

# Synthesis, Reactions and Characterization of 1,1'-(1,4-Phenylenebis(3-amino-6-methyl-1H-pyrazolo[3,4-b]pyridine-4,5-diyl))bis(ethan-1-one)

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## Abstract

Reaction of 4,4'-(1,4-phenylene)bis(5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile) (1) with methyl iodide afforded the 4,4'-(1,4-phenylene)bis(5-acetyl-6-methyl-2-(methylthio)nicotinonitrile) (2). The reaction of 2 with hydrazine hydrate followed by diazotization reaction afforded the 1,1'-(1,4-phenylenebis(3-amino-6-methyl-1H-pyrazolo[3,4-b]pyridine-4,5-diyl))bis(ethan-1-one) (3) and 1,1'-(1,4-phenylenebis(3-(chlorodiazonyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-4,5-diyl))bis(ethan-1-one) (4) respectively. On the other hand, reaction of 4 with malononitrile, 2-cyanoethanethioamide, ethyl acetoacetate, acetyl acetone, ethyl benzoylacetate, diethylmalonate, ethyl cyanoacetate and phenacylbromide aiming to build up pyrazolotriazine or pyrazole ring on the ring system of 4. Structures of all newly synthesized heterocyclic compounds in the present study were confirmed by considering the data of IR, <sup>1</sup>H NMR, mass spectra as well as that of elemental analyses.

## Keywords

Bis-1,2-dihydropyridine-3-carbonitrile, Bis-Nicotinonitrile, 1,1'-(1,4-Phenylenebis(3-(chlorodiazonyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-4,5-diyl))bis(ethan-1-one), Bis-dihydropyrido[2',3':3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carboxylate, Bis-1H-pyrazolo[3,4-b]pyridine

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## 1. Introduction

The chemistry of heterocyclic compounds has attracted attention in recent times due to its increasing importance in the field of pharmaceuticals and industries. In fact, the synthesis of bis-heterocyclic compounds exhibits various biological activities [1]-[8] including antibacterial, fungicidal, tuberculostatic, antiamebic, and plant growth regulative properties. Also, bis-compounds have received great attention [9] [10] not only for being model compounds for main chain polymers [11]-[16] but also because many biologically active natural and synthetic products have molecular symmetry [17]. The biological importance of both bis-compounds [18]-[21] and 2-thioxopyridine-3-carbonitriles [22]-[24] as well as the conjunction to our previous work [25]-[33] stimulated our interest to synthesize several derivatives of these ring systems that are required for several chemical transformations and medicinal chemistry programs.

## 2. Experimental

All melting points were uncorrected. I. R. (KBr discs) spectra were recorded on a Shimadzu FTIR-8201PC Spectrophotometer. <sup>1</sup>H NMR spectra were recorded on a Varian Mercury 300 MHz., and a Varian Gemini 200 MHz. Spectrometers using TMS as an internal standard and CDCl<sub>3</sub>, DMSO-d<sub>6</sub>, and (CD<sub>3</sub>)<sub>2</sub>CO as solvents. Chemical shifts were expressed as δ(ppm) units. Mass spectra were recorded on Agilent LC 1200/MS Ion Trap 6320 using APCI ionization source and the spectra was enhanced using acidified water/acetonitrile mobile phase and measured in the positive mode of the ion trap (Molecular weights of most compounds were protonated ([M+H]<sup>+</sup>)).

### 2.1. Synthesis of 2

Methyl iodide (3.6 g, 50 mmole) was added to a solution of **1** (22.9 g, 50 mmole) in methanol (100 mL) containing potassium hydroxide (2.8 g, 50 mmole) with stirring. The reaction mixture stir for 1 h, then the solid filtered and recrystallized from the dioxane to afford **2**.

**4,4'-(1,4-Phenylene)bis(5-acetyl-6-methyl-2-(methylthio)nicotinonitrile) (2)**: as orange crystals, yield 56%, mp > 330°C, IR (ν·cm<sup>-1</sup>): 3164.1 (Pyridine-NH), 3058.8 (aromatic-CH), 2948.2, 2855.1 (aliphatic-CH), 2228.4 (CN), and 1694.2 (Acetyl-CO); <sup>1</sup>H NMR (δppm): 2.43 (s, 6H, two SCH<sub>3</sub>), 2.53 (s, 6H, two CH<sub>3</sub>), 2.78 (s, 6H, two CH<sub>3</sub>CO), 7.1 - 7.57 (m, 4H, phenyl H's) MS: 487 ([M+H]<sup>+</sup>, 1.5%, corresponding to the molecular weight of the molecular formula C<sub>26</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> of the assigned structure), 471 (486-CH<sub>3</sub>, 12.6%), 456 (486-2CH<sub>3</sub>, 10.9%), 439 (486-SCH<sub>3</sub>, 23.5%), 392 (486-2SCH<sub>3</sub>, 5.7%), 349 (486-2SCH<sub>3</sub>, COCH<sub>3</sub>, 0.5%), 306 (486-2SCH<sub>3</sub>, 2COCH<sub>3</sub>, 100%); Anal. for C<sub>26</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> (486.6) Calcd./Found (%): C (64.17/64.19%) H (4.56/4.59%) N (11.51/11.55%) S (13.18/13.21%).

### 2.2. Synthesis of 3

A solution of **2** (4.86 g, 10 mmole) in hydrazine hydrate (10 ml), ethanol (20 mL) and pyridine (10 mL) was heated under reflux until the odor of methyl mercaptan ceased. The excess solvent was evaporated, and the solids so formed after cooling were collected by filtration, and recrystallized from ethanol to give the corresponding **3**.

**1,1'-(1,4-Phenylene)bis(3-amino-6-methyl-1H-pyrazolo[3,4-b]pyridine-4,5-diyl)bis(ethan-1-one) (3)**: as yellow crystals, yield 52%, mp 222°C, IR (ν·cm<sup>-1</sup>): 3385, 3333, 3185 (NH<sub>2</sub>, NH), 3055 (aromatic-CH), 2956, 2876 (aliphatic-CH) and 1697 (Acetyl-CO); <sup>1</sup>H NMR (δppm): 2.52 (s, 6H, two CH<sub>3</sub>), 2.78 (s, 6H, two CH<sub>3</sub>CO), 4.3 (s, br., 4H, two NH<sub>2</sub>), 7.0 - 7.55 (m, 4H, phenyl H's); 12.3 (s, br., 2H, two NH); MS: 455 ([M+H]<sup>+</sup>, 2.5%, corresponding to the molecular weight of the molecular formula C<sub>24</sub>H<sub>22</sub>N<sub>8</sub>O<sub>2</sub> of the assigned structure), 439 (454-CH<sub>3</sub>, 11.2%), 424 (454-2CH<sub>3</sub>, 18.1%), 411 (454-COCH<sub>3</sub>, 2.6%), 368 (454-2COCH<sub>3</sub>, 100%); Anal. for C<sub>24</sub>H<sub>22</sub>N<sub>8</sub>O<sub>2</sub> (454) Calcd./Found (%): C (63.43/63.40%) H (4.88/4.89%) N (24.66/24.65%).

### 2.3. Synthesis of 4

A solution of **3** (4.54 g, 10 mmole) in concentrated hydrochloric acid (10 mL) and glacial acetic acid (20 mL) was stirred in an ice bath. Sodium nitrite solution was added (4 g, dissolved in 20 ml cold water) drop wise with stirring for 50 minutes. The solids so formed were collected by filtration, washed with water and dried to give the corresponding **4**.

