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Paper

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2-Phenylsulfanylhydroquinone dimer mono-quinone derivative as a new fluorescence dye responding to reductive conditions

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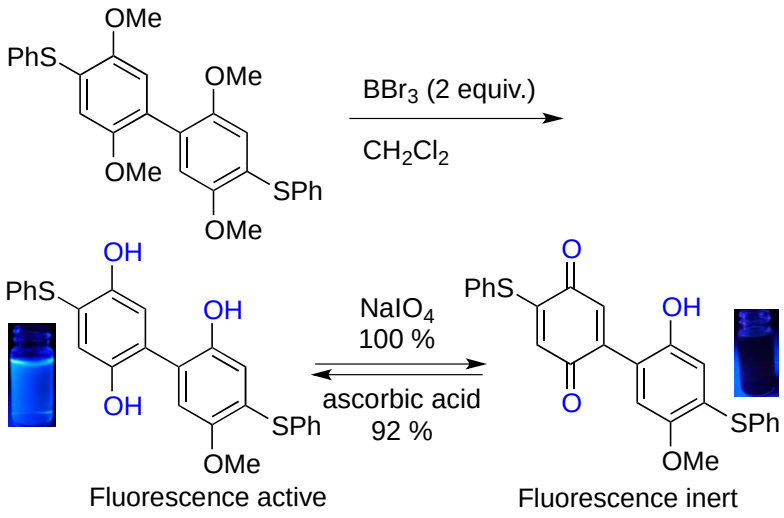
Dedication to Prof. Samir Zard

Received 09-14-2023 **Accepted Manuscript** 10-30-2023 **Published on line** 11-12-2023

Abstract

2-Phenylsulfanylhydroquinone dimer mono-quinone derivative was readily prepared via the selective deprotection and subsequent oxidation of 2-phenylsulfanylhydroquinone dimer tetramethyl ether. Controlled amounts of BBr_3 achieved the selective deprotection of the OMe group; and this one-step procedure provided a convenient preparation of mono-methylated derivative, which was fluorescence active. Oxidation using $NaIO_4$ quantitatively converted the latter to corresponding mono-quinone derivative, which did not exhibit fluorescence. Thus, this blue fluorescence activity was readily switched by oxidation or reduction between mono-methyl derivative and mono-quinone derivative.



Keywords: Fluorescence dye, hydroquinone dimer, reduction sensor, quinone

Cite as *Arkivoc* **2024** (2) 202312086

DOI: https://doi.org/10.24820/ark.5550190.p012.086

Introduction

Development of new fluorescence dyes has been of interest among organic chemists because it is regarded that such materials potentially open area of new science and technology.[1,2] Thus far, a variety of fluorescence dyes have been developed and widely used in the fields of biochemistry and material science.[3-25] Modified dyes are often used as fluorescence markers, which makes it easy to trace where the molecules are spread or distributed in biological systems. Some of these dyes are modified to exhibit fluorescence in response to chemical and/or biological stimuli, which allows to detect target molecules or reactions.[26-28] For example, cancer cells in vivo are readily detected using rhodamine-based dyes.[29]

Recently, we have developed a new fluorescence dye based on the 2-phenylsulfanylhydroquinone dimer,[30-32] which is readily prepared from commercially available benzoquinone and thiophenol. The molecule is easily synthesized at multi-gram scale and emits strong blue fluorescence under UV irradiation. Its quantum yield reached 0.39 in MeOH solution.[33] The fluorescence activity of the dye is controlled using the number of acyl units attached to it.[34] We modified the dye to achieve sufficient water solubility and installed a tether unit that connects to a peptide molecule. Subsequently, we found that the dye functions as a fluorescence marker of bovine albumin serum (BSA) peptides in aqueous solution.[35]

