Nucleophilic Substitutions of 2-Halonaphtho[2,3-*b*]furan-4,9-diones and 2-Nitronaphtho[2,3-*b*]furan-4,9-dione[1)]

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2-Chloronaphtho[2,3-*b*]furan-4,9-dione (4) was allowed to react with sodium phenoxide to produce 2-phenoxynaphtho[2,3-*b*]furan-4,9-dione (8) in 55% yield. Also, in a similar manner, 8 was obtained from the reactions of 2-bromonaphtho[2,3-*b*]furan-4,9-dione (5), 2-iodonaphtho[2,3-*b*]furan-4,9-dione (6) and 2-nitronaphtho[2,3-*b*]furan-4,9-dione (7) with sodium phenoxide. The reaction of 4 with sodium methoxide gave methyl 3-hydroxy-1,4-naphthoquinone-2-acetate (9) in which the furan ring was cleaved. 2-Phenylthionaphtho[2,3-*b*]furan-4,9-dione (11) and 2-methylthionaphtho[2,3-*b*]furan-4,9-dione (12) were obtained from the reactions of 4 with thiolates in 63% and 62% yields, respectively. Furthermore, 4 was treated with sodiomalonic ester to give diethyl 2-(naphtho[2,3-*b*]furan-4,9-dione-2-yl)malonate (13) in 28% yield. Compound 13 was also obtained from the reactions of 5 and 7 with sodiomalonic ester. All these nucleophilic substitutions were carried out at room temperature. It was found that 4—7 had a high reactivity with various nucleophilic reagents.

Key words aromatic nucleophilic substitution; naphthofuranquinone; cytotoxic activity; 2-halonaphtho[2,3-*b*]furan-4,9-dione; 2-nitronaphtho[2,3-*b*]furan-4,9-dione

A number of naphtho[2,3-*b*]furan-4,9-diones, which have interesting biological activities, have been isolated from various plants.[2)] For example, 2-acetylnaphtho[2,3-*b*]furan-4,9-dione (**1**) isolated from *Tabebuia cassinoides* (LAM.) DC. (Bignoniaceae) exhibits cytotoxic activity.[3)] Hayashi *et al.*[4)] reported that the cytotoxic activity of 2-methylnaphtho[2,3-*b*]furan-4,9-dione is three times that of **1**. As already mentioned, the activity of the 2-substituted naphtho[2,3-*b*]furan-4,9-diones varies with the type of substituent on the parent naphtho[2,3-*b*]furan-4,9-dione (**2**). Therefore, organic chemists have an interest in the syntheses of these compounds. Recently, we also became interested in the syntheses of the 2-substituted compounds, and reported the preparations of the parent compound **2**,[5)] the natural product **1**[1,6)] and 2-trimethylsilylnaphtho[2,3-*b*]furan-4,9-dione (**3**).[1)] The halodesilylations and nitrodesilylation of **3** have already been reported in connection with studies to prepare the 2-substituted compounds.[1)] No convenient method to prepare the 2-substituent compounds is yet available, except for our procedure. In the present paper, we report a new synthetic route to various 2-substituted compounds.

First, the carbodesilylation of **3** was carried out. Compound **3** was allowed to react with acetyl chloride (5 eq) in the presence of aluminum chloride (5 eq) in 1,2-dichloroethane, but **3** was recovered. Next, the carbodesilylation of **3** with ethyl iodide was examined, but the desired compound was not obtained, and iodonaphtho[2,3-*b*]furan-4,9-dione (**6**)[1)] was formed.

As mentioned above, it was considered that the electrophilic substitution of the trimethylsilyl group on **3** has limitations. The modification of the 2-position of **2** was carried out *via* nucleophilic substitutions of 2-chloronaphtho[2,3-*b*]furan-4,9-dione (**4**), 2-bromonaphtho[2,3-*b*]furan-4,9-dione (**5**), 2-iodo compound (**6**) and 2-nitronaphtho[2,3-*b*]furan-4,9-dione (**7**), which were prepared by the electrophilic reaction of **3** in our laboratory.[1)] First, the reactions of **4**—**7** with oxygen nucleophilic reagents were carried out. Compound **4** was treated with sodium phenoxide (2.5 eq) in dimethyl sulfoxide (DMSO) at room temperature to give 2-phenoxynaphtho[2,3-*b*]-furan-4,9-dione (**8**) in 55% yield. The reaction was completed in only 30 min. In a similar manner, **5**, **6**, and **7** were allowed to react with sodium phenoxide to give **8** in 48%, 21% and 55% yields, respectively (Chart 1). These compounds had a high reactivity in nucleophilic reactions, and the reactions were not dependent on the types of leaving groups at the 2-position.

