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Short communication

Rh-catalyzed selective synthesis of 1,5-dimethylhexahydro-1H-inden-4(2H)-one *via* hydroformylation of (*R*)-carvone

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ABSTRACT

This work reports domino hydroformylation, hydrogenation and intramolecular keto-aldol condensation reactions for the selective synthesis of 1,5-dimethylhexahydro-1H-inden-4(2H)-one obtained from (*R*)-carvone and dihydrocarvone under homogeneous hydroformylation condition. The synthesis of the desired product was achieved by using conventional rhodium/1,3-bis(diphenylphosphino)propane (Rh/dppp) catalyst and PPTS (pyridinium *p*-toluenesulfonate) as an acidic co-catalyst. The reaction conditions were optimized with respect to various reaction parameters like time, temperature, synthesis gas (CO/H_2) pressure, solvents, catalyst and co-catalyst loading. The experimental results showed that less planner carbon backbone in dihydrocarvone increases the steric hindrance around the reaction site and responsible for the reactivity difference between (*R*)-carvone and dihydrocarvone.

1. Introduction

Hydroformylation of olefins is one of the excellent tool for the synthesis of industrially important alkanals. These alkanals are important intermediates in the pharmaceuticals, agrochemicals, fragrances, in fuels, and for the synthesis of organic solvents [1]. According to techsci research report the global market of fine chemicals obtained *via* hydroformylation, estimated to exceed US$ 33.27 billion by 2025 published as “Global Oxo Chemicals Market By End Use, By Region, Forecast & Opportunities 2011-2025” in the year october 2016 [2]. The phosphine modified cobalt or rhodium metal-based complexes are used as a homogeneous or heterogeneous catalyst for hydroformylation reaction [3]. The tandem hydroformylation reaction is known for the synthesis of compounds like acetals, amines, alcohols, amides and amino acids [4]. Apart from various advantages of using such integrated processes, designing of the multifunctional or multicatalytic system is also a challenging task for the chemists to achieve multistep synthesis in one pot. The use of additives such as modified cyclodextrins [5,6], surfactant and ionic liquids in enhancing the activity, selectivity, solubility of reactant and interfacial area between two solvents is well known in the literature. Even such systems can also be adopted for consecutive secondary reactions in the tandem process in hydroformylation reaction. Tetrafluoroboric acid (HBF_4) was used as an additive to increase the conversion and selectivity towards branched amine in hydroaminomethylation of styrene with aniline catalyzed by $Rh(COD)_2BF_4$ /dppf (1,1′-bis(diphenylphosphino)ferrocene) (COD = 1,5-cyclooctadiene) [7]. Vieira et al. have developed a protocol for the synthesis of fragrance ingredient 4,8-dimethyl-bicyclo[3.3.1]non-7-en-2-ol *via* hydroformylation followed by an intramolecular carbonyl-ene reaction, catalyzed by rhodium complexes with PPTS as co-catalyst [8]. Fang et al. reported the effect of acid-base co-catalyst on the conversion and selectivity for the synthesis of ketones *via* hydroformylation/aldol condensation/hydrogenation using $[Rh(CO)_2(acac)]$/naphos (2,2′-bis(diphenylphosphinomethyl)-1,1′-binaphthyl) as a suitable catalytic system [9]. Limonene aldehyde, vertral and florhydral was used as an ingredient in perfumes, flavours, and foodstuffs industries through hydroformylation reaction [10]. Asakawa et al. reported a protocol for the synthesis and degradation of intense mossy odorous liverwort sesquiterpene alcohol “tamariscol” and studied its stereochemistry and absolute configuration [11]. They have successfully synthesized tamariscol by utilizing carbonyl compound *i.e.* (*1R,3aS,5R,7aS*)-1,5-dimethylhexahydro-1H-inden-4(2H)-one **(A)** (Scheme 1) obtained *via* multiple synthetic steps from (*R*)-carvone. This process can be made more efficient and sustainable if one can minimize the multiple synthetic steps using the multifunctional catalytic system through tandem reaction. In this regard, herein we report the selective synthesis of 1,5-dimethylhexahydro-1H-inden-4(2H)-one **(1d)** (Scheme 2) from (*R*)-carvone and dihydrocarvone using Rh/dppp as a catalyst in the presence of PPTS co-catalyst through tandem reactions. The developed catalytic system proceeds through various reaction sequence in one pot fashion *i.e.***(A)** selective hydroformylation of (*R*)-carvone gives **(1a)**; **(B)** hydrogenation of α,β-unsaturated C=C bond of enone **(1a)**;

