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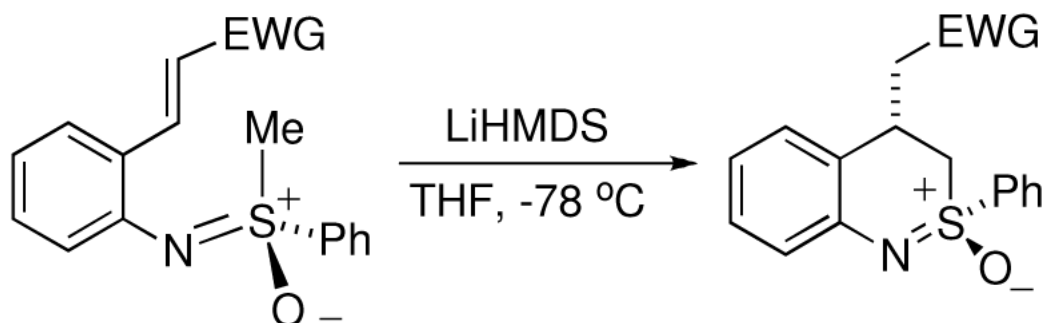
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Benzothiazines in Synthesis. Further Studies of the Intramolecular, Stereoselective Addition of Sulfonylimidoyl Carbanions to α,β -Unsaturated Functional Groups

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Abstract



A variety of alkenes substituted by electron-withdrawing groups serve as competent electrophiles for the stereoselective, intramolecular nucleophilic addition of sulfonylimidoyl 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 in of 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 *ortho*-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 *ortho*-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 curcumen and the antitubercular agents erogorgiaene and pseudopteroxazole, among others.^{4,5}

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Supporting Information Available. Spectroscopic data and experimental procedures for the reported compounds. 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>.

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 *ortho*-bromobenzaldehyde using 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, 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

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. Based on these data, the unequivocal results we have obtained with conjugated esters³ 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 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

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 CH₂Cl₂ (5 mL) and was filtered through a short pad of Celite. Excess solvent was removed under reduced pressure and the residue was purified by flash column 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, CDCl₃): 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); ¹³C NMR (62.5 MHz, CDCl₃): 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 C₁₇H₂₀NO₄PS: C, 55.88; H, 5.52. Found: C, 55.75; H, 5.70; [α]_D²⁵ = -197.94 (c 1.07, CHCl₃).

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 CH₂Cl₂ (3×10 mL). The combined organic layers were washed with brine, dried over MgSO₄, 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, CDCl₃): 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 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₇H₂₀NO₄PS [M + H]⁺ 366.0923; Found 366.0924; [α]_D²⁵ = -31.82 (c 0.44, CHCl₃).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

