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Heterocycles

[3+2]-Cycloadditions of *N*-Cyano Sulfoximines with 1,3-Dipoles

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In memory of Professor Dr. Rolf Huisgen

Abstract: Involving the cyano group of *N*-cyano sulfoximines in [3+2]-cycloaddition reactions with 1,3-dipoles provides practical routes for the construction of 5-membered heterocycles bearing sulfoximinoyl moieties. An ytterbium-catalyzed cycloaddition utilizing hydrazonoyl chlorides was developed, as well as a reaction involving imidoyl chlorides proceeding without the aid of a catalyst. Following these protocols, a range of sulfoximines with *N*-1,2,4-triazolyl and *N*-1,2,4-oxadiazolyl substituents was prepared.

Introduction

Being structurally related to the ubiquitous sulfamoyl group, the sulfoximinoyl moiety has in turn found significant interest in pharmaceutical and agrochemical industry.[1,2] Possessing a potential stereogenic sulfur and an additional site for further functionalization at the nitrogen atom, sulfoximines can be used to increase structural diversity, enable additional bonding interactions or generally improve pharmacokinetic properties.[1a] BSO,[3] Roniciclib,[1a] and Gö 4962[4] are examples for medicinal compounds, while Sulfoxaflor[5] is employed as pesticide (Figure 1).

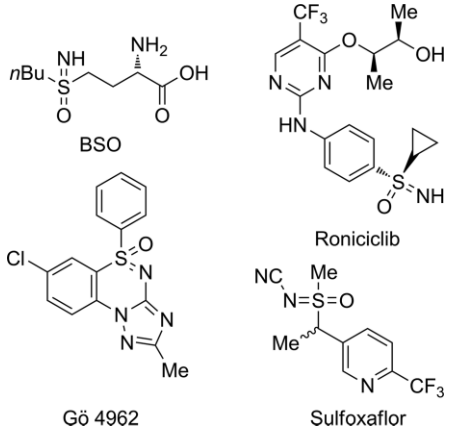

Figure 1. Examples of bioactive sulfoximines.

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Incorporating a sulfoximinoyl moiety into a complex molecular framework can still be challenging despite the impressive progress made in the development of complimentary synthetic routes in the last decades. For example, today's "synthetic tool box" includes sulfur oxidation/iminations,[6] C–S bond formations,[7] and a large variety of *N*-functionalizations such as acylations,[8] alkylations,[9] arylations,[10] alkynylations,[11] heteroatom introductions,[12] and annulations.[13]

N-Cyano sulfoximines **1** are easily accessible[14] and remarkably stable.[15] As a result, they have been applied as molecules with defined bioactivities such as pesticides (i.e. Sulfoxaflor)[5,14d] and enzyme inhibitors.[16] Furthermore, *N*-cyano sulfoximines proved useful as intermediates towards *N*H-sulfoximines, as the *N*-cyano group can be cleaved under well-defined reaction conditions.[14a,14b] In light of the rich chemistry of related compounds such as cyanamide,[17] it is surprising that chemical modifications of the *N*-cyano group of *N*-cyano sulfoximines keeping both the carbon and the nitrogen atom in the resulting molecular framework have only scarcely been studied. To the best of our knowledge, besides hydrolysis to the corresponding *N*-carbamoyl sulfoximine,[14a,14b,15] only three conversions have been reported: First, *N*-cyano sulfoximines were treated with azides providing the corresponding *N*-tetrazolyl derivatives **2** (Scheme 1, top).[18] Second, three-component denitrogenative [3+2] cycloadditions led to *N*-imidazolyl sulfoximines **3** (Scheme 1, middle),[19] and third, heterocyclizations via *N*(*N*-hydroxy guanidinyl) intermediates afforded sulfoximines with *N*-1,2,4-oxadiazolyl substituents **4** (Scheme 1, bottom).[20,21]

Considering the importance of functionalized heterocycles in pharmaceutical and agrochemical products,[22] we envisaged applying other heterocyclization reactions involving the CN group of *N*-cyano sulfoximines. Considering the large number of applications of 1,2,4-triazole and 1,2,4-oxadiazole derivatives in medicinal and agro chemistry,[23,24] synthetic protocols for compounds with *N*-1,2,4-triazolyl and *N*-1,2,4-oxadiazolyl substituents appeared particular attractive. Here, we report on two new transformations towards such compounds, which both proceed via in-situ formed propargyl-type 1,3-dipoles.[25,26]

