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New Synthesis of Benzothiazines and Benzoisothiazoles Containing a Sulfoximine Functional Group

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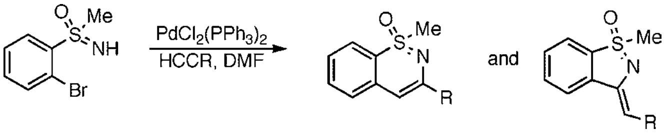
ABSTRACT

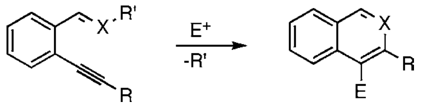


The reaction of *S*-2-bromophenyl-*S*-methylsulfoximine with terminal alkynes in the presence of a palladium catalyst resulted in the formation of both 1,2-benzothiazines and 1,2-benzoisothiazoles. A preference for the former was seen with alkylalkynes, while the latter were preferentially formed with alkynylarenes.

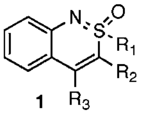
Very recently, there have been a number of new reactions reported involving the cyclization of alkynylarenes bearing a nucleophilic ortho substituent.[1] These reactions have included variations that involve the synthesis of a variety of heterocycles.[2] On certain occasions, the initial products were intermediates that could undergo further reaction (e.g., cycloaddition) to produce the isolated products.[3]

A general description of these reactions is shown in Scheme 1. In principle, the approach is a very general one, and virtually any nucleophilic group might be expected to participate in the key ring-forming step.

Scheme 1



We have had a longstanding interest in the synthesis of 2,1-benzothiazines represented by structures **1** and **2**. These can be prepared by the annulation reaction of either alkynes or alkenes with sulfonimidoyl chlorides[4] or by a domino sequence involving a Buchwald−Hartwig reaction[5] followed by ring formation.[6] These benzothiazines can also be described as cyclic sulfoximines.[7]



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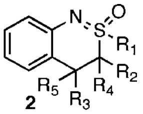

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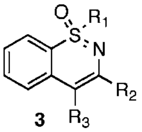

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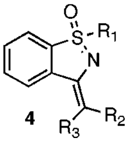

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In keeping with our interest in benzothiazines and sulfoximine chemistry in general, we were intrigued by the

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[1] For reviews, see: (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.

[2] For some recent examples, see: (a) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035. (b) Ohtaka, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 7339. (c) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139.

[3] (a) Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814. (b) Kusama, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 11592. (c) Zhu, J.; Germain, A. R.; Porco, J. R., Jr. *Angew.* Chem., Int. Ed. **2004**, *43*, 1239. (d) Sato, K.; Salprima, Y. S.; Asao, N.; Yamamoto, Y. *Synthesis* **2004**, 1409. (e) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458.

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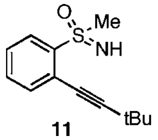
possibility of forming 1,2-benzothiazines **3** (or benzoisothiazoles **4**) using the chemistry illustrated in Scheme 1.[8] 1,2-Benzothiazines are of pharmaceutical interest, and a new general procedure for their synthesis opens the door for the creation of libraries of diversely functionalized compounds that may prove to be of value as leads in drug development.[9,10] From a more fundamental perspective, the nucleophilicity of the sulfoximine nitrogen atom is of general interest and further exploration of its reactivity is needed.[11] This Letter describes our successful initial exploration of the synthesis of 1,2-benzothiazines and 1,2-benzoisothiazoles using chemistry represented in Scheme 1.



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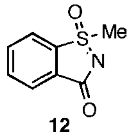

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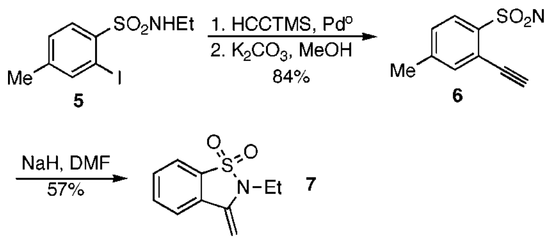
Our approach was inspired by the work of Snieckus and Lane, who showed that *ortho*-iodosulfonamide **5** could undergo a Sonogashira coupling to form **6**, which could be converted to benzoisothiazole **7** upon exposure to sodium hydride (Scheme 2).[12] We began our studies with the racemic bromosulfoximine **8**, easily prepared from 2-bromothiophenol using literature procedures (see Supporting Information). We planned to conduct a Sonogashira coupling with **8** and then attempt an electrophile-mediated cyclization to afford 1,2-benzothiazines **3**, hoping that the sulfoximine nitrogen was sufficiently nucleophilic to intercept any electrophilic species produced by activation of the alkyne.[13]

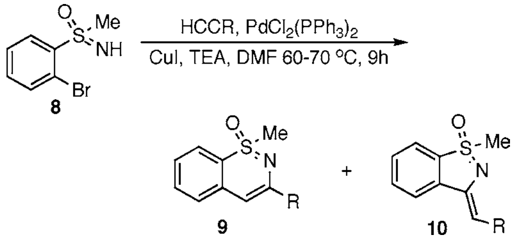
Scheme 2



In the course of our studies of the Sonogashira coupling, we found that treatment of **8** with terminal alkynes in the presence of Pd(PPh$_3$)$_2$Cl$_2$, CuI, and triethylamine in warm DMF afforded 1,2-benzothiazines directly and in good yield, along with 1,2-benzoisothiazoles resulting from a 5-exo-dig cyclization.

