A Convenient Synthesis of Naphtho[1,2-*b*]furans

Wen-Bing KANG, Takashi SEKIYA, Takeshi TORU, and Yoshio UENO*
Department of Applied Chemistry, Nagoya Institute of Technology, Nagoya 466
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Synopsis. Acid-catalyzed reductive cyclization of 2-alkyl-substituted 3-ethylthio- and 3-phenylthio-1,4-naphthoquinones gave naphtho[1,2-*b*]furans in high yields.

We have been interested in developing new methods for synthesis of naphthoquinone derivatives. Recently we found that 2-phenylthio- and 2-ethylthio-1,4-naphthoquinones (**1a** and **1b**) could be alkylated with lithium enolates[1,2] or pyridinium ylides[2] to give 2-(2-oxoalkyl)-3-phenylthio- and -3-ethylthio-1,4-naphthoquinones **2** in high yields, respectively, and that these alkylated 1,4-naphthoquinones **2** were cyclized successfully to naphtho[2,3-*b*]furan-4,9-dione derivatives. We have further studied on the synthesis of naphtho[1,2-*b*]furans by starting from 3-alkylated 2-thio-substituted 1,4-naphthoquinones **2**. Several naphtho[1,2-*b*]furan derivatives have interesting biological activities such as spasmolytic, local anesthetic,[3] and bactericidal activities.[4] The naphtho[1,2-*b*]furan moiety has also been used as synthetic intermediates for biologically interesting heterocycles.[5] We report here a new synthesis of naphtho[1,2-*b*]furan derivatives from 2-(2-oxoalkyl)-3-phenylthio- and -3-ethylthio-1,4-naphthoquinones **2**.

Treatment of 2-phenacyl-3-phenylthio-1,4-naphthoquinone **2a** (R^1=R^2=Ph)[2] with tin(II) chloride in the presence of hydrochloric acid in acetic acid at room temperature gave 2-phenyl-4-(phenylthio)naphtho[1,2-*b*]furan-5-ol **3a** in 78% yield. Transformation of 2-(2-oxoalkyl)-3-phenylthio-1,4-naphthoquinone **2b**—**2j** (R^1=Ph, R^2=aryl, alkyl) also afforded naphtho[1,2-*b*]furan derivatives **3b**—**3j** in 70—91% yields. The reaction of 1,4-naphthoquinone **2k** or **2l** having an ethylthio substituent also proceeded smoothly to give naphtho[1,2-*b*]furans **3k**—**3l** in 88—95% yields. All reactions of **2**, except **2i**, was carried out at room temperature during a peried of 10 to 60 min, while the reaction of **2i** (R^1=Ph, R^2=2-naphthyl) took 2.5 h at 40 °C. The structures of all these compounds were supported by spectral data and microanalyses. The results as well as the physical and analytical data of the products were summarized in Table 1.

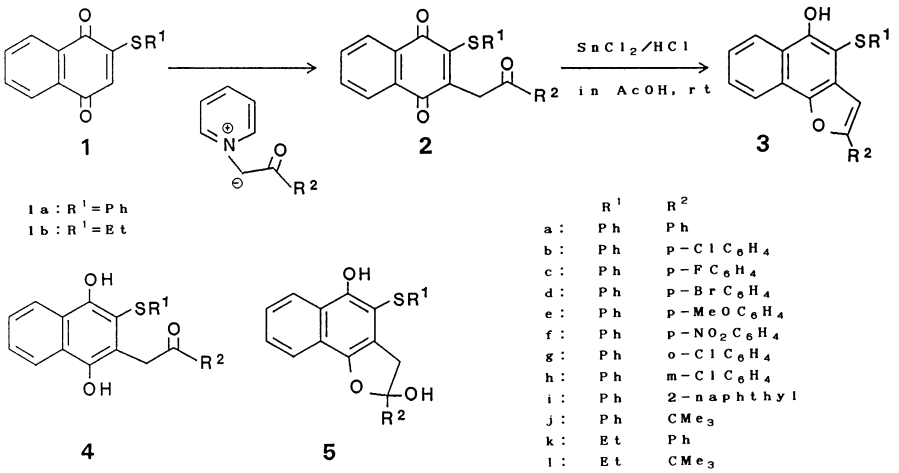
The reasonable mechanism of this reaction may be as follows: the alkylated 1,4-naphthoquinones **2** are reduced by the action of tin(II) chloride and hydrochloric acid[6] to give 1,4-naphthalenediol **4** which is cyclized by acid catalysis to dihydronaphtho[1,2-*b*]furans **5**. Dehydration of **5** affords substituted naphtho[1,2-*b*]furans **3**.

