# REACTION OF 2H-1-BENZOPYRANS WITH ORGANOMETALLIC REAGENTS. SYNTHESIS OF 4-(α,γ-DIALKYL-β-4-METHOXYPHENYLALLYL)RESORCINS

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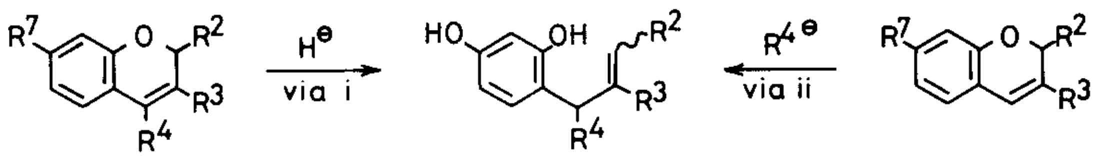
Abstract- The stereoselective synthesis of E- and Z-4-(α,γ-dialkyl-β-4-methoxyphenylallyl)resorcins was accomplished by reaction of 2-alkyl-7-hydroxy-4′-methoxy*iso*flavenes with organoaluminum and organomagnesium reagents. This way leads to better yields than the reduction of 2,4-dialkyl-7-hydroxy-4′-methoxy*iso*flavenes. The influence of substituents at different positions on the reduction was studied on model 2H-1-benzopyrans.

We have recently reported that 2H-1-benzopyrans react with organometallic compounds leading to o-allylphenols; the reactions are stereoselective, and the resulting double bonds have E- or Z-configuration depending on the experimental conditions.[1-3] The reduction is a competitive process leading to different amounts of reduced products, depending upon the organometallic used. These reductions are similar to previously described with aluminum hydride[4-6] and metal-acid systems.[7-10]
With this information in mind, we envisaged a synthesis of 4-(α,γ-dialkyl-β-4-methoxyphenylallyl)resorcin derivatives (III) from *iso*flavenes in two ways: i) Reduction of 2,4-dialkyl*iso*flavenes (I) and ii) Alkylation at C-4 of 2-alkyl*iso*flavenes (II)(Scheme I).

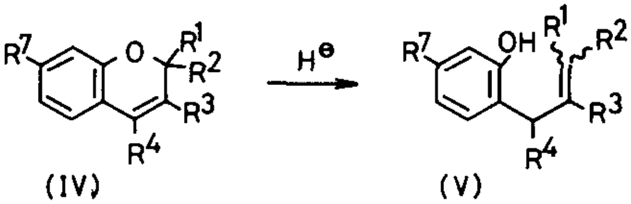


(I) (III) (II)

Scheme I

Initially we studied the feasibility of the reduction, and the influence of alkyl substituents at C-2 and C-4, aryl at C-3, and oxygenated substituents at C-7 on model compounds (IV a-i). The results are summarized on table 1.

Table 1. Reduction of 2H-1-Benzopyrans (IV) to o-allylphenols (V).