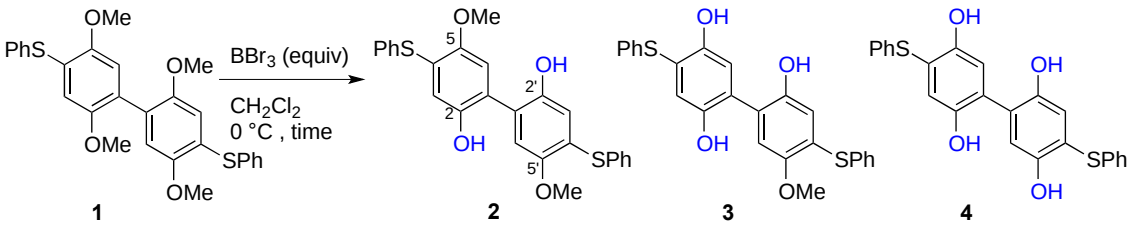
During our investigation for expanding the utility of the dye, we felt the need to develop a more convenient method for the chemical modification of the compound. After the dimerization reaction, 2-phenylsulfanylhydroquinone dimer contains four OMe groups that are expected to undergo deprotection reaction to the corresponding phenol. We deprotected all of the OMe groups using excess amounts of BBr_3, and subsequently obtained all OH derivative was selectively acetalized at the 2,2'-position.[33] Although this strategy provides a reasonable transformation, it requires a multistep sequence for preparing the desired derivatives. We speculated that if the selective deprotection of these OMe groups could be achieved using controlled amounts of BBr_3, this new strategy might provide a much shorter route for synthesizing the derivatives. In this paper, we report the selective deprotection of the four OMe groups using controlled amounts of BBr_3. With this procedure, we have successfully developed a new fluorescence dye based on 2-phenylsulfanylhydroquinone dimer mono-quinone derivative that responds to redox conditions.

Results and Discussion

Dimer **1**, which was prepared using our previously reported method,[33] was treated with various amounts of BBr_3 in CH_2Cl_2. The results are summarized in Table 1.

The reaction was carried out at 0 °C. When 1 equivalent of BBr_3 was used, the dimethoxy derivative **2** was obtained as the major product in 42% yield (entry 1), accompanied with unreacted **1** in 16%. The yield of **2** was improved to 52% when the reaction time was prolonged to 12 h (entry 2). Note that neither the tri-deprotected product **3** nor the tetra-deprotected product **4** was formed under these reaction conditions. When more than one equivalent of BBr_3 was used, mono-methyl product **3** and hydroquinone dimer **4** were obtained. For example, when 1.5 equivalents of BBr_3 was employed, compounds **2** and **3** were formed in 40% and 28% yields, respectively (entry 3). The highest yield of compound **3** was accomplished when 2.0 equivalents of BBr_3 was used (entry 4). As the amounts of BBr_3 used increased, the yield of the all-deprotected compound **4** increased (entry 5). Compounds **2**, **3**, and **4** were readily separated by simple column chromatography. Thus, compound **2** and **3** were conveniently prepared from compound **1** in one step using the above procedure.

Table 1. Selective deprotection of the methyl groups from tetramethyl ether **1**

