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Acid-catalyzed S_N^H(An) thiolation of *p*-dihydroxybenzene

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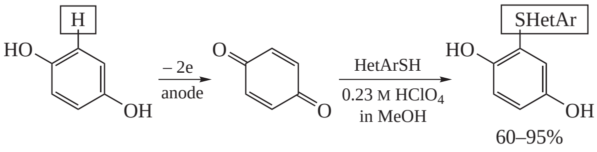
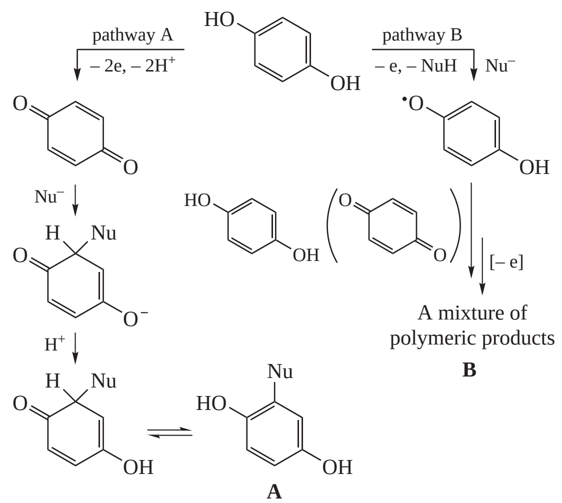
The anodic functionalization of *p*-dihydroxybenzene with poorly nucleophilic thiols is performed by acid activation of *p*-quinone electrogenerated at the first stage followed by treatment with thiols at the second stage. This two-stage process is preferable in terms of efficiency.

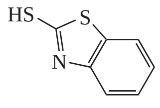


Functionally substituted *o*(*p*)-dihydroxybenzenes (DHB) manifest pharmacological activity,[1–4] which promoted a number of publications on the electrochemical functionalization of DHB with various nucleophiles (Nu).[3,4] These reactions may be considered[5] as electro-induced nucleophilic substitution of hydrogen S_N^H(An) that opens wide prospects for building C–C, C–N, C–S and other bonds.[6]

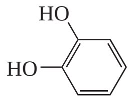
In general, such processes can be regarded as DHB electrooxidation with the generation of the corresponding quinone followed by Michael addition of Nu to give the functionalization product. In our previous study,[7] this process was implemented at the potentials of DHB oxidation in MeCN. Furthermore, we noted a number of its specific features depending both on the Nu properties and on the acidic properties of the DHB. These aspects were previously[7] overlooked within the electrochemical functionalization of DHB, where we tested nucleophiles with markedly different properties, namely, 2-mercaptobenzothiazole, 3,5-dimethylpyrazole and 4-nitropyrazolate anion (Scheme 1). Addition of 4-nitropyrazolate anion to the reaction mixture results in DHB deprotonation.[7] As a consequence, instead of pathway A to give the target product **A**, the process occurred *via* generation of a radical intermediate through pathway B to give a mixture of resinous products **B** (see Scheme 1). Based on these results, the general conclusion was made: for the successful electrochemical functionalization of DHB, the substituting reagent should be a sufficiently strong nucleophile to efficiently react with the electrogenerated quinone, on the one hand, and it should be a sufficiently weak base that cannot deprotonate the starting DHBs or the products of their functionalization, on the other hand.



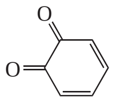
Scheme 1



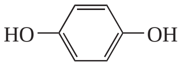
1
E_p^{ox} = 1.3 V



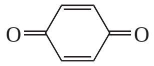
2
E_p^{ox} = 1.3 V



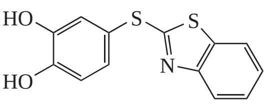
2′



3
E_p^{ox} = 1.1 V



3′



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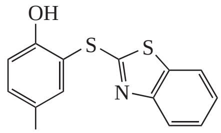
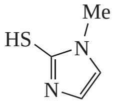


4′



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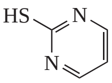

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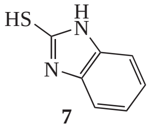

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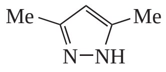

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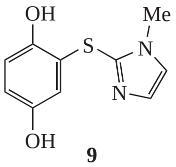

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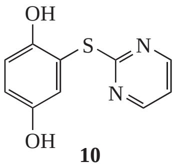

