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Efficient access to naphthoquinon-1,3-dithioles: formal cycloaddition and oxidation of quinones and amines with CS_2

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ABSTRACT

An efficient strategy for one-pot synthesis of a variety of naphthoquinon-1,3-dithiole derivatives has been developed. The combined action of the formal cycloaddition and oxidation reaction of quinones and amines in the presence of CS_2 without additional oxidant produced naphthoquinon-1,3-dithiole derivatives in good yields.

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1. Introduction

During the past decade, a multicomponent reaction, offering a straightforward route to generate complexity and diversity in a single operation, became an extremely powerful tool in combinatorial chemistry and drug discovery.[1] There are numerous biological active molecules with five-membered rings, containing two heteroatoms, which have antimalarial, antibacterial, antifungal, antiviral, antitumor, anti-inflammatory, and herbicidal activities.[2] Compounds containing the sulfur heterocycles have shown a wide range of pharmacological activities.[1i,3] Additionally, derivatives of sulfur heterocycles such as 1,3-dithiole have been widely explored as new materials because of their superconducting, optical, and electronic switching properties.[4] Especially, tetrathiafulvalenes (TTFs) are the most successful class of heterocycles in terms of creating highly conducting and low-temperature superconducting organic crystalline materials.[5] What's more, TTF–quinones constitute a promising field of applications due to the interesting optoelectronic properties they exhibit.[6]

There are few protocols for the corresponding reactions involving C–S bond formation comparing to the new C–N and C–O bond-forming technologies, despite the importance of sulfur-containing compounds. Recently, carbon disulfide is often used as sulfur reagent in constructing of various sulfur heterocycles.[1i,3b,c,4b–g,7] Itoh[7a] reported ruthenium-catalyzed cycloaddition of 1,6-diynes with isothiocyanates and carbon disulfide. One-pot reaction of amines, CS_2, and alkyl halides under catalyst and solvent-free to synthesize dithiocarbamates was established.[7d] Nozaki reported the first successful synthesis of sulfur-rich polymers with completely alternating copolymerization of episulfide with CS_2.[4e] Noteworthily, Ma and co-workers have utilized CS_2 as a substrate to construct 2-*N*-substituted benzothiazoles[7h] and 2-thio-substituted benzothiazoles.[4g] During the past few years we have reported the novel reactions of C_{60} with amino-acid esters and CS_2 affording fullerene derivatives.[7b]

Interest in 1,3-dithioles derivatives continues unabated due to their wide usefulness as biologically active agents and key intermediates in the organic synthesis.[8] At the same time, the quinone structure is common in numerous natural products[9] and important pharmacophores.[10] Furthermore, a number of natural occurring quinone structures are associated with anticancer, antibacterial, antimalarial, and fungicidal activities.[11] Based on their biological and structural properties, we investigated a novel, one-pot synthesis of a series of new 1,3-dithioles derivatives, which combine quinone structures and amines.

In the course of our studies on the reaction of naphthoquinone and amine, we were pleased to find that the new product **4** was obtained in the presence of CS_2. Herein we disclosed the details of our results.

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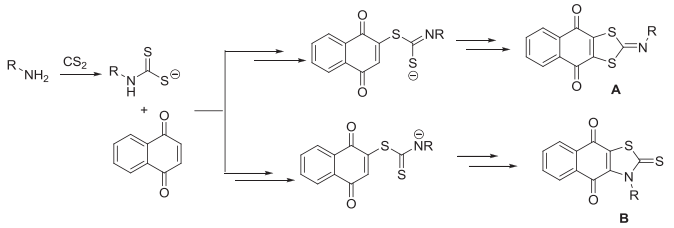
2. Results and discussion

In this reaction, it had two possible reaction routes to the different products of **A** with sulfur-attack and **B** with nitrogen-attack (Scheme 1). In order to validate the structure of product **4**, the single crystal of **4a** was cultured and determined by X-ray crystallographic analysis. Finally, it was unambiguously confirmed that the structure of product **4a** was **A** (Fig. 1).[12] Therefore, it had been identified two-step sulfur-attack to obtain **4** in this reaction system.



Scheme 1. Two possible reaction routes.

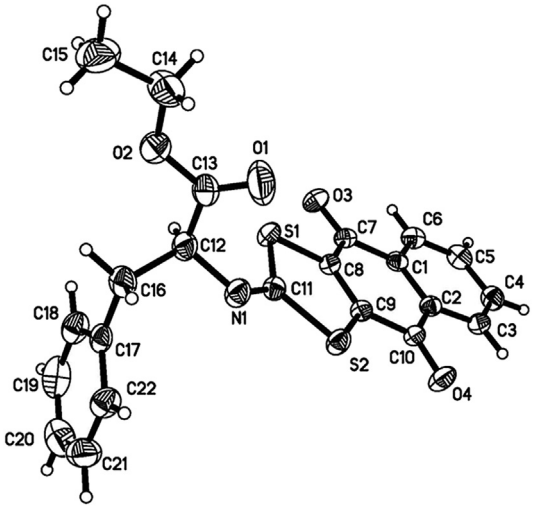
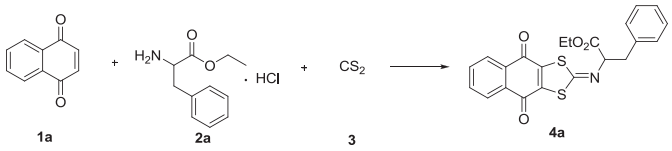


Fig. 1. X-ray crystallography for **4a**.

