Reaction between Phenols and Isoprene under Zeolite Catalysis. Highly Selective Synthesis of Chromans and *o*-Isopentenylphenols

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Abstract: Chromans **3** and *o*-isopentenylphenols **4** are synthesized in satisfactory to good yields and selectivities by the reaction of phenols and isoprene in the presence of the commercially available acid faujasite zeolite HSZ-360.

Key words: heterogeneous catalysis, zeolite HSZ-360, isoprene, chromans, *ortho*-isopentenylphenols

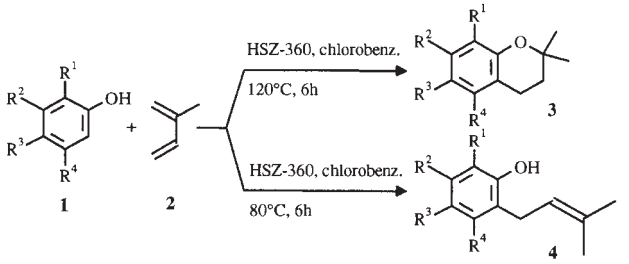
The preparation of fine chemicals following environmentally friendly strategies represents a challenging goal in the field of synthetic organic chemistry.[1] In the last ten years this approach has had a great development, mainly due to the use of solid acids such as clays and zeolites, (up to that time nearly exclusively employed in petrochemical processes).[2] It is now well stated that the use of these heterogeneous catalysts represents the best answer both to the new environmental legislation and to the old chemistry requirements: the processes they promote produce the minimum of pollution and show good[3] yields frequently accompanied by excellent selectivities.

As part of a programme designed to develop new selective and preparatively useful methods based on the use of solid acids as catalysts for the preparation of fine chemicals, previous investigations of our laboratory have described the synthesis of 2*H*-1-benzopyrans from phenols and α-alkynols using a commercial HY-zeolite in typically a heterogeneously catalyzed process.[4]

The α-alkynols, first dehydrate into the corresponding enynes which subsequently react with phenols in a regioselective way to form 2*H*-1-benzopyrans; in all cases the sole products arise from interaction of the phenol oxygen with the olefinic double bond and the *ortho* carbon of the phenol ring with the acetylenic framework of the enyne intermediate. On the basis of these results we investigated the reaction of isoprene with phenols to produce chromans (3,4-dihydro-2*H*-1-benzopyrans) over solid acid catalysts.

The synthesis of chromans or *o*-isopentenylphenols [2-(3-methylbut-2-enyl)phenols],[5] important classes of natural and biologically active compounds, has been extensively studied by many researchers, but it's chemo- and regioselective control is only achieved by using sophisticated catalytic systems such as conveniently prepared acid-base combinations[6] or transition metal complexes,[7] whereas the simple acid catalysis is described to result in less selective reactions.[8]

After preliminary studies with *p*-methoxyphenol (**1a**) and isoprene (**2**) under different conditions, compound **3a** was obtained in 65% yield and 85% selectivity by reacting **1a** (50 mmol) and **2** (50 mmol) in chlorobenzene (50 mL) in the presence of zeolite HSZ-360[9] (5 g) previously heated at 500°C for 5 hours. The reaction was performed by efficiently stirring the heterogene.[10] eous mixture at 120°C for 6 hours in a small autoclave.



3,4	R^1	R^2	R^3	R^4
a	H	H	OCH_3	H
b	H	H	CH=CH-CH=CH	
c	CH=CH-CH=CH		H	H
d	H	O-CH_2-O		H
e	H	H	H	H
f	H	H	OH	H
g	CH_3	CH_3	OH	CH_3
h	H	H	Cl	H
i	H	OCH_3	OCH_3	OCH_3

Scheme 1

Extension of the procedure to **1 b–i** gave the corresponding products **3** in good yields (40–85%) and selectivities (75–90%). As we isolated traces (~5%) of *o*-isopentenylphenols **4** from the reaction mixtures, we performed the synthesis of compounds **4** by conveniently modifying the experimental conditions. To this end we carried out the model reaction between *p*-methoxyphenol (**1a**) and isoprene (**2**) at 80°C obtaining compound **4a** in 45% yield and with 80% selectivity. Furthermore, variously substituted isopentenylphenols were synthesized according to the same procedure (Scheme 1). In all cases the only side product detected in traces by GC-MS analysis (MW 136) was presumably a dimer of isoprene.

