Chemistry of Heterocyclic Compounds, Vol. 36, No. 6, 2000

SYNTHESIS OF 2,5-BIS(2-AMINOTHIAZOL-5-YL)-3,6-DICHLORO-1,4-BENZOQUINONES

N. G. Batenko, R. Valters, and G. Karlivans

A series of 2-(2-aminothiazol-5-yl)-3,6-dichloro-5-diethylaminoethenyl-1,4-benzoquinones was synthesized from 2-(2-aminothiazol-5-yl)-3,5,6-trichloro-1,4-benzoquinones using acetaldehyde and diethylamine in toluene solution. Refluxing these compounds with substituted thioureas in acetonitrile in the presence of hydrochloric acid gives the corresponding 2,5-bis(2-aminothiazol-5-yl)-3,6-dichlorohydroquinones which can be oxidized to the target products with ferric chloride in aqueous DMF.

Keywords: 2-(2-aminothiazol-5-yl)-3,6-dichloro-5-diethylaminoethenyl-1,4-benzoquinones, 2-(2-aminothiazol-5-yl)-3,5,6-trichloro-1,4-benzoquinones, 1,4-benzoquinones, 2,5-bis(2-aminothiazol-5-yl)-3,6-dichloro-1,4-benzoquinones, thiazole, intramolecular charge transfer.

The aim of this work is the synthesis of 2,5-dihetaryl-1,4-benzoquinones from trichloro-1,4-benzoquinonylthiazoles. These compounds are of interest in connection with the presence in the molecule of a strong intramolecular charge transfer between the electron acceptor quinone fragment and the electron donor fragments of the thiazole.

Extending the work [1-3] with a study of the possible use of the previously developed method [1] for the synthesis of 2,5-dihetaryl-substituted 1,4-benzoquinones showed that, in the case of thiazole derivatives, the three component condensation reaction of trichloro-1,4-benzoquinonylthiazoles (**1**) with acetaldehyde and diethylamine in toluene gives the 5-N,N-diethylaminoethenyl derivatives (**2a-e**).

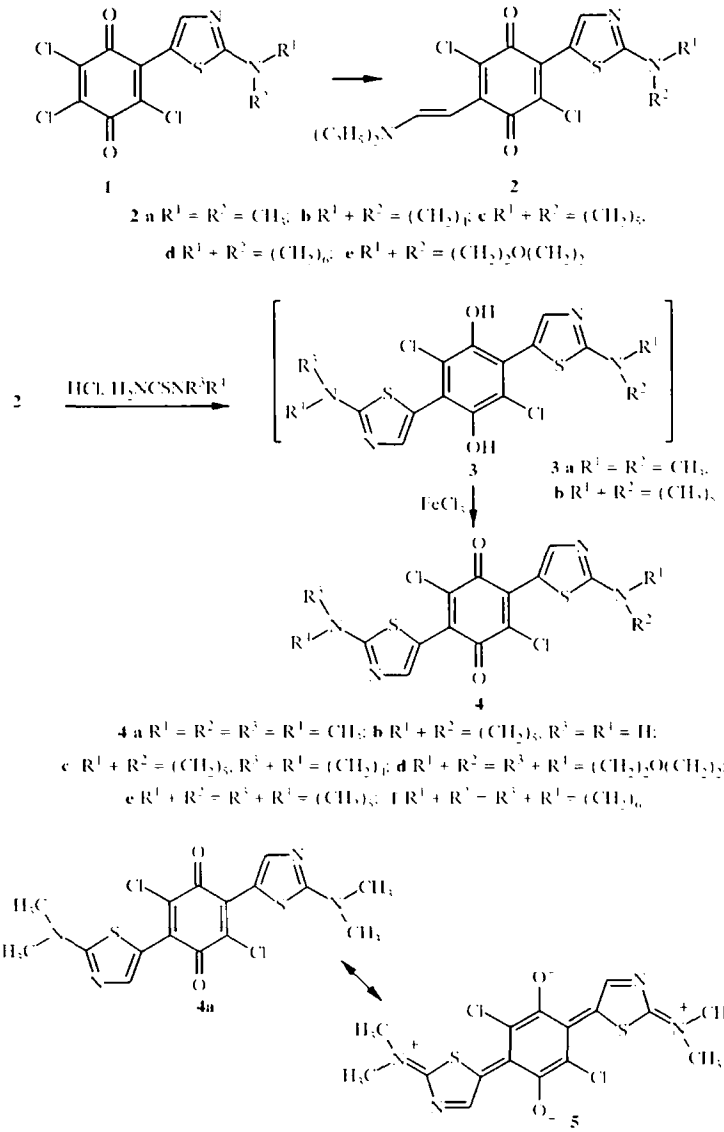
Compounds **2a-e** are deeply colored, crystalline materials (the yields in this reaction being in the range 32-96%). It was found that satisfactory results were obtained in the case where the amino group protons in the thiazole 2 position (compound **1**) are substituted. The use of magnesium sulfate in the course of the reaction increases the yield of the final product.

