A New and Efficient Synthesis of Coumestan and Coumestrol[1]

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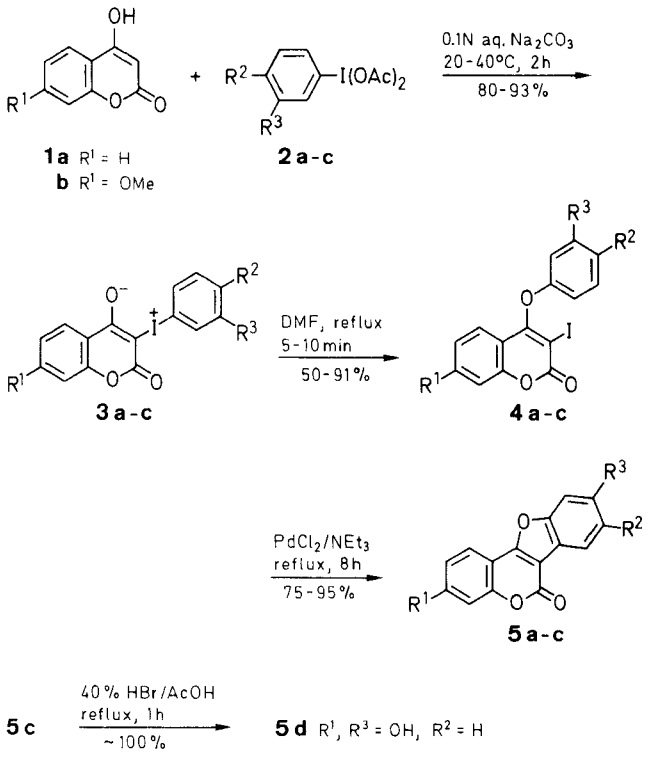
4-Aryloxy-3-iodocoumarins (4-aryloxy-3-iodo-2*H*-1-benzopyran-2-one), **4a–c**, which are readily available by known procedures starting from 4-hydroxycoumarins **1a,b** and diacetoxyiodobenzenes **2a–c**; are cyclized with palladium chloride in triethylamine to yield the coumestanes (6*H*-benzofuran[3,2-*c*][1]benzopyran-6-ones) **5a–c**.

Coumestan (6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one, **5a**) represents the basic ring system for a number of natural products,[2] such as coumestrol,[3] wedelolacton, desmethylwedeloactone, lucernol, psoralidin, isopsoralidin, erosnin, medicagol, and many others.[2] Coumestrol (3,9-dihydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one, **5d**), occurring naturally in ladino clover and alfalfa, shows estrogenic activity.[3] The synthesis of compounds closely related to coumestrol, containing the rigid *E*-stilbene moiety and hydroxy groups at the appropriate positions, leads to compounds with potent biological activity, either acting as estrogens or antiestrogens.[4] Some non-steroidal estrogen antagonists are already in use for the treatment of advanced breast cancer.[5]

Some years ago we reported a simple synthesis of coumestans[6] and coumestrol[7] by cyclodehydrogenation of the corresponding 3-aryl-4-hydroxy-coumarins on palladium at 250 °C. This methodology was also adopted by others to synthesize more complex coumestan derivatives.[8]



2	R^2	R^3	3–5	R^1	R^2	R^3
a	H	H	a	H	H	H
b	OMe	H	b	OMe	OMe	H
c	H	OMe	c	OMe	H	OMe

Later, we showed that the coumestan ring system can also be obtained by photocyclization of 4-phenyloxycoumarin in the presence of iodine, or from its 3-iodo derivative **4a** without the addition of iodine. However, the yields are low (42%)[9] and when the aryloxy substituent contains a methoxy group no cyclization at all occurs.[1,10]

These negative results prompted us to study the Ullmann[11] and Heck reaction[12] with the 4-aryloxy-3-iodocoumarins **4**. While the Ullmann reaction with copper (also with the addition of copper salts) in the usual high boiling solvents failed, the Heck reaction turned out to be a good choice. Among the many tested conditions, the use of palladium chloride in triethylamine gave the best results. Phosphine–palladium complexes or other cocatalysts (such as copper salts, frequently used in the Heck reaction)[12] neither improved the yield nor allowed a reduction in the amount of palladium chloride required.

