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Iodinane- and Metal-Free Synthesis of *N*-Cyano Sulfilimines: Novel and Easy Access of *N*H-Sulfoximines

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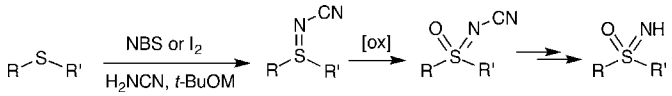
ABSTRACT



The synthesis of *N*-cyanosulfilimines can readily be achieved by reaction of the corresponding sulfides with cyanogen amine in the presence of a base and NBS or I_2 as halogenating agents. Oxidation followed by C–N bond cleavage affords synthetically useful *N*H-free sulfoximines.

The development of novel methods for the preparation of sulfilimines and sulfoximines has attracted significant attention over the past few years, since some derivatives proved useful as building blocks of chiral ligands[1] and structural units in pseudopeptides.[2] Two main routes are commonly followed to prepare these compounds.[3] They either involve an oxidative imination of a sulfide or sulfoxide or they utilize a nucleophilic displacement of the corresponding sulfin- or sulfonimidoyl halide or sulfonimidate.

In our own search for new and more efficient syntheses of sulfilimines and sulfoximines,[4] we recently focused our attention on sulfur iminations using cyanogen amine as nitrogen source.[5] In that context, we demonstrated that *N*-cyanosulfoximines were very appealing substrates for the preparation of *N*-heterocyclic sulfoximines.

Being attracted by the possibility of performing metal-free *N*-cyanosulfilimines syntheses,[6] we aimed to further simplify the synthetic protocol by avoiding the use of hypervalent iodinanes such as $PhI(OAc)_2$. For achieving this goal, an in situ formation of a sulfinimidoyl halide followed by a nucleophilic substitution with cyanogen amine was envisaged.[7] Herein, we report an easy procedure for the synthesis of various *N*-cyanosulfilimines, based on the use of low-cost reagents such as NBS or I_2. Furthermore, we demonstrate that *N*-cyanosulfilimines are valuable intermediates for the preparation of *N*-cyano- and *N*H-sulfoximines.

For the initial screening, benzyl methyl sulfide (**1a**) was chosen as substrate. First, the reaction of **1a** with cyanogen

(1) For examples of sulfoximines as chiral ligands, see: (a) Bolm, C.; Simic, O. *J. Am. Chem. Soc.* **2001**, *123*, 3830. (b) Harmata, M.; Ghosh, S. K. *Org. Lett.* **2001**, *3*, 3321. (c) Bolm, C.; Martin, M.; Simic, O.; Verrucci, M. *Org. Lett.* **2003**, *5*, 427. (d) Bolm, C.; Verrucci, M.; Simic, O.; Cozzi, P. G.; Raabe, G.; Okamura, H. *Chem. Commun.* **2003**, 2816. (e) Bolm, C.; Martin, M.; Gescheidt, G.; Palivan, C.; Neshchadin, D.; Bertagnolli, H.; Feth, M. P.; Schweiger, A.; Mitrikas, G.; Harmer, J. *J. Am. Chem. Soc.* **2003**, *125*, 6222. (f) Langner, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5984. (g) Mössner, C.; Bolm, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 7564. (h) Langner, M.; Rémy, P.; Bolm, C. *Synlett* **2005**, 781. (i) Langner, M.; Rémy, P.; Bolm, C. *Chem. Eur. J.* **2005**, *11*, 6254. (j) Reetz, M. T.; Bondarev, O. G.; Gais, H.-J.; Bolm, C. *Tetrahedron Lett.* **2005**, *46*, 5643.

(2) For the use of sulfoximines as building blocks for pseudopeptides, see: (a) Bolm, C.; Kahmann, J. D.; Moll, G. *Tetrahedron Lett.* **1997**, *38*, 1169. (b) Bolm, C.; Moll, G.; Kahmann, J. D. *Chem. Eur. J.* **2001**, *7*, 1118. (c) Tye, H.; Skinner, C. L. *Helv. Chim. Acta* **2002**, *85*, 3272. (d) Bolm, C.; Müller, D.; Hackenberger, C. P. R. *Org. Lett.* **2002**, *4*, 893. (e) Bolm, C.; Müller, D.; Dalhoff, C.; Hackenberger, C. P. R.; Weinhold, E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3207.

(3) For recent reviews, see: (a) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1. (b) Harmata, M. *Chemtracts* **2003**, *16*, 660. (c) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482. (d) Bentley, R. *Chem. Soc. Rev.* **2005**, *34*, 609.

