A Facile Synthesis of 2-Acetylnaphtho[2,3-*b*]furan-4,9-dione

Jyunichi Koyanagi, Katsumi Yamamoto, Kouji Nakayama, and Akira Tanaka*

Faculty of Pharmaceutical Science, Josai University, 1-1 Keyakidai, Sakado-shi, Saitama 350-02, Japan

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Reaction of the parent naphtho[2,3-*b*]furan-4,9-dione **2** with various electrophilic reagents was difficult, and only nitration of **2** gave small amounts of 2-nitronaphtho[2,3-*b*]furan-4,9-dione **4**. Then 2-acetylnaphtho[2,3-*b*]furan-4,9-dione **1** was not obtained by the acetylation of **2**. On the other hand, compound **1** that is isolated from *Tabebuia Cassinoides* and has cytotoxic activity, was obtained from 3-lithiofuran in five steps.

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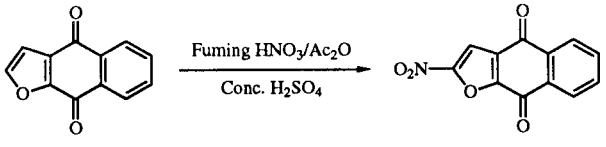
2-Acetylnaphtho[2,3-*b*]furan-4,9-dione **1** isolated from *Tabebuia Cassinoides* (Lam.) DC (*Bignoniaceae*) has cytotoxic activity [1a], and its derivatives are particularly interesting because of their biological activity. However, there are only a few reports [1] even about the synthesis of **1** which has a relatively simple structure, because the synthesis of the derivatives is very difficult. Also, some of the reports are not sufficient regarding the yield and large scale preparation. On the other hand, the authors have previously achieved the preparation of the parent naphtho[2,3-*b*]furan-4,9-dione **2** [2] by adding 3-lithiofuran [3] to phthalic anhydride followed by treating the formed 2-(3-furanoyl)benzoic acid **3** [2] with lithium diisopropylamide (LDA). In the present paper, we wish to report a new facile route, which utilized the above method, to prepare **1**.

First, in order to obtain 2-(1-hydroxyethyl)naphtho-[2,3-*b*]furan-4,9-dione, that could be regarded as a precursor to **1**, the reaction of the 2-lithio compound of **2** with acetaldehyde was carried out, but the attempt was unsuccessful because it was difficult to form the 2-lithio derivative from **2** by LDA [4]. Next, **2** was treated with a large excess of acetyl chloride in the presence of aluminum chloride, but only **2** was recovered. Therefore, in order to examine the reactivities of **2** in electrophilic substitutions, the reactions of **2** with various electrophiles were carried out, but 2-nitronaphtho[2,3-*b*]furan-4,9-dione **4** was obtained only in small amounts by nitration.

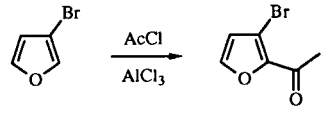
Scheme 1



2 **4**
yield: 20%

Thus, it was revealed that **2** is inactive in electrophilic substitution. Accordingly, the appropriate substituent group must be introduced onto the α-position of the furan ring before the cyclization. Then, with the expectation of obtaining 2-acetyl-4-bromofuran, 3-bromofuran [5] was allowed to react with acetyl chloride in the presence of aluminum chloride; however, only 2-acetyl-3-bromofuran **5** [6] instead of 2-acetyl-4-bromofuran was obtained.

