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Behavior of 4-(3,4-dimethyl-phenyl)-1(2*H*)-phthalazinone towards carbon electrophiles and carbon nucleophiles

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ABSTRACT

4-(3,4-Dimethyl-phenyl)-1(2H)-phthalazinone was used as key starting material for synthesis a new series of 1,4-disubstituted phthalazines, 2,4-disubstituted phthalazinones, and fused 1,2,4-triazolo-phthalazines depending on the principles of lactam-lactim dynamic equilibrium phenomena. The structure of the prepared compounds are elucidated using physical and spectral data like, FT-IR, [1]HNMR, and mass spectroscopy.

Keywords: 1(2*H*)-Phthalazinone, gluconyl-2*H*-phthalazin-1-one, *C*-nucleoside, *N*-nucleoside, 1,2,4-triazolo-phthalazine.

INTRODUCTION

A number of phthalazine and phthalazinone derivatives occur very widely in nature and are essential to life. Recently, they are derived from a wide range of biologically active natural products, troponoid family [1]. It is well known that phthalazinone derivatives like other members of isomeric diazine series have considerable biological and pharmaceutical activities. Indeed, several phthalazinone derivatives have been reported to possess antitumor [2-4], anticonvulsant [5], antihypertensive [6,7], antithrombotic [8], antidiabetic and hypolipidemic agents [9], antimicrobial [10-12], anti-inflammatory [13-15].

Moreover, phthalazinone derivatives represent key intermediate in the synthesis of various compounds with highly interesting pharmacological activities such as blood platelet aggregation inhibitors [16], poly(ADP-ribose)polymerase inhibitors [17], phosphodiesterase inhibitors [18]. In spite of higher stabilities of 4-(3,4-dimethyl-phenyl)-1(2*H*)-phthalazinone, it can be used as versatile building blocks in the synthesis of new phthalazinone derivatives with high functionality at the heterocyclic system, which might have good biological and medicinal application.

EXPERIMENTAL SECTION

Reagents and solvents were used as obtained from the supplier without further purification. All melting points reported are uncorrected and were determined on a Stuart electric melting point apparatus. Elemental analysis were carried out in the Micro Analytical Center, Cairo University, Giza, Egypt. Column chromatography was carried out on silica gel column. Thin-layer chromatography (TLC) was performed on Merk TLC aluminium sheets silica gel 60 F_{254} with detection by UV quenching at 254nm. ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer, with residual proton signal of the deuterated solvent as the internal reference (δ_H=7.26 ppm for $CDCl_3$ and δ_H=2.51 ppm for DMSO-d_6). Chemical shifts (δ) are given in parts per million (ppm). IR spectra were recorded on Nicolet Impact 400D FT-IR apparatus using OMNIC program and are reported in terms of frequency of absorption (cm^{-1}). EIMS were recorded on a gas chromatographic GCMS – Qploopx Shimadzu (Japan, 1990).

4-(3,4-Dimethyl-phenyl)-2*H*-phthalazin-1-one (1)
Prepared according to literature [13], the crude product was crystallized from toluene to afford 2.18g(87%) of **1**. Mp 252-254°C. IR (KBr) 1661 (CO), 3150 (NH). ^{1}H-NMR (DMSO-d_6)**:** δ 2.24 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.48 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.57-7.78 (m, 4H, Ar-H), 7.95 (d, *J* = 7.6 Hz, 1H, Ar-H), 8.03 (d, *J* = 8.1 Hz, 1H, Ar-H), 10.94 (s, 1H, NH). Anal. Calc. for $C_{16}H_{14}N_2O$: C 76.78, H 5.64, N 11.19; found: C 76.86, H 5.72, N 11.31.

Compounds (2a,b)
A mixture of phthalazinone **1** (2.50 g, 0.01 mol), ethyl bromoacetate (5.40 mL, 0.03 mol) and/or ethyl-2-bromopropionate (5.40 mL, 0.03 mol), and anhydrous potassium carbonate (4.10 g, 0.01 mol) in dry acetone (60 mL) was heated under reflux in water bath for 24 h. The excess solvent is distilled off under reduced pressure. The residue is treated with cold water and the solid obtained is filtered off, washed with water, and crystallized from ethanol to give 3.12 g (85%) of **2a** and/or 2.41 g (69%) of **2b** respectively.

[4-(3,4-Dimethyl-phenyl)-1-oxo-1*H*-phthalazin-2-yl]-acetic acid ethyl ester (2a) [13]**:** Mp 123°C (pet.ether 60-80°). IR (KBr): 1661, 1742 (CO). ^{1}H-NMR ($CDCl_3$)**:** δ 1.18 (t, *J* = 6.3 Hz, 3H, CH_3-ester), 2.28 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.14 (q, *J* = 6.3 Hz, 2H, CH_2-ester), 4.93 (s, 2H, NCH_2), 7.48 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.66-7.84 (m, 6H, Ar-H). Anal. Calc. for $C_{20}H_{20}N_2O_3$: C 71.41, H 5.99, N 8.33; found: C 71.56, H 5.72, N 8.42.

