Synthesis of Substituted 2*H*[1]Benzopyrans from Coumarins and Chromones

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A convenient route to substituted 2*H*[1]benzopyrans is described in which trialkylaluminium compounds are added to coumarins or chromones and the resultant *Z*-2-(3-hydroxy-1-propenyl)phenols are converted by thermal cyclization in the presence of silica gel to 2*H*[1]benzopyrans.

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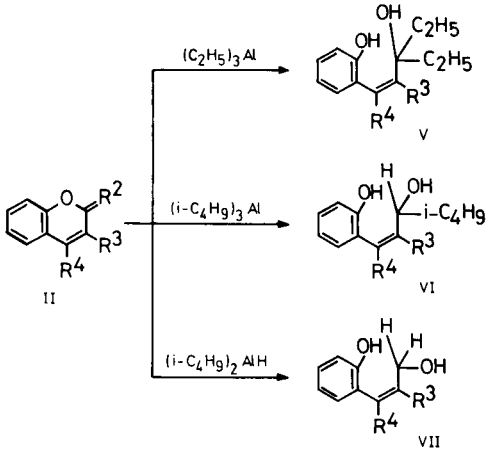
Several approaches to the Synthesis of 2*H*[1]benzopyrans I starting from coumarins II and chromones III have been described. However, these processes seem not to be general because the involved reactions between II or III and Grignard compounds led to complex mixtures of substances depending on both the nature of the organometallic derivative and the nature and position of the substituents at the heterocyclic ring (1-10).

In recent work (11,12) we have studied the transformations of II and III into substituted *Z*-2-(3-hydroxy-1-propenyl)phenols IV by the action of the aluminium trialkyls and observed that, in some cases, they are more useful reagents to open the heterocyclic system than Grignard derivatives. Therefore, as a convenient route to I we sought to combined the reaction between II or III and organoaluminium compounds with the thermal acid-catalysed cyclization of the resulting IV.

Depending on the organometallic employed, 3- or 4-substituted coumarins provided the 3,3-dialkylated V, 3-alkylated VI or reduced VII substituted *Z*-2-(3-hydroxy-1-propenyl)phenols (Table I).

Scheme 1



On the other hand, chromones also react with aluminium trialkyls leading to IV in good yields. In fact, 1,3-diethylated, 1,3-diisobutylated or 3-isobutylated-1-reduced substituted *Z*-2-(3-hydroxy-1-propenyl)phenols are obtained by reaction of III with aluminium triethyl or triisobutyl (Table II).

Table I

Reactions of Coumarins with Organoaluminium Compounds (Scheme 1)

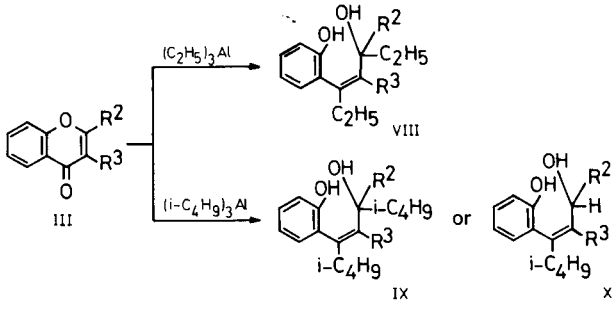
Coumarin	R^3	R^4	Products (%)		
IIa	H	H	Va (70),	VIa (30),	VIIa (73)
IIb	CH_3	H	Vb (69),	VIb (60),	VIIb (76)
IIc	C_2H_5	H	Vc (75),	VIc (55),	VIIc (75)
IId	$C_6H_5CH_2$	H	Vd (72),	VId (45),	VIId (78)
IIe	C_6H_5	H	Ve (65),	—	VIIe (76)
IIf	H	CH_3	Vf (70),	VIf (63),	VIIf (72)

Yields of V are comparable to those previously obtained by us in the reactions of II with ethylmagnesium bromide, except to IIe, that leads to Ve in 20% only.

Only yields of 4-8% in VI are reached in the reactions of II with isobutylmagnesium bromide.

Some coumarins have been previously converted to hemiacetals by diisobutylaluminium hydride (13). Other reducing agents (sodium borohydride, sodium hydride, diborane, *etc.*) do not yield these types of compounds (14,15).