In summary, the reductive cyclization reaction of 3-alkylated 2-thio-1,4-naphthoquinones, conveniently obtainable from the alkylation of 2-thio-1,4-naphthoquinones,[1,2] gives a general method for the synthesis of various naphtho[1,2-*b*]furan compounds. A further study on the bioactivities[7] of these substivituted naphtho[1,2-*b*]furans and application of this reaction is currently in progress in our laboratory.

Experimental

Mps were recorded on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were measured as KBr discs on a JASCO A-102 spectrometer. NMR spectra were determined with a Varian XL-200 spectrometer in deuteriochloroform with TMS as internal standard.

General Procedure for the Preparation of Naphtho[1,2-*b*]furans 3. To a suspension of thio-substituted 1,4-naphthoquinone **2** (0.5 mmol) in acetic acid (10 ml) was added a solution of tin(II) chloride dihydrate (2 mmol) in concentrated hydrochloric acid (4 ml). The reaction mixture was stirred for the time listed in Table 1, and then poured into water and extracted with toluene. The organic layer was washed successively with sodium hydrogencarbonate solution and water, and then dried over anhydrous sodium sulfate. After evaporation of solvent the residue was purified by column chromatography on silica gel using toluene as an eluent to afford **3**. All the compounds except **3l**, obtained as an oil, were recrystallized from methanol.



	R^1	R^2
a:	Ph	Ph
b:	Ph	p-ClC$_6$H$_4$
c:	Ph	p-FC$_6$H$_4$
d:	Ph	p-BrC$_6$H$_4$
e:	Ph	p-MeOC$_6$H$_4$
f:	Ph	p-NO$_2$C$_6$H$_4$
g:	Ph	o-ClC$_6$H$_4$
h:	Ph	m-ClC$_6$H$_4$
i:	Ph	2-naphthyl
j:	Ph	CMe$_3$
k:	Et	Ph
l:	Et	CMe$_3$

Table 1. Preparation of Naphtho[1,2-*b*]furans **3**[a]

