An Efficient Synthesis of *peri*-Hydroxy Aromatic Compounds: A Strong Base-Induced [4+2]Cycloaddition of 4-Phenylthio-Substituted Homophthalic Anhydrides with Various Sulfinyl-Substituted Dienophiles

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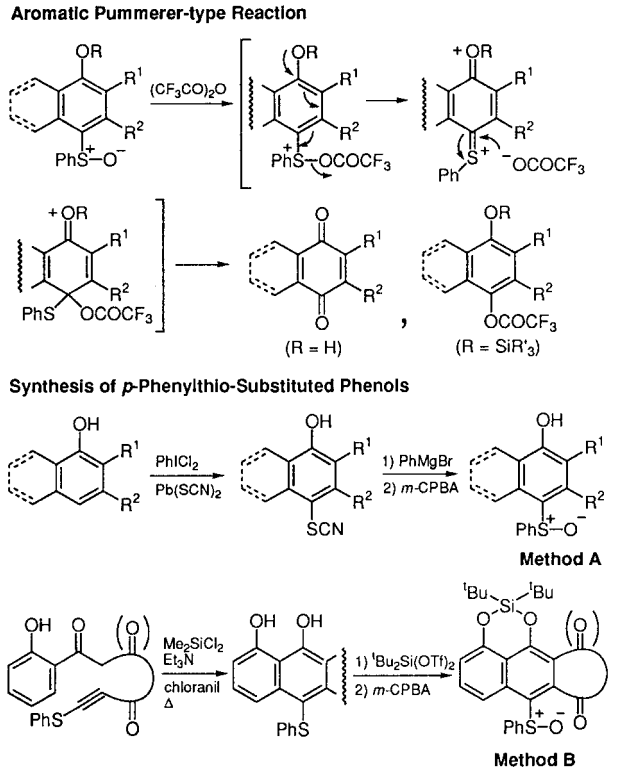
Abstract: As an extension of the strong base-induced [4+2]cycloaddition of homophthalic anhydrides studied previously, we found a general and versatile synthesis of *p*-phenylthio substituted phenols by the reaction of 4-phenylthio-substituted homophthalic anhydrides and various dienophiles. The use of the sulfinyl-substituted dienophile is essential to produce the desired reaction under mild conditions in good yield.

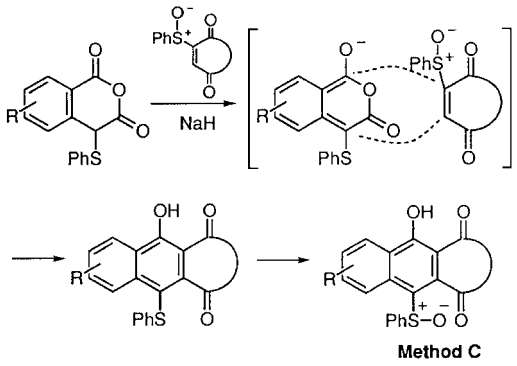
The general and efficient synthesis of *peri*-hydroxy aromatic compounds, which have useful biological activity, including anthracyclines and fredericamycin A, is significant in organic synthesis.[1,2]

Recently, we reported an aromatic Pummerer-type reaction of *p*-sulfinyl phenols and *p*-sulfinyl-substituted *peri*-hydroxy aromatic compounds leading to *p*-quinones and protected *p*-dihydroquinones.[3] With respect to the synthesis of the starting *p*-sulfinyl phenols, we have already reported the following two methods: (1) the *p*-specific thiocyanation of phenols using hypervalent iodine reagent and the conversion of the thiocyanato group to the sulfinyl group by treatment with Grignard reagent followed by oxidation with *m*-chloroperbenzoic acid (Method A)[3c,4] and (2) the oxidative intramolecular [4+2]cycloaddition of *o*-[(ω-phenylthioethynyl)acyl]phenols followed by oxidation of the sulfenyl group (Method B)[5] (Scheme 1).



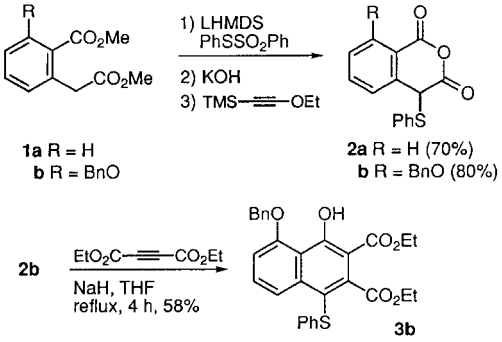
Scheme 1

As an extension of the strong base-induced [4+2]cycloaddition of homophthalic anhydrides studied previously,[6] we have studied the reaction of 4-phenylthio-substituted homophthalic anhydrides (**2a**, **b**) and various dienophiles leading to *p*-sulfenyl phenols. We now report a general, versatile and regioselective synthesis of *p*-phenylthio-substituted *peri*-hydroxy aromatic compounds (Method C) (Scheme 2).



Scheme 2

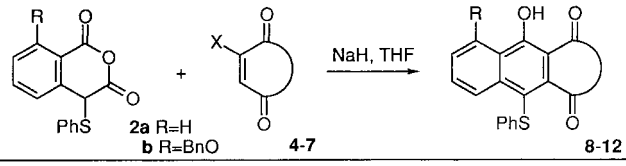
The starting 4-phenylthio-homophthalic anhydrides (**2a**, **b**) were readily prepared from the corresponding homophthalic acid dimethyl esters (**1a**, **b**) in 3 steps with 70-80% overall yields. Similar to the case of the corresponding homophthalic anhydride,[6a] the strong base-induced cycloaddition of **2b** with acetylenedicarboxylic acid diethyl ester directly gave the desired *p*-phenylthio-substituted adduct (**3b**) in 58% yield (Scheme 3).