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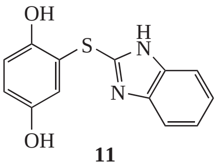
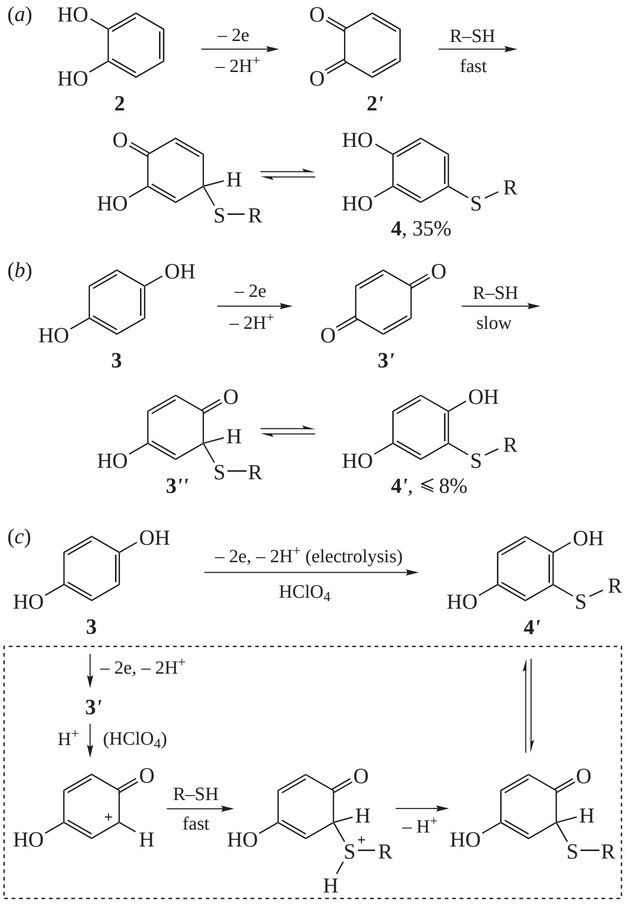


11

In view of this, we chose 2-mercaptobenzothiazole **1** as the most suitable Nu. For the DHB electrolysis in the presence of thiol **1**[7] a considerable difference in the efficiency of its reactions with *o*-quinone **2′** and *p*-quinone **3′**, *i.e.*, the products of electrooxidation of DHB **2** and DHB **3**, respectively, was noted. It fact, quinone **2′** is more reactive but less stable. As a result [Scheme 2(*a*)], the target product **4** was obtained in a moderate yield (35%), though the conversion of DHB **2** was complete. Conversely, quinone **3′** [Scheme 2(*b*)] is more stable but its reactivity is low. For this reason, the reaction mixture after the



Scheme 2

electrolysis contained a large amount of non-reacted quinone **3′**, whereas the target product **4′** was obtained in a minor yield ($\leqslant$ 8%). An attempt to accelerate the **3′** → **3′′** reaction using a threefold excess of thiol **1** with respect to DHB **3** failed, and the yield of product **4′** did not increase. However, the reaction mixture contained known (including NMR data)[8] di(benzothiazol-2-yl)disulfide (altax), which is a product of thiol **1** oxidation at a potential close to the oxidation potential of DHB. Since the data on the electrochemical thiolation of DHB **3** are practically absent in the literature, we studied herein this process in more detail.

It was found that the electrolysis of DHB **3** under these conditions in the presence of other thiols such as 2-mercapto-1-methylimidazole **5**, 2-mercaptopyrimidine **6** and 2-mercaptobenzoimidazole **7** also gave products of type **4′** in less than 15% yields.[†] Therefore, to increase the efficiency of the target process, it is insufficient to use relatively basic co-reagents or media (see above). At the same time, it is necessary to enhance the reactivity of quinone **3′**.

For example, it is known[9] that benzoquinone and its carbonyl-containing derivatives react with nucleophiles such as dimethylaniline, phenols and their ethers, and even alkylbenzenes under acid catalysis conditions. These reactions usually occur at room temperature[10] to give functionally substituted benzoquinones. It may therefore be expected that acid activation of quinone **3′** would enhance its electrophilicity, as shown in Scheme 2(*c*).

