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Short Communication

Electrochemical Initiation of Nucleophilic Substitution of Hydroquinone with 4, 6-Dimethylpyrimidine-2-thiol

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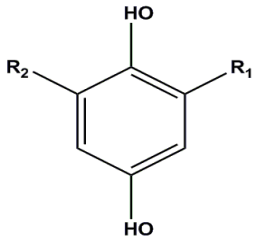
The electrochemical synthesis of (2,6-bis(4,6-dimethylpyrimidin-2-ylthio)benzene-1,4-diol(**6a**),3,5-bis (4,6-dimethylpyrimidin-2-ylthio)-2-methylbenzene-1,4-diol (**6b**), and 3,5-bis (4,6-dimethylpyrimidin-2-ylthio)-2-methoxybenzene-1,4-diol (**6c**) by anodic oxidation of hydroquinone (**1a**), 2-methyl hydroquinone (**1b**) and2-methoxy hydroquinone (**1c**)in the presence of 4,6-dimethylepyrimidne-2-thiol (**3**)as nucleophile in aqueous media are described. The results showed that quinones derived from hydroquinone participate in Michael addition reaction with (**3**) and converted to 2-((4, 6-dimethylpyrimidin-2-yl) thio) benzene-1, 4-diol (**4a-c**). All the three compounds (**6a**), (**6b**), and (**6c**) were characterized by ^{1}HNMR, ^{13}CNMR, FTIR and ESI-MS spectrometry.

Keywords: Hydroquinone, electro-oxidation, 4, 6-dimethylpyrimidine-2-thiol, Michael addition reaction

1. INTRODUCTION

Hydroquinone could be reversibly transformed to *p*-quinones by electrochemical oxidation. Quinones are quite reactive and react with majority of nucleophiles, such as methanol [1], 1, 3-diethyl-2-thiobarbtoiric acid [2], benzenesulfinic acids [3], acetyl acetone [4], 4-hydroxycoumarin [5], 4-hydroxy-6-methyl-2- pyrone [6], 3, 4-dihydroxybenzaldehyde [7], 4-methyl catechol [8], *β*-diketone and *β*-diester [9]. The synthesis of pyrimidine [10] and benzofuranes [11] is interesting for pharmacological use. Due to pharmacological uses of pyrimidine, the syntheses and pharmacological properties of pyrimidine derivatives have been investigated [12]. Here we synthesized some new

pyrimidine and its derivatives through electrochemical methods. Hydroquinone and their derivatives were oxidized by electrochemical method in the presence of 4, 6- dimethylepyrimidne-2-thiol, and some new pyrimidine derivatives were obtained in high purity and good yield as compare to catechols [13], the effects of electrolysis conditions on the yields were discussed.



R1=R2=H Hydroquinone (1a)
R1=CH3,R2= H 2- methylhydroquinone (1b)
R1=OCH3,R2=H 2-methoxyhydroquinone (1c)

2. EXPERIMENTAL

Cyclic voltammetry (CV), controlled-potential coulometry and preparative electrolysis were performed using an electrochemical workstation (CHI 660). A glassy carbon (GC) electrode (1.8mm in diameter) was used as the working electrode (WE), a platinum electrode as the counter electrode (CE) and saturated calomel electrode (SCE) were used as the standard electrode. The WE was polished with alumina powder before the experiment.

2.1. Chemicals and reagents

The entire chemicals (hydroquinone and 4, 6- dimethylpyrimidine-2-thiol) were purchased from Aldrich, CH_3COONa (Sodium acetate) of pro-analysis from E.Merk. All these chemicals were used without further purification.

2.2. Experimental procedures

2.3 Electro-organic synthesis of pyrimidine derivatives (6a-6c)

In the typical procedure, 0.15M of acetate buffer solution (CH_3COONa-CH_3COOH, pH=7.4) was pre-electrolyzed in an undivided electrolytic cell in range of -0.4~1.5V*vs* SCE at 50mV s^{-1}. Subsequently 1mM hydroquinone and 2mM of 4, 6-dimethylpyrimidine-2-thiol were added in the electrolytic cell. The electrolysis process was terminated when the decay of current became more than 95%. The electrolytic cell was interrupted during electrolysis several times and GC electrode washed in acetone in order to make it reactive. Few drops of acetic acid (CH_3COOH) were added to the electrolytic cell at the end of electrolysis. The cell was placed in refrigerator for 24h and precipitates

(ppt) were filtered by filtration. The ppt was washed with water several times and the products were purified with column chromatography over silica gel (70-230 mesh) eluting with the mixed solvent of *n*-hexane-ethyl acetate (7:3). The compounds were characterized by IR, ^{1}HNMR, ^{13}CNMRand MS.