**1,1'-(1,4-Phenylenebis(3-(chlorodiazanyl)-6-methyl-1H-pyrazolo[3,4-b]-pyridine-4,5-diyl))bis(ethan-1-one) (4)**: as pale yellow crystals, yield 44%, mp 98°C, IR ( $\nu\text{-cm}^{-1}$ ): 3184 (NH), 3066 (aromatic-CH), 2952, 2878 (aliphatic-CH) and 1687 (Acetyl-CO);  $^1\text{HNMR}$  ( $\delta\text{ppm}$ ): 2.42(s, 6H, two  $\text{CH}_3$ ), 2.82 (s, 6H, two  $\text{CH}_3\text{CO}$ ), 7.1 - 7.78 (m, 4H, phenyl H's); 11.7 (s, br., 2H, two NH); **MS**: 550 ( $[\text{M}+\text{H}]^+$ , 2.5%, corresponding to the molecular weight of the molecular formula  $\text{C}_{24}\text{H}_{18}\text{Cl}_2\text{N}_{10}\text{O}_2$  of the assigned structure), 534 (549- $\text{CH}_3$ , 9.2%), 519 (549- $2\text{CH}_3$ , 22.3%), 506 (549- $\text{COCH}_3$ , 4.1%), 463 (549- $2\text{COCH}_3$ , 34.2%), 427 (549-two  $\text{N}_2\text{Cl}$ , 100%); Anal. for  $\text{C}_{24}\text{H}_{18}\text{Cl}_2\text{N}_{10}\text{O}_2$  (549) Calcd./Found (%): C (52.47/52.50) H (3.30/3.33) N (25.50/25.53), Cl 12.91/12.89

## 2.4. Synthesis of 5, 6, 7, 8, 9, 10 and 12

A solution of **4** (1.64 g, 3 mmole) in ethanol (30 mL) containing 2.0 g sodium acetate and malononitrile, cyanothioacetamide, ethyl acetoacetate, acetylacetone, ethyl benzoylacetate, diethylmalonate and ethyl cyano-acetate (0.30 g, 0.25 g, 0.38 g, 0.30 g, 0.57 g, 0.48 g and 0.33 g 3 mmole) was stirred at room temperature for one hour. The reaction mixture was then poured onto ice-cold water formed precipitate were collected by filtration, washed with water and recrystallized from the proper solvent to afford **5**, **6**, **7**, **8**, **9**, **10** and **12** respectively.

**10,10'-(1,4-Phenylene)bis(9-acetyl-4-amino-8-methyl-6,10b-dihydro-pyrido[2',3':-3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carbonitrile) (5)**: as pale yellow crystals, yield 44%, mp > 301°C, IR ( $\nu\text{-cm}^{-1}$ ): 3288, 3279, 3184 ( $\text{NH}_2$ , NH), 3066 (aromatic-CH), 2952, 2878 (aliphatic-CH), 2218 (CN) and 1687 (Acetyl-CO);  $^1\text{HNMR}$  ( $\delta\text{ppm}$ ): 2.42 (s, 6H, two  $\text{CH}_3$ ), 2.82 (s, 6H, two  $\text{CH}_3\text{CO}$ ), 2.91 (s, br., 4H,  $2\text{NH}_2$ ), 7.1 - 7.78 (m, 4H, phenyl H's); 11.7 (s, br., 2H, two NH); **MS**: 613 ( $[\text{M}+\text{H}]^+$ , 2.5%, corresponding to the molecular weight of the molecular formula  $\text{C}_{30}\text{H}_{24}\text{N}_{14}\text{O}_2$  of the assigned structure), 611 (612-H, 65.3%), 610 (612-2H, 23.1%), 599 (612- $\text{CH}_3$ , 19.5%), 584 (612- $2\text{CH}_3$ , 15.8%), 569 (612- $\text{COCH}_3$ , 14.7%), 526 (612- $2\text{COCH}_3$ , 23.5%); Anal. for  $\text{C}_{30}\text{H}_{24}\text{N}_{14}\text{O}_2$  (612.6) Calcd./Found (%): C (58.82/58.85) H (3.95/3.93) N (32.01/32.03).

**10,10'-(1,4-Phenylene)bis(9-acetyl-4-amino-8-methyl-6,10b-dihydro-pyrido[2',3':-3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carbothioamide) (6)**: as yellow crystals, yield 44%, mp > 300°C, IR ( $\nu\text{-cm}^{-1}$ ): 3288, 3279, 3184 ( $\text{NH}_2$ , NH), 3061 (aromatic-CH), 2959, 2879 (aliphatic-CH) and 1679 (Acetyl-CO);  $^1\text{HNMR}$  ( $\delta\text{ppm}$ ): 2.23 (s, 6H, two  $\text{CH}_3$ ), 2.54 (s, 6H, two  $\text{CH}_3\text{CO}$ ), 2.59 (s, br., 8H, four  $\text{NH}_2$ ), 3.6 (s, 2H, triazine H-3), 4.7 (s, br., 2H, two NH), 7.1 - 7.78 (m, 4H, phenyl H's); **MS**: 613 ( $[\text{M}+\text{H}]^+$ , 2.5%, corresponding to the molecular weight of the molecular formula  $\text{C}_{30}\text{H}_{28}\text{N}_{14}\text{O}_2\text{S}_2$  of the assigned structure), 611 (612-H, 65.3%), 610 (612-2H, 23.1%), 599 (612- $\text{CH}_3$ , 19.5%), 584 (612- $2\text{CH}_3$ , 15.8%), 569 (612- $\text{COCH}_3$ , 14.7%), 526 (612- $2\text{COCH}_3$ , 23.5%); Anal. for  $\text{C}_{30}\text{H}_{24}\text{N}_{14}\text{O}_2$  (612.6) Calcd./Found (%): C (58.82/58.85%) H (3.95/3.93%) N (32.01/32.03%).

**10,10'-(1,4-Phenylene)bis(9-acetyl-4-amino-8-methyl-6,10b-dihydropyrido[2',3':3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carbothioamide) (7)**: as yellow crystals, yield 44%, mp 249°C, IR ( $\nu\text{-cm}^{-1}$ ): 3184 (NH), 3079 (aromatic-CH), 2978, 2859 (aliphatic-CH) and 1719 (CO ester), 1689 (Acetyl-CO);  $^1\text{HNMR}$  ( $\delta\text{ppm}$ ): 1.21 (t, 6H, two  $\text{CH}_3\text{CH}_2$ ), 1.7 (s, 6H, two  $\text{CH}_3$ ), 2.35 (s, 6H, two  $\text{CH}_3$ ), 2.63 (s, 6H, two  $\text{CH}_3\text{CO}$ ), 3.5 (s, 2H, triazine H-3), 4.3 (q, 4H, two  $\text{CH}_3\text{CH}_2$ ), 5.4 (s, br., 2H, two NH), 7.2 - 7.88 (m, 4H, phenyl H's); **MS**: 705 ( $[\text{M}+\text{H}]^+$ , 4.1%, corresponding to the molecular weight of the molecular formula  $\text{C}_{36}\text{H}_{36}\text{N}_{10}\text{O}_6$  of the assigned structure), 611 (612-H, 65.3%), 610 (612-2H, 23.1%), 599 (612- $\text{CH}_3$ , 19.5%), 584 (612- $2\text{CH}_3$ , 15.8%), 569 (612- $\text{COCH}_3$ , 14.7%), 526 (612- $2\text{COCH}_3$ , 23.5%); Anal. for  $\text{C}_{36}\text{H}_{36}\text{N}_{10}\text{O}_6$  (704.7) Calcd./Found (%): C (61.35/61.35%) H (5.15/5.13%) N (19.88/19.87%).

