Sci. J. Fac. Sci. Monoufia Univ. Vol. VIII (1994).

REACTIONS WITH ACTIVATED DOUBLE BOND: SYNTHESIS OF 4-SUBSTITUTED ANTIPYRINE DERIVATIVES

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ABSTRACT

*4-Formylantipyrine **1** reacted with β -aroyl-propionic acids **2** to give butenolides **3** which reacted with hydrazine hydrate to give pyridazines **5**. The hydrazone **8** was prepared through condensation of **7** with phenyl hydrazine. Addition reactions of cinnamonitriles **10** to active hydrogen reagents resulted in the formation of arylidenes **13** and **14**. Dimedone reacted with cinnamonitriles **10** in molar ratio 2:1 to give the adduct **15**. 4-Cyanoacetamidoantipyrine **17** reacted with chalcones **18** to yield pyridone derivatives **21**.*

INTRODUCTION

Polyfunctionally substituted butenolides and pyridazines are biologically interesting molecules and their chemistry has received considerable interest[1-7]. We report here about the results of our attempts to prepare substituted pyridazines to be treated as expected biologically active compounds.

RESULTS AND DISCUSSION

4-Formylantipyrine **1** could be condensed with β-aroylpropionic acids **2** to yield the corresponding butenolides **3**. These compounds reacted with hydrazine hydrate in refluxing ethanol containing conc.HCl to yield acyclic hydrazides **4**, which when cyclized directly to afford products that could be formulated as compounds **5**. Trials to isolate the intermediate **4** under milder conditions, by conducting the reaction at room temperature resulted in a mixture of products.

Antipyrinylhydrazones are efective compounds, as being easily complexed with metals[8]. For this reason hydrazone derivative **8** was prepared from hydrazone derivative 7 and phenyl-hydrazine. The formed product was identical with that obtained from the reported method[9] (m.p. and mixed m.p.) via reaction of diazotized 4-aminoantipyrine **9** and 3-methyl-1-phenylpyrazolone. Compound **8** is now in current use as a legand for complexing with metals.

Trials for addition reactions of cinnamonitriles **10** with the active hydrogen containing compounds: thiosemicarbazide **11a**, isonicotinic acid hydrazide **11b**, cyanoacetamide **12a** or 2-cyanomethyl-benzimidazole **12b** resulted only in the formation of arylidene derivatives **13, 14**. The formation of these products is assumed to proceed via elimination of active methylene moiety from the initially formed adduct. Similar elimination in reactions of **10** with active methylene compounds has been recently observed[10,11]. The structure of the formed products was elucidated, besides their correct elemental and spectral analysis, by their formation from 4-formylantipyrine **1** and the active hydrogen compounds, **11** and **12**.

Although trials for reaction of dimedone with **10** was un successful, it reacted with 4-formylantipyrine **1** in the ratio of 2:1 to give a condensation product for which structure **15** was suggested based on elemental and spectral analyses. Trials to affect ring closure of **15** to give **16** failed under a variety of different conditions.

4-Cyanoacetamidoantipyrine **17** reacted with arylidenes and heterocyclidene acetophenone **18** to yield the 2-pyridone derivatives **21**. This was obtained through an acylclic intermediate **19**, which cyclized and then aromatized to give the isolable products **21**.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1100 spectrophotometer. The ^{1}H-NMR spectra were measured on a Bruker AC 250 FT spectrometer using TMS as an internal standard and chemical shifts are expressed as ppm. Mass spectra were recorded on a Varian MAT 311 A spectrometer. The microanalyses were performed by the microanalytical unit at Cairo University.

α-(4-Antipyrinyl)-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides 3:

To a powdered mixture of each of β-aroylpropionic acid **2** (0.01 mol) and freshly fused CH_3COONa (0.01 mol), 4-formylantipyrine (0.01 mol) and 3 ml freshly distilled $(CH_3CO)_2O$ were added. The reaction mixture was heated on a boiling water bath till a yellow solid separated (≈ 2 h). The obtained solid product was triturated with alcohol, filtered off and then recrystallized from acetic acid.

4-Antipyrinylmethyl-6-aryl-3(2H) pyridazinones 5:

To a suspension of the butenolide **3** (1 g) in ethanol (20 ml), hydrazine hydrate (2 ml) and conc.HCl (1 ml) were added. The reaction mixture was heated under reflux for 1 h and then cooled. The product, so formed, was filtered off, washed with water and then recrystallized from ethanol.

