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Exploring the Reactivity of *N*-Alkynylated Sulfoximines: Acid-Catalyzed Cyclizations

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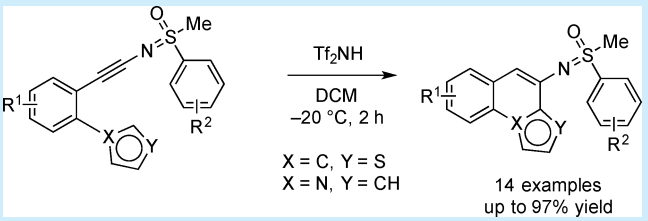
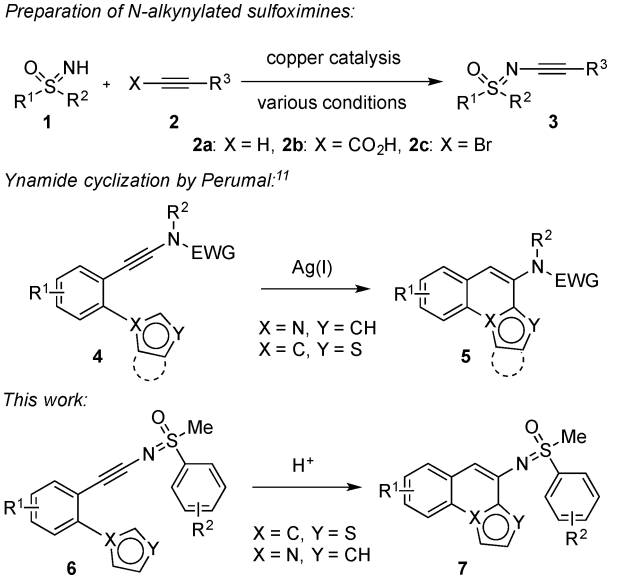
Supporting Information

ABSTRACT: *N*-Alkynylated sulfoximines undergo acid-promoted cyclization processes under mild reaction conditions. The transformations proceed in short reaction times affording sulfoximidoyl-functionalized naphtho[2,1-*b*]thiophenes or pyrrolo[1,2-*a*]quinolines in up to excellent yields.



Due to their versatile properties, sulfoximines are an interesting class of compounds with important applications in organic synthesis, crop protection, and medicinal chemistry.[1] In our continuous efforts to find new approaches for including sulfoximidoyl moieties into organic molecules,[2] we lately focused on the synthesis and application of *N*-alkynylated sulfoximines **3** (Scheme 1, top).[3] Synthetic strategies for accessing such compounds involved copper-catalyzed cross-couplings of *NH*-sulfoximes **1** with terminal alkynes **2a**,[4] aryl propiolic acids **2b**,[5] or bromoacetylenes **2c**.[6,7] Since *N*-alkynylated sulfoximines can be considered as chiral versions of ynamides,[8] they represent interesting substrates for various transformations leading to (chiral) sulfoximidoyl-tethered products with possible application in medicinal chemistry or crop protection. However, until now, only two reactivity studies for *N*-alkynylated sulfoximines have been described in literature including [2 + 2]-cycloadditions[9] and regioselective hydroacyloxylation and hydroamination processes.[10] In the context of ynamide chemistry, two recent publications caught our attention. First, Perumal and coworkers utilized ynamides in a silver(I)-catalyzed cyclization approach yielding indolo- or pyrrolo[1,2-*a*]quinolines and naphtho[2,1-*b*]thiophenes **5** (Scheme 1, middle),[11] and second, in 2015, Yamaoka and Takasu developed Brønsted acid-promoted cyclization reactions of ynamides providing 3*H*-pyrrolo[2,3-*c*]quinolines **7**.[12] As those fused heterocycles are found in natural products and possess a high potential as bioactive molecules,[13] we started wondering if analogous reactions with *N*-alkynylated sulfoximines **6** would allow a direct access to sulfoximidoyl-tethered heterocyclic products **7** (Scheme 1, bottom). Herein, we report the realization of this concept applying a cyclization approach to the *N*-alkynylated substrates.

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



To explore a potential cyclization process, *N*-alkynylated sulfoximine **8a** was treated with 1.2 equiv of TFA in DCM. To our delight, the desired product **9a** was formed in 42% yield after 30 min at room temperature (Table 1, entry 1). With the goal to increase the yield of **9a**, the effects of different acids were examined. The application of triflic imide (Tf_2NH) resulted in a 49% yield (Table 1, entry 2), while using TfOH only led to a trace amount of **9a** (Table 1, entry 3). Performing the reaction with triflic imide at 0 °C increased the yield of **9a** only slightly (56%; Table 1, entry 4). In the next step, the amount of triflic imide was varied (Table 1, entries 5−7). In this series, the best result was obtained with 10 mol % of the acid resulting in 72% of **9a** (Table 1, entry 6). Next, the reaction temperature was decreased to −20 °C, while the reaction time was extended to 1 h resulting in 92% yield of **9a** (Table 1, entry 9). Performing the reaction at −35 °C did not

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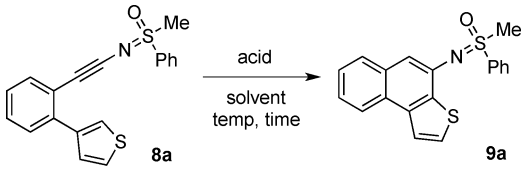
Table 1. Optimization of the Reaction Conditions[a]