In the method used for preparation of monohetaryl-substituted trichloro-1,4-benzoquinones [1, 3, 4], the subsequent step was the synthesis of 3,4,6,7-tetrachloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furan from 3,5,6-trichloro-2-(N,N-diethylaminoethenyl)-1,4-benzoquinone. However, the separation of its 6-(2-aminothiazol-5-yl)-substituted analog when heating compounds **2a-e** with hydrochloric was not successful in our hands. This lowers the yields of the final product and complicates the use of the given method for constructing other heterocycles.

The reaction of compounds **2a-e** with the corresponding thioureas in the presence of an excess of concentrated hydrochloric acid leads to formation of the hydroquinones **3**. The best solvent for this reaction proved to be acetonitrile since carrying out the reaction in dioxane give an oily precipitate which was not susceptible to purification. The hydroquinones are extremely difficult to separate in the pure state since they are readily oxidized in air to the corresponding 1,4-benzoquinones. This is indicated by the presence in the IR spectra of compounds **3a** and **3b** of absorption bands for the OH of the hydroquinone (3000, 3200 cm^{-1}) and the C=O group band of the 1,4-benzoquinone (1640, 1630 cm^{-1} respectively). The presence in the UV spectrum of compound **3b** of an absorption band typical of hetaryl substituted 1,4-benzoquinones (582 nm) confirmed this proposition. Because the final target is the preparation of 1,4-benzoquinones, the synthesized hydroquinones were immediately oxidized. Oxidation with ferric chloride in aqueous DMF solution occurred readily and in good yields.

Riga Technical University, Riga LV-1048, Latvia; e-mail: rvalters@latnet.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 835-839, June, 2000. Original article submitted January 20, 2000.

0009-3122/00/3606-0733$25.00©2000 KluwerAcademic/Plenum Publishers



2,5-Bis(2-aminothiazol-5-yl)-3,6-dichloro-1,4-benzoquinones (**4a-f**) are intensely blue colored, are poorly soluble in organic solvents, and give deeply colored solutions at low concentration. When heated above 250°C they gradually decompose. Use of this method permits the preparation of only one of two regioisomers (2,5-dihetaryl-3,6-dichloro- and 2,6-dihetaryl-3,5-dichloro-1,4-benzoquinones) - 2,5-bis(2-aminothiazol-5-yl)-3,6-dichloro-1,4-benzoquinone. This was confirmed by the ^{13}C NMR spectrum of 2,5-bis(2-piperidinothiazol-5-yl)-3,6-dichloro-1,4-benzoquinone (**4c**) which, as expected, showed nine ^{13}C signals (in the spectrum of its 2,6-regioisomer ten non-equivalent ^{13}C atom signals would be seen). When comparing the ^{13}C NMR spectra of **4a** and 2-(2-aminothiazol-5-yl)-3,5,6-trichloro-1,4-benzoquinone [2] with the spectrum of chloranil there is observed a common low field shift of 7-8 ppm for the $^{13}C_{(1,4)}$ signal. Assignment of the signals for the remaining ^{13}C signals in the spectrum of compound **4c** was made according to the data in [2] for 2-(2-N,N-dimethylaminothiazol-5-yl)-3,5,6-trichloro-1,4-benzoquinone and its 5-substituted derivatives. Obtaining ^{13}C NMR spectra for other compounds in this series was difficult because of their low solubility. There had recently appeared a report [5] concerning the nucleophilic substitution reaction of two bromines in the bromanil molecule for 2-(3-methylbutyl)indol-3-yl residues in which there was described the formation of a mixture (1:1) of both the 2,5- and 2,6-substituted regioisomers. However, it is known [6, 7] that the predominant direction of nucleophilic substitution of two halogen atoms in the chloranil molecule is 2,5-disubstitution.