The preparation of the key intermediates, the 4-aryloxy-3-iodocoumarins **4a–c**, follows the established reaction sequence.[1,9,13–15] Thus, the 4-hydroxycoumarins **1a,b** are treated with the required iodosylbenzenes prepared *in situ* from the corresponding (diacetoxy)iodoarenes **2a–c** with aqueous sodium carbonate solution to yield iodonium ylides **3a–c**. Thermal rearrangement of these ylides leads to **4a–c**, the actual starting material for the Heck reaction.

The rearrangement of **3** to **4** can be regarded as a variation of the Smiles rearrangement and a *spiro*-Meisenheimer complex has been proposed as an intermediate.[15] As a consequence, **3b** yields **4b** and **3c** gives **4c**. This means that starting with **2b** the methoxy group in **4b** is not in the correct position in order to give coumestrol dimethyl ether **(5c)** by the palladium-catalyzed ring closure, but rather **5b**. Fortunately, the benzofuran formation with the *meta* isomer **4c** occurrs only in the *para*-position with regard to the methoxy group, yielding **5c**. A product resulting from the ring closure at the *ortho*-position could not be detected. (There is a small amount of a strongly fluorescent substance present in the mother liquor of **5c**. However, it could be shown by mass spectrometry that this compound is not an isomer of **5c**; the structure of this minor byproduct is still unknown.) The coumestrol dimethyl ether **5c** can be cleaved with hydrobromic acid to coumestrol **5d** in quantitative yield according to the reported procedure.[7]

This new synthetic scheme allows the preparation of many closely related compounds for biological testing, and has also been extended to the synthesis of "aza-coumestrol" analogs, starting with 7-methoxy-2(1*H*)-quinolones instead of coumarins.[17]

Melting points are uncorrected and were obtained on a Gallenkamp Melting Point Apparatus, Mod. MFB-595 (open capillary tubes). ^{1}H-NMR-spectra were recorded on a Varian EM 360 instrument and on a Varian XL 200 instrument (TMS as internal

Table. 3-Aryliodonio-2-oxo-2*H*-benzopyran-4-olate **3a–c**, 4-Aryloxy-3-iodo-2*H*-1-benzopyran-2-ones **4a–c**, 6*H*-Benzofuro[3,2-*c*][1]-benzopyran-6-ones **5a–c**

