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Synthesis of *N*-(1*H*)-Tetrazole Sulfoximines

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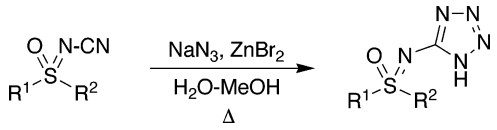
ABSTRACT



***N*-(1*H*)-Tetrazole sulfoximines are readily available by addition of sodium azide to the corresponding *N*-cyano derivatives in the presence of $ZnBr_2$. The use of these *N*-(1*H*)-tetrazoles as intermediates in the synthesis of other *N*-heterocyclic sulfoximines is demonstrated.**

Tetrazoles are appealing ligands in coordination chemistry and important compounds in pharmaceutical and material sciences.[1] Moreover, 1*H*-tetrazoles proved valuable for the preparation of substituted tetrazoles and other nitrogen-containing heterocycles.[2] The most direct and convenient route to 5-substituted-(1*H*)-tetrazoles is the [2 + 3]-cycloaddition between a nitrile and an azide.[3] Various synthetic approaches have been developed for this transformation. Most of them rely on the in situ generation of highly toxic and explosive hydrazoic acid through activation of the azide by expensive and toxic metals,[4] strong Lewis acids,[5] or amine salts.[6] Recently, Sharpless reported an efficient and safe procedure for the synthesis of tetrazoles using stoichiometric amounts of nontoxic $ZnBr_2$ in water.[7,8]

Encouraged by the intense research activity in the tetrazole field and in pursuit of our continuing interest in sulfoximine chemistry,[9,10] we envisioned the combination of these attractive functional groups by the synthesis of 1*H*-tetrazole sulfoximines **1** (Figure 1). Here, we report the synthesis of various *N*-cyano sulfoximines **2** and their conversion into tetrazole derivatives **1**.

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(3) A review: (a) Wittenberger, S. J. *Org. Prep. Proc. Int.* **1994**, *26*, 499.

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(9) 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. Reviews: (k) Harmata, M. *Chemtracts* **2003**, *16*, 660. (l) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482.

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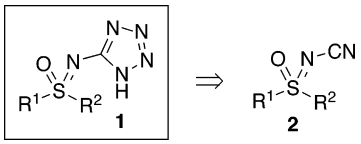
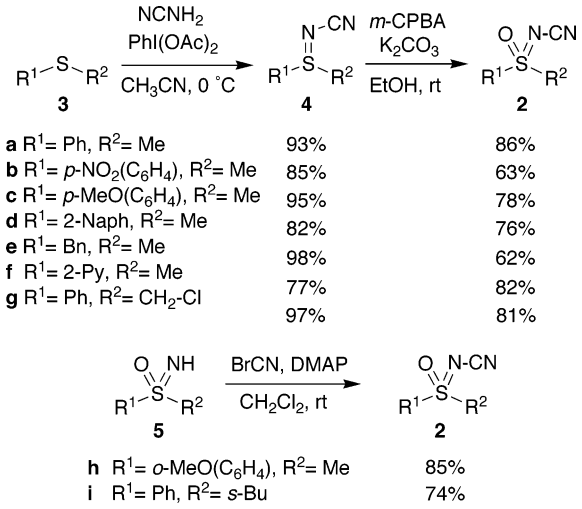


Figure 1. Target compounds **1** and their precursors **2**.

The most common approach toward sulfoximines consists of the direct imination of sulfoxides with a suitable nitrogen source.[11] Unfortunately, all attempts to perform such transformations with cyanogen amine were unsuccessful, and sulfoximines of type **2** remained inaccessible by this route. In contrast, diversely substituted *N*-cyano sulfilimines **4** could easily be prepared from the corresponding sulfides **3** by imination with cyanogen amine in combination with $PhI(OAc)_2$ (Scheme 1).[12] The reaction proceeded smoothly

Scheme 1



at 0 °C even in the absence of a metal catalyst.[13] Subsequent oxidation of sulfilimines **4** with *m*-CPBA and K_2CO_3 in ethanol gave the desired sulfoximines **2** in moderate to good yields (63−86%).