2-[4-(3,4-Dimethyl-phenyl)-1-oxo-1*H*-phthalazin-2-yl]-propionic acid ethyl ester (2b): Mp 141-143°C (pet.ether 60-80°). IR (KBr) 1656, 1752 (CO). ^{1}H-NMR ($CDCl_3$)**:** δ 1.21 (t, *J* = 6.8 Hz, 3H, $OCH_2\underline{CH_3}$), 1.41 (d, *J* = 7.3 Hz, 3H, $\underline{CH_3}CH$), 2.27 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.17 (q, *J* = 6.8 Hz, 2H, $O\underline{CH_2}CH_3$), 4.94 (q, *J* = 7.3 Hz, 1H, $\underline{CH}CH_3$), 7.28 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.62-7.79 (m, 4H, Ar-H), 7.93 (d, *J* = 7.6 Hz, 1H, Ar-H), 8.01 (d, *J* = 8.1 Hz, 1H, Ar-H). Anal. Calc. for $C_{21}H_{22}N_2O_3$: C 71.98, H 6.33, N 7.99; found: C 72.08, H 6.21, N 7.82.

Compounds (3a,b)
A mixture of compound **1** (2.50 g, 0.01 mol) and ethyl bromoacetate (5.40 mL, 0.03 mol) and/or ethyl-2-bromopropionate (5.40 mL, 0.03 mol) , and anhydrous potassium carbonate (4.10 g, 0.01 mol) in 1,4-dioxane (30 mL) was heated under reflux for 8h. The excess solvent is distilled off under reduced pressure and the solid that obtained is filtered off and recrystallized from benzene to give 2.63 g(72%) of **3a** and/or 2.65 g (76%) of **3b** respectively.

[4-(3,4-Dimethyl-phenyl)-phthalazin-1-yloxy]-acetic acid ethyl ester (3a): Mp 137°C. IR (KBr) 1753 (CO). Anal. Calc. for $C_{20}H_{20}N_2O_3$: C 71.41, H 5.99, N 8.33; found: C 71.33, H 6.12, N 8.58.

[4-(3,4-Dimethyl-phenyl)-phthalazin-1-yloxy]-propionic acid ethyl ester (3b): Mp 155-157°C. IR (KBr) 1758 (CO). ^{1}H-NMR ($CDCl_3$)**:** δ 1.28 (t, *J* = 6.8 Hz, 3H, $OCH_2\underline{CH_3}$), 1.39 (d, *J* = 6.5 Hz, 3H, $\underline{CH_3}CH$), 2.31 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.19 (q, *J* = 6.8 Hz, 2H, $O\underline{CH_2}CH_3$), 4.59 (q, *J* = 6.5 Hz, 1H, $\underline{CH}CH_3$), 7.13 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.38 (d, *J* = 2.8 Hz, 1H, Ar-H), 7.76-7.82 (m, 5H, Ar-H). Anal. Calc. for $C_{21}H_{22}N_2O_3$: C 71.98, H 6.33, N 7.99; found: C 72.09, H 6.24, N 8.18.

[4-(3,4-Dimethyl-phenyl)-1-oxo-1*H*-phthalazin-2-yl]-3-oxo-propionitrile (4)
A mixture of phthalazinone **1** (2.50 g, 0.01 mol), ethyl cyanoacetate (1.10 mL, 0.01 mol), and 0.5 g of sodium ethoxide in ethanol (50 mL) was heated gently for 15min. then heated under refluxing condenser at 70°C for 5h. The reaction mixture was allowed to cool and the separated solid was filtered off, dried and crystallized from toluene to afford 1.90 g (60%) of **4**. Mp 284-286°C. IR (KBr) 1663, 1698 (CO), 2200 (CN). ^{1}H-NMR (DMSO-d_6)**:** δ 2.23 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.48 (s, 2H, CH_2), 7.27 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.66-7.74 (m, 4H, Ar-H), 7.99 (d, *J* = 7.6 Hz, 1H, Ar-H), 8.04 (d, *J* = 7.6 Hz, 1H, Ar-H). Anal. Calc. for $C_{19}H_{15}N_3O_2$: C 71.92, H 4.76, N 13.24; found: C 71.84, H 4.59, N 13.11.

4-(3,4-Dimethyl-phenyl)-2-(2,3,4,5,6-pentahydroxy-hexanoyl)-2*H*-phthalazin-1-one (5)
An equimolar mixture of phthalazinone **1** (2.50 g, 0.01 mol) and *D*-glucono-1,5-lactone (1.70 g, 0.01 mol) in dry pyridine (20 mL) was heated under reflux for 3h. The reaction mixture was allowed to cool and then poured into ice/HCl mixture. The solid that separated was filtered off, washed with water, dried, and crystallized from ethanol to give 3.65 g (83%) of **5**. Mp 288°C. IR (KBr) 1662, 1717 (CO). Anal. Calc. for $C_{22}H_{24}N_2O_7$: C 61.67, H 5.65, N 6.54; found: C 61.78, H 5.53, N 6.63.

