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Dehydrative Reduction: A Highly Diastereoselective Synthesis of *syn*-Bisaryl(or Heteroaryl) Dihydrobenzoxathiins and Benzodioxane

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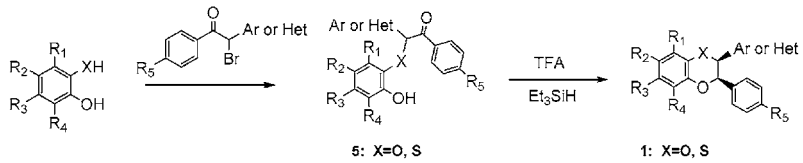
ABSTRACT



TFA/Et_3SiH-mediated cyclization of thioketones 5 derived from the reaction of functionalized thiophenols (catechols) with bromo ketones gave syn 2,3-bisaryl(or heteroaryl) dihydrobenzoxathiins and benzodioxane 1 with total diastereoselectivity (>99:1), in excellent yields.

Many benzodioxane and dihydrobenzoxathiin derivatives are of interest in several pharmaceutical areas,[1] since they exhibit a variety of biological properties[1a] such as antihypertensive, antidepressant, anxiolytic, and serenic activities as a consequence of their specific, observed affinities.[1b−g] Silybin[1f] and Americanol A,[1g] naturally occurring benzodioxane derivatives,[1h−i] were also found to have antihepatotoxic and neurotropic activities, respectively. In conjunction with a medicinal chemistry program targeting selective estrogen receptor modulators (SERMs), a method to synthesize *syn*-2,3-bisaryl-substituted dihydrobenzoxathiins and benzodioxanes **1** was needed. Although several methods were known to afford the anti isomer,[2] only a limited number of precedents were available in the literature prior to our study, which lead to the syn isomer.[3] Perhaps, this might be, in part, attributable to the difficulties associated with the diastereocontrolled chemistry necessary for the formation of the heterocyclic systems. Herein, we wish to report a novel diastereoselective synthesis of these substances by a dehydrative reduction of thioketones **5** under the conditions of the Kursanov−Parnes reaction[4] (TFA/Et_3SiH).

The cyclic oxocarbonium ion generated from the acid-promoted reaction of a ketal or a hemiketal has been

(1) (a) Boulton, A. J. *Compr. Heterocycl. Chem. II* 448. (b) Maria, W. Q.; Sayeed, K. T.; Alersandro, P.; Maria, O. G.; Gabriella, M.; Carlo, M. *J. Med. Chem.* **1993**, *35*, 1520. (c) Gaster, L. M.; Jenning, A. J. et al. *J. Med. Chem.* **1993**, *36*, 4121. (d) Quaglia, W.; Pigini, M.; Giannella, M. *J. Med. Chem.* **1990**, *33*, 2946. (e) Melchiorre, C.; Brasili, L.; Giardina, D.; Pigini, M. *J. Med. Chem.* **1984**, *27*, 1536. (f) Tanaka, H.; Shibata, M.; Ohira, K.; Ito, K. *Chem. Pharm. Bull.* **1985**, *33*, 1419. (g) Fukuyama, Y.; Hasegawa, T.; Toda, M.; Kodama, M.; Okazaki, H. *Chem. Pharm. Bull.* **1992**, *40*, 252. (h) Soukri, M.; Lazar, S.; Akssira, M.; Guillaumet, G. *Org. Lett.* **2000**, *2*, 1557. (i) Labrosse, J. R.; Lhoste, P.; Sinou, D. *Org. lett.* **2000**, *2*, 527. (j) Sweetner; Arnoldi, A.; Bassoli, A.; Merlini, L.; Ragg, E. *J. Chem. Soc., Perkin Trans 1.* **1993**, 1359.