As indicated in Table 1, the reaction conditions such as solvent, temperature, and bases were studied. It was found that the new compound **4a** was afforded in 78.9% yield through the reaction of 1,4-naphthoquinone (**1a**), phenylalanine ethyl ester hydrochloride (**2a**), and CS_2 (**3**) at room temperature and $NaHCO_3$ as base in ethanol (Table 1, entry 1). Encouraged by this result, we tried to optimize the reaction condition and the results were summarized in Table 1. The results demonstrated that the dichloromethane was more efficient than other solvents (Table 1, entry 5). As the carbon bisulfide was highly volatile, it was necessary to increase the ratio of CS_2 and the satisfactory yield 81.3% was obtained with 3 equiv of CS_2. However, when we tried to add more carbon bisulfide, the yield of **4a** didn't increase remarkably (Table 1, entry 7). Next, we screened different bases in place of $NaHCO_3$. Product **4a** was only yielded in 43.2% when pyridine was employed as base and the yield of **4a** was raised to 83.0% when Et_3N was used in this reaction (Table 1, entries 5, 8, and 9). Due to the byproduct urea produced by the side reaction of CS_2 and amine at room temperature, the yield of **4** was up to 86.0% when the temperature was dropped to 0 °C (Table 1, entry 10). Finally, the quantity of **2a** was increased to 1.2 equiv in order to make sure **1a** consumed completely and the yield of **4a** was 88.2% (Table 1, entry 9). On the basis of these results, the optimal condition involved the following parameters: Et_3N as a base, dichloromethane as a solvent, and reacted at 0 °C.

Table 1
Optimization between 1,4-naphthoquinone, CS_2, and phenylalanine ethyl ester hydrochlorides[a]



Entry	**1**/**2a**/**3**	Temperature	Solvent	Base	Yield[c] (%)
1	1:1:3	rt	Ethanol	$NaHCO_3$	78.9
2	1:1:3	rt	AcOEt	$NaHCO_3$	80.4
3	1:1:3	rt	Isopropanol	$NaHCO_3$	67.4
4	1:1:3	rt.	Toluene	$NaHCO_3$	69.6
5	1:1:3	rt	CH_2Cl_2	$NaHCO_3$	81.3
6	1:1:1	rt	CH_2Cl_2	$NaHCO_3$	56.1
7	1:1:5	rt	CH_2Cl_2	$NaHCO_3$	81.6
8	1:1:3	rt	CH_2Cl_2	Pyridine	43.2
9	1:1:3	rt	CH_2Cl_2	Et_3N	83.0
10	1:1:3	0 °C	CH_2Cl_2	Et_3N	86.0
11[b]	1:1.2:3	0 °C	CH_2Cl_2	Et_3N	88.2

[a] Reaction conditions: mixture of **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (3–5 mmol), base (1.0 mmol), and solvent (5.0 mL) was stirred for 4 h under corresponding temperature.
[b] Et_3N (1.2 equiv) was added.
[c] Yield of the isolated product.

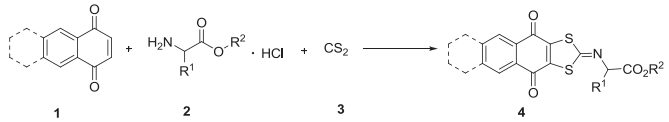
With the optimized reaction conditions established, we then examined the substrate scope of this reaction, and the results were summarized in Tables 2 and 3.

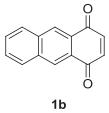
As highlighted in Table 2, a variety of amino-acid ester hydrochlorides **2a**–**2h** could react efficiently with **1a** in the presence of CS_2 to give the corresponding products in good to excellent yields (Table 2, entries 1–8). Unfortunately, the lower yields of **4c** and **4d** were obtained in 54.0 and 60.3%, the reason may be that the side reaction of urea was increased due to the small steric effect of glycine ester (Table 2, entries 3 and 4). The 1,4-anthraquinone **1b** was also applied to this reaction and obtained the corresponding products with middle yields in 40.3–55.8% because of the lower activity of 1,4-anthraquinone (Table 2, entries 9–13).

With the satisfactory results of amino-acid ester hydrochloride, we also investigated the aliphatic amines in this reaction to further extend the applicability of this reaction. Propylamine was used in order to establish the full scope of this interesting reaction at first. The corresponding product **4p** was only yielded in 60.1% when propylamine was used as the reactant under the same condition and the byproduct 2-thioxonaphtho[2,3-*d*][1,3]dithiole-4,9-dione **15** was found in 18.7% yield. Excitingly, the yield of **4p** was improved to 94.8% when propylamine hydrochloride and Et_3N was employed (Table 3, entry 3). Then, the different primary amines (**2i**–**2r**) bearing various linear and branched chain alkyl groups, benzyl group all yielded the corresponding products in 73.1–96.7% yield (Table 3, entries 1–9). Cyclohexylamine was obtained in 66.8% yield because of the low reactivity due to the steric hindrance of cyclohexylamine. When cyclohexylamine hydrochloride was up to 3 equiv, the yield of **4w** was up to 80.0%. A little byproduct **15** was found in about 10% yield when some amines used (Table 3, entries 2, 4, 6, 7, 10). 1,4-Anthraquinone was also examined with propylamine and the corresponding product (**4x**) was obtained in 60.1%. Furthermore, the corresponding product was not observed, but 2-(phenyl)amino-1,4-naphthoquinone **16** was obtained as the addition product of 1,4-naphthoquinone and phenylamine for the low activity of phenylamine (confirmed by NMR and GC–MS).

