Synthesis of Raspberry and Ginger Ketones by Nickel Boride-catalyzed Hydrogenation of 4-Arylbut-3-en-2-ones

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Raspberry and ginger ketones have been synthesized in good yield by the hydrogenation of the corresponding unsaturated precursors 4-(4′-hydroxyphenyl)but-3-en-2-one and 4-(4′-hydroxy-3′-methoxyphenyl)but-3-en-2-one, respectively, using a freshly prepared suspension of nickel boride in methanol as catalyst.

Key words: Raspberry Ketone, Zingerone, Enones, Hydrogenation, Nickel Boride

Introduction

Raspberry and ginger ketones **1** [1] and **2** [2] are well-known natural substances which became the objects of both laboratory and industrial synthesis. Owing to their intensive fragrance they found applications in perfumery, cosmetics and as food additives [3, 4]. Investigations of the biological activity of the phenolic compounds **1** and **2**, in particular antioxidant [5 – 7] and anti-inflammatory [6 – 8] actions, cancer prevention [8, 9] and influence on the metabolic rate [10, 11] are still ongoing. In addition to that, the preparation of these simple structures with unusual properties is interesting as an educational process [12].

One of the general approaches to the synthesis of ketones **1** and **2** includes an aldol condensation of 4-hydroxybenzaldehyde and 4-hydroxy-3-methoxybenzaldehyde (vanillin) with acetone followed by the reduction of the double bonds of the corresponding intermediate α,β-unsaturated ketones **3** and **4** (Schemes 1 and 2). The first step is simple and cheap to realize, however for the reduction of enones **3** and **4** rather expensive hydrogenation catalysts (palladium [1, 13], platinum [2], rhodium [12], or Raney nickel [14]) have been used. Transition metal catalysis except rhodium is also complicated by a partial reduction of the carbonyl function [12]. Some other specific methods and reagents such as sodium amalgam [15],
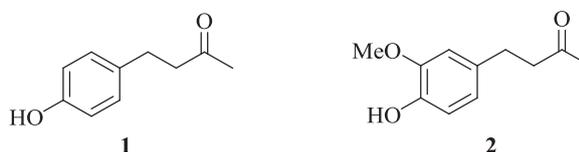
sodium hydrotelluride [16], baker's yeast [17, 18], and aluminum halide-induced ionic hydrogenation [19] were employed for the 1,4-reduction of compounds **3** or **4**. At last, highly efficient hydrogenation was achieved with neodymium oxide/polyethylene glycol-supported nickel boride [20]. In the present paper we report an easier and cheaper procedure for the transformation of enones **3** and **4** into raspberry and ginger ketones in good yield using nickel boride as hydrogenation catalyst.

Results and Discussion

Nickel boride (Ni_2B) can be prepared by the reaction of nickel(II) salts with sodium borohydride. This reagent was applied for the selective reduction of a number of functional groups [21]. In the presence of Ni_2B, as reported, the C=C double bond of α,β-unsaturated carbonyl compounds is reduced with an external source of hydrogen [22] and also without one, when the catalyst and the hydrogen are generated *in*
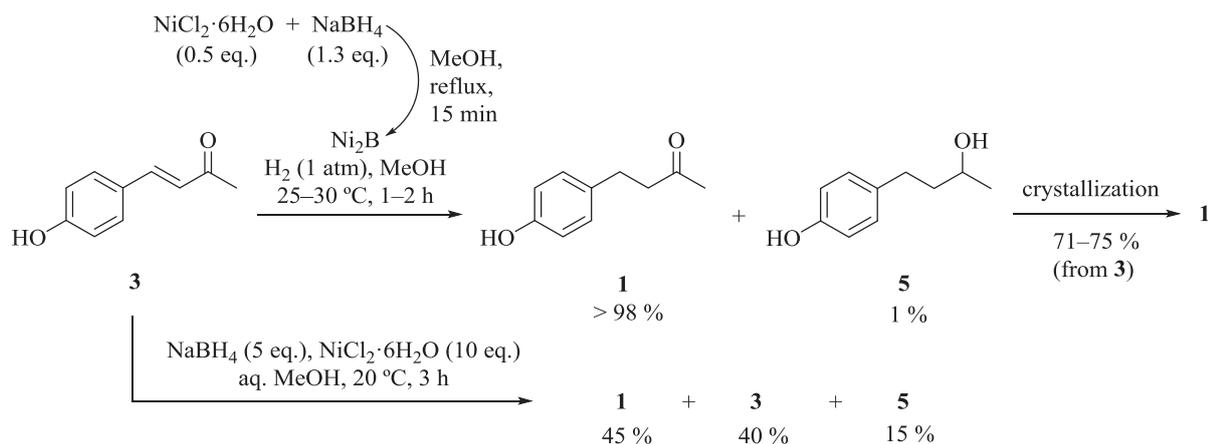
Scheme 1. Preparation of raspberry ketone **1**.

situ by the reaction of $NaBH_4$ with $NiCl_2$ in the mixture of methanol/dioxane [23] or in aqueous methanolic solution [24]. The second method, which is more easily handled, unfortunately appeared to be not effective for the preparation of raspberry ketone. Reduction of enone **3** with an excess of $NiCl_2$ and $NaBH_4$ [24] (Scheme 1) led to a difficultly separable mixture of saturated ketone **1** (45%), alcohol **5** (15%) and starting material (40%) as established by GC and ^1H NMR spectroscopy.

