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Benzothiazines in Synthesis. Further Studies of the Intramolecular, Stereoselective Addition of Sulfonimidoyl Carbanions to α,β-Unsaturated Functional Groups

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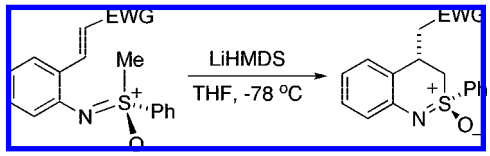
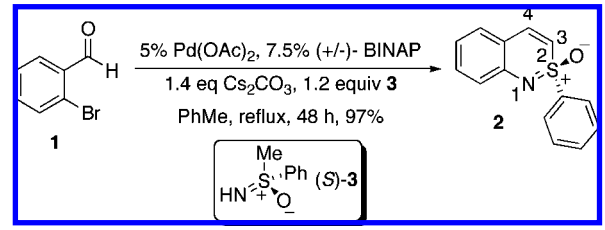


A variety of alkenes substituted by electron-withdrawing groups serve as competent electrophiles for the stereoselective, intramolecular nucleophilic addition of sulfonimidoyl carbanions to form benzothiazines. This reaction generally proceeds with complete stereoselectivity within the limits of our detection. In some cases, benzothiazine formation occurs in a single pot at relatively high temperatures during *N*-arylation of the simple sulfoximine used in this study. Yet, the process occurs with the same direction and extent of stereoselectivity as that seen when the Michael addition is performed at very low temperatures.

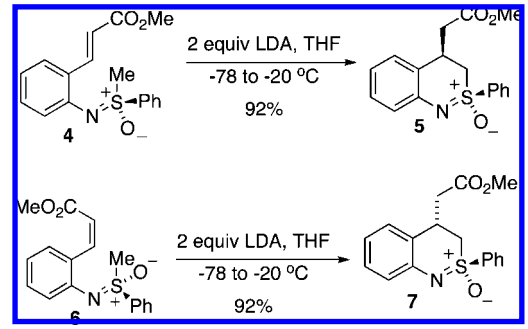
The use of heterocyclic templates in organic synthesis has a long and honored history.[1] Whether for simple bond formation or those including the generation of stereogenic centers, heterocycles have played a key role in organic synthesis, in addition to serving as targets themselves.

As part of our ongoing interest in this area, a number of years ago we reported the synthesis of benzothiazines in a one-pot process via the reaction of *o*-halobenzaldehydes with certain enantiomerically pure N−H sulfoximines using the Buchwald−Hartwig reaction (Scheme 1).[2] We extended this process to the synthesis of benzothiazines beginning with *o*-bromocinnamates in which an initial C−N bond forming event was generally followed by an intramolecular Michael addition that was completely stereoselective and stereospecific (Scheme 2).[3] This led to several applications, including the synthesis of curcumene and the antitubercular agents erogorgiaene and pseudopteroxazole, among others.[4,5]

SCHEME 1. Benzothiazine Synthesis



SCHEME 2. Stereospecific Conjugate Addition



In principle, the process is quite general, and we wondered the extent to which changing the electron-withdrawing group would affect the yield and stereochemical outcome of the intramolecular Michael addition reaction. This report details our first examination of this question.

Our initial goal was not to be exhaustive, but to survey a reasonable number of electron-withdrawing groups and build a database of reactivity and stereoselectivity that could be used as a basis for further studies and applications.

A series of substrates was prepared from *o*-bromobenzaldehyde with standard methods and details are provided in the Supporting Information. These compounds were coupled with (*S*)-**3** under our standard coupling conditions to afford *N*-aryl sulfoximines in high yield.[2,6] The results are summarized in Table 1. In general this reaction proceeded quite smoothly. However, in the case of **27**, when the reaction was conducted under standard conditions, the only product isolated in low yield was benzothiazine **2**. We assumed that this outcome arose via the mechanism shown in Scheme 3.

Nucleophilic attack of hydroxide on **27** afforded the 1,6-conjugate addition product **8**. This compound underwent a vinylogous retro-Claisen condensation to afford **1**, which then coupled with (*S*)-**3** as shown in Scheme 1. It is likely that other decomposition problems also intervened, given the low yield of **28**. Nevertheless, we hoped that by excluding water we could improve the reaction outcome. Indeed, performing the coupling in the presence of molecular sieves afforded **28** in 79% yield,

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(2) Harmata, M.; Pavri, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2419–2422.
(3) Harmata, M.; Hong, X. *J. Am. Chem. Soc.* **2003**, *125*, 5754–5756.
(4) (a) Harmata, M.; Hong, X.; Schreiner, P. R. *J. Org. Chem.* **2008**, *73*, 1290–1296. (b) Harmata, M.; Hong, X. *Tetrahedron Lett.* **2005**, *46*, 3847–3849.
(5) (a) Harmata, M.; Hong, X. *Org. Lett.* **2005**, *7*, 3581. (b) Harmata, M.; Hong, X.; Barnes, C. L. *Org. Lett.* **2004**, *6*, 2201.
(6) Bolm, C.; Hildebrand, J. P. *Tetrahedron Lett.* **1998**, *39*, 5731–5734.

