

**SYNTHESIS OF HETEROCYCLES
BASED ON PRODUCTS OF ANION
ARYLATION OF UNSATURATED
COMPOUNDS. 5.* REACTION OF 2-ARYL-
1,4-BENZOQUINONES WITH THIOUREA**

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2-Aryl-1,4-benzoquinones, that can be obtained by arylation of quinone by arenediazonium salts, regioselectively react with thiourea in acid medium to form 7-aryl-5-hydroxy-1,3-benzoxathiol-2-ones. In the presence of excess arylquinones at room temperature, 2-amino-6-hydroxybenzothiazoles are formed in the same reaction.

Keywords: 2-aryl-1,4-benzoquinones, thiourea.

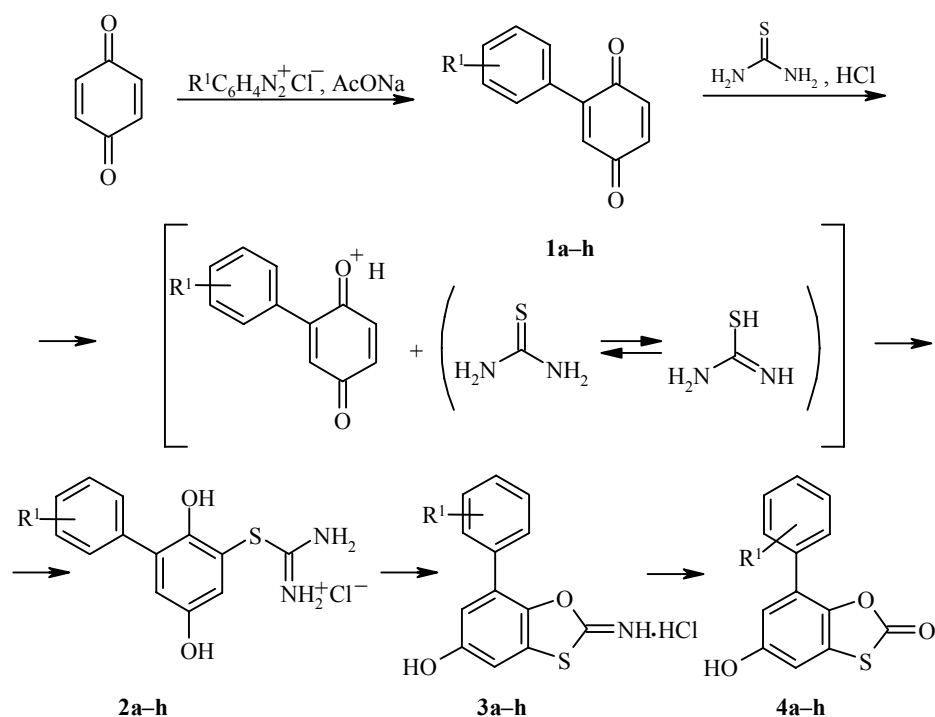
The products of haloarylation [1-4] and thiocyanatoarylation [5] of unsaturated compounds of arenediazonium salts are convenient reagents for synthesis of heterocycles. One variant of the Meerwein reaction (haloarylation or arylation of unsaturated compounds) is the reaction of quinones with arenediazonium salts, as a result of which generally monoaryl-substituted quinones are obtained [6, 7].

In this work, we have studied the possibility of synthesis of heterocycles based on the arylation products of *p*-benzoquinone **1a-h**. We know that quinones add to compounds with thiol groups, and using polyfunctional reagents in this reaction makes it possible to obtain different condensed heterocycles as a result of subsequent intramolecular cyclocondensations [8, 9]. When quinones react with thiourea, thiuronium salts are obtained for which the direction of further cyclization depends on the reaction conditions [10, 11]. We have established that arylquinones **1a-h** react with thiourea in acid medium to form 7-aryl-5-hydroxy-1,3-benzoxathiol-2-ones **4a-h** (Table 1).

