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SYNTHESIS OF SUBSTITUTED PHENYLAZOCOUMARIN RING BY CONDENSATION OF ACTIVATED NITRILES , 4-HYDROXY-5-PHENYLAZO SALICYLALDEHYDE AND KETONES BY MEANS OF AMMONIUM ACETATE

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تخليق مشتقات حلقة فينيل أزو كومارين بتكاثف النتريلات النشطة ، ٤ - هيدروكسى - ٥ - فينيل أزو ساليسالد هيد والكيتونات فى وجود خلات الامونيوم

الخلاصة: تم تحضير العديد من أريل أزو كومارين الجديدة من (٤-٩) بالتكاثف المباشر لسيانو أسيتاميد أو أثيل سيانو أسيتات مع ٥ - فينيل أزو - ٤ - هيدروكسى ساليسالد هايد والكيتونات فى وجود خلات الامونيوم .

Abstract- Several new arylazocoumarin (4-9)were prepared by the direct condensation of cyanoacetamide or ethyl cyanoacetate with 5-phenylazo-4-hydroxysalicylaldehyde and ketones in the presence of ammonium acetate.

1-Introduction

Previous papers have shown that pyran derivatives possess pronounced biological properties[1].On the other hand , substituted pyridines shows acricidal , insecticidal and herbicidal activities[2] . Moreover , pyrimidines are important analgesic and anti-inflammatory agents[3,4] . Compounds having a combination of benzopyran and pyridine and/or pyrimidine moieties can be expected to possess marked medicinal properties . Also , it has been reported that cresotolaldehyde condensed with malonitrile in presence of ammonium acetate afford substituted benzopyrano-3-carbonitrile derivatives[5] while naphthopyr anopyridopyrimidine derivatives were obtained from the condensation of malononitrile with 2-hydroxy-1-naphthaldehyde[6] .

As a continuation of this research program directed to prepare some new benzopyrane and naphthopyranopyridopyrimidine derivatives[5,6] , the present work deals with synthesis of some new arylazocyanocoumarinimide and/or brnzopyranopyridopyrimidine derivatives by the condensation of ethyl cyanoacetate and/or cyanoacetamid with , 5-arylazo-4-hydroxy salicylaldehyde and a variety of ketones in presence of ammonium acetate .

Phenyl diazonium salt (1) undergo a coupling reaction with 2,4-dihydroxybenzaldehyde (2) in ethanol containing sodium acetate to give 5-phenylazo -4-hydroxy salicylaldehyde (3). This dye has been characterized by elemental analysis as well as spectral analysis . When compound (3) was subjected to react with cyanoacetamide (equimolar ratio at RT. in ethanol and ammonium acetate (slight excess) gave 6-phenylazo -7-hydroxy-2-amino-3-coumarinamide derivative (4).

When 3 was heated with an excess of cyanoacetamide and ammonium acetate in ethanol ,6-phenylazo -7-hydroxy -3-cyanocoumarin was formed as the only main product (5). The same product was obtained when ethyl cyanoacetate was used instead of cyanoacetamide ,and the reaction was carried out under the same condition.

On the other hand , when the above reaction was carried out in the presence of a catalytic amount of TEA or piperidine instead of ammonium acetate , only compound (4) was formed as the main product . These facts are taken to indicate that in many cases in the present study the course of the reaction was markedly influenced by choice of the base catalyst . However , type (4) compound was formed under all conditions.

The infrared spectrum of (4) showed bands at 1680 ,1650,3450,3330 and 1555 cm $^{-1}$ characteristic for CO , C=N , NH2 , OH and -N=N- stretching respectively. While the IR spectrum of (5) revealed the presence of C≡N , C=N , OH and -N=N- absorption at 2220 , 1650 , 3350 and 1555 cm $^{-1}$ respectively .