It was the result of the combined action of the cycloaddition and oxidation reaction to yield the product of **4** in the absence of additional oxidant at this reaction system. Referring to the work of Miyamura[3a] and Wang,[13] we considered that the oxidation process was the result of the combined oxidation with oxygen and quinone itself in this

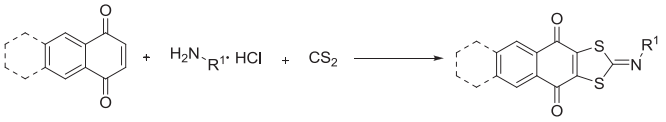
Table 2
Extending scopes using different amino-acid ester hydrochlorides

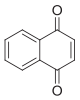
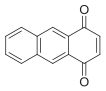


Entry[a]	1	R^1	R^2	4	Yield (%)
1		$PhCH_2$–	CH_3CH_2–	**4a**	88.2
2		$(CH_3)_2CH$–	CH_3–	**4b**	75.0
3		H–	CH_3CH_2–	**4c**	54.0
4		H–	CH_3–	**4d**	60.3
5		$(CH_3)_2CH$–	CH_3CH_2–	**4e**	79.3
6		CH_3–	CH_3CH_2–	**4f**	86.0
7			CH_3CH_2–	**4g**	71.2
8			CH_3CH_2–	**4h**	78.2
9		$PhCH_2$–	CH_3CH_2–	**4i**	55.8
10		H–	CH_3CH_2–	**4j**	46.1
11		$(CH_3)_2CH$–	CH_3CH_2–	**4k**	41.1
12		CH_3–	CH_3CH_2–	**4l**	48.1
13			CH_3CH_2–	**4m**	40.3

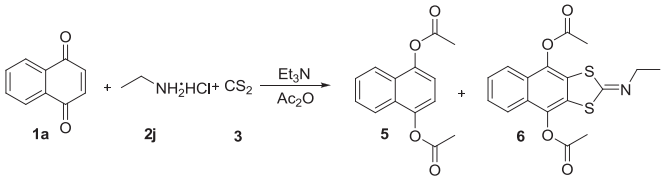
[a] Reaction conditions: the mixture of **1a** (1.0 mmol), **2** (1.2 mmol), **3a** (3 mmol), Et_3N (1.2 mmol), and CH_2Cl_2 (5.0 mL) was stirred for about 4 h under 0 °C.

Table 3
Extending scopes using different primary amine hydrochlorides

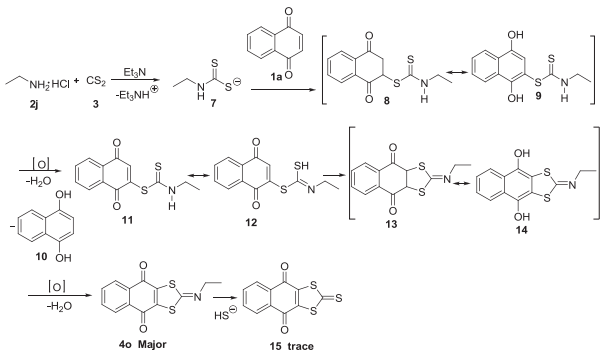


Entry	1	R^1	4	Yield (%)
1		CH_3–	**4n**	96.7
2		CH_3CH_2–	**4o**	86.7
3		$CH_3CH_2CH_2$–	**4p**	94.8
4		$(CH_3)_2CH$–	**4q**	81.0
5		$CH_3CH_2CH_2CH_2$–	**4r**	90.7
6		C_6H_{13}–	**4s**	85.5
7		$C_{10}H_{21}$–	**4t**	76.0
8		$C_{12}H_{25}$–	**4u**	73.1
9		$PhCH_2$–	**4v**	83.3
10			**4w**	80.0[a]
11		$CH_3CH_2CH_2$–	**4x**	60.1

[a] 3.0 equiv cyclohexylamine hydrochloride and 3.0 equiv Et_3N were added.



Scheme 2. Control experiment.



Scheme 3. Proposed reaction pathway.

reaction system. Some control experiments were carried out in order to probe the mechanism of this transformation. In order to capture the naphthol and prove the oxidation of naphthoquinone, the acetic anhydride was added to the reaction system at different conditions. When 4 equiv Ac_2O and Et_3N were added the reaction mixture of **1a**, **2o**, and **3** at standard condition for 2 h, the resulting products **5** and **6** were detected by GC–MS and ^1H NMR. It showed that naphthol was produced with the oxidation of quinone. The products **5** and **6** were 5.8% and 42.9% at air atmosphere, but 48.3% and 10.0% under the nitrogen atmosphere [see Supplementary data]. It showed that oxygen also has the same oxidation in this reaction (Scheme 2).

On the basis of the above results, the mechanism of this reaction is proposed in Scheme 3. Firstly, the amine **2j** added to CS_2 and formed adduct **7**.[7a,f,g,14] Subsequently, intermediate **7** attacked 1,4-naphthoquinone **1a** and formed the initial addition product **8** and it's tautomer **9**, which can be oxidized by quinine itself or O_2. Finally the final product of **4o** was obtained through another sulfur-attack reaction and oxidized procedure. The byproduct **15** was detected because the hydrogensulfide anion attacked final product **14** and the yield of **15** was increased when sodium sulfide was added to the reaction system [identified by NMR and GC–MS,[6] see Supplementary data]. We suspected the hydrogensulfide anion was formed with the side reaction of urea.