In the course of the reaction, at an intermediate stage S-(3-aryl-2,5-dihydroxyphenyl)thiuronium chlorides **2a-h***² and 7-aryl-5-hydroxy-2-imino-1,3-benzoxathioles **3a-h** [10] are formed. The latter are rapidly hydrolyzed under the reaction conditions to form compounds **4a-h**, and we did not isolate them in pure form. The structure of the end products of the reaction is due to the regiodirective nature of the addition of thiourea to *p*-benzoquinone.

* For Communication 4, see [1].

*² The salts **2a-h** can be isolated in pure form. The characteristics of compounds **2f,h** are presented in the Experimental section.



1-4 a R¹ = H, **b** R¹ = 3-Me, **c** R¹ = 4-Me, **d** R¹ = 4-MeO, **e** R¹ = 2-Cl, **f** R¹ = 3-Cl,
g R¹ = 4-Cl, **h** R¹ = 4-NO₂

Theoretically, in addition to compounds **4a-h** it is possible that isomers of type **5**, **6** can be formed. However, we found that the reaction occurs regioselectively: the thiourea adds in the *meta* position relative to the aromatic substituent (compounds **2a-h**). We draw such a conclusion based on the ¹H NMR spectroscopy data (Table 2). In the ¹H NMR spectra of these compounds, we observe two doublets from the aromatic protons *ortho* to the

TABLE 1. Characteristics of 7-Aryl-5-hydroxy-1,3-benzoxathiol-2-ones

Compound	Empirical formula	Found, %			mp, °C	Yield, %
		Calculated, %				
		C	H	S		
4a*	C ₁₃ H ₈ O ₃ S	63.74	3.19	13.11	176-177	91
		63.92	3.30	13.13		
4b	C ₁₄ H ₁₀ O ₃ S	64.91	3.82	12.30	153-154	51
		65.10	3.90	12.41		
4c	C ₁₄ H ₁₀ O ₃ S	64.95	3.87	12.48	170-171	50
		65.10	3.90	12.41		
4d	C ₁₄ H ₁₀ O ₄ S	61.27	3.53	11.67	165-166	93
		61.30	3.68	11.69		
4e	C ₁₃ H ₇ ClO ₃ S	55.90	2.48	11.39	167-168.5	70
		56.02	2.53	11.50		
4f	C ₁₃ H ₇ ClO ₃ S	55.85	2.42	11.37	204-205	70
		56.02	2.53	11.50		
4g	C ₁₃ H ₇ ClO ₃ S	56.10	2.46	11.56	175-176	72
		56.02	2.53	11.50		
4h	C ₁₃ H ₇ NO ₅ S	54.11	2.40	10.99	>300 (dec.)	81
		53.98	2.44	11.08		

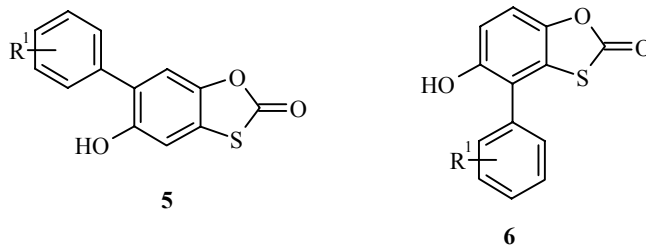
* The constants for the substance are consistent with literature data in [10].

