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A novel and efficient method for the synthesis of 6-amino-pyrimidine-2(1H)-thiones derivatives, pyrido [2,3-d] pyrimidine-2(1H)-thiones derivatives and their glycosides

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Simple condensation reaction of 6-amino-pyrimidine-2(1H)-thiones with aromatic aldhydes afforded 6-(arylidene-amino)-pyrimidine-2-(1H)-thiones derivatives, that react with ∞-nitrostyrene to give pyrido[2,3-d] pyrimidine-2-(1H)-thiones derivatives , the latter compounds served as key intermediate for the synthesis of a new class of pyrimidine-S-glycosides by the reaction with *α*-bromoglucose tetracetate. Deacetylation of glycoside have been achieved The structure of the compounds were established and confirmed on the basis of their elemental analysis and spectral data.

Capsule Summary: A novel synthesis of 6-amino-pyrimidine-thiones derivatives, pyrido [2,3-d] pyrimidine-2-(1H)-thiones derivatives and their glycosides are described.

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INTRODUCTION

The pyrimidinethione nucleosides were recently occupied a significant position in the search for effective antiviral agents and exert inhibitory effects on both DNA and RNA containing viruses (Elgemeie et al., 1990, 1995, 1997 and 2002a). During our studies of nucleoside analogues with novel H-bonding patterns (Elgemeie et al., 1989, 1994 and 2002b). A route for the synthesis of N- or S- nucleosides bearing a substituted pyrimidine ring as a heterocyclic was desired ((Elgemeie et al., 1995 and 2000) and such a route could provide access to a varity of analoguses of pyrimidine nucleosides with novel H-bonding patterns, such nucleosides might serve as components of an expanded genetic "alphabet" of display pharmaceutically useful antimetabolite activity (Elgemeie et al., 1999; Khalil, 2006; 2007).

On the basis of these findings, it was of interest to prepare modified analogous to search for more effective agents. We report here the result of investigation into the utility of the reaction of pyrimidine-2(1H)-thiones derivatives and pyrido [2.3-d] pyrimidine-2(1H)-thiones derivatives with 2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide for the synthesis of a new antimetabolites agents. A condensation reaction was adopted for the synthesis of 6-amino-pyrimidine-2(1H)-thiones with aromatic aldhydes afforded 6-(arylidene-amino)-pyrimidine-2-(1H)-thiones derivatives.

MATERIAL AND METHODS

All evaporations were carried out under reduced pressure at 40 °C M.p.s are uncorrected. Aluminum sheets coated with silica gel F_{254} (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, ^{1}H NMR and ^{13}C NMR spectra were measured on a Wilmad 270 MHz or on a Vairan 400 MHz Spectrometer for solution in $CDCL_3$ or $(CD_3)_2SO$ with $SiMe_4$ as internal standard. J values are given in Hz. Mass spectra were recorded on varion MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Center at Cairo University.

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.

6-(arylidine-amino)-pyrimidine-2(1H)-thinoes derivatives (7a-c)

General procedure: A solution of 6-amino-uracil (1) (0.01 mol) in ethanol as solvent (20 ml) was treated with different aromatic aldehyde compounds (0.01 mol) in presence of piperdine as catalyst, the reaction mixture was heated under reflux for 3h. the solid product was collected by filtration and crystallized from appropriate solvent.

7a: yellow from (EtOH), m.p: 230°C;yield (75%),IR: γ_{max}/cm^{-1} (KBr)2960(NH);$C_{11}H_9N_3OS$ (m/e = 231); calcd: C, 57.14; H, 3.89; N, 18.18; S, 13.85%. Found: C, 57.13; H, 3.87; N, 18.16; S, 13.84%.

7b: yellow from (EtOH), m.p: 255°C;yield (77%),IR: γ_{max}/cm^{-1} (KBr)2966(NH); ^{1}H NMR: δ_H 2.31(s,1H, CH), 2.50(s,3H, OCH_3), 7.10-7.36(m,4H, Ar-H),11.37(br,1H,NH), $C_{12}H_{11}N_3O_2S$ (m/e = 261); calcd: C, 55.17; H, 4.21; N, 16.09; S, 12.26%, Found: C, 55.15; H, 4.20; N, 16.08; S, 12.25%.

7c: yellow from (EtOH), m.p: 210°C;yield (70%),IR: γ_{max}/cm^{-1} (KBr)2962(NH);$C_{11}H_9N_3O_2S$ (m/e = 247); calcd: C, 53.44; H, 3.64; N, 17.00; S, 12.95%. Found: C, 53.45; H, 3.63; N, 16.98; S, 12.94%.

2-(2\,3\,4\,6\-tetra-*O*-acetyl-*β*-*D*-glucopyranosl-thio)-6-(arylidene-amino)- pyrimidine-4-one derivatives (9a-c)

General procedure: To a solution of condensed 6-(arylidine-amino)-4-one-pyrimidine-2(1*H*) thiones (7a-c) (0.01 mol) in aqueous potassium hydroxide [0.56 g, (0.01 mol) in distilled water (6 ml)] was added a solution of 2,3,4,6-tetra-*O*-acetyl-*α*-*D*-glucopyranosyl bromide (3) (4.10 g, 0.01mol) in acetone (30 ml) the reaction mixture was stirred overnight at room temperature, on the next day the mixture was evaporated under reduced pressure at 40°C and the residue was washed with distilled water to remove the potassium bromide formed. The product was dried and crystallized from the appropriate solvent.

9a: yellow from (EtOH): m.p: 110 °C; yield (70%), IR: γ_{max}/cm^{-1} (KBr): 1750 (C=O); $C_{25}H_{27}N_3O_{10}S$; (m/e=561); calcd: C, 53.47; H, 4.81; N, 7.48; S, 5.10%. Found: C, 53.44; H, 4.83; N, 7.42; S, 5.13%.

