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REACTION OF β-PINENE AND THIOLS IN THE PRESENCE OF LEWIS ACIDS

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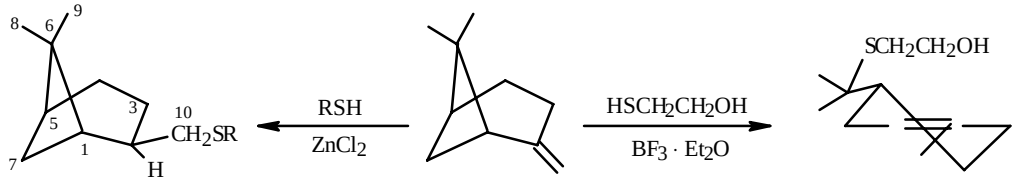
The reaction of β-pinene with thiols using zinc chloride catalyst occurred regiospecifically to synthesize pinane-type sulfides and to form anti-Markovnikov addition products. However, the pinane structure isomerized into menthane in the presence of boron trifluoride etherate.

Key words: β-pinene, catalytic electrophilic addition, thiols, Markovnikov rule.

A common method for sulfiding olefins is the reaction of them with thiols in the presence of mineral and Lewis acids. If mineral acids are used to catalyze the electrophilic addition of thiols to bicyclic monoterpenes, a complicated mixture of products is often formed due to isomerization of the initial molecular skeleton [1, 2]. It is advisable to use Lewis acids to perform regiospecific syntheses of S-containing terpenoids in reactions with thiols.

Our research on the catalyst selected for electrophilic addition of S-containing reagents (thiols and disulfides) to monoterpenes showed that $ZnCl_2$ is the most effective and simultaneously "soft" catalyst [3-5]. Therefore, we chose it as the catalyst for reactions of thiols with β-pinene.

Electrophilic addition of thiols (ethanedithiol, mercaptoethanol, mercaptoacetic acid and its methyl ester) to β-pinene was carried out in methylene chloride at room temperature in the presence of $ZnCl_2$. Pure compounds **2-5** were isolated as oily liquids using column chromatography over silica gel.



2 - 5 **1** **6**

2: R = CH_2CH_2SH; **3:** R = CH_2CH_2OH; **4:** R = CH_2COOH; **5:** R = CH_2COOCH_3

The strained four-membered ring in β-pinene (**1**) makes isomerization processes the principal reactions of this terpene with electrophiles. However, the pinane skeleton is retained in exceptional instances. Furthermore, it was unexpected that the pinane structure was retained in all reactions of thiols with β-pinene catalyzed by $ZnCl_2$.

According to elemental analyses, **2-5** were addition products of one thiol molecule to the double bond of β-pinene. The presence in PMR spectra of adducts **2-5** of signals for only two methyls (0.90 s and 1.11 s) indicated unambiguously that an anti-Markovnikov reaction had occurred (otherwise the spectra would have shown a signal for an additional methyl).

The question of isomerization or retention of the pinane structure was resolved using complex PMR analysis, DQF-COSY, ^{13}C NMR DEPT, COLOC, and HETCOR spectra of **2-5**. Formation of products with the menthane structure was excluded because the PMR spectra lacked signals for olefinic protons. The reaction with retention of the starting pinane structure should lead to the formation of structure **A** whereas isomerization into the bornane system would form structure **B**.

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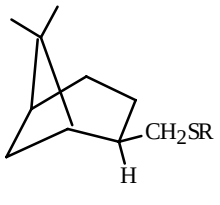
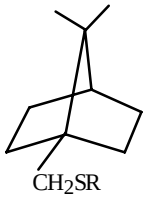


A



B

The presence in the ^{13}C NMR spectrum of **2** of one signal for tetrasubstituted C-7 (39.04), three signals for –CH– fragments [45.85 (C-1), 41.65 (C-6), and 41.44 (C-2)], six signals for methylenes [39.84, 39.67 (C-10, C-11), 36.72 (C-12), 33.76, 32.77 (C-3, C-4), and 22.49 (C-6)], and two signals for methyls [28.42 (C-9) and 23.69 (C-8)] was consistent with retention of the pinane structure in **A**.

For bornane structure **B**, the spectrum should have been different in principle. A detailed analysis of the HETCOR, COLOC, and DQF-COS spectra enabled signals to be assigned to distinct C and H atoms. According to the DQF-COSY spectrum of **2**, the C-2 methine proton (2.38 and 2.41 dd) had cross peaks with the methylene protons of C-10 (two AB systems near 2.51, 2.55 and 2.58, 2.62 pm, 12.5 Hz) and C-3 (m, 1.42 ppm) and with methine proton H-1 (m, 1.92 ppm). The signal for methine proton H-5 (dd, 1.82 ppm) correlated with signals of the CH_2 protons of C-4 (1.65 ppm) and C-6 (1.45 ppm), which, in turn, had cross peaks with protons of neighboring groups. The methylenes of the $–CH_2CH_2SH$ fragment in **2** appeared as singlets at 2.60 and 2.71 ppm.

