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10-Hydroxy-10,9-boroxarophenanthrenes: Versatile Synthetic Intermediates to 3,4-Benzocoumarins and Triaryls

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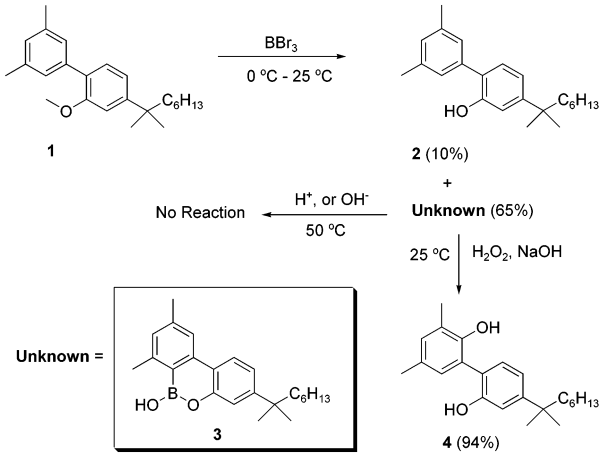
Abstract: 10-Hydroxy-10,9-boroxarophenanthrenes were obtained as unexpected major products upon BBr_3-mediated *O*-demethylation of 2-methoxybiaryls. The formation likely proceeds via intramolecular electrophilic aromatic cyclization of a reactive dibromoaryloxyborane intermediate. Essentially quantitative yields of 10-hydroxy-10,9-boroxarophenanthrenes were also obtained from 2-hydroxybiaryl and BCl_3/$AlCl_3$ with use of a modified literature procedure. As synthetic intermediates, 10-hydroxy-10,9-boroxarophenanthrenes were efficiently converted to 3,4-benzocoumarins and triaryls through Pd-catalyzed CO insertion and Suzuki reaction.

While carrying out the *O*-demethylation of **1** with BBr_3 under standard reaction conditions, we anticipated its clean conversion to cannabinoid mimetic **2** (Scheme 1).[1] To our surprise, an unknown compound **3** was isolated in 65% yield while the desired product **2** was isolated in only ~10% yield. Although the demethylation reaction was later accomplished in high yield with use of TMSI, we were intrigued by what had transpired during the BBr_3 treatment and by the structure of the anomalous product.

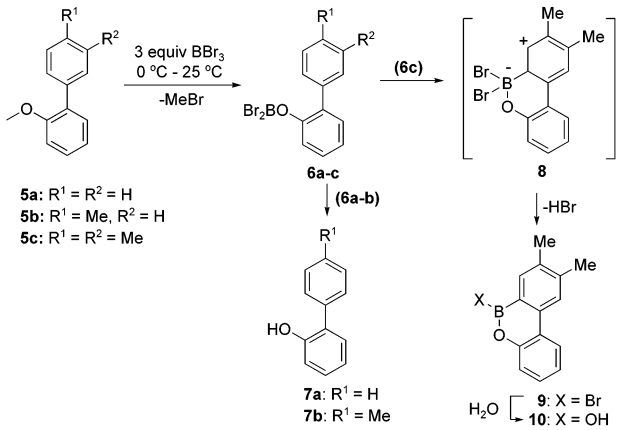
LC/MS analysis revealed that the unknown product was a single compound containing one boron atom. The material was stable to both strong aqueous acid and base at 50 °C. It was smoothly transformed via oxidative hydrolysis to a second unknown (94% yield), which was readily identified as 2,2′-dihydroxybiphenyl **4** by ^{1}H NMR, ^{13}C NMR, and LC/MS analysis (Scheme 1). This latter transformation indicated that the boron atom was attached directly to an aryl carbon atom. From these and spectroscopic studies, the unknown compound was assigned structure **3**, a substituted 10-hydroxy-10,9-boroxarophenanthrene.[2]

To investigate the unexpected formation of **3** further, we prepared 2-methoxybiphenyls **5a**−**c** (Scheme 2), and subjected them to the same reaction conditions as compound **1**. Interestingly, **5a**,**b** gave the anticipated phenols **7a**,**b** (100% yield), while **5c** furnished **10** in quantitative yield. It was clear that a 3′-methyl substituent was required to facilitate boroxarene formation. The reaction mechanism is believed to proceed through a common dibromophenoxyborane intermediate (**6**) which, in the absence of the 3′-methyl group (**6a**,**b**), hydrolyzes to give phenol. In the presence of the 3′-methyl group (**6c**), an alternative pathway ensues: intramolecular electrophilic aromatic substitution, re-aromatization upon loss of HBr, then hydrolysis (**8** → **9** → **10**). The strict electronic requirement within the biaryl substrate may explain why boroxarene formation has never been reported as a side reaction during BBr_3-mediated *O*-demethylation.

