Substitution and Elimination Reactions of 3- and 4-Alkyl-2*H*-1-benzopyrans with Organoaluminium and Organomagnesium Reagents

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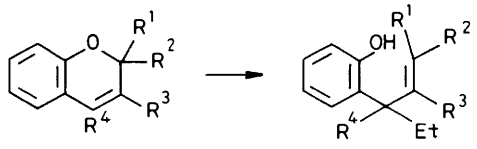
2,3-Dialkyl- and 2,2,3-trialkyl-2*H*-1-benzopyrans react with triethylaluminium or ethylmagnesium bromide yielding substituted *o*-allylphenols in good yield. The reactions of 2,3-dialkyl-2*H*-1-benzopyrans are stereoselective. Either the *E* or *Z* isomers can be formed preferentially depending upon the experimental conditions; the stereoselectivity increases with the bulk of the alkyl substituent at C-3. However 2,4-dialkyl- and 2,2,4-trialkyl-2*H*-1-benzopyrans lead to *o*-allylphenols only with ethylmagnesium bromide; the mixture of *E* and *Z* isomers thus formed was found to be very difficult to separate.

The reaction of 2-alkyl- and 2,2-dialkyl-2*H*-1-benzopyrans with triethylaluminium provides a good synthetic approach to *o*-allylphenols.[1] We have now investigated the behaviour of the 3-alkyl and 4-alkyl substituted 2*H*-1-benzopyrans under a variety of conditions as follows. Method A, reaction with triethylaluminium in benzene at 80 °C; method B, the same conditions but with u.v. irradiation; method C, reaction with ethylmagnesium bromide in toluene at 110 °C; and method D, in diethyl ether at 35 °C† and with u.v. irradiation. The purpose of this study is to determine the influence of the substitution at C-3 and C-4 upon the outcome of the reaction. The results obtained are summarized in Table 1.



(1) (2)

a; $R^1 = R^2 = R^4 = H, R^3 = Me$
b; $R^1 = Bu^i, R^2 = R^4 = H, R^3 = Me$
c; $R^1 = R^2 = Et, R^3 = Me, R^4 = H$
d; $R^1 = Bu^i, R^2 = R^4 = H, R^3 = Et$
e; $R^1 = R^2 = R^3 = Et, R^4 = H$
f; $R^1 = R^2 = R^4 = H, R^3 = Bz$
g; $R^1 = Bu^i, R^2 = R^4 = H, R^3 = Bz$
h; $R^1 = R^2 = Et, R^3 = Bz, R^4 = H$
i; $R^1 = R^4 = Et, R^2 = R^3 = H$
j; $R^1 = R^2 = Et, R^3 = H, R^4 = Me$
k; $R^1 = Bu^i, R^2 = R^3 = H, R^4 = Me$
l; $R^1 = Bu^i, R^2 = R^3 = H, R^4 = Bu^i$
m; $R^1,R^2 = -(CH_2)_4-, R^3 = H, R^4 = Me$
n; $R^1 = Me, R^2 = R^3 = R^4 = H$

Scheme 1.

In a general sense it can be established that the reactions of the 2,3-dialkyl- and 2,2,3-trialkyl-2*H*-1-benzopyrans are of synthetic interest. The 2,3-dialkyl derivatives react with organoaluminium and organomagnesium compounds in a stereoselective fashion. Depending on the experimental conditions either the *E*- (60—70%) or *Z*-alkenes (54—65%) can be obtained as exclusive or major products. Furthermore, the degree of stereoselectivity increases with the size of the substituent at C-3. The isomeric mixtures are separable by column chromatography on silica gel (eluant: hexane–benzene, 10:3).

We have studied only five examples of 2,4-dialkyl- and 2,2,4-trialkyl-2*H*-1-benzopyrans. They react quickly with triethylaluminium (methods A and B), isomerizing to give unstable butadienylphenols (**3**) which revert to the starting materials with slight heating.‡ However, using methods C and D, compounds (**1j**), (**1k**), and (**1m**) give the *o*-allylphenols. Compound (**2k**) was formed as a mixture of geometrical isomers (70%), not separable by column chromatography.