2-(2,3,4,6-tetra-*O*-acetyl-*β*-*D*-glucopyranosyl)-4-(3,4-dimethyl-phenyl)-2*H*-phthalazin-1-one (6)
Phthalazinone **1** (2.50g, 0.01 mol) was suspended in sodium carbonate solution (3 mL, 17%). The suspension was shacked well for 10 min. and the precipitate that formed was filtered off and dried. The resulting solid was dissolved

in *N*,*N*-dimethylformamide (10 mL) and *D*-glucopyranosyl bromide tetracetate (4.11 g, 0.01 mol) was added and the reaction mixture was heated gently (at 75°C) for 3h. The reaction mixture was concentrated under vacuum and the crude product obtained was purified using column chromatography using ethyl acetate : hexane (3:1) as eluent. Yield 2.61g (45%). Mp 178°C. IR (KBr) 1658, 1746 (CO). ^{1}H-NMR (DMSO-d_6)**:** δ 2.04, 2.05, 2.08, 2.10 (s, 4x3H, 4xCH_3CO), 2.23 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.74 (m, 1H, 5´-H), 4.29 (m, 2H, 6´-CH_2), 4.77 (m, 1H, 4´-H), 5.13-5.31 (m, 2H, 3´-H, 2´-H), 6.02 (d, *J* = 8.3 Hz, 1H, 1´-H), 7.23 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.65-7.81 (m, 4H, Ar-H), 7.95 (d, *J* = 7.7 Hz, 1H, Ar-H), 8.07 (d, *J* = 7.7 Hz, 1H, Ar-H). Anal. Calc. for $C_{30}H_{32}N_2O_{10}$: C 62.06, H 5.56, N 4.83; found: C 62.26, H 5.63, N 4.71.

Compounds (7a,b)

A solution of phthalazinone **1** (2.50 g, 0.01 mol) in dry benzene (50 mL) was treated with ethereal solution of ethyl magnesium iodide and/or phenyl magnesium bromide (0.03 mol) in the course of 30min. The reaction mixture was heated under reflux for 5h, left overnight at room temperature, and then decomposed in the usual way to give viscous oils which were triturated with light petrol. (60-80°). The solids that obtained were filtered off and crystallized from the proper solvent to give 1.67 g (64%) of **7a** and/or 2.21 g (71%) of **7b** respectively.

1-(3,4-Dimethyl-phenyl)-4-ethyl-phthalazine (7a): Mp 128-130°C. IR (KBr) 2922 (CH aliph.), 3067 (CH arom.). ^{1}H-NMR (DMSO-d_6)**:** δ 1.34 (t, *J* = 7.3 Hz, 3H, $CH_2\underline{CH_3}$), 2.26 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.95 (q, *J* = 7.3 Hz, 2H, $\underline{CH_2}CH_3$), 7.09 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.29-7.84 (m, 6H, Ar-H), 7.99 (d, *J* = 7.6 Hz, 1H, Ar-H), 8.04 (d, *J* = 7.6 Hz, 1H, Ar-H). Anal. Calc. for $C_{18}H_{18}N_2$: C 82.41, H 6.92, N 10.68; found: C 82.29, H 6.84, N 10.47.

1-(3,4-Dimethyl-phenyl)-4-phenyl-phthalazine (7b): Mp 141-142°C. IR (KBr) 2919 (CH aliph.), 3070 (CH arom.). ^{1}H-NMR (DMSO-d_6)**:** δ 2.29 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.13 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.31 (d, *J* = 2.4 Hz, 1H, ArH), 7.68-8.07 (m, 10H, Ar-H). Anal. Calc. for $C_{22}H_{18}N_2$: C 85.13, H 5.85, N 9.03; found: C 85.27, H 5.94, N 9.17. MS: m/z 580[M^+](17.3%), 331(6.8%), 249(100%), 59(23.4%).

1-Chloro-4-(3,4-dimethyl-phenyl)-phthalazine (8)

A solution of phthalazinone **1** (2.50 g, 0.01 mol) and 1 g of phosphorous pentachloride in phosphorous oxychloride (20 mL) was heated in water bath at 80°C for 2h. The reaction mixture was allowed to cool and then poured over cold water. The solid that separated was filtered off, washed with water, and crystallized from toluene to yield 1.72 g (64%) of **8**. Mp 138°C. IR (KBr) 2967 (CH aliph.), 3023 (CH arom.). Anal. Calc. for $C_{16}H_{13}ClN_2$: C 71.51, H 4.88, N 10.42; found: C 71.35, H 5.02, N 10.21.

