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The unique regioselectivity in the formation of disubstituted-1,4-benzoquinones generated from the reaction of 4-hydroxycoumarins with 1,4-benzoquinone

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Abstract—The 2,3-disubstituted 1,4-benzoquinones were synthesized through the regioselective addition of 4-hydroxycoumarins with 1,4-benzoquinone in aqueous acetone, which were different from 2,5-disubstituted adducts generated by the previously reported reaction of compounds possessing an activated methylene with 1,4-benzoquinone.

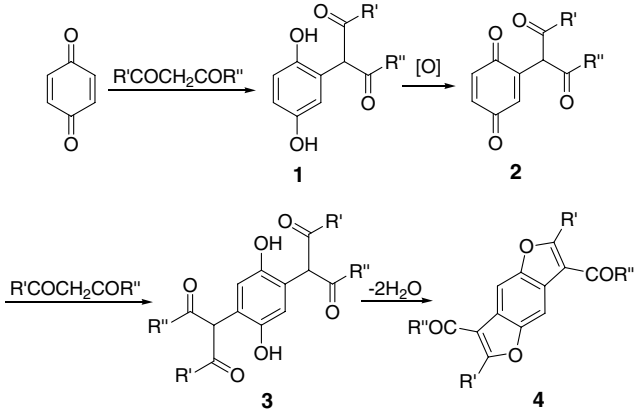
Quinones are widely distributed in nature and are produced by the chemical industry. The principle aspect of the application of quinones is their utilization as organic dyes. The importance of quinones is not, however, restricted to the chemistry of dyes. A number of quinones show interesting biological activities.[1] The nucleophilic reaction of quinones is an useful method to synthesize quinone derivatives, and is discussed in a review.[2]

The regioselectivity in the formation of disubstituted adducts through the Michael addition of 1,4-benzoquinone with nucleophiles is widely investigated by means of theory and experiment. The results show that nucleophiles would mainly attack the 5-position of donor-substituted 1,4-benzoquinones, and 3-position of acceptor-substituted 1,4-benzoquinones.[3] For example, the reactions of 1,4-benzoquinone with some compounds possessing an activated methylene afford 2,5-disubstituted adducts as intermediates or products.

Wood[4] and King[5] reported that the Michael addition of 1,4-benzoquinone with 1,3-dicarbonyl compounds afforded 2,5-disubstituted adduct **3**, which was dehydrated followed by subsequent cyclization to give furan derivatives **4** (Scheme 1).

A similar scheme took place in the reaction of 1,4-benzoquinone with acylcyanomethanes (Scheme 2).[2]

To our knowledge, there are no literature which reported the formation of 2,3-disubstituted adduct



Scheme 1. Michael addition of 1,4-benzoquinone with 1,3-dicarbonyl compounds.

Keywords: 4-Hydroxycoumarins; 1,4-Benzoquinone; Michael addition.
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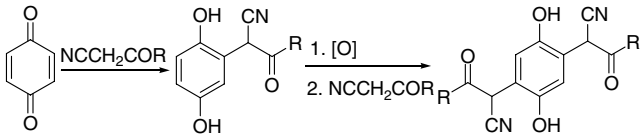
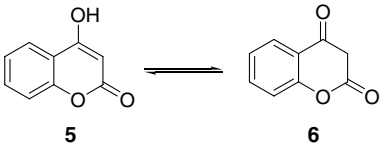


Scheme 2. Reaction of 1,4-benzoquinone with acylcyanomethanes.



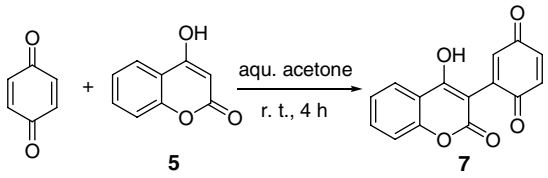
Scheme 3. Tautomerization of 4-hydroxycoumarin.

through the reaction of 1,4-benzoquinone with the activated methylene group.

4-Hydroxycoumarin **5**, recognized as the enol tautomer of 2,4-chromandione **6**, displays high nucleophilic reactivity on C-3 as 1,3-dicarbonyl compounds do (Scheme 3). A number of 4-hydroxycoumarin derivatives with biological activities can be synthesized through the Michael addition of 4-hydroxycoumarins to α,β-unsaturated carbonyl compounds utilizing the nucleophilicity of C-3.[6]

In our continuing investigation on the reaction of quinones with 4-hydroxycoumarins,[7] we found that 2,3-disubstituted products were generated in the reaction of 1,4-benzoquinone with 4-hydroxycoumarins, which were different from 2,5-disubstituted products obtained in the reaction of 1,4-benzoquinone with compounds possessing an activated methylene described above, and herein are reported the details of the results.

