A Novel Synthesis of Naphthazarin and Juglone Derivatives by Reaction of Naphthazarin and Juglone with Cyclic Enol Ethers[1)]

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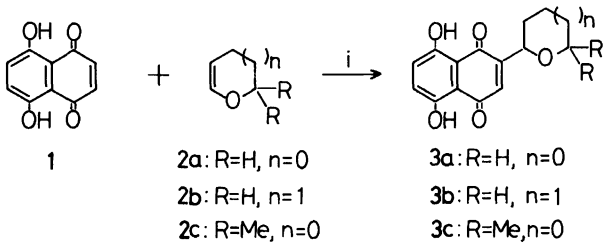
The reaction of naphthazarin with cyclic enol ethers in acetic acid in the presence of BF_3·OEt_2 gave naphthazarin derivatives such as cycloshikonin, having a cyclic ether substituent, in one step. Cyclic enol ethers did not attack the quinone ring of naphthazarin but the benzene ring, and the corresponding naphthazarin derivatives were produced after tautomerization. This reaction was applicable to juglone to give juglone derivatives bearing a cyclic ether substituent.

1,4-Naphthoquinone derivatives occur widely in nature and have been synthesized[2)] from interest in their biological activities. However, there are only a few studies[3)] on the introduction of a side chain into naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) (**1**). We have already reported syntheses of shikonin and cycloshikonin from 1,4,5,8-tetramethoxynaphthalene via many steps.[4)] Furthermore, we have found that the reaction of **1** with cyclic enol ethers gave naphthazarin derivatives having a cyclic ether substituent and we have already reported a part of the work.[5)] This paper describes detailed investigation of the reaction and its application to other naphthazarins, naphthols, and juglone (5-hydroxy-1,4-naphthoquinone) (**14**).

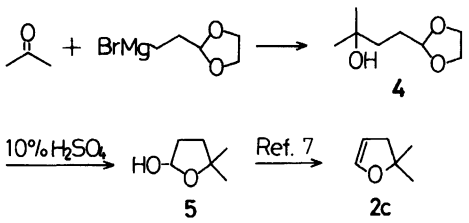
Results and Discussion

Treatment of **1** with commercially available cyclic enol ethers (1.2 equiv, 2,3-dihydrofuran (**2a**) and 3,4-dihydro-2*H*-pyran (**2b**)) in acetic acid in the presence of BF_3·OEt_2 (1.0 equiv) at room temperature for 18 h produced the corresponding naphthazarin derivatives (**3a**) and (**3b**) in the yields of 54% and 34%, respectively (Scheme 1). Treatment of **1** with 2,2-dimethyl-2,3-dihydrofuran (**2c**) under similar conditions gave cycloshikonin (**3c**)[4c)] in 40% yield. The dihydrofuran **2c** was prepared as shown in Scheme 2. Cyclization[6)] of 1,3-dioxolane **4** with 10% H_2SO_4 afforded tetrahydrofuran **5**, followed by dehydration with powdered NH_4NO_3 to yield the dihydrofuran **2c**. Conversion of **5** into **2c** was done by the method reported by Botteghi.[7)]

In an attempt to examine the reaction mechanism of this substitution, the reaction of several naphthazarins, naphthols, and quinones with 2,3-dihydrofuran in acetic acid in the presence of BF_3·OEt_2 were done and the results are listed in Table 1. The reaction of naphthazarins with **2a** (Entries 1—3) gave two products having a tetrahydrofuryl substituent on the benzene ring of naphthazarin. As shown in Entries 5—7, the naphthols gave the corresponding products bearing a tetrahydrofuryl substituent at the ortho position of the hydroxyl group. In cases of 1,4-naphthoquinone, 1,4-benzoquinone, 1,4-dimethoxynaphthalene, and quinizarin, no reaction occurred. On the other hand, Kometani et al.[8)] have reported that a boron trifluoride-catalyzed rearrangement of 2-(aryloxy)tetrahydropyrans gave 2-aryltetrahydropyrans. Terao et al.[9)] reported the preparation of 2-tetrahydrofurylhydroquinone by the reaction of hydroquinones with 2,3-dihydrofuran in the presence of (+)-10-camphorsulfonic acid. Our results and their reports seem to indicate the following interpretation for the reaction of Scheme 1: Cyclic enol ethers don't at-