SCHEME 1



SCHEME 2



The parent boroxarene **13** was previously prepared by Dewar[3] in 1960 upon treatment of 2-phenylphenol **7a** with BCl_3 gas in hexane followed by the addition of $AlCl_3$ (Scheme 3). Bridger[4] subsequently found that the stepwise addition of reagents was unnecessary. The yield in both reports was ca. 65%. Boroxarenes have found limited application in the literature, including their use as antioxidant lubricant additives,[5] Lewis acids for the aldol condensation,[6] and fungicides.[7] However, there are no reports employing boroxarenes as synthetic intermediates.

(1) (a) Worm, K. I.; Zhou, Q. J.; Dolle, R. E. *Solid-Phase Approach To Biaryl Cannabinoid Mimetics*; Abstracts of the 224th National Meeting of the American Chemical Society, Boston, MA; American Chemical Society: Washington, DC, 2002; ORGN 163. (b) Gareau, Y.; Dufresne, C.; Gallant, M.; Rochette, C.; Sawyer, N.; Slipetz, D. M.; Tremblay, N.; Weech, P. K.; Metters, K. M.; Labelle, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 189−194.

(2) This class of compound is collectively referred to herein as boroxarenes.

(3) Dewar, M. J. S.; Dietz, R. J. *J. Chem. Soc.* **1960**, 1344.

(4) Bridger, R. F. U.S. Patent 4 210 599, 1980.

(5) Braid, M. U.S. Patent 4 353 807, 1982.

(6) Davis, F. A.; Dewar, M. J. S. *J. Org. Chem.* **1968**, *8*, 3324.

(7) Kohn, G. K.; McMurtry, R. J. U.S. Patent 3 686 398, 1972.

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SCHEME 3

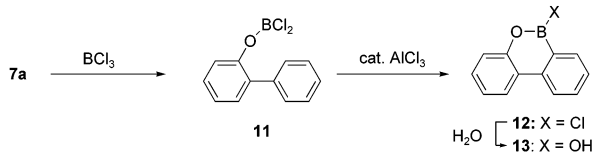
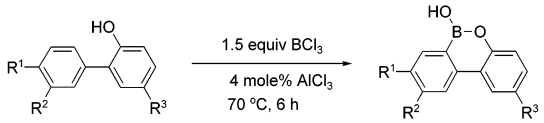
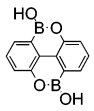
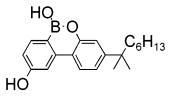


TABLE 1. Results of Boroxarene Formation



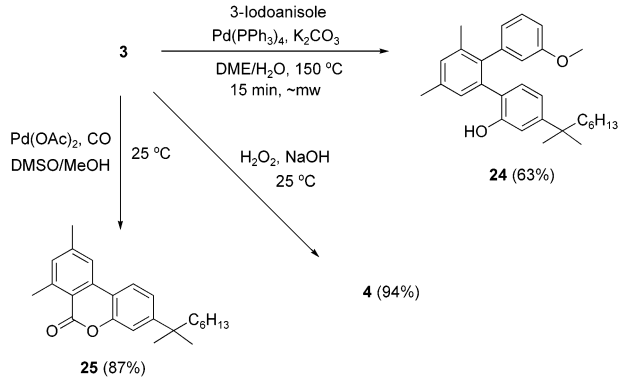
boroxarene	R^1	R^2	R^3	yield (%)
13	H	H	H	99[a,b]
14	H	CH_3	H	98[a]
15	CH_3	H	H	98[a]
16	H	H	CH_3	96[a]
17	H	H	F	99[a]
18	Cl	H	H	15[c]
19	F	F	H	0[c]
20	H	CH_3	H	0[c]
21	F	CH_3	H	80[c]
22				0[c,d]
23				80[e]

[a] Isolated yield. [b] Identical yield was obtained from 2-methoxybiphenyl with 3 equiv of BCl_3. [c] Determined by LC/MS. [d] 3 equiv of BCl_3, 8 mol % of $AlCl_3$, 90 °C. [e] From 4-(1,1′-dimethylheptyl)-3′-methoxy-biphenyl-2-ol, using 3 equiv of BCl_3.

