Benzannulation of Stannylquinones. A New Regiocontrolled Construction of Substituted Naphtho- and Anthraquinones

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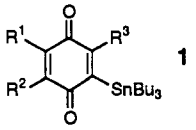
Recently, stannylquinones **1** have been shown to be versatile nucleophilic quinone synthons. These compounds hold great



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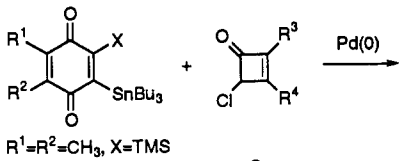
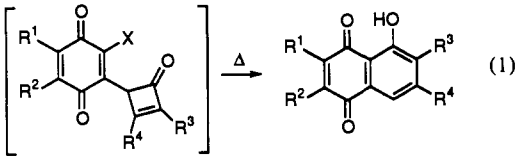
promise for use in the construction of complex quinones by direct carbon–carbon bond formation onto the quinone nucleus using palladium-catalyzed cross-coupling technology.[2-4] It has already been shown that stannylquinones undergo palladium-catalyzed allylation,[5] oxidative dimerization,[6] and cross-coupling with substituted aromatic and heteroaromatic iodides.[7] In this communication is documented a conceptually new synthesis of substituted 1,4-naphthoquinones and 9,10-anthraquinones which uses a palladium-catalyzed coupling of stannylquinones with 4-chlorocyclobutenones (eq 1). This new quinone construction



1a: $R^1=R^2=CH_3$, X=TMS
1b: $R^1=R^2$=benzo, X=TMS
1c: R^1=*i*-PrO, $R^2=CH_3$, X=H

2



3 **4**

(1)

is presumed to occur by formation of the cyclobutenone intermediate **3** shown in eq 1 which rearranges on gentle thermolysis to the benzannulated quinone **4**. This new process joins a growing family of synthetic methods based on cyclobutenone transformations that provide oxygenated aromatics and substituted quinones[5,7-30] bearing substitution patterns not easily established using traditional methods of synthesis.[31-33]

The requisite stannylquinones were produced by two complementary routes. Stannylquinones **1a** and **1b** were prepared by the Bu_3SnOCH_3-mediated thermolysis of 4-hydroxy-2,3-dimethyl-4-(2-(trimethylsilyl)ethynyl)cyclobutenone and 2-hydroxy-2-(2-(trimethylsilyl)ethynyl)benzocyclobutenone as described earlier.[5] The C(3) trimethylsilyl group provided enhanced stability to the stannylquinone. Stannylquinone **1c** was obtained by addition of lithium 2-(tri-*n*-butylstannyl)acetylide to 3-isopropoxy-4-methylcyclobutenedione followed by thermolysis of the intermediate 4-alkynyl-4-hydroxy-2-cyclobutenone.[18,34] Although it lacked the trimethylsilyl blocking group at C(3), stannylquinone **1c** was sufficiently stable to allow purification and handling for short periods of time.

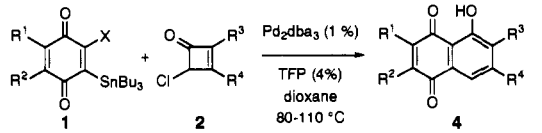
Treatment of equimolar **1a** and 4-chlorocyclobutenone **2a**[10] ($R^3=CH_3$, R^4 = *i*-PrO) in dioxane with Pd_2dba_3 (1 mol %) and tris(2-furyl)phosphine (4 mol %) followed by heating to 80–85 °C for 2–4 h and then heating at 100 °C for 1–2 h afforded the pentasubstituted naphthoquinone **4a** in 81% isolated yield (Table I, entry 1). Similarly, stannylquinones **1b** and **1c** coupled cleanly with a variety of 4-chlorocyclobutenones,[8,10] affording quinones **4b-4j** in 74–95% yield. The highly hindered substrate **2c**, bearing a *tert*-butyl group at C(2), required heating at 100 °C for 16 h to effect complete coupling but still afforded anthraquinone **4f** in 77% yield. The products derived from **1a** and **1b** were produced primarily as their trimethylsilyl ethers, with traces of the free phenol observed. An aqueous KF workup was employed to transform all of the product to the unprotected phenol. In all cases examined, a single quinone regioisomer was observed, resulting from exclusive coupling at the least-substituted terminus of the putative π-allyl palladium intermediate.[8-10] As can be seen from the examples in Table I, the quinone synthesis is quite general, tolerating dialkyl, alkylaryl, and alkylalkoxy substitution patterns on the 4-chlorocyclobutenone.