3. Conclusion

In conclusion, we have developed a simple, facile, and highly efficient method for the synthesis of naphthoquinon-1,3-dithiole derivatives, which relied on the combined action of the formal cycloaddition and oxidation reaction of 1,4-naphthoquinone and amines in the presence of CS_2 without additional oxidant. This

approach can compliment a lot of other existing methods for naphthoquinon-1,3-dithiole derivatives. Therefore the potential application of these compounds will be interested in academic, pharmaceutical, and material research. The application of this powerful strategy to the synthesis of natural products and more detailed mechanistic investigations are currently underway in our laboratory. Additionally, the successful application of CS_2 in synthesis of sulfur-containing heterocycle will stimulate the study on sulfur chemistry by employing these inexpensive reagents.

4. Experimental section

4.1. General

All chemicals were purchased from commercial vendors and were used as received without further purification; any exceptions are noted within the text and the vendors are noted within the context of use. The ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, in $CDCl_3$ using TMS as internal standard with a Bruker AM 500 spectrometer. Chemical shifts (δ) were reported as parts per million (ppm) and the following abbreviations were used to identify the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad and all combinations thereof can be explained by their integral parts. The GC–MS was taken on Aglient (GC431-MS210) and elementary analysis was on Thermo Electron Corporation Flash EA 1112. HRMS were recorded on a Bruker MicroTOF-QII mass instrument (ESI).

*4.1.1. Typical procedure for the preparation of ethyl 2-(4,9-dioxo-4,9-dihydronaphtho[2,3-d][1,3]-dithiol-2-imino)-3-phenylpropanoate(**4a**).* Typically, a mixture of 1,4-naphthoquinone (**1a**, 1.0 mmol, 0.158 g, 1.0 equiv), phenylalanine ethyl ester hydrochloride (**2a**, 1.2 mmol, 0.276 g, 1.2 equiv), CS_2 (**3a**, 5 mmol, 0.381 g, 5.0 equiv), triethylamine (1.2 mmol, 0.121 g 1.2 equiv) in CH_2Cl_2 (5.0 mL) was stirred at 0 °C under air condition for 4 h, determined by GC–MS and TLC. The solvent was removed under vacuum and the resulting crude product was purified by chromatography on silica gel eluted using CH_2Cl_2 as the eluent to afford the desired product **4a** as red solid (0.3735 g, yield 88.2%, mp=149–150 °C).

Yield 88.2%; mp 149–150 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.12–8.08 (m, 2H), 7.78–7.74 (m, 2H), 7.31–7.28 (m, 2H), 7.26–7.20 (m, 3H), 4.22 (q, J=7.0 Hz, 2H), 3.93 (dd, J_1=5.5 Hz, J_2=8.5 Hz, 1H), 3.32 (dd, J_1=5.0 Hz, J_2=13.5 Hz, 1H), 3.14 (dd, J_1=8.0 Hz, J_2=13.0 Hz, 1H), 1.26 (t, J=8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.1, 175.5, 169.6, 160.7, 143.6, 142.6, 136.6, 134.3 (2C), 132.0, 131.9, 129.6 (2C), 128.5 (2C), 127.1 (2C), 127.0, 73.4, 61.6, 39.1, 14.1; EIMS m/z 424.18 $[M+H]^+$. Anal. Calcd for $C_{18}H_{17}NO_4S_2$: C, 62.10; H, 4.50; N, 3.29; S, 15.07. Found: C, 62.39; H, 3.97; N, 3.17; S, 14.69.

*4.1.2. Methyl 2-(4,9-dioxo-4,9-dihydronaphtho[2,3-d][1,3]dithiol-2-imino)-3-methylbutanoate (**4b**).* Yield 75.0%; mp 142–143 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.13–8.11 (m, 2H), 7.79–7.76 (m, 2H), 3.78 (s, 3H), 3.52 (d, J=5.5 Hz, 1H), 2.41–2.34 (m, 1H), 1.01 (d, J=3.0 Hz, 3H), 0.99 (d, J=2.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.1, 175.5, 170.1, 160.0, 143.8, 142.6, 134.3, 134.3, 132.0 (2C), 127.1, 78.1, 52.2, 32.5, 19.3, 18.4 (2C). GC–MS m/z 362.3 $[M+H]^+$, 361.3 $[M]^+$, 318.4, 303.0 (100%), 104.5, 76.5, 55.3; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{16}NO_4S_2$ $[M+H]^+$ 362.0515, found 362.0515.

*4.1.3. Ethyl 2-(4,9-dioxo-4,9-dihydronaphtho[2,3-d][1,3]dithiol-2-imino)acetate (**4c**).* Yield 54.0%; mp 159–160 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.14–8.12 (m, 2H), 7.79–7.76 (m, 2H), 4.28 (q, J=7.0 Hz, 2H), 4.04 (s, 2H), 1.33 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.1, 175.5, 168.2, 161.4, 144.5, 142.7, 134.4, 134.3, 132.0 (2C), 127.2, 127.1, 61.6, 59.0, 14.2; GC–MS m/z 333.1 $[M]^+$, 261.3, 260.3 (100%), 220.3, 104.2, 76.2, 72.2, 50.1; HRMS (ESI-TOF) m/z calcd for $C_{15}H_{12}NO_4S_2$ $[M+H]^+$ 334.0202, found 334.0203.

