Asian Journal of Chemistry Vol. 22, No. 9 (2010), 7039-7042

Synthesis of Novel Benzothiazinedione

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3,4-Dihydro-2*H*-benzo[b][1,4]thiazine-6,7-dione was synthesized from the reaction of cysteamine with catechol in the presence of potassium hexacyanoferrate(III) in 9 different pHs. Structural elucidations by spectroscopic methods showed that the same product was produced in different acidic and basic pHs.

Key Words: Cysteamine, Catechol, Benzothiazinedione, Potassium hexacyanoferrate, Structure activity relationship.

INTRODUCTION

Thiazine and thiazinedione compounds show biological activities and have unique place in medicinal chemistry since they display diverse biological properties such as an anesthetic agent[1], antifungal[2], antiinflammatory[3], anti HIV[4], antipsoriatic[5], antitumour[6], antituberculosis[7], antiasthma and anti Parkinson[8], antimicrobial[9], antirheumatic[10] and antiradiation[11] activities. In some of them the structure-activity relationship evaluated for their anti proliferative activity against human cervical cancer (HeLa) cells[12], while some act as potent calcium antagonists selective for cardiovascular tissue[13].

Recently, a series of naphtho[2,3-b][1,4]-thiazine-5,10-diones were synthesized and evaluated for their antibacterial and antifungal activities. The structure-activity relationships (SAR) of these compounds were studied. The results show that one of them exhibited better antibacterial activity than gentamycin *in vitro* against *Staphylococcus aureus*. In addition it also imparted marked antifungal activity *in vitro* against *Cryptococcus neoformans*, *Sporothrix schenckii* and *Trichophyton mentagraphytes* when compared with fluconazole[14].

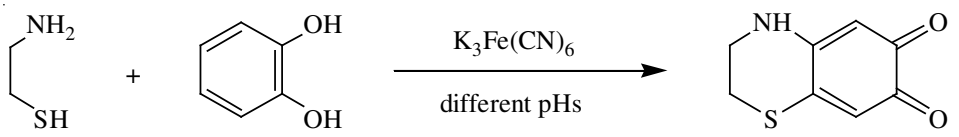
EXPERIMENTAL

Synthesis of 3,4-dihydro-2*H*-benzo[b][1,4]thiazine-6,7-dione: To a stirred phosphate buffer solution (80 mL, pHs = 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5 and 9.0), cysteamine (10 mmol) and catechol (10 mmol) were added. A solution of potassium hexacyanoferrate (60 mmol) dissolved in the phosphate buffer solution (20 mL) was added dropwise over 15 min during which time the solution became dark and a solid precipitated. After 24 h, the mixture was filtered and the filtrate was extracted with CH_2Cl_2 (2 mL × 25 mL). The combined organic layers was

dried and evaporated and recrystallization of the resulting brown precipitate from *n*-hexane gave the benzothiazinedione. m.p. 106.5-108.5 ºC, IR (KBr, ν_{max}, cm^{-1}): 3321, 2900, 1732, 1463, 1377, 1185, 1094, 1039, 847, 769, 740, 631, 564. ^1H NMR (90 MHz, $CDCl_3$): δ: 2.05 (N-H), 6.78 ($2CH_2$), 7.8 (2H quinone). ^{13}C NMR, (22.5 MHz, $CDCl_3$): δ: 30.59, 117.00, 121.59, 146.76, 182.73. MS: m/e (%): 181, 180, 110, 92, 81, 64, 63, 55, 53, 51, 50, 42, 41, 39, 38, 37, 29, 27, 25. Anal. (%) calcd. for $C_8H_7NO_2S$: C, 53.04; H, 3.87; N, 7.73; S, 17.68. Found: C, 52.84; H, 4.05; N, 7.86; S, 17.75.

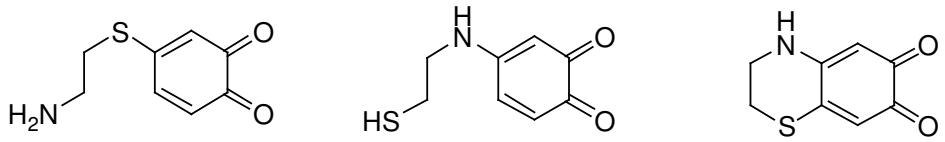
RESULTS AND DISCUSSION

In continuation of our studies on the synthesis of new heterocyclic compounds[15-20], we would like to report a synthesis of new 3,4-dihydro-2*H* benzo[b][1,4]thiazine-6,7-dione from the reaction of catechol with cysteamine (as a nucleophile) with potassium hexacyanoferrate(III) (as an oxidant) in 9 different acidic and basic pHs (**Scheme-I**).



