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Convenient One-Pot Synthesis of 4,8-Dimethyl-bicyclo[3.3.1]non-7-en-2-ol via Platinum/Tin Catalyzed Hydroformylation/Cyclization of Limonene

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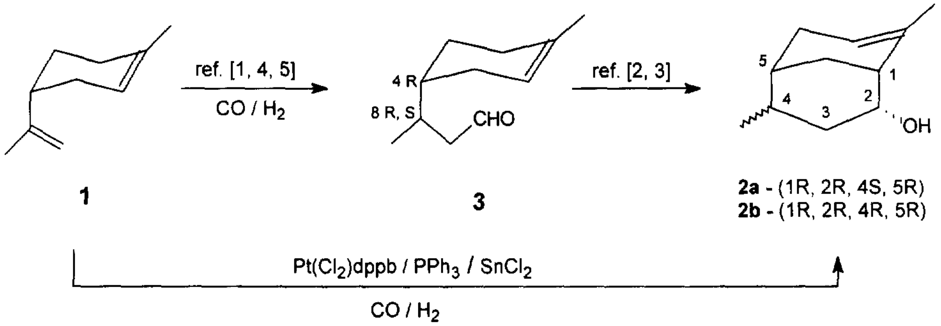
Abstract: Limonene (**1**) was converted in one step into two diasteroisomers of 4,8-dimethyl-bicyclo[3.3.1]non-7-en-2-ol (**2**), useful as perfumes, employing $PtCl_2(PPh_3)_2/PPh_3/SnCl_2$ and $PtCl_2(diphosphine)/PPh_3$ /$SnCl_2$ systems as bifunctional catalysts whose diphosphines were 1,3-bis(diphenylphosphino)propane (dppp) and 1,4-bis(diphenylphosphino)butane (dppb). In the presence of the $PtCl_2(dppb)/PPh_3$ /$SnCl_2$ system, which was found to be the most promising combination, the selectivity for **2** reached the value of 82% at 95% conversion of **1**.

Limonene (**1**) is sufficiently abundant and cheap enough to produce oxygenated derivatives of interest to perfumery. Aldehydes and alcohols derived from the naturally occurring terpenes are widely employed in the perfumery industry[1]. It was reported by the Mitsubishi Co. that two isomers of 4,8-dimethyl-bicyclo[3.3.1]non-7-en-2-ol (**2a** = 1R,2R,4S,5R; **2b** = 1R,2R,4R,5R) and their derivatives are useful as perfumes[2,3]. Their syntheses via cyclization of menthene (**3**), catalyzed by sulfuric acid[2] or by strongly acidic ion-exchange resins[3], were described in two patents of the Mitsubishi Co. Menthene can be synthesized by hydroformylation of limonene using phosphine-modified cobalt or rhodium complexes[1,4], or platinum-tin combinations[5] as catalysts.



In a previous work, we studied the hydroformylation of various monoterpenes in the presence of platinum(II)-phosphine-tin(II) catalytic systems[6]. It was observed that under certain reaction conditions these systems showed a marked acidic behavior promoting isomerization of **1** mainly into α-terpinolene and γ-terpinene. In addition, we detected small amounts of two by-products which were later identified as the isomeric bicyclic alcohols **2a** and **2b** probably formed by the acid catalyzed cyclization of the hydroformylation product **3**. To find the most favorable conditions for the synthesis of **2** directly from **1** without isolation of **3**, we have studied the effect of the reaction variables and the nature of the phosphine on the product distribution. We report herein a convenient one-pot synthesis of **2** via platinum-tin catalyzed hydroformylation/cyclization of **1** and preliminary results of the study of this reaction. To the best of our knowledge, this is the first example of the direct conversion of **1** into the 4,8-dimethyl-bicyclo[3.3.1]nonane derivatives under hydroformylation conditions described in the literature up to the present time.

The reaction of **1** with CO and H_2 was investigated using the following catalytic systems: $PtCl_2(PPh_3)_2/PPh_3/SnCl_2$ and $PtCl_2$(diphosphine)/$PPh_3/SnCl_2$ with different chelating diphosphines: 1,2-bis (diphenylphosphino)ethane (dppe), 1,3-bis(diphenylphosphino)propane (dppp) and 1,4-bis (diphenyl phosphino)butane (dppb). Benzene was employed as a solvent. The results are given in Table 1.

