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Access to *N*-Cyanosulfoximines by Transition Metal-Free Iminations of Sulfoxides

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A transition metal-free synthesis of *N*-cyanosulfoximines from sulfoxides using *N*-chlorosuccinimide (NCS) as oxidising agent and cyanamide as nucleophilic amine source is reported. The products are obtained in moderate to excellent yields. The protocol enables an easy access to *N*-cyanosulfoximines from readily available starting materials under inversion of configuration at a preexisting stereogenic center.

Since their discovery in the 1940s, sulfoximines represent a steadily diversifying class of compounds exhibiting highly interesting bioactivities.[1-4] Being identified as the responsible biotoxic agent for canine hysteria, methionine sulfoximine (MSO, **1**) was the first representative of such molecules ever reported.[5] Subsequently, sulfoximines have mostly been employed in asymmetric synthesis.[6,7] More recently, their potential in pesticide research and medicinal chemistry has been recognised,[1-4] where sulfoximines offer advantages over their non-aza analogues, sulfones, due to their solubility and their potential for structural diversification through nitrogen substitution at the stable stereogenic sulfur center.[6a,8] Examples of bioactive sulfoximines are the insecticide Sulfoxaflor (**2**)[4] and the two potent enzyme inhibitors BAY 1143572 (**3**)[1,2c] and AZD6738 (**4**)[2d], which have been promoted to clinical trials (Fig. 1).

For accessing sulfoximines from their corresponding sulfides two general pathways can be distinguished (Scheme 1, path A and path B).[9] The first one proceeds by sulfide imination and subsequent oxidation of the initially formed sulfilimine (path A). Along those lines we have reported the use of a combination of *N*-bromosuccinimide (NBS), potassium *tert*-butoxide (KO*t*Bu) and cyanamide for the first step followed by sulfilimine oxidation with *meta*-chloroperbenzoic acid (*m*-CPBA).[10] Alternatively, the sulfide imination can be performed with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and

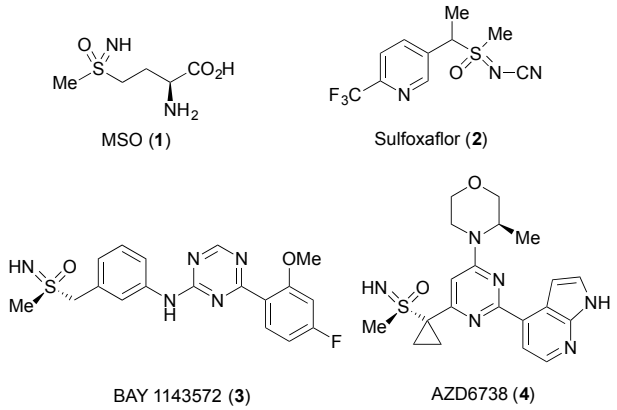

Fig. 1 Prominent bioactive sulfoximines.

trifluoroacetamide. Subsequent oxidation and concurrent deprotection with Oxone® then provides *N*H-sulfoximines.[11] If *N*-methylsulfoximines are targeted, a one-pot protocol by sequential imination/oxidation with methylamine, bromine and potassium permanganate can be applied.[12] The second route towards sulfoximines (Scheme 1, path B) reverses the imination/oxidation order. Also for this pathway, which involves a sulfoxide imination, several methods have been described.[9] Most of them rely on the use of a transition metal catalyst (based on iron,[13] copper,[14] ruthenium,[7b,15] rhodium,[16] silver[17])[18] and utilise amine sources such as azides or related nitrene-forming agents in combination with hypervalent iodine species.[19] Transition metal-free methods for sulfoxide iminations are also known,[20-25] however all of them employ the aforementioned critical reagents with respect to the nitrogen source and the oxidant hampering their synthetic applicability, in particular, on large scale.[24,25] Based on this analysis, we considered finding a new sulfoxide imination process with simple (harmless, non-toxic, low-cost) reagents as top priority. *N*-Cyanosulfoximines appeared particularly attractive because of their occurrence as bioactives[3b,4] and their relevance as intermediates towards *N*H-sulfoximines[10] and related derivatives.[26] The results of our search and

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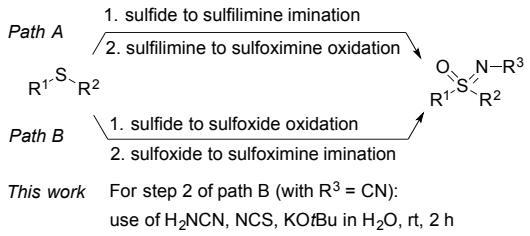

Scheme 1 Sulfide to sulfoximine conversions.

development are reported here (Scheme 1, path B, lower part).

