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Synthesis of aryl-butanal isomers by hydroformylation of substituted allylbenzene and propenylbenzene

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Abstract

The hydroformylation of two isomeric arylalkenes, 1-(4′-methoxy-phenyl)-propene and 3-(4′-methoxy-phenyl)-propene was investigated in the presence of in situ rhodium and platinum catalysts. While α- and β-substituted formyl regioisomers were formed in the hydroformylation of propenylarene type substrate by rhodium catalysts, all three regioisomers were isolated in platinum-catalyzed reactions. Very high chemoselectivities (> 99%) were obtained in the first case. The accompanying hydrogenation of the substrate took place to a very small extent. Due to isomerization of the terminal double bond lower chemoselectivities and the formation of chiral 2-(4′-methoxy)-butanal were observed with 3-(4′-methoxy-phenyl)-propene as substrate. E.e.'s up to 7.5% and 27.5% were obtained for 2-(4′-methoxy)-butanal in asymmetric hydroformylation of 1-(4′-methoxy-phenyl)-propene by rhodium–diop catalyst and in the hydroformylation of 3-(4′-methoxy-phenyl)-propene by platinum–tin(II)chloride catalyst, respectively.

Keywords: Hydroformylation; Anethol; Estragol; Rhodium–phosphine catalyst; Platinum–phosphine–tin(II)chloride catalyst

1. Introduction

The asymmetric hydroformylation represents a potential powerful synthetic tool for the synthesis of a large number of pharmacologically important compounds and various chiral building blocks. While much work has been done on asymmetric hydroformylation of vinylaromatics both with rhodium- [1–6] and platinum-containing systems [7–10] (for a recent review, see[11]) in recent years, little is known about the hydroformylation of propenyl and allylaromatics [12,13]. This is surprising, since the enantioselective hydroformylation of propenyl-benzene could result in the formation of optically active 2-phenyl-butanal, which could be oxidized with ease to 2-phenyl-butanoic acid, a direct precursor of sparmolitic Butetamate and antiinflammatory Indobufen [14] (Fig. 1, Eq. (1)). Substituted 3- and 4-aryl-butanal derivatives, which could be easily synthesized by the hydroformylation of the corresponding allylarenes, are important intermediates for the synthesis of substituted 2-methyl-indanons and α-tetralons, respectively [15] (Fig. 1, Eqs. (2) and (3)). Some substituted derivatives of allyl-benzenes and propenylbenzenes are easily available from natural resources

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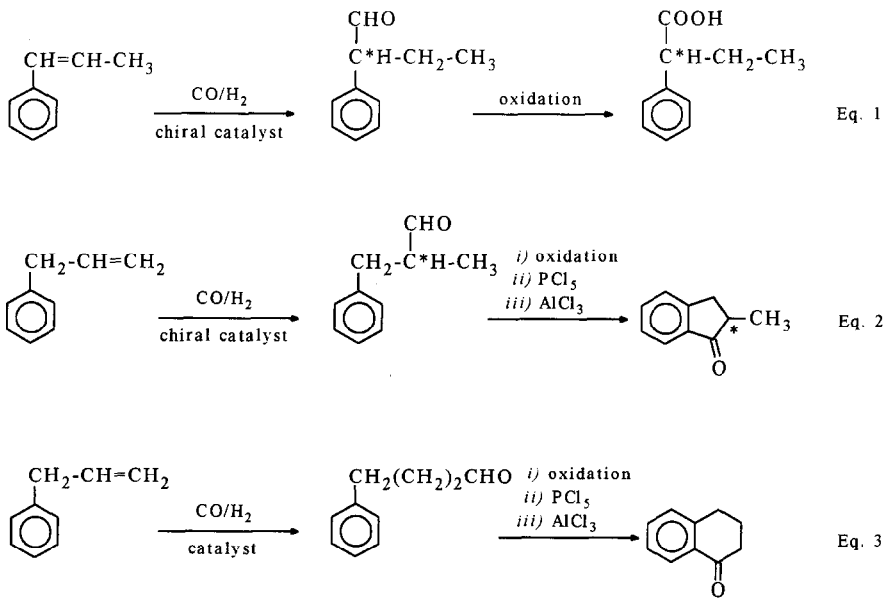

Fig. 1. Possible reactions of arylbutanals.

like pine oil and proved to be valuable starting materials in various syntheses. Their carbonylation products represent biologically active compounds or could be used in the perfume industry [16].

The synthesis of methyl arylbutanoate regioisomers by hydromethoxycarbonylation was reported in the presence of the widely used $PdCl_2(PPh_3)_2$ precursor with or without tin(II)chloride cocatalyst [17].

