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

M. A. El-Hashash¹ and Y. A. El-Badry²*

¹Chemistry department, Faculty of Science, Ain Shams University, Cairo, Egypt.
²Organic Chemistry lab., Faculty of Education, Ain Shams University, Cairo, Egypt.

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, ¹H NMR, and mass spectroscopy.

Keywords: 1(2H)-Phthalazinone, gluconyl-2H-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(2H)-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 Merck TLC aluminium sheets silica gel 60 F₂₅₄ with detection by UV quenching at 254nm. ¹H NMR spectra were recorded on a Bruker 400 MHz spectrometer, with residual proton signal of the deuterated solvent as the internal reference (δH=7.26 ppm for CDCl₃ and δH=2.51 ppm for DMSO-d₆). 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)-2H-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, 1742 (CO), 3150 (NH). ¹H-NMR (CDCl₃); δ 1.18 (t, J = 6.8 Hz, 3H, CH₂CH₃), 2.28 (s, 3H, CH₃), 2.46 (s, 3H, CH₃), 4.17 (q, J = 6.8 Hz, 2H, CH₂-O), 4.94 (q, J = 7.3 Hz, 1H, CH₂CH₃), 7.28 (s, 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 C₁₉H₁₅N₂O : C 71.98, H 6.33, N 7.99; found: C 71.86, H 6.12, N 7.82.

Compounds (2a,b)
A mixture of phthalazinone (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 1,4-dioxane (60 mL) was heated under reflux for 8h. The excess solvent is distilled off under reduced pressure and the solid that obtained is filtered off, washed with water, dried 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-1H-phthalazin-2-yl]-acetic acid ethyl ester (2a) [13]: Mp 123°C (pet.ether 60-80°C). IR (KBr): 1661, 1742 (CO), 3150 (NH). ¹H-NMR (CDCl₃); δ 1.18 (t, J = 6.8 Hz, 3H, CH₂CH₃), 2.28 (s, 3H, CH₃), 2.24 (s, 3H, CH₃), 2.24 (s, 3H, CH₃), 4.14 (q, J = 6.3 Hz, 2H, CH₂-ester), 4.93 (s, 2H, NCH₂), 7.48 (d, J = 8.1 Hz, 1H, Ar-H), 7.66-7.84 (m, 6H, Ar-H). Anal. Calc. for C₁₉H₁₅N₂O₂ : 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-1H-phthalazin-2-yl]-propionic acid ethyl ester (2b): Mp 141-143°C (pet.ether 60-80°C). IR (KBr) 1656, 1752 (CO). ¹H-NMR (CDCl₃); δ 1.21 (t, J = 6.8 Hz, 3H, OCH₂CH₃), 1.41 (d, J = 7.3 Hz, 3H, CH₂CH₃), 2.27 (s, 3H, CH₃), 2.41 (s, 3H, CH₃), 4.17 (q, J = 6.8 Hz, 2H, OCH₂CH₃), 4.94 (q, J = 7.3 Hz, 1H, CH₂CH₃), 7.28 (s, 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 C₁₉H₁₅N₂O₂ : 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 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]-propionic acid ethyl ester (3b): Mp 155-157°C. IR (KBr) 1758 (CO). ¹H-NMR (CDCl₃); δ 1.28 (t, J = 6.8 Hz, 3H, OCH₂CH₃), 1.39 (d, J = 6.5 Hz, 3H, CH₂CH₃), 2.47 (s, 3H, CH₃), 4.19 (q, J = 6.8 Hz, 2H, OCH₂CH₃), 4.59 (q, J = 6.5 Hz, 1H, CH₂CH₃), 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 C₁₉H₁₅N₂O₃ : 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-1H-phthalazin-2-yl]-3-oxo-propionitrile (4)
A mixture of phthalazinone (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). ¹H-NMR (DMSO-d₆); δ 2.23 (s, 3H, CH₃), 2.38 (s, 3H, CH₃), 3.48 (s, 2H, CH₂), 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). Anal. Calc. for C₁₉H₁₅N₂O₂ : C 71.92, H 4.76, N 13.24; found: C 71.84, H 4.59, N 13.11.

