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ENAMINONES IN HETEROCYCLIC SYNTHESIS: NEW ONE POT SYNTHESIS OF SOME POLYFUNCTIONALLY SUBSTITUTED PYRIDINES

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ABSTRACT

Several new pyridine derivatives were prepared *via* reacting the enaminones **1a-d** with active hydrogen reagents. Reaction of **1a-c** with 4-acetylantipyrine **2** yielded the pyridines **3** Condensation of the enaminonitrile **1d** with **2a-b** and **8** give the pyridines **6** and **10** respectively. Also, **1a** reacted with active methylenes in **12** and **15** to afford the pyridine derivatives **14** and **15** respectively.

INTRODUCTION

The elaboration of efficient synthetic 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 years [El-Taweel, (1995); **El-Taweel et al., (2001) and Abdel-Rahman et al., (2002)**]. Recently, enaminones have successfully utilised as a building block for the synthesis of polyfunctionalised heteroaromatics and other related condensed systems [**Abdel-Rahman, et al., (2002); Abdel-Khalik & Elnagdi (2002); Abu Elmaati (2002); Elassar & Abu El-Khair (2003) and Jackse et al., (2004)**]. In view of our interest in developing an efficient synthesis of polyfunctionally substituted hetero-aromatics using the readily obtainable enaminones as starting materials [**Abdel-Rahman et al., (2002) and Jackse et al., (2004)**], it is worthwhile to explore their potential utilization for synthesis of polyfunctionally substituted pyridines, because of their biological and medicinal activities [**Dolle, et al., (1997); Troschutz & Karger (1997); Robertson, (1996) and Alousi, et al., (1983)**].

RESULTS AND DISCUSSION

It has been found that, the enaminones **1a-c** reacted with 4-acetylantipyrine **2a** in refluxing acetic acid and in presence of ammonium acetate to yield products that may formulated as **3** or isomeric **4**. While initial Michael addition of the methyl ketones in **2** across the activated double bond in **1a-c** and subsequent cyclization could lead to structures **3**, initial condensation of the methyl moiety in **2** with the carbonyl function of the enaminones **1a-c** and subsequent cyclization might afford compound **4**. However, structures **3** were established as reaction products based on similarity with recent reported formation of similar systems **[Agamey, et al. (2001)]**.

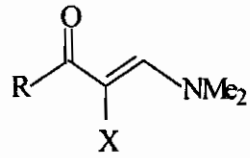
Similar to the behaviour of the enaminones **1** towardes **2a** , the enaminonitrile **1d [Abu Elmaati, (2002)]** reacted with **2b-d** to yield the pyridine derivatives **6** or **7**. Structures **7** were readily eliminated based on IR spectra of the reaction products which cleary indicates the absence 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 enaminones **1a-c** with 2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-oyl)acetonitrile **8** using the above reaction conditions.

Also, 3-dimethylamino-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro -1*H*pyrazole-4-oyl)acrylonitrile **(1d) [Abu Elmaati, (2002)]** reacted with **8** to yield pyridine derivative **10** as a sole product. The possible isomeric **11** was excluded based on IR spectrum which clearly showed the presence of an amino group at γ = 3455,3397 cm^{-1} and cyano group at γ = 2220 cm^{-1} (cf. Scheme 3).