3. RESULTS AND DISCUSSION

Cyclic voltammetry of 1mM hydroquinone (**1a**) in acetate buffer solution was studied, as shown in Fig.1b. There is a pair of anodic peak (centered at 0.1V) and cathodic peak (centered at 0.0V) corresponding to transformation of **1a** between *p*-quinones (**2a**) in a quasi-reversible two-electron process. The ratio of peak current Ip^{C1}/Ip^{A1} kept nearly unity in about 20 times circular scanning, which can be considered as an evidence of the stability of *p*-quinone produced under the experimental condition and no dimerizaation[14] or hydroxylation[15] occurred. The CV curve of GC electrode with **1a** and **3** in the electrolyte was shown in Fig.1c. It is shown that the anodic peak shifted about to 0.25V and the intensity of cathodic peak around 0.01V decreased dramatically, which means **1a** was oxidized to **2a**, but only a little **2a** was reduced to **1a**. That is to say, **2a** reacted with **3** once it was generated. The extra anodic peak at about 1.0 V could be assigned to the electro- oxidation of that intermediate (such as **5a**). Figure 2 shows the multi-cycle CV curves of GC electrode with **1a** and **3** in the electrolyte. During the following circular scanning the intensity of anodic peak around 0.25V was decreased observably. It is inferring that a thin film of product formed at the surface of the electrode, which inhibit to a certain extent the performance of the electrode process [16-17].

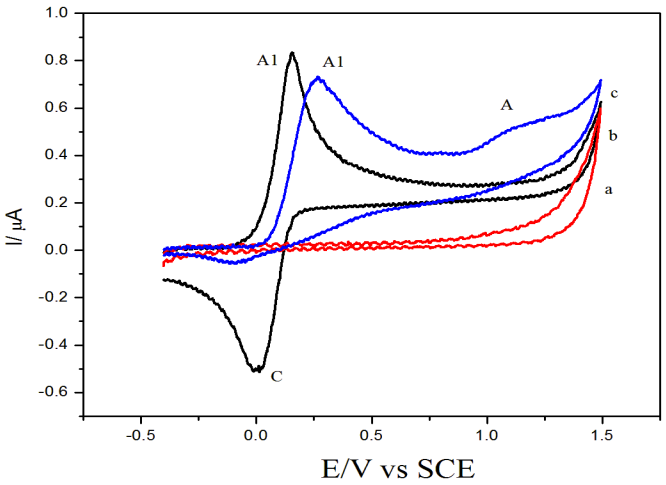


Figure 1. Cyclic voltammograms of GC electrode in acetate buffer solution(a) blank (b) 1mM hydroquinone(c) 2mM hydroquinone; scan rate: 100 mVs^{-1}; T: 25±1 °C.

During second and third cycle scanning, the peak around 1.0V decreased due to the consumption of **3** and the decreased of the amount of **5a**. From figure 3 it is clear that, increased potential sweep rate, the peak height of **1a** also increase (curve a-e). The same condition is observed

when the concentration of **3** is decreased. The current ratio (*I*pC/*I*pA) virus scan rate for mixture of **1a** and **3,** conformed the reactivity of **2a** towards **3**, appearing as an increase in the height of the C peak at higher scan rates.