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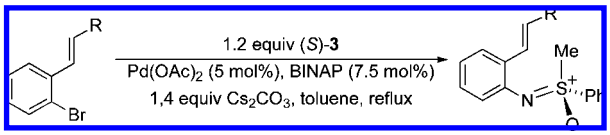
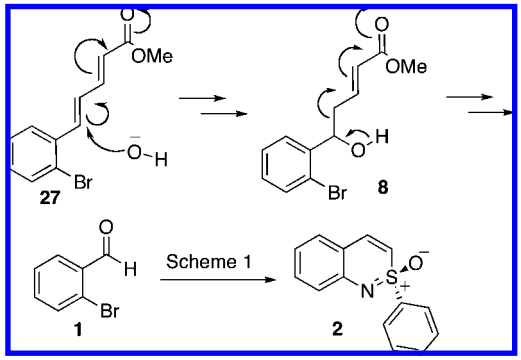
TABLE 1. Synthesis of *N*-Aryl Sulfoximines



entry	educt, R	time (h)	product	yield (%)
1	**9**, SO_2Ph	36	**10**	93
2	**12**, Ph	36	**13**	92
3	**15**, SPh	48	**16**	97
4	**18**, $CONMe_2$	36	**19**	91
5	**21**, $PO(OMe)_2$	36	**22**	95
6	**24**, Ph*p*CN	48	**25**	96
7	**27**, (*E*)-CH=$CHCO_2Me$	44	**28**	79[a]
8	**30**, $CON(CH_2)_5$	48	**31**	89
9	**33**, COPh*o*OMe	36	**34**	66
10	**36**, COPh*p*OMe	18	**37**	81
11	**39**, COPh*p*Cl	48	**40**	84
12	**42**, CO*t*Bu	48	**43**	93
13	**45**, COPh	96	**46**	47[b]
14	**48**, CO(2-furyl)	48	**49**	67
15	**51**, $POPh_2$	36	**52**	57[c]
16	**54**, CN	21	**55**	85[d]

[a] The reaction was performed in the presence of 4 Å molecular sieves. [b] 91% yield based on recovered starting material. [c] A 42% yield of **53** was obtained. [d] A 10% yield of **56** was obtained.

SCHEME 3. Proposed Mechanism for the Formation of 2 from 27



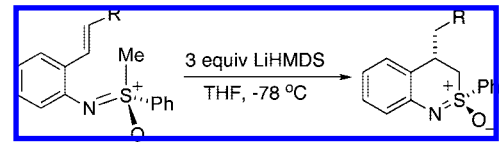
supporting the idea that water and/or hydroxide destroyed **27** under the initial reaction conditions.

It should be pointed out that in two cases, coupling also led to the formation of benzothiazines. Thus, under coupling conditions, substrates **51** and **54** led to the corresponding benzothiazines **53** and **56** in 42% and 10% yields, respectively. We have observed this behavior before,[3] but have not tried to optimize for the result in any systematic way.

With *N*-aryl sulfoximines in hand, we proceeded with our study of the intramolecular Michael addition reaction. We chose to use excess base, as we had previously observed that excess base generally resulted in higher yields in benzothiazine formation in this process. Further, since our main purpose in this study was to examine the yield and stereochemical outcome of the reaction, we chose not to attempt optimization with respect to the nature and amount of base used in the reaction. Thus, all of the *N*-aryl sulfoximines were treated with 3 equiv of LiHMDS in THF at −78 °C.[7]

(7) During the course of our studies, we have found that the nature of the base, including the cation, has no effect on the stereochemical outcome of the reaction, at least with esters as the electron-withdrawing group. Details will be reported elsewhere.

TABLE 2. Synthesis of Benzothiazines



entry	educt, R	product	yield (%)
1	**10**, SO_2Ph	**11**	88
2	**13**, Ph	**14**	NR
3	**16**, SPh	**17**	NR
4	**19**, $CONMe_2$	**20**	85
5	**22**, $PO(OMe)_2$	**23**	83
6	**25**, Ph*p*CN	**26**	NR
7	**28**, (*E*)-CH=$CHCO_2Me$	**29**	42[a]
8	**31**, $CON(CH_2)_5$	**32**	88
9	**34**, COPh*o*OMe	**35**	66
10	**37**, COPh*p*OMe	**38**	63
11	**40**, COPh*p*Cl	**41**	65
12	**43**, CO*t*Bu	**44**	82
13	**46**, COPh	**47**	81
14	**49**, CO(2-furyl)	**50**	53
15	**52**, $POPh_2$	**53**	75
16	**55**, CN	**56**	88

[a] The substrate was added to base.

The results of the study are shown in Table 2. In general, the base was added to the benzothiazines. However, in the case of **28**, the reaction succeeded only when the substrate was added to a solution of base, presumably due to side reactions like polymerization through conjugate addition when the substrate was exposed to a limited amount of base.

