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Preliminary Communication

Hydroformylation of cinnamic acid derivatives catalyzed by rhodium complexes *

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Abstract

The hydroformylation of methyl cinnamate catalyzed by various rhodium complexes affords the aldehyde **1a** with good chemo- and regio-selectivity, while in the case of methyl *p*-chlorocinnamate the predominant reaction is the substrate hydrogenation. Higher yields of the desired aldehydes **1a** and **1b** are obtained by hydroformylation of the cinnamaldehyde and *p*-chlorocinnamaldehyde diethylacetal, respectively, under the same reaction conditions. These aldehyde products are valuable drug precursors.

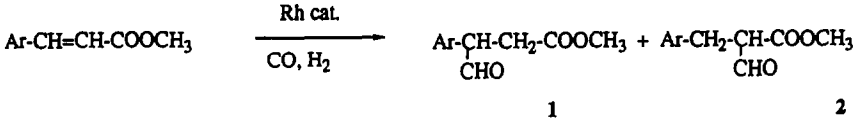
The hydroformylation of olefins containing functional groups is a powerful and not yet fully exploited, synthetic tool for the preparation of pharmacologically active compounds [1,2]. In particular, cinnamic acid esters, when hydroformylated regioselectively to give the aldehydes **1** (Scheme 1) are valuable precursors for phenylsuccinic acids and hence of the antiepilectic agent *N*-methyl-2-phenylsuccinimide (Phensuximid®) [3]. Moreover, the aldehydes **1** are easily converted by catalytic reductive amination using dihydrogen and ammonia [4] to the corresponding γ-aminoacids, a class of miorelaxing agents, among which β-(aminomethyl)-*p*-chlorohydrocinnamic acid (Baclofen®) is important [5].

Few reports have appeared on the hydroformylation of cinnamic acid esters and none on *p*-chlorocinnamic derivatives [6–8]. Generally this catalytic reaction suffers from unsatisfactory chemoselectivity even when using rhodium complexes, due to definic double bond hydrogenation and/or formation of lactones *via* reduction of the aldehyde group under the reaction conditions [6,7]. High-molecular-weight by-products also occur, expecially if cobalt catalysts are employed [8].

In a first set of experiments, methyl cinnamate was hydroformylated in the presence of different, readily accessible, rhodium derivatives, suitable for industrial application under standard conditions. Most catalytic precursors promote extensive hydrogenation of the substrate, but no lactones were found among the reaction products, and only occasionally a limited amount of high-boiling compounds (Table 1). The best results were obtained using the zwitterion complex [Rh(COD)BPh_4] (COD = 1,5-cyclooctadiene) [9], that afforded nearly 75% chemoselectivity and more than 94% regioselectivity in the formation of the aldehyde **1a**.

Various catalytic systems such as anhydrous Rh_2O_3, Rh_2O_3/PPh_3, [{Rh(COD)Cl_2}$_2$] and [{Rh(COD)Cl_2}$_2$]/2,2′-bipyridine gave aldehyde **1a** almost regiospecifically, but the chemical yields are very low. Increasing the reaction temperature from 80 to 120°C generally improves the substrate conversion, but the chemoselectivity is worse.

The more reactive and selective catalytic precursors for methyl cinnamate hydroformylation were also tested with methyl *p*-chlorocinnamate. The data in Table 2



1 **2**

1a, 2a : Ar = C_6H_5

1b, 2b : Ar = p-Cl-C_6H_4

Scheme 1.

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* Dedicated to Professor G.P. Chiusoli on the occasion of his 70th birthday and in recognition of his important contributions to organometallic chemistry and its application to organic synthesis.

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TABLE 1. Hydroformylation of methyl cinnamate in the presence of various rhodium complexes

