

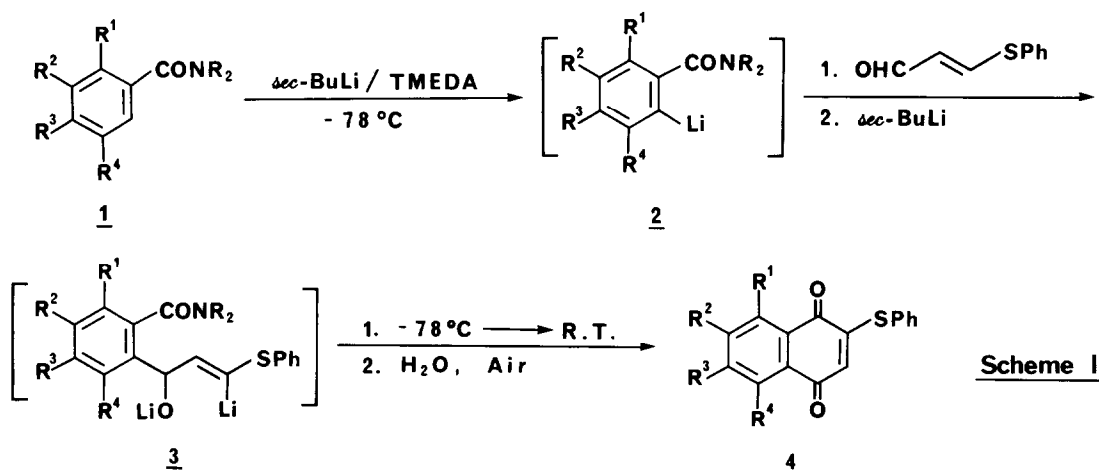
## A NOVEL NAPHTHOQUINONE SYNTHESIS VIA TANDEM DIRECTED LITHIATIONS

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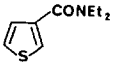
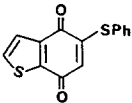
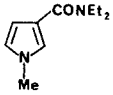
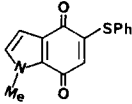
**Summary:** A convenient one-pot synthesis of 1,4-naphthoquinones from tertiary benzamides has been devised using tandem directed lithiations.

During the past decade substantial efforts have been devoted to the regioselective synthesis of highly substituted quinones owing to the significant biological activities of naturally occurring quinone derivatives.<sup>1</sup> For the preparation of 1,4-naphthoquinone nucleus, Diels-Alder reaction,<sup>2</sup> phthalide annulation,<sup>3</sup> and cycloaddition reactions *via* aryl chromium-carbene complexes<sup>4</sup> or phthaloyl cobalt complexes<sup>5</sup> have been developed. In this Letter, we report on a novel anionic one-pot 1,4-naphthoquinone synthesis *via* tandem directed lithiations.<sup>6</sup> The strategy shown in the Scheme I involves consecutively *a*) *ortho* lithiation of tertiary benzamides<sup>7</sup> [1→2], *b*) condensation of 2 with 3-(phenylthio)acrolein<sup>8</sup> followed by phenylsulfide-directed  $\alpha$  lithiation<sup>9</sup> of the condensation product [2→3], and *c*) intramolecular anionic cyclization and subsequent air oxidation [3→4].



