Al-Azhar Bull. Sci. Vol. 19, No. 2 (Dec.): pp. 119-134, 2008.

UTILITY OF N-2-PYRIDYL–3-OXOBUTANAMIDE IN HETEROCYCLIC SYNTHESIS: SYNTHESIS OF NEW DIHYDROPYRIDINE, FUSED PYRIDINE, PYRIDOPYRIDONE, PYRIDAZINE AND PYRIDOPYRIMIDINETHIONE DERIVATIVES

I.S. ABDEL HAFIZ[*a], A.E. KHODAIR[b], SAFAA M.BAKER[a] and A.M HUSSEIN[c,]

[a] *Department of Chemistry, Faculty of Education, Suez Canal University, Al-ArisH, Egypt.*

[b] *Department of Chemistry, Faculty of Science, Suez Canal University, ismailia, Egypt.*

[c] *Department of Chemistry, Faculty of Science, Al Azhar University, Assiut 71524, Egypt.*

e-mail: dr_ibrahim_Saad@maktoob.com

Abstract

2-Aminopyridine was fused with ethyl acetoacetate for two hours to yield the N-2-pyridyl–3-oxobutanamide (1). However, when the reaction time was increased to 5 hours compound 3 was obtained. Condensation of 3 with benzaldehyde gave 4. The reaction of pyridopyridone 3 with arylidenemalononitrile 7a-c afforded 4H-pyran derivatives 10a-c. In contrast to the behavior of arylidenemalononitriles 7a-c towards pyridopyridine 3, benzylidenemalononitrile 7d reacted with compound 3 to give the product 11. Compound 1 was allowed to react with arylidenemalononitriles to give the dihydropyridine derivatives 17a-d. Alkylation of compound 1 with alkylating agents has been also reported. Thus, compound 1 was condensed with [DMF-DMA] in refluxing dioxane to yield 18, but under the reaction conditions we obtained only 21. The pyridopyridone 3 reacted with benzoyl isothiocyanates 25a,b to give thiourea derivatives 26a,b. Cyclization of 26a,b in dry dioxane and conc. sulphuric acid afforded pyridopyrimidine-2-thione derivatives 27a,b. On the other hand, coupling of pyridopyridone 3 with the aryl diazonium salts 28a-e afforded the corresponding azo products 29a-e. Boiling of compound 29 in ethanol and HCl afforded the azo products 30a-e. Treatment of arylhydrazone 30a with malononitrile afforded the pyridazine derivative 31.

Keywords: pyridine, pyridopyridone, pyridazine and pyridopyrimidinethione derivatives.

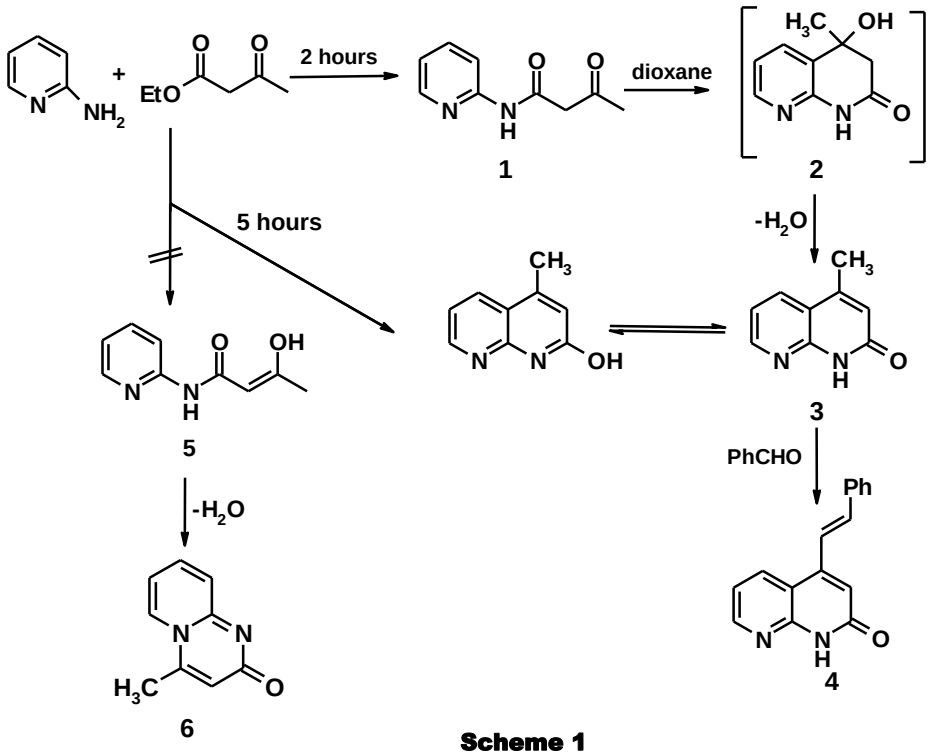
Introduction

In the last few years, we have been involved in a program aimed at developing new efficient synthetic approaches for the synthesis of heterocyclic compounds of

biological interest [1-3]. In previous studies, we reported the synthesis of polyfunctionally substituted pyridines [4,5]. In continuation of this work we use here N-2-Pyridyl-3-oxobutanamide for the synthesis of polyfunctionally substituted pyridines and pyridazines.

