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Exploring the Reactivity of *N*-Alkynylated Sulfoximines: [2 + 2]-Cycloadditions

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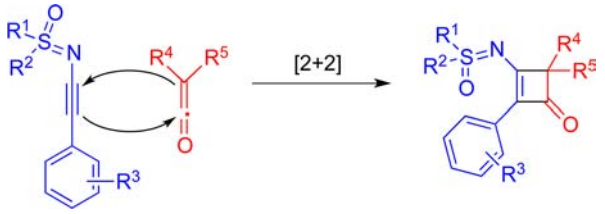
ABSTRACT



To assess the potential of *N*-alkynylated sulfoximines as new (chiral) reagents for organic synthesis, their reactivity profile in numerous synthetic processes is under investigation. When reacted with ketenes, the alkynylated-sulfoximines undergo a [2 + 2]-cycloaddition process to afford sulfoximine-functionalized cyclobutenones in excellent yields.

Sulfoximines have been widely applied in organic synthesis, medicinal chemistry, and agrochemistry.[1] The development of new methods that facilitate the incorporation of the sulfoximidoyl moiety into organic molecules using mild conditions is a continuing goal of our research group.[2] To this end, we recently reported the synthesis of a new class of compounds, *N*-alkynylated sulfoximines **3**, through an oxidative copper-catalyzed coupling of terminal alkynes **2** with *N*H-sulfoximines **1** (Scheme 1).[3,4]

In recent years, ynamides have been successfully employed in numerous transformations including cycloadditions, nucleophilic addition reactions, cycloisomerizations, and metal-catalyzed cross-coupling reactions.[5] To this end, it was envisaged that the sulfoximine ynamide analogs **3** also possessed significant potential as reagents that would allow the incorporation of the (chiral) sulfoximidoyl moiety into a broad variety of synthetic molecules.

Furthermore, cyclobutanones have been applied as useful synthetic intermediates in a range of organic and natural product syntheses often in processes that include ring-opening and ring-expansion reactions.[6] One of the

(1) For selected recent examples regarding sulfoximines, see: (a) Zhu, Y.; Loso, M. R.; Watson, G. B.; Sparks, T. C.; Rogers, R. B.; Huang, J. X.; Gerwick, B. C.; Babcock, J. M.; Kelley, D.; Hegde, V. B.; Nugent, B. M.; Renga, J. M.; Denholm, I.; Gorman, K.; DeBoer, G. J.; Hasler, J.; Meade, T.; Thomas, J. D. *J. Agric. Food Chem.* **2011**, *59*, 2950. (b) Park, S. J.; Buschmann, H.; Bolm, C. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4888. (c) Gais, H. J. *Heteroat. Chem.* **2007**, *18*, 472. (d) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482. (e) Lücking, U. *Angew. Chem.* **2013**, *125*, 9570. *Angew. Chem., Int. Ed.* **2013**, *52*, 9399.

(2) For recent work, see: (a) Wang, J.; Frings, M.; Bolm, C. *Angew. Chem.* **2013**, *125*, 8823. *Angew. Chem., Int. Ed.* **2013**, *52*, 8661. (b) Wang, L.; Priebbenow, D. L.; Zou, L. H.; Bolm, C. *Adv. Synth. Catal.* **2013**, *355*, 1490.

(3) Wang, L.; Huang, H.; Priebbenow, D. L.; Pan, F.-F.; Bolm, C. *Angew. Chem.* **2013**, *125*, 3562. *Angew. Chem., Int. Ed.* **2013**, *52*, 3478.

(4) In our recent publication (ref 3) we presented the only example of an alkynylated sulfoximine reported in the literature. However, as Professor Banert (TU Chemnitz) alerted us, the structure proposed in the original publication (Tanaka, R.; Yamabe, K. *J. Chem. Soc. Chem. Commun.* **1983**, 329.) was incorrect and our report was in fact the first describing access to *N*-alkynylated sulfoximines. For clarification, see: Banert, K.; Hagedorn, M.; Wutke, J.; Ecorchard, P.; Schaarschmidt, D.; Lang, H. *Chem. Commun.* **2010**, *46*, 4058.

(5) (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem.* **2010**, *122*, 2902. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840.

(6) (a) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485. (b) Wong, H. N. C.; Lau, K.-L.; Tam, K.-F. *Top. Curr. Chem.* **1986**, *133*, 84. (c) Bellus, D.; Ernst, B. *Angew. Chem.* **1988**, *100*, 820. *Angew. Chem., Int. Ed.* **1988**, *100*, 820.

(7) (a) Hyatt, J. A.; Raynolds, P. W. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1994; Vol. 45, pp 159–646. (b) Danheiser, R. L., Ed. *Science of Synthesis: Houben Weyl Methods of Molecular Transformations*; Thieme: Stuttgart, 2006; Vol. 23.

