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RESEARCH ARTICLE

SYNTHESIS OF PYRIDO [2,3-D]PYRIMIDIN-2,4(3H)-DIONE NUCLEOSIDE

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ABSTRACT

Pyrido[2,3-d](*1H*,*3H*)-pyrimidin-2,4-dione**2**ribosylated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- –D-ribofuranose3 by using the silylation method, afforded –anomeric of the benzoylated nucleoside **5**. Debenzoylation of compound**5** by sodium metal in dry methanol to afford the corresponding free nucleoside**6**. The structures of the newly synthesis compounds have been confirmed on the basis of elemental analyses, IR, ^{1}HNMR, ^{13}CNMR and Mass spectral data.

INTRODUCTION

The heterocyclic compounds have a great importance in medicinal chemistry. One of the most important heterocycles in medicinal chemistry are quinazolines and Pyrido[2,3-d]pyrimidines. Pyrido [2,3-d] pyrimidinones have been the most a wide range of biological activities, such as antibacterial, antiallergic, antitumor, anti folate, tyrosine kinase, antimicroibial, calcium channel antagonists, antibacterial, anti-inflammatory, analgesic, antihypertensive, antileishmanial, tuber culostatic, anticonvulsants, diuretic, potassium sparing, anti-aggressive activities and inhibitory activity against eukaryotic elongation factor-2 kinase (eEF-2K). (Bystryakova, D. *et al*, 1991; Deb, M. L & Bhuyan, P. J, 2006; Deyanov, A. B *et al*, 1991; Donkor, I.O *et al*, 1995; Ellingboe, J. W & Princeton, N. J, 1996; Fayed, A.A *et al*, 2009; Grivsky, E. M *et al*, 1880; and Ramakrishna Edupuganti *et al*, 2014).Pyrido[2,3-d]Pyrimidin-2,4-dione nucleosides are the most important in medicinal chemistry as potential antitumor agents.(Boshra H. Rizkalla. *et al*, 1972; Andrea B.Staubli& Peter B.Dervan, 1994; and Donald E. Bergstrom*et al*,1982),In the view of interest pyrido[2,3-*d*]pyrimidine-2,4(*3H*)-dione nucleosides [5,6] were synthesized and expected their biological activity.

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MATERIALS 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. ^{1}H NMR and ^{13}C 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.

Experimental

Pyrido [2,3-d] pyrimidin-2,4(*1H*,*3H*)-dione 2

2-Aminonicotinic acid 1 (0.01 mol, 1.38g) was dissolved in water (30 ml), acetic acid (1 ml) and potassium cyantate (0.02 mol, 0.16g),the mixture was stirred at room temperature for 2 hour. The mixture was cooled to 0-5 °C and Aqueous NaOH (1M, 10 ml) was added. The solvent was evaporated under vacuum and neutralized with few drops sulfuric acid. The obtained precipitate was filtered off, washed with water, dried

under vacuum and recrystallized from hot ethanol. White solid, yield = 92%; mp.340 °C (ethanol). ^{1}H-NMR (850 MHz): 11.98 (s, 1H, NH-1), 11.35 (s, 1H, NH-3), 7.67 (s, 1H, H-5), 6.97 (s, 1H, H-6), 6.64 (s, 1H, H-7); ^{13}C-NMR (850 MHz): 161.55 C4, 154.32 C2, 151.30, 128.24, 127.51, 125.10, 124.76.Anal. Calcd. for $C_7H_5N_3O_2$; M.wt. 163.13; C, 51.54; H, 3.09; N, 25.76 (%); Found: C, 51.16; H, 3.33; N,24.95 (%).

