DDQ Oxidation of 6- or 8-Allyl-7-hydroxycoumarins. A New Synthesis of Benzodipyrandiones and Furobenzopyranones

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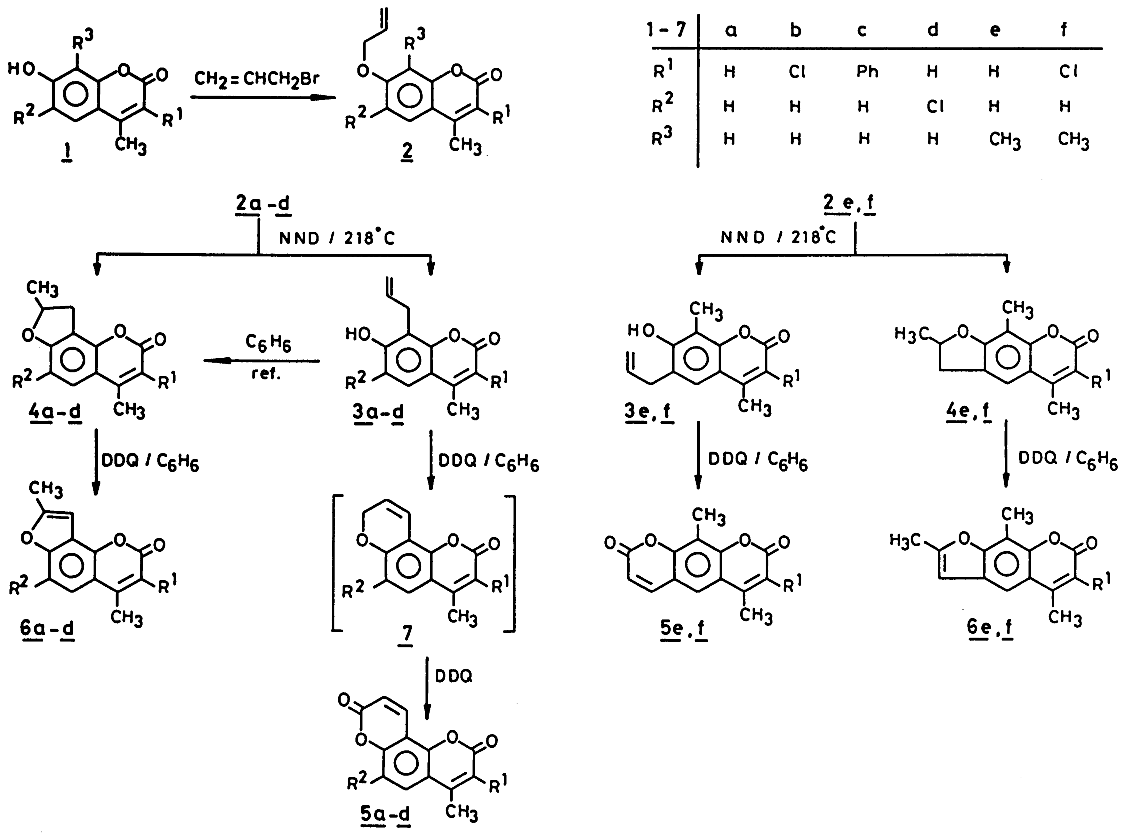
Synopsis. A novel synthesis of 2*H*,8*H*-benzo[1,2-*b*:3,4-*b*′]dipyran-2,8-diones, 2*H*,8*H*-benzo[1,2-*b*:5,4-*b*′]dipyran-2,8-diones, 2*H*-furo[2,3-*h*][1]benzopyran-2-ones, and 7*H*-furo[3,2-*g*][1]benzopyran-7-ones was achieved by developing 2-pyrone and furan ring over coumarin. 6- or 8-Allyl-7-hydroxycoumarins on oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) afforded benzodipyrandiones and furobenzopyranones. The structures of the compounds now synthesized were established by analytical, spectral, and comparison with authentic samples prepared by the known procedures.