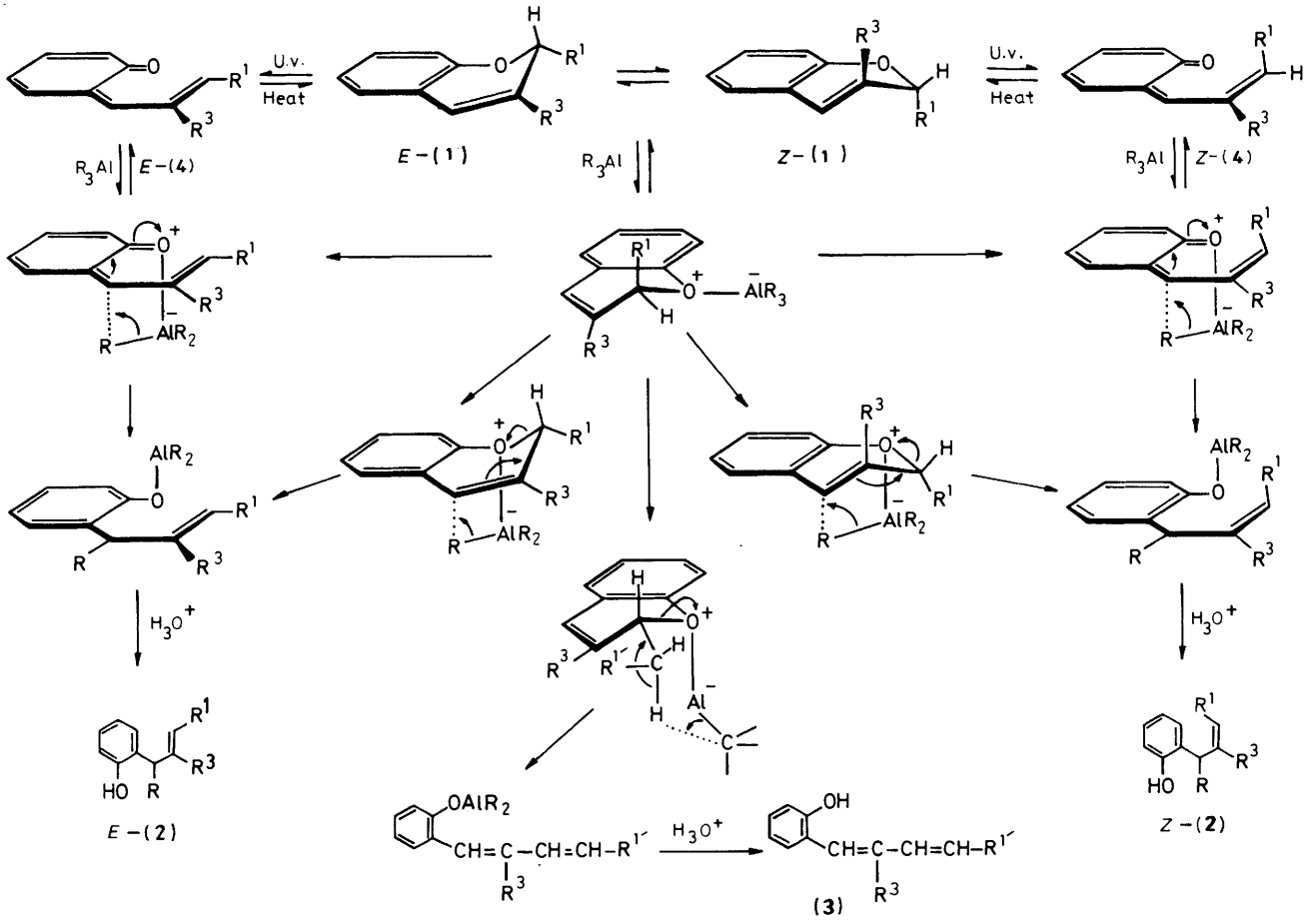
The experimental results allow us to make the following generalizations. (a) The reactivity of (**1**) [*i.e.* the rate of conversion into (**2**) and/or (**3**)] towards these organometallics is not related to the yields of the *o*-allylphenols (**2**). Consequently (**2**) and (**3**) could be formed by two independent and competitive routes. (b) The configuration of the double bond of (**2b**), (**2d**), (**2g**), (**2k**), and (**2n**) has been found to be dependent upon, (i) the Lewis acidity of the organometallics, (ii) the basicity of the solvents, and (iii) whether or not the system is irradiated.