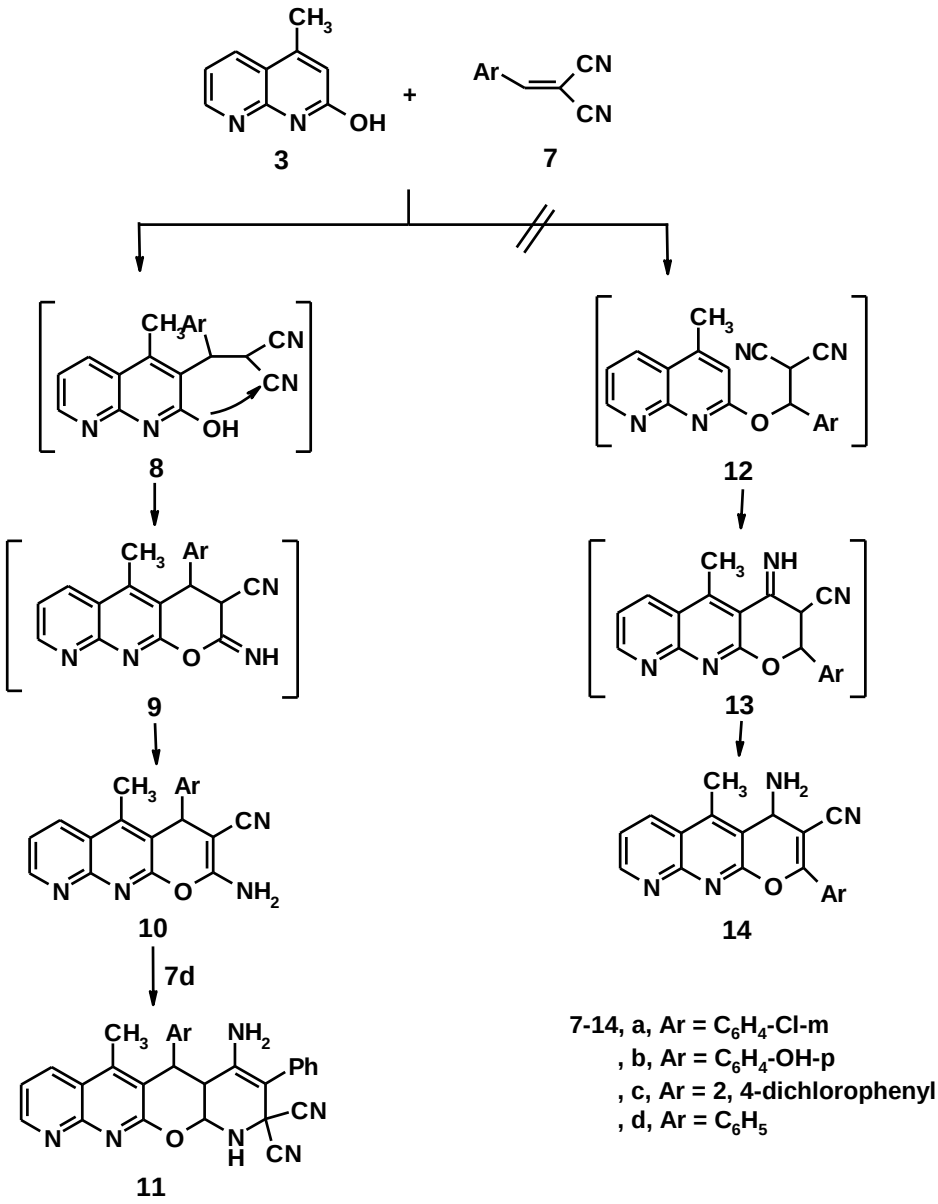
Results and discussion

It has been found that 2-aminopyridine was fused with ethyl acetoacetate for two hours to yield N-2-pyridyl–3-oxobutanamide **(1)**[6,7]**.** However, when the reaction time was increased to 5 hours a product with a molecular formula $C_9H_8N_2O$ and molecular weight 160 was obtained. This was assigned structure **3** or its isomeric pyridopyrimidine **6**. Structure **6** was ruled out based on the elemental analysis and the spectral data. Thus, ^{1}H NMR spectrum revealed the presence of a singlet signal at δ = 3.3 ppm corresponding to the methyl group, a multiplet signal at δ = 6.9-8.3 ppm corresponding to aromatic and olefinic protons and a singlet signal at δ = 11.7 corresponding to NH group. Furthermore, this conclusion was supported by the mass spectrum. Thus, it showed a very intense molecular ion peak at *m/z* = 160. It, also, showed fragments at 131 (M - C=O), at 94 (M - CH_3-C=C=O) and at 78 (pyridyl radical). This data are consistent with structure **3** and not structure **6**. Finally, structure **3** was confirmed via its preparation from N-2-pyridyl-3-oxobutanamide **(1)** according to the published procedure, using refluxing dioxane for 3 hours [mp, m.mp and TLC]. Therefore, formation of compound **3** from 2-aminopyridine and ethyl acetoacetate is believed to be formed via initial condensation of 2-aminopyridine with ethyl acetoacetate to form compound **1** which cyclizes to give the non isolable intermediate **2** that loses one molecule of water to give **3**. Further support of the structure **3** was obtained by its condensation with aromatic aldehydes. Thus, it was condensed with benzaldehyde in refluxing ethanol in the presence of a catalytic amount of piperidine to give **4** as literature procedure [8,9]. Establishing the structure of compound **4** was based on its elemental analysis and spectral data. Thus, ^{1}H NMR spectrum of compound **4** revealed the absence of methyl function and revealed the presence of two doublet signals at δ = 6.8 and 6.9 ppm corresponding to olefinic protons, a multiplet signal at δ = 7.2-8.2 ppm corresponding to aromatic protons and a singlet signal at δ = 11.7 ppm corresponding to NH group.



Scheme 1

The behavior of pyridopyridone **3** towards electrophilic reagents under an alkaline condition was also investigated. Thus, the reaction of pyridopyridone **3** with 3-chlorobenzylidinemalononitrile **7a** afforded a product that can be formulated as either 4H-pyran derivative **10a** or its isomeric structure **14a**. Structure **14a** was ruled out, while structure **10a** was established as the sole reaction product based on its spectral analysis. For example, the ^{1}H NMR spectrum of **10a** revealed the presence of a singlet signal at δ = 3.37 ppm corresponding to methyl function, a singlet function at δ = 4.45 ppm corresponding to 4H pyran, a multiplet signal at δ = 7.07-7.80 ppm corresponding to aromatic protons and a singlet signal at δ = 10.45 ppm corresponding to NH_2 group. Formation of compound **10** can be interpreted via intermediacy of Michael adduct **8a** which cyclizes to **9a** that tautomerizes into **10a**. Similarly, the reaction of pyridopyridone **3** with arylidenemalononitriles **7b,c** afforded the 4H pyran derivatives **10b,c**.

