Synthesis of 8-Trifluoromethyl-2-Thioquinazolin-(3H)-4-One Nucleosides

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Received: August 16, 2017   Accepted: October 12, 2017   Online Published: October 17, 2017
doi:10.5539/ijc.v9n4p82 URL: https://doi.org/10.5539/ijc.v9n4p82

Abstract

Synthesis of 8-trifluoromethyl-2-thioquinazolin-(1H,3H)-4-one 2, which have been ribosylated by coupling with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose 4 by using the silylation method, afforded β-anomeric of the benzoylated nucleoside derivatives 5. Debenzylation of 5 by sodium metal in dry methanol to afford the corresponding free nucleosides 6. The structures of the newly synthesis compounds have been confirmed on the basis of elemental analyses, IR, 1HNMR, 13CNMR and Mass spectral data.

Keywords: 1-O-Acetyl-2,3,5-trihydroxy-β-D-ribofuranose, Nucleosides, 2-thioquinazolin-4-one, trifluoromethyl

1. Introduction

Quinazolinone and thioquinazolinone are heterocyclic compounds that occupies a distinct and place in the field of medicinal chemistry. Many of them were showed antimicrobial, anti-inflammatory, anticonvulsant, analgesic and anticancer agents (Abbas S. E., et al, 2013; Kumar A. et al, 2011; Amin K.M. et al, 2010; Aly M.M., 2010; Al-Rashood S.T., 2006 and Mulakayala N., 2012).

Thioquinazoline derivatives have interesting antimicrobial activity against different species of Gram positive bacteria, Gram negative bacteria and pathogenic Fungi, a possible pharmacophore for antitubercular activity and antiviral activity against TMV (Kottke, K., et al, 1997; Zhihua Wan, 2015).

Quinazolinone and thioquinazolinone nucleosides were first synthesized by Stout and Robins in 1968 as pyrimidine nucleoside analogs (Stout M. G and Robins R. K.,1968) and consequent synthetic studies were contributed by Dunkel and Pfleiderer in the 1990s (Hiroshi Takahashi, 1979; Dunkel M and Pfleiderer W, 1991, 1992 and 1993).

Many familiar drugs and pharmacological studies contain trifluoromethyl groups. Quinazoline-2,4-diones and thioquinazolinones bearing a trifluoromethyl group derivatives were an inhibitor of human immunodeficiency virus-1 reverse transcriptase, antagonists at ionotropic glutamate receptors (Hao Chen et al, 2003; Tun-Cheng Chien et al, 2004; Vittoria Colotta, 2012) and anticancer compound trifluoromethyl-substituted pyrazole N-nucleoside (Saleh A. M. et al, 2016).

In this review, 8-trifluoromethyl-2-thioquinazolin-(3H)-4-one nucleosides containing trifluoromethyl and thione groups were designed as part of our continuing interest in the synthesis of new nucleosides as expected their biological activity.

2. Material and Methods

Melting points were measured on Gallenkamp melting point apparatus (UK) and are uncorrected. The purity of the compounds was checked by thin layer chromatography (TLC). Thin layer chromatography (TLC) was performed on silica gel sheets F1550 LS 254 of Schleicher & Schull and column chromatography on Merck silica gel 60 (particle size 0.063–0.20. Elemental analyses were obtained on an Elementary Vario EL 1150C analyzer. IR spectra were recorded on KBr discs on Fourier Transform infrared and Pie Unicom SP 300 Infrared Spectrophotometers at Taif University. 1H NMR and 13C NMR spectra were obtained on a Varian (850 MHz) EM 390 USA instrument at King Abdel-Aziz University by using TMS as the internal reference. Mass spectra were recorded on a JEOL-JMS-AX500 at King Abdel-Aziz University, Saudi Arabia.
3. Experimental

8-trifluoroethyl-2-thioquinazolin-(1H,3H)-4-one 2

2-Amino-3-trifluoroethyl benzoic acid 1 (Aldrich; 0.01mol, 2.05g) isothiocyanate KNCS (1.94mol, 0.02g) and triethylamine (1 ml) in absolute ethanol (30 ml) was heated under reflux for 3 h. The reaction mixture was left to cool and the solvent was removed under reduced pressure. The obtained solid was then washed with petroleum ether, dried and crystallized from ethanol (Alaeefy A. M., 2011; Al-Deeb A. O & Alaeefy A. M., 2008 and Kottke et al., 1977). The compound purified by column chromatography on silica gel with Chloroform : Ethylacetate (9:1) to afford yellow crystals.

Yield (92.30%), w. 3g, m.p. <193-195 °C yellow; crystals.

8-Trihydroxy-3-trifluoroethyl benzoic acid 2 (0.00151 mol, 1.45g), dry absolute methanol (20 ml) and sodium metal (0.055 g, 0.001mol) was stirred at room temperature for 48h. The solvent was evaporated under vacuum to give a colorless solid, which was dissolved in hot water and neutralized with few drops acetic acid. Purification of each compound by TLC chromatographic on silica gel with Chloroform : Ethylacetate (9:1) to afford colorless solid. The obtained solid was then washed with petroleum ether, dried and crystallized from ethanol (Alaeefy A. M., 2011; Al-Deeb A. O & Alaeefy A. M., 2008 and Kottke et al., 1977). The compound purified by column chromatography on silica gel with Chloroform : Ethylacetate (9:1) to afford yellow crystals.

