**3y**	89
26	**1k** (3-Me)	**2b** (Ph)	**4a**	91
27	**1l** (3-CHPh$_2$)	**2b** (Ph)	**4b**	76
28[d]	**1m** (3-CH$_2$CN)	**2b** (Ph)	**4c**	56

[a] Reaction conditions: indole **1** (0.40 mmol), sulfonyl hydrazide **2** (0.48 mmol), iodine (10 mol%), ethanol (1.0 mL), 70°C, open to air, 5 h. [b] No regioisomer was detected by ^{1}H NMR analysis. [c] Yield of isolated product. [d] 0.80 mmol of sulfonyl hydrazide **2** was used and the reaction was run for 8 h.

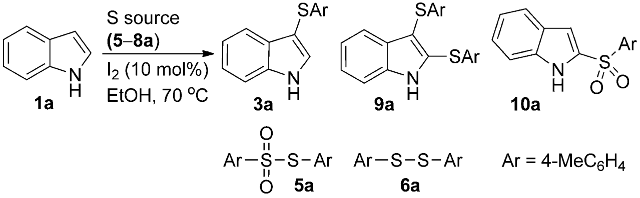


Scheme 1. Decomposition of the sulfonyl hydrazide **2a**.

2a, and tentatively identified two minor decomposition products of **2a**, 4-MeC$_6$H$_4$SO$_2$H (**7a**), and 4-MeC$_6$H$_4$SO$_2$Et (**8a**), according to the high-resolution mass data.[15]

Additional experiments were carried out under the developed reaction conditions to determine whether the decomposition products of sulfonyl hydrazides could be transformed into indole thioethers. As demonstrated by the results summarized in Table 2, the four decomposition products of **2a**, **5a**, **6a**, **7a**, and **8a**, were all transformed into **3a**, albeit in much lower yields than that from the reaction of **1a** with **2a** (Table 1, entry 1). Moreover, some of these reactions gave additional by-products, such as the dithioether **9a** and sulfone **10a**, which were not detected in the corresponding iodine-catalyzed sulfenylation reaction. Thus, it is unlikely for these decomposition products of the sulfonyl hydrazide to serve as major intermediates for the formation of the corresponding indole thioether.

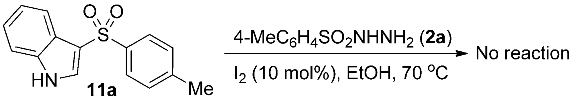
Table 2: Reactions of indole (**1a**) with the four decomposition products of sulfonyl hydrazide **2a**.[a]



Entry	S source	Yield [%][b]				
		3a	**9a**	**10a**	**5a**	**6a**
1	**5a**	48	20	–	–	–
2	**6a**	29	–	–	–	–
3	**7a**	28	12	11	14	trace
4	**8a**	62	14	–	–	–

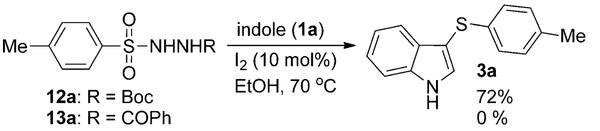
[a] Reaction conditions: indole (**1a**) (0.20 mmol), S source (1 equiv), iodine (10 mol%), ethanol (0.5 mL), 70°C, open to air, 5 h. [b] Yield of isolated product.

Furthermore, it is unlikely for an indolyl sulfone to serve as an intermediate in the sulfenylation reaction. As shown in Equation (2), our reaction conditions failed to reduce the sulfone **11a** to give **3a**. This result suggests that the removal of the two oxygen atoms from the sulfonyl group occurs prior to the carbon–sulfur bond formation between the indole and the sulfonyl hydrazide.



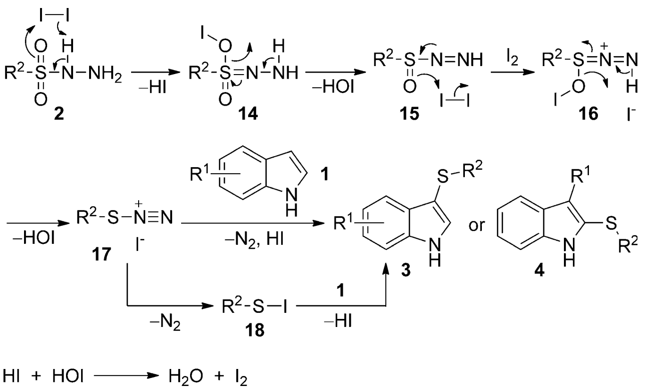
(2)

The reaction mixture of **1a** with **2a** became weakly acidic (pH 4–5) as determined by using pH paper. Moreover, the reaction conditions allowed *N*-Boc-*N'*-sulfonylhydrazine (**12a**) to be transformed into **3a** in 72% yield by taking advantage of the weak acidity to remove the Boc group [Eq. (3)]. In sharp contrast, no reaction was observed with *N*-benzoyl-*N'*-sulfonylhydrazine (**13a**) under the same reaction conditions. These results suggest that the NHNH$_2$ group is essential for the sulfonyl hydrazide to serve as an effective sulfenylating agent.