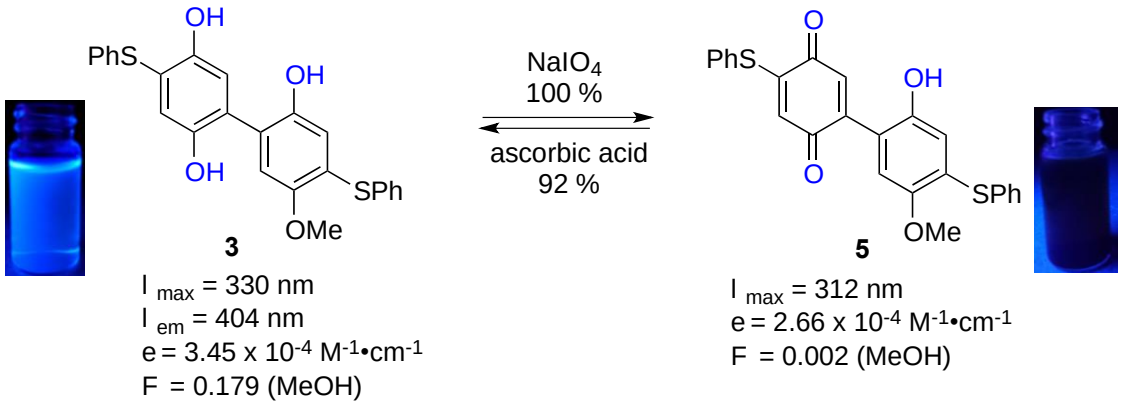


entry	Time (h)	BBr_3 (equiv.)	**2**; Yield (%)[a]	**3**; Yield (%)[a]	**4**; Yield (%)[a]	**1**; Revovery (%)[a]
1	5	1.0	42	0	0	16
2	12	1.0	52	0	0	8
3	5	1.5	40	28	0	0
4	5	2.0	16	39 (36)[b]	9	0
5	5	2.5	1	18	43	0

a) NMR yields. b) Isolated yield.

These results indicated that the deprotection of the methoxy groups at the 2-position occurred preferentially under these conditions, and the methyl groups in 5-position were deprotected more slowly. Hence, we assumed that BBr_3 preferred to be chelated by the OMe groups at the 2- and 2'-positions, and this chelating effect accelerated the deprotection reaction at these positions.

The obtained unsymmetrical hydroquinone dimers **3** was photoluminescent in MeOH solution and showed excellent blue fluorescence upon irradiation with 330 nm UV light. Its emission maximum appeared at 404 nm, and its quantum yield in MeOH reached 0.179. We assumed that the corresponding oxidation derivative, mono-quinone **5**, would be photoluminescently inactive. Indeed, this was true, and mono-quinone **5**, readily obtained quantitatively by treatment of **3** with $NaIO_4$ (Scheme 1), showed no fluorescence upon UV irradiation at its absorption peak observed at 312 nm. Its quantum yield was only 0.002, and we concluded that compound **5** was a non-fluorescent compound. Exposure of the mono-quinone **5** to ascorbic acid progressed smooth reduction to the mono-methyl derivative **3** in 92% yield. The reduction was also possible using aqueous $Na_2S_2O_4$.



Scheme 1. Redox reactions between the mono-methylderivative **3** and the mono-quinone **5**.

Changes in the UV and PL spectra of compounds **3** and **5** were investigated during their oxidation and reduction reactions. To a solution of **3** in MeOH was added aqueous $NaIO_4$ solution, and the UV and PL spectra of the resulting mixture were observed. After the addition of the oxidant, the UV spectra gradually changed and finally showed the spectra of compound **5** after 240 min. The fluorescence intensity decreased gradually and finally disappeared. In the UV spectra, we observed two isosbestic points at 314 and 361 nm. This indicated that the oxidation of mono-methyl derivative **3** to mono-quinone **5** progressed very cleanly and no significant side reaction occurred (Figure 1).

