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Short Report

The Reaction of (*R*)-Limonene with *S*-Thioacids

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A reação do (*R*)-limoneno com uma quantidade equimolar de ácidos *S*-tioacético ou *S*-tiobenzóico em tolueno sob refluxo ocorre com regiosseletividade anti-Markovnikoff produzindo os 9-[(4*R*, 8*RS*)-*p*-mentenil] *S*-tiocarboxilatos em 71 e 61% de rendimento, respectivamente. A mesma reação do ácido *S*-tioacético catalisada pela argila montmorilonita K-10 levou ao *S*-tioéster em 65% de rendimento, além de *p*-mentadienos e *p*-cimeno. Foi observado que a argila K-10 promove a isomerização do limoneno aos mentadienos, e sua disproporcionação para o *p*-cimeno

The reaction of (*R*)-limonene with equimolar amount of *S*-thioacetic or *S*-thiobenzoic acids in refluxing toluene proceeded regioselectively in anti-Markovnikoff fashion forming 9-[(4*R*, 8*RS*)-*p*-menthenyl] *S*-thiocarboxylates (71 and 61% yield, respectively). The montmorillonite K-10 clay-catalyzed reaction of (*R*)-limonene with *S*-thioacetic acid led to the *S*-thioester (65%) along with *p*-menthadienes and *p*-cymene. It was observed that K-10 clay promoted the isomerization of limonene to *p*-menthadienes and further disproportionation to *p*-cymene.

Keywords: (*R*)-limonene, *S*-thioester, montmorillonite K-10

Introduction

The natural terpene limonene (**1**) is widely found in nature.[1] The (*R*)-limonene (the most abundant enantiomer) is present in the essential oils of lemon, orange, and other citrus fruits, while the (*S*)-limonene is found in peppermint and the racemate in turpentine oil.[2] The percentage of (*R*)-limonene in orange is ca. 0.92% and it is largely used in the flavor and fragrance industry. As (*R*)-limonene can be obtained in high enantio purity from orange peels, it is an important, cheap and readily available chiral raw material in organic synthesis.[3]

Thio-compounds derived from limonene are used as flavors or flotation agents.[1] The addition of alkyl- and arylthio-compounds onto the acyclic double bond of limonene is promoted by catalysis with Lewis[4] or protic[5] acids in different regioselectivity. Recently we reported that Amberlyst-15, a strong acidic resin, catalyzes the addition of thio-compounds to limonene in high regio- and chemoselectivity.[6] On the other hand, the uncatalyzed reaction of *S*-thioacetic acid to limonene was studied more than a decade ago and led to a mixture of addition products to both double bonds along with diaddition products[7] (Scheme 1). A radical reaction of thiophenol with limonene in the presence of O_2 occurs at the acyclic double bond too and the product is reported to be a potential antimalarial.[8]

Continuing our interest in the chemistry of limonene[9] we revisited its reaction with *S*-thioacids and communicate our new results here.

Results and Discussion

Clays are efficient catalysts for diverse organic transformations due to their Bronsted and Lewis activities[10] and the commercially and readily available K-10 clay (a mild acidic montmorillonite[11]) has been shown to catalyzed several reactions with great selectivity in short reaction times.[12] Among of them, it can catalyze the addition of thio-compounds to alkenes.[13]

The reaction of (*R*)-limonene with *S*-thioacetic acid (1 mol equiv.) in the presence of catalytic K-10 clay (10% weight of limonene) in refluxing toluene for 3.5 h led to 9-[(4*R*)-*p*-menthenyl] *S*-thioacetate as a 1:1 mixture of diastereoisomers in 65% yield, along with unreacted limonene (10%) and several minor products, such as isomeric *p*-menthadienes (among of them terpinolene (**2**)) and *p*-cymene (**3**) – Scheme 2.

To our surprise, a comparison of this catalyzed-reaction with one performed in identical conditions in the absence

