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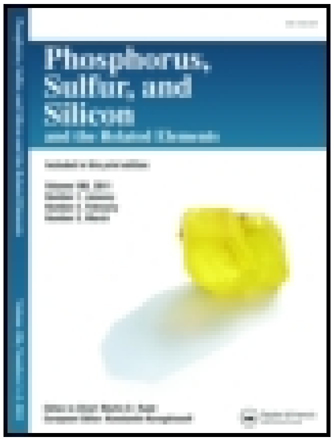

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ADDITION of THIO COMPOUNDS to (R)-LIMONENE CATALYZED by AMBERLYST-15

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ADDITION OF THIO COMPOUNDS TO (*R*)-LIMONENE CATALYZED BY AMBERLYST-15

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The addition of thioacids and thiophenol to (R*)-limonene catalyzed by Amberlyst-15 produced the corresponding 9-thioester- or 9-thioether-p-menthene chemo- and regioselectively.*

Keywords: Amberlyst-15; ion-exchange resin; limonene; thioether; thioester

The catalyzed addition of thio compounds to alkenes can be with Markovnikov (using montmorillonite K-10,[1] Lewis,[2] or protic acids[3]) or anti-Markovnikov (using zeolites[4] or radical conditions[5]) selectivity.

Thio compounds derived from limonene are used as flavors or flotation agents.[6] The uncatalyzed reaction of thioacetic acid with limonene (**1**) is not chemoselective, producing a mixture of addition products to both double bonds along with diaddition products.[7] On the other hand, the reaction of limonene with thiols catalyzed by boron trifluoride produces the 9-thio derivatives,[8] whereas the reaction of thiophenol catalyzed by $HClO_4$ produces in low yield the 8-thio derivative of difficult purification[9] (Scheme 1).

Continuing our interest in chemo- and regiospecific functionalization of the 8,9-double bond of (*R*)-limonene,[10] we studied the reaction of diverse thio compounds catalyzed by Amberlyst-15, a macroreticular strong acidic sulfonic ion-exchange resin ($H_0 = -2.2$),[11] and present our results here.

RESULTS AND DISCUSSION

The reaction of (*R*)-limonene (10 mmol) with thioacetic acid (10 mmol) in dichloromethane at room temperature and catalytic Amberlyst-15

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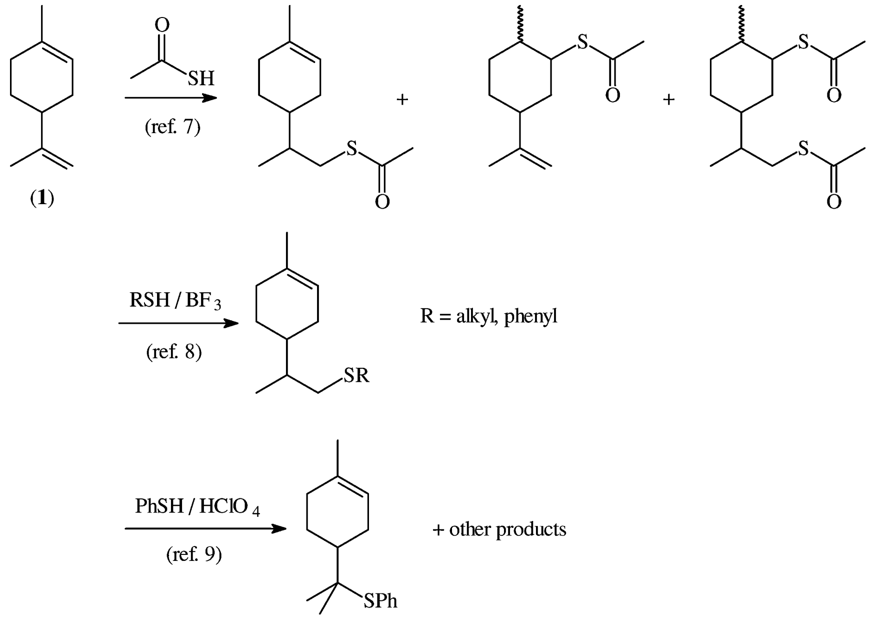
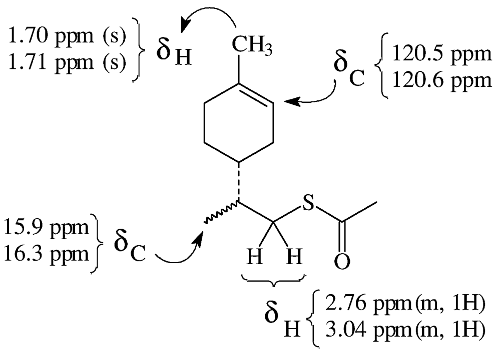


