GLOBAL JOURNAL OF ENGINEERING SCIENCE AND RESEARCHES

NEW AND ONE POT-SYNTHESIS OF FUNCTIONALLY SUBSTITUTED PYRIDINES FROM ENAMINOKETONES

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ABSTRACT

Several new pyridine derivatives were prepared *via* reacting the enaminoketones **1a-d** with active hydrogen reagents. Reaction of the enaminoketones **1a-c** with 4-acetyl-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one **2a** yielded the pyridines **3a-c**. Condensation of the enaminonitrile **1d** with **2b-d** or 3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-3-oxopropanenitrile **8** give the pyridine derivatives **6a-c** and **10** respectivly. Also, (*E*)-3-(3-(dimethylamino)acryloyl)-2*H*-chromen-2-one **1a** reacted with active methylenes in diethyl 3-oxopentanedioate **12** and 4-methyl-6-oxo-2-thioxo-1,2,5,6-tetrahydropyridine-3-carbonitrile **15** to afford the pyridine derivatives **14** and **16** respectively.

Keywords: Pyridine, Antipyrine, Coumarin.

I. INTRODUCTION

The elaboration of efficient synthesis protocols for a variety of aromatic and heteroaromatic systems as potential bio-active agents have been a major area of research interest in our laboratory, over the past several year [1- 7] . Recently, enaminones have successfully utilized as a builing block for the synthesis of polyfunctionlised heteroaromatics and other related condensed systems [8-10] In view of our interest in developing an efficient synthesis of polyfunctionally substituted heteroaromatics using the readily obtainable enaminoketones **1a-d** as starting materials. It is worthwhile to explore their potential utilization for synthesis of polyfunctionally substituted pyridines, because of their biological and medicinal activities.

II. EXPERIMENTAL

All melting points are uncorrected and measured on Griffin & George MBF 010(London) apparatus. Recorded on a Perkin Elmer SP-880 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 spectrometer in DMSO-d as solvent and TMS as an internal standard; chemical shifts are reported in δ units (ppm). Mass spectra were measured on MS 30 and MS 9 (AEI), eV. Microanalysis were performed on LECONCHNS-932. Micro analytical data were obtained from the Micro analytical Data unit at Cairo University.

General procedure for the preparation of the pyridine derivatives **3a-c, 6a-c, 10, 14.**

To a solution of (0.01 mole) of the enaminoketones **1a-c** in acetic acid (20 ml) containing (0.01 mole) of ammonium acetate, (0.01 mole) of the active methyl or the active methylene derivatives were added. The reaction mixture was refluxed for 3 hours and then the solvent was concentrated in vacuo and then left to cool to room temperature. The solids deposited were collected by filtration and recrystallized from ethanol to give **3a-c**, **6a-c**, **10** and **14** respectively.

1,5-Dimethyl-4-(6-(2-oxo-2H-chromen-3-yl)pyridin-2-yl)-2-phenyl-1H-pyrazol-3(2H)-one **3a**:Formed colorless crystals in 65 % yield,from ethanol,m.p.246-248^{o}C;IR(υ / cm^{-1}): 1729(CO coumarinyl),1649(CO antpyrinyl);^{1}-H-NMR(DMSO-d_6)(δ,ppm):2.29(s,3H,CH_3),3.37(s,3H,*N*-CH_3),7.42-8.45(m,12H,aromatic protons),8.89(s,1H,coumarin H-4).*Anal*. $C_{25}H_{19}N_3O_3$(409.45) :Calcd. :C,73.34;H,4.68;N,10.26;Found: C,73.60;H, 4.74;N,10.34; (M^+ = 409 m/z).

1,5-dimethyl-2-phenyl-4-(6-(thiophen-2-yl)pyridin-2-yl)-1H-pyrazol-3(2H)-one **3b** : Formed yellow crystals in 70 % yield,from ethanol ,m.p.165-167^{o}C;IR(υ / cm^{-1}): 1650(CO antpyrinyl) ;^{1}-H-NMR(DMSO-d_6)
(δ,ppm):2.40(s,3H,CH_3),3.35(s,3H,*N*-CH_3),7.21-8.24(m,11H,aromatic protons).*Anal*. $C_{20}H_{17}N_3SO$ (347.44) :Calcd. : C, 69.14; H, 4.93; N, 12.09; Found: C,69.24;H, 4.86;N,12.13; (M^+ = 347 m/z).