Scheme 1. i, BF_3·OEt_2 (1.0 equiv), AcOH, room temp, 18 h, **3a**, 54% (69%)[a)]; **3b**, 34% (53%); **3c**, 40% (54%). a) Number in parentheses represents yields based on the amount of consumed naphthazarin.



Scheme 2.

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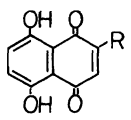
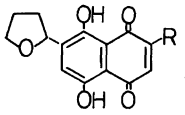
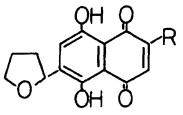
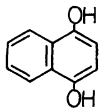
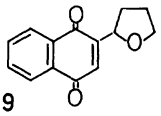
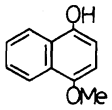
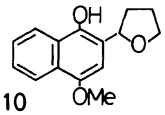
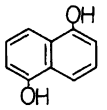
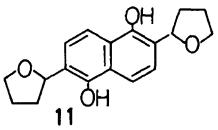
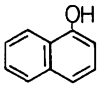
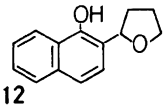
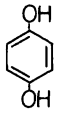
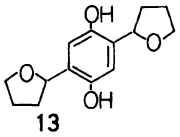
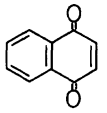
Table 1. Reaction of Naphthazarins, Naphthols, and Quinones with 2,3-Dihydrofuran[a)]

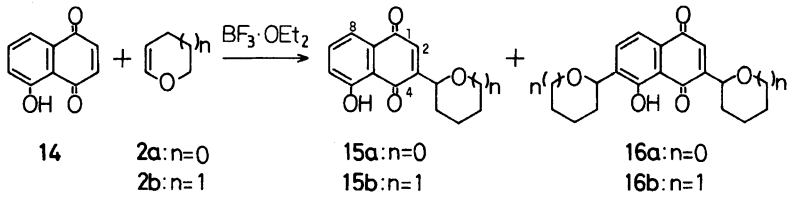
Entry	Substrate	Product	Ratio[b)]	Yield%[c)]
1	 R=Me	 **6a**	 **6b**	1 : 1	24(61)[d)]
2[e)]	OMe	**7a**	**7b**	1 : 6	13(25)
3	Cl	**8a**	**8b**	1 : 1	29(34)
4		 **9**			41
5		 **10**			44
6[f)]		 **11**			48
7[g)]		 **12**			27(52)
8		 **13**			18
9[h)]		—			0

a) Unless otherwise stated, all reactions were done using a substrate (100 mg), 2,3-dihydrofuran (1.2 equiv), and $BF_3 \cdot OEt_2$ (1.0 equiv) in AcOH (20 ml) at room temperature for 18 h. b) Determined by comparison of the intensity of the hydroxyl protons of two isomers in the ^1H NMR spectrum of the mixture. c) Isolated yields. d) Number in parentheses represents yield based upon the amount of the consumed starting material. e) 55 °C, 9 h. f) room temp, 8 h. g) 0.1 equiv $BF_3 \cdot OEt_2$, 0 °C, 1 h. h) In addition, 1,4-benzoquinone, 1,4-dimethoxynaphthalene, and quinizarin did not give the corresponding product and the starting materials were recovered.

tack the quinone ring of naphthazarin but the benzene ring, and primary products bearing cyclic ether substituent on the benzene ring are produced. Due to the tautomeric nature of the naphthazarin system, the primary products may be tautomerized to the more stable form (**3a**—**3c**) having a cyclic ether substituent on the quinone ring.

