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A NEW METHOD FOR THE SYNTHESIS OF 2,5-BISHETEROARYL-3,6-DICHLORO-1,4-BENZOQUINONES

Nelli G. Batenko, Gatis A. Karlivans, and Raimonds E. Valters*

Faculty of Material Science and Applied Chemistry, Riga Technical University, Azenes St. 14/24, Riga LV-1048, Latvia

rvalters@latnet.lv

Abstract – A new method for the synthesis of symmetrical and asymmetrical 2,5-bisheteroaryl-3,6-dichloro-1,4-benzoquinones with sulfur and/or nitrogen containing heterocycles has been elaborated on the basis of easily obtainable benzofuran (**2**).

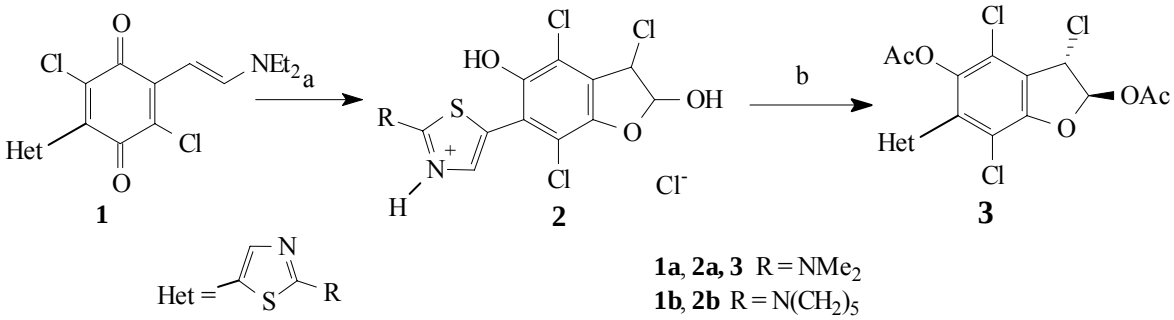
INTRODUCTION

Benzoquinones are a class of compounds found as subunits in many natural products.[1] Compounds containing the benzoquinone group have been shown to have chemotherapeutic value as antitumor,[2] antifungal,[3] and antibacterial[3] drugs. Recently it was shown that the derivatives of 3,6-bis(indol-3-yl)-2,5-dihydroxybenzoquinones, fungal metabolites (asterriquinones) exhibit antitumor activity and act as insulin mimetics in several biochemical and cellular assays.[4] General and efficient synthetic methods that allow easy preparation of structurally diverse heteroaryl-substituted quinones are rare,[4] except the above mentioned bisindolylquinones. [2]

RESULTS AND DISCUSSION

We have previously shown [5] that different monoheteroaryl-substituted trichloro-1,4-benzoquinones can be formed on the basis of 3,4,6,7-tetrachloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furan. In such a way monoheteroaryl-substituted trichloro-1,4-benzoquinones containing a thiazole or thiazoline,[6] selenazole,[7] 1,3,4-thiadiazine, [8] pyrazole, [9] or 1,3-dithiol-2-one [10] ring were synthesized. Initial furan is easily obtainable in two-step synthesis from tetrachlorobenzoquinone.[11] The interest in 2,5-bisheteroaryl-substituted benzoquinones led us to explore this synthetic method for the introduction of the second similar or different heterocycle moiety into the 1,4-benzoquinone ring in position 5. In this paper, we report the synthesis of such 2,5-bisheteroaryl-substituted 1,4-benzoquinones using thiazolyl-substituted benzofuran

derivative (**2**) as initial synthone. This strategy is based on the introduction of the α-chloroacetaldehyde group in the 5-position of the monoheteroaryl-substituted quinones. The benzofuran (**2**) is a cyclic tautomeric form [12] of an o-hydroxyaryl-substituted α-chloroacetaldehyde. The reaction of benzofuran (**2**) with various bifunctional compounds proceeds *via* substitution of a chlorine atom in position 3 in the first stage and further opening of the dihydrobenzofuran ring with subsequent cyclization to the corresponding heterocycle.