4-(4'-Antipyrinylazo)-3-methyl-1-phenyl-5-pyrazolone 8:

To a mixture of the hydrazone **7** (0.01 mol) in alcohol (20 ml), was added phenylhydrazine (0.01 mol). The mixture was refluxed for 2 h and then cooled. The product, so formed, was collected by filtration and recrystallized from ethanol. Yield 80% M.p. 200°C.

Preparation of Arylidenes 13a,b and 14a,b:

a) Reaction of cinnamonitriles 10 with active hydrogen containing compounds:

To a suspension of each of the cinnamonitriles **10** (0.01 mol) in absolute ethanol (20 ml) containing 1 ml triethylamine, each of the active hydrogen compounds viz : thiosemicarbazide, isonicotic acid hydrazide, cyanoacetamide or 2-cyanomethyl-benzimidazole (0.01 mol) was added. The mixture was refluxed for 2 h and then cooled. The formed product was collected by filtration and crystallized from alcohol. [The m.p. of each of **13a,b** gave no depression when a sample was admixed with an authentic specimen prepared by reaction of 4-formylantipyrine and each of **11a,b**[12]]. For experimental data for compounds **14a,b** (cf. Table 1 and Table 2).

b) Reaction of 4-formylantipyrine (1) with active hydrogen containing compounds:

To a suspension of 4-formylantipyrine (0.01 mol) in ethanol (20 ml) containing 1 ml triethylamine, **11a,b** or **12a,b** (0.01 mol), was added. The mixture was refluxed for 2 h. After cooling, the product was filtered off and then recrystallized from ethanol to give **13a,b** or **14a,b** (the melting points were undepressed when admixed with samples prepared by method a).

Reaction of 1 with dimedone:

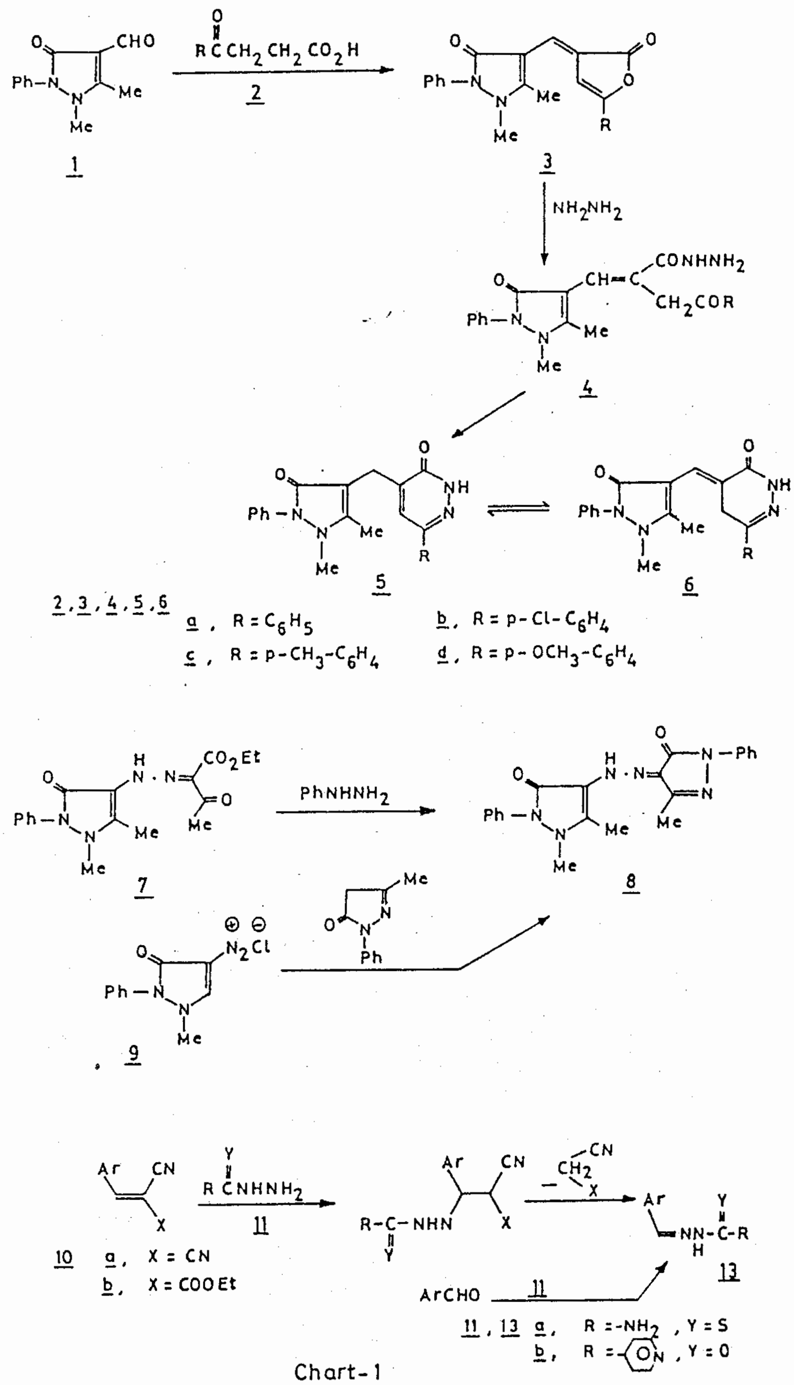
To a suspension of 4-formylantipyrine **1** (0.01 mol) in alcohol (30 ml) containing 1 ml conc. HCl, was added dimedone (0.02 mol). The mixture was refluxed for 10 minutes and then cooled. The formed solid was collected by filtration and then recrystallized from ethanol-water, to give **15**.