Compound **4**, which showed a moderate yield in the above reaction, was allowed to react with alkoxides. However, when **4** was treated with sodium methoxide (2.5 eq) in DMSO at room temperature, it gave only an intractable complex mixture. When the solvent was changed from DMSO to methanol, **9** was isolated as yellow needles, mp 140—141 °C. The ^{1}H-NMR spectrum of **9** showed the presence of two kinds of aromatic protons at δ 8.03 (2H, m, Ph) and δ 7.67 (3H, m, Ph and OH), and the signal of the furan ring was not observed. The MS of **9** showed a molecular ion peak at $m/z=246$, and fragment peaks were observed at $m/z=215$ (M^+-OMe) and $m/z=187$ ($M^+-COOMe$). From these results, **9** was determined to be methyl 3-hydroxy-1,4-naphthoquinone-2-acetate. The structure was supported by the IR and elemental analysis results. On the other hand, it has been reported that the furan ring of naphtho[2,3-*b*]furan-4,9-diones is cleaved to give 1,4-naphthoquinones by alkaline hydrolysis.[7)] It is thought that the furan ring of 2-methoxynaphtho[2,3-*b*]furan-4,9-dione, formed by the nucleophilic substitution of **4** with sodium methoxide, was cleaved under basic conditions to give **9**. Ethyl

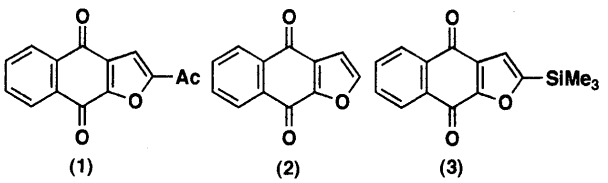

Fig. 1

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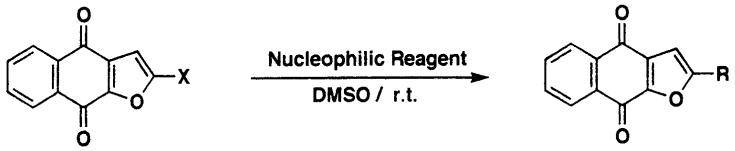

Substrates	X	Nucleophilic Reagent	Time	Products	R	Yield (%)
(4)	Cl	PhONa (2.5eq.)	0.5hr	(8)	OPh	55
(5)	Br	PhONa (2.5eq.)	0.5hr	(8)	OPh	48
(6)	I	PhONa (2.5eq.)	0.5hr	(8)	OPh	21
(7)	NO_2	PhONa (2.5eq.)	0.5hr	(8)	OPh	55
(4)	Cl	PhSNa (2.5eq.)	0.5hr	(11)	SPh	63
(5)	Br	PhSNa (2.5eq.)	0.5hr	(11)	SPh	58
(6)	I	PhSNa (2.5eq.)	0.5hr	(11)	SPh	63
(7)	NO_2	PhSNa (2.5eq.)	0.5hr	(11)	SPh	63
(4)	Cl	MeSNa (2.5eq.)	5min	(12)	SMe	62
(4)	Cl	$NaCH(COOEt)_2$ (5.0eq.)	6hr	(13)	$CH(COOEt)_2$	28
(5)	Br	$NaCH(COOEt)_2$ (5.0eq.)	7hr	(13)	$CH(COOEt)_2$	36
(6)	I	$NaCH(COOEt)_2$ (5.0eq.)	24hr	(13)	$CH(COOEt)_2$	—
(7)	NO_2	$NaCH(COOEt)_2$ (5.0eq.)	0.3hr	(13)	$CH(COOEt)_2$	6

Chart 1

3-hydroxy-1,4-naphthoquinone-2-acetate (**10**) was also obtained from the reaction of **4** with a large excess of sodium ethoxide in ethanol (Chart 2). It was found that the substitutions of **4**—**7** with sodium phenoxide gave the desired 2-substituted compound, though 1,4-naphthoquinones were obtained from the reaction of **4** with alkoxides which have a strong basicity. The latter method may be used to prepare various 1,4-naphthoquinones. Rao and Kingston[3] have reported that lapachol isolated from several *Tabebuia* species (Bignoniaceae) has cytotoxic activity. We were also interested in the biological activities of **9** and **10**, because these compounds have a 3-hydroxy-1,4-naphthoquinone structure that is the same as that of lapachol.