Following an alternative sequence, **2h** and **2i** were synthesized from *N*H-sulfoximines **5** by *N*-cyanation with BrCN.[14] As demonstrated later, this approach permits the synthesis of optically active products from enantiopure *N*H-sulfoximines.

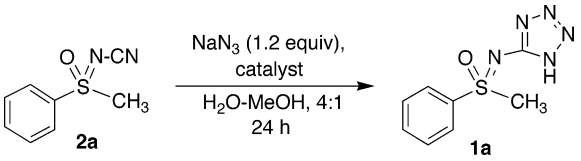
(11) For previous contributions on iminations of sulfur compounds, see: Rh-catalyzed: (a) Okamura, H.; Bolm, C. *Org. Lett.* **2004**, *6*, 1305. Ag-catalyzed: (b) Cho, G. Y.; Bolm, C. *Org. Lett.* **2005**, *7*, 4983. Fe-catalyzed: (c) García Mancheño, O.; Bolm, C. *Org. Lett.* **2006**, *8*, 2349. Metal-free: (d) Cho, G. Y.; Bolm, C. *Tetrahedron Lett.* **2005**, *46*, 8007.

(12) For previous synthesis of *N*-cyano sulfilimines, see: (a) Swern, D.; Ikeda, I.; Whitfield, G. F. *Tetrahedron Lett.* **1972**, *13*, 2635. (b) Kemp, J. E. G.; Ellis, D.; Closier, M. D. *Tetrahedron Lett.* **1979**, *20*, 3781. (c) Hutchins, M. G. K.; Swern, D. *Tetrahedron Lett.* **1981**, *22*, 4599. (d) Zhu, Y.; Rogers, R. B.; Huang, J. X. US Patent 20050228027 A1, 2005.

(13) When the imination of **3a** was performed in the presence of $Fe(acac)_3$ (10 mol %) in combination with PhI=O or $PhI(OAc)_2$, the reaction was faster (0.5 h vs 2 h) and the yield of **4a** was about the same.

Next, the [3 + 2]-cycloaddition reaction between *N*-cyano phenyl methyl sulfoximine (**2a**) and sodium azide to form the corresponding *N*-(1*H*)-tetrazole sulfoximine **1a** was studied (Table 1). Due to the poor water solubility of **2a**,

Table 1. *N*-(1*H*)-Tetrazole Sulfoximine **1a**[a]



entry	catalyst (mol %)	T (°C)	yield (%)[b]
1	−	120	−
2	−	160	nd[c]
3	aq sat NH_4Cl (excess)[d]	120	decomp
4	$Me_2NH{\cdot}HCl$ (20)	120	decomp
5	CuI (20)	120	15−35
6	$ZnBr_2$ (120)	120	84 (82)[e]

[a] Reaction conditions: sulfoximine **2a** (1 equiv), NaN_3 (1.2 equiv), and catalyst in H_2O−MeOH 4:1 (0.4 M) in a sealed pressure tube. [b] Yield after column chromatography. [c] An inseparable 1:1 mixture of tetrazole **1a** and *N*H-sulfoximine was obtained. [d] Used as solvent instead of H_2O. [e] Yield after trituration with Et_2O−pentane 1:1.

the addition of methanol (H_2O−MeOH 4:1) was required to improve its dispersion. Consequently, the reactions were performed in sealed glass pressure tubes.

Initially, the cycloaddition was carried out in the absence of a catalyst at 120 °C. At this temperature, no reaction occurred after 24 h, and in order to obtain the desired tetrazole sulfoximine **1a**, it was necessary to overheat the mixture to 160 °C. Unfortunately, under those conditions, an inseparable 1:1 mixture of the desired tetrazole and the corresponding *N*H-sulfoximine resulted (Table 1, entry 2). In the presence of amino salts such as $Me_2NH{\cdot}HCl$ (20 mol %) or an aqueous solution of NH_4Cl, *N*-cyano sulfoximine **2a** decomposed (entries 3 and 4).