Exp.	Catalytic precursor	t (h)	Substrate conversion (%)	Hydrogenated product yield (%)	Total aldehyde yield (%)	**2a/1a** [g] molar ratio
1	Rh_2O_3	7	19.7	–	19.7	0/100
2 [a]	Rh_2O_3	7	100	31.2	68.8	0/100
3	$[HRh(CO)(PPh_3)_3]$	7	69.3	11.7	57.6	28/72
4	$[\{Rh(COD)Cl\}_2]$	7	59.1	19.6	39.5	0/100
5 [b]	$[\{Rh(COD)Cl\}_2]$/2,2'-bipiridine	7	75.1	53.8	21.3	0/100
6 [c]	$[Rh(COD)(BPh_4)]$	22	94.6	15.5	79.0	5.6/94.4
7 [d,f]	Rh_2O_3/PPh_3	22	14.1	1.3	11.1	66.5/33.5
8 [f]	$[\{RhCl(CO)_2\}_2]$	16	71.7	17.8	52.1	5.2/94.8
9	$[HRh(PPh_3)_4]$	7	67.5	11.3	56.6	8.8/91.2
10 [e]	$[\{RhCl(CO)_2\}_2]$	7	100	37.8	62.2	2.6/97.3
11 [e]	$[RhCl(CO)(PPh_3)_2]$	7	46.4	14.2	32.2	33.9/62.1
12 [e]	$[Rh(COD)(BPh_4)]$	22	97.7	28.7	69.0	2.5/97.5

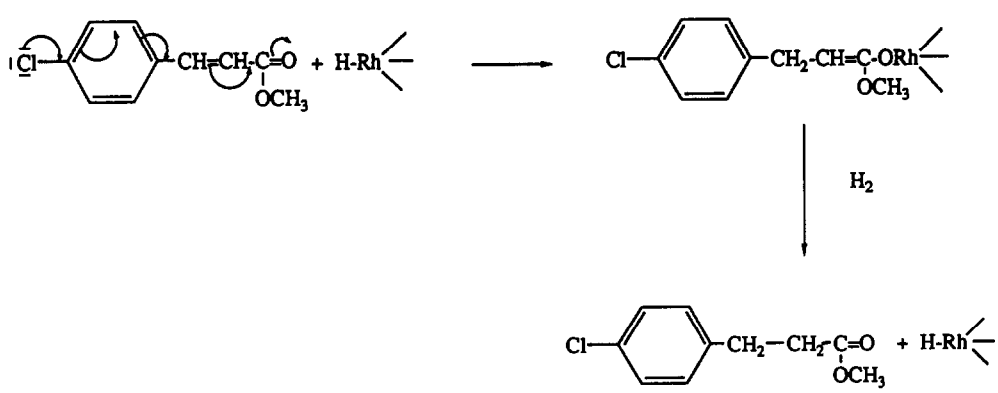
Methyl cinnamate: 12.3 mmol; substrate/catalyst = 1000/1 molar ratio; benzene: 20 ml; $P(CO) = P(H_2) = 50$ atm; $T = 80$°C. [a] Experiment carried out at $T = 120$°C. [b] $[\{Rh(COD)Cl\}_2]$/2,2'-bipyridine = 1/2 molar ratio. [c] Substrate/Catalyst = 54/1 molar ratio (according to ref. 9). [d] $Rh_2O_3/PPh_3 = 1/5$ molar ratio. [e] Experiment carried out at $T = 100$°C. [f] About 2% high boiling by-products are present. [g] Determined by GC using an OV17 packed column heated at 120°C. The structure of the predominant isomer **1a** was determined by the proton intramolecular NOE effect.

TABLE 2. Hydroformylation of methyl *p*-chlorocinnamate in the presence of various rhodium complexes

Exp.	Catalytic precursor	t (h)	Substrate conversion (%)	Hydrogenated product yield (%)	Total aldehyde yield (%)	**2b/1b** [c] molar ratio	High boiling by-products yield (%)
1 [a]	$[Rh(COD)(BPh_4)]$	22	100	95.8	2.2	0/100	2.0
2 [b]	Rh_2O_3/PPh_3	22	100	93.4	2.8	0/100	3.8
3	$[HRh(CO)(PPh_3)_3]$	7	100	95.2	1.4	0/100	3.4
4	$[\{Rh(COD)Cl\}_2]$	7	4.6	4.6	–	–	–
5	$[HRh(PPh_3)_4]$	6	75.0	29.1	44.6	4.6/95.4	1.3

Substrate: 12.4 mmol; substrate/catalyst = 1000/1 (molar ratio); benzene = 20 ml; $P(CO) = P(H_2) = 50$ atm; $T = 80$°C. [a] Substrate/Catalyst = 54/1 molar ratio. [b] $Rh_2O_3/PPh_3 = 1/5$ molar ratio. [c] Determined by GC using an OV17 packed column heated at 140°C. The structure of the predominant isomer **1b** was determined by the proton intramolecular NOE effect.

