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Taurine as a green bio-organic catalyst for the preparation of bio-active barbituric and thiobarbituric acid derivatives in water media

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ABSTRACT

Taurine, a *β*-amino acid that is abundantly available in the tissues of human and animals, is efficiently used as a green bio-organic catalyst in the preparation of some of the biologically active barbituric and thiobarbituric acid derivatives. In the presence of taurine, 5-Arylidene (thio) barbituric acid derivatives were prepared *via* Knovenagel reaction between aldehydes and (thio)barbituric acid. Using this reagent also pyrano[2,3-*d*]pyrimidinone(thione) derivatives were synthesized through a three-component reaction between aldehydes, (thio)barbituric and malononitrile. Both reactions are performed in water with good to excellent yields during acceptable reaction times. No organic solvent was used during reaction or separation steps and no extra-purification was exerted. Meanwhile, reusability of taurine was easy and noticeably high.

1. Introduction

For the first time, pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione or barbituric acid was synthesized and nominated in 1863 by Adolf von Baeyer through reduction of dibromo alloxan (5,5-dibromo barbituric acid) by hydrocyanic acid [1]. In 1879 Eduard Grimaux used $POCl_3$, urea and malonic acid [2] (today is replaced with diethyl malonate) [3,4] to achieve barbituric acid. In 1887 thiobarbituric acid was synthesized by Arthur Michael [3] and its first disubstituted derivative (5,5-diethyl-2-thiobarbituric acid) was synthesized by Emil Fischer in 1904 [5].

Despite having no pharmacological activity by its own, substituted barbituric acid derivatives show good bioactivity. In a research, it was shown that only C(5) substituted derivatives of barbituric and thiobarbituric acids possess significant hypnotic, anticonvulsant or anesthetic activities [6]. Also because of their high acidity, barbituric acid and thiobarbituric acid are not suitable to be used directly in the human body but their C(5) derivatives can be used since their two acidic protons are substituted [7]. 5-Arylidene barbituric acid derivatives are an important part of seductive and hypnotic drugs. On the other hand, arylidene thiobarbituric acid derivatives are noticeable for the preparation of heterocyclic compounds, aryl-thiobarbituric acid derivatives, antioxidants and thermal stabilizers [8,9]. Also, thiobarbituric reactive substances (TBRS) are famous for the determination of lipid peroxides [10].

Pyrano[2,3-*d*]pyrimidinone(thione) derivatives are very important because of their essential biological properties such as antihypertensive, antihepatotoxicity [11], antitumor [12,13], antibronchitic and anticardiotonic activities [14]. These compounds also are available as important units of some natural products such as polyethers, antibiotics, carbohydrates, phormones, iridoids and alkaloids [15,16].

Many catalysts have been used for the preparation of 5-arylidene (thio)barbituric acid derivatives such as [DABCO]$(SO_3H)_2(HSO_4)_2$ [17], sodium acetate [18], bi-SO_3H DABCO chloride [19], SBA-Pr-SO_3H [20], BF_3/nano-γ-Al_2O_3 [21], CuO-NPs [22], L-Tyrosine [23], $CoFe_2O_4$-NPs [24], NaOH/fly ash [25], sodium *p*-toluene sulfonate [26], PVP-Ni NPs [27], silicotungstic acid [28], aminosulfonic acid [29], 1-*n*-butyl-3-methylimmidazolium tetrafluoroborate [30], ethylammonium nitrate [31], cetyltrimethyl ammonium bromide [32], and CMZO mixed metal oxide [33].

Also several catalysts have been reported capable for the promotion of the formation of pyrano[2,3-*d*]pyrimidinone (thione) derivatives including [DABCO]$(SO_3H)_2(HSO_4)_2$ [17], nano-sawdust-OSO_3H [34], Al-HMS-20 [35], silica-bonded *N*-propyltriethylenetetramine [36], Nano Al_2O_3, [37], $CaHPO_4$ [38], DABCO [39], KBr [40], choline chloride·$ZnCl_2$ [41] Alum [42],

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Zn[L-proline]$_2$ [43], L-proline [44], succinimidinium hydrogensulfate [45], nano CuO/ZnO [46], trichloroisocyanuric acid [47], nano-titania sulfuric acid and $B(OH)_3$ [48] and *n*-butyl-3-methylimidazolium tetra-fluoroborate [49].