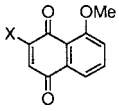
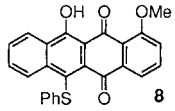
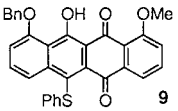
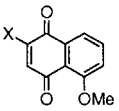
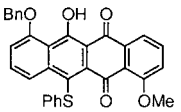
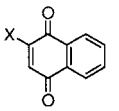
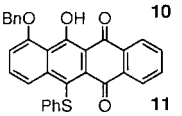
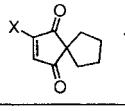
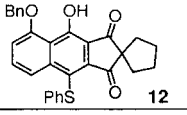


Scheme 3

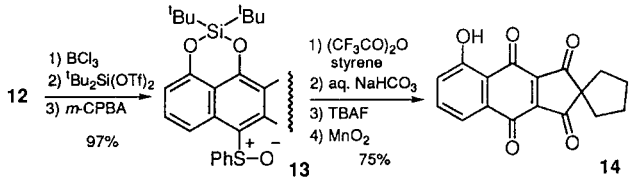
Next, we examined the regioselective synthesis of *p*-phenylthio-substituted *peri*-hydroxy aromatic compounds using dienophiles attached with various leaving groups. Although the reaction of **2** with **4a-c**, **5a**, **6a** and **7a** (X = Cl, Br, SPh)[7] took a long time and gave the desired products in low yields (runs 1-3, 5, 7, 9, 11 in Table 1), the reaction of **2** with sulfinyl-substituted dienophiles[8] (**4d**, **5b**, **6b**, **7b**) immediately occurred at r.t. and gave the desired products (**8-12**) in good yields (runs 4, 6, 8, 10, 12).[9,10] These results are listed in Table 1.

Table 1. Reaction of 4-Phenylthio-Substituted Homophthalic Anhydrides (2)



run	2	dienophiles	reaction conditions	product	yield (%)
1	2a	 **4a** X = Cl	r.t., 4 d		58
2	//	**b** X = Br	r.t., 2 d		67
3	//	**c** X = SPh	reflux, 15 h		N.R.
4	//	**d** X = S(O)Ph	r.t., 1 h		72
5	2b	**4b** X = Br	r.t., 7 d		48
6	//	**d** X = S(O)Ph	r.t., 1 h		73
7	//	 **5a** X = Br	r.t., 3 d		52
8	//	**b** X = S(O)Ph	r.t., 1 h		67
9	//	 **6a** X = Br	r.t., 7 d		48
10	//	**b** X = S(O)Ph	- 20 to 0 °C, 2 h		66
11	//	 **7a** X = Br	r.t., 3 d		32
12	//	**b** X = S(O)Ph	r.t., 0.5 h		82

We applied this anionic cycloaddition to the synthesis of the ABCD-ring analog of fredericamycin A. In the case of **7b**, the reaction smoothly occurred at r.t. to give **12** in 82% yield (run 12). Debenzylation of **12** cleanly occurred by treatment with BCl_3. Sequential silylene-protection of both phenol groups with $^tBu_2Si(OTf)_2$ followed by oxidation of the phenylsulfenyl group gave **13** in 97% overall yield. The aromatic Pummerer-type reaction of **13** provided the ABCD-ring analog **14** in good yield (Scheme 4).[3b]



Scheme 4

In conclusion, we have succeeded in developing a general and versatile synthesis of *p*-regioselective phenylthio-substituted *peri*-hydroxy aromatic compounds, whose structure is expected to receive various modifications. In this cycloaddition, using sulfinyl-substituted dienophile is crucial, and this method offers very mild reaction conditions and the direct formation of the desired compound in good yield.

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(9) *Typical procedure*: Under nitrogen atmosphere, a mixture of **2b** (94 mg, 0.25 mmol) and NaH (60% in mineral oil, 11 mg, 0.27 mmol) in anhydrous THF (8 ml) was stirred at 0 °C for 1.5 h. A solution of **7b** (53 mg, 0.19 mmol) in anhydrous THF (8 ml) was added to the mixture at 0 °C. The whole was allowed to warm to room temperature, and stirred for 0.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and AcOEt. The organic layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (hexane-AcOEt) to give **12** (75 mg, 82%) as yellow crystals: mp 164-165 °C (recryst. from CH_2Cl_2-Et_2O), IR (KBr) 2950, 1734, 1705, 1671, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91-2.00 (8 H, m), 5.33 (2 H, s), 7.04-7.08 (3 H, m), 7.13-7.16 (3 H, m), 7.39-7.46 (3 H, m), 7.55 (2 H, d, *J* = 7.5 Hz), 7.62 (1 H, t, *J* = 8.5 Hz), 8.49 (1 H, d, *J* = 8.5 Hz), 11.26 (1 H, s); Anal. Calcd for $C_{30}H_{24}O_4S$: C, 74.98; H, 5.03; S, 6.67. Found: C, 74.63; H, 5.08; S, 6.59.

(10) Satisfactory spectral data (IR, ^1H NMR, HRMS) and/or elemental analyses for unknown compounds (**2**, **3b**, **4d**, **5b**, **7**-**12**) were obtained.