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Hydroformylation of *m*-diisopropenylbenzene and 1-isopropyl-3-isopropenylbenzene for the preparation of the fragrance Florhydral®

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Abstract

An hydroformylation-based approach to the synthesis of the odorant Florhydral® has been investigated. The hydroformylation of *m*-diisopropenylbenzene (**2**) in the presence of rhodium catalysts leads to mixtures of 3-(3-isopropenylphenyl)butyraldehyde (**3**), which is an immediate precursor of Florhydral® and of the dialdehyde 3-[3-(1-methyl-3-oxopropyl)phenyl]butyraldehyde (**4**), which is a useless side product. The **3/4** ratio is dependent on the substrate conversion: when it is pushed over 40%, the formation of **4** becomes increasingly important. Interestingly, the reaction can be carried out in aqueous biphasic systems using a rhodium catalyst precursor either in the presence of sulphonated triphenyl phosphine or human serum albumin (HSA) as the ligands. Good results were also obtained using rhodium complexes immobilized on silica; in this case it was possible to exclusively obtain the sought aldehyde **3** by limiting the substrate conversion at about 41%.

As an alternative approach, 1-isopropyl-3-isopropenylbenzene (**8**) was synthesized and hydroformylated. In both homogeneous and biphasic systems, in the presence of rhodium catalysts, the reaction leads to the formation of Florhydral® with high reaction rates and complete chemo- and regioselectivity. The use of chiral phosphino ligands, in order to obtain enantiomerically enriched Florhydral®, gave very poor ees.

Keywords: Hydroformylation; Rhodium; Biphasic catalysis; Asymmetric catalysis; Fragrances; *m*-Diisopropenylbenzene

1. Introduction

The hydroformylation of functionalized olefins is a useful synthetic tool which can be conveniently employed in the preparation of a wide variety of fine chemicals [1–4]. In particular, hydroformylation-based synthetic approaches are of the foremost importance in perfume industry since they allow to transform a large number of readily available olefinic precursors into the corresponding aldehydes which represent one of the most important classes of odorants [5]. In this connection, it is worth mentioning that BASF has developed processes based on the hydroformylation of functionalized alkenes such as α-pinene [6], *tert*-butyldihydrodioxepine [7] or β-isophorone [8] and that also mono- or polycyclic aldehydes have been advantageously obtained by hydroformylation of the corresponding cyclic olefins [9–11]. In addition, it is to remind that differently substituted allyl- and propenylbenzenes such as safrole, isosafrole, eugenol and isoeugenol have been hydroformylated in the presence of rhodium complexes to produce the corresponding aldehydes which are valuable perfume components and/or odour boosters [12–14].

A new trend in modern perfumery is the preparation of fragrances having a delicate marine and watery touch [15]. Among the synthetic odorants employed to convey the fresh marine and ozonic note, one of the most important is 3-(3-isopropylphenyl)butyraldehyde (**1**) (Scheme 1), which is marketed by Givaudan under the trade name of Florhydral®. According to two patents issued by Givaudan, a very advantageous synthesis of Florhydral® implies the rhodium catalyzed hydroformylation of the cheap and readily available *m*-diisopropenylbenzene (**2**) (Scheme 1). The reaction affords the unsaturated aldehyde **3** which is then hydrogenated to give

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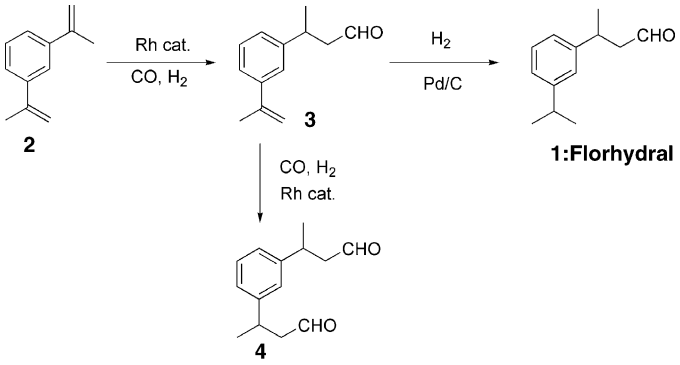

Scheme 1.

the sought fragrance. The major drawback of the process is represented by the formation of the undesired dialdehyde **4** which is formed by the double hydroformylation of the starting olefin [16,17].

Owing to our interest in the application of the oxo-reaction in fine chemistry [18–23], we deemed it interesting to reinvestigate the hydroformylation of *m*-diisopropenylbenzene in the presence of some rhodium catalysts modified with phosphino ligands looking for higher selectivities in the formation of aldehyde **3**; moreover, in order to easily recover and recycle the expensive rhodium-based catalyst, we decided to perform the oxo-process in biphasic systems by using water soluble or heterogenized rhodium catalysts.

