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# Regioselective Addition Reaction of Lithium Enolates to Thio-Substituted 1,4-Naphthoquinones. Convenient Synthesis of a Naphthofuran-4,9-dione Ring System

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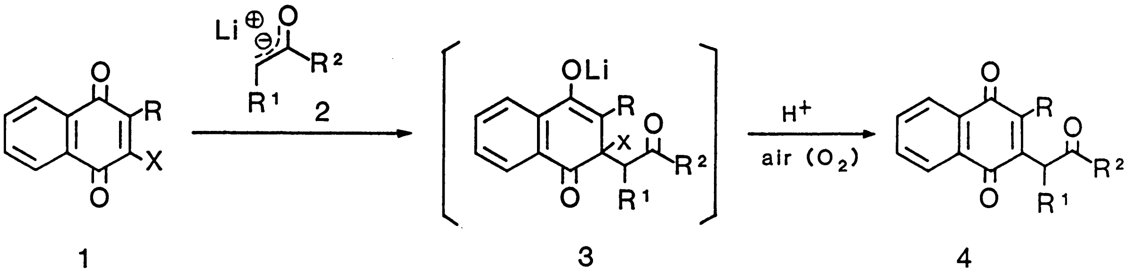
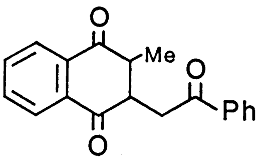
The regioselective addition of lithium enolates to thio-substituted 1,4-naphthoquinones gave alkylated 1,4-naphthoquinones via 1,4-addition products. A phenacyl 1,4-naphthoquinone was cyclized to a naphthofuran-4,9-dione ring system.

It is of great interest to achieve the selective 1,2- or 1,4-addition of carbon nucleophiles to quinones since introduction of a functionalized alkyl chain into the quinone skeleton is one of the most attractive synthetic route to biologically important naturally-occurring quinones.1) Reactions of quinones with tin(II) enolates or silyl enol ethers have been reported to give 1,2- or 1,4-addition products,2) whereas the Michael addition of lithium enolates to quinones has been less studied.3) Here we wish to report the successful 1,4-addition of lithium enolates to thio-substituted 1,4-naphthoquinones (1).

Reaction of 2-phenylthio-1,4-naphthoquinone (1a) and 2-ethylthio-1,4-naphthoquinone (1b)4) with lithium enolates 2a-c gave 2-(2-oxoalkyl)-3-phenylthio-1,4-naphthoquinones 4a-d in excellent yields, which were derived from the initially formed 1,4-addition products 3 through the air-oxidation as shown in Scheme 1. No formation of other addition products was observed in these reactions. On the other hand, reaction of 2-methyl-1,4-naphthoquinone (1c) with lithium enolate 2c afforded 2,3-dihydro-2-methyl-3-(2-oxo-2-phenylethyl)-1,4-naphthoquinone (5) and 2,3-dihydro-2-methyl-2-(2-oxo-2-phenylethyl)-1,4-naphthoquinone (6) in 48 and 32% yields, respectively. It should be noted that the thio-substituted group at the 2-position of the parent 1,4-naphthoquinone (1) has a crucial role to determine the regiochemistry in these reactions.5) The addition of lithium enolate 2b to 2-butylthio-3-chloro-1,4-naphthoquinone (1d) also occurred regioselectively at the 3-position to give naphthoquinone 4e in 70% yield via elimination of a chloride ion. These results are summarised in Table 1.



Scheme 1.