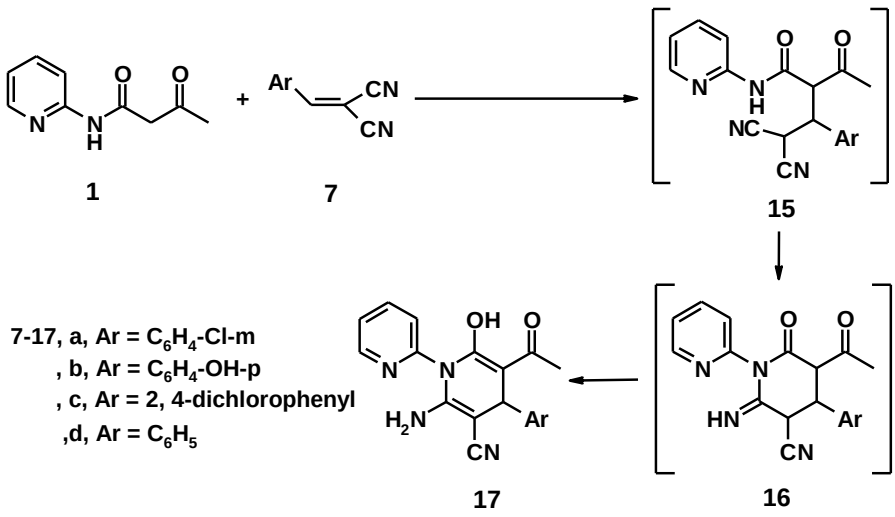


7-14, a, Ar = C_6H_4-Cl-m
, b, Ar = C_6H_4-OH-p
, c, Ar = 2, 4-dichlorophenyl
, d, Ar = C_6H_5

Scheme 2

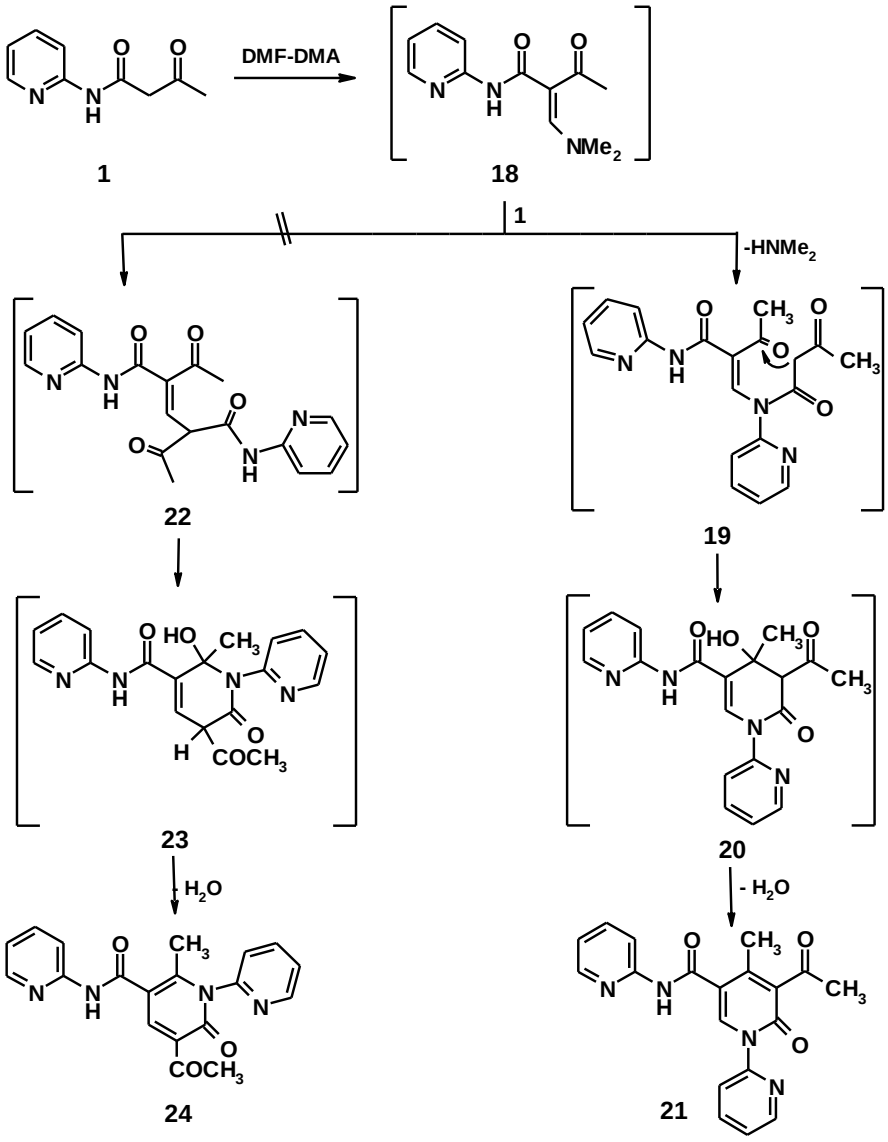
In contrast to the behavior of arylidenemalononitriles **7a-c** towards pyridopyridone **3**, but 2 moles of benzylidenemalononitrile **7d** reacted with **3** to give a product with a molecular formula $C_{29}H_{20}N_6O$ (468). This product was assigned structure **11** on the bases of its elemental analysis and spectral data. Thus, ^{1}H NMR spectrum revealed the presence of a singlet signal at δ = 3.38 ppm corresponding to methyl group, a singlet function at δ = 4.80 ppm corresponding to 4H-pyran, a multiplet signal at δ = 7.31-8.02 ppm corresponding to aromatic protons and NH group and a singlet signal at δ = 8.60 ppm corresponding to amino group. The mass spectrum of compound **11** showed the molecular ion peak at m/z = 468. It also showed fragment at 313 (M-benzylidenemalononitrile).

The results obtained from the behavior of **3** towards arylidenemalononitriles prompted us to investigate further behavior of N-2-pyridyl-3-oxobutanamide **(1)** towards arylidenemalononitrile **7a-d**. Thus, N-2-pyridyl-3-oxobutanamide **(1)** was allowed to react with 3-chlorobenzylidinemalononitrile to give dihydropyridine derivative **17a** (Scheme 3**)**. Establishing structure **17a** was based on its elemental analysis and spectral data. For example, the IR spectrum of compound **17a** revealed the presence of a peak at 3200 cm^{-1} corresponding to amino function, a peak at 2214 cm^{-1} corresponding to nitrile function and a peak at 1681 cm^{-1} corresponding to carbonyl function. ^{1}H NMR of the same product revealed the presence of a singlet signal at δ = 1.23 ppm corresponding to methyl group, a singlet signal at δ = 1.66 ppm corresponding to phenolic hydroxyl, a singlet signal at δ = 3.79 ppm corresponding to 4H pyridine and a multiplet signal at δ = 7.24-8.35 ppm corresponding to aromatic protons and amino group. The mass spectrum of the same product is in accordance with the proposed structure. Thus, it showed a molecular ion peak at 363. It also showed fragments at 323 (M-C-C=O) and 281(M-pyridine). Formation of **17a** from reaction of N-2-pyridyl-3-oxobutanamide (**1)** and 3-chlorobenzylidenemalononitrile is believed to be formed via intermediacy of Michael adduct **15a** which cyclizes to give **16** that tautomerizes readily to give the dihydropyridine **17a.** Similarly, N-2-pyridyl-3-oxobutanamide **(1)** was allowed to react with arylidinemalononitrile derivatives **7b-d** to give the dihydropyridine derivatives **17b-d** (Scheme 3).



