Ceric Ammonium Nitrate Mediated Cycloaddition of Hydroxyquinones with Alkenes for the One-Step Construction of Furoquinone Derivatives

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A one-step formation of furoquinones, such as naphtho[2,3-*b*]furan-4,9-dione, naphtho[1,2-*b*]furan-4,5-dione, benzofuran-4,7-dione, and benzofuran-4,5-dione derivatives, by the ceric ammonium nitrate mediated [3+2] type cycloaddition of 2-hydroxy-1,4-naphthoquinones and 2-hydroxy-1,4-benzoquinones with alkenes or phenylacetylene is described.

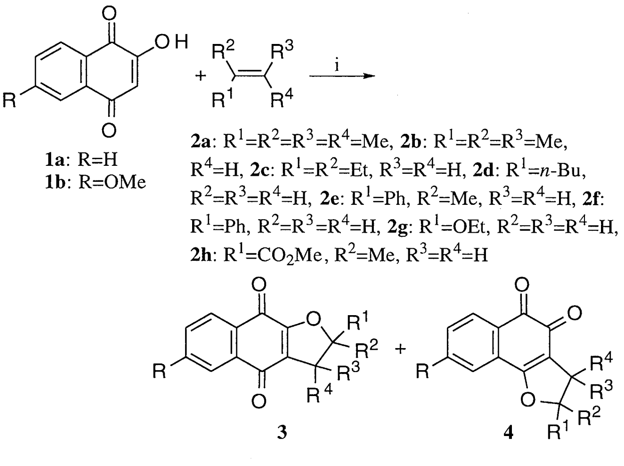
The synthesis of furoquinones has recently attracted much attention, because a number of these derivatives have been found in nature and some of them have proven to exhibit a wide range of biological activities.[1] Although many strategies have been used for the construction of furoquinone skeletons,[2] most of approaches employ several steps to secure the target skeletons from readily available precursors. In previous papers we reported a new [3+2] type regioselective photoaddition of 2-hydroxy-1,4-naphthoquinones and 2-hydroxy-1,4-benzoquinones with alkenes (or alkynes) yielding naphtho[2,3-*b*]furan-4,9-dione[3] and benzofuran-4,7-dione derivatives,[4] respectively. In this paper we describe that a similar cycloaddition can be mediated by ceric ammonium nitrate (CAN)[5] to give these furo-*p*-quinones along with the corresponding furo-*o*-quinone derivatives.

We began our investigation by first examining the reaction between 2-hydroxy-1,4-naphthoquinones (**1a**) and 2,3-dimethyl-2-butene (**2a**). An acetonitrile solution of **1a** and **2a** (10 eq.) was treated with CAN (2 eq.) at 0 °C. TLC analysis of the reaction mixture after 20 min showed only a trace of unreacted **1**, and the presence of two products. A usual work-up followed by subsequent purification by preparative TLC on silica gel afforded two pure products. The major and more mobile product was identified as 2,3-dihydro-2,2,3,3-tetramethylnaphtho[2,3-*b*]furan-4,9-dione (**3a**) (61%) by a direct comparison with an authentic sample previously prepared by us.[3] The minor and less mobile one was identified as 2,3-dihydro-2,2,3,3-tetramethylnaphtho[1,2-*b*]furan-4,5-dione (**4a**) (10%) from its spectroscopic data, which characterize an orthoquinone structure.[6] Reactions between 2-hydroxy-1,4-naphthoquinones **1** and a variety of alkenes **2** were then carried out under the same reaction conditions, and the corresponding furonaphthoquinones **3** and **4** were produced (Scheme 1). The formation of each product was completely regioselective. The results obtained are given in Table 1. The reactions with 2-methyl-2-butene or 2-ethyl-1-butene gave the corresponding adducts in good yields (Entries 2, 3, 9, and 10). 1-Hexene, on the other hand, gave **3d** and **4d** in a low yield (Entry 4). However, it is worth noting that no [3+2] cycloaddition product could be obtained by the photochemical reaction of **1a** with terminal alkenes.[3] Styrenes were found to react more smoothly to give the adducts in higher yields and seem to favor the formation of **4** (Entries 5 and 6). The reaction of **1a** with ethyl vinyl ether was carried out in the presence of 1 equiv. of $NaHCO_3$ to afford **3g** as the sole isolated product (Entry 7). The corresponding furo-*o*-quinone was not isolated probably due to its instability under the reaction and/or work-up conditions. Although lower in yield, methyl methacrylate gave the products (Entry 8). Methyl acrylate and acrylonitrile could not give any addition products under these conditions. While the adducts could be obtained in MeOH as well, the yield was considerably lower than that in acetonitrile.