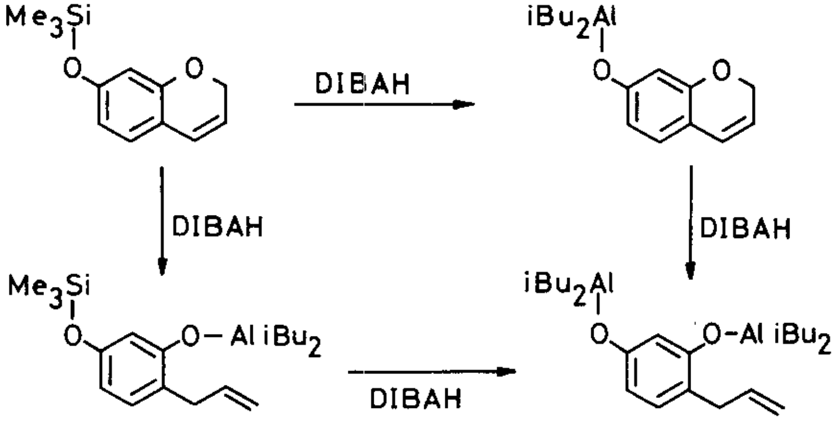
| Run | Comp. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^7$ | Reaction Conditions | o-allylphenol (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | IVa | $-(CH_2)_4$ | | H | H | H | LAH ether, 5 h. | ---- |
| 2 | | | | | | | DIBAH toluene, 12 h. | ---- |
| 3 | | | | | | | LAH ether, 6 h.[a] | Va (50) |
| 4 | | | | | | | DIBAH pentane, 2.5 h.[a] | Va (80) |
| 5 | IVb | Et | Et | H | Me | H | LAH ether 12 h. | Vb (15) |
| 6 | | | | | | | DIBAH toluene 12 h. | Vb (10) |
| 7 | | | | | | | LAH ether 5.5 h.[a] | Vb (82) |
| 8 | | | | | | | DIBAH pentane 2 h.[a] | Vb (83) |
| 9 | IVc | H | Et | Ph | Et | H | LAH ether 3.5 h.[a] | E-Vc (15) |
| 10 | | | | | | | DIBAH pentane 6 h.[a] | E-Vc/Z-Vc (12/16) |
| 11 | IVd | Et | Et | Ph | H | H | LAH ether 10 h. | Vd (10) |
| 12 | | | | | | | DIBAH toluene 12 h. | Vd (5) |
| 13 | | | | | | | LAH ether 4 h.[a] | Vd (85) |
| 14 | | | | | | | DIBAH pentane 2 h.[a] | Vd (88) |
| 15 | IVe | Me | Me | H | H | OH | LAH ether 10 h.[a] | Ve (15) |
| 16 | | | | | | | DIBAH pentane 6 h.[a] | Ve (80) |
| 17 | IVf | Et | Et | H | Me | OH | LAH ether 5 h.[a] | Vf (82) |
| 18 | | | | | | | DIBAH pentane 6 h.[a] | Vf (75) |
| 19 | IVg | Et | Et | H | H | OTMS | LAH ether 8 h.[a] | Vg (83) |
| 20 | IVh | Et | Et | H | Me | OTMS | LAH ether 4 h.[a] | Vh (88) |
| 21 | | | | | | | DIBAH pentane 6 h.[a] | Vh (85) |
| 22 | IVi | Et | Et | H | Me | OTMS | LAH ether 4 h.[a] | Vi (95) |
| 23 | | | | | | | DIBAH pentane 4 h.[a] | Vi (80) |

[a] Reactions under irradiation

The starting benzopyran was practically recovered unchanged by reaction with lithium aluminum hydride (LAH) under thermal conditions (runs 1, 5 and 11), and diisobutylaluminum hydride (DIBAH), under refluxing toluene, leads to complex mixtures of dienic phenols; the yields of o-allylphenols were intolerably lows again (runs 2, 6 and 12).

As previously reported[1], the reaction with LAH or DIBAH was improved by irradiation, leading to o-allylphenols in excellent yields ( runs 4,7,8, 13, 14 and 16- 23). Only the 2,4-dialkyl-3-aryl trisubstituted benzopyran (IVc) shows a low conversion

into the corresponding allylphenols ( runs 9 and 10).
The presence of a hydroxyl group at C-7 has not influence on the final yield, but it is necessary to add a twofold excess of hydride and, in some cases, to increase the reaction time, probably as a consequence of the formation of the less reactive conjugated base[14]. The protection of the hydroxyl group as trimethylsilyl ether was effective only in part because the Si-O bond was broken by DIBAH before the total transformation of the benzopyran into o-allylphenoxide (Scheme II).



Scheme II

All these facts were confirmed on the reactions of 2-methyl-4-ethyl-4'-methoxy-7-trimethylsilyloxy*iso*flavene (Ia) and its isomer (Ib) with both LAH and DIBAH (table 2). The E-o-allylphenols (IIIa) and (IIIb) were formed in low yield when the reactions were carried under irradiation.