The reaction of ethylcyanoacetate or cyanoacetamide and 5-phenylazo-4-hydroxy-salicylaldehyde (3) with ketones was carried out by heating for 2 hours, a mixtrue of nitrile , aldehyde ,ketone , and ammonium acetate (molar ratio 1:1:1:1-1.5) in ethanol. In this case ,the dehydration of the amio group of amidinocoumarinimide (6) and the carbonyl group of the ketones ,cyclization between the methyl or methylene group of the ketone and the 4-position of the coumarin ring , and subsequent dehydrogenation took place to form the product 8-arylazo-9-hydroxy-3-amino -5-phenyl pyrido [3,4-c] coumarin (7).The IR spectrum of (6) showed absorption bands in the 1640-1500 region , 3330,3250 and 1555 cm $^{-1}$ attributed to a hetero ring , OH , NH and -N=N- groups respectively , but did not show any band for the amino , groups.

The cyclization reaction in the present study ,therefore , can reasonably be explained in terms of a two-steps condensation . Nitriles and salicylaldehyde derivative condensed to give 3-cyanocoumarin,wich in turn converts readily to 3-amidinocoumarin (6).

Then , 3-amidinocoumarin condenses with ketones to give heterocyclic compounds of the type (7).

Reaction with cyclic ketone proceeded much as in the case of the reaction with the aromatic ketones described above. In this case ,cyclization occurred between the methylene group adjacent to the carbonyl group of the ketone and the 4-position of the coumarin ring to form 5-amino-9-hydroxy-10-phenylazo-6-oxo-7-oxabenz[f] -2,3-dihydro-1H-cyclopent[c] isoquinoline (8a) (from cyclopentanone) and 6-amino-10-hydroxy-11-phenylazo-7-oxo-8-oxa-1,2,3,4-tetrahydrobenzo[k] phenan- thridine (8b) (from cyclohexanone). These structures were supported by a study of the infrared and NMR spectra . The IR spectra showed bands at 3470-3350 , 3130,1710,1550 cm $^{-1}$ due to the presence of NH2 ,OH,CO,and -N=N- groups respectively , while the ^{1}H nmr spectrum of 8a (CF_3COOH) showed peaks at δ2.3-2.9(m,2H) , 3.1-3.9(m, 4H)and multiplets 7.5-8.5 due to aromatic protons respectively. The ^{1}H nmr spectrum of 10b showed bands at δ1.8-2.3 (br , 4H), 2.9-3.5 (br,4H) and multiplats at δ7.5-8.5 of the aromatic protons. Similarlly , Heating of (3) with *p*-(N,N-dimethylamino) benzaldehyde , aminonium acetate in ethanol for 2h , afforded 8-arylazo-9-hydroxy-5- p-(N,N-dimethylaminophenyl) pyrimidino[3,4-c] coumarine(9) in 35% yield.

Experimental

The details of obtianing analytical and spectral data are given in an earlier paper[7] .

2-Synthesis of 5-phenylazo-4-hydroxy salicylaldehyde (3a-h):

A well stirred solution of the base aromatic amine (0.1 mol) in 2N hydrochloric acid (125 ml) was cooled in an ice-salt bath and diazotized with 1N-sodium nitrite solution (100 ml).

The above cold diazonium solution was added slowly to a wellstirred solution of 2,4-dihydroxy benzaldehyde (0.1 mol) in ethanol (150 ml) containing 10% sodium acetate solution (50 ml) ,and the mixture was cooled in an ice-salt bath.

After the coupling reaction was complete , the reaction mixture was stirred for 15 min at room temperature to coagulate the dye particles . The crude product was filtered ,dried ,and recrystallized from ethanol to give red crystals of 5-phenylazo -4-hydroxysalicylaldehyde (3).(Table 1). IR spectra of compounds (3) showed bands at 3350 (OH) ,1710 (CO) and 1550 cm $^{-1}$ (-N=N-) respectively.

3-Reaction of cyanoacetamide with phenylazosalicylaldehyde derivative (3):

A mixture of cyanoacetamide (0.1 mol), aldehyde (3) and ammonium acetate (0.2 mol) in ethanol (20-30 ml) was left to stand at room temperature for 3 hr . Deep red crystals are precipitated and were collected and washed with ethanol to give 6-phenyl-7-hydroxy-2-imino-3-coumarinamide- derivative (4) (cf.Table 1). νmax 3350-3280 (OH,NH),1680 (CO), 1650 (C=NH) , 1550 cm-1(-N=N-).

The reaction mixture (nitriles , 0.35 mol ;3a , 0.1 mol; ammonium acetate , 0.2 mol) was heated for 2 hrs in ethanol it gave a deep red crystals of 6-phenylazo -7-hydroxy-3-cyanocoumarine (5). νmax 3350 (OH), 2220 (C ≡N) and 1555 cm $^{-1}$ (-N=N-). NMR ($CDCl_3$):
4.5(s,1H,OH) , 7.5-8.5 (m,7H,ArH).

When the latter reaction mixture was heated for 2 hr using a catalytic amount of TEA (5 drops) as a base medium instead of ammonium acetate to give (4) in 30 % yield , MS(m/z)M^+;290.

4-Reaction of nitriles , 3, and acetophenone :

To a mixture of nitriles (0.03 mol), phenylazosalicylaldehyde (3 , 0.03 mol), and acetophenone (0.03 mol) in ethanol (20 ml),ammonuim acetate (0.04 mol) was added and heated for 2 hr. The reaction mixture gave compound (7) in 60 % yield ; NMR ($CDCl_3$);4.1 (5, 2H , NH2) , 4.5 (s,1H,OH), 7.5-8.5 (m,12H-Ar-H). Carrying this reaction in ethanol (20 ml) and TEA (4 drops), the reaction mixture afforded (10 %) of 4 , (4%) of 6 and (6%) of 7 respectively. The IR spectrum of 6 gave bands I.R at 3420 , 3330 (NH2),3280 (NH),1650 (C=NH) and 1550 cm $^{-1}$ (-N=N-) ; MS(m/z):M^+-430.

5-Reaction of malononitrile , phenylazosalicylaldehyde and cyclic ketones:

A mix of nitriles (0.03 mol), 3(0.03 mol), cyclopentanone or cyclohexanone (0.03 mol) and ammonium acetate (0.034 mol) in ethanol was heated for 1 hr. A deep red crystals precipitated out during the reaction ;this was collected and recrystallized from ethanol -pyridine to afford 8a and 8b respectively .

6-Reaction of nitriles with aromatic aldehyde:

A mixture of 3 (0.1 mol) , P-(N,N-dimethylamino) benzaldehyde (0.1 mol) and ammonium acetate (0.15 mol) in ethanol (20 ml) was heated for 2hrs . The precipitated crystals were collected and recrystallized from ethanolpyridine to give 9 as deep red needless.(cf.table 1).

Table 1 : Characterization Data of the newly prepared compounds

Compound no.	Yield %	M.P °c	Mol.formula	Analysis, Calcd (found) C	H
3	61	156	$C_{13}H_{10}N_2O_3$	64.5 (64.4)	4.1 (4.0)
4	67	265	$C_{16}H_{11}N_3O_4$	66.5 (66.3)	3.7 (3.5)
5	60	240	$C_{16}H_9N_3O_3$	65.9 (65.6)	3.1 (3.0)
6	63	220	$C_{16}H_{12}N_4O_3$	62.3 (62.1)	3.9 (3.7)
7	66	275	$C_{24}H_{16}N_4O_3$	70.5 (70.3)	3.9 (3.9)
8a	70	300	$C_{21}H_{16}N_4O_3$	67.7 (67.5)	4.3 (4.1)
8b	62	280	$C_{22}H_{18}N_4O_3$	68.4 (68.1)	4.7 (4.5)
9	53	281	$C_{25}H_{20}N_5O_3$	68.5 (68.3)	4.6 (4.5)

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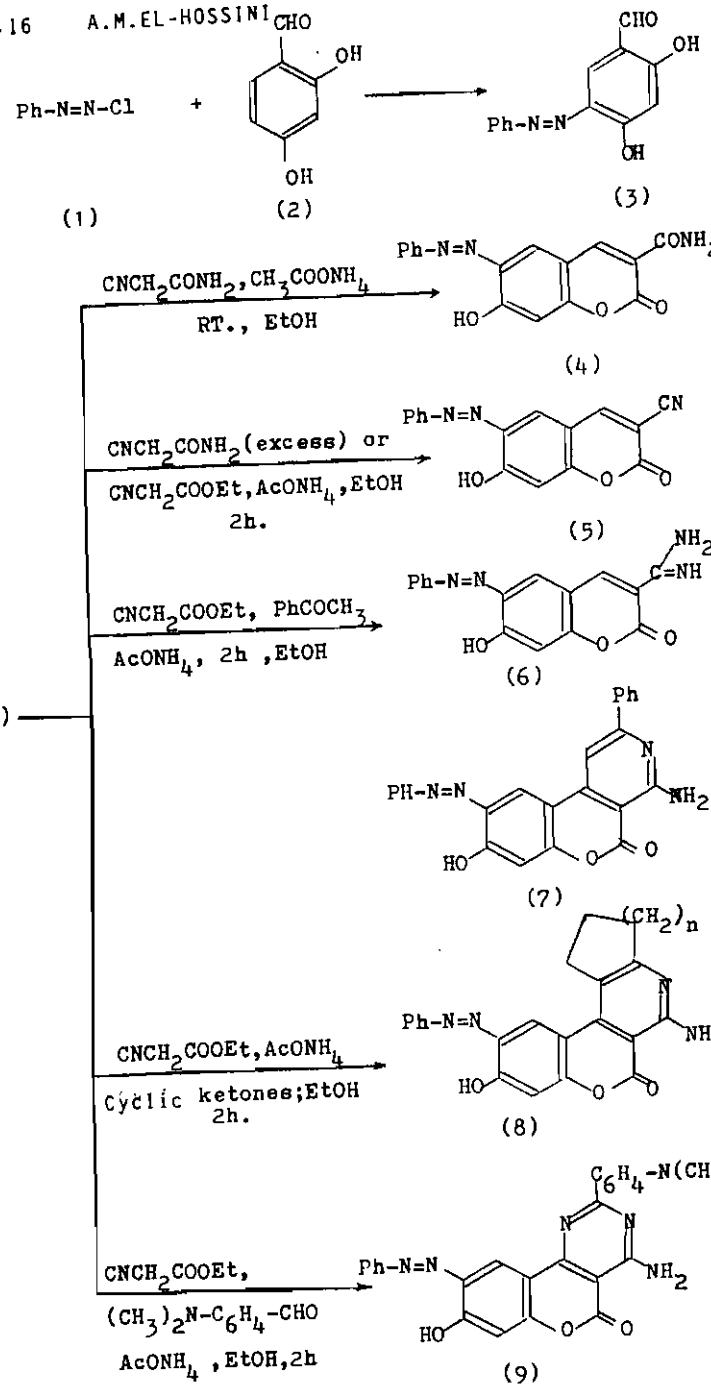
Ph-N=N-Cl
(1)
(2)
(3)
CNCH2CONH2, CH3COONH4
RT., EtOH
(4)
CNCH2CONH2(excess) or
CNCH2COOEt, AcONH4, EtOH
2h.
(5)
CNCH2COOEt, PhCOCH3
AcONH4, 2h, EtOH
(6)
(7)
CNCH2COOEt, AcONH4
Cyclic ketonee; EtOH
2h.
8a, n=1
8b, n=2
(8)
CNCH2COOEt,
(CH3)2N-C6H4-CHO
AcONH4, EtOH, 2h
(9)