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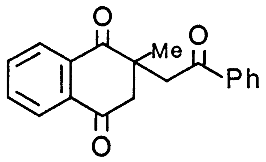

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Table 1. Reaction of Naphthoquinone with Lithium Enolates

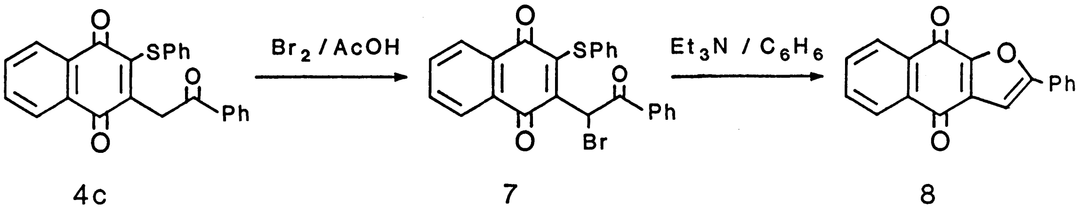
| Entry | 1 | | | 2 | | | Products a) |
|---|---|---|---|---|---|---|---|
| | R | X | | $R^1$ | $R^2$ | | (Yield/%)b) |
| 1 | SPh | H | (1a) | $-(CH_2)_3-$ | | (2a) | 4a (76) |
| 2 | SPh | H | (1a) | $-(CH_2)_2-$ | | (2b) | 4b (75) |
| 3 | SPh | H | (1a) | H | Ph | (2c) | 4c (62) |
| 4 | SEt | H | (1b) | $-(CH_2)_3-$ | | (2a) | 4d (64) |
| 5 | Me | H | (1c) | H | Ph | (2c) | 5 (48) and 6 (32) |
| 6 | SBu | Cl | (1d) | $-(CH_2)_2-$ | | (2b) | 4e (70) |

a) All the products gave satisfactory IR, NMR, and mass spectra.

b) Isolated yields.

A typical procedure of this reaction is as follows: butyllithium (2 mmol, hexane solution) was added dropwise over 5 min to a stirred solution of dicyclohexylamine (2 mmol) in THF (8 ml) at -45 °C under argon. After the addition the mixture was cooled to -78 °C. A solution of a ketone (2 mmol) in THF was added slowly and the mixture was stirred until it became a clear solution (10-15 min). Then HMPA (1 ml) was added. After stirring for 10 min at -78 °C, the resulting solution was added to a solution of naphthoquinone 1 (2 mmol) in THF (15 ml) and HMPA (1 ml) at -70 °C. The reaction mixture was stirred for 15 min and then 5% hydrochloric acid (10 ml) was added. Purification of the crude mixture with column chromatography (silica gel, toluene-hexane, 1:1) gave naphthoquinone 4.

Associated with this successful 1,4-addition reaction of thio-substituted 1,4-naphthoquinones, we attempted the transformation of a product to a naphthofuran-4,9-dione ring system. Thus, 2-(2-oxo-2-phenylethyl)-3-phenylthio-1,4-naphthoquinone 4c was brominated in acetic acid at room temperature for 12 h to give the crude brominated naphthoquinone 7 which was treated with triethylamine (1 equiv.) in benzene at room temperature for 10 min to give 2-phenylnaphtho[2,3-b]furan-4,9-dione (8)$^{6,7)}$ in 45% yield.



Scheme 2.

Regioselective introduction of 2-oxoalkyl chains into thio-substituted 1,4-naphthoquinones could be achieved by use of lithium enolates. Cyclization of the resulting 2-(2-oxoalkyl)-3-phenylthio-1,4-naphthoquinones (4) provides an efficient method for the synthesis of naphthofuran-4,9-dione derivatives. A further study on the synthesis of naturally-occurring cytotoxic naphthofuran-4,9-diones$^{8)}$ is now in progress.

References

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5) The reaction of 2-bromo-1,4-naphthoquinone and 2-methoxy-1,4-naphthoquinone with lithium enolate 2a gave many products from which the addition products corresponding to 4 could not be isolated.

6) Compound 9 had mp 246-247 °C (Lit.7) mp 246.5-247.5 °C); $^1$HNMR (CDCl$_3$) $\delta$=7.24 (s, 1H), 7.53 (m, 3H), 7.80 (m, 2H), 7.90 (m, 2H), 8.26 (m, 2H).

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