Electrochemical Oxidation of Catechols (= Benzene-1,2-diols) in the Presence of Benzoylacetonitrile: Synthesis of New Derivatives of 5,6-Dihydroxybenzofuran

by **Davood Nematollahi***, **Ali Reza Atlasi-Pak**, and **Roya Esmaili**

Faculty of Chemistry, Bu-Ali Sina University, Hamedan, Zip Code 65178-38683, Iran
(phone: +98-811-8380647; fax: +98-811-8380709; e-mail: nemat@basu.ac.ir)

The electrochemical oxidation of catechol (= benzene-1,2-diol; **1a**) and some of its derivatives in H_2O/MeCN 1:1 containing benzoylacetonitrile (= β-oxobenzenepropanenitrile; **3**) as a nucleophile was studied by cyclic voltammetry and controlled-potential coulometry. The voltammetric data showed that electrochemically generated *o*-benzoquinones (= cyclohexa-3,5-diene-1,2-diones) from catechol (**1a**) and 3-methylcatechol (**1b**) participate in a *Michael*-addition reaction with **3** to form the corresponding 5,6-dihydroxybenzofuran-3-carbonitrile **8** (*Scheme 1*). In this work, we report an efficient one-pot method with high atom economy for the synthesis of new substituted 5,6-dihydroxybenzofuran-3-carbonitriles in an undivided cell under ambient conditions.

Introduction. – Catechol (= benzene-1,2-diol; **1a**) and its mono-substituted derivatives are active in part against *Pseudomonas*. Also, many flavonoids and catechol derivatives turned out to be antimicrobial agents [1]. On the other hand, many compounds having a dihydroxybenzofuran moiety as the core structure show interesting pharmacological activities [2–5]. For example, a series of (2*Z*)-2-benzylidene-6,7-dihydroxybenzofuran-3(2*H*)-ones (*cf. Fig. 1*) were identified as potent inhibitors of bacterial chorismate synthase [2].

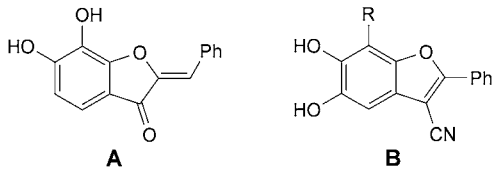


Fig. 1. *Synthase inhibitor (2*Z*)-2-benzylidene-6,7-dihydroxybenzofuran-3(2*H*)-one* (**A**) *and synthesized 5,6-dihydroxybenzofuran-3-carbonitrile derivatives* **B**

The importance of dihydroxybenzofuran compounds has prompted us to synthesize a number of these compounds by electrochemical oxidation of catechols in the presence of some nucleophiles derived from CH-acids such as acetylacetone [6], dimedone [7], 3-hydroxy-1*H*-phenalen-1-one [8], and cyanoacetone [9]. In the present work, in order to extend the above-mentioned strategy, we describe the preparation of some other new dihydroxybenzofurans using the electrochemical oxidation of catechol (**1a**) and 3-methylcatechol (**1b**) in the presence of benzoylacetonitrile (= β-oxobenzenepropanenitrile; **3**). The present work led to the development of a facile and

reagentless method with high atom economy for the synthesis of some new 5,6-dihydroxybenzofuran derivatives under ambient conditions in an undivided cell equipped with a carbon electrode.

Results and Discussion. – *Electrochemical Oxidation of Catechol* (**1a**; R = H) *and 3-Methylcatechol* (**1b**; R = Me) *in the Presence of Benzoylacetonitrile* (**3**). The cyclic voltammogram of a 1.0 mM solution of catechol (**1a**) in H_2O/MeCN 1:1 containing 0.20M phosphate buffer (pH 7.0) showed one anodic (A_1) and corresponding cathodic peak (C_1) (*Fig. 2*), which correspond to the transformation of catechol (**1a**) to *o*-benzoquinone (=cyclohexa-3,5-diene-1,2-dione; **2a**) and *vice versa* within a quasi-reversible two-electron process [10] (*Scheme 1*, *Eqn. 1*). A peak-current ratio (I_{pC_1}/I_{pA_1}) of near unity can be considered as a criterion for the stability of *o*-benzoquinone (**2a**) produced at the surface of the electrode under the experimental conditions. In other words, any other reactions such as hydroxylation [11][12], dimerization [13–15], or oxidative ring cleavage [16][17] of electrochemically generated **2a** were too slow to be observed at the time scale of cyclic voltammetry.