(3)

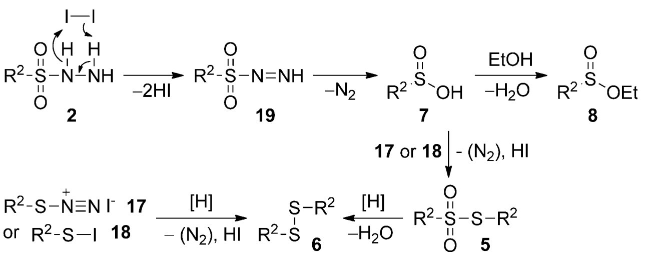
On the basis of the above experimental results, we propose the major reaction pathways as depicted in Scheme 2 for the iodine-catalyzed sulfenylation of indoles with sulfonyl hydrazides. Stepwise removal of the hydrogen and oxygen atoms from the SO$_2$NHNH$_2$ group in **2** with iodine leads to the formation of the thiodiazonium **17**,[18]



Scheme 2. Proposed reaction pathways for the iodine-catalyzed sulfenylation of indoles with sulfonyl hydrazides.

which undergoes a regioselective Friedel–Crafts reaction with **1** to give either the thioether **3** or **4**, depending on whether or not a substituent occupies the C3 position of **1**. Alternatively, extrusion of molecular nitrogen from **17** gives the sulfenyl iodide **18**,[8b,d] which is attacked by **1** to give either **3** or **4**. In these steps, iodine is converted into HI and HOI, the two of which react to give water and regenerate iodine to continue the catalytic cycle.

Possible reaction pathways have also been proposed for the iodine-promoted decomposition of sulfonyl hydrazides (Scheme 3). Oxidation of **2** with iodine and subsequent extrusion of molecular nitrogen gives **7**,[13f] which undergoes esterification with ethanol (solvent) under acidic conditions to give the sulfinate ester **8**. Alternatively, **7** undergoes nucleophilic substitution with **17** (or **18**) to give the sulfonothioate **5**. Reduction of **17**, **18**, or **5**, by ethanol/iodine gives **6**. The generation of HI and **7** as by-products in small amounts by such a reaction pathway accounts for the weak acidity of the reaction mixture.



Scheme 3. Proposed reaction pathways for the iodine-promoted decomposition of sulfonyl hydrazides.

In summary, we have developed an unprecedented sulfenylation reaction of indoles with sulfonyl hydrazides through the cleavage of sulfur–oxygen and sulfur–nitrogen bonds. In the presence of 10 mol% iodine, a range of aryl-, heteroaryl-, and alkylsulfonyl hydrazides smoothly underwent sulfenylation with indoles to give structurally diverse indole thioethers in moderate to excellent yields with extremely high regioselectivity. The current study paves the way for the use of sulfonyl hydrazides as unique sulfur electrophiles in chemical synthesis.

Received: February 19, 2013

Keywords: heterocycles · hydrazides · iodine · regioselectivity · synthetic methods

---

[1] For reviews, see: a) A. R. Katritzky, C. A. Ramsden, J. A. Joule, V. V. Zhdankin, *Handbook of Heterocyclic Chemistry*, 3rd ed., Elsevier, Oxford, **2010**; b) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875.

[2] G. La Regina, M. C. Edler, A. Brancale, S. Kandil, A. Coluccia, F. Piscitelli, E. Hamel, G. De Martino, R. Matesanz, J. F. Díaz, A. I. Scovassi, E. Prosperi, A. Lavecchia, E. Novellino, M. Artico, R. Silvestri, *J. Med. Chem.* **2007**, *50*, 2865.

[3] P. C. Unangst, D. T. Connor, S. R. Stabler, R. J. Weikert, M. E. Carethers, J. A. Kennedy, D. Thueson, J. C. Chestnut, R. L. Adolphson, M. C. Conroy, *J. Med. Chem.* **1989**, *32*, 1360.

[4] a) P. Hamel, *J. Org. Chem.* **2002**, *67*, 2854; b) H. M. Gilow, C. S. Brown, J. N. Copeland, K. E. Kelly, *J. Heterocycl. Chem.* **1991**, *28*, 1025; c) M. Raban, L.-J. Chern, *J. Org. Chem.* **1980**, *45*, 1688.