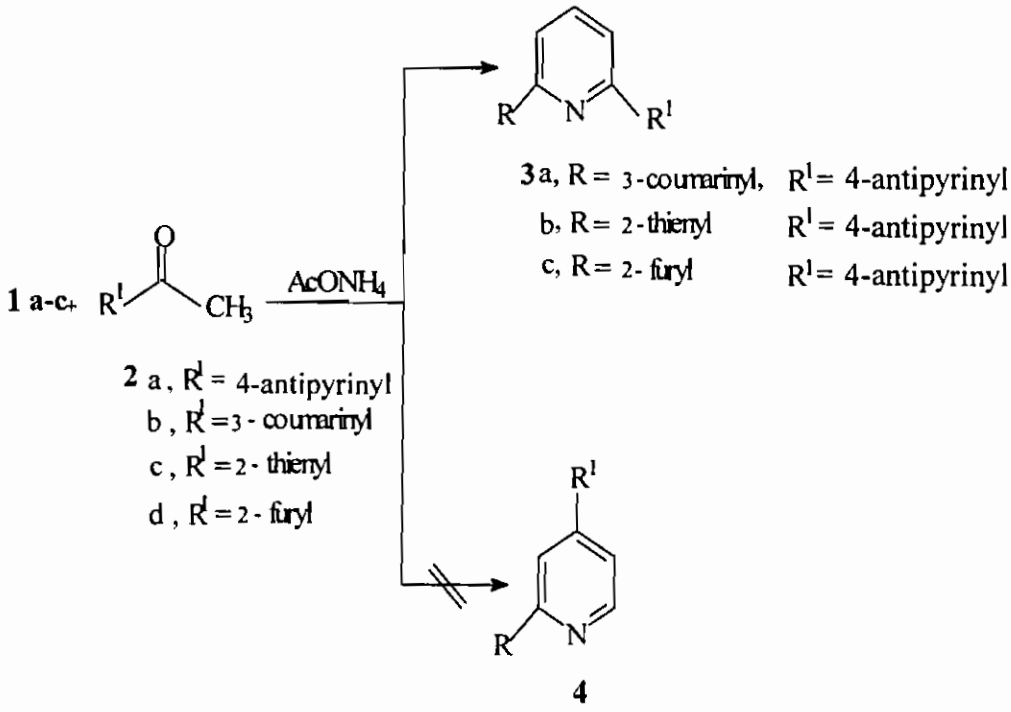
The enaminones **1a** also reacted with diethyl 3-oxoglutarate **12** in acetic acid catalysed by ammonium acetate to afford either diethyl 2-hydroxybenzene-1,3-dicarboxylate **13** or the pyridine derivatives **14**. However, the elemental analysis and spectral data of the reaction products are compatible only with the pyridine structure **14**. The later compound was assumed to be formed *via* addition of the active methylene in **12** across the double bond in **1** followed by cyclization with ammonia.

Reacting the enaminone **1a** with 1,2,5,6-tetrahydro-6-oxo-2-thioxo-3-cyano-4-methylpyridine (**15**) in ethanol and a catalytic amount of piperidine afforded a condensation product *via* dimethylamine