In this paper the hydroformylation and enantioselective hydroformylation of 1-(4′-methoxyphenyl)-propene and 3-(4′-methoxy-phenyl)-propene with rhodium and platinum catalysts are described.

2. Experimental

2.1. Reagents

The $PtCl_2$(bdpp) and $[Rh(nbd)Cl]_2$ complexes were prepared by standard methods [18,19]. Toluene was distilled under argon from sodium in the presence of benzophenone.

The compositions of the reaction mixtures were determined by GLC with a Hewlett Packard 5830A gas chromatograph fitted with SP-2100. ^1H NMR spectra were recorded in $CDCl_3$ solutions on a Varian Unity 300 spectrometer.

2.2. Hydroformylation experiment

In a typical experiment a solution of 0.0125 mmol $[Rh(nbd)Cl]_2$ and 0.0275 mmol diop in 30 ml toluene containing 70 mmol **1** (or **2**) was transferred under argon into a 150 ml stainless steel autoclave. The vessel was pressurized to 80 bar total pressure ($CO/H_2 = 1/1$) and placed into an oil bath and the mixture was stirred with a magnetic stirrer. The pressure was monitored throughout the reaction. After cooling and venting of the autoclave, the reddish-brown solution was removed and immediately analyzed by GC, then fractionally distilled in vacuo. The formyl-products were isolated as colorless liquids.

The determination of optical purity of **4** was carried out by ^1H NMR in the presence of chiral shift reagent ($Eu(dcm)_3$). Sufficient separation

of CHO signals of the two enantiomers was achieved ($\Delta\delta = 1.2$ ppm, $\Delta\Delta\delta = 0.035$ ppm, the $Eu(dcm)_3$/**4** molar ratio was 0.4). The determination of the optical purity of **5** by the same technique failed.

2.3. Characterization of the products

2.3.1. 2-(4'-methoxyphenyl)-butanal (4)

^{1}H NMR (δ, $CDCl_3$): 0.9 (t, 7 Hz, 3H, CH_2CH_3); 1.7 (ddq, 7 Hz, 7.5 Hz, 14.2 Hz, 1H, $CH^aH^bCH_3$); 2.05 (ddq, 7 Hz, 7.5 Hz, 14.2 Hz, 1H, $CH^aH^bCH_3$); 3.34 (td, 7.5 Hz, 2.1 Hz, 1H, $CHCH_2$); 3.8 (s, 3H, OCH_3); 6.9 (d, 2H, aromatic protons); 7.1 (d, 2H, aromatic protons); 9.64 (d, 2.1 Hz, 1H, CHO); MS (*m/z*/rel. int.): 178/15 (M^+); 149/95 (M^+–CHO); 121/100 (M^+–C_2H_4–CHO).

2.3.2. 2-(4'-methoxybenzyl)-propanal (5)

^{1}H NMR (δ, $CDCl_3$): 1.1 (d, 6.6 Hz, 3H, $CHCH_3$); 2.55 (dd, 5.8 Hz, 13 Hz, 1H, CH^aH^bCH); 2.6 (m, 1H, CHCHO); 3.0 (dd, 5.8 Hz, 13 Hz, 1H, CH^aH^bCH); 3.8 (s, 3H, OCH_3); 6.8 (d, 2H, aromatic protons); 7.0 (d, 2H, aromatic protons); 9.68 (d, 1.5 Hz, 1H, CHO); MS (*m/z*/rel. int.): 178/13 (M^+); 121/100 (M^+–C_2H_4–CHO).

2.3.3. 4-(4'-methoxyphenyl)-butanal (6)

^{1}H NMR (δ, $CDCl_3$): 1.9 (qi, 6.6 Hz, 2H, CH_2CH_2CHO); 2.4 (td, 1.5 Hz, 6.6 Hz, 2H, CH_2CHO); 2.6 (t, 6.6 Hz, 2H, $CH_2(CH_2)_2$); 3.8 (s, 3H, OCH_3); 6.9 (d, 2H, aromatic protons); 7.1 (d, 2H, aromatic protons); 9.70 (t, 1.5 Hz, 1H, CHO); MS (*m/z*/rel. int.):178/13 (M^+); 134/100 (M^+–CH_3–CHO); 121/83 (M^+–CH–CH_3–CHO).

3. Results and discussion

Two isomeric naturally occurring olefins (trivial names set in italic), 1-(4'-methoxyphenyl)-propene (**1**, *anethol*) and 3-(4'-methoxy-phenyl)-propene) (**2**, *cavicol methyl ether, estragole*) were hydroformylated in the presence of $PtCl_2$(bdpp) + $SnCl_2$ and $[Rh(nbd)Cl]_2$ + PPh_3 (or diop) catalysts (bdpp = (2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane; diop = (4*R-trans*)-[(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(diphenylphosphine)) (Fig. 2).