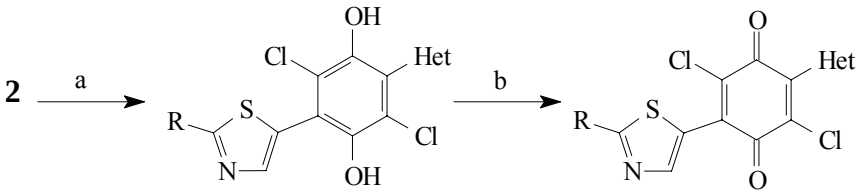


Reagents and conditions:(a) HCl, MeCN, 60^0 C, 2 h; (b) Ac_2O, H_3PO_4, 60^0 C, 1 h.

Scheme 1

For the synthesis of benzofuran (**2**) we adopted our two-step protocol involving the synthesis [13] of the compound (**1**) from 2-dialkylamino-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazole and further its reaction with HCl (Scheme 1). Thus, by this method benzofurans (**2a,b**) were prepared with yields 68-73%. Their ^{1}H NMR spectra show two doublets (J = 4.8 Hz) and two doublets (J ~ 0.5 Hz) indicative of the 2-H, 3-H *cis/trans* stereochemistry (for **2a** *cis/trans* ratio 16:84, for **2b** - 36:64, both in DMSO-d_6). The benzofuran (**2**) was isolated from the reaction mixture in the form of its hydrochloride. The treatment of benzofuran (**2a**) with acetic anhydride in the presence of catalytic amount of orthophosphoric acid led to acylation of both hydroxy groups yielding compound (**3**). Reaction of equimolar amounts of benzofuran (**2b**) and 1-phenylthiosemicarbazide in ethanol under reflux for 3 h and following oxidation led to *4H*-1,3,4-thiadiazine derivative (**5a**). The quinone (**5a**) is deeply colored and in UV spectrum two long-wave bands (λ = 403 and 718 nm in $CHCl_3$) can be associated with strong intramolecular charge transfer. Benzofurans (**2a,b**) produced corresponding 2,5-bis-(2-dialkylaminothiazol-5-yl)-3,6-dichloro-hydroquinones (**4b,c**) in the reactions with variously substituted thioureas. The compounds (**5b,c**) were obtained in high yield by oxidation of **4b,c** with ferric chloride in aqueous DMF. The ^{13}C-NMR spectral data of the compound (**5b**) (first obtained [13] by the oxidation of the reaction product of **1b** with *N,N*-pentamethylenthiourea in the presence of hydrochloric acid) confirm the 2,5-position of the heterocycles in the benzoquinone ring. The spectral characteristics of the compounds (**5b,c**) are identical to the data previously reported, [13] but the yields are higher.

The reactions of benzofurans (**2a,b**) with 4,4-dialkylthiosemicarbazides proceeded with extrusion of sulfur atom from 1,3,4-thiadiazine intermediate and the formation of pyrazole derivatives (**4d,e**) which



4 **5**

Reagents and conditions: (a) XC(S)Y, EtOH, reflux; (b) $FeCl_3$, DMF, H_2O

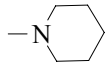
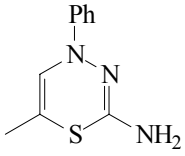
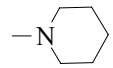
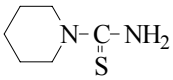
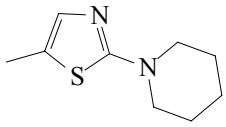
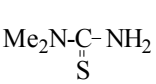
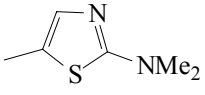
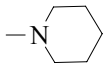
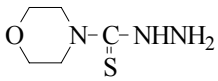
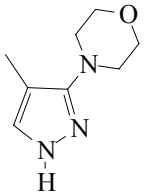
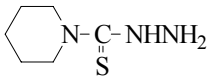
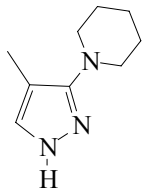
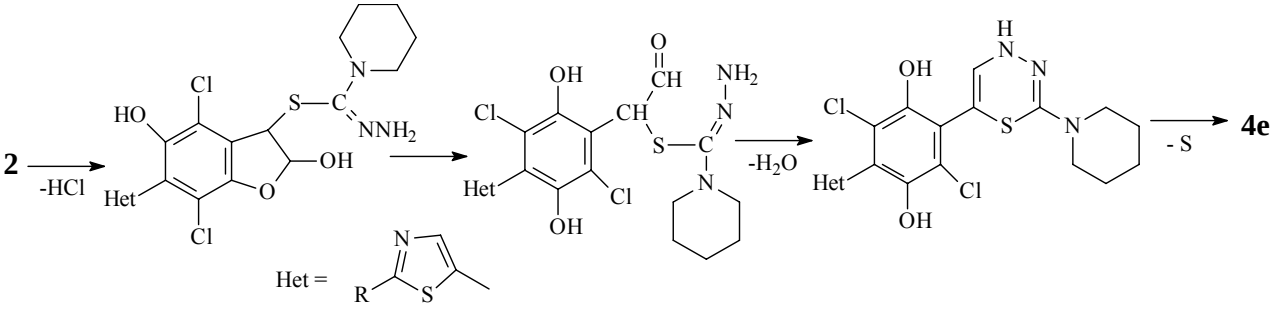
entry	R	XC(S)Y	Het	product	yield, %
1				**4a**	62
				5a	64
2				**4b**	89
				5b	74
3				**4c**	92
				5c	65
4				**4d**	68
				5d	54
5				**4e**	47
				5e	