TABLE 1. Electronic Spectroscopic Characteristic for Compounds **2a-d** and **4a-f** in Ethanol

Compound	λ_{max}, nm	log λ
2a	351, 557	4.5; 4.45
2b	352, 563	4.58; 4.48
2c	353, 563	4.33; 4.21
2d	352, 566	4.48; 4.37
4a	363, 400, 610, 743	3.89; 3.85; 3.82; 3.84
	364, 601, 718 (sh)*	4.41; 4.14; 3.81
4b*[2]	359, 563, 718 (sh)	
4c	352, 604*	4.21; 3.93
4d	347, 562	3.50; 3.22
4e	358, 587	4.30; 4.18
4f*[2]	360, 593	

In the UV spectra of compounds **4a-f** (Table 1) the absorption band in the region 562-610 nm is due to charge transfer in the molecule and is more intense when compared with trichloro-1,4-benzoquinonylthiazoles [1]. When compared with 2-amino-5-(3,5,6-trichloro-1,4-benzoquinonyl)thiazoles, the UV spectra of 2,5-bis(2-N,N-dimethylaminothiazol-5-yl)-3,6-dichloro-1,4-benzoquinone (**4a**) and 2-(2-aminothiazol-5-yl)-5-(2-piperidino-thiazol-5-yl)-3,6-dichloro-1,4-benzoquinone (**4b**) show a further absorption maximum at 743 and 718 nm respectively. For compound **4a**, an intramolecular charge transfer can exist in the mesomeric form **5**.

In the IR spectra of identically substituted amino groups in the 2 position of the thiazole ring there is found a strong C=O stretching band at 1628 cm^{-1} whereas in the case of unsymmetrical substitutents the stretching band is found at 1643 cm^{-1}, similarly to 2-amino-5-(3,5,6-trichloro-1,4-benzoquinonyl)thiazole.

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 instrument for suspensions in nujol (in the range 1900-1500 cm^{-1}, NaCl prism) or in hexachlorobutadiene (3800-2000 cm^{-1}, LiF prism). UV spectra were taken on a Specord M-40 instrument for solutions in ethanol or chloroform (concentration 2.5×10^{-5} mol/l). ^1H NMR spectra were obtained on a Bruker WH-90/DS instrument using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. ^{13}C NMR spectra were taken on a Varian Mercury BB 200 (50.3 MHz) instrument for $CDCl_3$ solutions. The purity of the compounds was monitored by TLC on Silufol UV-254 covered silica gel plates, eluent acetone–hexane, UV light detection.

2-(2-N,N-Dialkylaminothiazol-5-yl)-3,5,6-trichlorobenzoquinones **1a-d** were prepared according to method [1].