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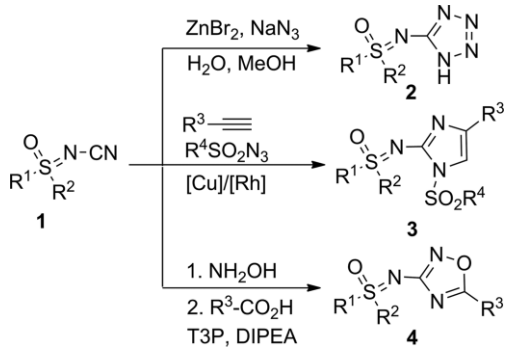
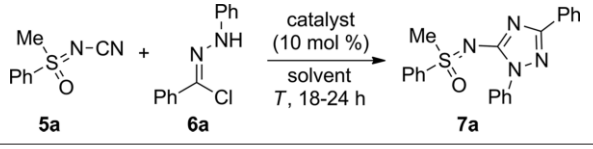


Scheme 1. Previous reactions at the cyano group of *N*-cyano sulfoximines; T3P = 1-propanephosphonic anhydride.

Results and Discussion

Hydrazonoyl chlorides are known to undergo dehydrohalogenation reactions providing highly reactive nitrilimines.[27] If those react with nitriles by 1,3-dipolar cycloaddition, 1,2,4-triazoles result. For the study reported here, we chose sulfoximine **5a** and hydrazonoyl chloride **6a** as representative starting materials. As numerous methods for the dehydrohalogenation of the betaine precursors exist, the rate of release of the active 1,3-dipole can be tailored to the reactivity of the dipolarophile. Our initial attempt revealed that refluxing the reactants in toluene was insufficient, with **6a** being almost fully recovered (Table 1, entry 1). Subsequently, various bases were added (Table 1, entries 2–4), and $NaHCO_3$ was identified as most effective, yielding *N*-triazolyl sulfoximine **7a** in 59 %. Being inspired by a report of Su and co-workers,[28] $Yb(OTf)_3$ was tested as catalyst. Even without base, the presence of 10 mol-% of $Yb(OTf)_3$ led to **7a** in 44 % yield (Table 1, entry 5). Most likely, the Lewis acid supported the cycloaddition reaction by activation of **5a** through coordination to the *N*-cyano group. Alternatively, $Yb(OTf)_3$ facilitated the dehydrohalogenation of **6a** leading to a high concentration of the respective dipole. Subsequently, various other reaction parameters such as the solvent type and the temperature were evaluated (Table 1, entries 6–10). Finally, keeping a combination of the substrates with 10 mol-% of $Yb(OTf)_3$ and 1.5 equiv. of $NaHCO_3$ in benzene at 120 °C for 24 h using a sealed tube in an aluminum heating block proved optimal providing **7a** in 99 % yield (Table 1, entry 10). Using toluene as solvent under the same conditions gave **7a** in 97 % yield (Table 1, entry 11).

Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	Base	Catalyst	Yield [%][b]
1	Toluene	–	–	5
2[c]	Toluene	Et_3N	–	45
3[c]	Toluene	$NaHCO_3$	–	59
4[c]	Toluene	K_2CO_3	–	39
5[d]	Toluene	–	$Yb(OTf)_3$	44
6[d]	H_2O	–	$Yb(OTf)_3$	38
7[d]	EtOH	–	$Yb(OTf)_3$	9
8[d]	MeCN	–	$Yb(OTf)_3$	43
9[d]	Benzene	–	$Yb(OTf)_3$	75
10[c]	Benzene	$NaHCO_3$	$Yb(OTf)_3$	99[e]
11[c]	Toluene	$NaHCO_3$	$Yb(OTf)_3$	97[e]

[a] Reaction conditions: **5a** (0.20 mmol), **6a** (0.30 mmol), base (0.30 mmol), catalyst (0.02 mmol, 10 mol-%), solvent (0.5 mL), 120 °C, 18 h. [b] Determined by quantitative ^1H NMR spectroscopy with dimethylsulfone as internal standard (except for entries 10 and 11). [c] Reaction time: 24 h instead of 18 h. [d] Reaction temperature: 100 °C instead of 120 °C. [e] After column chromatography.