TABLE 2. ^1H NMR Spectra for 7-Aryl-5-hydroxy-1,3-benzoxathiol-2-ones, δ , ppm

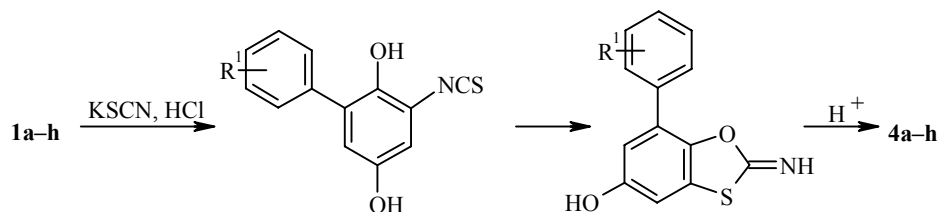
Compound	Me or OMe, 3H, s	4-H, 1H, d	6-H, 1H, d	J_{46}	H_{arom} in RC_6H_4	OH, 1H, s
4a	—	6.87	7.15	2.5	7.48 (3H, m*); 7.61 d (2H)	9.94
4b	2.38	6.85	7.14	2.7	7.24 (1H, m*); 7.39 (3H, m*)	9.86
4c	2.36	6.84	7.13	2.4	7.30 (2H, d); 7.50 (2H, d)	9.89
4d	3.82	6.84	7.09	2.4	7.06 (2H, d); 7.56 (2H, d)	9.81
4e	—	6.72	7.21	2.1	7.46 (3H, m*); 7.59 (1H, d)	9.90
4f	—	6.88	7.18	1.0	7.53 (3H, m*); 7.67 (1H, s)	9.89
4h	—	6.96	7.25	2.1	7.90 (2H, d); 8.34 (2H, d)	10.05

* Centers of multiplets are indicated.

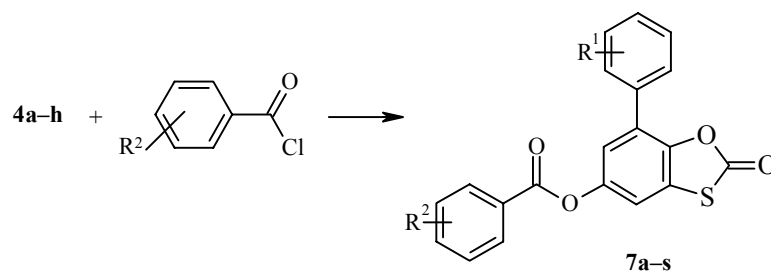
hydroxy group (4-H, 6-H), with characteristic long-range spin-spin coupling constants (J_{46}). The signals that were typical for the isomers **5**, **6** are missing in the spectra. Only when using 2-(4-nitrophenyl)-1,4-benzoquinone do we observe formation of isomers **4** and **5** in ~ 5:1 ratio.



We also attempted to synthesize compounds **4** by reaction of arylquinones with thiocyanic acid (such an approach to synthesis of similar compounds is described in [12]). However, this process is complicated by side reactions, which makes it difficult to isolate the target products **4a-h**.



Compounds **4a-h** are rather easily acylated by acid chlorides in benzene in the presence of bases. The characteristics of 5-aryloxy-7-aryl-1,3-benzoxathiol-2-ones **7a-s** are given in Table 3, and the ^1H NMR spectral data are given in Table 4.




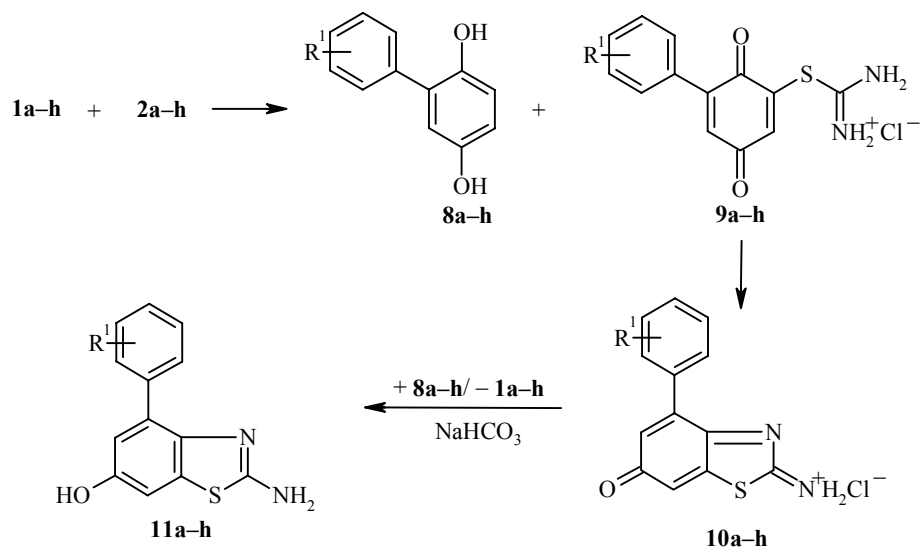
7 R¹ = H, R² = H (**a**), 4-NO₂ (**b**); R¹ = H, instead of R²C₆H₄ -  (**c**),
 R¹ = 3-Me, R² = 2-Cl (**d**), 4-Cl (**e**); R¹ = 4-Me, R² = H (**f**), 2-Cl (**g**), 4-Cl (**h**);
 R¹ = 4-OMe, R² = H (**i**), 2-Cl (**j**), 4-Cl (**k**); R¹ = 2-Cl, R² = H (**l**), 2-Cl (**m**),
 4-Cl (**n**), 4-Br (**o**); R¹ = 4-Cl, R² = H (**p**), 2-Cl (**q**), 4-Cl (**r**), 4-Br (**s**)