*4.1.4. Methyl 2-(4,9-dioxo-4,9-dihydronaphtho[2,3-d][1,3]dithiol-2-imino)acetate (**4d**).* Yield 60.3%; mp 196–197 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.14–8.12 (m, 2H), 7.79–7.77 (m, 2H), 4.05 (s, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.1, 175.4, 168.7, 161.6, 144.5, 142.6, 134.4, 134.3, 132.0 (2C), 127.2, 127.1, 58.8, 52.5; GC–MS m/z 319.3 $[M+H]^+$, 261.6, 260.6 (100%), 220.5, 191.5, 149.5, 134.5, 104.3; HRMS (ESI-TOF) m/z calcd for $C_{14}H_9NO_4S_2Na$ $[M+Na]^+$ 341.9865, found 341.9874.

*4.1.5. Ethyl 2-(4,9-dioxo-4,9-dihydronaphtho[2,3-d][1,3]dithiol-2-imino)-3-methylbutanoate (**4e**).* Yield 79.3%; mp 132–133 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.12–8.09 (m, 2H), 7.77–7.76 (m, 2H), 4.24 (q, J_1=7.0 Hz, J_2=14.0 Hz, 2H), 3.49 (d, J=6.0 Hz, 1H), 2.40–2.34 (m, 1H), 1.31 (t, J=7.5 Hz, 3H), 1.0 (d, J=6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.1, 175.5, 169.6, 159.7, 143.7, 142.7, 134.3, 134.2, 132.0 (2C), 127.1, 78.1, 61.3, 32.4, 19.3, 18.3, 14.2 (2C); GC–MS m/z 376.0 $[M+H]^+$, 332.1, 303.3, 302.3 (100%), 104.1, 76.1, 55.0. Anal. Calcd for $C_{18}H_{17}NO_4S_2$: C, 57.58; H, 4.56; N, 3.73; S, 17.08. Found: C, 57.75; H, 4.46; N, 3.49; S, 17.06.

*4.1.6. Ethyl 2-(4,9-dioxo-4,9-dihydronaphtho[2,3-d][1,3]dithiol-2-imino)propanoate (**4f**).* Yield 86.0%; mp 169–170 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.11–8.09 (m, 2H), 7.78–7.75 (m, 2H), 4.23 (q, J_1=7.5 Hz, J_2=14.0 Hz, 2H), 3.81 (d, J_1=7.0 Hz, J_2=14.0 Hz, 1H), 1.52 (d, J=7.0 Hz, 3H), 1.30 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.0, 175.5, 170.6, 159.5, 143.9, 142.7, 134.3 (2C), 132.0, 131.9, 127.2, 127.1, 66.5, 61.5, 17.6, 14.2; GC–MS m/z 348.0 $[M+H]^+$, 274.1 (100%), 104.1, 86.0, 76.2, 60.0; HRMS (ESI-TOF) m/z calcd for $C_{16}H_{14}NO_4S_2$ $[M+H]^+$ 348.0359, found 348.0361.

*4.1.7. Ethyl 2-(4,9-dioxo-4,9-dihydronaphtho[2,3-d][1,3]dithiol-2-imino)-3-(4-hydroxyphenyl)propanoate (**4g**).* Yield 71.2%; mp 163–164 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.11–8.08 (m, 2H), 7.77–7.74 (m, 2H), 7.12–7.09 (m, 2H), 6.77–6.74 (m, 2H), 5.13 (s, 1H), 4.22 (q, J=6.5 Hz, 2H), 3.88 (dd, J_1=5.0 Hz, J_2=8.0 Hz, 1H), 3.24 (dd, J_1=5.0 Hz, J_2=14.0 Hz, 1H), 3.06 (dd, J_1=8.0 Hz, J_2=13.5 Hz, 1H), 1.27 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.1, 175.5, 169.8, 160.7, 154.7, 143.6, 142.6, 134.3 (2C), 132.01, 132.0, 130.8 (2C), 128.6, 127.1 (2C), 115.5 (2C), 73.7, 61.7, 38.2, 14.2; EIMS m/z 440.03 $[M+H]^+$; HRMS (ESI-TOF) m/z calcd for $C_{22}H_{17}NO_5S_2Na$ $[M+Na]^+$ 462.0440, found 462.0444.

*4.1.8. Ethyl 2-(4,9-dioxo-4,9-dihydronaphtho[2,3-d][1,3]dithiol-2-imino)-2-(1H-indol-3-yl)acetate (**4h**).* Yield 78.2%; mp 129–130 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.20 (s, 1H), 8.00–7.96 (m, 2H), 7.68–7.65 (m, 2H), 7.22 (d, J=7.0 Hz, 2H), 7.13–7.07 (m, 2H), 7.00 (d, J=2.5 Hz, 1H), 4.22 (q, J=4.5 Hz, 2H), 4.02 (t, J=5.5 Hz, 1H), 3.45 (dd, J_1=5.5 Hz, J_2=14.5 Hz, 1H), 3.28 (dd, J_1=8.0 Hz, J_2=14.0 Hz, 1H), 1.26 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 175.8, 175.2, 170.2, 160.6, 143.2, 142.4, 136.1, 134.2, 134.1, 131.8, 131.7, 127.4, 126.9 (2C), 123.6, 122.1, 120.0, 118.7, 111.3, 110.7, 72.9, 61.7, 28.8, 14.2; EIMS m/z 463.71 $[M+H]^+$; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{18}N_2O_4S_2Na$ $[M+Na]^+$ 485.0600, found 485.0602.