Synthesis of protection nucleoside of 8-trifluoroethyl-2-thioquinazolin-(1H,3H)-4-one 2.

General Procedure.

Silylation of 8-trifluoroethyl 2-thioquinazolin-(1H,3H)-4-one 2 (0.0121 mol 3g) with hexamethyl-disilazane (HMDS) (20 ml) was refluxed for 3days with a catalytic a few crystals of ammonium sulfate under exclusion of moisture. Excess Silylation of 8-trifluoroethyl 2-thioquinazolin-(1H,3H)-4-one 2 (0.001mol) was stirred at room temperature for 48h. The reaction mixture was left to cool and the solvent was removed under reduced pressure. The obtained solid was then washed with petroleum ether, dried and crystallized from ethanol (Alaeefy A. M., 2011; Al-Deeb A. O & Alaeefy A. M., 2008 and Kottke et al., 1977). The compound purified by column chromatography on silica gel with Chloroform : Ethylacetate (9:1) to afford yellow crystals.

Yield (62.50%), w. 2.3 g, m.p. 118oC white; IR ν (cm−1) (KBr) 3342, 1725, 1680; 1HNMR (850MHz); (CDCl3): δ9.47(s, 1H) H3Amide, 8.36 (d, 1H, J = 7.5 Hz) H5, 7.93 (d, 1H, J = 7.2 Hz) H7, 7.92 (dd, 1H, J = 15.7 Hz) H6, 7.81-7.25 (m, 15H) HAr-H, 5.98 (d, 1H, J = 7.5 Hz) H1`, 5.36 (dd, 1H, J = 8.4 Hz) H2`, 5.09 (t, 1H, J = 13. 4 Hz) H3`, 4.72-4.70 (dd, 1H, J = 4.6 Hz) H4`, 6.49-4.36 (m, 1H, H5`). 13CNMR (850MHz) (CDCl3): δ189.2 C=S, 167.13,165.71,165.53 and 158.25 C=O γ-carbons 137.61-124.73 Ar-carbons, 119.32 CF3, 89.52 C1`, 76.47 C2`, 74.93 C3`, 71.98 C4`, 63.82 C5` sugar carbons. Anal. Calcd. for C14H13F3N2O5S; M.wt: 378.32; C,44.45; H,3.45; F,8.17; N, 4.06; S, 4.64 (%); Found: C, 44.26; H, 3.73; F,8.17; N,3.95; S, 4.01 (%).

Deprotection of protection nucleoside to afford the free nucleosides.

General Procedure.

The pure anomer of each β 5 and (0.00151 mol, 1.45g), dry absolute methanol (20 ml) and sodium metal (0.055 g, 0.001mol) was stirred at room temperature for 48h. The solvent was evaporated under vacuum to give a colorless solid, which was dissolved in hot water and neutralized with few drops acetic acid. Purification of each compound by TLC chromatographic on silica gel with chloroform: ethyl acetate (9:1) to afford colorless and white crystals of the following Zemplen et al.’s method (Zemplen et al, 1939) to afford the free nucleosides 6.

β-1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-8-trifluoroethylquinazolin-2,4-2-thione. The protected nucleoside was separated by column chromatography on silica gel with chloroform: Ethylacetate (9:1) as eluent to afford a white crystal pure β-anomeric 5, in good yields.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-8-trifluoroethyl-2-thioquinazolin-(3H)-4-one 5

Yield (62.50%), w. 2.3 g, m.p. 118°C white; IR ν (cm−1) (KBr) 3342, 1725, 1680; 1HNMR (850MHz); (CDCl3): δ 9.47(s, 1H) H3Amide, 8.36 (d, 1H, J = 7.5 Hz) H5, 7.93 (d, 1H, J = 7.2 Hz) H7, 7.92 (dd, 1H, J = 15.7 Hz) H6, 7.81-7.25 (m, 15H) HAr-H, 5.98 (d, 1H, J = 7.5 Hz) H1`, 5.36 (dd, 1H, J = 8.4 Hz) H2`, 5.09 (t, 1H, J = 13. 4 Hz) H3`, 4.72-4.70 (dd, 1H, J = 4.6 Hz) H4`, 6.49-4.36 (m, 1H, H5`). 13CNMR (850MHz) (CDCl3): δ189.2 C=S, 167.13,165.71,165.53 and 158.25 C=O γ-carbons 137.61-124.73 Ar-carbons, 119.32 CF3, 89.52 C1`, 76.47 C2`, 74.93 C3`, 71.98 C4`, 63.82 C5` sugar carbons. Anal. Calcd. for C14H13F3N2O5S; M.wt: 378.32; C,44.45; H,3.45; F,8.17; N, 4.06; S, 4.64 (%); Found: C, 40.26; H, 3.73; F,8.17; N,3.95; S, 4.01 (%).