9b: yellow from (EtOH): m.p: 120 °C; yield (73%), UV: λ_{max}: 267.5, 734.5; IR: γ_{max}/cm^{-1} (KBr): 1725 (C=O); ^{1}H NMR: δ_H 1.92-2.05 (4s, 12H, 4XOAc); 4.05 (m, 2H, 6\-H_2); 4.20 (t, 1H, 5\-H), 5.05 (m, 1H, 4\-H); 5.20 (m, 1H, 3\-H); 5.51 (t, 1H, 2\-H); 6.10 (d, 1H, 1\-H); 7.23-7.59 (m, 5H, Ar-H); 8.03 (m, 5H, phenyl-H); 11.76 (br, s, 1H, NH), ^{13}C NMR: δ_C 21.2 (4XCH_3), 61.7 (CH_2-6\); 67.8(CH-4\); 69.1 (CH-2\); 74.9 (CH-3\); 76.2 (CH-5\); 80.02(C-1\) 105 (C-5); 121-134 (Ar-C); 161 (=C-S-); 152.2 (C-6); 168.3-170.2 (4XC=O); $C_{26}H_{29}N_3O_{11}S$ (m/e=591); calcd: C, 52.79; H, 4.90; N, 7.10; S, 5.41%. Found: C, 52.75; H, 4.86; N, 7.11; S, 5.45%.

9c: yellow from (EtOH): m.p: 127 °C; yield (70%), IR: γ_{max}/cm^{-1} (KBr): 1730 (C=O); ^{1}H NMR: δ_H 1.93-2.0 (4s, 12H, 4XOAc); 4.02 (m, 2H, 6\-H_2); 4.23 (t, 1H, 5\-H); 5.03 (m, 1H, 4\-H); 5.17 (m, 1H, 3\-H); 5.50 (t, 1H, 2\-H); 6.12 (d, 1H, 1\-H); 7.23-7.59 (m, 5H, Ar-H); 8.06 (m, 5H, phenyl-H); 11.73 (brs, 1H, NH); $C_{25}H_{27}N_3O_{11}S$ (m/e=577); Calcd: C, 51.99; H, 4.67; N, 7.27; S, 5.54; Found: C, 52.01; H, 4.69; N, 7.25; S, 5.51.

2-(2\,3\,4\,6\-tetra-*O*-acetyl-*β*-*D*-gluco-pyranosl-thio)-6-amino-pyrimidine-4-one (4)

General procedure: The above procedure for preparation of compounds (9a-c) was followed. 4: white from (H_2O); m.p: 265°C; yield: (78%); IR: γ_{max}/cm^{-1} (KBr): 1725 (C=O); UV: λ_{max}: 267.5, 734; ^{1}H NMR: δ_H 1.95-2.06 (4s, 12H, 4XOAc); 4.07 (m, 2H, 6\-H_2); 4.21 (t, 1H, 5\-H); 5.03 (m, 1H, 4\-H); 5.21 (m, 1H, 3\-H); 5.53 (t, 1H, 2\-H); 6.12 (d, 1H, 1\-H); $C_{18}H_{23}N_3O_{10}S$ (m/e = 473; Calcd: C, 45.66; H, 4.86; N, 8.87; S, 6.76; Found: C, 45.69; H, 4.88; N, 9.01; S, 7.02%.

7-aryl-6-nitroso-5-Phenyl-pyrido-(2,3-d) pyrimidine-2(1*H*) thione-4-one deri-vatives (13a-c)

General procedure: To a solution of 6-(arylidene-amino)-pyrimidine (7a-c) (0.01 mol) in DMF (20 ml) and few drops of piperidene was added *α*-nitrostyrien (12) (0.01 mol), the reaction mixture was heated under reflux for 4h , the solid product formed after pouring into ice/water, the precipitate was filtered off and crystallized from the appropriate solvent.

