SHORT PAPER

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Heteroaromatization with 4-hydroxycoumarin Part I:Synthesis of some new pyranocoumarins and coumarinopyranopyrimidines†

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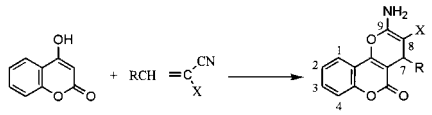
Considerable interest has been shown in coumarin derivatives, on account of their excellent pharmacological activity[1-3]. In continuation of our work[4-6], it was of interest to synthesize new coumarin derivatives, which might be biologically active. Thus condensation of 4-hydroxycoumarin **1** with various substituted α-cyanocinnamonitrile **2a-n** in ethanolic piperidine afforded pyrano[3,2-c]coumarin derivatives **3a-n** (Scheme 1).

Structure **3** was established on the basis of the ^{1}H NMR spectra which showed 7-H at δ 4.49(3d), δ 3.39(quartet, 3g), δ 4.92(3m) and δ 4.90 ppm (3n). The UV spectrum of **3e** revealed a weak shoulder[7,8], characteristic for a 4H-pyran at λ_{max} (CH_3COCH_3) 275 (log ε 8.31) and **3f,i,k,m,n** at λ_{max} (CH_3COCH_3) 275 nm (log ε 8.23-8.51).



1	2	3	
a; R= Ph;	X= CN	h; R= C_6H_3OMe-3, OH-4	X=CN
b; R=$C_6H_4NO_2$-p	X= CN	i, R= Ph	X= CO_2Et
c; R=C_6H_4Br-p	X= CN	j, R= C_6H_4Cl-p	X= CO_2Et
d; R= C_6H_4Cl-p	X= CN	k; R= C_6H_4Br-p	X= CO_2Et
e; R= C_6H_4Me-p	X= CN	l, R= $C_6H_4NO_2$-p	X= CO_2Et
f, R= C_6H_4OMe-p	X= CN	m,R= C_6H_4Me-p	X= CO_2Et
g, R= Me	X= CN	n, R= C_6H_4OMe-p	X= CO_2Et

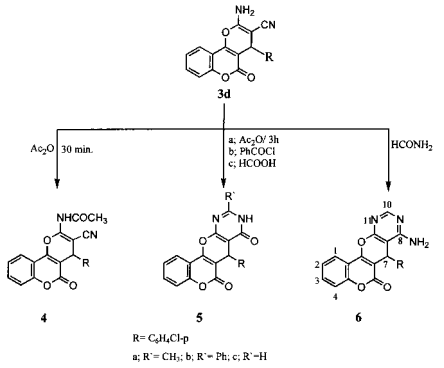
Scheme 1

Interaction of 9-amino-7-(p-chlorophenyl)-8-cyano-7H-pyrano[3,2-c]coumarin **3d** with acetic anhydride for 30 min. afforded the N-acetyl derivative **4**, while heating of **3d** with acetic anhydride under reflux for 3h afforded the coumarinopyranopyrimidin-8-one derivative **5a** (Scheme 2). Treatment of **3d** with benzoyl chloride or formic acid gave the coumarino-pyranopyrimidine-8-one derivative **5b,c**, while with formamide afforded the coumarino-pyranopyrimidin-8-amine derivative **6** (Scheme 2). Structures **4–6** were established by spectral data and analogy with our previous work[8,9]. Structure **6** is also supported by independent synthesis of the same product by ammonolysis of **7a** in methanol at room temperature (m.p. and mixed m.p.) (Scheme 3).

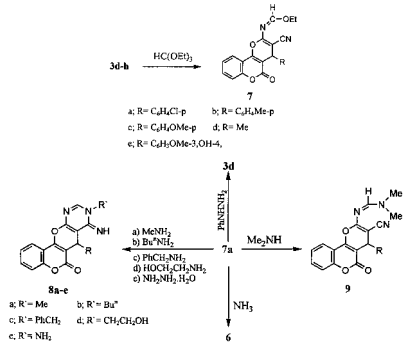
Treatment of **3d–h** with triethyl orthoformate in acetic anhydride at reflux gave the corresponding ethoxymethylideneamino derivative **7** (Scheme 3). Structure **7** was established by spectral data and analogy with our previous work[8,10].

