

Benzothiazines in Organic Synthesis. The Preparation of Enantiomerically Pure 4-Substituted Quinolones

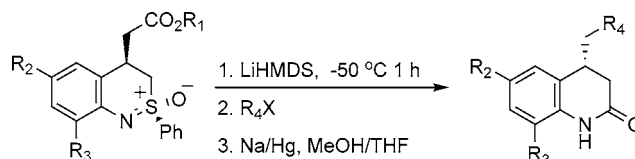
Michael Harmata* and Xuechuan Hong

Department of Chemistry, University of Missouri–Columbia,
Columbia, Missouri 65203

harmatam@missouri.edu

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ABSTRACT



3,4-Dihydroquinolin-2(1H)-ones have potential biological and pharmacological significance. Enantiomerically pure benzothiazines, readily available via an intramolecular addition of a sulfoximine-stabilized carbanion to an α,β -unsaturated ester, could be used as templates for making a series of enantiomerically pure 3,4-dihydroquinolin-2(1H)-ones under mild conditions.

Quinolin-2(1H)-ones are ubiquitous structural motifs that can be found in many naturally and non-naturally occurring compounds (Figure 1).¹ Many of these heterocycles possess interesting biological properties and have been developed as drugs that are antibiotics,^{1b} HIV-1 reverse transcriptase inhibitors,^{1c} NMDA antagonists,^{1d} and 5-HT₃ receptor antagonists.^{1e} Their importance in medicinal chemistry has stimulated considerable attention from organic chemists and encouraged the development of new synthetic pathways to prepare these compounds.

A number of syntheses of quinolin-2(1H)-ones have been reported that rely on radical cyclizations of a secondary amide,^{2a,b} solid-phase synthesis,^{2c} asymmetric cyclocarbonylation of 2-vinylanilines by palladium^{2d–h} or rhodium catalysts,²ⁱ Friedlander-type methods or Friedel–Crafts cyclization,^{2j–l} and multicomponent reactions.^{2m} Most of the

syntheses of quinolin-2(1H)-ones give racemic compounds or low enantiomeric excesses under relatively harsh reaction

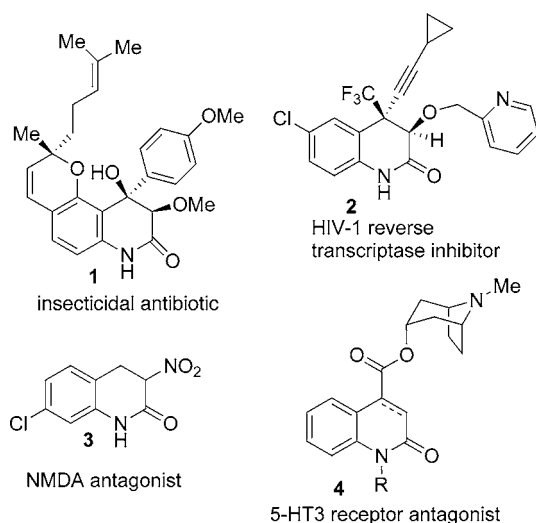
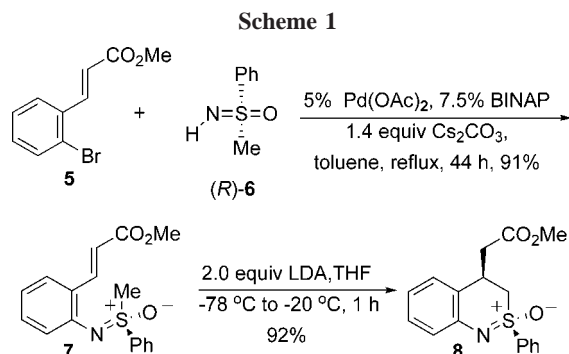


Figure 1. Examples of tetrahydroquinolone-containing natural and non-natural products.

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conditions. The use of radical cyclization to build six-membered rings has some limitations as well, often resulting in very low yields.

We recently reported the stereoselective, intramolecular Michael addition of sulfoximine carbanions to α,β -unsaturated esters as exemplified in Scheme 1.³ The preparation of



sulfoximine **7** was conducted by using the methodology introduced by Bolm and co-workers.⁴ Subsequent treatment of sulfoximine **7** with LDA afforded **8** as a single stereoisomer in high yield. The reaction is stereospecific and offers a way of establishing benzylic stereocenters with high fidelity. We are interested in using these benzothiazines as useful synthons in a variety of ways.

