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Benzothiazines in Organic Synthesis. Stereoselectivity in the Intermolecular Michael Addition Reactions of Benzothiazines

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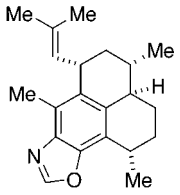
ABSTRACT

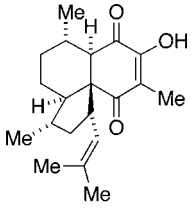
A study of the intermolecular Michael addition of certain benzothiazine anions demonstrated that stereoselectivity could be extremely high, though achieving control over the direction of relative stereoselectivity was in general not straightforward.

As part of our program involving the synthesis and application of chiral, nonracemic benzothiazines,[1] we have been involved in the synthesis of natural products that possess antitubercular activity, such as the amphilectane diterpene pseudopteroxazole (**1**),[2,3] which was isolated from the sea whip *Pseudopterogorgia elisabethae*.[4] Elisabethin A (**2**) is a related structure also isolated from the same organism, but its biological activity has not been defined.[5] At the outset of our work, no synthesis of **2** existed. Mulzer and co-workers reported a synthesis of **2**,[6] but the accuracy of this report has been challenged.[7]

A key step in our projected synthesis of **2** involved the reaction of the anion of **3** with a Michael acceptor such as ethyl crotonate. Our premise was that chelation control would obtain and that **4** would be produced as the major product of the reaction (Scheme 1).



1, pseudopteroxazole



2, elisabethin A

The intermolecular Michael addition of sulfoximine anions to Michael acceptors is well-known in the case of allylic sulfoximines.[8] For example, a report by Pyne demonstrated that the Michael addition of the anion of racemic **6** to chalcone proceeded with high stereoselectivity to afford **8**, presumably via a transition state resembling **7** (Scheme 2).[8b,c] This result suggested that our expectations for the reaction of **3** might be well-founded.

From a more general perspective, the Michael addition of sulfoximine anions has not been extensively studied,[9] and

(1) Harmata, M.; Hong, X. *J. Am. Chem. Soc.* **2003**, *125*, 5754.
(2) Davidson, J. P.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 13486.
(3) (a) Harmata, M.; Hong, X.; Barnes, C. L. *Org. Lett.* **2004**, *6*, 2201. (b) Harmata, M.; Hong, X. *Org. Lett.* **2005**, *7*, 3581.
(4) Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I.; González, E. *Org. Lett.* **1999**, *1*, 527.
(5) Rodríguez, A. D.; González, E.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 7083.
(6) Heckrodt, T. J.; Mulzer, J. *J. Am. Chem. Soc.* **2003**, *125*, 4680.
(7) Zanoni, G.; Franzini, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4837.
(8) (a) Harmata, M.; Claassen, R. J., III. *Tetrahedron Lett.* **1991**, *32*, 6497. (b) Pyne, S. G.; Dong, Z.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **1997**, *62*, 2337. (c) Pyne, S. G.; Dong, Z. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *95*−*96*, 425. (d) Pyne, S. G.; Dong, Z.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Chem. Commun.* **1994**, 751.

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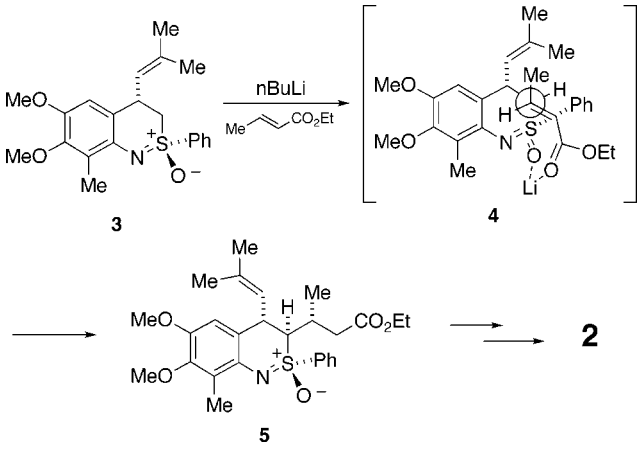
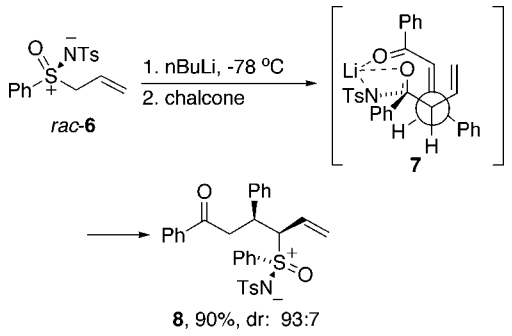
Scheme 1



