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## $\beta$ -oxoanilides in heterocyclic synthesis: A convenient synthetic route to polyfunctionally substituted pyridazines and pyridines

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### ABSTRACT

Coupling of N-naphthalen-1-yl-3-oxo-butyramide (**1**) with equimol of aryl diazonium chloride salts (**2**) yield the corresponding hydrazone products (**3a-d**). The arylhydrazones (**3a-d**) condensed with ethyl cyanoacetate (**4a**) to give the pyridazinone derivatives (**6a-d**). Similarly, hydrazones (**3a-d**) condensed with malononitrile (**4b**) yielding the pyridazinimines (**7a-d**). The reaction of compound (**1**) with equimolar amounts of malononitrile upon refluxing in ethanolic piperidine afforded compound (**10**). In contrast to the behavior of compound (**1**) towards cyano thioacetamide, it reacted with cyanoacetamide (**4d**) to yield the expected pyridine (**14**). Condensation of compound (**1**) with aromatic aldehydes (**15**) afforded compounds (**16a-d**). Compound (**1**) reacted with arylidenemalononitrile (**17a-c**) under basic conditions yielding (**21a-c**). Similarly, Compound (**1**) easily reacted with arylidenecyano thioacetamide (**17a-c**) to yield the pyridinethione (**25a-c**). The structure of the synthesized compounds was established from their analytical and spectral data. © 2008 Trade Science Inc. -INDIA

### INTRODUCTION

$\beta$ -Oxoanilides are important building blocks in synthetic heterocyclic chemistry and their utility for the preparation of azines has been reported recently<sup>[1-12]</sup>. Following previous work in our laboratory<sup>[13-16]</sup>, we have reported several new synthesis of this class of heterocyclic synthesis.

In continuation of our research in this area, we report here results that enabled us to develop several new efficient synthesis for differently substituted pyridazines and pyridines from  $\beta$ -Oxoanilide derivative<sup>[17]</sup>. So, it has been observed that the active methylene moiety in compound (**1**) underwent an electrophilic substitution upon coupling with equimolecular of aryl diazonium chloride salts yield the corresponding hydrazone coupling products (**3a-d**). Compound (**3**) proved to exist pre-

dominantly in the hydrazone form rather than the azo form on the basis of <sup>1</sup>H NMR data. Thus e.g. (**3a**) revealed besides the expected signals, the presence of a singlet signals exchangeable with D<sub>2</sub>O at  $\delta$ 13.74 and 14.69 ppm attributed to the hydrazone NH and imide NH functions. Furthermore, its UV spectrum showed absorption maxim at  $\lambda$  384 nm and 302 nm in accordance with those for hydrazo functions which are reported<sup>[18,19]</sup> to exhibit strong absorption at wave length higher than 310 nm. So, the obtained arylhydrazones have been utilized as starting materials for preparing the targeted pyridazine ring system. Thus, the aryl hydrazones (**3a-d**) condensed readily and smooth with ethyl cyanoacetate (**4a**) in the presence of ammonium acetate in oil bath without solvent yielding product of water and ethanol elimination which thus be formulated as the pyridazinone derivatives (**6a-d**). Assignment of

structure (6) for the reaction product based on its correct elemental analyses and compatible spectroscopic data. The, IR spectrum of compound (6a) as example showed absorption bands at  $\nu$  3395  $\text{cm}^{-1}$  (NH), 2195  $\text{cm}^{-1}$  (CN) and 1657, 1628  $\text{cm}^{-1}$  (2CO). Its  $^1\text{H}$  NMR spectrum ( $\text{DMSO}-d_6$ ) showed a singlet signals (3H) at  $\delta$  2.49 ppm assigned for  $\text{CH}_3$  protons, a singlet at  $\delta$  10.64 ppm assigned for the NH proton which underwent facial hydrogen deuterium exchange and disappeared upon addition of  $\text{D}_2\text{O}$  to the NMR sample. The formation of 6 from (3) is assumed to proceed via intermediate of no isolable (5).

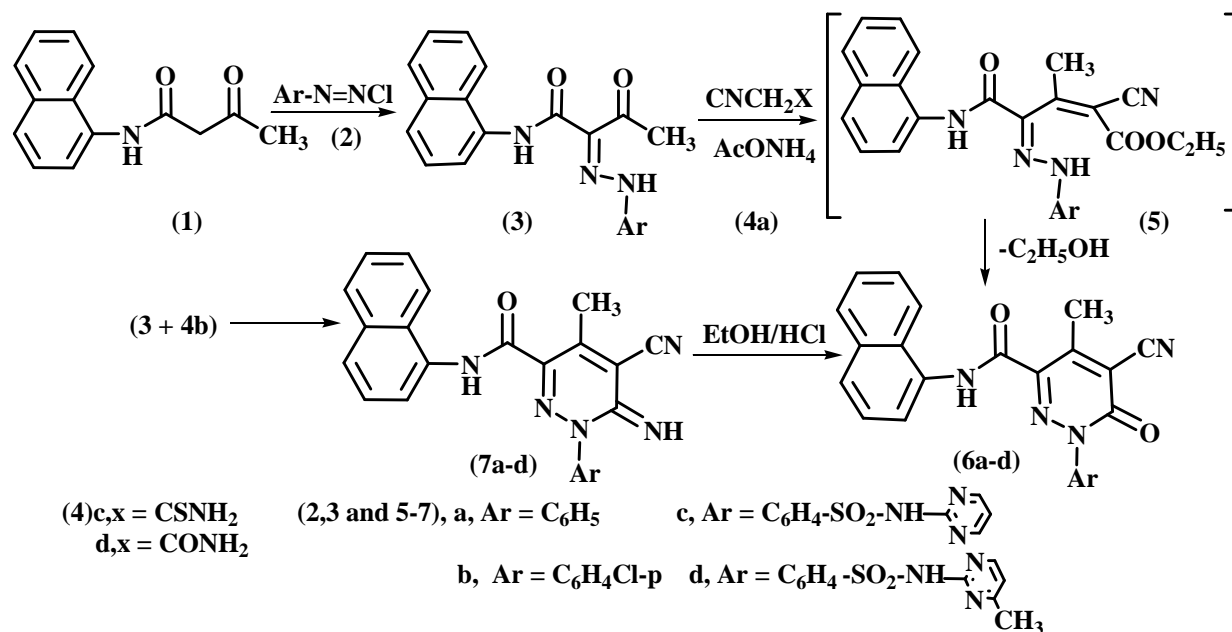
Similarly, hydrazones (3a-d) condensed with malononitrile (4b) yielding the pyridazinimines (7a-d). The structure of (7a-d) was established based on the elemental analysis and spectral data. Thus, the  $^1\text{H}$  NMR of compound (7a) as example revealed a singlet signal (1H) at  $\delta$  11.88 ppm and  $\delta$  13.52 ppm assigned for the 2NH protons besides the expected protons in the molecule.