Since sulfur nucleophilic reagents have a strong nucleophilicity and weak basicity, the reactions of **4**—**7** with these reagents were examined. Compound **4** was allowed to react with sodium benzenethiolate (2.5 eq) in DMSO to give 2-phenylthionaphtho[2,3-*b*]furan-4,9-dione (**11**) in 63% yield. The reaction was completed in only 30 min at room temperature. The reactions of **5**, **6** and **7** with sodium benzenethiolate also gave **11** in 58%, 63% and 63% yields, respectively (Chart 1). The leaving ability of the leaving groups had little effect on the yield.

2-Methylthionaphtho[2,3-*b*]furan-4,9-dione (**12**) was obtained from the reaction of **4** with sodium methanethiolate (2.5 eq) in 62% yield (Chart 1). The reaction was completed in only 5 min at room temperature. As can be seen from the results, the reactions of **4** with sulfur nucleophilic reagents represent a facile route to the naphtho[2,3-*b*]furan-4,9-dione-2-yl thioethers.

Organometallic compounds (*e.g.* Grignard reagents, alkyllithiums) are considered as carbanions, but these reagents may react with the carbonyl groups of naphthofuranquinones. The reaction of **4** with sodiomalonic ester, which gave a stable enolate anion, was then examined. Compound **4** was treated with the sodium salt of diethyl malonate (5 eq) in DMSO at room temperature for 6 h to give diethyl 2-(naphtho[2,3-*b*]furan-4,9-dione-2-yl)malonate (**13**) in 28% yield. Compounds **5** and **7** were treated with sodiomalonic ester to give **13** in 36% and 6%

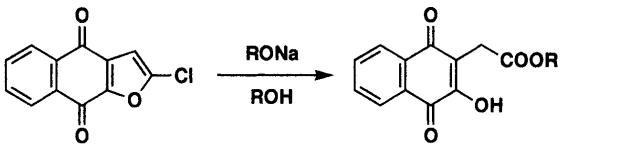

Chart 2

yields, respectively (Chart 1). The reaction of **6** with sodiomalonic ester was also attempted, but only a small amount of **6** was recovered. For this reason, it is thought that the decomposition of **7** proceeds in preference to the substitution, because **7** is susceptible to the base due to the influence of the nitro group. Aryl halides do not ordinarily react with sodiomalonic esters, but **13** was obtained from **4**, **5** and **7**. This result shows that these compounds have a high reactivity for nucleophilic substitutions.

In conclusion, it was found that **4**—**7** easily react with oxygen and sulfur nucleophilic reagents at the 2-position. Compounds **9** and **10**, which cleaved the furan ring, were obtained from the reaction of **4** with alkoxide, because naphthofuranquinones were unstable under basic conditions. Furthermore, **4**, **5** and **7** were treated with sodiomalonic ester to give **13**. All these substitutions were carried out at room temperature. Although these compounds have a high reactivity with various nucleophilic reagents, the desired compounds were obtained only in moderate yields. Nucleophilic substitutions of the naphthofuranquinones may compete with decomposition, because the parent **2** is susceptible to basic conditions. Further work on the nucleophilic substitutions of **5** with amines is in progress. These results will be reported in due course.

Experimental

All melting points (open capillaries) were determined using a Yamato MP-21 and are uncorrected. The ^{1}H-NMR spectra were determined at 60 MHz with a Nippon Denshi JNM PMR-60 SI spectrometer with tetramethylsilane as the internal reference. The IR spectra were measured with a JASCO IR-810 spectrometer. The MS were obtained using a

Nippon Denshi JMS-700 spectrometer at 70 ev. Chromatography was carried out using silica gel (Wakogel C-300, Wako Pure Chemical Industries, Ltd.). Methanethiol sodium salt (*ca.* 15% in water, Tokyo Chemical Industry Co., Ltd.) was commercially obtained.