Table 2. Reduction of 2,4-dialkyl-4'-methoxy-7-trimethylsilyloxy*iso*flavenes (*via* i)

| Run | Isoflavene | $R^2$ | $R^4$ | $R^7$ | Reaction conditions | | | o-Allylphenol (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | Ia | Me | Et | OTMS | LAH | ether | 7 h. | ---- |
| 2 | | | | | LAH | ether | 7 h.[a] | E-IIIa (12) |
| 3 | | | | | DIBAH | benzene | 10 h. | ---- |
| 4 | | | | | DIBAH | benzene | 12 h.[a] | E-IIIa (15) |
| 5 | Ib | Et | Me | OTMS | LAH | ether | 5 h. | ---- |
| 6 | | | | | LAH | ether | 10 h.[a] | E-IIIb (14) |
| 7 | | | | | DIBAH | benzene | 8 h. | ---- |
| 8 | | | | | DIBAH | benzene | 10 h.[a] | E-IIIb (16) |

[a] Reactions under irradiation.

The alternative synthesis of o-allylphenols by alkylation (via ii) was studied on isoflavenes (IIa-c)(Table 3). It is interesting to note that, under thermal conditions, Z-Vc was obtained as a single isomer by alkylation of IIc in low yield, but better than by reduction of IVc ( compare runs 6 and 7 in table 3 versus 9 and 10 in table 1); on the other hand, it is possible to obtain both isomers of IIIa, in high yield by alkylation of IIa with ethylmagnesium bromide under irradiation, and by heating with triethylaluminum ( runs 1 and 2), and Z-IIIb as a pure isomer from IIb by reaction with triethylaluminum (run 4).

Table 3. Reactions of 2-alkylisoflavenes with organometallics (via ii)

| Run | Compound | $R^2$ | $R^3$ | $R^7$ | Reaction conditions | | | o-allylphenol (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | IIa | Me | p-$MeOC_6H_4$ | OTMS | EtMgBr | ether | 5 h.[a] | E-IIIa (75) |
| 2 | | | | | $Et_3Al$ | benzene | 9 h. | Z-IIIa (84) |
| 3 | IIb | Et | p-$MeOC_6H_4$ | OTMS | MeMgI | ether | 7 h.[a] | E-IIIb/Z-IIIb(45/15) |
| 4 | | | | | $Me_3Al$ | benzene | 8 h.[a] | Z-IIIb (65) |
| 5 | IIc | Et | $C_6H_5$ | H | EtMgBr | ether | 4 h.[a] | E-Vc (70) |
| 6 | | | | | EtMgBr | toluene | 12 h. | Z-Vc (20) |
| 7 | | | | | $Et_3Al$ | benzene | 18 h. | Z-Vc (19) |
| 8 | | | | | $Et_3Al$ | toluene | 3 h.[a] | E-Vc/Z-Vc (32/30) |

[a] Reactions under irradiation.

## EXPERIMENTAL

Mp's were taken on an oppen capillary tube and are uncorrected. Nmr spectra were taken on a Varian T60 A or a Bruker WP-200 SY spectrometers, and chemical shifts are reported in ppm downfield from TMS used as internal standard. Ir were obtained on a Pye-Unicam SP-1100 spectrometer. The geometry E- or Z-isomers was assigned based upon their spectroscopic charactristics as previously reported[2,3].

The benzopyran (IVa)[3] was obtained by reduction and dehydration of 2H-1-benzopyran-2-spirocyclopentane[12], while compounds (IVb-d) were synthesized by dehydration of the corresponding 2-(3-hydroxyprop-1-enyl)phenols obtained from benzopyranones by reaction with organometallics[14,15].

Compounds (Ia-b), (IIa-b) and (IVg-h) were obtained from the corresponding 7-hydroxyderivative[11-13] by silylation with hexamethyldisilazane as previously described.

2,2-Diethyl-4-methyl-7-methoxy-2H-1-benzopyran (IV i). On a cooled (ice-water) solution of 0.3 moles of ethylmagnesium bromide in 200 ml of anhydrous ether under nitrogen was slowly dropped 19 g (0.1 moles) of 4-methyl-7-methoxycoumarin in 100 ml of ether. The reaction mixture was stirred for 24 h at room temperature, and additional 2 h at reflux. The mixture was cooled, added over ice, acidified just until the magnesium oxides were dissolved and extracted with ether.