Scheme 2

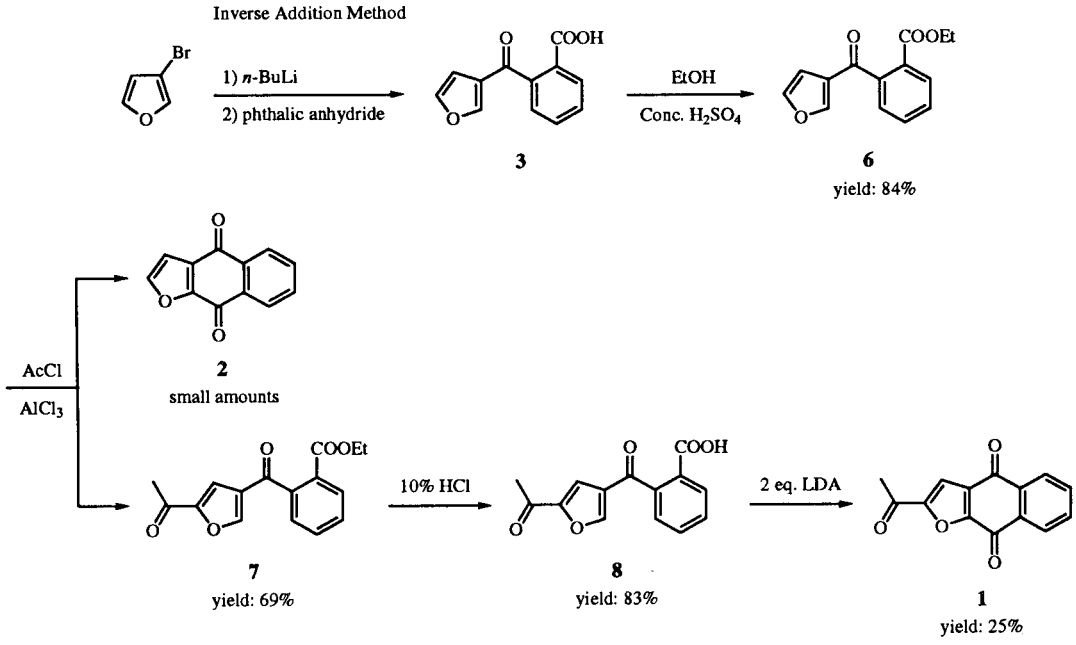


5
yield: 51%

It is thought that the acetylation of furans, bearing an electron-withdrawing group at the 3-position, predominantly yields 2,4-disubstituted furans. Compound **3**, a raw material of **2**, was then esterified in the usual way followed by heating the obtained ester ethyl 2-(3-furanoyl)-benzoate **6** with a large excess of acetyl chloride and aluminum chloride in dichloromethane to give the desired ethyl 2-(2-acetyl-4-furanoyl)benzoate **7** in 69% yield. It is interesting that small amounts of **2** were formed as a by-product. Further, the acetylation of **6** required a longer reaction time compared with the acetylation of 3-bromofuran owing to the carbonyl group at the 3-position of the furan ring. Hydrolysis of the ester **7** was attempted under basic conditions (sodium hydroxide or lithium hydroxide), but the expected 2-(2-acetyl-4-furanoyl)benzoic acid **8** was not obtained, because **7** was unstable under basic conditions. The ester **7** was then heated with 10% hydrochloric acid to give **8** in a good yield. Next, the cyclization of **8** to **1** was attempted using polyphosphate ester (PPE), but only an intractable complex mixture was obtained. Finally, for the purpose of cyclization under basic conditions, **8** was treated with two equimolar amounts of LDA in a manner similar to the cyclization of **3** to give **1**.

In conclusion, **1** which has cytotoxic activity, was obtained from 3-lithiofuran in only five steps. Further, the method is very useful for preparing naphtho[2,3-*b*]furan-4,9-dione derivatives, because the introduction of various substituent groups at the 2-position of the parent quinone

Scheme 3



2 is possible. Further work on the reduction of the acetyl group at the 2-position of **1** 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. All boiling points are uncorrected. The pmr spectra were determined at 60 MHz with a Nippon Denshi JNM PMR-60SI spectrometer with TMS as an internal reference. The ir spectra were measured with a JASCO IR-810 spectrometer. The mass spectra were obtained on a Nippon Denshi DX-300 spectrometer at 70 eV. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately prior to use. Chromatography was carried out using silica gel (Wakogel C-300, Wako Pure Chemical Industries Ltd.).

