New route for the synthesis of 4-amino-pyrimidine-2(1H)-thiones derivatives and their nucleosides

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INTRODUCTION

Synthesis and biological activities of sugar modified nucleoside analogues have been active research areas for many years, since many of these compounds have found useful application in the chemotherapy of cancer and viral infections. Several base modified nucleosides have been reported to act as antiviral and anticancer agents most likely due to their capability to mimic natural counterparts and function (Towensend, 1991). A variety of nucleosides derivatives have been prepared through the deletion or change in natural of the functional group present on the heterocyclic base or their sugar moieties. Such analogues permit the synthesis of oligo-nucleosides in which a single functional group at a preselected position has been deleted or otherwise altered. (Elgemeie et al., 1994, 1997, 1999). As a part of our program directed towards the development of new, simple and efficient procedures for the synthesis of antimetabolites, we reported here the results of our investigation into the utility of the reaction of 4-amino pyrimidine-2(1H)-thiones derivatives with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromides for the synthesis of a new class of pyrimidine S-glucosides (Elgemeie et al., 2002a, 2002b, 2002c).

MATERIAL AND METHODS

All evaporation were carried out under reduced pressure at 40 °C. M.ps are uncorrected. Aluminum sheets coated with silica gel F254 (Merck) were used for TLC. Detection was effected by viewing under a short-wavelength UV lamp. IR spectra were obtained (KBr disk) on a Pye Unicam spectra 1000, 1H NMR and 13C NMR spectra were measured on a Wilmad 270 MHz or on a Vairan 400 MHz Spectrometer for solution in CDCl3 or (CD3)2SO with SiMe4 as internal standard J values are given in Hz. Mass spectra were recorded on varion MAT 112 spectrometer biological activity

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The starting 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (5) was prepared as reported in Vogel’s Textbook of Practical Organic Chemistry.

4-amino-5-alkyl/ or arylidine-6-hydroxy-pyrimidine 2(1H) thiones derivatives (3a–e).

General procedure
A solution of alkyl/or aryl aldehydes (0.01 mol) and ethyl cyano acetate (0.01 mol) in acetone (30 ml) was heated under reflux in the presence of ethyl alcohol and few drops of piperidine for 30 min to 2h, cool a yellowish white precipitate is formed, take (0.01 mol) of alkyl/or arylidene ethyl cyano acetate and (0.01 mol) of thiourea in sodium ethoxide (70 ml) and refluxed in water bath for 2h to give white yellow precipitate after dry make neutralization by HCl ice/H2O.

7a: yellow, from (EtOH); m.p: 150 °C; yield: (50 %), IR: \(\nu_{\text{max}}/\text{cm}^{-1} (\text{KBr}) 1728 \text{ cm}^{-1} (\text{C-O}), \) \(\nu_{\text{OH}}/\text{cm}^{-1}, 3323, 2930, 1720 \text{ cm}^{-1}(\text{C}=\text{O})\). Anal. Calcd. For C17H17N3O4S: m/z = 319. Found: C, 52.70; H, 5.06; N, 7.09; S, 6.59. Found: C, 52.73; H, 5.11; N, 7.13; S, 5.44.

7b: pale yellow, from (EtOH); m.p: 175 °C; yield: (58%), IR: \(\nu_{\text{max}}/\text{cm}^{-1} (\text{KBr}) 1710 \text{ cm}^{-1} (\text{C-O}), \) Anal. Calcd. For C16H12N3O2S: m/z = 283. Found: C, 48.02; H, 5.25; N, 8.43; S, 6.41%.

7c: yellow, from (EtOH); m.p: 180 °C; yield: (60%); U.V: \(\lambda_{\text{max}} 229, 267, 734.\) IR: \(\nu_{\text{max}}/\text{cm}^{-1} (\text{KBr}) 1748 \text{ cm}^{-1} (\text{C-O}), \) \(\nu_{\text{OH}}/\text{cm}^{-1}, 3323, 2930, 1720 \text{ cm}^{-1}(\text{C}=\text{O}).\) Anal. Calcd. For C17H17N3O4S: m/z = 319. Found: C, 52.70; H, 5.06; N, 7.09; S, 6.59. Found: C, 52.73; H, 5.11; N, 7.13; S, 5.44.

7d: yellow, from (EtOH); m.p: 120 °C; yield: (58%), IR: \(\nu_{\text{max}}/\text{cm}^{-1} (\text{KBr}) 1715 \text{ cm}^{-1} (\text{C-O}), \) Anal. Calcd. For C16H12N3O2S: C, 52.70; H, 5.06; N, 7.09; S, 6.40. Found: C, 52.73; H, 5.11; N, 7.13; S, 5.54.