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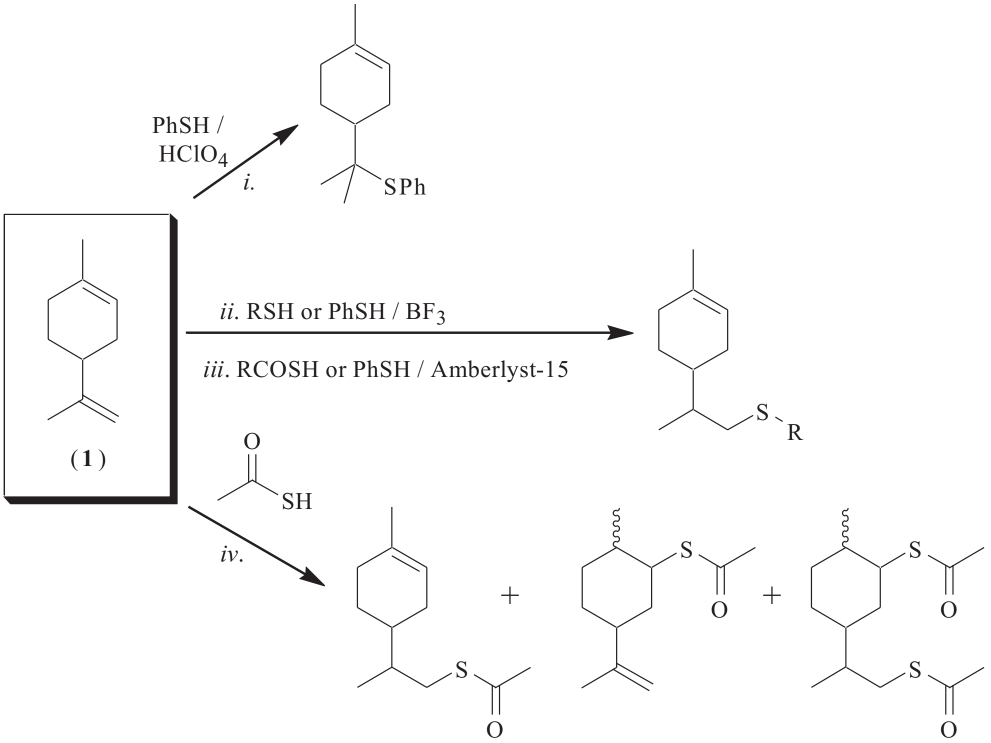
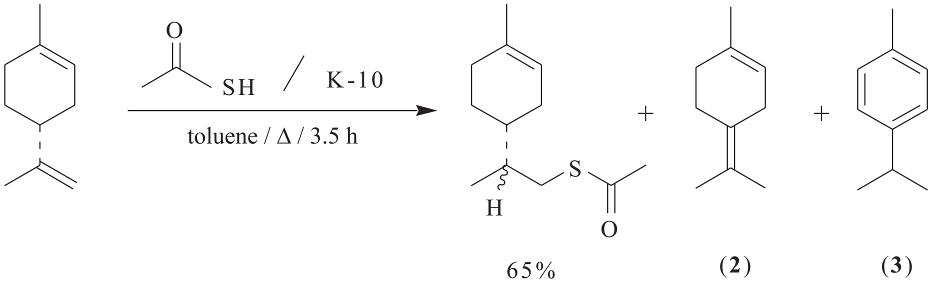


Scheme 1. *i*. from reference 5; *ii*. from reference 4; *iii*. from reference 6; *iv*. from reference 7.



Scheme 2.

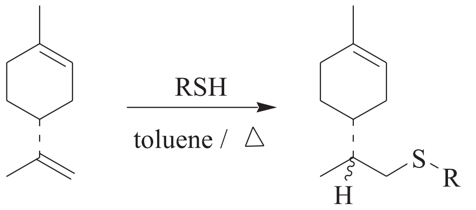
of any catalyst led to the same results, *i.e.*, formation of the 9-*S*-thioacetate in 71% yield, along with unreacted limonene (21%).

A kinetic study comparing both K-10 clay-catalyzed and the uncatalyzed reaction was performed at room temperature to avoid the formation of the minor byproducts and the results are shown in Figure 1. It can be noticed that after 15 min the equilibrium was achieved and the conversion of limonene into 9-*S*-thioacetate in both reactions occurs in very similar rates and ca. 40% yield.

Based on the above results, we studied the uncatalyzed reaction of (*R*)-limonene with thio-compounds. *S*-Thiobenzoic acid added onto the acyclic double bond of the substrate to produce the 9-*S*-thiobenzoate as a 1:1 mixture of diastereoisomers in 61% yield after 4 h at reflux. On the other hand, the addition of thiophenol and propylthiol to limonene in diverse conditions failed. In the former case, diphenyldisulphide was isolated in 40% yield and with the alkylthiol no product was detected in the crude reaction mixture after several hours of reflux. All the results are summarized in Table 1.

The reaction of *S*-thioacids with (*R*)-limonene took place in anti-Markovnikoff fashion and controlled experimental conditions to avoid radical reactions led to the same results. This can be explained in terms of a concerted S-H addition to the acyclic double bond of the substrate with steric factors controlling the regio-selectivity.[13] Another possible explanation could be the attack of the acyclic double bond of limonene onto the protonated *S*-thioacid to afford a tertiary carbenium ion

Table 1. Uncatalyzed reaction of (*R*)-limonene with thio-compounds



R	time/h	Yield/(%)[a]
CH_3CO	3.5	71
PhCO	4	61
Ph	8	–[b]
Pr	12	–

[a] Yield of pure product, based on limonene; [b] Diphenyldisulphide formed in 40% yield.