Reaction of **7a** with various amines in ethanol at room temperature yielded the pyrimidine derivatives **8a–d**, while with hydrazine hydrate or dimethyl amine gave, the coumarino-[2′,1′:5,6]pyrano[2,3-d]pyrimidin-9-amine derivative **8e** and dimethylamino-ethylideneamino derivative **9** (Scheme 3).

When **7a** was treated with phenylhydrazine in ethanol at room temperature, an addition product formed, from which elimination of ethyl formate phenylhydrazone gave the enaminonitrile **3d**[8,11].



Scheme 2



Scheme 3

Experimental

Mps are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratories of the Faculty of Science, Cairo University. IR spectra (KBr) were measured on a FT IR/5300 spectrometers. Ultraviolet spectra were recorded on Perkin Elmer Lambda-3B UV-Visible spectrophotometer. ^{1}H NMR spectra on a Varian Gemini (200 MHz), Varian Mercury (300 MHz) spectrometer and mass spectra on a Shimadzu GC-MS-QP 1000 EX spectrometer.

*Reaction of 4-hydroxycoumarin with **2a–n:*** A solution of 4-hydroxycoumarin **1** (0.01 mol) in ethanol (30 ml) was treated with various substituted α-cyanocinnamonitriles **2a–n** (0.01 mol) and piperidine (0.5 ml). The reaction mixture was heated until complete precipitation (reaction time:30 min. for **2a–h**; 120 min for **2i–n**). The solid product which formed was collected by filteration and recrystallized from a suitable solvent to give **3a–n** (70-90% yield) (Table 1)**. 3d**: ν_{max}/cm^{-1} 3381, 3290 (NH_2), 3188 (CH stretching), 2193 (CN), 1713 (CO δ-lacton), 1676 (C=C); δ_H([$^2H_6$]DMSO) 7.33-7.92 (8H,m,arom.), 7.29 (2H,br,NH_2), 4.49 (1H,s,pyran CH). **3e**: ν_{max}/cm^{-1} 3400, 3292 (NH_2), 3192 (CH stretching), 2195 (CN), 1715 (CO δ-lacton), 1678 (C=C). **3f**: ν_{max}/cm^{-1} 3400, 3292, (NH_2), 3190, 2958, 2839 (CH stretching), 2191 (CN), 1707 (CO δ-lacton), 1670 (C=C). **3g**: ν_{max}/cm^{-1} 3393, 3317, (NH_2), 3194, 3063, 3047, 2960, 2930 (CH stretching), 2195 (CN), 1707 (CO δ-lacton), 1670 (C=C). δ_H([$^2H_6$]DMSO) 7.33-7.84 (4H,m,arom.), 7.26 (2H, br, NH_2), 3.39

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

(1H, q, pyran CH, J=6.6Hz), 1.31 (3H, d, CH_3, J=6.6 Hz). **3j**: ν_{max}/cm^{-1} 3452, 3302 (NH_2), 2949 (CH stretching), 1736 (CO δ-lacton), 1693 (CO ester), 1665 (C=C). **3m**: ν_{max}/cm^{-1} 3396, 3283, (NH_2), 3136, 2986, 2935, 2922, 2866 (CH stretching), 1701 (CO δ-lacton), 1681 (CO ester), 1649 (C=C), $\delta_H([^2H_6]CDCl_3)$ 7.06-7.87 (8H,m,arom.), 6.46 (2H, br, NH_2), 4.92 (1H, s, pyran CH), 4.12 (2H, q, CH_2, J=7.2 Hz), 2.30 (3H,s,CH_3), 1.22 (3H,t,CH_3, J=7.2 Hz). **3n**: ν_{max}/cm^{-1} 3398, 3287, (NH_2), 3045, 2907, 2831(CH stretching), 1697 (CO δ-lacton), 1653 (CO ester), 1609 (C=C),$\delta_H([^2H_6]CDCl_3)$ 7.29-7.86 (8H,m,arom.), 6.47 (2H,br, NH_2), 4.90 (1H, s, pyran CH), 4.11 (2H, q, CH_2, J=7.2 Hz), 3.77 (3H,s,OCH_3), 1.21 (3H,t,CH_3, J=7.2 Hz).

