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One-Pot Synthesis of Naphtho[2,3-*b*]furan-4,9-diones by Sequential Coupling/Ring Closure Reactions

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Abstract: Treatment of 3-phenyliodonio-1,2,4-trioxo-1,2,3,4-tetrahydronaphthalenides with terminal acetylenes in the presence of a bis(triphenylphosphine)palladium chloride-cuprous iodide catalyst or cuprous oxide in *N*-methylpiperidine or pyridine, respectively, furnished the corresponding 2-substituted naphtho[2,3-*b*]furan-4,9-diones in moderate to good yields. The utility of this method was demonstrated in the synthesis of a cytotoxic natural product, 2-(1-hydroxyethyl)naphtho[2,3-*b*]furan-4,9-dione.
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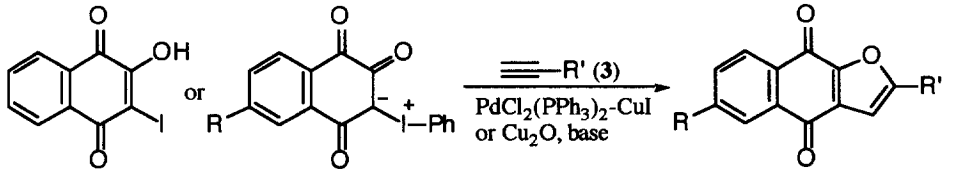
Although transition metal-catalyzed coupling reactions of aryl halides carrying an appropriate functional group at the *o*-position with terminal acetylenes, followed by ring closure, have been successfully employed for synthesizing a variety of heterocyclic compounds,[1] studies on the synthesis of heterocycle-fused quinones have so far remained unreported.[2] In continuation of our studies on the preparation of quinone derivatives,[3] we have begun work on exploring an approach to the direct synthesis of furonaphthoquinone derivatives by a method based on the utilization of the transition metal-catalyzed coupling/ring closure sequence. In this paper, we wish to describe the results of our preliminary investigation, which show for the first time that the strategy is applicable to iodoquinone derivatives **1** and **2**, thus providing a novel method for the synthesis of 2-substituted naphtho[2,3-*b*]furan-4,9-dione derivatives **4**, including a cytotoxic natural product, 2-(1-hydroxyethyl)naphtho[2,3-*b*]furan-4,9-dione (**4d**) (Scheme 1). While there have been a number of reports[4] concerning the synthesis of naphtho[2,3-*b*]furan-4,9-dione derivatives because of their biological activities,[5] few one-step syntheses have been reported.[3a,d,6]



1 **2** **4**

Scheme 1.

We initiated our investigation by reacting 2-hydroxy-3-iodo-1,4-naphthoquinone (**1**)[10] with phenylacetylene (**3a**) under conditions similar to those reported by Sonogashira et al.[11] for the coupling of aryl

Table 1. Preparation of Naphtho[2,3-*b*]furan-4,9-diones **4**.

Entry	**1** or **2**	**3** (eq.)	Conditions[a]	**4** (Yield/%)[b]
1	**1**	**3a** [R'=Ph] (10)	A	**4a**[g] (20)
2	**2a** (R=H)	**3a** (10)	A	**4a** (66)
3	**2b** (R=OMe)	**3a** (10)	A[f]	**4b** (61)
4	**2a**	**3c** [R'=*n*-C_4H_9][c] (5)	A	**4c**[h] (57)
5	**2a**	**3a**[d] (5)	A	**4a** (59)
6	**2a**	**3d** [R'=CH(OH)Me][e] (5)	A	**4d**[i] (20)
7	**2a**	**3d** (10)	B	**4d** (45)
8	**2a**	**3e** [R'=CH_2OH] (10)	B	**4e** (45)
9	**2a**	**3f** [R'=CH_2OMe] (10)	B	**4f** (42)

