Quinazolinediones and Quinazolinethiones by Intramolecular Ester Amidation

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(Received on 18th August 2010, accepted iin revised form 21st September 2010)

Summary: A new synthetic route was devised for synthesis of Quinazoline-2,4(1H,3H)-dione **5** in which salicylic acid **1** was treated with urea **2** to afford urea arylated ortho-urahydroxy benzoic acid **4**. Ortho-urahydroxy benzoic acid **4** is the intermediate moiety which upon cyclization corroborated the cyclic formation of 2, 4-quinazolinedione **5**. To form the quinazoline derivative 2, 3-dihydro-2-thioxoquinazolin-4(1H)-one **5a** thiourea **3** is used in place of urea **2**. Thiourahydroxy benzoic acid **4a** is another intermediate compound formed by reacting salicylic acid **1** with thiourea **3**. Thiourahydroxy benzoic acid **4a** upon interamolecular ester amidation gave final product 2, 3-dihydro-2-thioxoquinazolin-4(1H)-one **5a**. This new method replaces the isocyanates and cyanides usage for the formation of quinazolinediones because the incorporation of isocyanates and cyanides is extremely poisonous and cause fatal diseases and immediate death upon contact.

Introduction

Due to vital biological role of heterocyclic compounds the hetrocyclic chemistry has attracted considerable attentions in the fields of pharmaceutical, agriculture and veternary sciences [1-3]. Benzoylene urea (2, 4-quinazolinediones) **5** is a class of heterocyclic biomolecules which caused remarkable developments in the field of combinatorial chemistry and solid phase organic synthesis [4-6]. Quinazolines and its derivatives are known for their anti inflammatory, antimalarial, analgesics, anticonvulsants, serotonin uptake inhibitors, antihypertensive, cardiovascular, bactericidal and fugicidal activities [7-17]. The quinazolinedione pattern present in a large number of bioactive molecules including serotonergic, dopaminergic and adrenergic receptor ligands and inhibitors of aldose reductase, lipoxygenase, cyclooxygenase, couagenase and carbonic anhydrase [18, 19].

Many literature methods used for corroborating this simple hetrocyclic templates i-e quinazolines quinazolinediones are time consuming and tedious [20, 23].

In this paper we report the new synthetic route that involves a very simple and short time method i.e. the fusing of salicylic acid and urea on heating to get ortho-urahydroxy benzoic acid **4** which upon cyclization gave 2, 4-quinazolinediones (benzoyleneurea) **5**. Chemicals which have been used for the preparation of benzoylene urea reported in the literature [14, 19-21] are toxic like cyanides, isocyanate and cyanide salts. This method was employed since it avoids the incorporation of isocyanates and cyanides which are extremely poisonous and cause immediate death upon contact.

Results and Discussion

This is a two step single pot reaction in which urea **2** or thiourea **3** was treated with salicylic acid **1** and its derivatives (**1a, 1b, 1c and 1d**) to form quinazoline-2, 4-dione **5** and its thio-derivatives **5a** upon heating or microwave fusing. Salicylic acid skeleton (salicylic acid and its derivatives) fused with urea **2** and thiourea **3** on heating to form condensational products (**4a, 4b, 4c and 4d)** which on intramolecular cyclization form ester amide products *i-e.* Quinazoline-2, 4-Dione **5** and 2, 3-dihydro-2-thioxoquinazolin-4(1H)-one **5a** (Scheme 1) [24].

Chemistry of the Reaction

The electron density of urea nitrogen attacks on the carbonyl carbon of salicylic acid in first step of fusing and the removal of water takes place in this step [22, 23]. The 3-D structural study showed that two carbon atoms of salicylic acid **1** are sterically hindered i-e to which hydroxyl group and carboxylic acid group are attached while in case of other carbon atoms of aromatic ring of salicylic acid the nucleophilic attack of nitrogen density of urea is not possible due to their nucleophilic nature of benzene. So the attack on carbonyl carbon of carboxylic acid