A convergent synthesis of hexasubstituted anthraquinones was also developed, exploiting the recently reported method for the construction of highly substituted benzocyclobutenediones (Scheme I).[8] Protection of the C(3) oxygen of benzocyclobutenedione **5**[8] as the *tert*-butyldimethylsilyl ether (TBSCl, DMAP, imidazole, CH_2Cl_2) was expected to direct nucleophilic addition to C(1) with high selectivity.[35] Indeed, slow addition of lithium (tri-

(1) National Institutes of Health Postdoctoral Fellow, 1991–1993.
(2) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.
(3) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
(4) Mitchell, T. N. *Synthesis* **1992**, 803.
(5) Liebeskind, L. S.; Foster, B. F. *J. Am. Chem. Soc.* **1990**, *112*, 8612.
(6) Liebeskind, L. S.; Riesinger, S. W. *Tetrahedron Lett.* **1991**, *32*, 5681.
(7) Liebeskind, L. S.; Riesinger, S. W. *J. Org. Chem.* **1993**, *58*, 408.
(8) Edwards, J. P.; Krysan, D.; Liebeskind, L. S. *J. Org. Chem.* **1993**, *58*, 3942.
(9) Liebeskind, L. S.; Wang, J. *J. Org. Chem.* **1993**, *58*, 3550.
(10) Krysan, D. J.; Gurski, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 1412.
(11) Lee, K. H.; Moore, H. W. *Tetrahedron Lett.* **1993**, *34*, 235.
(12) Gayo, L. M.; Winters, M. P.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896.
(13) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 326.
(14) Xu, S.; Yerxa, B. R.; Sullivan, R. W.; Moore, H. W. *Tetrahedron Lett.* **1991**, *32*, 1129.
(15) Heerding, J. M.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 4048.
(16) Enhsen, A.; Karabelas, K.; Heerding, J. M.; Moore, H. W. *J. Org. Chem.* **1990**, *55*, 1177.
(17) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 1897.
(18) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975.
(19) Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149.
(20) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.
(21) Danheiser, R. L.; Cha, D. D. *Tetrahedron Lett.* **1990**, *31*, 1527.
(22) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693.
(23) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, *29*, 4917.
(24) Liebeskind, L. S.; Granberg, K. L.; Zhang, J. *J. Org. Chem.* **1992**, *57*, 4345.
(25) Liebeskind, L. S.; Zhang, J. *J. Org. Chem.* **1991**, *56*, 6379.
(26) Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1991**, *113*, 2771.
(27) Liebeskind, L. S. *Tetrahedron* **1989**, *45*, 3053.
(28) Durst, T.; Breau, L. Cyclobutene Ring Opening Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 6, pp 675.
(29) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821.
(30) Moore, H. W.; Yerxa, B. R. *Chemtracts: Org. Chem.* **1992**, *5*, 273.
(31) Thomson, R. H. *Naturally Occurring Quinones III*; Chapman and Hall: London, 1987; Vol. III.
(32) Thomson, R. H. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons, Inc.: New York, 1992; Vol. 8, pp 311.
(33) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455.
(34) All new compounds were spectroscopically characterized and furnished adequate elemental analysis (C, H ± 0.4%) or high-resolution mass-spectral data. Details are provided in the supplementary material.
(35) Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* **1986**, *51*, 3065.