(4) For previous contributions on iminations of sulfur compounds, see the following references. Rh-catalyzed: (a) Okamura, H.; Bolm, C. *Org. Lett.* **2004**, *6*, 1305. Ag-catalyzed: (b) Cho, G. Y.; Bolm, C. *Org. Lett.* **2005**, *7*, 4983. Metal-free: (c) Cho, G. Y.; Bolm, C. *Tetrahedron Lett.* **2005**, *46*, 8007. Fe-catalyzed: (d) García Mancheño, O.; Bolm, C. *Org. Lett.* **2006**, *8*, 2349. For comparative metal-catalyzed iminations of sulfoxides, see: (e) García Mancheño, O.; Bolm, C. *Chem. Eur. J.* **2007**, *13*, 6674.

(5) García Mancheño, O.; Bolm, C. *Org. Lett.* **2007**, *9*, 2951.

(6) For previous synthesis of *N*-cyanosulfilimines, see: (a) Swern, D.; Ikeda, I.; Whitfield, G. F. *Tetrahedron Lett.* **1972**, *13*, 2635. (b) Hutchins, M. G. K.; Swern, D. *Tetrahedron Lett.* **1981**, *22*, 4599. (c) Kemp, J. E. G.; Ellis, D.; Closier, M. D. *Tetrahedron Lett.* **1979**, *20*, 3781. (d) Zhu, Y.; Rogers, R. B.; Huang, J. X. US 20050228027 A1.

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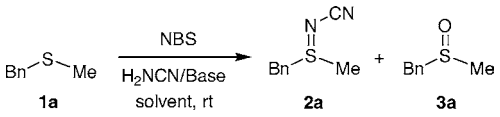
amine and NBS in the presence of *t*-BuOK was carried out in methanol (Table 1, entry 1). Under these conditions

Table 1. Imination of Sulfide **1a**[a]



1a **2a** **3a**

entry	solvent	base	**2a/3a**[b]
1	MeOH	*t*-BuOK	85:15 to 90:10
2	dry MeOH	*t*-BuOK	71:29
3	MeOH/H_2O (4:1)	*t*-BuOK	87:13
4	dry MeOH + MS 4Å	*t*-BuOK	16:84
5	EtOH	*t*-BuOK	64:36
6	*t*-BuOH	*t*-BuOK	2:98
7	MeCN	*t*-BuOK	88:12
8	THF	*t*-BuOK	71:29
9	THF	NaH	90:10
10	MeOH	K_2CO_3	

[a] Reaction conditions: sulfide **1a** (1 equiv), base (1.2 equiv), H_2NCN (1.3 equiv), and halogen source (1.5 equiv) at room temperature. [b] The **2a**/**3a** ratio was determined by ^1H NMR of the crude mixture.

N-cyanosulfilimine **2a** was the major product. However, the formation of 10−15% of the corresponding sulfoxide **3a** was also observed. In order to avoid this side product, the effect of the solvent was explored (Table 1).

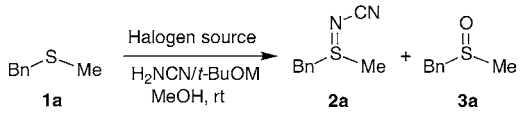
Neither the use of dry or degassed MeOH (entry 2) nor the addition of water (entry 3) helped to increase the ratio of **2a**/**3a**.[8] Moreover, the addition of molecular sieves 4 Å dramatically favored the formation of the sulfoxide (entry 4). THF and other alcohols such as EtOH and *t*-BuOH were also tested. Finally, with *t*-BuOK as base, MeOH and MeCN provided the highest **2a**/**3a** ratios (entries 1 and 7).[9]

The role of the base was also evaluated. Sulfoxide formation was observed in a similar **2a**/**3a** ratio (90:10) when NaH was used (entry 9). Finally, no reaction occurred when the weaker base K_2CO_3 was employed (entry 10).

Next, the effect of the halogen source on the **2a**/**3a** ratio was evaluated with methanol as solvent (Table 2).

To our delight, we found that the use of iodine instead of NBS as halogenating agent (in combination with *t*-BuOK) led to the exclusive formation of sulfilimine **2a**. Whereas with 1.2 equiv of I_2 the desired product was only obtained

Table 2. Optimization: Effect of the Halogen Source[a]



1a **2a** **3a**

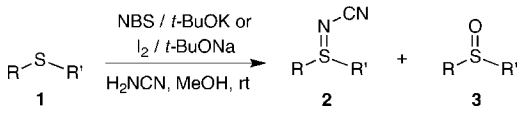
entry	halogen source	*t*-BuOM	yield of **2a**[b] (%)	**2a/3a**[c]
1	NCS	*t*-BuOK	nd	45:55
2	NBS	*t*-BuOK	83	90:10
3	Br_2	*t*-BuOK	nd	2:98
4	NIS	*t*-BuOK	33	100:0
5	I_2	*t*-BuOK	39	100:0
6	I_2[d]	*t*-BuOK	55	100:0
7	I_2[d]	*t*-BuONa	81	100:0