4-(6-(Furan-2-yl)pyridin-2-yl)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one **3c** : Formed pale

yellow crystals in 60 % yield,from ethanol ,m.p.170-172°C;IR(υ / cm^{-1}): 1660(CO antpyrinyl) ; ^{1}H-NMR(DMSO-d_6) (δ,ppm):2.43(s,3H,CH_3),3.36(s,3H,*N*-CH_3),7.38-8.30(m,11H,aromatic protons).*Anal*. $C_{20}H_{17}N_3O_2$(331.37):Calcd. : C, 72.49; H, 5.17; N, 12.68; Found: C72.62;H, 5.22;N,12.53; (M^+ = 331 m/z).

4-(2-Amino-6-(2-oxo-2H-chromen-3-yl)nicotinoyl)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one **6**a : Formed yellow crystals in 70 % yield,from ethanol,m.p.208-210°C;IR(υ / cm^{-1}):3426(NH_2), 1735(CO coumarinyl),1670(side chain CO),1645(CO antpyrinyl);^{1}H-NMR (DMSO-d_6) (δ,ppm):2.44(s,3H,CH_3),3.37(s,3H,*N*-CH_3),6.68 (s,2H,NH_2) ,7.44-8.62 (m,11H,aromatic protons),9.02(s,1H,coumarin H-4).*Anal*. $C_{26}H_{20}N_4O_4$ (452.46) :Calcd. : C, 69.02; H, 4.46; N, 12.38;Found: C, 69.23; H, 4.62 ; N,12.25; (M^+ = 452 m/z).

4-(2-Amino-6-(thiophen-2-yl)nicotinoyl)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one **6**b : Formed yellow crystals in 63 % yield,from ethanol,m.p.140-142°C;IR(υ / cm^{-1}):3360(NH_2), ,1670(side chain CO), 1660(CO antpyrinyl);^{1}H-NMR (DMSO-d_6) (δ,ppm):2.35 (s,3H, CH_3), 3.16(s,3H,*N*-CH_3), 7.26-8.52 (m,10H,aromatic protons), 8.97 (s,2H , NH_2).*Anal*. $C_{21}H_{18}N_4O_2S$ (390.46) :Calcd. : C, 64.60; H, 4.65; N, 14.35; Found: C, 64.46; H, 4.54 ; N,14.23; (M^+ = 390m/z).

4-(2-Amino-6-(furan-2-yl)nicotinoyl)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one **6**c : Formed yellow crystals in 63 % yield,from ethanol ,m.p.169-171°C;IR(υ / cm^{-1}):3430(NH_2), ,1675(side chain CO), 1665 (CO antpyrinyl);^{1}H-NMR (DMSO-d_6) (δ,ppm):2.41 (s,3H, CH_3), 3.30 (s,3H, *N*-CH_3),6.80(s,2H,NH_2), 7.34-8.35 (m,10H,aromatic protons) .*Anal* $C_{21}H_{18}N_4O_3$ (374.39) :Calcd. : C, 67.37; H, 4.85; N, 14.96; Found: C, 67.42; H, 4.76 ; N,14.79; (M^+ = 374 m/z).

6-Amino-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-5-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carbonyl) nicotinonitrile **10** : Formed yellow crystals in 65 % yield,from ethanol ,m.p.270-272°C;IR(υ / cm^{-1}):3455,3424(NH_2), 2220(conjugated CN), 1673(side chain CO), 1665 (CO antpyrinyl);^{1}H-NMR (DMSO-d_6) (δ,ppm) :2.34 (s,3H, CH_3), 3.35 (s,3H, *N*-CH_3),6.65(s,2H,NH_2), 7.33-8.35 (m,11H,aromatic protons) .*Anal* $C_{29}H_{25}N_7O_3$ (519.55) :Calcd. : C, 67.04; H, 4.85; N, 18.87; Found: C, 67.13; H, 4.98 ; N,18.75; (M^+ = 519 m/z).