In an attempt to optimize the process [see Scheme 2(*c*)] for electrolysis of DHB **3** in the presence of thiol **1** as an example, we tried to estimate the effect of the nature of the acid additives, namely, perchloric, *p*-toluenesulfonic and sulfuric acids (*cf.* ref. 11). To our delight, the electrolysis of DHB **3** in the presence of thiol **1** with $HClO_4$ additive resulted in a considerable increase in the reactivity of quinone **3′**: the yield of the target product **4′** reached 65% instead of previous 8%.[‡] The use of the other acids also raised the yield of product **4′** but this growth was smaller (~30%).

In all the above cases, the electrooxidation of DHB **3** in the presence of thiol **1** was performed as a one-stage process. However, the reaction mixture always contained an admixture of the disulfide, a product of thiol **1** oxidative dimerization. Meantime, the stability of quinone **3′** noted previously[7] made it possible to perform the functionalization of DHB **3** as a two-stage process involving the electrogeneration of quinone **3′** as the first stage followed by the treatment of this quinone with thiol **1** at the second stage. This two-stage process proved to be more efficient: the disulfide was not formed, and the yield of **4′** approached to 80% even at an equimolar ratio between **3′** and **1**.[§] However, in a series of similar syntheses with thiols **5**–**7**, the corresponding products **9**–**11** were obtained in moderate yields (40–55%) after column chromatography, and these results were poorly reproducible. The duration of this procedure significantly influenced the degree of destruction of the target products. This stimulated further

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[†] ^{1}H NMR spectra of the products in DMSO-d_6 were obtained on a Bruker Avance 300 spectrometer (300.13 MHz). HRMS spectra were recorded on a Bruker micrOTOF II instrument. The electrolyses were performed in a divided (with a tracing paper diaphragm) temperature-controlled (25 °C) cell (V = 60 ml) with coaxially arranged cylindric Pt electrodes (S_{anode} = 26 cm^2, S_{cathode} = 10 cm^2), using an Elins P30JM potentiostat (a reference SCE was separated from the working solution by a salt bridge with the supporting electrolyte). All the reagents and solvents were purchased from Acros Organics.

Co-electrolysis of DHB **3** *with thiols* **1**, **5**–**7** *in neutral MeCN*. A solution (50 ml) of 0.1 M $NaClO_4$ in MeCN containing 0.001 mol of DHB **3** and 0.001 (0.003) mol of thiol **1** or 0.001 mol of thiol **5** (**6**, **7**) was placed into the anodic compartment. A 0.1 M solution of $NaClO_4$ in MeCN (10 ml) was placed into the cathodic compartment. The process was carried out at a potential of 1.1 V by passing the theoretically required amount of electricity (2 F per mole of the starting DHB). Then the electrolysis was stopped and the mixture was stirred for 5 h. The subsequent treatment of the mixture and identification of the products were performed as reported previously.[7] The yields of target products **4′**, **9**–**11** were $\leqslant$ 15%.

[‡] *Co-electrolysis of DHB* **3** (**2**) *with thiol* **1** *in acidified MeCN*. The supporting electrolyte (50 ml, MeCN containing 2 ml of 70% aqueous $HClO_4$, or 2 ml of 96% aqueous H_2SO_4, or 1.5 g of 98% $TsOH{\cdot}H_2O$), 0.001 mol of DHB **3** (or **2**) and 0.001 mol of thiol **1** were placed into the anodic compartment. The supporting electrolyte (10 ml) was placed into the cathodic compartment. The electrolysis was carried out at a potential of 1.1 V (**3**) or 1.3 V (**2**) by passing 2 F per mole of the starting DHB. The electrolysis was stopped, the mixture was stirred for 5 h, and the acid was neutralized with excess AcONa. The subsequent treatment of the mixture and identification of the products were performed as reported previously.[7] The yield of product **4′** was 37 to 65% (depending on the nature of the acid), and the yield of product **4** was ~35%.

[§] *General two-stage procedure*. At the first stage, 0.001 mol of DHB **3** in MeOH (MeCN) containing 2 ml of 70% aqueous $HClO_4$ was electrooxidized by passing 2 F per mole of the starting DHB to generate quinone **3′**. At the second stage, 0.001 mol of a thiol (**1**, **5**–**7**) or pyrazole **8** was added, the mixture was stirred for 5 h, and then $HClO_4$ was neutralized with excess AcONa. The solution was concentrated to obtain a paste, then 60 ml of water was added and the mixture was extracted with CH_2Cl_2 (4 × 40 ml). The extracts were combined, evaporated *in vacuo* (45 °C, 30 Torr), and the residue was dried in the air. The yields of products **4′**, **9**–**11** are shown in Table 1. The known products **4**, **4′**, **11** were identified referring to the literature data.[7,12]