Scheme 3

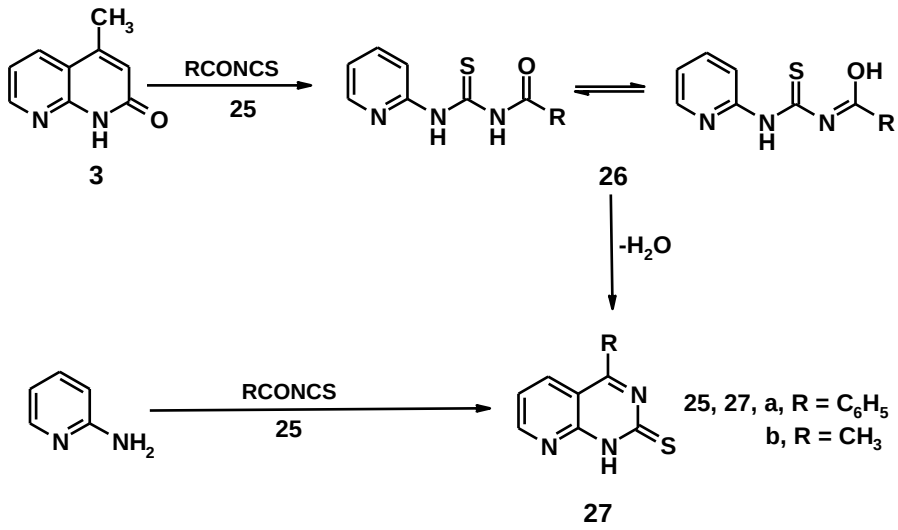
Ready oxidation of dihydroazines into azines has been reported earlier under mild conditions [10]. Alkylation of compound **1** with alkylating agents has been also reported. Thus, N-2-pyridyl-3-oxobutanamide **(1)** was condensed with N,N-dimethylformamide-dimethylacetal [DMF-DMA] in refluxing dioxane to yield the product which may be formulated as 2-dimethylaminomethylene-3-oxo-N-2-pyridylbutyramide **18**. But under the reaction condition we obtained only a product with a molecular mass m/z = 349 (M+1) corresponding to a molecular formula $C_{19}H_{16}N_4O_3$, this was considered to be either **21** or its isomeric structure **24**. Structure **21** was actually the only reaction product based on its spectral data. Thus, ^{1}H NMR spectrum revealed the presence of a singlet signal at δ = 2.12 ppm corresponding to methyl group, a singlet signal at δ = 3.34 ppm corresponding to methyl group, a multiplet signal at δ = 7.13-8.71 ppm corresponding to aromatic protons and a singlet signal at δ = 11.11 ppm corresponding to NH group. Formation of compound **21** is assumed to proceed via initial condensation of N-2-pyridyl-3-oxobutanamide **(1)** with one molecule of DMF-DMA to yield the unstable enaminone **18**, which in turn, reacts with nother molecule of **1** to give intermediate **19** via losing dimethylamine molecule. Intermediate **19** cyclized into structure **20**, then, loses H_2O to yield the final product **21**. (Scheme 4).



Scheme 4

The behavior of pyridopyridone **3** towards isothiocyanate reagents was also investigated. Thus, when **3** was reacted with benzoyl isothiocyanate and acetyl isothiocynate **25a,b** which, in turn prepared from benzoylchloride or acetylchloride with ammonium thiocyanate in refluxing acetone, afforded the acyclic thiourea

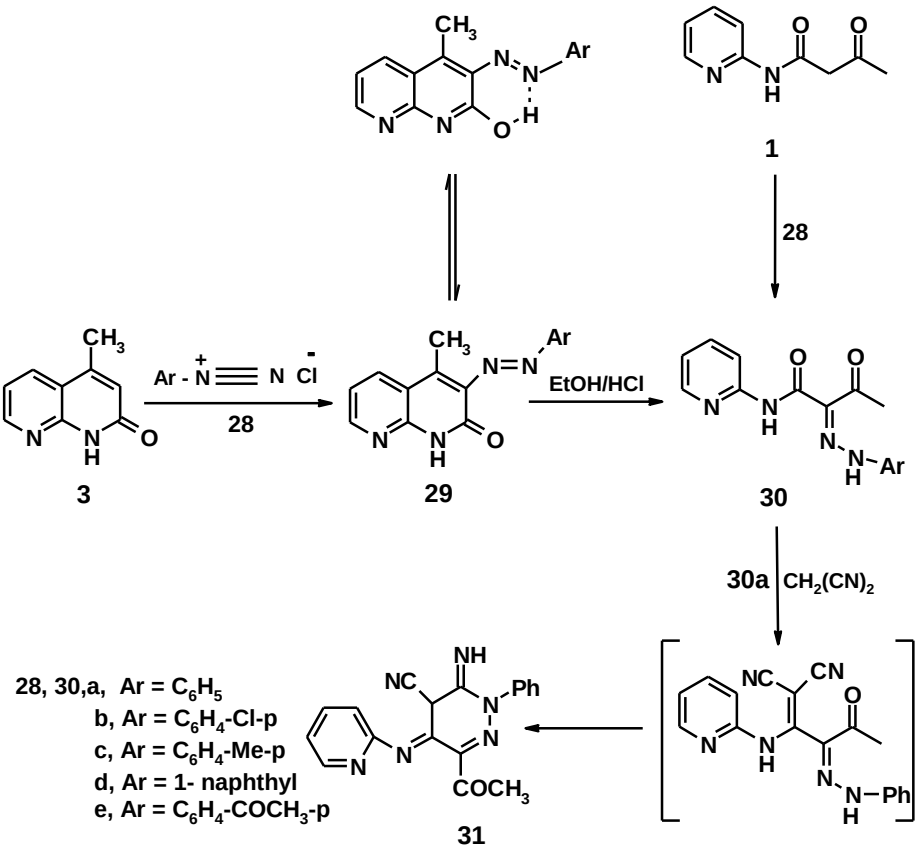
derivatives **26a,b** based on their elemental analysis and spectral data. Formation of **26a,b** from the reaction of pyridopyridone **3** and benzoyl isothiocynate is believed to be formed via initial ring opening in pyridopyridone **3** and subsequent loss of crotonaldehyde molecule. Cyclization of thiourea derivatives **26a,b** in dry dioxane and conc. sulphuric acid afforded pyridopyrimidinethione derivatives **27a,b** (Scheme 5).