9-Acetylamino-7-(p-chlorophenyl)-8-cyano-7H-pyrano[3,2-c]coumarin (4): A solution of 9-amino-7-(p-chlorophenyl)-8-cyano-7H-pyrano[3,2-c]coumarin **3d** (0.01 mol) in acetic anhydride (20 ml) was heated under reflux for 30 min. to give the N-acetyl derivative **4**, 85% yield (Table 1), ν_{max}/cm^{-1} 3383 (NH), 3190, 3045 (CH stretching), 2193 (CN), 1713 (CO δ-lacton), 1676 (CO acetyl), 1649 (C=C).

7-(p-Chlorophenyl)-10-methyl-7,9-dihydrocoumarino[2′,1′:5,6] pyrano[2,3-d]-pyrimidin-8-one (5a): A solution of **3d** (0.01 mole) in acetic anhydride (20 ml) was heated under reflux for 3h to give **5a** (85% yield) (Table 1), ν_{max}/cm^{-1} 3400 (NH), 2910, 2860 (CH stretching), 1701(CO δ-lacton), 1679 (CO), 1625 (C=N), $\delta_H([^2H_6]DMSO)$ 12.80 (1H,br,NH), 7.28-7.95(8H,m,arom.), 4.83 (1H, s, pyran CH), 2.33(3H,s, CH_3).

7-(p-Chlorophenyl)-10-phenyl-7,9-dihydrocoumarino[2′,1′:5,6] pyrano[2,3-d]-pyrimidin-8-one (5b): A solution of **3d** (0.01 mol) in benzoyl chloride (20 ml) was heated under reflux for 6h to give **5b** (75% yield) (Table 1), ν_{max}/cm^{-1} 3270 (NH), 1713 (CO δ-lacton), 1659 (CO), 1639 (C=N), m/z 455 (M^++1, 27%), 379 (17), 343 (100), 285 (54), 221 (45), 175 (35), 131 (63), 71 (40).

7-(p-Chlorophenyl)-7,9-dihydrocoumarino[2′,1′:5,6] pyrano[2,3-d]-pyrimidin-8-one(5c): A solution of **3d** (0.01 mol) in formic acid (20 ml) was heated under reflux for 6h. to give **5c** (78% yield); (Table 1), ν_{max}/cm^{-1} 3190 (NH), 1719 (CO δ-lacton), 1641 (CO), 1607 (C=N).

7-(p-Chlorophenyl)-7,9-dihydrocoumarino[2′,1′:5,6]pyrano[2,3-d]-pyrimidin-8-amine (6): (a) A solution of **3d** (0.01 mol) in formamide (20 ml) was heated under reflux for 6h to give **6** (70% yield) (Table 1), ν_{max}/cm^{-1} 3186 (NH_2), 1665 (CO δ-lacton), 1630 (C=N).

(b) A stream of NH_3 gas was passed through **7a** (0.01 mol) in methanol for 1h. The solid product formed on cooling was collected to give **6** (90% yield), (Table 1).