4-(1,3-Benzothiazol-2-ylsulfanyl)benzene-1,2-diol **4**: pale yellow solid, mp 196–198 °C. ^{1}H NMR, δ: 6.93 (dd, 1H, C^{6}H, $J_{6,5}$ 8.2 Hz, $J_{6,3}$ 0.7 Hz), 7.07 (dd, 1H, C^{5}H, $J_{5,6}$ 8.2 Hz, $J_{5,3}$ 2.2 Hz), 7.14 (dd, 1H, C^{3}H, $J_{3,5}$ 2.2 Hz, $J_{3,6}$ 0.7 Hz), 7.29 (ddd, 1H, C$^{6'}$H, 2-$C_7H_4NS_2$, $J_{6',7'}$ 8.2 Hz, $J_{6',5'}$ 7.1 Hz, $J_{6',4'}$ 1.2 Hz), 7.41 (ddd, 1H, C$^{5'}$H, 2-$C_7H_4NS_2$, $J_{5',4'}$ 8.2 Hz, $J_{5',6'}$ 7.1 Hz, $J_{5',7'}$ 1.2 Hz), 7.80 (ddd, 1H, C$^{4'}$H, 2-$C_7H_4NS_2$, $J_{4',5'}$ 8.2 Hz, $J_{4',6'}$ 1.1 Hz, $J_{4',7'}$ 0.7 Hz), 7.89 (ddd, 1H, C$^{4'}$H, 2-$C_7H_4NS_2$, $J_{7',6'}$ 8.1 Hz, $J_{7',5'}$ 1.2 Hz, $J_{7',4'}$ 0.7 Hz), 9.57 (br. s, 1H, 4-OH), 9.77 (s, 1H, 1-OH). Found (%): C, 56.82; H, 3.18; N, 5.14. Calc. for $C_{13}H_9NO_2S_2$ (%): C, 56.71; H, 3.29; N, 5.09.

Table 1 Functionalization of DHB **3** at the controlled potential electrolysis (1.1 V) *via* intermediate quinone **3′** in the presence of $HClO_4$ followed by treatment with thiols.

Entry	Thiol	Product	Yield (%)
1	**1**	**4′**	95
2	**5**	**9**	70
3	**6**	**10**	60
4	**7**	**11**	72

optimization of the procedure. We found that the use of MeOH as a solvent instead of MeCN provided good to excellent yields of products **4′**, **9–11** (Table 1). Isolation was simple: after the extraction and evaporation operations no further purification was required.

However, reactions with relatively basic nucleophiles such as pyrazole **8** turned to be inefficient since acid additive caused their protonation and deactivation. As noted above, quinone **2′** is unstable, so acid additive did not affect the functionalization of DHB type **2** [the yield of the target product remained at 35%, as shown in Scheme 2(*a*)].

In conclusion, acid activation is an important factor for efficient reactions of quinone **3′** with low-reactivity nucleophiles. Moreover, two-stage functionalization of DHB **3** prevents nucleophile oxidation.

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2-(1,3-Benzothiazol-2-ylsulfanyl)benzene-1,4-diol **4′**: white solid, mp 224–226 °C. ^{1}H NMR, δ: 6.88 (dd, 1H, C^5H, $J_{5,6}$ 8.8 Hz, $J_{5,3}$ 2.7 Hz), 6.93 (dd, 1H, C^6H, $J_{6,5}$ 8.8 Hz, $J_{6,3}$ 0.6 Hz), 7.02 (dd, C^3H, $J_{3,5}$ 2.7 Hz, $J_{3,6}$ 0.6 Hz), 7.29 (ddd, 1H, $C^{6'}H$, 2-$C_7H_4NS_2$, $J_{6',7'}$ 8.2 Hz, $J_{6',5'}$ 7.1 Hz, $J_{6',4'}$ 1.1 Hz), 7.42 (ddd, 1H, $C^{5'}H$, 2-$C_7H_4NS_2$, $J_{5',4'}$ 8.1 Hz, $J_{5',6'}$ 7.1 Hz, $J_{5',7'}$ 1.2 Hz), 7.82 (ddd, 1H, $C^{4'}H$, 2-$C_7H_4NS_2$, $J_{4',5'}$ 8.1 Hz, $J_{4',6'}$ 1.1 Hz, $J_{4',7'}$ 0.7 Hz), 7.90 (ddd, 1H, $C^{4'}H$, 2-$C_7H_4NS_2$, $J_{7',6'}$ 8.2 Hz, $J_{7',5'}$ 1.2 Hz, $J_{7',4'}$ 0.7 Hz), 9.20 (br. s, 1H, 4-OH), 9.68 (s, 1H, 1-OH). Found (%): C, 56.80; H, 3.23; N, 5.13. Calc. for $C_{13}H_9NO_2S_2$ (%): C, 56.71; H, 3.29; N, 5.09.