[a] Reaction conditions: Sulfide **1a** (1 equiv), base (1.2 equiv), H_2NCN (1.3 equiv), and halogen source (1.5 equiv) in MeOH at room temperature. [b] Yield after column chromatography. [c] The **2a**/**3a** ratio was determined by ^1H NMR of the crude mixture. [d] Use of 4 equiv of I_2.

in 39% yield, use of 4 equiv of the dihalide afforded **2a** in 55% yield (entry 6). Finally, *t*-BuONa proved to be a more efficient base, improving the yield of **2a** to 81% (entry 7).

Next, the substrate scope of this imination reaction was investigated (Table 3). A variety of sulfides were treated with

Table 3. Substrate Scope[a]



1 **2** **3**

entry	R, R′	sulfide	halogen source	yield of **2**[b] (%)	**2/3**[c]
1	Ph, Me	**1b**	NBS	91	100:0
2			I_2	67	100:0
3	*p*-$OMeC_6H_4$, Me	**1c**	NBS	95	100:0
4			I_2	90	100:0
5	*p*-$NO_2C_6H_4$, Me	**1d**	NBS	92	100:0
6			I_2	30	100:0
7	2-Naph, Me	**1e**	NBS	85	100:0
8			I_2	70	100:0
9	2-Py, Me	**1f**	NBS	95	100:0
10			I_2	58	100:0
11	Ph, Ph	**1g**	NBS	99	100:0
12			I_2	<10	nd
13	$-(CH_2)_2-$	**1h**	NBS	83	90:10
14			I_2	<10	nd
15	*t*-Bu, Me	**1i**	NBS	71	100:0
16			I_2	<10	nd

[a] Reaction conditions: sulfide **1** (1 mmol, 1 equiv), H_2NCN (1.3 equiv), and the combination of NBS (1.5 equiv)/*t*-BuOK (1.2 equiv) or I_2 (4.0 equiv)/*t*-BuONa (1.2 equiv) in MeOH (3 mL) at room temperature. [b] Yield after column chromatography. [c] The **2a**/**3a** ratio was determined by ^1H NMR of the crude mixture.

NBS or I_2 in MeOH to form cyanosulfilimines **2**. Both halogenating agents showed a high selectivity in the formation of the sulfilimines, with iodine providing lower yields compared to NBS (entries 2, 4, 6, 8, and 10). Moreover,

(7) For previous examples of nucleophilic substitution with amides or aromatic amines, see: (a) Ringer, J. W.; Pearson, D. L.; Scott, C. A.; Wallin, A. P.; WO 9821178. (b) Vilsmaier, E.; Reichert, K. *Liebigs Ann. Chem.* **1980**, 1075. (c) Tseng, C. P. US 4484939. (d) Mock, W. L.; Tsay, J. T. *Synth. Commun.* **1988**, *8*, 769. (e) Shimizu, H.; Ikedo, K.; Hamada, K.; Ozawa, M.; Matsumoto, H.; Kamata, K.; Nahamura, H.; Ji, M.; Kataoka, T.; Hori, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, *7*, 1733. (f) Nummy, L. J.; EP 598396. (g) Benin, V.; Kaszynski, P.; Pink, M.; Young, V. G. *J. Org. Chem.* **2000**, *65*, 6388. (h) Zienkiewicz, J.; Kaszynski, P.; Young, V. G. *J. Org. Chem.* **2004**, *7*, 2551. (i) Hamilton, C. T. US 2005215570 A1. (j) Kislitsyn, P. G.; Kuchero, F. A.; Chukhrov, L. N.; Zlotin, S. G.; Satrikova, Z. A.; Dolgushin, F. M., *Russ. Chem. Bull.* **2004**, *4*, 916.

(8) For NBS-mediated oxidations of sulfides in aqueous media, see: Surenda, K.; Krishnaveni, N.; Srilakshmi, K.; Pavan, V.; Sridhar, R.; Rao, K. *Tetrahedron Lett.* **2005**, *46*, 4581.