Table 1

after subsequent oxidation yield the compounds (**5d,e**). The mechanism of the formation of the compounds (**4a-e**) from benzofuran (**2**) may be assumed as shown in Scheme 2 (example for the formation of **4e**).

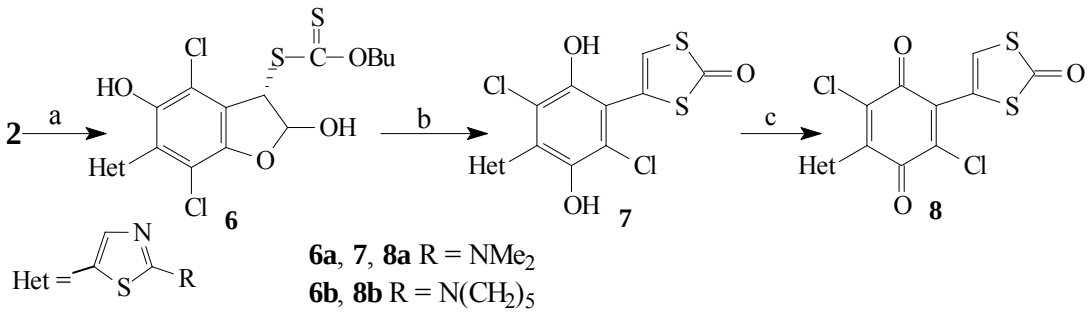


Scheme 2

The reaction of the benzofurans (**2a,b**) with potassium *O*-butylxanthate provided the substitution products of the chlorine atom at the position 3 (Scheme 3).

Treatment of **6a,b** with concentrated sulfuric acid at 60^0 C led to its recyclization with removal of the butoxy group and the formation of 1,3-dithiol-2-one hydroquinone derivatives (**7**).

After their oxidation by iron (III) trichloride in aqueous DMF benzoquinones (**8a,b**) were obtained.



Reagents and conditions: (a) $BuOC(S)S^-K^+$, MeOH, rt; (b) 1. H_2SO_4 2. H_2O; (c) $FeCl_3$, DMF, H_2O

Scheme 3

In summary, we have elaborated an efficient synthetic method to obtain both symmetrical and asymmetrical 2,5-bisheteroaryl-3,6-dichloro-1,4-benzoquinones with sulfur and/or nitrogen containing heterocycle moieties.

EXPERIMENTAL

Materials and Methods. ^{1}H and ^{13}C NMR spectra were obtained with a Varian Mercury BB 200 NMR spectrometer (200 MHz) using tetramethylsilane as an internal standard, and the chemical shifts were reported in δ values. Samples were dissolved in DMSO-d_6 and $CDCl_3$. IR spectra were recorded on a Specord M-80 spectrophotometer. UV spectra were recorded on a Specord M-40 spectrophotometer. Analytical thin-layer chromatography (TLC) was carried out on Silufol-254 plates. 2-(2-Dialkylamino-thiazol-5-yl)-5-(*N,N*-diethylamino)ethenyl-3,6-dichloro-1,4-benzoquinones (**1a,b**) were prepared as reported. [13] Hydrochlorides (**2a,b**) and hydroquinones (**4a-e, 7**) were not recrystallized because their heating in solvents led to partial dehydrochlorination (**2a,b**) or partial oxidation (**4a-e, 7**).