Taurine (2-aminoethanesulfonic acid) (Fig. 1) is a β-amino acid that is found in high amounts in the body of living organisms especially animals. This reagent is the important part of the bile and it forms one-tenth percent of total human weight [50]. Despite other homologs that are not dissociated in biological pH, taurine is in the zwitterionic shape in water and this leads to essential biological and medicinal properties [51]. This formation in water is proved by computational and NMR investigations [52]. This β-amino acid is used in the diet supplements, energy drinks and also has several biological properties in the human body [53].

2. Experimental section

2.1. General methods

All the chemicals were purchased from Merck, Aldrich and Fluka Chemical Companies and used without any further purification. All the products were separated and characterized by their physical properties and comparison with the reported samples. Both the purity determination of the substrates and reaction monitoring were accompanied by thin layer chromatography (TLC) using silica gel SIL G/UV 254 plates. Melting points were determined using a Buchi B-545 apparatus. FT-IR spectra were recorded by Perkin-Elmer spectrum BX series spectrophotometer (KBr disks). The ^{1}H NMR and ^{13}C NMR spectra were recorded by Bruker Avance 400 and 500 MHz instrument using deuterated solvents.

2.1.1. General procedure for the preparation of 5-benzylidene (thio) barbituric acid derivatives

In a 25 mL round-bottomed flask a mixture of aldehyde (1.0 mmol), (thio)barbituric acid (1.0 mmol) and taurine (0.025 g, 20 mol%) in water (3 mL) was heated at 90 °C for the appropriate time (Table 2, entries 1–17). After the completion, which was monitored by TLC (*n*-hexane:EtOAc 3:1), 10 mL of water was added and stirred for 2 min. During this time the product was precipitated and separated by filtration. The separated product was washed several times with water. After drying, the pure product was obtained while there was no need to further purification process and addition of organic solvent was not necessary. In continue, water was evaporated from the filtrate to obtain taurine.

2.1.2. General procedure for the synthesis of pyrano[2,3-d] pyrimidinone (thione) derivatives

In a 25 mL round-bottomed flask a mixture of aldehyde (1.0 mmol), (thio)barbituric acid (1.0 mmol), malononitrile, (1.1 mmol) and taurine (0.025 g, 20 mol%) in water (3 mL) was heated at reflux temperature for the appropriated time (Table 4, entries 1–14). After the completion, of the reaction which was monitored by TLC (*n*-hexane:EtOAc 3:1 then neat EtOAc), 10 mL of water was added and stirred for 2 min. During this time the product was precipitated and separated by filtration. The separated product was washed several times with water. After drying, the pure product was obtained while there was no need to further purification process and addition of organic solvent was not necessary. In continue, water was evaporated from the filtrate to obtain taurine.

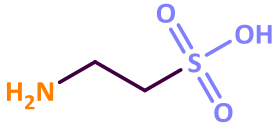

Fig. 1. Taurine (2-aminoethanesulfonic acid).

2.2. Spectroscopic data of the selected previously introduced and new compounds

2.2.1. 5-(2-Nitrobenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione [Table 2, Entry 2]

IR (KBr, cm^{-1}): 3325, 3197, 3091, 2836, 2751, 1735, 1687, 1572, 1513, 1433, 1389, 1345, 1123, 974, 794, 733; ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm) = 7.58 (d, J = 7.6, 1H), 7.68 (dt, J_1 = 8.0, J_2 = 0.8, 1H), 7.79 (dt, J_1 = 7.6, J_2 = 1.2, 1H), 8.24 (dd, J_1 = 8.0, J_2 = 1.2, 1H), 8.61 (s, 1H), 11.26 (s, 1H), 11.51 (s, 1H); ^{13}C NMR (100 MHz, DMSO d_6): δ (ppm) = 120.9, 124.51, 130,6, 130.8, 132.1, 134.2, 146.7, 150.7, 152.9, 161.6, 162.8.

2.3.2. 5,5′-(1,3-Phenylenebis(methanylylidene))bis(2-thioxodihydropyrimidine-4,6 (1H,5H)-dione) [Table 2, Entry 16].

