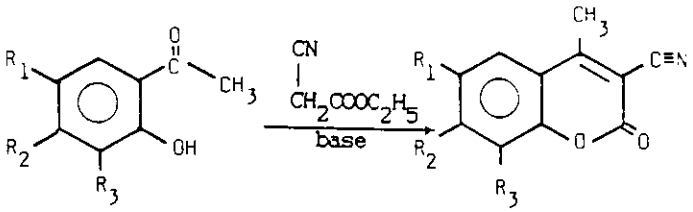
SYNTHESIS AND REACTIONS OF SOME 3-CYANO-4-METHYLCOUMARINS

Hassan M. F. Madkour

Chemistry Department, Faculty of Science, Ain Shams University, Cairo, A. R. Egypt

Abstract- o-Hydroxy ketones (I) were converted into 3-cyano-4-methylcoumarins (II) *via* condensation with ethyl cyanoacetate in presence of piperidine or ammonium acetate as a catalyst. The behavior of compound (II) towards Grignard and Michael reactions was investigated. The reactions of 3-acetylcoumarin (III) with hydrazines under different conditions were carried out to give the hydrazone (IV a), phenylhydrazone (IV b) and pyrazole (V) derivatives. Also, the 4-styryl derivatives (VI) were obtained by condensation of II with different aromatic and heterocyclic aldehydes. A one pot synthesis of Michael product (VII) from the reaction of VI with malononitrile was described.

The condensation of an equimolar amount of 5-chloro-2-hydroxyacetophenone, 5-methyl-2-hydroxyacetophenone, 2-acetyl-1-naphthol and 2-acetyl-4-bromo-1-naphthol and ethyl cyanoacetate in presence of a basic catalyst such as piperidine or ammonium acetate afforded the 4-methyl-3-cyanocoumarins (II a-d) respectively.[1] The coumarin (IIa) is prepared by just stirring of the reaction mixture at room temperature whereas other coumarins (II b-d) can be obtained by refluxing the reaction mixture in benzene containing acetic acid and ammonium acetate.