Scheme 5

On the other hand, coupling of pyridopyridone **3** with the aryl diazonium salt **28a** [11, 12] afforded the corresponding azo product **29a**. Establishing structure **29a** was based on its spectral data. For example, the mass spectrum of compound **29a** showed a molecular ion peak at m/z = 264 (M^+) corresponding to the molecular formula $C_{15}H_{12}N_4O$. Also, ^{1}H NMR of compound **29a** revealed the presence of a singlet signal at δ = 2.3 ppm corresponding to methyl function, a multiplet signal at δ = 6.9-8.5 ppm corresponding to aromatic protons and singlet signals at δ = 13.13, 14.45 ppm corresponding to NH and OH groups. Similarly, coupling of pyridopyridine **3** with aryl diazonium salts **28b-e** afforded the azo products **29b-e** (Scheme 6). Boiling compounds **29a-e** in ethanol and HCl afforded the azo products **30a-e**. Spectral data are in favor with the proposed azo form. For example the IR spectrum of **30d** showed absorption bands at 3100, 3058 cm^{-1} corresponding to NH, and absorption bands at 1662 and 1635 cm^{-1} corresponding to amidic arbonyl and

acetylcarbonyl respectively. ^{1}H NMR revealed to the presence of a singlet signal at δ = 2.60 ppm corresponding to methyl group, a multiplet signal at δ = 7.04-8.42 ppm corresponding to aromatic protons and a singlet signal at δ = 11.90 ppm corresponding to NH group. Moreover, the mass spectrum of **30d** showed the molecular ion peak at m/z = 332 (M+1). Treatment of arylhydrazone **30a** with malononitrile in absence of solvent and in presence of a little amount of ammonium acetate afforded the pyridazine derivatives **31** as demonstrated in (Scheme 6). Establishing structure **31** was based on its elemental analysis and the spectral data.



Scheme 6

Experimental

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν, cm^{-1}). The ^1H NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ at 200 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Elemental analyses were carried out by the Micro analytical Research Center, Faculty of Science, Cairo University.

Preparation of N-2-pyridyl–3-oxobutanamide (1):

A mixture of 2-aminopyridine (9.4 g, 0.1mol) and ethyl acetoacetate (13 g, 0.1mol) was fused at 130°C for 2 hrs. The reaction mixture was cooled and treated with petroleum ether (40-60). The solid was collected and crystallized from ethanol to give **1** s colorless crystals (60 %); mp 99-100 ^OC; ν_{max}/ cm^{-1}(KBr) 3243, 3190 (NH), 1721, 1667 (C=O); Found: C, 60.62; H, 5.70; N, 15.80; Calcd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.61; N, 15.73%.

Preparation o f 1,2-Dihydro-4-methyl[1,8]naphthyridine-2-one(3):

A mixture of 2-aminopyridine (9.4 g, 0.1 mol) and ethyl cetoacetate (13 g, 0.1 mol) was fused at 130°C for 5 hrs. The reaction mixture was allowed to cool and treated with petroleum ether (40-60), the solid product, so formed, was collected by filtration and crystallized from ethanol. It was obtained as colorless crystals (50%); mp 162-164°C; ν_{max} /cm^{-1} (KBr) 3150 (NH), 1651 (C=O); δ_H (DMSO-d_6) 3.3 (s, 3H, CH_3), 6.9-8.3 (m, 4H, aromatic H), 11.7 (s, 1H, NH); m/z =160 (M). Found: C, 67.40; H, 5.10; N, 17.42; Calcd for $C_9H_8N_2O$: C, 67.50; H, 5.00; N, 17.50%.

Preparation of 4-(2-styryl)naphthryidin-2-one (4):

A mixture of pyridopyridone **3** (1.6 g; 0.01 mol) and benzaldehyde (1.06 g; 0.01 mol) in ethanol (30ml) was treated with a catalytic amount of piperidine (1 ml). The reaction mixture was refluxed for 2 hrs and left to cool. The solid product was collected by filtration and crystallized from ethanol. It was obtained as colorless crystals (50%); mp 166-168°C; ν_{max} /cm^{-1} (KBr) 3444 (NH), 2923 (CH-aliph), 1651 (C=O); δ_H ($CDCl_3$) 6.8 (d, 1H, alkenyl proton), 6.9 (d, 1H, alkenyl proton), 7.2-8.2 (m, 9H, aromatic-H), 11.7 (s, 1H, NH); m/z 248 (M); Found: C, 77.50; H, 4.80; N, 11.35; Calcd for $C_{16}H_{12}N_2O$: C, 77.41; H 4.83; N, 11.29 %.

Preparation of fused pyran derivatives (10a-c and 11):

General procedure: A mixture of pyridopyridone derivative **3** (1.60 g; 0.01 mol) and arylidenemalononitriles (0.01 mol) in ethanol (30 ml) was treated with few drops of piperidine and heated under reflux for 3 hrs. The reaction mixture was allowed to cool and poured onto crushed ice then acidified with HCl, The solid product was collected by filtration and crystallized from the proper solvent.

***2-Amino-4-(3-chlorophenyl)-5-methyl-4H-1-oxa-9,10-diaza-anthracene-3-carbonitrile* (10a):**

It was obtained as pale yellow crystals from ethanol (62 %); mp 268-270°C; ν_{max} /cm^{-1} (KBr) 3307 (NH_2), 3080 (CH-arom), 2966 (CH-aliph), 2203 (CN); δ_H (DMSO-d_6) 3.06 (s, 3H, CH_3), 4.4 (s, 1H, 4H pyran), 7.07-7.80 (m, 7H, aromatic H), 10.45 (s, 2H, NH_2); m/z = 348 (M); Found: C, 65.50; H, 3.58; N, 16.20; Calcd for $C_{19}H_{13}N_4OCl$: C 65.42; H, 3.73; N, 16.06 %.