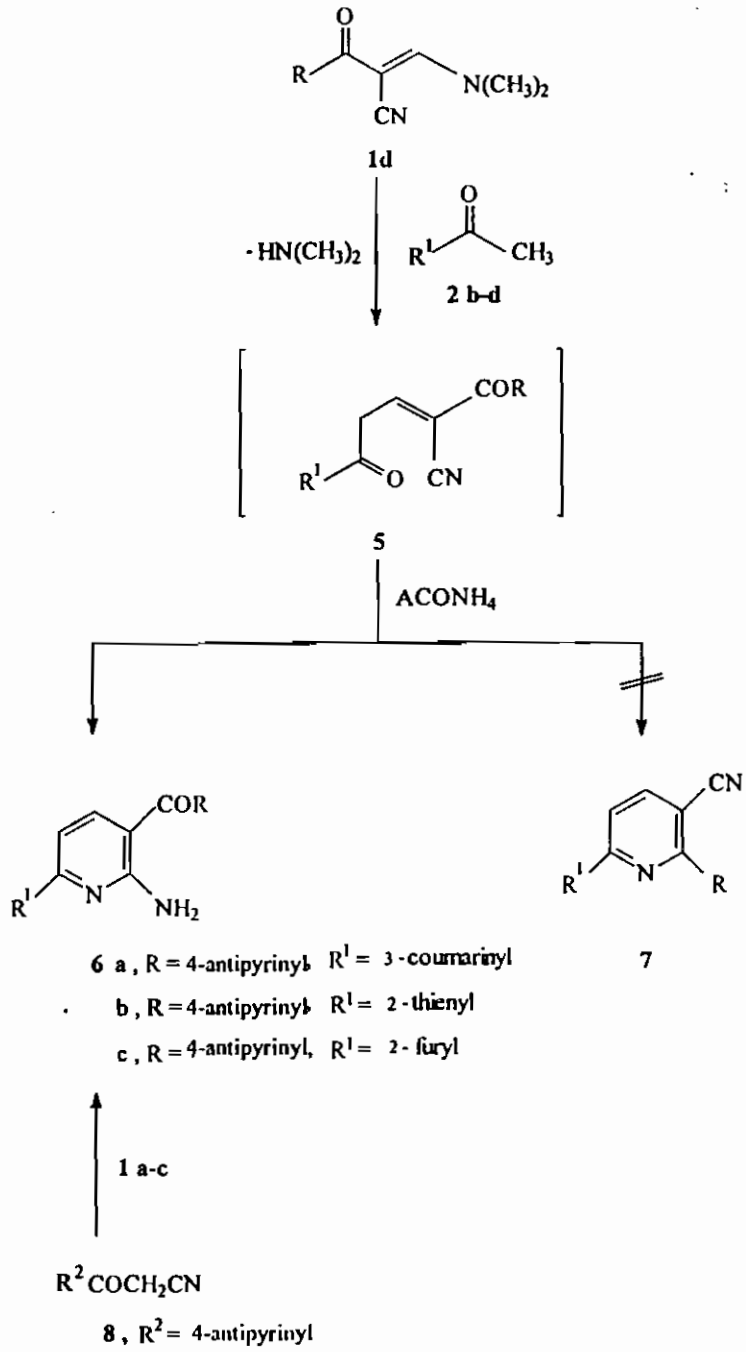
elimination. Elemental and spectral data are in good agreement with the pyridine structure **16** (cf. Scheme **4**).



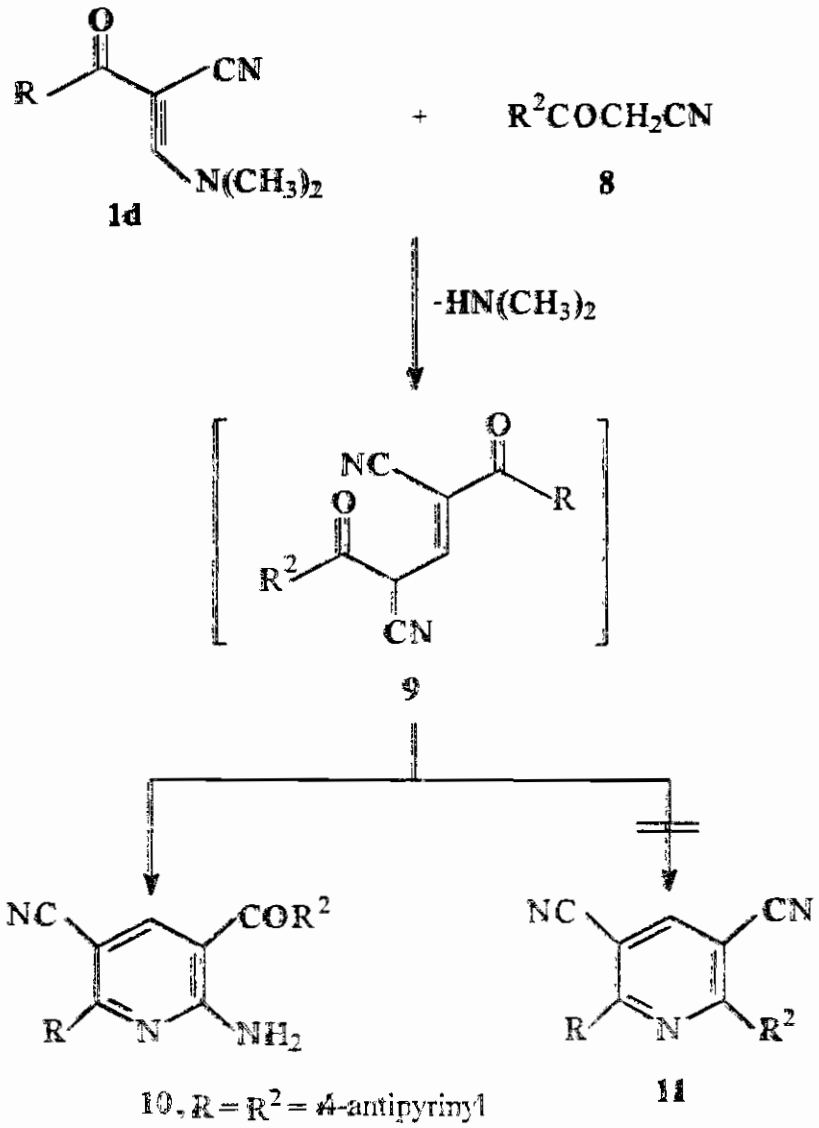
1a, R = 3-coumarinyl, X = H
b, R = 2-thienyl X = H
c, R = 2-furyl X = H
d, R = 4-antipyrinyl X = CN