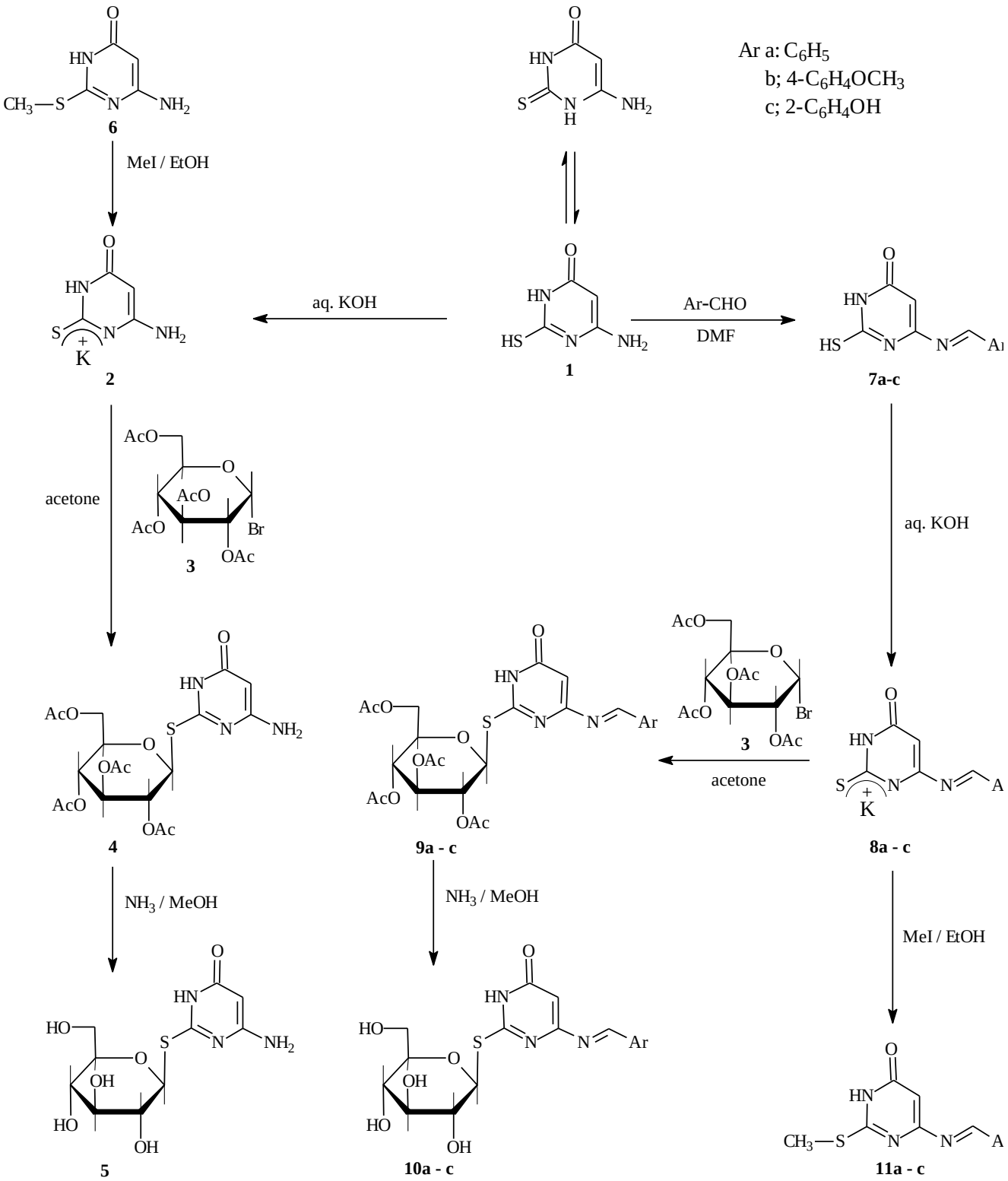
13a: yellow from (EtOH), m.p: 185°C;yield (75%),IR: γ_{max}/cm^{-1} (KBr)3430(OH),2983(NH);$C_{20}H_{12}N_4O_3S$ (m/e = 376); calcd: C, 60.63; H, 3.19; N, 14.89; S, 8.51%. Found: C, 60.65; H, 3.23; N, 14.94; S, 8.54%.

13b: yellow from (EtOH), m.p: 165°C;yield (70%),IR: γ_{max}/cm^{-1} (KBr)3431(OH),2981(NH);$C_{20}H_{14}N_4O_4S$ (m/e = 407); calcd: C, 59.11; H, 3.44; N, 13.79; S, 7.88%. Found: C, 59.15; H, 3.48; N, 13.83; S, 7.92%.

13c: yellow from (EtOH), m.p: 172°C;yield (80%),IR: γ_{max}/cm^{-1} (KBr)3428(OH)2986(NH); ^{1}H NMR: δ_H 7.27-7.48(m,5H, Ar-H); 7.50-7.96(m,5H, Ph-H), 10.34(s,1H, OH); $C_{19}H_{12}N_4O_4S$ (m/e=393); calcd: C, 58.16; H, 3.06; N, 14.28; S, 8.16%, Found: C, 58.22; H, 3.10; N, 14.31; S, 8.21%.

2-(2\,3\,4\,6\-tetra-*o*-acetyl-*β*-*D*-glucopyranosl-thio)-7-aryl-6-nitroso-5-phenyl-pyrido (2,3-d) pyrimidine-4-ol derivatives (15a-c)

The above procedure for preparation of compounds (9a-c) and (4) were followed.



Scheme 1: Synthesis procedure

15a: yellow from (EtOH): m.p: 192 °C; yield (70%), IR: γ_{max}/cm^{-1} (KBr): 1725 (C=O); ^1H NMR: δ_H 1.95-2.03(4s, 12H, 4XOAc), 4.02 (m, 2H, 6\-H_2); 4.26 (t, 1H, 5\-H); 5.10-5.53 (m, 3H, 4\-H, 3\-H, 2\-H); 6.13 (d, 1H, 1\-H); 7.20-7.52 (m, 5H, Ar-H); 8.86 (m, 5H, phenyl-H);$C_{33}H_{30}N_4O_{12}S$; (m/e): 706; calcd: C, 56.09; H, 4.24; N, 7.93; S, 4.53%. Found: C, 56.06; H, 4.21; N, 7.92; S, 4.55%.

15b: yellow from (EtOH): m.p: 180 °C; yield (75%), IR: γ_{max}/cm^{-1} (KBr): 1725 (C=O); $C_{34}H_{32}N_4O_{13}S$ (m/e) = 736; calcd: C, 55.43; H, 4.34; N, 7.60; S, 4.34%. Found: C, 55.46; H, 4.37; N, 7.64; S, 4.36%.

15c: yellow from (EtOH): m.p: 140 °C; yield (73%), UV: λ_{max}: 214.5, 257.5, 733.5; IR: γ_{max}/cm^{-1} (KBr): 1730 (C=O); ^1H NMR: δ_H 1.95-2.15 (4s, 12H, 4XOAc); 4.05 (m, 2H, 6\-H_2); 4.20 (t, 1H, 5\-H), 5.05-5.50 (m, 3H, 4\-H, 3\-H); 5.53 (t, 1H, 2\-H); 6.13 (d, 1H, 1\-H); 7.47 (m, 4H, Ar-H); 8.76 (m, 5H, phenyl-H); ^{13}C NMR δ_C 21.5 (4XCH_3), 61.8 (6\-CH_2); 67.4(4\-CH); 69.3 (2\-CH); 75.01 (3\-CH); 76.3 (5\-CH); 80.1 (1\-CH); 105 (C-5); 120-134 (Ar-C); 167.1 (=C-S-); 151.3 (C-6); 168.1-170.2 (4XC=O); $C_{33}H_{30}N_4O_{13}S$; (m/e) = 722; calcd: C, 54.84; H, 4.15; N, 7.75; S, 4.43%. Found: C, 54.81; H, 4.11; N, 7.73; S, 4.42%.

