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Efficient electrosynthesis of 1,2,4-triazino[3,4-*b*]-1,3,4-thiadiazine derivatives

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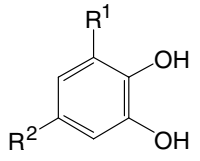
Abstract—Electrochemical oxidation of catechols **1a–d** has been studied in the presence of 4-amino-6-methyl-1,2,4-triazine-3-thion-5-one **3** as a nucleophile in aqueous solutions, using cyclic voltammetry and controlled-potential coulometry, leading to the efficient synthesis of 1,2,4-triazino[3,4-*b*]-1,3,4-thiadiazines.

Electrochemistry provides a versatile means for the selective reduction and oxidation of organic compounds. The importance of an electrochemical synthesis lies not only in the selectivity of the reaction, but also in the formation of electrons at the electrode surface. Hence, since the electrons are reagent free, pollution of the environment by spent reagents can be avoided. In addition, electrosynthesis can lead to efficient and sometimes unexpected synthesis of compounds, which cannot be easily prepared by conventional organic synthesis.

Several compounds containing a thiadiazine core have been demonstrated to have antimicrobial properties. Some thiadiazines are efficient antibacterial and antifungal compounds[1] and their use against the bacterium *Helicobacter pylori* and as reverse transcriptase inhibitors of human immunodeficiency virus has been reported.[2] Several drugs such as doxorubicin, daunorubicin and mitomycin C, used in cancer chemotherapy, contain quinones,[3] and other quinones exhibit antitumour and antimalarial activities.[4,5] In recent years, there has been interest in the study of the reactions between quinones produced by the oxidation of catechols and a variety of nucleophiles including 4-hydroxycoumarin,[6] 4-hydroxy-6-methyl-2-pyrone,[7] barbituric acids,[8] benzenesulfinic acid,[9] dimedone[10] and acetylacetone.[11] Herein, we report a new synthetic strategy involving the electrochemical oxidation of catechols **1a–d** in the presence of 4-amino-6-methyl-1,2,4-triazine-3-thion-5-one **3** as a nucleophile. The present work has led to the development of an electrochemical method for the synthesis of some new 1,2,4-triazino[3,4-*b*]-1,3,4-thiadiazines using the bidendent nucleophile **3**.



R^1=H	R^2=H	**1a,** catechol
R^1=OCH_3	R^2=H	**1b,** 3-methoxycatechol
R^1=CH_3	R^2=H	**1c,** 3-methylcatechol
R^1=H	R^2=COOH	**1d,** 3,4-dihydroxybenzoic acid

Cyclic voltammetry of a 1 mM aqueous solution of catechol **1a** containing 0.2 M phosphate buffer (pH 7.0) shows one anodic (A) and a corresponding cathodic peak (C), which correspond to the transformation of catechol **1a** into its related *o*-benzoquinone **2a** and vice versa within a quasi-reversible two-electron process (Fig. 1, curve a). The oxidation of catechol **1a** in the presence of 4-amino-6-methyl-1,2,4-triazine-3-thion-5-one **3** was studied in some detail. Figure 1 (curve b) shows the cyclic voltammogram obtained for a 1 mM solution of **1a** in the presence of 1 mM of **3**. The voltammogram exhibits one anodic peak at 0.29 V and the cathodic counterpart at 0.02 V versus Ag/AgCl (C), which shows a decrease in comparison to the cathodic

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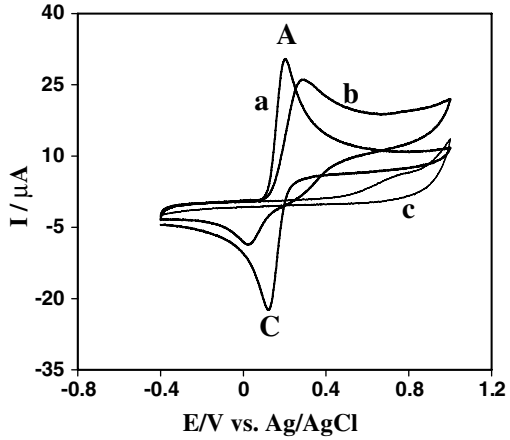


Figure 1. Cyclic voltammograms of 1 mM aqueous catechol **1a**: (a) in the absence, (b) in the presence of 1 mM 4-amino-6-methyl-1,2,4-triazine-3-thion-5-one **3**, (c) 1 mM 4-amino-6-methyl-1,2,4-triazine-3-thion-5-one **3** in the absence of catechol **1a** at the glassy carbon electrode in aqueous phosphate buffer ($c = 0.2$ M, pH = 7.0), scan rate: 100 mV s^{-1}.