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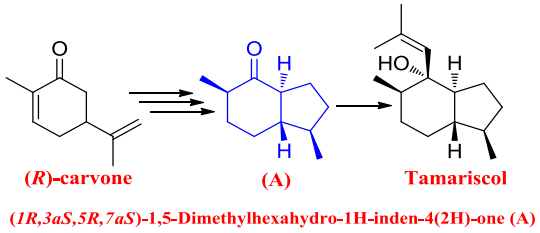
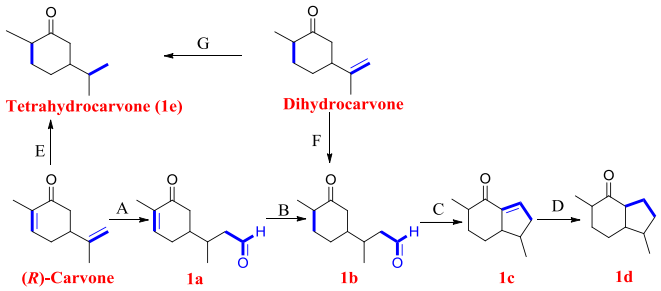


Scheme 1. Synthesis of tamariscol.



Scheme 2. Hydroformylation of (*R*)-carvone and dihydrocarvone.

(C) intramolecular keto-aldol condensation of **(1b)** catalyzed by PPTS; **(D)** hydrogenation of α,β-unsaturated C═C bond of newly formed enone **(1c)**; **(E)** hydrogenation of both C═C bonds of carvone gives by-product **(1e)**; **(F)** hydroformylation of dihydrocarvone gives keto-aldehyde **(1b)** and **(G)** hydrogenation of C═C bond of dihydrocarvone gives by-product **(1e)** as shown in (Scheme 2).

2. Experimental

2.1. Materials and instruments

All the materials *i.e.* (*R*)-carvone, dihydrocarvone, PPTS, rhodium metal precursor, phosphine ligand *etc.* were procured from the reputed chemical supplier and used without further purification. The quantitative analysis and qualitative product formation were confirmed by using GC–MS-QP 2010 instrument (Rtx-17, 30 m × 25 mm ID, the film thickness(df) = 0.25 μm) (column flow 2 mL min^{-1}, 65 °C to 240 °C at 10 °C min^{-1} rise). The FT-IR (Fourier Transform Infrared) spectra were recorded on Brucker Perkin Elmer-100 spectrometer in the wavelength range from 400 to 4000 cm^{-1}. ^1H NMR spectra of the final product **(1d)** were obtained with a Bruker Avance 400 MHz NMR spectrometer with $CDCl_3$ as the solvent [15].