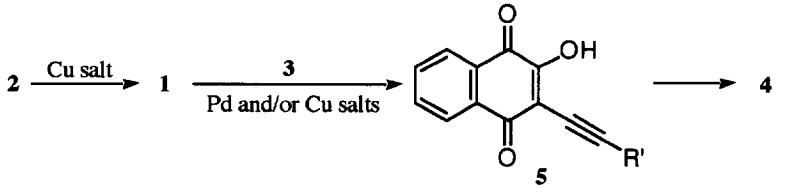
[a]Reactions were carried out on a 0.25-1 mmol reaction scale. A: $PdCl_2(PPh_3)_2$ (2.8 mol %) and CuI (5.2 mol %) in NMP, r. t., 18 h. B: Cu_2O in pyridine, 80 °C, 2 h. [b]Isolated yields. [c]1-(Tributylstannyl)-1-hexyne (ref. 7) was used. [d]Phenyl(tributylstannyl)acetylene was used. [e]1-(Tributylstannyl)-3-(tributylstanyloxy)-1-butyne was used. [f]DMF was used as a solvent. [g]Refs. 3a and 8. [h]Ref. 3a. [i]A metabolite from *Tabebuia cassinoides* and *Crescentia cujute* (ref. 9). Mp 155-157 °C (MeOH) (lit.,[9] 156.5-157.5 °C).

halides with terminal alkynes (Conditions A). Thus, treatment of **1** with **3a** (3 equiv.) in the presence of bis(triphenylphosphine)palladium dichloride (2.8 mol%) and cuprous iodide (5.2 mol%) in *N*-methylpiperidine (NMP)[12] at room temperature for 18 h gave 2-phenylnaphtho[2,3-*b*]furan-4,9-dione (**4a**)[3a,8] in 13% yield. The low yield would probably be due to not only the non-availability of **1** in a pure form but also the competitive consumption of **3a** by oxidative coupling during the course of the reaction since a considerable amount of 1,4-diphenyl-1,3-butadiyne was obtained from the reaction mixture. When the reaction was carried out by using 10 equiv. of **3a**, a slightly improved result (20%) was achieved (Table 1, Entry 1). However, the use of more than 10 equivalents of **3a** did not result in further improvement. The satisfactory result was obtained by using 3-phenyliodonio-1,2,4-trioxo-1,2,3,4-tetrahydronaphthalenide (**2a**), prepared from 2-hydroxy-1,4-naphthoquinone by simply treating with (diacetoxyiodo)benzene in nearly quantitative yield,[10] instead of **1**. Thus, treatment of **2a** with 10 equiv. of **3a** under the same conditions for the reaction of **1** with **3a** gave **4a** in rather improved 66% yield (Entry 2). The reaction of methoxylated trioxonaphthalenide **2b**[13] with **3a** also gave the corresponding furoquinone **4b** in 61% yield, though the use of DMF as solvent was essential for the satisfactory production (Entry 3). In the absence of either of the palladium salt or cuprous iodide, no formation of the desired product was observed. Subsequently, the reaction of **2a** with an aliphatic terminal acetylene such as 1-hexyne was examined. We found that it was very sluggish and the desired furoquinone **4c** was produced only in 12% yield even at 100 °C. Fortunately, the use of (1-tributylstannyl)-1-hexyne (**3c**) instead of 1-hexyne proved to give a satisfactory yield (57%) of **4c** (Entry 4). Phenyl(tributylstannyl)acetylene also worked well to give **4a** in 59% yield (Entry 5).

