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SUBSTITUTION OF A HALOQUINONE BY PHENOLS UNDER PYRIDINE-FREE CONDITIONS: SYNTHETIC, MECHANISTIC, AND SOLID-STATE CONSIDERATIONS INVOLVING 2,3-DICHLORO-1,4-NAPHTHOQUINONE

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Abstract – Benzoquinones fused to heterocycles, like most benzoquinones, have the potential for a wide-array of applications but their inherent reactivity can present a synthetic dilemma. The issue is that a synthesis may target one desired outcome, yet yield a range of side products. In efforts to understand the reaction pathways of haloquinone substitution, while minimizing undesired product formation, four examples of reactions between 2,3-dichloro-1,4-naphthoquinone and phenolic nucleophiles are presented. Two of the products were confirmed and analyzed by X-ray crystallography. The reaction with orcinol was optimized for yield and investigation of this mechanism indicates a novel pathway under pyridine-free conditions.

Examples of benzoxaheterocycles fused to naphthoquinones (**1** & **2**) can be found in natural products,¹ show potential for use as organic electronics,² and hold promise as anti-cancer drugs.³ The diversity of applications for these conjugated structures has prompted our lab to investigate the mechanism and conditions for substitution reactions of 2,3-dichloro-1,4-naphthoquinone (**3**) since the molecule can be utilized as a synthetic precursor to **1**, **2**, and analogs (Figure 1).

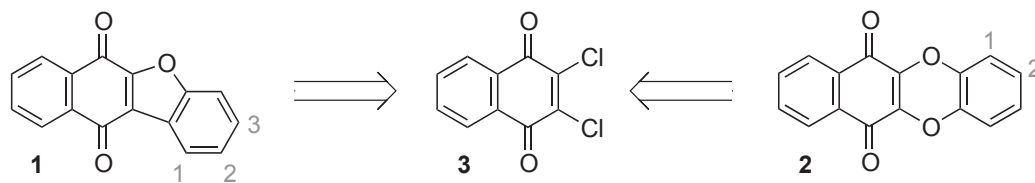
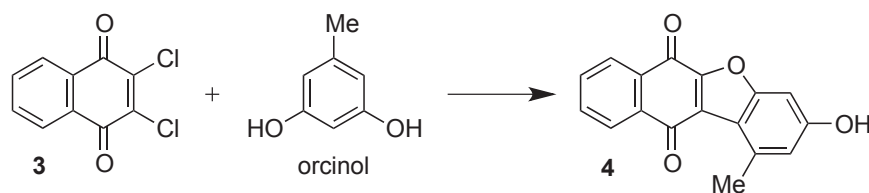


Figure 1. Retrosynthetic analysis of furan (**1**) and dioxane (**2**) illustrating that 2,3-dichloro-1,4-naphthoquinone (**3**) can be used as a common precursor

2,3-Dichloro-1,4-naphthoquinone (**3**) is a useful building block because the quinone is an inexpensive fungicide.⁴ Furthermore, haloquinone rings can react through a variety of pathways such as carbonyl addition, single electron transfer, alkene (cyclo)addition, reduction, and halogen substitution (nucleophilic addition-elimination, Ad_N-E).⁵ In this communication, we describe general and mild reaction conditions that give selective preference of the Ad_N-E mechanism when **3** is reacted with a diverse set of phenolic nucleophiles.

Initially a mild substitution of **3** with resorcinols was sought because this reaction is known to afford 3-hydroxy derivatives of **1**.^{1,3,5d,6} However, the reaction is commonly conducted with pyridine as the solvent (see Supporting Information). While these conditions produce products such as **4** in good yields when carbonate is also utilized (e.g., Table 1, entry 9), pyridine also can cause unwanted side reactions. Towards this goal, we targeted reasonable yields of **4** under pyridine-free conditions.

Optimization with orcinol⁷ revealed that replacing pyridine with a polar, non-nucleophilic solvent like DMSO (Table 1, entries 1-3), DMF (entry 4), or THF (entry 5) does convert **3** to product **4**.⁸ The choice of base employed proved to be crucial as enhancing the nucleophilicity of the base by using fluoride (entry 6), triethylamine (entry 7), or pyridine (base and solvent, entry 8) gave little to no product. Subtle, but mechanistically important, differences appeared when the reaction conditions were modified (see mechanistic discussion below). For convenience and brevity, DMSO was employed as the solvent and 2 h was set as the common reaction time, then three otherwise identical reactions were conducted at varying temperatures (entries 1-3). The lowest temperature tested (80 °C, entry 1) gave the highest yield of product, however, it could not be completely purified (*vide infra*). As the temperature was increased (100 °C, entry 2), the remaining side products were separated by column chromatography offering a pure form of **4** in a reasonable yields (as high as 40% in the highest yielding reaction of the five attempts). When the temperature was further increased (120 °C, entry 3) the conversion to product was significantly attenuated.

