[Chem. Pharm. Bull. 32(9)3384—3395(1984)]

Synthesis and Reactions of 6-Aryl- and 6-Styryl-3-cyano-4-methylthio-2*H*-pyran-2-ones

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(Received December 22, 1983)

The reaction of various types of acetyl compounds with a ketene dithioacetal, methyl 2-cyano-3,3-bis(methylthio)acrylate, in the presence of potassium hydroxide gave the corresponding 6-aryl- and 6-styryl-3-cyano-4-methylthio-2*H*-pyran-2-one derivatives. The methylthio group on the pyrone ring reacted readily with nucleophiles such as amines, active methylene compounds and methoxy anion to yield the corresponding displacement products in good yields.

Keywords——ketene dithioacetal; methyl 2-cyano-3,3-bis(methylthio)acrylate; 2*H*-pyran-2-one; 4-amino-2*H*-pyran-2-one; 4-methoxy-2*H*-pyran-2-one; displacement reaction

It is now well known that the ketene dithioacetal derivatives are very useful reagents for the preparation of heterocyclic compounds.[1] We have also recently reported the synthesis of a number of heterocyclic compounds by the application of ketene dithioacetals.[2] The present paper deals with the synthesis of 2*H*-pyran-2-one derivatives by the reaction of various types of acetyl compounds with a ketene dithioacetal, methyl 2-cyano-3,3-bis(methylthio)acrylate (**1**), and the reaction of their pyrones with nucleophiles.

We have recently reported the reaction of acetophenones with 2-nitro-1,1-bis(methylthio)ethene, giving 1-benzoyl-3-nitro-2-methylthio-1-propenes in good yields.[3] In the present investigation, we applied this reaction to the formation of 2*H*-pyran-2-one derivatives. Namely, reaction of acetophenone (**2a**) with **1** in the presence of powdered potassium hydroxide in *N,N*-dimethylformamide (DMF) gave 3-cyano-3-methylthio-6-phenyl-2*H*-pyran-2-one (**3a**) in 48% yield. In the same manner, 3-cyano-4-methylthio-6-(4-methoxy, 4-bromo, 4-chloro, 3,4-dimethoxy, and 3,4-methylenedioxy)phenyl-2*H*-pyran-2-ones (**3b**, **c**, **d**, **e**, and **f**) were obtained in good yields, as shown in Table I. Other 6-heteroaryl-2*H*-pyran-2-ones (**3g**, **h**, and **i**) were also synthesized from the corresponding heterocyclic acetyl compounds (3-acetylpyridine, 2-acetylquinoline, and 2-acetylthiophene) in a manner similar to that used for the preparation of **3a**. The above synthesis should be generally useful for the preparation of 6-aryl-2*H*-pyran-2-ones. Compounds **3f** and **3g** have the basic skeletons of paracotoin and anibine, respectively.

Next, the reaction of benzylideneacetone (**2j**) with **1** under similar conditions gave a 5,6-dehydrokawain derivative, 3-cyano-4-methylthio-6-styryl-2*H*-pyran-2-one (**3j**) in 35% yield. The nuclear magnetic resonance (NMR) spectrum of **3j** showed signals due to two protons of the ethenyl group at 6.28 ($J=16$ Hz) and 7.70 ($J=16$ Hz) ppm. Therefore, **3j** was assigned the *trans* configuration. Similarly, the reaction of other benzylideneacetone derivatives [4-methoxybenzylideneacetone (**2k**), 4-chlorobenzylideneacetone (**2l**)] with **1** also afforded 6-styryl-2*H*-pyran-2-ones (**3k** and **l**) in 43 and 45% yields, respectively. When the reaction time was short and the reaction mixture was treated with hydrochloric acid solution, **1** and **2j** were partly recovered and yellow crystals with mp 158 °C were obtained. On the bases of the spectroscopic data and elemental analysis (see Experimental), the isolated compound was

determined to be 3-cyano-4-methylthio-6-(2-phenyl-2-methylthio)ethyl-2*H*-pyran-2-one (**4**), which would be formed by the addition of a methanethiol group to the ethenyl group.