there are no examples of anionic, cyclic sulfoximines such as benzothiazines serving as nucleophiles in Michael addition processes.[10] Thus, we sought to obtain data that would be useful in further applications of the chemistry we were developing.

Scheme 2



Our initial investigations with model systems were fraught with a number of problems. Electrophiles such as simple alkyl crotonate esters afforded crude reaction mixtures that were quite messy.[11] The same was true of diethyl crotonamide and crotonitrile.

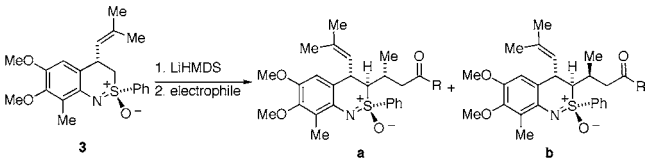
We chose to examine a number of esters that we thought might react more cleanly in that they would inhibit 1,2-addition via steric bulk and prevent processes such as anionic polymerization. The results are summarized in Table 1. Though we were ultimately interested in using esters of *tert*-butylhydroxytoluene (BHT) or related species, we decided to investigate simpler, less sterically hindered phenol esters, as well, in order to get a complete picture of the process.

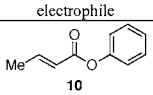
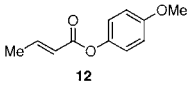
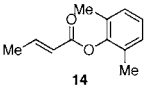
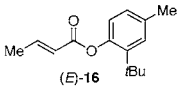
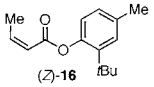
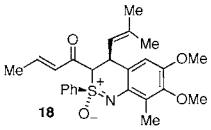
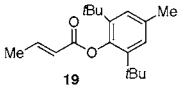
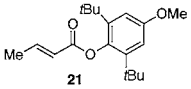
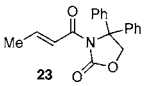
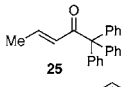
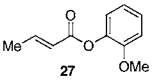
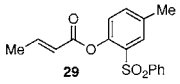
(9) Johnson, C. R.; Kirchhoff, R. A.; Reischer, R. J.; Katekar, G. F. *J. Am. Chem. Soc.* **1973**, *95*, 4287.

(10) Diastereoselective alkylation of cyclic sulfoximines is well-known. See, for example: (a) Harmata, M.; Kahraman, M.; Jones, D. E.; Pavri, N.; Weatherwax, S. E. *Tetrahedron* **1998**, *54*, 9995. (b) Bosshammer, S.; Gais, H.-J. *Synthesis* **1998**, 919.

(11) Methyl, ethyl, isopropyl, and *t*-butyl crotonates were investigated.

Table 1. Metalation and Michael Addition Reactions of Benzothiazine **3**



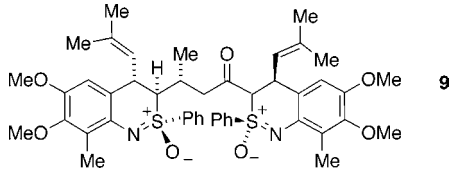
entry	electrophile	product	ratio (a:b)[a]	yield (%)[b]	yield (%)[b] **9**	ratio (a+b:**9**)
1	 **10**	**11**	0:1	29	29	1:1
2	 **12**	**13**	0:1	28	29	1:1
3	 **14**	**15**	0:1	90	0	-
4	 (*E*)-**16**	**17**	0:1	91	trace	-
5	 (*Z*)-**16**	**17**	0:1	59	14	4:1
6	 **18**	**9**	-	-	87	-
7	 **19**	**20**	1:1	87	0	-
8	 **21**	**22**	1:1	90	0	-
9	 **23**	**24**	1:13	89	0	-
10	 **25**	**26**	1:6.2	87	0	-
11	 **27**	**28**	0:1	91[c]	0	-
12	 **29**	**28**	0:1	92[c]	0	-

[a] Product ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. [b] Yields based on **3**. [c] The product was a primary amide.