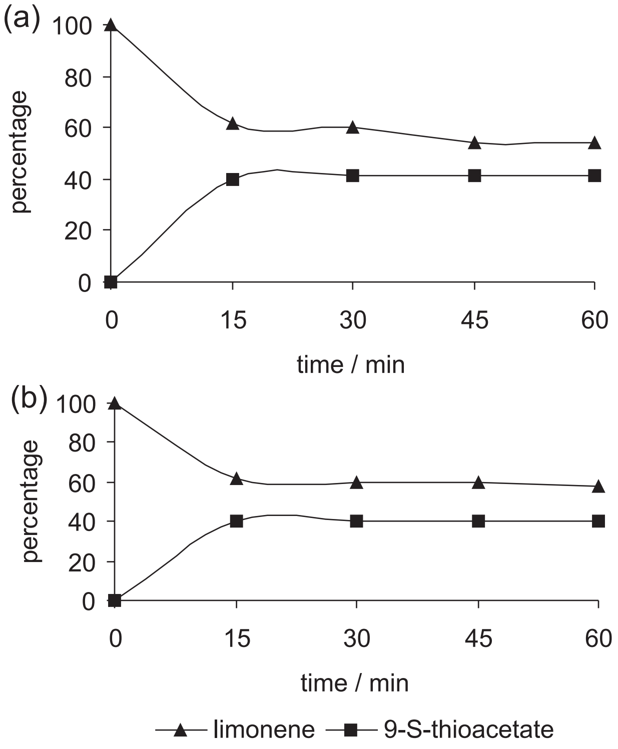


Figure 1. Kinetics of the conversion of (*R*)-limonene into 9-[(4*R*, 8*RS*)-*p*-menthenyl] *S*-thioacete in the presence of K-10 clay (a) and without any catalyst (b).

followed by deprotonation where the bulky thio-group remains at the least sterically loaded carbon atom.[4] Furthermore, in our conditions, we did not detected the products early reported by Davletina *et al.*[7]

Figure 2 shows the ratio limonene / 9-*S*-thioacetate for the reaction of (*R*)-limonene with *S*-thioacetic acid for both K-10-catalyzed and uncatalyzed reactions. It can be noticed that, even after the equilibrium has been achieved, the concentration of limonene decreases in the catalyzed reaction. This result shows that limonene is destroyed by the catalyst (no more addition product is formed) through isomerization to *p*-menthenes and further disproportionation to *p*-cymene. Control experiments heating (*R*)-limonene in the presence of K-10 clay confirmed these observations.[14]

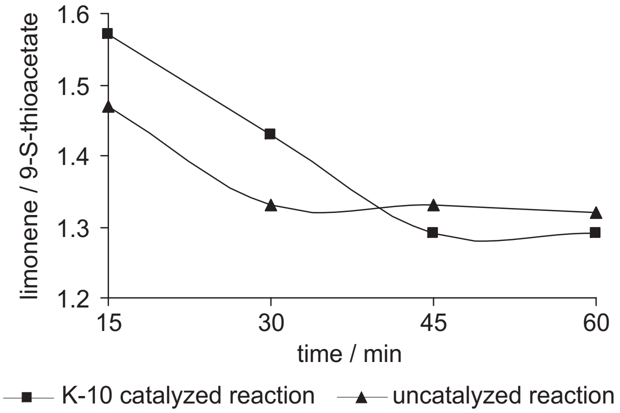


Figure 2. Ratio of limonene / 9-[(4*R*, 8*RS*)-*p*-menthenyl] *S*-thioacete in the reactions of (*R*)-limonene with *S*-thioacetic acid.

K-10 clay presents acidic sites at its surface (H_0 = 1.1-1.5).[15] The formation of terpinolene and other *p*-menthadienes (Scheme 3) is consistent with the chemoselective protonation of the acyclic double bond of limonene[16] by the acidic K-10 clay to produce the terpinyl carbenium (**4**) followed by fast deprotonation (or hydrogen shift and deprotonation).[17] Further disproportionation of *p*-menthadienes produces *p*-cymene.[18] This behavior of limonene to produce *p*-menthadienes derivatives when in the presence of acidic clays was recently observed by Fernandes *et al.* too.[19]

