Stereoselective Synthesis of Aryl-substituted *o*-Allylphenols

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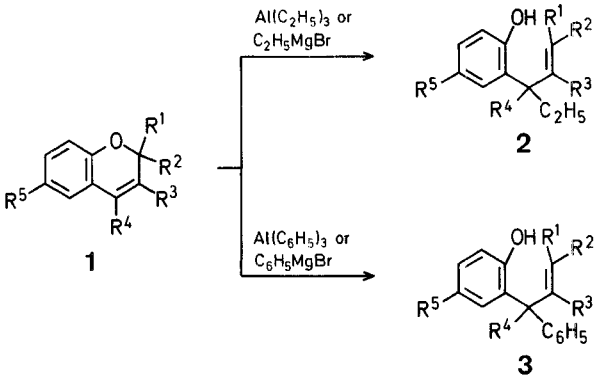
The reaction of 2-alkyl- and 2,2-dialkyl-2*H*-1-benzopyrans with trialkylaluminium reagents provides a good synthetic route to *o*-allylphenols[1]. On the other hand, the 2,3-dialkyl- and 2,2,3-trialkyl-2*H*-1-benzopyrans react with triethylaluminium or ethylmagnesium bromide in a stereoselective fashion, yielding either (*E*)- (60–70%) or (*Z*)- (54–65%) *o*-allylphenols depending upon the experimental conditions[2]. The transformations of 2,4-dialkyl- and 2,2,4-trialkyl-2*H*-1-benzopyrans[2] are also of preparative interest.



We now report the synthesis of aryl-substituted *o*-allylphenols by the reaction of (a) alkylbenzopyrans with phenylmagnesium bromide or triphenylaluminium, and (b) arylbenzopyrans with organomagnesium and organoaluminium derivatives. This strategy allows us to prepare different aryl-substituted *o*-allylphenols from the same 2*H*-1-benzopyran (Table 1).

In a general sense the following observations can be established:

(a) The reactivity of the substrate, and the yield and stereoselectivity [i.e., the formation of (*E*)- or (*Z*)-isomer] of this process are dependent upon the organometallic compound and solvent employed, the position of the substituents at the starting 2*H*-1-benzopyran, and whether or not the system is irradiated.

(b) The yield is not apparently related with the reactivity of the substrate. It increases if the starting 2*H*-1-benzopyran is aryl-substituted at C-2 and the system is under U.V. irradiation, and decreases when the substituents are at C-3 or C-4 (the influence of aryl groups at C-2, C-3, and C-4 is greater than that of alkyl substituents at the same positions[1,2]) or when ether is used as solvent.