The PMR, DQF-COSY, ^{13}C DEPT, COLOC, and HETCOR spectra of **3**-**5** were similar in principle to those of **2**. The difference was only the signals for the thiols. For example, the methylene protons of the mercaptoethanol fragment in the PMR spectrum of **3** appeared as triplets at 2.58 (SCH_3) and 3.61 (CH_2O) ppm. Spectra of **4** and **5** had a singlet at 3.05 ppm that corresponded with protons of the methylene on the S. The spectrum of **4** had a singlet for the carboxylic proton at 10.82 ppm. The acetyl protons of **5** appeared as a singlet at 3.50 ppm.

Based on the splitting of the signal for the C-2 methine proton in the PMR spectrum of **5**, we concluded that the addition was stereospecific. A doublet of doublets at 2.38 and 2.41 ppm (J = 3.7 and 7.5 Hz) indicated unambiguously that the *endo*-isomer had formed because there was no coupling between methine protons H-2 and H-1. This agreed with the literature, according to which the magnitude of this constant is small and in the range 0-2 Hz. If the *exo*-isomer had formed, then H-2 would have had the same chemical shift but would have been a multiplet.

According to the literature, the vicinal constant of 3.7 Hz is due to coupling of the C-2 and C-3 *exo*- and *endo*-protons of the ring; the SSCC of 7.5 Hz; coupling of two *exo*-protons [6].

The spectral properties of products **2-4** from the reaction of β-pinene with ethanedithiol, mercaptoethanol, and mercaptoacetic acid were also completely consistent with the pinane structure with an *endo* $–CH_2SR$ group.

Obviously using the "soft" Lewis acid $ZnCl_2$ enabled isomerization of the pinane skeleton to be avoided. However, use of the stronger acceptor $BF_3 \cdot Et_2O$ as a catalyst for the reaction of β-pinene with mercaptoethanol produced **6** with the menthene structure. The PMR spectrum of **6** contained signals for the C-8 *gem*-dimethyl protons (1.02 s), the olefin methyl (1.60 s, 3H-7), the proton of the double bond (5.30 s, H-2), two triplets corresponding to mercaptoethanol protons [2.52 t (SCH_2, J = 6.6 Hz) and 3.48 t (CH_2O, J = 6.6 Hz)], and signals for protons of the cyclohexane ring and the hydroxyl.

We assumed that the formation in the presence of $ZnCl_2$ of reaction products (**2-4**) with the pinane structure and anti-Markovnikov *endo* $–CH_2SR$ groups was a consequence of the high sensitivity of the reactions to steric factors because the addition of a complex reagent (thiol—catalyst) to the β-pinene double bond is concerted and effected from the side opposite the *gem*-dimethyl fragment.

The transition states of model reactions of ethylene and isobutylene with methanethiol were calculated using the DFT method (density functional PBE/3z, three-exponential polarized basis set) and showed that the activation energy of the reaction with $ZnCl_2$ catalyst is lowered considerably (Table 1).

A structural analysis of the transition state for the reaction of isobutylene and methanethiol in the presence of $ZnCl_2$ showed that the proton is coordinated to the tertiary C atom (Fig. 1), remaining partially bound to the S atom. This is consistent with the H—S distance of 1.92 Å whereas the sum of the van der Waal radii of H and S is 2.94 Å [1.74 Å (S) and 1.2 Å (H)]. Simultaneously the S atom is already partially bound to the primary C atom [the difference of the sum of the van der Waal radii of S and C and the calculated distance between these atoms in the transition state is 0.34 Å (1.74 + 1.4 - 2.80)].

TABLE 1. Energy of Formation of π-Complex, Transition State, and Reaction (kcal/mol) Calculated by the DFT Method

Reaction	ΔH_a^{π}	$\Delta H^{\neq}$	ΔH^r
$C_2H_4+CH_3SH$	-0.09	35.14	-22.3
$C_2H_4+CH_3SH$ ($ZnCl_2$)	-2.43	25.68	-14.61
$C_2H_4+2(CH_3SH)$ ($ZnCl_2$)	-1.87	25.92	-16.11

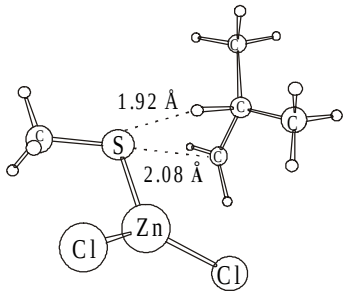


Fig. 1. Structure of π-complex from reaction of isobutylene and methanethiol catalyzed by $ZnCl_2$.

The calculated heats of formation of the regioisomeric addition products also indicated that the anti-Markovnikov thiol addition product is thermodynamically more favored ΔH^r (anti-Markovnikov) = 17.52 kcal/mol; ΔH^r (Markovnikov), 14.95 kcal/mol].

The concerted nature of thiol addition to β-pinene in the presence of $ZnCl_2$ was indirectly confirmed by the retention of the pinane structure because the formation of isomerized products is more probable if particles with localized charges are involved in the reaction.