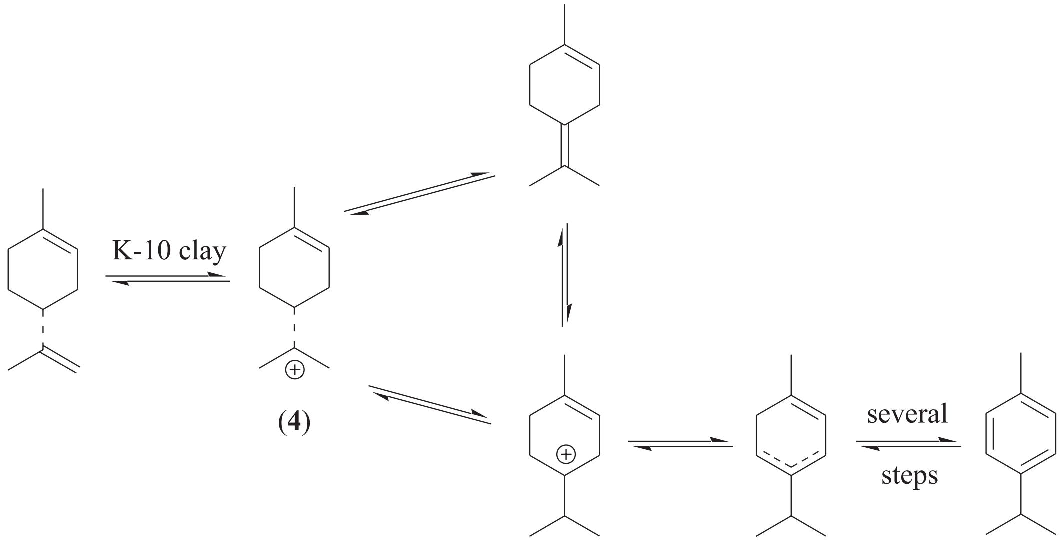
Conclusions

We have shown that the reaction of *S*-thioacids with (*R*)-limonene is a very attractive route to 9-(*p*-menthenyl) *S*-thiocarboxylates. As in the case of related monoterpene sulfides,[20] the products offer great potentials as starting materials for a multistep preparation of bisabolanes.

Experimental

General

(*R*)-Limonene (Dierberger) was previously distilled at 177 °C (lit.: 178 °C)[21] and stored in a freezer. Thio-compounds and K-10 clay (Aldrich) and other chemicals were used without further purification. ^1H NMR and ^{13}C NMR spectra were acquired on a Bruker AC-200 (200 MHz and 50 MHz, respectively) spectrometer in $CDCl_3$



Scheme 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 (HRGC) 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^{-1}) as carrier gas (split 1:20).

K-10-Catalyzed reaction of (R)-limonene with S-thioacetic acid

A suspension of (*R*)-limonene (5 mmol), *S*-thioacetic acid (5 mmol) and K-10 clay (70 mg) in toluene (10 cm^3) was refluxed for 3.5 h. The catalyst was filtered off and the solution was extracted with CH_2Cl_2 (2 × 10 cm^3). The combined liquid was washed with 10% Na_2CO_3 (2 × 10 cm^3), water (2 × 10 cm^3) and then dried (Na_2SO_4). After evaporation of the solvent, the residue was analyzed by HRGC.

Uncatalyzed reaction of (R)-limonene with S-thioacids

A stirred solution of (*R*)-limonene (10 mmol) and the *S*-thioacid (10 mmol) in toluene (25 cm^3) was heated under reflux. After the time shown in Table 1, the solution was extracted with CH_2Cl_2 (2 × 10 cm^3). The combined liquid was washed with 10% Na_2CO_3 (2 × 10 cm^3), water (2 × 10 cm^3) and then dried (Na_2SO_4). After evaporation of the solvent, the residue was analyzed by HRGC.

9-[(4R, 8RS)-p-Menthenyl] S-thioacetate (1:1 mixture of diastereoisomers)

^{1}H NMR δ 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). ^{13}C NMR δ 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. IR (KBr) ν_{max}/cm^{-1}: 2961, 2924, 2836, 1693, 1451, 1354, 1135, 1109, 955, 800, 629. MS *m/z* 214 (M^++2), 212 (M^+), 173, 171, 136 (100%), 123, 121, 107, 94, 79.

9-[(4R, 8RS)-p-Menthenyl] S-thiobenzoate (1:1 mixture of diastereoisomers)

^{1}H NMR δ 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). ^{13}C NMR δ 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. MS *m/z* 276 (M^++2), 274 (M^+), 171, 169, 105, 77 (100%).

Kinetic study

The addition of *S*-thioacetic acid to (*R*)-limonene with and without catalyst was performed at room temperature as described above. The conversion of the substrate into 9-*S*-thioacetate at different reaction times in both reactions was monitored by HRGC using octadecane as internal standard.

Acknowledgments

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