Synthesis and behavior of 4- arylphthalazin-1(2H)thione derivatives towards carbon and nitrogen electrophiles

M.A.El-Hashash; A.H-Moustafa; R.S.Ali

Abstract— 4-methylphenylphthalazin-1(2H)-thione (4-a) has been reacted with alkylating agents namely propargil bromide, allyl bromide, epichlorohydrin-2,3,4,6-tetracetyl-β-D-glucopyranosyl bromide, and peracetylated ribose and yielded the S-alkylated products. Interaction of 4-(3,4-dimethylphenyl) phthalazin-(2H)-one with D-glucono-1,5 lactone and 2,3,4,6-tetraacetoxy-α-D-glucopyranosyl bromide yielded the N-nucleosides 10 and 11 respectively.

Interaction of 4-(3,4-dimethylphenyl) phthalazin-(2H)-one with D-glucono-1,5 lactone and 2,3,4,6-tetraacetoxy-α-D-glucopyranosyl bromide yielded the N-nucleosides 10 and 11 respectively.

Treatment of (3,4-dimethylphenyl) phthalazin-1-(2H)-thione(4b) with hydrazine hydrate afforded the hydrazine derivative 12. Heteroring opening of D-glucono-1,5-lactone by the hydrazine derivative 12 gave the N-nucleoside derivative 17.

Furthermore, reaction of the hydrazine derivative with D-glucose gave the corresponding hydrazone 13. Treatment of hydrazone 13 with acetic anhydride followed by bromination gave acetylated cyclic C-nucleoside 15 which converted to free C-nucleoside via its reaction with ammonium hydroxide and methanol.

Index Terms— methylphthalazine – D-glucopyranosylbromide – peracetylatedribose - D-glucono-1,5 lactone -2,3,4,6- tetraacetoxy-α-D-glucopyranosyl bromide - N-nucleoside - acetylated cyclic C-nucleoside.

1 INTRODUCTION

Nitrogen containing heterocyclic molecules constitutes the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals. Phthaiazin-1(2H)-ones are important building blocks in the construction of new molecular systems for biologically active molecules (1-3).

The development of new and efficient methodologies for synthesis of potentially bioactive phthaiazin-1(2H)-one derivative is important. Phthaiazin-1(2H)-ones are of considerable interest due to their antidiabetic(4), antiallergic(5), vasrelaxant(6), PDE4 inhibitors(7), VEGF (vascular endothelial growth factor) receptor tyrosine kinesis for the treatment of cancer(8,9), antiasthmatic agents with dual activities of thromboxane A2 (TXA2) synthetase inhibition and bronchodilation(10), herbicidal(11), like activities. A number of established drug molecules like hydralazine(12,13), budralazine(14,15), azelastine(16,17), ponalrestat(18) and zopolrestat(19) are prepared from the corresponding phthaiazinones.

Due to the nature of the phthaiazine nucleus, Synthesis of new derivatives becomes an important issue. There has been little reported in the literature concerning phthaiazin-
1(2H)-thione. It was for that reason that we decide to synthesize new phthaiazin-1(2H)-thione derivatives.

**Results and discussion**

In this article we report the synthesis of new 4-arylphthaiazin-1(2H)-thione derivatives 4a and b according to (scheme 1). Compound 3 was obtained by cyclization of acylbenzoic acid 2 using hydrazine hydrate. The later was made through a friedel-crafts reaction between aromatic hydrocarbon and phthalic anhydride.

![Reaction scheme 1](image1.png)

**Scheme (1)**

Reation of compound 3 with phosphorus penta sulphide in boiling xylene afforded 4 arylyphthaiazin-1(2H)-thione (4a) and (4b). IR spectrum displayed absorption bands in the region 3450-3460 and 1240-1255 Cm\(^{-1}\) NH and C=S groups. \(^1\)HNMR showed a signal at δ 12.72 ppm for NH or SH from SH group. Here the \(^1\)HNMR spectra of N\(_2\)sulphide in tautomer is pulling of the bromide anhydrous and acetone CO\(_2\) in the presence of K\(_2\)CO\(_3\) using hydrazine hydrate. The later was glucopyranosyl bromide and peracetylated 2-SH experimental. Nitrile is more thermodynamically stable than the conjugate base derived from thioamide tautomer via the back donation involving the vacant d-orbital of the sulphur atom. Therefore, the iminothiol tautomer is more predominate under such conditions.