Scheme 2



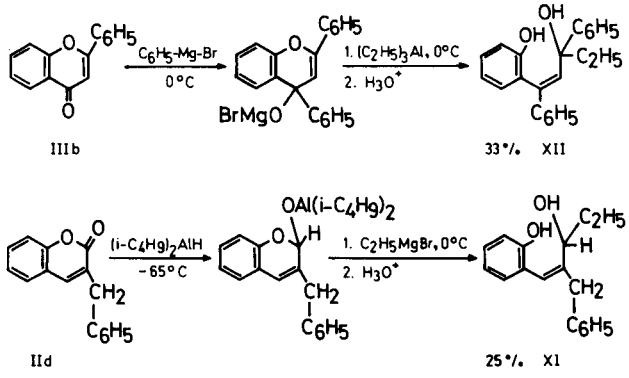
A number of substituted *Z*-2-(3-hydroxy-1-propenyl)-phenols have been obtained by reaction of III with a Grignard derivative, followed by treatment of the intermediate alcoxide with an organoaluminium compound. Compound IV has also been synthesized by the action of a dialkylaluminium hydride upon II and by treatment of the resulting hemiacetal alcoxide with an alkyl magnesium halide (13) (Scheme 3).

Table II

Reactions of Chromones with Aluminium Trialkyls (Scheme 2)

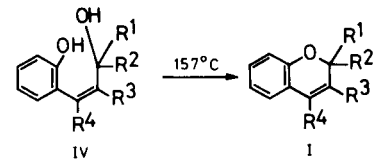
Chromone	R^2	R^3	AIR_3	Products (%)
IIIa	H	H	R = C_2H_5	VIIIa (70)
IIIa	H	H	R = isoC_4H_9	IXa (65)
IIIb	C_6H_5	H	R = C_2H_5	VIIIb (35)
IIIc	H	C_6H_5	R = C_2H_5	VIIIc (60)
IIId	$C_6H_5CH_2$	H	R = isoC_4H_9	Xd (45)

Scheme 3



The cyclization of IV to benzopyrans, in different acidic solutions (1,3), does not always lead to high yields. We report now a clean and more general method for the synthesis of I based on the thermal cyclization (mesitylene at reflux) of IV in the presence of silicagel (Table III).

Scheme 4



The yields of these reactions depend on the nature and position of the substituent at the heterocycle (the highest yields when $R^4 \neq H$, and the lowest if $R^1 = R^2 = H$). This difference in reactivity can be employed to produce the cyclization of some substituted *Z*-2-(3-hydroxy-1-propenyl)-phenols (if $R^1 \neq H$) under mild conditions (reflux of toluene or xylene) in the presence of other phenols of the same group (when $R^1 = R^2 = H$).

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were obtained using a Pye-Unicam 1100 spectrometer. The ^1H nmr spectra were recorded on a Varian T-60A spectrometer, using TMS as an internal standard. Column chromatography was carried out on Merck silica gel, 70-230 mesh, and a mixture of methylene chloride-diethyl ether as the solvent.

Benozopyranones are commercial products, except 3-ethylcoumarin (16), 3-benzylcoumarin and 2-benzylcoumarin (17).

3-Benzylcoumarine.

A mixture of 90 g (0.73 mole) of freshly distilled salicylaldehyde, 320 g (1.13 moles) of phenylpropionic anhydride and 270 g (1.56 moles) of anhydrous sodium phenylpropionate was heated in an oil bath at 240° for 24 hours, after which the mixture was cooled to room temperature