The difference between the catalytic activity of the rhodium- and platinum-containing systems is much higher with **2** than with **1**. A few amount of **2** was converted in the presence of platinum catalyst. The chemoselectivity of hydroformylation is unexpectedly high. However, all three aldehyde regioisomers (**4**, **5** and **6**) were formed both in case when **1** and **2** were showing the C=C double bond isomerization. Hydroformylation of **1** in the presence of platinum catalyst yielded also the linear aldehyde (**6**) due to the unexpectedly high extent of isomerization of the conjugated double bond of **1** to the terminal double bond of **2**. As a consequence of this reaction, with progress of the hydroformylation the relative amount of **6** was increased (run 2 and 3) (Table 1).

The use of rhodium catalysts resulted in the formation of even less 1-(4'-methoxy-phenyl)-propane (**3**, hydrogenation product) in all cases.

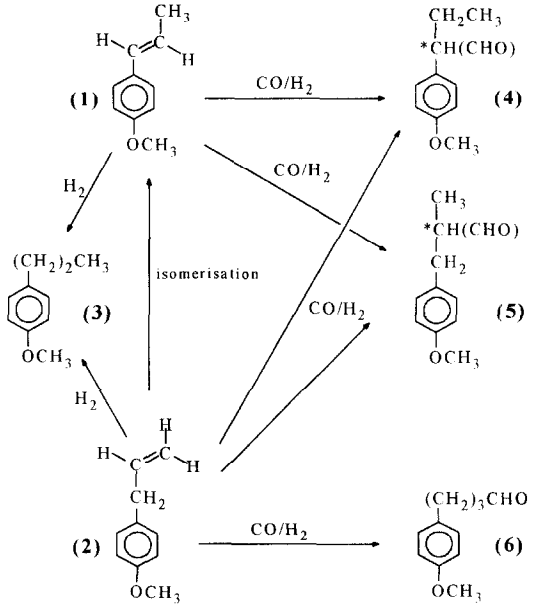

Fig. 2. Product formation in the hydroformylation of **1** and **2**.

Both substrates were converted to the mixture of aldehyde regioisomers. Unlike the platinum case, no isomerization of the internal double bond of **1** took place, and as a consequence of that, the two branched aldehyde regioisomers, **4** and **5** were formed only (run 4 and 5).

Due to the insertion of **2** in the [Rh]–H bond and consecutive deinsertion of **1**, partial isomerization of the terminal double bond of **2** was observed in all cases in the presence of rhodium catalysts (Fig. 3). The formation of the three possible Rh–alkyl intermediates is shown in the figure. The carbon monoxide insertion leading to the acyl-complex and its hydrogenolysis in the aldehyde-forming step are indicated by an arrow. (The reversibility of these steps is not indicated.)

Both the aldehyde selectivity and the ratio of aldehyde regioisomers are very similar using PPh_3 and diop-containing rhodium catalysts (run 6 and 7).

The composition of the reaction mixture during hydroformylation of **2** by the Rh–PPh_3 system is shown in Fig. 4. (The amount of **3** is negligible throughout the reaction and not indicated in the diagram.) The α-formyl derivative (**4**) is formed only when **1** is already present in a relatively large amount. With progress of the reaction the **4/5/6** ratio was shifted towards **4**

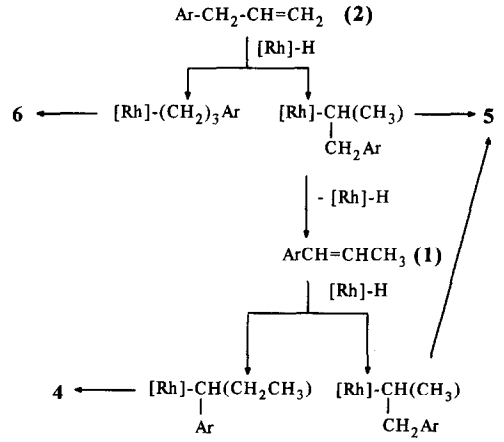

Fig. 3. Simplified scheme for the formation of the isomerization (**1**) and hydroformylation products (**4**, **5** and **6**) formed under 'oxo-conditions' from **2** (Ar = 4-OMe-C_6H_4).

due to the hydroformylation of the isomerization product (**1**).