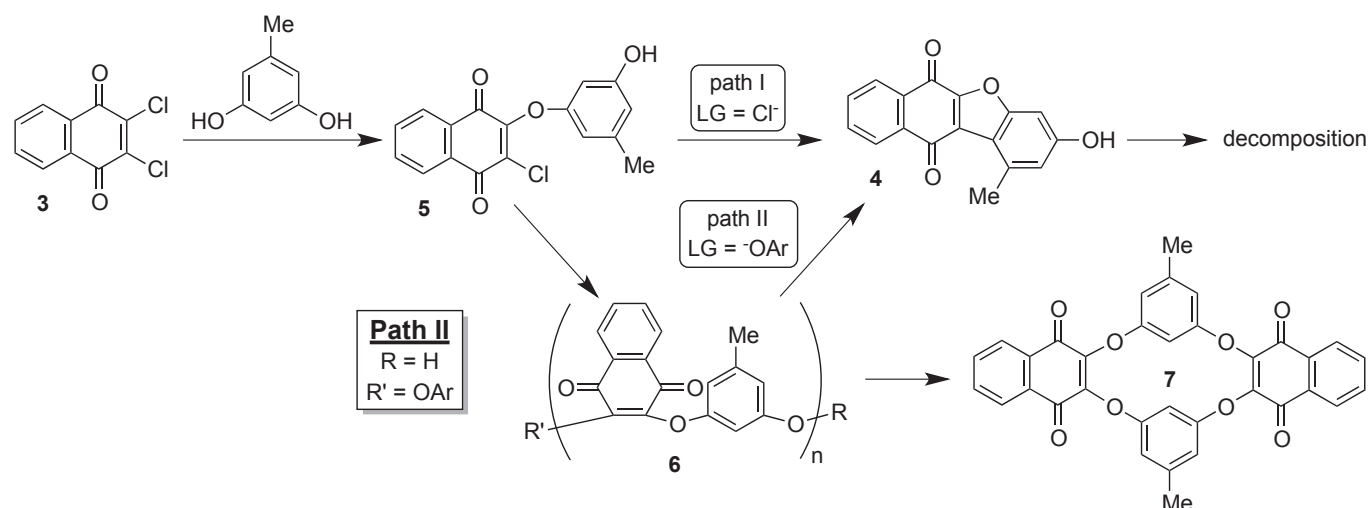
Table 1. Optimization of the synthesis of **4**

Entry	Base	Solvent	Time	Temperature	Conversion ^a	Yield ^b
1	Cs ₂ CO ₃	DMSO	2 h	80 °C	- ^c	34% ^d
2	Cs ₂ CO ₃	DMSO	2 h	100 °C	38% ^e	33% ^e
3	Cs ₂ CO ₃	DMSO	2 h	120 °C	27%	23%
4	Cs ₂ CO ₃	DMF	2 h	100 °C	- ^c	27%
5	Cs ₂ CO ₃	THF	32 h	60 °C	32%	26%
6	CsF	DMSO	2 h	100 °C	23%	18%
7	Et ₃ N	DMSO	32 h	60 °C	<5%	- ^f
8	-	pyridine	3 h	100 °C	<5%	- ^f
9	Cs ₂ CO ₃	pyridine	16 h	90 °C	- ^c	76%

^aConversions were estimated by ¹H NMR analysis of the sample prior to chromatographic purification.

^bIsolated yield after chromatographic purification. ^cConversion could not be measured due to presence of a solvent peak in the naphthoquinone signal region of the NMR spectrum. ^dProduct could not be completely purified, likely contains oligomers (**6**). ^eMedian of five runs. ^fNo attempt was made to isolate the pure compound because it was not observed in the crude ¹H NMR spectrum.