Reaction of cyanoacetamidoantipyrine 17 with chalcones 18:

To a suspension of each of **18** (0.005 mol) in absolute ethanol (20 ml), cyanoacetamidoantipyrine **17** (0.005 mol) and 0.5 ml of triethylamine were added. The reaction mixture was refluxed for 5 h then cooled. The solid product, so formed, was collected by filtration and recrystallized from DMF to give compounds **21**.

Acknowldgement

The authors wish to express their thanks to DANIDA for the support throughout the work.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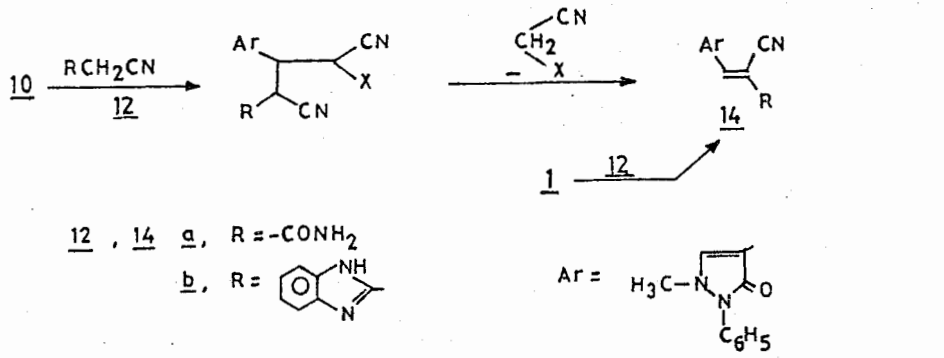
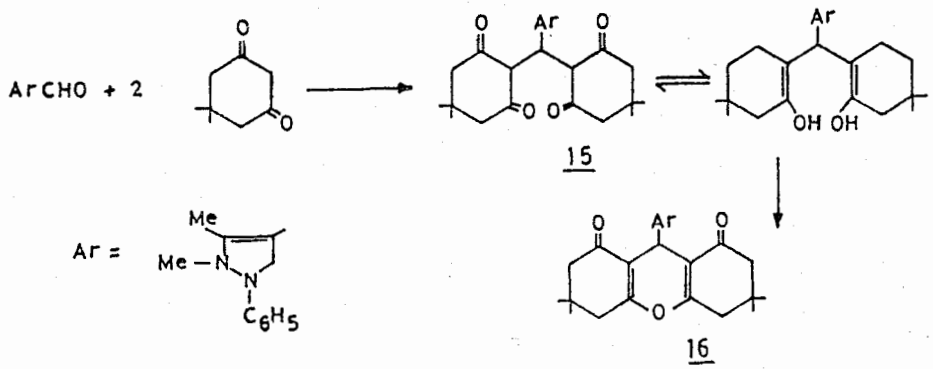
Ph-N
Me
1
RCCH2CH2CO2H
2
3
NH2NH2
CONHNH2
CH2COR
4
5
6
2,3,4,5,6 a, R = C6H5
b, R = p-Cl-C6H4
c, R = p-CH3-C6H4
d, R = p-OCH3-C6H4
CO2Et
7
PhNHNH2
8
N2Cl
9
Ar CN
10 a, X = CN
b, X = COOEt
RCNHNH2
11
R-C-NHN
ArCHO
NN-C-R
13
11, 13 a, R = -NH2, Y = S
b, Y = O