7e: yellow, from (EtOH); m.p: 192 °C; yield: (61%), IR: \(\nu_{\text{max}}/\text{cm}^{-1} (\text{KBr}) 1720 \text{ cm}^{-1} (\text{C-O}), \) Anal. Calcd. For C16H12N3O2S: C, 51.90; H, 4.84; N, 7.26; S, 5.53. Found: C, 51.93; H, 4.89; N, 7.28; S, 5.59%.

2-(α-D-glucopyranosylthio)-4-amino-5-alkyl/ or arylidine-6-hydroxy-pyrimidine derivatives (8a–e).

General procedure
Dry gaseous ammonia was passed through a solution of protected nucleoside (7a-e) (0.5 gm) in dry methanol (20 ml) at 0 °C for 0.5h. then the mixture was stirred at 0 °C for 6h. The mixture was evaporated at 40 °C to give a solid residue which was crystallized from the appropriate solvent.

8a: yellow, from (MeOH); m.p: 176 °C; yield: (42%), IR: \(\nu_{\text{max}}/\text{cm}^{-1} (\text{KBr}) 3425(\text{OH}), \) \(\nu_{\text{N}}/\text{cm}^{-1}, 1777, 3323, 2930, 1720 \text{ cm}^{-1}(\text{C}=\text{O}).\) Anal. Calcd. For C17H17N3O4S: m/z = 319. Found: C, 48.02; H, 5.25; N, 8.43; S, 6.41.

8b: yellow, from (EtOH); m.p: 150 °C; yield: (50 %), IR: \(\nu_{\text{max}}/\text{cm}^{-1} (\text{KBr}) 1728 \text{ cm}^{-1} (\text{C-O}), \) \(\nu_{\text{OH}}/\text{cm}^{-1}, 3323, 2930, 1720 \text{ cm}^{-1}(\text{C}=\text{O})\). Anal. Calcd. For C17H17N3O4S: m/z = 319. Found: C, 52.70; H, 5.06; N, 7.09; S, 6.59. Found: C, 52.73; H, 5.11; N, 7.13; S, 5.44.

8c: yellow, from (EtOH); m.p: 175 °C; yield: (58%), IR: \(\nu_{\text{max}}/\text{cm}^{-1} (\text{KBr}) 1710 \text{ cm}^{-1} (\text{C-O}), \) Anal. Calcd. For C16H12N3O2S: C, 52.70; H, 5.06; N, 7.09; S, 6.40. Found: C, 52.73; H, 5.11; N, 7.13; S, 5.54.

8d: yellow, from (EtOH); m.p: 120 °C; yield: (58%), IR: \(\nu_{\text{max}}/\text{cm}^{-1} (\text{KBr}) 1715 \text{ cm}^{-1} (\text{C-O}), \) Anal. Calcd. For C16H12N3O2S: C, 52.70; H, 5.06; N, 7.09; S, 6.40. Found: C, 52.73; H, 5.11; N, 7.13; S, 5.54.

8e: yellow, from (EtOH); m.p: 192 °C; yield: (61%), IR: \(\nu_{\text{max}}/\text{cm}^{-1} (\text{KBr}) 1720 \text{ cm}^{-1} (\text{C-O}), \) Anal. Calcd. For C16H12N3O2S: C, 51.90; H, 4.84; N, 7.26; S, 5.53. Found: C, 51.93; H, 4.89; N, 7.28; S, 5.59%.

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**Scheme 1:** Synthesis scheme

41.5; H, 5.03; N, 13.20; S, 10.06. Found: C, 41.53; H, 5.08; N, 13.25; S, 10.04%.

8b: yellow, from (MeOH), m.p: 162 °C; yield: (55%). IR: \( \nu_{\text{max}}/\text{cm}^{-1} \) (KBr) 3383 (OH); Anal. Calcd. For C\(_7\)H\(_8\)N\(_3\)O\(_3\): C, 43.37; H, 5.42; N, 12.65; S, 9.63. found: C, 43.39; H, 5.46; N, 12.68; S, 9.67%.