0002-7863/93/1515-9868$04.00/0

Table I. Synthesis of Naphthoquinones and Anthraquinones

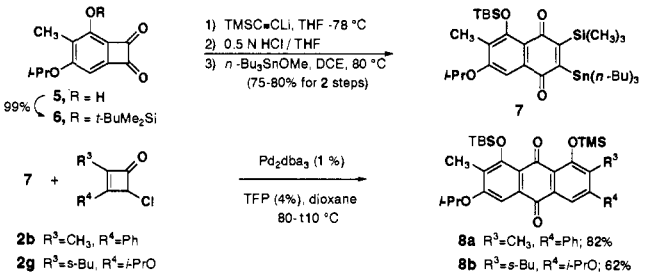


1 2 4

entry	R^1	R^2	R^3	R^4	1	2[a]	product	yield, %
1	CH_3	CH_3	CH_3	*i*-PrO	**1a**	**2a**	**4a**	81
2	CH_3	CH_3	CH_3	Ph	**1a**	**2b**	**4b**	74
3	*i*-PrO	CH_3	CH_3	*i*-PrO	**1c**	**2a**	**4c**	77
4	*i*-PrO	CH_3	CH_3	Ph	**1c**	**2b**	**4d**	81
5	benzo		CH_3	*i*-PrO	**1b**	**2a**	**4e**	75
6	benzo		*t*-Bu	*i*-PrO	**1b**	**2c**	**4f**	77
7	benzo		Ph	*i*-PrO	**1b**	**2d**	**4g**	76
8	benzo		CH_3	Ph	**1b**	**2b**	**4h**	82
9	benzo		Ph	CH_3	**1b**	**2e**	**4i**	94
10	benzo		Et	Et	**1b**	**2f**	**4j**	95

[a] For the synthesis of **2a**, **2b**, and **2e** see ref 10; for **2c**, **2d**, and **2f** see ref 8.

Scheme I



methylsilyl)acetylide to **6**, isolation of the crude 1,2-addition product, and then thermolysis in the presence of *n*-Bu_3SnOCH_3 (dichloroethane, reflux, 15 min) afforded stannylnaphthoquinone **7** in 75–85% yield and with >30:1 regioselectivity (Scheme I). Palladium-catalyzed coupling of **7** and **2b** proceeded smoothly to afford an 82% yield of anthraquinone **8a** as a 25:1 mixture of regioisomers. Interestingly, silyl group transfer was very efficient, and the resulting anthraquinone thus has three differently protected hydroxyls. The reaction of **7** with the more sterically demanding 4-chlorocyclobutenone **2g**,[8] bearing a *sec*-butyl group at C(2), was sluggish, and the longer reaction time (18 h at 85 °C) resulted in a lower yield (62%) of **8b**.

In conclusion, a general and regiocontrolled benzannulation approach to the synthesis of substituted naphthoquinones and anthraquinones from stannylquinones and 4-chlorocyclobutenones has been developed. The growing list of substitution patterns available for cyclobutenediones and benzocyclobutenediones,[8,14,36-46] the precursors to the reactants used above, bodes well for the potential utility of this process. Efforts to expand the generality of this new preparation of quinones and applications to natural product synthesis are currently in progress.

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Supplementary Material Available: Details of experimental procedures (11 pages). Ordering information is given on any current masthead page.

(36) Ohno, M.; Yamamoto, Y.; Shirasaki, Y.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 263.
(37) Liebeskind, L. S.; Yu, M. S.; Fengl, R. W. *J. Org. Chem.* **1993**, *58*, 3543.
(38) Sidduri, A.; Budries, N.; Laine, R. M.; Knochel, P. *Tetrahedron Lett.* **1992**, *33*, 7515.
(39) Liebeskind, L. S.; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293.
(40) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359.
(41) Liebeskind, L. S.; Wirtz, K. R. *J. Org. Chem.* **1990**, *55*, 5350.
(42) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482.
(43) Reed, M. W.; Pollart, D. J.; Perri, S. T.; Foland, L. D.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477.
(44) Schmidt, A. H.; Künz, C. *Synthesis* **1991**, 78.
(45) Liebeskind, L. S.; Lescosky, L. J.; McSwain, C. M., Jr. *J. Org. Chem.* **1989**, *54*, 1435.
(46) South, M. S.; Liebeskind, L. S. *J. Org. Chem.* **1982**, *47*, 3815.