7-Aryl/alkyl-8-cyano-9-ethoxymethylideneamino-7H-pyrano[3,2-c]coumarin (7a-e).: A mixture of **3d-h** (0.01 mol), triethyl orthoformate (0.01 mol) and acetic anhydride (20 ml) was refluxed for 5h. The solvent was removed under vacuum. The residue obtained was recrystallized from benzene to give **7a-e** (65-80% yield) (Table 1). **7a**: ν_{max}/cm^{-1} 2982, 2980 (CH stretching), 2216 (CN), 1709 (CO δ-lacton), 1666 (C=N), $\delta_H([^2H_6]DMSO)$ 8.94 (1H,s,CH), 7.43-8.23 (8H,m,arom.), 4.76 (1H, s, pyran CH), 4.40 (2H,q, CH_2 J=7 Hz), 1.35 (3H,s,CH_3, J=7Hz). **7b**; $\delta_H(CDCl_3)$ 8.50 (1H,s,CH), 7.19-7.82 (8H,m,arom.), 4.74 (1H, s, pyran CH), 4.61 (2H,q, CH_2 J=7.2 Hz), 2.34 (3H,s,CH_3), 1.44 (3H,t,CH_3). **7c**: m/z 402 (M^+, 52%), 345 (29), 279 (64), 239 (100), 121 (72), 66 (40). **7d**: ν_{max}/cm^{-1} 2980, 2937, 2885 (CH stretching), 2212 (CN), 1720 (CO δ-lacton), 1672 (C=N), $\delta_H([^2H_6]DMSO)$ 8.40 (1H,s,CH), 7.29-7.70 (4H,m,arom.), 4.45 (2H,q,CH_2 J=7.2 Hz), 3.63 (1H,q,pyran CH, J=6.8Hz), 1.49 (3H,d,CH_3,J=6.8 Hz), 1.40 (3H,t,CH_3, J=7.2 Hz).

Reaction of 7a with various amines and hydrazine hydrate (8a–e) and 9: A solution of 7-(p-chlorophenyl)-8-cyano-9-ethoxymethylideneamino-7H-pyrano[3,2-c]coumarin **7a** (0.01 mol) and various amines (0.01 mol) or hydrazine hydrate (99%, 5 ml) in ethanol (50 ml) was stirred for 45 min. The colouress solid obtained was filtered off and crystallized from benzene to give **8a-e** and 7-(p-chlorophenyl)-8-cyano-9-dimethylamino-methylidene-amino-7H-pyrano[3,2-c]coumarin **9** (70-78% yield) (Table 1). **8a**: ν_{max}/cm^{-1} 3340 (NH), 3051, 2930, 2874 (CH stretching), 1724 (CO δ-lacton), 1666 (C=N), 1620 (C=N). $\delta_H([^2H_6]DMSO)$ 8.20 (1H,s,pyrimidine CH), 7.31-7.93 (8H,m,arom.), 6.96 (1H,br,NH), 4.97 (1H, s, pyran CH), 3.29 (3H,s, N-CH_3), **8b**: ν_{max}/cm^{-1} 3150 (NH), 2960, 2928 (CH stretching), 1722 (CO δ-lacton), 1644 (C=N). **8c**: ν_{max}/cm^{-1} 3348 (NH), 3032 (CH stretching), 1718 (CO δ-lacton), 1664 (C=N). **8d**: ν_{max}/cm^{-1} 3325 (OH), 3180 (NH), 3086, 2826 (CH stretching), 1720 (CO δ-lacton), 1658 (C=N). **8e**: ν_{max}/cm^{-1} 3568, 3547 (NH_2), 3337 (NH), 1718 (CO δ-lacton), 1653 (C=N). **9**: ν_{max}/cm^{-1} 2980, 2920, 2871 (CH stretching), 2203 (CN), 1720 (CO δ-lacton), 1660 (C=N). $\delta_H([^2H_6]CDCl_3)$ 8.27 (1H,s,pyrimidine CH), 7.31-7.39 (8H,m,arom.), 4.69 (1H, s, pyran CH), 3.24, 3.18 (6H,s, N-$(CH_3)_2$, 2 nonequivalent CH_3).

Reaction of 7a with phenylhydrazine: A solution of **7a** (0.01 mol) and phenylhydrazine (0.01 mol) in ethanol (50 ml) was stirred for 45 min. to give **3d** (m.p. and mixed m.p.) (Table 1).