2-(*β-D*-gluco-pyranosylthio)-6-(arylidene-amino)pyrimidine-4-one derivatives (10a-c)

General procedure: Dry gaseous ammonia was passed through a solution of protected nucleoside (9a-c) (0.5 gm) in dry methanol (20 ml) at 0°C for (1h) and keep the mixture stirring at 0°C until reaction was judged to be complete (2-6h), the mixture was evaporated at 40°C to give a solid residue which was purified by chromatography or by crystallized from the appropriate solvent.

10a: white from (MeOH), m.p: 173 °C, yield (58%), IR: γ_{max}/cm^{-1} (KBr): 3200 -3600 (OH); ^1H NMR: δ_H 2.06 (s, 1H, CH); 4.01-4.18 (m, 6H, 6\-H_2, 5\-H, 4\-H, 3\-H); 4.88 (m, 1H, 4\-OH); 4.92 (m, 1H, 2\-OH); 4.95 (m, 1H, 3\-OH); 5.20 (m, 1H, 4\-OH); 5.49 (d, 1H, 1\-H); $C_{17}H_{19}N_3O_6S$; (m/e) = 393; calcd: C, 51.90; H, 4.83; N, 10.68; S8.14%. Found: C, 51.93; H, 4.87; N, 10.69; S, 8.15%.

10b: white from (MeOH), m.p: 161 °C, yield (62%), IR: γ_{max}/cm^{-1} (KBr): 3200 -3600 (OH); ^1H NMR: δ_H 1.98 (s, 1H, CH); 3.25-3.72 (m, 6H, 6\-H_2, 5\-H, 4\-H, 3\-H); 4.88 (m, 1H, 4\-OH); 4.92 (m, 1H, 2\-OH); 4.95 (m, 1H, 3\-OH); 5.20 (m, 1H, 4\-OH); 5.49 (d, 1H, 1\-H); ^{13}C NMR δ_C 58.1 (CH, C-8); 60.08 (CH_2, 6\-H_2), 69.10 (CH, C-4\); 69.20 (CH, C-2\); 75.50 (CH, C-3\); 80.03 (CH, C-5\); 82.5 (CH, C-1\); 123.10 (CH, C-5); 161.0 (=C-S); $C_{18}H_{21}N_3O_7S$; (m/e=423); calcd: C, 51.06; H, 4.96; N, 9.92; S, 7.56%. Found: C, 51.09; H, 5.01; N, 9.90; S, 7.58%.

10c: pale yellow from (MeOH); m.p: 193 °C, yield (55%), IR: γ_{max}/cm^{-1} (KBr): 3200 -3600 (OH); $C_{17}H_{19}N_3O_7S$; (m/e=409); calcd: C, 49.78; H, 4.64; N, 10.26; S, 7.82%. Found: C, 49.75; H, 4.61; N, 10.29; S, 7.78%.

2(*β-D*-gluco-pyranosyl thio)-6-amino-pyrimidine-4-one (5)

The above procedure for preparation of compounds (10a-c) and (4) were followed.

5: white from (MeOH), m.p: 179 °C, yield (56%), IR: γ_{max}/cm^{-1} (KBr): 3200 -3600 (OH); ^1H NMR: δ_H 1.96 (s, 1H, CH); 3.25-3.72 (m, 6H, 6\-H_2, 5\-H, 4\-H, 3\-H); 4.92-4.99 (m, 3H, 4\-OH, 2\-OH, 3\-OH); 5.39 (m, 1H, 4\-OH); 5.43 (d, 1H, 1\-H); 10.20 (br, 2H, NH2); $C_{10}H_{15}N_3O_6S$; (m/e) = 305; calcd: C, 39.34; H, 4.91; N, 13.77; S, 10.49%. Found: C, 39.31; H, 4.95; N, 13.79; S, 10.46%.

2-(*β-D*-gluco-pyranosylthio)-7-aryl-6-nitroso-5-phenyl-pyrido (2,3-d) pyrimidine-4-ol derivatives (16a-c)

The above procedure for preparation of compounds (10a-c) and (5) were followed.

16a: yellow from (MeOH), m.p: 123 °C, yield (63%), IR: γ_{max}/cm^{-1} (KBr): 3200 -3600 (OH); ^1H NMR: δ_H 3.42-3.66 (m, 6H, 6\-H_2, 5\-H, 4\-H, 3\-H); 4.95 (m, 1H, 4\-OH, 2\-OH); 5.08 (m, 1H, 2\-OH); 5.17 (m, 1H, 3\-OH); 5.23 (m, 1H, 4\-OH); 562 (d, 1H, 1\-H); 7.23 (m, 5H, Ar-H); 7.50-8.06 (m, 5H, phenyl-H); $C_{25}H_{22}N_4O_8S$; (m/e) = 538; calcd: C, 55.76; H, 3.11; N, 10.40; S, 5.95%. Found: C, 55.72; H, 3.14; N, 10.46; S, 5.98%.

16b: yellow from (MeOH), m.p: 119 °C, yield (60%), IR: γ_{max}/cm^{-1} (KBr): 3200 -3600 (OH); $C_{26}H_{24}N_4O_9S$; (m/e) = 568; calcd: C, 54.92; H, 4.22; N, 9.85; S, 5.63%. Found: C, 54.96; H, 4.20; N, 9.81; S, 5.65%.