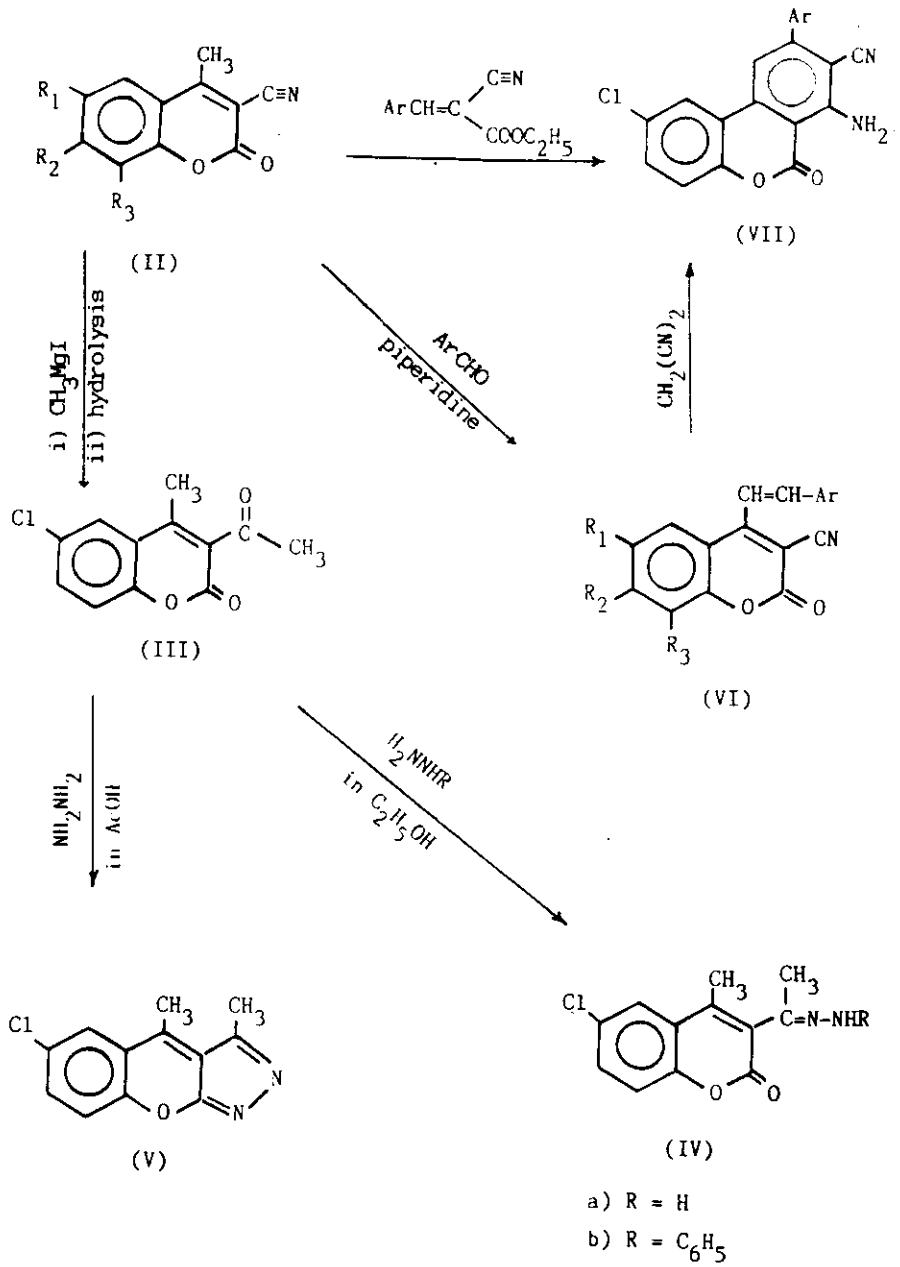


(I) (II)

	R_1	R_2	R_3
a)	Cl	H	H
b)	CH_3	H	H
c)	H	-CH=CH-CH=CH-	
d)	Br	-CH=CH-CH=CH-	

The ir spectra of II a-d exhibited well defined absorption bands at 2220-2240* and 1730-1740 attributable to ν CN and ν CO of coumarin. The ^{1}H-nmr of IIa showed the following signals at δ 7.30-7.80 (m, 3H, ArH) and 2.80 (s, 3H, CH_3). Also, the ^{1}H-nmr of IIc showed the following signals at δ 2.20 (s, 3H, CH_3) and 7.60-8.50 (m, 6H, ArH). The mass spectrum of compound (IIb) exhibited the molecular ions with m/z 199 which is the parent peak corresponding to the molecular ion M^+, 173 (19) attributable to $[M-CN]^+$, 134 (18) due to $[M-CH_3C{\equiv}C-CN]^+$ and 65 (17) attributed to $[CH_3C{\equiv}CCN]^+$. The author extends this work by the conversion of cyano group of the cyanocourmarin (IIa) into acetyl function by treatment of Grignard reagent. The reaction of IIa with methylmagnesium iodide[2] gave 3-acetyl-6-chloro-4-methylcoumarin (III) in 58% yield. Ir spectrum of III showed characteristic absorption bands at 1760 and 1730 attributable to ν CO of acetyl and ν CO of coumarin. The ^{1}H-nmr of III has the following signals at

* In cm^{-1} throughout the paper


(II)
(VII)
(III)
(VI)
(V)
(IV)
i) CH_3MgI
ii) hydrolysis
ArCHO
piperidine
$CH_2(CN)_2$
NH_2NH_2
in AcOH
H_2NNHR
in C_2H_5OH
a) R = H
b) R = C_6H_5

Scheme 1

δ 1.50 (s, 3H, $COCH_3$), 2.60 (s, 3H, $CH_3C=C-$) and 7.00-7.50 (m, 3H, ArH). The author tends to study the relative reactivity of the carbonyl group at position 3 and that of coumarin nucleus at position 2.[3] Thus, the condensation of compound (III) with hydrazine hydrate or phenylhydrazine in boiling ethanol produced a hydrazone or a phenylhydrazone (IV a,b), respectively. The ir of IV displayed absorption bands attributable to ν CO of coumarin at 1685-1675, ν C=N at 1640-1630, ν NH_2 (doublet) at 3480 and 3410 (for IV a), ν NH at 3450 (for IV b). The ^{1}H-nmr of compound (IV b) exhibited the following signals at δ 2.65 (s, 6H, $2CH_3$), 3.60 (s, 1H of NH) and 7.25- 7.80 (m, 8H, ArH).