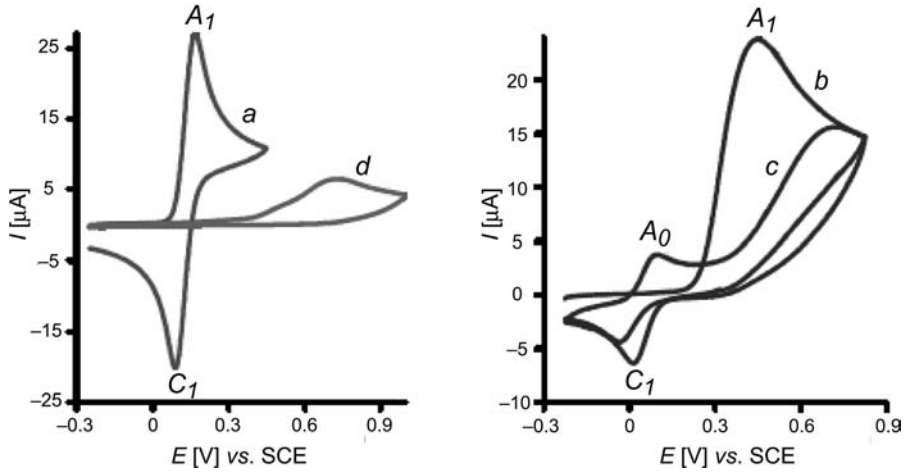
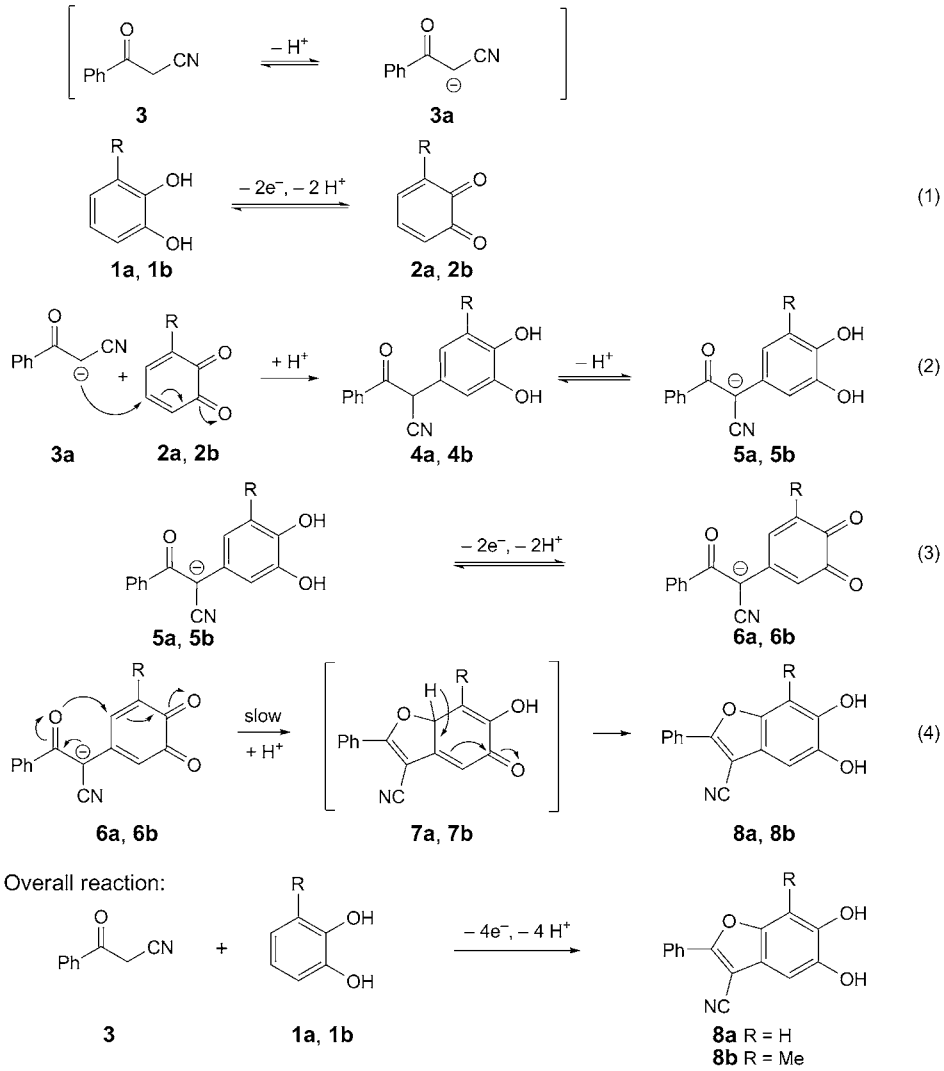