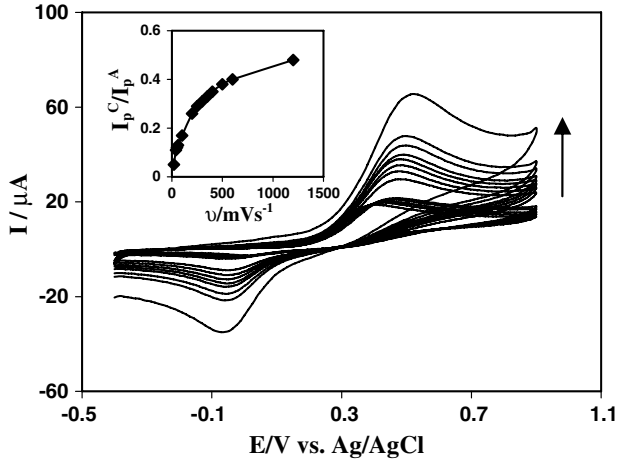


Figure 2. Typical voltammograms of 1 mM aqueous catechol **1a** in the presence of 4-amino-6-methyl-1,2,4-triazine-3-thion-5-one **3** at the glassy carbon electrode, in phosphate buffer ($c = 0.2$ M, pH = 7.0), scan rates: 20, 40, 50, 60, 100, 200, 250, 300, 350, 400, 500, 600, 1200 mV s^{-1}. Inset: variation of peak current ratio (I_p^C/I_p^A) versus scan rate.

peak of catechol **1a** in the absence of the nucleophile. In this Figure, curve c is the voltammogram of **3** under the same conditions but in the absence of catechol **1a**.

Furthermore, it can be seen that proportional to the increase of the potential sweep rate, the height of the cathodic C peak of **1a** increases (Fig. 2). A similar situation was observed when the ratio of **3** to **1a** was decreased. A plot of peak ratio (I_p^C/I_p^A) versus scan rate for a mixture of **1a** and **3** leads to an increase in the height of the cathodic peak C at higher scan rates (Fig. 2, inset). On the other hand, the current function for the anodic A peak ($I_p^A/v^{1/2}$) decreased with increasing scan rate. These observations allowed us to propose the following mechanism (Scheme 1).

Under the experimental conditions, the formation of *o*-quinone **2a** from the starting material **1a** is evident, and one could expect that **2a** would undergo two alternative reactions (pathways **I** and **II**, Scheme 1). Thus *o*-quinone **2a** might be attacked by the SH group of **3** (pathway **I**) or the NH_2 group (pathway **II**). According to our results, in the case of **1a**,**b**, the most likely pathway is **I**, while reaction of 3-methylcatechol **1c** proceeds via pathway **II**. Pathway **I** shows the *o*-quinone being attacked by the SH group of **3**, leading to intermediates **4a**,**b**. Oxidation of these compounds is easier than oxidation of the parent starting molecules **1a**,**b** by virtue of the presence of an electron-donating group (formation of **5a**,**b**). Finally products **6a**,**b** result from cyclization via attack by the NH_2 group.