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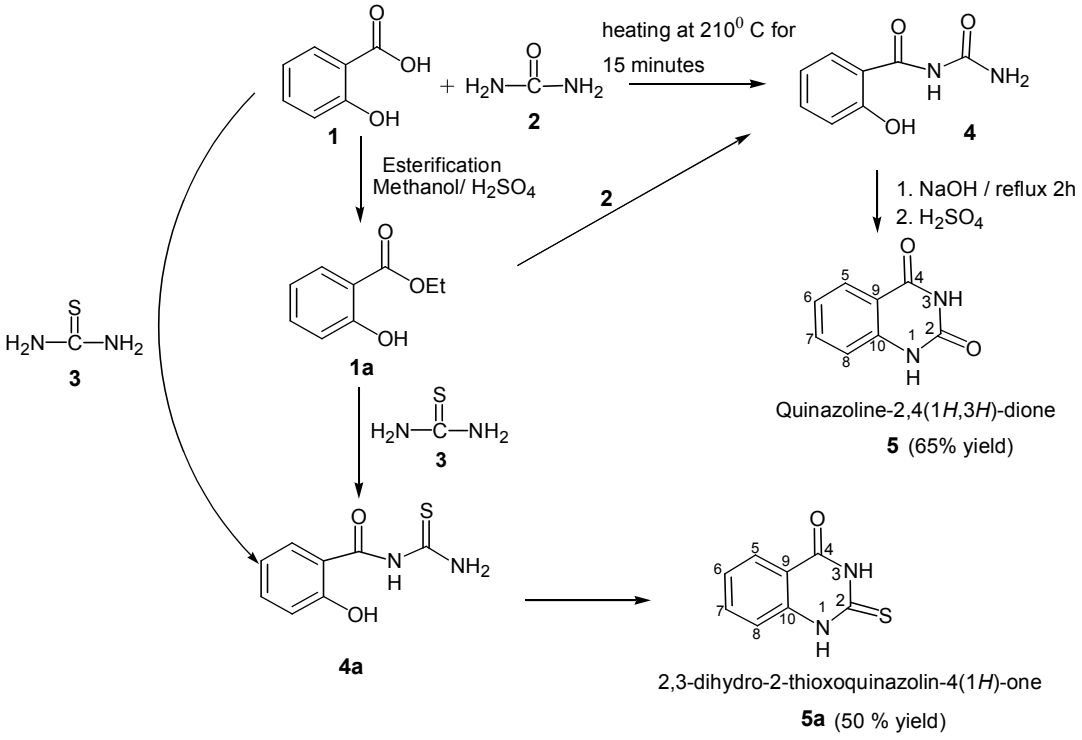
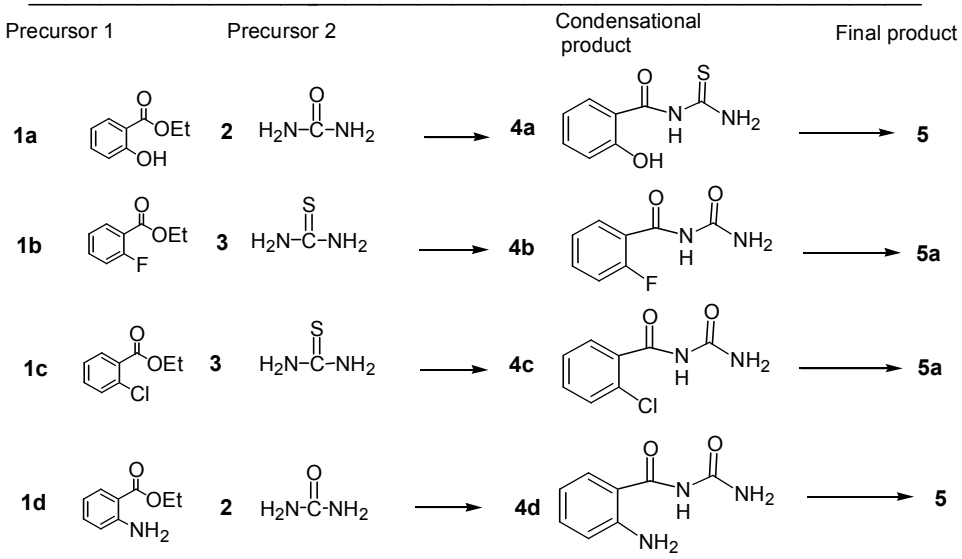
was possible due to its less steric energy value and greater bond length of C-O [22, 23]. The carbonyl carbon of urea **2** is also sterically hindered due to the nitrogen of amino group therefore it is not possible for lone pair of oxygen of hydroxyl group or electron density of the ring to attack on carbonyl carbon of urea [22, 23]. The condensational product **4** in second step is cyclized in NaOH to form quinazolinedione **5** shown in Scheme 1**.** The main cause of adding NaOH in procedure "*a"* is to dissolve the unreacted salicylic acid and urea so that our product will be crystal out on cooling state. In case of procedure "*b"* acetone is used as a solvent with K_2CO_3 for the formation of product. Thiourea causes the formation of quinazolinethione **5a** when treated with salicylic acid pattern. The ease of cyclization of condensational product depends upon stability of leaving group, bond energy or bond length of carbon atom with leaving group electronegative atom.





Scheme 1

Experimental

Melting points (°C) were taken in open capillaries and are uncorrected. Microanalyses were conducted on a Heraeus instrument; results are within ± 0.6% of the three theoretical values. IR Spectra were taken on Perkin Elmer and its model No. RX1 using (32 x 3) mm cell. The instrument used for Low-resolution electron impact mass spectra was Finningan MAT 311 with MASPEC data system. Peak matching, field desorption (FD) and field ionization (FI) were recorded on MAT 312 mass spectrometer. Jeol JMS HX 110 mass spectrometer was used for High resolution mass spectra and fast atomic bombardment (FAB) measurements using glycerol and thioglycerol as a matrix with cesium iodide (CsI) as an internal standard. ^{1}H-NMR was taken in $CDCl_3$ solvent using TMS as internal standard at 500 MHz on Bruker AM-500 with aspect 3000 data systems at a digital resolution of 32K.^{13}C-NMR spectra were recorded in $CDCl_3$ solvent at 125 MHz on the Bruker AM-500. The pulse conditions used for ^{1}H-NMR spectra were Spectrometer frequency (SF) 500.13 MHz , acquisition time (AQ) 1.79s, number of transients (NS) 64, receiver gain (RG) 161.3 , temperature(TE) 300.0 K, dwell time (DW)54.8 usec , per scan delay (DE) 6.00 usec and dummy scans (DS) 0.