Wagh et al.[8] reported the reaction of 1,4-benzoquinone with 4-hydroxycoumarin, and obtained the monosubstituted 1,4-benzoquinone **7** (Scheme 4).



Scheme 4.

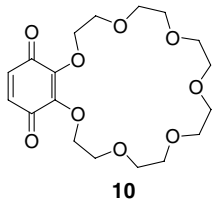


Figure 1.

We performed the reaction under Wagh's condition, and obtained also a yellowish orange colored solid,[9] which was identified as the disubstituted 1,4-benzoquinone by MS-(ESI) and ^{1}H NMR. Several factors of the reaction, including (i) the reaction temperature (rt, 40 °C, 50 °C), (ii) the ratio of the reactants (4-hydroxycoumarin–1,4-benzoquinone = 4:1, 3:1, 2:1, 1:2, 1:3, 1:4 (mol/mol)), and (iii) the solvent (methanol, ethanol) were tested, but the outcome was only the disubstituted adduct.

Unfortunately, we could not determine that the adduct was 2,5-disubstituted 1,4-benzoquinone **8** or 2,3-disubstituted 1,4-benzoquinone **9a** just by MS-(ESI), and ^{1}H NMR (Scheme 5) because the two hydrogen atoms on the quinone moiety of both compounds **8** and **9a** should display one single signal. The single peak of the two quinone hydrogen atoms of compound **9a** was proved indirectly by that of compound **10** (Fig. 1).[10]

Finally, the adduct of the reaction of 1,4-benzoquinone with 4-hydroxycoumarin was unambiguously deter-

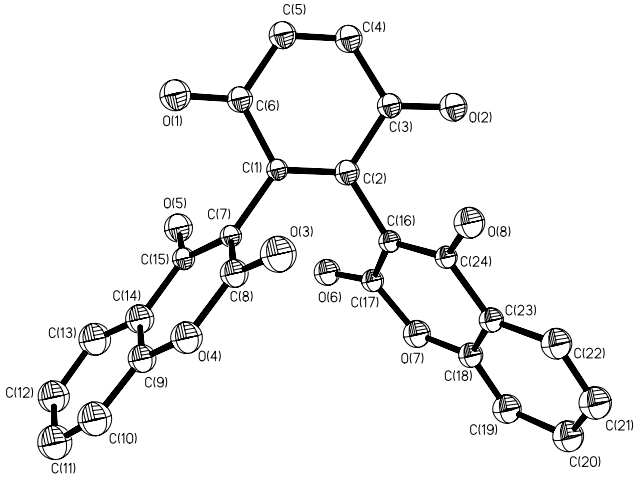
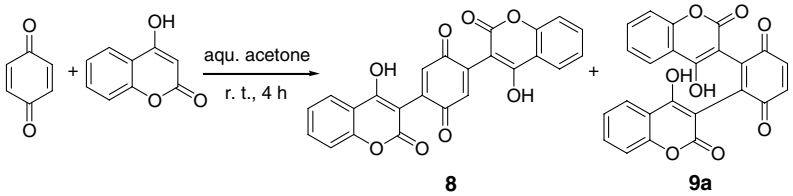
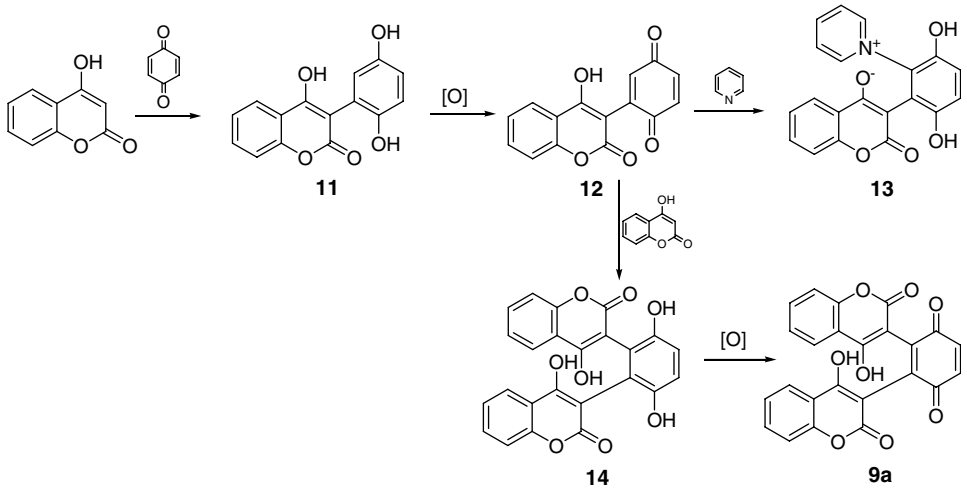


Figure 2. Perspective view of the X-ray structure of **9a**.

