Direct Synthesis of 5-Substituted Naphthoquinones

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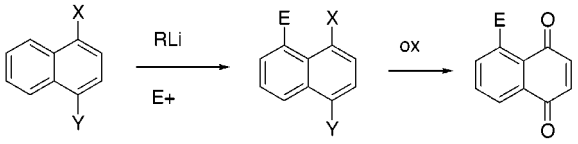
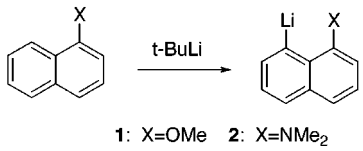
Abstract: Peri-metalation of 4-(dimethylamino)-1-*tert*-butyldimethylsilyloxynaphthalene (**5**) followed by reaction with an electrophile and Jones' oxidation affords 5-substituted naphthoquinones.

In the context of our studies on the regioselective Diels−Alder reactions of substituted quinones, we required a direct and versatile preparation of 5-substituted naphthoquinones.[1] Although a wealth of procedures have been reported for the synthesis of 2-substituted or 2,3-disubstituted naphthoquinones, there are very few general methods for the synthesis of 5-substituted naphthoquinones.[2−4] We evaluated peri-metalation as a strategy for constructing 5-substituted naphthoquinones and report our results herein. Our basic strategy is shown below.

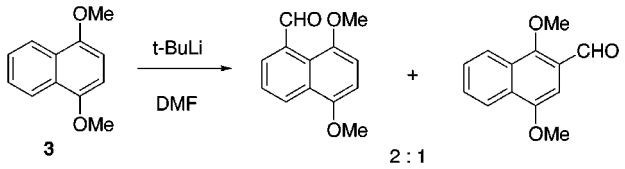


Barnes and Kirby have reported that 1-methoxynaphthalene (**1**) and 1-dimethylaminonaphthalene (**2**) can be selectively metalated at the 8-position using *tert*-butyllithium.[5,6] A synthesis of 5-substituted naphthoquinones could be realized if oxidation to the quinone could be achieved. In view of the results shown below, we studied the metalation of 1,4-dimethoxynaphthalene (**3**), a ready precursor to a naphthoquinone. Unfortunately, the selectivity for peri-metalation (as evidenced by trapping with DMF) was reduced to 2:1.

We reasoned that the attenuated selectivity relative to **1** was due to the inductive effect of the 4-methoxyl group enhancing metalation at C-2. Because 4-amino-1-naphthol is readily available, we converted it into **4** using acetic acid, paraformaldehyde, and sodium cyanoborohydride in 84% yield according to the method of Gribble.[7]

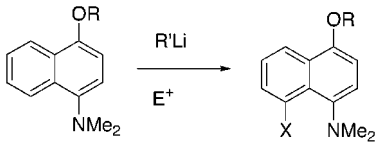


1: X=OMe **2**: X=NMe$_2$



3 2 : 1

Unfortunately, attempted metalation of **4** using 2.2 equiv of *tert*-butyllithium in ether over 48 h led to a complex mixture of products. The phenol was then protected as the TBS ether **5** using TBSCl and sodium hydride in THF. Metalation of **5** using *tert*-butyllithium in cyclohexane for 72 h at ambient temperature followed by trapping with methyl iodide led to a 54% yield of **6** (X = Me) plus recovered starting material. Metalation of **5** using *n*-butyllithium afforded lower yields.



4: R=H
5: R=TBS

6

5 was considerably more stable to storage than was phenol **4** and could be prepared in a one-pot procedure. In addition, the TBS ether sterically inhibited metalation at C-2 and C-8. To test the suitability of **5** as a precursor to naphthoquinone, **5** was treated with Jones' reagent in acetone at 0 °C.[8] After 30 min at 0 °C, 1,4-naphthoquinone was generated in quantitative yield.

The successful oxidation of **5** prompted us to react the anion of **5** with a variety of electrophiles. The results are collated in Table 1. The anion of **5** reacted successfully with several electrophiles. Quenching the anion solution with D_2O afforded an 87% yield of deuterium incorporation. The anion did not react well with propylene oxide, benzyl chloride, or benzyl bromide. Attempts to trap the alkoxide intermediate in the propylene oxide reaction did not lead to improved yields.