As noted above, a wide range of yields for the reaction of **3** with resorcinols under a variety of basic conditions have been previously reported.⁸ The disparity between these higher yielding reaction conditions (e.g., entry 9) and the trends observed in Table 1 prompted us to investigate the mechanistic aspects of this reaction more closely. In entry 1, after chromatographic purification, additional compounds remained visible in the ¹H NMR spectrum of the sample containing product **4**. When the temperature was increased to 100 °C (entry 2), **4** was more easily separated from the side products. This observation led us to propose the mechanistic pathway shown in Scheme 1, where side products are formed by oligomerization. Indeed, MS of a crude sample obtained under the conditions in entry 2⁹ revealed the presence of linear (i.e., **6**) and cyclic (i.e., **7**) oligomers. Though oligomerization occurs, it is not yet clear whether product **4** is directly obtained from **5** (i.e., path I with chloride as the leaving group), from an oligomer (i.e., path II with a phenoxide as the leaving group where likely R = H and R' = oligomer chain), or a combination of both. Path II of the oligomerization mechanism has precedence in a similar poly(*m*-phenylene oxide) system where macrocyclic rings, analogous to **7**, are energetically favored due to the all *meta*-geometry.¹⁰

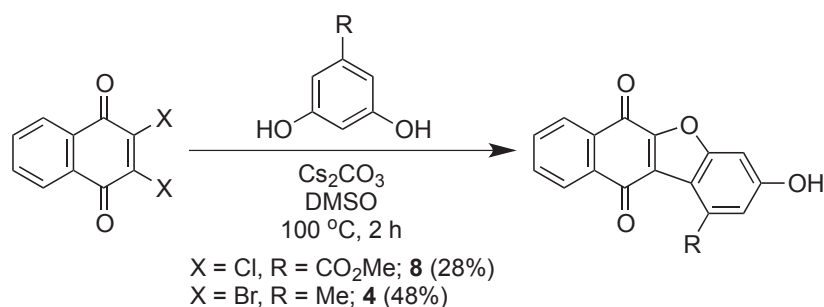


Scheme 1. Possible reaction pathways for the reaction of **3** + orcinol

Previous reports on the synthesis of **4** and analogs have not provided much insight into the mechanism.^{3,5d,6a} However, mechanistic results of the reaction between **3** and other nucleophiles under pyridine and pyridine-free conditions have been reported.^{11,12} In these cases, isolation of intermediates indicates that the chloride leaving group is susceptible to displacement by any nucleophile present in the reaction (see Supporting Information). Thus, we hypothesize that the mechanism of the reaction between **3** and resorcinol nucleophiles can be controlled based on the nucleophiles present. If the only nucleophile present is the resorcinol then oligomers and macrocyclic species (e.g., **7**) will not be cleaved by other nucleophiles (e.g., pyridine) and can be isolated.¹³

Further investigation revealed that product **4** is not completely stable under the carbonate and DMSO reaction conditions. In entry 3, ¹H NMR analysis of the crude reaction mixture showed a decrease in conversion compared to entry 2. This result seemed to suggest that after product **4** forms, it begins to decompose. Indeed, re-subjection of pure **4** to the reaction conditions at 100 °C revealed shifting and broadening of the aromatic proton peaks by ¹H NMR analysis.¹⁴ Therefore, the furan products synthesized under these conditions are likely only metastable. However, these carbonate and DMSO conditions are attractive because they are mild and can be used to access a diverse range of structures.

The generality of the carbonate and DMSO conditions can be seen in examples of reactions of **3** with other resorcinol nucleophiles (Scheme 2). Changing the methyl group on the resorcinol to a methoxycarbonyl yields the furan product (**8**) in similar yield (29%) but shows no sign of transesterification, which is likely under previously reported conditions.^{3,5d,6a} Changing the leaving groups on the naphthoquinone to bromine dramatically increases the yield of product **4** (48%), likely due to the enhanced leaving group ability.



Scheme 2. General reaction conditions applied to analogous starting materials

Single crystals of **4** were grown by slow evaporation of a mixture of chloroform and DMSO (50:1 v/v). X-Ray analysis revealed the molecule to crystallize in the monoclinic space group $C2/c$. A disordered DMSO solvent molecule is present in the asymmetric unit (Figure 2a).¹⁵ The hydroxyl group of **4** engages in an O-H...O hydrogen bond (O...O (Å): 2.575(7)) with the included DMSO solvent. The naphthoquinone-benzofuran rings of neighboring molecules engage in offset face-to-face π -forces (3.5 Å) along the crystallographic b -axis, with the packing of **4** being dominated C-H... π interactions that extend in the ac -plane (Figure 2b).