The results of our study are shown in Table 1. Alkyl-substituted terminal alkynes afforded benzothiazines **9** in 53–73% yield along with 13–27% yields of the corresponding benzoisothiazoles **10** (Table 1, entries 1–8). Steric effects

Table 1. Synthesis of 1,2-Benzothiazines and 1,2-Benzoisothiazoles



entry	R[a]	products	% (**9**)[b]	% (**10**)[b]
1	propyl	**9a/10a**	70	20
2	butyl	**9b/10b**	73	27
3	pentyl	**9c/10c**	60	19
4	hexyl	**9d/10d**	58	16
5	$-(CH_2)_3OBn$	**9e/10e**	54	18
6	$-(CH_2)_3Ph$	**9f/10f**	53	13
7	$-(CH_2)_3CCH$	**9g/10g**	56	19
8	cyclohexyl	**9h/10h**	50	18
9	*tert*-butyl	**9i/10i**	0[c]	0[c]
10	1-cyclohexenyl	**9j/10j**	52	d
11	cyclopropyl	**9k/10k**	56	19
12	phenyl	**9l/10l**	0	81
13	4-methylphenyl	**9m/10m**	21	73
14	4-*tert*-butylphenyl	**9n/10n**	16	69

[a] Between 2 and 10 equiv of alkyne was used. Further optimization to reduce the amount of alkyne must be performed. [b] Yields are for isolated products. [c] Only coupling product was formed. See text. [d] Product could not be isolated in pure form.

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(7) (a) Bosshammer, S.; Gais, H.-J. *Synthesis* **1998**, *6*, 919. (b) Hwang, K. J.; Logusch, E. W.; Brannigan, L. H.; Thompson, M. R. *J. Org. Chem.* **1987**, *52*, 3435. (c) Schaffner-Sabba, K.; Tomaselli, H.; Henrici, B.; Renfroe, H. B. *J. Org. Chem.* **1977**, *42*, 952.

(8) A limited number of cyclic sulfoximines related to **3** are known. See: (a) Williams, T. R.; Cram, D. J. *J. Org. Chem.* **1973**, *38*, 20. (b) Stoss, P.; Satzinger, G. *Chem. Ber.* **1972**, *105*, 2575. (c) Williams, T. R.; Cram, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 7333.

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(12) (a) Lane, C.; Snieckus, V. *Synlett* **2000**, 1294. But see also: (b) Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777. (c) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764.

(13) At the suggestion of a referee, we conducted a reaction with **8** and an internal alkyne. The reaction of **8** with 4-octyne under our reported reaction conditions afforded recovered starting material (50%) as well as a small amount of an unidentified product that did not incorporate 4-octyne and was not a benzothiazine or isobenzothiazole.

can preclude the formation of any heterocyclic product. For example, the reaction of **8** with *tert*-butylacetylene resulted only in the formation of the Sonogashira coupling product **11** with no evidence for the formation of either possible heterocycle (Table 1, entry 9). As might be expected, alkynylarenes preferentially cyclized to benzoisothiazoles, the aryl group activating the alkyne toward 5-exo-dig ring closure (Table 1, entries 12−14). Other potentially activating groups such as the cyclopropyl and cyclohexenyl did not change the course of the reaction vis-à-vis that observed for simple alkynes.

The structures of **9** and **10** were easily established on the basis of NMR analysis. The stereochemistry of benzoisothiazoles **10** was assigned on the basis of a NOESY experiment performed on **10b**.

The compounds produced in this reaction are *N*-vinyl sulfoximines, cyclic version of *N*-vinyl sulfoximines, a relatively unstudied class of compounds.[14] Benzothiazines **9** appear to be stable compounds. Indeed, resonance delocalization should stabilize these compounds.

On the other hand, benzoisothiazoles **10** do not appear to be very stable. Attempted isolation of **10e** after several days on the benchtop resulted in the isolation of **12** via recrystallization.[15] Its structure was confirmed by spectroscopic analysis and single-crystal X-ray analysis. Furthermore, exposure of **10n** to an oxygen atmosphere for 12 h resulted in significant decomposition and the formation of **12** and *tert*-butylbenzaldehyde, as evidenced by proton NMR analysis of the crude reaction mixture.[16] The mechanism of this process is presently not clear, and the temptation to consider a dioxetane intermediate is offset by the expectation that the generation of such an intermediate would require the presence of singlet oxygen.[17]

In summary, we have established a new approach to 1,2-benzothiazines possessing a sulfoximine functional group. In certain cases, 1,2-benzoisothiazoles can be selectively produced. Learning how to control the regiochemistry of the cyclization, expanding the scope of the reaction, and developing the chemistry of the “enamine” double bond of both heterocycles will be pursued. Developments will be reported in due course.

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Supporting Information Available: X-ray structure data for **12**, detailed experimental procedures, and copies of ^{1}H and ^{13}C NMR and other characterization data for all new compounds (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Stoss, P.; Satzinger, G. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 76.

[16] After 12 h of stirring in $CDCl_3$ under an oxygen atmosphere, proton NMR analysis suggested the formation of a 25% yield of **12**. After 36 h, *tert*-butylbenzaldehyde was isolated in 20% yield along with 61% of recovered **10n**. Compound **12** did not elute from the silica column, even after flushing with polar solvents.

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