**1,1'-(10,10'-(1,4-Phenylene)bis(4,9-dimethyl)-6,10b-dihydropyrido[2',3':3,4]pyrazolo[5,1-c][1,2,4]triazine-10,9-diyl)-diethanone (8)**: as yellow crystals, yield 44%, mp > 330°C, IR ( $\nu\text{-cm}^{-1}$ ): 3184 (NH), 3073 (aromatic-CH), 2974, 2851 (aliphatic-CH) and 1689 (Acetyl-CO);  $^1\text{HNMR}$  ( $\delta\text{ppm}$ ): 1.3 (s, 6H, two  $\text{CH}_3$  at triazine), 2.11 (s, 6H,  $2\text{CH}_3$  at pyridine), 2.58 (s, 6H, two  $\text{CH}_3\text{CO}$  at triazine), 2.69 (s, 6H, two  $\text{CH}_3\text{CO}$  at pyridine), 3.8 (s, 2H, triazine H-3), 5.1 (s, br., 2H, two NH), 7.1 - 8.01 (m, 4H, phenyl H's); **MS**: 645 ( $[\text{M}+\text{H}]^+$ , 3.5%, corresponding to the molecular weight of the molecular formula  $\text{C}_{34}\text{H}_{32}\text{N}_{10}\text{O}_4$  of the assigned structure), 644 (643-H, 15.1%), 642 (644-2H, 12.3%), 629 (644- $\text{CH}_3$ , 22.3%), 601 (644- $\text{COCH}_3$ , 31.6%), 558 (644- $2\text{COCH}_3$ , 100%); Anal. for  $\text{C}_{36}\text{H}_{36}\text{N}_{10}\text{O}_6$  (644.7) Calcd./Found (%): C (63.34/63.35%) H (5.00/5.03%) N (21.73/21.77%).

**1,1'-(10,10'-(1,4-Phenylene)bis(3-benzoyl-4-hydroxy-8-methyl-6,10b-dihydropyrido[2',3':3,4]pyrazolo[5,1-c][1,2,4]triazine-10,9-diyl)-diethanone (9)**: as yellow crystals, yield 44%, mp > 312°C, IR ( $\nu\text{-cm}^{-1}$ ): 2559 - 3321 (broad band OH), 3058 (aromatic-CH), 2979, 2889 (aliphatic-CH) and 1689 (Benzoyl-CO);  $^1\text{HNMR}$  ( $\delta\text{ppm}$ ): 1.8 (s, 6H, two  $\text{CH}_3$  at pyridine), 2.65 (s, 6H, two  $\text{CH}_3\text{CO}$  at pyridine), 3.8 (s, 2H, triazine H-3), 4.4 (s, br., 2H, two NH), 7.3 - 8.4 (m, 14H, phenyl H's), 11.3 (s, br., 2H, two OH); **MS**: 773 ( $[\text{M}+\text{H}]^+$ , 0.5%, corres-

ponding to the molecular weight of the molecular formula  $C_{42}H_{32}N_{10}O_6$  of the assigned structure), 771 (643-H, 15.1%), 770 (772-2H, 9.1%), 757 (772- $CH_3$ , 12.5%), 729 (772- $COCH_3$ , 42.1%), 686 (772- $2COCH_3$ , 11.0%), 667 (772- $PhCO$ , 51.1%), 562 (772- $2PhCO$ , 62.2%), 476 (772- $2PhCO$ ,  $2CH_3CO$ , 100%); Anal. for  $C_{42}H_{32}N_{10}O_6$  (772.7) Calcd./Found (%): C (65.28/65.30%) H (4.17/4.20%) N (18.13/18.17%).

**Tetraethyl 2,2'-(2,2'-(4,4'-(1,4-phenylene)bis(5-acetyl-6-methyl-2,3-di-hydro-1H-pyrazolo[3,4-b]pyridine-4,3-diyl))bis(hydrazin-2-yl-1-ylidene))dimalonate (10):** as yellow crystals, yield 44%, mp 243°C, **IR** ( $\nu\text{-cm}^{-1}$ ): 3188, 3166 (NH), 2877-2965 (C-H aliphatic), 3072 (aromatic-CH), 1723 (Ester-CO) and 1689 (CO-Acetyl);  **$^1H$ NMR** ( $\delta$ ppm): 1.09 (t, 8H,  $4CH_3CH_2$ ), 1.5 (s, 6H, two  $CH_3$  at pyridine), 2.34 (q, 12H,  $4CH_3CH_2$ ), 2.62 (s, 6H,  $2CH_3CO$ ), 3.9 (s, 2H, triazine H-3), 4.1 (s, br., 4H, 2NH), 6.8 (s, br., 2H, 2NH), 7.2 - 8.1 (m, 4H, phenyl H's); **MS**: 801 ( $[M+H]^+$ ), 3.1%, corresponding to the molecular weight of the molecular formula  $C_{38}H_{44}N_{10}O_{10}$  of the assigned structure), 799 (800-H, 4.6%), 798 (800-2H, 12.4%), 785 (800- $CH_3$ , 22.1%), 757 (800- $COCH_3$ , 14.5%), 714 (800- $2COCH_3$ , 32.1%), 710 (800- $2EtO$ , 5.3%), 620 (800- $2EtO$ , 12.5%), 508 (800- $4COOEt$ , 30.4%), 456 (800- $2N=C(COOEt)_2$ , 100%); Anal. for  $C_{38}H_{44}N_{10}O_{10}$  (800.8) Calcd./Found (%): C (56.99/57.00%) H (5.54/5.53%) N (17.49/17.50%).

**Diethyl 2,2'-(2,2'-(4,4'-(1,4-phenylene)bis(5-acetyl-6-methyl-2,3-di-hydro-1H-pyrazolo[3,4-b]pyridine-4,3-diyl))bis(hydrazin-2-yl-1-ylidene))bis(3-cyanopropano-ate) (12):** as yellow crystals, yield 44%, mp > 300°C, **IR** ( $\nu\text{-cm}^{-1}$ ): 3180, 3166 (NH), 2879 - 2966 (C-H aliphatic), 3078 (aromatic-CH), 2219 (CN), 1722 (Ester-CO) and 1688 (CO-Acetyl);  **$^1H$ NMR** ( $\delta$ ppm): 1.11 (t, 4H,  $2CH_3CH_2$ ), 1.62 (s, 6H, two  $CH_3$  at pyridine), 2.1 (s, br., 2H, 2NH-pyrazolidine), 2.45 (s, 6H,  $2CH_3CO$ ), 2.61 (s, 4H,  $2CH_2CN$ ), 3.7 (s, 2H, triazine H-3), 4.4 (s, br., 2H, 2NH-pyrazolidine), 4.69 (q, 6H,  $2CH_3CH_2$ ), 6.8 (s, br., 2H, 2NH-hydrazidic), 7.0 - 8.3 (m, 4H, phenyl H's); **MS**: 735 ( $[M+H]^+$ ), 1.9%, corresponding to the molecular weight of the molecular formula  $C_{36}H_{38}N_{12}O_6$  of the assigned structure), 733 (734-H, 1.6%), 732 (734-2H, 2.4%), 718 (734- $CH_3$ , 12.3%), 690 (734- $COCH_3$ , 11.9%), 647 (734- $2COCH_3$ , 32.5%), 603 (734- $EtO, 2COCH_3$ , 17.8%), 575 (734- $EtOOC, 2COCH_3$ , 32.1%), 502 (734 -  $2COOEt, 2COCH_3$ , 63.5%), 480 (734- $2COOEt, 2CH_2CN, 2N$ , 100%); Anal. for  $C_{36}H_{38}N_{12}O_6$  (734.7) Calcd./Found (%): C (58.85/58.90%) H (5.21/5.23%) N (22.88/22.90%).