3. Results and discussion

In the initial stage, we have optimized the reaction parameters for the hydroformylation reaction. The hydroformylation reaction was performed by taking (*R*)-carvone (600 mg, 4 mmol), $Rh(CO)_2(acac)$ (2.58 mg, 0.01 mmol), dppe (1,2-bis(diphenylphosphino)ethane, 15.92 mg, 0.04 mmol; M/L 1:4), PPTS (5.00 mg, 0.02 mmol), synthesis gas (CO/H_2, 1:1) pressure ranging from 550 psi to 750 psi in toluene (10 mL) at 110 °C for 24 h at 700 rpm stirring speed (Table 1, entries 1–3). At 550 psi of synthesis gas pressure, only 60% of conversion and selectivity was observed with considerable amount intermediates **(1a)** and **(1c)** (Table 1, entry 1). With the increase in synthesis gas pressure from 550 psi to 650 psi, the conversion was enhanced up to 96% with 90% selectivity for **1d** (Table 1, entry 2). With further increase in the synthesis gas pressure to 750 psi leads to double hydrogenation of starting material and gives tetrahydrocarvone **(1e)** (Table 1, entry 3) as a side product. Next, the effect of temperature towards conversion of (*R*)-carvone and selectivity for **(1d)** was studied (Table 1, entries 4–6). It has been observed that change in reaction temperature significantly affects the net conversion and selectivity of the desired product. When the reaction was carried out at 120 °C it gave 100% conversion with 91% selectivity for compound **(1d)** (Table 1, entry 4). Further increase in temperature up to 130 °C had no significant impact (Table 1, entry 5). However at 140 °C, the conversion remains same but the rate of substrate hydrogenation was increased and gives **(1e)** (Table 1, entry 6). The effect of reaction temperature and pressure on the conversion and selectivity of products under hydroformylation condition for (*R*)-carvone was not studied in earlier reports [12]. In the catalyst screening, the performance of different rhodium metal sources for better selectivity with conversion towards desired product was tested. It is been found that the use of $[RhCl_3]$ and $[Rh(COD)Cl]_2$ (Table 1, entries 7, 8) are not ideal for the given set of reaction sequences and gives low *i.e.* 40% and 70% conversion respectively. With $[RhCl_3]$ and $[Rh(COD)Cl]_2$ complexes, an inhibition period always observed before hydroformylation began. Such inhibition period in $[RhCl_3]$ and $[Rh(COD)Cl]_2$ complexes may be responsible for a slow formation of catalytically active Rh-hydride species by hydrogenolysis and less reactivity in the developed catalytic system. Desire results for compound **(1d)** were obtained only by using $[Rh(CO)_2(acac)]$ as a rhodium metal precursor and gives the highest selectivity up to 91% with 100% conversion (Table 1, entry 4). The appropriate choice of ligand ancillary was found to be a crucial step as it plays an important role in conversion and selectivity towards formation of **(1d)** (Table 1, entries 9–14). The phosphine containing aryl (PPh_3 (triphenylphosphine); Table 1, entry 10), alkyl (PBu_3 (tributylphosphine); PCy_3 (tricyclohexylphosphine); Table 1, entries 11, 12) backbone gave acceptable conversion but high reactivity towards the hydrogenation leads to the generation of **(1e)** in the final product and hence it eliminates their applicability for the synthesis of **(1d)**. Whereas the use of dppp ligand gives 97% selectivity for **(1d)** shows similar conversion as of dppe (Table 1, entries 9). Use of wide bite angle containing bulky bidentate phosphine ligand like xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) is well-known ligand reported for the hydroformylation chemistry and known for its excellent selectivity towards normal aldehyde product. And hence use of xantphos as phosphine ancillary displays very high selectivity for the hydroformylation reaction and gives **(1a)** in the highest ratio (Table 1, entry 13) but retards next consecutive hydrogenation reaction of **(1a)** to form intermediate product **(1b)**. The low conversion and highest percent composition of side product **(1e)** in reaction mixture disclose the importance of phosphine ancillary in the developed in the present catalytic system (Table 1, entry 14). The diphosphine ligands are reported in the literature for hydroformylation of various olefins and their performance in terms of conversion and selectivity is correlated with their bite angle. We also observed results which are in line with the reported results for other olefins. *i.e.* increase in conversion and selectivity ratio with respect bite angle [13,14].

In the next set of experiments, the effect of metal to ligand ratio was studied (Table 1, entries 15, 16). It was observed that the decrease in Rh/dppp ratio from 1:4 to 1:2 considerably brings down the net conversion up to 91% and selectivity (Table 1, entry 15). However when metal to ligand ratio increased from 1:4 to 1:6, hydrogenation reactions get decelerate and gives intermediate **(1a)** and **(1c)** in notable concentration (Table 1, entry 16). From above observations, it can be concluded that metal to ligand ratio of 1:4 is necessary for the optimal conversion and selectivity.

The pyridinium-based organic salts like pyridinium chloride (Py.HCl), pyridinium sulfate ($Py.H_2SO_4$) and pyridinium nitrate ($Py.HNO_3$) were also examined. But the promising result was obtained with PPTS as co-catalyst (Table 2, entries 1–4). When the reaction was carried out in the absence of co-catalyst considerable amount of intermediate aldehyde **(1b)** was detected in the final product, this indicates that co-catalyst is necessary to accelerate intramolecular keto-aldol reaction to give intermediate **(1c)** (Table 2, entry 5). Further, it has been observed that ligand to co-catalyst ratio in reaction medium