We next tried a sequence of reactions involving metalation, trapping with an electrophile, and oxidation without purification of intermediates. The results are shown in Table 2.

The reaction with iodine generated two products. When 1 equiv of sulfuric acid was added to the metalation product (to protonate the amine) before Jones' reagent was added and when the oxidation reaction was conducted at −78 °C, a 44% yield of **18** and a 3% yield of **19** were obtained.

The metalation of **5** followed by trapping with halides, carbonyl groups, and stannanes and oxidation produces naphthoquinones in good overall yields. These products

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(1) Kraus, G. A.; Zhang, N.; Melekhov, A.; Jensen, J. *Synlett* **2001**, *4*.

(2) Gallagher, P. T. *Contemp. Org. Synth.* **1996**, *3*, 433. Thomson, R. H. *Total Synth. Nat. Prod.* **1992**, 311. Lien, J. C.; Huang, L. J.; Wang, J. P.; Teng, C. M.; Lee, K. H.; Kuo, S. C. *Bioorg. Med. Chem.* **1998**, *6*, 251. You, Y. J.; Kim, Y.; Song, G. Y.; Ahn, B. Z. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2301.

(3) 5-Iodonaphthoquinone: Ishii, H.; Hanaoka, T.; Asaka, T.; Harada, Y.; Ikeda, N. *Tetrahedron* **1976**, *32*, 2693.

(4) 5-Formylnaphthoquinone: Rozeboom, M. D.; Tegmo-Larsson, I. M.; Houk, K. N. *J. Org. Chem.* **1981**, *46*, 2338.

(5) Barnes, R. A.; Nehmsmann, L. J. *J. Org. Chem.* **1962**, *27*, 1939.

(6) Kirby, A. J.; Percy, M. *Tetrahedron* **1988**, *44*, 6903.

(7) Gribble, G. W.; Nutaitis, C. F. *Synthesis* **1987**, 709.

(8) Stolow, R. D.; Krikorian, R. R. *Org. Prep. Proced. Int.* **1971**, *3*, 39.

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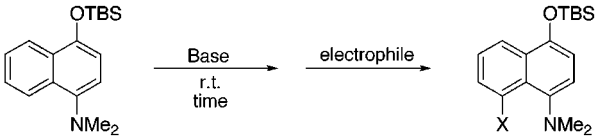
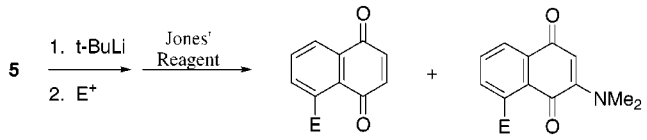
Table 1



base	solvent	time (h)	electrophile	X	yield (%)	conversion (%)	
n-BuLi	ether	48	MeI	Me	26	41	7
1.2 equiv	ether	72	MeI		34	51	7
	cyclohexane	72	MeI		6	37	7
t-BuLi	cyclohexane	72	MeI	Me	54	94	7
1.2 equiv							
t-BuLi	cyclohexane	72	DMF	CHO	30	[a]	8
1.2 equiv			$(PhS)_2$	SPh	46	[a]	9
			CO_2	CO_2H	45	95	10
t-BuLi	cyclohexane	72	CO_2	CO_2H	41	53	10
2.0 equiv			(gas)				
t-BuLi	cyclohexane	72	PhCHO	PhCHOH	35	44	11
1.2 equiv			propylene oxide	$CH_2CHMeOH$	17	54	12
			BnBr	Bn	27	47	13
			n-Bu_3SnCl	$SnBu_3$	50	83	14

[a] Starting material was not isolated.