Table III

Cyclization of *Z*-2-(3-Hydroxy-1-propenyl)phenols to 2*H*-1-Benzopyrans I

Starting Compound	R^1	R^2	R^3	R_4	Products (%)
Va	C_2H_5	C_2H_5	H	H	Ia (60)
Vb	C_2H_5	C_2H_5	CH_3	H	Ib (72)
Vc	C_2H_5	C_2H_5	C_2H_5	H	Ic (65)
Vd	C_2H_5	C_2H_5	$C_6H_5CH_2$	H	Id (45)
Ve	C_2H_5	C_2H_5	C_6H_5	H	Ie (61)
Vf	C_2H_5	C_2H_5	H	CH_3	If (75)
VIa	H	iso-C_4H_9	H	H	Ig (60)
VIb	H	iso-C_4H_9	CH_3	H	Ih (64)
VIc	H	iso-C_4H_9	C_2H_5	H	Ii (68)
VId	H	iso-C_4H_9	$C_6H_5CH_2$	H	Ij (70)
VIf	H	iso-C_4H_9	H	CH_3	Ik (76)
VIIa	H	H	H	H	Il (45)
VIIb	H	H	CH_3	H	Im (60)
VIIc	H	H	C_2H_5	H	In (58)
VIId	H	H	$C_6H_5CH_2$	H	Io (45)
VIIe	H	H	C_6H_5	H	Ip (47)
VIIIa	H	C_2H_5	H	C_2H_5	Iq (72)
VIIIb	C_2H_5	C_6H_5	H	C_2H_5	Ir (77)
VIIIc	C_2H_5	H	C_6H_5	C_2H_5	Is (75)
IXa	H	iso-C_4H_9	H	iso-C_4H_9	It (75)
Xd	H	$C_6H_5CH_2$	H	iso-C_4H_9	Iu (80)
XI	H	C_2H_5	$C_6H_5CH_2$	H	Iv (61)
XII	C_6H_5	C_2H_5	H	C_6H_5	Ix (85)

Table IV

Physical Data of Substituted *Z*-2-(3-Hydroxy-1-propenyl)phenols

Compound	Mp (°C)	Method of separation	Yield (%)	^{1}H NMR Spectral Data of Allylic Protons (TMS, deuteriochloroform)	Molecular formula	Elemental Analyses Found (Calcd.) C	H
Va (18)	67	A	70	6.3 (d, 1H), 5.6 (d, 1H)	$C_{13}H_{18}O_2$	75.68 (75.70);	8.80 (8.74)
Vb	96	A	69	6.3 (broad s, 1H)	$C_{14}H_{20}O_2$	76.48 (76.40);	9.04 (9.11)
Vc	86	A	75	6.3 (broad s, 1H)	$C_{15}H_{22}O_2$	76.99 (76.92);	9.29 (9.40)
Vd	101	A	72	6.05 (broad s, 1H)	$C_{20}H_{24}O_2$	80.90 (81.08);	8.02 (8.10)
Ve (11)	96	A	65	6.3 (s, 1H)	$C_{19}H_{22}O_2$	80.61 (80.80);	7.92 (7.80)
Vf (11)	96	A	70	5.55 (broad s, 1H)	$C_{14}H_{20}O_2$	76.61 (76.40);	9.00 (9.09)
VIa (11)	56	B	30	6.4 (d, 1H), 5.7 (c, 1H), 4.3 (m, 1H)	$C_{13}H_{18}O_2$	75.61 (75.70);	8.81 (8.74)
VIb	86	A—B	60	6.3 (b s, 1H), 4.5 (m, 1H)	$C_{14}H_{20}O_2$	76.23 (76.40);	9.11 (9.09)
VIc	96	A—B	55	6.3 (b s, 1H), 4.7 (m, 1H) (a)	$C_{15}H_{22}O_2$	77.01 (76.92);	9.23 (9.40)
VId	104	B	45	6.05 (s, 1H), 4.6 (t, 1H)	$C_{20}H_{24}O_2$	81.23 (81.08);	7.98 (8.10)
VIf	64	A	63	5.5 (m, 1H), 4.15 (m, 1H)	$C_{14}H_{20}O_2$	76.25 (76.40);	9.21 (9.09)
VIIa (19)	114	A	73	6.56 (d, 1H), 5.85 (sext., 1H), 4.4 (m, 2H) (a)	$C_9H_{10}O_2$	72.12 (72.00);	6.72 (6.66)
VIIb	121	A	76	6.35 (s, 1H), 4.15 (s, 2H)	$C_{10}H_{12}O_2$	74.01 (73.78);	7.21 (7.37)
VIIc	94	A	75	6.4 (s, 1H), 4.2 (s, 2H)	$C_{11}H_{14}O_2$	74.30 (74.15);	7.93 (7.86)
VIId	88	A	78	6.4 (s, 1H), 4.2 (s, 2H)	$C_{16}H_{16}O_2$	80.20 (80.00);	6.71 (6.66)
VIIe	99	A	76	6.75 (s, 1H), 4.4 (s, 1H)	$C_{15}H_{14}O_2$	79.48 (79.60);	6.34 (6.19)
VIIIa (12)	65	A	70	5.6 (d, 1H), 4.0 (m, 1H)	$C_{13}H_{18}O_2$	75.51 (75.70);	8.80 (8.74)
VIIIb (12)	97	A—B	35	6.2 (broad s, 1H)	$C_{19}H_{22}O_2$	80.92 (80.80);	7.81 (7.80)
VIIIc (12)	144	A	60	4.1 (t, 1H)	$C_{19}H_{22}O_2$	80.61 (80.80);	7.81 (7.80)
IXa (12)	93	A	65	5.55 (d, 1H), 4.1 (m, 1H)	$C_{17}H_{26}O_2$	81.01 (80.90);	10.2 (10.3)
Xd (12)	123	B	45	5.7 (d, 1H), 4.1 (m, 1H)	$C_{20}H_{24}O_2$	81.00 (81.08);	8.14 (8.10)
XI	111	B	25	6.05 (s, 1H), 4.3 (t, 1H)	$C_{16}H_{20}O_2$	80.48 (80.60);	7.51 (7.46)
XII	96	A—B	33	6.75 (s, 1H)	$C_{23}H_{22}O_2$	83.48 (83.63);	6.79 (6.66)