2-Nitronaphtho[2,3-*b*]furan-4,9-dione **4**.

Fuming nitric acid (0.7 ml, d = 1.52) was added to acetic anhydride (1.6 ml) at -5° with stirring, and one drop of sulfuric acid was added. To the above, **2** (0.2 g, 1 mmole) was added slowly at -5°, and the mixture was stirred for 3 hours at the same temperature and poured into ice-cold water. The solution was neutralized with sodium bicarbonate and extracted with ether. The ether layer was washed with brine and dried over anhydrous sodium sulfate, and then the solution was evaporated. The residue was recrystallized from ethanol-water to give **4** 50 mg (20%) as brown needles, mp 226~227°; ir (potassium bromide): 1685, 1675 (C=O), 1550, 1340 (NO_2) cm^{-1}; pmr (DMSO-d_6): δ 8.17 (1H, s, F-3), 8.10~7.77 (4H, m, Ph); ms: m/z 243 (M^+).

Anal. Calcd. for $C_{12}H_5NO_5$: C, 59.27; H, 2.07; N, 5.76. Found: C, 59.34; H, 2.36; N, 5.54.

2-Acetyl-3-bromofuran **5**.

To a suspension of anhydrous aluminum chloride (8.0 g, 60 mmoles) in anhydrous dichloromethane (20 ml), acetyl chloride (5.0 g, 64 mmoles) in anhydrous dichloromethane (20 ml) was added at 0~5° with stirring. To the above, 3-bromofuran (3.0 g, 20 mmoles) in anhydrous dichloromethane (40 ml) was added at 0~5° with stirring; the mixture was stirred for 15 minutes at the same temperature and then poured into ice-cold water. The solution was extracted with dichloromethane, the dichloromethane layer was washed with water, 5% sodium bicarbonate solution and brine, and then dried over anhydrous sodium sulfate. The solution was evaporated and the residue was purified by chromatography on silica gel with (chloroform:hexane = 3:2) to give **5** 2.0 g (51%) as white needles, mp 35~36° (mp 43.5~44° [6b]); ir (potassium bromide): 1660 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 7.38 (1H, d, F-5, 2 Hz), 6.52 (1H, d, F-4, 2 Hz), 2.50 (3H, s, CH_3); ms: m/z 190 (M^++2), 188 (M^+), 173 (M^+-Me).

Exact Mass Calcd. for $C_6H_5BrO_2$: 187.9473. Found: 187.9490.

Ethyl 2-(3-Furanoyl)benzoate **6**.

To a solution of **3** (6.0 g, 28 mmoles) in absolute ethanol (100 ml), sulfuric acid (2.0 g) was added. The mixture was refluxed with stirring for 8 hours. At the end of the reaction, excess ethanol was evaporated, and the solution was then poured into ice-cold water. The solution was extracted with ether, the ether layer was washed with 5% sodium bicarbonate solution, water, then brine and dried over anhydrous sodium sulfate. The solution was evaporated and the residue was redistilled under reduced pressure to give **6** 5.7 g (84%) as a yellowish liquid, bp 167~169°(7 mm Hg); ir (neat): 1725 (COOEt), 1670 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 7.94 (1H, m, Ph), 7.58~7.36 (5H, m, F and Ph), 6.78 (1H, d, F-4), 4.15 (2H, q, CH_2, 7 Hz), 1.17 (3H, t, CH_3, 7 Hz); ms: m/z 244 (M^+), 199 (M^+-OEt).

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.81; H, 5.11.

Ethyl 2-(2-Acetyl-4-furanoyl)benzoate **7**.

