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Tetrahedron Letters 45 (2004) 5429–5432
Tetrahedron Letters

syn-2,3-Disubstituted-2,3-dihydro-1,4-benzoxathiin rings: preparation from quinone ketals and 2-mercaptoethanols ☆

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Received 11 March 2004; revised 9 May 2004; accepted 11 May 2004

Abstract—A general method for the preparation of *syn*-2,3-disubstituted-2,3-dihydro-1,4-benzoxathiin rings from 2-mercaptoethanols and quinone ketals is presented. This ring system is produced by Michael addition of a 2-mercaptoethanol to a quinone ketal, followed by cyclization of the initial Michael adduct, and subsequent aromatization to afford a *syn*-2,3-disubstituted-1,4-benzoxathiin in fair to good chemical yield. Several chiral *syn*-2,3-disubstituted-2,3-dihydro-1,4-benzoxathiin rings were prepared with this method from enantioenriched 2-mercaptoethanols. No loss of enantiopurity was observed.

The 2,3-dihydro-1,4-benzoxathiin ring system **1** is a useful scaffold for the synthesis of selective estrogen receptor modulators (SERM).[1] Derivatives of this ring core are of interest for treatment of disorders such as hypertension, hot flashes, osteoporosis, endometriosis, vaginal dryness, breast cancer, and uterine cancer in post-menopausal women.[1,2] Few examples, which report the preparation of 2,3-dihydro-1,4-benzoxathiins have appeared in the literature. Most deal with unsubstituted,[3] monosubstituted,[4,5d] or 2,3-*anti*-disubstituted-2,3-dihydro-1,4-benzoxathiins.[5] Relatively few examples for the preparation of *syn*-2,3-disubstituted-2,3-dihydro-1,4-benzoxathiins have appeared in the open literature.[1a,5d,6]

Preparation of the *syn*-isomer is typically accomplished via a Diels–Alder cyclization of an *ortho*-thioquinone with an olefin, however regioisomer formation in this approach is often problematic.[6a] Recently, Kim et al.[1a] and Dininno et al.[1b,c] reported the dehydrative reductive cyclization of alpha-thioketones to provide 2,3-*syn*-dihydro-1,4-benzoxathiins in good yield and selectivity.

As part of a program directed toward the synthesis of a novel SERM, we required a practical route to *syn*-2,3-dihydro-1,4-benzoxathiins **1**. Herein, we report a novel methodology to prepare *syn*-2,3-dihydro-1,4-benzoxathiins and demonstrate its synthetic utility in the preparation of racemic and chiral dihydrobenzoxathiins **1a**–**f**. Retrosynthetically, **1** might arise from enone **2** after aromatization (Scheme 1). Enone **2** could in turn arise from **4** and **5** through Michael addition and cyclization, respectively.

Condensation of **4a**[7] with dimethyl ketal **5a** (R=H)[8] in methanol (Scheme 2) with catalytic triethylamine afforded a ~1.6:1 mixture of diastereomers **6** and **7**, which could be separated by chromatography (55%). To our disappointment, when this mixture was treated with trifluoroacetic acid (TFA), only a small amount of **1a** was produced. Independent treatment of the major Michael diastereomer **6** with TFA afforded only small amount of **1a** along with ketals **8** and **9** (>20:1); these could be isolated from the reaction mixture by silica gel chromatography.

Keywords: Quinone ketal; 2-Mercaptoethanol; Michael addition; 2,3-Dihydro-1,4-benzoxathiin.
☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.05.047
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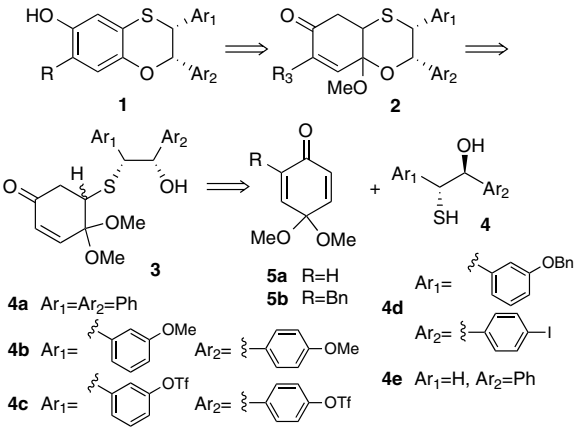
doi:10.1016/j.tetlet.2004.05.047

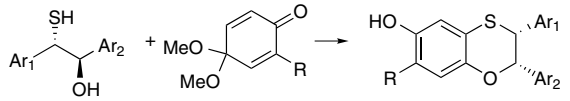


Scheme 1.

Of interest, in the presence of TFA only the minor ketal **9** converted (overnight) to **1a**, while the major ketal **8** proved resistant to aromatization. The addition of trimethysilyl triflate (TMSOTf) to the reaction mixture was necessary to effect aromatization of the ketal **8**.[9] In contrast to **6**, exposure of the minor Michael diastereomer **7** to TFA resulted in rapid and clean conversion to **1a**.