While 3-acetyl-6-chloro-4-methylcoumarin (III) was allowed to react with hydrazine hydrate in boiling glacial acetic acid, a pyrazole derivative (V) was obtained.[2] The ir of the product (V) showed bands at 1620 (ν C=N) and 1590 (ν C=C) with disappearance of ν C=O of acetyl group and ν C=O of coumarin. The ^{1}H-nmr of compound (V) exhibited signals at δ 2.50 (s, 6H, 2 CH_3) and 7.20-7.90 (m, 3H ArH).

Condensation of 3-cyano-4-methylcoumarins (II a-c) with aromatic or heterocyclic aldehydes in presence of piperidine[4,5] yielded 3-cyano-4-styrylcoumarins (VI a-m) (see Table 2). The ir of the styryl derivatives showed strong absorption bands at 2220-2240, 1700-1730, 1590-1620, and 1100-1150 due to ν C≡N, ν CO of coumarin, ν C=C and ν -O- , respectively.

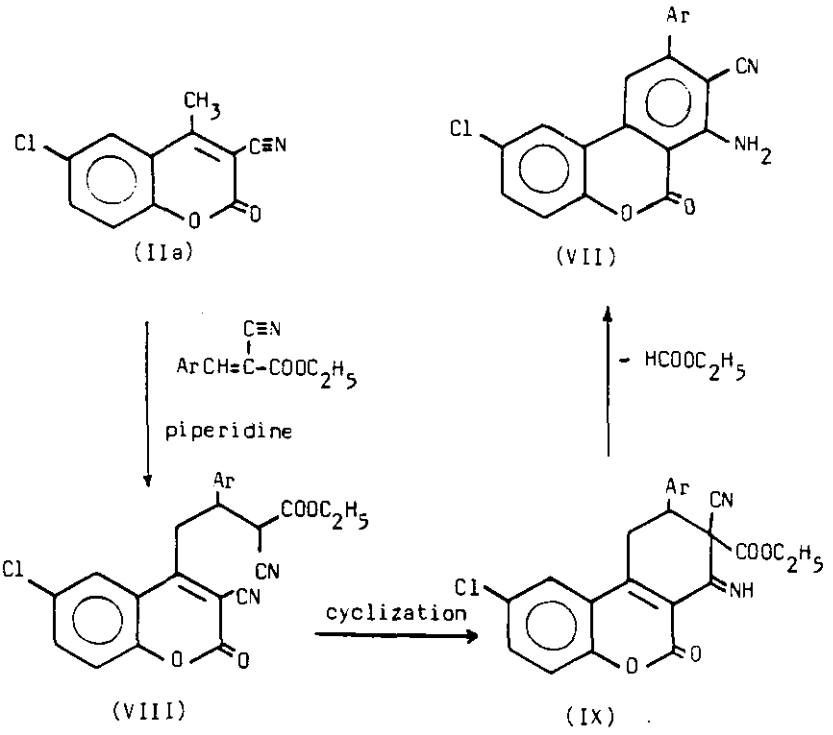
The mass spectrum of VIb showed characteristic molecular ions with m/z values followed by % of abundance : 342(M^+, 54), 341(M^+-1, 100), 315(M^+-HCN, 96), 137(M^+-C_8H_6Cl, 56). The M+2 peak is (67%) relative to the molecular ion peak, M+3 (9.9) and M+4 (1.7). The intensity 67% of the M+2 peak demonstrates that two chlorine atoms are in the structure which

agreed well with the proposed structure. The ^{1}H-nmr spectrum of VI f displayed the following signals at δ 2.68 (s, 3H, CH_3, attached to the benzene nucleus), 3.18(s, 3H, OCH_3), 6.27 (d, J= 9 Hz, 1H, CH_3-C$_6$H$_4$-CH=CH-), 6.50(d, J= 9 Hz, 1H, CH_3O-C$_6$H$_4$-CH=CH-). and at 6.68-7.21 (m, 7H, ArH). Also, the ^{1}H-nmr of VI j showed the following signals at δ 6.70 (d, J= 8 Hz, 1H, -CH=CH-C$_6$H$_5$), 7.10 (d, J= 8 Hz, 1H, -CH=CH-C$_6$H$_5$) and at 7.80-8.30 (m, 11H, ArH).

