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Use of 5-[2-Ethoxyquinazolin-4-one-3-yl]-2-phthalimidomethylthiadiazole in the Synthesis of *N*- and *C*-Glycosides via Amadori Rearrangement

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Abstract
Synthesis of novel 5-[2- aminoquinazolin-4-one-3-yl]-2- phthalimidomethylthiadiazole **2** from 5-[2-ethoxyquinazolin-4-one-3-yl]-2-phthalamidomethylthiadiazole **1**. The behavior of **2** as a nitrogen nucleophile towards an α-hydroxy-aldehyde, such as glucose and formation of Amadori rearrangement product (ARP) **8** that has had occurred during the course of reaction was discussed.

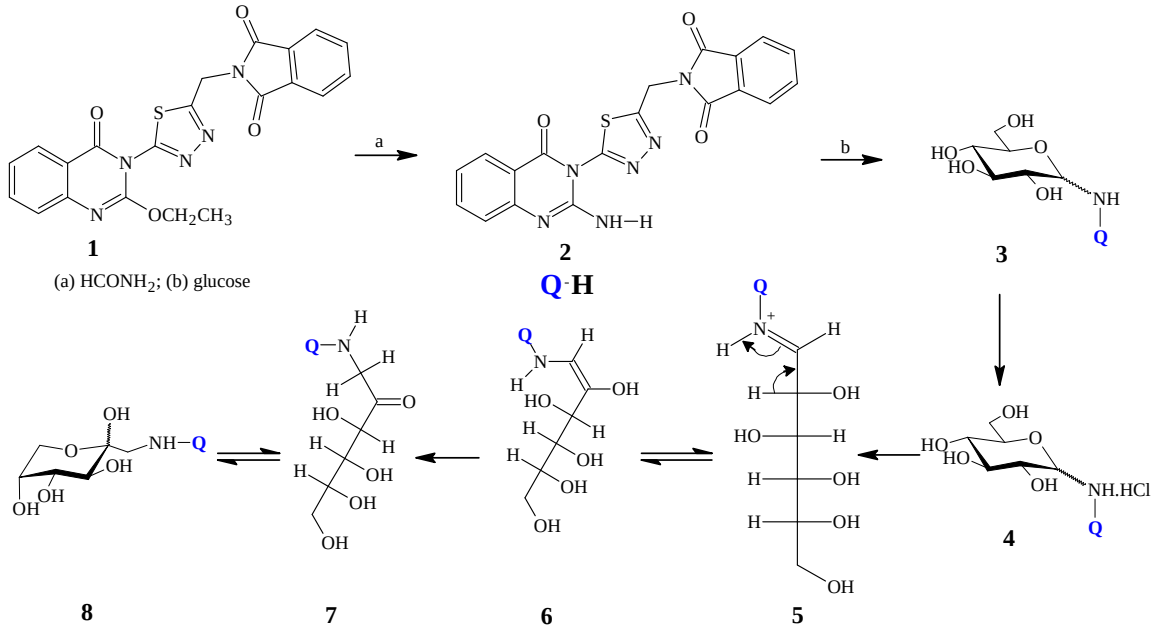
Keywords: *N*-Glycosides, *α*-bromoglucose, Amadori rearrangement, quinazolinone

1. Introduction

In recent years there has been an increasing interest in the chemistry of 4(3*H*)-quinazolinone derivatives because of their biological importance. Many of them show antifungal (Partoli *et al* 1998), antibacterial (Abdel-Hamid *et al* 1997), anticancer (Barker 1995), anti-inflammatory (Bakhit *et al* 1998), anticonvulsant (Gursoy *et al* 1995), immunotropic (Nawrocka *et al* 1997), hypolipidemic (Kuroji *et al* 1996), antitumor (Hame *et al* 1996), antiulcer (Terashima *et al* 1995), analgesic (Hemalatha *et al* 2011), antiproliferative (Raffa *et al* 1999) activities and inhibitory effects for the thymidylate synthase and poly (ADP-ribose) polymerase (PARP) (Baek *et al* 1998). Some of 4-anilinoquinazolines have been found to be potential and highly selective inhibitors of human immunoglobulin E (Berger *et al* 2001) and epidermal growth factor receptor tyrosine kinase (Bridges 2001) which regulates the cell growth and proliferation, so they can work as potent anti-allergic or anti-cancer agents, respectively.

2. Results and Discussion

It is well known that cyclic and acyclic nucleosides often enhance the biological activity of heterocyclic derivatives (Wang *et al* 2010). Herein we synthesized a novel 5-[2-aminoquinazolin-4-one-3-yl]-2-phthalimidomethylthiadiazole from our previously reported biologically active quinazolinone 5-[2-ethoxy-quinazolin-4-one-3-yl]-2-phthalamidomethylthiadiazole (El-Hashash *et al* 2011), and then discussed and reported its behavior as nitrogen nucleophile towards an α-hydroxy-aldehyde, such as glucose. In this paper, it is so important to pay attention to the so-called Amadori rearrangement that has had occurred during the course of reaction. The Amadori reaction, which is the first step in "Maillard browning" (Maillard 1912, Ibid 1912, Ledl *et al* 1990), is a potential non-enzymatic way to link reducing carbohydrates to complex biomolecules with reactive amino groups. The Amadori-rearrangement involves the reaction of α-hydroxy-aldehydes with suitable amine leading to the corresponding glycosylamine and the following rearrangement to the corresponding ketosamine, i.e. the Amadori-rearrangement product (ARP). The early mechanism for the Amadori-rearrangement was suggested by Kuhn and Weygand (1937). The initial reaction between the anomeric position of glucose and amino group of derivative **2** leads to the formation of glycosylamine **3** (Scheme 1). After the protonation the Schiff base **5** is formed by ring opening, which is in equilibrium with the enol **6**. This enol is stabilized by the formation of 1-amino-1-deoxyketohexose **7**, which undergoes ring closure to the corresponding hemiketal **8**.