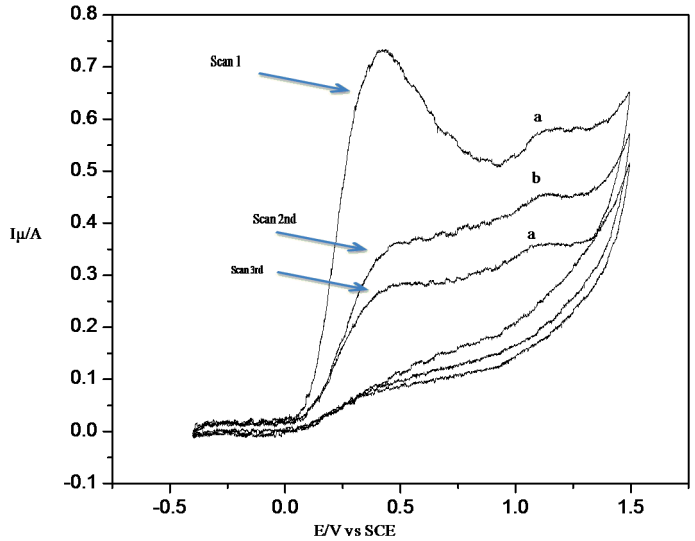


Figure 2. Multi-cyclic voltammograms of (**1a**) in the presence of (**3**) on GC electrode in aqueous acetate Solution (a) the first circle; (b) for the second circle; (c) for the third circle. (pH 7.4); Scan rate: 100 mVs-1; T 25±1°C.

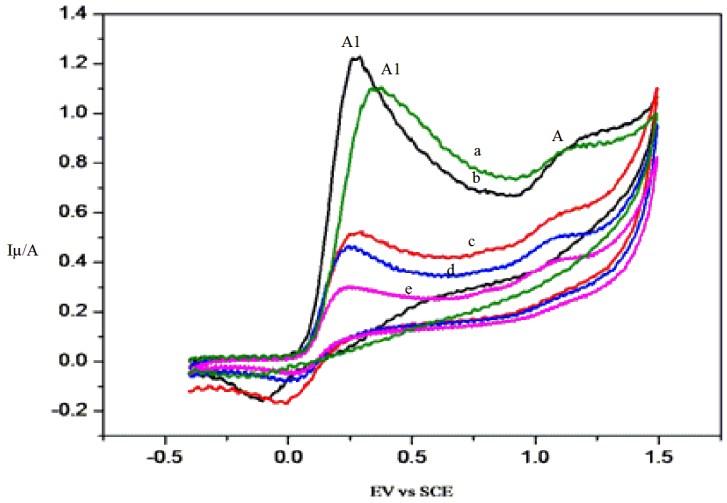


Figure 3. Typical voltammograms of 1 mM hydroquinone(**1a**) in the presence of 2 mM 4, 6 dimethylpyrimidine-2-thiol(**3**) at a glassy carbon electrode (1.8 mm diameter) and at various scan rates. Scan rates of a, b; c, d and e are 20, 40, 50, 80 and 100 mVs^{-1}, respectively. Supporting electrolyte: 0.15 M sodium acetate buffer solution: pH 7.4

2mM **1a** and 2mM **3** were used for control-potential coulometry at 0.45 *vs* SCE. The anodic and cathodic peaks are disappearing, due to the advancement of coulometry and on consumption of

4electrons per molecule. The electrolysis process was monitored using cyclic voltammetry as shown in Fig 4.

