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SYNTHESIS OF COUMARAN-5-OLS - NEW MODEL COMPOUNDS FOR BIOANTIOXIDANTS

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Abstract - Based on a Heck type reaction a new access to coumaran-5-ols has been developed. The reaction, its analytical and synthetical features as well as the nature of some by-products are discussed.

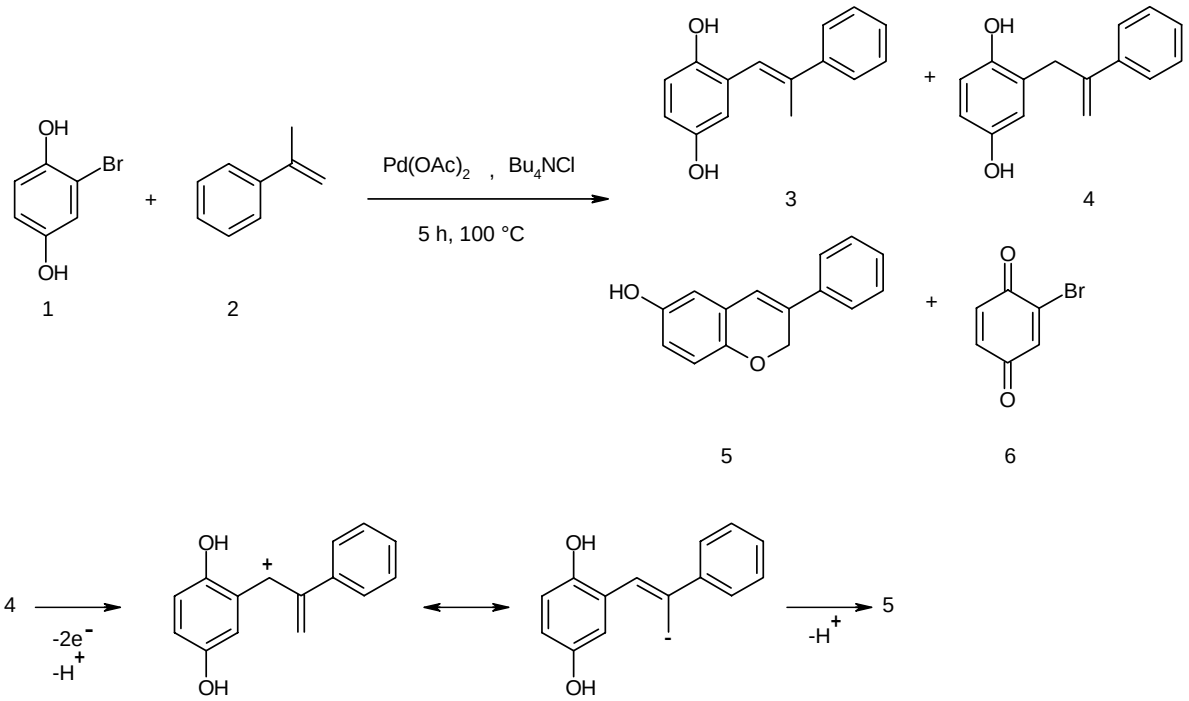
INTRODUCTION

Coumaran-5-ols are of increasing interest since they were found to be biological effective antioxidants exceeding even vitamin E (α-tocopherol) in efficiency, to which they are structurally related.[1] Despite their promising properties there has only little work been done on the synthesis of these compounds. There did not exist any efficient method to synthesise coumaran-5-ols with unsubtituted positions at the aromatic ring in tolerable yield, which are of importance as analogues for β- and γ-tocopherol.

RESULTS AND DISCUSSION

We tried to solve this problem with the Heck type reaction. As model system we chose the reaction of monobromohydroquinone (**1**) with α-methylstyrene (**2**) as olefinic component which is not only a cheap educt but has a boiling point which allows working under classical Heck conditions, i.e. temperatures of 80~100 °C. For this system it proved best to work in DMF with stoichiometric amounts of phase transfer catalyst Bu_4NCl, sodium carbonate as base and 5.1 mol% palladium acetate as catalyst (Scheme 1). Formation of **6** can not be totally suppressed but formation of compound (**5**)[2] is avoided and a mixture of isomers (**3**) and (**4**) is obtained in very good yield (92%). For this case the existence of two isomers in an almost 1:1 ratio does not matter as they are both easily cyclised to **7** in formic acid withcatalytic amounts of sulfuric acid (Scheme 2). The problem of the isomeric ratio becomes crucial if there are alkyl groups attached to the aromatic ring as 2*H*-chromen-6-ols like **5** then become the major products. The