Addition of catalytic TMSOTf to the toluene/TFA reaction mixture accelerated the aromatization of ketals **8**–**10** significantly (60–90 min, Table 1, entry 2). Boron trifluoride–etherate could be used in place of TFA with similar results, however the use of TMSOTf was still required to effect aromatization of the major ketal **8** (Table 1, entry 1). Repeating the cyclization/aromatization sequence for the diastereomeric mixture of **6** and **7** with an optimized process[10] afforded **1a** (50% HPLC assay, 44% isolated). Also observed were small amounts of stilbene (<5%) and methyl ether **12** (<10%). The formation of undesired **12** was minimized by running both the cyclization and aromatization steps in toluene and at a reduced pressure to remove any excess methanol. Presumably, **12** resulted from ketalization of **8** prior to elimination of methanol.

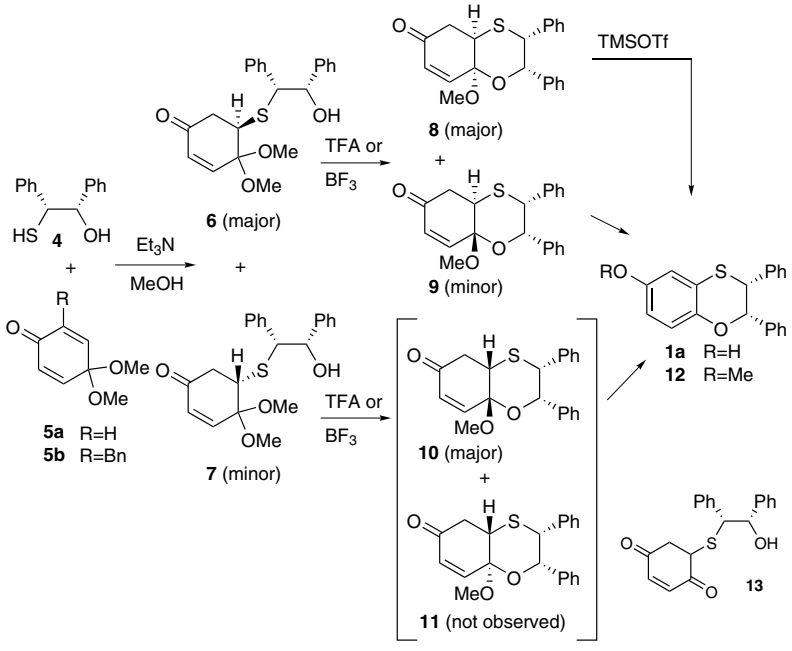
Table 1. Synthesis of *syn*-2,3-disubstituted-2,3-dihydro-1,4-benzoxathiins



4a-e **5a** R=H, **5b** R=Bn, **1a-f**, **1f** Ar_1=Ar_2=Ph, R=Bn

Entry[a]			1	Yield[b]	
				Assay[c]	Isolated
1	**4a**	**5a**	**1a**	50	44
2[d]	**4a**	**5a**	**1a**	50	30
3[d]	**4b**	**5a**	**1b**	n/a	18
4[d]	**4c**	**5a**	**1c**	50	29
5	**4d**	**5a**	**1d**	50	41
6	**4e**	**5a**	**1e**	30	15
7	**4a**	**5b**	**1f**	77	61
8[e]	(+)-**4a**	**5a**	(+)-**1a**	n/a	27
9[e]	(−)-**4a**	**5b**	(−)-**1f**	85	63
10[e]	(+)-**4d**	**5a**	(+)-**1d**	47	40

[a] Cyclization/aromatization using BF_3-TMSOTf except where noted. See supplementary section for representative procedure.
[b] Three-step overall yield from the starting 2-mercaptoethanol **4**.
[c] Assay yield from HPLC monitoring of reaction.
[d] TFA-TMSOTf used for cyclization/aromatization steps. See supplementary section for representative procedure.
[e] Enantiomeric excesses (ee) were measured by chiral supercritical fluid chromatography (SFC). See supplementary materials for details. For (+)-**1a**, (−)-**1f**, (+)-**4a**, (−)-**4a**, ee were ⩾99%. For (+)-**4d** and (+)-**1d**, ee were 89% and 87%, respectively.

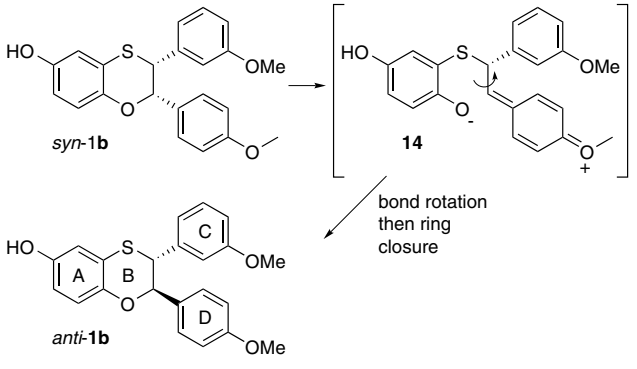


Scheme 2.