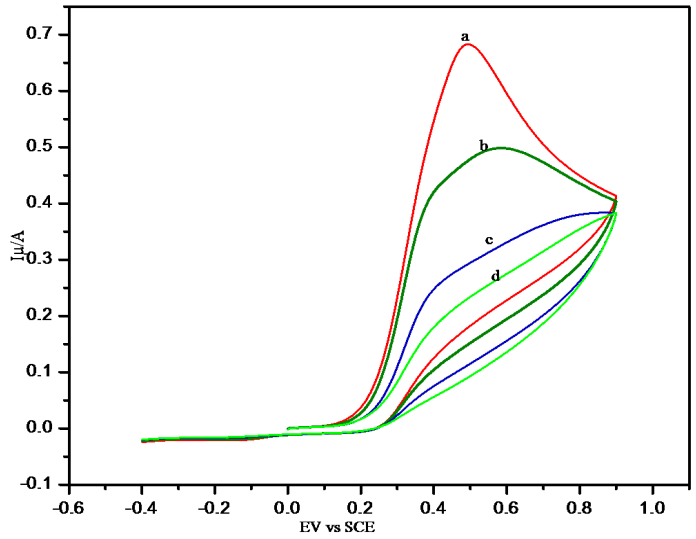
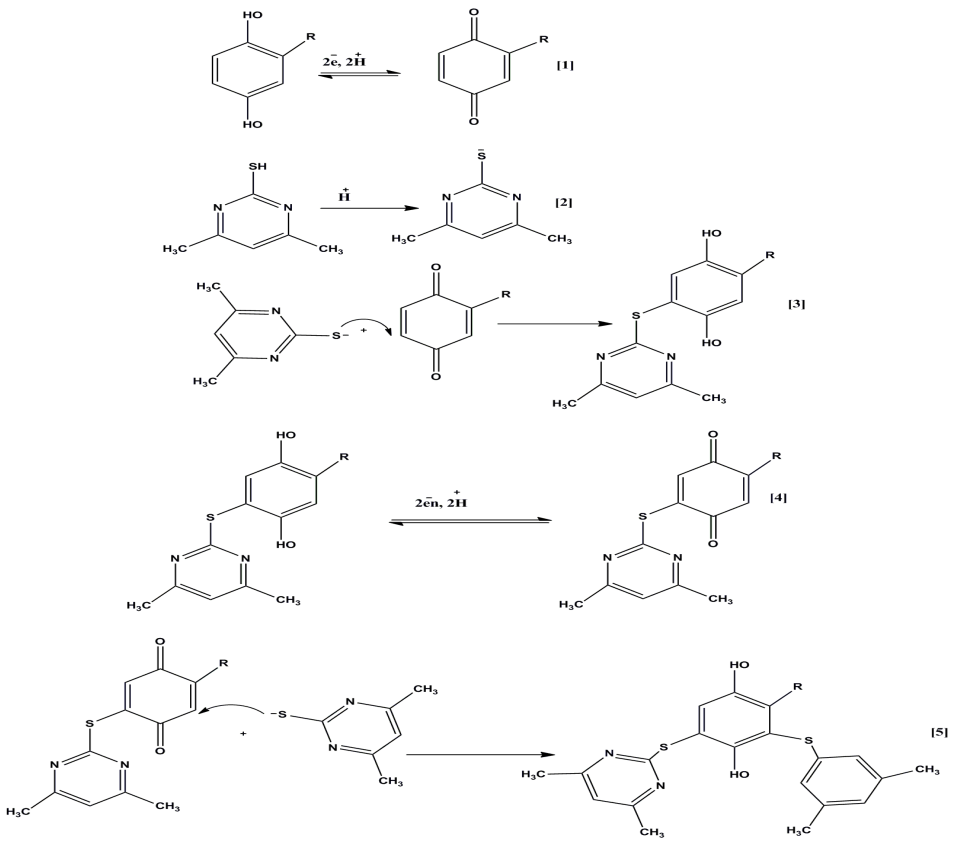
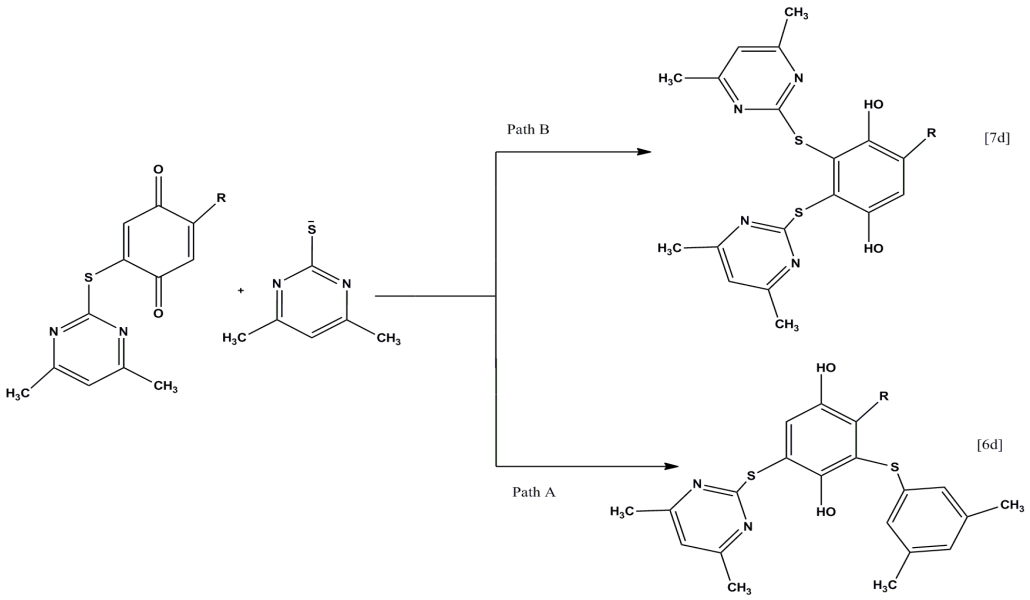