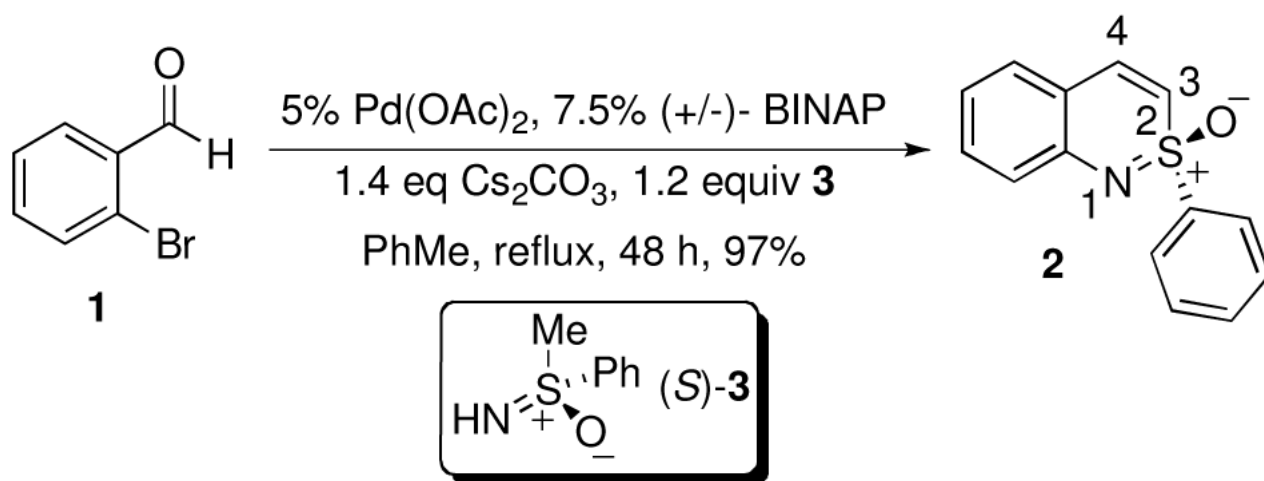
Acknowledgement

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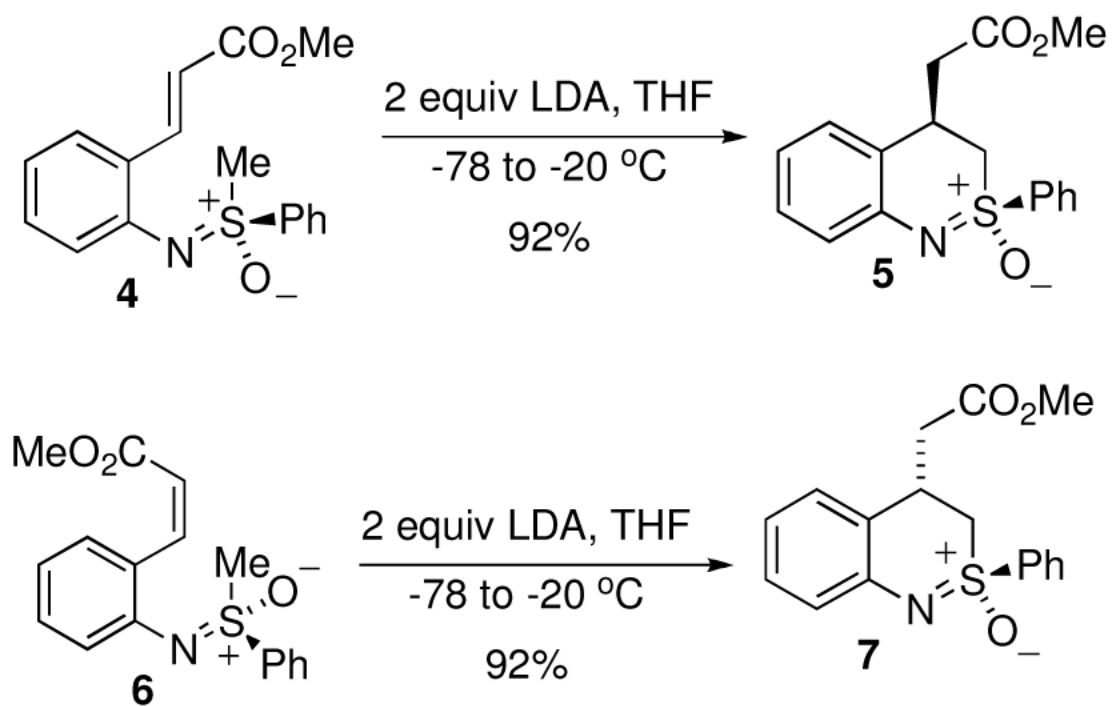
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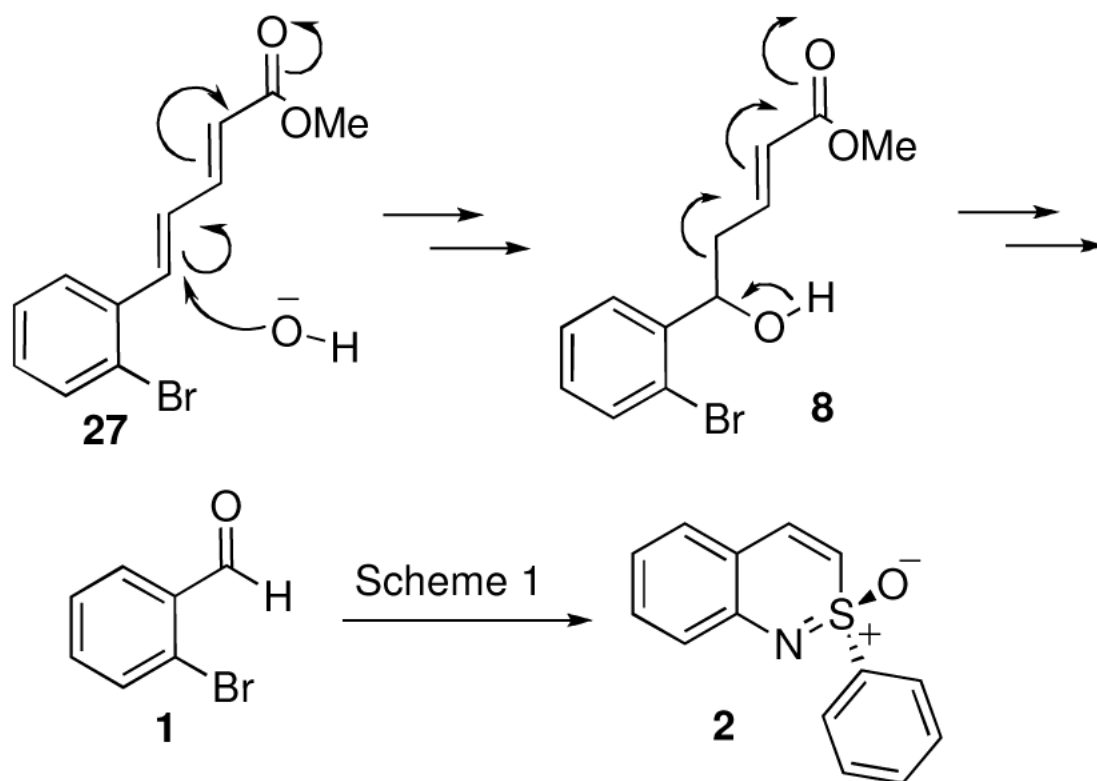
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- (7). During the course of our studies, we have found that the nature of the base, including the cation, has no effect on the stereochemical outcome of the reaction, at least with esters as the electron-withdrawing group. Details will be reported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