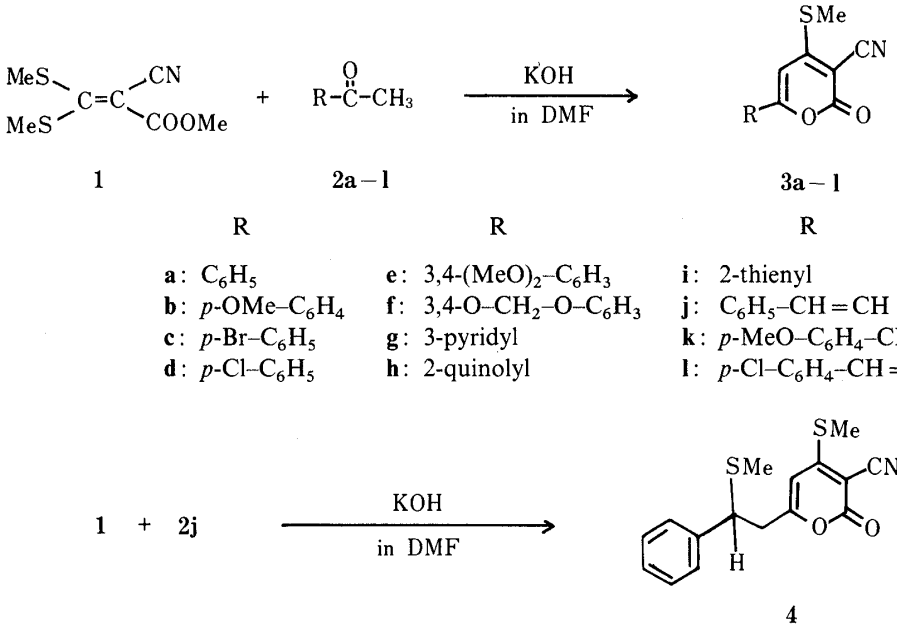


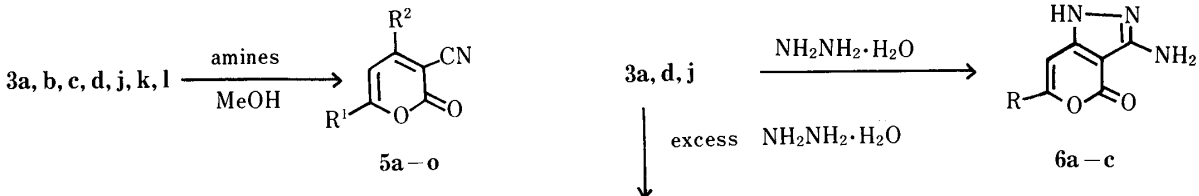
Chart 1

Recently, we reported that the reaction of condensed 4-methylthio-2*H*-pyran-2-one derivatives with nucleophiles such as amines and active methylene compounds gave the products resulting from replacement of the methylthio group by the nucleophiles in good yields.[4]

Various 4-hydroxy-2*H*-pyran-2-ones and their ethers, which have a variety of pharmacological properties, have been synthesized and tested for biological activities.[5] We attempted the synthesis of 4-amino-6-phenyl- and 4-amino-6-styryl-2*H*-pyran-2-ones because of their pharmacological potential (antibacterial activity and antifungal activity). The reaction of **3** with amines (benzylamine, phenethylamine, piperidine, morpholine, dimethylamine, monoethanolamine) in methanol gave the corresponding 4-amino-2*H*-pyran-2-one derivatives (**5a**, **b**, **c**, **d**, **e**, **f**, **g**, **h**, **i**, **j**, **k**, **l**, **m**, **n**, and **o**) in good yield. On the other hand, the reaction of **3a** with hydrazine hydrate in methanol afforded 3-amino-1,4-dihydro-4-oxo-6-phenylpyrano[4,3-*c*]pyrazole (**6a**) in 64% yield. Similarly, **6b** and **6c** were obtained from **3d** and **3j** in 95 and 21% yields, respectively. Compound **3a** was allowed to react with an excess of hydrazine hydrate, giving 3,5-diamino-4,5-dihydro-4-oxo-6-phenyl-1*H*-pyrazolo[4,3-*c*]-pyridine (**7**) in 20% yield. The structures of all these condensed pyrazoles were supported by the spectral and analytical data (see Experimental).

Reaction of **3** (**a**, **c**, **e**, **j**, and **l**) with dimethyl malonate or diethyl malonate in the presence of potassium carbonate in DMF gave displacement products (**8a**, **b**, **c**, **d**, **e**, and **f**) of the methylthio group in **3** in good yields. When **3** was reacted with methyl cyanoacetate in a manner similar to that used for the preparation of 8,3-substituted 6,8-dihydroxy-5-methoxycarbonyl-1-oxo-1*H*-pyrano[3,4-*c*]pyridines (**9a** and **b**) were obtained in 75 and 67% yields, respectively. The use of ethyl acetoacetate instead of methyl cyanoacetate as a nucleophile in the above reaction gave 5-ethoxycarbonyl-8-hydroxy-6-methyl-3-phenyl-1-oxo-1*H*-pyrano[3,4-*c*]pyridine (**9c**) in 55% yield.

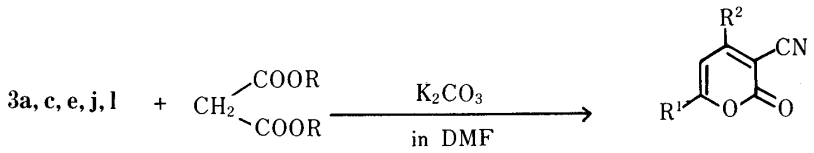
Compound **3** (**a**, **b**, **f**, **j**, and **k**) was treated with sodium methoxide in methanol to give the corresponding 4-methoxy-6-phenyl- or 4-methoxy-6-styryl-2*H*-pyran-2-one derivatives (**10a**, **b**, **c**, **d**, and **e**) in good yields. These methyl ether compounds should be very useful intermedi-



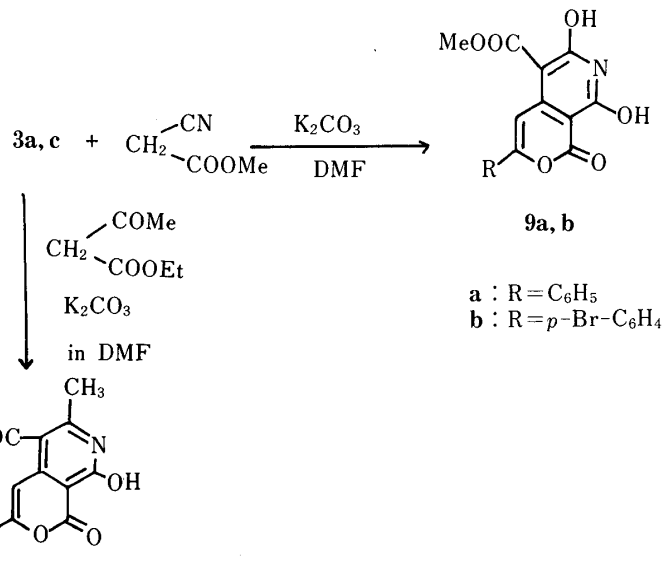
	R^1	R^2
a:	C_6H_5	benzylamino
b:	C_6H_5	phenethylamino
c:	C_6H_5	piperidino
d:	C_6H_5	morpholino
e:	C_6H_5	dimethylamino
f:	*p*-MeO–C_6H_4	phenethylamino
g:	*p*-MeO–C_6H_4	morpholino
h:	*p*-Cl–C_6H_4	cyclohexylamino
i:	*p*-Br–C_6H_4	piperidino
j:	C_6H_5–CH=CH	benzylamino
k:	C_6H_5–CH=CH	morpholino
l:	C_6H_5–CH=CH	cyclohexylamino
m:	C_6H_5–CH=CH	ethanolamino
n:	*p*-MeO–C_6H_4–CH=CH	benzylamino
o:	*p*-MeO–C_6H_4–CH=CH	morpholino