General Method for Preparing 2-(2-Aminothiazol-5-yl)-5-N,N-diethylaminoethenyl-3,6-dichloro-1,4-benzoquinones (2a-e). Compound **1** (3 mmol) was dissolved in toluene (30-60 ml), magnesium sulfate added, then acetaldehyde (3 mmol), and finally diethylamine (6 mmol) was slowly added dropwise. The product was further stirred at room temperature for 30 min and the magnesium sulfate filtered off. The toluene solution was evaporated to half volume, hexane (20-40 ml) was added, and after 48 h, the precipitate separated. Compounds **2a-d** could be recrystallized from ethanol and **2e** from ethyl acetate: mp > 250°C (decomp.).

3,6-Dichloro-5-N,N-diethylaminoethenyl-2-(2-N,N-dimethylaminothiazol-5-yl)-1,4-benzoquinone (2a). Yield 32%. IR spectrum (thin layer): 2924 (C–H), 1636 (C=O), 1570 cm^{-1} (C=C). ^1H NMR spectrum ($CDCl_3$): 8.71 (1H, s, 4-H thiazole); 8.38 (1H, d, ^3J = 14 Hz, N–C(H)=C); 5.58 (1H, d, ^3J = 14 Hz, C=C–H); 3.35 (4H, q, $CH_3\underline{CH_2}$); 3.17 (6H, s, N–CH_3); 1.23 ppm (6H, t, $\underline{CH_3}CH_2$). Found, %: Cl 18.03; S 8.40. $C_{17}H_{19}Cl_2N_3O_2S$. Calculated, %: Cl 17.72; S 8.0.

3,6-Dichloro-5-N,N-diethylaminoethenyl-2-(2-pyrrolidinothiazol-5-yl)-1,4-benzoquinone (2b). Yield 34%. IR spectrum (thin layer): 3008 (C–H), 1633 (C=O), 1579 (C=C), 1553 (C=C–N), 1511 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 8.78 (1H, s, 4-H thiazole); 8.40 (1H, d, ^3J = 13 Hz, N–C(H)=C); 5.60 (1H, d, ^3J = 13 Hz, C=C–H); 3.51 (4H, t, N–CH_2 pyrrolidine); 3.37 (4H, q, $CH_3\underline{CH_2}$); 2.07 (4H, m, CH_2); 1.24 ppm (6H, t, $\underline{CH_3}CH_2$). Found,%: Cl 16.55; S 7.40. $C_{19}H_{21}Cl_2N_3O_2S$. Calculated, %: Cl 16.25; S 7.35.

3,6-Dichloro-5-N,N-diethylaminoethenyl-2-(2-piperidinothiazol-5-yl)-1,4-benzoquinone (2c). Yield 96%. ^1H NMR spectrum (DMSO-d_6): 8.59 (1H, s, 4-H thiazole); 8.36 (1H, d, ^3J = 13 Hz, N–C(H)=C); 5.56 (1H, d, ^3J = 13 Hz, C=C–H); 3.60 (4H, t, N–CH_2 piperidine); 2.9 (4H, q, $CH_3\underline{CH_2}$); 1.65 (6H, m, CH_2 piperidine); 1.57 ppm (6H, t, $\underline{CH_3}CH_2$). found, %: Cl 16.43; S 7.46. $C_{20}H_{23}Cl_2N_3O_2S$. Calculated, %: Cl 16.12; S. 7.28.

3,6-Dichloro-5-N,N-diethylaminoethenyl-2-(2-perhydroazepinothiazol-5-yl)-1,4-benzoquinone (2d). Yield 89%. IR spectrum (thin layer): 2932 (C–H), 1636 (C=O), 1584 (C=C), 1512 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 8.81 (1H, s, 4-H thiazole); 8.44 (1H, d, ^3J = 14 Hz, N–C(H)=C); 5.64 (1H, d, ^3J = 14 Hz, C=C–H); 3.64 (4H, t, N–CH_2 perhydroazepine); 3.33 (4H, q, $CH_3\underline{CH_2}$); 1.80 (4H, m, CH_2 perhydroazepine); 1.58 (4H, m, CH_2 perhydroazepine); 1.20 ppm (6H, t, $\underline{CH_3}CH_2$). Found, %: Cl 15.32; S 7.59. $C_{21}H_{25}Cl_2N_3O_2S$. Calculated, %: Cl 15.61; S. 7.06.