## 2.5. Synthesis of 11 and 13

A solution of **4** (1.64 g, 3 mmole) in ethanol (30 ml) diethylmalonate and ethyl cyanoacetate (0.48 g and 0.33 g 3 mmole) in presence of piperidine drops, was heated under reflux for 4 hours. The excess solvent was evaporated. The reaction mixture was then cooled and the solids were collected by filtration, dried, and crystallized to give **11** and **13** respectively.

**Diethyl 10,10'-(1,4-phenylene)bis(9-acetyl-4-hydroxy-8-methyl-6,10b-dihydropyrido[2',3':3,4]pyrazolo [5,1-c][1,2,4]triazine-3-carboxylate) (11):** as yellow crystals, yield 44%, mp 300°C, **IR** ( $\nu\text{-cm}^{-1}$ ): 2566 - 3288 (broad band, OH), 2879 - 2982 (C-H aliphatic), 3079 (aromatic-CH), 1722 (Ester-CO) and 1679 (CO-Acetyl);  **$^1H$ NMR** ( $\delta$ ppm): 1.31 (t, 6H,  $2CH_3CH_2$ ), 1.82 (s, 6H, two  $CH_3$  at pyridine), 2.67 (s, 6H,  $2CH_3CO$ ), 3.62 (s, 2H, triazine H-3), 4.1 (s, br., 2H, 2NH), 4.51 (q, 4H,  $2CH_2CH_3$ ), 7.2 - 8.1 (m, 4H, phenyl H's), 13.4 (s, br., 2H, 2OH); **MS**: 709 ( $[M+H]^+$ ), 6.0%, corresponding to the molecular weight of the molecular formula  $C_{34}H_{32}N_{10}O_8$  of the assigned structure), 691 (708-OH, 12.3%), 674 (708-2OH, 24.7%), 663 (708- $OCH_2CH_3$ , 7.9%), 635 (708- $EtOOC$ , 23.8%), 590 (708- $EtO, COOEt$ , 7.1%), 562 (708- $4COOEt$ , 42.1%), 519 (708- $2(COOEt)_2, COCH_3$ , 61.3%), 476 (800- $2(COOEt)_2, 2COCH_3$ , 100%); Anal. for  $C_{34}H_{32}N_{10}O_8$  (708.7) Calcd./Found (%): C (57.62/57.70%) H (4.55/4.53%) N (19.76/19.72%).

**Diethyl 10,10'-(1,4-phenylene)bis(9-acetyl-4-amino-8-methyl-6,10b-dihydropyrido[2',3':3,4]pyrazolo [5,1-c][1,2,4]triazine-3-carboxylate) (13):** as yellow crystals, yield 44%, mp 243°C, **IR** ( $\nu\text{-cm}^{-1}$ ): 3358, 3256, 3187 ( $NH_2, NH$ ), 2877 - 2989 (C-H aliphatic), 3082 (aromatic-CH), 1721 (Ester-CO) and 1679 (CO-Acetyl);  **$^1H$ NMR** ( $\delta$ ppm): 1.30 (t, 6H,  $2CH_3CH_2$ ), 1.87 (s, 6H, two  $CH_3$  at pyridine), 2.68 (s, 6H,  $2CH_3CO$ ), 2.91 (s, br., 4H,  $2NH_2$ ), 3.87 (s, 2H, triazine H-3), 4.1 (s, br., 2H, 2NH), 4.51 (q, 4H,  $2CH_2CH_3$ ), 7.2 - 8.1 (m, 4H, phenyl H's); **MS**: 709 ( $[M+H]^+$ ), 6.0%, corresponding to the molecular weight of the molecular formula  $C_{34}H_{34}N_{12}O_6$  of the assigned structure), 691 (708-OH, 12.3%), 674 (708-2OH, 24.7%), 663 (708- $OCH_2CH_3$ , 7.9%), 635 (708- $EtOOC$ , 23.8%), 590 (708- $EtO, COOEt$ , 7.1%), 562 (708- $4COOEt$ , 42.1%), 519 (708- $2(COOEt)_2, COCH_3$ , 61.3%), 476 (800- $2(COOEt)_2, 2COCH_3$ , 100%); Anal. for  $C_{34}H_{32}N_{10}O_8$  (708.7) Calcd./Found (%): C (57.62/57.70%) H (4.55/4.53%) N (19.76/19.72%).

## 2.6. Synthesis of 14 and 15

A solution of **4** (1.64 g, 3 mmole) and 2-bromo-1-phenyl-ethanone, 2-bromo-1-*p*-chlorophenylethanone (0.59 g or 0.69 g, 3 mmole) in dimethyl-formamide (10 ml) containing KOH (0.16 g, 3 mmole) was stirred at room temperature for 2 hours. The formed precipitates were collected by filtration, washed with water and crystallized to give **14** and **15**.

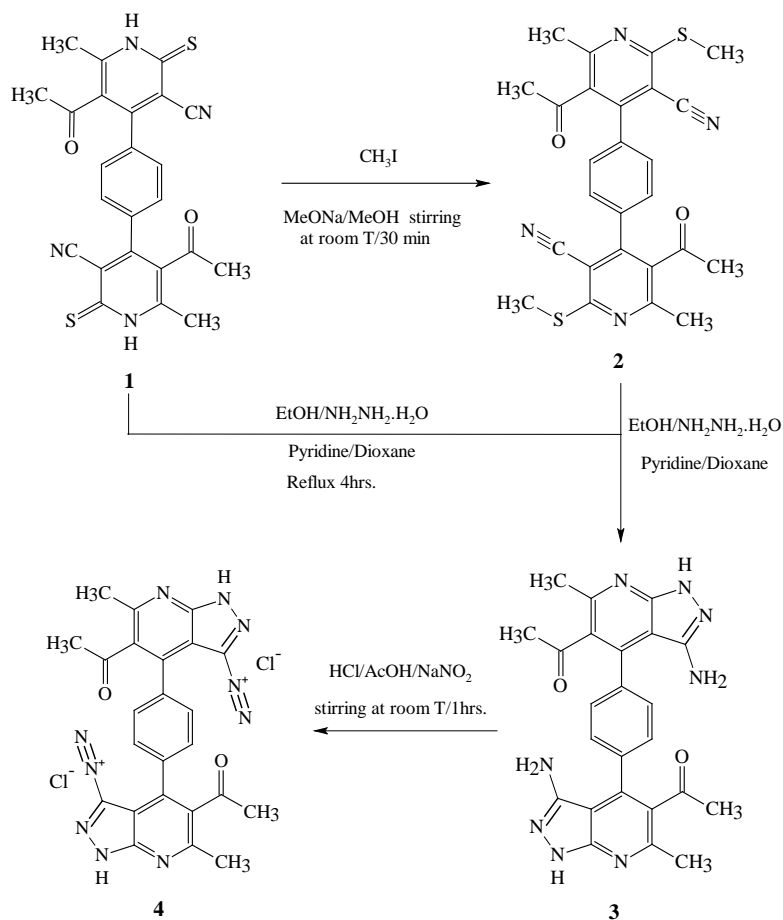
**2,2'-(4,4'-(1,4-Phenylene)bis(5-acetyl-3-amino-6-methyl-1H-pyrazolo-[3,4-b]pyridine-4,1-diy))bis(1-phenylethanone) (14)**: as yellow crystals, yield 44%, mp > 300°C, IR ( $\nu\text{-cm}^{-1}$ ): 3354, 3262 (NH<sub>2</sub>), 2873 - 2987 (C-H aliphatic), 3070 (aromatic-CH), 1705 (CO-benzoyl) and 1668 (CO-Acetyl); <sup>1</sup>HNMR ( $\delta\text{ppm}$ ): 1.72 (s, 6H, two CH<sub>3</sub> at pyridine), 2.55 (s, 6H, 2CH<sub>3</sub>CO), 4.01 (s, br., 4H, 2NH<sub>2</sub>), 5.01 (s, 4H, 2CH<sub>2</sub>CO), 7.1 - 8.3 (m, 14H, phenylH's); MS: 691 ([M+H]<sup>+</sup>, 0.6%, corresponding to the molecular weight of the molecular formula C<sub>40</sub>H<sub>34</sub>N<sub>8</sub>O<sub>4</sub> of the assigned structure), 689 (690-H, 10.8%), 688 (690-2H, 12.1%), 663 (708-OCH<sub>2</sub>CH<sub>3</sub>, 7.9%), 635 (708-EtOOC, 23.8%), 590 (708-EtO, COOEt, 7.1%), 562 (708-4COOEt, 42.1%), 519 (708-2(COOEt)<sub>2</sub>, COCH<sub>3</sub>, 61.3%), 476 (800-2(COOEt)<sub>2</sub>, 2COCH<sub>3</sub>, 100%); Anal. for C<sub>40</sub>H<sub>34</sub>N<sub>8</sub>O<sub>4</sub> (690.7) Calcd./Found (%): C (69.55/69.57%) H (4.96/4.94%) N (16.22/16.24%).