For the initial reactivity screening, methylphenylsulfoxide (**5a**) was selected as starting material. Targeting *N*-cyano-sulfoximine **6a** as product, cyanamide was regarded as optimal nitrogen source. Although the standard procedures for sulfide iminations proved largely unsuitable for converting sulfoxide **5a**, small quantities of **6a** were detected when NBS, DBDMH, or trichloroisocyanuric acid were used as oxidants. The subsequent optimisation studies included variations of the base, the solvent, and the temperature and additional applications of the chlorine-based oxidants NCS and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH).[27] The results obtained from reactions performed in methanol as solvent at ambient temperature for 2 h are summarised in Table 1.

To our delight, the imination protocol could significantly be improved, and a major advance was achieved when NCS was used as oxidant, which proved superior to all other oxidising agents (Table 1, entries 1-5).[28] In this manner and with KO*t*Bu as base, sulfoximine **6a** was obtained in 77% yield.

Two more factors proved critical: The type of base and the order of reagent formation and addition. Thus combinations of NCS with sodium acetate, cesium carbonate, or triethylamine were unsuitable and did not lead to product formation (Table 1, entries 6-8). In contrast, with K_2CO_3, K_3PO_4, NaOMe, NaO*t*Bu or KOH as base, NCS provided **6a**, albeit in lower yields as with KO*t*Bu (Table 1, entries 1, 9-13). As the details in the series reveal, the strength of the base as well as the cation type (with, for example, K^+ being superior over Na^+) played a significant role. The importance of reagent formation and addition sequence was indicated by the following observations: If NCS was added to the sulfoxide before cyanamide and KO*t*Bu, the yield of **6a** was significantly lower and substantial amounts of sulfone **7** were detected (Table 1, entry 14). Both NCS and KO*t*Bu were crucial for the imination of **5a**, and in the absence of either of these reagents, no product was formed (Table 1, entries 15 and 16). From these results we conclude that the imination proceeds via deprotonated cyanamide, which reacts with an NCS-activated sulfoxide. Thus, the success of the reaction depends on the concurrent presence of all reagents and their in situ selfsorting.

Table 1 Screening of oxidant and base[a]

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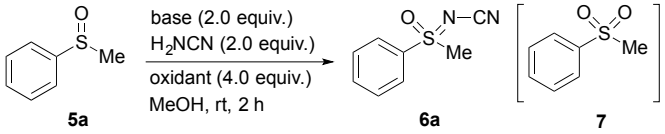
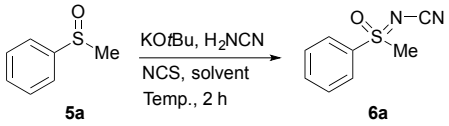


Entry	Oxidant	Base	Yield (%)[b]
1	**NCS**	**KO*t*Bu**	**77**
2	DCDMH	KO*t*Bu	55
3	NBS	KO*t*Bu	Trace
4	DBDMH	KO*t*Bu	Trace
5	Trichloroisocyanuric acid	KO*t*Bu	40
6	NCS	NaOAc	n.r.
7	NCS	Cs_2CO_3	n.r.
8	NCS	Et_3N	n.r.
9	NCS	K_2CO_3	60
10	NCS	K_3PO_4	56
11	NCS	NaOMe	34
12	NCS	NaO*t*Bu	38
13	NCS	KOH	75
14[c]	NCS	KO*t*Bu	37
15	NCS	-	n.r.
16	-	KO*t*Bu	n.r.

[a] Reactions were performed with **5a** (0.20 mmol), base (0.40 mmol), cyanamide (0.40 mmol), oxidant (0.80 mmol), MeOH (1 mL). [b] n.r. = no reaction. [c] Addition of NCS 10 min before addition of base and cyanamide.

