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Novel synthesis of 2-aryl pyridazinone via condensation of 3-oxo-3-substituted-2-arylhydrazonals with active methylenenitriles

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ABSTRACT

The reaction of 3-oxo-3-phenyl-2-arylhydrazonal with functionally substituted and heteroaromatics substituted acetonitrile by using eco-friendly solvent (ethanol) and less amount of catalyst (piperidine) could established to yield arylpyridazine imine derivatives, but these compounds are readily hydrolyzed under reaction conditions to yield arylpyridazinone as final products, which was confirmed by spectral analysis; MS, FTIR, ^{1}H-NMR and ^{13}CNMR.

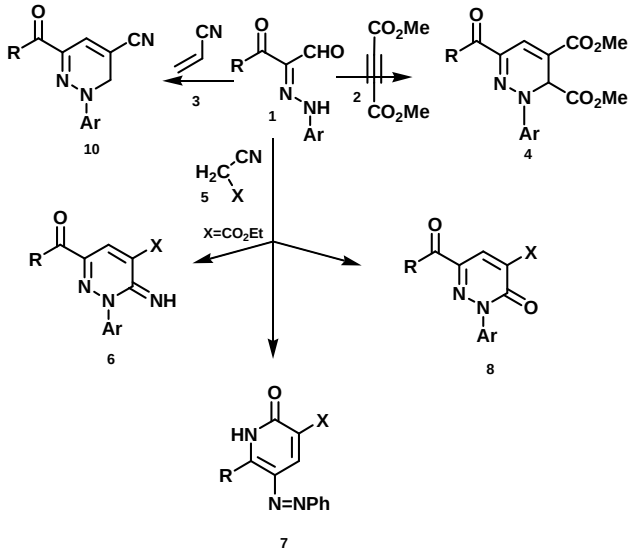
KEYWORDS

3-oxo-3-phenyl-2-phenylhydrazonal;
Pyridazine imine;
Pyridazinone.

INTRODUCTION

3-oxo-3-substituted-2-arylhydrazonals 1 are versatile readily obtainable reagents[1] that have been extensively utilized for synthesis of polyfunctional substituted aromatics and heteroaromatics[2,3]. In the past Elnagdi *et al*[4,5] have reported novel synthesis of polyfunctional pyridazines *via* heating 1 with dimethylacetylene dicarboxylate 2 as well as acrylonitrile 3 in presence of triphenylphosphine or a tertiary base. They have also reported that condensing active methylene nitriles 5 with 1 affords products that were believed to be the pyridazine imines 6[6]. Recently however Al-Mousawy *et al*[7] could realize that this structure cannot be correct as reported ^{13}CNMR data for the product lacked a carbonyl carbon at $\delta > 175$. (Scheme1)

However in some cases pyridazinones 8 were the reaction products rather than nicotine 7. In the present article we report on reactivity of 1a-b forward a variety of derivative of 5 where we noted that these reaction



Scheme 1

produce derivative of 8. Recently Elnagdi *et al*[8] reported novel synthesis of 3-Arylazonicotinates.

pyridazine derivatives have been reported[9] to possess a wide range of biological activities, these include antiviral and anticancer,[10] antituberculosis,[11] antihypertensive,[12] anti-inflammatory,[13] and antimicrobial,[14] ac-

tivities. Pyridazine derivatives have also been the subject of extensive research in the agrochemical areas[15-18]. Recently have been explored as new R-helix mimetics[19].

MATERIALS AND METHODS

General

All melting points are uncorrected. IR spectra were run in Nicolet FTIR model 205 spectrophetometer. ^{1}HNMR spectra (deuterodimethylsulfoxides δ = ppm) were recorded on a Varian Bruker (400 MH_z) Tetramethylsilane was used as internal standard. Mass spectra were recorded on a mass spectrometer MS q(AGt) El made. The microanalyses were performed at Microanalytical Center, Cairo University Egypt.

General procedure for the reaction between compound 1 and 5

A mixture of **(1a-b)** (0.01mmol), and active methylene nitrile derivatives **(5a,b, 9, 10)** and ethylacetoacetate **(18)** (0.01mmol) in presence of piperidine (3 drops) and ethanol (10ml) as a solvent was refluxed for 1-2 hr. the reaction mixture was evaporated. The solid product, so formed, was crystallized from proper solvent

6-Benzoyl-3-oxo-2-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid hydrazide (11)

Orange crystals from ethanol, M.P 105°c, yield 98%, IR: 3399-3266 cm^{-1}(NH_2), 1614 cm^{-1} (C=N), 1680 (CO), M.S: M/Z (75%)= (333.1), ^{1}HNMR (DMSO) =7.26-7.28 (d,2H,NH2); 7.38-7.55 (m,10H,2Ph); 8.43(S,1H,NH); 8.55(S,1H,pyridazine C-H). ^{13}C NMR: =190.76, 190.50, 164.61, 159.67, 142.05, 141.29, 139.36, 137.37, 137.27, 131.81, 130.45, 130.19, 129.52, 127.81, 124.44, 142.35, 115.67, 115.05.

