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FUNCTIONALIZATION OF BENZOTHIAZINES VIA A SULFOXIMINE STABILIZED VINYL CARBANION

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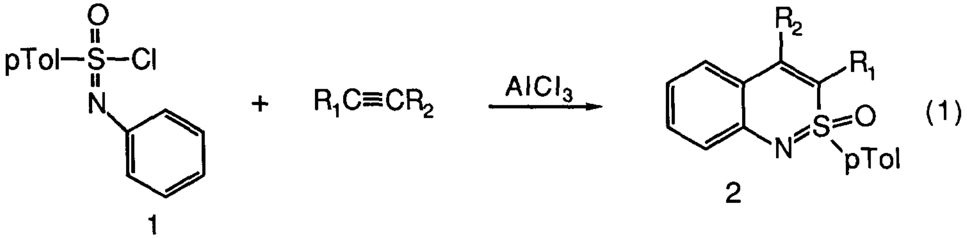
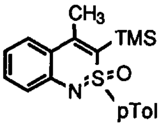
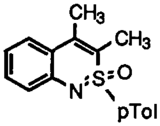
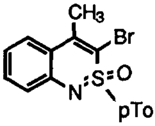
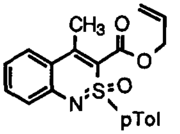
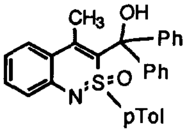
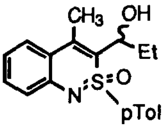
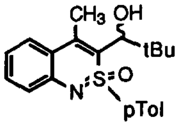
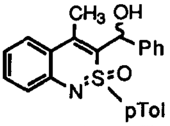
Summary: Benzothiazine **2b** is readily deprotonated by n-BuLi to give the first example of a sulfoximine stabilized vinyl carbanion. The latter reacts efficiently with a variety of electrophiles.

Recently, we reported a general regioselective cyclization reaction between N-phenyl-(4-methylphenyl)sulfoximidoyl chloride **1** and alkynes which leads to benzothiazines **2** in good yield (Equation 1).[1] The process leads to Markownikoff type addition products. While the reaction represents a powerful yet simple method for accessing benzothiazines **2** when simple alkynes are used, we anticipated some difficulties in the use of alkynes which contained acid labile functionality. In an effort to expand the scope of the reaction, we have begun a study of the chemistry of these benzothiazines.[2] Of special interest is the advantageous use of the sulfoximine functionality contained in **2**, particularly with respect to asymmetric induction.



As shown in equation 2 benzothiazine **2a** is rapidly desilylated by tetra-n-butylammonium fluoride in THF at -78°C to give an excellent yield of **2b**.[3] The facility of this process led us to the straightforward conclusion that deprotonation of **2b** should occur with equal ease, due to the presence of the sulfoximine functionality.[4] Concerns regarding the regiochemistry of the deprotonation (vinylic vs. allylic) were put to rest upon execution of the metalation sequence. Thus, treatment of a solution of **2b** in THF at -78°C (dry ice/isopropanol; ~.2M) with 1.1 equivalents of n-BuLi led to a pale peach-colored slurry after 15 minutes.[5]

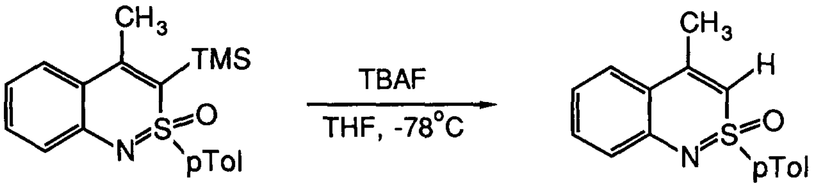
Table 1

Entry	Electrophile	Product	Yield(%)
1	TMSCl	2a 	89
2	CH_3I	2c 	79
3	$C_2Br_2Cl_4$	2d 	98
4	$ClCO_2C_3H_5$	2e 	76
5	Ph_2CO	2f 	65
6	EtCHO	2g 	83[a]
7	tBuCHO	2h 	76[b]
8	PhCHO	2i 	84[c]

a: Isomer ratio= 1.9:1

b: Isomer ratio= 2.4-2.8:1

c: Isomer ratio= 1.2:1



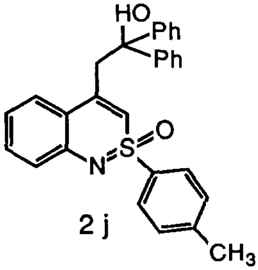
2a 2b (2)

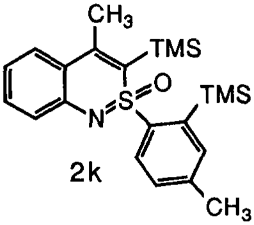
Quenching the anion with various electrophiles led to high yields of products functionalized almost exclusively at carbon 3. The results are presented in Table 1. A byproduct in the synthesis of **2f**, namely **2j**, apparently derived from an allylic anion, was isolated in low yield on a large scale run.