Pyrano and furocoumarins are isolated from natural sources and are reported to have a variety of biological activity.[1,2] 2,5,9-Trimethyl-7*H*-furo[3,2-*g*][1]benzopyran-7-one (trioxsalen) has photodynamic activity and used in the treatment of leucoderma.[1] Earlier from our laboratory we reported the synthesis of benzodipyran-4,8-diones[3] by DDQ oxidation of 8-allyl-7-hydroxyflavones. Now we report on the results obtained in oxidation of 6- or 8-allyl-7-hydroxycoumarins using DDQ. It was now observed that 2*H*-furo[2,3-*h*][1]benzopyran-2-ones and 7*H*-furo[3,2-*g*][1]benzopyran-7-ones (furocoumarins) are formed in addition to 2*H*,8*H*-benzo[1,2-*b*:3,4-*b*′] and [1,2-*b*:5,4-*b*′]dipyran-2,8-diones (2-pyronocoumarins).

Results and Discussion

4-Methyl-7-hydroxycoumarin (**1a**) on condensation with allyl bromide in acetone–potassium carbonate medium afforded 7-allyloxy-4-methylcoumarin (**2a**). Allyloxycoumarin (**2a**) on Claisen rearrangement in *N,N*′-diethylaniline (218 °C) gave a mixture of two compounds.[4] They were separated by column chromatography over silica gel in benzene–ethyl acetate (9 : 1) mixture. Their structures were inferred as 8-allyl-7-hydroxy-4-methylcoumarin (**3a**), mp 198 °C (58% yield) and 8,9-dihydro-4,8-dimethyl-2*H*-furo[2,3-*h*][1]benzopyran-2-one (**4a**), mp 116 °C (22% yield) by spectral evidence, [**3a** ^{1}H NMR ($CDCl_3$) δ=3.55 (2H, dd, J=10.0, 2.0 Hz, $C_{1'}$–H_2), 5.94 (1H, m, $C_{2'}$–H), 5.00 (2H, m, $C_{3'}$–H_2), 7.45 (1H, d, J=8.5 Hz, C_5–H), 6.93 (1H, d, J=8.5 Hz, C_6–H), 6.00 (1H, s, C_3–H), 2.34 (3H, s, C_4–CH_3); **4a** ^{1}H NMR ($CDCl_3$) δ=3.00 (1H, dd, J=15.0, 7.0 Hz, C_9–H), 3.60 (1H, dd, J=15.0, 10.0 Hz, C_9–H), 5.10 (1H, m, C_8–H), 7.33 (1H, d, J=8.5 Hz, C_5–H), 6.82 (1H, d, J=8.5 Hz, C_6–H), 6.06 (s, C_3–H), 1.30 (d, J=5.5 Hz, C_8–CH_3)



1 - 7	a	b	c	d	e	f
R¹	H	Cl	Ph	H	H	Cl
R²	H	H	H	Cl	H	H
R³	H	H	H	H	CH₃	CH₃

Scheme 1.

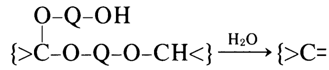
2.43 (3H, s, C_4–CH_3)].

3a and DDQ (1 : 3 mol) in benzene were refluxed for 12 h on a steam bath. The reaction mixture upon chromatographic purification yielded two compounds. The major product (highly polar) was analyzed for $C_{13}H_8O_4$, mp 240 °C, M^+ *m*/*z* 228 (**5a**). The IR spectrum shows absorptions for two lactone carbonyls (1720 and 1735 cm^{-1}). The ^1H NMR spectrum ($CDCl_3$) reveals two AB doublets at δ=8.20 (C_{10}–H, *J*=10.0 Hz) and 6.50 (C_9–H, *J*=10.0 Hz) which are characteristic of α,β-protons of 2-pyrone ring system. In addition to these other doublets due to C_5 and C_6 coumarin protons appear at δ=7.80 and 7.43 (*J*=8.0 Hz each). C_3–H and C_4–CH_3 resonate at δ=6.40 and 2.40. Based on the above spectral data the structure of the compound (**5a**) has been inferred as 4-methyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*′]dipyran-2,8-dione. This was confirmed by its synthesis from 8-formyl-7-hydroxy-4-methylcoumarin by Perkin reaction using Ac_2O/NaOAc.[5]