6-[2-(*N,N*-Dimethylamino)thiazol-5-yl]-3,4,7-trichloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furan hydrochloride (2a)[14] **and 6-(2-piperidinothiazol-5-yl)-3,4,7-trichloro-2,5-dihydroxy-2,3-dihydro-benzo[*b*]furan hydrochloride (2b)**[14]**:** 35 % HCl (0.5 mL) was added dropwise to a solution of 2-[2-(*N,N*-dialkylamino)thiazol-5-yl]-5-(*N,N*-diethylamino)ethenyl-3,6-dichloro-1,4-benzoquinone (**1a**) or (**1b**) (1 mmol) in acetonitrile (5 mL) and the reaction mixture was stirred for 1 h at 60^0 C. The precipitate was collected by filtration and washed with hot acetonitrile and hexane. (**2a**): yield 0.32 g (73%), mp >250^0 C. ^{1}H NMR (DMSO-d_6): δ 10.00 (br s, 1H), 7.51 (s, 1H), 6.11 (d, J = 4.89 Hz), 6.02 (d, J = 0.49 Hz), 5.67 (d, J = 4.89 Hz), 5.40 (d, J = 0.49 Hz), 3.27 (s, 6H). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 169.6, 164.9, 148.8,

147.1, 133.3, 125.9, 115.9, 107.6, 62.0, 41.4. IR (nujol): 3163, 2945, 2780, 1634 cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2O_3Cl_4S$: C, 37.34; H, 2.90; N, 6.70. Found: C, 37.54; H, 3.04; N, 6.86. (**2b**): yield 0.31 g (68%), mp >250^0 C. ^{1}H-NMR (DMSO-d_6): δ 7.56 (s, 1H), 6.13 (d, *J* = 4.75 Hz), 6.02 (d, *J* = 0.5 Hz), 5.67 (d, *J* = 4.75 Hz), 5.43 (d, *J* = 0.5 Hz), 3.69 (br s, 4H), 1.72 (br s, 6H). Anal. Calcd for $C_{16}H_{16}N_2O_3Cl_4S$: C, 41.94; H, 3.52; N, 6.11. Found: C, 41.56; H, 3.63; N, 6.15.

6-[2-(*N*,*N*-Dimethylamino)thiazol-5-yl]-3,4,7-trichloro-2,5-diacetoxy-2,3-dihydrobenzo[*b*]furan (3).[15] A solution of benzofuran (**2a**) (1.25 g, 3 mmol) and 0.1 mL (1.5 mmol) of H_3PO_4 in acetic anhydride (10 mL) was stirred at 50^0 C for 1 h. After cooling, water (50 mL) was added to this mixture, the mixture was extracted with methylene chloride and the organic layer was dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was recrystallized from ethanol to yield **3** (0.86 g, 62%), mp 186-188^0 C.^{1}H-NMR (DMSO-d_6): δ 7.31 (s, 1H), 6.85 (s, 1H), 5.87 (s, 1H), 3.15 (s, 6H), 2.24 (s, 3H), 2.10 (s, 3H). IR (nujol): 2964, 2820, 2740, 1768, 1738, 1560 cm^{-1}. Anal. Calcd for $C_{17}H_{15}N_2O_5Cl_3S$: C, 43.84; H, 3.25; N, 6.02. Found: C, 44.21; H, 3.38; N, 6.07.

2-(2-Amino-4-phenyl-*4H*-1,3,4-thiadiazin-6-yl)-5-(2-piperidinothiazol-5-yl)-3,6-dichlorohydroquinone (4a). A mixture of benzofuran (**2b**) (1.37 g, 3 mmol) and 1-phenylthiosemicarbazide (0.5 g, 3 mmol) in ethanol (20 mL) was stirred for 2 h and then refluxed for 3 h. The obtained solution was cooled to 5^0 C and kept at this temperature for 12-15 h. The precipitate was collected and washed with ethanol. Yield 0.99g (62%), mp >250^0 C. ^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1H), 7.96 (m, 2H), 7.51 (m, 3H), 7.29 (s,1H), 5.78 (br s, 2H) 3.49 (br s, 4H), 1.67 (br s, 6H). Anal. Calcd for $C_{23}H_{21}N_5O_2Cl_2S_2$: C, 51.69; H, 3.96; N, 13.10. Found: C, 51.59; H, 3.55; N, 12.78.