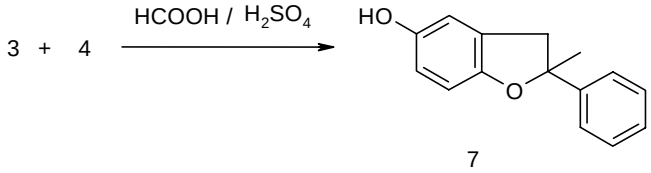
circumstances leading to the formation of 2*H*-chromen-6-ols can only be anticipated. Palladium(II) ions which are also responsible for the oxidation of bromohydroquinone (**1**) to the corresponding quinone (**6**) could as well as the ladder oxidize isomer (**4**) to an allyl cation. This cation could cyclise to give **5** (Scheme 1, below). Additional electron donor substituents at the hydroquinone would stabilise the allyl cation thus favouring the formation of 2*H*-chromen-6-ols as observed by us in reactions of monobromo-5,6-dimethylhydroquinone.



Scheme 1.

Table 1. Heck reaction of monobromohydroquinone with α-methylstyrene

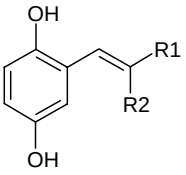
solvent	base	additives	**3** : **4**	yield (%)	**5** yield (%)	**6** yield (%)
MeCN	Na_2CO_3	-	47 : 53	35	-	16
DMF	AcOK	-	56 : 44	40	12	10
DMF	Et_3N	-	50 : 50	5	-	14
DMF	Na_2CO_3	-	46 : 54	92	-	6
DMF	Na_2CO_3	Ag_2CO_3	-	-	-	8
DMF	Na_2CO_3	$AgNO_3$	-	-	-	-
DMF	Na_2CO_3	$(C_6H_5)P$	55 : 45	47	8	12



Scheme 2.

Therefore, several attempts were made to change the isomeric ratio as the 2*H*-chromen-6-ols can be formed out of the isomer with the terminal double bond only. However, we did not yet succeed in getting isomeric pure compounds. Silver salts, which are usually used in this case, oxidise the hydroquinone.[3] Triphenylphosphine which was proposed in some works[4] is already known to lower the yield in Heck reactions of phenols. The same happened to our hydroquinones while there was no real change in the isomeric ratio observed (Table 1).

While there remains a lot of work to be done for Heck type reactions of alkyl substituted hydroquinones the introduction of different olefins into monobromohydroquinone is very promising as a wide range of olefins can be used. Simple olefins like 1-hexene or styrene are added in almost quantitative yield (the latter forming the *trans*-adduct)[5] to give compounds of the general structure of **8**. Subsequent ring closure to the coumaran-5-ols could not be achieved which is probably due to the formation of a benzyl cation under acidic conditions instead of getting the positive charge at the carbon next to the R-groups (Scheme 3).



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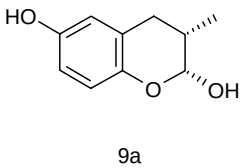
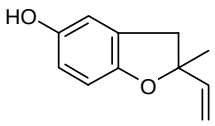
R1	R2	
Bu	-H	**8a**
phenyl	-H	**8b**
phenyl	phenyl	**8c**



9a



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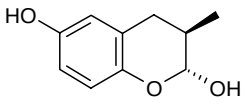

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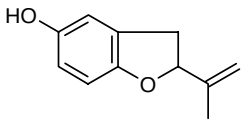

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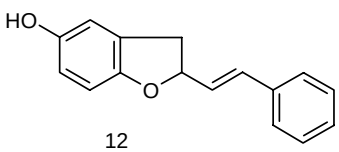

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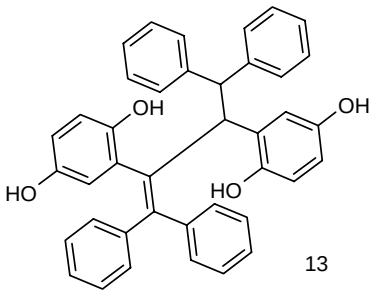

13

Scheme 3.