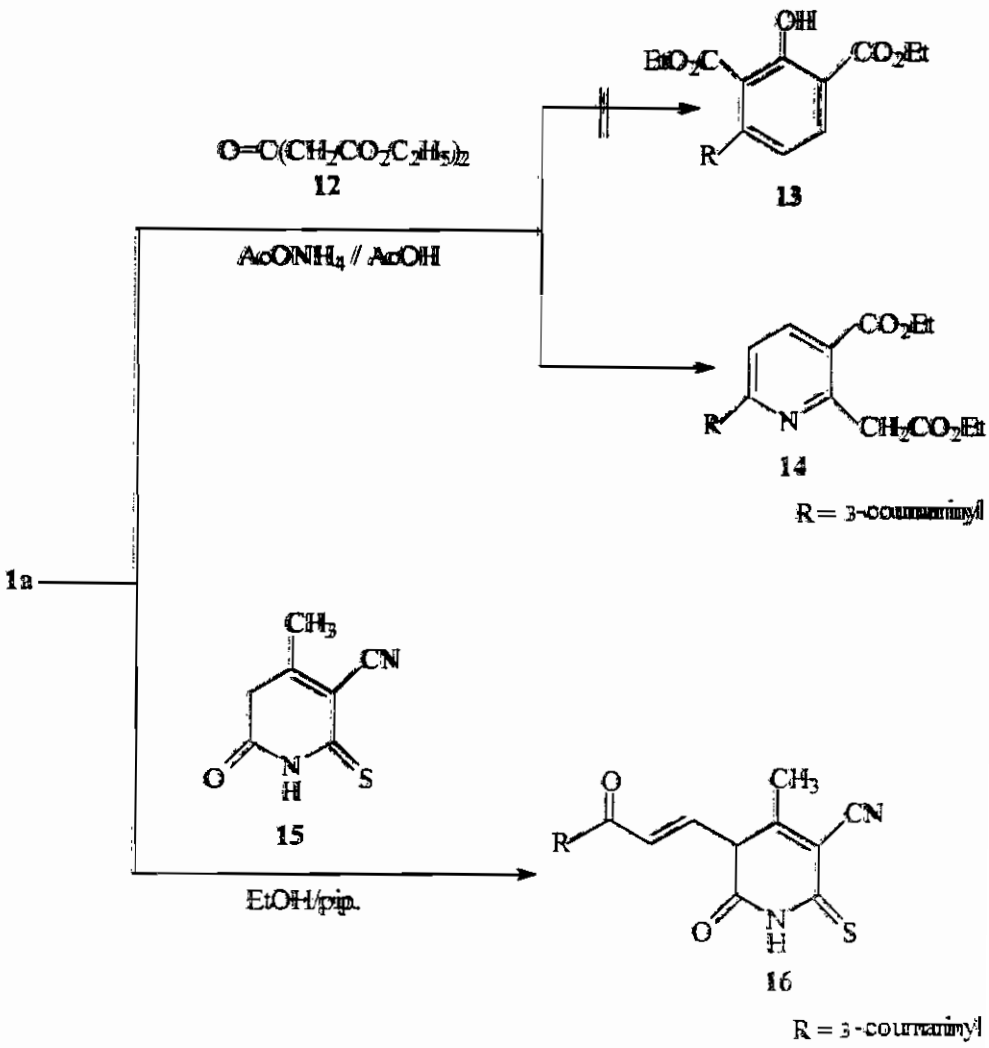
Scheme 1


O
R
N(CH3)2
CN
1d
-HN(CH3)2
O
R1
CH3
2 b-d
COR
R1
O
CN
5
ACONH4
COR
R1
N
NH2
CN
R1
N
R
6 a , R = 4-antipyrinyl R1 = 3-coumarinyl
b , R = 4-antipyrinyl R1 = 2-thienyl
c , R = 4-antipyrinyl, R1 = 2-furyl
7
1 a-c
R2COCH2CN
8 , R2 = 4-antipyrinyl

Scheme 2


O
R
CN
N(CH3)2
1d
+
R2COCH2CN
8
-HN(CH3)2
NC
O
R
O
R2
CN
9
NC
COR2
R
N
NH2
NC
CN
R
N
R2
10, R = R2 = 4-antipyrinyl
11

Scheme 3


O=C(CH2CO2C2H5)2
12
AcONH4 / AcOH
13
14
R = 3-coumarinyl
1a
15
EtOH/pip.
16
R = 3-coumarinyl

Scheme 4

EXPERIMENTAL

All melting points are uncorrected and measured on Griffin & George MBF 010T (London) apparatus. Recorded yields corresponds to the pure products. IR (KBr) spectra were recorded on a Perkin Elmer SP-880 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 spectrometer in [$^2H_6$] DMSO 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 LECOCHNS-932. Microanalytical data were obtained from the Microanalytical Data unit at Cairo University.

General procedure for the preparation of the pyridine derivatives 3 , 6 , 10 , 14 .

To a solution of (10 mmole) of the enaminones **1** in acetic acid (20 ml) containing (10 mmole) of ammonium acetate, (10 mmole) 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 **3**,**6**,**10** and **14** respectively.