Scheme-I

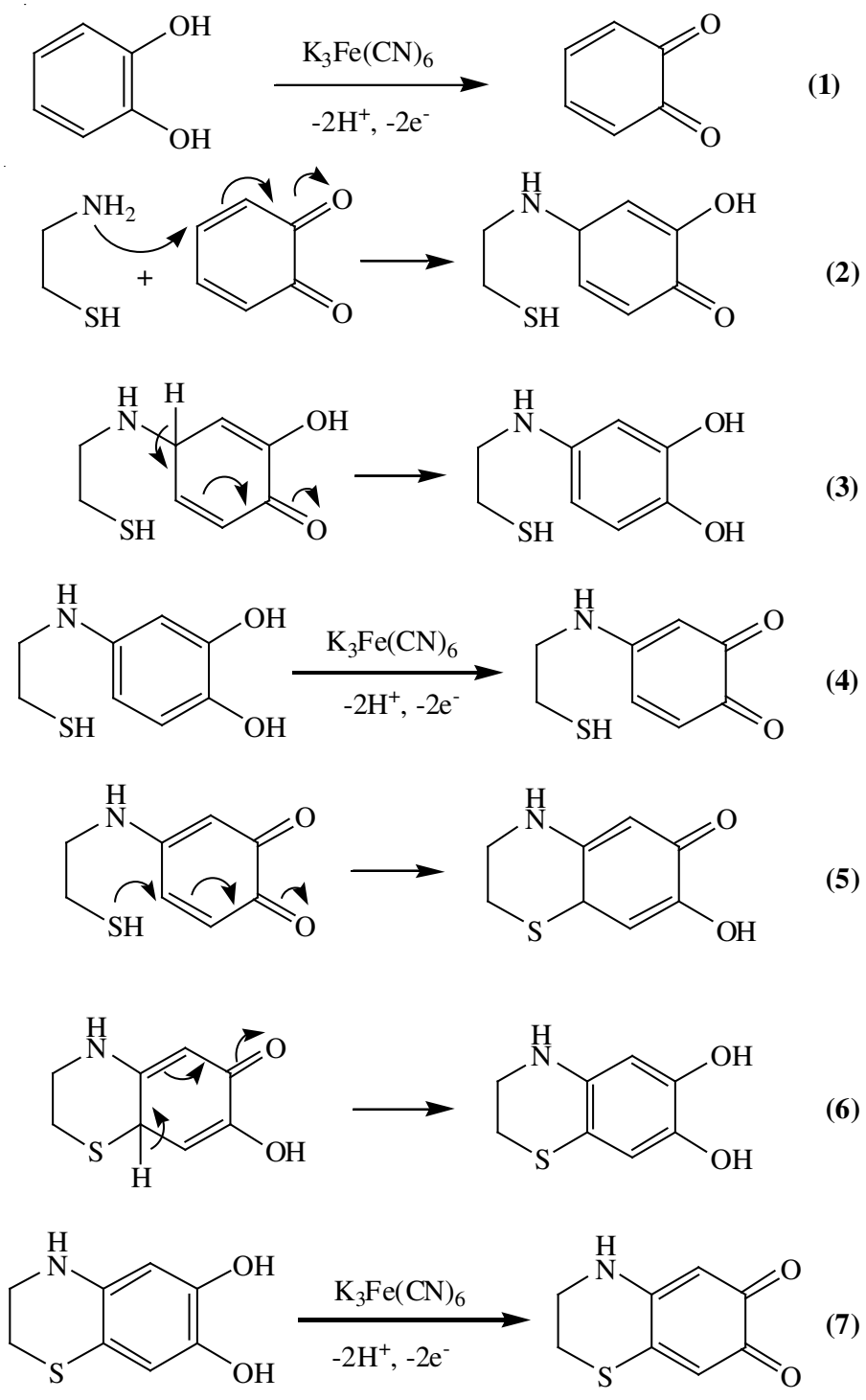
According to our previous experiences, we expected to get the following three different products in different pHs (Fig. 1). In the acidic pHs, the -NH_2 group will be protonated faster than the -SH and the nucleophilic attack of this group to the quinone form of catechol will decrease. Thus the -SH head has priority and will attack better and we expected to get the product **1**; while in the basic pHs the -NH_2 head will become stronger and so the nucleophilic attack of this group to the quinone form of catechol will increase and we expected obtain the product **2**.



1 **2** **3**

Fig. 1. Probable products in different pHs

Surprisingly, despite application of the 9 different acidic and basic pHs, product **3** obtained. Apparently, the carbonyl groups in the quinone form of catechol were activated in the acidic media and both the -NH_2 and -SH heads attacked to the quinone ring. The proposed mechanism might be as below (**Scheme-II**).


OH
OH
K3Fe(CN)6
-2H+, -2e-
O
O
(1)
NH2
+
SH
O
O
H
N
OH
SH
O
(2)
H
N
H
OH
SH
O
H
N
OH
SH
OH
(3)
H
N
OH
SH
OH
K3Fe(CN)6
-2H+, -2e-
H
N
O
SH
O
(4)
H
N
O
SH
O
H
N
O
S
OH
(5)
H
N
O
S
OH
H
H
N
OH
S
OH
(6)
H
N
OH
S
OH
K3Fe(CN)6
-2H+, -2e-
H
N
O
S
O
(7)

Scheme-II

ACKNOWLEDGEMENT

The authors gratefully acknowledged the financial support from the Bu Ali Sina University, Hamedan 651783868, Iran.

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(*Received*: 14 January 2010; *Accepted*: 18 June 2010) AJC-8796