[4-(3,4-Dimethyl-phenyl)-phthalazin-1-yl]-hydrazine (9)

A mixture of the Chlorophthalazinone **8** (2.69 g, 0.01 mol) and hydrazine hydrate (1.5 g, 0.03 mol) in ethanol (30 mL) was heated under reflux for 8h. The excess solvent was distilled off and the solid that separated after cooling was filtered off, dried and crystallized from toluene to give 2.06 g (78%) of **9**. Mp 268°C. IR (KBr) 1606 (C=N), 2916 (CH aliph.), 3068 (CH arom.), 3389, 3450 (NH). Anal. Calc. for $C_{16}H_{16}N_4$: C 72.70, H 6.10, N 21.20; found: C 72.79, H 5.96, N 21.07. MS: m/z 264[M^+](2.6%), 233(100%), 115(23.4%), 77(31.5%).

***N*-[4-(3,4-Dimethyl-phenyl)-phthalazin-1-yl]-acetic acid hydrazide (10)**

A solution of compound **9** (2.64 g, 0.01 mol) in freshly distilled acetic acid anhydride (15 mL) was heated under reflux for 2h. The reaction mixture was left overnight and the solid that separated was filtered off, washed with water several times and crystallized from ethanol to give 1.78 g (58%) of **10**. Mp 183-185°C. IR (KBr) 1666(CO), 3152(NH). Anal. Calc. for $C_{18}H_{18}N_4O$: C 70.57, H 5.92, N 18.29; found: C 70.67, H 5.97, N 18.06.

6-(3,4-Dimethyl-phenyl)-3-methyl-[1,2,4]triazolo[3,4-a]phthalazine (11)

A solution of the acid hydrazide **10** (3.06 g, 0.01 mol) in *n*-butanol (15 mL) was heated under reflux for 48h. The reaction mixture was allowed to cool and the separated solid was filtered off, dried and recrystallized from *n*-butanol to give 2.23 g (77%) of **11**.

Another procedure:

A mixture of chlorophthalazine **8** (2.69 g, 0.01 mol) and acetic acid hydrazide **10** (3.06 g, 0.01 mol) in *n*-butanol (20 mL) was heated under reflux for 24h. The reaction mixture was allowed to cool and the solid that separated was filtered off, dried, and crystallized from *n*-butanol to give 2.33 g (81%) of **11**. Mp 280-282°C. IR (KBr) 1609(C=N), 2921(CH aliph.), 3064(CH arom.). ^{1}H-NMR (DMSO-d_6)**:** δ 2.27(s, 3H, CH_3), 2.38(s, 3H, CH_3), 2.49(s, 3H, CH_3), 7.58-7.84(m, 6H, Ar-H), 8.21(d, *J* = 8.3 Hz, 1H, Ar-H). Anal. Calc. for $C_{18}H_{16}N_4$: C 74.98, H 5.59, N 19.43; found: C 75.14, H 5.32, N 19.58.

6-(3,4-Dimethyl-phenyl)-2*H*-[1,2,4]triazolo[3,4-a]phthalazin-3-one (12)
A solution of compound **9** (2.64 g, 0.01 mol) in ethyl chloroformate (2 mL, 0.02 mol) was heated at 65°C in water bath for 7h. The reaction mixture after cooling was poured into cold water, the solid that formed was washed with water several times and crystallized from ethanol to give 1.84 g (63%) of **12**. Mp 276-278°C. IR (KBr) 1621 (C=N), 1667 (CO), 3171 (NH). ^{1}H-NMR (DMSO-d_6)**:** δ 2.14 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 7.53-7.73 (m, 5H, Ar-H), 8.03 (d, *J* = 7.6 Hz, 1H, Ar-H), 8.17 (d, *J* = 7.6 Hz, 1H, Ar-H), 9.34 (s, 1H, NH). Anal. Calc. for $C_{17}H_{14}N_4O$: C 70.33, H 4.86, N 19.30; found: C 70.45, H 4.97, N 19.44.

6-(3,4-Dimethyl-phenyl)-3-phenyl-2,3-dihydro-[1,2,4]triazolo[3,4-a] phthalazine (13)
A mixture of compound **9** (2.64 g, 0.01 mol), benzaldehyde (1.06 g, 0.01 mol), and few drops of piperidine was refluxed in boiling ethanol (20 mL) for 12h. After cooling, the collected solid is crystallized from toluene to give 2.89 g (82%) of **13**. Mp 178-180°C. IR (KBr) 1611 (C=N), 3394 (NH). ^{1}H-NMR (DMSO-d_6)**:** δ 2.23 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 5.84 (s, 1H, CH), 7.43-7.84 (m, 12H, Ar-H), 9.84 (s, 1H, NH). Anal. Calc. for $C_{23}H_{20}N_4$: C 78.38, H 5.72, N 15.90; found: C 78.21, H 5.60, N 15.99.