(a) Solvent perdeuterioacetone.

Table V

Physical Data of Substituted Benzopyrans

Compound	Bp/torr (Mp)	Yield (%)	^{1}H NMR Spectral Data of Allylic Protons (TMS, carbon tetrachloride)	Molecular formula	Elemental Analyses Found (Calcd.) C	H
Ia (18)	99/2.8	60	6.3 (d, 1H), 5.3 (d, 1H)	$C_{13}H_{16}O$	83.02 (82.97);	8.58 (8.51)
Ib	103/1.7	72	6.2 (m, 1H)	$C_{14}H_{18}O$	83.12 (83.16);	8.88 (8.91)
Ic	102/1.5	65	6.2 (s, 1H)	$C_{15}H_{20}O$	83.31 (83.33);	9.29 (9.26)
Id	(104)	45	5.8 (m, 1H)	$C_{20}H_{22}O$	86.16 (86.33);	7.70 (7.91)
Ie	(57)	61	6.4 (s, 1H)	$C_{19}H_{20}O$	86.21 (86.36);	7.41 (7.57)
If	81/1.0	75	5.1 (m, 1H)	$C_{14}H_{18}O$	83.20 (83.16);	8.87 (8.91)
Ig (20)	84/1.2	60	6.0 (m, 1H), 5.0 (c, 1H), 4.5 (m, 1H)	$C_{13}H_{16}O$	83.01 (82.97);	8.55 (8.51)
Ih	90/0.9	64	6.0 (s, 1H), 4.5 (m, 1H)	$C_{14}H_{18}O$	83.22 (83.16);	8.97 (8.91)
Ii	98/1.1	68	6.0 (m, 1H), 4.6 (c, 1H)	$C_{15}H_{20}O$	83.25 (83.33);	9.22 (9.26)
Ij	(70)	70	6.0 (m, 1H), 4.6 (c, 1H)	$C_{20}H_{22}O$	86.22 (86.33);	7.70 (7.91)
Ik	103/2.0	76	5.2 (m, 1H), 4.7 (m, 1H)	$C_{14}H_{18}O$	83.15 (83.16);	8.89 (8.91)
Il (21)	51/1.2	45	6.2 (m, 1H), 5.5 (m, 1H), 4.7 (m, 2H)	C_9H_8O	81.78 (81.81);	6.09 (6.06)
Im (10)	52/0.5	60	6.0 (m, 1H), 4.5 (m, 2H)	$C_{10}H_{10}O$	82.33 (82.19);	6.87 (6.84)
In (10)	60/0.4	58	6.1 (m, 1H), 4.6 (m, 2H)	$C_{11}H_{12}O$	82.34 (82.50);	7.52 (7.50)
Io	(31)	45	6.0 (m, 1H), 4.5 (m, 2H)	$C_{16}H_{14}O$	86.31 (86.48);	6.19 (6.30)
Ip (10)	(94)	47	6.8 (t, 1H), 5.2 (d, 2H)	$C_{15}H_{12}O$	86.45 (86.53);	5.72 (5.77)
Iq	65/1.1	72	5.3 (m, 1H), 4.6 (m, 1H)	$C_{13}H_{16}O$	83.21 (82.97);	8.55 (8.51)
Ir	(44)	77	5.6 (s, 1H)	$C_{19}H_{20}O$	86.17 (86.36);	7.55 (7.58)
Is	(48)	75	4.6 (c, 1H)	$C_{19}H_{20}O$	86.21 (86.36);	7.60 (7.58)
It	97/0.6	75	5.3 (m, 1H), 4.7 (m, 1H)	$C_{17}H_{24}O$	83.75 (83.60);	9.80 (9.83)
Iu	142/0.5	80	5.4 (d, 1H), 4.9 (m, 1H)	$C_{20}H_{22}O$	86.52 (86.33);	7.96 (7.91)
Iv	(65)	61	6.0 (m, 1H), 4.5 (c, 1H)	$C_{18}H_{16}O$	86.27 (86.40);	7.18 (7.20)
Ix	(105)	85	5.9 (s, 1H)	$C_{23}H_{20}O$	88.56 (88.46);	6.39 (6.41)