2-(2-Amino-4-phenyl-*4H*-1,3,4-thiadiazin-6-yl)-5-(2-piperidinothiazol-5-yl)-3,6-dichlorocyclohexa-2,5-diene-1,4-dione (5a). A 20% solution of ferric chloride (25 mL, 31 mmol) was added dropwise to a stirred solution of hydroquinone (**4a**) (1.6 g, 3 mmol) in DMF (20 mL). The reaction mixture was stirred at rt for 1 h and then diluted with 20 mL of water. The precipitate was filtered, washed with water and recrystallized from chloroform/hexane. Yield 1.02 g (64%), mp >250^0 C. ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.73 (s, 1H), 8.04 (m, 2H), 7.55 (m, 3H), 3.73 (br s, 4H), 1.74 (br s, 6H). UV-VIS, λ_{max} (log ε, $CHCl_3$): 335 (4.14); 403 (4.18); 715 (3.70) nm. Anal. Calcd for $C_{23}H_{19}N_5O_2Cl_2S_2$: C, 51.88; H, 3.60; N, 13.15. Found: C, 51.76; H, 3.43; N, 12.97.

2-(3-Morpholynopyrazol-4-yl)-5-(2-piperidinothiazol-5-yl)-3,6-dichlorohydroquinone (4d): A mixture of benzofuran (**2b**) (1.37 g, 3 mmol) and 4,4-dimethyleneoxadimethylenethiosemicarbazide (0.48 g, 3 mmol) in ethanol (20 mL) was stirred at rt for 2 h and then refluxed for 2 h with 0.05 mL of H_2SO_4. 0.2 g of activated carbon was added and the hot solution was filtered off. After cooling, precipitate was collected by filtration and washed with hexane. Yield 1.0 g (68%), mp >250^0 C (decomp). ^{1}H NMR (DMSO-d_6): δ 9.23 (br s, 2H), 7.87 (s, 1H), 7.43 (s, 1H), 3.67 (br s, 4H), 3.49 (t, *J* = 7 Hz, 4H), 3.03 (t,

J = 7 Hz, 4H), 1.67 (br s, 6H). IR (nujol): 3392, 2924, 2850, 1510 cm^{-1}. Anal. Calcd for $C_{21}H_{23}N_5O_3Cl_2S$: C, 50.81; H, 4.67; N, 14.11. Found: C, 51.05; H, 4.86; N, 14.37.

2-(3-Piperidinopyrazol-4-yl)-5-[2-(*N*,*N*-dimethylamino)thiazol-5-yl]-3,6-dichlorohydroquinone (4e): A mixture of benzofuran (**2a**) (1.25 g, 3 mmol) and 4,4-pentamethylenthiosemicarbazide (0.47 g, 3 mmol) in ethanol (20 mL) was stirred at rt for 2 h and then refluxed for 3 h with a drop of H_2SO_4. 0.2 g of activated carbon was added and the hot solution was filtered off. After cooling, the precipitate was filtered and washed with hexane. Yield 0.64 g (47%), mp >250^0 C (decomp). ^{1}H NMR (DMSO-d_6): δ 9.27 (br s, 2H), 7.98 (s, 1H), 7.47 (s, 1H), 3.23 (s, 6H), 3.01 (br s, 4H), 1.54 (br s, 6H). IR (nujol): 3104, 2924, 2856, 1516 cm^{-1}. Anal. Calcd for $C_{19}H_{21}N_5O_2Cl_2S$: C, 50.23; H, 4.66; N, 15.41. Found: C, 50.45; H, 4.98; N, 15.48.