The minor product (lesser polar) analyzed for $C_{13}H_{10}O_3$, mp 183 °C, M^+ *m*/*z* 214 (**6a**). The IR spectrum shows absorption for only one carbonyl group (1730 cm^{-1}). The ^1H NMR spectrum ($CDCl_3$) reveals signals for a methyl substituted furan ring system; δ=2.52 (s, C_8–CH_3), 6.75 (s, C_9–H), aromatic doublets appear at δ=6.90 and 7.23 (C_6–H and C_5–H, *J*=8.0 Hz each), C_3–H and C_4–CH_3 resonate at 6.25 and 2.46 respectively. The above spectral data establishes the structure **6a** to be 4,8-dimethyl-2*H*-furo[2,3-*h*][1]benzopyran-2-one (4,8-dimethylfuro[2,3-*h*]coumarin). It was confirmed by its synthesis from **3a** by using $PdCl_2(PhCN)_2$.[6]

The formation of compounds **5a** and **6a** can be explained as follows (Scheme 1). 8-Allyl-7-hydroxy-4-methylcoumarin (**4a**) undergoes oxidative cyclization (cyclodehydrogenation) to pyranocoumarin (**7a**) by using one mole of DDQ. This pyranocoumarin is immediately further oxidizes to 2-pyronocoumarin (**5a**)[3,7] via bis ether which is formed by hydride ion abstraction from the pyranocoumarin (**7a**) by DDQ. Bis ether on reaction with another mole of DDQ followed by facile hydrolysis with the traces of water present in the reaction medium yields 2-pyronocoumarin (**5a**). The sequence of reactions can be represented as follows by partial structures:

$$\{>CH_2 \xrightarrow{DDQ} \underset{\text{Bis ether}}{\{>CH\text{-}O\text{-}Q\text{-}O\text{-}CH<\}} \xrightarrow{DDQ}$$



$$\{>\overset{O\text{-}Q\text{-}OH}{\overset{|}{C}}\text{-}O\text{-}Q\text{-}O\text{-}CH<\} \xrightarrow{H_2O} \{>C{=}O$$

5a is the major product in the reaction (55% yield). **6a** arises from **4a** by dehydrogenation.[8] **4a** is formed from **3a** during the reaction by thermal cyclization of **3a**. To verify the thermal isomerization of **3a** to **4a**, **3a** was

Table 1. Characterization Data of 2-Pyronocoumarins (**5a**—**f**)