Ethyl 2-(2-ethoxy-2-oxoethyl)-6-(2-oxo-2H-chromen-3-yl)nicotinate **14**: Formed orange crystals in 65 % yield,from ethanol/dimethylformamide , m.p.149-151°C;IR(υ / cm^{-1}):1730(CO coumarinyl), 1720(CO ester);^{1}H-NMR (DMSO-d_6) (δ,ppm) :1.23-1.26(t,J = 7Hz ,3H,CH_3),1.36-1.38(t,J = 7Hz ,3H,CH_3),3.36(s,2H,CH_2),4.14-4.21(q,J = 7Hz,2H,CH_2),4.33-4.4-(q, J = 7Hz,2H,CH_2),7.54-8.43(m,6H,aromatic protons),8.98 (s,1H, coumarin H-4) .*Anal* $C_{21}H_{19}NO_6$ (381.38) :Calcd. : C, 66.13; H, 5.02; N, 3.67; Found : C, 66.23; H, 5.11 ; N,3.53; (M^+ = 381 m/z).

(E)-4-methyl-6-oxo-5-(3-oxo-3-(2-oxo-2H-chromen-3-yl)prop-1-en-1-yl)-2-thioxo-1,2,5,6-tetrahydropyridine-3-carbonitrile **16**

A solution of **1a** (0.01 mole) in absolute ethanol (50 ml) was mixed with the appropriate pyridine (0.01 mole) and few drops of piperidine. The reaction mixture was heated under reflux for one hour, then left to cool. The solid deposited was collected by filtration and recrystallized to give **16**.Compound **16** formed orange crystals in 75 % yield,from ethanol/dimethylformamide , m.p.> 300°C; IR(υ / cm^{-1}):3439 (NH) , 1715 (CO coumarinyl), 1683(CO side chain)1650 (CO amide);^{1}H-NMR (DMSO-d_6)(δ,ppm) : 1.82(s,3H,CH_3), 3.81 (s.1H, H-3),6.59(d, J = 15Hz,1H,CH),6.97(d, J = 15Hz, 1H,CH) ,7.42-7.84 (m, 4H,aromatic protons),8.57 (s,1H, coumarin H-4); ^{13}C-NMR (DMSO-d_6) (δ,ppm) :12.3(CH_3),59.8(C-3),133.4 (CH),156.7(CH), 147.2,159.4,165.8, 172.7, 183.7(CO),115.9(CN),107.4,116.1,118.2,125.4,127.9 ,128.5(aromatic carbons) .*Anal* $C_{19}H_{12}N_2O_4S$ (364.37) :Calcd. : C, 62.63; H, 3.32; N, 7.69; Found : C, 62.71; H, 3.43 ; N,7.52; (M^+ = 364 m/z).

III. RESULTS AND DISCUSSION

It has been found that, the enaminoketones **1a-c** reacted with 4-acetyl-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one **2a** in refluxing acetic acid and in presence of ammonium acetate to yield products that may formulated as the 2,6-disubstituted pyridines **3** or isomeric 2,4- disubstituted pyridines **4**. While initial Michael addition of the methyl ketone across the activated double bond in **1a-c** and subsequent cyclization could lead to structures **3**, initial condensation of the methyl function in **2** with the carbonyl function of the enaminoketones **1a-c** and subsequent cyclization might afford compound **4**.