The reaction mentioned above was observed with juglone (**14**) instead of naphthazarin. Treatment of **14** with **2a** (1.0 equiv) in the presence of $BF_3 \cdot OEt_2$ (0.01 equiv) produced two juglone derivatives (**15a**)[10)] and (**16a**) in 39% yield and 27%, respectively (Scheme 3). Furthermore, treatment of **14** with 1.0 equiv of **2b** afforded two juglone derivatives (**15b**)[10)] and (**16b**) in the yields of 25 and 12%, respectively. When 3.0 equiv of **2b** to **14** was used, their yields rose to 33 and 48%, respectively.

The structure of **15a** was determined from two-dimensional NMR spectra (long-range C–H COSY spectra). When the average J_{CH}-values were set at 10 and 5 Hz, the correlations of C-4 (δ=190.29)–H-2 (δ=6.99) and C-1 (δ=184.35)–H-8 (δ=7.57) were observed respectively. Therefore, the tetrahydrofuryl group was found to be substituted on the 3-position in juglone.



Scheme 3.

Table 2. Analitical and Spectral Data of the New Compounds

Product	Mp, Bp/Pa °C	Formula	Found(Calcd)/% C	H	IR(KBr) ν/cm^{-1}	MS m/z	^{1}H NMR, ^{13}C NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	134.5—135.5	$C_{14}H_{12}O_5$	64.70 (64.61)	4.79 4.65)	1608 (C=O)	260 (M^+)	5.07 (1H, m), 7.15 (1H, d, J=1.7 Hz), 7.19 (2H, s), 12.50 (1H, s), 12.52 (1H, s)
3b	167—168.5	$C_{15}H_{14}O_5$	66.07 (65.69	5.30 5.14)	1612 (C=O)	274 (M^+)	4.58 (1H, m), 7.17 (3H, s), 12.49 (1H, s), 12.57 (1H, s)
4	78—80/267	$C_8H_{16}O_3$			3420 (OH)	159 (M^+-1)	1.22 (3H, s), 1.38 (3H, s), 1.8—2.1 (5H, m), 3.71 (4H, m), 5.06 (1H, m)
6a, 6b	87—93	$C_{15}H_{14}O_5$	65.61 (65.69	5.57 5.14)	1602 (C=O)	274 (M^+)	6.92 (1H, m), 7.24 (1H, s), 12.69 and 12.72 (each **6a**, 1H, s), 12.50 and 12.90 (each **6b**, 1H, s)
7a, 7b	157—160	$C_{15}H_{14}O_6$	61.92 (62.07	5.32 4.86)	1608 (C=O)	290 (M^+)	6.15 (1H, s), 7.37 (1H, s), 12.61 and 12.68 (each **7a**, 1H, s), 12.29 and 13.07 (each **7b**, 1H, s)
8a, 8b	134—140	$C_{14}H_{11}ClO_5$	56.59 (57.06	3.78 3.76)	1610 (C=O)	296 (M^++2) 294 (M^+)	7.32, 7.26, 7.30, 7.31 (each 1H, s), 12.53 and 12.69 (each **8a**, 1H, s), 12.42 and 12.79 (each **8b**, 1H, s)
9	95—96	$C_{14}H_{12}O_3$	73.60 (73.67	5.33 5.30)	1653 (C=O)	228 (M^+)	5.0 (1H, m), 7.04 (1H, d, J=1.6 Hz), 7.5—7.9 (2H, m), 7.9—8.2 (2H, m)
10	oil	$C_{15}H_{16}O_3$	m/z 244.1095 (m/z 244.1099)		3270 (OH)	244 (M^+)	5.1 (1H, m), 6.31 (1H, s), 7.3—7.6 (2H, m), 8.0—8.3 (2H, m), 9.02 (1H, s)
11	191—192	$C_{18}H_{20}O_4$	72.20 (71.98	6.73 6.71)	3210 (OH)	300 (M^+)	5.1 (2H, m), 7.01 (2H, d, J=8.6 Hz), 7.71 (2H, d, J=8.6 Hz), 9.43 (2H, s)
13	198—199.5	$C_{14}H_{18}O_4$	66.79 (66.78	7.22 7.25)	3330 (OH)	250 (M^+)	1.9—2.3 (8H, m), 3.8—4.2 (4H, m), 4.93 (2H, m), 6.50 (2H, s), 8.10 (2H, s)
15a	105—106	$C_{14}H_{12}O_4$	69.28 (68.85	5.13 4.95)	1455 (C=C)	244 (M^+)	^{1}H: 6.99 (1H, d, J=1.6 Hz), 7.57 (1H, dd, J=7.4, 1.6 Hz), 11.93 (1H, s); ^{13}C: 132.87, 152.29, 184.35, 190.29
16a	161.5—162.5	$C_{18}H_{18}O_5$	69.13 (68.78	5.81 5.77)	1425 (C=C)	314 (M^+)	6.99 (1H, d, J=1.8 Hz), 7.57 (1H, d, J=7.8 Hz), 7.80 (1H, d, J=7.8 Hz), 12.31 (1H, s)
15b	121.5—122	$C_{15}H_{14}O_4$	69.81 (69.76	5.48 5.46)	1449 (C=C)	258 (M^+)	^{1}H: 7.02 (1H, d, J=1.5 Hz), 7.25 (1H, m), 7.55 (1H, m), 7.65 (1H, m), 11.98 (1H, s); ^{13}C: 184.32, 189.64
16b	164—165	$C_{20}H_{22}O_5$	70.26 (70.16	6.54 6.48)	1425 (C=C)	342 (M^+)	7.00 (1H, d, J=1.5 Hz), 7.59 (1H, d, J=7.8 Hz), 7.83 (1H, d, J=7.8 Hz), 12.40 (1H, s)