**2,2'-(4,4'-(1,4-Phenylene)bis(5-acetyl-3-amino-6-methyl-1H-pyrazolo[3,4-b]pyridine-4,1-diy))bis(1-(4-chlorophenyl)ethanone) (15)**: as yellow crystals, yield 44%, mp > 300°C, IR ( $\nu\text{-cm}^{-1}$ ): 3347, 3253 (NH<sub>2</sub>), 2878 - 2967 (C-H aliphatic), 3075 (aromatic-CH), 1700 (CO-benzoyl) and 1672 (CO-Acetyl); <sup>1</sup>HNMR ( $\delta\text{ppm}$ ): 1.67 (s, 6H, two CH<sub>3</sub> at pyridine), 2.59 (s, 6H, 2CH<sub>3</sub>CO), 4.05 (s, br., 4H, 2NH<sub>2</sub>), 5.12 (s, 4H, 2CH<sub>2</sub>CO), 7.0 - 8.1 (m, 12H, phenyl H's); MS: 760 ([M+H]<sup>+</sup>, 2.1%, corresponding to the molecular weight of the molecular formula C<sub>40</sub>H<sub>32</sub>Cl<sub>2</sub>N<sub>8</sub>O<sub>4</sub> of the assigned structure), 761 (M+ +2689 (690-H, 10.8%), 688 (690-2H, 12.1%), 663 (708-OCH<sub>2</sub>CH<sub>3</sub>, 7.9%), 635 (708-EtOOC, 23.8%), 590 (708-EtO, COOEt, 7.1%), 562 (708-4COOEt, 42.1%), 519 (708-2(COOEt)<sub>2</sub>, COCH<sub>3</sub>, 61.3%), 476 (800-2(COOEt)<sub>2</sub>, 2COCH<sub>3</sub>, 100%); Anal. for C<sub>40</sub>H<sub>32</sub>Cl<sub>2</sub>N<sub>8</sub>O<sub>4</sub> (759.6) Calcd./Found (%): C (63.24/63.27%) H (4.25/4.24%) Cl (9.33/9.34) N (14.75/14.74%).

## 3. Results and Discussion

An unequivocal support for the structure of compound **1** [20] came from the series of reactions concerning the presence and synthetic potentiality of NH, C=S and CN functional groups in 4,4'-(1,4-phenylene)bis(5-acetyl-6-methyl-2-thioxo-1,2-dihydro-pyridine-3-carbonitrile) **1** and this stimulated our interest to use it as the good starting material for the present study aiming for further chemical transformation required for our medicinal chemistry programs. Thus, it has been found that **1** reacted with methyl iodide in sodium methoxide under stirring at room temperature for 15 minutes to give the corresponding 2-methylthio derivative **2**. The IR ( $\text{cm}^{-1}$ ) and <sup>1</sup>HNMR ( $\delta\text{ppm}$ ) of **2** showed neither bands nor signals for NH groups and instead that of SCH<sub>3</sub> groups were detected. Moreover, its mass spectrum gave the parent peak at  $m/z = 486$ , which corresponding to the molecular weight of the molecular formula C<sub>26</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> of the assigned structure **2** (cf. Experimental Part). The neighboring and the chemical reactivity of both SCH<sub>3</sub> and CN functions in **2** were investigated *via* its reaction with hydrazine hydrate under reflux till the odor of methyl mercaptan ceased. The reaction seemed to proceed *via* the cleavage of SCH<sub>3</sub> groups simultaneously with the ring closure of 2-hydrazino derivatives to afford the corresponding 1,1'-(4,4'-(1,4-phenylene)bis(3-amino-6-methyl-1H-pyrazolo[3,4-b]pyridine-5,4-diy))diethanone **3**. Authentically, compound **3** obtained *via* the reaction of **1** with hydrazine hydrate under reflux through the removing of H<sub>2</sub>S molecule. The IR ( $\text{cm}^{-1}$ ) of **3** showed no absorption bands of CN function and instead the newly formed NH<sub>2</sub> function was detected. The elemental analyses and <sup>1</sup>H NMR spectral data used to elucidate the structures of this reaction product (cf. Experimental Part). Moreover, its mass spectrum gave the parent peak (M<sup>+</sup>) at  $m/z = 454.19\%$  which corresponding to the molecular weight of the molecular formula C<sub>24</sub>H<sub>22</sub>N<sub>8</sub>O<sub>2</sub> of the assigned structure **3**. In addition to the parent peaks (M<sup>+</sup>), other peaks at  $m/z = (M^+-H)$ , (M<sup>+</sup>-2H) and (M<sup>+</sup>-NH<sub>2</sub>) which gave the further confirmation of the **3** structure (cf. Experimental Part and Scheme 1).