In an attempt to have broader access to boroxarenes to evaluate their potential utility in synthesis, we reinvestigated the original literature procedure for the preparation of **13**. After a thorough study, we developed an optimized procedure. The literature's one-pot protocol slowly passed BCl_3 gas into a solution of **7a** in hexane at room temperature (Scheme 3). Under these conditions BCl_3 is initially the limiting reagent and the putative intermediate 2-biphenyl chloroboronite **11** may react with the starting material to form a boronate dimer/trimer (the major side product of the reaction). The undesired dimer/trimer cannot undergo intramolecular cyclization to form boroxarene, but rather is hydrolyzed upon aqueous workup regenerating starting phenol. We reasoned that by keeping BCl_3 in excess throughout the reaction, this may minimize dimer/trimer formation and potentially improve the reaction yield. When this small modification in protocol was carried out, i.e., the addition of the phenol **7a** into a dilute solution of BCl_3 in hexane (ca. 0.1 M) followed by addition of $AlCl_3$ (~4 mol %), a quantitative yield of **13** was obtained. Strict control of anhydrous conditions as well as the use of fresh reagents was essential for a successful reaction. The optimized reaction conditions were then applied to a range of 2-arylphenols.

Table 1 displays the substrates and the yields of the corresponding boroxarenes. The presence of an electron-withdrawing group (EWG) in the pendent aryl ring where

SCHEME 4



electrophilic substitution occurs has a strong negative effect on the cyclization process, resulting in either marginal or no production of boroxarene (**18**, **19**, **20**). The presence of an electron-donating group (EDG) *para* to the site of electrophilic attack dramatically counteracts the influence of an EWG group as observed for the formation of **21** (80% versus 0% for **19**). In contrast, the presence of an EWG or an EDG in the phenolic ring has no influence on boroxarene synthesis (**16**, **17**). The failure to isolate bisboroxarene **22** (recovered starting material only) may result from unfavorable steric interactions of the putative 2,2′-bis(dichloroboronite)biphenyl and/or lack of electron-donating substituents as a driving force. Finally, the exclusive formation of products **14** and **21**[8] serves to demonstrate the regioselectivity of the intramolecular cyclization (less hindered sp^2 carbon atom).

Scheme 4 displays three chemical transformations of boroxarene **3**. The oxidative hydrolysis, which was mentioned in Scheme 1, converted **3** into 2,2′-dihydroxy compound **4** with 94% yield. Suzuki coupling with 3-methoxyphenyl iodide gave triaryl derivative **24** in 63% yield, despite the potential for steric hindrance. This particular reaction was carried out in the microwave; however, we did not find a dramatic difference between conventional heating methods and microwave conditions. Palladium-catalyzed carbonylation occurred in good yield as evidenced by isolation of the tricyclic lactone **25** (87% yield). None of the putative intermediate methyl ester was observed, suggesting facile conversion to the benzocoumarin ring system under the reaction conditions.

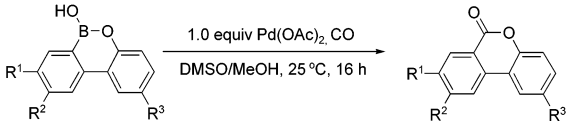
This preliminary success in using boroxarene **3** as a synthetic intermediate encouraged us to evaluate similar transformations for the boroxarenes listed in Table 1.

3,4-Benzocoumarin **26** and its derivatives are naturally occurring biologically active agents possessing valuable pharmaceutical properties.[9] Previous synthetic approaches to 3,4-benzocoumarins employed either strong oxidative conditions[10] or elaborate preconstruction of appropriately functionalized precursors in such a way that the final step (benzocoumarin formation) could be carried out in a mild and selective fashion.[11] As summarized in Table

(8) Structures were confirmed by ^1H NMR, ^{13}C NMR, and MS. See Supporting Information.

(9) (a) Gringauz, A. *J. Pharm. Sci.* **1976**, *65*, 291. (b) Liu, H.; Santostefano, M.; Lu, Y.; Safe, S. *Organohalogen Compd.* **1993**, 13. (c) Weidner-Wells, M. A.; Altom, J.; Fernandez, J.; Fraga-Spano, S. A.; Hilliard, J.; Ohemeng, K.; Barrett, J. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 97. (d) Douros, J. D., Jr.; McNelis, E. J. U.S. Patent 3 248 286, 1966.

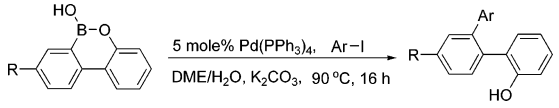
TABLE 2. Results of Carbonylation



product	R^1	R^2	R^3	yield (%)
26	H	H	H	90[a]
27	H	CH_3	H	100[a,b]
28	CH_3	H	H	96[a]
29	H	H	CH_3	80[a]
30	H	H	F	99[a]
31	Cl	H	H	95[c]

[a] Isolated yield. [b] Identical yield was obtained by using 10 mol % of $Pd(OAc)_2$, 20 mol % of DPPF, and 3 equiv of Et_3N. [c] Determined by LC/MS.