Table 1. Synthesis of 4,8-Dimethyl-bicyclo[3.3.1]non-7-en-2-ol (**2**) by Hydroformylation/Cyclization of Limonene (**1**) and Cyclization of Menthene (**3**) [a]

Run	Substrate	Catalyst	Conversion	Product distribution [b] (%)			
			(%)	Hydrogenation [c]	Isomerization [d]	**3**	**2 (2a/2b)** [e]
1	**1**	$PtCl_2(PPh_3)_2$	83	1	70	-	29 (50/50)
2	**1**	$PtCl_2$(dppp)	93	22	4	7	67(44/56)
3	**1**	$PtCl_2$(dppb)	95	11	4	3	82 (47/53)
4[f]	**1**	$PtCl_2$(dppb)	85	traces	80	-	20 (45/55)
5[g]	**1**	$PtCl_2$(dppb)	85	13	3	21	63 (47/53)
6	**3**	$PtCl_2$(dppb)	100	-	-	-	100(45/55)
7	**3**	-	< 1	-	-	-	traces
8[h]	**3**	$PtCl_2$(dppb)	<1	-	-	-	-

a) Reaction conditions: substrate (5 mmol), catalyst (0.05 mmol), $SnCl_2$ $2H_20$ (0.05 mmol), PPh_3 (0.1 mmol), benzene (5 mL), 130°C, 9 MPa (CO/H_2 = 1/1), reaction time 50 h. b) Determined by gas chromatography. c) The product of limonene hydrogenation -carvomenthene. d) The products of limonene isomerization, mainly, α-terpinolene and γ-terpinolene. e) The ratio of 1R,2R,4S,5R (**2a**) and 1R,2R,4R,5R (**2b**) (may be reversed). f) $SnCl_2$ $2H_20$ - 0.25 mmol. g) Reaction time 24 h. h) In the absence of $SnCl_2$ $2H_20$, reaction time 19 h.

In the absence of $SnCl_2$, all Pt complexes studied show no activity in the hydroformylation of **1**. We have found that the nature of the phosphorus-containing ligands exerts a strong effect on the activity of the catalytic system in the conversion of **1** and the product distribution. The combination with dppe, which can make up a strong chelate ring, is completely inactive in the hydroformylation of **1**. Neither **2** nor **3** are detected. A similar effect of dppe on the activity of the platinum-tin systems in the hydroformylation of 1-alkenes has been reported earlier[7]. Several transformations of **1** occur in the presence of the systems containing PPh_3, dppp, or dppb as ligands (Table 1): cyclization with the incorporation of CO and H_2 yielding the diastereomeric mixture of **2a** and **2b**, hydroformylation resulting in aldehyde **3**, isomerization of **1** mainly into α-terpinolene and γ-terpinene, and hydrogenation of the exocyclic double bond of **1** resulting in carvomenthene. Relative amounts of the products depend on the phosphine used, the Pt/Sn ratio, and the reaction time. A low selectivity for **2** (29%) and large amounts of the isomerization products (up to 70%) are observed when PPh_3 is employed as the only phosphine ligand (run 1). This system shows the lowest hydrogenation activity compared with the other ones. On the other hand, considerable amounts of carvomenthene (22%) and only 4% of the isomerization products are formed when the $PtCl_2$(dppp) complex is used, with the selectivity for **2** being rather high (67%) (run 2).

The best result is achieved employing a platinum complex containing dppb as ligand (run 3). The selectivity for **2** reaches the value of 82% at 95% conversion of **1** and Sn/Pt=1. The selectivity for **2** is strongly influenced by the tin/platinum atomic ratio and drastically decreases to 20% at Sn/Pt=5 (run 4). Small amounts of aldehyde **3** (3%, run 3) are detected in the reaction solution after 50 hours, while at shorter reaction time the relative amounts of **3** among the reaction products are significantly higher (21% at 24 hours, run 5). This allows to suggest a stepwise conversion of **1** into **2** with the intermediate formation of the hydroformylation product **3** followed by its cyclization into **2a** and **2b**. Indeed, **3** undergoes a complete conversion into **2a** and **2b** in the presence of the $PtCl_2(dppb)/PPh_3/SnCl_2$ system under the same reaction conditions (run 6). It is worthwhile noting that **1** is hydroformylated regiospecifically to give exclusively the linear aldehyde **3** (a mixture of 4R,8S and 4R,8R diasteroisomers in approximately equal amounts) and only the terminal double bond is selectively transformed. No trace of the branched aldehyde can be detected.

