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Exploring the Reactivity of *N*-Alkynylated Sulfoximines: Regioselective Hydroacyloxylations and Hydroaminations

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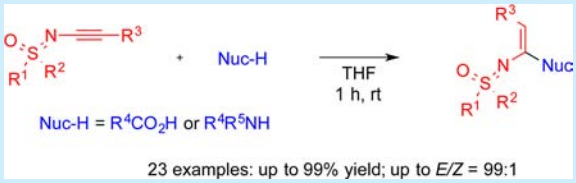
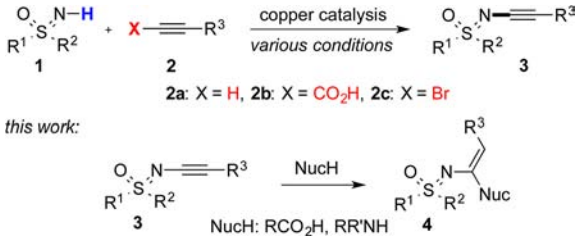
Supporting Information

ABSTRACT: *N*-Alkynylated sulfoximines undergo smooth transformations with benzoic acids and sulfonamides under mild conditions affording the corresponding hydroacyloxylation or hydroamination products. The transformations proceed in the absence of catalysts or additional reagents in short reaction times generating the products in excellent yields and very high stereoselectivities.



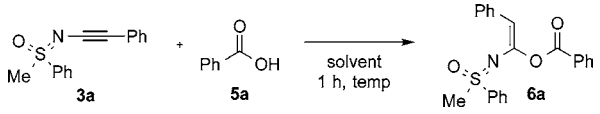
Since their discovery in 1950, sulfoximines have been widely applied in organic synthesis, medicinal chemistry, and crop protection.[1] The development of new synthetic strategies for the incorporation of the sulfoximidoyl moiety into organic molecules has therefore been of interest in our group for a long time.[2] Lately, we focused on the preparation of *N*-alkynylated sulfoximines **3** (Scheme 1, top),[3] and three cross-coupling protocols were developed.[4−6] All three rely on copper catalysis and utilize *NH*-sulfoximes **1** as starting materials. Synthetic variations result from the alkynylic coupling partners that can be either terminal alkynes **2a**,[4] aryl propiolic acids **2b**,[5] or bromoacetylenes **2c**.[6,7] Formally, *N*-alkynylated sulfoximines represent chiral versions of ynamides. However, whereas the chemistry of the latter compounds is well-investigated, *N*-alkynylated sulfoximines are virtually unexplored.[8] For ynamides various transformations including nucleophilic addition reactions, cycloadditions, ring-closing metathesis, cycloisomerizations and metal-catalyzed cross-coupling reactions are known allowing the synthesis of a variety of target molecules.[9] In this context, Lam and co-workers reported regio- and stereoselective Pd-catalyzed hydroacyloxylations of ynamides with carboxylic acids affording α-acyloxyenamides.[10] Additionally, a metal-free version for the same reaction was developed by Hu and Bi.[11] Recently, Cao described regio- and stereoselective hydroamination reactions of ynamides with diphenylsulfonimides leading to ketenaminals.[12] These and other findings[13] made us wonder about analogous reactions starting from *N*-alkynylated sulfoximines. Here, we report hydroacyloxylations and hydroaminations of such substrates (Scheme 1, bottom).

Scheme 1. Preparation of *N*-Alkynylated Sulfoximines and Focus of the Present Study



To investigate the hydroacyloxylation process, the initial reactions were performed applying *N*-alkynylated sulfoximine **3a** and benzoic acid (**5a**) as representative substrates using the conditions reported by Hu and Bi (toluene, 100 °C, 1 h).[11] To our delight, the desired product **6a** was formed in 70% yield (Table 1, entry 1). However, a mixture of *E*/*Z* isomers was obtained in a ratio of 47:53.[14] To optimize the reaction conditions, the effect of the reaction temperature was examined. When increasing the temperature to 120 °C, the isomer ratio

Table 1. Optimization of Reaction Conditions[a]



entry	temp (°C)	solvent	yield (%)	*E*/*Z*[b]
1	100	toluene	70	47:53
2	120	toluene	65	47:53
3	80	toluene	80	47:52
4	60	toluene	90	68:32
5	40	toluene	90	82:18
6	rt	toluene	90	93:7
9	0	toluene	99	94:6
10	−20	toluene	99	77:23
12	0	DCM	92	96:4
13	0	pentane	87	96:4
14	0	THF	83	98:2
15	rt	THF	96	99:1
16	rt	DCM	99	75:25

[a]Reaction conditions: **3a** (0.2 mmol) and **5a** (0.3 mmol) stirred in 1 mL of solvent under argon at indicated temperature for 1 h. [b]Ratio determined by ^{1}H NMR spectroscopy.