While for ^{13}C-NMR spectra conditions used were as follows Spectrometer frequency (SF) 125.71MHz , acquisition time (AQ) 0.547s, number of transients (NS) 20480, receiver gain (RG) 32768 , temperature (TE) 300 K, dwell time (DW)16.500 µsec, per scan delay (DE) 50.0usec and dummy scans (DS) 2. All chemicals and reagents used were purchased from Aldrich Chemical Co., USA.

Synthesis of Quinazoline-2,4(1H,3H)-dione (5)

Procedure a

Salicylic acid (13.8 g) and urea (6.0 g) mixture was fused to form slurry by heating for about ten minutes at 210° C and concentrated solution of sodium (1M) hydroxide was added into slurry with continuous stirring and reflux for 2 hours. The colorless salt of benzoylene urea was precipitated out on cooling reaction mixture. These precipitates were then filtered and dissolved in 200 ml hot water. Dilute sulfuric acid was added to precipitate out 2, 4-quinazolinedione as lustrous, colorless needles. The crude product is filtered and washed with water and purified by TLC and HPLC. Preparative plates of precoated silica gel GF-254 (20× 20 cm, 0.5 mm thick, E-Merck) were used for preparative TLC to check the purity of compounds.

Procedure b

Salicylic acid (13.8 g), urea (6.0 g) and anhydrous K_2CO_3 (2.5 g) mixture was reacted in acetone by heating for about fifteen minutes in microwave oven at 90 watt power. The colorless solid crystals of benzoylene urea (Quinazoline-2, 4 (1H, 3H)-dione) were precipitated out on *vacuo*. These precipitates were recrystallized in ethanol.

Synthesis of 2, 3-dihydro-2-thioxoquinazolin-4(1H)-one ***(5a)***

Salicylic acid (13.8 g) and Thiourea (7.4 g) mixture was fused to form slurry by heating for about ten minutes at 200° C and concentrated solution of sodium (1M) hydroxide was added into slurry with continuous stirring. The colorless salt of thioxoquinazolin-4(1H)-one was precipitated out on cooling reaction mixture. These precipitates were then filtered and dissolved in 200 ml hot water. Dilute sulfuric acid was added to precipitate out 2-thioxoquinazolin-4(1H)-one **5a** as lustrous, colorless needles. The crude product is filtered and washed with water and purified by TLC and HPLC. Preparative plates of precoated silica gel GF-254 (20× 20 cm, 0.5 mm thick, E-Merck) were used for preparative TLC.

Characterization

*Quinazoline-2,4(1H,3H)-dione (**5**)*

Yield 65%, m.p 300°C. IR (KBr) ν_{max} : 2846, 1719, 1626, 1653,1536, 1225 cm^{-1}. EIMS *m/z* (rel.int.%) : 162 (100), 161 (10), 134 (21). ^{1}H-NMR ($CDCl_3$, 500 MHz):δ 10.35 (2H, s, NH, H-3), 10.29 (2H, s, NH, H-1), 7.53 (1H, dd, *J* = 7.4, 2.5 Hz, H-5,), 7.95-7.80 (2H, m, H-6, H-7), 7.32 (1H, dd, *J* = 7.2, 3.1 Hz, H-8); ^{13}C-NMR ($CDCl_3$, 125 MHz): *δ* 153.9 (C-2), 158.8 (C-4), 127.6 (C-5), 123.7 (C-6), 132.3 (C-7) , 124.5 (C-8), 121.6 (C-9), 137.9 (C-10).

2, 3-dihydro-2-thioxoquinazolin-4(1H)-one ***(5a)***

Yield 50% m.p 289°C. IR (KBr) ν_{max} : 3134, 3248, 3028, 1664, 1488, 1529, 1340, 1402, 1203, 1271. EIMS *m/z* (rel.int.%) : 178 (100.0), 150 (25), 144 (46). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 12.22 (1H, s, NH, H-1), 11.72 (1H, s, NH, H-3), 7.69 (1H, dd, *J* = 7.1, 2.8 Hz, H-5), 7.75-7.63 (2H, m, H-6, H-7), 7.02 (1H, dd, *J* = 6.8, 2.5 Hz, H-8); ^{13}C-NMR ($CDCl_3$, 125 MHz): *δ* 165.5 (C-2), 151.7 (C-4), 127.5

(C-5), 123.4 (C-6), 132.0 (C-7), 120.1 (C-8), 121.0 (C-9), 139.8 (C-10).

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