The extract was washed with a solution of sodium bicarbonate, water, and dried over anhydrous magnesium sulfate; the solvent was ditilled, and the oily residue crystallized from hexane/benzene giving 22 g (88%) of 2-(3-ethyl-1-methyl-3-

hydroxypent-1-enyl)-5-methoxyphenol. Mp. 72-73ºC. Nmr ($CDCl_3$): 0.9 (t, 6H); 1.6 (m, 4H); 2.0 (d, 3H); 3.7 (s, 3H); 5.6 (broad s, 1H); 6.9-7.2 (m, 3H). $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86. Found C, 71.80; H, 8.79.

A mixture of 8 g of the above compound, 24 g of silica gel (Merck 60) and 150 ml of xylene was refluxed for 2 h on a Dean-Stark trap. The hot mixture was filtered and the silica gel washed with hot xylene (2x 100ml). The xylene was removed under vacuum and the residue was chromatographed on silica gel and hexane as eluent yielding 5.8 g (78%) of (IVi) as a colourless oil, bp 110-13ºC/0.5 mm. Nmr ($CDCl_3$): 0.9 (t, 6H); 1.6 (m, 4H); 2.0 (d, 3H); 3.7 (s, 3H); 5.2 (q, 1H); 6.4-7.2 (m, 3H).

2,2-Diethyl-7-hydroxy-4-methyl-2H-1-benzopyran (IVf). By the same method, from 20g of 4-methyl-7-trimethylsilyloxycoumarin and 0.24 moles of ethylmagnesium bromide it can be isolated 18 g of a yellow oil, that was refluxed with silica gel in xylene and chromatographed on silica gel ($CH_2Cl_2$ as solvent) to give 11.8 g (67.5 %) of(IVf) as a yellowish oil; bp. 118-20ºC/0.4 mm. Nmr ($CDCl_3$): 0.9 (t, 3H); 1.6 (m, 4H); 2.0 (d, 3H); 5.2 (q, 1H); 6.2-7.0 (m, 3H).

2,2-Dimethyl-7-hydroxy-2H-1-benzopyran (IVe). This compound was obtained after flash chromatography from the reaction mixture of 7-trimethylsilyloxycoumarin and trimethylaluminum in benzene (58 %) or methylmagnesium bromide in diethyl ether (49 %). Yellow oil, bp 94-96ºC/0.5 mm (lit.[16] oil).

2-Ethylisoflavene (IIc). This compound was obtained as minor product in the synthesis of 2,2-diethylisoflavene (IVd) from 3-phenylcoumarin and triethylaluminum[15]. The flash chromatography (silica gel/Hexane) allowed to isolate (IVd)(46 %) followed by 2-ethylisoflavene (IIc)(12 %). Colourless oil, bp 130-35ºC/0.2 mm. Nmr ($CDCl_3$): 1.0 (t, 3H); 1.7 (m, 2H); 5.2 (d d, $J_1$=8, $J_2$=4, H at C-2); 6.6 (s, H at C-4); 6.7-7.4 (m, 9H).

Reaction of 2H-1-Benzopyrans with Organometallics and Metal Hydride Complexes. General Method. A mixture of 2H-1-benzopyran (15 mmoles) and 30 mmoles of organometallic or metal hydride complex, in 50 ml of the corresponding solvent was refluxed under nitrogen for the time indicated in tables. When the reaction was finished, the solution was cooled, added on crushed ice and acidified just until hydroxides dissolve. The organic layer was washed with a saturated solution of sodium bicarbonate, water and brine, and dried over anhydrous magnesium sulfate. The solvent was distilled, and the residue chromatographed on silica gel and hexane/benzene: 5/2 for o-allylphenols (Va-d and Vi) or methylene chloride/diethyl ether: 20/1 for compounds (IIIa-b), (Ve-g). The reactions under irradiation were carried out on a pyrex flask using a quertz-lamp of 125 W[3].

2-(3,3-(1,4-Butanediyl)-2-propenyl)phenol (Va). Yellowish oil, bp 110-12ºC/0.4 mm. Nmr ($CDCl_3$): 1.6 (m, 4H); 2.2 (m, 4H); 3.3 (d, J= 7, 2H at α); 5.4 (m, H at β); 6.4-7.2 (m, 4H). Phenylurethane, white solid, mp 113-115ºC( from hexane/benzene). $C_{20}H_{21}NO_2$ requires C, 78.15; H, 6.89; N, 4.56. Found, C, 78.26; H, 6.80; N, 4.67.