6-{[4-(3,4-Dimethyl-phenyl)-phthalazin-1-yl]-hydrazono}-hexane-1,2,3,4,5-pentaol (14)
A mixture of compound **9** (2.64 g, 0.01 mol), α–*D*-glucose (1.84g, 0.01mol), and few drops of glacial acetic acid in ethanol (30 mL) was heated under reflux for 8h. The reaction mixture was allowed to cool and the separated solid was filtered off, dried, and crystallized from ethanol/H_2O to give 3.24 g (76%) of **14**. Mp >300°C. IR (KBr) 1629 (C=N), 3148 (NH), 3432 (OH). Anal. Calc. for $C_{22}H_{26}N_4O_5$: C 61.96, H 6.15, N 13.14; found: C 61.82, H 6.10, N 13.23.

2,3,4,5-Tetracetoxy-1-{[4-(3,4-Dimethyl-phenyl)-phthalazin-1-yl]-hydrazonomethyl}- acetic acid pentylester (15)
A solution of the ester **14** (4.26 g, 0.01 mol) in a mixture of acetic acid anhydride and pyridine (1:1, 10 mL) was stirred at room temperature for 24h. The reaction mixture was poured into ice/HCl mixture, the solid that separated was collected by filtration, washed with water, dried and recrystallized from *n*-butanol to give 4.17 g (66%) of **15**. Mp 165-166°C. IR (KBr): 1260 (C-O), 1722 (CO), 3100 (NH). Anal. Calc. for $C_{32}H_{36}N_4O_{10}$: C 60.37, H 5.66, N 8.80; found: C 60.44, H 5.60, N 8.96.

(1S)-Per-O-acetyl-1-C-[4-(3,4-dimethyl-phenyl)-[1,2,3]triazolo[5,1-a]phthalazin-2-yl]-*D*-arabinitol (16)
To a solution of the ester **15** (6.36 g, 0.01 mol), a solution of bromine (1.58 g, 0.01 mol) in glacial acetic acid (5 mL) was added drop wise with vigorous stirring at room temperature during 10min. Then, the reaction mixture was heated under reflux for 1h. The reaction mixture was allowed to cool down, poured into cold water with stirring. The solid that formed was collected, washed with water, dried, and crystallized from ethanol to give 3.36 g (53%) of **16**. Mp 207-208°C. IR (KBr): 1646 (C=N), 1734 (CO). ^{1}H-NMR (DMSO-d_6)**:** δ 1.93-2.06 (m, 15H, 5xOAc), 2.29 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.57 (m, 2H, CH_2), 4.32-4.53 (m, 4H, 4CH), 7.19-7.34 (m, 7H, Ar-H). Anal. Calc. for $C_{32}H_{34}N_4O_{10}$: C 60.56, H 5.36, N 8.83; found: C 60.46, H 5.42, N 8.92.

(1S)-C-[4-(3,4-dimethyl-phenyl)-[1,2,3]triazolo[5,1-a]phthalazin-2-yl]-*D*-arabinitol (17)
To a solution of the ester **16** (6.34 g, 0.01 mol) in anhydrous methanol (20 mL), ammonium hydroxide solution (5 mL, 35%) was added, then the reaction mixture was stirred at room temperature for 3h. The excess solvent was distilled off under reduced pressure and the residue was purified on silica gel column using Chloroform : methanol (4:1) as an eluent to give 2.16 g (51%) of **17**. Mp >300°C. IR (KBr) 1644(C=N), 3332(NH). Anal. Calc. for $C_{22}H_{24}N_4O_5$: C 62.25, H 5.70, N 13.20; found: C 62.34, H 5.61, N 13.39.

2,3,4,5,6-Pentahydroxy-*N*-[4-(3,4-Dimethyl-phenyl)-phthalazin-1-yl]-hexanoic acid hydrazide (18)
A mixture of phthalazinone **1** (2.64 g, 0.01 mol) and *D*-glucono-1,5-lactone (1.7 g, 0.01 mol) in dry pyridine (20 mL) was heated under reflux for 2h. The reaction mixture after cooling was poured over ice/HCl mixture. The solid that separated was filtered off, washed with water, dried, and recrystallized from ethanol/H_2O to afford 3.73 g, (84%) of **18**. Mp >300°C. IR (KBr): 1675 (CO), 3148 (NH), 3381 (OH). Anal. Calc. for $C_{22}H_{26}N_4O_6$: C 59.72, H 5.89, N 12.66; found: C 59.88, H 5.94, N 12.79. MS: m/z 442[M^+](43.7%), 337(9.4%), 249(54.1%), 210(36.2%), 105(100%).