The relative stereochemistries were assigned for the major and minor ketals **8** and **9** using gradient NOE.[11] Characterization and assignment of the relative stereochemistry for ketal **10** was achieved from in situ monitoring (NMR) of the BF_3 promoted cyclization (toluene-d_8) of the minor Michael adduct **7**. Of interest, dihydroquinone **13** was also observed to slowly form (−20 °C, 5 h, <15%) in the NMR tube during this reaction presumably due to hydrolysis of dimethylketal **7**. Upon gradual warming the reaction mixture from −20 to +67 °C, both ketal **10** and quinone **13** were converted to the aromatized material **1a**.

While only the *syn* isomer of **1a** was observed in the cyclization/aromatization sequence of the initial Michael adduct (Table 1, entry 1), the presence of an electron donating group (e.g., OMe) in the *para*-position of the D-aromatic ring gave a mixture of *syn* and *anti* isomers (Scheme 3). For example, with $Ar_1 = 3$-methoxyphenyl and $Ar_2 = 4$-methoxyphenyl (**4b**, Table 1, entry 3) cyclization of the initial Michael adducts (from **4b** and **5a**) and subsequent aromatization, using the TFA/toluene/TMSOTf conditions, afforded a 1:1.6 *syn*:*anti* mixture **1b**. Formation of the *anti* isomer of **1b** might occur as proposed in Scheme 3. Ring opening of *syn*-**1b** would afford the intermediate quinone **14**. Bond rotation, followed by 1,6-addition of the phenoxide to the quinone would then produce *anti* isomer **1b**. This pathway can be suppressed by destabilizing quinone **14** through replacement of the *para*-methoxy group in the D-ring with a less electron donating group. The use of triflate on both the aryl rings of the mercaptoethanol (**4c**, Table 1, entry 4) afforded only the *syn* isomer **1c** (50% assay, 29% isolated) upon treatment of the Michael adduct with TFA/toluene/−20 °C followed by TMSOTf/−40 °C. Substitution of a halide for methoxy in the *para* position of the D-ring (**4d**, Table 1, entry 5) afforded only the *syn*-2,3-dihydro-1,4-benzo-benzoxathiin **1d**.

As demonstrated above, the method works well for disubstituted 2-mercaptoethanols (Table 1, entries 1–5). It is possible to utilize mono-substituted 2-mercaptoethanols. For example, **4e** (Table 1, entry 6) afforded **1e** in modest yield. Importantly, enantioenriched 2-mercaptoethanols[12,13] may also be used (Table 1, entries 8–10) with no erosion of stereochemistry in the cyclization/aromatization sequence. For example, when the Michael



Scheme 3.

adducts from (+)-**4a** (>99% ee) and **5a** (entry 8) were cyclized with BF_3 etherate and then aromatized with TMSOTf, product (+)-**1a** was obtained with no loss of enantiopurity. Similar results were obtained with enantioenriched 2-mercaptoethanols (−)-**4a** and (+)-**4d** (entries 9 and 10), with no loss of enantiopurity upon conversion to (−)-**1f** and (+)-**1d**, respectively. Analogs of the quinone ketal could also be utilized (entries 7 and 9). The benzyl-substituted analog **5b**, 2-benzyl-4,4-dimethoxycyclohexa-2,5-dien-1-one, when reacted with 2-mercapto-1,2-diphenylethanol **4a** (entry 7) afforded the Michael adduct, which was cyclized and then aromatized to produce **1f** in 61% yield.

In conclusion, a novel, convenient, and effective synthetic route to *syn*-2,3-disubstituted-2,3-dihydro-1,4-benzoxathiins was developed. The starting materials are readily available. The method lends itself to the preparation of a plethora of derivatives in good chemical yield and high enantiopurity. Most importantly, chiral *syn*-2,3-disubstituted-2,3-dihydro-1,4-benzoxathiins can be readily prepared from enantioenriched mercaptoethanols without any loss of optical activity.

Supplementary material

Representative experimental procedures for the preparation of 2-mercaptoethanols (**4d**) and for the Michael addition, cyclization, and aromatization reactions (**4d**+**5a**→**1d**). Also included is characterization data for compounds **1a**–**f**, **4a**–**e**, **5a**–**b**, **8**–**10**.

Acknowledgements

We would like to thank Ms. Mirlinda Biba for the chiral SFC and HPLC method development and enantiopurity determinations. Also, we would like to thank Dr. Thomas J. Novak for obtaining high resolution mass spectroscopic data.

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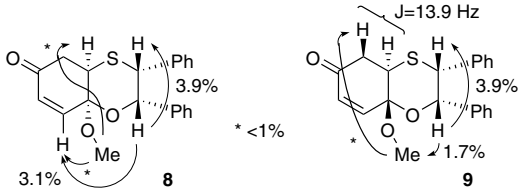

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12. Resolved using semi-preparative chiral SFC. See supplementary materials for details.
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