Table 2



E+	E	yield (%)			
CO_2	CO_2H	42	**16**	0	
DMF	CHO	55	**17**	0	
I_2	I	40	**18**	20	**19**
I_2	I	44	**18**	3[a]	**19**

[a] An extra equiv of sulfuric acid was used.

will be useful intermediates for the construction of heterocyclic quinones.[9]

Experimental Section

4-Dimethylamino-1-*tert*-butyldimethylsilyloxynaphthalene (5). To a stirred suspension of 4-amino-1-naphthol (1 g, 4.60 mmol) and paraformaldehyde (1.38 g, 46.0 mmol) in AcOH (30 mL) at 25 °C under argon was added in 1 portion sodium cyanoborohydride (1.445 g, 23 mmol) and dry THF (6 mL). The resulting mixture was stirred at room temperature for 24 h. The pale pink suspension was then quenched with saturated aqueous Na_2CO_3 (40 mL) at 0 °C and extracted. The organic layer was dried over $MgSO_4$ and concentrated under vacuum (overnight) to give a red, oily residue. The residue was dissolved in dry THF (10 mL) under argon, cooled to 0 °C, and treated with sodium hydride (221 mg, 9.2 mmol). The reaction mixture was stirred for 2 h at 0 °C, and then TBDMSCl (832 mg, 5.52 mmol) was added. The reaction was warmed to room temperature and stirred for 8 h before being quenched with MeOH. The residue was adsorbed on silica gel and then purified by SGC (hexane/ether 40:1), yielding **5** (1.27 g, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, J = 18.0, 7.6 Hz, 2H), 7.50 (m, 2H), 6.98 (d, J = 8.0 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 2.86 (s, 6 H), 1.12 (s, 9H), 0.30 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 147.7, 144.8, 130.4, 128.9, 125.8, 125.2, 124.0, 123.2, 114.3, 112.1, 45.8, 26.1, 18.6, −4.0; R_f (hexane/EtOAc 2:1) = 0.96.

Representative Procedure for in Situ Oxidation. To a solution of **5** (294 mg, 0.975 mmol) in cyclohexane (3 mL) under argon was added *tert*-butyllithim (690 μL, 1.7 M in pentane) at 0 °C. The solution was stirred at room temperature for 3 days. The resulting red solution was cooled to 0 °C, and DMF (113 μL, 1.46 mmol) was added. After 1 h at 0 °C, the reaction mixture was warmed to room temperature (the addition of THF (1 mL) is necessary for MeI, Bu_3SnCl, propylene oxide, iodine, benzyl bromide, and diphenyl disulfide) and then quenched with MeOH. After removal of the solvent in vacuo, the residue was dissolved in acetone (10 mL), cooled to 0 °C, and treated with Jones' reagent (1.1 mL, 2.7 M). The solution was stirred at 0 °C for 30 min and then quenched with 2-propanol (1 mL). The organic layer was extracted with $CHCl_3$ and dried over $MgSO_4$. The products were purified by silica gel flash column chromatography.

Compound 7: NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 6.4 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 3.02 (s, 3H), 2.71 (s, 6H), 1.14 (s, 9H), 0.32 (s, 6H); IR (KBr) 3057, 2957, 2928, 1592 cm^{-1}; HRMS *m/e* (EI) for $C_{19}H_{29}ONSi$ $(M)^+$ calcd 315.2018, measured 315.2022; CMR ($CDCl_3$) δ 148.5, 146.5, 135.2, 130.8, 130.2, 129.9, 124.8, 121.4, 117.0, 112.0, 46.2, 26.2, 23.8, 18.6, −4.0. R_f (hexane/EtOAc 8:1) = 0.87.

Compound 9: NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.4 Hz, 1H), 7.64 (dd, J = 8.0, 1.6 Hz, 2H), 7.44 (m, 3H), 7.23 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 2.75 (s, 6H), 1.10 (s, 9 H), 0.29 (s, 6H); HRMS *m/e* (EI) for $C_{24}H_{31}ONSSi$ $(M)^+$ calcd 409.1896, measured 409.1903; CMR ($CDCl_3$) δ 149.0, 145.3, 138.1, 136.4, 136.2, 129.9, 129.7, 129.3, 128.6, 125.0, 124.4, 119.3, 119.0, 112.7, 46.1, 26.1, 18.6, −4.0. R_f (hexane/EtOAc 8:1) = 0.77.

