ORGANIC LETTERS

2007
Vol. 9, No. 14
2701−2704

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

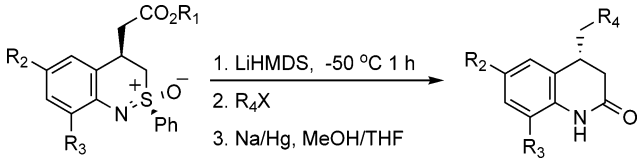
Michael Harmata* and Xuechuan Hong

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

harmatam@missouri.edu

Received May 3, 2007

ABSTRACT



3,4-Dihydroquinolin-2(1*H*)-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(1*H*)-ones under mild conditions.

Quinolin-2(1*H*)-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(1*H*)-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(1*H*)-ones give racemic compounds or low enantiomeric excesses under relatively harsh reaction

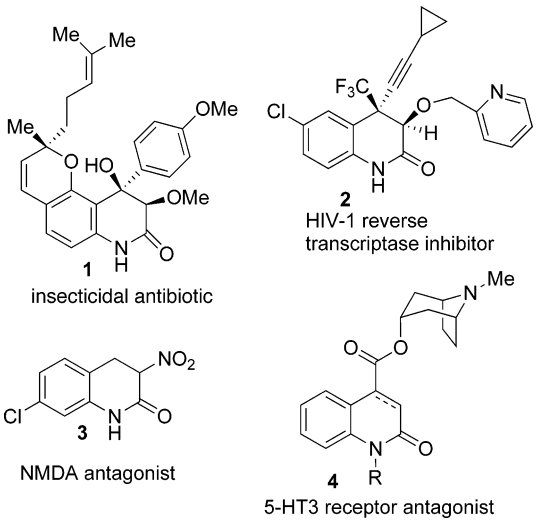


Figure 1. Examples of tetrahydroquinolone-containing natural and non-natural products.

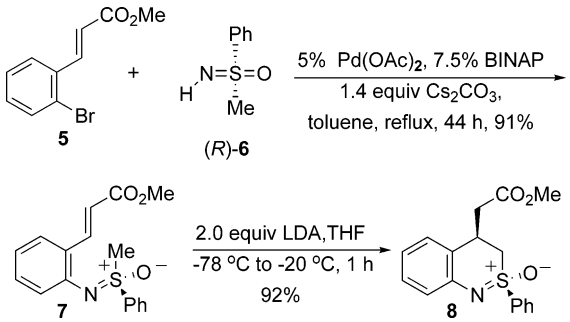
(1) (a) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; p 167. (b) Uchida, R.; Imasato, R.; Shiomi, K.; Tomoda, H.; Omura, S. *Org. Lett.* **2005**, *7*, 5701. (c) Patel, M.; McHugh, R. J.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1943. (d) Carling, R. W.; Leeson, P. D.; Moore, K. W.; Smith, J. D.; Moyes, C. R.; Mawer, I. M.; Thomas, S.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Tricklebank, M. D.; Saywell, K. L. *J. Med. Chem.* **1993**, *36*, 3397. (e) Hayashi, H.; Miwa, Y.; Miki, I.; Ichikawa, S.; Yoda, N.; Ishii, A.; Kono, M.; Suzuki, F. *J. Med. Chem.* **1992**, *35*, 4893.

10.1021/ol0710358 CCC: $37.00
Published on Web 06/08/2007

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

Scheme 1

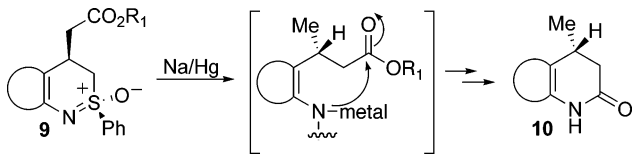


sulfoximine **7** was conducted by using the methodology introduced by Bolm and co-workers.[4] Subsequent treatment of sulfoximine **7** with LDA afforded **8** as a single stereoisomer in high yield. The reaction is stereospecific and offers a way of establishing benzylic stereocenters with high fidelity. 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]