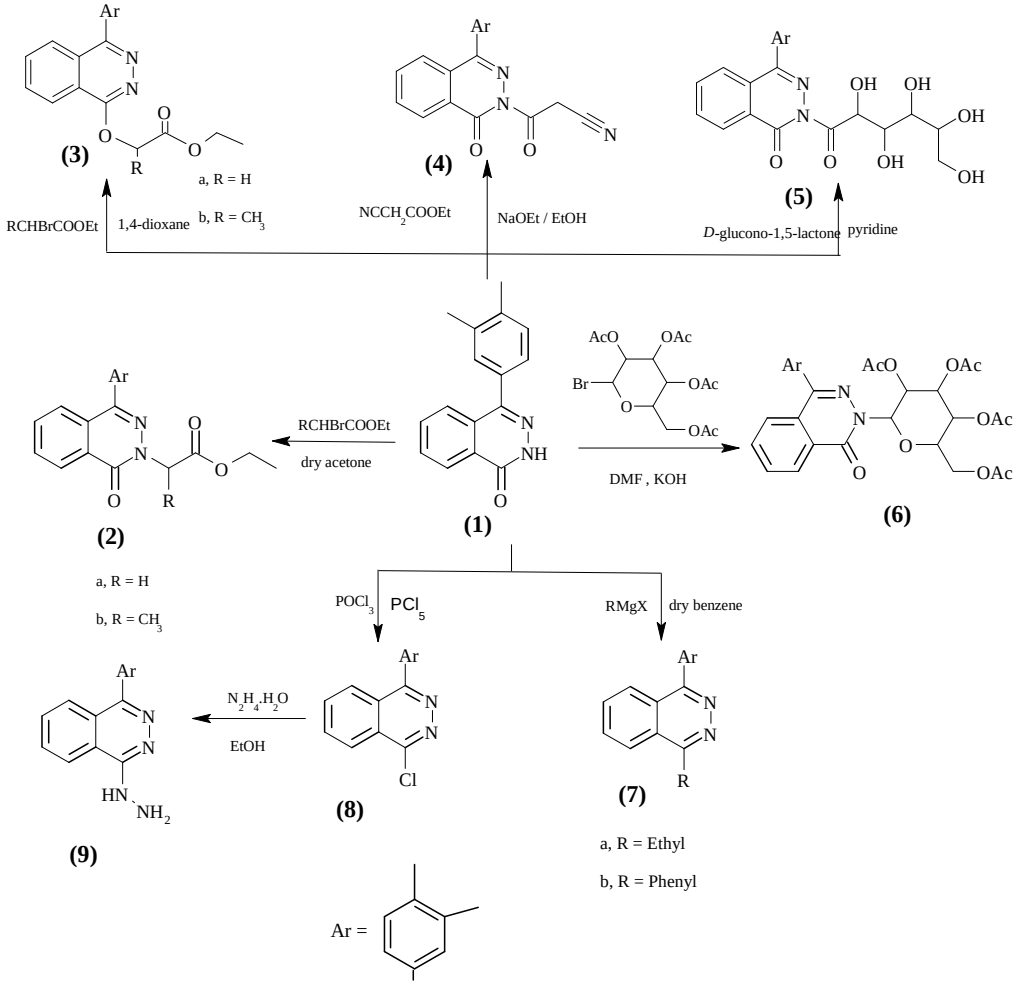
RESULTS AND DISCUSSION

4-(3,4-dimethyl-phenyl)-1(2*H*)-phthalazinone **(1)** was obtained according to reported method [13] via interaction of 2-(3,4-dimethyl)benzoylbenzoic acid with hydrazine hydrate in boiling ethanol

It was reported that, polar solvent strongly affects and favors the amide-like structure of the α- and γ-pyridone tautomers, the same was shown with pyrimidone system [19,20]. Therefore, one can consider our phthalazinone system to exhibit this phenomena, specially when discussing the nature of that system. Lactam-lactim dynamic equilibrium is a classical medium-dependent equilibrium. Thus, substituted phthalazinones were prepared by converting 1(2*H*)-phthalazinone **1** into ethyl-[4-(3,4-dimethyl-phenyl)-1-oxo-(2*H*)-phthalazin-2-yl]acetate **(2a)** and/or ethyl-[4-(3,4-dimethyl-phenyl)-1-oxo-(2*H*)-phthalazin-2-yl]propionate **(2b)** by the action of ethyl bromoacetate and/or ethyl-2-bromopropionate respectively in the presence of anhydrous potassium carbonate as a catalyst in boiling dry acetone [21], [Scheme 1].

On the other hand, when the reaction was conducted in 1,4-dioxane instead of dry acetone the products were identified as ethyl[4-(3,4-dimethyl-phenyl)phthalazin-1-yl]glycolate **(3a)** and ethyl[4-(3,4-dimethyl-phenyl)phthalazin-1-yl]-2-methylglycolate **(3b)** respectively, [Scheme 1]. The FT-IR spectra of phthalazine derivatives **3a,b** revealed absorption bands in the region 1745-1750cm^{-1} and devoid any band for cyclic amide. Here the author concluded that, in presence of acetone the lactam form is the predominant conformer while in 1,4-dioxane the lactim form is the predominant conformer (dioxane has lower polarity than acetone).