The general procedure for the Michael addition consisted of treating a THF solution of compound **3** with 2.0 equiv of LHMDS at −78 °C. After 40 min, a THF solution of the Michael acceptor (1.3 equiv) was added dropwise into the nucleophile solution. After 1 h, the reaction was quenched. Further details are given in the Supporting Information. Two equivalents of base was used because yields improved with excess base.

Simple phenol esters gave reactions with the anion of **3** that were very stereoselective (Table 1, entries 1 and 2). Two products were formed in each case, **11b** and **13b**, both "contaminated" with **9**. Only a single diastereomer of each

product was formed! While the "**a**" series of diastereomers bears the incorrect relative configuration for our ultimate synthetic goals, **9** formed with perfect stereocontrol in the desired sense.



9

We presume that **9** resulted from the initial attack of the anion of **3** on the carbonyl carbon of **10** or **12** to afford the corresponding ketone. Michael addition to this ketone then gave **9**. This was corroborated when **18** was reacted with metalated **3**. Only compound **9** was obtained in very high yield (Table 1, entry 6).

The use of more sterically hindered phenols essentially eliminated this side reaction. For example, the ester (*E*)-**16** led to **17b** in very high yield, as did its corresponding *Z* isomer (Table 1, entries 4 and 5). In the latter case, however, a significant amount of **9** was formed, perhaps due to conformational effects on reactivity in (*Z*)-**16**.

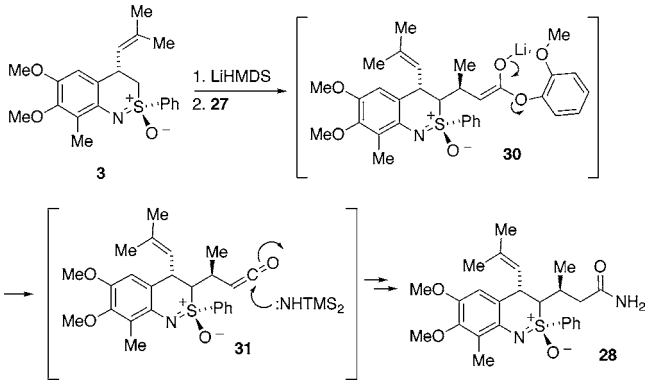
Interestingly, the BHT ester **19** afforded a 1:1 mixture of **20a** and **20b**. We speculate that, in the case of (*E*)-**16**, reaction takes place on a conformer in such a way as to minimize steric interactions with the *t*-butyl group. With **19**, it is likely that the *t*-butyl groups lie on either side of the π system, forcing a steric interaction and leading to a mechanistic change that favors the formation of the **a** diastereomer series. This idea is corroborated in the reaction of **21** (Table 1, entry 8) but not in the reactions of either **23** or **25**, a result that we found surprising (Table 1, entries 9 and 10).

The fact that **18** reacted with the anion of **3** to give only **9**, formally a diastereomer in the **a** family, led us to explore phenols bearing ortho hetereoatom substituents that would be capable of chelating a lithium ion. Were this interaction responsible for the high diastereoselectivity of the reaction of **18**, it might be possible to completely change the diastereoselectivity of the reaction vis-à-vis that of ester **16**. In the event, esters **27** and **29** favored the formation of **28b**. We have not yet found a simple way to selectively control the stereochemical outcome of the Michael addition process.

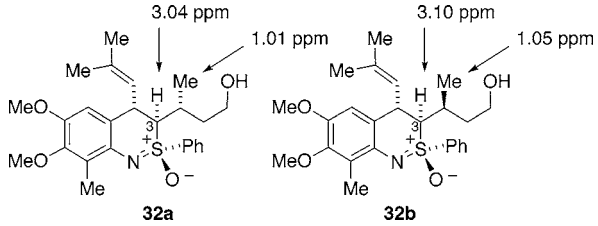
Interestingly, both **27** and **29** led to a product that was not an ester but a primary amide. We believe that, in these cases, Michael addition was followed by elimination to form a ketene (e.g., **31**) that was trapped by hexamethylsilylamide. This elimination may have been facilitated by chelation, though we have not yet done experiments to support this idea. Desilylation upon workup then gave the primary amide (Scheme 3).

