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Benzothiazolopyrimidinone through oxidative coupling of catechols and propylthiouracil

Mohsen Sargordan-Arani[a*] and Behrooz Mirza[b]

[a]*Department of Chemistry, Faculty of Science, Yadegar-e-Imam Khomeini (RAH), Shahre Rey Branch, Islamic Azad University, Tehran, Iran*
[b]*Department of Chemistry, Karaj Branch, Islamic Azad University, Karaj, Iran.*

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Abstract: Catechol derivatives' chemical oxidation with potassium ferricyanide as an oxidizing agent (Decker oxidation) has been studied in the presence of 6-propyle-2-thiouracil as nucleophile in aqueous media. The results indicated that catechol and its derivatives participate in a 1, 4 Michael addition reaction with 6-propyle-2-thiouracil (**ptu**) to form the new and novel benzo thiazolopyrimidinone compounds. The chemical synthesis of this compound has been successfully performed at a good yield, characterizedby IR, ^{1}HNMR and ^{13}C NMR and MS spectroscopy.

Keywords: Propylthiouracil, Catechol, *o*-benzoquinones, Oxidative coupling, Potassium ferricyanide.

Introduction

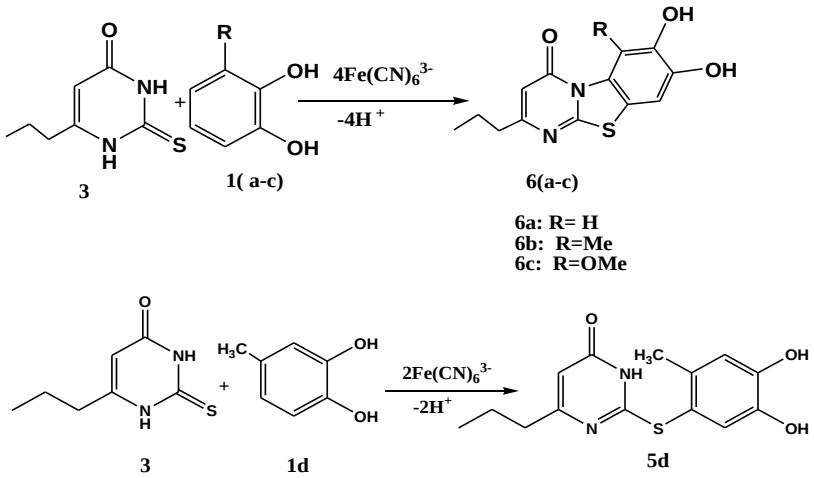
Of the nuisances the chemists are facing in organic chemistry is to develop some simple and efficient chemical processes and methods for synthesizing the extensively applied organic compounds from easily available reagents**.** The chemical oxidation of catechol derivatives (1a-d) has been described and revealed that these compounds can be oxidized to o-benzoquinones (**2a-d**) [1-3]. The chemically generated **o**-benzoquinones (**2a-d**) are quite reactive Michael acceptor and can be attacked by a variety of nucleophiles undergo various mechanisms with the consumption of 2, 4 electrons per molecule of catechols derivatives**.** [4, 5].On the other hand, 6-Propyl-2-thiouracil,**(ptu)** is of the recognized drugs belonging to thionamides and of the crucial agents in thyrotoxicosis treatment. Propylthiouracil inhibits the thyroid gland peroxidase' activity, and consequently, blocks iodine organification in the gland.

*Corresponding author. Tel: (+98) 9126096940, Fax: (+98) 21 77194107; E-mail: mohsenfard555@yahoo.com

Thisaction is also common for other thionamides like methimazole andcarbimazole [6]. Another characteristic of **ptu** is its ability to block the conversion of tetraiodothyronine (T_4) into triiodothyronine (T_3) in the peripheral tissues. It directly interferes with thyroid synthesis by preventing iodine from combining with thyroglobulin, leading to thyroid hormone levels' decrease [7]. **ptu** also exhibits anti-herpes virus activities in men [8, 9]. In this respect, to the best of our knowledge, no Propylthiouracil based in situ chemical oxidation reaction generated benzoquinones derivatives (3) has been previously reported, while the electrochemical oxidation of only catechol with thiouracil has been given earlier [10]. This way, we have investigated the catechol derivatives' chemical oxidation in the presence of 6-propil-2-thiouracil as a nucleophile and discovered an easy and one-pot chemical method for the synthesis of new and novel thiazdiazafluorenone compounds via a 1, 4 Michael addition reaction in aqueous solutions using potassium ferricyanide as an oxidizing agent in high yield and purity.