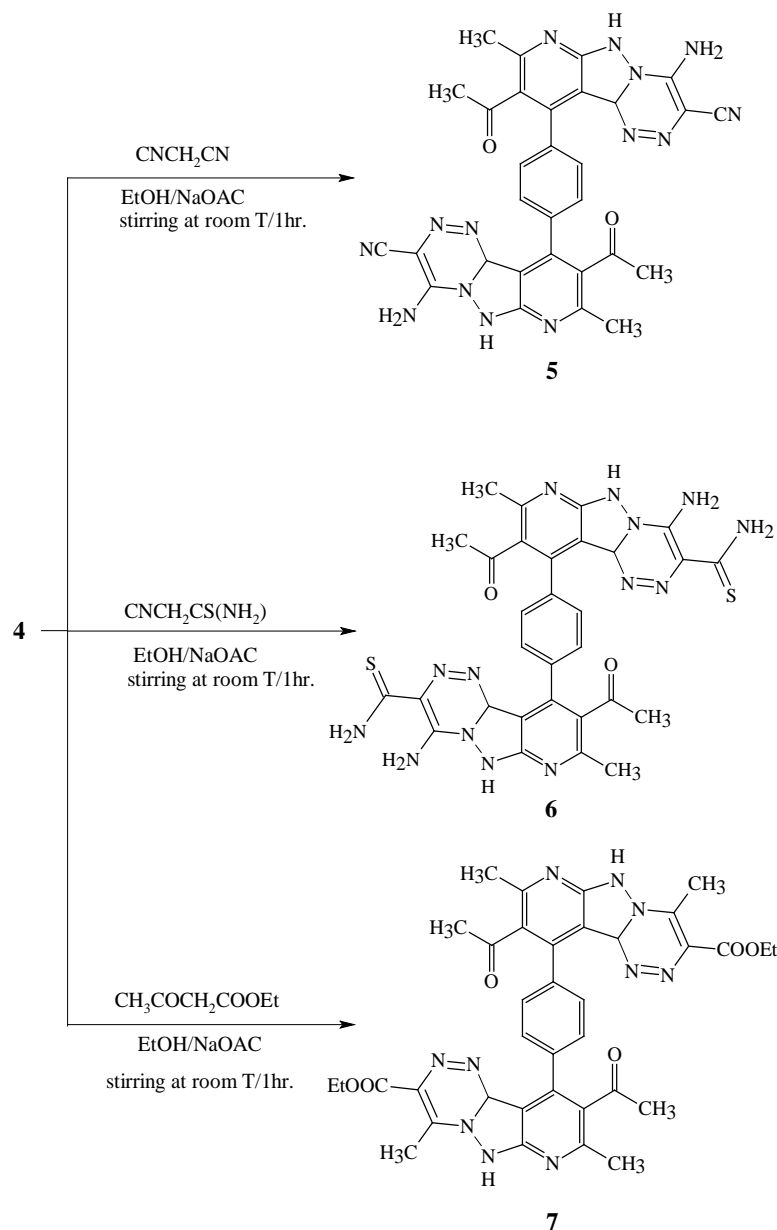
The chemical reactivity of NH<sub>2</sub> in **3** was investigated *via* its reaction with nitrous acid under stirring at room temperature to give the corresponding diazonium salt **4** which in turn, used as the good coupling reagents to synthesize several pyridopyrazolo-triazines (cf. Experimental Part). Thus, compound **4** was reacted with malonitrile and 2-cyanoethane-thioamide in ethanol (30 mL) containing sodium acetate (2 g) under stirring at room temperature for 1h to give the corresponding 10,10'-(1,4-phenylene)bis(9-acetyl-4-amino-8-methyl-6,10b-dihydropyrido[2',3':3,4]-pyrazolo[5,1-c][1,2,4]triazine-3-carbonitrile) **5** and 10,10'-(1,4-phenyl-ene)bis(9-acetyl-4-amino-8-methyl-6,10b-dihydropyrido[2',3':3,4]pyrazolo-[5,1-c][1,2,4]triazine-3-carbothioamide) **6** respectively.



Scheme 1. Synthesis of compound 2-4.

The IR ( $\text{cm}^{-1}$ ) spectrum of **5** showed the bands of CN and  $\text{NH}_2$  functions while that of **6** showed no absorption bands of CN function and instead  $\text{CSNH}_2$  functions were detected. Also, the  $^1\text{H}$  NMR ( $\delta$ ppm) spectra of each of **5** and **6** revealed the signals of  $\text{NH}_2$ , pyridine and aromatic protons. Compound **6** further confirmed *via* the presence of **S** by the element test. In addition to the elemental analyses data, the mass spectra of each of **5** and **6** gave the parent peaks ( $M^+$ ) at  $m/z = 612.22$  and  $680.20$  which corresponding to the molecular weights of the molecular formulas  $\text{C}_{30}\text{H}_{24}\text{N}_{14}\text{O}_2$  and  $\text{C}_{30}\text{H}_{28}\text{N}_{14}\text{O}_2\text{S}_2$  of the assigned structures **5,6** respectively and such results used as good evidence for further confirmation of their structures (cf. Scheme 2 and Experimental Parts).

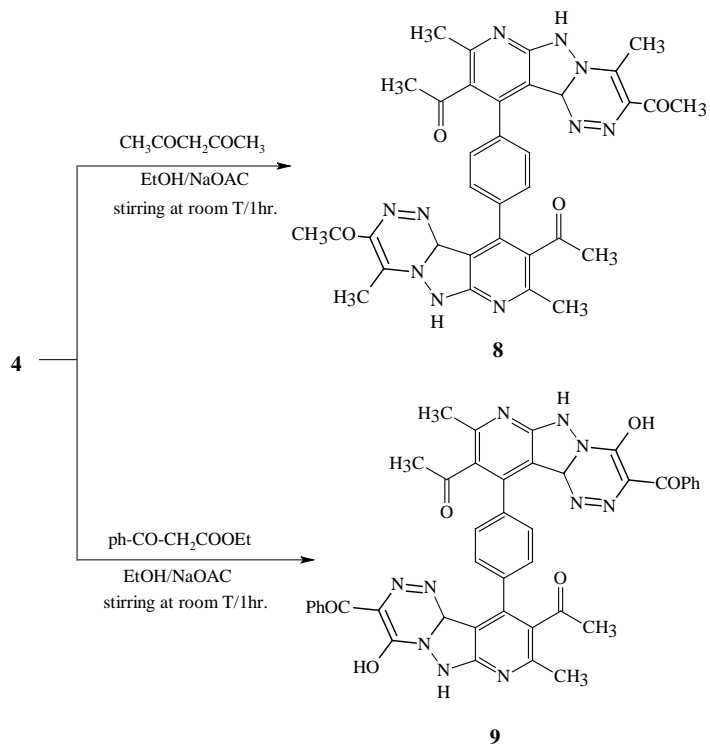
In a similar behavior, compound **4** was reacted with ethyl 3-oxobutanoate to give ethyl 10,10'-(1,4-phenylene)bis(9-acetyl-4,8-dimethyl-6,10b-dihydropyrido[2',3':3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carboxylate)**7**. The mass spectra of this reaction product gave the parent peak ( $M^+$ ) at  $704.28\%$  which corresponding to the molecular weight of the molecular formula  $\text{C}_{36}\text{H}_{36}\text{N}_{10}\text{O}_6$  of the assigned structure **7**. Moreover, the  $^1\text{HNMR}$  ( $\delta$ ppm) spectral data of this reaction product revealed the signals of  $-\text{COOCH}_2\text{CH}_3$  protons (cf. Scheme 2 and Experimental Part). Similarly, compound **4** was reacted with pentan-2,4-dione in ethanol (30 mL) containing sodium acetate (2 gm) under stirring at room temperature for 1h to give the reaction product **8**. The IR ( $\text{cm}^{-1}$ ) of this reaction product showed the absorption band of  $\text{CH}_3\text{CO}$  groups. Moreover, its mass spectrum gave the parent peak ( $M^+$ ) at  $m/z = 644$  which corresponding to the molecular weight of the molecular formula  $\text{C}_{34}\text{H}_{32}\text{N}_{10}\text{O}_4$  for the assigned structure **8**. Also, several peaks at  $m/z = 629$  ( $M^+ - \text{CH}_3$ ) and  $601$  ( $M^+ - \text{COCH}_3$ ). Considering the above mentioned compound **8** formulated as 1,1'-(10,10'-(1,4-phenylene)bis(3,8-dimethyl)-6,10b-dihydropyrido[2',3':3,4]pyrazolo[5,1-c][1,2,-4]triazine-10,9-diyl)-diethanone (cf. Experimental Part Scheme 3). Also, compound **4** reacted with ethyl 3-oxo-3-phenylpropanoate to give the reaction product 10,10'-(1,4-phenylene) bis(3-benzoyl-4-hydroxy-8-methyl-6,10b-dihydropyrido[2',3':3,4]-pyrazolo[5,1-c][1,2,4]triazine-10,9-diyl))diethanone **9**. The  $^1\text{H}$  NMR spectra revealed the signal of OH and phenyl protons. Also, the mass spectra of this