3,6-Dichloro-5-N,N-diethylaminoethenyl-2-(2-morpholinothiazol-5-yl)-1,4-benzoquinone (2e). Yield 65%, after recrystallization 45%. IR spectrum (thin layer): 2900 (C–H), 1676, 1640 (C=O); 1586 (C=C), 1522 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 8.69 (1H, s, 4-H thiazole); 8.40 (1H, d, ^3J = 14 Hz, N–C(H)=C); 5.57 (1H, d, ^3J = 14 Hz, C=C–H); 3.80 (4H, t, O–CH_2); 3.64 (4H, t, N–CH_2); 3.36 (4H, q, $CH_3\underline{CH_2}$); 1.24 ppm (6H, t, $\underline{CH_3}CH_2$). Found, %: Cl 17.3; S 7.4. $C_{19}H_{21}Cl_2N_3O_3S$. Calculated, %: Cl 16.03; S 7.25.

General Method for Preparing 2,5-Bis(2-aminothiazol-5-yl)-3,6-dichloro-1,4-benzoquinones (4a-f). Compound **2** (3 mmol) was dissolved in acetonitrile (20–40 ml), concentrated hydrochloric acid (4.5 ml) was added slowly dropwise, then the corresponding thiourea (3 mmol) was added, and the product was refluxed for 1.5 h. The precipitate formed was filtered off. If the precipitate did not form immediately the solution was allowed to stand overnight in a fridge. The precipitate was then dissolved in DMF (10-30 ml), an aqueous solution of ferric chloride (25%, 50 ml) was added, and the whole was shaken for 1.5 h. The precipitate obtained was filtered off and washed thoroughly on the filter with water; mp > 250°C (decomp.).

2,5-Bis(2-N,N-dimethylaminothiazol-5-yl)-3,6-dichloro-1,4-benzoquinone (4a). Yield 65%. IR spectrum (thin layer): 2926 (C–H), 1628 (C=O), 1572 (C=C), 1510 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 8.71 (2H, s, 4-H thiazole); 3.20 ppm (12H, s, N–CH_3). Found, %: Cl 16.13; S 15.20. $C_{20}H_{14}Cl_2N_4O_2S_2$. Calculated, %: Cl 16.51; S 14.90

2-(2-Aminothiazol-5-yl)-3,6-dichloro-5-(2-piperidinothiazol-5-yl)-1,4-benzoquinone (4b). Yield 45%. IR spectrum (thin layer): 3368 (NH_2), 2936 (C–H), 1643 (C=O), 1540 (C=C), 1505 cm^{-1}. ^1H NMR spectrum (DMSO-d_6): 8.48 (1H, s, 4-H thiazole); 8.37 (1H, s, 4-H thiazole); 8.10 (2H, br. s, NH_2); 3.58 (4H, br. s, N–CH_2); 1.59 ppm (6H, br. s, CH_2). Found, %: Cl 16.61; S 14.19. $C_{17}H_{14}Cl_2N_4O_2S_2$. Calculated, %: Cl 16.07; S 14.54.

3,6-Dichloro-2-(2-piperidinothiazol-5-yl)-5-(2-pyrrolidinothiazol-5-yl)-1,4-benzoquinone (4c). Yield 52%. IR spectrum (thin layer): 2924 (C–H), 1630 (C=O), 1545 (C=C), 1502 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 8.80 (1H, s, 4-H thiazole); 8.69 (1H, s, 4-H thiazole); 3.68 (4H, br. s, N–CH_2); 3.55 (4H, br. s, N–CH_2); 2.14 (4H, s, CH_2 pyrrolidine); 1.69 ppm (6H, br. s, CH_2 piperidine). Found, %: Cl 14.83; S 12.84. $C_{21}H_{20}Cl_2N_4O_2S_2$. Calculated, %: Cl 14.31; S. 12.94.