4-(3-Dimethyl-phenyl)-2-(2,3,4,5,6-pentahydroxy-hexanoyl)-2H-phthalazin-1-one (5)
An equimolar mixture of phthalazinone (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 C₂₀H₂₁N₃O₇ : 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)-2H-phthalazin-1-one (6)
Phthalazinone (2.50g, 0.01 mol) was suspended in sodium carbonate solution (3 mL, 17%). The suspension was shaken 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 tetracete (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 (C=O). 1H-NMR (DMSO-d$_6$): δ 2.04, 2.05, 2.08, 2.10 (s, 4xH, 4xCH$_2$CO), 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$_{39}$H$_{23}$O$_{10}$: 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 (2.50 g, 0.01 mol) in dry benzene (50 mL) was treated with ethereal solution of ethyl 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°C). 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):** A solution of phthalazinone (2.69 g, 0.01 mol) and acetic acid hydrazide (0.01 mol) in freshly distilled acetic anhydride (15 mL) was heated under reflux for 8h. The excess solvent was distilled off and the solid that separated was filtered off, washed with water and crystallized from toluene to give 1.72 g (64%) of 7a. Mp 138-139°C. IR (KBr) 3068 (C-H), 3389, 3450 (N-H). 1H-NMR (DMSO-d$_6$): δ 1.34 (t, J = 7.5 Hz, 3H, 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$_{21}$H$_{23}$N$_2$: C 82.39, H 6.92, N 10.68; found: C 82.29, H 6.84, N 10.47.

**1-Chloro-4-(3,4-dimethyl-phenyl)-phthalazine (8):** A solution of chlorophthalazine (1.50 g, 0.01 mol) and phosphorous pentachloride in phosphorous oxychloride (2.69 g, 0.01 mol) and acetic acid hydrazide (0.01 mol) in ethanol (30 mL) was heated under reflux for 48h. The excess solvent was distilled off, washed with water, and crystallized from toluene to yield 1.72 g (64%) of 8. Mp 138°C. IR (KBr) 2967 (C-H), 3023 (C-H). 1H-NMR (DMSO-d$_6$): δ 2.89 (s, 3H, CH$_3$), 2.40 (s, 3H, CH$_3$). 2.29 (s, 3H, 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$_{21}$H$_{23}$N$_2$: C 82.41, H 6.92, N 10.68; found: C 82.29, H 6.84, N 10.47.

**1-Chloro-4-[3,4-(dimethyl-phenyl)-phthalazine (8):** A solution of phthalazinone (2.69 g, 0.01 mol) and hydrazine hydrate (0.03 mol) in ethanol (30 mL) was heated under reflux for 8h. The excess solvent was distilled off, washed with water, and crystallized from toluene to give 1.72 g (64%) of 9. Mp 138°C. IR (KBr) 1609 (C=N), 1606 (C=N), 3068 (CH arom.), 3389, 3450 (NH). Anal. Calc. for C$_{21}$H$_{23}$N$_2$: C 72.70, H 6.10, N 21.20; found: C 72.70, H 5.96, N 21.07. MS: m/z 264[M$^+$](2.6%), 233(100%), 115(23.4%), 77(31.5%).

**6-(3,4-Dimethyl-phenyl)-3-methyl-[1,2,4-triazolo[3,4-a]phthalazine (11):** A solution of the acid hydrazide (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 then poured out, filtered off, dried and recrystallized from n-butanol to give 2.23 g (77%) of 11. Another procedure: A mixture of chlorophthalazine (2.69 g, 0.01 mol) and 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$_{21}$H$_{23}$N$_2$:O: C 70.57, H 5.92, N 18.29; found: C 70.67, H 5.97, N 18.06.

**[1,3,4-Dimethyl-phenyl]-4-(phenyl)-phthalazine (11):** A solution of compound (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$_{21}$H$_{23}$N$_2$:O: C 70.57, H 5.92, N 18.29; found: C 70.67, H 5.97, N 18.06.
6-(3,4-Dimethyl-phenyl)-2H-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). 1H-NMR (DMSO-d6): δ 6.14 (s, 3H, CH3), 2.27 (s, 3H, CH3), 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 C17H14N4O: 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 2.16 g (51%) of 13. Mp >300 C. IR (KBr) 1629 (C=N), 3148 (NH), 3432 (OH). Anal. Calc. for C23H18N4O: C 60.56, H 5.36, N 8.83; found: C 60.46, H 5.42, N 8.92.