Firstly, in the presence of K\(_2\)CO\(_3\) anhydrous and acetone the conjugate base of the iminothiol tautomer is more thermodynamically stable than the conjugate base derived from thioamide tautomer via the back donation involving the vacant d-orbital of the sulphur atom. Therefore, the iminothiol tautomer is more predominate under such conditions.

Secondly, sulphur anion is strong nucleophile than nitrogen anion (nucleophilicity is kinetic control). Thus, the iminothiol tautomer is more thermodynamically and kinetically favored than the thio amide tautomer, which practically spells out the reactivity of the iminothiol tautomer.

Compound 4a undergoes alkylation with 2,3,4,6-tetra acetoxy-β-D-glucopyranosyl bromide and peracetylated ribose in presence of anhydrous K\(_2\)CO\(_3\) and dry acetone to give 4-(4-methylphenyl)-1-(2,3,4,6-tetra acetoxy) -β-D-...
glucopyranosyl) thiophthalazine (6) and 4-(4-methylphenyl)-1-(2,3,5triacetoxy)β-D-ribofuranosyl)thiophthalazine (7) with very low yield. A 10% riboside 7 was obtained by MW irradiation of 4a with peracetylated ribose for 5 min.

The IR spectra for S-nucleosides 6 and 7 showed absorption bands at 1737 and 1739 cm$^{-1}$ for acetoxy groups. $^1$HNMR spectrum of glycoside 6 showed signals at $\delta$ 81.81, 1.93, 1.95 and 2.02 for 4-acetoxy groups and at 56.35 PPM as doublet signal characteristic for anomeric proton with coupling constant ($j=9.6$Hz) indicate the formation of B-configuration. While $^1$HNMR spectrum of ribose 7 showed signals at $\delta$ 2.03 and 2.07 and 2.09 characteristic for 3-acetoxy groups and doublet signal at 6.44 PPM characteristic for anomeric proton. The elemental analysis data assigned structure of S-nucleosides 6 and 7. (cf. experimental part.)

The deprotection of S-nucleosides 6 and 7 in presence of MeOH/TEA and few drops of water afforded the free nucleosides 8 and 9 respectively in 85% yields.

The IR spectra are in agreement with the structureand revealed the absence of V of acetoxy groups and presence of bands at 3595 and 3415 cm$^{-1}$ for free VOH groups of free nucleosides.$^1$HNMR spectra of nucleosides 8 and 9 showed the absence of the methyl protons for the acetoxy groups and presence of signals for the OH groups which exchangeable with D$_2$O, in addition to signals at $\delta$ 5.72 and 6.25 PPM with coupling constant ($j=6.6, 3.8$ HZ) characteristic for the anomeric protons.

**Scheme(2):** Alkylation with functionalized alkyl halides

In this investigation the outer sought to investigate heterotiring opening of D-glucono-1,5-lactone with phthalazinone derivative 3b with the aim of obtaining N-nucleoside incorporated with phthalazinone moiety.

Actually, some N-nucleoside was shown to exhibit prominent and versatile biologically activity$^{20,21}$. Indeed, the phthalazinone 3b was allowed to react with with D-glucono-1,5-lactone in pyridine afforded N-nucleoside derivative, 2-gluconyl-4(3,4-dimethylphenyl)-2H-phtha;azin-1-one (10). Additionally, when
phthalazinone 3b was glycosidated by coupling with 2,3,4,6-tetraacetoxy-α-D-glucopyranosylbromide (α-ABG) in the presence of sodium carbonate solution in N,N-dimethylformamide, it gave 2-(2,3,4,6-tetra acetoxy)-β-D-glucopyranosyl)-4-(3,4 dimethyl-phenyl)-2H-phthalazine-1-one(11).

\[ \text{Scheme (3)} \]