The structure (7) was further confirmed on the bases of its chemical transformation to compound (6) upon refluxing with a mixture of ethanol and HCl, SCHEME 1.

Next, it was of interest to explore the scope limitations and generality of (1) as a precursor for the synthesis of some polyfunctionally substituted pyridines. Thus, reactions of 1 with equimolar amounts of

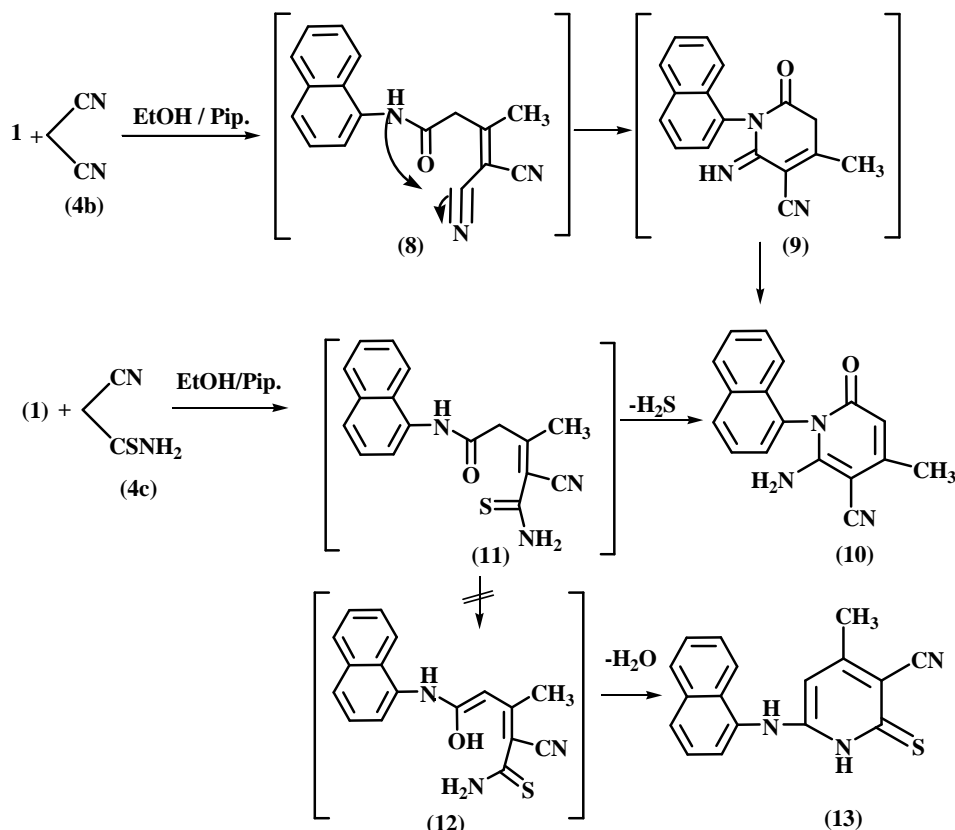
malononitrile upon refluxing in ethanolic piperidine, the corresponding 2-amino-4-methyl-1-naphthalen-1-yl-6-oxo-1, 6-dihydro-pyridine-3-carbonitrile (10) was obtained in good yield (SCHEME 2). The identity of the product was established on the bases of elemental analysis and spectral background in each case. The, IR spectrum of (10) as example showed absorption bands at  $\nu$  3456, 3307  $\text{cm}^{-1}$  ( $\text{NH}_2$ ), 2205  $\text{cm}^{-1}$  (CN) and 1669  $\text{cm}^{-1}$  (CO). Its  $^1\text{H}$  NMR spectrum showed a singlet signals (3H) at  $\delta$  2.24 ppm assigned for  $\text{CH}_3$  protons, a singlet at  $\delta$  5.74 ppm assigned for the CH protons of pyridine moiety in addition to the aromatic protons at  $\delta$  7.33-7.66 ppm. Formation of (10) is believed to be via initial condensation of active methylene moiety in malononitrile (4b) with acetyl carbonyl group of compound (1) to afford the intermediate (8) which then cyclized via an internal addition of the NH group to the CN group to afford (9) and aromatized by rearrangement to the pyridone (10).

On the other hands, the reaction of compound 1 with cyanothioacetamide (4c) afforded the pyridone (10) rather than the expected pyridinethione (13) was ruled out based on spectral data. This structure was confirmed by identical spectral data, mp and mixed mp. with those corresponding to compound (10). We assume that the reaction product is formed via initial condensation of active methylene moiety in cyanothio



SCHEME 1

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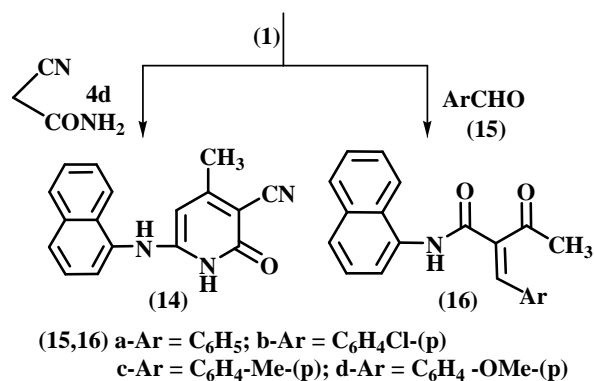
SCHEME 2

acetamid (**4c**) with acetyl carbonyl in compound (**1**) to afford the intermediate **(11)** which loss  $\text{H}_2\text{S}$  and cyclized to **(9)** and rearrange to pyridine **(10)**, SCHEME 2.

