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Rhodium-catalyzed hydroformylation of 1-allylpyrrole as an unexpected way to 5,6-dihydroindolizine synthesis

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Abstract

When 1-allylpyrrole was subjected to hydroformylation conditions with $Rh_4(CO)_{12}$ as the catalyst precursor, at 120 atm total pressure, at 20 and 100°C, 5,6-dihydroindolizine was found unexpectedly, together with the expected branched aldehyde, the linear isomer being obtained in traces amounts only. An annulation via a nucleophilic attack of the pyrrole C2 carbon atom on the carbonyl group of the linear aldehyde, followed by dehydration of the intermediate alcohol, possibly generates the indolizine structure.

Keywords: Hydroformylation; 1-Allylpyrrole; Rhodium; Catalysis; Indolizine

1. Introduction

Hydroformylation, one of the most important catalytic reactions for the functionalization of a double bond, has become in the last few years a useful tool for fine chemical synthesis [1]. Among unsaturated aromatic substrates, styrenes with different substituent groups on the aromatic ring [2,3] as well as vinylheteroaromatic compounds such as vinylfurans [4] and vinylthiophenes [5] have been investigated extensively. Recently, the synthesis of arylbutanal isomers by hydroformylation of substituted allylbenzene and propenylbenzene has also been carried out [6]. Our studies on the rhodium-catalyzed hydroformylation of the new vinyl- and divinylpyrroles [7] demonstrated that, in spite of the reported instability of these substrates [8], pyrrolyl mono- and dialdehydes can conveniently be obtained under oxo conditions. Within this context, it seemed interesting to carry out the hydroformylation of allylpyrroles, a class of compounds that, unlike the analogous allylbenzenes [6], has never been investigated before. We found and report here that hydroformylation of 1-allylpyrrole (**1**) in the presence of $Rh_4(CO)_{12}$, a good catalyst precursor for vinylaromatic substrates [9,10], surprisingly gives 5,6-dihydroindolizine (**2′**) together with the branched aldehyde (**3**), while the linear aldehyde (**2**) was present in traces only (Scheme 1). This result constitutes the first example of one-pot 5,6-dihydroindolizine synthesis under hydroformylation conditions.

The hydroformylation experiments on 1-allylpyrrole (**1**) were carried out in toluene with $Rh_4(CO)_{12}$ as the catalyst precursor, at 20 and 100°C, at 120 atm total pressure ($CO-H_2 = 1:1$), using a 250:1 and 500:1 substrate–rhodium ratio, respectively. The substrate conversion and the composition of the reaction mixtures were analyzed at different times by GC and GC–MS, using acetophenone as internal standard.

As far as the **3**–**2** ratio is concerned, it ranged from 80:20 at 20°C to 59:38 at 100°C (Table 1). These values, characterized by a prevalence of the branched aldehyde (**3**) at both temperatures, are similar to the ones reported for the hydroformylation of allylbenzene with rhodium-based catalyst precursors [6]. The influence of the temperature on the regioselectivity is in agreement with the well-documented increase of the linear alde-

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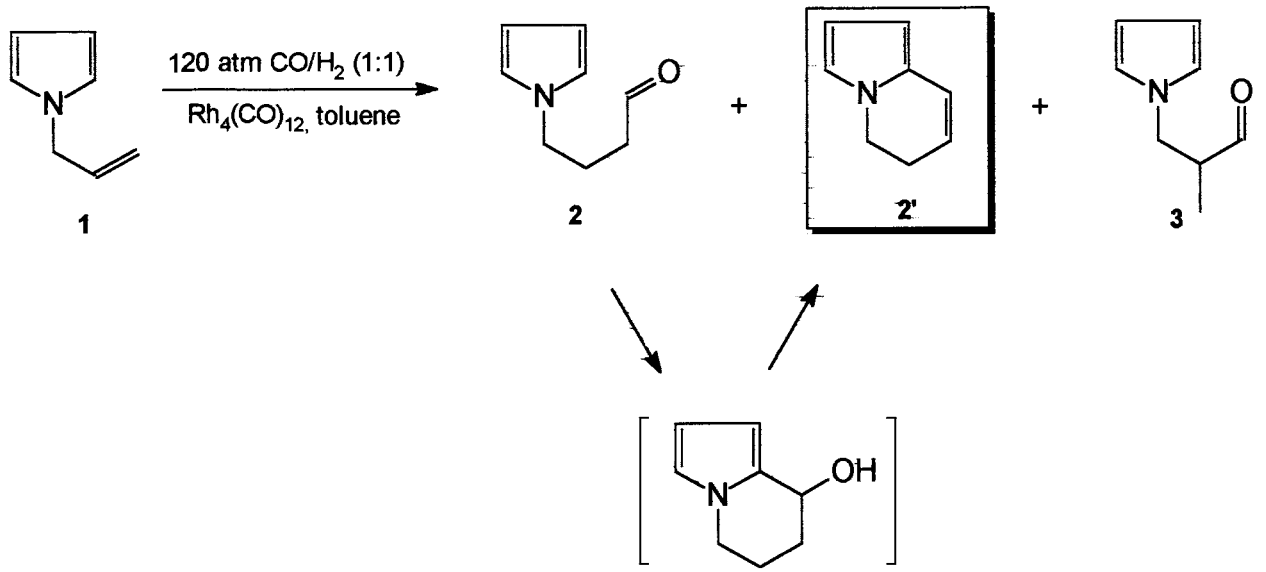
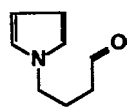
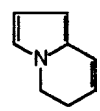
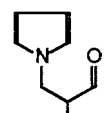


Scheme 1.

hyde content with increasing temperature in the hydroformylation of other vinylsubstrates [7a,10] (Table 1).