- a) D-glucono-1,5-lactone/pyridine
- b) 2,3,4,6-tetraacetoxy-α-D-glucopyranosylbromide (α-ABG), Na2CO3/DMF
- c) N2H4/ethanol

\[ 3b, X=O \]
\[ 4b, X=S \]

2,3,4,6-tetraacetoxy-α D-glucopyranosylbromide (α-ABG) in the presence of sodium carbonate solution in N,N-dimethylformamide, it gave 2-(2,3,4,6-tetra acetoxy)-β-D-glucopyranosyl) -4-(3,4 dimethyl-phenyl)-2H-phthalazine-1-one(11).

\[ \text{Scheme (4): Synthesis of N-nucleoside and C-nucleoside analogues} \]

- d) D-glucose/AcOH
- e) AcO/pyridine
- f) Br2/AcOH
- g) NH4OH/MeOH
- f) D-glucono-1,5-lactone/pyridine

Deprotection of 15 using ammonium hydroxide solution in methanol gave the target free cyclic C-nucleosides 16. This reaction was suggested to proceed via dimroth type rearrangement where the triazolo [1, 5-a]phthalazine was converted to triazolo[3,4-a]phthalazine.1 HNMR spectrum of compound 16 revealed signals of the D2O exchangeable OH protons at δ3.10-3.50 and 3.7 (m, 2H, proton of triazole moieties) and the absence of the acetyl protons. The IR data of compound 16 showed also the absence of the acetyl function and the appearance of the characteristic OH’s band at 3370cm. Finally, the hydrazinophthalazine 12 react...
with D-glucono-1,5-lacton in pyridine and gave the

EXPERIMENTAL

Melting points are uncorrected. IR spectra (KBr disc) were recorded on FTIR-400, (Perkin-Elmer) spectrophotometer. \(^1\)H, \(^13\)CNMR spectra were recorded on a Varian 200,500 MHz and 300MHZ all chemical shifts were reported as \(\delta\) ppm scale using TMS as the standard and coupling constant values are given in HZ. The elemental analysis was determined at Microanalysis center, Cairo University.

General procedure for synthesis of (4-arylphthalazin-1(2H)-thione)(a and b).

The phthalazines (3a and b) (0.01 mol) in dry xylene (30mL) was treated with phosphorus penta sulphide (0.01 mol) and then the reaction mixture was stirred under reflux for 1 hour. Filtered off and concentrate the solvent and the solid obtained was crystallized from

4-(4-Methylphenyl)phthalazin-1-(2H)-thione(4a):

Yield 96% mp 230-231°C IR (KBr) 3450 (v NH), 1243 (v C=O).\(^1\)HNMR(DMSO-d6) \(\delta\): 2.39(s,3H,CH\(_3\)), 7.31(d,2H,J=8.00 HZ, ArH), 7.43(d,2H,J=7.80 HZ,ArH), 7.65-8.32(m,4H,ArH), 12,72(s,1H,NH).\(^1\)3CNMR: 21,40(CH\(_3\)), 123,61, 24,2,125,3,127,1,129,6,130,2,133,3,133,5,134,1,139,3,1, and 179.5 (Ar-C, C=N and C=S). Anal. Calculated for C\(_{18}\)H\(_{18}\)N\(_2\)S (252.33): C, 71.41, H, 4.79, N, 11.10 Found: C, 71.48; H, 4.75; N, 11.13.

4-(3,4-Diphenylmethylene)phthalazin-1(2H)thionone(4b):

Yield 87% mp 187-188°C IR (KBr) 3460(v NH), 1255(v C=O).\(^1\)HNMR(DMSO-d6) \(\delta\): 1.57(s,3H,CH\(_3\)), 7.28(s,1H,ArH), 7.45(d,2H,J=7.82HZ,ArH), 7.66-8.31(m,4H,ArH), 12.51(s,1H,SH) Anal. Calculated for C\(_{20}\)H\(_{17}\)N\(_2\)S (266.36): C, 72.15; H, 5.30; N, 10.52 Found C, 72.35; H, 5.15; N, 10.90.