In contrast to the behavior of compound (**1**) towards cyanothioacetamide, it reacted with cyanoacetamide (**4d**) to yield the expected pyridine (**14**). Assignment of structure (**14**) for the reaction product was based on its correct elemental analysis and compatible spectroscopic data.

Thus, its IR spectrum showed absorption bands at  $\nu$  3407, 3276  $\text{cm}^{-1}$  (2NH), 2197  $\text{cm}^{-1}$  (CN) and 1633  $\text{cm}^{-1}$  for (amidic CO). its  $^1\text{H}$  NMR spectrum showed a singlet signals (3H) at  $\delta$  2.49 ppm assigned for  $\text{CH}_3$  protons, a singlet at  $\delta$  9.15 ppm assigned for the NH proton in addition to the aromatic protons and (CH-pyridine +NH) protons at  $\delta$  7.47-8.25 ppm.

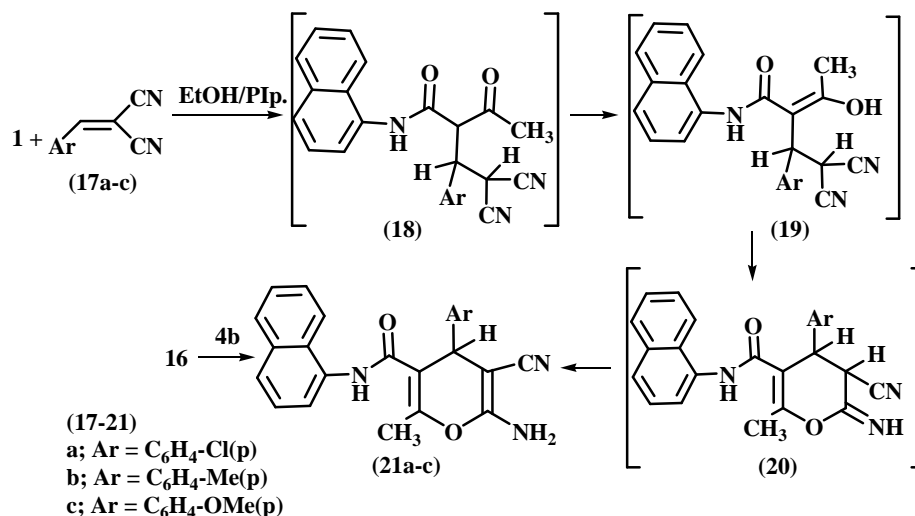
The condensation of compound (**1**) with aromatic aldehyde (**15**) by refluxing in ethanolic piperidine afforded (**16a-d**). Structure (**16**) was actually established based on spectral data IR and  $^1\text{H}$  NMR. The  $^1\text{H}$  NMR



SCHEME 3

spectrum of compound (**16c**) for example revealed a singlets (3H) at  $\delta$  2.17, 2.36 ppm assigned for two  $\text{CH}_3$  protons, a singlet signal (1H) at  $\delta$  6.20, 6.97-7.89 and 9.87 ppm assigned for the CH protons besides the aromatic and NH protons.

Similar to the reported reactivity of active methylene toward  $\alpha,\beta$ -unsaturated nitrile<sup>[20]</sup>. Compound (**1**) reacted with arylidenemalononitrile (**17a-c**) under basic conditions to yield (**21a-c**), most likely via Michael



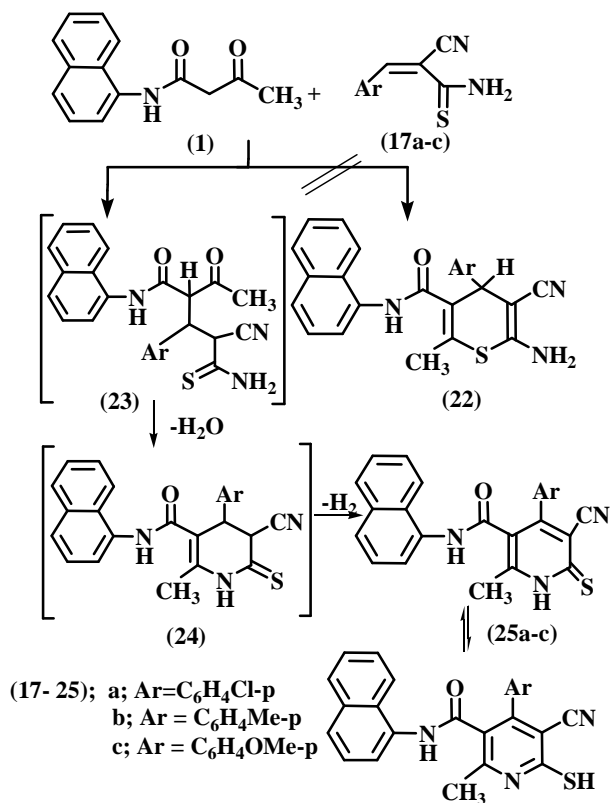
SCHEME 4

adduct (**18**) which then cyclized to (**20**) through the adduct (**19**). Compound (**20**) was rearrangement to the 4H pyran (**21**). Establishing of structure (**21**) for the reaction product was based on its correct elemental analysis and compatible spectroscopic data.

Thus, the IR spectrum of compound (**21a**) as example showed absorption band at  $\nu$  3456, 3381, 2177 and 1641 cm<sup>-1</sup> assigned to NH<sub>2</sub>, CN and CO respectively. Its <sup>1</sup>H NMR spectrum revealed the presence of singlet signal at  $\delta$  4.69 ppm assigned to 4H-pyran beside the other signal in the molecule.