Since the two branched chiral aldehydes (**4** and **5**) are precursors of pharmacologically important compounds (see Introduction), preliminary experiments have been done for the synthesis of their enantiomers. Unfortunately, the optical yields for **4** are lower (up to 27.5%) than those obtained with vinyl-aromatics in the presence of rhodium-containing catalysts [11]. However, the highest e.e. is comparable to those

Table 1
Hydroformylation of **1** and **2** in the presence of Rh and Pt catalysts

Run	Catalyst [a]	Substrate	R. time (h)	Conv. (%)	Composition of the reaction mixture (%)						Ratio of **4/5/6**	R_C [b]
					1	**2**	**3**	**4**	**5**	**6**		
1	**I** + $SnCl_2$	**2**	27	8.5	1	91.5	0.5	2	3	2	28.5/43/2 8.5	82
2	**I** + $SnCl_2$	**1**	7	18	82	0.5	2	8.5	5	2	55/32/13	86
3	**I** + $SnCl_2$	**1**	21	44.5	55.5	0.5	2	22 [c]	14	6	52.5/33.5/14	94
4	**II** + 4.4PPh_3	**1**	7	84	16	0.5	0.5	71	12	0	85/15/0	99
5	**II** + 2.2diop	**1**	14	51	49	0	0	44 [d]	7	0	86/14/0	100
6	**II** + 4.4PPh_3	**2**	7	97	10	3	1	21	30	35	24/35/41	89
7	**II** + 2.2diop	**2**	7	99.5	4.5	0.5	1	23 [e]	32	39	24/34/42	94

Reaction conditions: 30 ml toluene, 0.07 mol substrate, $p(CO) = p(H_2) = 40$ bar, reaction temperature 100°C.
[a] **I** = $PtCl_2$(bdpp); **II** = $[Rh(nbd)Cl]_2$.
[b] **(4 + 5 + 6)/(2 + 3 + 4 + 5 + 6)** × 100 (substrate **1**) or **(4 + 5 + 6)/(1 + 3 + 4 + 5 + 6)** × 100 (substrate **2**).
[c] e.e. = 27.5%.
[d] e.e. = 7.4%.
[e] e.e. = 3.6% (determined in the mixture of formyl products).

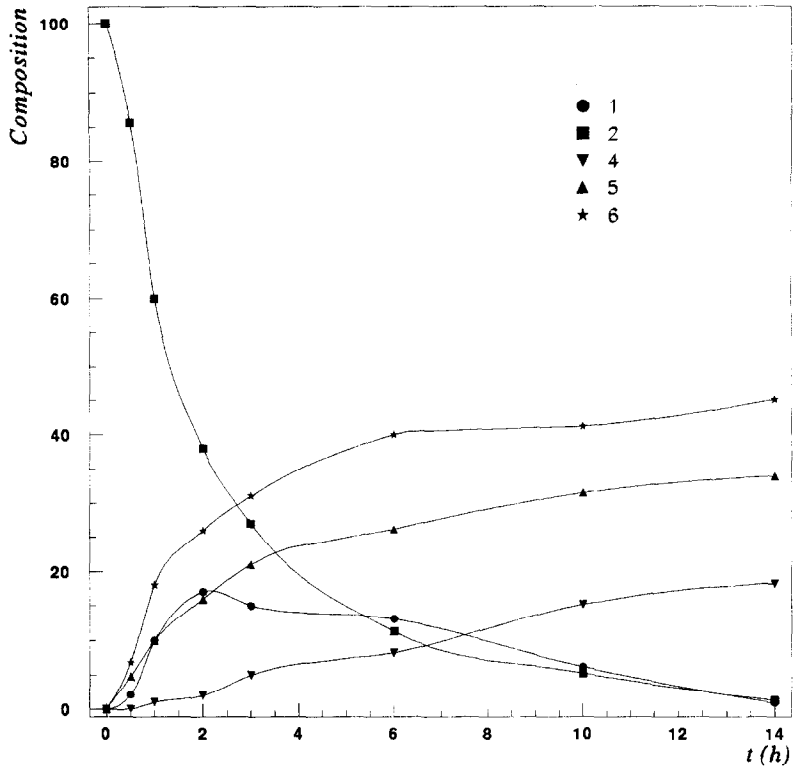

Fig. 4. Product distribution versus reaction time diagram of the hydroformylation of **2** by Rh–PPh_3 catalyst (the amount of **3** is less than 1.5% even after 14 h and has been omitted for clarity).

obtained with the same catalyst under similar conditions [10].

The lower enantiomeric excesses obtained at longer reaction times are the result of product racemization via keto-enol tautomerism under reaction conditions. When the isolated **4** possessing 27.5% e.e. (containing less than 3% **5**) was stirred in toluene in the presence of platinum catalyst under the given reaction conditions for 20 h, the e.e. was reduced to 12%.

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