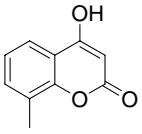
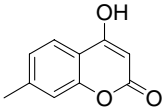
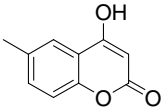
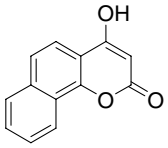
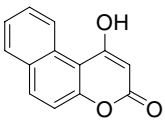
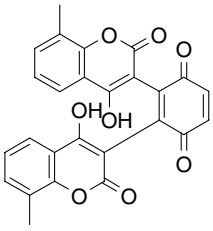
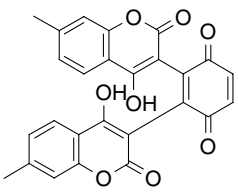
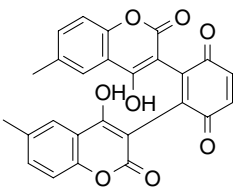
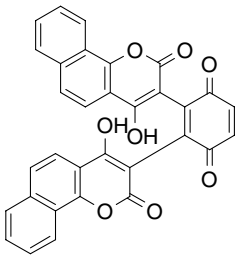
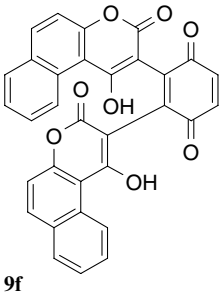


Scheme 5. Reaction of 4-hydroxycoumarin with 1,4-benzoquinone.



Scheme 6. Mechanism of reaction of 4-hydroxycoumarin with 1,4-benzoquinone.

Table 1. Products generated by reaction of 4-hydroxycoumarins with 1,4-benzoquinone

Entry	1	2	3	4	5
4-Hydroxy-coumarins					
Products					
	9b	**9c**	**9d**	**9e**	**9f**
Yield (%)	55	48	66	52	56

mined to be compound **9a** through single crystal X-ray diffraction (Fig. 2).[†]

In a previous communication,[7a] we reported the synthesis of zwitterionic 4-hydroxycoumarin derivative **13** through the reaction of 4-hydroxycoumarin with 1,4-benzoquinone, and pyridine in aqueous acetone (Scheme 6).

Obviously, the formation of both compounds **9a** and **13** followed the same reaction mechanism (Scheme 6). We reported that compound **13** was generated through regioselective attack of pyridine on the activated 3-position of the intermediate **12**, which resulted from the addition of 4-hydroxycoumarin with 1,4-benzoquinone, and subsequent oxidation. The synthesis of compound **13** displayed the high reactivity of 3-position of **12**, which was activated by the substituent. In the absence of pyridine, the second 4-hydroxycoumarin molecule would attack 3-position of the intermediate **12** to afford compound **14**, which was subsequently oxidized to give compound **9a**. The reason, as to why compound **13** could not be further oxidated to afford quinone in reaction mixture, was ascribed to the high electron-withdrawing effect of the pyridinium moiety. The reaction mechanism also confirmed the molecular structure of compound **9a** as 2,3-disubstituted 1,4-benzoquinone.

Under similar reaction conditions for the synthesis of compound **9a**, five other 2,3-disubstituted 1,4-benzoquinones **9b–f** were also prepared (Table 1).

In summary, we described here the reaction of 4-hydroxycoumarins with 1,4-benzoquinone in aqueous acetone.

[†] CCDC 604206 contains the supplementary crystallographic data for this letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Six 2,3-disubstituted 1,4-benzoquinones were obtained through this unique regioselective addition.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.076.

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9. Typical procedure for synthesis of compound **9a**: 4-Hydroxy-coumarin (0.80 g, 5 mmol) and 1,4-benzoquinone (0.54 g, 5 mmol) were dissolved in aq acetone (30 ml, v:v = 1:1). The resulting dark brown solution was magnetically stirred for 4 h at room temperature. The reaction mixture was filtered to afford a yellowish orange colored solid, which was recrystallized from dimethylformamide as orange needles (0.65 g, 61%): ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.87 (2H, dd, $J_1 = 7.7$ Hz, $J_2 = 1.5$ Hz), 7.61 (2H, td, $J_1 = 8.2$ Hz, $J_2 = 1.5$ Hz), 7.33 (2H, td, $J_1 = 8$ Hz, $J_2 = 1$ Hz), 7.26 (2H, dd, $J_1 = 8$ Hz, $J_2 = 1$ Hz), 7.03 (2H, s) ppm. ESI-MS(m/z): 427 $(M-1)^-$.
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