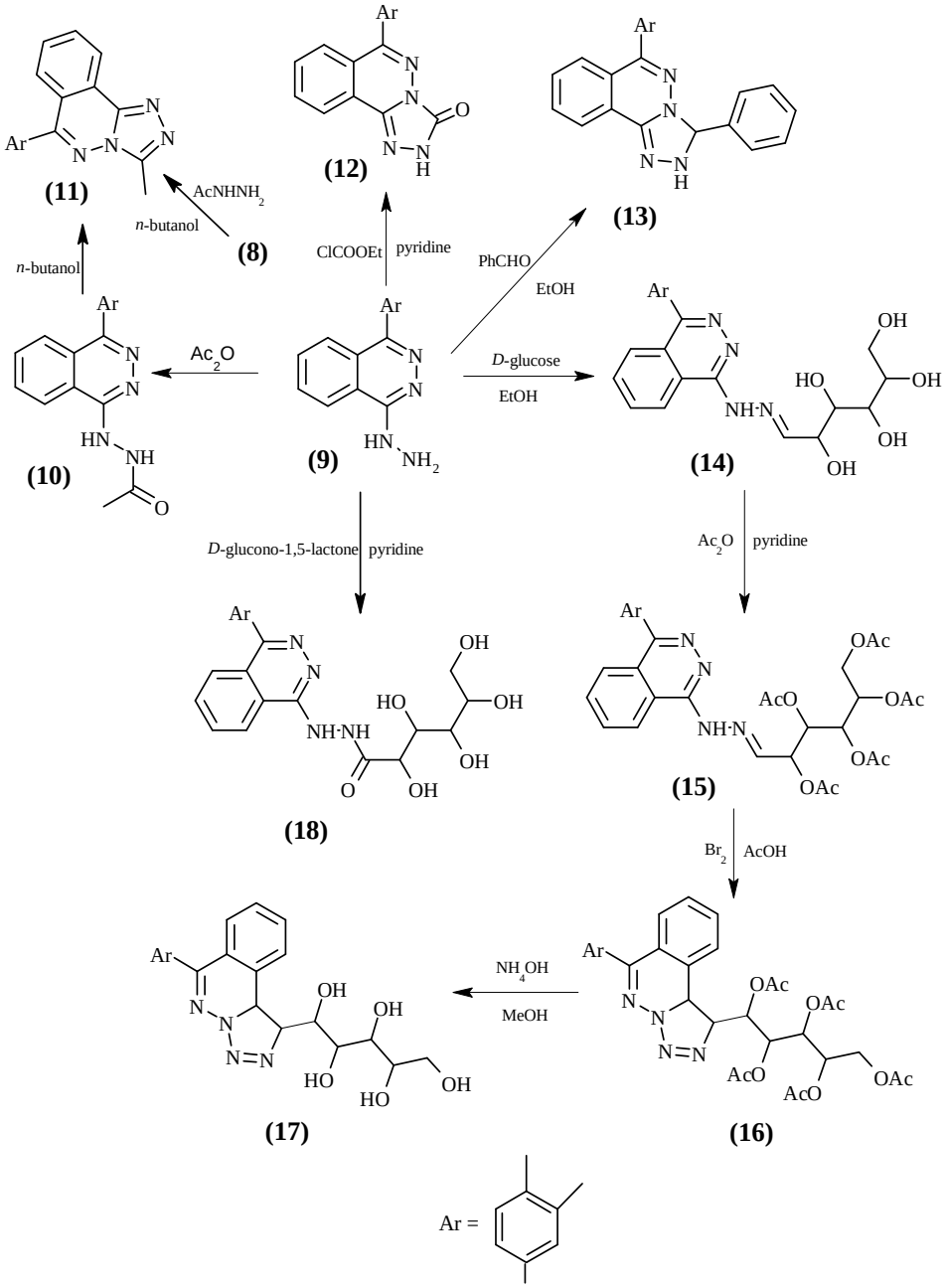
Interaction of the phthalazinone **1** with ethyl cyanoacetate in the presence of sodium ethoxide, cyanoacetylation takes place and yielded 2-cyanoacetyl-4-(3,4-dimethyl-phenyl)-2*H*-phthalazin-1-one **(4)**. This reaction suggested to take place on the acyl moiety via tetrahedral mechanism. Thereafter, the author sought to investigate heteroring opening of *D*-glucono-1,5-lactone with phthalazinone **1** with the aim of obtaining *N*-nucleoside incorporated by phthalazinone moiety. Actually, some *N*-nucleoside was shown to exhibit prominent and versatile biological activity [22-24]. Indeed, the phthalazinone **1** was allowed to react with *D*-glucono-1,5-lactone in pyridine and afforded the *N*-nucleoside derivative, 2-gluconyl-4-(3,4-dimethyl-phenyl)-2*H*-phthalazin-1-one **(5)**. Additionally, when phthalazinone **1** was glycusidated by coupling with 2,3,4,6-tetra-*O*-acetyl-*α*-*D*-glucopyranosylbromide (α-ABG) in the presence of sodium carbonate solution in *N*,*N*-dimethyl formamide, it gave 2-(2,3,4,6-tetra-*O*-acetyl-*β*-*D*-glucopyranosyl)-4-(3,4-dimethyl-phenyl)-2*H*-phthalazin-1-one **(6)**, [Scheme 1], as the only isolable one product as judged by TLC analysis.