Fig. 2. *Cyclic voltammograms of 1.0 mM catechol* (**1a**)*:* a) *in the absence of benzoylacetonitrile* (**3**), b) *and* c) *first and second scan in the presence of 1.0 mM* **3**, *and* d) *in the presence of 1.0 mM* **3** *but in the absence of* **1a**, *all at a glassy carbon electrode in H_2O/MeCN 1:1 containing 0.2M phosphate buffer* (pH 7.0). Scan rate 100 mV s^{-1}. *T* 25 ± 1°.

The oxidation of **1a** in the presence of benzoylacetonitrile (**3**) as a nucleophile was studied in some detail. The cyclic voltammogram obtained for a 1.0 mM solution of **1a** in the presence of 1.0 mM **3** (*Fig. 2*, *Curve b*) exhibited a remarkable decrease in the current of peak C_1 due to the chemical reaction of **2a** with **3** [10]. The second-cycle voltammogram of **1a** in the presence of **3** (*Curve c*) showed that concomitantly to the shift of the peak A_1 in a positive direction and peak C_1 in negative direction, a new anodic peak (A_0) appeared at a less positive potential (*Fig. 2*, *Curve c*). This new peak suggested the presence of a relatively stable intermediate in the electrochemical

Scheme 1. *Electrochemical Oxidation of Catechol* (**1a**; R = H) *and 3-Methylcatechol* (**1b**; R = Me) *in the Presence of Benzoylacetonitrile* (**3**)



oxidation of **1a** in the presence of **3**. The shift of the peaks A_1 and C_1 in the presence of **3** was due to the formation of a thin film of product at the surface of the electrode, inhibiting to a certain extent the performance of the electrode process. The voltammogram of **3** (*Fig. 2*, *Curve d*) is established a totally irreversible electron-transfer process. Additionally, proportional to the increase of the potential scan rate, the peak-current ratio I_{pC_1}/I_{pA_1} increased (*Fig. 3*). A plot of the peak current ratio I_{pC_1}/I_{pA_1} *vs.* the scan rate for a mixture of **1a** and **3** confirmed the reactivity of *o*-benzoquinone **2a** towards **3**.