Another aspect which spurred us to investigate the synthesis of **1** via hydroformylation is the presence of a chiral carbon atom in the Florhydral® molecule. As it happens with other fragrances, the two enantiomers induce a different biological activity and it has been shown by Fuganti and co-workers, who succeeded in independently preparing the two enantiomers resorting to an enzymatic approach [24], that (+)-Florhydral® is an odorant much more powerful than the opposite stereomer. There currently is a great interest in preparing chiral odorants as pure enantiomers; in fact, by producing and marketing only the more olfactory active isomer it will be possible to reduce the amount of these molecules which are eventually dispersed in the biosphere. These considerations encouraged us to devise an asymmetric hydroformylation-based scheme for the synthesis of enantiomerically enriched Florhydral®.

2. Experimental

2.1. General remarks

Commercial solvents (Fluka or Aldrich) were purified according to literature [25]. *m*-Diisopropenylbenzene, 3-isopropylphenol, trifluoromethanesulfonic anhydride, formic acid, 3-(mercapto)propyl-functionalyzed silica gel and 3-(1-thioureido)propyl-functionalyzed silica gel were purchased from Aldrich. $HRh(CO)(PPh_3)_3$, $Rh(CO)_2(acac)$, Xantphos and DPPB were Strem products. Sulfonated triphenylphosphine (TPPTS) was obtained from Fluka. Human serum albumin (HSA) was a Sigma product. (*R*)-BINAP (**III**), (*R*)-(−)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine (**IV**) and (*R*)-(−)-1[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyl-di(3,5-dimethylphenyl)phosphine (**V**) were purchased from Strem. The silica gel tethered rhodium catalysts **Rh-I** and **Rh-II** were prepared according to Ref. [23].

Flash chromatographies were performed using Merck 60 silica gel, 230–400 mesh. NMR spectra were recorded on a Bruker Avance 300 spectrometer using $CDCl_3$ as the solvent. GLC analysis were carried out on an Agilent 6850A gas chromatograph, using an HP1 column (30 m × 0.32 mm × 0.25 μm). GC–MS analyses were performed by using an Agilent MS Network 5937 apparatus using an HP-5MS column (30 m × 0.25 mm × 0.25 μm). Optical rotation values were measured with a Perkin-Elmer Mod. 241 polarimeter.

2.2. Synthesis of 1-isopropyl-3-isopropenylbenzene (*8*)

2.2.1. 4-(3-Isopropylphenyl)-2-methylbut-3-yn-2-ol (*6*)

To an aqueous solution of NaOH (40.0 g in 400 mL) were added 40.3 g (0.30 mol) of 3-isopropylphenol and the mixture was stirred until complete dissolution. Then 83.5 g (0.30 mol) of trifluoromethanesulfonic anhydride dissolved in 85 mL of CCl_4 were added dropwise. After stirring for 2 h, the organic phase was separated and the aqueous layer washed with CCl_4 (4 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and rotoevaporated to give a brown oil. Distillation under reduced pressure afforded 65.0 g (81% yield) of trifluoromethanesulfonic acid 3-isopropylphenyl ester as a colourless oil (bp 49–51 °C/0.01 mmHg).

Trifluoromethanesulfonic acid 3-isopropylphenyl ester. MS: *m/z* 268 [M^+], 253, 135, 119, 103, 91. ^{1}H NMR ($CDCl_3$, δ): 1.29 (d, J = 7.0 Hz, 6H, CH_3), 2.98 (m, 1H, CH), 7.10–7.15 (m, 2H, arom.), 7.29 (s, 1H, arom.), 7.35–7.40 (m, 1H, arom.). ^{13}C NMR ($CDCl_3$, δ): 23.6, 33.9, 118.5, 118.8 (q, CF_3, J_{C-F} = 320.5 Hz), 119.3, 126.5, 130.0, 149.8, 152.0.

Under an inert atmosphere, in a 500 mL three-necked round bottom flask equipped with a reflux condenser and a nitrogen inlet, were placed, in the order, 41 mg of palladium(II) acetate (0.18 mmol), 140 mg of triphenylphosphine (0.54 mmol), 19.3 g (72.0 mmol) of trifluoromethanesulfonic acid 3-isopropylphenyl ester, 69 mg (0.36 mmol) of CuI, 6.0 g (72.0 mmol) of 2-methylbut-3-yn-2-ol and 125 mL of piperidine. The resulting solution was stirred at 75 °C for 20 h, then was cooled at rt and the piperidine was distilled off. The brown residue was treated with 70 mL of 5N HCl at 0 °C. The mixture was extracted with diethyl ether, and the aqueous phase washed with diethyl ether (3 × 50 mL), and with dichloromethane (3 × 50 mL). The combined organic extracts were washed with $NaHCO_3$, then with brine, dried over $MgSO_4$ and rotoevaporated. The resulting crude brown oil can be used in the subsequent step without further purification, but if needed, **6** can be obtained as a pale yellow oil after flash chromatography (silica gel, *n*-hexane/diethyl ether = 95/5).

4-(3-Isopropylphenyl)-2-methylbut-3-yn-2-ol (**6**). MS: *m/z* 202 [M^+], 187, 170, 159, 128, 91. ^{1}H NMR ($CDCl_3$, δ): 1.29 (d, J = 7.0 Hz, 6H, CH_3), 1.66 (s, 6H, CH_3), 2.45 (br s, 1H, OH), 2.98