TABLE 3. Characteristics of 5-Aroyloxy-7-aryl-1,3-benzoxathiol-2-ones

Com- pound	Empirical formula	Found, %		mp, °C	Yield, %
		Calculated, %			
		C	H		
7a	C ₂₀ H ₁₂ O ₄ S	<u>68.72</u>	<u>3.40</u>	97-98	51
		68.95	3.47		
7b	C ₂₀ H ₁₁ NO ₆ S	<u>61.20</u>	<u>2.85</u>	190-191	55
		61.07	2.82		
7c	C ₂₂ H ₁₁ ClO ₄ S ₂	<u>60.09</u>	<u>2.47</u>	181-182	65
		60.20	2.53		
7d	C ₂₁ H ₁₃ ClO ₄ S	<u>63.28</u>	<u>3.25</u>	102-103	59
		63.56	3.30		
7e	C ₂₁ H ₁₃ ClO ₄ S	<u>63.62</u>	<u>3.27</u>	134-135	57
		63.56	3.30		
7f	C ₂₁ H ₁₄ O ₄ S	<u>69.41</u>	<u>3.88</u>	135-136	67
		69.60	3.89		
7g	C ₂₁ H ₁₃ ClO ₄ S	<u>63.32</u>	<u>3.18</u>	123-124	50
		63.56	3.30		
7h	C ₂₁ H ₁₃ ClO ₄ S	<u>63.53</u>	<u>3.25</u>	163-164	50
		63.56	3.30		
7i	C ₂₁ H ₁₄ O ₅ S	<u>66.36</u>	<u>3.72</u>	154-155	76
		66.65	3.73		
7j	C ₂₁ H ₁₃ ClO ₅ S	<u>60.89</u>	<u>3.12</u>	176-177	49
		61.10	3.17		
7k	C ₂₁ H ₁₃ ClO ₅ S	<u>61.14</u>	<u>3.08</u>	174-175	53
		61.10	3.17		
7l	C ₂₀ H ₁₁ ClO ₄ S	<u>62.60</u>	<u>2.77</u>	138-139	60
		62.75	2.90		
7m	C ₂₀ H ₁₀ Cl ₂ O ₄ S	<u>57.33</u>	<u>2.34</u>	134-135	55
		57.57	2.42		
7n	C ₂₀ H ₁₀ Cl ₂ O ₄ S	<u>57.67</u>	<u>2.50</u>	141-142	71
		57.57	2.42		
7o	C ₂₀ H ₁₀ BrClO ₄ S	<u>51.84</u>	<u>2.23</u>	168-169	56
		52.03	2.18		
7p	C ₂₀ H ₁₁ ClO ₄ S	<u>62.61</u>	<u>2.85</u>	141-142	61
		62.75	2.90		
7q	C ₂₀ H ₁₀ Cl ₂ O ₄ S	<u>57.38</u>	<u>2.37</u>	152-153	52
		57.57	2.42		
7r	C ₂₀ H ₁₀ Cl ₂ O ₄ S	<u>57.69</u>	<u>2.47</u>	178-179	48
		57.57	2.42		
7s	C ₂₀ H ₁₀ BrClO ₄ S	<u>51.90</u>	<u>2.11</u>	181-182	57
		52.03	2.18		

The thiuronium salts **2a-h** can be oxidized by arylquinones **1a-h** [11]. Therefore, if we use an excess of compounds **1a-h** in the reaction with thiourea and we carry out the reaction in the presence of a mineral acid at room temperature, then 2-amino-4-aryl-6-hydroxybenzothiazoles **11a-h** are formed rather than compounds **4a-h**. The most probable mechanism for such a reaction includes intermediates **9**, **10a-h** [11].