$C_{18}H_{14}N_4O_3$ (334) Calc.: **(C)** 64.66, **(H)** 4.22, N 16.76 %. Found: **(C)** 64.49, **(H)** 4.11, N 16.62 %.

Synthesis of 6-Benzoyl-3-oxo-2-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid benzylidene-hydrazide (12).

A mixture of **(11)** (0.1mol) and benzaldehyde in (20 ml) ethanol as a solvent and (3 drops) of piperdine was reflux for 3 h. The reaction mixture was evaporated. The solid product was formed as orange crystals from ethanol, M.P 220°c, yield 98%, IR: 3449 cm^{-1}(NH), 1638.23 cm^{-1} (C=O), 1536.02 (Ph), M.S: M/Z (65%)= (421.1), ^{1}HNMR (DMSO) =7.09-8.04 (m,15H,3Ph); 8.42 (S,1H,NH); 8.87(S,1H,pyridazine C-H). $C_{24}H_{18}N_4O_3$ (422) Calc.: **(C)** 71.08, **(H)** 4.29, N 13.26 %. Found: **(C)** 69.94, **(H)** 4.13, N 13.20 %.

6-Benzoyl-3-oxo-2-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid amide (13)

Yellow crystals from ethanol, M.P 254°c, yield 95% IR: 3402- 3200 cm^{-1}(NH_2), 1629 cm^{-1} (C=N), 1670 cm^{-1} (CO), M.S: M/Z (75%)= (319), ^{1}HNMR (DMSO) =7.20 (d,2H,NH2); 7.38-7.55 (m,10H,2Ph); 8.55(S,1H,pyridiazine C-H).(figure 52).

$C_{18}H_{13}N_3O_3$ (319) Calc.: C 67.71, H 4.10, N 13.16 %. Found: C 67.62, H 4.00, N 13.09 %.

Synthesis of 6-Benzoyl-3-oxo-2-phenyl-2,3-dihydro-pyridazine-4-carbaldehyde (14).

A mixture of **(13)** (0.1mol), and Zn powder (2gm) in acetic acid (20ml) was reflux for 2 hr. then filtrate on hot,The reaction mixture was cooled to room temperature and then was poured onto ice-water. The solid, so formed,was collected by filtration and crystallized from AcOH to give faint green ppt yield. 80% M.P 160°c, M.S: M/Z (15%)= (305), ^{1}HNMR (DMSO) =7.49-7.60 (m,10H,2Ph); 8.56 (S,1H,pyridazine C-H); 9.58(S,1H,CHO).

$C_{18}H_{12}N_2O_3$ (304) Calc.: **(C)** 71.05, **(H)** 3.97, **(N)** 9.21 %. Found: **(C)** 70.99, **(H)** 3.80, **(N)** 9.19 %.

6-Benzoyl-4-(1H-indole-2-carbonyl)-2-phenyl-2H-pyridazin-3-one (15).

Brown crystals from AcOH, M.P up300°c, yield 80%, IR : 1680 cm^{-1} (CO), 1620 (C=N), 1550 (C=C), M.S: M/Z (15%)=(419), ^{13}C NMR: =189.21, 176.05, 142.80, 141.40, 140.84, 137.18, 136.98, 135.37, 135.33, 132.42, 130.47, 130.30, 129.55, 129.16, 128.95, 128.44, 127.38, 126.91, 125.57,125.44, 123.55, 122.71,121.77,118.95,115.91, 112.65.

$C_{26}H_{17}N_3O_3$ (419) Calc.: **(C)** 74.45, **(H)** 4.09, **(N)** 10.02 %. Found: **(C)** 74.30, **(H)** 4.00, **(N)** 10.00 %.

4-Benzothiazol-2-yl-6-benzoyl-2-phenyl-2H-pyridazin-3-one (16).

Brown crystal from ethanol., M.P 202°c, yield 95%,

IR : 1640 cm^{-1} (CO), 1620 (C=N), 1567 (C=C), M.S: M/Z (20%)=(409).

$C_{24}H_{15}N_3O_2S$ (409) Calc.: **(C)** 70.40, **(H)** 3.69, **(N)** 10.26 %. Found: **(C)** 70.40, **(H)** 3.54, **(N)** 10.12 %.

3-Oxo-2-phenyl-6-(thiophene-2-carbonyl)-2,3-dihydro-pyridazine-4-carboxylic acid hydrazide (17).