2,5-Bis(2-morpholinothiazol-5-yl)-3,6-dichloro-1,4-benzoquinone (4d). Yield 47%. ^1H NMR spectrum ($CDCl_3$): 8.67 (2H, s, 4-H thiazole); 3.77 (8H, s, (O–CH_2); 3.64 ppm (8H, br. s, N–CH_2). Found, %: Cl 13.96; S 12.94. $C_{20}H_{18}Cl_2N_4O_4S_2$. Calculated, %: Cl 13.81, S 12.49.

2,5-Bis(2-piperidinothiazol-5-yl)-3,6-dichloro-1,4-benzoquinone (4e). Yield 74%. IR spectrum (thin layer): 2596 (C–H), 2512 (C–H), 1628 C=O), 1546 (C=C), 1505 cm^{-1}. ^1H NMR spectrum (200 MHz, $CDCl_3$): 8.76 (2H, s, 4-H thiazole); 3.67 (8H, br. s. N–CH_2); 1.69 ppm (12H, br. s, CH_2). ^{13}C NMR spectrum: 23.97 ($C_{(4)}$ piperidine); 25.28 ($C_{(3,5)}$ piperidine); 49.63 ($C_{(2,6)}$ piperidine) ; 116.19 ($C_{(2,5)}$ benzoquinone); 127.12 ($C_{(3,6)}$ benzoquinone), 134.68 ($C_{(4)}$ thiazole); 152.80 ($C_{(5)}$ thiazole); 177.03 and 177.46 ppm ($C_{(2)}$ thiazole and/or $C_{(1,4)}$ benzoquinone). Found, %: Cl 14.06; S 12.96. $C_{22}H_{22}Cl_2N_4O_2S_2$. Calculated, %: Cl 13.92; S 12.59.

2,5-Bis(2-perhydroazepinothiazol-5-yl)-3,6-dichloro-1,4-benzoquinone (4f). Yield, 57%. IR spectrum (thin layer): 2932 (C–H), 1638 (C=O), 1544 (C=C), 1504 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 8.71 (2H, s, 4-H thiazole); 3.77 (8H, t, N–CH_2); 1.84 (8H, m, CH_2); 1.56 ppm (8H, m, CH_2). Found, %: Cl 13.88; S 12.46. $C_{22}H_{20}Cl_2N_4O_2S_2$. Calculated, %: Cl 13.55; S 12.25.

REFERENCES

1. M. F. Utinans, R. E. Valters, G. A. Karlivans, E. E. Liepin'sh, and A. S. Edzhinya, *Khim. Geterotsikl. Soedin.*, No. 5, 692 (1988).
2. M. F. Utinans, Yu. V. Gulbis, R. E. Valters, E. E. Liepin'sh, G. A. Karlivans, and A. S. Edzhinya, *Khim. Geterotsikl. Soedin.*, No. 3, 410 (1991).
3. R. Valters, G. Karlivans, J. Gulbis, M. Utinans, and A. Bace, *Phosph. Sulf.*, **95-96**, 457 (1994).
4. R. E. Valter, E. E. Liepin'sh, G. A. Karlivan, V. R. Zin'kovska, and M. F. Utinan, *Zh. Org. Khim.*, **21**, No. 2, 436 (1985).
5. G. D. Harris, A. Nguyen, H. App, P. Hirth, G. McMahon, and Cho Tang, *Organic Letters*, **1**, 431 (1999).
6. K. Th. Finley, in: *The Chemistry of Quinonoid Compounds* (ed. S. Patai), Vol. **1**, Part 2, Wiley, New York (1974), p. 877.
7. K. Th. Finley, in: *The Chemistry of Quinonoid Compounds* (eds. S. Patai and Z. Rapoport), Vol. **2**, Part 1, Wiley, Chichester (1988), p. 537.