16c: yellow from (MeOH), m.p: 110 °C, yield (66%), UV: λ_{max}: 238.5, 259.5, 733.5; IR: γ_{max}/cm^{-1} (KBr): 3200 -3600 (OH); ^1H NMR: δ_H 3.40-3.63 (m, 6H, 6\-H_2, 5\-H, 4\-H, 3\-H); 4.92 (m, 1H, 4\-OH); 5.02 (m, 1H, 2\-OH); 5.13 (m, 1H, 3\-OH); 5.21 (m, 1H, 4\-OH); 5.42 (d, 1H, 1\-H); ^{13}C NMR δ_C 60.0 (CH_2, 6\-H); 69.1 (CH, 4\-C); 69.2 (CH, 2\-C); 75.5 (CH, 3\-C); 80.0 (CH, 5\-C); 89.01 (CH, 1\-C); 167.0 (=C-S); $C_{25}H_{22}N_4O_9S$; (m/e) = 554; calcd: C, 54.15; H, 3.97; N, 10.10; S, 5.77%. Found: C, 54.77; H, 3.95; N, 10.13; S, 6.01%.

2-Methylthio-6-amino-pyrimidine-4-one (6)

General procedure: A solution of compound (1) (0.01 mol), methyl iodide (0.01 mol) and potassium hydroxide (0.01 mol) (16 ml) and ethanol (20 ml) was stirred at 60°C, a white solid began to precipitate immediately, stirring was continued for (30 min) and the mixture allowed to cool, the solid was collected, wash with water, dried and recrystallized from ethanol.

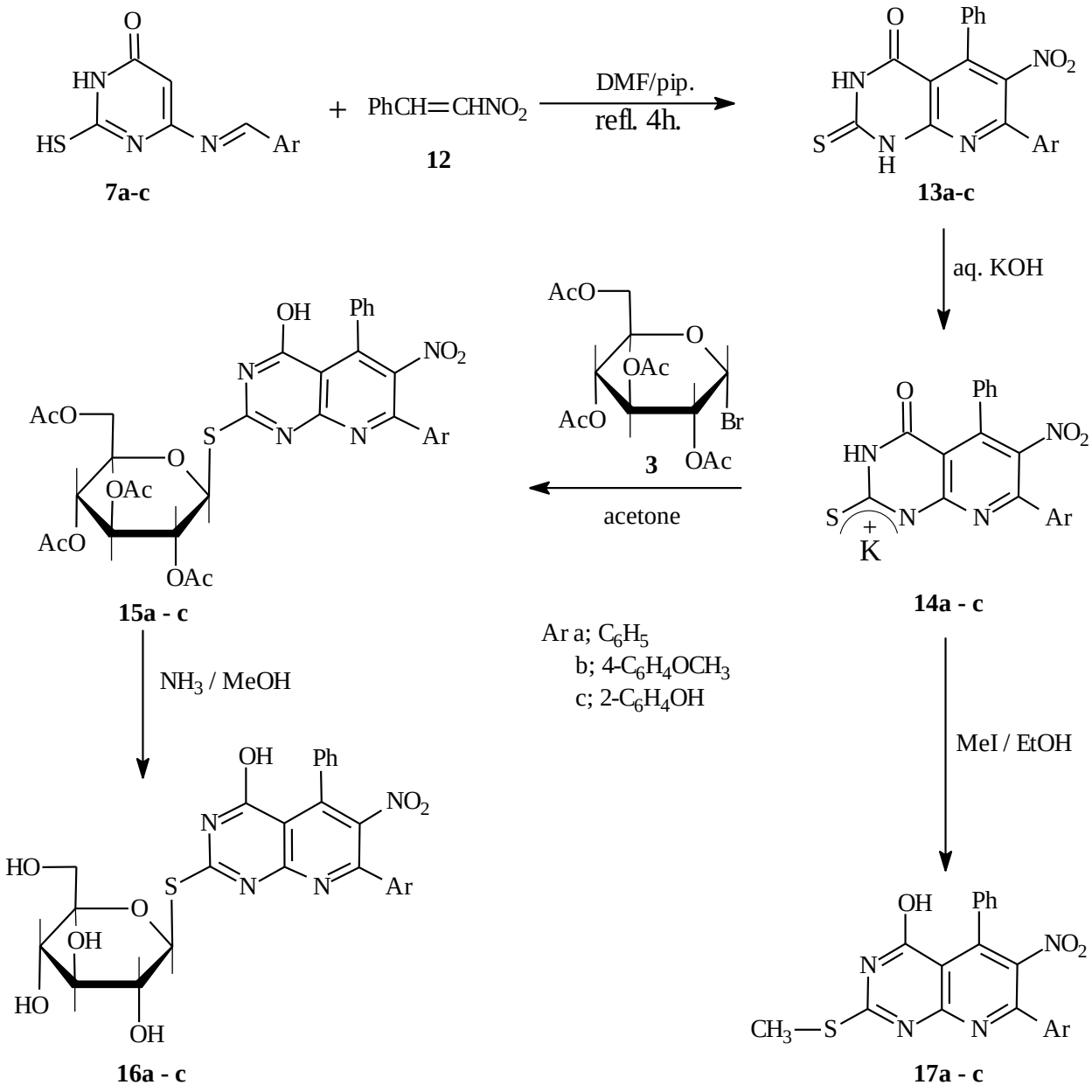
6: yellow from (EtOH), m.p: 203 °C, yield (80%), IR: γ_{max}/cm^{-1} (KBr): 1551 cm^{-1} (C=N); UV: λ_{max}, 213, 267, 733; ^1H NMR: δ_H 2.50 (s, 3H, CH_3); 1.9 (t, 1H-CH); 3.34 (m, 1H-4-OH); 6.83 (br, 2H, NH_2); 7.33-7.41 (d, 1H, pyrimidine-H); $C_5H_7N_3OS$; (m/e) = 157; calcd: C, 38.21; H, 4.45; N, 26.75; S, 20.38%. Found: C, 38.18; H, 4.41; N, 26.79; S, 20.42%.

2-methylthio-6-(arylidine-amino)-pyrimidine-4-one derivatives (11a-c)

The above procedure for preparation of compound (6) was followed.