Although we have not performed mechanistic investigations, Scheme 2 suggests[1] two alternative paths to (**2**): namely, 1,4-addition to the quinone methides (**4**) or S_N' substitution of the allyl ether system, the latter being a base-induced elimination leading to (**3**). The *E*/*Z* ratios might be explained, among other considerations, by a conformational preference for the formation of *E*-(**4**) or *Z*-(**4**).

The stereochemistry of the S_N' path is not discussed and we

† The 2*H*-1-benzopyrans react with ethylmagnesium bromide (ether at 35 °C) only if the mixture is subjected to u.v. irradiation.

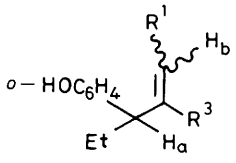
‡ Butadienylphenols are obtained as minor products in all of these reactions, and we have characterized the compounds derived from (**1d**) and (**1g**) by ^1H n.m.r. spectroscopy. The ^1H n.m.r. spectra do not however permit assignment of *E* or *Z* geometry to the double bond. Nevertheless the facile conversion of the compounds into the starting 2*H*-1-benzopyrans allows the assignment of the *cis* configuration[2] to the 1′ double bond.



Scheme 2.

have shown only some of the possible transition states. The substitution can also be performed in an intermolecular fashion by a second equivalent of organometallic.

The use of (**2n**) as a reference compound allows the assignment of *E* and *Z* configurations to (**2b**), (**2d**), and (**2g**) based upon ^{1}H n.m.r. spectral comparisons. The chemical shift of H_a in the compounds obtained by methods A and C is at higher field (25—40 Hz) than the corresponding isomer prepared by method D (Table 2); δ H_b varies in a reverse sense but to a lesser degree.



The geometry of (**2n**) can be unequivocally assigned from its i.r. spectrum.* The isomer obtained by method A possesses absorption typical of a *trans* double bond at 970 cm^{-1}, but the isomer obtained by method D does not.

Generalizing these experimental results to include the other compounds enables us to conclude that the resonance of H_a in the *E* isomer is at higher field than that of the *Z*, whilst the reverse is true of the H_b resonance. Further, that the *E* isomers are obtained by method A, B, or C, and method D leads to the *Z* isomers. The strong diastereotopy of H_c in the *E* isomer must be attributed to the hindered rotation of the benzyl group *cis* with respect to the isobutyl substituent. The *Z* isomer does not

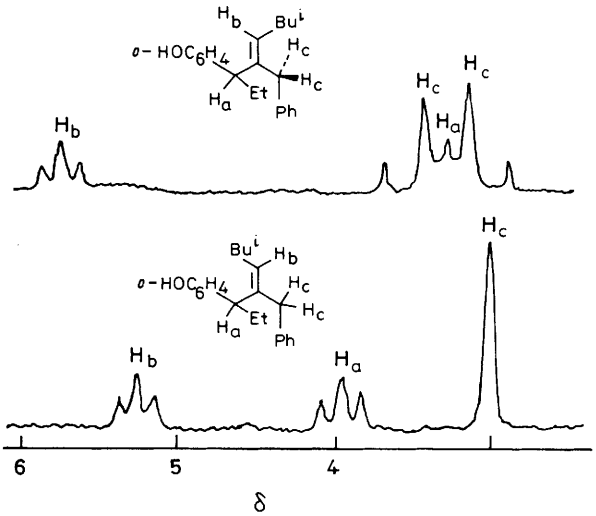


Figure.