Compound 10: NMR (300 MHz, $CDCl_3$) δ 8.84 (dd, J = 7.2, 1.5 Hz, 1H), 8.49 (dd, J = 8.4, 1.5 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.45 (d, J = 8.4, 1H), 6.92 (d, J = 8.4, 1H), 2.92 (s, 6H), 1.09 (s, 9H), 0.31 (s, 6H); HRMS *m/e* (EI) for $C_{19}H_{27}O_3NSi$ $(M)^+$ calcd 345.1760, measured 345.1766; CMR ($CDCl_3$) δ 170.8, 152.5, 136.9, 136.5, 130.1, 130.1, 127.9, 127.8, 125.4, 120.5, 111.9, 46.0, 26.0, 18.6, −4.1. R_f (hexane/EtOAc 1:2) = 0.17.

Compound 11: NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, J = 8.0, 1.6 Hz, 1H), 8.26 (bs, 1H), 7.39−7.27 (m, 8H), 6.86 (d, J = 8.4 Hz, 1H), 6.28 (s, 1H), 2.70 (s, 3H), 2.22 (s, 3H), 1.10 (s, 9H), 0.29 (s, 6H); IR (KBr) 3395, 2929, 1595 cm^{-1}; HRMS *m/e* (EI) for $C_{25}H_{33}O_2NSi$ $(M)^+$ calcd 407.2281, measured 407.2288; CMR ($CDCl_3$) δ 150.8, 145.4, 143.2, 139.1, 130.7, 130.5, 130.2, 128.1, 127.2, 126.7, 124.5, 123.8, 120.9, 112.3, 77.1, 48.5, 46.7, 26.1, 18.6, −4.0, −4.1. R_f (hexane/EtOAc 2:1) = 0.27.

Compound 12: NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J = 8.4, 1.6 Hz, 1H), 7.39 (t, J = 8.4 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 3.98 (m, 1H),

(9) Tisler, M. *Adv. Heterocycl. Chem.* **1989**, *45*, 37. Middleton, R. W.; Parrick, J. *Chem. Quinonoid Compd.* **1988**, *2*, 1019.

3.76 (dd, J = 13.2, 3.6 Hz, 1H), 3.23 (dd, J = 13.6, 7.6 Hz, 1H), 2.84 (bs, 1H), 2.75 (s, 3H), 2.67 (s, 3H), 1.19 (d, J = 6 Hz, 3H), 1.11 (s, 9H), 0.30 (s, 6H); IR (KBr) 3415, 2928, 2778, 1593 cm^{-1}; HRMS *m/e* (EI) for $C_{21}H_{33}O_2NSi$ $(M)^+$ calcd 359.2281, measured 359.2285; CMR ($CDCl_3$) δ 149.2, 145.1, 135.2, 131.5, 130.6, 129.6, 124.8, 122.9, 117.7, 111.9, 69.9, 47.1, 46.9, 45.8, 26.1, 23.3, 18.6, −4.0. R_f (hexane/EtOAc 3:1) = 0.36.

Compound 13: NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 6.8 Hz, 1H), 7.19 (t, J = 7.2 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 7.6 Hz, 2H), 6.81 (d, J = 8.4 Hz, 1H), 4.85 (s, 2H), 2.48 (s, 6H), 1.13 (s, 9H), 0.31 (s, 6H); HRMS *m/e* (EI) for $C_{25}H_{33}ONSi$ $(M)^+$ calcd 391.2331, measured 391.2338; CMR ($CDCl_3$) δ 148.8, 146.1, 143.9, 136.8, 131.2, 130.4, 130.2, 128.4, 128.1, 125.1, 124.8, 122.3, 118.3, 112.1, 46.2, 42.4, 26.1, 18.6, −4.0. R_f (hexane/EtOAc 8:1) = 0.80.