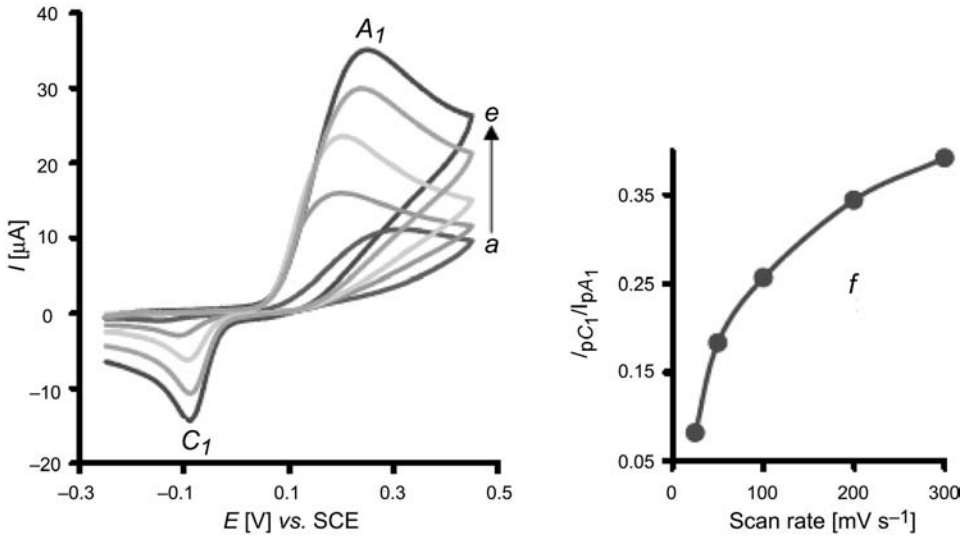


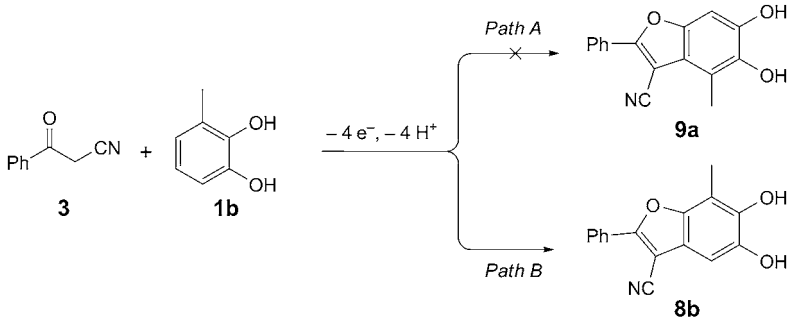
Fig. 3. a)–e) *Cyclic voltammograms of 1.0 mM catechol* (**1a**) *in the presence of 1.0 mM benzoylacetonitrile* (**3**) *at a glassy carbon electrode in H_2O/MeCN* 1:1 *containing 0.2M phosphate buffer* (pH 7.0)*, with the scan rates 25, 50, 100, 200, and 300 mV s^{-1} from* a) *to* e)*, resp.* f) *Variation of peak current ratio* (I_{pC_1}/I_{pA_1}) vs. *scan rate. T* 25 ± 1°.

Controlled-potential coulometry was employed for determining the number of transferred electrons (n) during the electrode process. In this work, controlled-potential coulometry of **1a** (0.15 mmol) in the presence of **3** (0.15 mmol) at 0.30 V *vs.* SCE in H_2O/MeCN 1:1 verified the transfer of four electrons per molecule of **1a**.

Diagnostic criteria of cyclic voltammetry, including decreasing of peak C_1 during the reverse scan in cyclic voltammetry of **1a** in the presence of **3** (*Fig. 2*) and reappearance of it with increasing scan rate (*Fig. 3*) on the one hand, and controlled-potential coulometry (consumption of *ca.* 4 e^-) on the other hand, accompanied by the IR and ^{1}H- and ^{13}C-NMR data (see *Exper. Part*) and a molecular mass of 251 of the final product, indicated that the reaction mechanism of electrochemical oxidation of **1a** and **1b** in the presence of **3** is of the type *ECEC* (electron transfer, chemical reaction, electron transfer, and then chemical reaction). According to our data, the intermolecular *Michael*-addition reaction of the anion **3a** of benzoylacetonitrile (enolate) to *o*-benzoquinone (**2a**) leads *via* **4a** to the intermediate **5a**. In the next step, **5a**, *via* another two-electron oxidation process is converted into *o*-benzoquinone **6a**. In the final step, an intramolecular *Michael*-addition reaction and aromatization converts **6a** *via* **7a** into **8a** as the final product. Consequently, the anodic peak A_1 pertained to the oxidation of **1a** to **2a**, peak C_1 corresponded to the reduction of **2a**, and the new anodic peak A_0 was related to the oxidation of **5a** to *o*-benzoquinone **6a**.