The relative stereochemistry of **17b**, **20a**, **9**, and **28b** was established by X-ray crystallographic analysis of these compounds or certain derivatives. ^{1}H NMR data were used to correlate the stereochemistry of the remaining compounds. For example, compound **17b** could be reduced to its corresponding alcohol (**32b**). The chemical shift for the proton at C-3 and the methyl group appeared at 3.10 and 1.05 ppm,

Scheme 3

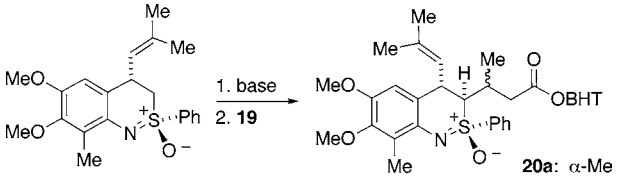


respectively. A 1:1 mixture of **32a** and **32b** could be obtained from a mixture of **20a** and **20b**. This showed upfield shifts for the same signals, which occurred at 3.04 and 1.01 ppm, respectively. We could thus use both X-ray data and chemical shift data to obtain stereochemical information on mixtures of Michael adducts that we produced.



In order to evaluate other variables in the reaction and establish that product formation was under kinetic and not thermodynamic control, we undertook another small series of experiments using **19** as the electrophile. The results are summarized in Table 2. Interestingly, when NaHMDS was

Table 2. Cation, Solvent, and Temperature Variation in the Michael Addition of **3** and **19**



entry	temp (°C)	base	solvent	ratio (**a**:**b**)[a]	yield (%)
1	−78	NaHMDS	THF	0:1	86
2	−78	LiHMDS	toluene	1:1	88
3	−95	LiHMDS	THF	1.3:1	91
4	−95	LiHMDS	THF/HMPA[b]	1.4:1	87
5	−78	LiHMDS[c]	THF	1.7:1	84[d]

[a] Ratio determined by ^{1}H NMR of the crude reaction mixture. [b] 10% HMPA by volume. [c] 2 equiv of $MgBr_2$ added to anion prior to addition of electrophile. [d] Based on 92% conversion.

used as a base in THF, the stereochemical outcome of the Michael addition reaction changed dramatically, so that only **20a** was obtained (Table 2, entry 1). This contrasts with the 1:1 mixture of diastereomers obtained with the use of LiHMDS (Table 1, entry 7). A change to toluene had no effect on this ratio (Table 2, entry 2). While conducting the reaction at −95 °C increased the yield of **20a** a small amount, the addition of HMPA had no effect on the stereochemical outcome at this temperature. Nevertheless, still thinking that chelation was involved in determining the stereochemical outcome of the reaction, we added $MgBr_2$ to the anion of **3**. Subsequent Michael addition with **19** afforded a 1.7:1 ratio of **20a**/**20b** in 84% yield (92% conversion, Table 2, entry 5). Further studies of the impact of different metal ions on the stereochemical outcome of the reaction are in progress. In order to determine whether the reactions were under kinetic control, as we had assumed, we conducted several experiments. Compound **20b** was treated with both LiHMDS and NaHMDS at −78 °C for 2 h in THF and was recovered unchanged. A 1:1 mixture of **20a** and **20b** experienced the same fate. This suggests the Michael addition reactions are under kinetic control.

In conclusion, we have described what we believe are the first examples of highly diastereoselective Michael additions of 2,1-benzothiazines (cyclic sulfoximines). Further studies of this process and others that demonstrate the synthetic utility of these chiral species are in progress. Further results will be reported in due course.

Acknowledgment. This work was supported by the NIH (1R01-AI59000-01A1) to whom we are very grateful.

Supporting Information Available: Experimental procedures, as well as characterization and copies of proton and carbon spectra for all previously unreported compounds. X-ray data for **9**, **17b**, **20a**, and **28b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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