*4.1.9. Ethyl 2-(4,11-dioxo-4,11-dihydroanthra[2,3-d][1,3]dithiol-2-imino)-3-phenylpropanoate(**4i**).* Yield 55.8%; mp >300 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.55 (d, J=7.0 Hz, 2H), 8.02 (s, 2H), 7.70 (d, J=4.0 Hz, 2H), 7.34–7.22 (m, 2H), 4.24 (q, J=7.0 Hz, 2H), 3.96 (dd, J_1=6.0 Hz, J_2=8.0 Hz, 1H), 3.35 (dd, J_1=5.0 Hz, J_2=14.0 Hz, 1H), 3.17 (dd, J_1=8.5 Hz, J_2=14.0 Hz, 1H), 1.28 (t, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 175.5, 175.0, 169.6, 160.8, 145.2, 144.2, 136.7,

134.6, 130.4, 130.3 (2C), 129.9, 129.6 (2C), 128.5 (2C), 128.0, 127.9, 127.0, 73.4, 61.7, 39.1, 14.2; EIMS *m/z* 472.39 $[M-H]^+$; HRMS (ESI-TOF) *m/z* calcd for $C_{26}H_{20}NO_4S_2$ $[M+H]^+$ 474.0827, found 474.0828.

*4.1.10. Ethyl 2-(4,11-dioxo-4,11-dihydroanthra-[2,3-d][1,3]dithiol-2-imino)acetate (**4j**).* Yield 46.1%; mp 205–206 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.64 (d, *J*=3.5 Hz, 2H), 8.07 (d, *J*=4.5 Hz, 2H), 7.74 (d, *J*=5.5 Hz, 2H), 4.31 (q, *J*=6.5 Hz, 2H), 4.06 (s, 2H), 1.36 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 175.8, 175.1, 168.3, 161.6, 146.2, 144.4, 134.8 (2C), 130.5, 130.4, 130.3 (2C), 130.1 (2C), 128.1, 128.0, 61.7, 59.1, 14.2; EIMS *m/z* (%) 384.23 $[M+H]^+$; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{14}NO_4S_2$ $[M+H]^+$ 384.0359, found 384.0368.

*4.1.11. Ethyl 2-(4,11-dioxo-4,11-dihydroanthra-[2,3-d][1,3]dithiol-2-imino)-3-methylbutanoate(**4k**).* Yield 41.1%; mp 199–200 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.64 (d, *J*=1.5 Hz, 2H), 8.08–8.06 (m, 2H), 7.75–7.73 (m, 2H), 4.26 (q, *J*=7.5 Hz, 2H), 3.52 (d, *J*=6.5 Hz, 1H), 2.53–2.36 (m, 1H), 1.33 (t, *J*=6.5 Hz, 3H), 1.03 (d, *J*=3 Hz, 3H), 1.02 (d, *J*=2.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 175.8, 175.3, 169.7, 160.0, 145.5, 144.4, 134.8, 134.7, 130.6, 130.5, 130.4 (2C), 130.3, 130.0, 128.2, 128.1, 78.2, 61.4, 32.5, 19.3, 18.4, 14.3; EIMS *m/z* 424.09 $[M-H]^+$; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{20}NO_4S_2$ $[M+H]^+$ 426.0828, found 426.0815.

*4.1.12. Ethyl 2-(4,11-dioxo-4,11-dihydroanthra-[2,3-d][1,3]dithiol-2-imino)propanoate(**4l**).* Yield 48.1%; mp 232–233 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.66 (d, *J*=2.5 Hz, 2H), 8.10–8.07 (m, 2H), 7.76–7.74 (m, 2H), 4.26 (q, *J*=6.5 Hz, 2H), 3.86 (q, *J*=6.5 Hz, 1H), 1.56 (t, *J*=10.0 Hz, 3H), 1.33 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 175.7, 175.3, 170.8, 159.8, 145.8, 144.4, 134.8 (2C), 130.5, 130.4, 130.3 (2C), 130.1 (2C), 128.2, 128.1, 66.5, 61.6, 17.7, 14.2; EIMS *m/z* 398.16 $[M+H]^+$; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{16}NO_4S_2$ $[M+H]^+$ 398.0495, found 398.0631.

*4.1.13. Ethyl 2-(4,11-dioxo-4,11-dihydroanthra-[2,3-d][1,3]dithiol-2-imino)-3-(4-hydroxyphenyl)-propanoate (**4m**).* Yield 40.3%; mp >300 °C ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.60 (d, *J*=8.5 Hz, 2H), 8.06–8.04 (m, 2H), 7.13 (d, *J*=8.0 Hz, 2H), 6.78 (d, *J*=8.0 Hz, 2H), 5.00 (s, 1H), 4.23 (q, *J*=6.5 Hz, 2H), 3.90 (q, *J*=2.5 Hz, 2H), 3.26 (dd, J_1=5.0 Hz, J_2=14.0 Hz, 1H), 3.08 (dd, J_1=8.0 Hz, J_2=14.0 Hz, 1H), 1.28 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 175.7, 175.2, 169.8, 161.7, 154.7, 144.3, 142.6, 135.0 (2C), 134.7 (3C), 130.7, 130.4 (2C), 130.3, 123.0, 128.1, 128.0, 115.4 (2C), 73.6, 61.6, 38.2, 14.2; EIMS *m/z* 489.03 $[M]^+$; HRMS(ESI-TOF) *m/z* calcd for $C_{26}H_{19}NO_5S_2Na$ $[M+Na]^+$ 512.0594, found 512.0601.