Table 1. Preparation of furoquinones **3** and **4**

Entry	1	2	3 (Yield/%)[a]	4 (Yield/%)[a]
1	**1a**	**2a**	**3a**[d] (61)	**4a** (10)
2	**1a**	**2b**	**3b**[d] (70)	**4b** (12)
3	**1a**	**2c**	**3c** (72)	**4c** (17)
4	**1a**	**2d**	**3d** (12)	**4d** (14)
5	**1a**	**2e**	**3e**[e] (38)	**4e**[e] (48)
6	**1a**	**2f**	**3f**[d] (39)	**4f**[e] (33)
7[b]	**1a**	**2g**	**3g**[d] (34)	—
8	**1a**	**2h**	**3h**[d] (12)	**4h** (3)
9	**1b**[c]	**2b**	**3i**[d] (47)	**4i** (24)
10	**1b**[c]	**2c**	**3j** (48)	**4j** (20)

[a]Isolated yields. [b]$NaHCO_3$ (1 eq.) was used. [c]Ref. 9. [d]Ref. 3. [e]Ref. 6.

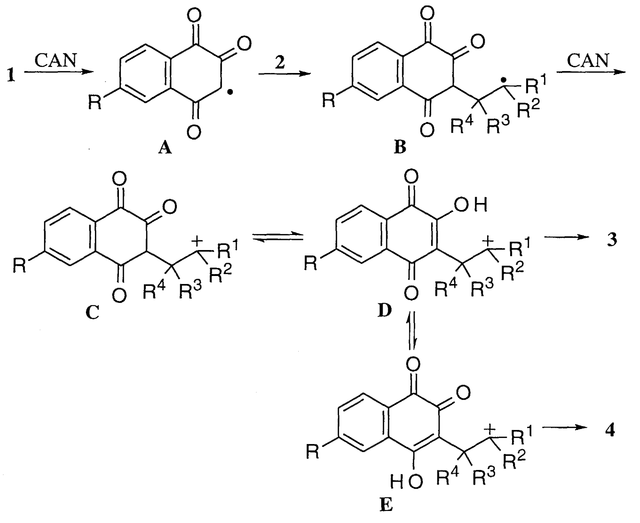


2a: $R^1=R^2=R^3=R^4=Me$, **2b**: $R^1=R^2=R^3=Me$, $R^4=H$, **2c**: $R^1=R^2=Et$, $R^3=R^4=H$, **2d**: $R^1=n\text{-}Bu$, $R^2=R^3=R^4=H$, **2e**: $R^1=Ph$, $R^2=Me$, $R^3=R^4=H$, **2f**: $R^1=Ph$, $R^2=R^3=R^4=H$, **2g**: $R^1=OEt$, $R^2=R^3=R^4=H$, **2h**: $R^1=CO_2Me$, $R^2=Me$, $R^3=R^4=H$

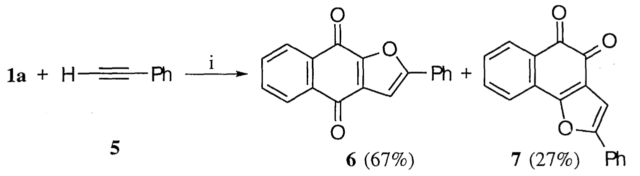
Reagents and conditions: i, 2 eq. CAN, CH_3CN, 0 °C.

Scheme 1.

The foregoing results indicate that the pathway to the products of the present cycloaddition is analogous to that proposed previously;[5] the initial formation of a reactive radical intermediate **B** (through **A**) and its oxidation gives a carbonium ion intermediate **C**, which is intramolecularly trapped with the hydroxyl group of 2-hydroxy- **D** or 4-hydroxy-tautomer **E** to give **3** or **4**, respectively (Scheme 2).



Scheme 2.