a : R = C_6H_5
b : R = *p*-Cl–C_6H_4
c : R = C_6H_5–CH=CH

Chart 2

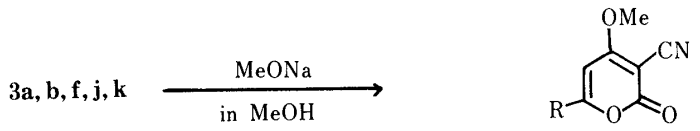


	R^1	R^2
a:	C_6H_5	$CH(COOMe)_2$
b:	*p*-Br–C_6H_4	$CH(COOMe)_2$
c:	3,4-$(MeO)_2$–C_6H_3	$CH(COOEt)_2$
d:	C_6H_5–CH=CH	$CH(COOMe)_2$
e:	*p*-Cl–C_6H_4–CH=CH	$CH(COOMe)_2$
f:	*p*-Cl–C_6H_4–CH=CH	$CH(COOEt)_2$



a : R = C_6H_5
b : R = *p*-Br–C_6H_4

Chart 3



10a—e

R

a: C_6H_5
b: *p*-MeO–C_6H_4
c: 3,4-O–CH_2–O–C_6H_3
d: C_6H_5–CH=CH
e: *p*-MeO–C_6H_4–CH=CH

Chart 4

ates for the preparation of natural 2*H*-pyran-2-one derivatives.

Experimental

All melting points were determined in a capillary tube and are uncorrected. Infrared (IR) spectra were recorded in KBr pellets on a JASCO IRA-2 spectrometer, ultraviolet (UV) absorption spectra were determined on a Hitachi EP-S2 spectrometer in 95% EtOH, and NMR spectra were obtained with a JNM-PS-100 (100 MHz) spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS-01SG double-focusing mass spectrometer.

General Method for the Preparation of 6-Aryl- and 6-Styryl-3-cyano-4-methylthio-2*H*-pyran-2-ones (3a—l)——A mixture of 0.01 mol of an acetyl compound (acetophenone, 4-methoxyacetophenone, 4-bromoacetophenone, 4-chloroacetophenone, 3,4-dimethoxyacetophenone, 3,4-methylenedioxyacetophenone, 3-acetylpyridine, 2-acetylquinoline, 2-acetylthiophene, benzylideneacetone, 4-methoxybenzylideneacetone, or 4-chlorobenzylideneacetone), 0.01 mol of methyl 2-cyano-3,3-bis(methylthio)acrylate (**1**),[1a] 0.02 mol of powdered KOH, and 50 ml of DMF was stirred at room temperature for 6 h. The rection mixture was poured into 300 ml of ice-water and the whole was stirred at room temperature for 4—5 h. The yellow precipitates that appeared were collected by filtration, washed with water and recrystallized from C_6H_6–MeOH or MeOH to give the corresponding 2*H*-pyran-2-one.

3-Cyano-4-methylthio-6-(2-phenyl-2-methylthio)ethyl-2*H*-pyran-2-one (4)——A mixture of 1.46 g (0.01 mol) of benzylideneacetone, 2.03 g (0.01 mol) of **1**, 1.12 g (0.02 mol) of powdered KOH, and 50 ml of DMF was stirred at room temperature for 30 min. The reaction mixture was poured into 300 ml of 10% HCl and the whole was stirred at room temperature for 4 h. The brown gummy product that appeared was collected by decantation and washed with 30 ml of MeOH; it crystallized to give 0.062 g (20%) of yellow prisms. An analytical sample was recrystallized from MeOH to give yellow prisms, mp 158 °C. The MeOH washing solution contained the starting materials (**1** and benzylideneacetone) and other products. IR ν(KBr) cm^{-1}: 2200 (CN), 1715 (C=O). UV λ_{max}^{EtOH} nm (log ε): 235 (4.22), 303 (4.12), 350 (4.06). NMR ($CDCl_3$) δ: 1.87 (3H, s, SMe), 2.44 (3H, s, SMe), 3.00 (2H, d, J=8 Hz, CH_2–), 4.13 (1H, t, J=8 Hz, –CH<), 5.92 (1H, s, 5-H), 7.29 (5H, s, phenyl-H). MS *m/e*: 309 (M^+). *Anal.* Calcd for $C_{16}H_{15}NO_2S_2$: C, 60.56; H, 4.77; N, 4.41; S, 20.21. Found: C, 60.44; H, 4.64; N, 4.29; S, 19.90.