*2-[(1-Methyl-1*H*-imidazol-2-yl)thio]benzene-1,4-diol* **9**: cream color solid, mp 189–191 °C. ^{1}H NMR, δ: 3.6 (s, 3H, NMe, 2-$C_4H_5N_2S$), 5.85 (dd, 1H, C^3H, $J_{3,5}$ 2.9 Hz, $J_{3,6}$ 0.6 Hz), 6.43 (dd, 1H, C^5H, $J_{5,6}$ 8.9 Hz, $J_{5,3}$ 2.3 Hz), 6.55 (dd, 1H, C^6H, $J_{6,5}$ 8.9 Hz, $J_{6,3}$ 0.6 Hz), 7.12 (d, $C^{5'}H$, 2-$C_4H_5N_2S$, $J_{5',4'}$ 1.5 Hz), 7.50 (d, $C^{4'}H$, 2-$C_4H_5N_2S$, $J_{4',5'}$ 1.5 Hz), 8.84 (s, 1H, 4-OH), 9.49 (s, 1H, 1-OH). HRMS (ESI), *m/z*: 223.0535 (calc. for $C_{10}H_{10}N_2O_2S$, *m/z*: 223.0536 $[M+H]^+$). Found (%): C, 54.20; H, 4.45; N, 12.67. Calc. for $C_{10}H_{10}N_2O_2S$ (%): C, 54.04; H, 4.53; N, 12.60.

2-(Pyrimidin-2-ylthio)benzene-1,4-diol **10**: pale yellow solid, mp 202–204 °C. ^{1}H NMR, δ: 6.70 (dd, 1H, C^5H, $J_{5,6}$ 8.7 Hz, $J_{5,3}$ 2.8 Hz), 6.77 (dd, 1H, C^6H, $J_{6,5}$ 8.7 Hz, $J_{6,3}$ 0.6 Hz), 6.85 (dd, C^3H, $J_{3,5}$ 2.8 Hz, $J_{3,6}$ 0.6 Hz), 7.18 (t, 1H, $C^{5'}H$, 2-$C_4H_3N_2S$, $J_{5',6'(5',4')}$ 4.8 Hz), 8.56 (d, 2H, $C^{4'}H$, $C^{6'}H$, 2-$C_4H_3N_2S$, $J_{4',6'(4',5')}$ 4.8 Hz), 8.94 (s, 1H, 4-OH), 9.13 (s, 1H, 1-OH). HRMS (ESI), *m/z*: 219.0222 (calc. for $C_{10}H_8N_2O_2S$, *m/z*: 219.0223 $[M-H]^+$). Found (%): C, 54.41; H, 3.77; N, 12.61. Calc. for $C_{10}H_8N_2O_2S$ (%): C, 54.53; H, 3.66; N, 12.72.

*2-[(1*H*-Benzo[*d*]imidazol-2-yl)thio]benzene-1,4-diol* **11**: white solid, mp 218–220 °C. ^{1}H NMR, δ: 6.58–6.69 (m, 2H, C^4H, C^5H), 6.82 (dd, 1H, C^6H, $J_{6,5}$ 8.9 Hz, $J_{6,3}$ 0.7 Hz), 7.14–7.24 (m, 2H, $C^{5'}H$, $C^{6'}H$, 2-$C_7H_5N_2S$), 7.45–7.55 (m, 2H, $C^{4'}H$, $C^{7'}H$, 2-$C_7H_5N_2S$), 10.38 (br. s, 3H, 1-OH, 4-OH, NH, 2-$C_7H_5N_2S$). HRMS (ESI), *m/z*: 259.0536 (calc. for $C_{13}H_{10}N_2O_2S$, *m/z*: 259.0536 $[M+H]^+$). Found (%): C, 60.51; H, 3.88; N, 10.88. Calc. for $C_{13}H_{10}N_2O_2S$ (%): C, 60.45; H, 3.90; N, 10.85.