The electrochemical oxidation of 3-methlycatechol (**1b**) in the presence of benzoylacetonitrile (**3**) in phosphate buffer solution (pH 7.0, 0.2M) proceeded in a similar way to that of **1a**. But, the presence of the Me group at C(3) of **1b** may cause the *Michael* acceptor **2b** to be attacked by **3** at C(4) (*Path A*) and/or C(5) (Path B) to yield

Scheme 2. *Possible Products of the Electrochemical Oxidation of 3-Methylcatechol* (**1b**) *in the Presence of Benzoylacetonitrile* (**3**)



two types of products (*Scheme 2*). The experimental and calculated ^{13}C-NMR chemical shift [18] of the Me group for the obtained product **8b** and the second possible structure **9b** in the *Table* suggested that *o*-benzoquinone **2b** was attacked at C(5) (*Path B*) by **3** leading to the formation of the product **8b**.

Table 1. *Experimental and Calculated ^{13}C-NMR Data for the Me Group of the Product from* **1b** *and* **3** (cf. *Scheme 2*)

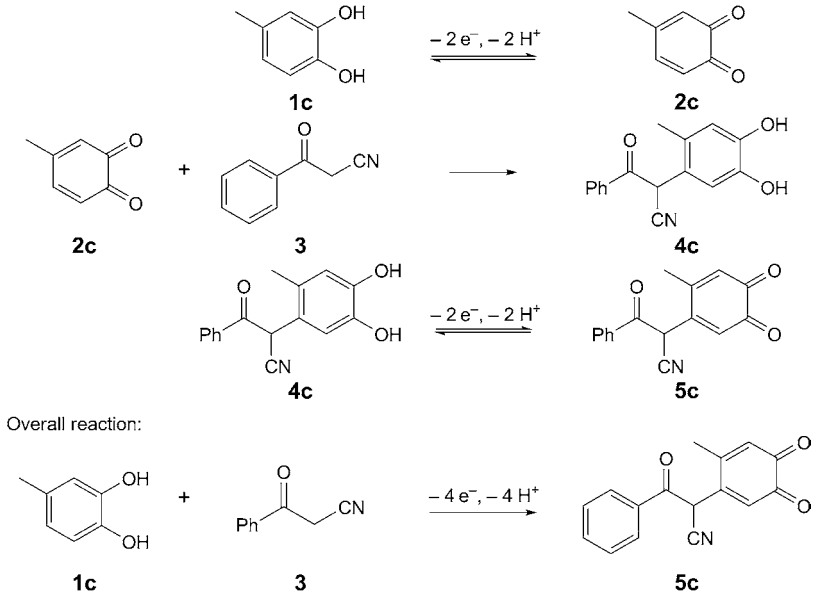
	δ(C) of Me
Experimental[a])	9.7
Calculated for **8b**	8.6
Calculated for **9b**	12.1

[a]) Experimental data obtained for the filtered product without any purification.

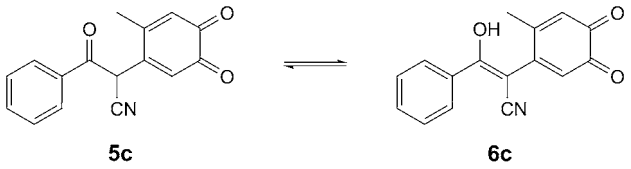
Electrochemical Oxidation of 4-Methylcatechol (**1c**) *in the Presence of Benzoylacetonitrile* (**3**). The voltammetric responses and coulometry results of the electrochemical oxidation of 4-methylcatechol (**1c**) in the presence of **3** showed a similar behavior to that of **1a**. But contrary to these data, the ^{1}H-NMR spectrum of the isolated product exhibited a different pattern from that observed for **8a** and **8b**: a single peak appeared at δ(H) 4.77 which was assigned to the H-atom of the C(O)CHCN moiety of **5c** (*Scheme 3*). These observations allowed us to propose the pathway illustrated in *Scheme 3* for the electrochemical oxidation of **1c** in the presence of **3**.