The sterically demanding 1,1-diphenylethene was introduced in good yield[6] but upon treatment with catalytic amounts of sulphuric acid in formic acid did not give ring closure but formed dimer (**13**) which might be caused by steric hindrance and traces of water.

Olefins bearing additional functionalities were also added fairly well giving spontaneous ring closure in all cases. With 2-methyl-2-propen-1-ol we surprisingly received the diastereomeric 6-hydroxychromans (**9a**) and (**9b**) in a 50: 50 ratio. Isoprene yielded the two products (**10**) and (**11**), which were to be expected in an 18:82 ratio. In order to increase conversion reaction was carried out for one week. When 1,3-dienes with only one unsubstituted double bound are reacted only one isomer is formed. So, phenyl-1,3-butadiene gave compound (**12**) in 92% yield.

EXPERIMENTAL

General methods: Melting points were received with a Kofler-Boetius apparatus and are corrected. ^{1}H-NMR, ^{13}C-NMR, and 2D-NMR spectra (NOESY, COSY, HSQC, HMBC) were recorded either on a Bruker AC-200P or on a Bruker DRX-500 spectrometer. Spectra are reported in ppm downfield from TMS as internal standard. Elemental analysis was determined on a CHN-S analyser (Carlo Erba). Analytical TLC was performed using Merck prepared plates (silica gel 60 F-254 on aluminium). Merck silica gel (63-200 μm) was used for chromatography.

Typical procedure for the Heck reaction of monobromohydroquinone (1) with olefins: To a stirred solution of **1** (1g, 5.29 mmol) in dry DMF (15 mL) kept at rt under argon were added dry and well grounded sodium carbonate (1.69 g, 16 mmol), tetrabutylammonium chloride (1.75 g, 6.3 mmol), palladium acetate (0.06 g, 0.27 mmol) and the olefin (20 mmol). The mixture was heated to 100 °C for 5 h. Then ethyl acetate (15 mL) and water (15 mL) were added. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (15 mL). The combined organic layers were washed with water (2×15 mL) and dried over sodium sulfate. After evaporation of the solvent the residue was chromatographed on silica gel (*n*-pentane/ethyl acetate 4:1).

2-(2-Phenyl-1-propenyl)hydroquinone (3): brown oil; ^{1}H-NMR ($CDCl_3$, 500.13 MHz): δ 2.12 (s, 3H), 5.10 (s, 2H), 6.66 (m, 1H), 6.67 (m, 2H), 6.71 (s, 1H), 6.79 (d, 1H, J = 8.4 Hz), 7.31 (t, 1H, J = 7.4 Hz), 7.38 (t, 2H, J = 7.4 Hz), 7.53 (d, 2H, J = 7.3 Hz); ^{13}C-NMR ($CDCl_3$, 125.8 MHz): δ 17.2; 115.4; 116.0; 116.2; 121.0; 125.4; 125.9; 127.7; 128.4; 141.1; 142.1; 146.9; 148.9. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.36; H, 6.12.

2-(2-Phenyl-2-propenyl)hydroquinone (4): brown oil; ^{1}H-NMR ($CDCl_3$, 500.13 MHz): δ 3.76 (s, 2H), 5.01 (d, 1H, J = 1.1 Hz), 5.10 (s_{br}, 2H), 5.50 (s, 1H), 6.56 (dd, 1H, J = 8.5, 3.0 Hz), 6.63 (d, 1H, J = 2.9 Hz), 6.66 (d, 1H, J = 8.4 Hz), 7.26 (d, 1H, J = 7.7 Hz), 7.30 (t, 2H, J = 7.7 Hz), 7.47 (d, 2H,

J = 7.8 Hz); ^{13}C-NMR ($CDCl_3$, 125.8 MHz): δ 35.9; 114.1; 114.2; 116.6; 117.4; 126.0; 126.7; 127.7; 128.3; 140.3; 145.7; 147.7; 149.4. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.36; H, 6.12.