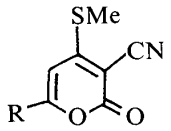
4-Amino-3-cyano-2*H*-pyran-2-ones (5a—o)——A mixture of 0.01 mol of **3** (**a**, **b**, **c**, **d**, **j**, **k**), 0.015 mol of an amine (benzylamine, phenethylamine, piperidine, morpholine, dimethylamine, cyclohexylamine, or monoethanolamine), and 100 ml of MeOH was refluxed on a boiling water bath for 2 h. After removal of the solvent, the residue was recrystallized from MeOH to give the corresponding amine derivative.

3-Amino-1,4-dihydro-4-oxo-6-phenylpyrano[4,3-*c*]pyrazole (6a)——A mixture of 2.43 g (0.01 mol) of **3a**, 1 g (0.02 mol) of hydrazine hydrate, and 50 ml of MeOH was refluxed for 1 h. After evaporation of the solvent and excess hydrazine, the residue was recrystallized from MeOH to give 1.45 g (64%) of yellow needles, mp 233 °C. IR ν(KBr) cm^{-1}: 3400, 3300 (NH), 1710 (C=O). UV λ_{max}^{EtOH} nm (log ε): 236 (4.26), 300 (4.17), MS *m/e*: 227 (M^+, 100). *Anal.* Calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.32; H, 3.92; N, 18.43.

3-Amino-6-(4-chlorophenyl)-1,4-dihydro-4-oxopyrano[4,3-*c*]pyrazole (6b)——This compound was synthesized in 95% yield, from **3d** and hydrazine hydrate in a manner similar to that used for the preparation of **6a**. An analytical sample was recrystallized from MeOH to give yellow needles, mp 274 °C. IR ν(KBr) cm^{-1}: 3400, 3300 (NH), 1715 (C=O). UV λ_{max}^{EtOH} nm (log ε): 240 (4.26), 303 (4.21). *Anal.* Calcd for $C_{12}H_8ClN_3O_2$: C, 55.08; H, 3.08; N, 16.06. Found: C, 55.15; H, 3.00; N, 15.98.

3-Amino-1,4-dihydro-4-oxo-6-styrylpyrano[4,3-*c*]pyrazole (6c)——This compound was synthesized in 21% yield, from **3j** and hydrazine hydrate in a manner similar to that used for the preparation of **6a**. An analytical sample was recrystallized from C_6H_6–MeOH to give yellow needles, mp 253 °C. IR ν(KBr) cm^{-1}: 3340 (NH), 1715 (C=O). UV λ_{max}^{EtOH} nm (log ε): 260 (4.12), 302 (3.89). *Anal.* Calcd for $C_{14}H_{11}N_3O_2$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.17; H,

TABLE I. 6-Substituted 3-Cyano-4-methylthio-2*H*-pyran-2-ones



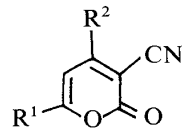
No.	R	Yield (%)	mp (°C)	Recryst. solvent	Appearance	Formula	Analysis (%) Calcd (Found)			
							C	H	N	S
3a	C_6H_5	48	201	MeOH	Yellow needles	$C_{13}H_9NO_2S$	64.20	3.73	5.76	13.16
							(63.93	3.76	6.02	12.98)
3b	*p*-MeO–C_6H_4	35	215	MeOH–C_6H_6	Yellow needles	$C_{14}H_{11}NO_3S$	61.54	4.06	5.31	11.73
							(61.59	3.82	5.10	11.69)
3c	*p*-Br–C_6H_4	42	230	MeOH–C_6H_6	Yellow needles	$C_{13}H_8BrNO_2S$	48.44	2.48	4.34	9.98
							(48.71	2.58	4.00	10.36)
3d	*p*-Cl–C_6H_4	44	240	MeOH–C_6H_6	Yellow needles	$C_{13}H_8ClNO_2S$	56.22	2.90	5.04	11.55
							(56.04	2.73	5.01	11.58)
3e	3,4-$(MeO)_2$–C_6H_3	40	221	MeOH–C_6H_6	Yellow needles	$C_{15}H_{13}NO_4S$	59.40	4.32	4.62	10.57
							(59.68	4.41	4.46	10.30)
3f	3,4-O–CH_2–O–C_6H_3	55	266	MeOH–C_6H_6	Yellow needles	$C_{14}H_9NO_4S$	58.54	3.16	4.88	10.52
							(58.43	3.11	4.87	10.49)
3g	3-Pyridyl	58	192	MeOH	Yellow needles	$C_{12}H_8N_2O_2S$	59.01	3.30	11.47	13.13
							(59.38	3.22	11.53	12.56)
3h	2-Quinolyl	47	240	MeOH	Yellow needles	$C_{16}H_{10}N_2O_2S$	66.29	3.42	9.52	10.89
							(65.97	3.38	9.52	10.74)
3i	2-Thienyl	44	253	MeOH–C_6H_6	Yellow needles	$C_{11}H_7NO_2S_2$	52.99	2.83	5.62	25.72
							(52.77	2.73	5.56	25.71)
3j	C_6H_5–CH=CH	35	221	MeOH	Yellow needles	$C_{15}H_{11}NO_2S$	66.91	4.12	5.20	11.88
							(66.79	4.00	5.34	12.11)
3k	*p*-MeO–C_6H_4–CH=CH	43	255	MeOH–C_6H_6	Orange needles	$C_{16}H_{10}NO_3S$	64.21	4.38	4.64	10.69
							(64.39	4.30	4.81	10.61)
3l	*p*-Cl–C_6H_4–CH=CH	45	261	MeOH–C_6H_6	Yellow needles	$C_{15}H_{10}ClNO_2S$	59.30	3.32	4.61	10.59
							(59.37	3.43	4.56	10.50)

TABLE I. (continued)