The mechanism of the intramolecular cyclization of **3** under the hydroformylation conditions is not yet fully understood. It is interesting to note a high diasteroseletivity of this reaction. A stereospecific interaction of the carbonyl group with the endocyclic double bond in each of two diasteroisomers of **3** results in the formation of only one diasteroisomer of **2**. The product **2a** is formed from the 4R,8S isomer of **3**, while 4R,8R isomer forms **2b**. We have to note that the configuration R of the asymmetric carbon atoms 1 and 2 of both **2a** and **2b** was suggested on the basis of molecular model structures and are in agreement with the data reported in ref. 2. Our preliminary study revealed that catalytically active species probably contain both platinum and tin atoms. Cyclization of **3** did not occur in the absence of either a platinum complex (run 7) or $SnCl_2$ (run 8). Only the starting material was recovered after these runs. Thus, it seems unlikely that $SnCl_2$ alone acts as a Lewis acid catalyzing the transformation of **3** into **2**. The nature of the active complex remains to be clarified.

In conclusion, we have described a synthesis of 4,8-dimethyl-bicyclo[3.3.1]non-7-en-2-ol from limonene and preliminary results of the study of this reaction. The $PtCl_2(dppb)/PPh_3/SnCl_2$ combination represents a selective bifunctional catalyst that promotes both the hydroformylation of limonene and then the intramolecular cyclization of the aldehyde formed in a convenient one-pot reaction.

Experimental: The products were analyzed by gas chromatography (CG) using a Shimadzu 14B instrument fitted with a Carbowax 20 M capillary column and a flame ionization detector. NMR spectra were obtained using a Brucker CXP-400 spectrometer with tetramethylsilane as an internal standard in $CDCl_3$. IR spectra were recorded on a Mattson FTIR 3000/ Calaxy Series spectrophotometer. Mass spectra were obtained on a Hewlett-Packard MSD 5890/Series II instrument operating at 70 eV. Platinum complexes were synthesized by literature methods[8,9]. Phosphorus(III) compounds and $SnCl_2 \cdot 2H_2O$ were purchased from Aldrich and used without further purification. Benzene was purified under reflux with sodium wire/benzophenone for six hours and then distilled under nitrogen. R-(+)-Limonene was distilled before use.

In a typical run a platinum complex (0.05 mmol), $SnCl_2 \cdot 2H_2O$ (0.05 mmol), PPh_3 (0.1 mmol), **1** (5 mmol), and benzene (5 mL) were transferred under nitrogen into a glass lined 30 mL stainless steal reactor. The reactor was pressurized to 9 MPa total pressure (CO/H_2= 1/1), placed in an oil bath, and magnetically stirred at 130°C for 50 h unless otherwise indicated. After cooling to room temperature, the excess CO/H_2 was slowly vented. The solution was analyzed by GC and GC/MS. A mixture **2a/2b** was isolated from the reaction solution by column chromatography (silica) using mixtures of hexane, CH_2Cl_2, and methanol as eluents; and analyzed by IR, ^1H and ^{13}C-NMR spectroscopy.

4,8-dimethyl-bicyclo[3.3.1]non-7-en-2-ol (**2a/2b**). IR ν_{max}(film)/cm^{-1}: 3400, 2900, 1450, 1370, 1070, 1030, 900, 800. MS (*m/z*/rel.int.): 166/13 (M^+); 148/30; 133/20; 121/12; 106/26; 93/100. ^1H NMR: δ 0.92 (d, 3H, C*H*$_3$, J=6.5Hz); 1.03 (d, 3H, C*H*$_3$, J=7.4Hz); 1.21-1.25 (m, 2H); 1.49-1.53 (m, 4H); 1.63-1.68 (m, 6H); 1.78 (s, 3H, C*H*$_3$); 1.79 (s, 3H, C*H*$_3$); 1.98-2.01 (m, 3H); 2,32-2.34 (m, 3H); 3.84-3.88 (m, 1H, C*H*OH); 3.98-4.09 (m, 1H, C*H*OH); 5.55-5.58 (m, 2H, C*H*= (**2a**), C*H*= (**2b**)). ^{13}C NMR: δ 19.46; 19.88; 25.33; 25.68; 25.91; 31.09; 31.27; 31.89; 34.01; 34.19; 35.56; 36.37; 36.79; 40.82; 41.87; 69.67; (C-OH); 74.46 (C-OH); 123.68 (C=C); 124.33 (C=C); 133,69 (C=C); 134.21 (C=C). Spectral simulations performed with the ADC/CNMR program were in agreement with the spectra observed.

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