General procedure for synthesis of compounds [a-c]

A mixture of the appropriate alkyl halide namely propargyl bromide, allyl bromide and epichlorohydrin (0.02 mol), thione 4a (0.01 mol) and anhydrous potassium carbonate (0.04 mol) in dry acetone (50 mol) was heated under reflux for 15 hrs. The excess solvent was removed by evaporation, then the reaction mixture was diluted with water, the solid that obtained was filtered off and crystallized from ethanol.

1-(prop-2-ynythio)-4-(4-Methylphenyl)phthalazine(5a):

Yield 65%; mp 133-134°C.\(^1\)HNMR (DMSO-d6) 82.43 (s,3H, ArCH), 3.21 (t,1H,J=1.5 HZ,acetylenic proton), 4.32(d,2H,J=2.4 HZ,SCH), 7.39(d,2H,J=7.6 HZ, ArH), 7.58(d,2H,J=7.90 HZ,ArH), 8.00-8.32 (m,4H,ArH).\(^1\)3CNMR : 8 19.50 and 21.40 (SCH and CH), 74 and 80.50 (C ArC, 123.6, 124.6, 125.2, 127.1, 129.6, 130.2, 133.2, 134.0, 139.3, 157.3, 157.7(ArC and 2 C=N). Anal. Calculated for C\(_{18}\)H\(_{18}\)N\(_2\)S (290.38): C, 74.75,H,4.86;N,9.65 Found : C, 74.52; H, 4.88; N, 9.98.

1-(allythiolio)-4-(4-Methylphenyl)phthalazine (5b):

Yield 70%; mp 144-146°C.\(^1\)HNMR (DMSO-d6) \(\delta\): 82.34 (s,3H,ArCH), 4.12 (m,2H,SCH), 5.50-5.18 (m,2H,terminal olefinic proton), 6.00 (m,1H,olefinic proton), 7.28 (d,2H,J=7.8 HZ,ArH), 7.49 (d,2H,J=7.70 HZ,ArH), 7.99-8.28 (m,4H,ArH). Anal. Calculated for C\(_{18}\)H\(_{18}\)N\(_2\)S (292.40): C, 73.94,H,5.52;N,9.58 Found : C,73.90;H,5.56;N,9.49.

1-(oxiran-2-ylmethylthio)-4-(4-Methylphenyl)phthalazine (5c):

Yield 65% mp 118-120°C.\(^1\)HNMR (DMSO-d6) \(\delta\): 82.34 (s,3H,ArCH), 2.623,95 (DD,2H,J=9.10,1.80HZ,CH), 4.23,4.51 (DD,2H,J=7.10,5.3 HZ,diasterotopic protonsofoxiranering), 6.22 (m,1H,sterogenic protons of oxiran ring), 7.35 (d,2H,J=7.06HZ,ArH), 7.46(d,2H,J=7.90 HZ,ArH), 7.57-8.32 (m,4H,ArH).\(^1\)3CNMR: 21.4(CH\(_3\)), 32.8(SCH\(_3\)), 53.3 and 55.3 and 55.80 (CH\(_2\)O and CHO of oxiran ring) 127.1,127.6,128.6, 129.5, 129.8, 132.2, 132.4,134.1, 139.2 , 146.7 , 157.5 and 158.2 (Ar-C and 2 C=N) . Anal. Calculated for C\(_{18}\)H\(_{18}\)N\(_2\)O\(_2\) (308.40): C, 70.10 , H, 5.23; N, 9.08 Found: c, 70.12; H, 5.20; N, 9.09.