(2) (a) Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C. *J. Org. Chem.* **1997**, *62*, 2611. (b) Tanaka, H.; Shibata, M.; Ohira, K.; Ito, K. *Chem. Pharm. Bull.* **1985**, *33*, 1419. (c) Procopiou, P. A.; Brodie, A. C.; Deal, M. J.; Hayman, D. F. *Tetrahedron Lett.* **1993**, *34*, 7483. (d) Guz, N. R.; Stermitz, F. R.; Johnson, J. B.; Belson, T. D.; Willen, S.; Hsiang, J. Lewis, K. *J. Med. Chem.* **2001** *44*, 261. (e) Li, L.; Hang, T. *Org. Lett.* **2001**, *3*, 739. (f) Ganesh, T.; Davidkrupadanam, G. L. *Synth. Commum.* **1998**, *28*, 3121. (g) She, X.; Jing, X.; Pan, X.; Chan, A. S. C.; Yang, T. K. *Tetrahedron Lett.* **1999**, *40*, 4567. (h) Matsumoto, K.; Takahashi, H.; Miyake, Y.; Fukuyama, Y. *Tetrahedron Lett.* **1999**, *40*, 3185. (i) Gu, W.; Jing, X.; Pan, X.; Chan, A. S. C.; Yang, T. K. *Tetrahedron Lett.* **2000**, *41*, 6079. (j) Arnoldi, A.; Bassoli, A.; Caputo, R.; Merlini, L.; Palumbo, G.; Pedatella, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1241. (k) Tegeler, J.; Org, H. H.; Profih, J. A. *J. Heterocycl. Chem.* **1983**, *20*, 867.

(3) (a) Nair, V.; Mathew, B. *Tetrahedron lett.* **2000**, *41*, 6919. (b) Corsano, S.; Proietti, G.; Castagnino, E.; Strappaghetti, G. *Farmaco Ed. Sci.* **1982**, *38*, 265. (c) Schonberg, A.; Awad, W. I.; Mousa, G. A. *J. Am. Chem. Soc.* **1955**, *77*, 3850.

(4) Kursanov, D. N.; Parnes, Z. N.; Lolm, N. M. *Synthesis* **1974**, 633.

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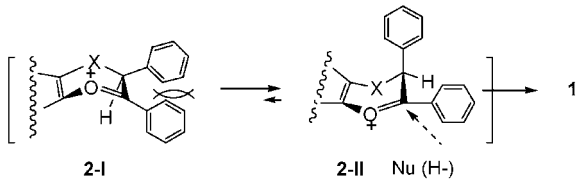
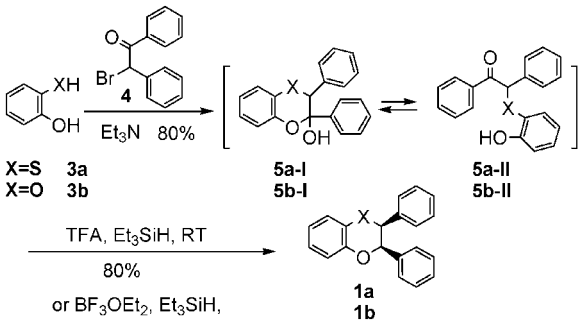
considered to be an important intermediate in organic synthesis, particularly in the most common nucleophilic capture strategies for C−C bond formation[5] (e.g., silicon-containing nucleophiles such as silylenol ethers, silylketene acetals, allylsilanes, etc.). Also, there have been many recent reports concerning the diastereoselective outcome of the incoming nucleophile to the oxocarbonium ion, which appears to be governed by both steric and stereoelectronic factors.[6] We, therefore, postulated that the most stable configuration of the oxocarbonium ion **2** would be **2-II** wherein placement of one of the aryl groups in the pseudo-axial position would alleviate the severe steric interaction of the two aryl groups found in **2-I**. Consequently, the phenyl group at the C-3 position of intermediate **2-II** would then differentiate the approach of the nucleophile to the prochiral oxocarbonium ion, such that hydride delivery away from it,[7] at the more stereoelectronically favorable α face, was anticipated to afford the requisite syn product **1** (Scheme 1).