11a: yellow from (EtOH), m.p: 195 °C, yield (78%); IR: γ_{max}/cm^{-1} (KBr): 1553 cm^{-1} (C=N); $C_{11}H_{11}N_3OS$; (m/e) = 233; calcd: C, 56.65; H, 4.72; N, 18.02; S, 13.73%. Found: C, 56.61; H, 4.68; N, 18.06; S, 13.69%.

11b: yellow from (EtOH), m.p: 187 °C, yield (75%); UV: λ_{max}, 229, 267, 734; IR: γ_{max}/cm^{-1} (KBr): 1551 cm^{-1} (C=N); ^1H NMR: δ_H 2.58 (s, 3H, SCH_3); 3.90 (s, 3H, OCH_3); 7.65-7.72 (m, 4H, Ar-H); ^{13}C NMR: δ_C 13.23 (CH_3); 104 (Ar-C); 161 (=C-S); $C_{13}H_{13}N_3O_2S$; (m/e) = 275; calcd: C, 56.72; H, 4.72; N, 15.27; S, 11.63%. Found: C, 56.70; H, 4.75; N, 15.31; S, 11.66%.



Scheme 2: Synthesis procedure

11c: yellow from (EtOH), m.p: 250 °C, yield (65%); IR: γ_{max}/cm^{-1} (KBr): 755 cm^{-1} (C-S); $C_{12}H_{11}N_3O_2S$; (m/e) = 261; calcd: C, 55.17; H, 4.21; N, 16.09; S, 12.26%. Found: C, 55.21; H, 4.25; N, 16.05; S, 12.29%.

2-Methyl thio-7-aryl-6-nitroso-5-phenyl-pyrido (2,3-d) pyrimidine-4-ol derivatives (17a-c)

The above procedure for preparation of compounds (6) and (11a-c) was followed.

17a: white from (EtOH), m.p: 234 °C, yield (60%); UV: λ_{max}, 243.5, 257.5, 733.5; IR: γ_{max}/cm^{-1} (KBr): 1551 cm^{-1} (C=N); $C_{20}H_{14}N_4O_3S$; (m/e=390); calcd: C, 61.53; H, 3.58; N, 14.35; S, 8.20%. Found: C, 61.56; H, 3.61; N, 14.32; S, 8.18%.

17b: white from (EtOH), m.p: 241 °C, yield (68%); IR: γ_{max}/cm^{-1} (KBr): 1496 cm^{-1} (C=N); ^{13}C NMR: δ_C 14.2 (CH_3); 105 (Ar-C); 121 (Ph-C); 166.5 (=C-S); $C_{21}H_{16}N_4O_4S$; (m/e) = 420; calcd: C, 60.0; H, 3.80; N, 13.33; S, 7.61%. Found: C, 59.97; H, 3.84; N, 13.30; S, 7.64%.

17c: white from (EtOH), m.p: 170 °C, yield (73%); ^1H NMR: δ_H 2.53 (s, 3H, SCH_3); 6.98-7.73 (m, 5H, Ar-H); 8.03 (m, 5H, phenyl-H); $C_{20}H_{14}N_4O_4S$; (m/e) = 406; calcd: C, 59.0; H, 3.44; N, 13.79; S, 7.88%. Found: C, 59.15; H, 3.48; N, 13.82; S, 7.91%.

RESULTS AND DISCUSSION

Heating of thiourea with ethylcyanoacetate in sodium ethoxide for 2h gave the corresponding 6-amino-pyrimidin-2(1H)-thione (1) (scheme 1). Simple condensation reaction of 6-amino pyrimidin-2(1H)-thione (1) with appropriate aromatic aldehydes in *N*,*N*-dimethyl formamid with few drops of acetic acid afforded the corresponding condensation products 6-(arylidene-amino)-pyrimidine-2(1H)-thiones derivatives (7a-c) in good yields, the structure of compounds (7a-c) were established on the basis of their elemental analysis and spectral data thus, the structure of compound (7b) is supported by its mass and ^{1}H NMR the latter include a broad band at δ_H (11.37) assigned to the NH proton. Compounds (7a-c) and (1) can be coupled with different classes of sugar halied to give a novel ring of glycosides. Thus, it has been found that compounds (7a-c) reacted with 2,3,4,6-tetra-*O*-acetyl-*α*-*D*-glucopyranosyl bromide (3) in the presence of aqueous potassium hydroxide to give the corresponding S-glycosides (9a-c). the structure of the reactions products (9a-c) were established and confirmed for the reaction products on the basis of their elemental analysis and spectral data (MS, IR, ^{1}H NMR, UV, ^{13}C NMR). Thus, the analytical data for (9b) revealed a molecular formula $C_{26}H_{29}N_3O_{11}S$ (m/z = 591). ^{1}H NMR spectroscopy was used to confirm this structure for the product. Thus ^{1}H NMR spectrum showed the anomeric proton as doublet at δ_H 6.21 ppm with spin-spin coupling contant of (J = 11.28 Hz) corresponding to a diaxial orientation of H-1\ and H-2\ proton indicating the β-configuration. The other six protons of the glucopyranosyl ring resonated in the δ_H 4.05-5.51 ppm region the remaining four acetoxy groups appear as four singlet at δ_H 1.92-2.05 ppm; IR spectrum of compound (9b) was characterized by the presence of acetoxy carbonyl groups at 1725 cm^{-1}. The ^{13}C NMR spectrum was characterized by a signal at δ_C 80.02 corresponding to the C-1\ atom of the *β*-*D*-glucopyranose the four signals appearing at δ_C 168.3-170.2 were due to the four acetoxy carbonyl carbon atoms while the four signals at δ_C 20.02-20.18 were attributed to the acetate methyl carbons. Another five signals at δ_C 61.7, 67.8, 69.1, 74.9 and 76.2 were assigned to C-6\, 4\, 2\, 3\ and 5\ of the glucose part, respectively. It could have been argued that the coupling reaction of (7a-c) with (3) happened on the nitrogen atom to give the corresponding N-glycosides. However, the formation of the *S*-glycosides (9a-c) 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 (11a-c) also, the UV spectra of compound (9a-c) proved that the reaction had led selectively to the formation of *S*-glycosyl derivatives since the corresponding *S*-methyl derivatives (11a-c) gave the same UV absorption maxima. For example, the *S*-methyl derivative (11b) showed two maxima at 267.5 and 733.5 nm and its corresponding glucosyl derivative (9b) also exhibited two maximum absorption bands at 267 and 733 nm. Also, it was proved using ^{13}C NMR which revealed the absence of the thione carbon at δ_C 178 ppm and appearance of C-2 at δ_C 161 ppm nearly the same value as the corresponding *S*-methyl derivatives (11a-c) scheme 1 (Still et al 1976)(Stefaniak. I. 1979).