Compd	Mp °C	Molecular formula	Elemental analysis/% Found (F:), Calcd (C:) C	H	UV_{max}^{MeOH} nm (log ε)	IR (KBr) CO (cm^{-1})	^1H NMR ($CDCl_3$) δ/ppm	MS (*m*/*z*) M^+
5a	240	$C_{13}H_8O_4$	F: 68.28 C: 68.42	3.45 3.50	214 (4.54) 295 (4.80)	1720 1735	2.40 (s, 3 H, C_4–CH_3), 6.42 (s, 1 H, C_3–H), 6.50 (d, 1 H, C_9–H, *J*=10.0 Hz), 7.43 (d, 1 H, C_6–H, *J*=8.0 Hz), 7.82 (d, 1 H, C_5–H, *J*=8.0 Hz), 8.23 (d, 1 H, C_{10}–H, *J*=10.0 Hz)	228
5b	250	$C_{13}H_7ClO_4$	F: 59.39 C: 59.54	2.54 2.67	212 (4.31) 294 (2.11)	1720 1740	2.50 (s, 3 H, C_4–CH_3), 6.50 (d, 1 H, C_9–H, *J*=10.0 Hz), 7.43 (d, 1 H, C_6–H, *J*=8.0 Hz), 7.82 (d, 1 H, C_5–H, *J*=8.0 Hz), 8.22 (d, 1 H, C_{10}–H, *J*=10.0 Hz)	262
5c	275	$C_{19}H_{12}O_4$	F: 74.94 C: 75.00	3.80 3.94	208 (4.35) 300 (4.22)	1700 1720	2.40 (s, 3 H, C_4–CH_3), 6.52 (d, 1 H, C_9–H, *J*=10.0 Hz), 7.00—7.50 (m, 6 H, C_3–Ph and C_6–H), 7.82 (d, 1 H, C_5–H, *J*=8.0 Hz), 8.23 (d, 1H, C_{10}–H, *J*=10.0 Hz)	304
5d	246	$C_{13}H_7ClO_4$	F: 59.24 C: 59.54	2.62 2.67	210 (4.32) 296 (4.16)	1700 1720	2.40 (s, 3 H, C_4–CH_3), 6.42 (s, 1 H, C_3–H), 6.55 (d, 1 H, C_9–H, *J*=10.0 Hz), 8.25 (s, 1 H, C_{10}–H, *J*=10.0 Hz), 7.82 (s, 1 H, C_5–H)	262
5e	261	$C_{14}H_{10}O_4$	F: 69.30 C: 69.42	4.00 4.13	206 (3.94) 272 (3.90) 334 (3.63) 352 (3.60)	1720 1750	2.43 (s, 3 H, C_4–CH_3), 2.54 (s, 3 H, C_{10}–CH_3), 6.35 (s, 1 H, C_3–H), 6.53 (d, 1 H, C_7–H, *J*=10.0 Hz), 7.42 (s, 1 H, C_5–H), 7.60 (d, 1 H, C_6–H, *J*=10.0 Hz)	242
5f	270	$C_{14}H_9ClO_4$	F: 60.72 C: 60.86	3.30 3.26	208 (3.82) 276 (3.89) 335 (3.72) 354 (3.62)	1720 1750	2.54 (s, 3 H, C_4–CH_3), 2.62 (s, 3 H, C_{10}–CH_3), 6.45 (d, 1 H, C_7–H, *J*=10.0 Hz), 7.74 (d, 1 H, C_6–H, *J*=10.0 Hz), 7.59 (s, 1 H, C_5–H)	276

refluxed in benzene for 12 h, when it afforded **4a** in 25% yield. The compound **6a** is the minor product in the reaction (20% yield). The compounds **5b**—**f** and **6b**—**f** were similarly synthesized from the correspondingly substituted 6- or 8-allyl-7-hydroxycoumarins by DDQ oxidation. All compounds were fully characterized by analytical and spectral data (Table 1). Spectral data of furo compounds (**6a**—**f**) is available in literature.[6] We conclude that DDQ oxidation of 6- or 8-allyl-7-hydroxycoumarins provides a general method for the synthesis of 2-pyrono and furocoumarins.

Experimental

All melting points reported are uncorrected. IR spectra were recorded on a Perkin-Elmer infrared 337 spectrometer. ^{1}H NMR spectra were run on a Varian A-60 D (80 MHz) instrument in $CDCl_3$ (chemical shift in δ, ppm). The mass spectra were recorded on a UG-Micromass 7070 H instrument.

General Procedure for Preparation of 2-Pyrono and Furocoumarins. A solution of 6- or 8-allyl-7-hydroxy-4-methylcoumarins (**3a**—**f**) (0.001 mol) in benzene and DDQ (0.003 mol) were refluxed for 12 h on a steam bath. A hydroquinone that separates was filtered off and benzene solution was washed with saturated sodium hydrogensulfite ($NaHSO_3$) solution (3×500 ml) followed by water (3×500 ml). Benzene layer was dried over anhydrous sodium sulfate (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting residue on chromatographic purification (silica gel, ACME, 200 mesh) by elution with benzene-ethyl acetate (4 : 1, 600 ml) afforded two products, furocoumarins (**6a**—**f**) and 2-pyronocoumarins (**5a**—**f**) in 16—22% and 50—55% yields respectively.

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