Scheme 1



Initially, we prepared the simple compounds **5a**/**5b**,[8] according to a reported method,[9] which were reacted with TFA in CH_2Cl_2 containing Et_3SiH at room temperature to give indeed the syn compounds **1a**/**1b** (>99% diastereoselectivity), as no anti isomer was detected, which is described in Scheme 2. BF_3 etherate could also be used, but the former

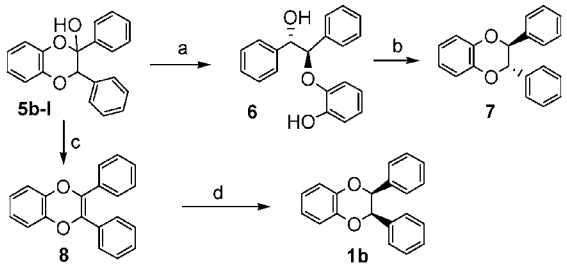
Scheme 2



seemed to give better yields. The structural assignment of **1a** was based on its ^1H NMR spectral data, in which H-2 resonated at δ 5.6 ppm as a doublet (J = 2.2 Hz) and H-3 at 4.46 ppm as a doublet (J = 2.2 Hz). Based on the magnitude of the coupling constant,[10] the aryl groups at C-2,3 were believed to be cis.

Further proof of the cis configuration was provided by an alternative synthesis of **1b**[11] and the corresponding trans isomer **7**, as depicted in Scheme 3.[12] The ^1H NMR of **1b** was quite distinguishable from that of the trans compound **7**, as **1b** exhibited a singlet at δ 5.48 vs 4.5 ppm for **7**.

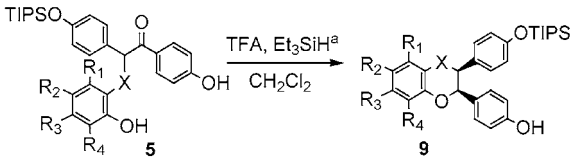
Scheme 3[a]



[a] Reaction conditions: (a) $NaBH_4$, EtOH, quantitative; (b) PPh_3, DIAD, THF, rt, >80%; (c) $SOCl_2$, 40°C, 35%; (d) 10% Pd, H_2, EtOAc, 100%.

Encouraged by this result, we were prompted to further explore the synthetic potential of this process. As illustrated in Table 1, the dehydrative reduction was found to be quite general (>99% diastereoselectivity) and to proceed in good to excellent yield[13] for most of the thioketones. Significant

Table 1. Cyclization of Representative Phenylthioketones

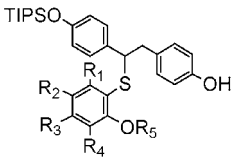


entry	X	R_1	R_2	R_3	R_4	temp (°C)	time (h)	yield[b] (%)
a	S	H	H	BnO	H	rt	10	30[c]
b	S	F	H	BnO	H	rt	10	34[d]
c	S	H	H	BnO	Me	rt	6	55
d	S	Et	H	BnO	H	rt	5	65
e	S	H	H	BnO	Et	rt	5	75
f	S	BnO	H	BnO	H	rt	4	50
g	S	H	BnO	H	H	0	2	85[e]
h	S	F	BnO	H	H	0	10	73
i	S	H	BnO	H	Cl	0	3	85
j	S	H	BnO	H	Me	0	2	91
k	S	Br	BnO	Br	H	0	20	80

[a] Reaction conditions: 10 equiv of TFA and 3−4 equiv of Et_3SiH in CH_2Cl_2 (ca. 0.05 M). [b] All cases showed total diastereoselectivity (>99:1) with J_{H-H} = 2.2 Hz. [c] Low yield may be due to the formation of over-reduced products such as **10**. [d] Mostly starting material was recovered. [e] Trans isomer synthesized by an independent route showed a large coupling constant (J_{H-H} = 9.0 Hz).

(5) (a) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc*. **2000**, *122*, 168. (b) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 447. (c) Hoffmann, R. W. *Chem. Rev*. **1989**, *89*, 1841. (d) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043.