On the other hand, reduction of enone **3** under a hydrogen atmosphere in the presence of a freshly prepared suspension of Ni_2B in methanol proceeded smoothly at 25 – 30 °C to give raspberry ketone **1** as the main product (Scheme 1). The reaction mixture as detected by GC contained more than 98% of saturated ketone **1** and about 1% of the corresponding saturated alcohol **5**. These compounds were also distinguished by the chemical shift of the methyl group in the ^1H NMR spectra ($\delta = 2.14$ ppm for **1**, 1.24 ppm for **5**, and 2.40 ppm for **3**). The target raspberry ketone **1** was easily purified by crystallization from mixtures of methanol/water or toluene/ethyl acetate.

Noteworthy, in the course of hydrogenation we clearly observed the completion of the reduction of the C=C double bond by the disappearance of the green color of the reaction mixture. We terminated the reaction at this moment because overtime of the hydrogen treatment gradually increased the amount of saturated alcohol as observed by TLC and ^1H NMR spectroscopy. When using nickel boride generated from $NaBH_4$, it is necessary to prevent the reduction of the carbonyl function by residual $NaBH_4$ [22]. For this reason, the suspension of the catalyst in methanol should be refluxed for several hours [22]. However, by our observations, this caused a significant loss of catalytic activity and decreased the rate of hydrogen absorption. In our experiments, if a suspension of Ni_2B was initially refluxed for 3 h, the hydrogenation of enone **3** was incomplete after 24 h at 25 – 30 °C. We limited the thermal treatment of the catalyst to 15 min, and in this case the hydrogenation process was accomplished in a short time.

Ginger ketone **2**, also called zingerone, was prepared in the same manner by the hydrogenation of
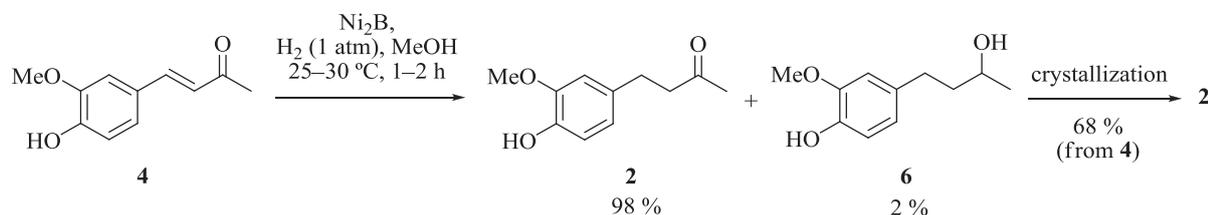
Scheme 2. Preparation of ginger ketone (zingerone) **2**.

enone **4** (Scheme 2). The reaction mixture contained about 98% of ketone **2** and 2% of alcohol **6** based on GC. Due to a low melting point, we had some trouble with the crystallization of zingerone **2** and preferred column chromatography for its purification. However, we also succeeded in crystallization of crude **2** using seed crystals of the pure product and a mixture of methanol/water as solvent.

Conclusion

Readily available products of the aldol condensation of 4-hydroxybenzaldehyde or vanillin with acetone were hydrogenated in the presence of cheap nickel boride to give raspberry and zinger ketones, respectively, in good yield. The advantage of the reported procedures is that a two-step sequence (preparation of catalyst and hydrogenation) can be carried out in a one-pot reaction and in a short time.

Experimental Section

Melting points were determined with a capillary apparatus. IR spectra were recorded on a Vertex 70 spectrometer. GC-MS analyses were performed using a Shimadzu GCMS-QP2010 instrument equipped with an Equity^{TM}-5 capillary column (30 m, 0.25 mm ID, 0.25 μm film thickness) in the electron impact ionization mode at 70 eV. The carrier gas helium was applied. ^{1}H NMR spectra were recorded on a Bruker AC 400 instrument at 400 MHz, CHCl$_3$ was used as internal standard ($\delta = 7.26$ ppm). Elemental analyses were performed using a Thermo Scientific^{TM} Flash 2000 CHNS/O analyzer. Methanol was freshly distilled from magnesium methoxide. Petroleum ether of b. p. 40 – 70 °C was used. Silica gel 60 F 254 plates were used for TLC analysis, and column chromatography was performed on silica gel 70 – 230 mesh using 10 – 30% solutions of ethyl acetate in petroleum ether as eluent. Starting compounds (*E*)-4-(4′-hydroxyphenyl)but-3-en-2-one (**3**) and (*E*)-4-(4′-hydroxy-3-methoxyphenyl)but-3-en-2-one (**4**) were prepared by NaOH-catalyzed condensation of acetone with 4-hydroxybenzaldehyde and 4-hydroxy-3-methoxybenzaldehyde, respectively (see for example ref. [12]).

