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SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 1713–1716

# An efficient electrochemical method for a unique synthesis of new derivatives of 7*H*-thiazolo[3,2-*b*]-1,2,4-triazin-7-one

L. Fotouhi,[a,*] D. Nematollahi,[b,*] M. M. Heravi[a] and E. Tammari[b]

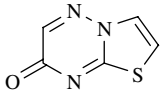
[a]*Department of Chemistry, Faculty of Sciences, Al-Zahra University, PO Box 1993891167, Tehran, Iran*
[b]*Department of Chemistry, Faculty of Sciences, Bu-Ali-Sina University, PO Box 65174, Hamadan, Iran*

Received 8 December 2005; revised 5 January 2006; accepted 12 January 2006

**Abstract**—The electrochemical oxidation of catechols (**1a**–**c**) has been studied in the presence of 6-methyl-1,2,4-triazine-3-thion-5-one **3** in aqueous sodium acetate, using cyclic voltammetry and controlled-potential coulometry. A plausible mechanism for the oxidation of catechols and their reaction with **3** is presented. All the catechol derivatives (**1a**–**c**) were converted into 7*H*-thiazolo[3,2-*b*]-1,2,4-triazin-7-one derivatives (**6a**–**c**) through a Michael-type addition reaction of **3** to anodically generated *o*-quinones. The electrochemical syntheses of **6a**–**c** were successfully performed in one pot in an undivided cell using an environmentally friendly method with high atomic economy.


## 1. Introduction

Bartlett et al. described 7*H*-thiazolo[3,2-*b*]-1,2,4-triazin-7-ones as antiinflammatory agents with immunomodulating properties.[1] They reported that these compounds are effective not only in preventing, but also curing established arthritic disorders in rats. They also reported that these compounds effectively inhibited the carrageenan-induced paw oedema, attenuated the active Arthus reaction, and demonstrated antierythema as well as antipyretic activity. Part of the antiinflammatory effects of these compounds is most probably related to their antioxidative activity, as well as to the inhibition of lipoxygenase metabolites.[1]



7*H*-thiazolo[3,2-*b*]-1,2,4-triazin-7-one

With due attention to our experiences in electrochemical oxidation of catechols in the presence of nucleophiles,[2] we envisaged that attachment of a catechol ring to a thiazolo-triazine might cause an enhancement of its antioxidative activity. This idea prompted us to investigate the electrochemical oxidation of catechol and some of its derivatives in the presence of 6-methyl-1,2,4-triazine-3-thion-5-one as a nucleophile and thus we discovered an easy and one-pot electrochemical method for the synthesis of some new 7*H*-thiazolo[3,2-*b*]-1,2,4-triazin-7-one derivatives (**6a**–**c**) in high yield and purity, in an undivided cell, using an environmentally friendly method with high atom economy.

## 2. Results and discussion

The cyclic voltammogram of 1 mM catechol **1a** in phosphate buffer ($c = 0.2$ M, pH = 7.0) is shown in Figure 1, curve a. As can be seen, at the scan rate of 0.10 V $s^{-1}$, one anodic peak ($A_1$) was observed at 0.22 V versus SCE. On the reverse scan, the counterpart of this peak ($C_1$) appeared at an $E_p$ value of 0.15 V, which corresponds to the transformation of catechol **1a** into *o*-benzoquinone **2a** and vice versa within a two-electron process (Scheme 1, Eq. 1). A peak current ratio ($I_p^{C_1}/I_p^{A_1}$) of nearly unity, particularly during the repetitive recycling of potential, can be considered as a criterion for the stability of *o*-quinone produced at the

*Keywords*: Electrochemical oxidation; Michael-type addition; Quinone; 6-Methyl-1,2,4-triazine-3-thion-5-one; 7*H*-Thiazolo[3,2-*b*]-1,2,4-triazin-7-one.
* Corresponding authors. Tel.: +98 21 88044051; fax: +98 21 88047861 (L.F.); tel.: +98 811 8271541; fax: +98 811 8272404 (D.N.); e-mail addresses: lfotouhi@alzahra.ac.ir; nemat@basu.ac.ir