1-(Coumarin-3-oyl)-2-(1,2,5,6-tetrahydro-6-oxo-2-thioxo-3- cyano -4-methylpyridin-5-yl)ethene (16).

A solution of **12** (10 mmole) in abs. ethanol (50 ml) was mixed with **15** (10 mmole) 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 from DMF to give **16**.

Table 1. Analytical data of the compounds 3,6,10,14 and 16.

Compd.	Yield (%)	M.p.(°C)	Molecular formula (g/mol)	Microanalysis Calcd. / Found C	H	N
3a	**65**	**248**	$C_{25}H_{19}N_3O_3$	73.34	4.68	10.26
			(409.45)	73.60	4.74	10.34
3b	**70**	**165**	$C_{20}H_{17}N_3SO$	69.14	4.93	12.09
			(347.44)	69.24	4.87	12.13
3c	**60**	**170**	$C_{20}H_{17}N_3O_2$	72.49	5.17	12.68
			(331.38)	72.62	5.22	12.53
6a	**70**	**208**	$C_{26}H_{20}N_4O_4$	69.20	4.46	12.38
			(452.47)	69.23	4.62	12.25
6b	**63**	**140**	$C_{21}H_{18}N_4SO_2$	64.60	4.67	14.35
			(390.47)	64.46	4.54	14.23
6c	**60**	**169**	$C_{21}H_{18}N_4O_3$	67.37	4.85	14.96
			(374.40)	67.42	4.76	14.79
10	**62**	**270**	$C_{29}H_{25}N_7O_3$	67.04	4.85	18.87
			(519.57)	67.13	4.98	18.82
14	**60**	**149**	$C_{21}H_{19}NO_6$	66.14	5.02	3.67
			(381.38)	66.23	5.11	3.53
			($M^+ = 381$)			
16	**65**	**>300**	$C_{19}H_{12}N_2SO_4$	62.63	3.32	7.69
			(364.38)	62.71	3.43	7.52
			($M^+ = 364$)			

a) **Compounds 3,6,10 and 14** were recrystalized from ethanol.
b) **Compound 16** was recrystalized from dimethylformamide.