SCHEME 1.
Benzothiazine Synthesis



SCHEME 2.
Stereospecific Conjugate Addition



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

TABLE 1

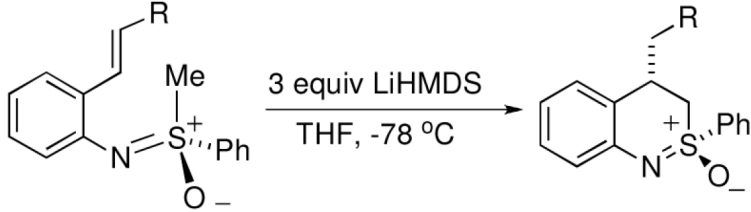
Synthesis of N-Aryl Sulfoximines

entry	educt, R	time (h)	product	yield (%)
1	9 , SO ₂ Ph	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 ₂ CN	48	25	96
7	27 , (<i>E</i>)-CH=CHCO ₂ Me	44	28	79 ^a
8	30 , CON(CH ₂) ₅	48	31	89
9	33 , COPh ₂ OMe	36	34	66
10	36 , COPh ₂ OMe	18	37	81
11	39 , COPh ₂ Cl	48	40	84
12	42 , CO ₂ tBu	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

^aThe reaction performed in the presence of 4Å molecular sieves.^b91% yield based on recovered starting material.^cA 42% yield of **53** was obtained.^dA 10% yield of **56** was obtained.

TABLE 2

Synthesis of Benzothiazines



entry	educt, R	product	yield (%)
1	10 , SO ₂ Ph	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 ₂ CN	26	NR
7	28 , (<i>E</i>)-CH=CHCO ₂ Me	29	42 ^a
8	31 , CON(CH ₂) ₅	32	88
9	34 , COPh ₂ OMe	35	66
10	37 , COPh ₂ OMe	38	63
11	40 , COPh ₂ Cl	41	65
12	43 , CO ₂ 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

^aThe substrate was added to base.