2-(3-Morpholynopyrazol-4-yl)-5-(2-piperidinothiazol-5-yl)-3,6-dichlorocyclohexa-2,5-diene-1,4-dione (5d) and 2-(3-piperidinopyrazol-4-yl)-5-[2-(*N*,*N*-dimethylamino)thiazol-5-yl]-3,6-dichloro-cyclohexa-2,5-diene-1,4-dione (5e): $FeCl_3$ (20% in water, 30 mL, 37 mmol) was added to a solution of hydroquinone (**4d**) or **(4e**) (2 mmol) in ethanol (30 mL). The reaction mixture was stirred for 1 h and then was extracted twice with 20 mL methylene chloride, the organic layer was dried over magnesium sulfate. The solvent was evaporated under reduced pressure and then the precipitate was recrystallized from ethanol. **5d:** yield 0.53 g (54%), mp >250^0 C (decomp). ^{1}H NMR (DMSO-d_6): δ 8.64 (s, 1H), 7.87 (s, 1H), 3.60 (br s, 4H), 3.41 (t, *J* = 7 Hz, 4H), 3.03 (t, *J* = 7 Hz, 4H), 1.67 (br s, 6H). IR (nujol): 2928, 2860, 1656, 1612 cm^{-1}. UV-VIS: λ_{max} (log ε, $CHCl_3$): 344 (4.10); 640 (3.65) nm. Anal. Calcd for $C_{21}H_{21}N_5O_3Cl_2S$: C, 51.02; H, 4.28; N, 14.17. Found: C, 51.24; H, 4.49; N, 14.37. **5e:** yield 0.44 g (48%), mp >250^0 C (decomp). ^{1}H NMR (DMSO-d_6): δ 8.49 (s, 1H), 7.94 (s, 1H), 3.18 (s, 6H), 3.07 (br s, 4H), 1.54 (br s, 6H). IR (nujol): 2929, 2856, 1632 cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_5O_2Cl_2S$: C, 50.45; H, 4.23; N, 15.48. Found: C, 50.63; H, 4.47; N, 15.61.

***O*-Butyl *S*-[6-(2-(*N*,*N*-dimethylamino)thiazol-5-yl)-4,7-dichloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]-furan-3-yl]xanthate (6a)[15] and *O*-Butyl *S*-[6-(2-piperidinothiazol-5-yl)-4,7-dichloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furan-3-yl]xanthate (6b)[15]:** A solution of potassium *O*-butylxanthate (0.6 g, 3.2 mmol) in 20 mL of methanol was added dropwise to a stirred solution of the benzofuran (**2a,b**) (3 mmol) in 20 mL of methanol. The reaction mixture was stirred at rt for 3 h, poured into 150 mL of water. The product was extracted with methylene chloride, then the organic layer was dried over magnesium sulfate and the solvent was evaporated. The precipitate was recrystallized from carbon tetrachloride. **6a**: Yield 1.03 g (69%), mp 190-192^0 C. ^{1}H NMR (DMSO-d_6): δ 9.43 (s, 1H), 8.18 (d, *J* = 6 Hz, 1H), 7.23 (s, 1H), 6.01 (dd, *J*= 6 Hz, *J* < 0.5 Hz, 1H), 5.07 (d, *J* < 0.5 Hz, 1H), 4.65 (t, *J* = 6 Hz, 2H), 3.07 (s, 6H), 1.72 (quintet, *J* = 6 Hz, 2H), 1.29 (sextet, *J* = 6 Hz, 2H), 0.89 (t, *J* = 6 Hz, 3H). Anal. Calcd for $C_{18}H_{20}N_2O_4Cl_2S_3$: C, 43.64; H, 4.07; N, 5.65. Found C, 43.86; H, 4.39; N, 5.48. **6b**: Yield 0.98 g (61%), mp 185-187^{0}C. ^{1}H NMR (DMSO-d_6): δ 9.41 (s, 1H), 8.18 (d, *J* = 6.2 Hz, 1H), 7.23 (s, 1H), 5.96 (dd, *J* = 6.2 Hz, *J* < 0.5 Hz, 1H), 5.07

(d, $J < 0.5$ Hz, 1H), 4.65 (t, 2H), 3.45 (br s, 4H), 1.63 (br s, 8H), 1.36 (m, 2H), 0.91 (t, 3H). Anal. Calcd for $C_{21}H_{24}N_2O_4Cl_2S_3$: C, 47.10; H, 4.52; N, 5.23. Found: C, 47.49; H, 4.21; N, 4.85.