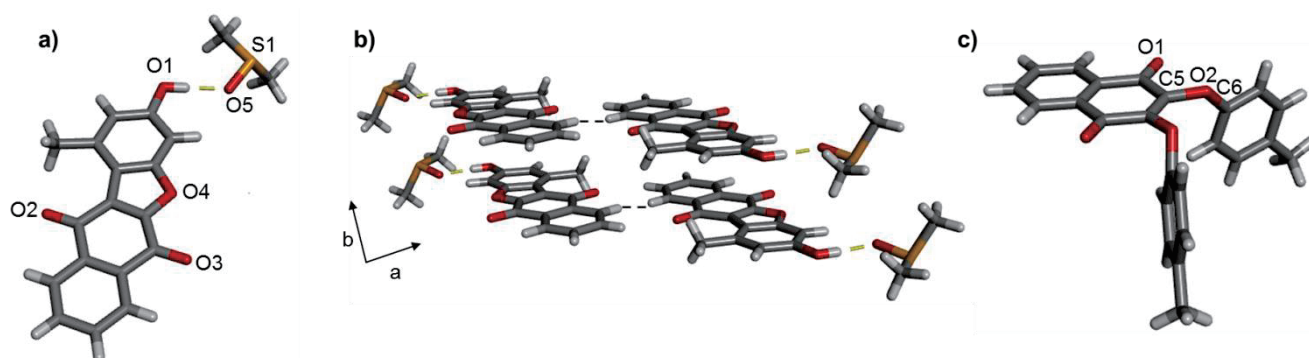
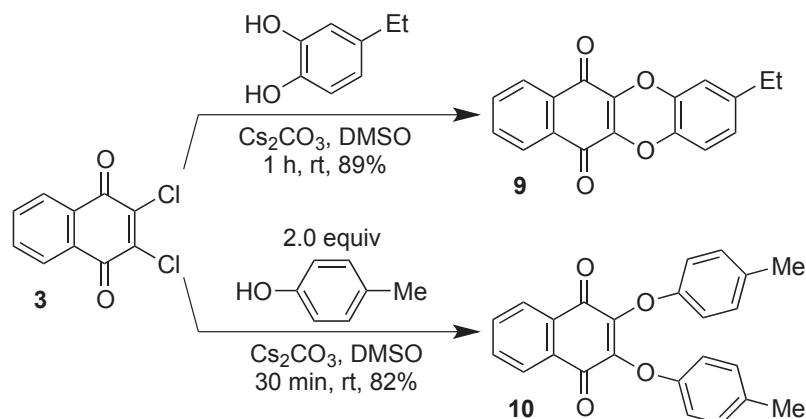


Figure 2. X-Ray crystal structures of **4** (a & b) showing hydrogen bonding with included DMSO and **10** (c) showing conformation as defined by phenoxy groups. Highest occupancies for disordered DMSO shown for clarity

Reactions that only yield C-O bond formation between **3** and a phenol proceed with high selectivity and high yields under pyridine-free conditions in two examples. The reaction of 4-ethylcatechol with **3** under carbonate and DMSO conditions at rt for 1 h gave **9** in 89% yield and in good purity without need for chromatographic purification¹⁶ and no detection of the furan product from C-C bond formation. The enhanced yield can be explained by facile annulation of the two phenoxide nucleophiles to form a dioxine. Thus, these general conditions also work quite well to form benzooxaheterocycles fused to naphthoquinones.



Scheme 3. General reaction conditions applied to the synthesis of **9** and **10**

The formation of **10** from **3** and 2.0 equiv of *p*-cresol proceeded smoothly at rt for 30 min. These conditions afforded the highest yield reported¹⁷ for substitution of **3** with a monophenol in solution. Single crystals of **10** were grown by slow evaporation from a chloroform solution. X-Ray analysis revealed the molecule to crystallize in the non-centrosymmetric orthorhombic space group *Pmn*2₁ (Figure 2c).¹⁵ The conformation of the molecule is defined by both phenoxy substituents pointing along the same side of the plane of naphthoquinone ring system, subtending an angle from the quinone to the phenoxy (C5-O2-C6) of 117.5°. The packing is dominated by C-H(methyl)•••O(quinone) interactions approximately along the crystallographic *a*-axis, while, similar to **4**, C-H••• π interactions dominate in the *bc*-plane. The naphthoquinone rings of neighboring molecules are also engaged in offset face-to-face π -forces (3.7 Å).