Table 1. Reactions of 2*H*-1-Benzopyrans **1** with Organometallic Reagents

Substrate No.	R^1	R^2	R^3	R^4	R^5	Organometallic Reagent	Solvent (reflux)	Time [h]	Products	Yield[a] [%]
1a[3]	H	H	H	H	H	$(C_6H_5)_3Al$	toluene	24	**3a**	80
1b[4]	CH_3	H	H	H	H	C_6H_5MgBr	toluene	5	(*E*)-**3b**	15
1c[5]	C_2H_5	C_2H_5	H	CH_3	H	C_6H_5MgBr	ether	24[b]	**3c**	60
1d[6]	C_6H_5	H	H	H	H	$(C_2H_5)_3Al$	benzene	6	(*E*)-**2d**	87
						C_2H_5MgBr	ether	7[b]	(*E*)-**2d** + (*Z*)-**2d**	31 + 42
1e[5]	H	H	C_6H_5	H	H	$(C_2H_5)_3Al$	benzene	4	**2e**	< 5[c]
						$(C_2H_5)_3Al$	benzene	15[b]	**2e**	40
1f[7]	4-H_3CO—C_6H_4	H	H	H	H	$(C_2H_5)_3Al$	benzene	2	(*E*)-**2f**	70
1g	C_6H_5	H	CH_3	H	CH_3	$(C_2H_5)_3Al$	benzene	1	(*E*)-**2g**	70
						$(C_2H_5)_3Al$	benzene	0.25	(*E*)-**2g**	73
						$(C_2H_5)_3Al$	ether	5.5[b]	(*E*)-**2g** + (*Z*)-**2g**	30 + 60
						C_2H_5MgBr	ether	14	(*E*)-**2g** + (*Z*)-**2g**	28 + 54
						C_2H_5MgBr	toluene	10	(*E*)-**2b**	80
						C_2H_5MgBr	THF	5.5[b]	(*E*)-**2g** + (*Z*)-**2g**	43 + 21
						$(C_6H_5)_3Al$	ether	8[b]	(*E*)-**3g** + (*Z*)-**3g**	68 + 24
						$(C_6H_5)_3Al$	toluene	9	(*E*)-**3g**	77
						C_6H_5MgBr	ether	11[b]	(*E*)-**3g** + (*Z*)-**3g**	35 + 54
						C_6H_5MgBr	toluene	4	(*E*)-**3g**	37
1h	C_2H_5	C_2H_5	C_6H_5	H	H	$(C_2H_5)_3Al$	benzene (20°C)	4	**2h**	< 5[c]
						$(C_2H_5)_3Al$	benzene	2[b]	**2h**	10
						C_2H_5MgBr	ether	9.5[b]	**2h**	60
						C_6H_5MgBr	ether	11[b]	**3h**	48
1i	—$(CH_2)_4$—		H	H	H	C_6H_5MgBr	ether	14[b]	**3i**	66
						C_6H_5MgBr	toluene	4	**3i**	70
1j	—$(CH_2)_4$—		H	CH_3	H	C_6H_5MgBr	ether	25[b]	**3j**	82
1k	—$(CH_2)_4$—		H	C_6H_5	H	CH_3MgBr	ether	20[b]	—[d]	—[c]
1l[5]	C_6H_5	C_2H_5	H	C_6H_5	H	C_2H_5MgBr	ether	7[b]	—[e]	—
1m[5]	H	C_2H_5	C_6H_5	C_2H_5	H	$(C_2H_5)_3Al$	benzene	5	**2m**	< 5[c]

[a] Yield of pure, isolated product. The by-products of the reactions are reduced *o*-allylphenols[1], *o*-propenylphenols[1], dienic phenols[2], rearranged products [i.e. *o*-(1-phenyl-1-butenyl)-phenol from (*E*)-**3b**], and phenol.

[b] Reactions under U.V. irradiation.

[c] **1e** (90 =), **1h** (70%), **1k** (50%), and **1m** (90%), respectively are recovered unchanged.

[d] Product **3k** cannot be isolated from the reaction mixture.

[e] The starting material is completely transformed but **3l** cannot be isolated.

(c) The reactions without U.V. irradiation yield (*E*)-*o*-allylphenols almost exclusively. On the contrary, the reactions under U.V. irradiation in ether lead to a mixture of geometrical isomers, that are separable by column chromatography (silica gel, hexane/benzene: 10/3). The amount of the (*Z*)-isomer increases with the bulk of the substituent at C-3[1].

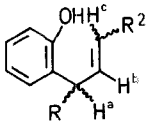
(d) The yield of *o*-allylphenols is improved in the case of reactions with Grignard reagents by working in diethyl ether as solvent and under U.V. irradiation. In reactions that lead to a mixture of (*E*/*Z*)-isomers, the latter is obtained as the major product. Using organoaluminium reagents, the best results are obtained with toluene/triphenylaluminium or benzene/triethylaluminium at reflux temperature if the starting compound is a 4-substituted-2*H*-1-benzopyran. The yields of (*E*)-*o*-allylphenols are higher by this procedure than in the reactions with organomagnesium compounds.

Table 2. Chemical Shifts of H^a, H^b, and H^c of the Geometrical Isomers of **2** and **3**

Isomer	Chemical Shift δ [ppm] H^a	H^b	H^c
(*E*)-**2d**	3.65	6.30	6.35
(*Z*)-**2d**	3.90	5.80	6.45
(*E*)-**2g**	3.50	—	6.60
(*Z*)-**2g**	3.95	—	6.40
(*E*)-**3g**	5.10	—	6.15
(*Z*)-**3g**	5.50	—	6.65

The probable reaction mechanisms have been proposed in earlier communications[1,2]. The geometry of (*E*)-*o*-allylphenols (**2d, 2f,** and **3b**) is unequivocally assigned by its typical I.R. absorption at 965 cm^{-1}, whereas the chemical shift and coupling constants of the olefinic protons do not allow the assignation of the configuration in some cases [i.e., (*E*)-**2d** and (*E*)-**2f**, $\delta_{H^c} \simeq \delta_{H^c}$ and $J_{trans} \simeq 0$].