Table II. IR and ^{1}H-NMR of the compounds **3,6,10,14 and 16.**

Compd.	IR(KBr)(cm^{-1})	^{1}H-NMR (Solvent) δppm
3a	1729 (CO coumairnyl); 1649 (CO antipyrinyl).	(DMSO-d_6): δ=2.29(s,3H,CH_3); 3.37(s, 3H,N-CH_3); 7.42-8.42 (m,12H,arom-H); 8.98 (s, 1H, coumarinH-4).
3b	1650 (CO antipyrinyl).	(DMSO-d_6): δ=2.40(s, 3H,CH_3); 3.35(s, 3H, N-CH_3); 7.21-8.24 (m, 11H, arom-H).
3c	1660 (CO antipyrinyl).	(DMSO-d_6): δ=2.43(s, 3H, H_3); 3.36(s, 3H, N-CH_3);7.38-8.30(m, 11H, arom-H).
6a	3426 (NH_2);1735(CO coumairnyl); 1670 (CO side chain);1645 (CO antipyrinyl).	(DMSO-d_6): δ=2.44(s, 3H, CH_3); 3.37(s, 3H, N-CH_3);6.86(s,2H, NH_2); 7.44-8.62 (m, 11H, arom-H); 9.02(s, 1H, coumarin H-4).
6b	3360 (NH_2); 1670 (CO side chain); 1660 (CO antipyrinyl)	(DMSO-d_6): δ=2.35(s, 3H, CH_3); 3.16(s, 3H, N-CH_3);7.26-8.52 (m,10H, arom-H); 8.97(s, 2H, NH_2).
6c	3430 (NH_2); 1675 (CO side chain); 1665 (CO antipyrinyl).	(DMSO-d_6): δ=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, arom-H).
10	3455,3424,3397(NH_2);2220 (CN); 1673 (CO side chain); 1665 (CO antipyrinyl).	(DMSO-d_6): δ= 2.34(s,6H,2CH_3): 3.35(s, 6H, 2N-CH_3); 6.65(s, 2H, NH_2); 7.33-8.35(m, 11H, arom).
14	1730 (CO coumarinyl); 1720 (CO ester).	(DMSO-d_6): δ=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); 4.33-4.40 (q , J = 7Hz. 2H, CH_2); 7.54-8.43 (m, 6H, arom-H); 8.98(s, 1H, coumarin H-4).
16	3439 (NH); 1715 (CO coumarinyl) 1683 (CO side chain); 1650 (CO amide).	(DMSO-d_6): δ_H(Insoluble).

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تحضير الحلقات الغير متجانسة من الإينامينونات :
طريقة جديدة لتحضير مشتقات البيريدن

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تم في هذا البحث تحضير العديد من مشتقات البيردين من تفاعل الإينامينونات مع المركبات ذات مجموعة المثيلين النشيطة. تفاعل المركبات **1a-c** مع ٤- أستيل أنتيبيرين أنتج البيريدينات رقم **3**. تكاثف الإينامينونيتريل **1d** مع المركبات رقم **2** و**8** ليعطى البيريدينات رقم **6** و **10** على التوالي. كما تفاعل الإينامينون **1a** مع مجموعات الميثيلين النشيطة فى المركبات رقم **12** و **15** لتعطى مشتقات البيريدين رقم **14** و **15** على التوالي.

تم إثبات التركيب البنائى للمركبات الجديدة باستخدام التحليل العنصري والطيفي.