Chart-1





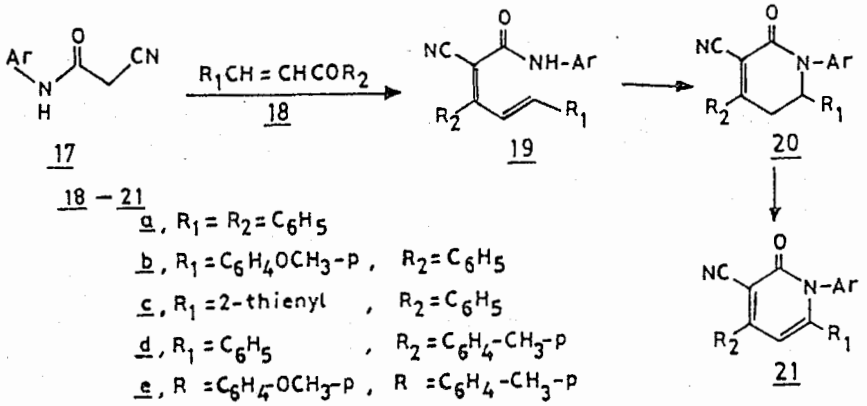


Chart - 2

Table 1: Experimental data for the newly synthesized compounds.

Comp. No.	Mol. form. Mol wt.	M.p.* °C	Yield %	% Analysis (Calcd./Found) C	H	N
3a	$C_{22}H_{18}N_2O_3$ (358.40)	250a	56	73.7 73.0	5.0 5.0	
3b	$C_{22}H_{17}ClN_2O_3$ (392.84)	275a	51	67.3 67.8	4.3 4.3	7.1 7.1
3c	$C_{23}H_{20}N_2O_3$ (372.42)	260a	52	74.2 74.4	5.4 5.2	7.5 8.1
3d	$C_{23}H_{20}N_2O_4$ (388.72)	262a	51	71.1 70.8	5.2 4.8	
5a	$C_{22}H_{20}N_4O_2$ (372.53)	238b	78	71.1 71.0	5.3 5.5	
5b	$C_{22}H_{19}ClN_4O_2$ (406.87)	225b	73	64.9 64.6	4.7 4.4	
5c	$C_{23}H_{22}N_4O_2$ (386.55)	235b	55	71.5 72.0	5.7 6.0	
5d	$C_{23}H_{22}N_4O_3$ (402.45)	260b	60	68.6 68.2	5.5 5.2	
14a	$C_{15}H_{14}N_4O_2$ (282.30)	210c	61	63.8 63.4	5.0 5.3	19.8 20.0
14b	$C_{21}H_{17}N_5O$ (355.40)	180d	52	70.9 70.7	4.8 4.9	19.7 19.9
15	$C_{28}H_{32}N_2O_4$ (460.60)	200e	50	73.0 72.8	7.0 6.6	
21a	$C_{29}H_{22}N_4O_2$ (458.52)	230d	59	76.0 76.0	4.8 5.4	12.2 12.5
21b	$C_{30}H_{24}N_4O_3$ (488.54)	242d	78	73.7 73.2	5.9 5.5	11.4 11.0
21c	$C_{27}H_{20}N_4O_2S$ (464.53)	204d	63	69.8 69.1	4.3 4.9	12.1 12.5
21d	$C_{30}H_{24}N_4O_2$ (472.54)	213d	65	76.2 75.6	5.1 5.3	11.9 12.2
21e	$C_{31}H_{26}N_4O_3$ (502.57)	235d	60	74.0 73.5	5.2 5.8	11.1 10.8

* Crystallized from a = acetic acid, b = ethanol, c = chloroform, d = DMF, e = ethanol-water

Table 2: Spectral data of the newly synthesized compounds.