Benzo[c]coumarin derivatives (VII a-e) are easily obtainable by refluxing of cyanocoumarin (IIa) with arylidenecyanoacetate in ethanol containing few drops of piperidine.[4] The structures given for compounds (VII a-e) were elucidated from their analytical data together with their ir and mass spectra. The ir spectra showed absorption bands at 3400 and 3300, 2220-2200, 1720-1700 and 1600-1590 cm^{-1} attributable to ν NH_2 which appears as two bands due to NH asymmetric and NH symmetric stretching, ν CN, ν CO of coumarin and ν C=C respectively.

The mass spectrum of VI b showed the following molecular ions with m/z values followed by % of abundance: 381 (M^+, 26), 380 (M^+-1, 100) and 382 (M^++1, 68). The M+2 peak is (66.5 %) relative to the molecular ion peak, M+3 (9.6) and M+4 (1.7). The intensity of the M+2 peak illustrates that two chlorine atoms are in the structure assigned.

The formation of the product (VII) probably proceed *via* Michael addition pathway of the reactive methyl function of II to the highly activated double bond of the arylidenecyanoacetate to yield the open chain Michael adduct (VIII) which underwent cyclization to give the cyclic intermediate (IX). The latter is assumed to proceed elimination of carboethoxy group to afford the final isolated product (VIII).



The compounds (VII a-e) were also obtained by heating of the styryl derivatives (VI a-e) with malononitrile in boiling ethanol containing a catalytic amount of piperidine. The formation of VII a-e on the reaction of VI a-e with malononitrile is a satisfying chemical evidence for the structure assigned to the products (VII a-e).

EXPERIMENT

All melting points reported are uncorrected. Ir spectra were recorded on a Beckmann IR-20 and Pye Unicam spectrophotometers using KBr Wafer technique. The ^{1}H-nmr spectra were determined on a Varian T-60 using TMS as the internal standard and $CDCl_3$ as a solvent and all chemical shifts are in

ppm downfield from TMS. The mass spectra were recorded on a AEL MS-902 mass spectrometer at 70 eV. The physical data of new synthesised products are listed in Tables 1-3.

Reaction of o-Hydroxyketones with Ethyl Cyanoacetate; Synthesis of 3-Cyano-4-methylcoumarins (II a-d):

Method (A): Formation of IIa

A mixture of 5-chloro-2-hydroxyacetophenone (Ia) (1.70 g, 0.01 mol), ethyl cyanoacetate (0.81 g, 0.01 mol) and piperidine (0.5 ml) was stirred for 1 h at room temperature. The reaction mixture was poured onto hydrochloric acid (50 ml; 1 N) and the solid was collected by filtration, washed with water, dried and finally recrystallized from ethanol to afford IIa (1.90 g, 87 %).

Method (b): Formation of II b-d:

A solution of the appropriate ketone (0.01 mol) and cyanoacetate (0.81 g, 0.01 mol) in benzene (100 ml) containing ammonium acetate (2.00 g, 26 mmol) and acetic acid (2.00 ml) was refluxed for 6 h using a water separator. The solution was cooled, the II b-d were precipitated, collected by filtration as white crystalline solid which was recrystallized from the proper solvent.

Reaction of 6-Chloro-3-cyano-4-methylcoumarin (II a) with Methylmagnesium Iodide:

Formation of 3-Acetyl-6-chloro-4-methylcoumarin (III):

An ethereal solution of II a (2.199 g, 0.01 mol) was added dropwise to methylmagnesium iodide (5.00 g, 0.03 mol) in dry ether (100 ml) within 15 min. The reaction mixture was refluxed on a water bath for 4 h then poured into HCl (50 ml; 1N) and the solid material that deposited was collected

by filtration and recrystallized to give III (1.37 g, 58 %).

Reaction of III with Hydrazines; Formation of IV:

A solution of acetylcoumarin (III) (2.35 g, 0.01 mol) and hydrazine hydrate (0.64 g, 0.02 mol) or phenylhyrazine (2.16 g, 0.02 mol) in ethanol (50 ml) was refluxed for 4 h. The reaction mixture was left to cool, then poured onto HCl (30 ml; 1 N) and the solid separated out was collected by filtration, washed with water, dried and recrystallized to give the hydrazone or phenylhydrazone (IV a,b) respectively.