Compound (**21**) are formed most likely via an established reaction by the synthesis of the same product via reacting of compound (**16**) with malononitrile (**4b**) to give product identical in all respects (mp, mixed mp, TLC and spectral data) with those corresponding to the 4H-pyran derivatives (**21**), SCHEME 4.

Similarly, N-naphthalen-1-yl-3-oxo-butylamide (**1**)<sup>[21-26]</sup> easily reacted with arylidene cyanothioacetamide (**17a-c**) in refluxing ethanolic piperidine yielding a product that may be either structure (**25a-c**) or its isomeric structure (**22**). Establishing the exact structure of the reaction product as structure (**25a-c**) rather than (**22**) based on the spectral data. Thus, the <sup>1</sup>H NMR spectrum of compound (**25a**) as example revealed the presence of a singlet signal at  $\delta$  = 10.30 and 14.50 ppm assigned to 2NH groups and no signal at range  $\delta$  = 4-5 ppm assigned for the thiopyran CH-4. So, the pyridinethione (**25**) is considered to be only the reaction product. Also, the mass spectrum of (**25a**) is com-



SCHEME 5

patible with the molecular ion peak  $m/z$  = 429(M<sup>+</sup>) Corresponding to the molecular formula C<sub>24</sub>H<sub>16</sub>N<sub>3</sub>OS.

Compound (**25**) is assumed to proceed via an initial addition of the active methylene moiety in (**1**) to the active double bond in (**17a-c**), thus forming the acyclic Michael adduct (**23**), then cyclized to (**24**) by a loss of water and loss of hydrogen to yield the aromatic final

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product (25), SCHEME 5.

### EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer ( $\nu$ ,  $\text{cm}^{-1}$ ). The  $^1\text{H}$  NMR spectra were recorded in  $\text{DMSO-d}_6$  and  $\text{CDCl}_3$  at 200, 400 MHz on a Varian Gemini NMR spectrometer ( $\delta$ , ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 eV. U.V spectra carried out using a Labomed double-beam UV-visible programmable spectrophotometer equipped with 1 cm quartz cells controlled by a PC running the spectrophotometric software UV Win version 5.0. Elemental analysis were carried out by the Microanalytical Research Center, Faculty of Science, Cairo University and Al-azhar university, faculty of science, Department of chemistry, Assiut branched.

#### Preparation of compounds (3a-d)

##### General procedure

A solution of 1 (0.01 mole) in ethanol (30 ml) containing sodium acetate (2.0 g) was cooled to  $0^\circ\text{C}$ , stirred and treated gradually with cooled solution of aryl diazonium chloride (prepared from 0.01 mole of amine and the appropriate quantities of  $\text{HCl}$  and  $\text{NaNO}_2$ ). The solid product formed on standing was collected and recrystallized from the appropriate solvent to give (3a-d).

#### N-Naphthalen-1-yl-3-oxo-2-(phenyl-hydrazono)-butyramide (3a)

It was obtained as brown crystals from dioxane/ethanol; yield 90 %; m.p  $174^\circ\text{C}$ ; IR (KBr)  $\nu$   $\text{cm}^{-1}$  3448 (NH), 3048 (CH-arom.), 2920 (CH-aliph.), 1642 ( $\text{C=O}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 2.34 (s, 3H,  $\text{CH}_3$ ), 7.00-8.34 (m, 12H, Ar-H), 13.74 (s, 1H, NH), 14.69 (s, 1H, NH), UV spectrum at  $\lambda$  = 384, 302 nm for hydrazone group. Elemental analysis:  $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_2$  (331), Calcd: C, 72.49; H, 5.17; N, 12.68%, Found: C, 72.53; H, 5.20; N, 12.70%.

#### 2-[(4-Chloro-phenyl)-hydrazono]-N-naphthalen-1-yl-3-oxo-butyramide (3b)

It was obtained as yellow crystals from dioxan/etha-

nol; yield 86%; m.p  $183^\circ\text{C}$ ; IR (KBr)  $\nu$   $\text{cm}^{-1}$  3468 (NH), 3050 (CH-arom.), 2926 (CH-aliph.), 1640, 1662 ( $\text{C=O}$ ). Elemental analysis:  $\text{C}_{20}\text{H}_{16}\text{ClN}_3\text{O}_2$  (365.5). Calcd: C, 65.67; H, 9.69; N, 11.49%, Found: C, 65.70; H, 9.75; N, 11.55%

#### N-Naphthalen-1-yl-3-oxo-2-[[4-(pyrimidin-2-ylsulfamoyl)-phenyl]-hydrazono]-butyramide (3c)

It was obtained as red crystals from ethanol; yield 87%; m.p  $185^\circ\text{C}$ ; IR (KBr)  $\nu$   $\text{cm}^{-1}$  3371, 3234 (2 NH), 3054 (CH-arom.), 2924 (CH-aliph.), 1663, 1628 ( $\text{C=O}$ );  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  = 2.64 (s, 3H,  $\text{CH}_3$ ), 6.89-8.32 (m, 15H, Ar-H + NH), 11.64 (s, 1H, NH), 14.07 (s, 1H, NH). Elemental analysis:  $\text{C}_{24}\text{H}_{20}\text{N}_6\text{O}_4\text{S}$  (488), Calcd: C, 59.01; H, 4.13; N, 17.20; S, 6.56%; Found: C, 59.53; H, 4.26; N, 17.35; S, 6.64%.