2-Amino-4-(4-hydroxyphenyl)-5-methyl-4H-1-oxa-9,10-diaza-anthracene-3-carbonitrile (10b):

It was obtained as orange crystals (35%); mp 230-232°C; ν_{max} /cm^{-1} (KBr) 3336 (OH), 3220 (NH_2), 2202 (CN); Found: C, 69.30; H, 4.15; N, 16.77; Calcd for $C_{19}H_{14}N_4O_2$: C, 69.09; H 4.24; N, 16.96 %.

2-Amino-4-(2,4-dichlorophenyl)-5-methyl-4H-1-oxa-8,10-diaza-anthracene-3-carbonitrile (10c) :

It was obtained as yellow crystals from ethanol (25%); mp 263-265°C; ν_{max} /cm^{-1} (KBr) 3433, 3321 (NH_2), 3070 (CH-arom), 2218 (CN); m/z = 383 (M+1); Found: C, 59.60; H, 3.19; N, 14.70 Calcd for $C_{19}H_{12}N_4OCl_2$: C, 59.68; H 3.14; N, 14.65 %.

7-Amino-5-methyl-6,8-diphenyl-6,10-dihydro-11-oxa-1,10,12-triaza-naphthacene-9,9-dicarbonitrile (11) :

It was obtained as pale yellow crystals from ethanol (51 %); mp >300°C; νmax /cm-1 (KBr) 3468 (NH2), 3321 (NH), 3029 (CH-arom), 2927 (CH-aliph), 2206 (CN); δH (DMSO-d6) 3.29 (s, 3H, CH3), 4.9 (s, 1H, 4 H pyran), 7.11-8.11 (m, 15H, aromatic H and NH2), 8.6 (s, 1H, NH), m/z = 468 (M); Found: C, 74.30; H, 4.15; N, 17.82; Calcd for C29H20N6O: C, 74.35; H, 4.27; N, 17.94%.

Preparation of 4H-pyridine derivatives 17a-d:

General procedure: A mixture of N-2-pyridyl-3-oxobutanamide **1** (1.78 g; 0.01 mol) and arylidenemalononitriles (0.01 mol) in ethanol (30 ml) was treated with few

drops of piperidine and heated under reflux for 3 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl, The solid product was collected by filtration and crystallized from the proper solvent.

5-Acetyl-2-amino-4-(3-chlorophenyl)-6-hydroxy-4H-[1,2]bipyridinyl-3-carbonitrile (17a) :

It was obtained as canarian yellow crystals from ethanol (64 %); mp 310-311°C; ν_{max} /cm^{-1} (KBr) 3200 (NH_2), 3090 (CH-arom), 2927 (CH-aliph), 2214 (CN), 1681 (C=O); δ_H ($CDCl_3$) 1.23 (s, 3H, CH_3), 1.66 (s, 1H, OH), 3.79 (s, 1 H, 4 H pyridine), 7.24-8.35 (m, 10H, aromatic H and NH_2); m/z = 363 (M-3); Found: C, 62.30; H, 4.15; N, 15.12; Calcd for $C_{19}H_{15}N_4O_2Cl$:s C, 62.21; H, 4.09; N, 15.27 %.

***5-Acetyl-2-amino-6-hydroxy-4-(4-hydroxyphenyl)-4H-[1,2]bipyridinyl-3-carbonitrile* (17b):**

It was obtained as orange crystals from ethanol (68.5 %); mp 180-182°C; m/z = 348 (M); Found: C, 65.33; H, 4.55; N, 16.02; Calcd for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.59; N 16.09 %.

5-Acetyl-2-amino-4-(2,4-dichlorophenyl)-6-hydroxy-4H-[1,2]bipyridinyl-3-carbonitrile (17c):

It was obtained as pale yellow crystals from ethanol (68.4 %); mp 160-162°C; ν_{max} /cm^{-1} (KBr) 3271 (NH_2), 2214 (CN), 1650 (C=O); δ_H ($CDCl_3$) 1.46 (s, 3H, CH_3), 1.8 (s, 1H, OH), 4.35 (s, 1 H, 4 H pyridine), 6.98-7.31 (m, 9H, aromatic H and NH_2), m/z = 398 (M-3); Found: C, 56.80; H, 3.45; N, 13.82; Calcd for $C_{19}H_{14}N_4O_2Cl_2$: C, 56.85; H, 3.49; N, 13.96 %.

5-Acetyl-2-amino-6-hydroxy-4-phenyl-4H-[1,2]bipyridinyl-3-carbonitrile (17d):

It was obtained as pale yellow crystals from ethanol (72.4 %); mp 140-142°C; ν_{max} /cm^{-1} (KBr) 3259, 3215 (NH_2), 3101 (CH-arom), 2960 (CH-aliph), 2194 (CN), 1706 (C=O); m/z = 333 (M+1); Found: C, 68.54; H, 4.75; N, 16.82; Calcd for $C_{19}H_{16}N_4O_2$: C, 68.67; H, 4.81; N, 16.86 %.

Preparation of 5-Acetyl-4-methyl-6-oxo-6H-[1,2]bipyridinyl-3-carboxylic acid pyridin-2-ylamide (21):

To a solution of N-2-pyridyl-3-oxobutanamide **(1)** (1.78 g; 0.01 mol) in dry dioxane, dimethylformamidedimethyl acetal (0.01 mol) was added. The reaction mixture was heated under reflux for 2 hrs, and then cooled. The precipitate was

filtered off, washed with ether and crystallized from ethanol. It was obtained as pale yellow crystals (50 %) mp 245-247°C; ν_{max} /cm^{-1} (KBr) 3241 (NH), 3022 (CH-arom), 2920 (CH-aliph), 1774, 1672, 1655(3 C=O); δ_H (DMSO-d_6) δ = 2.12 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 7.13-8.38 (m, 9H, aromatic H), 11.11(s, 1H, NH); m/z = 349 (M+1); Found: C, 65.88; H, 4.33; N, 16.15 Calcd for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.59; N, 16.09 %.