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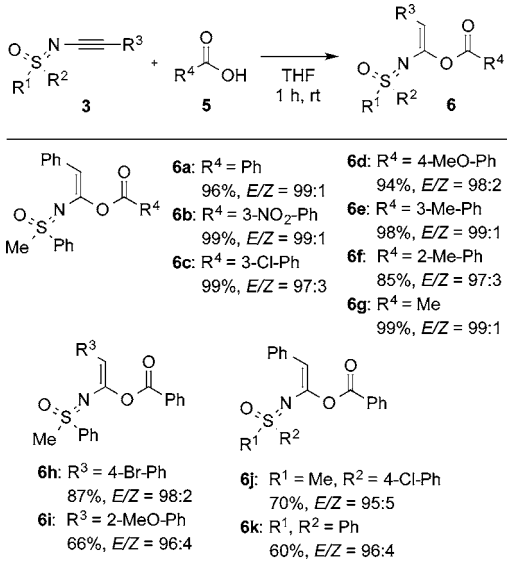
remained unchanged, while the yield dropped to 65% (Table 1, entry 2). Lowering the reaction temperature affected both the yield of **6a** and the *E*/*Z* ratio (Table 1, entries 3−10). The best result in this series was obtained at 0 °C resulting in a 99% yield of **6a** having an *E*/*Z* ratio of 94:6 (Table 1, entry 9). A solvent screening (DCM, pentane, THF; entries 9, 12−14) at 0 °C revealed that THF provided the highest *E*/*Z* selectivity (98:2, Table 1, entry 14). Since product **6a** was now obtained in only 83% yield, the hydroacyloxylation in THF was trialed at room temperature. Delightfully, product **6a** formed in 96% yield with an *E*/*Z* selectivity of 99:1 (Table 1, entry 15).

Under the optimized conditions (THF, room temperature, 1 h), various carboxylic acids **5** were reacted with *N*-alkynylated sulfoximine **3a** first (Scheme 2). For aromatic acids electronic

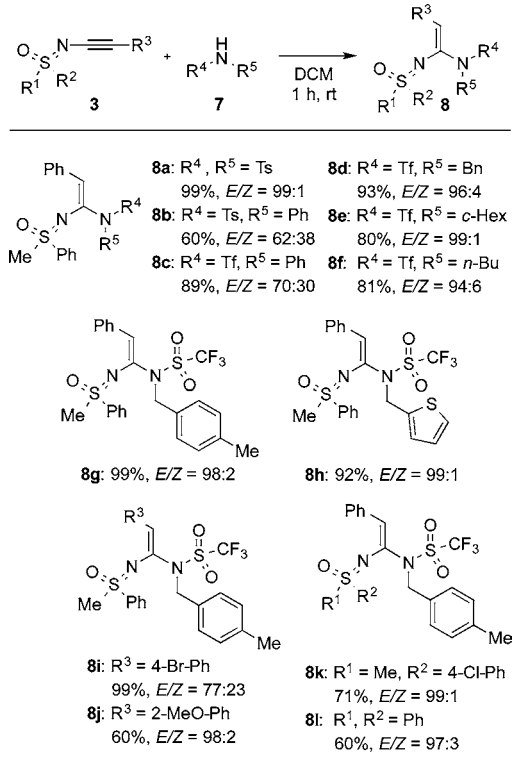
Scheme 2. Scope of Hydroacyloxylations of *N*-Alkynylated Sulfoximines



effects induced by substituents did not significantly influence the yield and the stereochemistry of the corresponding products (**6a−f**). Thus, both benzoic acids with electron-donating and -withdrawing substituents gave the addition products in very high to excellent yields (85%−99%, Scheme 2). In all cases, the stereoselectivities were excellent (97:3−99:1). Then, acetic acid, representing an acid with an aliphatic rest, was reacted with **3a**. Again, both the yield (99%) and the *E*/*Z* ratio (99:1) of the resulting product (**6g**) were excellent. Finally, the yne-sulfoximine component was varied and couplings with benzoic acid (**5a**) were studied. Although the yields (60%−87%) of **6h−k** were not as high as before (Scheme 2), those substrate combinations proved applicable demonstrating the wide scope of the coupling process. Summarizing this part of the study, it is worth noticing that, compared to the chemistry of ynamides,[10,11] *N*-alkynylated sulfoximines undergo hydroacyloxylation reactions under much milder reaction conditions revealing an increased reactivity.