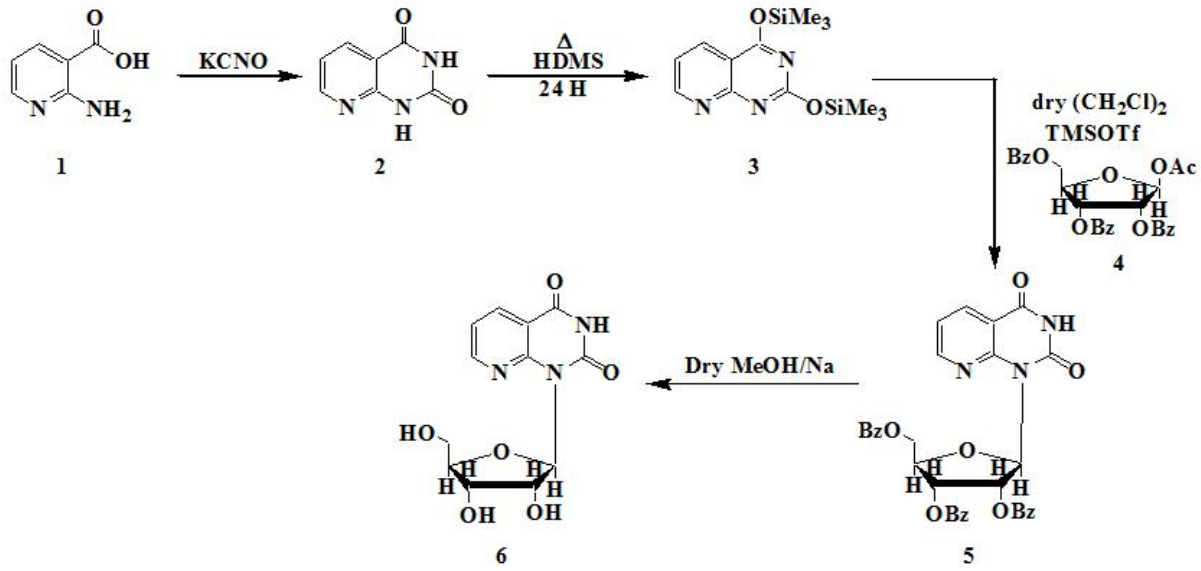
2,4-bis-(trimethylsiIlyloxy)Pyrido[2,3-d]pyrimidine 3

Pyrido[2,3-d]pyrimidin-2,4(*IH,3H*)-dione 2 (0.009mol, 1.5g) with hexamethyldisilazane (HMDS) (20 ml) was refluxed for 48h with a catalytic a few crystals of ammonium sulfate under exclusion of moisture. Excess of HMDS was removed in vacuo by co-evaporation with dry 1,2-dichloroethane gave a colorless oil of the silyated derivative 3, using the Vorbruggen'ssilylation method (Vorbruggen *et al*, 1981).

^{13}CNMR (850MHz) (DMSO): δ 168.02, 165.56, 164.89, 155.83, 146.02, $_{C=O's\ groups}$, 138.62, 137.24, 135.87, 133.68, 133.45, 133.21, 132.92, 131.38, 130.78, 129.44, 129.40, 129.57, 129.31, 129.24, 128.92, 128.89, 128.78, 128.59, 128.62, 128.31, 128.26, 127.64, 127.35,126.15, 121.10$_{Ar\text{-}carbons}$, 92.31 $C_{1'}$, 83.41 $C_{2'}$, 77.98 $C_{3'}$, 74.12 $C_{4'}$, 63.04 $C_{5'sugar\ carbons}$. Anal. Calcd. for $C_{35}H_{25}N_3O_9$; M.wt. 607.57; C, 65.24; H, 4.15; N, 6.92 (%); Found: C, 59.26; H, 3.89; Cl, 14.8; N,3.95 (%).

-1-(2,3,5-Trihydroxy-D-ribofuranosyl)-Pyrido [2,3-d] Pyrimidin-2,4-(*3H*)-dione6

Deprotection of -anomer**5** (0.0032mol, 2g), in dry absolute methanol (15 ml) and sodium metal (0.011 g, 0.0005mol) was stirred at room temperature for two days. The solvent was evaporated under vacuum to give a colorless solid, which was



Scheme (1): Synthesis of Prido[d]pyrimidin-2,4(*3H*)-dione Nucleosides

-1-(2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl)-Pyrido [2,3-d] Pyrimidin-2,4-dione 5

The residue of the silyated derivative **3** was dissolved in 20 ml of dry 1,2-dichloroethane and then 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose4 (0.009mol, 4.5g) was added. The mixture was added dropwise onto a mixture (2ml) of (10 ml trimethylsilyltrifluoromethanesulfonate (TMSOTf) in dry 1,2-dichloroethane (50 ml)). The mixture was stirred for three days at room temperature, and then washed with a saturated solution of aqueous sodium bicarbonate (3 × 50 ml), washed with water (3 × 50 ml), and dried over anhydrous sodium sulfate. The solvent was removed under vacuum gave an anomeric of -1-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)pyrido[2,3-d]pyrimidin-2,4(*3H*)-dione 5. The protected nucleoside was separated by column chromatography on silica gel with chloroform: Acetone (9:1) as eluent to afford a white crystal pure -anomeric5(Scheme 1).