8c: yellow, from (MeOH); m.p.: 130 °C; yield: UV: \( \lambda_{\text{max}} \) 243, 260, 733 (60%). IR: \( \nu_{\text{max}}/\text{cm}^{-1} \) (KBr) 3600-3200(OH). \(^1\)H NMR: \( \delta \) 1.82(s, 1H, CH); 3.35(br, s, 2H, NH\(_2\)); 4.01(m, 2H, H\(_2\)-6'); 4.07(m, 1H, H-5); 4.11(m, 1H, H-4'); 4.14(m, 1H, H-3'); 4.96(m, 1H, H-2'); 4.98(t, 1H, 2'-OH); 5.02(t, 1H, 3'-OH), 5.13(t, 1H, 4'-OH), 5.60(d, 1H, 6'-OH), 5.88(d, 1H, H-1'), 7.56-8.06(m, 4H, Ar-H). \(^{13}\)C NMR: \( \delta \) 61.2(C-6'); 69.9(C-4'); 74.1(C-2'); 82.1(C-3'); 82.2(C-5'); 84.5(C-1'); 168(C-S). MS: (m/z = 395). Anal. Calcd. For C\(_{10}\)H\(_{12}\)N\(_3\)O\(_3\): C, 51.77; H, 5.07; N, 10.65; S, 8.12. Found: C, 52.01; H, 5.09; N, 10.07; S, 8.10%.

8d: pale yellow, from (MeOH), m.p: 150 °C; yield: (75%). IR: \( \nu_{\text{max}}/\text{cm}^{-1} \) (KBr) 3480-3334 (OH); Anal. Calcd. For C\(_{10}\)H\(_{12}\)N\(_3\)O\(_3\): C, 50.94; H, 5.18; N, 9.90; S, 7.54. found: C, 50.79; H, 5.21; N, 9.93; S, 7.51%.

8e: yellow, from (MeOH), m.p: 187 °C; yield: (60%). IR: \( \nu_{\text{max}}/\text{cm}^{-1} \) (KBr) 3200-3600(OH). \(^1\)H NMR: \( \delta \) 1.82(s, 1H, CH);
3.35(br, s, 2H, NH2); 4.01(m, 2H, H-2)); 4.07(m, 1H, H-5)); 4.10(m, 1H, H-4)); 4.14(m, 1H, H-3)); 4.96(m, 1H, H-2)); 4.98(t, 1H, 2'-OH); 5.02(t, 1H, 3'-OH); 5.15(t, 1H, 4'-OH); 5.62(d, 1H, 6'-OH); 5.97(d, 1H, H-1)); 7.65-8.21(m, 4H, Ar-H); 10.2(s,1H,OH); 10.4(s,1H,OH) \(^1\)C NMR: c 61.2(C-6)); 69.9(C-4)); 73.4(C-2)); 80.6(C-3)); 82.5(C-5)); 84.8(C-1)); 169.2(C-S). Anal. Calcd. For C\(_{24}\)H\(_2\)N\(_2\)O\(_5\): C, 45.75; H, 5.43; N, 22.82; S, 17.39. Found: C, 45.61; H, 5.40; N, 22.85; S, 18.02%.

9c: yellow, from (MeOH); m.p.: 140 °C; yield: (65%). Anal. Calcd. For C\(_{12}\)H\(_{11}\)N\(_3\)O\(_5\): C, 45.65; H, 5.43; N, 22.82; S, 17.39. Found: C, 45.61; H, 5.40; N, 22.85; S, 18.02%.

9d: yellow, from (MeOH); m.p.: 165 °C; yield: (75%). U.V: \(\lambda\)max248, 734. IR: \(\text{cm}^{-1}\) (KBr) 2983(C=O); 1.43(s, 1H, CH)); 2.55(s, 3H, SCH3); 3.31(s, 2H, NH2). \(^1\)C NMR: c 13.23(CH3); 24.25(SCH3); 168(C-2). MS: \(m/z = 170\). Anal. Calcd. For C\(_{12}\)H\(_{11}\)N\(_3\)O\(_5\): C, 45.65; H, 5.43; N, 22.82; S, 17.39. Found: C, 45.61; H, 5.40; N, 22.85; S, 18.02%.

9e: pale yellow, from (MeOH); m.p.: 145 °C; yield: (55%). Anal. Calcd. For C\(_{12}\)H\(_{11}\)N\(_3\)O\(_5\): C, 45.62; H, 5.07; N, 15.21; S, 11.59. Found: C, 56.49; H, 5.11; N, 15.19; S, 12.04%.