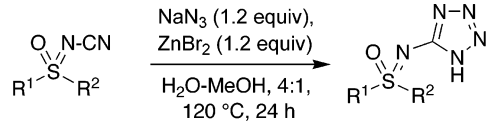
To avoid the cleavage of the *N*-cyano group or the decomposition of the sulfoximine, various metal salts were tested as catalysts.[15] Finally, the most suitable method for the synthesis of *N*-(1*H*)-tetrazole sulfoximines **1** was found to be the addition of sodium azide in the presence of a stoichiometric amount of $ZnBr_2$.[7] Thus, when *N*-cyano sulfoximine **2a** was treated with a 1:1 mixture of NaN_3 and $ZnBr_2$ (1.2 equiv), tetrazole sulfoximine **1a** was obtained in 84% yield (Table 2, entry 7). Due to the highly crystalline nature of 1*H*-tetrazoles, a simple trituration with a 1:1 mixture of Et_2O−pentane permitted pure tetrazole sulfoximine **1a** to be obtained in high yield (82%).

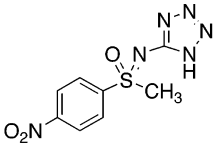
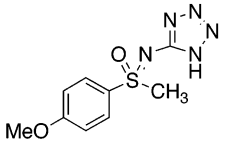
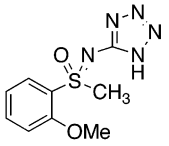
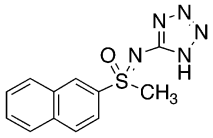
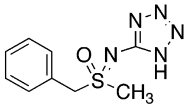
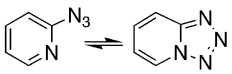
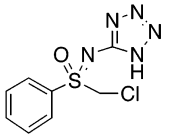
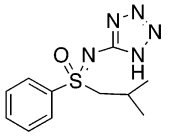
To determine the generality of this transformation, other *N*-cyano sulfoximines **2b**−**i** were applied as substrates (Table

(14) (a) Stoss, P.; Satzinger, G. *Tetrahedron Lett.* **1973**, *14*, 267. For the synthesis and application of *N*-cyano sulfoximines as insecticides, see ref 12d.

(15) The $AlMe_3$ mediated cycloaddition between **2a** and NaN_3 in dry toluene or THF at room temperature did not proceed.

Table 2. Synthesis of *N*-(1*H*)-Tetrazole Sulfoximines[a]



entry	sulfoximine	tetrazole		yield (%)[b]
1	**2b**		**1b**	68
2	**2c**		**1c**	83
3	**2h**		**1h**	86
4	**2d**		**1d**	65[c]
5	**2e**		**1e**	87
6	**2f**		**1f**	90[d]
7	**2g**		**1g**	82
8	**2i**		**1i**	68

[a] Reaction conditions: sulfoximine **2** (1 equiv), NaN_3 (1.2 equiv), and $ZnBr_2$ (1.2 equiv) in H_2O−MeOH 4:1 (0.4 M) at 120 °C in a sealed pressure tube. [b] Yield after trituration with Et_2O−pentane 1:1. [c] Yield after acidification and filtration. [d] Yield after purification by column chromatography.

2). All reactions proceeded to completion in less than 24 h, and tetrazole sulfoximines **1** were isolated in moderate to good yields (65−87%). The purification involved either acidification followed by simple filtration or extraction and subsequent trituration with Et_2O−pentane mixtures.[16] In general, electronic and steric modifications had no significant effect on the reactivity of the *N*-cyano sulfoximine. The best results were obtained with nitriles **2c**, **2h**, and **2e** containing electron-rich substituents at sulfur (83, 86, and 87%; entries 2, 3, and 5, respectively). In contrast, cycloaddition of 2-pyridyl sulfoximine **2f** did not give the desired tetrazole. Not surprisingly, **1f** was obtained by displacement of the sulfoximidoyl group at the pyridine core with NaN_3 (90%, entry 7). The IR absorption of the azido group in **1f** was weak, indicating the presence of the more stable ring-closed isomer, tetrazolo[1,5-α]pyridine.[17]

Next, the value of the 1*H*-tetrazole sulfoximines as intermediates for the synthesis of *N*-substituted tetrazoles and other *N*-heterocyclic sulfoximines was demonstrated (Scheme 2).