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doi:10.1016/j.tetlet.2006.01.053

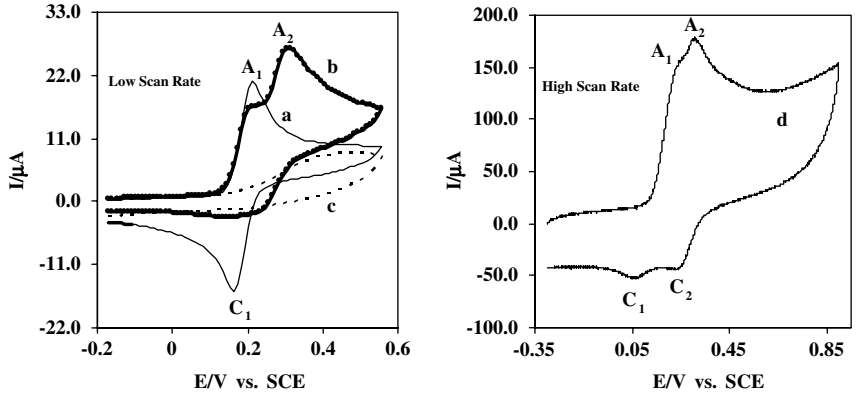
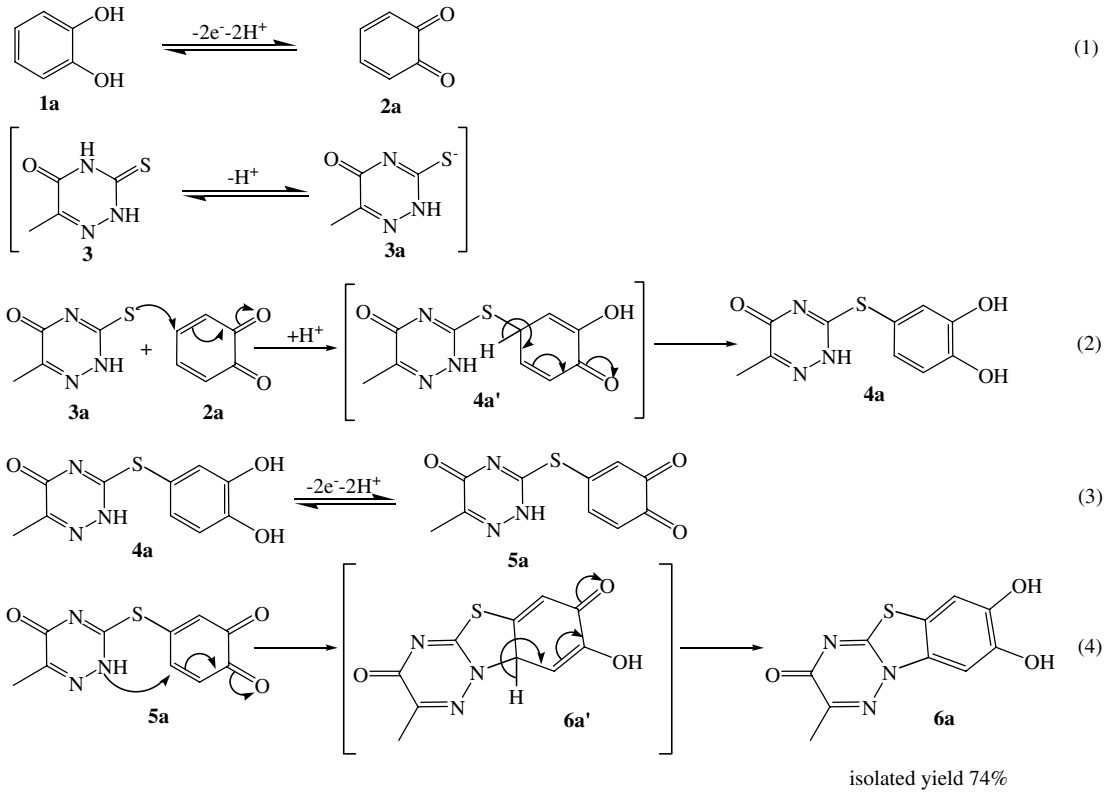