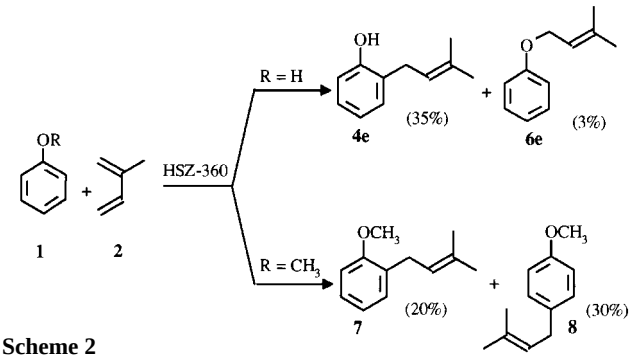
Synthetic results reported are consistent with a typical electrophilic substitution process (compare, e.g., products **3e** and **3h** or **4a** and **4e**). It is worthwhile to note that the reaction shows complete *ortho*-regioselectivity (products **3e** and **4e**) and that in the heterocyclic framework the two methyl groups are next to the oxygen atom. This was confirmed by ^{1}H NMR 2D NOESY spectroscopy experiments: for example, compound **3f** shows a strong cross-peak correlation between the doublet due to H-5 on the

phenolic ring and the triplet due to the methylene H-4 (see experimental section).

Of particular interest is the synthesis of compound **4i** (40% yield, 95% selectivity), a natural product isolated from *Piper clarkii*, which was recently recognized as a powerful anticancer agent and has been synthesized to date in a multistep process.[11] Furthermore, in the reaction with trimethylhydroquinone **1g** we observed the competitive formation of the more important 3,5,6-trimethyl-2-(3-methylbut-2-enyl)-1,4-benzoquinone (**5g**)[12] which has been obtained as the sole product in 53% yield by bubbling oxygen through the flask at the end of the reaction.

Concerning the mechanistic pathway, there is no guarantee that all phenol allylation reactions proceed in the same manner. However, in many instances it has been shown that the reaction involves previous formation of allyl aryl ethers followed by [1,3] or [3,3] sigmatropic rearrangement.[13] Our results confirm that the phenol OH group plays a crucial role in the *ortho*-regioselective control.

Indeed the phenol reacts with isoprene at 80°C for 6 hours in the presence of zeolite HSZ-360 giving the *o*-isopentenylphenol **4e** in 35% yield accompanied by a small amount of the isopentenyl phenyl ether (**6e**, 3%) according to Scheme 2. On the contrary, the same reaction with anisole leads to a mixture of *o*- and *p*-isopentenylanisoles **7** and **8** in 20 and 30% yield respectively (Scheme 2). A detailed study of the alkylation of anisole with dienes promoted by K10 Montmorillonite has been recently published.[14]

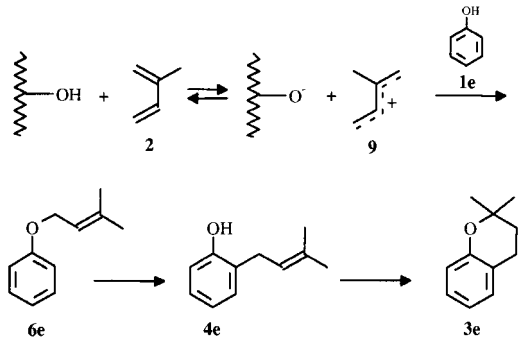


Scheme 2

Moreover both compounds **4e** and **6e** afford the chroman **3e** as the sole product in 80% yield by heating the reaction mixture at 120°C. Finally, by stirring at 80°C a slurry of the ether **6e**[13a] and zeolite HSZ-360 in chlorobenzene, compound **4e** was obtained in 87% yield accompanied by a small amount of phenol (4% yield). The pathway shown in Scheme 3 accounts for all data observed.