Yield (47.6%), w. 2.6g, m.p. 123-125 °C white; ^{1}HNMR (850MHz); (DMSO): ¢ 9.49 (d, 1H, J= 8.5Hz) 8.21(d, 1H, J= 7.5Hz), 8.91(d, 1H, J= 8.5Hz), 8.75-7.76(m, 15H)$_{H's\ benzyl\ groups}$, 6.85 (d, 1H,J= 7.5Hz) $H_{1'}$, 5.72 (d, 1H, J= 7.5Hz) $H_{2'}$, 5.65-5.61(m,1H) $H_{3'}$, 5.55-5.39 (m,1H) $H_{5'}$, 4.73-4.46(m,1H) $H_{4'}$, dissolved in hot water and neutralized with few drops acetic acid. Purification of compound6 by TLC chromatographic on silica gel with ($CHCl_3$: $CH_3COOCH_2CH_3$) (9 : 1) to afford white crystals of the following Zemplen *et al*.'s method (Zemplen *et al*, 1939) to afford the free nucleoside 6.Yield (82.3 %), w. 0.8g, m.p. <300 °C white color; IR *v* (cm^{-1}) (KBr) 3450, 1714, 1690; ^{1}HNMR (850MHz); (CD_3OD): ¢ 8.53 (s, 1H), 7.92(d,1H), 7.38-7.36 (t, 1H), 7.33-7.32(t, 1H), 6.57 (d, 1H, J= 7.5 Hz) $H_{1'}$; 5.23(d,1H, J= 4.5 Hz) $H_{2'}$, 3.82(d, 1H, J= 7.5 Hz) $H_{3'}$, 3.78-3.75 (m, 1H) $H_{4'}$, 3.78-3.73 (m, 1H) $H_{5'}$, 3.69 (s, 1H) $OH_{2'}$, 3.64-3.62 (m, 1H) $OH_{3'}$,3.53 (s, 1H) $OH_{5'}$. ^{13}C NMR CD_3OD, 168.28, 163.48, 155.71, 136.73, 132.09, 130.23, 127.67$_{Ar\text{-}carbons}$, 84.35 $C_{1'}$, 81.62 $C_{2'}$, 76.04 $C_{3'}$, 65.45 $C_{4'}$, 63.15 $C_{5'}$., MS m/z: 295 (M^+, 27%). Anal. Calcd. for $C_{12}H_{13}N_3O_6$; M.wt. 295.25; C, 48.82; H, 4.44; N,14.23 (%); Found: C, 48.82; H, 4.44; N,14.23 (%).

RESULTS AND DISCUSSION

^{1}H NMR spectra showed a doublet signals at δ 6.85 (d, 1H,*J*= 7.5Hz) $H_{1'}$for compound 5assigned to the anomeric proton of the ribose moiety with spin–spin coupling constant ($J_{1',2'}$) equal to 7.5 Hz, which confirms the *β*-anomeric configuration. (Break , 2017-2015; Break *et al*, 2014; Break *et al*, 2013;

Break &Mosselhi, 2012; and Abdullah Hijazi, 1988). The ^{1}H NMR spectra of nucleosides free showed a doublet signals at δ 6.57 (d, 1H, J= 7.5 Hz) $H_{1'}$for compound 6 spin– spin coupling constant ($J_{1',2'}$) equal to 7.5 Hz -anomeric configuration. The ^{1}H NMR of compounds 5 showed the expected base moiety protons in addition to the sugar moiety protons (see the Experimental section).The ^{13}C NMR ofPyrido[2,3-d]Pyrimidin-2,4(*1H, 3H*)-dione 2 appearedtwo signals of carbonyl amide groups at¢ 161.55 and 154.32. While nucleoside products revealed the signals are due to the three benzoyl carbonyl groupsand the two signals of carbonyl amide groups, at¢168.02, 165.56, 164.89, 155.83 and 146.02 for compound 5, while showed the two signals ofamide carbons at 168.28, and 163.48 for compound 6. The twenty five signals at 138.62-121.10 Aromatic carbons for compound 5. The five signals of free nucleosides at 155.71, 136.73, 132.09, 130.23, 127.67 Aromatic carbons for compound 6.The five signals were assigned to C-1', C-2', C-3' , C-4', and C-5' of the sugar moiety, at δ 92.31 $C_{1'}$, 83.41 $C_{2'}$, 77.98 $C_{3'}$, 74.12 $C_{4'}$ and 63.04 $C_{5'}$for compound 5, at δ 84.35 $C_{1'}$, 81.62 $C_{2'}$, 76.04 $C_{3'}$, 65.45 $C_{4'}$ and 63.15 $C_{5'}$ for compound6.The IR spectrum of compound5 showed the stretching vibration frequencies of the carbonyl C=O groups at 1725 cm^{-1}. IR spectra of compound6 showed absorptions around 3450 cm^{-1} for (OH) and 1715 cm^{-1} for (C=O).

Conclusion

Ribosylation of Pyrido[2,3-d]Pyrimidin-2,4-dione 2 with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose3 afforded mixture -anomeric of the benzoylated nucleoside derivatives 5. Debenzoylation of the latter affording the corresponding free N-nucleosides 6. Nucleosides obtained have been identified by their spectral analysis.

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