#### 2-[[4-(4-Methyl-pyrimidin-2-ylsulfamoyl)-phenyl]-hydrazono]-N-naphthalen-1-yl-3-oxo-butyramide (3d)

It was obtained as red crystals from ethanol; yield 89%; m.p.  $180^\circ\text{C}$ ; IR (KBr)  $\nu$   $\text{cm}^{-1}$  3379, 3332 (2 NH), 3053 (CH-arom.), 2863 (CH-aliph.), 1663, 1627 ( $\text{C=O}$ );  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\lambda$  = 2.32 (s, 3H,  $\text{CH}_3$ ), 2.49 (s, 3H,  $\text{CH}_3$ ), 6.89-8.33 (m, 13H, Ar-H + pyrimidine-H), 11.87 (s, 1H, NH), 13.92 (s, 1H, NH), 14.23 (s, 1H, NH), UV spectrum at  $\lambda$  = 502, 381 nm for hydrazone group. Elemental analysis:  $\text{C}_{25}\text{H}_{22}\text{N}_6\text{O}_4\text{S}$  (502), Calcd: C 59.75; H 4.41; N 16.72; S 6.38%, Found: C 59.79; H 4.45; N 16.77; S 6.40%.

#### Preparation of compounds (6a-d, 7a-d)

##### General procedure

A mixture of (3a-d) (0.01 mole), appropriate active methylene reagent (ethylcyanoacetate and malononitrile) (0.01 mole) and ammonium acetate (2 gm) was fused for 30 min. The reaction mixture was left to stand and then triturated with ethanol. The solid product so formed was collected by filtration and recrystallized from the proper solvent to give (6a-d, 7a-d).

#### 5-Cyano-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylic acid naphthalen-1-ylamide (6a)

It was obtained as brown crystals from ethanol; yield 62%; m.p  $270^\circ\text{C}$ ; IR (KBr)  $\nu$   $\text{cm}^{-1}$  3395 (NH), 3055 (CH-arm.), 2969 (CH-aliph.), 2195 (CN), 1657,

1628 (2C=O).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.49 (s, 3H,  $\text{CH}_3$ ), 7.12-8.36 (m, 12H, Ar-H), 10.64 (s, 1H, NH), UV spectrum Show disappearance of all bands for hydrazone group. Elemental analysis:  $\text{C}_{23}\text{H}_{16}\text{N}_4\text{O}_2$  (380), Calcd: C, 72.62; H, 4.24; N, 14.73%, Found: C, 72.68; H, 4.27; N, 14.78%.

**1-(4-Chloro-phenyl)-5-cyano-4-methyl-6-oxo-1,6-dihydro-pyridazine-3-carboxylic acid naphthalen-1-ylamide (6b)**

It was obtained as brown crystals from ethanol; yield 64%; m.p. 260°C; IR (KBr)  $\nu$   $\text{cm}^{-1}$  3399 (NH), 3056 (CH-arm.), 2972 (CH-aliph.), 2231 (CN), 1679, 1648 (2C=O);  $^1\text{H}$  NMR (DMSO)  $\delta$  = 2.26 (s, 3H,  $\text{CH}_3$ ), 6.98-8.30 (m, 11H, Ar-H), 11.79 (s, 1H, NH). Elemental analysis:  $\text{C}_{23}\text{H}_{15}\text{ClN}_4\text{O}_2$  (414), Calcd: C, 66.59; H, 3.64; N, 13.51%, Found: C, 66.74; H, 3.87; N, 13.64%.

**5-Cyano-4-methyl-6-oxo-1-[4-(pyrimidin-2-yl sulfamoyl)-phenyl]-1,6-dihydro-pyridazine-3-carboxylic acid naphthalen-1-ylamide (6c)**

It was obtained as brown crystals from DMF/ethanol; yield 66%; m.p. 290°C; IR (KBr)  $\nu$   $\text{cm}^{-1}$  3368 (NH), 3059 (CH-arm.), 2962 (CH-aliph.), 2191 (CN), 1670, 1627 (2C=O);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.62 (s, 3H,  $\text{CH}_3$ ), 7.27-8.08 (m, 16H, Ar-H + pyrimidine-H + 2NH). Elemental analysis:  $\text{C}_{27}\text{H}_{19}\text{N}_7\text{O}_4\text{S}$  (537), Calcd: C, 60.33; H, 3.56; N, 18.24, S, 5.96% Found: C, 60.36; H, 3.59; N, 18.27; S, 5.99%.

**5-Cyano-4-methyl-1-[4-(4-methyl-pyrimidin-2-yl sulfamoyl)-phenyl]-6-oxo-1,6-dihydro-pyridazine-3-carboxylic acid naphthalen-1-ylamide (6d)**

It was obtained as green crystals from DMF/ethanol; yield 63%; m.p. > 300°C; IR (KBr)  $\nu$   $\text{cm}^{-1}$  3339, 3324 (2NH), 2924 (CH-aliph.), 2196 (CN), 1674, 1626 (2C=O);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.48 (s, 3H,  $\text{CH}_3$ ), 2.68 (s, 3H,  $\text{CH}_3$ ), 6.76-8.53 (m, 14H, Ar-H + pyrimidine-H + NH), 10.67 (s, 1H, NH), UV spectrum Show disappearance of all bands for hydrazone group. Elemental analysis:  $\text{C}_{28}\text{H}_{21}\text{N}_7\text{O}_4\text{S}$  (551), Calcd: C, 60.97; H, 3.84; N, 17.78; S, 5.81%, Found: C, 61.51; H, 3.90; N, 17.82; S, 5.85%.

**5-Cyano-6-imino-4-methyl-1-phenyl-1,6-dihydro-pyridazine-3-carboxylic acid naphthalen-1-ylamide**

(7a)

It was obtained as brown crystals from dioxane/ethanol; yield 75%; m.p. > 300°C; IR (KBr)  $\nu$   $\text{cm}^{-1}$  3343, 3201 (2NH), 3051 (CH-arom.), 2924 (CH-aliph.), 2193 (CN), 1626 (C=O);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.26 (s, 3H,  $\text{CH}_3$ ), 6.93-8.35 (m, 12H, Ar-H), 11.88 (s, 1H, NH), 13.52 (s, 1H, NH). Elemental analysis:  $\text{C}_{23}\text{H}_{17}\text{N}_5\text{O}$  (379), Calcd: C, 72.81; H, 4.52; N, 18.46%, Found: C, 72.85; H, 4.66; N, 18.54%.