We next examined the reaction of **2a** with 3-butyn-2-ol (**3d**), aiming at direct synthesis of the natural product **4d**. The reaction of **2a** with **3d** resulted in formation of an intractable mixture of products containing no more than a trace of the desired product. However, the reaction of **2a** with 1-(tributylstannyl)-3-(tributylstannyloxy)-1-butyne[14] gave **4d**[9] in 20% yield (Entry 6). In addition, cuprous oxide was found to be more effective for its production. Thus, treatment of **2a** with **3d** in pyridine in the presence of a molar amount

of cuprous oxide at 80 °C for 2h gave **4d** in 45% yield (Entry 7). These conditions are similar to those reported by Owen et al. for the synthesis of benzofurans from 2-iodophenols and terminal acetylenes.[1b] Longer reaction times not only failed to further enhance the yield, but rather tended to decrease it through secondary decomposition. Similarly, the reactions of **2a** with propargyl alcohol (**3e**) and 3-methoxypropyne (**3f**) under the cuprous oxide conditions afforded the corresponding furonaphthoquinones **4e** and **4f** (Entries 8 and 9). Interestingly, no trace of the corresponding *o*-furoquinone was produced in all the present reactions.[13]

It should be noted that similar reactions of phenyliodonium ylides, derived from 1,3-dicarbonyl compounds, with simple acetylenes induced photochemically[15] or by $Cu(acac)_2$[16] have been reported by Spyroudis et al. Although they have proposed the intermediacy of a carbene or iodane species in their reactions, it appears to us that our reactions using the iodonium ylides **2** proceed through formation of the corresponding 2-hydroxy-3-iodo-1,4-naphthoquinones as outlined in Scheme 2. This may be supported by TLC analysis during the course of the reactions, which indicated the presence of these iodo quinones in the reaction mixtures. Their formation, followed by coupling with a terminal acetylene, gives rise to the alkynylated hydroxy quinones **5**, which subsequently undergo intramolecular ring closure to give **4**.



Scheme 2.

In conclusion, we have developed a novel method for the one-step preparation of naphtho[2,3-*b*]furan-4,9-diones using the transition metal-mediated heteroannulation. Additional mechanistic and synthetic aspects of the present reactions are presently under investigation. The results will be reported in a forthcoming full paper.

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13. All the new products in this study gave satisfactory analytical results. Physical and spectral data for the products are as follows. **2b**: Mp 120-122 °C ($CHCl_3$); IR (KBr disk) 1739, 1707, 1671, 1582, 1556, 1269 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) δ 3.92 (3H, s), 7.22 (1H, dd, *J*=8.4, 2.6 Hz), 7.40 (2H, dd, *J*=7.9, 7.4 Hz), 7.45-7.55 (2H, m), 7.85 (2H, d, *J*=7.9 Hz), 7.94 (1H, d, *J*=8.4 Hz). **4b**: Mp 215-218 °C (CH_2Cl_2); IR (KBr disk) 1676, 1660 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.97 (3H, s), 7.16 (1H, s), 7.19 (1H, dd, *J*=8.7, 2.5 Hz), 7.4-7.55 (3H, m), 7.64 (1H, d, *J*=2.5 Hz), 7.88 (2H, dd, *J*=8.3, 1.8 Hz), 8.17 (1H, d, *J*=8.7 Hz); MS, *m/z* 304 (M^+, 100). **4e**: Mp 177-179 °C (hexane-$CHCl_3$); IR (KBr disk) 3498, 1676 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.64 (1H, s), 4.81 (2H, s), 6.90 (1H, s), 7.7-7.8 (2H, m), 8.15-8.25 (2H, m); MS, *m/z* 229 (36), 228 (M^+, 24), 139 (42), 97 (100). **4f**: Mp 129-130 °C (hexane-Et_2O); IR (KBr disk) 1673 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.47 (3H, s), 4.57 (2H, s), 6.90 (1H, s), 7.7-7.8 (2H, m), 8.15-8.25 (2H, m); MS, *m/z* (%) 242 (M^+, 48), 183 (100).
14. Prepared by a successive treatment of 3-butyn-2-ol with 2 equiv. each of *n*-butyllithium and chlorotributyltin in Et_2O at -78 °C: bp 230 °C (bath temp)/0.18 Torr; IR (neat) 2134 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.1-2.3 (57H, m) and 4.82 (1H, q, *J*=6.8 Hz).
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