TABLE 3. Results of Triaryl Formation



product	R	Ar	yield (%)
32	CH_3	Ph	81[a]
33	H	*m*-CHO-Ph	65[b]
34	H	*p*-MeO-Ph	64[b]

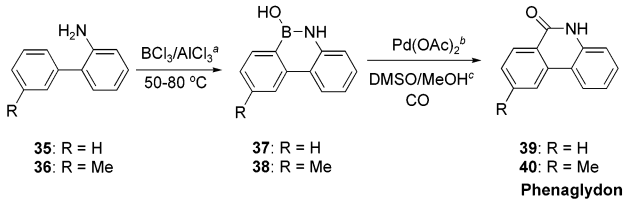
[a] Isolated yield. [b] Determined by LC/MS.

2, the Pd-catalyzed CO insertion of boroxarenes provides an alternative method for their construction under mild conditions with high regioselectivity. In this reaction, 1 equiv of $Pd(OAc)_2$ was used and the reactions were essentially complete within 2−4 h, affording 3,4-benzocoumarins in excellent yields. Little or no purification was needed other than a simple aqueous workup and filtration. This reaction proceeds with equal ease and efficiency with use of a catalytic amount of the $Pd(OAc)_2$ (10 mol %) accompanied by DPPF (20 mol %).

The Pd-catalyzed Suzuki coupling of boroxarene was likewise straightforward. Three additional examples **32**−**34** were carried out under conventional conditions with results virtually identical with those found for **24** as summarized in Table 3.

The optimized reaction conditions were also applied to 2-aminobiphenyls (**35** and **36**), attempting to prepare the

SCHEME 5



[a] 2−3 equiv of BCl_3, 4−8 mol % of $AlCl_3$, 50−80 °C for 16 h. [b](1) 10 mol % of $Pd(OAc)_2$, 20 mol % of DPPF, Et_3N; (2) 1 equiv of $Pd(OAc)_2$. Both conditions gave similar results. [c]When R = Me, heating in acetic acid at 50 °C for 16 h resulted in 49% yield.

10-hydroxy-10,9-borazarophenanthrenes **37** and **38** (Scheme 5). Quantitative conversion was achieved under relatively forcing conditions (2−3 equiv of BCl_3, 4−8 mol % of $AlCl_3$, 50−90 °C, 16 h). However, the borazarenes so obtained showed aggregate characteristics: higher masses present in the LC/MS and complex proton NMR spectra. Carbonylation of these aggregates generated the desired lactams **39** and **40** in only 17% yield as determined by LC/MS.

Harris *et al*. reportedly isolated monomer **37** by recrystallizing from 50% aqueous acetic acid.[12] Considering this, the carbonylation of **38** was carried out in acetic acid at 50 °C overnight. The yield of lactam **40** significantly increased to 49%. Lactam **40** is a natural product known as phenaglydon that was subsequently isolated and its structure was confirmed by comparing the ^1H and ^{13}C NMR and MS of the synthetic material with the literature data.[13]

In summary, we demonstrated regioselective boroxarene formation from 2-hydroxybiphenyl and 2-methoxybiphenyl under mild conditions. As synthetic intermediates, boroxarenes were converted to 3,4-benzocoumarins through CO insertion and triaryls through Suzuki coupling. Application of this chemistry to commercially available 3′-methyl-biphenyl-2-ylamine resulted in an efficient two-step synthesis of phenaglydon.

Acknowledgment. We thank Clay Rutledge and Bill Barker for their valuable NMR and LC/MS service.

Supporting Information Available: Experimental details for compounds **3**, **4**, **7a**, **7b**, **10**, **13**−**18**, **21**, **23**-**34**, and **37**−**40**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049343W

(10) Migachev, G. I.; Andrievskii, A. M.; Poplavskii, A. N.; Dokunikhin, N. S. U.S. Patent 591 473, 1978. (b) Olah, G. A.; Wang, Q.; Trivedi, N. J.; Prakash, G. K. S. *Synthesis* **1991**, *9*, 739.

(11) Harayama, T.; Yasuda, H. *Heterocycles* **1997**, *46*, 61.

(12) Harris, K. D. M.; Kariuki, B. M.; Lambropoulos, C.; Philp, D.; Robinson, J. M. A. *Tetrahedron* **1997**, *53*, 8599.

(13) Wurz, G.; Hofer, O.; Greger, H. *Nat. Prod. Lett.* **1993**, *3*, 177.