To a suspension of anhydrous aluminum chloride (34.0 g, 255 mmoles) in anhydrous dichloromethane (80 ml), **6** (6.0 g, 25 mmoles) in anhydrous dichloromethane (80 ml) was added with stirring at 0~5°; and the mixture was stirred for 30 minutes at the same temperature. To the above, acetyl chloride (20.0 g, 255 mmoles) in anhydrous dichloromethane (80 ml) was added at 0~5°; the mixture was refluxed with stirring for 30 hours and poured into ice-cold water. The solution was extracted with dichloromethane. The dichloromethane 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 purified by chromatography on silica gel with (hexane:ethyl acetate = 2:1). First **2** 30 mg (0.6%) as yellow needles, mp 220~222° (mp 220~221° [2]) was eluted. Next, **7** 4.8 g (69%) was obtained as yellow needles, mp 44~45°; ir (potassium bromide): 1720 (COOEt), 1690 (COMe), 1675 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 7.97 (1H, m, Ph), 7.72 (1H, s, F-5), 7.63~7.25 (3H, m, Ph), 7.41 (1H, s, F-3), 4.19 (2H, q, CH_2, 7 Hz), 2.48 (3H, s, CH_3), 1.23 (3H, t, CH_3, 7 Hz); ms: m/z 286 (M^+), 271 (M^+-Me), 241 (M^+-OEt).

Exact Mass Calcd. for $C_{16}H_{14}O_5$: 286.0841. Found: 286.0827.

2-(2-Acetyl-4-furanoyl)benzoic Acid **8**.

To a solution of **7** (2.0 g, 7 mmoles) in dioxane (40 ml), 10% hydrochloric acid (100 ml) was added. The mixture was refluxed with stirring for 9 hours and poured into ice-cold water. The solution was extracted with ethyl acetate. The desired compound **8** was extracted with 5% sodium bicarbonate solution from the ethyl acetate layer. The aqueous solution was made acidic with 10% hydrochloric acid and then extracted with ethyl acetate. The ethyl acetate layer was washed with brine and dried over anhydrous sodium sulfate. The solution was evaporated and the residue was recrystallized from benzene-hexane to give **8** 1.5 g (83%) as white needles, mp 155°; ir (potassium bromide): 1685 (COOH, COMe), 1670 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 7.94 (1H, m, Ph), 7.60 (1H, s, F-5), 7.51~7.15 (3H, m, Ph), 7.33 (1H, s, F-3), 7.17 (1H, bs, OH), 2.45 (3H, s, CH_3); ms: m/z 258 (M^+), 243 (M^+-Me).

Anal. Calcd. for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90. Found: C, 64.82; H, 3.99.

2-Acetylnaphtho[2,3-*b*]furan-4,9-dione **1**.

n-Butyllithium (6.2 ml of 1.63 *M*-solution in hexane, 10 mmoles) was added to diisopropylamine (1.4 ml, 10 mmoles, freshly distilled from solid potassium hydroxide) with stirring at -10° in an atmosphere of argon. After 15 minutes, the resulting viscous oil was diluted with THF (20 ml), cooled to -78° and **8** (1.3 g, 5 mmoles) in THF (15 ml) was added. The mixture was stirred at -78° for 30 minutes; then the mixture was warmed to 0° for 20 minutes and poured into ice-cold water. The solution was made acidic with 10% hydrochloric acid and extracted with ether. The ether 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 **1** 0.3 g (25%) as yellow needles, mp 218~219°(mp 220° [1a]); ir (potassium bromide): 1690 (COMe), 1675 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 8.15 (2H, m, Ph), 7.73 (2H, m, Ph), 7.50 (1H, s, F-3), 2.63 (3H, s, CH_3); ms: m/z 240 (M^+), 225 (M^+-Me).

Anal. Calcd. for $C_{14}H_8O_4$: C, 70.00; H, 3.36. Found: C, 69.98; H, 3.56.

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[4] To make sure that the 2-lithio compound was obtained from the reaction of **2** with LDA, the parent **2** was treated with LDA; then the mixture was poured into deuterium oxide, but only **2** was recovered.

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