Realising that the counterion of the base played such a major role, we wondered about solvation effects. Hence, a range of solvents was tested next (Table 2). While no conversion of **5a** was observed in reactions performed in toluene, DCM, DCE, diethyl ether, and trifluoroethanol, the previously applied methanol could be substituted by several other polar solvents. Thus, formation of **6a** was observed in ethyl acetate and THF, but due to incomplete conversion of **5a** and the generation of side products the results were unsatisfying (Table 2, entries 1 and 2). Reactions in acetonitrile and ethanol were almost as good as in methanol (77% yield), providing **6a** in 66% and 62% yield, respectively (Table 2, entries 3-5). Water proved to be superior to all other solvents leading to **6a** in 89% yield (Table 2, entry 6). Finally, adjusting the reagent amounts (Table 2, entries 6-9) and applying equimolar quantities of base, amine and oxidant (2.0 equiv. each) allowed isolating sulfoximine **6a** in 93% yield. Using KOH instead of KO*t*Bu was possible too, giving **6a** in 85% yield (Table 2, entry 10). Higher temperatures led to lower yields, performing the imination at 0 °C increased the yield of **6a** only insignificantly (to 95%; Table 2, entries 11-13).

Table 2 Optimisation of solvent, stoichiometry and temperature[a]



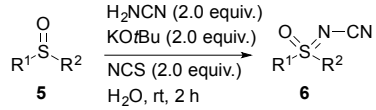
Entry	Solvent	Equiv. of base/ amine/oxidant	Temp. (°C)	Yield (%)[b]
1	ethyl acetate	2.0/2.0/4.0	rt	n.d.
2	THF	2.0/2.0/4.0	rt	n.d.
3	MeCN	2.0/2.0/4.0	rt	66
4	EtOH	2.0/2.0/4.0	rt	62
5	MeOH	2.0/2.0/4.0	rt	77
6	H_2O	2.0/2.0/4.0	rt	89
7	H_2O	1.0/2.0/2.0	rt	39
8	H_2O	1.5/1.5/1.5	rt	79
9	**H_2O**	**2.0/2.0/2.0**	**rt**	**93**
10[c]	H_2O	2.0/2.0/2.0	rt	85
11	H_2O	2.0/2.0/2.0	100	59
12	H_2O	2.0/2.0/2.0	50	75
13	H_2O	2.0/2.0/2.0	0	95

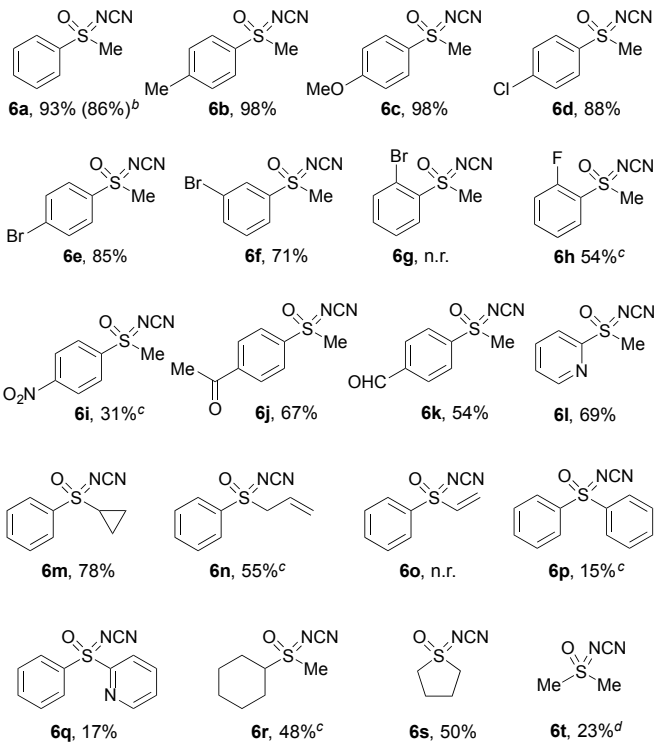
[a] Reactions were performed with **5a** (0.20 mmol), base, cyanamide, oxidant, solvent (1 mL). [b] n.d. = not determined. [c] Use of KOH instead of KO*t*Bu as base.

