A Short-step Synthesis of Naphtho[2,3-*b*]furan-4,9-dione

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Phthalic anhydride in THF was added to 3-lithiofuran **2** in THF to give 3,3-di-(3-furyl)-1,3-dihydroisobenzofuran-1-one **4**. On the other hand, **2** in THF was added to phthalic anhydride in THF to give 2-(3-furanoyl)benzoic acid **3** by the inverse addition method. Further, the parent naphtho[2,3-*b*]furan-4,9-dione **1** was obtained from the reaction of **3** with two equimolar amounts of LDA.

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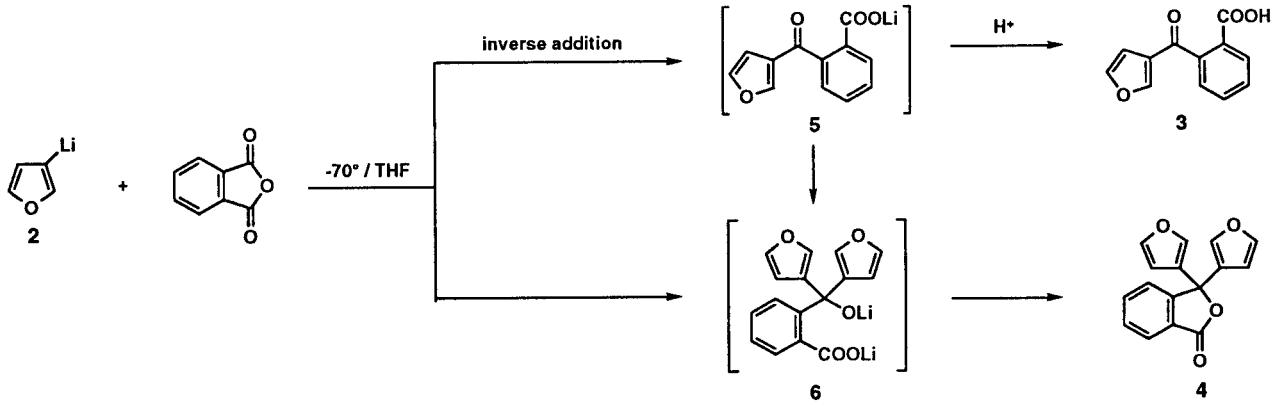
A number of naphtho[2,3-*b*]furan-4,9-diones, which have interesting biological activities, have been isolated from various plants [1]. For example, 2-acetylnaphtho[2,3-*b*]furan-4,9-dione having an acetyl group at the 2-position of the parent naphtho[2,3-*b*]furan-4,9-dione **1** shows cytotoxic activity [2]. Also, Maturone, having a methyl group at the 5-position and a hydroxymethyl group at the 3-position of **1**, has been used for the treatment of diabetes [3]. As previously mentioned, since naphtho[2,3-*b*]furan-4,9-diones exhibit different biological activities depending upon the position and kinds of substituent groups, an organic chemist is particularly interested in studying the synthesis of **1** and its derivatives. While there are a few reports about the synthesis of **1** [4], they are not convenient because all methods require many steps. In the present paper, we wish to report the short-step synthesis of **1** from 3-lithiofuran **2** [5].

First, the synthesis of 2-(3-furanoyl)benzoic acid **3** was examined as an intermediate to prepare **1**. It is expected that **3** is easily obtained by the reaction of **2** with phthalic anhydride. Thus, phthalic anhydride in THF was added to **2** in THF at -70° in an atmosphere of nitrogen. However, 3,3-di-(3-furyl)-1,3-dihydroisobenzofuran-1-one **4** was only obtained. The structure of **4** was confirmed from the various spectral data and the elemental analyses. These results suggest that the lithium salt **5**, once formed, further reacts with unreacted **2** to give the dilithium salt **6** , followed by lactonization of **6** to give **4**. Next, to prevent the second nucleophilic addition to **5**, a similar reaction was attempted using the inverse addition method. That is, **2** in THF was added to phthalic anhydride in THF at -70° for 1 hour in an atmosphere of nitrogen to give **3** in 41% yield (Scheme 1). Compound **3** is a new substance, and the structure was confirmed from the various spectral data and elemental analyses.

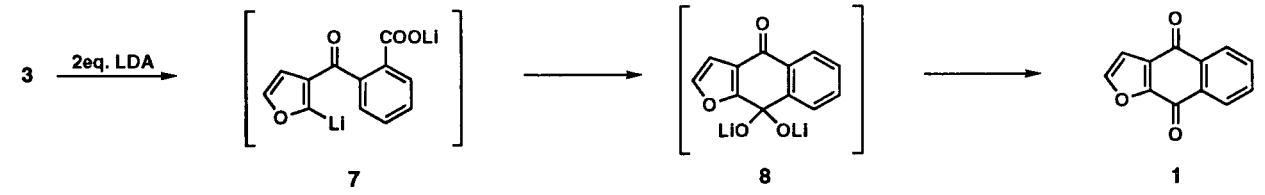
Moreover, to cyclize **3** to **1** under Friedel-Crafts conditions, the chlorination of the acid **3** was examined by using thionyl chloride or phosphorus pentachloride, but the attempt was unsuccessful. Further, cyclodehydration of **3** was tried by using polyphosphate ester or trimethylsilyl polyphosphate, but an intractable complex mixture was also obtained. For these reasons, it is shown that the furan ring is labile under acidic conditions. Consequently, the cyclization of **3** was tried under basic conditions. As shown in Scheme 2 , it was expected that the treatment of compound **3** with two equimolar amounts of lithium diisopropylamide (LDA) would give the desired compound **1** *via* the dilithium salt **7** and the dilithio adduct **8**. As already mentioned, compound **3** was allowed to react with two equimolar amounts of LDA in THF under an atmosphere of nitrogen to afford compound **1** in 20% yield.