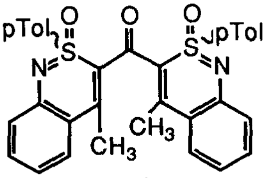
The only limitation in this reaction was observed when ketones were used as the electrophilic trapping agent. With either cyclohexanone or 2-pentanone enolization competed to the exclusion of adduct formation. Efforts are underway to modify reaction conditions to prevent this. Interestingly, addition of 2-pentanone to a solution of the anion from **2b** in THF/HMPA (HMPA added after metalation) was accompanied by a flash of blue color, perhaps suggesting more than simple proton transfer in the enolization process.

The most exciting results were anticipated to arise from adducts **2g**, **2h**, and **2i**. In these cases, diastereoselection is possible by virtue of the chirality of **2b** associated with the sulfoximine function.[4] The diastereomeric ratios of **2g** and **2i** were a meager 1.9:1 and 1.2:1, respectively.[6] Surprisingly, for **2h** the ratio was only 2.4-2.8:1 as determined by NMR analysis. There does not appear to be a dramatic steric effect on diastereoselectivity in this reaction. Somewhat better results have been observed for the diastereoselective addition of sulfoxide stabilized vinyl anions to aldehydes.[7] The relative stereochemical relationships in **2g** through **2i** have not yet been determined. The structures of both the benzothiazine and aldehyde as well as reaction conditions need to be examined thoroughly to optimize diastereoselectivity in this reaction.

It appears that deprotonation at the ortho position of the p-tolyl group of **2b** is also possible. A small amount of **2k**, identified by NMR, was isolated as a byproduct in the synthesis of **2a**. Thus, care must be exercised with respect to the amount of n-BuLi used in the metalation step.


2 j


2k


2 l

Kinetic resolution was observed in the formation of a byproduct during the synthesis of **2e**. Ketone **2l** was isolated as a 8.5:1 mixture of isomers (meso and d,l) in 10% yield. We are currently in the process establishing structures for these isomers.

In summary, the functionalization of benzothiazine **2a** is possible via a lithiation-alkylation sequence. This work, to the best of our knowledge, presents the first example of a sulfoximine stabilized vinyl carbanion. Yields for the alkylation step are high for many electrophiles save enolizable ketones. Studies are underway to improve diastereoselectivity in this series and to investigate more generally the chemistry of vinylic and allylic sulfoximine stabilized carbanions.[8,9]

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References and Notes

1. Harmata, M.; Schlemper, E.O. **Tetrahedron Lett.** 1987, 5997.

2. For a review of benzothiazine chemistry, see: Lombardino, J.G.; Kuhla, D.E. in "Advances in Heterocyclic Chemistry", Vol. 28, Katritsky, A.R.; Boulton, A.J. Eds.; Academic Press: New York, 1981, pp 73-126.

3. Data for **2b**: mp 106-9°C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.77 (d, 2H, J=8.3), 7.66 (dd, 1H, J=1.3, 8.1), 7.45 (ddd, 1H, J=1.5, 7.0, 8.3), 7.34 (d, broadened, 3H, J=8.5), 7.05 (ddd, 1H, J=1.3, 7.0, 8.1), 6.26 (d, 1H, olefinic H, J=0.8), 2.48 (d, 3H, J=0.8), 2.44 (s, 3H); IR(CCl$_4$) 3066w, 3046w, 3034w, 2988w, 2960w, 2925w, 2858w, 1605s, 1588s, 1535s, 1494w, 1471w, 1439s, 1401w, 1377m, 1361m, 1334s, 1301w, 1281m, 1256s, 1226s, 1179s, 1160m, 1135s, 1100s, 1065w, 1037m, 1001m, 992m. Anal. Calcd for C$_{16}$H$_{15}$NOS: C, 71.35; H, 5.62. Found: C, 71.18; H, 5.56.

4. For a review of sulfoximine chemistry by a leader in the field, see: Johnson, C.R.; **Aldrichim. Acta** 1985, **18**, 3.

5. Attempted metalation in the presence of HMPA resulted in a dark red solution and the formation of a number of unidentified products.

6. Diastereomeric ratios were determined by integration of the appropriate NMR signals or by HPLC (Silica, 5u, 250x5mm, eluant: hexane/isopropanol)

7. (a) Solladie, G.; Moine, G. **J. Am. Chem. Soc.** 1984, **106**, 6097. (b) House, S.; Jenkins, P.R.; Fawcett, J.; Russell, D.R. **J. Chem. Soc. Chem. Comm.** 1987, 1844.

8. This work was presented in part at the 194th National Meeting of the American Chemical Society, New Orleans, LA; ORGN 295.

9. All new compounds exhibited acceptable 1H NMR and IR spectra as well as satisfactory combustion or HRMS data. All yields are for chromatographically purified materials.

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