With the optimized conditions (Table 1, entry 10) in hand, the substrate scope was explored. The results are shown in Figure 2. First, the sulfoximine structure was varied, and hydrazonoyl chloride **6a** was used as coupling partner. In the series of methyl sulfoximines (leading to products **7a**–**h**) neither electron-donating nor -withdrawing groups on the arene showed a significant effect on the efficiency of the heterocyclization. In most cases, the yields were high (with up to 99 %). The only exceptions were 4-acetyl and 4-nitro-substituted substrates **5d** and **5h**. Whereas the former afforded product **7d** in 84 % yield, the reaction with the latter provided only unidentified degradation products. The failure of converting 4-nitrophenyl-substituted *N*-cyano sulfoximine **5h** is in line with observations described later related to the attempted synthesis of **9e** (see Figure 4) indicating an intrinsic instability of compounds with such substitution pattern. *S*-Phenyl sulfoximines with *S*-ethyl, *S*-isopropyl, and *S*-cyclopropyl groups reacted as well leading to the corresponding product **7i**–**k** in yields of 98 %, 89 %, and 85 %, respectively.

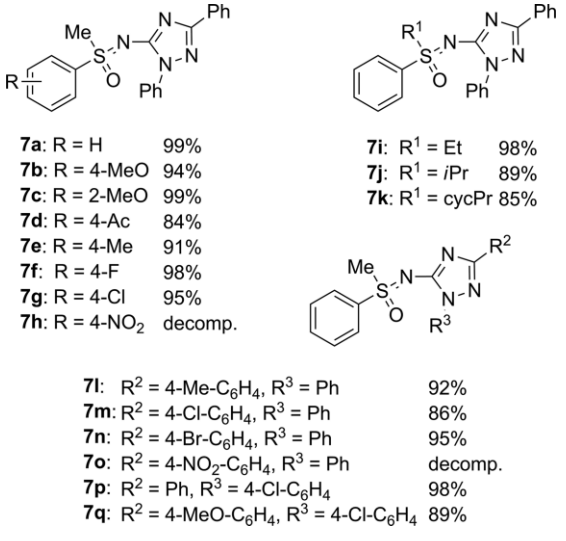


Figure 2. Substrate scope for the syntheses of *N*-1,2,4-triazolyl sulfoximines **7** from sulfoximines **5** and hydrazonoyl chlorides **6** (under conditions shown in Table 1, entry 10).

Applying sulfoximine **5a** in reactions with other hydrazonoyl chlorides **6** revealed the flexibility of the approach (Figure 2). In general, the yields of the corresponding products (**7l**–**7q**) were high (> 86 %) again, with the only exception of nitro-containing targeted product **7o** where decomposition was observed.

With the intention to expand the reaction portfolio of *N*-cyano sulfoximines with in-situ formed propargyl-type 1,3-di-

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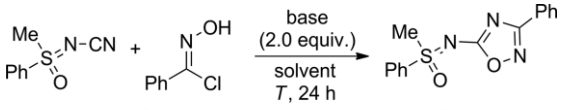
poles obtained by dehydrohalogenations of respective betaine precursors we turned our attention to a potential use of imidoyl chlorides. In relation to the studies by Saravanan and co-workers,[19,20] this approach presented a synthetic alternative towards *N*-1,2,4-oxadiazolyl-sulfoximines.

Imidoyl chlorides are readily available by chlorination of aldoximes, and their subsequent dehydrohalogenations leads to nitrile oxides, which undergo a wide range of 1,3-dipolar cycloaddition reactions.[29] Usually, nitrile oxides are generated at room temperature and an equimolar amount of the dipolarophile is sufficient to provide the products in high yield and selectivity. The attempt to follow this protocol here with *N*-cyano sulfoximine **5a** and imidoyl chloride **8a** as starting materials remained unsuccessful. In all cases, the yield of *N*-1,2,4-oxadiazolyl-sulfoximine **9a** remained unsatisfying, independent of the type of base or the solvent (Table 2, entries 1–8). At best, **9a** was obtained in 44 % yield, when the transformation was carried out in DCM in the presence of sodium bicarbonate (Table 2, entry 4). Attempts to mediate or catalyze the reaction with metal salts (such as CuCl in the absence or presence of amine ligands) were also unsuccessful (details not shown). However, increasing the temperature proved beneficial, being in line with a thermal activation of the intended 1,3-dipolar cycloaddition. Finally, product **9a** could be isolated in 94 % yield after carrying out the reaction in toluene at 120 °C for 24 h (Table 2, entry 9). The addition of a base proved unnecessary.