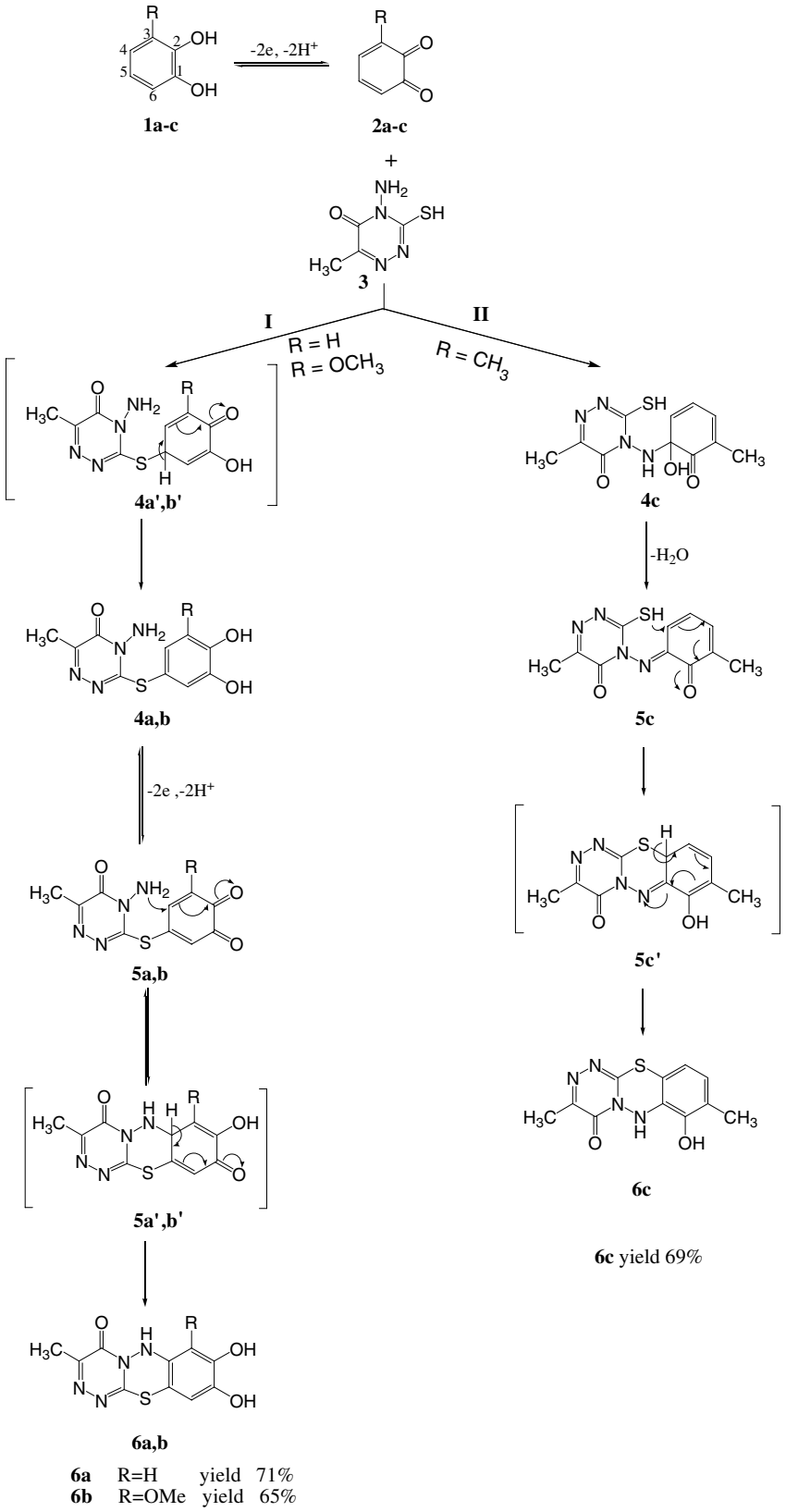
The electro-oxidation of 3-methoxycatechol **1b** in the presence of **3** as a nucleophile in phosphate buffer solution (pH 7.0, 0.2 M) proceeded in a similar way; however, the presence of a methoxy group at C-3 probably causes the Michael acceptor **2b** to be attacked by the SH group at C-4 and/or C-5, to yield two different products (Fig. 3). The experimental and calculated[12] ^{1}H NMR data for the product obtained suggested possible structures **6b** and **6b′** (Table 1). According to the ^{1}H NMR results, we suggest that *o*-quinone **2b** is probably attacked only at C-5 leading to the formation of product **6b**.

In order to study the effect the presence of a group at a reactive site on the catechol ring, the electrochemical oxidation of 3,4-dihydroxybenzoic acid **1d** was studied in the presence of **3**. From the electrochemical and spectroscopic data, we propose a comparable mechanism involving an electro-decarboxylation (Scheme 2).

The oxidation of **1c** in the presence of **3** in an aqueous solution proceeds via pathway **II** (Scheme 1). Here, the nucleophilic attack occurs in the form of a 1,2-addition reaction, which leads to **6c** as the final product. A suggested reason for this difference is probably due to stabilization of intermediate **4b** of 3-methoxycatechol **2b** by H-bonding between the methoxy group of **2b** and the amino group of nucleophile **3** (in the 1,4-addition reaction), which is not possible in 3-methylcatechol **3c**.

Reaction equipment was described in an earlier paper.[13] 4-Amino-6-methyl-1,2,4-triazine-3-thion-5-one was prepared by the procedure reported previously.[14]

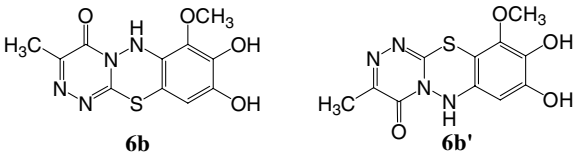
Electrosynthesis of **6a**–**c**: In a typical procedure, 80 ml of an aqueous solution containing 0.15 M sodium acetate (or phosphate buffer 0.20 M, pH 7.0) was pre-electrolyzed at 0.40 V versus saturated Ag/AgCl, in an individual cell. Subsequently, 1 mmol each of catechol **1a**–**d** and 4-amino-6-methyl-1,2,4-triazine-3-thion-5-one **3** was added to the cell. The electrolysis was terminated when the decay of the current became greater than 95%. The procedure was interrupted during the electrolysis and the carbon anode was washed in acetone in order to reactivate it. At the end of electrolysis, a few drops of acetic acid were added to the solution and the cell was placed in a refrigerator overnight. The



Scheme 1.

resulting precipitate was filtered off and washed with water. All products were characterized using IR, ^{1}H NMR and MS spectroscopy.