**1-(4-Chloro-phenyl)-5-cyano-6-imino-4-methyl-1,6-dihydro-pyridazine-3-carboxylic acid naphthalen-1-ylamide (7b).**

It was obtained as brown crystals from dioxane/ethanol; yield 71%; m.p. > 300°C; IR (KBr)  $\nu$   $\text{cm}^{-1}$  3424 (2NH), 3053 (CH-arom.), 2923 (CH-aliph.), 2199 (CN), 1626 (C=O);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.25 (s, 3H,  $\text{CH}_3$ ), 6.98-8.34 (m, 11H, Ar-H), 11.81 (s, 1H, NH), 13.38 (s, 1H, NH). Elemental analysis:  $\text{C}_{23}\text{H}_{16}\text{ClN}_5\text{O}$  (413), Calcd: C, 66.75; H, 3.90; N, 16.92%, Found: C, 66.83; H, 3.56; N, 16.68%.

**5-Cyano-6-imino-4-methyl-1-[4-(pyrimidin-2-yl sulfamoyl)-phenyl]-1,6-dihydro-pyridazine-3-carboxylic acid naphthalen-1-ylamide (7c).**

It was obtained as brown crystals from DMF/ethanol; yield 76%; m.p. > 300°C; IR (KBr)  $\nu$   $\text{cm}^{-1}$  3422, 3486, 3386 (3NH), 3061 (CH-arom.), 2926 (CH-aliph.), 2198 (CN), 1624 (C=O). Elemental analysis:  $\text{C}_{27}\text{H}_{20}\text{N}_8\text{O}_3\text{S}$  (536), Calcd: C, 60.44; H, 3.76; N, 20.88, S, 5.98%, Found: C, 60.48; H, 3.68; N, 20.92, S, 5.51%.

**5-Cyano-6-imino-4-methyl-1-[4-(4-methyl-pyrimidin-2-yl sulfamoyl)-phenyl]-1,6-dihydro-pyridazine-3-carboxylic acid naphthalen-1-ylamide (7d)**

It was obtained as brown crystals from dioxan/ethanol; yield 80%; m.p. 280°C; IR (KBr)  $\nu$   $\text{cm}^{-1}$  3445, 3386 (2NH), 3045 (CH-arom.), 2929 (CH-aliph.), 2200 (CN), 1629 (C=O);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.26 (s, 3H,  $\text{CH}_3$ ), 2.59 (s, 3H,  $\text{CH}_3$ ), 7.03-8.52 (m, 14H, Ar-H + pyrimidine-H + NH), 10.52 (s, 1H, NH), 11.65 (s, 1H, NH). Elemental analysis:  $\text{C}_{28}\text{H}_{22}\text{N}_8\text{O}_3\text{S}$  (550), Calcd: C, 61.08; H, 4.03; N, 20.35; S, 5.82%, Found: C, 61.13; H, 4.08; N, 20.40; S, 5.87%.

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### Preparation of compound (10)

#### General procedure

**Method A:** A mixture of (1) (0.01mole), appropriate active methylene reagent (malononitrile) in ethanol (30ml) was treated with a few drops of piperidine and refluxed for 12 hrs. The solid precipitate produced on hot was collected by filtration and recrystallized from the proper solvent to give (10).

**Method B:** A mixture of (1) (0.01mole), cyanothio acetamide (0.01mole) and few drops of piperidine, was refluxed in ethanol (30 ml) for 18hrs. The obtained solid on heating recrystallized from ethanol to give (10).

#### 2-Amino-4-methyl-1-naphthalen-1-yl-6-oxo-1,6-dihydro-pyridine-3-carbonitrile (10)

It was obtained as white crystals from dioxan/ ethanol; yield 84%; m.p. 340°C; IR (KBr)  $\nu$  cm<sup>-1</sup> 3456, 3307 (NH<sub>2</sub>), 3096 (CH-arom.), 2992 (CH- aliph.), 2205 (CN), 1669 (C=O); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  = 2.24 (s, 3H, CH<sub>3</sub>), 5.74 (s, 1H, pyridine-H), 6.79 (s, 2H, NH<sub>2</sub>), 7.33-7.66 (m, 7H, Ar-H), MS: m/z = 276 (M<sup>+</sup>). Elemental analysis: C<sub>17</sub>H<sub>13</sub>N<sub>3</sub>O (275), Calcd: C, 74.17; H, 4.76; N, 15.26%, Found: C, 74.20; H, 4.79; N, 15.29%

#### 4-Methyl-6-(naphthalen-1-ylamino)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (14).

A mixture of (1)(0.01mole), cyanoacetamide (0.01mole) in ethanol and few drops of piperidine, was refluxed for 8hrs. The obtained solid product on heating recrystallized from dioxan/ethanol to give (14) as white crystals; yield; 72%; m.p.299°C; IR (KBr)  $\nu$ cm<sup>-1</sup> 3407, 3276 (2NH), 3050(CH-arom.), 2197 (CN), 1633 (C=O); <sup>1</sup> H NMR (DMSO-d<sub>6</sub>)  $\delta$  = 2.49 (s, 3H, CH<sub>3</sub>), 7.47-8.25 (m, 9H, Ar-H + pyridine-H+NH), 9.15(s,1H,NH). Elemental analysis: C<sub>17</sub>H<sub>13</sub>N<sub>3</sub>O (275), Calcd: C, 74.17; H, 4.76; N, 15.26%, Found: C, 74.22; H, 4.80; N, 15.60%

### Preparation of compound (16a-d)

#### General procedure

A mixture of compound (1) (0.01mole), aromatic aldehydes (0.01mole) and few drops of piperidine in ethanol (30ml) was refluxed for 8hrs. The solid precipitate produced on hot was collected by filtration and recrystallized from the proper solvent to give (16a-d).