* The ^{1}H n.m.r. spectrum of (**2n**) shows the olefinic protons as being split into a second-order system, and its coupling constants do not allow the ready assignation of the configuration.

Table 1. Reactions of 2*H*-1-benzopyrans with organometallic compounds

2*H*-1-Benzopyran	Method	Time (h)	*o*-Allylphenols (%)
(**1a**)	A	25	(**2a**) (<5) [a]
(**1a**)	B	15	(**2a**) (55) [b]
(**1b**)	A	2	*E*-(**2b**) (68)
(**1b**)	B	0.5	*E*-(**2b**) (70)
(**1b**)	C	10	*E*-(**2b**) (55)
(**1b**)	D	13	*E*-(**2b**) (32), *Z*-(**2b**) (54) [c,d]
(**1c**)	A	3	(**2c**) (50)
(**1c**)	B	0.75	(**2c**) (50)
(**1c**)	C	10	(**2c**) (35)
(**1c**)	D	10	(**2c**) (70)
(**1d**)	A	5	*E*-(**2d**) (60)
(**1d**)	B	3.5	*E*-(**2d**) (48)
(**1d**)	C	25	*E*-(**2d**) (20)
(**1d**)	D	8	*E*-(**2d**) (24), *Z*-(**2d**) (69)
(**1d**)	*	20	*E*-(**2d**) (35), *Z*-(**2d**) (7)
(**1e**)	A	2	(**2e**) (25)
(**1e**)	B	1.5	(**2e**) (20)
(**1e**)	C	20	(**2e**) (<5)
(**1e**)	D	20	(**2e**) (70)
(**1f**)	A	25	(**2f**) (<5) [e]
(**1f**)	B	12	(**2f**) (30) [c,f,g]
(**1g**)	A	6	*E*-(**2g**) (66)
(**1g**)	B	3.5	*E*-(**2g**) (51)
(**1g**)	C	20	*E*-(**2g**) (21)
(**1g**)	D	4	*E*-(**2g**) (27), *Z*-(**2g**) (68)
(**1h**)	A	3.5	(**2h**) (10)
(**1h**)	B	2	(**2h**) (10)
(**1h**)	C	20	(**2h**) (<5)
(**1h**)	D	24	(**2h**) (62)
(**1i**)	A	3	
(**1j**)	A	13	(**2j**) (<5)
(**1j**)	C	4	(**2j**) (64)
(**1j**)	D	21	(**2j**) (87)
(**1k**)	D	20	*E*-(**2k**) (60), *Z*-(**2k**) (17) [c,d]
(**1l**)	A	3	
(**1m**)	C	4	(**2m**) (80)
(**1m**)	D	28	(**2m**) (82)
(**1n**)	A	2	*E*-(**2n**) (73),
(**1n**)	D	25	*E*-(**2n**) (41), *Z*-(**2n**) (25) [c,d]

[a] Starting material recovered in 50% yield. [b] (**1a**) (10%) also obtained. [c] Yield was determined by g.l.c. and ^{1}H n.m.r. spectroscopy before separation of the reaction mixture. [d] The separation of *E* and *Z* isomers by the general chromatographic method (silica gel–hexane–benzene) is very difficult. [e] (**1f**) (90%) also present. [f] Because of its instability the compound was not obtained pure by the chromatographic method. [g] (**1f**) (13%) also present.

* $AlEt_3$ in diethyl ether with u.v. irradiation.

possess this steric hindrance and the protons H_c became magnetically equivalent (see Figure).

Experimental

M.p.s are uncorrected. I.r. spectra were recorded with a Pye-Unicam SP 1100 instrument, and ^{1}H n.m.r. were obtained on a Varian T-60A spectrometer at 60 MHz, using $SiMe_4$ as internal standard. G.l.c. was carried out on a Hewlett-Packard 5710-A chromatograph using nitrogen as carrier gas and a column packed with DEGS (20%) on Chromosorb W-HMDS 80/100.