RESULTS AND DISCUSSION

Compounds (3a-e) were prepared by the reaction of alkyl/or arylidene ethyl cyan acetate (1a-e) with thiourea (2) in sodium ethoxide for 2h to give the corresponding 4-amino-5-alkyl/or arylidene-pyrimidine-2(1H) thiones (3a-e) scheme (1). The structures of compounds (3a-e) were established on the basis of their elemental analysis and spectral data. Thus, structure of (3c) is supported by its mass and \(^1\)H NMR spectra, the latter included a broad band at \(\delta\) 13.09 assigned to the NH proton. Compounds (3a-e) can be coupled with different classes of sugar halides to give a novel ring system of glycosides. Thus it has found that compounds 4-amino-pyrimidine-2-(1H) thiones (3a-e) reacted with 2,3,4,6-tetra-\(\text{O}\)-acetyl-\(\text{β}\)-D-glucopyranosyl bromide (5a) in the presence of aqueous potassium hydroxide to give the corresponding S-glycosides (7a-e) scheme (1). The structure of the reaction products (7a-e) was established on the basis of their elemental analysis and spectral data (MS, \(^1\)H NMR, \(^13\)C NMR). Thus, the analytical data for (7a) revealed a molecular formula C\(_{18}\)H\(_{2}\)N\(_2\)O\(_5\) (m/z 486). IR spectrum of compound (7a) was characterized by the presence of acetoxycarbonyl groups at 1728 cm\(^{-1}\). \(^1\)H NMR spectroscopy was used to confirm this structure for the product. Thus, \(^1\)H NMR spectrum showed the anomic proton as doublet at \(\delta\) 5.01 ppm corresponding to a diaxial orientation of H-1 and H-2 protons indicating the \(\text{β}\)-configuration. The other six protons of the glucopyranosyl ring resided in the \(\delta\) 4.12-5.58 ppm region. The remaining four acetoxycarbonyl groups appear as four singlets at 1.96-2.04 ppm. \(^13\)C NMR spectra were characterized by a signal at 80.4 corresponding to the C-1' atom of the \(\text{β}\)-D-glucopyranose. The four signals appearing at 169.2-169.8 ppm are due to the four acetoxycarbonyl carbon atoms, while the five signals at 20.2-20.4 are attributed to the acetate methyl carbons. Another five signals at \(\delta\) 61.8, 67.7, 69.3, 72.3 and 75.3 were assigned to C-6, A2, V3 and 5 respectively. It may be argued that the coupling reaction of (3) with (5) happened on the nitrogen atom to give the corresponding S-glycosides. However, the formation of the S-glycosides (7a-e) was proved using IR spectra which revealed the absence of the vibration of (C=S) near 1100 cm\(^{-1}\) and appearance of absorbing in (C-S) stretching vibration region about 600-700 cm\(^{-1}\), the same value of the corresponding S-methyl derivatives (9a-e), also the UV spectra of compounds (7a-e) proved that the reaction had led selectively to the formation of S-glycosyl derivatives since the corresponding S-methyl derivatives (9a-e) gave the same UV absorption maxima (Elgemie et al 2005, 2014). For example, the S-methyl derivative (9c) showed two maxima at 248 and 734 nm and its corresponding glucosyl derivative (7c) exhibited three maximum absorption bands at 229, 267 and 734 nm. Also, it was proved using \(^13\)C NMR which revealed the absence of the thione carbon at \(\delta\) 178 ppm and appearance of C-2 at \(\delta\) 169.27 ppm nearly the same value as the corresponding S-methyl derivatives (9a-e). (still et al,1976). Also it was proved using H NMR spectra which characteristic by the presence of band at 11.74 assigned to the NH proton. The protected nucleosides (7a-e) were deblocked through treatment with methanolic ammonia to give the free glycosides (8a-e) after chromatographic purification scheme (1). TLC of compounds (8a-e) showed that a single unique compound was produced and their structures were confirmed by their elemental analysis and spectral data. Thus, the analytical data for compound (8e) revealed a molecular formula C\(_{18}\)H\(_{2}\)N\(_2\)O\(_5\) (m/z = 395). The IR absorption spectra of this compound showed a characteristic band at 3200-3600 cm\(^{-1}\) due to the hydroxyl groups of the glucose moiety. The \(^1\)H NMR spectroscopy was used to confirm this structure for the product. Thus, \(^1\)H NMR spectra

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revealed the presence of a doublet at δ -5.97 ppm, indicating the presence of only the β-D-glucopyranose. The other six glucose protons appear as a multiplet at δ 3.99-4.10 ppm, while the four hydroxyl groups of glucose moiety resonated at δ 4.96, 5.13, 5.16, 5.20 ppm (exchangeable by D₂O). ¹³C NMR spectra were characterized by a signal at δ 80.46 ppm corresponding to the C-1\ atom of β-D-glucopyranose. Another five signals at δ -61.8, 66.2, 72.8, 75.03 and 80.4 ppm were assigned to C-6\, -4\, -2\, -3\ and -5\ of glucose respectively.

CONCLUSIONS

The work describes an efficient synthetic access to S-D-glucosides of pyrimidine-2(1H)-thiones as starting materials for further synthesis transformation. It also expands the synthesis as well as the utility of both base-modified and sugar-modified nucleosides of possible application in the chemotherapy of cancer and viral infections.

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