β-1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-8-trifluoroethylquinazolin-(3H)-4-one 6

Yield (63.00%), w. 0.5g, m.p. <300 °C white color; IR ν (cm−1) (KBr) 3450, 3032, 1715, 1625; 1HNMR (600MHz)(DMSO-D6): δ 11.59 (s, 1H) H3Amide, 8.06 (d, 1H, J = 5.5 Hz) H5, 7.80-7.79 (d, 1H, J = 8.7 Hz) H7, 7.77-7.76 (d, 1H, J = 5.2 Hz) H6, 5.17 (d, 1H, J = 7.5 Hz) H1`, 4.87 (s, 1H) H2`, 4.27 (m, 1H) H3`, 4.15 (t, 1H) H5`, 4.03 (s, 1H) H4`, 3.78-3.76 (m, 1H) H2OH, 3.66-3.61 (m, 1H) H3OH, 3.58-3.41 (m, 1H) H2OH. 13CNMR: 191.0 C=S, 165.07 C=O, 153.63 C5, 139.6, 133.73, 129.92, 128.86, 123.01, 118.96 CF3, 89.89 C1`, 79.31 C2`, 76.41 C3`, 69.29 C4`, 61.63 C5` (Chloroform: Acetone) (9:1); MS m/z: 378 (M+, 11%). Anal. Calcd. for C9H5F3N2O8S; M.wt: 378.32; C,44.45; H,3.45; F,15.07; N, 7.40; S,8.48 (%); Found: C, 44.12; H, 3.75; F,15.51; N,7.10; S, 8.03 (%).
4. Results and Discussion

The structures of the products 2-6 were established and confirmed on the bases of their elemental analyses and spectral data (IR, $^1$H and $^{13}$C NMR) (see the Experimental section) (Scheme 1). Thus, their $^1$H NMR spectra of compound 2 showed doublet signals at assigned to the aromatic protons of H-5 H-6 and H-7 and two a singlet signal of amide NH-3 and NH-1 at δ 11.62, and 11.31, respectively.

$^1$H NMR spectra of compound 5 and 6 showed in each case a doublet signals at δ 5.98 (d, 1H, $J = 7.5$ Hz) H$_1$ for compound 5 and at δ 5.17 (d, 1H, $J = 7.5$ Hz) H$_1$ for free nucleoside compound 6 assigned to the anemic proton of the ribose moiety with spin–spin coupling constant ($J_{1',2'}$) equal to 7.5 Hz, which confirms the $\beta$-anomeric configuration. (Break, 2017; Break et al, 2014; Break et al, 2013; Break & Mosselhi, 2012; Mosselhi & Break, 2011; Break et al, 2010; Chien T.-C. et al, 2005 and Abdullah Hijazi, 1988). The $^1$H NMR of compounds 5 and 6 showed the expected base moiety protons in addition to the sugar moiety protons (see the Experimental section).

The $^{13}$C NMR of nucleoside products revealed the signals are due to the four carbonyl groups at 167.13, 165.71, 165.53 and 158.25C=O's groups for compound 5, while showed the one signal of amide carbons at 165.07 for compound 6. The twenty one signals at 137.61-124.73 Aromatic carbons for compound 5, while disappeared the signals of benzoyl carbons for free nucleoside 6.

The five signals were assigned to C-1', C-2', C-3', C-4', and C-5' of the sugar moiety, at δ 89.52 C$_1'$, 76.47 C$_2'$, 74.93 C$_3'$, 71.98 C$_4'$ and 63.82 C$_5'$ for compound 5, and at δ 89.89 C$_1'$, 79.31 C$_2'$, 76.41 C$_3'$, 69.29 C$_4'$, 61.63 C$_5'$ for compound 6. The $^{13}$C NMR of CF$_3$ group showed at δ 119.80, 119.32 and 118.96 of compounds 2, 5 and 6 respectively (Break, 2016 and Break, 2015. $^{13}$C NMR shifts of C=S group: those of derivatives 2, 5, and 6 lie in the region of 188.2, 189.2 and 190.1 ppm, respectively that of thion groups. (Hanusek J., et al; 2001).

The IR spectrum of compounds 5 and 6 showed the stretching vibration frequencies of the carbonyl C=O groups at 1725 cm$^{-1}$. IR spectra of compounds 6 showed absorptions around 3450 cm$^{-1}$ for (OH) and 1715 cm$^{-1}$ for (C=O).

5. Conclusion

Thioquinazolinone nucleosides are scientific importance in many biologically active compounds. So synthesis and characterization of 8-trifluoromethyl-2-thioquinazolin-(3$H$)-4-one 2. Ribosylation of compound 3 with 1-O-acetyl-2,3,5-tri-O-benzoyl-$\beta$-D-ribofuranose 4 afforded $\beta$-anomeric of the benzoylated nucleoside derivatives 5. Debenzoylation of the latter affording the corresponding new free N-nucleosides 6. Compounds obtained have been identified by their spectral analysis.
References


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