The aminothiazoles **11a-h** were not isolated in pure form; they were identified using ^1H NMR spectroscopy and chromatographic mass spectroscopy. In this case, fairly small amounts of the isomers and products of side reactions were also formed, which we did not study more closely.

TABLE 4. ^1H NMR Spectra of 5-Aroyloxy-7-aryl-1,3-benzoxathiol-2-ones **7a-s**, δ , ppm*

Compound	4-H, 1H, d* ²	6-H, 1H, d* ²	R ¹ C ₆ H ₄	R ² C ₆ H ₄
1	2	3	4	5
7a	7.46	7.78	7.44-7.65 (5H, m)	7.69-7.77 (3H, m); 8.16 (2H, d; <i>o</i> -H)
7b	7.61	7.83	7.50 (3H, m); 7.71 (2H, d)	8.39 (2H, d); 8.44 (2H, d)
7c	7.58	7.84	7.70 (4H, m)	
7d	7.39	7.70	7.50 (3H, m) 2.44 (3H, s, CH ₃); 7.25 (1H, d); 7.37-7.50 (3H, m)	8.03 (1H, d); 8.19 (1H, d); 7.52-7.66 (3H, m); 8.10 (1H, d, <i>o</i> -H)
7e	7.38	7.68	2.44 (3H, s, CH ₃); 7.24 (1H, d); 7.39-7.50 (3H, m)	7.62 (2H, d); 8.16 (2H, d)
7g	7.39	7.69	2.43 (3H, s, CH ₃); 7.32 (2H, d); 7.58 (2H, d)	7.50-7.65 (3H, m); 8.10 (1H, d, <i>o</i> -H)
7h	7.36	7.64	2.41 (3H, s, CH ₃); 7.30 (2H, d); 7.57 (2H, d)	7.61 (2H, d); 8.15 (2H, d)
7i	7.46	7.71	3.81 (3H, s, CH ₃ O); 7.07 (2H, d); 7.65 (2H, d)	7.59-7.80 (3H, m); 8.14 (2H, d, <i>o</i> -H)
7j	7.38	7.65	3.85 (3H, s, CH ₃ O); 7.05 (2H, d); 7.63 (2H, d)	7.50-7.65 (3H, m); 8.10 (1H, d, <i>o</i> -H)
7k	7.35	7.64	3.83 (3H, CH ₃ O); 7.03 (2H, d); 7.60 (2H, d)	7.61 (2H, d); 8.15 (2H, d)

TABLE 4 (continued)

1	2	3	4	5
7l	7.23	7.77	7.48 (3H, m)	7.59 (3H, m) 7.71 (1H, t); 8.15 (2H, d, <i>o</i> -H)
7m	7.27	7.82		7.45–7.68 (7H, m) 8.09 (1H, d, <i>o</i> -H)
7n	7.24	7.79	7.49 (3H, m); 7.57 (1H, d)	7.61 (2H, d); 8.15 (2H, d)
7o	7.24	7.80	7.49 (3H, m); 7.59 (1H, m)	7.77 (2H, d); 8.07 (2H, d)
7p	7.41	7.70	7.52 (2H, d); 7.72 (2H, d)	7.60 (2H, m); 7.70 (1H, m); 8.16 (2H, d, <i>o</i> -H)
7q	7.44	7.74	7.53 (2H, d); 7.72 (2H, d)	7.50–7.67 (3H, m); 8.10 (1H, d, <i>o</i> -H)
7r	7.43	7.71	7.52 (2H, d); 7.72 (2H, d)	7.62 (2H, d); 8.15 (2H, d)
7s	7.41	7.70	7.52 (2H, d); 7.72 (2H, d)	7.78 (2H, d); 8.08 (2H, d)

* In the case of narrow multiplets, their centers are given.