SCHEME 1

(ca. 5% in weight) led to a product **2a** along with some unreacted substrate (determined by high-resolution gas chromatography). After low-pressure distillation, **2a** was isolated in 73% yield and its MS spectra indicated incorporation of one unit of thioacetic acid to limonene (m/z 212 and 214). The IR spectra of the product showed characteristic signals of thioesters (1693, 1135, and 1109 cm^{-1}) and the disappearance of the signal of the disubstituted double bond of limonene (890 cm^{-1}), indicating a chemoselectivity to the acyclic double bond of the substrate. The ^{1}H NMR spectra showed two multiplets at 2.76 and 3.04 ppm (1H each) of a CH$_2$ linked to thioester, indicating both an anti-Markovnikov addition and a diastereoisomeric mixture of products. The fact the **2a** is a pair of diastereoisomers (ca. 1:1) is confirmed by two signals of methyl at 1.70 and 1.71 ppm. The ^{13}C NMR spectrum showed a mixture of diastereoisomers too, as there were many signals with very close shifts (e.g., ring CH at 120.6 and 120.8 ppm, CH$_3$ of isopropyl at 15.9 and 16.3 ppm). Based on these informations the proposed structure for **2a** is shown in Figure 1.

To our surprise, an anti-Markovnikov product was obtained and it was unexpected, because its formation is consistent with a radical process.[5] Furthermore, the addition of alcohols to limonene catalyzed by Amberlyst-15 produced regioselectively the 8-substituted terpinyl



2a

FIGURE 1 Selected NMR data for **2a** (mixture of diastereoisomers).

ethers.[12] Control experiments with freshly distilled limonene,[13,*] rigorous exclusion of air, or reaction in the presence of free radicals inhibitors[14] led to the same product **2a** in similar yield. On the other hand, in the absence of the catalyst, the reaction of limonene with thioacetic acid was incomplete after several hours, producing the thioester **2a** in low yield along with unreacted substrate (in our hands no mixture of several products was detected as previously described[7]).

A possible explanation for the formation of the anti-Markovnikov product could be an initial complexation of limonene with the resin. In analogy to the case with zeolites,[4] due to steric constraints the bulkier Markovnikov adduct could not be retained in the resin and the attack of the thioacid occurs at the less hindered primary carbon of the complex, producing the anti-Markovnikov product.

Based on the above results, it was decided to demonstrate the generality and utility of the Amberlyst-15 catalyzed reaction of (*R*)-limonene with other thio compounds. In all cases the corresponding 9-thio-p-menthenes were obtained as a ca. 1:1 mixture of diastereoisomers (Table I summarizes the results).

The reaction of (*R*)-limonene with thiobenzoic acid produced the thioester **2b** in 65% isolated yield after 20 h [methylene adjacent to thioester at 2.73 and 3.03 ppm (m, 1H each)]. The reaction of (*R*)-limonene with thiophenol produced the thioether **2c** in 51% isolated yield [methylene adjacent to thioester at 2.75 and 3.06 ppm (m, 1H each)] along with unreacted limonene (ca. 30% recovered), diphenyldisulphide (ca. 5%) and diaddition products (ca. 10%).

On the other hand, the reactions of (*R*)-limonene with 1-propanethiol and 2-propanethiol were disappointing as the substrate was recovered

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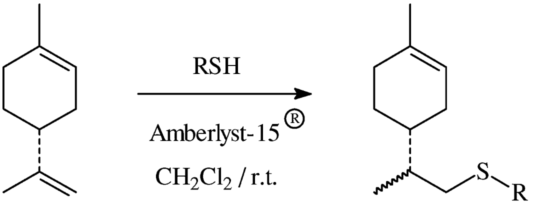
[*] It is known that limonene produces peroxides quickly.

TABLE I Yields of **2** Obtained



2a-e

Entry	R	Time (t/h)	Yield of 2 (%)[a]
a	$CH_3C(O)$	18	73
b	PhC(O)	20	65
c	Ph	48	51
d	Pr	>60	—[b]
e	*i*-Pr	>48	—[b]

[a] Yield of pure product based on limonene.
[b] Limonene recovered.

and no product was detected by the analytical techniques employed (high-resolution gas chromatography, ^{1}H and ^{13}C NMR spectroscopy). Several attempts to perform the reaction changing the conditions (reaction time, temperature, and addition of more catalyst) proved unsuccessful too.