Scheme 1

The interesting reaction of NH-acidic phthalazinones with organometallic compounds leading to novel C-C-bond has been investigated. Where, phthalazinone **1** was submitted to react with ethyl magnesium iodide and/or phenyl magnesium bromide under Grignard reaction conditions and yielded 1-(3,4-dimethyl-phenyl)-4-[ethyl and/or phenyl]-phthalazine **7a** and/or **7b** respectively, [Scheme 1].

Chlorination of the titled phthalazinone **1** using phosphorous pentachloride in the presence of phosphorous oxychloride afforded the 1-chloro-4-(3,4-dimethyl-phenyl)-phthalazine **8**, [Scheme 1]. This reaction under went in agreement with our previous foundation for chlorination of cyclic amides [25], compound **1** in the presence of $POCl_3$ solution exhibits the phenomena of lactam=lactim dynamic equilibrium, where the reaction takes place via interaction of PCl_4^+ ($2PCl_5 = PCl_4^+ + PCl_6^-$ in solid state) with lone pair of oxygen group for lactim form, followed by lose of H^+ ($H^+ + PCl_6^- = HCl + PCl_5$) and gave the intermediate organophosphorous compound, which undergoes internal nucleophilic substitution reaction S_Ni in which part of the leaving group must be able to attack the substrate, detaching itself from the rest of the leaving group in the process.



Scheme 2

The hydrazinophthalazinone **9** was obtained from the interaction of chlorophthalazine **8** with hydrazine hydrate via S_N2 mechanism on the electron deficiency center (C(1) in phthalazine nucleus which activated by the adjacent

nitrogen atom). Our approach to the heterocyclic designed was achieved by the synthesis of hydrazinophthalazine **9** which contains "$NHNH_2$" moiety and are well known to be highly reactive and used as intermediate for synthesis of fused annulated heterocycle with phthalazine nucleus [26], specially when the heterocycle is 1,2,4-triazole; the biological properties are markedly enhanced [27]. In this circumstance, interaction of hydrazino derivative **9** with acetic acid anhydride afforded acetohydrazino intermediate **10**, which undergoes ring reclosure by boiling in *n*-butanol and the 6-(3,4-dimethyl-phenyl)-3-methyl-[1,2,4]triazolo[3,4-a]phthalazine **11** was obtained. The solid evidence for the structure of compound **11** came from its independent synthesis by interaction of the chlorophthalazine **8** with acetic acid hydrazide (acetylhydrazine) in refluxing *n*-butanol for 24 hours, and identified via m.p and mixed m.p determination, [Scheme 2].

Thereafter, the hydrazinophthalazine **9** was allowed to react with ethyl chloroformate in pyridine and provided 6-(3,4-dimethyl-phenyl)-2*H*-[1,2,4]triazolo[3,4-a]phthalazin-3-one (**12)**. On the other hand, the hydrazinophthalazinone **9** was submitted to react with benzaldehyde in boiling ethanol and gave 6-(3,4-dimethyl-phenyl)-3-phenyl-2,3-dihydro-[1,2,4]triazolo[3,4-a]phthalazine (**13)**. Interaction of hydrazinophthalazinone **9** with α*–D*-glucose in the presence of catalytic amounts of glacial acetic acid yielded the hydrazone **14**. Here the author soughs to convert the hydrazone **14** to the corresponding *C*-nucleoside via acetylation of the hydrazone derivative **14** at room temperature and gave the *O*-acetylated derivative **15**. Oxidative cyclisation of compound **15** by using bromine/acetic acid afforded the *O*-acetylated cyclic *C*-nucleoside **16**. Deprotection of **16** using ammonium hydroxide solution in methanol gave the target free cyclic *C*-nucleoside **17**. This reaction was suggested to proceed via Dimroth type rearrangement where the triazolo[1,5-a]phthalazine was converted into triazolo[3,4-a]phthalazine. Finally, interaction of the hydrazinophthalazine **9** with D-glucono-1,5-lactone in pyridine afforded the heteroring opening adduct **18**, [Scheme 2].

CONCLUSION

Successfully we reported here the designing and resynthesizing of 4-(3,4-dimethyl-phenyl)-1(2H)-phthalazinone as key starting material. Therefrom, a series of 1,4-disubstituted phthalazines, 2,4-disubstituted phthalazinones, and fused 1,2,4-triazolo-phthalazines are furnished.

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