***trans*-Hex-1-enylhydroquinone (8a):** yield 96%; colourless crystals; mp 106 °C; ^{1}H-NMR (DMSO-d_6, 300.13 MHz): δ 0.90 (t, 3H, J = 7.0 Hz), 1.37 (m, 4H), 2.15 (q, 2H, J = 6.9 Hz), 6.05 (m, 1H), 6.44 (dd, 1H, J = 8.55, 2.9 Hz), 6.53 (d, 1H, *J* = 16 Hz, 1'-H), 6.60 (d, 1H, *J* = 8.6 Hz, 6-H), 6.73 (d, 1H, J = 2.8 Hz), 8.60 (s, 1H), 8.74 (s, 1H); ^{13}C-NMR (DMSO-d_6, 75.5 MHz): δ 13.7; 21.6; 31.1; 32.4; 111.6; 114.5; 116.1; 124.4; 124.7; 129.4; 146.7; 149.7. Anal. Calcd for $C_{12}H_{16}O_2$: C, 81.34; H, 5.12. Found: C, 81.12; H, 4.98.

***trans*-2,5-Dihydroxystilbene (8b)[5]:** yield 98%; mp 165-167; ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 111.4; 115.2; 116.1; 123.4; 124.0; 125.6; 126.4; 127.0; 127.8; 137.3; 147.4; 149.4.

2-(2,2-Diphenylvinyl)hydroquinone (8c)[6]: brown oil; yield 68%; ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 6.12 (d, 1H, J = 2.8 Hz), 6.39 (dd, 1H, J = 8.6, 2.9 Hz), 6.58 (d, 1H, J = 8.6 Hz), 7.00 (s, 1H), 7.20 (m, 10H), 7.83 (s, 1H), 8.23 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 114.8; 115.3; 115.5; 123.4; 124.5; 126.5; 127.1; 127.3; 127.6; 129.8; 139.8; 140.7; 143.2; 148.2; 148.5.

***cis*-3-Methylchromane-2,6-diol (9a):** yellow oil; yield 12%; ^{1}H-NMR (DMSO-d_6/$CDCl_3$, 500.13 MHz): δ 0.96 (d, 3H, J = 6.8 Hz), 1.88 (m, 1H), 2.41 (dd, 1H, J = 16.0, 5.5 Hz), 2.50 (dd, 1H, J = 15.8, 5.8 Hz), 5.18 (d, 1H, J = 2.2 Hz), 6.39 (s, 1H), 6.46 (m, 1H), 6.47 (m, 1H); ^{13}C-NMR (DMSO-d_6/$CDCl_3$, 125.8 MHz): δ 15.8; 27.9; 31.0; 93.4; 111.8; 113.7; 116.3; 122.2; 144.2; 150.4. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.49; H, 6.68.

***trans*-3-Methylchromane-2,6-diol (9b):** yellow oil; yield 12%; ^{1}H-NMR (DMSO-d_6/$CDCl_3$, 500.13 MHz): δ 0.90 (d, 3H, J = 6.9 Hz), 1.89 (m, 1H), 2.25 (dd, 1H, J = 9.8, 6.1 Hz), 2.83 (dd, 1H, J = 9.7, 5.8 Hz), 4.94 (d, 1H, J = 4.8 Hz), 6.39 (s, 1H), 6.44 (m, 1H), 6.46 (m, 1H); ^{13}C-NMR (DMSO-d_6/$CDCl_3$, 125.8 MHz): δ 15.9; 29.0; 31.0; 95.9; 111.8; 113.7; 116.2; 121.4; 144.7; 150.4. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.49; H, 6.68.

2-Methyl-2-vinylcoumaran-5-ol (10): yield 10%; light brown oil; ^{1}H-NMR ($CDCl_3$, 500.13 MHz): δ 1.54 (s, 3H), 2.94 (d, 1H, J = 15.8 Hz), 3.08 (d, 1H, J = 15.8 Hz), 5.10 (d, 1H, *J* = 10.5 Hz, vinyl-CH_2), 5.30 (d, 1H, J = 17.6 Hz), 6.03 (dd, 1H, J = 17.4, 10.7 Hz), 6.62 (m, 1H), 6.65 (m, 1H), 6.71 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125.8 MHz): δ 25.6; 42.0; 87.7; 109.2; 112.5; 112.7; 114.25; 127.4; 141.2; 149.4; 142.5. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.77; H, 6.72.

2-Isopropenylcoumaran-5-ol (11): yield 42%; light brown oil; ^{1}H-NMR ($CDCl_3$, 500.13 MHz): δ 1.75 (s, 3H), 2.95 (dd, 1H, J = 15.9, 9.0 Hz), 3.22 (dd, 1H, J = 15.9, 9.0 Hz), 4.70 (s, 1H), 5.09 (s, 1H), 5.13 (t, 1H, J = 8.9 Hz), 6.63 (m, 2H), 6.73 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125.8 MHz): δ 16.9; 34.7; 85.7; 108.9;

112.0; 112.3; 114.2; 127.5; 143.6; 149.4; 153.0. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.77; H, 6.72.