In all the compounds, and also in the alkyl-substituted 2*H*-1-benzopyrans[2], the resonance of H^a in the (*E*)-isomer is at higher field than that of the (*Z*)-compound. The assignation of the configuration of *o*-allylphenols with trisubstituted double bonds (Table 2) was made on the base of the above observations and the analogous chemical behaviour with the alkyl-substituted 2*H*-1-benzopyrans[2].



The 2*H*-1-benzopyrans **1a–f, 1h, 1l,** and **1m** are prepared by reported methods[3–7].

3,6-Dimethyl-2-phenyl-2*H*-1-benzopyran (1g):
Prepared from 3,6-dimethylflavanone by the method reported[8] for the synthesis of 1-methyl-2-phenyl-2*H*-1-benzopyran; white solid; yield: 77%; m.p. 61–62°C (from ethanol).

$C_{17}H_{16}O$	calc.	C 86.40	H 6.82
(236.3)	found	86.45	6.83

Spiro[2*H*-1-benzopyran-2,1′-cyclopentane] (1i):
A suspension spiro[4-chromanone-2,1′-cyclopentane][9] (40 g, 0.2 mol) and lithium aluminium hydride (3.7 g) in ether (300 ml) is refluxed for 4 h. After treatment with dilute acetic acid (100 ml), the ether layer is washed with water (500 ml), and aqueous sodium hydrogen carbonate (100 ml), dried with sodium sulfate, and concentrated to dryness. The crystalline product, without further purification, and *p*-toluenesulphonic acid (0.1 g) are refluxed in toluene (400 ml) for 20 min with azeotropic removal of water (Dean-Stark trap). The solution is cooled, washed with water (300 ml), dried, and the solvent evaporated under reduced pressure. The residue is vacuum-distilled, giving **2i** as a colourless liquid; yield: 28.27 g (76%); b.p. 92°C/1 torr.

$C_{13}H_{14}O$	calc.	C 83.83	H 7.58
(186.2)	found	83.80	7.60

Table 3. Characterisation of Compounds **2** and **3**

Product	m.p. [°C] or b.p. [°C]/torr	Molecular formula[a]	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm] (allylic protons only)	Phenylurethane Molecular formula[b]	Phenylurethane m.p. [°C]
3a	183–185°/12	Ref.[10], b.p. 183–185°/12 torr	6.30 (dq, H^b, J_{ab}=6 Hz, J_{bc}=18 Hz, J_{bd}=10 Hz); 4.8–5.35 (m, H^a, H^c, H^d)	—	90–91°
(*E*)-**3b**	oil	—	5.80 (q, H^b, J_{ab}=6 Hz, J_{bc}=14 Hz); 5.35 (q, H^c, J_{cd}=6 Hz); 4.85 (d, H^a)	$C_{23}H_{21}NO_2$ (343.4)	97–98°
3c	134–138°/1	—	5.95 (br. s, 1 H)	$C_{27}H_{29}NO_2$ (399.5)	117–118°
(*E*)-**2d**	120–122°/0.5	—	6.35 (s, H^c); 6.30 (d, H^b, J_{ab}=4 Hz); 3.65 (m, H^a)	$C_{24}H_{23}NO_2$ (357.4)	104–105°
(*Z*)-**2d**	136–138°/1	—	6.45 (d, H^c); 5.80 (dd, H^b, J_{ab}=11 Hz, J_{bc}=12 Hz); 3.9 (m, H^a)	$C_{24}H_{23}NO_2$ (357.4)	111–112°
2e	122–124°/0.5	—	5.45 (s, 1 H); 5.25 (s, 1 H); 4.10 (t, H^a, J=7 Hz)	$C_{24}H_{23}NO_2$ (357.4)	115–116°
(*E*)-**2f**	101°	$C_8H_{20}O_2$ (132.2)	6.25 (s, H^c); 6.20 (d, H^b, J_{ab}=6 Hz); 3.55 (m, H^a)	—	—
(*E*)-**2g**	168–170°/1.2	—	6.60 (s, 1 H); 3.50 (t, H^a, J_{ad}=7 Hz)	$C_{26}H_{25}NO_4$ (415.5)[c]	117–118°[c]
(*Z*)-**2g**	54°	$C_{19}H_{22}O$ (266.4)	6.40 (s, 1 H); 3.95 (t, H^a, J_{ad}=8 Hz)	$C_{26}H_{25}NO_2$ (383.5)	114–115°
(*E*)-**3g**	87°	$C_{23}H_{22}O$ (314.4)	6.15 (br. s, 1 H); 5.10 (s, 1 H)	$C_{30}H_{27}NO_2$ (433.5)	130–131°
(*Z*)-**3g**	80°	$C_{23}H_{22}O$ (314.4)	6.65 (s, 1 H); 5.50 (s, 1 H)	$C_{30}H_{27}NO_2$ (433.5)	146–147°
2h	125–128°/0.5	—	4.20 (t, H^a, J_{ad}=8 Hz)	$C_{28}H_{31}NO_2$ (413.5)	138–139°
3h	66°	$C_{25}H_{26}O$ (342.5)	5.70 (s, 1 H)	$C_{32}H_{31}NO_2$ (461.6)	126–127°
3i	95–100°/0.5	—	5.75 (br. d, H^b, J_{ab}=9 Hz); 5.00 (d, H^a)	$C_{26}H_{25}NO_2$ (383.5)	125–126°
3j	170–173°/2.5[d]	—	6.10 (br. s, 1 H)	$C_{27}H_{27}NO_2$ (397.5)	127–128°