4-(4′-Hydroxyphenyl)butan-2-one (*1*)

NaBH$_4$ (0.46 g, 12.1 mmol) was added portionwise at 0 °C to a stirred solution of NiCl$_2$·6H$_2$O (1.10 g, 4.63 mmol) in methanol (20 mL). Once the addition was complete, the suspension was stirred for 15 min at 0 °C followed by re-

fluxing under argon atmosphere for 15 min. Then, the mixture was cooled to room temperature, and unsaturated ketone **3** (1.50 g, 9.25 mmol) was added. The stirred mixture was treated with hydrogen (~1 atm) keeping the external temperature at 25 – 30 °C. Once the green color of the methanolic solution had disappeared (about 1 – 2 h), the hydrogenation was stopped, and the mixture was filtered. The nickel boride cake was washed with methanol, and the combined filtrates were evaporated under reduced pressure. Then, the residue was treated with saturated aqueous NH$_4$Cl (20 mL) and ethyl acetate (20 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (10 mL). The combined organic phases were washed with brine (10 mL), dried with Na$_2$SO$_4$, and evaporated under reduced pressure. According to GC analysis, the unpurified reaction mixture contained > 98% of product **1** ($t_R = 21.3$ min), 1% of by-product **5** ($t_R = 21.6$ min) and traces of starting enone **3** ($t_R = 25.5$ min). The residue was recrystallized from a mixture of methanol/water (1 : 3) to give pure raspberry ketone **1** in a yield of 1.14 g (75%) as colorless crystals; m. p. 82 – 83 °C (lit. [12]: m. p. 80 – 82 °C). Alternatively, the residue was recrystallized from the mixture of toluene-ethyl acetate (4 : 1), the yield of compound **1** being 1.08 g (71%), m. p. 81 – 83 °C. – IR (KBr): $\nu = 3373$ (OH), 1691 (C=O) cm^{-1}. – ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 2.14$ (s, 3H, CH$_3$), 2.71 – 2.76 (m, 2H, CH$_2$), 2.80 – 2.85 (m, 2H, CH$_2$), 6.29 (br s, 1H, OH), 6.75 – 6.79 (m, 2H, aromatic CH), 7.00 – 7.04 (m, 2H, aromatic CH) ppm. The spectral data were similar to those reported in the literature [12, 20]. – MS: m/z (%) = 164 (20) [M]$^+$, 149 (5) [M–CH$_3$]$^+$, 131 (3) [M–CH$_3$–H$_2$O]$^+$, 121 (11) [M–CH$_3$CO]$^+$, 107 (100) [M–CH$_3$COCH$_2$]$^+$. – C$_{10}$H$_{12}$O$_2$ (164.2): calcd. C 73.15, H 7.37; found C 73.28, H 7.28.

4-(4′-Hydroxy-3′-methoxyphenyl)butan-2-one (*2*)

Compound **2** was prepared from enone **4** (1.78 g, 9.26 mmol) in accordance to the procedure for raspberry ketone **1**. As shown by GC analysis, the unpurified reaction mixture contained 98% of product **2** ($t_R = 23.6$ min) and 2% of by-product **6** ($t_R = 24.1$ min). The crude product was purified by column chromatography to give zingerone **2** as a colorless liquid which was crystallized in a refrigerator. Yield 1.69 g (94%); m. p. 39 – 40 °C (lit. [2]: m. p. 40 – 41 °C). Alternatively, the crude product was recrystallized from a mixture of methanol/water (1 : 3) using seed crystals, the yield of compound **2** being 1.23 g (68%); m. p. 41 – 42 °C. – IR (KBr): $\nu = 3400$ (OH), 1705 (C=O) cm^{-1}. – ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 2.13$ (s, 3H, CH$_3$), 2.71 – 2.76 (m, 2H, CH$_2$), 2.79 – 2.84 (m, 2H, CH$_2$), 3.86 (s, 3H, CH$_3$O), 5.63 (br s, 1H, OH), 6.64 – 6.67 (m, 1H, aromatic CH), 6.68 – 6.69 (m, 1H, aromatic CH), 6.81 – 6.83 (m, 1H, aromatic CH) ppm. The spectral data were similar to

those reported in the literature [12, 14]. – MS: m/z (%) = 194 (37) $[M]^+$, 179 (2) $[M–CH_3]^+$, 161 (1) $[M–CH_3–H_2O]^+$, 151 (12) $[M–CH_3CO]^+$, 137 (100) $[M–CH_3COCH_2]^+$. – $C_{11}H_{14}O_3$ (194.2): calcd. C 68.02, H 7.27; found C 68.07, H 7.22.

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