*² $J_{46} \sim 2\text{--}2.5$ Hz.

EXPERIMENTAL

The ¹H NMR spectra of compounds **4a-f,h**, **7e**, **11a-h** were taken on a Varian VXR-300; the spectra for compounds **7a-d**, **f-s** were taken on a Bruker WM-250 in DMSO-*d*₆, internal standard HMDS. The mass spectra were taken on a Finnigan MAT INKOS-50 chromatographic mass spectrometer.

The 2-aryl-1,4-benzoquinones **1a-h** were obtained by a procedure close to that described in [13] in the following yields: **1a**, 070%; **1b**, 84%; **1c**, 85%; **1d**, 62%; **1e**, 82%; **1f**, 85%; **1g**, 75%; **1h**, 91%. The constants for these substances agree with literature data [13,14].

5-Hydroxy-7-phenyl-1,3-benzoxathiol-2-one (4a). A solution of 2-phenyl-1,4-benzoquinone (3.7 g, 0.02 mol) in acetic acid (20 ml) was added to a solution of thiourea (2.3 g, 0.03 mol) in 2 N hydrochloric acid (40 ml). The mixture was heated for 1 h and then cooled; the precipitate formed was filtered off and crystallized from aqueous alcohol. Compounds **4b-h** were obtained similarly.

When the reaction mixture was held without heating, a precipitate of thiuronium salt **2a-h** was formed. The compounds **2e,h** were isolated and characterized.

S-[3-(3-Chlorophenyl)-2,5-dihydroxyphenyl]thiuronium Chloride (2f). Yield 72%; mp 133-134°C. ¹H NMR spectrum, δ , ppm: 6.91 (2H, d, H_{dihydroxyphenyl}); 7.30-7.57 (4H, m, H_{arom}); 8.62 (2H, br. s, NH₂); 8.90 (1H, s, OH); 9.35 (2H, br. s, NH₂⁺); 9.40 (1H, s, OH). Found, %: C 46.92; H 3.60; N 8.52. C₁₃H₁₂Cl₂N₂O₂S. Calculated, %: C 47.14; H 3.65; N 8.46.

S-[2,5-Dihydroxyphenyl-3-(4-nitrophenyl)]thiuronium Chloride (2h). Yield 74%; mp 210-212°C. Found, %: C 45.80; H 3.49; N 12.11. C₁₃H₁₂ClN₃O₄S. Calculated, %: C 45.68; H 3.54; N 12.29.

Reaction of 2-Aryl-1,4-benzoquinones 1a-h with HSCN. A mixture of arylquinone **1a-h** (0.01 mol), KSCN (1.45 g), 2 N hydrochloric acid (20 ml), and acetic acid (15 ml) were heated for 1.5 h. The precipitate formed was filtered off. The presence of compounds **4a-h** in the precipitate was established by TLC and ¹H NMR spectroscopy.

7-Aryl-5-aryloxy-1,3-benzoxathiol-2-ones (7a-s) (Table 3). N-methylmorpholine (1.01 g, 0.01 mol) and the corresponding acid chloride (0.01 mol) were added to a solution of compound **4a-h** (0.01 mol) in benzene (30 ml). The mixture was heated for 1 h, the precipitate of N-methylmorpholinium chloride was filtered off, the filtrate was evaporated down to formation of a precipitate of compounds **7a-s**, which were crystallized from an acetone-alcohol or DMF-alcohol mixture.

2-Amino-4-aryl-6-hydroxybenzothiazoles (11a-h). A solution of arylquinone **1a-h** (13.4 mmol) in ethanol (20-30 ml) was added to a mixture of thiourea (0.51 g, 6.7 mmol) and concentrated hydrochloric acid in ethanol (15 ml). The mixture was held for 24 h at room temperature, then the ethanol was evaporated off, water was added to the residue and it was heated until the hydrochlorides of amines **11a-h** were dissolved. The mixture was filtered and NaHCO₃ was added to the filtrate. A precipitate formed that, judging from the ¹H NMR spectra and the mass spectra, consisted mainly of 2-amino-4-aryl-6-hydroxybenzothiazoles.

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