Scheme 1: Synthetic pathway of the Amadori rearrangement product **8**

3. Experimental:

General

All melting points recorded are uncorrected. The IR spectra were recorded on a Pye Unicam SP 1200 spectrophotometer using the KBr wafer technique. The ^{1}H-NMR spectra were determined on a Varian FT-200, or Bruker AC-200 MHz instrument using TMS as an internal standard. The chemical shifts (δ) are expressed in ppm. The mass spectra were determined using MP model NS-5988 and Shimadzu single focusing mass spectrometer (70 eV). All solvents used were of HPLC/AnalaR grade. All reagents were used as received from Alfa Aesar.

Synthesis of Compounds **2**, **3** and **8**

A mixture of equimolar amounts of 5-[2-ethoxyquinazolin-4(3*H*)-one-3-yl]-2-phthalimidomethylthiadiazole **1** and formamide (0.01 mol) was heated under reflux for 5 h. The mixture was cooled and then poured onto ice/water with frequent stirring. The brown solid that separated out was filtered, washed with water, dried and crystallized from DMF to afford **2**. Stirring derivative **2** (0.01 mol) with glucose (3 equivalents) in methanol (25 mL) at 40 °C for 12 h afforded brownish white syrupy solid of derivative **3**. Protonation of derivative **3** was achieved by washing with an equimolar quantity of dilute hydrochloric acid (0.01 mol), affording light brown precipitate of **4** as the hydrochloride form. The presence of halogen was verified by a green flame with a copper wire. Treatment of product **4** with sodium bicarbonate solution (0.01 mol each) produced a dark brown precipitate which was filtered, washed frequently with water, dried and then crystallized with DMF affording derivative **8**. Purification and separation of **8** was achieved using column chromatography (3:1 EtOAc: Hexane).

5-[2-Aminoquinazolin-4(3H)-one-3-yl]-2-phthalamidomethylthiadiazole **2**: Brown crystals from DMF; m.p. 303-304 ºC; yield 85%. Anal. for $C_{19}H_{12}N_6O_3S$ (m.w. 404): found: C, 56.55; H, 2.99; N, 20.84; S, 7.99; Calcd: C, 56.44; H, 2.97; N, 20.79; S, 7.92. IR υ (cm^{-1}) 1631 (C=N), 1670, 1727, 1776

(3xC=O). MS: *m/z* (int. %) $[M+H]^+$ 404 (58.0), 435 (22.8), 245 (36.4), 247 (3.4), 191(100), 193 (56.1), 186 (78.0), 188 (12.7), 175 (30.1), 177 (8.1), 157 (3.2), 159 (0.1), 147 (8.3), 149 (0.3), 130 (48.3), 132 (6.4), 122 (4.5), 124 (0.2), 78 (0.3), 80 (0.1);^{1}H-NMR (DMSO-d_6) δ 5.16 (s, 2H; CH_2, phthalimidomethyl), 7.32-7.86 (m, 4H, quinazolinone), 7.94-8.03 (m, 4H, phthalimido-H), 9.38(bs, 1H, NH).

2-{[(3S, 5S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl]amino}quinazolin-4(3H)-one **3**: Brownish white syrupy solid from methanol; m.p. > 300 °C; yield 80%. Anal. for $C_{25}H_{22}N_6O_8S$ (m.w. 566): found: C, 56.48; H, 3.01; N, 20.83; S, 7.96; Calcd: C, 56.44; H, 2.97; N, 20.79; S, 7.92. IR υ (cm^{-1}) 1634 (C=N), 1671, 1724, 1776 (3xC=O).

3-(5-Phthalimidomethyl-1,3,4-thiadiazol-2-yl)-2-{[(2,3,4,5-tetrahydroxytetrahydro-2H-pyran-2-yl)methyl)amino} quinazolin-4(3H)-one **8**: Brown crystals from DMF; m.p. 303-304 °C; yield 85 %. Anal. for $C_{25}H_{22}N_6O_8S$ (m.w. 566): found: C, 53.06; H, 3.98; N, 14.92; S, 5.72; Calcd: C, 53.0; H, 3.93; N, 14.84; S, 5.65. IR υ (cm^{-1}) 1631 (C=N), 1670, 1727, 1776 (3xC=O). MS: *m/z* (int. %) $[M+H]^+$ 566 (58.0), 568 (22.8), 245 (36.4), 247 (3.4), 191 (100), 193 (56.1), 186 (78.0), 188 (12.7), 175 (30.1), 177 (8.1), 157 (3.2), 159 (0.1), 147 (8.3), 149 (0.3), 130 (48.3), 132 (6.4), 122 (4.5), 124 (0.2), 78 (0.3), 80 (0.1); ^{1}H-NMR (DMSO-d_6) δ 3.19 (dd, 1H, pyran-H-4), 3.28 (d, 1H, pyran-H-3), 3.55 (m, 1H, pyran-H-5), 3.72 (s, 2H, NHCH_2), 3.81, 3.87 (2 dd, 2H, pyran-H-$6_{a,b}$), 5.17 (s, 2H, phthalimido-CH_2), 7.31-7.75 (m, 4H, quinazolinone), 7.72-7.88 (m, 4H, phthalimido-H), 9.42 (br s, 1H, *NH*).

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