2-(3-Ethyl-1-methyl-2-pentenyl)phenol (Vb). Yellow oil, bp 91-93ºC/0.1 mm. Nmr ($CDCl_3$): 0.9 (t, 6H); 1.3 (d, J=7, $CH_3$ at α); 2.0 (q, 4H); 3.9 (m, H at α); 5.2 (d, J=9, H atβ ); 6.5-7.2 (m, 4H). Phenylurethane, white solid,mp 106-107ºC. $C_{21}H_{25}NO_2$ requires: C, 77.98; H, 7.79; N, 4.33. Found C, 78.17; H, 7.66; N, 4.21.

2-(3-Ethyl-2-phenyl-2-pentenyl)phenol (Vd). Yellowish oil, bp 126-28ºC/2mm. Nmr ($CDCl_3$): 0.9 (t, 3H); 1.1 (t, 3H); 2.0 (q, 2H); 2.3 (q, 2H); 3.7 (s, 2H); 6.3-7.2 (m, 9H). Phenylurethane, white solid, mp 112-13ºC. $C_{26}H_{27}NO_2$ requires: C, 81.01;

H, 7.06; N, 3.63. Found, C, 80.88; H, 7.19; N, 3.51.

Z-2-(1-Ethyl-2-phenyl-2-pentenyl)phenol (Z-Vc). Colourless oil, decomp by heating. Nmr ($CDCl_3$): 0.9 (t, 3H); 1.0 (t, 3H); 1.8 (m, $CH_2$ at α and $CH_2$ at γ); 3.7 (t, J=7, H at α); 5.6 (t, J=7, H at γ); 6.5-7.2 (m, 9H). Phenylurethane, white solid, mp 165-66ºC. $C_{26}H_{27}NO_2$ requires: C, 81.01; H, 7.06; N, 3.63. Found, C, 80.82; H, 7.19; N, 3.49.

E-2-(1-Ethyl-2-phenyl-2-pentenyl)phenol (E-Vc). Colourless oil, bp 135-37ºC/ 2 mm. Nmr ($CDCl_3$): 0.9 (t, 3H); 1.0 (t, 3H); 1.7 (m, $CH_2$ at α); 2.4 (m, $CH_2$ at γ); 4.1 (d d, $J_1$= 9, $J_2$= 6, H at α); 5.4 (t, J=7, H at γ); 6.5-7.2 (m, 9H).Phenylurethane, white solid, mp 176-77ºC. $C_{26}H_{27}NO_2$ requires: C, 81.01; H, 7.06; N, 3.63. Found, C, 80.80; H, 6.91; N, 3.72.

4-(3-Methyl-2-butenyl)-1,3-benzenediol (Ve). Yellowish oil, bp 105-107ºC/0.4 mm. (lit.[17] 126-28ºC/2 mm). Nmr ($Cl_4C$): 1.7 (s, 6H); 3.2 (d, 2H at α, J=7); 5.3 (t, J=7, H at β); 6.2-7.0 (m, 3H). Diphenylurethane, white solid,mp 147-49ºC. $C_{25}H_{24}N_2O_4$ requires: C, 72.10; H, 5.81; N, 6.73. Found, C, 71.87; H, 5.69; N, 6.61.

4-(3-Ethyl-1-methyl-2-pentenyl)-1,3-benzenediol (Vf). Colourless oil, bp 145-47ºC/ 0.4 mm. Nmr ($CDCl_3$): 1.0 (t, 6H); 1.3 (d, J=7, $CH_3$ at α); 2.1 (q, 4H); 3.8 (m, H at α); 5.1 (d, J=9, H at β); 6.1-7.0 (m, 3H). Diphenylurethane,white solid, mp 174-75ºC. $C_{28}H_{30}N_2O_4$ requires: C, 73.34; H, 6.59; N, 6.11. Found, C, 73.21; H, 6.70 N, 6.27.