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/H2O to give 3.24 g (76%) of 14. Mp >300°C. IR (KBr) 1629 (C=N), 3148 (NH), 3432 (OH). Anal. Calc. for C23H26N4O5: C 61.96, H 6.15, N 13.14; found: C 61.82, H 6.10, N 8.96.

RESULTS AND DISCUSSION
4-(3,4-dimethyl-phenyl)-1(2H)I-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 equilibriums is a classical medium-dependent equilibriums. Thus, substituted phthalazinones were prepared by converting 1(2H)-phthalazinone 1 into ethyl-[4-(3,4-dimethyl-phenyl)-1-oxo-(2H)-phthalazin-2-yl]acetate (2a) and/or ethyl-[4-(3,4-dimethyl-phenyl)-1-oxo-(2H)-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 1745-1750 cm⁻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)-2H-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)-2H-phthalazin-1-one (5). Additionally, when phthalazinone 1 was glycosidated by coupling with 2,3,4,6-tetra-O-acetyl-β-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)-2H-phthalazin-1-one (6), [Scheme 1], as the only isolable one product as judged by TLC analysis.

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 1745-1750 cm⁻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).
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 POCI₃ solution exhibits the phenomena of lactam=lactim dynamic equilibrium, where the reaction takes place via interaction of PCl₅ (2PCl₅ = PCl₄⁺ + PCl₆⁻ in solid state) with lone pair of oxygen group for lactim form, followed by lose of H⁺ (H⁺ + PCl₆⁻ = HCl + PCl₅) and gave the intermediate organophosphorous compound, which undergoes internal nucleophilic substitution reaction SNi 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.

The hydrazinophthalazinone 9 was obtained from the interaction of chlorophthalazine 8 with hydrazine hydrate via SN2 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 hydrazinophthalazinone 9 which contains "NHNH₂" 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 anhydride afforded acetoxyhydrazino intermediate 10, which undergoes ring reclosure by boiling in n-butanol and the 6-(3,4-dimethyl-phenyl)-3-methyl-1H-[1,2,4]triazolo[3,4-alphathalazine 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 hydrazinophthalazinone 9 was allowed to react with ethyl chloroformate in pyridine and provided 6-(3,4-dimethyl-phenyl)-2H-[1,2,4]triazolo[3,4-alphathalazin-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)-2,3-dihydro-[1,2,4]triazolo[3,4-alphathalazine (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-alphathalazine. Finally, interaction of the hydrazinophthalazinone 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)-phthalazine as key starting material. Therefrom, a series of 1,4-disubstitued phthalazines, 2,4-disubstitued phthalazinones, and fused 1,2,4-triazolo-phthalazines are furnished.

REFERENCES

[3] S Zhang; Y Zhao; Y Liu; D Chen; W Lan; Q Zhao; C Dong; L Xia; P Gong. Eur. J. Med. Chem., 2010, 45, 3504.
[10] H Brad; C Guo-Qiang; PC Partha; RF James; P Liping; MR Robert; BR Anthony; R Andreas; S Kelvin; T Maya; PW Ryan; X Shimin; Z Dawei; H Faye; RI Matthew; S Rashed; L Vivian; G Daved; HP Matthew; H Bradley; S Lisa; M Scot; M W Lu; S T Andrew. J. Med. Chem., 2008, 51, 6271.
[12] N Napoletano; G Norcini; F Pellacini; G Marchin; P Morazzoni; F Ferlenga; L Pradella. J. Med. Chem., 2009, 52, 3954.
[22] G Blod; K Altmann; J Frei; M Lang; PW Manley; P Traxler; B Wietfeld; J Bruggen; E Buchdunger; R Cozens; S Ferrari; D Wietfeld; J Wood. *J. Med. Chem.* 2000, 43, 3200.