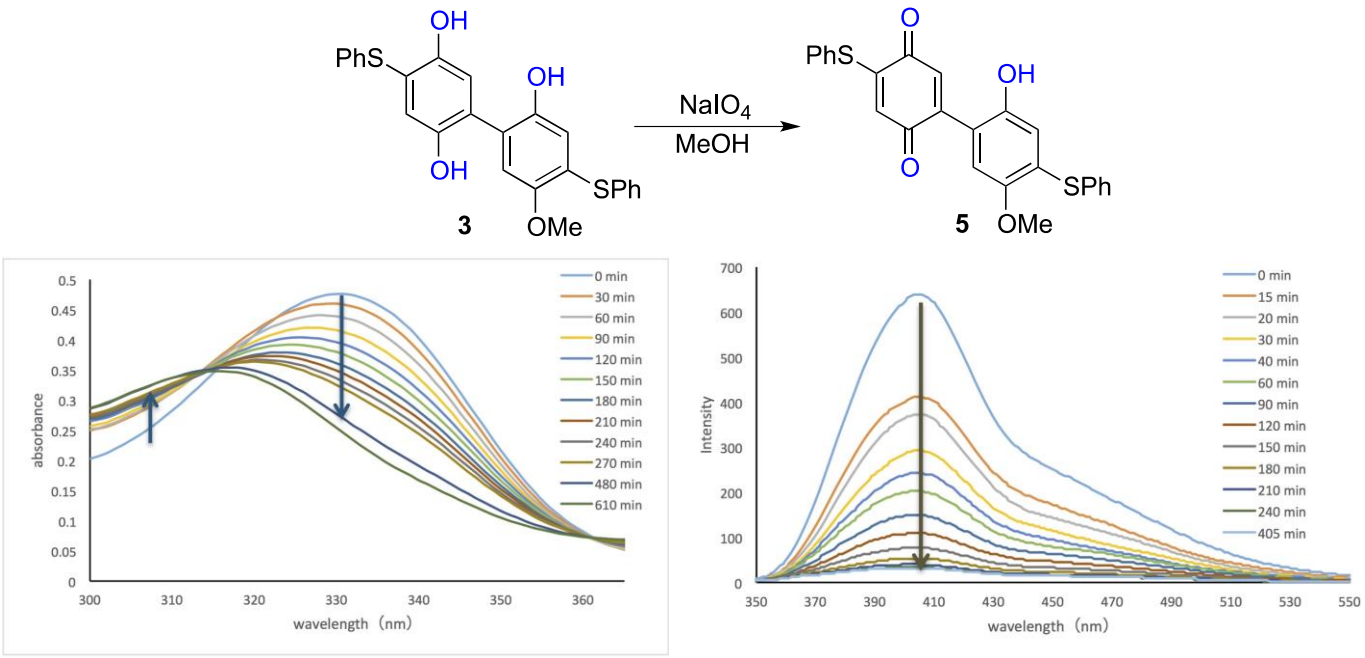


Figure 1. Changes of the UV and PL spectra of the mono-methyl derivative **3** during oxidation.