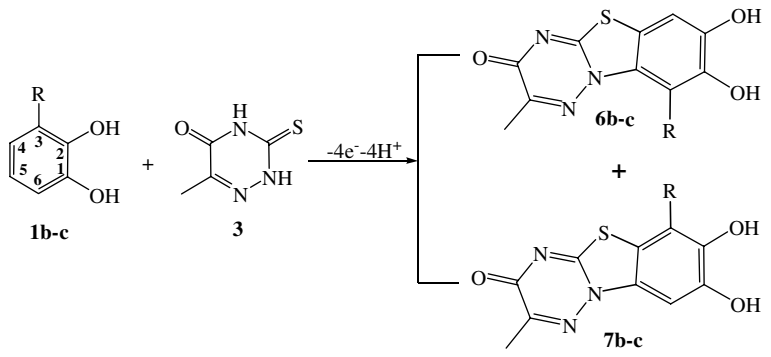

**Figure 1.** Cyclic voltammograms of 1 mM catechol (a) in the absence, (b) in the presence of 1 mM of **3** and (c) 1 mM of **3** in the absence of catechol, scan rate 0.10 V $s^{-1}$, curve (d) as (b) in scan rate 2.0 V $s^{-1}$: at a glassy carbon electrode, in phosphate buffer ($c = 0.2$ M, pH = 7.0).




(1) (2) (3) (4)

**Scheme 1.**

surface of the electrode under the experimental conditions. This implies that hydroxylation[3] or dimerization[4] reactions did not occur on the time scale of cyclic voltammetry. In Figure 1, curve b shows the cyclic voltammogram of catechol **1a** in the presence of 6-methyl-1,2,4-triazine-3-thion-5-one **3** as a nucleophile. The voltammogram exhibits two anodic peaks ($A_1$ and $A_2$) and the cathodic counterpart of the anodic peaks is virtually absent. The anodic and cathodic peaks $A_2$ and $C_2$ correspond to the oxidation of intermediate **4a** to *o*-quinone **5a** and vice versa. In Figure 1, curve c is the cyclic voltammogram of 6-methyl-1,2,4-triazine-3-thion-5-one **3**. Furthermore, it is seen that proportional to the augmentation of potential scan rate the anodic peaks current ratio ($I_p^{A_1}/I_p^{A_2}$) increases and cathodic counterparts of them ($C_1$ and $C_2$) appears (Fig. 1, curve d). The peak current ratio of these peaks ($I_p^{C_1}/I_p^{C_2}$) increases in proportion to increasing of potential scan rate. Also, a plot of peak current ratio ($I_p^{A_1}/I_p^{C_1}$) versus $\log v$, for a mixture of catechol and 6-methyl-1,2,4-triazine-3-thion-5-one **3** confirmed the reactivity of *o*-benzoquinone **2a** towards **3**, appearing as an increase in the height of the cathodic peak $C_1$ at higher scan rates. A similar situation was observed when the concentration of **3** was decreased relative to **1a**. On the other hand, the current function for the $A_1$ peak, ($I_p^{A_1}/v^{1/2}$), decreased on increasing the scan rate and we suggest that such behavior is indicative of an ECEC mechanism.[5]




**Scheme 2.**

Controlled-potential coulometry was performed in an aqueous solution containing 1 mmol of **1a** and 1 mmol of **3** at a potential 0.5 V versus SCE. The progress of the electrolysis was monitored by cyclic voltammetry. It is shown that proportional to the advancement of coulometry, anodic peaks $A_1$ and $A_2$ decreased. All anodic and cathodic peaks disappeared when the charge consumption became about $4e^-$ per molecule of **1a**. These observations allow us to propose the pathway represented in Scheme 1. According to our results, it seems that the intermolecular Michael addition of **3a** to *o*-quinone **2a** is faster than other secondary reactions, leading to intermediate **4a**. The reaction product **6a** is obtained after oxidation of **4a** (Scheme 1, Eq. 3) followed by a rapid intramolecular Michael-type addition (Scheme 1, Eq. 4). The final product **6a** could also be oxidized in principle, however, over oxidation of **6a** was avoided during the preparative reaction because of the insolubility of the product in reaction medium.