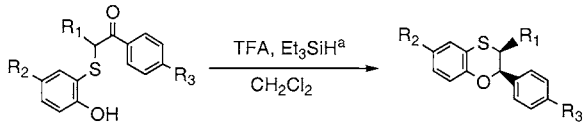
electronic effects, however, were observed depending upon the substituents. For example, *meta*-benzyloxy-substituted phenolic thioketones (entries a−f) gave typically lower yields and required longer reaction times, due perhaps to the inductive effect of the substituent, which resulted in reduced nucleophilicity of the phenol. Similar inductive effects were also observed for the reaction of fluoro-substituted thioketones (entries b and h[14]). On the other hand, *para*-benzyloxy-substituted phenolic thioketones exhibited dramatic differences in yield and rate (entries g−k), presumably due to the electron donation to the phenol, thus enhancing the rate of cyclization in the first step. Interestingly, the yield of this process could also be greatly improved by the addition of alkyl groups (entries c−e and j), which inferred that the reaction could be influenced by steric factors as well as electronic factors. In those cases examined, wherein the rate of cyclization was slow, the major byproduct was identified as **10**.[15]



10: R_5=H or TES

Having succeeded in our original goal, we then focused on the extension of the optimal cyclization process to other thioketones in which both heteroaromatic and various alkyl groups would be located at the eventual pendant position of the benzoxathiin. As shown in Table 2, the cyclization was effective for electron-rich heteroaromatics (entries 1 and 2) and also proceeded with high diastereoselectivity. However, the reaction with pyridine-substituted thioketones (entries 3 and 4) required extended times and gave relatively poor yields, suggesting a possible enolization of the ketone, assisted by the electron-deficient pyridinium substituent, thereby hampering nucleophilic addition of the phenol to the carbonyl group.

Table 2. Cyclization of Representative Thioketones



entry	R_1	R_2	R_3	temp (°C)	time (h)	yield[a] (%)
1		OH	OTIPS	rt	1.5	90
2		OH	OTIPS	0	4	77
3		BnO	OTIPS	rt	20	45
4		BnO	OTIPS	0 to rt	5	43
5		BnO	OH	-40	1	90
6		OH	OH	-20	2	90
7	H	BnO	OTIPS	-23	0.5	73[b]
8	Methyl	BnO	OTIPS	-23	1	77[c]
9	Ethyl	BnO	OTIPS	-23	0.75	72[d]
10	i-Propyl	BnO	OH	-20	7	76[e]
11	t-Butyl	OH	OTIPS	-40	9	76
12	i-Butyl	OH	OTIPS	-40 to -10	2	92
13		OH	OTIPS	-40 to -10	2	95
14		BnO	OH	-30 to -20	19	60
15		OH	OH	-20	2	90[f]

[a] See Table 1 or as indicated. [b] With 20% over-reduction product (ORP). [c] With 12% ORP. [d] With 17% ORP. [e] Cis:trans = 20:1. [f] Cis:trans = 11:1.

(6) 1,3-Stereoselectivity: (a) Colobert, F.; Mazery, R. D.; Solladie, G.; Carreno, M. C. *Org. Lett.* **2002**, *4*, 1723. (b) Ghosh, A.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027. (c) Paquette, L. A.; Barriault, L.; Pissarnitski, D. *J. Am. Chem. Soc.* **1999**, *121*, 4542. (d) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208. (e) Jaouen, V.; Jegou, A.; Lemee, L.; Veyrieres, A. *Tetrahedron* **1999**, *55*, 9245. (f) Jaouen, V.; Jegou, A.; Lemee, L.; Veyrieres, A. *Tetrahedron* **1999**, *55*, 9245. (g) Mukaiyama, T.; Shimpuku, T.; Takashima, T.; Kobayashi, S. *Chem. Lett.* **1989**, 145. (h) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983, 209. (i) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (j) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032.

(7) Kraus observed that axial delivery of hydride (Et_3SiH) to a cyclic oxoniumion was favored to avoid $A^{1,2}$ strain; see: (a) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Chem. Soc., Chem. Commum.* **1986**, 1568. (b) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273.

(8) For **5a**, the major tautomeric form would be **5a-II**; γ(CO and OH) 1675, 3391 cm^{-1} (see: Shtsuka, Y.; Oishi, T. *Chem. Pharm. Bull.* **1983**, *31*, 443). For **5b**, the major tautomeric form would be **5b-I** (see: Dzvinchuk, I. B.; Lozinskii, M. O. *Zh. Org. Khim.* **1991**, *27*, 560).