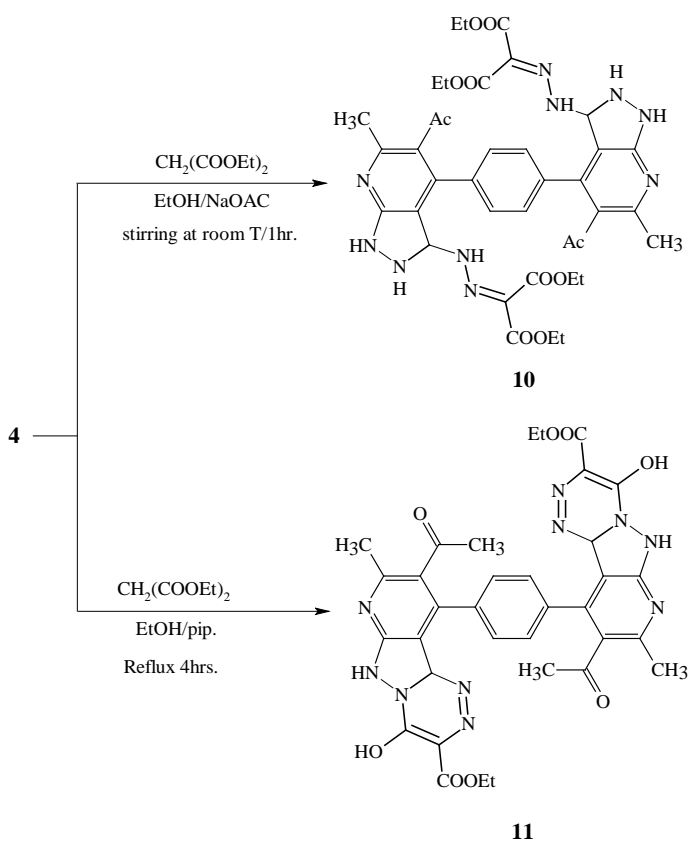
**Scheme 2.** Synthesis of compound 5-7.

reaction product gave the parent peak at  $m/z = 772.25$  which corresponding to the molecular weight of the molecular formula  $C_{42}H_{32}N_{10}O_6$  of the assigned structure **9** (cf. **Scheme 3** and Experimental Part).

Moreover, compound **4** reacted with diethylmalonate in ethanol (30 mL) containing sodium acetate (2 g) under stirring at room temperature for 1h to give the corresponding tetraethyl 2,2'-(2,2'-(4,4'-(1,4-phenylene)bis(5-acetyl-6-methyl-2,3-dihydro-1H-pyrazolo[3,4-b]pyridine-4,3-diyl))bis-(hydrazin-2-yl-1-ylidene))dimalonate **10**. The IR of this reaction product showed the absorption bands of ester CO function and  $^1\text{H}$ NMR spectra revealed the signals of  $\text{COOCH}_2\text{CH}_3$ . Moreover, the mass spectrum gave the parent peak at  $m/z = 800.32\%$  which corresponding to the molecular weight of the molecular formula  $C_{38}H_{44}N_{10}O_{10}$  of the assigned structure **10** in addition to several peaks that gave further confirmation of this structure (cf. **Scheme 4** and Experimental Part). Thus, it has been found that compound **4** reacted with diethylmalonate in ethanol (30 mL) containing the catalytic amount of piperidine under reflux to give a new triazine ring corresponding to diethyl 10,10'-(1,4-phenylene)bis(9-acetyl-4-hydroxy-8-methyl-6,10b-dihydropyrido[2',3':3,4]pyrazolo[5,1-c][1,2,-4]triazine-3-c



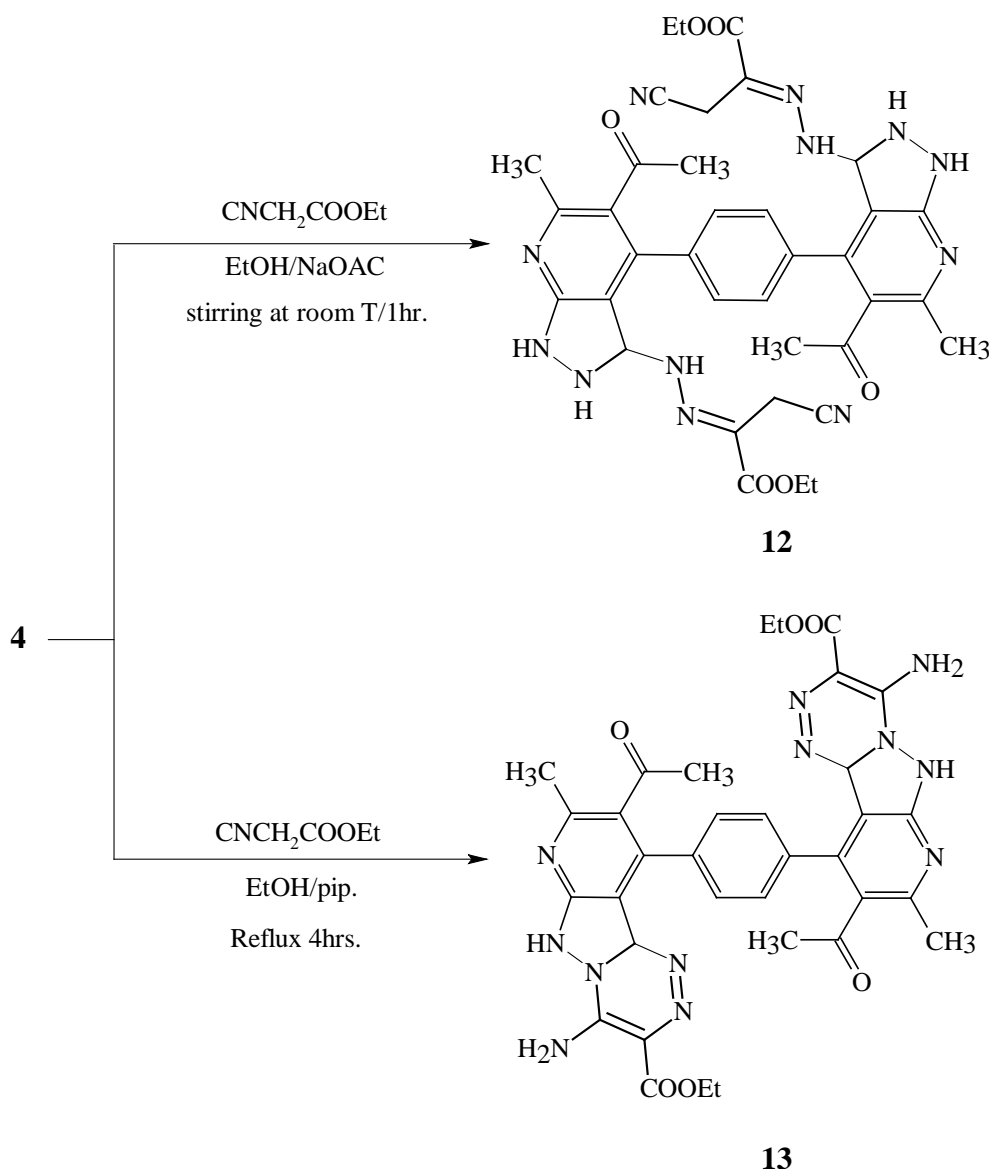
**Scheme 3.** Synthesis of compound **8** and **9**.