In our continuing efforts to expand the utility of 2,1-benzothiazine chemistry, we thought that our enantiopure 2,1-benzothiazines[3] would be ideal to construct enatiomerically 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**

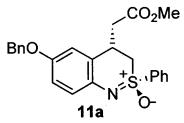
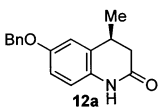
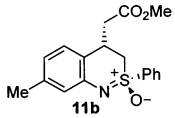
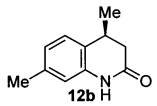
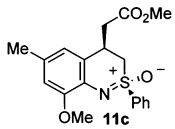
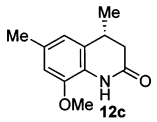
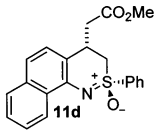
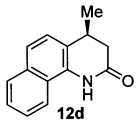
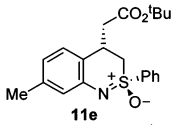
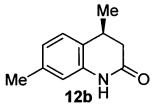
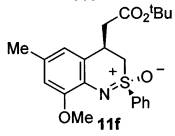
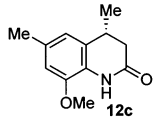
Scheme 2



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**[3] 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*H*)-one	yield (%)
1	 **11a**	12	 **12a**	89
2	 **11b**	14	 **12b**	93
3	 **11c**	14	 **12c**	91
4	 **11d**	14	 **12d**	71
5	 **11e**	15	 **12b**	83
6	 **11f**	13	 **12c**	78

(2) (a) Binot, G.; Zard, S. Z. *Tetrahedron Lett.* **2005**, *46*, 7503. (b) Clark, A. J.; Jones, K.; McCarthy, C.; Storey, J. M. D. *Tetrahedron Lett.* **1991**, *3*, 2829. (c) Turner, K. L.; Baker, T. M.; Islam, S.; Procter, D. J.; Stefaniak, M. *Org. Lett.* **2006**, *8*, 329. (d) Touzani, R.; Alper, H. *J. Mol. Catal. A*: *Chem.* **2005**, *227*, 197. (e) Dong, C.; Alper, H., *Tetrahedron*: *Asymmetry* **2004**, *15*, 35. (f) Okuro, K.; Kai, H.; Alper, H. *Tetrahedron*: *Asymmetry* **1997**, *8*, 2307. (g) El Ali, B.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264. (h) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2004**, *6*, 2433. (i) Fujita, K.; Takahashi, Y.; Owaki, M.; Yamamoto K.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 2785. (j) Jones G. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon Press: Oxford, UK, 1984; Vol. 2 (8). (k) Li, K.; Foresee, L. N.; Tunge, J. A. *J. Org. Chem.* **2005**, *70*, 2881. (l) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 6772. (m) Marcaccini, S.; Pepino, R.; Pozo, M. C.; Basurto, S.; García-Valverde, M.; Torroba, T. *Tetrahedron Lett.* **2004**, *45*, 3999.

(3) Harmata, M.; Hong, X. *J. Am. Chem. Soc.* **2003**, *125*, 5754.

(4) (a) Bolm, C.; Hildebrand, J. P. *Tetrahedron Lett.* **1998**, *39*, 5731. (b) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169.