Initial attempts to prepare *N*-benzyl substituted tetrazoles **6** and/or **7** by reaction of **1a** with benzyl azide or the in situ formed organic azide (generated from NaN_3 and BnBr) failed.[18] Therefore, the alkylation of 1*H*-tetrazole **1a** in the presence of bases, which can provide both 1*N*- and 2*N*-alkyl substituted tetrazoles, was studied.[1a] The use of Et_3N in combination with a catalytic amount of DMAP in acetone at room temperature gave a 1.1:1 mixture of the *N*-benzylated regioisomers **6** and **7** (67%).[19] In contrast, with Et_3N alone, an inverse regioselectivity favoring the alkylation at N(1) was observed, leading to tetrazoles **6** and **7** in 32 and 59% yields, respectively.

The preparation of other five-membered heterocycles was studied next. In particular, we were interested in the well-established reaction of tetrazoles with anhydrides, which is of great importance for the synthesis of unsymmetrically substituted 1,3,4-oxadiazoles. Here, the reaction of 1*H*-tetrazole **1a** with highly reactive trifluoroacetic anhydride proceeded smoothly in acetonitrile at room temperature, leading after 2 h to the corresponding oxadiazole **8** in 81% yield.

On the other hand, treatment of **1a** with acetic anhydride under typical thermal conditions[2] (120 °C, 16 h) gave a complex product mixture, and the desired oxadiazole **9** was only obtained in a low yield (31%). Application of microwave irradiation (200 W, 120 °C), however, led to an excellent result in this reaction,[20] and after only 2 h, oxadiazole **9** was cleanly obtained in 70% yield.

(16) In the case of tetrazole sulfoximine **1d**, which was highly insoluble in water, the low pK_a of the tetrazole allowed complete precipitation by simple acidification. For the other tetrazoles **1**, this precipitation was inefficient, and most of the ones shown in Table 2 were obtained after trituration.

(17) (a) Wentrup, C.; Winter, H.-W. *J. Am. Chem. Soc.* **1980**, *102*, 6159. (b) Klump, S. P.; Shechter, H. *Tetrahedron Lett.* **2002**, *43*, 8421.

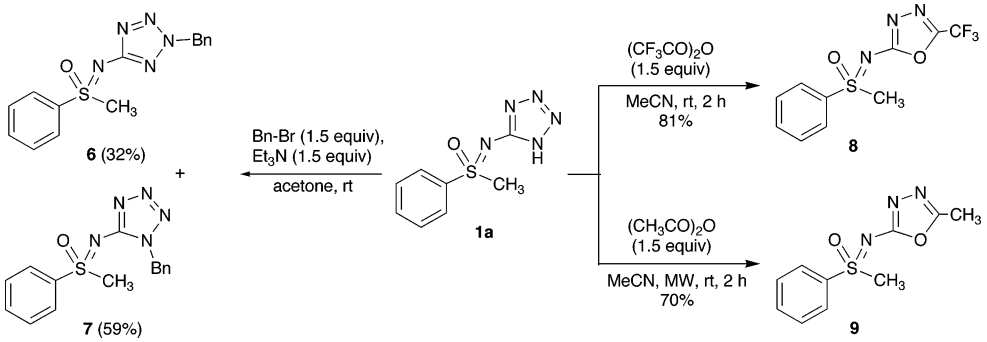
(18) For a recent example of cycloadditions of acylcyanides with aliphatic azides, see: Demko, Z. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2113.

(19) The structures of isomers **6** and **7** were assigned based on their ^1H and ^{13}C NMR spectra. Characteristically, the benzylic protons of the 2*N*-benzylated tetrazoles resonate at lower field than those of the corresponding 1*N*-benzylated isomers.