Taking all results into account, the subsequent substrate screening was performed with an equimolar amount of cyanamide, KO*t*Bu, and NCS (2.0 equiv. each) in water at room temperature for 2 h. Under these optimised reaction conditions, various sulfoxides **5a**-**t** were applied (Table 3). *S*-Aryl-*S*-methyl derivatives with electron-donating substituents on the arene gave very good to excellent yields of the corresponding *N*-cyanosulfoximines **6a-f**. Presumably due to steric reasons, no reaction was observed with *ortho*-bromo-substituted sulfoxide **5g**. In contrast, the analogous *ortho*-fluoro derivative gave sulfoximine **6h** in 54% yield. *S*-Methyl sulfoxides **5i**-**k** with electron-withdrawing aryl substituents led to the corresponding products **6i**-**k** in moderate to good yields. *S*-Methyl-*S*-2-pyridinyl-substituted sulfoximine **6l** was formed in 69% yield. Changing the *S*-methyl group to another alkyl or aryl group significantly affected the yield of the resulting sulfoximine depending on the individual substituent. Whereas *S*-cyclopropyl-*S*-phenylsulfoximine **6m** and *S*-allyl-*S*-phenyl-sulfoximine **6n** were formed in 78% and 55% yield, respectively, the yields for *S,S*-diphenylsulfoximine **6p** and *S*-phenyl-*S*-(2-pyridinyl)sulfoximine **6q** were only 15% and 17%. The low yields in the latter two cases were attributed to poor substrate solubilities in the solvent (H_2O) and the formation of the corresponding sulfones as favoured products. *S*-Phenyl-*S*-vinylsulfoximine **6o** remained inaccessible. The yields of *S,S*-dialkyl-substituted sulfoximines **6r**-**t** were low to moderate presumably due to their high water solubility which hampered their isolation.

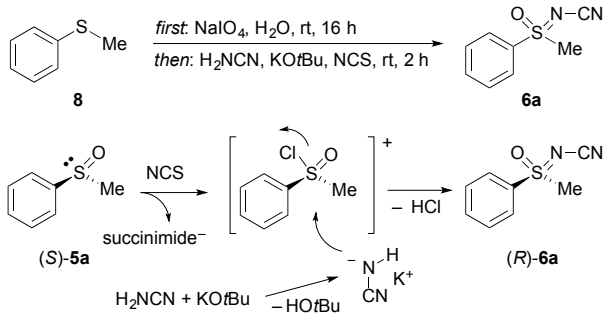
The scalability of the process was proven by performing the reaction starting from **5a** on a 50 mmol scale providing the desired product **6a** in 86% yield. Finally, a one-pot procedure for direct conversions of sulfides to *N*-cyanosulfoximines **6** via sulfoxides **5** was developed (Scheme 2, top, and ESI). As demonstrated for the reaction of methylphenylsulfide (**8**), the oxidation of **8** with $NaIO_4$ followed by imination of the resulting sulfoxide **5a** under the optimised conditions afforded *N*-cyanosulfoximine **6a** in 85% over two steps.

Table 3 Evaluation of the substrate scope[a]





[a] Reactions were performed on a 0.20 mmol scale in H_2O (1 mL). n.r. = no reaction. [b] In parentheses, yield of **6a** obtained in a reaction on a 50 mmol scale. [c] Isolated product contains small amounts (<5%) of impurities (such as solvents). [d] Yield of **6t** obtained in a reaction on a 5 mmol scale.



Scheme 2 Top: One-pot sulfide-to-sulfoximine conversion; bottom: mechanistic proposal.

The stereochemical path of this process was investigated by subjecting a sample of enantiomerically enriched sulfoxide **5a** to the imination conditions (Scheme 2, bottom). For the subsequent analysis, the obtained *N*-cyanosulfoximine **6a** was converted to its *N*H-analogue **9** without affecting the stereogenic center.[10] Analysing compound **9** by chiral HPLC and comparing the retention times with known data revealed that the imination was stereospecific converting **5a** to **6a** under inversion of configuration (for details, see ESI). This result could be explained by a retentive oxidative chlorination of the sulfoxide followed by invertive nucleophilic substitution by the deprotonated cyanamide.

Conclusions

We discovered an unprecedented imination of sulfoxides that proceeds under mild reaction conditions leading to *N*-cyanosulfoximines in moderate to excellent yields. The protocol is scalable, avoids the use of transition metal and thermally labile reagents. Chiral sulfoxides can stereospecifically be converted with inversion of configuration.

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