The fact that thiophenol added to limonene while alkylthiols failured could be explained in terms of the proton affinity of these thio compounds. The proton affinity of alkylthiols is 3 kcal/mol higher than thiophenol (189.3 *vs* 186.3 kcal/mol[15]) and consequently the more basic* alkylthiols could be protonated by the acidic resin ($H_0 = -2.2$[11]). Hence, a nucleophilic attack of thiophenol to the limonene-resin complex is possible while protonated alkylthiols do not react at all.

In summary, we have developed a very attractive route to 9-thio-p-menthanes. As in the case of related monoterpene sulfides,[16] the products offer great potentials as starting materials for multistep preparation of bisabolanes.

EXPERIMENTAL

(*R*)-Limonene (Dierberger) was distilled at 177°C (lit.[17] 178°C) and stored in a freezer. Amberlyst-15 (Rohm & Haas), thio compounds

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*As the solvent (CH_2Cl_2) does not efficiently solvate the thiols, the basicity in the gas phase can be assumed to be the same as in solution.

(Aldrich) and other chemicals were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker AC-200 (200 MHz and 50 MHz respectively) spectrometer in $CDCl_3$ solutions with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer (KBr film). MS were obtained on a Hewlett-Packard HP 5896-A HRGC-MS using electron impact (70 eV). Analyses by high-resolution gas chromatography were performed on a HP 5890-II gas chromatograph with FID by using a 25 m (length), 0.53 mm (ID) and 0.50 μm (phase thickness) RTX-5 silica capillary column (Restek Co.) and He (flow rate 50 cm/s) as carrier gas (split 1:20).

General Procedure for the Addition of Thio Compounds to Limonene Catalyzed by Amberlyst-15

To a stirred solution of (*R*)-limonene (10 mmol) and the thio compound (10 mmol) in CH_2Cl_2 (25 ml) was added Amberlyst-15 (70 mg) at room temperature. After the time shown in Table I, the catalyst was filtered off and washed with CH_2Cl_2 (10 ml). The combined liquid was washed with water (10 ml), 5% $NaHCO_3$ (10 ml), water (10 ml) and then dried (Na_2SO_4). After evaporation of the solvent, the residue was distilled at reduced pressure.

(2RS, 3′R)-1-[4′-Methylcyclohex-3′-enyl)propylthio]ethan-1-one (2a) ca. 1:1 Mixture of Diastereoisomers

It was obtained 1.54 g (73%), b.p. 120–122°C/1 Torr. δ_H 0.92 (m, 3H), 1.25 (m), 1.70 (s, CH_3), 1.71 (s, CH_3), 2.35 (s), 2.76 (m, 1H), 3.04 (m, 1H), 5.37 (broad s, 1H) ppm. δ_C 15.9, 16.3, 23.6, 25.5, 27.3, 27.8, 29.4, 30.4, 30.6, 30.8, 34.1, 34.3, 37.8, 37.9, 38.0, 120.5, 120.6, 134.2, 196.3 ppm. ν_{max} 2961, 2924, 2836, 1693, 1451, 1354, 1135, 1109, 955, 800, 629 cm^{-1}. m/z 214 (M^++2), 212 (M^+), 173, 171, 136 (100%), 123, 121, 107, 94, 79.

(2RS, 3′R)-2-(4′-Methylcyclohex-3′-enyl)propylthio Phenyl Ketone (2b) ca. 1:1 Mixture of Diastereoisomers

It was obtained 1.75 g (65%), b.p. 185–187 °C/1 Torr. δ_H 1.03 (m, 3H), 1.61–1.84 (m), 1.70 (s, CH_3), 1.92–1.96 (m), 2.73 (m, 1H), 3.03 (m, 1H), 5.37 (broad s, 1H), 7.45–8.00 (m) ppm. δ_C 16.1, 23.6, 30.4, 30.6, 31.6, 34.2, 38.2, 38.3, 38.4, 41.4, 120.2, 120.3, 128.7, 129.7, 131.1, 137.3, 137.7, 139.3, 197.0 ppm.

(2RS, 3′R)-2-(4′-Methylcyclohex-3′-enyl)propylthio]benzene (2c) ca. 1:1 Mixture of Diastereoisomers

It was obtained 1.24 g (51%), b.p. 150–153°C/1 Torr. δ_H 1.00 (dd), 1.63 (s, CH_3), 1.77 (m), 2.75 (m, 1H), 3.06 (m, 1H), 5.36 (broad s, 1H), 7.29 (m) ppm. δ_C 15.9, 16.4, 23.6, 25.5, 29.7, 30.8, 30.9, 37.3, 37.4, 39.0, 39.1, 120.8, 127.3, 129.0, 129.2, 137.2, 137.7, 196.2 ppm. m/z 248 ($M^+ + 2$), 246 (M^+), 136 (100%), 123, 107, 94, 79.

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