Yellow crystals from AcOH, M.P = 258°c, yield 95%, IR : 1680 cm^{-1} (CO), 1620 (C=N), 1550 (C=C), M.S: M/Z (20%)=(339), ^{1}HNMR (DMSO) =7.17-7.29 (t,3H,thiol); 7.4-7.5 (m,5H,ph); 8.43(S,1H,NH)., 8.54 (S,1H,Pyridazine C-H),. ^{13}C NMR: =180.13, 179.90, 164.60, 159.75, 142.09, 141.95, 140.83, 138.17, 136.16, 135.07, 130.04, 129.65, 127.58, 124.52, 128.44, 116.28.

$C_{16}H_{12}N_4O_3S$ (340) Calc.: **(C)** 56.46, **(H)** 3.55, **(N)** 16.46 %. Found: **(C)** 56.40, **(H)** 3.44, **(N)** 16.32 %.

4-Acetyl-2-phenyl-6-(thiophene-2-carbonyl)-2H-pyridazin-3-one (19).

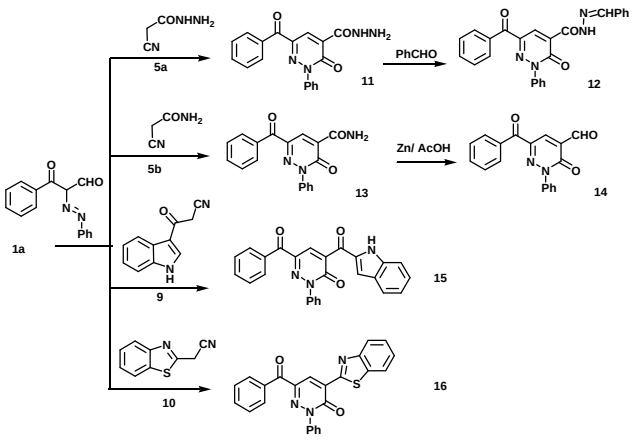
Buff crystal from ethanol, M.P = 184°c, yield 95%, IR : 1638 cm^{-1} (CO), 1620 (C=N), 1558 (C=C), M.S: M/Z (100%)=(324), ^{1}HNMR (DMSO) =2.63 (S,3H,CH3); 7.26-7.28 (t,1H,pyridazine C-H); 7.52-7.72(m,5H,Ph)., 8.10 -8.22 (m,3H, thiole),. ^{13}C NMR: =196.28, 178.59, 157.68, 141.42, 140.90, 138.28, 137.68, 136.80, 129.69, 129.03, 128.92, 128.48, 125.94, 30.34.

$C_{17}H_{12}N_2O_3S$ (324) Calc.: **(C)** 62.95, **(H)** 3.73, **(N)** 8.64 %. Found: **(C)** 62.82, **(H)** 3.54, **(N)** 8.42 %.

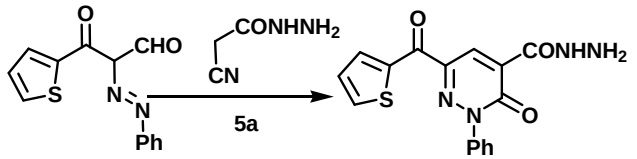
RESULTS AND DISCUSSION

Compound **(1a-b)** reacted with active methylene nitrile derivatives **(5a-b, 9,10)** yielding the pyridazinone **(11-13,15,16)** and **(17)**, respectively as indicated from presence of carbonyl carbon absorption in ^{13}C NMR at $\delta > 175$ compound **(13)** can be reduced by zinc and acetic acid to form **(14)** (Scheme 2,3).

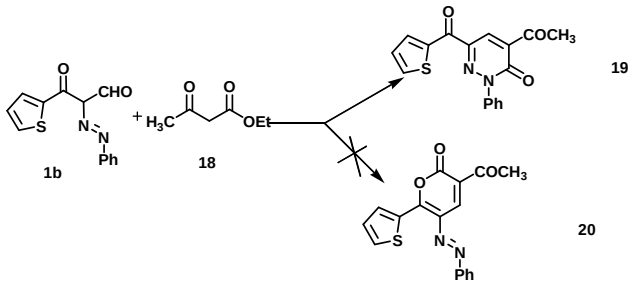
Ethylacetoacetate **(18)** condensed with **(1b)** to yield acetylpyridazinone **(19)**. possible formation of arylazo acetylpyranone **(20)** has been elimination base on ^{13}CNMR spectra that reveled to carbonyl carbon δ= 178.59 in addition amide carbonyl carbon at δ= 196.78 (scheme 4).



Scheme 2



Scheme 3



Scheme 4

CONCLUSION

In conclusion to this it has been formed that 5 condensed with 1 to yield pyridazinones 8 as indicted from presence of carbonyl carbon as $\delta > 175$ ppm. Initially formed imines 6 in this case are readily hydrolyzed under reaction conditions to yield final products 8. In fact this finding supports our belief that heterocyclic imines like 6 are difficult to isolate as they readily afford the more aromatic one derivative.

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