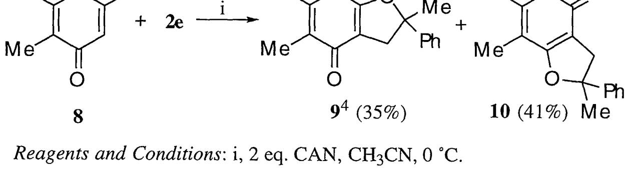


Reagents and Conditions: i, 2 eq. CAN, CH_3CN, 0 °C.

Scheme 3.

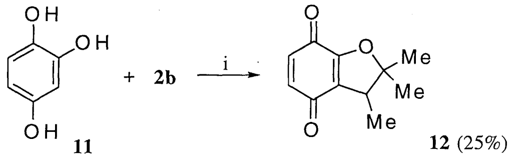
Analogous cycloaddition can be achieved with phenylacetylene instead of alkenes (Scheme 3). Formation of the products **6** and **7** was almost quantitative. The attempted cycloaddition of **1a** with other alkynes such as diphenylacetylene or 1-hexyne, however, resulted in the formation of an intractable mixture in each case.

The reactions of 2-hydroxy-1,4-benzoquinones were also carried out in order to examine the scope of the present cycloaddition. When 2-hydroxy-5,6-dimethyl-1,4-benzoquinone (**8**)[7] was allowed to react with **2e** in the presence of CAN under the above-mentioned conditions, benzofurandiones **9** and **10** were obtained in 35 and 41% yield, respectively (Scheme 4). 2-Hydroxy-1,4-benzoquinone, which is too unstable to be isolated,[8] has proven to be usable in the present reaction. When 1,2,4-benzenetriol (**11**)[8] was treated with 4 eq. of CAN in the presence of **2b** at 0 °C for 35 min, the cycloaddition took place, via 2-hydroxy-1,4-benzoquinone, to afford 2,3-dihydro-2,2,3-trimethylbenzofuran-4,7-dione (**12**) in 25% yield (Scheme 5).



Reagents and Conditions: i, 2 eq. CAN, CH_3CN, 0 °C.

Scheme 4.



Reagents and Conditions: i, 4 eq. CAN, CH_3CN, 0 °C.

Scheme 5.

This work shows that ceric ammonium nitrate can mediate the regioselective [3+2] type cycloaddition reaction between hydroxyquinones and alkenes (or phenylacetylene), which allows the formation of furonaphthoquinones and furobenzoquinones. The present procedure has additional advantages over the photochemical procedure developed by us;[3] not only the production of the furo-*o*-quinone derivatives but also milder reaction conditions, simpler manipulations, and applicability to a wider range of alkenes. Therefore, it may offer a more convenient method for the preparation of a variety of furoquinone derivatives. Further work is now in progress to investigate the scope of the present CAN mediated reaction.[10]

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References and Notes

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5 Several metal compounds have been used for the production of 1,2-dihydrofuran derivatives by the cycloaddition of 1,3-dicarbonyls to alkenes. For leading references see: K. Ichikawa, S. Uemura, and T. Sugita, *Tetrahedron*, **22**, 407 (1966); E. I Heiba and R. M. Dessau, *J. Org. Chem.*, **39**, 3456 (1974); E. Baciocchi and R. Ruzziconi, *Synth. Commun.*, **18**, 1841 (1988) and references cited therein. In particular, high efficiency of this cerium compound has been recently reported: V. Nair and J. Matthew, *J. Chem. Soc., Perkin Trans. 1*, **1993**, 187. An electrochemical procedure has also been successfully employed: J. Yoshida, K. Sakaguchi, and S. Isoe, *Tetrahedron Lett.*, **27**, 6075 (1986).

6 **4a**: a viscous oil; R_f 0.46 (1:2 EtOAc-hexane); IR (neat) 1701, 1640, 1614 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.34 (6H, s), 1.46 (6H, s), 7.5-7.65 (3H, m), 8.05 (1H, d, J=7.6 Hz); MS, *m/z* (%) 256 (M^+, 84), 241 (100). Found: C, 74.69; H, 6.01%. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29%. cf. K. Kobayashi, A. Sasaki, H. Takeuchi, and H. Suginome, *J. Chem. Soc., Perkin Trans. 1*, **1993**, 115.

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10 All new compounds showed satisfactory spectroscopic data (IR, ^1H NMR, and MS) together with elemental analyses.