and then poured into water. The organic material was extracted with ether and the ethereal solutions were dried over anhydrous calcium chloride. The solvent was removed and the residue fractionated under reduced pressure. The distillate was diltuted with acetone and the resultant precipitate of 3-benzylcoumarin was filtered (82 g, 47%) and recrystallized from acetone, mp 104-105°.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.35; H, 5.08. Found: C, 81.39; H, 5.00.

Reactions of Benzopyranones with Organoaluminium Compounds. General Method.

To a magnetically stirred solution of the organoaluminium compound (0.45 mole) in 200 ml of dry benzene [In the reactions with diisobutylaluminium hydride, a commercially available solution (20% in hexane) was employed.] in a three necked flask supplied with a continual nitrogen flush, was dropped at 0° 0.15 mole of benzopyranone in benzene (150 ml). [When the benzopyranone was not soluble the compound was added as a solid.] The nitrogen flush was stopped and the solution was maintained at room temperature during 24 hours and then refluxed 2 more. The solution was cooled, poured into an ice-water mixture and acidified until aluminium hydroxide was just dissolved. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent eliminated under reduced pressure.

General Method of Purification and Separation.

The method of separation and purification of hydroxycinnamyl alcohols depends upon the abundance of the substrate in the final reaction mixture.

Method A.

In reactions of high yields the substrates crystallize by evaporation of the reaction solvent or appear as a heavy oil that solidifies by addition of hexane and cooling. The products were recrystallized from hexane-benzene.

Method B.

In the reactions of lower yields, the final reaction mixture, after the solvent was removed, was chromatographed on a column (500 g of Merck Kieselgel-60, 15 g of mixture) using methylene chloride-diethyl ether (20:3) or pure methylene chloride as the eluent.

Table IV summarizes the physical data of all these compounds.

Cyclization of *Z*-2-(3-Hydroxy-1-propenyl)phenols to 2*H*[1]benzopyrans.

The following general procedure of reaction is representative.

A mixture of 0.1 mole of the substrate in 250 ml of dry mesitylene and 80 g of silica gel (Merck, Kieselgel-60) recently activates at 120° was refluxed for 2-5 hours. [The process was monitored by thin layer chromatography (silicagel and methylene chloride-diethyl ether, 20:3); the reaction time was, in general, 2 hours for 4-substituted chromenes and 5 hours for the rest.] The hot mixture filtered off and the silica gel washed twice with 100 ml of hot mesitylene. The filtrate was fractionated and the resultant oil chromatographed on silicagel-hexane. The solid compounds (Id, Ie, Ij, Ip, Ir, Is, Iv and Ix) crystallized when the concentrated solution in mesitylene was diluted with ethanol.

The data of all of these substances is recorded in Table V.

Reaction of Flavone with Phenylmagnesium Bromide and Triethylaluminium.

The flavone (19 g, 0.85 mole) was added slowly to an ethereal solution of phenylmagnesium bromide (made from 15.7 g (1 mole) of bromobenzene and 2.5 g (1.03 moels) of magnesium turnings) at 0° and the resultant mixture was allowed to stand for 12 hours at room temperature after which the diethyl ether was replaced by an equivalent amount of dry benzene and 30 ml (2.22 moles) of triethyl aluminium was added dropwise at 0°. After stirring the mxiture for 12 hours at room temperature, it was hydrolyzed, the organic layer removed and fractionated as was described in method B (methylene chloride was mobile phase). The main fraction (9.3 g, 33%) was identified as *Z*-2-(1,3-diphenyl-3-hydroxy-1-pentenyl)phenol, mp 95.5-96.5 (from hexane-benzene).

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