In all cases studied, only a single stereoisomer of product was obtained from isomerically pure starting materials. The stereochemistry of **11** and **35**, **41**, **44**, and **47** was established by X-ray analysis. On the basis of these data, the unequivocal results we have obtained with conjugated esters[3] and the fact that single stereoisomers of products were obtained, we surmise that the stereochemical outcome of the benzothiazine formation is the same throughout the series of substrates studied.

In summary, we have demonstrated that the formation of benzothiazines occurs readily from a number of *N*-aryl sulfoximines bearing electron-deficient alkenes ortho to the sulfoximine functional group. The reactions are highly stereoselective. Stereospecificity as a function of the electron-withdrawing group remains to be determined and a rationale for the stereoselectivity needs to be developed.[8] Further exploration of the reaction and applications of the process in synthesis will be reported in due course.

Experimental Section

General Procedure for the *N*-Arylation Reaction: Synthesis of 22. A 15 mL round-bottomed flask equipped with a reflux condenser was charged with $Pd(OAc)_2$ (7.73 mg, 0.034 mmol), *rac*-BINAP (32.2 mg, 0.052 mmol), and dry toluene (3.4 mL). Phosponate **21** (0.200 g, 0.687 mmol), (*S*)-**3** (0.128 g, 0.824 mmol), and cesium carbonate (0.313 g, 0.962 mmol) were added. The reaction mixture was heated in an oil bath at 115−120 °C for 36 h. After the reaction was complete, the mixture was diluted by CH_2Cl_2 (5 mL) and filtered through a short pad of Celite. Excess solvent was removed under reduced pressure and the residue was purified by flash column

(8) For example, we know that the reaction is stereospecific with respect to alkene geometrical isomers substituted with ester groups: *E* isomers give one product, the *Z* isomers uniquely afford a different diastereomer.[3] Whether this is true for other electron-withdrawing groups remains to be seen.

chromatography (5% MeOH/ EtOAc) to provide 0.239 g (95%) of a yellow oil: IR (neat) 3015, 2950, 1605, 1593, 1475, 1442, 1266, 1189, 1025 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.21 (dd, J = 17.8, 23.5 Hz, 1H), 7.95−7.91 (m, 2H), 7.60−7.46 (m, 4H), 7.09−7.00 (m, 2H), 6.91−6.83 (m, 1H), 6.28 (dd, J = 17.8. 19.8 Hz, 1H), 3.82 (d, J = 2.8 Hz, 3H), 3.78 (d, J = 2.8 Hz, 3H), 3.28 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 147.2, 147.1, 144.6, 139.0, 133.3, 130.8, 129.6, 128.5, 128.3, 128.1, 127.2, 122.4, 121.6, 112.5, 109.4, 52.4 (d, J = 4.1 Hz) 52.2 (d, J = 4.1 Hz), 46.2. Anal. Calcd for $C_{17}H_{20}NO_4PS$: C, 55.88; H, 5.52. Found: C, 55.75; H, 5.70. $[\alpha]^{25}_D$ −197.94 (*c* 1.07, $CHCl_3$).

General Procedure for Intramolecular Michael Addition: Synthesis of 23. A 10 mL round-bottomed flask was charged with compound **22** (0.050 g, 0.137 mmol) in dry THF (1.4 mL) at −78 °C. A 1.25 M solution of LiHMDS in THF (0.328 mL, 0.410 mmol) was added dropwise. The reaction mixture was stirred at −78 °C until the starting material was consumed, as indicated by TLC. The mixture was quenched with water and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (5% MeOH/EtOAc) to provide 0.042 g (83%) of a colorless oil: IR (neat) 3064, 2953, 2848, 1712, 1597, 1478, 1446, 1297, 1270, 1110, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 7.8 Hz, 2H), 7.70−7.57 (m, 3H), 7.28−7.13 (m, 3H), 6.95 (t, J = 7.5 Hz, 1H), 3.92 (dd, J = 4.3, 13.2 Hz, 1H), 3.80−3.72 (m, 1H), 3.73 (d, J = 10.9 Hz, 3H), 3.63 (d, J = 10.8 Hz, 3H), 3.35 (dd, J = 10.5, 13.2 Hz, 1H), 2.52 (ddd, J = 4.3, 15.8, 20.0 Hz, 1H), 2.06 (ddd, J = 10.5, 15.8, 15.9, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 139.0, 133.8, 129.4, 128.9, 128.8, 125.5, 124.8, 124.6, 124.4, 121.0, 52.7 (d, J = 6.8 Hz), 52.4 (d, J = 6.8 Hz), 52.2 (d, J = 3.8 Hz), 30.0 (d, J = 3.8 Hz), 27.2 (d, J = 140.2 Hz); HRMS calcd for $C_{17}H_{20}NO_4PS$ $[M + H]^+$ 366.0923, found 366.0924; $[\alpha]^{25}_D$ −31.82 (*c* 0.44, $CHCl_3$).

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Supporting Information Available: Spectroscopic data and experimental procedures for the reported compounds and X-ray data (CIF files) for **11**, **35**, **41**, **44**, and **47**. This material is available free of charge via the Internet at http://pubs.acs.org.

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