Table 2. Optimization of reaction conditions **1**.[a]



5a **8a** (2 equiv.) **9a**

Entry	Solvent	Base	Temp.	Yield [%][b]
1	DCM	Pyridine	r.t.	2
2	DCM	Et_3N	r.t.	11
3	DCM	Na_2CO_3	r.t.	31
4	DCM	$NaHCO_3$	r.t.	44
5	Et_2O	$NaHCO_3$	r.t.	31
6	EtOH	$NaHCO_3$	r.t.	34
7	H_2O	$NaHCO_3$	r.t.	32
8	H_2O/EtOH	$NaHCO_3$	r.t.	26
9	Toluene	–	120 °C	95 (94)[c]

[a] Reaction conditions: **5a** (0.2 mmol), **8a** (0.4 mmol, 2 equiv.), base (0.4 mmol), solvent (0.5 mL), 120 °C, 24 h. [b] Determined by quantitative ^{1}H NMR spectroscopy with dimethylsulfone as internal standard. [c] In parentheses: After column chromatography.

The molecular structure of **9a** (Figure 3) was unequivocally proven by X-ray crystal structure analysis.[30]

Next, the optimized conditions (Table 2, entry 9) were applied on other substrate combinations. The results are summarized in Figure 4. Again, the sulfoximine structure was varied first. In the series of *S*-aryl-*S*-methyl sulfoximines, the yields of the corresponding *N*-oxadiazolyl-sulfoximines **9a–i** showed a wider distribution than those for the previously described *N*-triazolyl sulfoximines **7** (Figure 2). Generally, sulfoximines with electron-donating substituents on the arene performed better than those with electron-withdrawing substituents. For example, product **9f** having a methoxy group in the 4 position of the *S*-aryl was obtained in 97 % yield. In contrast, **9h** bearing a 4-acetyl substituent was only formed in 48 %. Similar trends were observed with the halogenated derivatives **9b–d**. Also in this series, the nitro-containing product (**9e**) could not be isolated due to decomposition of sulfoximine **5e** under these otherwise optimal conditions. Presumably due to a steric effect the yields of **9f** and **9g** differ significantly (97 % vs. 67 %). Both products have methoxy-groups on the arene, but while the former bears the substituent on the 4 position, the latter has it in 2 position leading to a more pronounced steric impact.[31] An analogous behavior was seen when the *S*-methyl group on the sulfoximine is substituted by *S*-ethyl and *S*-cyclopropyl. While **9a** (with *S*-methyl) and **9j** (with *S*-ethyl) are formed in almost identical yields of 95 % and 97 %, respectively, **9k** bearing a sterically more demanding α-branched cyclopropyl substituent is only isolated in 70 % yield. Also halo-containing aryl imidoyl chlorides reacted with sulfoximine **5a** albeit the yields of the resulting products **9l–n** remained only moderate (39–49 %). Presumably, the dimerization rate of the intermediately formed nitrile oxide was too high to compete with the desired cycloaddition at the *N*-cyano group of sulfoximine **5a**. Substrate decomposition was observed in the attempt to react aliphatic acetimidoyl chloride (**9o**) with *N*-cyano sulfoximine **5a** under the standard conditions. As a result, parts of **5a** could be recovered, and **9o** remained inaccessible.

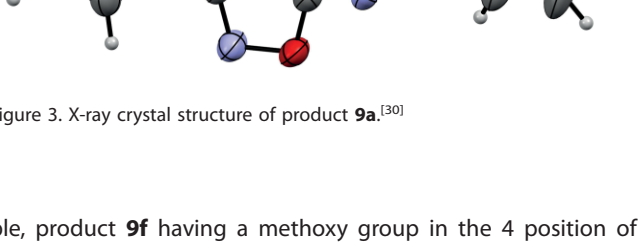
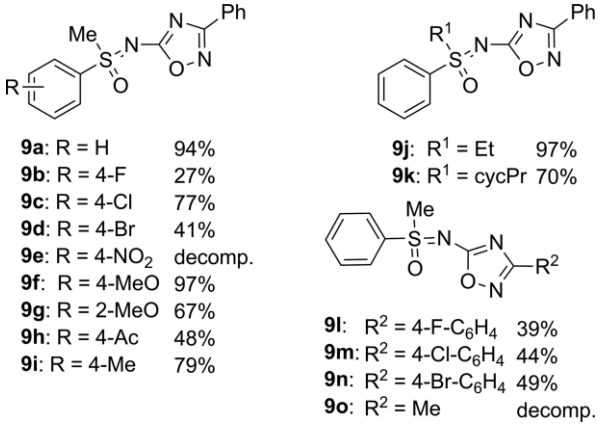