The presence of substituents at the catechol **1** is important for the type of the final product of the reaction of the electrochemically generated *o*-benzoquinone **2** with nucleophiles. The presence of the Me group at one of the reaction sites of catechol **1** prevented the oxidative cyclization of intermediate **4c** into a benzofuran derivative (see *Scheme 1*, *Eqn. 4*) and caused the formation of the substituted *o*-benzoquinone **5c** as the final product. The ^{13}C-NMR spectrum of **5c**, surprisingly showed two peaks at δ(C) 19.6 and 22.3 (instead of one peak) and an unexpected peak at δ(C) 87.7, which were not consistent with the structure **5c**. These results established that **5c** was in equilibrium with its tautomeric form **6c** (*Scheme 4*).

Scheme 3. *Electrochemical Oxidation of 4-Methylcatechol* (**1c**) *in the Presence of Benzoylacetonitrile* (**3**)



Scheme 4. *Tautomerization Equilibrium* **5c** ⇌ **6c**



Conclusions. – The mechanism of the reaction of electrochemically generated *o*-benzoquinones **2** with benzoylacetonitrile (**3**) was investigated, and a method of general applicability for their high-yield transformation under mild experimental conditions was provided. We observed an interesting diversity in the mechanism of the electrochemical oxidation of catechols **1a**–**1c** in the presence of **3**. In the case of 3-methylcatechol (**1b**) (and of catechol (**1a**)), the final product, a dihydroxybenzofuran, was obtained after intermolecular and intramolecular *Michael*-addition reactions, whereas in the case of 4-methylcatechol (**1c**), the final product was the *o*-benzoquinone **5c** that was obtained after the intermolecular *Michael*-addition reaction. The different results of the electrochemical oxidation of 3-methylcatechol (**1b**) and 4-methylcatechol (**1c**) in the presence of **3** was attributed to the blocking of one of the reaction sites of the catechol by a Me group in 4-methylcatechol (**1c**). In conclusion, we can state that the addition of benzoylacetonitrile to catechol derivatives **1** is an interesting reaction that provides direct access to new 5,6-dihydroxybenzofuran and *o*-benzoquinone derivatives.

We acknowledge the Bu-Ali Sina University Research Council and the *Center of Excellence in Development of Chemical Methods* (CEDCM) for their support of this work.

Experimental Part

General. Catechols and benzoylacetonitrile were from *Aldrich* and *Fluka*, MeCN, H_3PO_4 (phosphoric acid) and phosphate salts were of pro-analysis grade from *E. Merck*. These chemicals were used without further purification. Cyclic voltammetry: *Sama-500* instrument. Controlled-potential coulometry and prep. electrolysis: *Behpajoh-BHP*-2050 potentiostat/galvanostat. The working electrode used in the voltammetry experiments was a glassy carbon disc (1.8 mm^2 area), and Pt-wire was used as a counter electrode. The working electrode used in the controlled-potential coulometry and macroscale electrolysis was an assembly of four graphite rods, and a large stainless-steel gauze constituted the counter electrode. The working electrode potentials were measured *vs.* SCE (all electrodes from *Azar Electrode Co.*, Iran).

Electrochemical Synthesis of **8a**, **8b**, *and* **5c**: *General Procedure*. A soln. (*ca.* 80 ml) of 0.2M phosphate buffer (pH 7.0) in H_2O/MeCN 1:1 containing 1.0 mmol of a catechol **1** and 1.0 mmol of benzoylacetonitrile (**3**) was electrolyzed at a potential of 0.40 V in the case of **1a** and 0.30 V in the cases of **1b** and **1c**, in an undivided cell equipped with a carbon anode and a large stainless-steel gauze as cathode, at 25°. The electrolysis was terminated when the current decayed to 5% of its original value. The process was interrupted during the electrolysis, and the carbon anode was washed in acetone to reactivate it. At the end of the electrolysis, the cell was placed in a refrigerator overnight. The solid precipitated was collected by filtration and washed several times with H_2O. The product was purified by column chromatography. The yields of isolated **8a**, **8b**, and **5c** were 78, 73, and 82%, resp.