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula Lit. mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H-NMR (solvent/TMS) δ, J (Hz)
3a	93	136 (MeOH)	136[9]	1720, 1700, 1680, 1650, 1600, 1590, 1560, 1540	DMSO-d_6: 7.00–7.50 (m, 6H$_{arom}$), 7.65–7.75 (m, 2H$_{arom}$), 7.85 (dd, 5H, J = 1.5, 0.7)
3b	90	159–160 (EtOH)	$C_{17}H_{13}IO_5$ (424.2)	1670, 1610, 1590, 1545	DMSO-d_6: 3.75, 3.80 (2s, 3H each, OCH$_3$), 6.75–6.85 (m, 3H$_{arom}$), 7.70, 7.95 (dd, 4H$_{arom}$, J = 1, 0.7)
3c	80	138–140 (PrOH)	$C_{17}H_{13}IO_5$ (424.2)	1670, 1610, 1590, 1520	DMSO-d_6: 3.75, 3.85 (2s, 3H each, OCH$_3$), 6.80–6.90 (m, 2H$_{arom}$), 7.85 (m, 1H$_{arom}$), 7.34–7.45 (m, 3H$_{arom}$), 7.80–7.85 (m, 1H$_{arom}$)
4a	91	138–139 (MeOH)	138–139[9]	1735, 1720, 1700, 1610, 1590, 1500	DMSO-d_6: 6.80–7.30 (m, 7H$_{arom}$), 7.35–7.50 (m, 1H$_{arom}$), 7.60 (dd, 5H, J = 1, 0.7)
4b	77	167–169 (MeOH)	$C_{17}H_{13}IO_5$ (424.2)	1720, 1610, 1995, 1530	CDCl$_3$: 3.74, 3.83 (2s, 3H each, OCH$_3$), 6.65–7.00 (m, 6H$_{arom}$), 7.35 (d, 1H$_{arom}$, J = 7)
4c	50	149–150 (EtOH)	$C_{17}H_{13}IO_5$ (424.2)	1725, 1615, 1590, 1545	CDCl$_3$: 3.80, 3.90 (2s, 3H each, OCH$_3$), 6.45–6.80 (m, 4H$_{arom}$), 6.90 (s, 1H$_{arom}$), 7.25 (t, 1H$_{arom}$, J = 7), 7.42 (d, 1H$_{arom}$, J = 7)
5a	95	182–183 (cyclohexane)	181–182[6,9]	1735, 1625, 1600	CDCl$_3$: 7.15–7.90 (m, 7H$_{arom}$), 7.95–8.15 (m, 1H$_{arom}$)
5b	90	208–209[a] (EtOH)	$C_{17}H_{12}O_5$ (296.2)	1725, 1635, 1600	DMSO-d_6: 3.88, 3.93 (2s, 3H each, OCH$_3$), 7.04–7.15 (m, 2H$_{arom}$), 7.22, 7.28 (2s, 2H$_{arom}$), 7.75, 8.00 (2d, 2H$_{arom}$, J = 7)
5c	75	195[b] (EtOH)	197[7]	1735, 1630, 1610	DMSO-d_6: 3.90, 3.95 (2s, 3H each, OCH$_3$), 7.05–7.15 (m, 2H$_{arom}$), 7.20, 7.25 (2s, 2H$_{each}$), 7.65, 7.92 (2d, 2H$_{arom}$, J = 7)

[a] Purification by sublimation 175 °C/11 mmHg. [b] Purification by sublimation 210 °C/15 mmHg.

standard). Microanalyses were performed on a C,H,N-Automat Carlo Erba 1106. IR spectra were recorded on a Perkin-Elmer 298 (KBr pellets).

3-Aryliodonio-2-oxo-2*H*-1-benzopyran-4-olates 3a–c; General Procedure:

(Diacetoxy)iodoarenes[16] (**2a–c**, 10 mmol) are suspended in a solution of $Na_2CO_3 \cdot 10H_2O$ (2.86 g, 10 mmol) in water (100 mL) and stirred magnetically at r.t. for 30 min. This suspension is added to a solution of 4-hydroxycoumarin (**1a,b**, 10 mmol) and $Na_2CO_3 \cdot 10H_2O$ in water (100 mL). After stirring at r.t. for 2 h, the precipitate is filtered off, washed with water (100 mL) and recrystallized (Table).

4-Aryloxy-3-iodo-2*H*-1-benzopyran-2-ones (4-Aryloxy-3-iodocoumarins) 4a–c; General Procedure:

Compounds **3a–c** (10 mmol) are heated in DMF (50 mL) under reflux for 5 to 10 min. The solvent is removed *in vacuo* and the residue is digested with EtOH (50 mL). Water (50 mL) is added to the product **4a** instead of EtOH (Table).

6*H*-Benzofuro[3,2-*c*][1]benzopyran-6-ones (Coumestans) 5a–c; General Procedure:

Compounds **4a–c** (1 mmol) and $PdCl_2$ (0.09 g, 0.5 mmol) are heated in NEt_3 (20 mL) under reflux for 8 h. Isolation of the product is accomplished by diluting the reaction mixture with hot acetone (100 mL), removing the catalyst by filtration and the organic solvents *in vacuo*. After the addition of water (100 mL) to dissolve triethylammonium hydrochloride, the product is recrystallized (Table).

3,9-Dihydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (Coumestrol, 5d):

According to ref.[7] **5c** was heated for 1 h at reflux temperature in 40% HBr/AcOH. Yield almost quantitative, m.p. above 360 °C.[3,7]

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