(8) For selected examples, see: (a) Hassner, A.; Dillon, J. L., Jr. *J. Org. Chem.* **1983**, *48*, 3382. (b) Danheiser, R. L.; Sard, H. *Tetrahedron Lett.* **1983**, *24*, 23. (c) Hasek, R. H.; Gott, G. P.; Martin, J. C. *J. Org. Chem.* **1964**, *29*, 1239. (d) Wasserman, H. H.; Piper, J. U.; Dehmlow, E. V. *J. Org. Chem.* **1973**, *38*, 1451. (e) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693. (f) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575.

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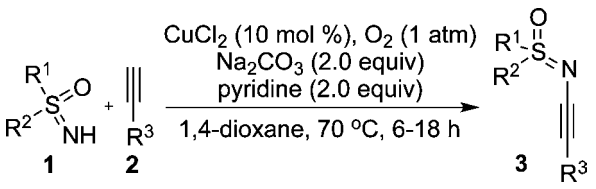
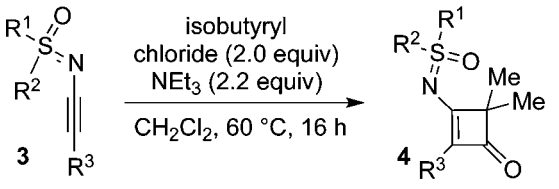
Scheme 1. Preparation of *N*-Alkynylated Sulfoximines



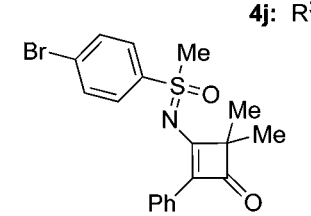
most common methods employed to access cyclobutanone derivatives is the [2 + 2]-cycloaddition of ketenes with alkynes.[7] To date, a wide range of alkynes containing aryl, alkyl, amino-, silyoxy-, or alkoxy-substitutents have been successfully employed in the cycloaddition process with ketenes.[8]

In 2006, Danheiser and co-workers reported the [2 + 2]-cycloaddition reaction of ynamides with ketenes that were generated from the reaction of suitable acyl chlorides with an organic base.[9] To explore the potential reactivity of *N*-alkynlated sulfoxmines in an analogous process, sulfoximine **3a** (R^1 = Me, R^2 = Ph, R^3 = Ph) was reacted with isobutyryl chloride in the presence of triethylamine (Scheme 2). A simple workup of the reaction mixture after refluxing for 16 h revealed that sulfoximine-functionalized cyclobutenone **4a** had formed in an exceptional yield of 98%.

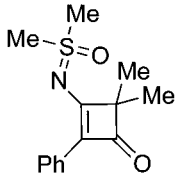
Scheme 2. Investigation into the [2 + 2]-Cycloaddition of *N*-Alkynylated Sulfoximines



4a: R^3 = Ph (98%)
4b: R^3 = 4-MePh (80%)
4c: R^3 = 2-MePh (70%)
4d: R^3 = 4-CNPh (55%)
4e: R^3 = 2-BrPh (75%)
4f: R^3 = 4-CF_3Ph (84%)
4g: R^3 = $SiEt_3$ (56%)
4h: R^3 = 3-ClPh (67%)
4i: R^3 = 2,5-MePh (90%)
4j: R^3 = 2,4,6-MePh (55%)



4k (74%)

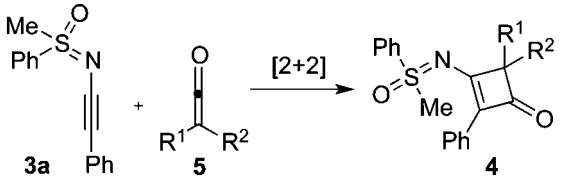


4l (61%)

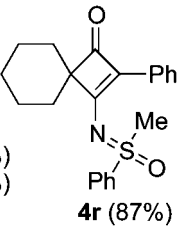
(9) Kohnen, A. L.; Mak, X. Y.; Lam, T. Y.; Dunetz, J. R.; Danheiser, R. L. *Tetrahedron* **2006**, *62*, 3815.

To further explore this reaction process, a series of alkynylated sulfoximines containing variations in both the alkyne functionality and the sulfoximine substituents were then reacted with the dimethyl ketene generated *in situ* from isobutyryl chloride (Scheme 2). The steric properties of the alkynylated sulfoximines did not appear to significantly affect the yield, with *ortho*-functionalized aryl alkynes **4c** and **4e** performing well in the cycloaddition. In addition, both electron-withdrawing and electron-donating substituents on the aryl alkyne were tolerated. Of note, the triethylsilyl-functionalized cyclobutenone **4g** was also formed, albeit in only moderate yield.