*4.1.14. 2-(Methylimino)naphtho[2,3-d][1,3]dithiole-4,9-dione (**4n**).* Yield 96.7%; mp 182–183 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.11 (dd, J_1=3.5 Hz, J_2=5.5 Hz, 2H), 7.76 (dd, J_1=3.0 Hz, J_2=5.5 Hz, 2H), 3.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.2, 175.6, 157.5, 144.1, 143.1, 134.3, 134.2, 132.0 (2C), 127.1 (2C), 45.3; GC–MS *m/z* 262.2 $[M+H]^+$, 261.3 (M, 100%), 220.3, 188.3, 160.3, 104.2, 76.3, 50.2; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_8NO_2S_2$ $[M+H]^+$ 261.9991, found 261.9999.

*4.1.15. 2-(Ethylimino)naphtho[2,3-d][1,3]dithiole-4,9-dione (**4o**).* Yield 86.7%; mp 199–200 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.09 (dd, J_1=1.0 Hz, J_2=5.5 Hz, 2H), 7.75 (dd, J_1=3.5 Hz, J_2=5.5 Hz, 2H), 3.26 (q, *J*=7.0 Hz, 2H), 1.35 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.1, 175.5, 155.3, 143.9, 143.1, 134.2, 134.1, 132.0 (2C), 127.1, 127.0, 53.9, 14.8; GC–MS *m/z* 276.1 $[M+H]^+$, 275.2, 260.4, 188.3, 160.2, 132.3, 104.2, 76.3, 50.2; HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{10}NO_2S_2$ $[M+H]^+$ 276.0148, found 276.0151.

*4.1.16. 2-(Propylimino)naphtho[2,3-d][1,3]dithiole-4,9-dione (**4p**).* Yield 94.8%; mp 130–131 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.09 (dd, J_1=3.5 Hz, J_2=5.0 Hz, 2H), 7.75 (dd, J_1=3.0 Hz, J_2=5.0 Hz, 2H), 3.18 (t, *J*=7.0 Hz, 2H), 1.80–1.73 (m, 2H), 1.00 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.2, 175.6, 155.3, 143.9, 143.2, 134.2, 134.1, 132.1, 132.0, 127.1 (2C), 61.5, 23.3, 11.9; GC–MS *m/z* 289.9 $[M+H]^+$, 288.9 $[M]^+$, 261.0, 260.0 (100%), 220.0, 160.1, 132.3, 104.1; HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{12}NO_2S_2$ $[M+H]^+$ 290.0304, found 290.0305.

*4.1.17. 2-(Isopropylimino)naphtho[2,3-d][1,3]dithiole-4,9-dione (**4q**).* Yield 81.0%; mp 153–154 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.07 (dd, J_1=1.0 Hz, J_2=5.0 Hz, 2H), 7.73 (dd, J_1=3.5 Hz, J_2=6.0 Hz, 2H), 3.24–3.18 (m, 1H), 1.25 (d, *J*=6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.1, 175.7, 153.5, 143.6, 143.2, 134.2, 134.1, 132.1, 132.0, 127.1 (2C), 61.4, 22.3; GC–MS *m/z* 290.2 $[M+H]^+$, 289.5, 274.8, 273.8, 245.7, 105.3; HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{12}NO_2S_2$ $[M+H]^+$ 290.0304, found 290.0311.

*4.1.18. 2-(Butylimino)naphtho[2,3-d][1,3]dithiole-4,9-dione (**4r**).* Yield 90.7%; mp 108–109 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.07 (dd, J_1=4.0 Hz, J_2=5.5 Hz, 2H), 7.74 (dd, J_1=3.0 Hz, J_2=5.5 Hz, 2H), 3.21 (t, *J*=6.5 Hz, 2H), 1.73–1.68 (m, 2H), 1.46–1.39 (m, 2H), 0.96 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.1, 175.5, 155.1, 143.8, 143.1, 134.2, 134.1, 132.0, 131.9, 127.1, 127.0, 59.4, 31.9, 20.5, 13.8; GC–MS *m/z* 303.0 $[M]^+$, 285.9, 270.1 (100%), 260.3, 220.2, 104.1, 76.1, 72.1, 50.0; HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{14}NO_2S_2$ $[M+H]^+$ 304.0461, found 304.0465.

*4.1.19. 2-(Hexylimino)naphtho[2,3-d][1,3]dithiole-4,9-dione (**4s**).* Yield 85.5%; mp 80–81 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.04 (dd, J_1=3.5 Hz, J_2=5.5 Hz, 2H), 7.72 (dd, J_1=3.5 Hz, J_2=6.0 Hz, 2H), 3.18 (t, *J*=7.0 Hz, 2H), 1.73–1.67 (m, 2H), 1.41–1.35 (m, 2H), 1.32–1.30 (m, 4H), 0.89 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 175.9, 175.4, 155.0, 143.8, 143.1, 134.7, 134.2, 134.1, 132.0, 131.9, 127.0, 126.8, 59.7, 31.6, 29.8, 27.1, 22.6, 14.1; GC–MS *m/z* 331.0$[M]^+$, 298.2 (100%), 260.3, 247.1, 220.2, 104.1, 76.1, 41.0; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{18}NO_2S_2$ $[M+H]^+$ 332.0774, found 332.0780.