The protected nucleosides (9a-c) were deblocked through treatment with methanolic ammonia to give the free glycosides (10a-c) after chromatographic purification. TLC of compounds (10a-c) showed that a single unique compound was produced, and their structure were confirmed by their elemental analysis and spectral data. Thus the analytical data for compound (10b) revealed a molecular formula $C_{18}H_{21}N_3O_7S$ (m/z = 423). ^{1}H NMR spectroscopy was used to confirm this structure for the product. Thus, ^{1}H NMR spectra revealed the presence of a doublet at δ_H 5.49 ppm (J = 10.75 Hz) indicating the presence of only the *β*-*D*-glucopyranose the other six glucose protons appear as a multiplet at δ_H 3.25-3.72 ppm while the four hydroxyl groups of glucose moiety resonated at δ_H 4.88, 4.92, 5.20 and 5.39 ppm (exchangeable by D_2O). 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 ^{13}C NMR spectrum was characterized by a signal at δ_C 82.5 corresponding to the C-1\ atom of the *β*-*D*-glucopyranose the four signals appearing at δ_C 168.3-170.2 were due to the four acetoxy carbonyl carbon atoms while the four signals at δ_C 20.02-20.18 were attributed to the acetate methyl carbons. Another five signals at δ_C 60.08, 69.01, 69.2, 75.5 and 80.03 were assigned to C-6\, 4\, 2\, 3\ and 5\ of the glucose part respectively.

6-(arylidene-amine)-pyrimidine-2(1H)-thiones (7a-c) react with α-nitrostyrene in *N*,*N*-dimethyl formamide and catalytic amount of piperidine reflux for (4h) to give pyrido-[2,3-*d*]-pyrimidine-2(1*H*)-thiones derivatives (13a-c) (scheme 2). The structures of compounds (13a-c) were established on the basis of their elemental analysis and spectral data. Thus, structure of compound (13c) is supported by its mass and ^{1} H NMR. The latter include abroad band at (14.21 ppm) assigned to the NH proton. Compounds (13a-c) can be coupled with different classes of sugar halides to give a novel ring system of glycosides. Thus it has found that compounds pyrido [2,3-*d*] pyrimidine-2(1*H*)-thiones (13a-c) reacted with 2,3,4,6-tetra-*O*-acetyl-*α*-*D*-glucopyranosyl bromide (3) in the presence of aqueous potassium hydroxide to give the corresponding S-glycosides (15a-c), the structure of the reaction products (15a-c) was established on the basis of their elemental analysis and spectral data (MS, IR, ^{1}H NMR, UV, ^{13}C NMR). Thus, the analytical data for (15c) revealed a molecular formula $C_{33}H_{30}N_4O_{13}S$ (m/z = 722). ^{1}H NMR spectroscopy was used to confirm this structure for the product, thus ^{1}H NMR spectrum showed the anomeric proton as doublet at δ_H 6.13ppm with spin-spin coupling constant of (J = 11.23 Hz) corresponding to a diaxial orientation of H-1\ and H-2\ protons indicating the *β*-configuration. The other six protons of glucopyranosyl ring resonated in the δ_H 4.05-5.53 ppm the remaining four acetoxy groups appear as four singlet at δ_H 1.5-205 ppm. IR spectrum of compound (15c) was characterized by the presence of actoxy carbonyl groups at 1730 cm^{-1}. The formation of *S*-glycosides (15a-c) was proven using IR spectra which showed the absence of the vibration of (C=S)

near 1100 cm^{-1} and appearance of absorbing in (C-S) stretching viberation region about 600-700 cm^{-1}, the same value of the corresponding S-methyl derivatives (17a-c). Also, the UV spectra of compound (15a-c) proved that the reaction had led selectively to the formation of *S*-glucosyl derivatives since the corresponding *S*-methyl derivatives (17a-c) gave the same UV absorption maxima. For example, the *S*-methyl derivative (17a) showed maxima at 243.5, 257.5 and 733.5 nm and its corresponding glucosyl derivative (15c) also exhibited maximum absorption bands at 236, 257.5, 733.5 nm. Also, it was proved using ^{13}C NMR which revealed the absence of the thione carbon at δ_C 178 ppm and appearance of C-2 at δ_C 167 ppm nearly the same value as the corresponding *S*-methyl derivatives (17a-c).