Results and Discussion

Formerly, catechols' oxidation to o-quinones in the presence of a variety of nucleophiles such as 4-mercaptocoumarin, [11] 4-mercapto-6-mehyl-2H-pyran-2-one, [12] β –diketones, [13] and barbituric acidshas been presented. [14] The formed o-quinones are quite reactive and can be attacked by nucleophiles and converted into the corresponding 4-(Dihydroxyphenylthio)-2 H-chromen-2-one, [11] 4-(Dihydroxyphenylthio)-6-methyl-2H-pyran-2-One [12] benzofuran, [13] and pyrimidine derivatives [14], respectively. In the present work, we have performed the oxidation of catechols (1a-d) in the presence of **ptu** (**3**) as possible nucleophiles in aqueous sodium acetate solution using potassium ferricyanide as the oxidizing agent (Scheme **1**). A suitable oxidizing agent is a compound able to only oxidize catechols (**1a-d**) to the related o-benzoquinones without any effect on Propylthiouracil (**ptu**) (**3**). Potassium ferricyanide is a stable, easily handled and commercially available oxidizing agent. Recently, we have depicted the suitability of potassium ferricyanide with an oxidation potential of 0.24 V vs. SCE for catechols' oxidation (Scheme **1**) [15].



Scheme 1: Catechols (**1a-d**) chemical oxidation in the presences of 6-propyl-2-thiouracile using ferricyanide

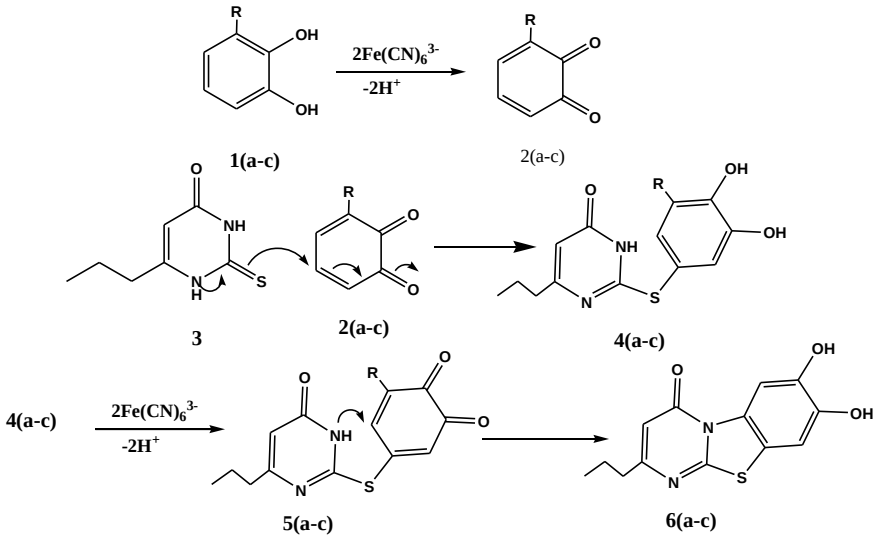
The proposed mechanism for 1a-c oxidation in the presence of **3** is presented in Scheme **2**. According to our results, it seems that 1, 4-addition (Michael) reaction of 3 to o-quinone (**2a-c**) leads to intermediate (**4a-c**). The oxidation of this compound (**4a-c**) is easier than that of parent-starting molecules (**1a-c**) due to the presence of an electron-donating group. The reaction products (**6a-c**) can also be oxidized at a lower potential than the starting 1a compound. However, over-oxidation of 6a-d was circumvented during the preparative reaction because of the product's insolubility in water/acetonitrile solvent medium. In 3-methyl or 3- methoxy state, catechol causes relevant Michael acceptor to be attacked by **3** at C-4 and C-5 positions to form two products in each case .Since in o-benzoquinones **2b** and **2c** C-5, and in o-quinone**2d,** C-4 position is more electropositive, it has been suggested that o-benzoquinones **2b** and **2c** be selectively attacked at C-5 and o-quinone**2d** at C-4 position by 3, leading to the formation of the products, namely, **6b** and **6c**, respectively (Scheme **2**). [16–18].