4-(3-Ethyl-2-pentenyl)-1,3-benzenediol (Vg). Brownish oil, decomp by heating. Nmr ($Cl_4C$): 1.0 (t, 6H); 2.1 (q, 4H); 3.3 (d, J=7, 2H at α); 5.2 (t, H at β); 6.1-7.0 (m, 3H). Diphenylurethane, white solid,mp 151-53ºC. $C_{27}H_{28}N_2O_4$ requires: C, 72.95; H, 6.35; N, 6.30. Found, C, 72.80, H, 6.49; N,6.20.

2-(3-Ethyl-1-methyl-2-pentenyl)-5-methoxyphenol (Vi). Colourless oil, bp 115-20ºC/ 0.4 mm. Nmr ($Cl_4C$): 0.9 (t, 3H); 1.0 (t,3H); 1.3 (d, J=7, $CH_3$ at α); 2.0 (q, 2H); 2.1 (q, 2H); 3.7 (s, 3H); 3.8 (m, H at α); 5.1 (d, J=9, H at β); 6.0-7.0 (m, 3H). Phenylurethane, white solid, mp 71-72ºC. $C_{22}H_{27}NO_2$ requires: C, 74.76; H, 7.67; N, 3.96. Found, C, 74.89; H, 7.56; N, 3.82.

Z-4-(1-Ethyl-2-(4-methoxyphenyl)-2-butenyl)-1,3-benzenediol (Z-IIIa). Yellow oil, decomp by heating. Nmr (methanol-$d_4$): 0.9 (t, 3H); 1.5 (d, J=7, $CH_3$ at γ); 1.6 (m, $CH_2$ at α); 3.7 (s, 3H); 3.8 (t, J=8, H at α); 5.5 (q, J=7, H at γ); 6.0-7.0 (m, 7H). Diphenylurethane, white solid, mp 182-83ºC. $C_{33}H_{32}N_2O_5$ requires: C, 73.86; H, 6.01; N, 5.22. Found, C, 73.72; H, 5.89; N, 5.37.

E-4-(1-Ethyl-2(4-methoxyphenyl)-2-butenyl)-1,3-benzenediol (E-IIIa). White solid, mp 72-73ºC. Nmr (methanol-$d_4$): 0.9 (t, 3H); 1.6 (m, $CH_2$ at α); 1.9 (d, J=7, $CH_3$ at γ); 3.7 (s, 3H); 4.3 (t, J=7, H at α); 5.4 (q, H at γ); 6.0-7.0 (m, 7H). Diphenylurethane, white solid, mp 168-69ºC. $C_{33}H_{32}N_2O_5$ requires: C, 73.86; H, 6.01; N; 5.22. Found, C, 73.81; H, 6.12; N, 5.10.

Z-4-(1-Methyl-2-(4-methoxyphenyl)-2-pentenyl)-1,3-benzenediol (Z-IIIb). Yellow oil, decomp on distillation. Nmr (methanol-$d_4$): 0.9 (t, 3H); 1.3 (d, J=7, $CH_3$ at α); 1.9 (m, $CH_2$ at γ); 3.7 (s, 3H); 4.1 (q, H at α); 5.4 (t, J=7, H at γ); 6.0-7.0 (m, 7H). Diphenylurethane, white solid, mp 159-60ºC. $C_{33}H_{32}N_2O_5$ requires: C, 73.86; H, 6.01; N, 5.22. Found, C, 73.98; H, 6.14; N, 5.11.

E-4-(1-Methyl-2-(4-methoxyphenyl)-2-pentenyl)-1,3-benzenediol (E-IIIb). Yellow oil, decomp on distillation. Nmr (methanol-$d_4$): 1.0 (t, 3H); 1.3 (d, J=7, $CH_3$ at α); 2.3 (m, $CH_2$ at γ); 3.7 (s, 3H); 4.4 (q, H at α); 5.2 (t, J=7, H at γ); 6.1-7.0 (m, 7H). Diphenylurethane, white solid, mp 146-47ºC. $C_{33}H_{32}N_2O_5$ requires: C, 73.86; H, 6.01; N, 5.22. Found, C, 73.70; H, 5.86; N, 5.09.

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