*4.1.20. 2-(Decylimino)naphtho[2,3-d][1,3]dithi-ole-4,9-dione (**4t**).* Yield 76.0%; mp 104–105 °C; ^1H NMR (500 MHz, $CDCl_3$): δ(ppm) 8.12 (dd, J_1=3.5 Hz, J_2=5.5 Hz, 2H), 7.76 (dd, J_1=3.0 Hz, J_2=5.0 Hz, 2H), 3.23 (t, *J*=7.0 Hz, 2H), 1.76–1.70 (m, 2H), 1.43–1.28 (m, 14H), 0.89 (t, *J*=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.2, 175.6, 155.2, 143.9, 143.2, 134.2, 134.1 (2C), 132.0, 127.1 (2C), 59.8, 31.9, 29.9, 29.6 (2C), 29.3 (2C), 27.4, 22.7, 14.1; GC–MS *m/z* 387.3 $[M]^+$, 354.3 (100%), 316.3, 283.4, 247.2, 166.5, 76.3, 41.2. Anal. Calcd for $C_{21}H_{25}NO_2S_2$: C, 65.08; H, 6.50; N, 3.61; S, 16.55. Found: C, 65.09; H, 6.60; N, 3.42; S, 17.06.

*4.1.21. 2-(Dodecylimino)naphtho[2,3-d][1,3]dithiole-4,9-dione (**4u**).* Yield 73.1%; mp 98–99 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.07 (dd, J_1=4.0 Hz, J_2=5.5 Hz, 2H), 7.73 (dd, J_1=4.0 Hz, J_2=6.0 Hz, 2H), 3.50 (t, *J*=6.0 Hz, 1H), 3.20 (t, *J*=6.5 Hz, 2H), 1.74–1.66 (m, 3H), 1.41–1.26 (m, 16H), 0.88 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.0, 175.5, 155.0, 143.7, 143.1, 134.1 (2C), 132.0, 131.9, 127.0 (2C), 59.7, 45.0, 31.9, 31.3, 30.0, 29.8, 29.6 (3C), 27.4, 22.6, 14.1; EIMS *m/z* 416.13 $[M+H]^+$; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{30}NO_2S_2$ $[M+H]^+$ 416.1713, found 416.1721.

*4.1.22. 2-(Benzylimino)naphtho[2,3-d][1,3]dithiole-4,9-dione (**4v**).* Yield 83.3%; mp 162–163 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.14 (dd, J_1=3.0 Hz, J_2=5.5 Hz, 2H), 7.77 (dd, J_1=3.5 Hz, J_2=6.0 Hz, 2H), 7.38–7.36 (m, 4H), 7.32–7.29 (m, 1H), 4.44 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 176.2, 175.6, 157.3, 144.2, 143.0, 137.4, 134.3, 134.2, 132.1, 132.0, 128.7 (2C), 127.8 (2C), 127.5, 127.2 (2C), 62.6; GC–MS *m/z* 338.5 $[M+H]^+$, 337.5 (M, 100%), 232.6, 91.5,

65.5, 50.2; HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{12}NO_2S_2$ $[M+H]^+$ 338.0304, found 338.0312.

*4.1.23. 2-(Cyclohexylimino)naphtho[2,3-d][1,3]dithiole-4,9-dione (**4w**).* Yield 66.8%; mp 153–154 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.04 (dd, J_1=3.5 Hz, J_2=5.5 Hz, 2H), 7.72 (dd, J_1=3.5 Hz, J_2=6.5 Hz, 2H), 2.91–2.86 (m, 1H), 1.83–1.79 (m, 4H), 1.66–1.63 (m, 1H), 1.50–1.42 (m, 2H), 1.38–1.27 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 175.8, 175.4, 153.0, 143.4, 143.1, 134.1, 134.0, 131.9, 131.8, 129.9 (2C), 69.3, 32.1 (2C), 25.39 (2C), 24.4 (2C); GC–MS *m*/*z* 330.3 $[M+H]^+$, 329.3 (M, 100%), 296.5, 141.5, 104.3, 67.3, 55.2, 41.2; HRMS (ESI-TOF) *m*/*z* calcd for $C_{17}H_{16}NO_2S_2$ $[M+H]^+$ 330.0617, found 330.0621.

*4.1.24. 2-(Propylimino)anthra[2,3-d][1,3]dithiole-4,11-dione (**4x**).* Yield 60.1%; mp 214–215 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.62 (s, 2H), 8.06–8.05 (m, 2H), 7.73–7.72 (m, 2H), 3.22 (t, *J*=6.5 Hz, 2H), 1.82–1.75 (m, 2H), 1.02 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 175.8, 175.3, 155.7, 145.6, 144.8, 140.1, 137.7, 134.7, 130.6, 130.4, 130.3, 130.2, 129.9, 128.2, 128.1, 61.4, 23.3, 11.9; EIMS *m*/*z* 340.10 $[M+H]^+$; HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{14}NO_2S_2$ $[M+H]^+$ 340.0467, found 340.0460.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.04.050.

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12. CCDC 915881 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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