[a] Satisfactory microanalyses obtained for solid *o*-allylphenols: C ±0.04, H ±0.05.
[b] Satisfactory microanalyses obtained for the derivatives: C ±0.05, H ±0.06, N ±0.03.
[c] Values for the *p*-nitrobenzoate derivative.
[d] The product decomposes partially during distillation.

4-Methylspiro[2*H*-1-benzopyran-2,1′-cyclopentane] (1j):
A solution of spiro[4-chromanone-2,1′-cyclopentane][9] (35 g, 0.17 mol) in anhydrous ether (100 ml) is added dropwise at −10°C to a solution of methylmagnesium iodide (0.22 mol) in ether (100 ml). After the addition is complete, the mixture is stirred for 1 h at room temperature. The magnesium complex is decomposed with saturated ammonium chloride solution (200 ml). The ether layer is separated, washed with water (200 ml), dried, and the solvent is evaporated. The residual oil is added to a solution of *p*-toluenesulphonic acid (0.1 g) in toluene (300 ml), and the mixture is refluxed slowly for 15 min. The solution is cooled, washed with water (300 ml), and dried with magnesium sulfate. The solvent is removed under reduced pressure, and the resultant oil chromatographed over silica gel using hexane as eluent to give the product; yield: 18 g (53%); b.p. 100–102°C/1 torr.

$C_{14}H_{16}O$	calc.	C 83.96	H 8.05
(200.3)	found	83.98	8.07

4-Phenylspiro[2*H*-1-benzopyran-2,1′-cyclopentane] (1k):
Prepared from spiro[4-chromanone-2,1′-cyclopentane] and phenylmagnesium bromide as described for **1j**; yield: 6%; white solid; m.p. 67–68°C.

$C_{19}H_{18}O$	calc.	C 86.99	H 6.92
(262.3)	found	86.95	6.94

Reaction of 2*H*-1-Benzopyrans with Organometallic Compounds; General Procedure:
A solution of the 2*H*-1-benzopyran (0.015 mol) and the organometallic compound (0.045 mol) in solvent (50 ml) is refluxed under nitrogen (Table 1). The solution is cooled, poured into ice/water (100 ml), and acidified until the metal hydroxide is just dissolved. The organic layer is washed with a sodium hydrogen carbonate solution (200 ml) and dried with anhydrous magnesium sulphate. The products are purified by chromatography of the reactions mixtures through a silica gel column, using benzene/*n*-hexane (3/10) as eluent, and vacuum distillation or recrystallisation (*n*-hexane). The irradiation reactions are carried out in a Pyrex flask one centimeter from the light source (quartz lamp, 125 W).

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