No.	IR ν(KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)		NMR δ (ppm)
3a	2200 (CN) 1715 (C=O)	239 (4.05), 255 (4.22), 332 (4.29), 368 (4.23)	C+T (1:1)	2.82 (3H, s, SMe), 7.15 (1H, s, 5-H), 7.52—7.76 (3H, m, 3′,4′,5′-H), 7.84—7.99 (2H, m, 2′,6′-H)
3b	2200 (CN) 1715 (C=O)	250 (4.21), 342 (4.28), 395 (4.45)	T	2.79 (3H, s, SMe), 3.99 (3H, s, OMe), 7.09 (1H, s, 5-H), 7.15 (2H, dd, J=1, 8 Hz, 3′,5′-H), 7.99 (2H, dd, J=1, 8 Hz, 2′,6′-H)
3c	2200 (CN) 1715 (C=O)	243 (4.03), 262 (4.18), 337 (4.33), 372 (4.26)	T	2.81 (3H, s, SMe), 7.18 (1H, s, 5-H), 7.40 (2H, d, J=8 Hz, 3′,5′-H), 7.95 (2H, d, J=8 Hz, 2′,6′-H)
3d	2200 (CN) 1720 (C=O)	243 (4.07), 261 (4.23), 336 (4.34), 371 (4.27)	C+T (1:1)	2.73 (3H, s, SMe), 6.86 (1H, s, 5-H), 7.58 (2H, dd, J=1, 8 Hz, 3′,5′-H), 7.91 (2H, dd, J=1, 8 Hz, 2′,6′-H)
3e	2190 (CN) 1710 (C=O)	225 (4.19), 249 (4.14), 355 (4.16), 402 (4.39)	T	2.84 (3H, s, SMe), 4.04 (6H, s, OMe), 7.12 (1H, s, 5-H), 7.16 (1H, d, J=8 Hz, 5′-H), 7.61 (1H, d, J=1.5 Hz, 2′-H), 7.70 (1H, dd, J=1.5, 8 Hz, 6′-H)
3f	2200 (CN) 1710 (C=O)	228 (4.13), 251 (4.12), 360 (4.14), 402 (4.21)	T	2.80 (3H, s, SMe), 6.08 (2H, s, O–CH_2–O), 6.97 (1H, d, J=8 Hz, 5′-H), 7.12 (1H, s, 5-H), 7.61 (1H, d, J=1.5 Hz, 2′-H), 7.70 (1H, dd, J=1.5, 8 Hz, 6′-H)
3g	2200 (CN) 1720 (C=O)	247 (4.16), 327 (4.24), 365 (4.10)	T	2.88 (3H, s, SMe), 7.50 (1H, s, 5-H), 8.34 (1H, dd, J=7, 8 Hz, 5′-H), 9.06 (1H, d, J=7 Hz, 6′-H), 9.25 (1H, dd, J=1, 8 Hz, 4′-H), 9.61 (1H, d, J=1 Hz, 2′-H)
3h	2200 (CN) 1725 (C=O)	258 (4.16), 304 (3.68), 355 (4.07), 374 (4.06)	T	2.95 (3H, s, SMe), 7.94 (1H, s, 5-H), 8.04—8.44 (3H, m, 5′,6′,7′-H), 8.70 (1H, d, J=8.5 Hz, 3′-H), 8.78 (1H, near d, J=8.5 Hz, 8′-H), 9.30 (1H, d, J=8.5 Hz, 4′-H)
3i	2200 (CN) 1715 (C=O)	218 (3.99), 267 (4.11), 349 (4.23), 402 (4.34)	T	2.73 (3H, s, SMe), 6.97 (1H, s, 5-H), 7.24 (1H, dd, J=3.5, 5 Hz, 4′-H), 7.86 (1H, d, J=5 Hz, 5′-H), 7.98 (1H, d, J=3.5 Hz, 3′-H)
3j	2200 (CN) 1710 (C=O)	235,[a] 279, 313, 365, 395	C	2.64 (3H, s, SMe), 6.24 (1H, s, 5-H), 6.28 (1H, d, J=16 Hz, ethenyl-H), 7.70 (1H, d, J=16 Hz, ethenyl-H), 7.24—7.56 (5H, m, phenyl-H)
3k	2200 (CN) 1715 (C=O)	242 (4.13), 415 (4.30)	D	2.68 (3H, s, SMe), 3.77 (3H, s, OMe), 6.76 (1H, s, 5-H), 6.92 (1H, d, J=16 Hz, ethenyl-H), 6.96 (2H, d, J=8 Hz, 3′,5′-H), 7.52 (1H, d, J=16 Hz, ethenyl-H), 7.64 (2H, d, J=8 Hz, 2′,6′-H)
3l	2200 (CN) 1710 (CO)	228,[a] 284, 310, 355, 390	T	2.71 (3H, s, SMe), 6.68 (1H, s, 5-H), 6.74 (1H, d, J=16 Hz, ethenyl-H), 7.36 (2H, d, J=9 Hz, 3′,5′-H), 7.50 (2H, d, J=9 Hz, 2′,6′-H), 7.72 (1H, d, J=16 Hz, ethenyl-H)

a) Insufficient solubility. T, CF_3COOH; C, $CDCl_3$; D, DMSO-d_6.