Benzothiazines that we have prepared have been directly converted to indoles,^{5a} allylanilines,^{5b} 2-alkylanilines,^{5b-d} and 2-alkenylanilines.^{5e} Further, we have demonstrated that the C_2 -symmetric bis-benzothiazines could be used as chiral ligands in asymmetric allylic alkylations.^{5f} We also applied benzothiazines to the total syntheses of (+)-curcuphenol, (+)-curcumene,⁶ erogorgiaene,⁷ and pseudopteroxazole.⁸

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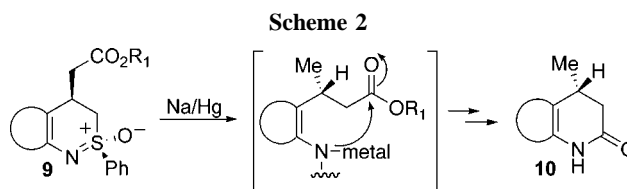
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In our continuing efforts to expand the utility of 2,1-benzothiazine chemistry, we thought that our enantiopure 2,1-benzothiazines³ would be ideal to construct enantiomerically pure 3,4-dihydroquinolin-2(1*H*)-ones. We anticipated that reductive desulfurization with sodium amalgam would result in a transient metal amide that would condense intramolecularly with the ester functional group to produce a lactam (Scheme 2). Indeed, reductive desulfurization of **9**



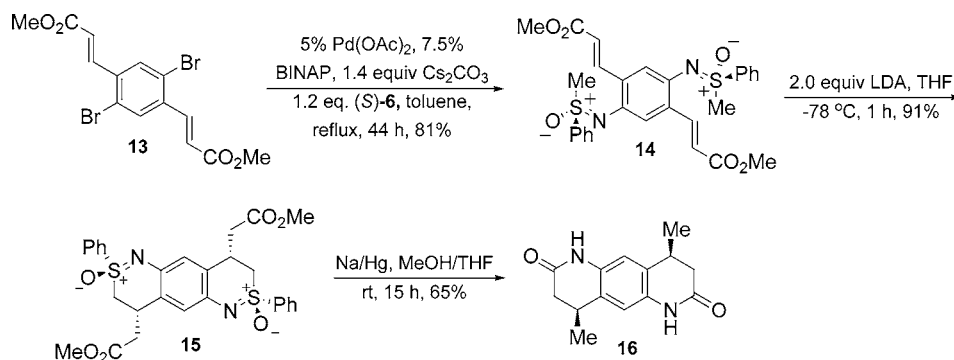
would yield 3,4-dihydroquinolin-2(1*H*)-one **10** in a concise and especially straightforward way. Herein we reported the first synthesis of enantiopure 3,4-dihydroquinolin-2(1*H*)-ones under mild conditions.

Our initial evaluation of the reductive desulfurization of benzothiazines was carried out using a simple system (Table 1). Treatment of benzothiazines **11a–d** with excess sodium amalgam in methanol/tetrahydrofuran at room temperature

Table 1. Conversion of Benzothiazines **11** to 4-Methyl-3,4-dihydroquinolin-2(1*H*)-ones **12**

entry	benzothiazine	Time (h)	dihydroquinolin-2(1 <i>H</i>)-one	yield (%)
1		12		89
2		14		93
3		14		91
4		14		71
5		15		83
6		13		78

Scheme 3



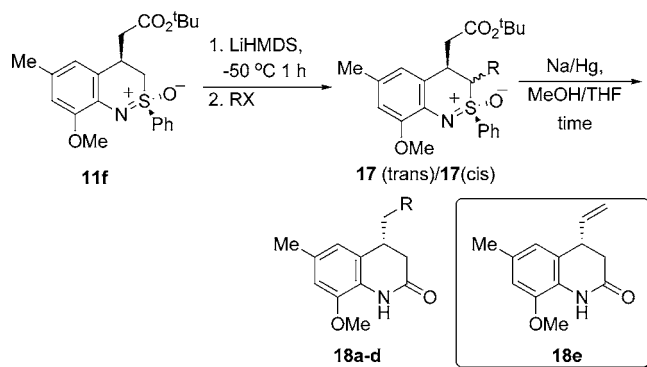
for several hours resulted in the formation of 4-methyl-3,4-dihydroquinolin-2(1*H*)-ones **12a–d** in excellent yields with high enantiopurity (entries 1–4). Benzothiazines **11e,f** displayed similar reactivity to **11b,c**, giving 4-methyl-3,4-dihydroquinolin-2(1*H*)-ones **12b** and **12c** in 83% and 78% yields, respectively. Enantiomerically pure bis-benzothiazine **15** was prepared as per our published procedures³ involving the reaction of sulfoximine **14** with LDA. Compound **15** could be reduced and condensed to **16** in 65% yield (Scheme 3).