Experimental

All melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were taken on a JEOL JNM-FX60 spectrometer. The analytical and spectral data of the new compounds are summarized in Table 2. Naphthol **12** is described in Ref. 8.

2-(3-Hydroxy-3-methylbutyl)-1,3-dioxolane (4). The crude product that was obtained by the reaction of acetone with 2-(1,3-dioxolane-2-yl)ethylmagnesium bromide was distilled under reduced pressure to give **4** (22%) as an oil.

General Procedure for the Reaction of Naphthazarins, Naphthols, and Juglone with Cyclic Enol Ethers. The reaction of naphthazarin (**1**) with 2,2-dimethyl-2,3-dihydrofuran (**2c**) is described as a typical example. The dihydrofuran **2c** (61.9 mg, 0.63 mmol) was added to a solution of **1** (100 mg, 0.53 mmol) in AcOH (20 ml) at room temperature and stirred for 30 min. To this solution was added BF_3·OEt_2 (75 mg, 0.53 mmol), stirred at room temperature for 18 h, poured into ice-water, and extracted with chloroform. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by thin-layer chromatography on silica gel to give the product **3c** (60 mg, 40%) and the starting material **1** (25 mg).

We would like to thank Professor Kazunori Sakata (Kyushu Institute of Technology) for the measurement of NMR and MS spectra and elemental analyses and Professor Hitoshi Takeshita (Kyushu University) for the measurement of two-dimensional NMR spectra.

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9) M. Shiraishi and S. Terao, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1591.

10) The products **15a** and **15b** appear to be obtained by the reaction of the tautomer (**b**) in juglone with cyclic enol ethers (Chart 1).

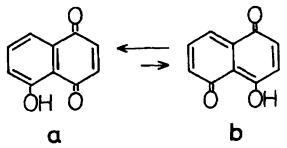

Chart 1.