Figure 3. X-ray crystal structure of product **9a**.[30]



9a: R = H 94%
9b: R = 4-F 27%
9c: R = 4-Cl 77%
9d: R = 4-Br 41%
9e: R = 4-NO_2 decomp.
9f: R = 4-MeO 97%
9g: R = 2-MeO 67%
9h: R = 4-Ac 48%
9i: R = 4-Me 79%

9j: R^1 = Et 97%
9k: R^1 = cycPr 70%

9l: R^2 = 4-F-C_6H_4 39%
9m: R^2 = 4-Cl-C_6H_4 44%
9n: R^2 = 4-Br-C_6H_4 49%
9o: R^2 = Me decomp.

Figure 4. Substrate scope for the syntheses of *N*-1,2,4-oxadiazolyl sulfoximines **9** from sulfoximines **5** and hydrazonoyl chlorides **8** (under conditions shown in Table 2, entry 9).

Conclusions

In summary, sulfoximines with *N*-bound five-membered heterocycles have been prepared by [3+2] cycloaddition reactions of *N*-cyano sulfoximines and nitrilium betaines derived from hydrazonoyl and imidoyl chlorides. While the former type of transformations benefits from the presence of catalytic amounts of $Yb(OTf)_3$, the latter proceed metal-free. Future investigations will focus on applying other 1,3-dipoles on *N*-cyano sulfoximines with the goal of expanding the chemical space around this interesting class of compounds.

Experimental Section

Typical Procedure for the Synthesis of *N*-1,2,4-Triazolyl Sulfoximines 7: To an oven-dried 10 mL tube equipped with a stirring bar was added *N*-cyano sulfoximine **5** (0.2 mmol), hydrazonoyl chloride **6** (0.3 mmol, 1.5 equiv.), $NaHCO_3$ (25.2 mg, 0.3 mmol, 1.5 equiv.), ytterbiumtriflate (12.4 mg, 0.02 mmol, 0.1 equiv.) and benzene (0.5 mL). After sealing, the tube was placed in a preheated aluminum heating block, and the reaction mixture was stirred at 120 °C for 24 h. Then, the solvent was removed under reduced pressure, and the reaction mixture subjected to flash column chromatography on silica gel using the specified gradient.

Typical Procedure for the Synthesis of *N*-1,2,4-Oxadiazolyl Sulfoximines 9: To an oven-dried 10 mL tube equipped with a stirring bar was added *N*-cyano sulfoximine **5** (0.2 mmol), imidoyl chloride **8** (0.4 mmol, 2.0 equiv.) and toluene (0.5 mL). The tube was sealed, placed in a preheated aluminum heating block, and the reaction was stirred at 120 °C for 24 h. Then, the solvent was removed under reduced pressure, and the reaction mixture subjected to flash column chromatography on silica gel using the specified gradient.

Acknowledgments

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Keywords: Betaines · Cycloaddition · 1,3-Dipole · Oxadiazole · Triazole

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[30] CCDC 1984075 (for **9a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

[31] The presence of 10 mol-% of $Yb(OTf)_3$ had no significant effect on the product formation as shown for the reaction between **5g** (0.2 mmol) and **8a** (0.4 mmol) in 0.5 mL of toluene at 12 °C for 24 h, which led to **9g** in 65 % yield.

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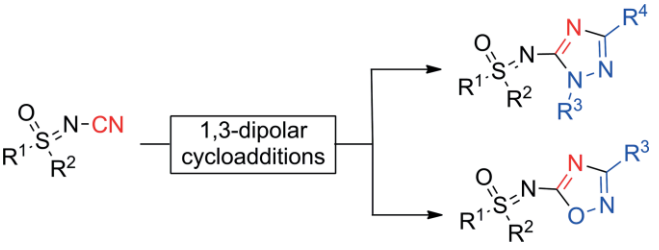
Heterocycles



In the present study reports 1,3-dipolar cycloaddition reactions starting from easily accessible *N*-cyano sulfoximines. In a straightforward manner, sulfoximines with *N*-1,2,4-triazolyl and *N*-1,2,4-oxadiazolyl substituents are prepared in good yields, While the former reactions require the presence of $Yb(OTf)_3$ in catalytic amounts, the latter proceed metal-free.

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