(20) For the first example of using microwave irradiation in the preparation of 1,3,4-oxadiazoles from tetrazoles, see: Lukyanov, S. M.; Bliznets, I. V.; Shorshnev, S. V.; Aleksandrov, G. G.; Stepanov, A. E.; Vasil'ev, A. A. *Tetrahedron* **2006**, *62*, 1849.

(21) Sulfoximine (*S*)-**5a** was prepared following literature procedures: (a) Fusco, R.; Tenconi, F. *Chim. Ind. (Milan)* **1965**, *47*, 61. (b) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418. For an improved protocol, see: (c) Brandt, J.; Gais, H.−J. *Tetrahedron: Asymmetry* **1997**, *8*, 909.

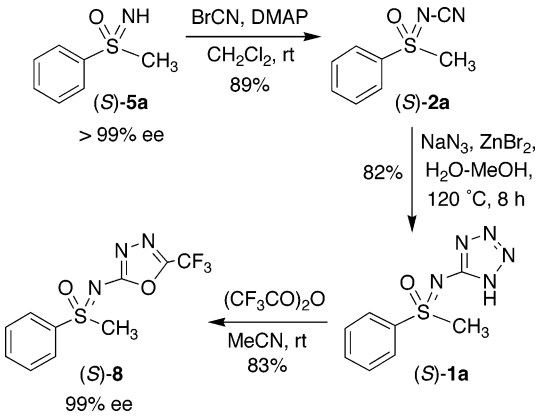
Scheme 2



Finally, the stereospecificity of the Zn-mediated [2 + 3]-cycloaddition leading to *N*-tetrazole sulfoximines was studied (Scheme 3).

For this purpose, sulfoximine (*S*)-**5a**[21,22] with >99% ee was converted into (*S*)-**2a** by *N*-cyanation with BrCN.[23] Subsequent reaction of (*S*)-**2a** under standard conditions with NaN_3 afforded *N*-tetrazole sulfoximine (*S*)-**1a**. Unfortunately, all attempts to determine its enantiomer ratio by chiral HPLC or GC techniques remained unsuccessful. Treatment of (*S*)-**1a** with trifluoroacetic anhydride at room temperature gave 1,3,4-oxadiazole (*S*)-**8** in 83% yield (corresponding to 61% over three steps from sulfoximine **5a**). Finally, the enantiomer ratio determination of (*S*)-**8** revealed that the entire reaction sequence had proceeded without loss of enantiopurity.[24]

Scheme 3



In summary, various *N*-cyano sulfoximines have been synthesized from readily available sulfides and cyanogen amine in two synthetic steps or by direct cyanation of the corresponding *N*H-sulfoximines. A [3 + 2]-cycloaddition reaction of the *N*-cyano sulfoximines with NaN_3 using inexpensive and nontoxic $ZnBr_2$ in H_2O−MeOH mixtures at 120 °C led to tetrazole sulfoximines. The reaction is stereospecific, constituting an easy access to novel enantiopure sulfoximines from the corresponding optically active *N*-cyano derivatives. Finally, the transformation of these compounds into *N*-benzylated tetrazole and 5-substituted 1,3,4-oxadiazole sulfoximines has been accomplished.

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

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(22) The enantiomeric excess of (*S*)-**5a** was determined by HPLC using a chiral column: Chiralcel OJ; heptane/*i*-PrOH = 85:15; 0.5 mL/min; 254 nm; $t_R(R)$ = 36.9 min, $t_R(S)$ = 48.9 min.

(23) Since this and the subsequent transformations do not involve the stereogenic center, we assume retention of configuration at sulfur.

(24) The enantiomeric excess of (*S*)-**8** was determined by HPLC using a chiral column: Chiralcel OJ; heptane/*i*-PrOH = 90:10; 0.7 mL/min; 254 nm; $t_R(R)$ = 89.8 min, $t_R(S)$ = 101.4 min.