IR (KBr, cm^{-1}): 3457, 3221, 3074, 2844, 1757, 1682, 1571, 1427, 1389, 1333, 800, 512; ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm) = 7.55 (t, J = 7.6 Hz, 1H), 8.20 (dd, J_1 = 7.8 Hz, J_2 = 1.6 Hz, 2H), 8.29 (s, 2H), 8.49 (s, 1H), 11.29 (s, 2H), 11.44 (s, 2H); (100 MHz, DMSO d_6) δ(ppm) = 120.3, 128.0, 132.9, 135.9, 137.6, 150.6, 153.9, 161.9, 163.6.

2.3.3. 5,5′-(1,4-Phenylenebis(methanylylidene))bis(2-thioxodihydropyrimidine-4,6(1H,5H)- dione)[Table 2, Entry 14]

IR (KBr, cm^{-1}): 3495, 3202, 3085, 2839, 1749, 1685, 1548, 1436, 1336, 1208, 808, 523; ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm) = 8.05 (s, 4H), 8.29 (s, 2H), 11.30 (s, 2H),11.45 (s, 2H); ^{13}C NMR (100 MHz, DMSO d_6) δ (ppm) = 120.9, 132.3, 136.1, 150.6, 153.4, 161.9, 163.6.

2.3.4. 5-(4-Hydroxy-3-methoxy-5-nitrobenzylidene)pyrimidine-2,4,6 (1H,3H,5H)-trione [Table 2, Entry 10]

IR (KBr, cm^{-1}): 3196, 3075, 3027, 2838, 1685, 1612, 1545, 1464, 1407, 1365, 1335,1268, 1231, 1106, 1046; ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm) = 3.94 (s, 4H), 8.26 (s, 1H), 8.29 (d, J = 2.0 Hz,1 H), 8.10 (d, J = 2.0 Hz, 1H), 9.89 (s, 1H), 11.30 (s, 1H), 11.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO d_6) δ (ppm) = 120.9, 124.51, 130,6, 130.8, 132.1,134.2, 146.7, 150,7,152.9, 161.6, 162.8.

2.3.5. 5-(4-(Methylthio)benzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione) [Table 2, Entry 11]

IR (KBr, cm^{-1}): 3214, 3067, 2841, 1731, 1689, 1533, 1490, 1429, 1200, 1090. ^{1}H NMR (400 MHz, DMSO d_6): δ (ppm) = 2.57 (s, 3H), 7.35 (d, J = 8.0 Hz, 2H), 8.21 (d, J = 8.0 Hz, 2H), 8.24 (s, 1H), 11.24 (s, 1H), 11.37 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO d_6): δ (ppm) = 14.32, 117.61, 124.76, 128.98, 135.10, 146.53, 150.56, 150.66, 154.94, 162.33, 162.44, 164.04, 164.15 ppm.

2.3.6. 7-Amino-5-(2-nitrophenyl)-4-oxo-2-thioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile [Table 4, entry 12]

FT-IR (KBr, cm^{-1}): 3426, 3317, 3273, 3182, 3062, 2955, 2892, 2197, 1675, 1573, 1518, 1469, 1395, 1349, 1278, 1250, 1126, 788; ^{1}H NMR: (400 MHz, DMSO d_6) δ (ppm) = 5.06 (s, 1H), 7.34 (s, 2H),7.48 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.54 (dd, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H), 7.67 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.86 (dd, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H), 12.43 (s, 1H), 13.67 (brs, 1H); ^{13}C NMR (100 MHz, DMSO d_6) δ (ppm) = 30.7, 56.9, 93.4, 119.0, 124.2, 128.6, 131.5, 133.9, 138.0, 149.7, 152.1, 158.6, 160.7, 174.4.

2.3.7. 7-Amino-2,4-dioxo-5-(o-tolyl)-1,3,4,5-tetrahydro-2H-pyrano [2,3-d] pyrimidine-6-carbonitrile [Table 4, entry 10]

IR (KBr, cm^{-1}): 3439, 3349, 3056, 2824, 2202, 1719, 1681, 1636, 1582, 1511, 1396, 1339, 1274, 1097; ^{1}H NMR (400 MHz, DMSO d_6): δ = 2.45 (s, 3H), 4.54 (s, 1H), 7.02–7.17 (m, 4Ar-H + 2H NH_2), 11.05 (s, 1H), 12.08 (brs, 1H) ppm; ^{13}C NMR (125 MHz, DMSO d_6):