2-(2-[*N,N*-Dimethylamino)thiazol-5-yl]-5-(1,3-dithiol-2-on-4-yl)-3,6-dichlorohydroquinone (7). Xanthate (**6a**) (1.49 g, 3 mmol) was dissolved in H_2SO_4 (15 mL) and then heated at 60^0 C for 30 min. After cooling the reaction mixture was poured into 100 mL of water. The precipitate was filtered and washed with water. Yield 0.85 g (67%), mp $>250^0$ C. ^{1}H NMR (DMSO-d_6): δ 9.27 (br s, 2H), 7.43 (s, 1H), 7.23 (s, 1H), 3.16 (s, 6H). Anal. Calcd for $C_{14}H_{10}N_2O_3Cl_2S_3$: C, 39.91; H, 2.39; N, 6.65. Found: C, 40.12; H, 2.48; N, 7.16. 2-(2-Piperidinothiazole-5-yl)-5-(1,3-dithiol-2-on-4-yl)-3,6-dichlorohydroquinone, prepared by an analogous procedure, was used directly for the following oxidation reaction without full characterization.

2-(2-(*N,N*-Dimethylamino)thiazol-5-yl)-5-(1,3-dithiol-2-on-4-yl)-3,6-dichlorocyclohexa-2,5-diene-1,4-dione (8a) and 2-(2-piperidinothiazol-5-yl)-5-(1,3-dithiol-2-on-4-yl)-3,6-dichlorocyclohexa-2,5-diene-1,4-dione (8b). A solution of $FeCl_3$ in water (20% solution, 30 mL, 37 mmol) was added dropwise to a stirred solution of corresponding hydroquinone (3 mmol) in DMF (20 mL). The reaction mixture was stirred at rt for 2 h, then diluted with water. Precipitate was collected by filtration and recrystallized from ethanol. **8a**: Yield 1.09 g (87%), mp $>240^0$ C (decomp). ^{1}H NMR ($CDCl_3$): δ 8.72 (s, 1H), 7.23 (s, 1H), 3.31 (s, 6H). IR (nujol): 3040, 2924, 1674, 1614, 1578, 1510 cm^{-1}. UV-VIS, λ_{max} (log ε, $CHCl_3$): 356 (4.19); 480 (3.57); 683 (3.80) nm. Anal. Calcd for $C_{14}H_8N_2O_3Cl_2S_3$: C, 40.10; H, 1.92; N, 6.68. Found: C, 40.43; H, 2.18; N, 7.03. **8b**: Yield 0.96 g (76%), mp $>250^0$ C (decomp). ^{1}H NMR ($CDCl_3$): δ 8.69 (s, 1H), 7.27 (s, 1H), 3.69 (br s, 4H), 1.72 (br s, 6H). Anal. Calcd for $C_{17}H_{12}N_2O_3Cl_2S_3$: C, 44.45; H, 2.63; N, 6.10. Found: C, 44.14; H, 2.85; N, 6.37.

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14. Compounds (**2a**) and (**2b**) exist as mixtures of 2-H, 3-H *cis/trans* stereoisomers. ^{1}H NMR for **2a**: *cis*-isomer: 2-H, δ 6.11 (d, J = 4.89 Hz), 3-H, δ 5.67 (d, J = 4.89 Hz); *trans*-isomer 2-H, δ 6.02 (d, J = 0.49 Hz), 3-H, δ 5.40 (d, J = 0.49 Hz). *Cis/trans* ratio in DMSO-d_6 : 16:84. ^{1}H NMR for **2b**: *cis*-isomer: 2-H, δ 6.13 (d, J = 4.75 Hz), 3-H, δ 5.67 (d, J = 4.75 Hz); *trans*-isomer 2-H, δ 6.02 (d, J = 0.5 Hz), 3-H, δ 5.43 (d, J = 0.5 Hz). *Cis/trans* ratio in DMSO-d_6 : 36:64.
15. Compounds (**3**, **6a** and **6b**) exist as *trans* stereoisomers because the coupling constant between 2-H and 3-H is J < 0.5 Hz.