clearly show that with the latter the hydrogenation of the olefinic double bond is the preferred reaction; only $[RhH(PPh_3)_4]$ gave the desired aldehyde (*ca.* 45% with *ca.* 95% regioselectivity). This can be tentatively explained, assuming that the halogen atom acts as an electron donor. This causes electron density enhancement on the oxygen atom, thus favouring the 1,4-addition of the catalytically active hydridorhodium com-

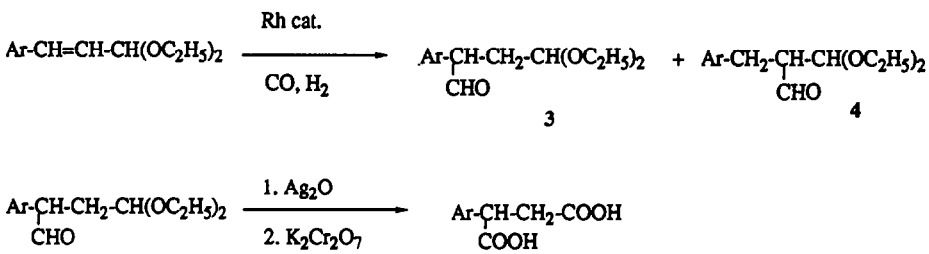


Scheme 2.

TABLE 3. Hydroformylation of cinnamaldehyde diethylacetal (A) and of *p*-chlorocinnamaldehyde diethylacetal (B) in the presence of various rhodium complexes

Exp.	Catalytic precursor	Substrate	*t* (h)	Substrate conversion (%)	Hydrogenated product yield (%)	Total aldehyde yield (%)	4/3 [a] molar ratio
1	$[HRh(PPh_3)_4]$	A	3	100	–	100	3/97
2	$[HRh(PPh_3)_4]$	A	0.75	86.9	–	86.9	1.3/98.7
3	$[HRh(CO)(PPh_3)_3]$	A	1.5	95	–	95	1.6/98.4
3	$[HRh(PPh_3)_4]$	B	3	97.9	–	97.9	3.1/96.9
5	$[HRh(PPh_3)_4]$	B	0.75	43.9	–	43.9	2.2/97.8
6	$[HRh(CO)(PPh_3)_3]$	B	1.5	60.8	–	60.8	2/98

Substrate: 12.4 mmol; substrate/catalyst = 1000/1 (molar ratio); benzene = 20 ml; $T = 80°C$; $P(CO) = P(H_2) = 50$ atm. [a] Determined by GC using an OV17 packed column heated at 120°C when the substrate is A and at 140°C when the substrate is B. The structure of the predominant isomer 3 was determined by the proton intramolecular NOE effect.



3a, 4a : Ar = C_6H_5

3b, 4b : Ar : p-Cl-C_6H_4

Scheme 3.

plex to the conjugated olefinic double bond-carbonyl system, which undergoes hydrogenolysis only, giving the saturated ester (Scheme 2) [10,11].

Higher reaction rates and chemical yields are achieved in the hydroformylation of cinnamaldehyde diethylacetal [12] using rhodium catalysts (Table 3). The aldehyde **3a** is formed almost regioselectively and is easily transformed by oxidation into 2-phenylsuccinic acid [13] (Scheme 3). The absence of the electron-withdrawing group $-COOCH_3$ facilitates hydroformylation. For example, *p*-chlorocinnamaldehyde diethylacetal [14*] is smoothly and conveniently converted into the desired *p*-chlorophenylsuccinaldehyde monodiethylacetal in the presence of some rhodium complexes (Table 3). As with *p*-chlorostyrenes, the presence of a halogen atom does not appreciably influence either the chemo- or the regio-selectivity of the reaction with respect to the oxo-process of non-halogenated substrates [18,19]. However, the reaction rates are slower as compared to the non-halogenated acetal (Table 3).

These results show that only the cooperative effect between the electron-withdrawing group $-COOCH_3$ and the electron-donor halogen atom seems to cause the low chemoselectivity obtained in the hydroformylation of methyl *p*-chlorocinnamate.

Acknowledgment

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