ISSN 2348 – 8034

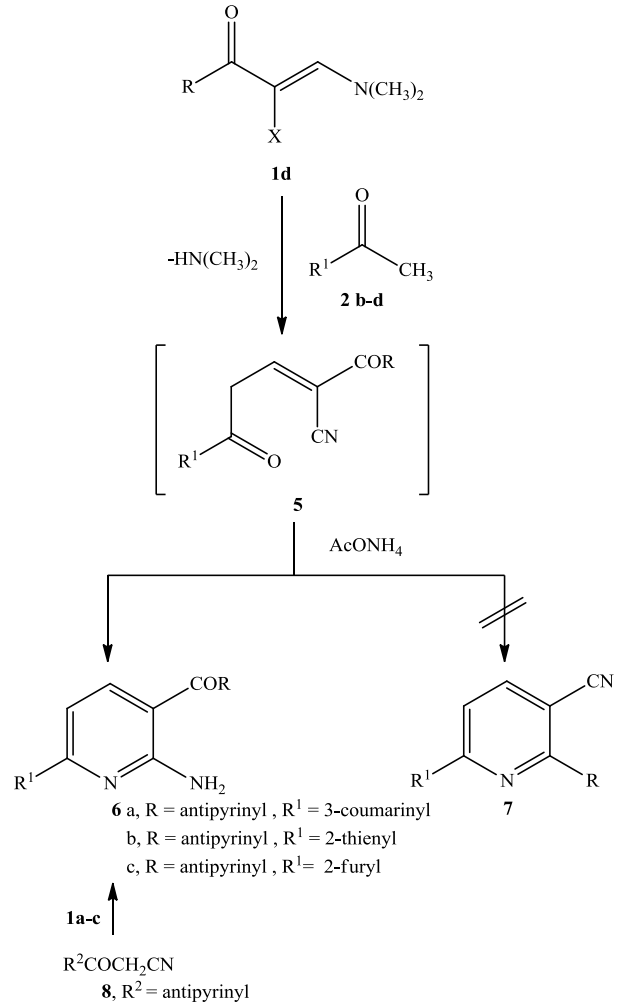
However, structures **3** were established as reaction products based on similarity with recent reported formation of similar systems[10] *cf*. Scheme **1**).

Similar to the behavior of the enaminoketones **1a-c** towards 4-acetyl-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one **2a**, (*E*)-2-(1,5-dimethyl-3-oxo -2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbonyl)-3-(dimethylamino) acrylonitrile **1d** reacted with **2b-d** to yield the pyridine derivatives **6a-c** or **7**.Structures **7** were readily eliminated based on IR spectra of the reaction products which cleary indicates the absence of signals due to cyano groups. Consequently, the pyridine structures **6** can be assigned to the reaction products. Compounds **6** were also synthesized *via* reacting the enaminoketones **1a-c** with 3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-3-oxopropanenitrile **8** using the above reaction conditions *cf*. Scheme **2**).

Also, (*E*)-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbonyl)-3-(dimethylamino)acrylonitrile **1d** reacted with 3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-3-oxopropanenitrile **8** to yield pyridine derivative **10** as the sole product. The possible isomeric **11** was excluded based on IR spectrum which cleary showed the presence of an amino group at γ= 3455, 3397 cm-1 and cyano group at γ = 2220 cm^{-1} (*cf*. Scheme **3**).