Preparation of thiourea derivatives (26a,b):

Procedure (A): To a solution of pyridopyridone **3** (1.6 g; 0.01 mol) in dry acetone (50 ml), benzoyl or acetyl isothiocyanate (0.01 mol) was added. The reaction mixture was heated under reflux for 2 hrs, and then poured onto cold water. The solid product was collected by filtration and crystallized from the proper solvent.

Procedure (B): To a solution of 2-aminopyridine (0.94 g; 0.01 mol) in dry acetone (50 ml), benzoyl or acetyl isothiocyanate (0.01 mol) was added. The reaction mixture was heated under reflux for 2 hrs, and then poured onto cold water. The solid product was collected by filtration and crystallized from the proper solvent.

N-pyridin-2-yl-N-benzoylthiourea (26a):

It was obtained as yellow crystals from ethanol (64.4 %); mp 180-182°C; ν_{max} /cm^{-1} (KBr) 3274, 3152 (NH), 1678 (C=O); δ_H (DMSO-d_6) 6.8-8.2 (m, 9H, aromatic H), 11.2 (s, 1H, NH), 12.4 (s, 1H, NH); m/z = 257 (M); Found: C, 60.65; H, 4.33; N, 16.13; Calcd for $C_{13}H_{11}N_3OS$: C, 60.70; H, 4.28; N, 16.34 %.

N-pyridin-2-yl-N-acetylthiourea (26b):

It was obtained as yellow crystals from ethanol (60 %); mp 258-260°C; ν_{max} /cm^{-1} (KBr) 3250, 3200 (NH), 1693 (C=O); δ_H (DMSO-d_6) 2.39 (s, 3H, CH_3), 6.7-8.8 (m, 4H, aromatic H), 11.3 (s,1H, NH), 13.6 (s,1H, NH); m/z = 195 (M); Found: C, 49.15; H, 4.55; N, 21.43; Calcd for $C_8H_9N_3OS$: C, 49.23; H, 4.61; N, 21.53 %.

Preparation of pyridopyrimidinethione derivative (27a,b):

General procedure: To a solution of thiourea derivatives **26a,b** (0.01 mol) in dry dioxane (50 ml), conc. sulphuric acid (0.01 mol) was added. The reaction mixture was heated under reflux for 2 hrs, and then poured onto cold water. The solid product was collected by filtration and crystallized from the proper solvent.

4-phenyl-1H-pyrido[2,3-d]pyrimidine-2-thione (27a).

It was obtained as pale yellow crystals from ethanol (55.4 %); mp > 300°C; ν_{max} /cm^{-1} (KBr) 3100 (NH); m/z = 239 (M); Found: C, 65.20; H, 3.65; N, 17.53; Calcd for $C_{13}H_9N_3S$: C, 65.27; H, 3.76; N, 17.57 %.

4-Methyl-1H-pyrido[2,3-d]pyrimidine-2-thione (27b):

It was obtained as pale yellow crystals from ethanol (63.8%); mp > 300°C; ν_{max} /cm^{-1} (KBr) 3371 (NH); δ_H (DMSO-d_6) 2.13 (s, 3H, CH_3), 7.21-7.36 (m, 3H, aromatic H), 10.45 (s, 1H, NH); Found: C, 65.20; H, 3.65; N, 17.53; Calcd for $C_8H_7N_3S$: C, 65.27; H, 3.76; N, 17.57 %.

Preparation of compounds (29a-e) and (30a-e):

General procedure: A cold solution of diazonium salt (prepared by adding a solution of sodium nitrite, 1.5 g into 10 ml H_2O, is added to the cold solution of the corresponding amine hydrochloride, 0.1 mol in 10 ml concentrated HCl, The mixture was stirred in an ice bath). The resulting solution of diazonium salt was then added to cold solution of either N-2-pyridyl-3-oxobutanamide **(1)** or pyridopyridone **3** (0.01 mole) in ethanol (30 ml) containing 2 g sodium acetate at 0°C for 1 hr. The resulting solid was collected by filtration, washed with water and crystallized from the proper solvent.

4-Methyl-3-phenylazo-1H-[1,8]naphthyridin-2-one (29a):

It was obtained as yellow crystals from ethanol (87%); mp 195-197°C; ν_{max} /cm^{-1} (KBr) 3200 (NH), 1639 (CO); δ_H ($CDCl_3$) 2.32 (s, 3H, CH_3), 6.97-8.50 (m, 8H, aromatic H), 13.13 (s, 1/2H, NH), 14.45 (s, 1/2H, OH); m/z = 264 (M); Found: C, 68.19; H 4.61; N, 21.27; Calcd for $C_{15}H_{12}N_4O$: C, 68.18; H, 4.54; N, 21.21 %.

3-(4-Chlorophenylazo)-4-methyl-1H-[1,8]naphthyridin-2-one (29b):

It was obtained as yellow crystals from ethanol (85 %); mp 201-203 °C; δH (CDCl3) 2.30 (s, 3H, CH3), 7.03-8.49 (m, 7H, aromatic H), 13.13 (s, 1/2H, NH) 14.47 (s, 1/2H, OH); m/z = 298 (M); Found: C, 60.45; H, 3.75; N, 18.83; Calcd for $C_{15}H_{11}N_4OCl$: C, 60.40; H, 3.69; N, 18.79 %.

4-Methyl-3-p-tolylazo-1H-[1,8]naphthyridin-2-one (29c):

It was obtained as yellow crystals from ethanol (96 %); mp 182-184°C; ν_{max} /cm^{-1} (KBr) 3290 (NH), 1635 (CO); δ_H ($CDCl_3$) 2.31 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.96-8.22 (m, 7H, aromatic H), 13.20 (s,1/2H, NH), 14.45 (s, 1/2H, OH); m/z = 278 (M); Found: C, 69.10; H, 5.00; N, 20.16; Calcd for $C_{16}H_{14}N_4O$: C, 69.06; H, 5.03; N, 20.14%.

4-Methyl-3-(naphthalene-1-ylazo)-1H- [1,8]naphthyridin-2-one (29d)*:*

It was obtained as deep yellow crystals from ethanol (80%); mp 223-225°C; Found: C, 72.50; H, 4.50; N, 17.66; Calcd for $C_{19}H_{14}N_4O$: C, 72.61; H, 4.45; N, 17.83 %.