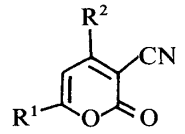
TABLE II. 6-Substituted 4-Amino-3-cyano-2*H*-pyran-2-ones



No.	R^1	R^2	Yield (%)	mp (°C)	Appearance	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν(KBr) cm^{-1}
5a	C_6H_5	Benzylamino	55	226	Colorless needles	$C_{19}H_{14}N_2O_2$	75.48 (75.45	4.67 4.49	9.27 9.40)	3250 (NH) 2200 (CN) 1660 (C=O)
5b	C_6H_5	Phenethylamino	25	181	Colorless needles	$C_{20}H_{16}N_2O_2$	75.93 (76.28	5.10 5.06	8.86 8.74)	3280 (NH) 2180 (CN) 1650 (C=O)
5c	C_6H_5	Piperidino	78	211	Pale yellow leaflets	$C_{17}H_{16}N_2O_2$	72.84 (72.99	5.75 5.64	9.99 10.32)	2180 (CN) 1680 (C=O)
5d	C_6H_5	Morpholino	48	221	Pale yellow leaflets	$C_{16}H_{14}N_2O_3$	68.07 (68.03	5.00 4.90	9.92 9.88)	2180 (CN) 1690 (C=O)
5e	C_6H_5	Dimethylamino	21	246	Pale yellow needles	$C_{14}H_{12}N_2O_2$	69.99 (69.89	5.03 5.01	11.66 11.61)	2180 (CN) 1680 (C=O)
5f	*p*-MeO–C_6H_4	Phenethylamino	60	224	Colorless needles	$C_{21}H_{18}N_2O_3$	72.82 (72.77	5.24 5.23	8.09 7.85)	3280 (NH) 2200 (CN) 1680 (C=O)

5g	*p*-MeO–C_6H_4	Morpholino	42	273	Pale yellow needles	$C_{17}H_{16}N_2O_4$	65.37 (65.25	5.16 5.00	8.97 8.64)	2180 (CN) 1680 (C=O)
5h	*p*-Cl–C_6H_4	Cyclohexylamino	60	291	Colorless needles	$C_{18}H_{17}ClN_2O_2$	65.75 (65.60	5.21 5.22	8.52 8.54)	3260 (NH) 2200 (CN) 1660 (C=O)
5i	*p*-Br–C_6H_4	Piperidino	45	248	Pale yellow leaflets	$C_{17}H_{15}BrN_2O_2$	56.83 (56.61	4.18 4.08	7.80 7.58)	2180 (CN) 1675 (C=O)
5j	C_6H_5–CH=CH	Benzylamino	70	235	Yellow needles	$C_{21}H_{16}N_2O_2$	74.97 (75.46	6.29 6.22	8.74 8.74)	3280 (NH) 2200 (CN) 1710 (C=O)
5k	C_6H_5–CH=CH	Morpholino	68	204	Yellow needles	$C_{18}H_{16}N_2O_3$	70.11 (70.27	5.23 5.20	9.09 9.20)	2200 (CN) 1690 (C=O)
5l	C_6H_5–CH=CH	Cyclohexylamino	75	219	Yellow needles	$C_{20}H_{20}N_2O_2$	74.97 (74.46	6.29 6.22	8.74 8.74)	3260 (NH) 2180 (CN) 1680 (C=O)
5m	C_6H_5–CH=CH	Ethanolamino	58	199	Yellow needles	$C_{19}H_{18}N_2O_2$	74.49 (74.07	5.92 6.01	9.15 8.94)	2180 (CN) 1680 (C=O)
5n	*p*-MeO–C_6H_4–CH=CH	Benzylamino	80	244	Yellow needles	$C_{22}H_{18}N_2O_3$	73.73 (73.74	5.06 4.97	7.82 7.51)	3260 (NH) 2200 (CN) 1705 (C=O)
5o	*p*-MeO–C_6H_4–CH=CH	Morpholino	77	280	Yellow needles	$C_{19}H_{18}N_2O_4$	67.44 (67.23	5.36 5.32	8.26 8.00)	2200 (CN) 1680 (C=O)

TABLE III. 4,6-Disubstituted 3-Cyano-2*H*-pyran-2-ones

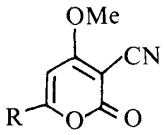


No.	R^1	R^2	Yield (%)	mp (°C)	Recryst. solvent	Appearance	Formula	Analysis (%) Calcd (Found)		
								C	H	N
8a	C_6H_5	$CH(COOMe)_2$	97	159	MeOH	Yellow needles	$C_{17}H_{13}NO_6$	59.13 (59.34	4.38 4.32	4.00 3.76)
8b	*p*-Br–C_6H_4	$CH(COOMe)_2$	90	176	MeOH	Yellow needles	$C_{17}H_{12}BrNO_6$	50.27 (50.28	2.98 2.84	3.45 3.29)
8c	3,4-$(MeO)_2$–C_6H_3	$CH(COOEt)_2$	50	145	EtOH	Yellow needles	$C_{21}H_{21}NO_8$	60.72 (60.42	5.10 5.07	3.37 3.36)
8d	C_6H_5–CH=CH	$CH(COOMe)_2$	30	200	MeOH–C_6H_6	Yellow needles	$C_{19}H_{15}NO_6$	64.52 (64.30	4.28 4.26	3.76 3.99)
8e	*p*-Cl–C_6H_4–CH=CH	$CH(COOMe)_2$	34	188	MeOH–C_6H_6	Yellow needles	$C_{19}H_{14}ClNO_6$	55.84 (58.56	3.63 3.63	3.61 3.27)
8f	*p*-Cl–C_6H_4–CH=CH	$CH(COOEt)_2$	29	185	EtOH–C_6H_6	Yellow needles	$C_{21}H_{18}ClNO_6$	60.65 (60.14	4.36 4.22	3.36 3.22)