2-Iodonaphtho[2,3-*b*]furan-4,9-dione (6) Ethyl iodide (780 mg, 5 mmol) in 1,2-dichloroethane (3 ml) was added to a suspension of anhydrous aluminum chloride (670 mg, 5 mmol) in 1,2-dichloroethane (3 ml) with stirring at 0—5 °C. To this mixture, **3**[1] (270 mg, 1 mmol) in 1,2-dichloroethane (3 ml) was added at 0—5 °C; the mixture was refluxed for 13 h and poured into ice-cold water. The solution was extracted with dichloromethane. The organic layer was washed with 5% sodium bicarbonate solution and brine, and then dried over anhydrous sodium sulfate. The solution was evaporated and the residue was recrystallized from ethanol–water to give 80 mg (25%) of **6** as yellow needles, mp 170—172 °C (lit.,[1] mp 172—173 °C).

2-Phenoxynaphtho[2,3-*b*]furan-4,9-dione (8) Phenol (240 mg, 2.5 mmol) in DMSO (4 ml) was added to 60% sodium hydride (100 mg) and vigorously stirred. To this mixture, **4**[1] (230 mg, 1 mmol) in DMSO (20 ml) was added at room temperature, then the mixture was stirred at the same temperature for 30 min and poured into ice-cold water. The solution was extracted with dichloromethane. The organic layer was washed with brine, and then dried over anhydrous sodium sulfate. The solution was evaporated and the residue was recrystallized from ethanol–water to give 160 mg (55%) of **8** as yellow needles, mp 136—138 °C; IR (KBr): 1670 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.02 (2H, m, Ph), 7.62 (2H, m, Ph), 7.18 (5H, m, OPh), 5.80 (1H, s, F-3); MS: *m/z* 290 (100), 233 (36), 105 (16), 101 (17), 77 (51), 51 (26). *Anal.* Calcd for $C_{18}H_{10}O_4$: C, 74.48; H, 3.47. Found: C, 74.22; H, 3.70. In a similar manner, **8** was obtained from the reactions of **5**,[1] **6** and **7**[1] with sodium phenoxide in 48%, 21% and 55% yields, respectively.

Methyl 3-Hydroxy-1,4-naphthoquinone-2-acetate (9) Compound **4** (230 mg, 1 mmol) in methanol (100 ml) was added to a solution of sodium methoxide (2160 mg, 40 mmol) in methanol (40 ml) at room temperature. The mixture was stirred for 4 h at the same temperature and poured into ice-cold water. The solution was made acidic with 10% hydrochloric acid and extracted with dichloromethane. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solution was evaporated and the residue was recrystallized from methanol–water to give 100 mg (41%) of **9** as yellow needles, mp 140—141 °C; IR (KBr): 3210 (OH), 1720 (COOMe), 1685 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.03 (2H, m, Ph), 7.67 (3H, m, Ph and OH), 3.70 (3H, s, CH_3), 3.63 (2H, s, CH_2); MS: *m/z* 246 (22), 218 (98), 215 (24), 214 (17), 187 (80), 186 (87), 159 (100), 158 (51), 105 (24), 104 (15), 103 (22), 102 (25), 77 (37), 76 (25), 59 (17). *Anal.* Calcd for $C_{13}H_{10}O_5$: C, 63.42; H, 4.09. Found: C, 63.19; H, 4.20.

Ethyl 3-Hydroxy-1,4-naphthoquinone-2-acetate (10) Compound **4** (230 mg, 1 mmol) in ethanol (120 ml) was added to a solution of sodium ethoxide (680 mg, 10 mmol) in ethanol (20 ml) at room temperature. The mixture was stirred for 2.5 h at the same temperature and poured into ice-cold water. The solution was made acidic with 10% hydrochloric acid and extracted with dichloromethane. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solution was evaporated and the residue was recrystallized from ethanol–water to give 60 mg (23%) of **10** as yellow needles, mp 155—157 °C; IR (KBr): 3240 (OH), 1735 (COOEt), 1670 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.98 (2H, m, Ph), 7.60 (3H, m, Ph and OH), 4.14 (2H, q, CH_2, 7 Hz), 3.60 (2H, s, CH_2), 1.25 (3H, t, CH_3, 7 Hz); MS: *m/z* 260 (20), 232 (68), 215 (37), 188 (58), 187 (100), 186 (37), 160 (23), 159 (65), 158 (21), 105 (21), 103 (16), 102 (16), 77 (27), 76 (18). *Anal.* Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.43; H, 4.68.