In conclusion, it is interesting that phthalic anhydride was added to **2** to give **4**. On the other hand, **2** was added

Scheme 1



Scheme 2



to phthalic anhydride by the inverse addition method to give **3**. It is noteworthy that though the yield is not satisfactory, the parent compound **1** of the biologically interesting natural products was obtained from **2** in only two steps. Further work on the substitutions 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. The pmr spectra were determined at 270 MHz using a Nippon Denshi JEOL-GX270FT NMR spectrometer with TMS as the internal reference. The ir spectra were measured using 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. Petroleum benzin refers to the fraction of bp 50-90°.

3,3-Di-(3-furyl)-1,3-dihydroisobenzofuran-1-one **4**.

3-Bromofuran (3.6 g, 24 mmoles) was added to *n*-butyllithium (18.0 ml of 1.68 *M*-solution in hexane, 30 mmoles) with stirring at -70° in an atmosphere of nitrogen. The mixture was allowed to react for 10 minutes. To the mixture, phthalic anhydride (3.9 g, 26 mmoles) in THF (40 ml) was added at -70°. The mixture was warmed to room temperature for 30 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 brine, and then dried over anhydrous sodium sulfate, and then the solution was evaporated. The residue was recrystallized from petroleum benzin to give **4**, 0.4 g (12%) as white prisms, mp 103°; ir (potassium bromide): 1765 cm^{-1} (C=O); pmr (deuteriochloroform): δ 7.94 (1H, d, Ph), 7.72 (1H, m, Ph), 7.60 (1H, dd, Ph), 7.53 (1H, t, Ph), 7.40 (2H, t, F-5 x 2), 7.35 (2H, t, F-2 x 2), 6.35 (2H, t, F-4 x 2); ms: m/z 266(M^+).

Anal. Calcd. for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79. Found: C, 72.23; H, 3.95.

2-(3-furanoyl)benzoic Acid **3**.

3-Bromofuran (10.8 g, 73 mmoles) was added to *n*-butyllithium (55.3 ml of 1.63 *M*-solution in hexane, 90 mmoles) with stirring at -70° in an atmosphere of nitrogen. The mixture was allowed to react for 10 minutes. The mixture was then added to phthalic anhydride (11.7 g, 79 mmoles) in THF (60 ml) at -70° in an atmosphere of nitrogen for 1 hour. The mixture was warmed to room temperature for 30 minutes and then poured into ice-cold water. The solution was made acidic with 10% hydrochloric acid and extracted with ether. The desired compound **3** was extracted with 5% sodium bicarbonate solution from the ether layer. The aqueous solution was made acidic with 10% hydrochloric acid and then extracted with ether. The ether layer was washed with brine, and dried over anhydrous sodium sulfate. The solution was evaporated, and the residue was recrystallized from water to give **3**, 6.5 g (41%) as white scales, mp 129°; ir (potassium bromide): 1715 (COOH), 1645 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 10.19 (1H, bs, OH), 8.05 (1H, dd, Ph), 7.64 (1H, m, Ph), 7.60 (1H, q, F-2), 7.55 (1H, m, Ph), 7.44 (1H, d, F-5), 7.42 (1H, dd, Ph), 6.81 (1H, d, F-4); ms: m/z 216 (M^+).

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.42; H, 3.98.

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

n-Butyllithium (30.5 ml of 1.66 *M*-solution in hexane, 51 mmoles) was added to diisopropylamine (7 ml, 50 mmoles, freshly distilled from solid potassium hydroxide) with stirring at -10° in an atmosphere of nitrogen. After 15 minutes the resulting viscous oil was diluted with THF (100 ml), cooled to -78° and **3** (5.5 g, 25 mmoles) in THF (75 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, then brine, and dried over anhydrous sodium sulfate. The solution was evaporated, and the residue was recrystallized in ethanol-water to give **1**, 1.0 g (20%) as yellow needles, mp 220-221° (mp 225-225.5° [4a]); ir (potassium bromide): 1685 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 8.23-8.16 (2H, m, Ph), 7.79-7.72 (2H, m, Ph), 7.77 (1H, m, F-2), 7.00 (1H, m, F-3); ms: m/z 198 (M^+).

Anal. Calcd. for $C_{12}H_6O_3$: C, 72.73; H, 3.05. Found: C, 72.48; H, 3.10.

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