Reaction of 3-Acetyl-6-chloro-4-methylcoumarin (III) with Hydrazine Hydrate, in Glacial Acetic Acid; Formation of the Pyrazole Derivative (V):

A solution of acetylcoumarin (III) (2.35 g, 0.01 mol) and hydrazine hydrate (0.96 g, 0.03 mol) in glacial AcOH (30 ml) was refluxed for 6 h. The reaction mixture was allowed to cool down, then poured into water. The solid that deposited was collected, dried and finally recrystallized, to yield V (1.65 g, 72%).

Condensation of 3-Cyano-4-methylcoumarins (II a-d) with Aldehydes; Synthesis of 4-Styrylcoumarins (VI a-m):

A mixture of an equimolar of 3-cyano-4-methylcoumarin (0.01 mol) and the appropriate aldehyde (0.01 mol) and few drops of piperidine in ethanol (30 ml) or dimethylformamide (20 ml) (for VI f-m) was heated under reflux for 2 h (for VI a-e) or heated for 4 h on a water bath at 100°C (for VI f-m). The condensation products which separated upon cooling were collected and recrystallized from the proper solvent to give the 4-styryl derivatives (VI)

Reaction of 6-Chloro-3-cyano-4-methylcoumarin (IIa) with Arylidenencyano-acetate Derivatives; Synthesis of Benzo[c]coumarins (VII a-c):

A solution of cyanocoumarin (IIa) (2.19 g, 0.01 mol) and arylidenecyanoacetate derivatives (0.01 mol) in ethanol (30 ml) containing few drops piperidine was refluxed for 3 h. Most of the solvent was distilled off, and the solid was collected and recrystallized.

Effect of Malononitrile on 4 Styryl Derivatives (VI a-e) Formation of Benzo[c]coumarin (VII a-e):

Malononitrile (1.32 g, 0.02 mol) was added to the styryl derivative (VI) (0.015 mol) together with few drops of piperidine in ethanol (30 ml). The reaction mixture was refluxed for 2 h and the solids obtained after concentration were collected, washed with ethanol and finally recrystallized from suitable solvent to give the benzo[c]coumarin derivatives (VII a-e).

Table 1: Physical data of synthesised products (II-v)

Compd No.	R_1	R_2	R_3	Crystallization Solvent (% yield)	mp° C		Analysis Found/Calcd(%) C	H	N
IIa	Cl	H	H	E (87)	187-189	$C_{11}H_6NO_2Cl$	60.34	2.60	6.22
							60.14	2.73	6.38
IIb	CH_3	H	H	E (79)	202-204	$C_{12}H_9NO_2$	72.50	4.90	7.21
							72.36	4.52	7.03
IIc	H	-CH=CH-CH=CH-		T (74)	282-283	$C_{15}H_9NO_2$	76.84	4.00	5.75
							76.59	3.82	5.95
IId	Br	-CH=CH-CH=CH-		E (72)	205-207	$C_{15}H_8NO_2Br$	57.11	2.71	4.19
							57.37	2.54	4.45
III				E (58)	120-122	$C_{12}H_9O_3Cl$	60.77	3.72	-
							60.86	3.80	-
IVa				E (84)	200-201	$C_{12}H_{11}N_2O_2Cl$	57.60	3.45	11.07
							57.49	3.39	11.18
IVb				E (76)	255-256	$C_{18}H_{15}N_2O_2Cl$	66.03	4.50	8.65
							66.16	4.59	8.58
V				B (72)	225-227	$C_{12}H_9N_2OCl$	61.86	3.80	11.96
							61.94	3.84	12.02

Table 2: Physical data of synthesised products (VI a-m)