The electrooxidation of 3-methylcatechol **1b** and 3-methoxycatechol **1c** in the presence of **3** proceeded in a similar way to that of **1a**. The presence of a methyl or methoxy group at the C-3 position of **1b** and **1c** could mean that the corresponding *o*-benzoquinones could be attacked by the thiolate anion at either or both C-4 and C-5 to yield two isomeric products. In the case of **1b**, products **6b** and **7b** were formed in a ratio of 2:1 (Scheme 2), as assessed by the ratio of integrals for $^1$H NMR signals at $\delta$ 7.20 for **6b** and 7.13 for **7b**.[6] However, in the case of **1c**, according to $^1$H NMR analysis, only one product was produced. A comparison of experimental and calculated[6] $^1$H NMR shifts for the aromatic proton in the product was obtained, and the two possible structures (**6c** and **7c**, Scheme 2), showed that only **6c** was formed.

## 3. Experimental

Reaction equipment was described in an earlier paper.[2c] 6-Methyl-1,2,4-triazine-3-thion-5-one was prepared by the procedure reported previously.[7]

### 3.1. Electroorganic synthesis of 6a–c

In a typical procedure, 80 ml of an aqueous solution containing 0.15 M sodium acetate (or phosphate buffer, $c = 0.2$ M, pH = 7.0) was pre-electrolyzed at 0.50 V versus SCE, in an undivided cell, subsequently, 1 mmol each of catechol (**1a**–**c**) and 6-methyl-1,2,4-triazine-3-thion-5-one **3** (1 mmol) were added to the cell. The electrolysis was terminated when the decay of the current became more than 95%. The process was interrupted during the electrolysis and the carbon anode was washed in acetone in order to re-active 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 resulting precipitate was filtered and washed with water. All products were characterized using IR, $^1$H NMR, $^{13}$C NMR and MS.

Data for **6a** ($C_{10}H_7N_3O_3S$). Mp 345–346 °C. IR (KBr): $\nu$ ($cm^{-1}$) = 3383, 3070, 2961, 1620, 1477, 1415, 1336, 1274. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 2.29$ (s, 3H), 7.20 (s, 1H), 7.33 (s, 1H), 9.65 (br, 1H), 9.90 (br, 1H); $^{13}$C NMR, (125.8 MHz DMSO-$d_6$): $\delta = 17.0$, 99.4, 109.3, 110.5, 128.4, 145.5, 146.7, 152.4, 159.6, 163.6; MS (EI) $m/z$ (relative intensity): 249 $[M]^{+\cdot}$ (46), 208 (100), 180 (47), 153 (12), 85 (37), 69 (36), 42 (19).

Data for mixture of **6b** and **7b** ($C_{11}H_9N_3O_3S$). IR (KBr): $\nu$ ($cm^{-1}$) = 3524, 3043, 1623, 1491, 1375, 1329, 1289. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 2.24$ (s, 3H), 2.29 (s, 3H), 2.31 (s, 3H), 2.60 (s, 3H), 7.13 (s, 1H), 7.20 (s, 1H), 9.5–10.0 (br, 2H); MS (EI) $m/z$ (relative intensity): 263 $[M]^{+\cdot}$ (38), 222 (100), 194 (21), 176 (17), 138 (10), 111 (19), 85 (25), 69 (46), 41 (54).

Data for **6c** ($C_{11}H_9N_3O_4S$). Mp 254–255 °C. IR (KBr): $\nu$ ($cm^{-1}$) = 3165, 1626, 1499, 1403, 1375, 1343, 1304, 1245. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 2.30$ (s, 3H), 3.81 (s, 3H), 7.14 (s, 1H), 9.30 (br, 1H), 9.86 (br, 1H); MS (EI) $m/z$ (relative intensity): 279 $[M]^{+\cdot}$ (21), 238 (31), 220 (56), 195 (31), 143 (36), 86 (48), 69 (54), 56 (75), 41 (100).

## Acknowledgements

The authors gratefully acknowledge the partial financial support from the research council of Alzahra University.

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