Figure 4. Control-potential coulometry at 0.45V of 2mM Hydroquinone (**1a**) in the presence of 4mM 4, 6- dimethylpyrimidine-2-thiol (**3**). Variation of peaks current ($Ip^{Al)}$; charge consumed. Scan rate $50mVs^{-1}$±1°C.



Scheme 1



Scheme 2

3.2Electro-oxidation of methyl hydroquinone (1b) in the presence of 4, 6- dimethylpyrimidine-2-thiol (3)

CV curve of 1mMmethyl hydroquinone (**1b**) has been studied in aqueous solution using sodium acetate 0.15M as supporting electrolyte, which exhibits two peaks, one is anodic and other is cathodic peaks, corresponding to the quesi-reversible two electron transformations, (**1b**) to (**2b**), as shown in Fig.5 (curve b).

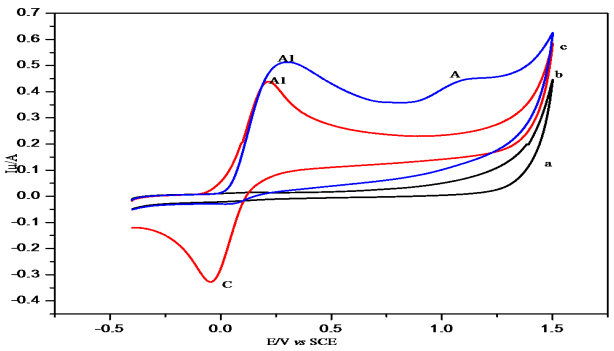


Figure 5. Cyclic voltammograms of GC electrode in acetate buffer solution(a) blank (b) with 1mM methyl hydroquinone (**1b**)(c) and 2mm 4, 6- dimethylpyrimidine-2-thiol (**3**); scan rate: 100 mVs^{-1}; T =25±1 °C.

Quinones produced from the oxidation of catechols and other nucleophiles due to the mechanistic [18, 19] and synthetic [20, 21] importance of these reactions. 3-methylhydroquinone (**2b**) is oxidized in the presence of 4, 6- dimethylpyrimidine-2-thiol (**3)**, in a similar way of **1a**. Due to the presence of methyl group, **2b** reacts faster as compare to **2a**, because it activates the quinone towards

nucleophile (**3**) [2]. (Fig 5 curve c). Controlled potential coulometry was performed in acetate buffer solution, containing 2mM 1b and 2mM (3) at 0.40V vs SCE [22]. The electrolysis progresses monitored by cyclic voltammetry, both the anodic peaks become decrease and cathodic and anodic peaks are disappear when the charges of electron become 4*e* per molecule. The electrochemical reaction between **1b** and **3** is same to the previous case. The result show the reaction between **1b** and **3** is fast enough and leads to final product **6b**.

Multi cyclic voltammetry shows that, during second and third cycle scanning, the peak around 1.2 V decreased due to the consumption of **3** and the decreased of the amount of **5b**, like **5a**. During second (b) and third (c),scan, the peaks is dramatically decrease, it is due to methyl group, that activate **2b**, to react with **3,** as shown in fig 6.