Compd No.	R_1	R_2	R_3	Ar	Crystallization Solvent (% yield)	mp°C		Analysis Found/Calcd(%) C	H	N
VIa	Cl	H	H	3,4-$OCH_2OC_6H_3$	B (83)	296-298	$C_{19}H_{10}NO_4Cl$	64.39	3.01	4.03
								64.49	2.84	3.98
VIb	Cl	H	H	p-ClC_6H_4	B (94)	302-303	$C_{18}H_9NO_2Cl_2$	63.16	2.72	4.20
								63.32	2.63	4.10
VIc	Cl	H	H	p-$CH_3OC_6H_4$	B (92)	243-244	$C_{19}H_{12}NO_3Cl$	67.37	3.65	4.10
								67.56	3.55	4.15
VId	Cl	H	H	p-BrC_6H_4	B (90)	311-313	$C_{18}H_9NO_2BrCl$	55.68	2.39	3.76
								55.89	2.33	3.62
VIe	Cl	H	H	2-furyl	B (85)	220-222	$C_{16}H_8NO_3Cl$	68.21	2.96	5.12
								68.11	2.84	4.97
VIf	CH_3	H	H	p-$CH_3OC_6H_4$	A (88)	223-225	$C_{20}H_{15}NO_3$	76.66	5.01	4.33
								76.70	4.73	4.41
VIg	CH_3	H	H	p-ClC_6H_4	DMF(89)	294-296	$C_{19}H_{12}NO_2Cl$	70.73	3.81	4.42
								70.91	3.73	4.35
VIh	CH_3	H	H	2-thienyl	A (76)	175-177	$C_{17}H_{11}NO_2S$	69.81	3.66	4.61
								69.62	3.75	4.77
VIi	CH_3	H	H	2-furyl	A (72)	360	$C_{17}H_{11}NO_3$	73.82	3.81	5.27
								73.64	3.47	5.05

Table 2: (cont.)

VIj	H	-CH=CHCH=CH-	C_6H_5	DMF(70)	269-270	$C_{22}H_{13}NO_2$	81.55	4.21	4.03
							81.73	4.02	4.33
VIk	H	-CH=CHCH=CH-	p-$CH_3OC_6H_4$	DMF(68)	272-273	$C_{23}H_{15}NO_3$	78.42	4.37	3.81
							78.18	4.25	3.96
VIl	H	-CH=CHCH=CH-	2-thienyl	A (72)	248-250	$C_{20}H_{11}NO_2S$	72.50	3.58	4.48
							72.44	3.34	4.25
VIm	H	-CH=CHCH=CH-	2-naphthyl	DMF(66)	284-286	$C_{26}H_{15}NO_2$	83.81	3.97	3.62
							83.65	4.02	3.75

Table 3: Physical data of synthesised products (VI a-m)

Compd No.	Ar	Crystallization Solvent(% yield)	mp°C		Analysis Found/Calcd(%) C	H	N
VIIa	3,4-$OCH_2OC_6H_3$	B (81)*	312	$C_{12}H_{11}N_2O_4Cl$	64.46	2.84	7.12
					64.53	2.82	7.17
VIIb	p-ClC_6H_4	B (93)	313-315	$C_{20}H_{10}N_2O_2Cl_2$	63.19	2.62	7.32
					62.99	2.62	7.35
VIIc	p-$CH_3OC_6H_4$	B (85)	287-288	$C_{21}H_{13}N_2O_3Cl$	67.07	3.39	7.39
					66.93	3.45	7.44
VIId	p-BrC_6H_4	B (91)	311	$C_{20}H_{10}N_2O_2BrCl$	56.62	2.28	6.67
					56.54	2.36	6.66
VIIe	2-furyl	B (79)**	260-262	$C_{18}H_9N_2O_3Cl$	64.34	2.55	8.12
					64.19	2.67	8.32

* Yields are based on reaction II with arylidenecyanoacetate.

** E= ethanol, T= toluene B= benzene, DMF= dimethylformamide, A= acetone

REFERENCES

1. C. H. Schroeder and K. P. Link, J. Am. Chem. Soc., 1953, 75, 1886.

2. A. A. Hamed, A. I. Hashem, M. A. Salem, and H. F. Madkour, Egypt. J. Chem., 1986, 29, 89.

3. A. Sammour, M. I. Selim, and M. El-Kady, Egypt. J. Chem., 1971, 14, 261.

4. E. A. Hafez, M. H. Elnagdi, A. A. Elagamey, and F. M. El-Taweel, Heterocycles, 1987, 26, 903.

5. D. R. Shridhar, C. V. Reddy Sastry, N. K. Vaidya, S. R. Moorty, G. S. Reddi and G. S. Thapar, Indian J. Chem., 1978, 16, 704.

Received, 22nd April, 1992