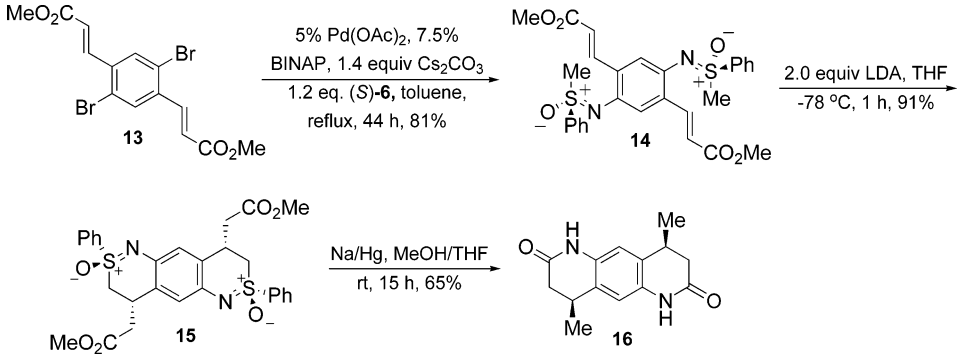
(5) (a) Harmata, M.; Herron, B. F. *Tetrahedron* **1991**, *47*, 8855. (b) Harmata, M.; Jones, D. E. *Tetrahedron Lett.* **1995**, *36*, 4769. (c) Harmata, M.; Herron, B. F. *Tetrahedron* **1991**, *47*, 8855. (d) Harmata, M.; Claassen, R. J., II; Barnes, C. L. *J. Org. Chem.* **1991**, *56*, 5059. (e) Harmata, M.; Kahraman, M. *Synthesis* **1994**, 142. (f) Harmata, M.; Ghosh, S. K. *Org. Lett.* **2001**, *3*, 3321.

(6) Harmata, M.; Hong, X.; Barnes, C. L. *Tetrahedron Lett.* **2003**, *44*, 7261.

(7) Harmata, M.; Hong, X. *Tetrahedron Lett.* **2005**, *46*, 3847.

(8) (a) Harmata, M.; Hong, X.; Barnes, C. L. *Org. Lett.* **2004**, *6*, 2201. (b) Harmata, M.; Hong, X. *Org. Lett.* **2005**, *7*, 3581.

Scheme 3

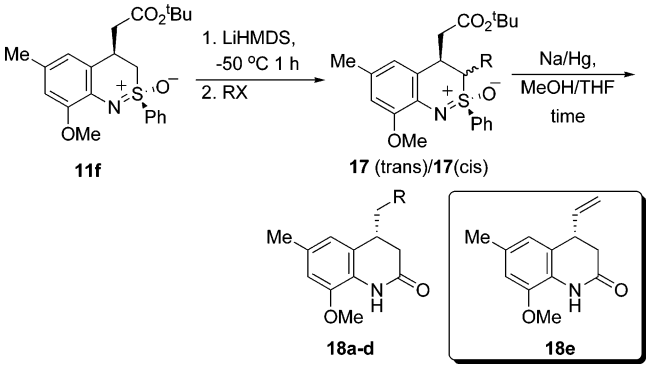


for several hours resulted in the formation of 4-methyl-3,4-dihydroquinolin-2(1*H*)-ones **12a**−**d** in excellent yields with high enantiopurity (entries 1−4). Benzothiazines **11e**,**f** displayed similar reactivity to **11b**,**c**, giving 4-methyl-3,4-dihydroquinolin-2(1*H*)-ones **12b** and **12c** in 83% and 78% yields, respectively. Enantiomerically pure bis-benzothiazine **15** was prepared as per our published procedures[3] 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 °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

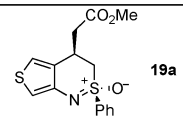
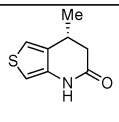
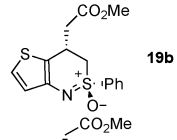
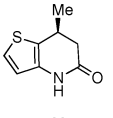
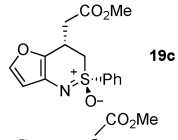
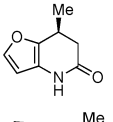
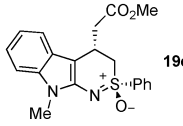
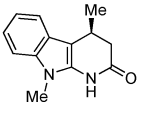
Table 2. Conversion of Benzothiazine **11f** to 4-Alkyl-3,4-dihydroquinolin-2(1*H*)-ones **18**



entry	RX	product	yield (%,**17**)	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 ^{1}H 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(1H)-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).

In summary, we have developed a new, convenient route for the synthesis of enatiomerically 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.

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

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.

OL0710358

(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 Gais[11] 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.

(11) Brandt, J.; Gais, H.-J. *Tetrahedron*: *Asymmetry* **1997**, *8*, 909.