Table 1 Characterization data for newly synthesized compounds

Compound	Melting point (*T*/°C)[a]	Molecular formula	Elemental analyses found (required) % C	H
3a	242[b]	$C_{19}H_{12}N_2O_3$	72.10 (72.15)	3.70 (3.79)
3b	250[c]	$C_{19}H_{11}N_3O_5$	62.90 (63.15)	2.80 (3.04)
3c	254	$C_{19}H_{11}Br\ N_2O_3$	57.70 (57.73)	2.80 (2.78)
3d	261[d]	$C_{19}H_{11}ClN_2O_3$	65.10 (65.06)	3.10 (3.13)
3e	255[e]	$C_{20}H_{14}N_2O_3$	72.70 (72.72)	4.20 (4.24)
3f	227[f]	$C_{20}H_{14}N_2O_4$	69.30 (69.36)	3.40 (4.04)
3g	235	$C_{14}H_{10}N_2O_3$	66.10 (66.14)	3.90 (3.93)
3h	264	$C_{20}H_{14}N_2O_5$	66.30 (66.29)	3.80 (3.86)
3i	196[h]	$C_{21}H_{17}NO_5$	69.40 (69.42)	4.70 (4.68)
3j	192[h]	$C_{21}H_{16}ClNO_5$	63.40 (63.40)	4.00 (4.02)
3k	215[h]	$C_{21}H_{16}BrNO_5$	56.70 (57.02)	3.60 (3.62)
3l	223[h]	$C_{21}H_{16}N_2O_7$	61.70 (61.76)	3.90 (3.92)
3m	190[h]	$C_{22}H_{19}NO_5$	70.10 (70.02)	5.00 (5.03)
3n	160[h]	$C_{22}H_{19}NO_6$	67.10 (67.17)	4.80 (4.83)
4	212[h]	$C_{21}H_{13}ClN_2O_4$	64.20 (64.21)	3.30 (3.31)
5a	348[i]	$C_{21}H_{13}Cl\ N_2O_4$	64.20 (64.21)	3.30 (3.31)
5b	<360[i]	$C_{26}H_{15}ClN_2O_4$	68.60 (68.66)	3.30 (3.30)
5c	185[h]	$C_{20}H_{11}ClN_2O_4$	63.40 (63.42)	2.90 (2.90)
6	230[h]	$C_{20}H_{12}ClN_3O_3$	63.50 (63.56)	3.10 (3.17)
7a	236[g,h]	$C_{22}H_{15}ClN_2O_4$	64.90 (64.95)	3.60 (3.60)
7b	225[h]	$C_{23}H_{18}N_2O_4$	71.50 (71.50)	4.70 (4.66)
7c	195[h]	$C_{23}H_{18}N_2O_5$	68.60 (68.65)	4.40 (4.47)
7d	205[h]	$C_{17}H_{14}N_2O_4$	65.80 (65.80)	4.50 (4.51)
7e	208[h]	$C_{23}H_{18}N_2O_6$	66.00 (66.02)	4.30 (4.30)
8a	243[h]	$C_{21}H_{14}ClN_3O_3$	64.40 (64.37)	3.60 (3.57)
8b	248[h]	$C_{24}H_{20}ClN_3O_3$	66.40 (66.44)	4.56 (4.60)
8c	220[h]	$C_{27}H_{18}ClN_3O_3$	69.30 (69.31)	3.80 (3.85)
8d	240[h]	$C_{22}H_{16}ClN_3O_4$	62.60 (62.64)	3.70 (3.79)
8e	250[h]	$C_{20}H_{13}Cl\ N_4O_3$	61.10 (61.15)	3.30 (3.31)
9	270[h]	$C_{22}H_{16}ClN_3O_3$	65.10 (65.11)	3.20 (3.94)

[a]From dioxane unless indicated otherwise, [b]Lit.[12], 258–260°C, [c]Lit.[12], 255–256°C. [d]Lit.[12], 252–254°C, [e]Lit.[12], 242–244°C, [f]Lit.[12], 232–234°C, [g]Lit.[12], 221–223°C, [h]from benzene and [i]from DMF

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