4-(4-Methylphenyl)-1-(2,3,4,6-tetraacetoxy-\(\beta\)-D-glucopyranosylthio)phthalazine(6):

A Solution of 2,3,4,6-tetraacetoxy-B-D-glucopyranosyl bromide (0.015 mol), anhydrous potassium carbonate (0.02 mol) and compound 4a (0.01 mol) in dry acetone (50 mL) was heated under reflux for 24 hrs. The excess solvent was removed by distillation, then the reaction was dilute with water, the solid that obtained was filtered off and crystallized from ethanol. Yield 25%, mp 95-97°C. IR (KBr)1737(vC=Oacetoxyugar).1HNMR(DMSO-d6) \(\delta\): 1.81,m1.93,1.95and2.02(4s,12H,4-CH\(_3\)CO), 2.49(s,3H, ArCH\(_3\)), 4.01(m,2H,H5andH-6), 4.36(m,2H,CH\(_2\)OCOCH\(_3\)).
phthalazine(7):

Method A
A mixture of thione 4a (0.01mol), anhydrous potassium carbonate (0.02mol), peracetylated ribose (0.015mol) in dry acetone 50 mL was heated under reflux for 24 hrs. the excess solvent was removed by distillation, then the reaction mixture was diluted with water, and the solid that separated was crystallized from ethanol to give riboside 7 (yield Ca 10%).

Method B:
A mixture of thione 4a (0.01mol), and peracetylated ribose (0.015mol), was dissolved in methylene chloride, then 1 gm silica gel (200-400mesh) was added, the solvent was removed by evaporation and dried residue was irradiated for 5 minutes in a domestic microwave oven. The product was extracted with methylene chloride evaporated to dryness and purified by recrystallization from ethanol.

Yield 20% mp 92-94 °C. IR(KBr) 1739(ν C=O acetoxy group).1H NMR (DMSO-d6): δ2.03, 2.07 and 2.09 (3x, CH3-CHO), 2.49 (s, 3H, CH3), 4.05 (dd, 1H, J 5.5=11.2 Hz, H3-H5), 4.11 (dd, 1H, J 4.5=4.6 Hz, 4.5=5.5 Hz, H4-H5). 5.38 (t, 1H, J2,3=3Hz, H2), 6.44 (d, 1H, J1.2=2.4 Hz, H-1), 7.37 (d2, HJ1,2=7.8 Hz, ArH), 7.50 (d, 2H, J7.8 Hz, ArH), 7.78-8.08 (m, 4H, ArH). Anal. Calculated for C29HsN15O9 (496.53) ;C, 60.47; H, 4.87; N, 5.64 Found: C, 60.19; H, 4.12; N, 5.48.

4-(3,4-Methylphenyl)-2-glucosyl-(2H)phthalazine-1-one(10):
A mixture of compound 3a (0.01mol), D-glucosyl-1,5-lactone (0.015) in pyridine (30mL) was heated under reflux for 2 hours. The reaction mixture after cooling was poured on to ice / hydrochloric acid. The solid that obtained was filtered off and crystallized from ethanol. Yield 72%; mp 288 °C. IR(KBr) 1665, 1675 (ν C=O), 3390 (νOH).1H NMR (DMSO-d6): δ2.02, 2.38 (s, 2Ar-CH3), 3.539 (m, 3H, H5-H5-H3), 6.44 (m, 3H, H1-H2-H3), 3.84 (m, 4H, 4-H2-OH, 3-OH, 4-OH, 5-OH), 4.81 (s, 1H, 1-OH), 7.37-8.22 (m, 7H, ArH). Anal. Calculated for C39H29N15O13 (657.54); C, 61.68; H, 5.60; N, 6.54 Found C, 61.62; H, 5.60; N, 6.56.

2-(2,3,4,6-Tetraacetoxy-B-D-glucopyranosyl)-4-(3,4-dimethylphenyl)-2H-phthalazine-1-one(11):
A mixture of compound 3a (0.01 mol), 2,3,4,6-Tetraacetoxy-B-D-glucopyranosyl bromide (0.015mol), Na2CO3 (0.02mol) in DMF (40mL) was heated under reflux for 6 hours. The reaction mixture was diluted with water and the solid that obtained was filtered off and crystallized from ethylacetate/hexane. Yield 45%; mp180 °C. IR (KBr) 1665, 1745, 3370 of νmax carbonyl groups and νOH.1H NMR (DMSO-d6/D2O): δ2.22, 2.40 (2s, 6H, Ar-CH3), 4.11, 4.26 (2dd, 2H, GERMINAL PROTONS OF 6-Ha and with coupling constant at 3.05, 5.35 and 12.25HZ.
corresponding to j,5,6b,j6b,6a respectively),5.12-5.61(3H,2-H,3-H,4-H),6.11(d,J=5.53Hz,1-H),7.37-8.22(m,7H,ArH). Anal.Calculated for C₆H₅N₂O₁₆ (580) C,62.06;H,5.51;N,4.82 Found : C,62.08; H,5.54; N,4.81.