Compound 14: NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J = 8.4, 1.2 Hz, 1H), 7.72 (dd, J = 6.4, 1.2 Hz, 1H), 7.43 (dd, J = 8.0, 6.4 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 2.61 (s, 6H), 1.51−1.42 (m, 6H), 1.34−1.25 (m, 6H), 1.1 (s, 9H), 1.04−0.99 (m, 6H), 0.84 (t, J = 7.2 Hz, 9H), 0.28 (s, 6H); HRMS *m/e* (EI) for $C_{30}H_{53}ONSiSn$ $(M)^+$ calcd 591.2918, measured 591.2925; CMR ($CDCl_3$) δ 149.1, 146.6, 138.3, 136.6, 136.1, 128.9, 124.9, 123.1, 115.3, 111.9, 47.9, 29.5, 27.9, 26.2, 18.7, 14.0, 11.9, −4.0. R_f (hexane/EtOAc 30:1) = 0.79.

Compound 15: NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 7.6 Hz, 2H), 7.24 (d, J = 8.0 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 2.67 (s, 6H), 1.13 (s, 9H), 0.31 (s, 6H); IR (KBr) 2925, 2855, 1589 cm^{-1}; HRMS *m/e* (EI) for $C_{18}H_{26}ONISi$ $(M)^+$ calcd 427.0829, measured 427.0834; CMR ($CDCl_3$) δ 147.9, 144.2, 142.1, 130.1, 128.7, 125.9, 124.0, 118.9, 113.0, 88.1, 45.7, 26.1, 18.6, −4.0. R_f (hexane/EtOAc 2:1) = 0.89.

Compound 16: NMR (400 MHz, CD_3CN/CD_3OD) δ 8.85 (dd, J = 8.0, 1.2 Hz, 1H), 8.58 (t, J = 7.6 Hz, 1H), 8.47 (dd, J = 7.6, 1.2 Hz, 1H), 7.74 (s, 2H); IR (KBr) 3327, 2930, 1695, 1671 cm^{-1}; HRMS *m/e* (EI) for $C_{11}H_6O_4$ $(M)^+$ calcd 202.0266, measured 202.0269; CMR (CD_3CN/CD_3OD) δ 185.7, 185.6, 172.1, 140.1, 139.6, 136.1, 135.2, 133.6, 133.3, 129.7, 128.3. R_f (hexane/EtOAc 1:1) = 0.07.

Compound 17: NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.30 (dd, J = 7.6, 1.2 Hz, 1H), 8.06 (dd, J = 7.6, 1.2 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.04 (s, 2H); IR (KBr) 3081, 2887, 1694, 1669, 1659 cm^{-1}; HRMS *m/e* (EI) for $C_{11}H_6O_3$ $(M)^+$ calcd 186.0317, measured 186.0320; CMR ($CDCl_3$) δ 192.5, 186.6, 184.0, 139.4, 138.4, 137.9, 134.2, 133.5, 132.7, 131.5, 130.9. R_f (hexane/EtOAc 1:1) = 0.37.

Compound 18: NMR (300 MHz, $CDCl_3$) δ 8.38 (dd, J = 7.8, 1.2 Hz, 1H), 8.17 (dd, J = 7.5, 1.2 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.04 (d, J = 10.5 Hz, 1H), 6.96 (d, J = 10.2 Hz, 1H); IR (KBr) 3055, 1669 cm^{-1}; HRMS *m/e* (EI) for $C_{10}H_5O_2I$ $(M)^+$ calcd 283.9334, measured 283.9338; CMR ($CDCl_3$): δ 183.8, 183,4, 148.4, 139.9, 137.3, 134.5, 133.9, 130.9, 127.8, 92.9. R_f (hexane/EtOAc 5:1) = 0.31.

Compound 19: NMR (300 MHz, $CDCl_3$) δ 8.298 (dd, J = 8.1, 1.5 Hz, 1H), 8.04 (dd, J = 7.8, 1.5 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 5.87 (s, 1H), 3.19 (s, 6H); HRMS *m/e* (EI) for $C_{12}H_{10}O_2NI$ $(M)^+$ calcd 326.9756, measured 326.9761; CMR ($CDCl_3$) δ 182.8, 181.0, 151.7, 148.1, 135.3, 132.3, 131.1, 127.8, 107.9, 91.3, 42.4. R_f (hexane/EtOAc 2:1) = 0.38.

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Supporting Information Available: NMR data for Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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