(9) (a) Ganesh, T.; Kumar, H.; Krupadanam, G. L. *Synth. Commum.* **1999**, *29*, 2069 and references therein. The functionalized thiophenols **3** were prepared by the known procedure with minor modifications. (b) Werner, G.; Biebrich, W. U.S. Patent 2,276,553; 2,332,418. (c) Hanzlik, R. P.; Weller, P. E.; Desai, J.; Zheng, J.; Hall, L. R.; Slaughter, D. E. *J. Org. Chem.* **1990**, *55*, 2736.

(10) The coupling constant for the trans isomers in related compounds is in the range of 7−9 Hz, while the cis isomers exhibit couplings of 2−3 Hz (see refs 1g, 2b, and: Pfundt, G.; Farid, S. *Tetrahedron* **1966**, *22*, 2237). The trans isomer that was independently synthesized (see ref 2j) exhibited a large coupling constant (J = 9.0 Hz) for H2,3.

(11) In contrast, hydrogenation of the analogous benzoxathiin returned only starting material (>90%), even at high pressures, presumably due to catalyst poisoning by the sulfur atom.

(12) (a) Adam, W. et al. *J. Org. Chem.* **1984**, *49*, 3920. (b) Procopiou, P. A. et al. *Tetrahedron Lett.* **1993**, *34*, 7483.

(13) Typical procedure is exemplified for the synthesis of **9g**: To a flask charged with thioketone **5g** (1.35 g, 2.2 mmol) in dichloromethane (ca. 0.04 M) at 0 °C under an atmosphere of nitrogen was added slowly TFA (1.8 mL, 10 equiv). Then, neat Et_3SiH (1.3 mL, 4 equiv) was slowly added and the reaction mixture was stirred until starting material was consumed as monitored by TLC. The reaction mixture was poured into saturated $NaHCO_3$−ice water, stirred for 10 min, and extracted with dichloromethane. The organic extract was washed with brine (2 × 100 mL), dried over Na_2SO_4, and concentrated in vacuo to afford a light yellow oil. Purification via flash chromatography (1:5 EtOAc−hexanes) provided 1.15 g (85%) of **9g** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.5−7.3 (m, 5H), 6.94 (d, 1H), 6.85 (d, 2H), 6.84 (d, 1H), 6.80 (d, 2H), 6.74 (dd, 1H), 6.65 (d, 2H), 6.64 (d, 2H), 5.43 (d, J = 2.1 Hz, 1H), 5.05 (s, 2H), 4.30 (d, J = 2.1 Hz, 1H), 1.23 (m, 3H), 1.10 (d, 18H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.7, 155.4, 153.9, 146.9, 137.3, 131.3, 131.0, 130.4, 128.8, 128.3, 128.2, 127.8, 119.7, 119.5, 114.9, 112.9, 112.1, 79.4, 70.9, 47.9, 18.2, 12.9; MS m/z 599.1 (M^+), 359.

(14) For the preparation of the fluoro-substituted thiophenol **3h**, see: Watanabe, M.; Date, M.; Tsukazake, M.; Furukawa, S. *Chem. Pharm. Bull.* **1989**, *37*, 36.

Although the cyclization reaction effected excellent control of diastereoselectivity for the majority of the substrates, the reaction occasionally gave some trans product (5−10%) [entries 10 and 15], which in entry 10 was shown to be temperature dependent, since raising the temperature to 0−10 °C increased the amount of the trans isomer to 33%. The success of the reaction was also dependent on the acid stability of the phenolic covering groups, wherein triisopropylsilyl and benzyl ethers, as well as acetate, were compatible with the standard reaction conditions, whereas, MOM and MEM groups suffered hydrolysis during the course of reaction.

In summary, the method described herein provides a high-yielding, mechanism-based synthesis of dihydrobenzoxathiins and benzodioxanes, and, in most instances, with total diastereoselective control. The application of this method for the synthesis of more complex, biologically active derivatives with an affinity for estrogen receptors will be reported in due course.

(15) We have shown that this product does not arise from the starting material **5**. For example, exposure of the silylated ketone, corresponding to entry 8 in Table 2, to the reaction conditions or at higher temperatures ranging from zero degrees to room temperature failed to yield any appreciable quantity of the analogous reduction product. Related experiments have also eliminated the product as the source and suggest the involvement of an intermediate leading to the oxonium species as the potential source.

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