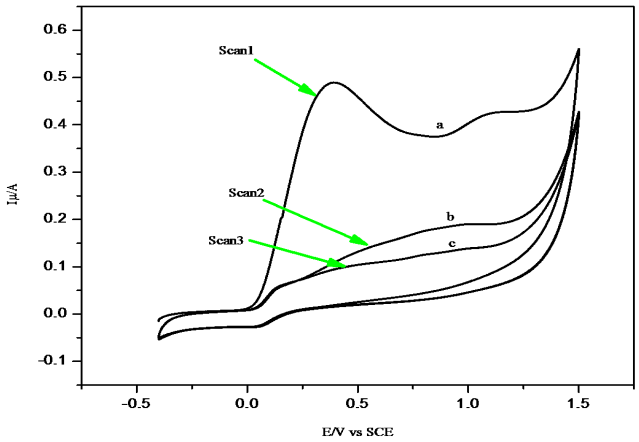


Figure 6. Multi-cyclic voltammograms of GC in acetate buffer solution with (1b) in the presence of (3) (a) for the first circle; (b) for the second circle; (c) for the third circle. Scan rate: 100 mVs^{-1}; T 25±1 °C.

3.3 Electro-oxidation of 3-methoxyhudroquinone (1c) in the presence of 4, 6- dimethylpyrimidine-2-thiol(3)

The electrochemical oxidation of methoxy hydroquinone (**1c**) in the presence of 4, 6-dimethylpyrimidine-2-thiol (**3**), as a nucleophile in acetate water solution was studied. The quinones formed are quite reactive and can be attacked by a variety of nucleophiles [23]. Like (**1a**) and (**1b**), (**1c**) also showed two peaks corresponding to transformation of (**1c**) *p*-quinones (**2c**) in a quasi-reversible two-electron process.2mM methoxy hydroquinone (**1c**), and 2mM 4, 6- dimethylpyrimidine-2-thiol (**3**), in acetate aqueous solution was used for controlled-potential coulometry at 0.40 V vs SCE [23] and for cyclic voltammetric analysis. All the anodic and cathodic peaks are disappearing at a rate corresponding 4*e* per molecule [2]. The electrochemical mechanism is similar as previous case: The presence of methoxy group, **2c**, reacts very fast as compares to parent compounds and **2a** and also **2b**. It is because methoxy group are strong activated group and it's activate the **2c**, to react with **3**.[2].Figure: 7

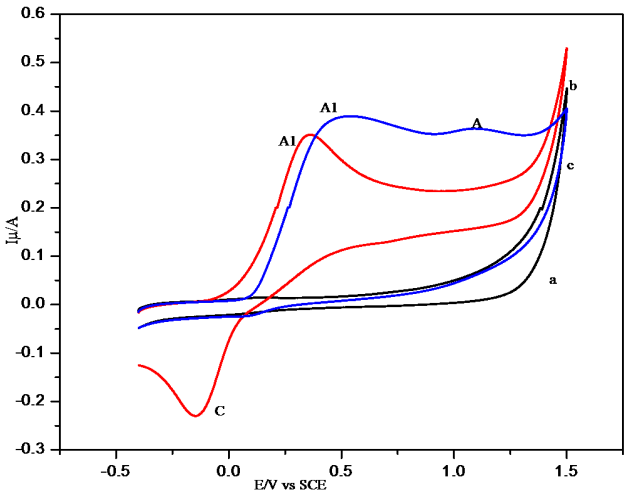


Figure 7. Cyclic voltammograms of GC in acetate buffer solution(a) blank (b) with1mM methoxy hydroquinone (1c), (c) 2mM4, 6- dimethylpyrimidine-2-thiol (3) , scan rate: 100 mVs-1; T: 25±1 °C.

From these observations, the reaction mechanism could be expressed in scheme 1. At the beginning **1a** is electrochemically oxidized to **2a** at potential of 0.01V. Then the generated **2a** reacts with coexisted **3** in the electrolyte through Michael addition reaction to generate 2-((4, 6-dimethylpyrimidin-2-) thio). Benzene-1, 4-diol (**4a**). The hydroquinone body of **4a** could be electrochemically oxidized to form 2-((4, 6-dimethylpyrimidin-2-yl) thio) cyclohexa-2, 5- diene-1, 4-dione (**5a**) at the potential of 1.0V. Then **5a** have attacked at C-3 position by **3** to form final product 2, 6-bis (4, 6-dimethylpyrimidin-2-ylthio) benzene-1, 4diol (**6a**). Fortunately, the over oxidation of **6a** was circumvented during the preparative procedure because of the insolubility of **6a** in acetate buffer solution media. The other derivatives of hydroquinone (**1b** and **1c**) can go through the same reaction paths to gave (**6b** and **6c**) products.