Data for **6a** ($C_{10}H_8N_4O_3S$). Mp >300 °C. IR (KBr): ν (cm^{-1}) 3550, 3378, 3097, 1676 (C=O), 1609 (C–O), 1483, 1378, 1275, 1078. ^{1}H NMR (300 MHz,



6b **6b'**

Figure 3. The two types of possible product from the electro-oxidation of 3-methoxycatechol **1b**.

Table 1. Experimental and calculated ^{1}H NMR data

Type	^{1}H NMR data[a]
Experimental[b]	6.44
Calculated for **6b**	5.96
Calculated for **6b′**	5.16

[a] Catechol ring proton.
[b] Experimental chemical shift of unpurified product.

DMSO-d_6): δ, 2.23 (s, 3H, CH_3), 5.97 (s, 1H, NH), 6.59–6.87 (m, 2H, Ar–H); MS (EI) *m/e* (relative intensity): 264 [$M^{+\cdot}$] (7), 111 (25), 110 (8), 105 (29), 97 (24), 81 (37), 71 (42), 69 (58), 57 (86), 41 (100).

Data for **6b** ($C_{11}H_{10}N_4O_4S$). Mp >300 °C. IR (KBr): *v* (cm^{-1}) 3425, 2925, 2854, 1725, 1633, 1462, 1376, 1287, 1228, 1106. ^{1}H NMR (300 MHz, DMSO-d_6): δ, 2.29 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 6.44 (s, 1H, Ar–H); MS (EI) *m/e* (relative intensity): 264 [M−OMe] (10), 127 (8), 78 (66), 63 (92), 44 (100).

Data for **6c** ($C_{11}H_{10}N_4O_2S$). Mp >300 °C. IR (KBr): *v* (cm^{-1}) 3418, 1622, 1470, 1283, 1075, 523. ^{1}H NMR (300 MHz, DMSO-d_6): δ (2.10 s, 1H, N–H), 2.18 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 6.50–6.70 (m, 2H, Ar–H); MS (EI) *m/e* (relative intensity): 260 [M−2]$^+$ (4), 258 (10), 256 (30), 224 (6), 194 (8), 192 (33), 160 (34), 128 (46), 97 (8), 64 (100), 57 (24).

Acknowledgement

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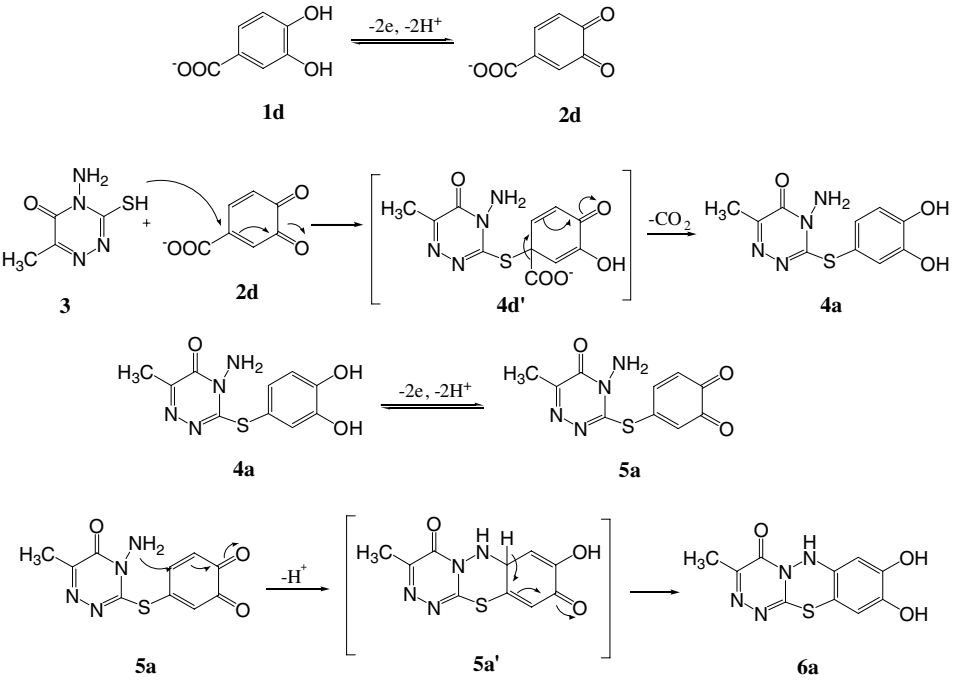

1d **2d** **3** **2d** **4d'** **4a** **4a** **5a** **5a** **5a'** **6a**

6a yield 71%

Scheme 2.

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