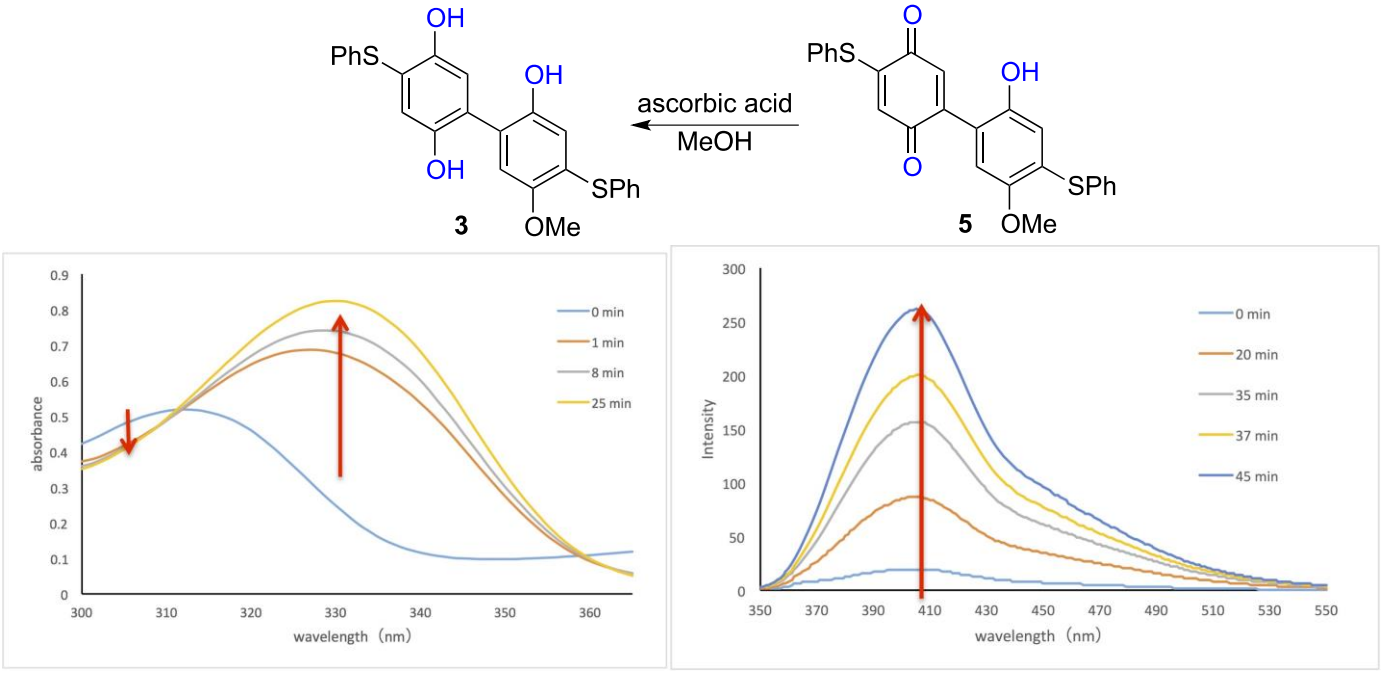


Figure 2. Changes of the UV and PL spectra of mono-quinone **5** during the reduction.

The reduction process of mono-quinone **5** using ascorbic acid was also examined (Figure 2). The addition of ascorbic acid changed the UV spectrum of **5** immediately and the UV spectrum of mono-methyl derivative **3** was observed within 30 min. Thus, the reduction of **5** under these conditions progressed very rapidly. We again observed two isosbestic points at 312 and 359 nm. These observations confirmed that the reduction reaction from **5** to **3** was also a clean reaction. In addition, the two isosbestic points during the oxidation and reduction processes are very close. Hence, this redox reaction is very clean and potentially useful for repeating the redox process between 3 and 5 for several times. Note that the blue fluorescence resumes as the reduction reaction of **5** progresses, and the emission spectrum to compound **3** is finally observed at the end of the reaction. This was also observed when the MeOH solution of mono-quinone **5** was irradiated with black light (λ_{max}; 365 nm), and the blue fluorescence resumed and gradually became more intense as the reaction progressed (Figure 3).

Figure 3. Appearance of fluorescence when ascorbic acid solution was added to a solution of compound 5 in MeOH. The top row from left to right: pictures after 0 sec., 1 sec., and 2 sec. The bottom row from left to right: pictures after 3 sec., 4 sec., and 5 sec.

Conclusions

We have achieved selective removal of the methyl groups from the 2-phenylsulfanylhydroquinone dimer tetramethyl ether in one step using controlled amounts of BBr_3. This simple and convenient process provides a one-step preparation of two-demethylated and three-demethylated derivatives. The 2-phenylsulfanylhydroquinone dimer mono-quinone derivative may serve as a potential fluorescence sensor that responds to reductive conditions. Further application and improvement of the fluorescence properties of the dye are now under investigation in our laboratory.

Experimental Section

General. All ^{1}H and ^{13}C NMR spectra were recorded on a JEOL Lamda-500 or JNM-ECA 500 Delta2 (500 MHz for ^{1}H and 126 MHz for ^{13}C) spectrometer. High-resolution mass spectra (HRMS) were measured using a Waters Xevo G2-XS QTof ESI mass spectrometer. UV-vis spectra were measured using a SHIMADZU UV-1650PC spectrometer. Fluorescence spectra were measured using a JASCO FP-6200 fluorescence spectrometer. Absolute quantum yields were measured using a Hamamatsu Photonics C9920-02G absolute quantum yield spectrometer. All the reactions in this study were performed using dried solvent under nitrogen atmosphere unless otherwise mentioned. Compound **1**, was prepared by the method reported in ref. 33, and compound **2** and **4** prepared in this method are confirmed by comparison with physical data reported in the same reference.