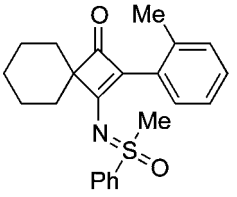
Scheme 3. Investigation into the Range of Ketenes Applicable in the [2 + 2]-Cycloaddition



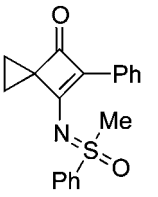
4m: R^1 = H, R^2 = $(CH_2)_5CH_3$ (80%)
4n: R^1 = H, R^2 = $(CH_2)_2CH_3$ (67%)
4o: R^1 = H, R^2 = Ph (81%)
4p: R^1 = H, R^2 = CH_2Ph (77%)
4q: R^1 = Et, R^2 = Ph (75%)



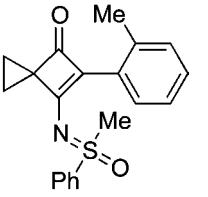
4r (87%)



4s (87%)



4t (93%)



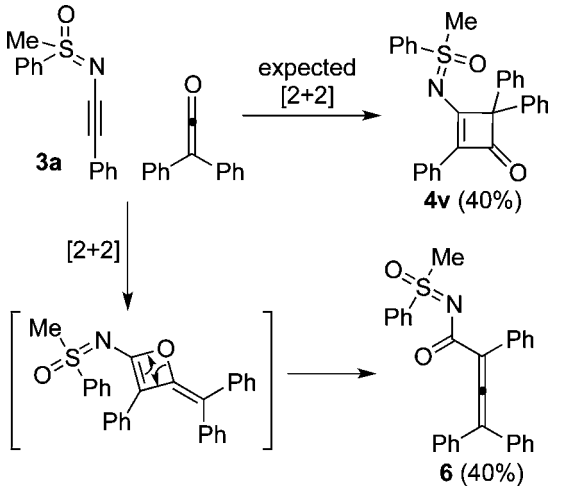
4u (90%)

Next, a range of alkyl- and aryl-substituted ketenes **5** were subjected to the cycloaddition conditions (Scheme 3). It was found that all of them were applicable in the [2 + 2]-cycloaddition process with *N*-alkynylated sulfoximine **3a** providing the cyclobutenone derivatives in yields ranging from 67% to 93%. When employing cyclohexane or cyclopropane carbonyl chlorides, spiro-cyclobutenones **4r**–**u** containing two contiguous carbocyclic rings were obtained in high yields.

Unfortunately, in all cases using nonsymmetrical ketenes, no significant diastereoinduction from the sulfoximine moiety was observed, and the products were isolated as inseparable mixtures of diastereomers (typically in a ratio of 1:1 to 2:3). As no diastereoselectivity was observed, application of the enantiopure sulfoximine-containing cyclobutenones was not pursued.

(10) See Supporting Information for details.

Scheme 4. Results of the [2 + 2]-Cycloaddition with the Sterically Hindered Diphenyl Ketene



An interesting result was observed when alkynylated sulfoximine **3a** was reacted with the diphenylketene generated from diphenylacetyl chloride (Scheme 4). A separable 1:1 mixture of the expected cycloaddition product **4v** (40% yield) and a byproduct, subsequently identified as the tetrasubstituted allene **6** (40% yield), was obtained. The formation of the allene derivative **6** was supposedly due to steric interactions which forced the cycloaddition to occur from the opposite end of the ketene resulting in a highly strained four-membered cyclic ether which subsequently rearranged to afford sulfoximine **6** (Scheme 4), the structure of which was subsequently confirmed by X-ray analysis.[10] The formation of amido-allenes during the [2 + 2]-cycloaddition process has been previously described by several other groups.[11] Steric factors appear to have a larger influence on this reaction process than electronic ones.[12]

In summary, it was determined that *N*-alkynylated sulfoximines can be applied in [2 + 2]-cycloaddition reactions with ketenes affording a series of valuable sulfoximidoyl-functionalized cyclobutenones in moderate to exceptional yields. These results indicate that, with the sulfoximidoyl group attached, the alkyne moiety is sufficiently electron rich to behave as a nucleophile in the presence of a suitable electrophile. Additional investigations into the reactivity patterns of the *N*-alkynylated sulfoximines in other synthetic transformations are currently underway and will be reported in due course.

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Supporting Information Available. Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

(11) (a) Kuehne, M. E.; Sheeran, P. J. *J. Org. Chem.* **1968**, *33*, 4406. (b) Ficini, J.; Pouliquen, J. *Tetrahedron Lett.* **1972**, 1135. (c) Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1987**, *52*, 3289. (d) Schulte, N.; Möller, M. H.; Rodewald, U.; Würthwein, E.-U. *Chem. Ber.* **1994**, *127*, 1287.

(12) During this investigation, trace amounts of such allene byproducts were identified in some of the cycloaddition reactions performed.

The authors declare no competing financial interest.