Interestingly, in case of 4-methylcatechol (1**d**) , because of the existence of methyl group at its C-4 position as a reactive site of cyclization, it proceeds in a different manner from that of 1a-c (Scheme **3**).

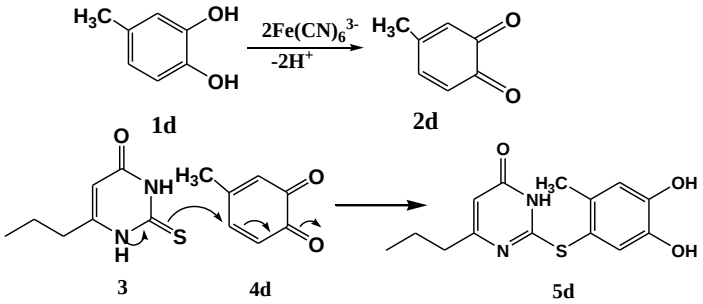
Experimental

Materials and Methods:

All reagents and solvents have been of reagent grade. The melting points have been determined in Bamsteadelectrothermal B4300 system open capillaries. IR Spectra have been taken on a THERMO ICO TNEXUS 870-FT spectrometer in KBr pellets and reported in cm^{-1}. NMR spectra were measured on a Bruker DPX 300 MHz spectrometer in Acetone-d_6 with chemical shift given in ppm relative to TMS as the internal standard. Mass spectra have been obtained with Thermofinnigan MAT95XL spectrometer system. The related data have been tabulated as m/ z. The elemental analyses have been performed using a Thermofinnigan Flash EA 1112 instrument.



Scheme 2: Catechols (**1a-c**) oxidation mechanism and its reaction with 6-propyl-2-thiouracile



Scheme 3*:* proposed mechanism for 4-methyl catechols (**1d**) and its reaction with 6-propyl-2-thiouracile

General method for synthesis of 6a-d.

To an aqueous sodium acetate 0.2 M/ acetonitrile (60/40), 6-Propyl-2-thiouracil (3) (1 mmol) solution which is being stirred, potassium ferricyanide has been added (4 mmol in the cases of 1a-c and 2 mmol in the case of 1d). A solution of catechols (**1a-d**) (1 mmol) in relevant solution has been prepared and added dropwise to the stirred solution within 20–30 min. The reaction mixture has been kept at r .t. with occasional stirring (1 h for **1a**, **1d** and 2.5 h for **b, c**). The solution has got dark and formed precipitates at the end of the reaction, a few drops of acetic acid have been added and the mixture has been placed in a refrigerator overnight. The formed solid has been collected by filtration and washed several times with water to extract the product. In case of **b**, **c**, the resulting residue has been charged on a silica gel column and eluted with a mixture of ethyl acetate/ n – hexane/chloroform (1.5/1/1) to extract the products. The final products have been characterized by IR, ^{1}HNMR, $^{1\,3}$CNMR, and MSspectroscopy

6, 7-dihydroxy benzo[d]thiazolo[2,3, b]6- propyl 4(1H) pyrimidin-one (6a):

Light yellow,Yield 90%, m.p. 245°C; IR (vmax: 3461, 3122, 3064, 2955, 2864, 1648,1520, 1454,1309, 869, cm^{-1}; ^{1}H NMR (300 MHz, acetone-d6) δ 0.88 (t, J = 7.5 Hz, 3H, CH_3), 1.72 (m, J= 7.5 Hz, 2H, CH_2), 2.54 (t, J= 7.5 H, CH_2), 6.14 (s, CH), 7.36 (s, H, ArH), 8.62 (s, H, ArH), 9.27 (s br, 2H, ArOH) ; ^{13}C NMR (acetone-d6); 13.4, 21.1, 40.8,105.8, 107.1, 108.1, 123.1, 128.7, 129.5, 144.9, 145.7, 160.8, 166.1 ppm δ; MS m/z (%): 276. (M^+, 60), 260. (30), 245 (55), 229 (21), 220 (65), 67 (15), 51 (18); Anal.Calcd.for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14; Found: C, 56.65; H, 4.50; N, 9.98.