2-Phenylthionaphtho[2,3-*b*]furan-4,9-dione (11) Thiophenol (280 mg, 2.5 mmol) in DMSO (4 ml) was added to 60% sodium hydride (100 mg) and the mixture was vigorously stirred. To this mixture, **4** (230 mg, 1 mmol) in DMSO (20 ml) was added at room temperature; the whole was stirred at the same temperature for 30 min and poured into ice-cold water. The solution was extracted with dichloromethane. The organic layer was washed with brine, and then dried over anhydrous sodium sulfate. The solution was evaporated and the residue was recrystallized from ethanol–water to give 190 mg (63%) of **11** as yellow needles, mp 135—136 °C; IR (KBr): 1685 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.03 (2H, m, Ph), 7.63 (2H, m, Ph), 7.30 (5H, m, SPh), 6.75 (1H, s, F-3); MS: *m/z* 307 (20), 306 (100), 262 (22), 221 (31), 121 (16), 105 (22). *Anal.* Calcd for $C_{18}H_{10}O_3S$: C, 70.57; H, 3.29. Found: C, 70.50; H, 3.47. In a similar manner, **11** was obtained from the reactions of **5**, **6** and **7** with sodium benzenethiolate in 58%, 63% and 63% yields, respectively.

2-Methylthionaphtho[2,3-*b*]furan-4,9-dione (12) Compound **4** (230 mg, 1 mmol) in DMSO (20 ml) was added to methanethiol sodium salt (*ca.* 15% in water) (1170 mg, 2.5 mmol) at room temperature. The mixture was stirred for 5 min at the same temperature and poured into ice-cold water. The solution was extracted with dichloromethane. The organic layer was washed with brine, and then dried over anhydrous sodium sulfate. The solution was evaporated and the residue was recrystallized from ethanol–water to give 150 mg (62%) of **12** as red needles, mp 164—165 °C; IR (KBr): 1670 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.07 (2H, m, Ph), 7.63 (2H, m, Ph), 6.65 (1H, s, F-3), 2.60 (3H, s, SCH_3); MS: *m/z* 245 (14), 244 (100), 201 (66). *Anal.* Calcd for $C_{13}H_8O_3S$: C, 63.92; H, 3.30. Found: C, 63.78; H, 3.45.

Diethyl 2-(Naphtho[2,3-*b*]furan-4,9-dione-2-yl)malonate (13) Diethyl malonate (800 mg, 5 mmol) in DMSO (10 ml) was added to 60% sodium hydride (200 mg) and the mixture was vigorously stirred. Then **4** (230 mg, 1 mmol) in DMSO (20 ml) was added at room temperature. The reaction mixture was stirred for 6 h at the same temperature and poured into ice-cold water. The solution was extracted with dichloromethane. The organic layer was washed with brine, and then dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with (hexane : ethyl acetate = 3 : 1) to give a yellow powder (*Rf* = 0.37). The powder was recrystallized from ethanol–water to give 100 mg (28%) of **13** as yellow needles, mp 98—100 °C; IR (KBr): 1755 (COOEt), 1730 (COOEt), 1685 (C=O), 1675 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.03 (2H, m, Ph), 7.63 (2H, m, Ph), 6.98 (1H, s, F-3), 4.78 (1H, s, CH), 4.27 (4H, q, $CH_2 \times 2$, 7 Hz), 1.30 (6H, t, $CH_3 \times 2$, 7 Hz); MS: *m/z* 356 (21), 284 (71), 283 (32), 256 (100), 238 (37), 227 (27), 212 (29), 211 (48), 183 (18), 182 (20), 126 (19), 76 (17). *Anal.* Calcd for $C_{19}H_{16}O_7$: C, 64.04; H, 4.53. Found: C, 63.83; H, 4.57. In a similar manner, **13** was obtained from the reactions of **5** and **7** using the sodium salt of diethyl malonate, in 36% and 6% yields, respectively.

References and Notes

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