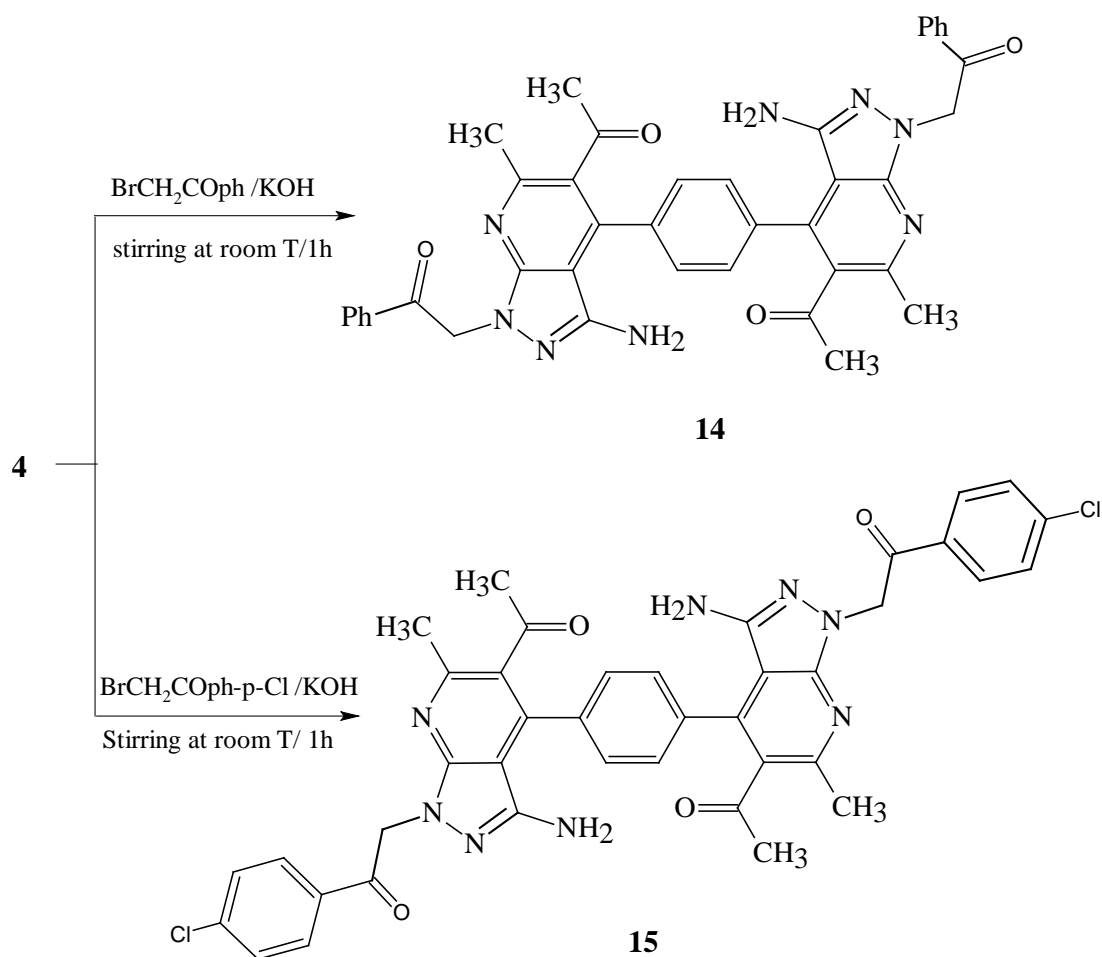
**Scheme 4.** Synthesis of compound **10** and **11**.



arboxylate) **11**. The  $^1\text{H}$  NMR spectra revealed the new signal of OH in addition to signals of  $\text{COOCH}_2\text{CH}_3$  protons. Also, the mass spectrum of this reaction product gave the parent peak at  $m/z = 708.24\%$  which corresponding to the molecular weight of the molecular formula  $\text{C}_{34}\text{H}_{32}\text{N}_{10}\text{O}_8$  of the assigned structure **11** (cf. **Scheme 4** and Experimental Part). In a similar behavior, ethyl cyanoacetate in ethanol (30mL) containing sodium acetate (2g) under stirring at room temperature for 1 h to afford the corresponding reaction product diethyl 2,2'-(2,2'-(4,4'-(1,4-phenyl-ene)bis(5-acetyl-6-methyl-2,3-dihydro-1H-pyrazolo[3,4-b]pyridine-4,3-diyl))bis(hydrazin-2-yl-1-ylidene))bis(3-cyanopropanoate) **12**. The IR ( $\text{cm}^{-1}$ ) of this reaction product showed the absorption band of each of ester carbonyl and CN and on the other hand, its  $^1\text{HNMR}$  ( $\delta\text{ppm}$ ) spectrum revealed the signals of  $-\text{COOCH}_2\text{CH}_3$  protons. Moreover, the mass spectrum gave the parent peak at  $m/z = 734.30$  which corresponding to the molecular weight of the molecular formula  $\text{C}_{36}\text{H}_{38}\text{N}_{12}\text{O}_6$  of the assigned structure **12**. (cf. **Scheme 5** and Experimental Part). Thus, it has been found that compound **4** reacted with ethyl cyanoacetate in ethanol (30 mL) containing the catalytic amount of piperidine under reflux to give the corresponding reaction product diethyl 10,10'-(1,4-phenylene)bis(9-acetyl-4-amino-8-methyl-6,10b-dihydropyrido[2',3':-3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carboxylate) **13**.



**Scheme 5.** Synthesis of compound **12** and **13**.



**Scheme 6.** Synthesis of compound **14** and **15**.

The IR ( $\text{cm}^{-1}$ ) of this reaction product showed the absorption band of each of ester carbonyl and  $\text{NH}_2$  and on the other hand, its  $^1\text{H NMR}$  ( $\delta\text{ppm}$ ) spectrum revealed the signals of  $-\text{COOCH}_2\text{CH}_3$  and  $\text{NH}_2$  protons and this confirmed that the cyclization proceeded *via* addition on the CN function. Also, the mass spectrum of this reaction product gave the parent peak at  $m/z = 706.27\%$  which corresponding to the molecular weight of the molecular formula  $\text{C}_{34}\text{H}_{34}\text{N}_{12}\text{O}_6$  of the assigned structure **13** (cf. **Scheme 5** and Experimental Part).

The chemical reactivity and synthetic potential of **4** were investigated *via* its chemical reaction with 2-bromo-1-phenylethano and 2-bromo-1-(4-chlorophenyl)ethano in dimethylformamide (10 mL) containing potassium hydroxide (1mmole) under stirring at room temperature for 1 h to afford the corresponding reaction product 2,2'-(4,4'-(1,4-phenylene)-bis(5-acetyl-3-amino-6-methyl-1H-pyrazolo[3,4-b]pyridine-4,1-diyl))bis-(1-phenylethano) and 2,2'-(4,4'-(1,4-phenylene)-bis(5-acetyl-3-amino-6-methyl-1H-pyrazolo[3,4-b]pyridine-4,1-diyl))bis(1-(4-chlorophenyl)ethano) **14** and **15** respectively. The IR ( $\text{cm}^{-1}$ ) of this reaction product showed the absorption band of  $\text{NH}_2$  function as well as its  $^1\text{H NMR}$  ( $\delta\text{ppm}$ ) spectrum revealed the signals of  $-\text{NH}_2$  protons. Moreover, their mass spectra gave the parent peaks at  $m/z = 690.27\%$  and  $758.19\%$  in respective manner which corresponding to their molecular weights of the molecular formulas  $\text{C}_{40}\text{H}_{34}\text{N}_8\text{O}_4$  and  $\text{C}_{40}\text{H}_{32}\text{Cl}_2\text{N}_8\text{O}_4$  of the assigned structures **14** and **15** (cf. **Scheme 6** and Experimental Part).

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