	IR ν(KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)		NMR δ (ppm)
8a	2200 (CN), 1745 (C=O)	254 (4.07), 274 (3.99), 368 (4.31)	C	3.80 (6H, s, OMe), 4.95 (1H, s, C–H), 7.13 (1H, s, 5-H), 7.50—7.68 (3H, m, 3′,4′,5′-H), 7.90—8.08 (2H, m, 2′,6′-H)
8b	2200 (CN), 1740 (C=O)	244 (3.84), 288 (4.04), 330 (3.99), 400 (3.73)	C	3.86 (6H, s, OMe), 5.05 (1H, s, C–H), 7.13 (1H, s, 5-H), 7.65 (2H, d, J=9 Hz, 3′,5′-H), 7.76 (2H, d, J=9 Hz, 2′,6′-H)
8c	2200 (CN), 1730 (C=O)	220 (4.32), 262 (3.99), 414 (4.38)	C	1.34 (6H, t, J=7 Hz, OCH_2–Me), 3.97 (6H, s, OMe), 4.27 (4H, q, J=7 Hz, OCH_2–Me), 5.00 (1H, s, C–H), 6.94 (1H, d, J=8.5 Hz, 5′-H), 7.05 (1H, s, 5-H), 7.34 (1H, d, J=2 Hz, 2′-H), 7.53 (1H, dd, J=8.5, 2 Hz, 6′-H)
8d	2200 (CN), 1760 (C=O), 1745 (C=O), 1735 (C=O)	240 (4.16), 268 (4.14), 283 (4.13), 428 (4.43)	T	3.98 (6H, s, OMe), 5.18 (1H, s, C–H), 6.89 (1H, d, J=16 Hz, ethenyl-H), 6.91 (1H, s, 5-H), 7.85 (1H, d, J=16 Hz, ethenyl-H), 7.30—7.69 (5H, m, phenyl-H)
8e	2200 (CN), 1750 (C=O), 1740 (C=O), 1710 (C=O)	224 (4.25), 269 (4.05), 288 (3.97), 304 (3.94), 368 (4.24)	C	3.82 (6H, s, OMe), 4.98 (1H, s, C–H), 6.60 (1H, s, 5-H), 6.62 (1H, d, J=16 Hz, ethenyl-H), 7.34 (2H, d, J=8 Hz, 3,5-H), 7.46 (2H, d, J=8 Hz, 2′,6′-H), 7.58 (1H, d, J=16 Hz, ethenyl-H)
8f	2200 (CN), 1750 (C=O), 1725 (C=O)	270 (4.16), 288 (4.12), 305 (4.06), 372 (4.34), 308 (4.36)	C	1.32 (6H, t, J=7 Hz, OCH_2–Me), 4.27 (4H, q, J=7 Hz, OCH_2–Me), 4.92 (1H, s, C–H), 6.64 (1H, s, 5-H), 6.66 (1H, d, J=16 Hz, ethenyl-H), 7.35 (2H, d, J=8 Hz, 3′,5′-H), 7.47 (2H, d, J=8 Hz, 2′,6′-H), 7.58 (1H, d, J=16 Hz, ethenyl-H)

C, $CDCl_3$; T, CF_3COOH.

TABLE IV. 6-Substituted 3-Cyano-4-methoxy-2*H*-pyran-2-ones



No.	R	Yield (%)	mp (°C)	Appearance	Formula	Analysis (%) Calcd (Found)		
						C	H	N
10a	C_6H_5	61	218	Pale yellow needles	$C_{13}H_9NO_3$	68.72 (68.50	3.99 3.92	6.17 5.96)
10b	*p*-MeO–C_6H_4	45	227	Pale yellow needles	$C_{14}H_{11}NO_4$	65.36 (65.22	4.31 4.22	5.45 5.25)
10c	3,4-O–CH_2–O–C_6H_3	55	291	Pale yellow needles	$C_{14}H_9NO_5$	61.99 (61.90	3.34 3.24	5.16 4.78)
10d	C_6H_5–CH=CH	89	255	Yellow needles	$C_{15}H_{11}NO_3$	71.14 (71.29	4.37 4.35	5.53 5.51)
10e	*p*-MeO–C_6H_4–CH=CH	43	266	Orange needles	$C_{16}H_{13}NO_4$	67.84 (67.40	4.63 4.51	4.95 4.95)

	IR ν(KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	NMR δ (ppm)
10a	2200 (CN) 1720 (C=O)	226 (4.17), 248 (4.27), 320 (4.18)	T 4.24 (3H, s, OMe), 7.05 (1H, s, 5-H), 7.40—7.64 (3H, m, 3′,4′,5′-H), 7.84—7.94 (2H, m, 2′,6′-H)
10b	2200 (CN) 1700 (C=O)	230 (4.20), 288 (3.75), 300 (3.74), 376 (4.45)	C 3.89 (3H, s, OMe), 4.16 (3H, s, OMe), 6.54 (1H, s, 5-H), 7.00 (2H, d, J=9 Hz, 3′,5′-H), 7.85 (2H, J=9 Hz, 2′,6′-H)
10c	2220 (CN) 1710 (C=O)	221,[a] 384	T 4.27 (3H, s, OMe), 6.06 (2H, s, O–CH_2–O), 6.93 (1H, s, 5-H), 6.96 (1H, d, J=8 Hz, 5′-H), 7.37 (1H, d, J=2 Hz, 2′-H), 7.60 (1H, dd, J=2, 8 Hz, 6′-H)
10d	2200 (CN) 1710 (C=O)	237 (4.13), 340 (4.37)	T 4.21 (3H, s, OMe), 6.52 (1H, s, 5-H), 6.83 (1H, d, J=16 Hz, ethenyl-H), 7.40—7.68 (5H, m, phenyl-H), 7.79 (1H, d, J=16 Hz, ethenyl-H)
10e	2200 (CN) 1710 (C=O)	230 (4.20), 415 (4.37)	D 3.76 (3H, s, OMe), 4.04 (3H, s, OMe), 6.84 (2H, d, J=8 Hz, 3′,5′-H), 6.88 (1H, d, J=16 Hz, ethenyl-H), 6.96 (1H, s, 5-H), 7.48 (1H, d, J=16 Hz, ethenyl-H), 7.60 (2H, d, J=8 Hz, 2′,6′-H)

a) Insufficient solubility. T, CF_3COOH; C, $CDCl_3$; D, DMSO-d_6.