Preparation of compound 3 (mono-methyl derivative). To a solution of compound **1** (0.9838 g, 2.005 mmol) in CH_2Cl_2 (40 mL) was added BBr_3 (4.1 mL in 1.0 M in CH_2Cl_2 solution, 4.1 mmol) at 0 °C, and the reaction mixture was stirred at the same temperature for 5 h. MeOH (20 mL) was added to the reaction mixture and the resulting solution was concentrated in vacuo. This manipulation was repeated for six times to remove borane-derived material as volatile $B(OMe)_3$. Residue was purified through silica gel column chromatography (hexane-EtOAc 5:1 then 3:1 v/v), and compound **3** was obtained in 36% yield (0.3243 g, 0.7230 mmol). Brown solid. mp 62.6-66.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, J = 7.8, 1.5 Hz, 2H), 7.44 – 7.35 (m, 3H), 7.28 (d, J = 8.1 Hz, 2H), 7.24 – 7.16 (m, 3H), 7.18 (s, 1H), 7.01 (s, 1H), 6.80 (s, 1H), 6.49 (s, 1H), 6.16 (s, 1H), 5.97 – 5.61 (br, 2H), 3.89 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.5, 151.0, 146.7, 146.6, 135.3, 133.9 (2C), 132.2, 129.7 (2C), 129.5 (2C), 129.3, 128.5 (2C), 127.7, 126.7 (2C), 124.3, 122.4, 117.6, 117.6, 117.3, 113.2, 56.7. HRMS (TOF-ES+): calcd for $C_{25}H_{21}O_4S_2$ 449.0881 [M + H^+], found 449.0884. λ_{max} 330 nm, $\varepsilon = 2.9 \times 10^4$ $M^{-1}cm^{-1}$ (MeOH, 1×10^{-5} M to 5.5×10^{-5} M). λ_{em} = 404 nm, Φ = 0.179 (1.3×10^{-5} M in MeOH).

Preparation of mono-quinone 5. To a solution of compound **3** (0.1798 g, 0.401 mmol) in MeOH (40 mL) was added aqueous $NaIO_4$ (0.0887 g, 0.4147 mmol) solution (2 mL) at room temperature, and the reaction mixture was stirred at the same temperature for 1.5 h. MeOH (20 mL) was removed by rotary evaporator and remaining aqueous mixture was extracted with CH_2Cl_2 (5 × 5 mL). The organic phase was combined and dried over Na_2SO_4. After filtration, the CH_2Cl_2 solution was concentrated and the obtained crude product was purified through silica gel column chromatography (hexane-EtOAc 4:1 v/v). Compound **5** was obtained in 77% yield (0.1385 g, 0.3102 mmol). Brown solid. mp 82.1 - 85.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.49 (m, 7H), 7.45 – 7.38 (m, 3H), 7.22 (s, 1H), 6.87 (s, 1H), 6.61 (s, 1H), 6.33 (s, 1H), 5.96 (s, 1H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.7, 183.7, 155.9, 150.0, 148.7, 147.4, 135.7 (2C), 135.2 (2C), 134.1, 134.1, 130.9, 130.7, 130.6 (2C), 129.9 (2C), 129.3, 126.7, 126.2, 118.6, 117.9, 112.0, 56.7. HRMS (TOF-ES+): calcd for $C_{25}H_{19}O_4S_2$ 447.0725 [M + H^+], found 447.0728. λ_{max} 312 nm, $\varepsilon = 3.7 \times 10^4$ $M^{-1}cm^{-1}$ (MeOH, 1.8×10^{-5} M to 3.1×10^{-5} M). λ_{em} = 402 nm, Φ = 0.002 (2.46×10^{-5} M in MeOH).

Reduction of mono-quinone 5. Aqueous ascorbic acid solution (60.6 mg, 0.346 mmol in 2 mL water) was added to a solution of compound **5** (138.5 mg, 0.310 mmol) in MeOH (20 mL) at room temperature, and the reaction mixture was stirred for 1 h. MeOH was evaporated and remaining aqueous solution was extracted with CH_2Cl_2 (3 × 5 mL). The organic phase was combined and dried over Na_2SO_4. After filtration, the CH_2Cl_2 solution was concentrated and compound **3** was obtained in 92% yield (128.5 mg, 0.287 mmol). NMR data were identical to compound **3**.

Acknowledgements

This study was partially supported by KAKENHI for Exploratory Research (26620031) and Scientific Research (B) (17H03023). We thank Ms. Karen Fukunaga for her experimental work partial supporting on this report. We are grateful for Professor Jun Kawamata, Yamaguchi University, for his helpful discussions and measuring the absolute quantum yields of these compounds.

Supplementary Material

Electronic supplementary information (ESI) available: copies of ^{1}H and ^{13}C NMR spectra and UV/PL spectra of compounds **3** and **5**. This material can be found via the "Supplementary material" section of this article's webpage.

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