#### 2-Benzylidene-N-naphthalen-1-yl-3-oxo-butylamide (16a)

It was obtained as pale green crystals from ethanol; yield 75%; m.p 240°C; IR(KBr)  $\nu$  cm<sup>-1</sup> 3236 (NH), 3035(CH-arom), 2970(CH- aliph.), 1655(C=O). Elemental analysis: C<sub>21</sub>H<sub>17</sub>NO<sub>2</sub> (315), Calcd: C, 79.98; H, 5.43; N, 4.44%, Found: C, 79.51; H, 5.65; N, 4.62%

#### 2-(4-Chloro-benzylidene)-N-naphthalen-1-yl-3-oxo-butylamide (16b)

It was obtained as yellow crystals from ethanol; yield 78%; m.p. 286°C; IR (KBr)  $\nu$  cm<sup>-1</sup> 3283 (NH), 3050(CH-arom.), 2921(CH- aliph.), 1685, 1655 (2C=O). Elemental analysis: C<sub>21</sub>H<sub>13</sub>ClNO<sub>2</sub> (349.5), Calcd: C 72.10; H 4.61; N 4.00%, Found : C 72.14; H 4.65; N 4.14%

#### 2-(4-Methyl-benzylidene)-N-naphthalen-1-yl-3-oxo-butylamide (16c)

It was obtained as yellow crystals from ethanol; yield 82%; m.p 282°C; IR (KBr)  $\nu$ cm<sup>-1</sup> 3265 (NH), 3045 (CH-arom.), 2974(CH- aliph), 1656 (C=O); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  = 2.17 (s, 3H, CH<sub>3</sub>), 2.36 (s, 3H, CH<sub>3</sub>), 6.20(s, 1H, C=CH-olefinic), 6.97-7.89 (m, 11H, Ar-H), 9.87(s, 1H, NH). Elemental analysis: C<sub>22</sub>H<sub>19</sub>NO<sub>2</sub> (329), Calcd: C, 80.22; H, 5.81; N, 4.25%, Found: C, 80.65; H, 5.74; N, 4.52%

#### 2-(4-Methoxy-benzylidene)-N-naphthalen-1-yl-3-oxo-butylamide (16d)

It was obtained as deep yellow crystals from ethanol; yield 85%; m.p 290°C; IR(KBr)  $\nu$  cm<sup>-1</sup> 3278 (NH), 3046(CH-arom.), 2928(CH-aliph), 1684, 1655 (2C=O). MS: m/z = 340(M<sup>+</sup>). Elemental analysis: C<sub>22</sub>H<sub>19</sub>NO<sub>3</sub> (345), Calcd: C, 76.50; H, 5.54; N, 4.06%, Found: C, 76.55; H, 5.46; N, 4.10%

### Preparation of compounds (21a-c)

#### General procedure

A mixture of 1 (0.01mole), arylidinemalononitrile (0.01mole) in ethanol 30 ml was treated with few drops of piperidine and heated under reflux for 8 hrs. The reaction mixture allowed to cool poured into crushed ice and acidified with HCl. The solid product was filtered off and recrystallized from the proper solvent to give (21a-c).

**6-Amino-4-(4-chloro-phenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylic acid naphthalen-1-ylamide (21a)**

It was obtained as yellow crystals from ethanol; yield 90%; m.p 180°C; IR (KBr)  $\text{vcm}^{-1}$  3456, 3381 ( $\text{NH}_2$ ), 3332 (NH), 3053 (CH-arom.), 2924 (CH- aliph.), 2177 (CN), 1641 (C=O).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 1.81 (s, 3H,  $\text{CH}_3$ ), 4.63 (s, 2H,  $\text{NH}_2$ ), 4.69 (s, 1H, 4H-pyrane), 7.15-8.00 (m, 11H, Ar-H), 12.37 (s, 1H, NH). Elemental analysis:  $\text{C}_{24}\text{H}_{18}\text{ClN}_3\text{O}_2$  (415.5), Calcd: C, 69.31; H, 4.36; N, 10.10%, Found: C, 69.68; H, 4.56; N, 10.28%

**6-Amino-5-cyano-2-methyl-4-p-tolyl-4H-pyran-3-carboxylic acid naphthalen-1-ylamide (21b)**

It was obtained as green crystals from ethanol; yield 88%; m.p 160°C; IR (KBr)  $\text{vcm}^{-1}$  3458, 3327 ( $\text{NH}_2$ ), 3190 (NH), 3049 (CH-arom.), 2918 (CH- aliph.), 2175 (CN), 1703 (C=O). Elemental analysis:  $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_2$  (395), Calcd: C, 75.93; H, 5.35; N, 10.63%, Found: C, 76.10; H, 5.40; N, 10.70%

**6-Amino-5-cyano-4-(4-methoxy-phenyl)-2-methyl-4H-pyran-3-carboxylic acid naphthalen-1-ylamide (21c)**

It was obtained as brown crystals from ethanol; yield 81%; m.p 165°C; IR (KBr)  $\text{vcm}^{-1}$  3458, 3332 ( $\text{NH}_2$ ), 3195 (NH), 3053 (CH-arom.), 2929 (CH- aliph.), 2176 (CN), 1702 (C=O). Elemental analysis:  $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_3$  (411), Calcd : C 72.98; H 5.14; N 10.21%, Found : C 72.54; H 5.50; N 10.52%

**Preparation of compound (25a-c)**

**General procedur**

A mixture of acetoacetanilide 1 (0.01 mole), arylidinedicyanothioacetamide (0.01 mole) in ethanol (30ml) was treated with few drops of piperidine and heated under reflux for 12 hrs. then cool, poured into crushed ice and acidified with HCl. The solid product was collected and recrystallized from the proper solvent to give (25a-c).