5,6-Dihydroxy-2-phenylbenzofuran-3-carbonitrile (**8a**): Black solid. M.p. 213–215°. IR (KBr): 3477 (OH), 2231 (CN), 1622, 1466, 1320, 1217, 1144, 838, 763, 682, 626. ^{1}H-NMR ((D_6)DMSO, 500 MHz): 6.97 (*s*, 1 H); 7.13 (*s*, 1 H); 7.54 (*m*, 3 H); 8.0 (*d*, *J* = 8.1, 2 H); 9.54 (br., OH, *ca.* 2 H). ^{13}C-NMR ((D_6)DMSO, 125 MHz): 88.0; 99.4; 103.9; 115.3; 118.6; 126.2; 128.6; 130.3; 131.6; 145.8; 147.6; 148.3; 160.0. EI-MS: 251 (100, M^+), 177 (15), 105 (40), 77 (30), 51 (15).

5,6-Dihydroxy-7-methyl-2-phenylbenzofuran-3-carbonitrile (**8b**): Dark brown solid. M.p. 223–225°. IR (KBr): 3400 (OH), 3300 (OH), 2227 (CN), 1627, 1452, 1301, 1234, 1101, 1008, 769, 690. ^{1}H-NMR ((D_6)DMSO, 500 MHz): 2.35 (*s*, 3 H); 6.85 (*s*, 1 H); 7.54 (*m*, 3 H); 8.03 (*d*, *J* = 7.3, 2 H); 8.92 (br., OH); 9.81 (br., OH). ^{13}C-NMR ((D_6)DMSO, 125 MHz): 9.7; 88.1; 100.8; 109.2; 115.4; 117.8; 126.2; 128.8; 130.3; 131.4; 145.2; 145.3; 147.9; 159.8. EI-MS: 265 (100, $M^{+\cdot}$), 190 (15), 105 (30), 77 (25).

2-(6-Methyl-3,4-dioxocyclohexa-1,5-dienyl)-3-oxo-3-phenylpropanenitrile (= *α-(6-Methyl-3,4-dioxocyclohexa-1,5-dien-1-yl)-β-oxobenzenepropanenitrile*; **5c**) *and (2*E*)-3-Hydroxy-2-(6-methyl-3,4-dioxocyclohexa-1,5-dienyl)-3-phenylprop-2-enenitrile* (= *(α*E*)-α-(Hydroxyphenylmethylene)-6-methyl-3,4-dioxocyclohexa-1,5-diene-1-acetonitrile*; **6c**): Brown solid. M.p. 105–107°. IR (KBr): 3442 (OH), 2922 (CH), 2229 (CN), 1631, 1469, 1333, 1219, 1150, 1025, 893, 841, 810, 765, 681. ^{1}H-NMR ((D_6)DMSO, 500 MHz): 1.70 (*s*, 3 H); 4.77 (*s*, 1 H); 6,78 (*s*, 1 H); 6.97 (*s*, 1 H); 7.35–7.53 (*m*, 4 H); 8.00 (*d*, *J* = 5.3, 1 H). ^{13}C-NMR ((D_6)DMSO, 125 MHz): 19.5; 22.5; 51.5; 87.7; 109.5; 114.4; 118.3; 129.1; 129.2; 129.3; 129.7; 130.1; 130.4; 130.9; 136.4; 143.9; 146.1; 167.5; 182.1; 190.4. EI-MS: 256 (3, M^+), 236 (15), 237 (6), 209 (4), 108 (4), 105 (87), 77 (100).

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Received January 22, 2012