3-(4-Acetylphenylazo)-4-methyl-1H-[1,8]naphthyridin-2-one (29e):

It was obtained as deep yellow crystals from ethanol (94 %); mp 234-6°C; ν_{max} /cm^{-1} (KBr) 3200 (NH), 1666 (CO); δ_H ($CDCl_3$) 2.31 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 6.97-8.50 (m, 7H, aromatic H), 13.09 (s, 1/2H, NH), 14.52 (s, 1/2H, OH); m/z = 305(M-1); Found: C, 66.63; H, 4.51; N, 18.28; $C_{16}H_{14}N_4O_2$: C, 66.66; H, 4.57; N, 18.30%.

Preparation of aryl azo derivatives (30a-e):

A suspension of arylazo pyridopyridinethione 29a-e in dil. hydrochloric acid solution was refluxed for 2 hrs. The reaction mixture was left to cool and neutralized with ammonia solution until complete precipitation. The solid product so formed was collected by filtration and crystallized by the proper solvent.

3-Oxo-2-(phenylazo)-N-pyridin-2-yl-butyramide (30a):

It was obtained as yellow crystals from ethanol (90.8 %); mp 178-179°C; ν_{max} /cm^{-1}(KBr) 3395, 3159 (NH), 1663, 1636 (C=O); δ_H ($CDCl_3$) 2.60 (s, 3H, CH_3), 7.04-8.41 (m, 9H, aromatic H), 11.85 (s, 1H, NH), 14.61 (s, 1H, NH); m/z = 282 (M); Found: C, 63.89; H, 4.65; N, 19.80; Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 4.60; N, 19.85%.

2-[(4-Chlorophenyl)- azo]-3-oxo-N-pyridin-2-yl-butyramide (30b):

It was obtained as reddish brown crystals from ethanol (77.4 %); mp 188-190°C; Found: C, 56.79; H, 4.05; N, 17.55; Calcd for $C_{15}H_{13}N_4O_2Cl$: C, 56.87; H, 4.10; N, 17.69%.

2-[(4-tolyl)-azo]-3-oxo-N-pyridin-2-yl-butyramide (30c):

It was obtained as yellow crystals from ethanol (98%); mp 180-182°C; ν_{max} /cm^{-1}(KBr) 3422, 3128 (2NH), 1658, 1718 (CO); δ_H ($CDCl_3$) 2.33 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 6.99-8.36 (m, 8H, aromatic H), 11.83 (s, 1H, NH), 14.58 (s, 1H, NH); m/z = 296 (M); Found: C, 64.89; H, 5.36; N, 18.90; Calcd for $C_{16}H_{16}N_4O_2$: C, 64.86; H, 5.40; N, 18.91%.

2-[(Naphthalen-1-ylazo)]-3-oxo-N-pyridin-2-yl-butyramide(30d):

It was obtained as reddish brown crystals from ethanol (83.3%); mp 210-212°C; ν_{max} /cm^{-1}(KBr) 3100, 3058 (NH), 1662, 1635 (CO); δ_H ($CDCl_3$) 2.60 (s, 3H, CH_3), 7.04-8.42(m, 11H, Ar-H), 11.90 (s,1H,NH), 15.49 (s, 1H, NH); m/z = 331 (M-1); Found: C, 68.60; H, 4.76; N, 16.90; Calcd for $C_{19}H_{16}N_4O_2$: C, 68.67; H, 4.81; N, 16.86%.

2-[(4-Acetyl-phenyl)-azo]-3-oxo-N-pyridin-2-yl-butyramide (30e):

It was obtained as brown crystals from ethanol (73.7 %); mp 223-225°C; Found: C, 62.85; H, 4.86; N, 17.30; $C_{17}H_{16}N_4O_3$: C, 62.96; H, 4.93; N, 17.28%.

6-Acetyl-3-imino-2-phenyl-5-(pyridine-2-ylimino)-2,3,4,5-dihydro-tetrahydropyridazine-4-carbonitrile (31):

A mixture of aryl hydrazo **30a** (2.82 g; 0.01 mol), malononitrile (0.66 g; 0.01 mol) and ammonium acetate (0.5 g) was fused for 30 minutes at 140°C. The reaction mixture was left to stand, and then triturated with ethanol. The solid product so formed was collected by filtration and crystallized from ethanol to give (**31**). It was obtained as gold crystals from ethanol (55%); mp 180°C; ν_{max} /cm^{-1}(KBr) 3168 (NH), 2200 (CN), 1663 (CO); δ_H (DMSO-d_6) 2.47 (s, 1H, aliph-H), 3.32 (s, 3H, CH_3), 7.19-8.36 (m, 9H, aromatic H), 11.67 (s,1H,NH); m/z = 330 (M); Found: C, 65.49; H, 4.30; N, 25.50; Calcd for $C_{18}H_{14}N_6O$: C, 65.45; H, 4.24; N, 25.45%.

References

1. R. KATRITZKY, S. ZHANG, A. M. HUSSEIN AND Y. FANG .*J .Org. Chem*, **66**, 5606(2001).
2. S. ABDEL HAFIZ, A. M. HUSSEIN AND V. F. MAHMOUD, Z. NATURFORSCH, **54b**, 923 (1999).
3. S. ABDEL-HAFIZ, A. M. HUSSEIN AND V. F. MAHMOUD, Z. Naturforsch, **54b**, 1568 (1999).
4. A. M. HUSSEIN, Heteroatom Chem., **8**, 1(1997).
5. A. M. HUSSEIN, Afinidad Lv1, **484**,377, (1999)
6. F. BIGI, B. FRULLANTI, R. MAGGI, G. SARTORI AND E. ZAMBONIN, J. Org. Chem., 64, 1004-1006 (1999).
7. M. H. ELNAGDI AND A. W. ERIAN, Bull. Chem. Sec. Jpn, **63**, 854 (1990).
8. A. S. S. RATHOD, B. N. BERAD, S. D. PATIL AND A. G. DOSHI, Orient. J. Chem., **16 (2)**, 315-318 (2000).
9. K. G. OJHA, J. NEERA AND T. HEER, Journal of the Indian Chemical Society, **79 (2),** 191-192 (2002).
10. H.G.GARG; S.S.JOSHI; J. Indian Chem., Soc. **37**, 626(1960).
11. A. D. MITCHELL; D. C. Nonhebel; Tetrahedron Lett. 3859 (1995).
12. H. H. El GHANDOUR; A. M. HUSSEIN; M. H. ELNAGDI; A. A. HARB AND S. A. METWALLY; J. Prakt. Chem., **334**, 723 (1992).