[5] a) E. Marcantoni, R. Cipolletti, L. Marsili, S. Menichetti, R. Properzi, C. Viglianisi, *Eur. J. Org. Chem.* **2013**, 132; b) C. C. Silveira, S. R. Mendes, L. Wolf, G. M. Martins, *Tetrahedron Lett.* **2010**, *51*, 2014; c) M. Tudge, M. Tamiya, C. Savarin, G. R. Humphrey, *Org. Lett.* **2006**, *8*, 565.

[6] S. Jain, K. Shukla, A. Mukhopadhyay, S. N. Suryawanshi, D. S. Bhakuni, *Synth. Commun.* **1990**, *20*, 1315.

[7] a) J. S. Yadav, B. V. S. Reddy, Y. J. Reddy, K. Praneeth, *Synthesis* **2009**, 1520; b) G. Wu, J. Wu, J. Wu, L. Wu, *Synth. Commun.* **2008**, *38*, 1036; c) J. S. Yadav, B. V. S. Reddy, Y. J. Reddy, *Tetrahedron Lett.* **2007**, *48*, 7034; d) Y. Maeda, M. Koyabu, T. Nishimura, S. Uemura, *J. Org. Chem.* **2004**, *69*, 7688; e) K. M. Schlosser, A. P. Krasutsky, H. W. Hamilton, J. E. Reed, K. Sexton, *Org. Lett.* **2004**, *6*, 819; f) J. A. Campbell, C. A. Broka, L. Gong, K. A. M. Walker, J.-H. Wang, *Tetrahedron Lett.* **2004**, *45*, 4073.

[8] a) W. Ge, Y. Wei, *Synthesis* **2012**, 934; b) W. Ge, Y. Wei, *Green Chem.* **2012**, *14*, 2066; c) Z. Li, J. Hong, X. Zhou, *Tetrahedron* **2011**, *67*, 3690; d) X.-L. Fang, R.-Y. Tang, P. Zhong, J.-H. Li, *Synthesis* **2009**, 4183; e) C. C. Browder, M. O. Mitchell, R. L. Smith, G. el-Stdayman, *Tetrahedron Lett.* **1993**, *34*, 6245.

[9] a) M. Matsugi, K. Murata, H. Nambu, Y. Kita, *Tetrahedron Lett.* **2001**, *42*, 1077; b) M. Matsugi, K. Murata, K. Gotanda, H. Nambu, G. Anilkumar, K. Matsumoto, Y. Kita, *J. Org. Chem.* **2001**, *66*, 2434.

[10] Q. Wu, D. Zhao, X. Qin, J. Lan, J. You, *Chem. Commun.* **2011**, *47*, 9188.

[11] For reviews, see: a) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2012**, *41*, 560; b) J. Barluenga, C. Valdés, *Angew. Chem.* **2011**, *123*, 7626; *Angew. Chem. Int. Ed.* **2011**, *50*, 7486; c) R. O. Hutchins, M. K. Hutchins in *Comprehensive Organic Synthesis*, *Vol. 8* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 327.

[12] For reviews, see: a) D. J. Pasto, R. T. Taylor, *Org. React.* **1991**, *40*, 91; b) D. J. Pasto in *Comprehensive Organic Synthesis*, *Vol. 8* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 471.

[13] a) X. Li, X. Xu, C. Zhou, *Chem. Commun.* **2012**, *48*, 12240; b) T. Taniguchi, A. Idota, H. Ishibashi, *Org. Biomol. Chem.* **2011**, *9*, 3151; c) I. V. Ukrainets, A. A. Tkach, V. V. Kravtsova, S. V. Shishkina, *Chem. Heterocycl. Compd.* **2008**, *44*, 677; d) S. Kamijo, M. Al-Masum, Y. Yamamoto, *Tetrahedron Lett.* **1998**, *39*, 691; e) R. Ballini, E. Marcantoni, M. Petrin, *Tetrahedron* **1989**, *45*, 6791; f) A. Deavin, C. W. Rees, *J. Chem. Soc.* **1961**, 4970.

[14] a) F.-L. Yang, X.-T. Ma, S.-K. Tian, *Chem. Eur. J.* **2012**, *18*, 1582; b) B. Liu, J. Li, F. Song, J. You, *Chem. Eur. J.* **2012**, *18*, 10830; c) X. Yu, X. Li, B. Wan, *Org. Biomol. Chem.* **2012**, *10*, 7479; d) O. Y. Yuen, C. M. So, W. T. Wong, F. Y. Kwong, *Synlett* **2012**, 2714.

[15] For details, see the Supporting Information.

[16] The reaction mixture turned purple, and it suggested that iodine was generated from NIS.

[17] Under the same reaction conditions the reaction with pyrrole and aniline afforded unsatisfactory yields. Moreover, no desired reaction was observed with less reactive aromatic compounds such as furan, phenol, and anisole.

[18] Since the reaction was not affected by the addition of a stoichiometric amount of 1,1-diphenylethene, a radical intermediate might not be involved in the formation of **17**.