Protonation of isoprene by the strongly acid zeolite HSZ-360 affords the isopentenyl cation **9**, which can be envisaged as crucial intermediate[15] and reacts at the oxygen as the more nucleophilic site of the phenol, leading to the ether **6e**. Subsequent *ortho*-regioselective [1,3] Claisen rearrangement yields **4e** which undergoes acid-promoted cyclization to give finally chroman **3e.**

In conclusion, we have shown the synthesis of chromans **3** and *o*-isopentenylphenols **4** starting from phenols and



Scheme 3

isoprene in a one-pot process under solid acid catalysis. The above compounds are obtained in satisfactory yields and good selectivities simply by carrying out the reaction at 120°C or at 80°C, respectively. The simplicity of the method and its workup, together with the low cost of the catalyst and the reagents make the present reaction a convenient route to chromans **3** and *o*-isopentenylphenols **4**. Some mechanistic details of the reaction are also given.

All reagents were of commercial quality. Zeolite HSZ-360 was supplied by Tosoh Corporation and was heated at 500°C before use. TLC analyses were performed on Stratocrom SIF silica gel plates (Carlo Erba) and developed with hexane/EtOAc mixtures. Silica gel (70–230 mesh) for preparative TLC was purchased from Merck. Mps were taken using a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC300 spectrometer at 300 MHz and on a Bruker AC100 spectrometer at 100 MHz; chemical shifts are expressed in ppm relative to TMS as internal standard; *J* values are given in Hz. IR spectra were recorded on a Nicolet PC5 spectrophotometer. MS were obtained in "EI mode" on a HP 5971 S instrument at 70 eV. Microanalyses were carried out by Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica dell'Università di Parma, Italy.

Synthesis of Chromans 3; General Procedure:
In a small autoclave (250 cm^3) the selected phenol (50 mmol), isoprene (5 mL, 50 mmol), zeolite HSZ-360 (5 g) and chlorobenzene (50 mL) were successively introduced. The reaction mixture was stirred at 120°C for 6 h and then cooled to r.t. After filtration, the catalyst was washed with Et_2O (100 mL); the solvents were distilled off under reduced pressure and the crude mixture was chromatographed on a silica gel column (hexane/EtOAc 5–15%) to give the products. The selectivities are calculated with respect to the phenol **1**.

*6-Methoxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran* (**3a**): orange oil; yield: 6.2 g (65%; selectivity: 85%); bp 84–86 °C/0.05 Torr.
^{1}H NMR ($CDCl_3$, 100 MHz): δ = 1.32 (s, 6H, 2 CH_3), 1.78 (t, 2H, *J* = 6.7 Hz, CH_2), 2.75 (t, 2H, *J* = 6.7 Hz, CH_2), 3.74 (s, 3H, OCH_3), 6.5–6.8 (m, 3H, H-arom.).
MS: *m/z* (%) = 192 (M^+, 72), 137 (100), 108 (13).

$C_{12}H_{16}O_2$	calcd	C	74.97	H	8.39
(192.26)	found		75.09		8.25

*3,3-Dimethyl-2,3-dihydro-1*H*-benzo[*d*][1]benzopyran* (**3b**): white solid; yield: 8.0 g (75%; selectivity: 85%); mp 74–76°C (lit.[16] mp 80°C).

*2,2-Dimethyl-3,4-dihydro-2*H*-benzo[*f*][1}benzopyran* (**3c**): white solid; yield: 9.0 g (85%; selectivity: 90%); mp 38–40°C (lit.[17] mp 35–36°C).

*2,2-Dimethyl-6,7-(methylenedioxy)-3,4-dihydro-2*H*-1-benzopyran* (**3d**): white solid; yield: 6.7 g (65%; selectivity: 90%); mp 78–80°C (lit.[18] mp 81–82°C).

*2,2-Dimethyl-3,4-dihydro-2*H*-1-benzopyran* (**3e**): yellow oil; yield: 6.5 g (80%; selectivity: 90%); bp 55–58 °C/0.05 Torr (lit.[6] bp 67–68 °C/2 Torr).
*6-Hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran* **(3f)**: white solid; yield: 4.5 g (50%; selectivity: 75%); mp 77–78 °C.
IR (KBr): ν = 3209 (OH) cm^{-1}.
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.30 (s, 6H, $2CH_3$), 1.75 (t, 2H, *J* = 6.8 Hz, CH_2), 2.68 (t, 2H, *J* = 6.8 Hz, CH_2 [position 4]), 5.7 (br s, 1H, OH), 6.54 (d, 1H, *J* = 2.9 Hz, H-5), 6.57 (dd, 1H, *J* = 8.6 and 2.9 Hz, H-7), 6.64 (d, 1H, *J* = 8.6 Hz, H-8).
MS: *m/z* (%) = 178 (M^+, 52), 163 (24), 123 (100).