Our efforts were subsequently directed at metalation of the benzothiazines **11f** and their reaction with electrophiles. The products of such reactions would place substituents other than a methyl group at the 4-position of the 4-alkyl-3,4-dihydroquinolin-2(1*H*)-ones obtained upon reduction (Table 2). In the initial attempt, deprotonation of **11f** with 1.1 equiv of LiHMDS at $-50\text{ }^{\circ}\text{C}$ for 1 h followed by reaction with 4.0 equiv of CH_3I for 1 h provided exclusively the product

with the methyl on the α position of the sulfoximine **11f** in 81% yield as a 16.3:1 mixture of isomers. The mixture of these two isomers of **17a** was treated with Na/Hg to provide 4-ethyl-3,4-dihydroquinolin-2(1*H*)-one **18a** in 63% yield via a reductive desulfurization/condensation process (entry 1).

Encouraged by these preliminary results, we considered applying these methods toward the installation of a range of other groups at the 4-position of the 3,4-dihydroquinolin-2(1*H*)-ones. Pleasingly, a variety of substituents could be installed in good yields. An ethyl, allyl, benzyl, or MEM group could be placed on the α position of the sulfoximine **11f** with the corresponding electrophiles in 44–83% yields with high diastereoselectivity.⁹ As expected, benzothiazines **17b–d** were readily converted to 3,4-dihydroquinolin-2(1*H*)-ones **18b–d** with different substituents at the 4-position. However, benzothiazine **17e** was converted to 4-vinyl-3,4-dihydroquinolin-2(1*H*)-one **18e**, instead. The formation of **18e** could be explained by assuming the formation of a negative charge adjacent to the alkoxy group during the course of the reduction. Elimination of the alkoxy group then resulted in the formation of the vinyl group. A related

Table 2. Conversion of Benzothiazine **11f** to 4-Alkyl-3,4-dihydroquinolin-2(1*H*)-ones **18**



entry	RX	product	yield (%) ^a	ratio (17, cis:trans) ^a	time, h	product	yield (%)
1	MeI	17a	80	16.3:1	36	18a	63
2	EtBr	17b	44	28.8:1	72	18b	65
3	allyl bromide	17c	83	5.1:1	48	18c	51
4	benzyl bromide	17d	79	16.4:1	72	18d	60
5	MEM-Cl	17e	48	24.1:1	72	18e	72

^a Determined by ^1H NMR analysis of the crude reaction mixture.

Table 3. Conversion of Thiazines **19** to Ring-Fused Pyridin-2(1*H*)-ones **20**

entry	thiazine	time (h)	pyridin-2(1 <i>H</i>)-one	yield (%)
1	19a	15	20a	87
2	19b	15	20b	81
3	19c	18	20c	90
4	19d	18	20d	68

sequence to introduce substituted alkenes is a potentially general process.

We were also curious to see if heterocyclic ring-fused thiazines **19a–d** could be used for the synthesis of ring-fused pyridin-2(1*H*)-ones. Gratifyingly, good results were obtained when thiophene, furan, and indole thiazines **19a–d** were treated with a similar reaction sequence (Table 3).

(9) Allylation of **11f** resulted in only a 5.1:1 mixture of the isomers of **17c** (entry 3, Table 2).

(10) We are assuming the dihydroquinolones are as enantiomerically pure as the sulfoximine **6**, which is used to prepare the benzothiazine precursors of the quinolones. The resolution of **6** is performed according to Gais¹¹ and the enantiomeric purity of the sulfoxime is checked by chiral column chromatography. We prepared enantiomerically pure **12a** and compared it to racemic material by chiral HPLC to validate this assumption.

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In summary, we have developed a new, convenient route for the synthesis of enantiomerically pure 3,4-dihydroquinolin-2(1*H*)-ones^{10,11} under mild conditions. Further investigations regarding the scope of the reaction presented and their application in organic synthesis will be reported in due course.

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Supporting Information Available: Experimental procedures, as well as characterization and copies of proton and carbon spectra for all previously unreported compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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