1-(3,4-dimethylphenyl)-2H-phthalazine-1-one(12):
A mixture of thione 4b (0.01mol),hydrazide hydrate “(0.03mol) in ethanol (50mL) was heated under reflux for 5 hours. The reaction mixture was allowed to cool and separated solid that obtained was filtered off and crystallized from dioxin. Yield 70% mp 268-270°C . EIMS m/s (264). Anal. Calculated for C,62.68;H,6.05;N,13.14. Found: C,62.67;H,6.05;N,13.14.

Aceticacid2,3,4,5-Tetraacetoxy-1-[4-(3,4-Dimethylphenyl)-phthalazine-1-yl]-hydrazonomethyl]pentylester(14):
A solution of compound 14 (0.01mol) in glacial acetic acid (20mL) was stirred at room temperature for 20 hours. The reaction mixture was poured into ice-water with stirring and the solid that separated was collected by filtration and crystallized from ethanol. Yield 65% mp 166-167°C . IR (KBr)1248(v ca),1605(v c=O ),1720(v c=O ) and 3100 (vNH) Anal.Calculated for C₆H₅N₂O₁₆ (580) C,62.27;H,5.92;N,9.68 Found: C,60.31;H,5.64;N,8.83.

(1S)-Per-O-acetyl-1-C-[4-(3,4-Dimethylphenyl)-1,2,4-triazolo[3,4-a]phthalazine-2-yl]-D-arabinitol(15):
To a solution of compound 15 (0.01mol) in glacial acetic acid (20mL),bromine (0.01mol) in glacial acetic acid(5mL),was added drop with at room temperature. The reaction mixture was heated under reflux for 1 hour, cooled, poured into water with stirring. The solid that separated was crystallized from ethanol. Yield 55% mp 210-212°C. IR(KBr)1640(vC=N ),1735(v c=O ).1HNMR(DMSO-d₆) δ 1.9-2.2(m,15H,5OCOC₆H₃),2.28 and 2.46(2s,6H,Ar-CH₃),4.05(m,2H,methyl-eneprotons),4.2-5.5(m,4H,4CHOAC)7.1-8.2(m,7H,ArH). Anal.Calculated for C₆H₅N₂O₁₆C,60.18;H,6.00;N,8.77 Found: C,60.46;H,5.37;N,8.85.

(1S)-C-[4-(3,4-Dimethylphenyl)-]1,2,4-triazolo[3,4-a]phthalazine-2-yl]-D-arabinitol(16):
To a solution of compound 15 (0.01mol) in anhydrous methanol (30mL), ammonium hydroxide solution (5mL,35%) was added,then the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was evaporated under reduced pressure and the residue was purified on silica gel column using chloroform methanol (4:1) as eluent to give 16. Yield 55% mp above 300°C . IR(KBr) 1644(vc=o),3341(vOH ). Anal. Calculated for C₂H₅N₂O₁₀ (428); C,61.67;H,6.59;N,13.08. Found: C,62.28;H,5.64;N,13.14.

2,3,4,5,6-Pentahydroxyhexanoicacid-N-[4-(3,4-dimethylphenyl)phthalazine-1-yl]hydrazid (17):
A mixture of compound 12 (0.01mol) and D-glucono-1,5-lactone (0.01mol) in pyridine (20mL) was refluxed for 2 hours. The reaction mixture was allowed to cool then poured into ice/HCl. The solid that separated, filtered off and crystallized from ethanol. Yield 85% mp above 300°C . IR(KBr) 1675(vc-o),3300(vOH ). Anal. Calculated for C₂H₅N₂O₁₀ (442); C,59.72;H,5.88;N,12.66. Found: C,59.72;H,5.80;N,12.61.

REFERENCES:


