SYNTHESIS OF 3-SUBSTITUTED-5-OXO-5H-[1]BENZOPYRANO[2,3-b]PYRIDINE DERIVATIVES

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Abstract ----- 3-Cyano-, 3-alkoxycarbonyl-, and 3-formyl-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine derivatives were prepared by reactions of 2-amino-4-oxo-4H-1-benzopyran-3-carboxaldehydes 1 with acetylene derivatives (methods A-C) or with reactive methylene compounds (methods D-E) and also by catalytic hydrogenation of 2-chloro-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carbonitriles 12 (method F).

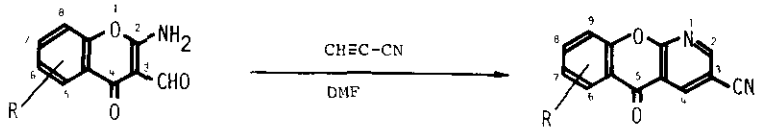
It has been reported that reactions of 2-amino-4-oxo-4H-1-benzopyran-3-carboxaldehyde 1a or 4-oxo-4H-1-benzopyran-3-carbonitriles with some reactive methylene compounds afford 2,3-di-substituted-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine derivatives.[1,2] However, there is no report on the synthesis of 3-substituted-5-oxo-5H-[1]benzopyrano[2,3-b]pyridines which carry no substituent at the 2-position. In this paper, the synthesis (methods A-F) of 3-cyano-, 3-alkoxycarbonyl- and 3-formyl-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine derivatives is described.

I Reaction of 2-amino-4-oxo-4H-1-benzopyran-3-carboxaldehydes 1 with acetylene derivatives (methods A-C)

5-Oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carbonitriles 2a-i were prepared by the following two methods : Method A is the reaction of 2-amino-4-oxo-4H-1-benzopyran-3-carboxaldehydes 1a-i with cyanoacetylene in DMF at 100°C for 1h and then at 140°C for 10h.: Method B is the reaction of 1c,d with α-chloroacrylonitrile in the presence of triethylamine in DMF at 120°C for 14h. In the case of method B, the intermediary adduct 3 was obtained. The adduct 3 afforded 2c in 65% yield on treatment with triethylamine in DMF at 120°C for 10h.

Ethyl 5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carboxylates 5a-d were prepared by the method C : A mixture of 1a,c,j, ethyl propiolate and triethylamine was heated in DMF at 90°C

for 40 min to afford the intermediate, aminoacrylates 4, (a, mp 201-203°C, 39%, b, mp 201-203° C, 52%, c, mp 228-230°C(dec), 29%) which on treatment with triethylamine in DMF at 130°C for 2.5h afforded 5a,b,d. In some cases, the compound 5 could be directly obtained from 1 without isolation of the aminoacrylate 4 as exemplified by the case of 5c (chart 1).

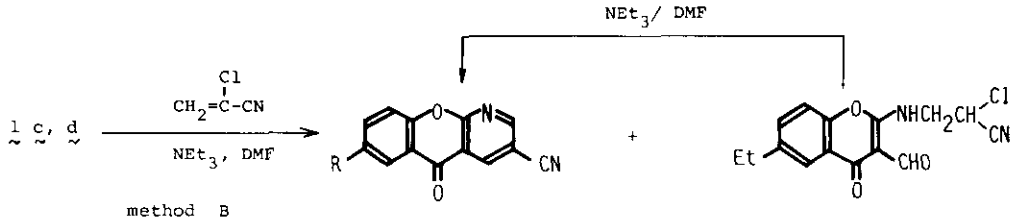


1

a: R= H f: R= 6,8-Me_2
b: R= 6-Me g: R= 6-Cl
c: R= 6-Et h: R= 6-i-PrO
d: R= 6-i-Pr i: R= 8-MeO
e: R= 6-t-Bu

2

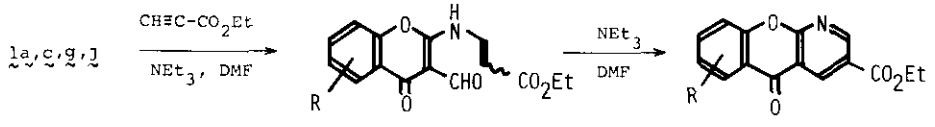
a: R= H f: R= 7,9-Me_2
b: R= 7-Me g: R= 7-Cl
c: R= 7-Et h: R= 7-i-PrO
d: R= 7-i-Pr i: R= 9-MeO
e: R= 7-t-Bu



2

c: R=Et
d: R=i-Pr

3



j: R=5,6-⟨

4

a: R= H
b: R= 6-Et
c: R= 5,6-⟨

5

a: R= H
b: R= 7-Et
c: R= 7-Cl
d: R= 6,7-⟨

Chart 1

II Reaction of 2-amino-4-oxo-4H-1-benzopyran-3-carboxaldehydes 1 with reactive methylene compounds (methods D-E)

When 2-amino-4-oxo-4H-1-benzopyran-3-carboxaldehydes 1a-d,g were treated with cyanoacetyl chloride or methyl malonyl chloride generated in situ by the reaction of cyanoacetic acid or malonic acid monomethyl ester with PCl_5 in CH_2Cl_2, in DMF at 60°C for 3h, 5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carbonitriles 2a-d,g or methyl 7-ethyl-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carboxylate 6 were prepared, respectively (chart 2, method D). To investigate the reaction mechanism, the following experiments were carried out. The reaction of 1c with cyanoacetyl chloride in CH_2Cl_2 at reflux for 2h gave the acylamino derivatives 7 (mp 170-175°C, 40%) which on treatment with pyridine at 80°C for 3h afforded the 3-cyano-2-hydroxy compound 8a (mp > 300°C, 55%). Treatment of 1c with cyanoacetyl chloride in diethylformamide or N-formylmorpholine at 65°C for 2h also gave 2c in 22 and 32% yield, respectively . However, when the reaction was carried out in formamide 2c was not obtained. A plausible mechanism to account for the above mentioned discrepancy can be depicted as shown in chart 3.

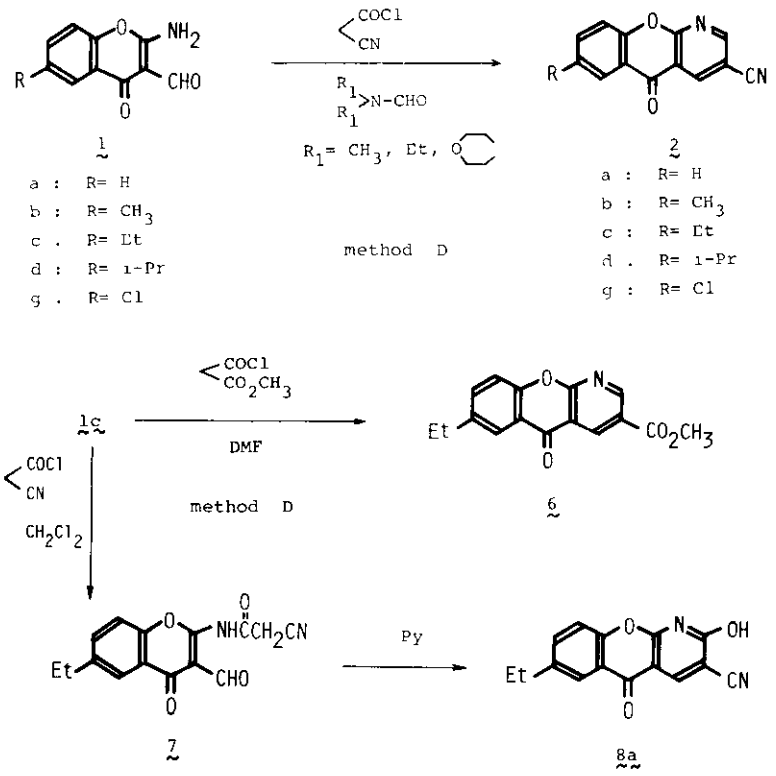


Chart 2

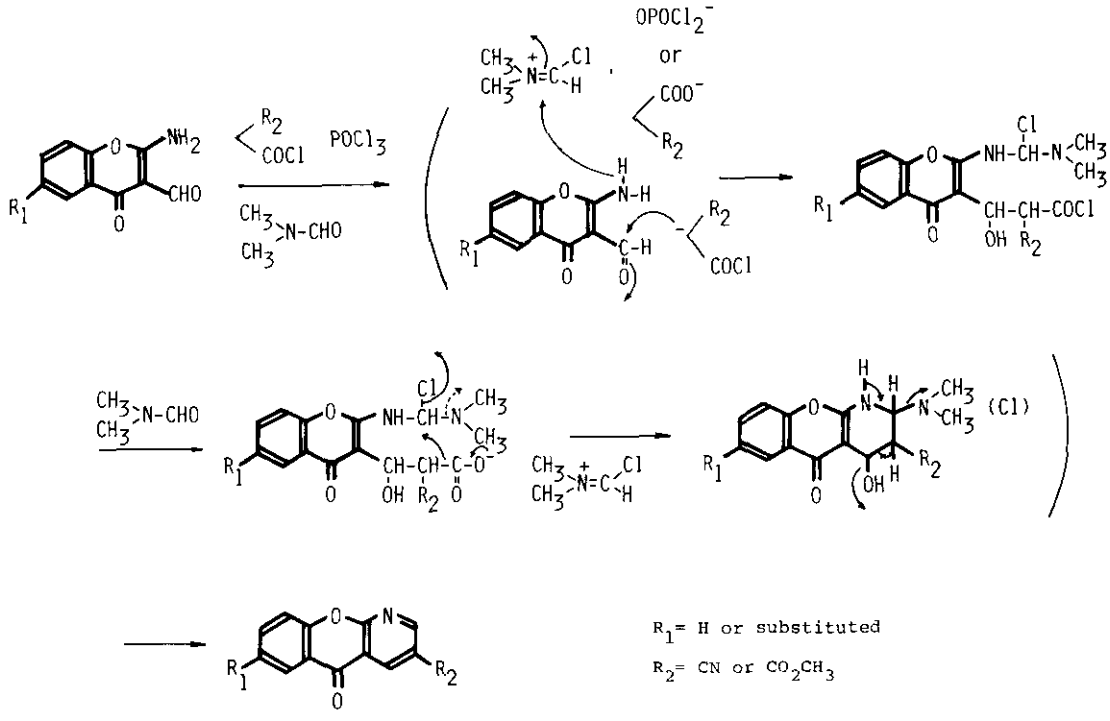
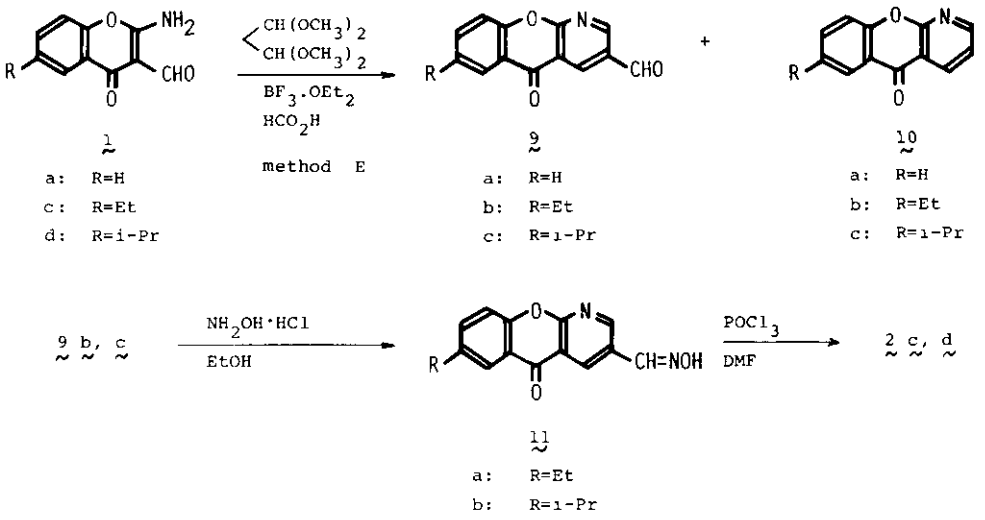


Chart 3

5-Oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carboxaldehydes 9a-c were synthesized by the method E (chart 4) : 9a-c were yielded by heating a mixture of 1a,c,d and malonaldehyde bis-(dimethylacetal) in boron trifluoride etherate containing formic acid at 60°C for 2h together with a small amount of the deformylated compounds 10a[3]-c[4]. The oximes 11 (a: mp 250-252°C, 93%, b: mp 247-249°C, 95%) which were obtained by treatment of 9b,c with hydroxylamine hydrochloride, were treated with $POCl_3$ in DMF at room temperature for 0.5h to give the nitriles 2 (c, 55%, d, 86%).



1
a: R=H
c: R=Et
d: R=i-Pr

9
a: R=H
b: R=Et
c: R=i-Pr

10
a: R=H
b: R=Et
c: R=i-Pr

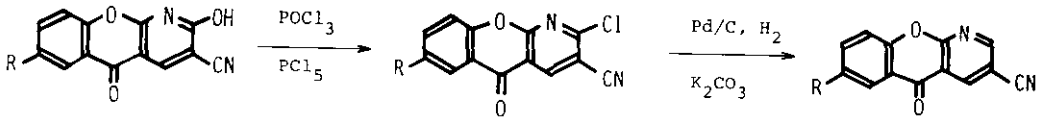
9 b, c → 11 → 2 c, d

11
a: R=Et
b: R=i-Pr

Chart 4

III Catalytic hydrogenation of 2-chloro-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carbonitriles (method F)

2-Hydroxy-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carbonitriles 8a,b[5] were converted to the 2-chloro compounds 12 (a, mp 233-234°C, 76%, b, mp 242-243°C, 74%) by the treatment with $POCl_3$-PCl_5 at 120°C for 2h. Catalytic hydrogenation of 12a,b over 5% Pd-C in the presence of K_2CO_3 in DMF at room temperature gave 2c,d (chart 5, method F).



8
a: R= Et
b: R= i-Pr

12
a: R= Et
b: R= i-Pr

method F

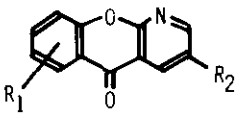
2
c: R= Et
d: R= i-Pr

Chart 5

3-Substituted-5-oxo-5H-[1]benzopyrano[2,3-b]pyridines which were synthesized by the above mentioned processes (methods A-F), are shown in Table I.

Table I

3-Substituted-5-oxo-5H-[1]benzopyrano[2,3-b]pyridines

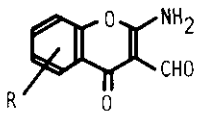


compd	R_1	R_2	mp °C	recrystn solvent	yield(%)	method
2a	H	CN	220-226	EtOH	32	A
					39	D
2b	7-Me	CN	240-242	AcOEt	30	A
					44	D
2c	7-Et	CN	183-185	CH_3CN	28	A
					33	B
					49	D
					76	F
2d	7-i-Pr	CN	203-205	EtOH	36	A
					35	B
					52	D
					72	F
2e	7-t-Bu	CN	247-249	CH_3CN	38	A
2f	7,9-Me_2	CN	254-257	CH_3CN	47	A
2g	7-Cl	CN	286-288	DMF	30	A
					41	D
2h	7-i-PrO	CN	259-261	$CHCl_3$-CH_3CN	23	A
					6	D
2i	9-MeO	CN	> 300	DMF	33	A
5a	H	CO_2Et	139-140	MeOH	49	C
5b	7-Et	CO_2Et	140-142	EtOH	62	C
5c	7-Cl	CO_2Et	176-177	EtOH	46	C
5d	6,7-⟨	CO_2Et	186-188	Me_2CO	53	C
6	7-Et	CO_2Me	156-157	MeOH	36	D
9a	H	CHO	220-222	CH_3CN	10	E
9b	7-Et	CHO	175-178	CH_3CN	31	E
9c	7-i-Pr	CHO	211-213	i-Pr_2O	18	E

The starting materials, 2-amino-4-oxo-4H-1-benzopyran-3-carboxaldehydes (1a-j), were synthesized from 4-oxo-4H-1-benzopyran-3-carbonitriles[6] by the modified method of the reference 1), i.e. in the presence of morpholine in DMF-H_2O at 60°C for 2h (Table II).

Table II

Conversion of 4-oxo-4H-1-benzopyran-3-carbonitriles into 2-amino-4-oxo-4H-1-benzopyran-3-carboxaldehydes 1



compd	R	mp °C	recrystn solvent	yield(%)
1a	H	252-255 (dec)	AcOH	70
		248-250 (dec)	EtOH	59[1]
1b	6-Me	282-284 (dec)	AcOH	69
1c	6-Et	246-249 (dec)	acetone	71
1d	6-i-Pr	206-208	AcOH	65
1e	6-t-Bu	240-242	AcOH	64
1f	6,8-Me_2	259-263 (dec)	AcOH	61
1g	6-Cl	308-310 (dec)	AcOH	67
1h	6-i-PrO	218-219	$CHCl_3$	60
1i	8-MeO	235-238	$CHCl_3$	68
1j	5,6-	258-260	AcOH	62

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References and Notes

1) U.Petersen and H.Heitzer, Liebigs Ann.Chem. 1976, 1659.

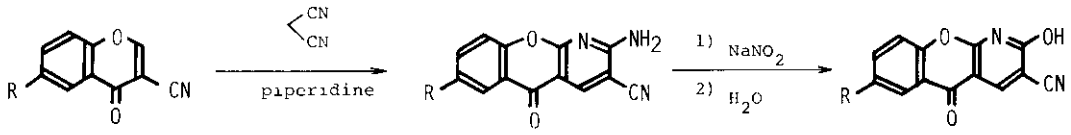
2) C.K.Ghosh, D.K.SinhaRoy and K.K.Mukhopadhyay, J.Chem.Soc.Perkin I, 1979, 1964 ; C.K.Ghosh, Synthetic Commun., 1978, 8, 487.

3) F.G.Mann and J.H.Turnbull, J.Chem.Soc., 1951, 761.

4) 10a[3], mp 187-188°C, 4%, 10b, mp 96-97°C, 3%, 10c, mp 101-102°C, 12%.

5) Compounds 8a,b were prepared by the following method : treatment of 13a,b with malononitrile in the presence of piperidine in EtOH at refluxing for 2.5h[2] afforded the aminonitriles 14 (a, mp>300°C, 92%, b, mp>300°C, 87%), which on reaction with $NaNO_2$ in

CF_3CO_2H for 1.5h followed by hydrolysis with H_2O gave 8 (a, mp>300°C, 60%, b, mp>300°C, 82%).



13

a: R= Et
b: R= i-Pr

14

a: R= Et
b: R= i-Pr

8

a: R= Et
b: R= i-Pr

6) A.Nohara, H.Kuriki, T.Saijo, H.Sugihara, M.Kanno and Y.Sanno, J.Med.Chem., 1977, 20, 141.

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