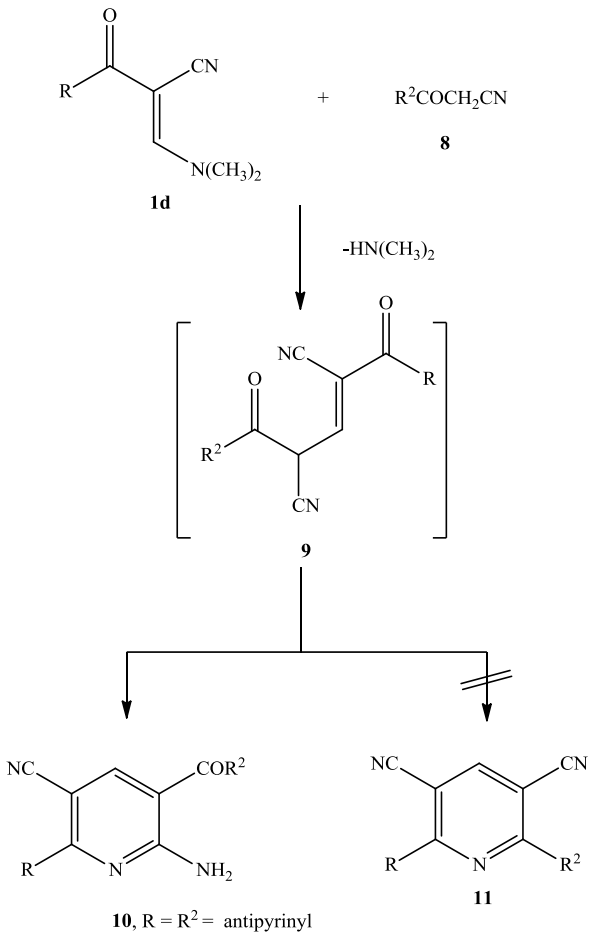
(*E*)-3-(3-(dimethylamino)acryloyl)-2*H*-chromen-2-one **1a** also reacted with diethyl 3-oxopentanedioate **12** in acetic acid catalysed by ammonium acetate to afford either diethyl 2-hydroxy-4-(2-oxo-2*H*-chromen-3-yl)isophthalate **13** or ethyl 2-(2-ethoxy-2-oxoethyl)-6-(2-oxo-2*H*-chromen-3-yl)nicotinate **14**. However, the elemental analysis and spectral data of the reaction products are compatible only with ethyl 2-(2-ethoxy-2-oxoethyl)-6-(2-oxo-2*H*-chromen-3-yl)nicotinate structure **14**. The later compound was assumed to be formed *via* addition of the active methylene in diethyl 3-oxopentanedioate **12** across the double bond in **1** followed by cyclization with ammonia.

Reacting (*E*)-3-(3-(dimethylamino)acryloyl)-2*H*-chromen-2-one **1a** with 1, 2, 5, 6-tetrahydro-6-oxo-2-thioxo-3-cyano-4-methylpyridine **15** in ethanol and in presence of catalytic amount of pipridine afforded a condensation product *via* dimethylamine elimination. Elemental and spectral data are in good agreement with the pyridine structure **16** (*cf*. Scheme **4**).

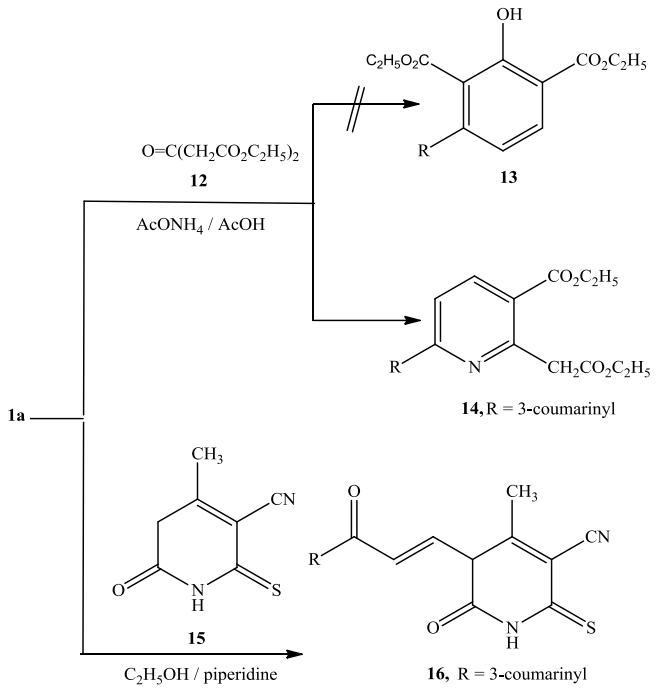


Scheme 2 : Preparation of the pyridines **6a-c**

ISSN 2348 – 8034



Scheme 3 : Preparation of the pyridine **10**



Scheme 4 : Synthesis of the pyridine derivatives **14** and **16**

IV. CONCLUSION

We conclude that,several new pyridine derivatives were prepared *via* reacting the enaminoketones with active hydrogen reagents with as readily obtainable starting materials that could be useful for biological evaluation studies.

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