Table 2. Chemical shift (p.p.m.) of H_a and H_b in the geometrical isomers of (**2**)

Compound	Method	δ H_a	δ H_b
(**2n**)	A	3.40	*ca.* 5.60
(**2n**)	D	3.85	*ca.* 5.60
(**2b**)	A	3.30	5.55
(**2b**)	D	3.95	5.45
(**2d**)	A	3.50	5.55
(**2d**)	D	4.00	5.45
(**2g**)	A	3.25	5.70
(**2g**)	D	3.95	5.20

Mass spectra were performed on a Hewlett-Packard 5930-A spectrometer.

Synthesis of 2H-1-*Benzopyrans*.—Compounds (**1a**)—(**1l**) were synthesized by dehydration of the corresponding *Z*-1-(3-hydroxyprop-1-enyl)phenols,[3] obtained from coumarins and organometallic compounds.[4]

2-Methyl-2*H*-1-benzopyran (**1n**) was prepared by a described procedure,[5] and 4-methyl-2*H*-1-benzopyran-2-spirocyclopentane (**1m**) as follows. A solution of 3,4-dihydro-4-oxo-2*H*-1-benzopyran-2-spirocyclopentane [6] (35 g, 0.17 mol) in anhydrous ether (100 ml) was added dropwise at −10 °C to a solution of ethylmagnesium iodide (0.22 mol) in ether (100 ml). After the addition was complete, the reaction mixture was stirred for 1 h at room temperature. The magnesium complex was decomposed with aqueous ammonium chloride. The ether layer was separated, washed with water, dried, and the solvent distilled. To the residual oil were added toluene (300 ml) and toluene-*p*-sulphonic acid (0.1 g) and the mixture was distilled slowly for 15 min. The solution was cooled, washed with water, and dried ($MgSO_4$). The solvent was distilled under reduced pressure and the resultant oil was chromatographed (silica gel–hexane) to give 4-*methyl*-2H-1-*benzopyran*-2-*spirocyclopentane* (18 g, 53%), b.p. 100—102 °C/1 Torr (Found: C, 84.0; H, 8.05. $C_{14}H_{16}O$ requires C, 83.96; H, 8.05).

Reaction of 2H-1-*Benzopyrans with Organometallic Compounds: General Procedure*.—A solution of the corresponding 2*H*-1-benzopyran (0.015 mol) and organometallic compound (0.045 mol) in solvent (50 ml) was refluxed under nitrogen (Table 1). At the end of the reaction (monitored by g.l.c.) the solution was cooled, poured into ice–water, and acidified until the metal hydroxide was just dissolved. The organic layer was decanted, washed with saturated aqueous $NaHCO_3$, and dried ($MgSO_4$). The mixture (after removal of the solvent) was chromatographed on silica gel (benzene–hexane, 3:10) and the products purified by distillation under reduced pressure. The irradiated reactions were carried out in a Pyrex flask at a distance of 1 cm from the light source (quartz lamp, 125 W). The characteristics of all the *o*-allylphenols obtained are summarized in Table 3.

For the following two butadienylphenols we have spectroscopic evidence only: 2-(2-*ethyl*-5-*methylhexa*-1,3-*dienyl*)-*phenol* (**3d**), δ(CCl_4) 6.75—7.25 (4 H, m), 6.30 (br, s, 1 H_a), 6.30 (d, 1 H_b), 5.85 (q, 1 H_c, J_{bc} 16 Hz, J_{ce} 6 Hz), 1.90—2.55 (m, 2 H_d and 1 H_e), 1.15 (t, 3 H), 0.95 (d, 6 H) [Found: 216 (M^+) $C_{15}H_{20}O$ requires *M*, 216]; 2-(2-*benzyl*-5-*methylhexa*-1,3-*dienyl*)*phenol* (**3g**), δ(CCl_4) 6.45—7.20 (m, 9 H), 6.15 (br, s, H_a), 6.20 (d, H_b), 5.75 (q, H_c, J_{bc}, 12 Hz, J_{ce} 6 Hz), 3.70 (s, 2 H), 2.15 (m, H_e), 0.95 (d, 6 H) [Found: 278 ($M^{+\cdot}$), $C_{20}H_{22}O$ requires *M*, 278].