Scheme I

Table. Synthesis of 2-Phenylthio-1,4-naphthoquinones

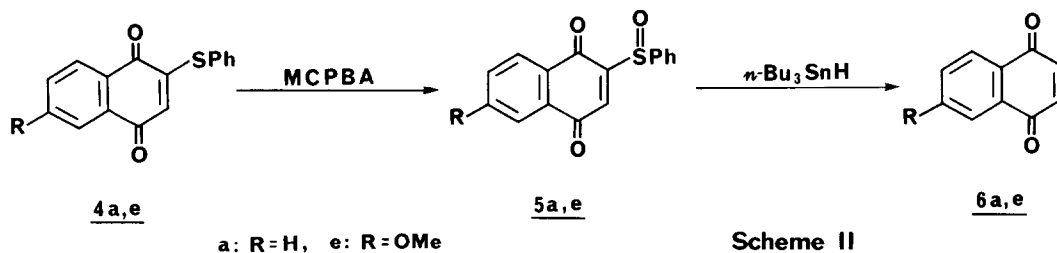
Amide	R	Quinone	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Yield/%	Mp/°C
<u>1a</u>	Et	<u>4a</u>	H	H	H	H	59	159-159.5 <sup>b</sup>
<u>1b</u>	Et	<u>4b</u>	H	H	Me	H	66	167-167.5
<u>1c</u>	Et	<u>4c</u>	H	H	F	H	33	167-168
<u>1d</u>	Me	<u>4d</u>	OMe	H	H	H	22	184.5-185
<u>1e</u>	Et	<u>4e</u>	H	H	OMe	H	66	200.5-201
<u>1f</u>	Et	<u>4f</u>	H	H	H	OMe	58 <sup>a</sup>	103.5-104.5
<u>1g</u>	Et	<u>4g</u>	H	Me	H	OMe	53 <sup>a</sup>	241-242
<u>1h</u>	Me	<u>4h</u>	OMe	H	OMe	H	31	222.5-223
<u>1i</u>	Et	<u>4i</u>	H	OMe	H	OMe	52	>300
<u>1j</u>	Me	<u>4j</u>	OMe	H	H	OMe	46 <sup>a</sup>	168.5-169
<u>1k</u>	Et	<u>4k</u>	H	H	OMe	OMe	52	145-145.5
<u>1l</u>	Et	<u>4l</u>	H	H	-O-CH <sub>2</sub> -O-		49	209-210
<u>1m</u>	Et	<u>4m</u>	-CH=CH-CH=CH-		H	H	21	191-191.5
<u>1n</u>		<u>4n</u>					44	146.5-147
<u>1o</u>		<u>4o</u>					63	139.5-140

<sup>a</sup>Yield after Ag<sub>2</sub>O oxidation. <sup>b</sup>Lit. mp 159-161 °C (Reference 11).

In a typical procedure, *N,N*-diethylbenzamide 1a was *ortho*-lithiated under the standard conditions<sup>10</sup> (1.1 eq *sec*-BuLi/TMEDA/THF/-78 °C/1 h) and the resulting lithiated amide 2a was subsequently treated at -78 °C with 3-(phenylthio)acrolein (1.1 eq) and *sec*-BuLi (1.1 eq) at an interval of two hours to generate 3a. After standing for one hour at -78 °C, the reaction mixture was warmed to room temperature and stirred for two hours to effect cyclization. The ring closure was indicated by the disappearance of the rusty color of 3a during this operation. Quenching the reaction mixture with aqueous NH<sub>4</sub>Cl and extractive workup followed by flash chromatography afforded 2-phenylthio-1,4-naphthoquinone 4a in 59% yield. The intermediate cyclization product is presumably air-oxidized during workup of chromatography. The structure of 4a was established by spectroscopic comparisons with an authentic sample<sup>11</sup> prepared from 1,4-naphthoquinone.

Under the similar conditions,<sup>12</sup> a variety of substituted 2-phenylthio-1,4-naphthoquinones 4b-1 listed in the Table were obtained regioselectively from the corresponding easily accessible tertiary benzamides 1b-1. The polycyclic and heterocyclic analogues 4m-o could also be available. In general, the yields of this annulation are good (>50%) for this type of strong base-induced cyclizations.<sup>6,13</sup> However, when *ortho*-substituted amides such as 1d, 1h, 1m, or halogenated amide 1c were used as starting materials, the yields decreased significantly. The poor yields would be attributable to the steric hindrance to cyclization in the former cases and to the benzyne formation in the latter.

Associated with this novel naphthoquinone synthesis, we have developed a mild method to remove the phenylthio group from the quinone ring under reductive conditions<sup>14</sup> (Scheme II). Thus the quinone 4a<sup>15</sup> was converted to its sulfoxide derivative 5a by *m*-chloroperbenzoic acid in 94% yield. When 5a was treated with tri-*n*-butyltin hydride<sup>16</sup> (1.1 eq) in toluene at 70 °C for ten minutes, 1,4-naphthoquinone 6a was obtained in 55% yield. In a similar manner, the quinone 4e was oxidized to 5e which was then desulfurized (70 °C, 30 min) to 6e in 70% yield.



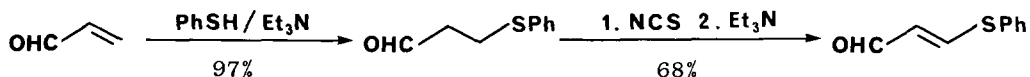
In conclusion, the synthetic method presented herein enables easy access of substituted 1,4-naphthoquinones which are not readily available by conventional methods. In addition, further regioselective functionalizations of the quinone ring may be possible through nucleophilic substitution<sup>17</sup> of the phenylthio or phenylsulfinyl group which would open the way to the synthesis of more complex naphthoquinone derivatives including biologically significant natural products. Studies along this line are in progress.

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