**4-(4-Chloro-phenyl)-5-cyano-2-methyl-6-thioxo-1,6-dihydro-pyridine-3-carboxylic acid naphthalen-1-ylamide (25a)**

It was obtained as yellow crystals from ethanol; yield 88%; m.p 285°C; IR (KBr)  $\text{vcm}^{-1}$  3358, 3200

(2NH), 3195 (NH), 3055 (CH-arom), 2973 (CH- aliph), 2227 (CN), 1653 (C=O);  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  = 2.60 (s, 3H,  $\text{CH}_3$ ), 7.15-7.92 (m, 11H, Ar-H), 10.30 (s, 1H, NH), 14.50 (hump, 1H, NH). MS:  $m/z$  = 429 ( $\text{M}^+$ ). Elemental analysis:  $\text{C}_{24}\text{H}_{16}\text{N}_3\text{OS}$  (429). Calcd: C, 67.05; H, 3.75; N, 9.77; S, 7.46% Found: C, 67.50; H, 3.82; N, 9.82; S, 7.70%

**5-Cyano-2-methyl-6-thioxo-4-p-tolyl-1,6-dihydro-pyridine-3-carboxylic acid naphthalen-1-ylamide (25b)**

It was obtained as yellow crystals from ethanol; yield 86%; m.p 298°C; IR (KBr)  $\text{v cm}^{-1}$  3368 (NH), 3045 (CH-arom.), 2922 (CH- aliph.), 2209 (CN), 1655 (C=O);  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  = 2.35 (s, 3H,  $\text{CH}_3$ ), 2.58 (s, 3H,  $\text{CH}_3$ ), 7.15-7.89 (m, 11H, Ar-H), 10.22 (s, 1H, NH), 14.36 (hump, 1H, NH). Elemental analysis:  $\text{C}_{25}\text{H}_{19}\text{N}_3\text{OS}$  (409), Calcd : C, 73.33; H, 4.68; N, 10.26; S, 7.83%, Found : C, 73.40; H, 4.72; N, 10.60 S, 7.67%

**5-Cyano-4-(4-methoxy-phenyl)-2-methyl-6-thioxo-1,6-dihydro-pyridine-3-carboxylic acid naphthalen-1-ylamide (25c)**

It was obtained as yellow crystals from ethanol; yield 89%; m.p 260°C; IR (KBr)  $\text{v cm}^{-1}$  3226, 3174 (2NH), 3051 (CH-arom), 2933 (CH- aliph.), 2216 (CN), 1647 (C=O). Elemental analysis:  $\text{C}_{25}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$  (425), Calcd : C, 70.57; H, 4.50; N, 9.88 S, 7.54%, Found : C, 70.62; H, 4.75; N, 9.92 S, 7.65%.

**REFERENCES**

- [1] R.M.A.Mohareb, S.Ibrahim, N.I.Abdel-Sayed, F.Z. El-Ablak; Collect.Czech.Chem.Comm., **54**(4), 947-53 (1993).
- [2] K.Mogilaiah, R.B.Rao; Indian Journal of Chemistry, **40B**, 713-714 (2001).
- [3] S.V.Ukhov, M.E.Konshin; Khim.Geterotsikl.Soedin., **2**, 238 (1989).
- [4] J.F.Giersson, J.F.Johannesdottir, J.Roynisson; Acta Chem.Scand., **51**, 348-350 (1997).
- [5] D.M.He, S.Wha, J.Heterocyclic Chem., **26**, 1447 (1989).
- [6] I.F.Kawa, H.Fujisawa, M.Kawazome, Y.Nakai, T.Ohta; Synthesis, **12**, 1715-17 (1998).
- [7] K.T.Koho; **62**, 283, 959, Chem.Abstr., **110**, 8049 (1986).

## Full Paper

- [8] J.K.F.Gerisson, J.F.Johannesdottir; J.Org.Chem., **61**, 7320-7325 (1996).
- [9] G.Gelbard, J.Lin, N.Roques; J.Org.Chem., **57**, 1789-1793 (1992).
- [10] S.E.Davis, B.S.Rauckman, J.H.Chan, B.Both; J.Med.Chem., **32**, 1936-1942 (1989).
- [11] H.Lee, K.A.Wayne; Tetrahydron Letters, **31** (31), 4405-4408 (1990).
- [12] Y.S.Lee; 9217, 452, Chem.Abstr., **119**, 117134 (1992).
- [13] A.M.Hussein; Afinidad Lvi, **484**, 377 (1999).
- [14] A.M.Hussein; Heteroatom Chemistry, **8**, 1 (1997).
- [15] A.M.Hussein, A.A.Atalla, A.M.Kamal El-Dean; Die.Pharmazie, **50**, 12, 788 (1995).
- [16] A.A.M.El-Adasy; Phosphorus, Sulfur, Silicon, **182**, 2625 (2007).
- [17] A.M.Hussein; M.S.A.El-Gaby, A.A.Abd El-Maged, A.M.Sh.El-sharief, Y.A.ammam; Under Publication.
- [18] H.C.Yao, P.J.Resnick; J.Am.Chem.Soc, **84**, 3514 (1962).
- [19] H.C.Yao; J.Org.Chem., **29**, 2959 (1964).
- [20] A.A.Harb, A.M.Hussein; S.A.Metwally, M.H.Elnagdi; Liebigs.Ann.Chem, 585 (1989).
- [21] G.E.H.Elgemeie, M.M.M.sallam, S.M.sherif, M.H.Elnagdi; Heterocycles **23**, 3107 (1985).
- [22] G.E.H.Elgemeie, S.M.sherif, F.A.M.Abdel-Ali, M.H.Elnagdi; Natur.Forsch, **41b**, 781 (1986).
- [23] F.M.Abdel-Galil, S.M.sherif, M.H.Elnagdi; Heterocycles, **24**, 2023 (1986).
- [24] A.A.Krauze, E.E.Liepin'sh, Z.A.Kalme, U.E.Pelchay, I.V.Dipan, Gya Dubur; Chem.Heterocycle Compounds, **21**, 77 (1985).
- [25] A.A.Krauze, E.E.Liepin'sh, Z.A.Kalme, U.E.pelchay, I.V.Dipan, Gya Dubur; Chem Heterocycle Compounds, **19**, 1202 (1983).
- [26] S.E.Zayed, E.L.Abou Elmagd, S.A.Metawally, M.H.Elnagdi; Collect.Gzech.Chem. Commun., **56**, 2175 (1991).