Next, hydroaminations of *N*-alkynylated sulfoximines were investigated (Scheme 3). To elaborate the optimal conditions, sulfonamide **7a** was reacted with **3a** in THF at room temperature. Delightfully, product **8a** was obtained in 99% yield after 1 h. Compared to the hydroacyloxylation process, a significant decrease of the *E*/*Z* ratio was observed (68:32). To improve the process, DCM was applied as a solvent, which

Scheme 3. Scope of Hydroaminations of *N*-Alkynylated Sulfoximines[a]



[a]Reaction conditions: Stirring of **3** (0.2 mmol) and **7** (0.3 mmol) in DCM (1 mL) under argon at room temperature for 1 h.

resulted in both an excellent yield of **8a** (99%) and a very high stereoselectivity (99:1). Next, various combinations of sulfonamides and *N*-alkynylated sulfoximines with alternations in both the alkyne substituent and the sulfoximine functionality were investigated. When the *N*-phenyl-tosyl amide was applied as the substrate in the reaction with **3a**, the yield of product **8b** was only 60% and the stereoselectivity dropped to 62:38. A better result was obtained with *N*-phenyl-triflyl amide, which gave **8c** in 89% yield and an *E*/*Z* ratio of 70:30. Apparently, the presence of the triflyl group had a positive effect on both the yield and the stereoselectivity, and thus, different *N*-substituted triflyl amides with benzyl, cyclohexyl, *n*-butyl, 4-methyl-benzyl, and thiophene-2-yl-methyl functionalities were utilized in the process next. All resulting products (**8d−h**, Scheme 3) were obtained in high to excellent yields (80%−99%) having *E*/*Z* ratios ranging from 94:6 to 99:1. Bis-triflic sulfonamide was unreactive with **3a** (product not shown in Scheme 3). Distinct substituent effects were observed when the sulfoximine component was changed from **3a** to compounds with substituted arene groups on the alkynyl fragment. Thus, **8i** having a *para*-bromo substituent on the arene was obtained in 99% yield and with an *E*/*Z* ratio of 77:23. In contrast, using the analogous substrate with a *para*-methoxy group led to the corresponding product (**8j**) in only 60% yield and with a stereoselectivity of 98:2. Varying the substituents at the sulfoximine core affected the yield (71% for *S*-aryl-*S*-methyl derivative **8k** and 60% for *S*,*S*-diphenyl analog **8l**), but the *E*/*Z* ratios remained high (99:1 and 97:3, respectively).

To demonstrate the synthetic applicability of the products, a catalytic oxidation to their corresponding diketo derivatives **9** was developed. Embedded in a fine-tuned molecular environ-

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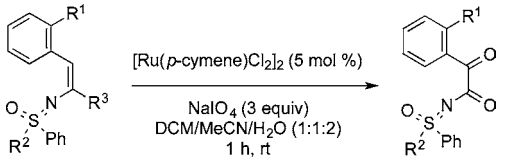
ment such products could reveal bioactivities[15] or serve as building blocks for heterocyclic compounds.[16] Based on previous results,[6,17] a ruthenium-catalyzed oxidation with $NaIO_4$ as an oxidant was chosen. Compounds **6a**, **8a**, and **8g** that had all been obtained from *N*-alkynylated sulfoximine **3a** gave diketone **9a** after 1 h in yields ranging from 77% to 97% (Table 2, entries 1−3). Starting from **8j** and **8l**, which varied by

Table 2. Oxidative Transformation of the Products to Diketo Derivatives[a]



entry	substrate	product	R^1	R^2	R^3	yield (%)
1	**6a**	**9a**	H	Me	OCOPh	77
2	**8a**	**9a**	H	Me	NTs_2	95
3	**8g**	**9a**	H	Me	NTsR[b]	97
4	**8j**	**9b**	OMe	Me	NTfR[b]	89
5	**8l**	**9c**	H	Ph	NTfR[b]	98

[a]Reaction conditions: Substrate **6** or **8** (0.5 mmol), [Ru(*p*-cymene)-$Cl_2]_2$ (0.025 mmol, 5 mol %), and $NaIO_4$ (1.5 mmol, 3 equiv) stirred in a mixture of DCM/MeCN/H_2O (1:1:2 mL) in air at room temperature for 1 h. [b]R = 4-Me-Ph-CH_2.

the substituent pattern of both the arene at the alkyne unit and the sulfoximine core, **9b** and **9c** were afforded in 89% and 98% yield, respectively (Table 2, entries 4 and 5). Finally, we established a one-pot procedure leading directly to the diketo derivatives **9**. Yne-sulfoximine **3a** was first reacted with benzoic acid (**5a**) or amide **7g** in DCM, and then the resulting product-containing mixture was subjected to the aforementioned oxidation protocol providing diketone **9a** in 87% and 92% yield, respectively.

In summary, we have shown that *N*-alkynylated sulfoximines undergo highly stereoselective hydroacyloxylation and hydroamination reactions under mild metal-free reaction conditions in short reaction times. The method provides products, which may directly find applications in various fields of chemistry. The same is true for the 1,2-diketones being accessible by oxidation of the initial hydroacyloxylation and hydroamination products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02477.

Experimental procedures and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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NOTE ADDED AFTER ASAP PUBLICATION

The SI file was replaced on September 25, 2015 in which ^{13}C coupling constants for compounds **7f**, **7h**, **8c-l** and ^{13}C chemical shifts for compounds **8i** and **8j** have been updated.

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