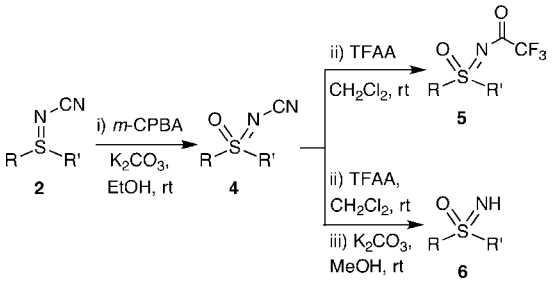
(9) The **2a**/**3a** ratio did not improve when the reaction was carried out at 0 °C (80:20).

attempted conversions of diarylsulfide **1g** and dialkylsufides **1h** and **1i** remained unsuccessful in reactions with iodine (entries 12, 14, and 16), whereas transformations with NBS led to the corresponding sulfilimines in satisfying yields (up to 99%; entries 11, 13, and 15). Only the NBS-mediated reaction of sulfide **1h**, which possessed two α-methylenic substituents, showed a lower selectivity, affording a 90:10 mixture of sulfilimine **2h** and sulfoxide **3h** (entry 13).[10] This result was consistent with the one observed in the conversion of sulfide **1a**, which also had methylene protons.

Finally, we were pleased to find that in the case of reactions with sulfides **1b**−**g** and **1i**, which have no α-methylenic positions, the formation of the corresponding sulfoxides was not detected, even when NBS was used as halogenating agent (Table 3, entries 1−12 and 15).

In order to demonstrate the synthetic value of the prepared *N*-cyanosulfilimines **2**, they were converted into trifluoroacetyl-protected and free *N*H-sulfoximines **5** and **6**, respectively. Interestingly, the latter transformation only required three steps, with no need of purification between the two final ones (Scheme 1).

Scheme 1



First, oxidation of **2** with *m*-CPBA afforded the *N*-cyanosulfoximines **4** in good yields (62−86%). The *N*-cyano group proved to be easily cleaved upon treatment with TFAA affording *N*-trifluoroacetylsulfoximines **5** (47−99%). Finally, sulfoximines **5** were converted into *N*H-free sulfoximines **6** by methanolysis of the trifluoroacetyl moiety (42−99%).[4a] For all substrates, each step of this sequence proceeded with high yields, except in the cases of the 2-pyridyl- and *p*-nitrophenyl-substituted compounds **2d** and **2f** (Table 4, entries 4 and 6, respectively). There, the final deprotection of these sulfoximines possessing electron-withdrawing groups occurred with only moderate yields (42% and 54%).

With the goal to expand the applicability of the cyano group cleavage, *N*-cyanosulfilimine **2b** was subjected to TFAA, and trifluoroacetyl-protected sulfilimine **7** was obtained in 99% yield (Scheme 2).

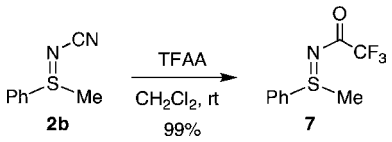
(10) When the reaction of **1h** was carried out on 10 mmol scale, a 60:40 ratio **2h**/**3h** was observed and sulfilimine **2h** was isolated in 50% yield.

Table 4. Synthesis of *N*H-Sulfoximines from Sulfilimines **1**[a]

entry	R, R′	sulfilimine	yield of **4**[b] (%)	yield of **5**[b] (%)	yield of **6**[b,c] (%)
1	Bn, Me	**2a**	62	84	81
2	Ph, Me	**2b**	86	93	72
3	*p*-OMeC$_6$H$_4$, Me	**2c**	78	99	99
4	*p*-NO$_2$C$_6$H$_4$, Me	**2d**	63	47	42
5	2-Naph, Me	**2e**	76	93	98
6	2-Py, Me	**2f**	82	92	54
7	Ph, Ph	**2g**	99	93	92
9	−(CH$_2$)$_2$−	**2h**	86	95	66

[a] See the Supporting Information for reaction conditions. [b] Yield after column chromatography. [c] Yield over two steps from **4**.

Scheme 2



In summary, we reported the synthesis of *N*-cyanosulfilimines from readily available sulfides and cyanogen amine using NBS or I_2 as halogenating reagents. The preparation of their corresponding *N*-cyanosulfoximines was easily achieved by common oxidation with *m*-CPBA under basic conditions. Finally, the access to synthetically valuable *N*H-sulfoximines was accomplished in two steps involving treatment with TFAA and subsequent methanolysis of the intermediately formed *N*-trifluoroacetyl sulfoximines.

Overall the described four-step-procedure for the formation of free *N*H-sulfoximines starting from sulfides has several advantages over the existing methodologies: the reagents involved are non-explosive, easy to handle, mild, and stable toward atmospheric moisture and oxygen. Thus, neither dried solvents nor an inert atmosphere are required.

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Supporting Information Available: Experimental procedures, full characterization of new compounds, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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