Comp. No.	MS (m/z) %	IR (cm^{-1})	^1H-NMR (ppm)
3a	358(M^+, 100)	1750 (C=O), 3000 (C=CH)	2.10 (s, CH_3), 3.13 (s, CH_3), 6.95-7.33 (m, 12H, 2xPh+2xCH).
3b	392 (M^+, 82)	1752 (C=O), 3000 (C=CH)	2.21 (s, CH_3), 2.53 (s, CH_3), 7.21-7.95 (m, 11H, arom.+2xCH).
3c	372 (M^+, 100)	1760 (C=O), 3000 (C=CH)	2.35 (s, CH_3), 2.55 (s, CH_3), 3.35 (s, CH_3), 7.25-7.85 (m, 11H, arom.+2xCH).
3d	388 (M^+, 100)	1640 (C=O), 3000 (C=CH)	2.25 (s, CH_3), 2.41 (s, CH_3), 3.40 (s, CH_3), 7.31-8.11 (m, 11H, arom.+2xCH).
5a	371 (M^+, 20)	1680 (C=O), 3250-3400(NH)	2.57 (s, CH_3), 3.55 (s, CH_3), 4.02 (sm, CH_2), 7.31-7.65 (m, 11H, arom.+CH).
5b	406 (M^+, 46)	1684 (C=O), 3250-3400(NH)	2.35 (s, CH_3), 3.40 (s, CH_3), 3.75 (s, CH_2), 7.20-7.85 (m, 10H, arom.+CH).
5c	386 (M^+, 74)	1685 (C=O) 3250-3400(NH)	2.45 (s, CH_3), 3.25 (s, CH_3), 3.80 (s, CH_2), 7.00-7.65 (m, 10H, arom.+CH).
5d	402 (M^+, 46)	1690 (C=O) 3250-3400(NH)	2.51 (s, CH_3), 3.35 (s, CH_3), 3.4 (s, CH_2), 7.31-7.85 (m, 10H, arom.+CH).
14a	282 (M^+, 70)	1650 (C=O) 2220 (CN)	2.45 (s, CH_3), 3.36 (s, CH_3), 7.34-7.81 (m, 8H, Ph, CH, NH_2).
14b	355 (M^+, 30)	1630 (C=O) 2220 (CN)	2.23 (s, CH_3), 2.55 (s, CH_3), 7.21-7.92 (m, 10H, arom.+CH).
15	460 (M^+, 100)	1650 (C=O) 3000 (C=CH)	0.91 (s, 2xCH_3), 1.02 (s, 2xCH_3), 2.51 (s, CH_3), 3.32 (s, CH_3), 2.9 (s, 2xCH_2), 4.22 (s, CH), 7.2-7.4 (m, 5H, Ph).
21a		2242 (CN), 1688 (C=O)	
21b	488 (M^+, 20)	2240 (CN) 1650 (C=O)	
21c	464 (M^+, 14)	2243 (CN), 1684 (C=O)	
21d	472 (M^+, 14)	2240 (CN)	
21e	502 (M^+, 18)	1684 (C=O)	

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تفاعلات مع الرابطة المزدوجة النشطة : تخليق ٤-مشتقات أنتيبيرين

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قسم الكيمياء - كلية العلوم - جامعة المنوفية - شبين الكوم - ج.م.ع

ملخص البحث :

يتفاعل ٤-فورميل أنتيبيرين مع الأحماض بيتا-أرويل بروبيونيك ليعطى بيوتينوليدات (٣) التى تتفاعل مع هيدرات الهيدرازين منتجة بيريدازينات (٥) . تم تحضير الهيدرازون (٨) بتكاثف (٧) مع الفينيل هيدرازين . عند إضافة السينامونيتريلات (١٠) إلى الجواهر المحتوية على ذرة الهيدروجين النشطة تعطى أريليدينات (١٣) ، (١٤) . تفاعل داى ميدون مع سينامونتريلات (١٠) بنسبة جزيئية ١:١ ليعطى مركب الإضافة (١٥) .

يتفاعل ٤-سيانو أسيتاميدوأنتيبيرين (١٧) مع الشالكونات (١٨) لتعطى مشتقات البيريدون (٢١) . وقد تم إثبات التركيب الكيميائى للمركبات الناتجة بالتحليل الدقيق وطيف الأشعة تحت الحمراء والرنين النووى المغناطيسى وكذا طيف الكتلة .