Quinone **2**	Reaction time/min	Product **3**	Yield %	Physical and analytical data of **3**			
				Mp °C	IR (cm^{-1}) (KBr)	^1H NMR δ/ppm ($CDCl_3$)	Anal.[b] (C, H)
2a	10	**3a**	78	170—171	3415, 3040, 1622, 1568	6.98 (1H, OH), 7.04—7.18 (8H), 7.20 (1H, 3-H), 7.51 (1H, 8-H), 7.67 (1H, 7-H), 7.78—7.88 (2H), 8.32 (2H, 6-H and 9-H)	$C_{24}H_{16}O_2S$
2b	40	**3b**	82	175—176	3400, 3040, 1625, 1572	7.07 (1H, OH), 7.09—7.31 (6H, 3-H and Ph), 7.41 (2H), 7.55 (1H, 8-H), 7.70 (1H, 7-H), 7.77—7.89 (2H), 8.35 (2H, 6-H and 9-H)	$C_{24}H_{15}O_2SCl$
2c	20	**3c**	82	149.5—150.5	3355, 3040, 1570	7.05 (1H, OH), 7.10—7.34 (8H), 7.59 (1H, 8-H), 7.75 (1H, 7-H), 7.86—7.95 (2H), 8.40 (2H, 6-H and 9-H)	$C_{24}H_{15}O_2SF$
2d	15	**3d**	88	192—193	3395, 1595	7.09—7.27 (6H, OH and Ph), 7.30 (1H, 3-H), 7.52—7.67 (3H), 7.68—7.82 (3H), 8.37 (2H, 6-H and 9-H)	$C_{24}H_{15}O_2SBr$
2e	45	**3e**	91	145.5—146.5	3380, 3030, 1605, 1565	3.38 (3H, CH_3), 6.98 (1H, OH), 7.00 (2H), 7.10—7.34 (6H, 3-H and Ph), 7.54 (1H, 8-H), 7.72 (1H, 7-H), 7.84 (2H), 8.37 (2H, 6-H and 9-H)	$C_{25}H_{18}O_3S$
2f	20	**3f**	70	207—208	3375, 1590, 1500	7.13—7.36 (7H, 3-H, OH, and Ph), 7.64 (1H, 8-H), 7.78 (1H, 7-H), 8.02 (2H), 8.10—8.30 (4H)	$C_{24}H_{15}NO_4S$
2g	60	**3g**	91	124—125	3385, 3050	7.10—7.65 (11H), 7.72 (1H, 7-H), 8.14 (1H), 8.38 (2H, 6-H and 9-H)	$C_{24}H_{15}O_2SCl$
2h	60	**3h**	75	149—150	3390, 3035, 1568, 1466	7.10—7.27 (6H, OH and Ph), 7.29 (1H, 3-H), 7.32—7.46 (2H), 7.58 (1H, 8-H), 7.74 (2H, 7-H), 7.89 (1H), 8.35—8.44 (2H, 6-H and 9-H)	$C_{24}H_{15}O_2SCl$
2i	210[c]	**3i**	76	191—192	3400, 3035, 1620	7.11—7.33 (6H), 7.43—7.66 (3H), 7.73 (1H, 7-H), 7.80—7.99 (5H), 8.35—8.47 (3H)	$C_{28}H_{18}O_2S$
2j	15	**3j**	85	130.5—131	3420, 2960, 1624, 1575	1.40 (9H, $3CH_3$), 6.47 (1H, OH), 7.06—7.30 (6H, 3-H and Ph), 7.51 (1H, 8-H), 7.68 (1H, 7-H), 8.27 (1H, 9-H), 8.36 (1H, 6-H)	$C_{22}H_{20}O_2S$
2k	10	**3k**	95	94.5—96	3360, 3050, 2920, 1572	1.25 (3H, CH_3), 2.84 (2H, CH_2), 7.25 (1H, OH), 7.32 (1H, 3-H), 7.35—7.58 (4H), 7.66 (1H, 7-H), 7.96 (2H), 8.33 (2H, 6-H and 9-H)	$C_{20}H_{16}O_2S$
2l	10	**3l**	88	Oil	3380, 3050, 2955, 1572	1.23 (3H, CH_3), 1.45 (9H, $3CH_3$), 2.81 (2H, CH_2), 6.59 (1H, OH), 7.28 (1H, 3-H), 7.48 (1H, 8-H), 7.62 (1H, 7-H), 8.22 (1H, 9-H), 8.31 (1H, 6-H)	$C_{18}H_{20}O_2S$

a) All reactions except that of **2i** were carried out at room temperature. b) Microanalyses for all compounds were satisfactorily done in ±0.3% of calculated values. c) This reaction was carried out at 40 °C.

References

1) W. B. Kang, S. Nan'ya, T. Toru, and Y. Ueno, *Chem. Lett.*, **1988**, 1415;

2) W. B. Kang, T. Sekiya, T. Toru, and Y. Ueno, *J. Chem. Soc., Perkin Trans. 1*, in press.

3) A. A. Stolyarchuk, T. I. Mukhanova, N. I. Ivanova, and V. V. Danil'chuk, *Fiziol. Akt. Veshchesstva*, **20**, 16 (1988).

4) C. Bilger, P. Demerseman, J. P. Buisson, R. Royer, P. Gayral, and J. Fourniat, *Eur. J. Med. Chem.*, **22**, 213 (1987).

5) H. Takahata, A. Anazawa, K. Moriyama, and T. Yamazaki, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1501; H. Takahata, A. Anazawa, K. Moriyama, and T. Yamazaki, *Chem. Lett.*, **1986**, 5; L. Capuano and P. Moersdorf, *Liebigs Ann. Chem.*, **1982**, 2178; H. E. Hoegberg, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2517.

6) D. B. Bruce and R. H. Thomoson, *J. Am. Chem. Soc.*, **76**, 1429 (1954).

7) A preliminary test for **3f** against HeLa cells was carried at the Research Center of Sankyo Company and the IC_{50} of **3f** was found to be 8.8 μg ml^{-1}.