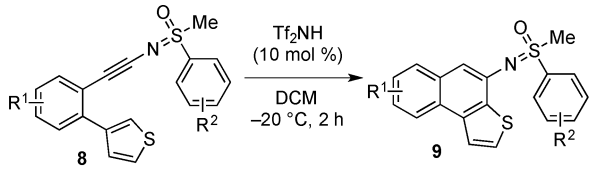
entry	temp (°C)	time (h)	acid (mol %)	solvent	yield (%)
1	rt	0.5	TFA (120)	DCM	42
2	rt	0.5	Tf_2NH (120)	DCM	49
3	rt	0.5	TfOH (120)	DCM	traces
4	0	0.5	Tf_2NH (120)	DCM	56
5	0	0.5	Tf_2NH (20)	DCM	68
6	0	0.5	Tf_2NH (10)	DCM	72
7	0	0.5	Tf_2NH (5)	DCM	61
8	−20	0.5	Tf_2NH (10)	DCM	78
9	−20	1	Tf_2NH (10)	DCM	92
10	−35	1	Tf_2NH (10)	DCM	70
11	−20	2	Tf_2NH (10)	DCM	94
12	−20	2	Tf_2NH (10)	THF	45
13	−20	2	Tf_2NH (10)	toluene	37

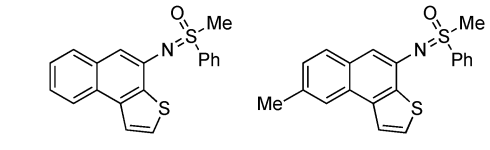
[a]Reaction conditions: **8a** (0.2 mmol) and acid stirred in the solvent (4 mL) under argon for the given time at the indicated temperature.

increase the yield (70%, Table 1, entry 10). However, extending the reaction time to 2 h at −20 °C led to 94% yield of **9a** (Table 1, entry 11). To investigate potential effects of the solvent, reactions were trialed in toluene and THF at −20 °C (Table 1, entries 12−13). However, using DCM as solvent provided the highest yield of the product (94%, Table 1, entry 11).

With the optimized conditions (10 mol % of Tf_2NH, DCM, −20 °C, 2 h) in hand, various *N*-alkynylated sulfoximines with thienyl groups **8** were explored in this reaction process (Scheme 2). Steric properties of the *N*-alkynylated sulfoximines did not significantly affect the yield of the resulting sulfoximine-naphtho[2,1-*b*]thiophenes **9** and using substrates with methyl or methoxy substituents attached to the arene group of the alkynyl fragment gave the corresponding products in good to high yields (**9b**, 71%; **9c**, 89%). Moreover, variation of the substitution pattern at the sulfoximine core did not influence the yield of the process. Electron-withdrawing substituents in *para*-position were well tolerated generating the corresponding products in high yields (**9d**, 87%; **9e**, 90%). An electron-withdrawing substituent in *meta*-position slightly decreased the yield of **9f** to 83%, while an electron-donating *meta*-methoxy substituent was well tolerated resulting in 91% yield of product **9g**.

Scheme 2. Scope of Acid-Catalyzed Cyclization towards Sulfoximidoyl-Containing Naphtho[2,1-*b*]thiophenes 9

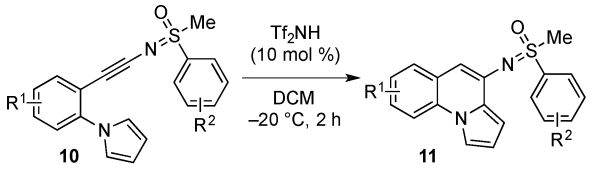


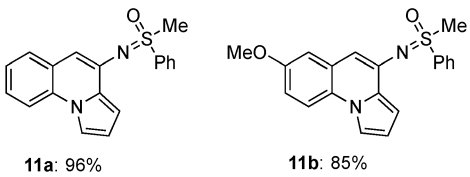


9a: 94%
9b: 71%
9c: 89%
9d: R^2 = *p*-Cl, 87%
9e: R^2 = *p*-Br, 90%
9f: R^2 = *m*-Br, 83%
9g: R^2 = *m*-OMe, 91%

Next, the cyclization process of *N*-alkynylated sulfoximines containing pyrrole fragments **10** was investigated (Scheme 3).

Scheme 3. Scope of Acid-Catalyzed Cyclization towards Sulfoximidoyl-Containing Pyrrolo[2,1-*a*]quinolines 11





11a: 96%
11b: 85%
11c: 97%
11d: R^2 = *p*-Cl, 89%
11e: R^2 = *p*-Br, 97%
11f: R^2 = *m*-Br, 94%
11g: R^2 = *m*-OMe, 88%

Delightfully, product **11a** was obtained in 96% yield when subjecting **10a** to the optimized reaction conditions. Then, various combinations of *N*-alkynylated sulfoximines with alternations in both the alkynyl substituent and the sulfoximine core were explored. When substrate **10b** having an electron-donating methoxy group at the alkyne functionality was applied in the cyclization process, product **11b** was obtained in 85% yield. A better result was achieved with an electron-withdrawing chloro substituent yielding **11c** in 97%. Varying the sulfoximine core did not affect the yield of the corresponding products. Thus, applying electron-withdrawing groups in *para* position resulted in high to excellent yields of the corresponding products (**11d**, 89%; **11e**, 97%). Also, substitution by *meta*-bromo or *meta*-methoxy led to the desired products in 94% yield of **11f** and 88% of **11g**, respectively.

In summary, we have shown that *N*-alkynylated sulfoximines can be applied in Brønsted-acid catalyzed cyclization reactions generating the corresponding products in short reaction times under mild reaction conditions. In this process, a variety of sulfoximidoyl-containing naphtho[2,1-*b*]thiophenes and

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pyrrolo[2,1-*a*]quinolines were obtained in good to excellent yields representing potentially useful substrates for different fields of chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01646.

Experimental procedures and full characterization for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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