Table 3. Physical data of allylic phenols and derivatives

	Allylic phenols		Derivative: phenylurethane				
Compound	B.p. (°C)/Torr [M.p.]	^{1}H N.m.r. spectral data of allylic protons ($SiMe_4$, CCl_4)	M.p. (°C)	Molecular formula	Elemental analysis: Found (Calc.) C	H	N
(2a)	76/1	5.00 (br, s, 2 H), 3.35 (t, 1 H)	96	$C_{19}H_{21}NO_2$	77.3 (77.26)	6.9 (7.17)	4.7 (4.74)
***E*-(2b)**	110/1	5.55 (t, 1 H), 3.30 (t, 1 H)	77	$C_{23}H_{29}NO_2$	78.7 (78.60)	8.4 (8.32)	3.9 (3.99)
***Z*-(2b)**	118/1.5	5.45 (t, 1 H), 3.95 (t, 1 H)	89	$C_{23}H_{29}NO_2$	78.5 (78.60)	8.4 (8.32)	3.9 (3.99)
(2c)	126/2	3.90 (q, 1 H)	131	$C_{23}H_{29}NO_2$	78.55 (78.60)	8.3 (8.32)	3.95 (3.99)
***E*-(2d)**	108/0.7	5.55 (t, 1 H), 3.50 (t, 1 H)	90	$C_{24}H_{31}NO_2$	78.8 (78.86)	8.6 (8.55)	3.8 (3.83)
***Z*-(2d)**	109/0.5	5.45 (t, 1 H), 4.00 (t, 1 H)	116	$C_{24}H_{31}NO_2$	78.9 (78.86)	8.6 (8.55)	3.8 (3.83)
(2e)	112/0.4	3.90 (t, 1 H)	121	$C_{24}H_{31}NO_2$	78.85 (78.86)	8.6 (8.55)	3.85 (3.83)
(2f) [a]		5.25 (br s, 1 H), 5.05 (br s, 1 H), 3.35 (t, 1 H)					
***E*-(2g)**	153/0.9	5.70 (t, 1 H), 3.25 (t, 1 H)	114	$C_{29}H_{33}NO_2$	81.5 (81.46)	7.7 (7.78)	3.3 (3.28)
***Z*-(2g)**	154/0.5	5.20 (t, 1, H), 3.95 (t, 1 H)	104	$C_{29}H_{33}NO_2$	81.5 (81.46)	7.75 (7.78)	3.25 (3.28)
(2h)	[44]	4.05 (t, 1 H)	158	$C_{29}H_{33}NO_2$	81.5 (81.46)	7.8 (7.78)	3.25 (3.28)
(2j)	86/0.5	5.10 (s, 1 H)	103	$C_{23}H_{24}NO_2$	78.6 (78.60)	8.35 (8.32)	3.95 (3.99)
***E*-(2k)**	75—90/0.2 [b]	6.10 (d, 1 H), 5.45 (m, 1 H) [b,c]					
(2m)	114/1	5.65 (m, 1 H)	126	$C_{23}H_{27}NO_2$	78.95 (79.05)	7.8 (7.79)	4.0 (4.01)
***E*-(2n)** [d]	106/2.5	*ca.* 5.6 (m, 2 H), 3.40 (q, 1 H)					
***Z*-(2n)**	78/1 [d]	*ca.* 5.6 (m, 2 H), 3.85 (q, 1 H) [d]					

[a] Unstable compound. [b] B.p. and signals determined in a mixture with *Z*-(**2k**) (15%). [c] Solvent CD_3SOCD_3. [d] B.p. and signals determined in a mixture with *E*-(**2n**) (10—12%).

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