The protected nucleosides (15a-c) were deblocked through treatment with methanolic ammonia to give the free glycosides (16a-c) after chromatographic purification TLC of compounds (16a-c) showed that a single unique compound was produced and their structure were confirmed by their elemental analysis and spectral data, thus the analytical data for compound (16c) revealed a molecular formula $C_{25}H_{22}N_4O_9S$ (m/z = 554). IR absorption spectra of the compound (16c) showed a characteristic band at 3200-3600 cm^{-1} due to the hydroxyl groups of the glucose moiety. The ^1H NMR spectra revealed the presence of a doublet at δ_H 5.62 ppm (J = 10.50 Hz), indicating the presence of only the *β-D*-glucopyranose, the other six glucose protons appear as a multiplet at δ_H 3.40-3.63 ppm, while the four hydroxyl groups of glucose moiety resonated at δ_H 5.02, 5.13, 5.21, 5.42 ppm (exchangeable by D_2O). The ^{13}C NMR spectrum was characterized by a signal at δ_C 82.1 corresponding to the C-1\ atom of the *β-D*-glucopyranose the four signals appearing at δ_C 168.3-170.2 were due to the four acetoxy carbonyl carbon atoms while the four signals at δ_C 20.02-20.18 were attributed to the acetate methyl carbons. Another five signals at δ_C 60.1, 69.1, 70.2, 75.5 and 81.9 were assigned to C-6\, 4\, 2\, 3\ and 5\ of the glucose part, respectively.

CONCLUSIONS

The formation of the S-glucosides was proven using ^{13}C NMR which revealed the absence of the thione carbon and the appearance of the C-2 carbon of the same value of the corresponding S-methyl derivative. Also the IR spectra showed the absence of the vibration of (C=S) and appearance of absorbing in C-S the same value of the corresponding S-methyl derivative and the UV spectra proved that the reaction had led selectively to the formation of S-glucosyl derivatives since the corresponding S-methyl derivatives gave the same UV absorpation maxima. In summary, we have achieved a regiospecific synthesis of interesting pyrimidine glycosides by the reaction of substituted pyrimidine-2(1*H*)-thiones derivatives with *α*-halosugers. The glycosides can be utilized as an excellent stating material for the synthesis of other carbohydrate derivatives and for biological evaluation studies.

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REFERENCES

Elgemeie, G.E.H., Attia, A.M., 1995, Synthesis of some N-hexapyranosyl-2-pyridones and -2-pyridinethioes Carbohydrate Research 32, 268-295.

Elgemeie, G.H., Ahmed, M.A., 2002**a**, A new class of biheterocyclic thioglycosides from pyridine 2-(1H)-thiones; Nucleosides Nucleotides and Nucleic acids 21(11,12), 837-847.

Elgemeie, G.E.H., Elfahham Hassan, A., Nabey Hesham A., 1988, *α*-β-unsaturated nitriles in heterocyclic synthsis of pyridines and thieno [2,3-b] pyridine derivatives, Bull chem. Bulletin of the Chemical Society of Japan 61, 4431-4433.

Elgemeie G.E.H., Attia, A.M.E., Farag, D.S., Sherif M.S., 1994. Direct route to condensed pyridine thione carbocyclic nucleosides related to 3-deazauridine, Journal of the Chemical Society, Perkin Transactions 1, 1285-1293.

Scala, S., Akhmed, N., Rao, U.S., Paull, K., Lan, L.B., Dickstein, B., Lee, J.S., Elgemeie, G.H., Stein, W.D., Bates, SE., 1997. P-glycoprotein substrates and antagonists cluster into two distinct groups. Molecular Pharmacology 51, 1024-1033.

Ussain Badria, A., Attia, Adel M., Elgemeie, G.E.H., 1999. Synthsis of N-glycoslated pyridines as new animetabolites agents; Nucleosides, Nucleotides and Nucleic acids 18, 2335-2343.

Elgemeie, G,E,, Attia, A,M,, Alkabai, S,S., 2000. Nucleic acid components and their analogues: New synthsis of bicyclic thiopyrimidine, Nucleosides. Nucleotides and Nucleic acids 19, 723

Elgemeie G.E.H., 2002b. A direct route to 2-(β-D-ribofuraoslthio) pyridine glycosides; Nucleosides, Nucleotides and Nucleic acids 21 (6,7), 411-416.

Furniss, B.S., Hannaford, A.J., Rogers, V., Smith, P.W.G., Tatchell, A.R., 1978. Vogel's Textbook of practical organic chemistry, 4th ed. Longman Group Limited: Harlow, UK, P: 457.

El-Sayed, H.A., Moustafa, A.H., Haikal, A.Z., Abdou, I.M., El-Ashry, E.S.H., 2008. Synthsis and evaluation of antimicrobial activity of some pyrimidine glucosides; Nucleosides, Nucleotides and Nucleic acids 27(9), 1061-1071.

Khalil, N.S.A.M., 2007. N- and S-*α*-L-arabino pyranosyl [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazoles. First synthsis and

biological evaluation, European Journal of Medicinal Chemistry 42, 1193-1199 .

Khalil, N.S.A.M., 2006. Efficient synthsis, structure and antimicrobial activity of some novel N- and S-β-D-glucosides of 5-pyridine-3-yl-1,2,4-triazoles, Carbohydrate Research 341, 2187-2199.

Elgemeie, G.E.H., Regaila, H.A., Shehata, N., 1990. Unexpected poducts of the reaction of cycloalkylidene (cyano)-thioacetamides with arylmethylenemalono nitriles: A different novel routes to condensed pyridine 2-(1H)-thiones and condensed carbocyclic nitriles. Journal of the Chemical Society, Perkin Transactions 1, 1267-1273.

Stefaniak., 1979. Nitrogen -14 and Carbon -13 NMR of Tantomeric Systems of Mercapto – and Amino –Pyridines Organic Magnetic Resonance 12, 379–382.

Still I.W.J., 1976. Carbon-13 nuclear magnetic resonance spectra of organic sulfur compounds. Comparison of chemical shifts for carbonyl and thiocarbonyl compounds in the pyrone, thiopyrone and pyridine series. Canadian Journal of Chemistry 54, 280–289.

Towensed, L.B., 1991, In Chemistry of Nucleosides and Nucleotides, Plenum Press, New York, Vol (1 and 2).