2-(4,5-dihydroxy-2-methylphenylthio)-6-propyl pyrimidin-4(3H)-one(5d):

Light yellow,Yield 85%, m.p. 185°C (dec); IR (vmax: 3450-3150, 2960, 3064, 2928, 2870, 1667,1509, 1279,1160, 836, cm^{-1}; ^1H NMR (300 MHz, Acetone-d6) δ 0.84 (t, J = 7.5 Hz, 3H, CH_3), 1.53 (m, J= 7.5 Hz, 2H, CH_2), 2.30 (t, J= 7.5 H, CH_2), 5.15(s br, NH), 5.90(s,CH), 6.82 (s, H, ArH), 7.01 (s, H, ArH), 9.15 (s br, 2H, ArOH) ; ^{13}C NMR (Acetone-d6); 13.5, 19.8, 22.1, 40.6,105.6, 115.3, 118.5, 124.4, 134.8, 144.5, 148.6, 166.3, 168.5, 174.4 ppm δ; MS m/z (%): 292. (M^+, 35), 274. (30), 264 (20), 249 (40), 209 (15), 123 (50), 96 (25), 91(25), 68(15), 43(25); Anal.Calcd.for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58; Found: C, 57.48; H, 5.60; N, 9.35.

5-Methyl 6, 7-dihydroxy benzo[d]thiazolo[2,3, b]6-propyl 4(1H) pyrimidin-one (6b):

Light yellow,Yield 83%, m.p. 160°C; IR (vmax: 3352, 3206, 2969, 2938, 2874,1792, 1662,1501, 1457,1306, cm^{-1}; ^1H NMR (300 MHz, Acetone-d6) δ 0.95 (t, J = 7.5 Hz, 3H, CH_3), 1.79 (m, J= 7.5 Hz, 2H, CH_2), 2.44(s,3H, CH_3), 2.55 (t, J= 7.5 H, CH_2), 6.06 (s,CH), 7.20 (s, H, ArH), 8.52 (s br, 2H, ArOH) ; ^{13}C NMR (Acetone-d6); 13.4, 16.2, 21.4, 38.6, 105.3, 105.5, 115.4, 118.6, 127.4,144.4, 145.1, 160.9, 163.1, 165.2 ppm δ; MS m/z (%): 290. (M^+, 60), 272. (30), 263 (20), 229 (10), 196 (20), 168 (30), 96 (15), 54(35); Anal.Calcd.for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65; Found: C, 57.85; H, 5.70; N, 9.45.

5-Methoxy 6, 7-dihydroxy benzo[d]thiazolo[2,3, b]6-propyl 4(1H) pyrimidin-one (6c):

Light yellow, Yield 65%, m.p. 280°C; IR (vmax: 3420, 2962, 2928, 2870, 1559,1499, 1104 cm^{-1}; ^1H NMR (300 MHz, Acetone-d6) δ 0.89 (t, J = 7.5 Hz, 3H, CH_3), 1.59 (m, J= 7.5 Hz, 2H, CH_2), 2.37(m, J= 7.5 H, CH_2), 3.86 (, s,3H, OCH_3), 5.92 (s, CH), 6.82 (s, H, ArH), 8.55 (s br, 2H, ArOH) ; ^{13}C NMR (Acetone-d6); 13.3, 21.1, 38.6, 60.8,103, 107.2, 111.7, 114.9, 116.4,117.1, 137.1, 146.5, 159.3, 164.9 ppm δ; MS m/z (%): 306 (M^+, 40), 288 (25), 252 (33), 220 (50), 212 (48), 138 (23), 86 (60), 43(15); Anal.Calcd.for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61; N, 9.14; Found: C, 54.65; H, 5.90; N, 9.45.

Conclusions

This work extracted results demonstrated that catechols are oxidized in water/acetonitrile to their respective o-benzoquinones. The quinones are then attacked by ptu (**3**) to form new benzothiazolopyrimidineonederivatives, a one-step reaction; the overall reaction mechanism for catechols' oxidation in the presence of ptu is given in Scheme **1**.

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