Thus, the use of $ZnCl_2$ catalyst for reactions of β-pinene with thiols led in most instances to regio- and stereospecific syntheses with retention of the pinane structure. However, the pinane structure isomerized into menthane in the presence of $BF_3 \cdot Et_2O$.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were measaured in $CDCl_3$ on a Varian Unity spectrometer (300 and 75.43 MHz) with TMS internal standard. IR spectra were obtained for samples in mineral oil on a 75-IR spectrometer.

Reaction of β-Pinene with Thiols. A solution of β-pinene (0.015 M) in CH_2Cl_2 was treated at room temperature and stirred with the appropriate thiol (0.0195 M) in CH_2Cl_2 (20 mL) and $ZnCl_2$ (0.2 g) (for preparation of **6**, $BF_3 \cdot Et_2O$, 0.5 mL). After 1-3 h the reaction mixture was treated with water (200 mL), extracted with CH_2Cl_2, and dried over $MgSO_4$. After solvent was removed, the reaction products were purified by column chromatography over silica gel (hexane:ether). Yields (%): 83 (**2**), 87 (**3**), 85 (**4**), 88 (**5**), and 79 (**6**).

{(6,6-Dimethylbicyclo[3.1.1]heptyl)*endo*-2-methylthio}ethanethiol (2). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.9 s, 1.11 s (6H, $2CH_3$), 1.42 m (1H, H-3), 1.45 m (2H, H-7), 1.65 m (2H, H-4), 1.82 m (2H, H-5), 2.38, 2.41 dd (1H, J = 3.7, 7.5, H-2), 2.51, 2.55 AB; 2.58, 2.62, A′B′ (2H, J = 12.5, H-10), 2.60 s, 2.70 s (4H, SCH_2CH_2SH).

^{13}C NMR spectrum (δ, ppm): 45.85 (C-1), 41.65 (C-6), 41.44 (C-2), 39.04 (C-7), 39.84, 39.67 (C-10,11), 36.72 (C-12), 33.76, 32.77 (C-3,4), 22.49 (C-7), 28.42 (C-9), 23.69 (C-8).

{(6,6-Dimethylbicyclo[3.1.1]heptyl)*endo*-2-methylthio}ethanol (3). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 s, 1.11 s (6H, $2CH_3$), 1.42 m (1H, H-3), 1.45 m (2H, H-7), 1.65 m (2H, H-4), 1.82 m (2H, H-5), 2.38, 2.41 dd (1H, J = 3.7, 7.5, H-2), 2.51, 2.55 AB; 2.58, 2.62 A′B′ (2H, J = 12.54, H-10), 2.58 t (2H, J = 6.6, SCH_2), 3.61 t (2H, J = 6.6, CH_2O).

^{13}C NMR spectrum (δ, ppm): 61.05 (C-12), 45.85 (C-1), 41.65 (C-6), 41.44 (C-2), 39.04 (C-7), 39.50, 39.16 (C-10,11), 33.76, 32.74 (C-3,4), 24.49 (C-7), 23.62 (C-9), 22.43 (C-8).

IR spectrum (ν, cm^{-1}): 3600-3200 (OH).

{(6,6-Dimethylbicyclo[3.1.1]heptyl)*endo*-2-methylthio}acetic Acid (4). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 s, 1.11 s (6H, $2CH_3$), 1.42 m (1H, H-3), 1.45 m (2H, H-7), 1.65 m (2H, H-4), 1.82 m (2H, H-5), 2.38, 2.41 dd (1H, J = 3.7, 7.5, H-2), 2.51, 2.55 AB; 2.58, 2.62 A′B′ (2H, J = 12.5, H-10), 3.05 s (2H, SCH_2), 10.82 s (1H, COOH).

^{13}C NMR spectrum (δ, ppm): 176.80 (C=O), 45.85 (C-1), 41.71 (C-2), 40.78 (C-7), 40.29 (C-11), 39.07 (C-7), 35.32 (C-10), 33.76, 32.77 (C-3,4), 26.6 (C-6), 73.66 (C-9), 21.69 (C-8).

IR spectrum (ν, cm^{-1}): 3500-3100 (OH).

Methyl{(6,6-dimethylbicyclo[3.1.1]heptyl)*endo*-2-methylthio}acetate (5). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 s, 1.11 s (6H, $2CH_3$), 1.42 m (1H, H-3), 1.45 m (2H, H-7), 1.65 m (2H, H-4), 1.82 m (2H, H-5), 2.38, 2.41 dd (1H, J = 3.7, 7.5, H-2), 2.51, 2.55 AB; 2.58, 2.62 A′B′ (2H, J = 12.5, H-10), 3.05 s (2H, SCH_2), 3.50 s (3H, OCH_3).

1-Methyl-4-(methylethyl)-8-hydroxyethylthiocyclohex-1-ene (6). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.02 s (6H, $2CH_3$), 1.60 s (3H, H-10), 2.03 s (OH), 2.52 t (2H, J = 6.0, SCH_2), 3.48 t (2H, J = 6.0, CH_2O), 5.30 s (1H, H-2).

IR spectrum (ν, cm^{-1}): 3600-3200 (OH), 1670 (>C=CH), 790.

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