$C_{11}H_{14}O_2$	calcd	C	74.13	H	7.92
(178.23)	found		74.20		8.00

*6-Hydroxy-2,2,5,7,8-pentamethyl-3,4-dihydro-2*H*-1-benzopyran* (**3g**): red oil; yield: 7.2 g (65%; selectivity: 85%); bp 77–80°C/0.05 Torr.
IR (KBr): ν = 3451 (OH) cm^{-1}.
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.28 (s, 6H, 2 CH_3), 1.78 (t, 2H, *J* = 6.9 Hz, CH_2), 2. 11 (s, 6H, 2 CH_3-Ar), 2.15 (s, 3H, CH_3-Ar), 2.61 (t, 2H, *J* = 6.9 Hz, CH_2), 4.2 (br s, 1H, OH).
MS: *m/z* (%) = 220 (M^+, 70), 164 (100).

$C_{14}H_{20}O_2$	calcd	C	6.33	H	9.15
(220.31)	found		76.51		9.03

*6-Chloro-2,2-dimethyl-3,4dihydro-2*H*-1-benzopyran* **(3**h): yellow oil; yield: 2.9 g (40%; selectivity: 80%); bp 83–85 °C/0.05 Torr (lit.[6] bp 94–95 °C/1 Torr).

Synthesis of *o*-Isopentenylphenols 4; General Procedure:
The reactions were carried out as described in General Procedure for the chromans **3** reducing the reaction temperature from 120°C to 80°C. Compounds **4** are accompanied by the corresponding aryl isopentenyl ethers (3–5%).

4-Methoxy-2-(3-methylbut-2-enyl)phenol (**4a**): yellow oil; yield: 4.3 g (45%; selectivity: 80%); bp 48–51 °C/0.1 Torr.
IR (NaCl): ν = 3410 (OH) cm^{-1}.
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.76 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 3.32 (d, 2H, *J* = 7.1 Hz, CH_2), 3.75 (s, 3H, OCH_3), 4.77 (s, 1H, OH), 5.3 (t, 1H, *J* = 7.1 Hz, CH), 6.64 (dd, 1H, *J* = 8.3 and 2.9 Hz, H-5), 6.67 (d, 1H, *J* = 2.9 Hz, H-3), 6.73 (d, 1H, *J* = 8.3 Hz, H-6).
MS: *m/z* (%) = 192 (M^+, 81), 137 (100), 108 (26).

$C_{12}H_{16}O_2$	calcd	C	74.97	H	8.39
(192.26)	found		75.12		8.45

1-(3-Methylbut-2-enyl)-2-naphthol (**4b**): pale brown oil; yield: 4.8 g (45%; selectivity: 85%); bp 60–63 °C/0.1 Torr.[19]

2-(3-Methylbut-2-enyl)-I-naphthol (**4c**): pale brown oil; yield: 4.2 g (40%; selectivity: 85%); bp 90–92 °C/0.1 Torr.[19]

2-(3-Methylbut-2-enyl)phenol (**4e**): yellow oil; yield: 2.8 g (35%; selectivity: 75%); bp 53–56 °C/0.1 Torr (lit.[20] bp 109–112 °C/5 Torr).

3,4,5-Trimethoxy-2-(3-methylbut-2-enyl)phenol (**4i**): white solid; yield: 5.0 g (40%; selectivity: 95%); mp 89–91 °C (lit.[11] mp 88–90°C).

3,5,6-Trimethyl-2-(3-methylbut-2-enyl)-1,4-benzoquinone (**5g**): yellow oil; yield: 5.8 g (53%; selectivity: 95%); bp 84–86 °C/0.1 Torr.[12]

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At 60 °C the yields in compounds **4** were lower. At a temperature higher than 120 °C, no yield increase in compounds **3** was observed.
No coke or tar formation on the calalyst surface was observed by carrying out the reaction at 120 °C for 6 h under the reported conditions.
A reaction carried out with the used catalyst (previously washed with acetone and heated for 6 h at 500 °C) gave a 40% yield of chroman **3a**.

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