4.43; N, 16.44.

3,5-Diamino-4,5-dihydro-4-oxo-6-phenyl-1*H*-pyrazolo[4,3-*c*]pyridine (7)——A mixture of 2.43 g (0.01 mol) of **3a** and 2 g (0.04 mol) of hydrazine hydrate was heated at 100 °C for 5 h. After cooling, the product was recrystallized from MeOH to give 0.75 g (30%) of yellow needles, mp >300 °C. IR ν(KBr) cm^{-1}: 3300 (br, NH), 1630 (C=O). UV λ_{max}^{EtOH} nm (log ε): 260 (4.12), 302 (3.89). MS *m/z*: 249 (M^+). *Anal.* Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.38; H, 4.47; N, 28.61.

Reaction of 3 with Active Methylene Compounds——An active methylene compound (dimethyl malonate or diethyl malonate) (0.02 mol) and 0.025 mol of K_2CO_3 were added with stirring to a solution of 0.01 mol of **3 (a, c, e, j, l)** in 50 ml of DMF at room temperature, and the mixture was stirred at the same temperature for 3 h. The reaction mixture turned reddish-brown. The precipitate was collected by filtration, washed with water and recrystallized from MeOH to give the corresponding product **8**.

6,8-Dihydroxy-5-methoxycarbonyl-1-oxo-3-phenyl-1*H*-pyrano[3,4-*c*]pyridine (9a)——A mixture of 2.43 g (0.01 mol) of **3a**, 1.9 g (0.02 mol) of methyl cyanoacetate, 3.45 g (0.025 mol) of K_2CO_3, and 50 ml of DMF was stirred at room temperature for 3 h. The reaction mixture was poured into 200 ml of ice-water and the whole was acidified with 10% HCl. The mixture was stirred at the same temperature for 10 h. The pale yellow precipitate was collected by filtration and recrystallized from C_6H_6–MeOH to give 2.35 g (75%) pale yellow needles, mp 310 °C. IR ν(KBr) cm^{-1}: 3300 (NH), 1775, 1690, 1660 (C=O). UV λ_{max}^{EtOH} nm (insufficient solubility): 254, 285, 370; λ min: 270, 320. MS *m/e*: 313 (M^+, 100). *Anal.* Calcd for $C_{16}H_{11}NO_6$: C, 61.34; H, 3.54; N, 4.47. Found: C, 61.45; H, 3.62; N, 4.32.

3-(4-Bromophenyl)-6,8-dihydroxy-5-methoxycarbonyl-1-oxo-1*H*-pyrano[3,4-*c*]pyridine (9b)——This compound was synthesized from **3c** and methyl cyanoacetate in 67% yield in a manner similar to that used for the preparation of **9a**. A analytical sample was recrystallized from C_6H_6–MeOH to give yellow needles, mp 310 °C. IR ν(KBr) cm^{-1}: 3300 (NH), 1770, 1700, 1670 (C=O). UV λ_{max}^{EtOH} nm (insufficient solubility): 273, 358; λ min: 300. *Anal.* Calcd for $C_{16}H_{10}BrNO_6$: C, 48.98; H, 2.55; N, 3.57. Found: C, 48.83; H, 2.49; N, 3.50.

5-Ethoxycarbonyl-8-hydroxy-6-methyl-3-phenyl-1-oxo-1*H*-pyrano[3,4-*c*]pyridine (9c)——This compound was synthesized from **3a** and ethyl acetoacetate in 55% yield in a manner similar to that used for the preparation of **9a**. An analytical sample was recrystallized from EtOH to give colorless needles, mp 291 °C. IR ν(KBr) cm^{-1}: 3400 (NH), 2800 (br, OH), 1765, 1720, 1620 (C=O). UV λ_{max}^{EtOH} nm (log ε): 231 (4.10), 271 (4.39), 350 (4.40). NMR (CF_3COOH) δ: 1.58 (3H, t, J=7 Hz, O–CH_2–Me), 2.87 (3H, s, 6-Me), 4.67 (2H, J=7 Hz, O–CH_2–Me), 7.56—7.68 (2H, m, phenyl protons), 7.69 (1H, s, 4-H), 7.92—8.05 (2H, m, phenyl protons). *Anal.* Calcd for $C_{18}H_{15}NO_5$: C, 66.45; H, 4.65; N, 4.31. Found: C, 66.42; H, 4.62; N, 4.15.

Synthesis of 4-Methoxy-2*H*-pyran-2-ones (10a, b, c, d, e)——Sodium methylate (0.01 mol) was added to a solution of 0.02 mol of **3** (**a**, **b**, **f**, **j**, and **k**) in 100 ml of MeOH and the mixture was refluxed on a boiling water bath for 3 h, then evaporated down to 20 ml. This concentrate was poured into 200 ml of water. The precipitate was collected by filtration and recrystallized from MeOH–C_6H_6.

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