We have reported a mild and effective synthesis for the substitution of both chlorines on 2,3-dichloro-1,4-naphthoquinone (**3**) with a variety of phenol nucleophiles. The only required additives are cesium carbonate and a polar, non-nucleophilic solvent, preferably DMSO. Because the conditions are mild and employ stoichiometrically equivalent amounts of the starting materials a wide range of functionalized 2,3-dihalo-1,4-naphthoquinones and phenols should be tolerated. In addition, the reaction conditions are general for the synthesis of benzoheterocyclic-naphthoquinone fused systems. Future work will continue on the mechanistic investigation into the substitution of **3** and its analogs with special attention being paid to the isolation and characterization of the oligomeric and macrocyclic species (e.g., **7**).

ACKNOWLEDGEMENTS

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SUPPORTING INFORMATION

The supporting information includes experimental information for compounds **4**, **8**, **9**, & **10**, HRMS spectra, ¹H NMR data from the degradation of **4**, brief summary of mechanistic results from reactions of **3** with other nucleophiles, tabular literature summary of the reactions of monophenols with **3**, and crystallographic data. The data associated with this article can be found, in the online version, at URL: <https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26176/98/3>.

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4. (a) 2,3-Dichloro-1,4-naphthoquinone (**3**) (<http://www.acros.com>, accessed 6/11/18) can be purchased for as little as 0.23 USD/g; (b) R. G. Owens and H. M. Novotny, *Contrib. Boyce Thompson Inst.*, 1958, **19**, 463.
5. These mechanisms, including reactions of **3**, have been previously reviewed: (a) K. T. Finley, The addition and substitution chemistry of quinones. In *Quinonoid Compounds*, Vol. 2, ed. by S. Patai, John Wiley & Sons, Chichester, 1974; (b) K. T. Finley, Quinones: The present state of addition and substitution chemistry. In *Hydroxyl, Ether and Peroxide Groups*, Vol. 2, ed. by S. Patai, John Wiley & Sons, Chichester, 1993; (c) A. A. Kuttyrev and V. V. Moskva, *Russ. Chem. Rev.*, 1991, **60**, 72; (d) M. F. Sartori, *Chem. Rev.*, 1963, **63**, 279.
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7. Orcinol was employed in lieu of resorcinol because it had better solubility properties and more straightforward analysis (especially ¹H NMR) of the products.
8. Higher yielding reactions of **3** with various resorcinols in pyridine have been previously reported (e.g., refs. 1, 3, & 6) and one set of conditions was repeated in this study (entry 9, Table 1).
9. The crude sample was obtained by following the procedure outlined in the Supporting Information with a slight excess of **3** (1.02 equiv). Figures S1 & S2 show negative and positive ion mode ESI spectra of several oligomers (**6**) where the chlorides have been hydrolyzed in the aqueous work up. Macrocycle **7** was further identified by chromatographic purification followed by HRMS but was

not isolated in high enough quantity or purity to obtain NMR spectra. See Supporting Information for HRMS spectra.

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11. See Schemes S1 & S2 in the Supporting Information for a summary of these mechanistic results.
12. D.-M. Lee, J. H. Ko, and K.-I. Lee, *Monatsh. Chem.*, 2007, **138**, 741.
13. We have isolated and characterized a macrocycle similar in structure to **7**, the results will be published in due course.
14. The decomposition products have yet to be identified, but we are investigating the kinetics of the reactions of nucleophiles with **3** and results will be published in due course. However we postulate that nucleophilic attack at the carbonyl could be facilitating the degradation. ¹H NMR data of degradation under the reaction conditions is shown in Figure S3.
15. CCDC 1429360 & 1429359 contain the supplementary crystallographic data for **4** and **10**, respectively.
16. (a) Similar reactions and products obtained have been previously reported (see b-e) and most without chromatographic purification (refs. 2 and 16b-c). Though our compound appears to be previously unreported, analogs described in ref. 2 were also formed in the good yields with an average of 60% in pyridine; (b) F. Ullmann and M. Ettisch, *Chem. Ber.*, 1921, **54**, 259; (c) S. Ishikawa, H. Hinoshita, M. Takagi, and K. Ueno, *Nippon Kagaku Kaishi*, 1988, 743; (d) V. K. Tandon and H. K. Maurya, *Tetrahedron Lett.*, 2010, **51**, 3843; (e) C. Ibis, S. S. Ayla, and H. Asar, *Synth. Commun.*, 2014, **44**, 121.
17. Table S1 (Supplementary Material) contains a comparison of 24 reactions of 2.0-2.2 equiv of phenol with **3** that could be located in our literature search.