Methyl and methoxy groups are electron-donating groups, which causes a diminution in activity of hydroquinone derivatives (**2b** and **2c**) as Michael acceptor toward addition [2]. However, it was confirmed by the ratio of reaction IpC_l/IpA_1 that the reaction between (**2b** and **2c**) and **3** was fast enough, leading to the formation of final products (**6b-c**) respectively. The proposed mechanism shows that there are two possibilities for **3** to attack **5c**, i.e. C-3 or C-6, which would result in two types of products (**6d**, **7d**). However, judging from ^{1}HNMR and TLC results, only (**6d**) but no (**7d**) was found in the products. It is implied that **3** attack only at C-3 of (**5c**), probably due to the steric hindrance. That is to say, **3** reacts with **5c** follows path **A** in scheme 2.

Characteristics of the products

2, 6-bis (4, 6-dimethylpyrimidin-2-ylthio) benzene-1, 4-diol (6a)

$C_{18}H_{18}N_4O_2S_2$(81% yield) m.p.>300°C, IR (KBr): υ (cm^{-1}) 3430, 1560,1450,1378, 1280, 835; ^{1}HNMR (400MHz $CHCl_3$, □/ppm): 2.24 (s, 12H, pyrimidine 4-methyl);(s, 2H, hydroquinone); 6.68

(1H, hydroquinone); 7.10 (s, 2H, pyrimidine); ^{13}NMR: 20,115,128,142,158,163,170; MS; m/e (relative intensity): 386 (30), 352 (15),248 (65), 140 (56).

3, 5-bis (4, 6-dimethylpyrimidin-2-ylthio)-2-methylbenzene1, 4-diol (6b)

$C_{19}H_{20}N_4O_2S_2$ (80%yield) m.p>300°C IR (KBr): υ (cm1), 3420, 2924, 1599, 1484, 1343, 1255, 1196, and 1067. ^{1}HNMR (400M Hz $CHCl_3$□□/ppm) :1.90 (s,3H,methyl); 2.22 (s,6H,pyrimidine); 2.24 (s,6H,pyrimidin), 6.68,6.40 (s,1H,hydroquinone) ;6.69 (s,1H,pyradamine),6.90 (s,1H,Pyrimidine); ^{13}NMR22,34,36,120,123, 128, 130, 132, 143, 148, 170, 173; MS:m/e (relative intensity): 400 (25), 368 (15), 313 (12),262 (83),226 (28), 138(5).

3, 5-bis (4, 6-dimethylpyrimidin-2-ylthio) 2methoxybenzene1, 4-diol (6c)

$C_{19}H_{20}N_4O_3S_2$(77% yield): m.p.>300°C, IR(KBr, υ(cm^{-1}): 3450, 2920, 1599, 1548, 1341, 1255, 1230,1135,1066.^{1}HNMR (300MHz $CHCl_3$,□□/ppm):2.10(s, 6H, pyrimidine 2 methyl), 2.23(s, 6H, pyrimidine 2-methyl), 4.33(s, 3H, -OCH_3),6.87(s,1H, hydroquinone), 6.92(s, 1H, pyrimidine), 7.00(s, 1H, pyrimidine); ^{13}NMR: 23, 31, 40, 118, 122, 127, 130, 135, 143, 150, 170; MS(m/e, relative intensity): 416(25), 383(95),368(18), 278(53), 138(51).

4. CONCLUSION

The hydroquinone is oxidized to *p*-quinone in aqueous media. The quinones are quite reactive species and reacted with 4, 6- dimethylepyrimidne-2-thiol which act as nucleophile, and formed the final products. The mechanism shows that quinones reacted with 4, 6-dimethylepyrimidne-2-thiol through Michael reaction and lead new pyrimidine derivatives.

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