2-[(*E*)-2-Phenylethenyl]coumaran-5-ol (12): yield 92%; yellowish crystals; mp 118 °C; ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 300.13 MHz): 2.94 (dd, 1H, *J* = 15.8, 7.8 Hz), 3.29 (dd, 1H, *J* = 15.7, 7.9 Hz), 5.22 (q, 1H, *J* = 8.0 Hz), 6.25 (dd, 1H, *J* = 15.8, 7.7 Hz), 6.53 (s, 2H, 6-H), 6.61 (d, 1H, *J* = 15.9 Hz), 6.64 (s, 1H), 7.17 (d, 1H, *J* = 6.9 Hz), 7.24 (t, 2H, *J* = 7.1 Hz), 7.33 (t, 2H, *J* = 7.1 Hz), 8.22 (s, 1H); ^{13}C-NMR ($CDCl_3$/DMSO-d_6, 75.5 MHz): δ 36.3; 82.9; 108.7; 111.9; 113.8; 126.2; 126.9; 127.5; 128.2; 128.3; 131.4; 135.8; 150.9; 151.9. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.94; H, 6.08.

Procedure for the ring closure of **3** and **4** and for the dimerisation of **9c**: The adducts received in the Heck reaction were heated under reflux overnight in formic acid (25 mL) to which 5 drops of sulfuric acid were added. Ice water (25 mL) was poured into the reaction mixture and the aqueous solution was extracted with ether (3×25 mL). The combined organic layers were washed with water (2×25 mL), dried over sodium sulfate, the solvent was evaporated *in vacuo* and the residue chromatographed on silica gel (*n*-pentane/ethyl acetate 4:1).

2-Methyl-2-phenylcoumaran-5-ol (7): yield 62%; brown oil; ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 1.68 (s, 3H), 3.24 (d, 1H, *J* = 15.6 Hz), 3.31 (d, 1H, *J* = 15.6 Hz), 4.46 (s, 1H), 6.53 (dd, 1H, *J* = 8.4, 2.6 Hz), 6.56 (d, 1H, *J* = 2.5 Hz), 6.65 (d, 1H, *J* = 8.4 Hz), 7.18 (m, 1H), 7.26 (t, 2H, *J* = 7.8 Hz), 7.39 (d, 2H, 7.8 Hz); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 29.2; 45.0; 89.2; 109.5; 112.4; 114.4; 124.5; 127.0; 127.6; 128.3; 146.8; 149.6; 153.0. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.66; H, 6.21.

2-[1-Benzhydryl-2-(2,5-dihydroxyphenyl)-3,3-diphenyl-2-propenyl]hydroquinone (13): yield 78%; brown oil, ^{1}H-NMR ($CDCl_3$, 300.13 MHz): 4.41 (d, 1H, *J* = 8.4 Hz), 4.65 (s, 1H), 4.91 (s, 1H), 5.43 (d, 1H, *J* = 8.4 Hz), 6.57 (dd, 1H, *J* = 2.6, 0.8 Hz), 6.60 (dd, 1H, *J* = 8.5, 2.7 Hz), 6.73 (dd, 2H, *J* = 8.6, 3.5 Hz), 6.78 (d, 1H, *J* = 2.4 Hz), 7.06 (dd, 2H, *J* = 7.8, 1.8 Hz), 7.23 (m, 14H), 7.31 (m, 1H), 7.36 (m, 4H), 7.54 (dd, 2H, *J* = 6.2, 1.9 Hz); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 58.1; 93.1; 105.0; 109.7; 111.5; 112.4; 113.3; 115.2; 117.4; 125.8; 126.9; 127.3; 127.6; 128.1; 128.30; 128.34; 128.6; 128.8; 128.9; 129.4; 129.6; 130.6; 131.1; 131.3; 132.8; 140.6; 141.3; 149.0; 150.1; 151.5; 151.7; 153.8. Anal. Calcd for $C_{40}H_{32}O_4$: C, 81.79; H, 6.10. Found: C, 81.39; H, 5.97.

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