At 20°C, at partial substrate conversion (16%), an almost complete chemoselectivity into the expected **2** and **3** aldehydes was observed, the 5,6-dihydroindolizine (**2′**) being in very low amount (< 1%). After 36 h, the dihydroindolizine (**2′**) was 20% of the total products, while the linear aldehyde **2** was present in traces only (Table 1). At 100°C the hydroformylation process was much faster, the substrate conversion reaching 95% after 0.25 h only. Also in this case, the chemoselectivity into isomeric aldehydes was very high, the (**3** + **2**)–**2′** molar ratio being 97:3. At total substrate conversion (> 99%) the linear aldehyde **2** disappeared and **2** was 40% of the total products (Table 1), the branched aldehyde (**3**) staying unreacted during all the reaction time. The 5,6-dihydroindolizine (**2′**) was isolated on column chromatography (SiO_2; hexane) and characterized by GC-MS, IR, ^{1}H-NMR and ^{13}C-NMR analyses [11,12] (Table 2). Aldehydes **2** and **3** are both new compounds. The predominant isomer 2-methyl-3-(pyrrol-1-yl)propanal (**3**) was isolated on column chromatography (SiO_2; hexane–AcOEt = 4:1) and characterized by GC-MS, IR, ^{1}H-NMR and ^{13}C-NMR analyses [13] (Table 2). 4-(Pyrrol-1-yl)butanal (**2**), being unstable under the chromatographic conditions adopted for **3**, was identified by the above analyses carried out on the crude hydroformylation mixture [14] (Table 2).

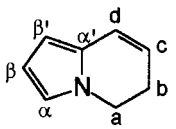
Table 1
Composition of the crude reaction mixtures resulting from the hydroformylation of 1-allylpyrrole (**1**) with $Rh_4(CO)_{12}$ at 20 and 100°C [a]

Entry	Temperature (°C)	Reaction time (h)	Conversion (%) [b]	Products (%) [b]		
				 **2**	 **2'**	 **3**
1	20	4	16	20	<1	80
2	20	36	99	–	20	80
3	100	0.25	95	38	3	59
4	100	3	99	–	40	60

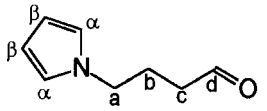
[a] Reaction conditions: 0.2 g 1-allylpyrrole, 6 ml toluene, substrate–Rh = 250:1 at 20°C, 500:1 at 100°C; autoclave volume 25 ml; 120 atm total pressure (CO–H_2 = 1:1).

[b] Determined by GLC using acetophenone as internal standard.

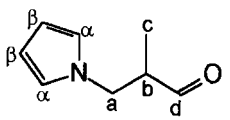
Table 2
^{1}H- and ^{13}C-NMR parameters for 5,6-dihydroindolizine (**2′**), 4-(pyrol-1-yl)butanal (**2**) and 2-methyl-3-(pyrol-1-yl)propanal (**3**)



2′



2



3

Products	Nucleus	Chemical shifts (δ) [a]							
		α	α′	β	β′	a	b	c	d
2′	^{1}H	6.61(m)		6.16 (m)	6.06 (m)	3.90 (t; $J = 7.5$)	2.52 (m)	5.74 (dt; $J = 9.7$, 4.5)	6.48 (d; $J = 9.7$)
	^{13}C	120.0	128.1	105.7	107.8	45.0	23.8	118.6	120.6
2	^{1}H	6.60 (t; $J = 2.4$)		6.14 (t; $J = 2.4$)		4.25 (t; $J = 7.2$)	2.10 (m)	2.46 (t; $J = 7.6$)	9.69 (t; $J = 0.6$)
	^{13}C	120.8		108.4		62.7	19.1	30.1	201.0
3	^{1}H	6.62 (t; $J = 2.4$)		6.15 (t; $J = 2.4$)		4.23 (dd; $J = 13.9$, 6.7) 3.95 (dd; $J = 13.9$, 6.7)	2.81 (m)	1.11 (d; 7.2)	9.67 (d; 1.1)
	^{13}C	120.8		108.4		49.2	48.0	11.5	202.4

[a] Referred to TMS as internal standard; $CDCl_3$ as solvent. Coupling constant values in Hertz.

The six-membered nature of the newly formed ring, together with the observation that the sum of the linear aldehyde **2** and the indolizine product (**2′**) gives a constant value with respect to the branched aldehyde (**3**), suggests that the indolizine structure comes from the pyrrolylbutanal **2** possibly via an intramolecular nucleophilic attack of the pyrrole C2 carbon atom on the carbonyl group of the linear aldehyde. Then a bicyclic alcohol should form, which undergoes water elimination very easily to give a double bond conjugated with the pyrrole ring (Scheme 1).

Under analogous hydroformylation conditions, 4-phenylbutanals arising from allylbenzenes do not give a cyclization process [6]. Then we can state that the strong nucleophilic character [15] of the carbon atom in the α positions of the pyrrole ring plays a crucial role in the annulation reaction.

Direct aliphatic C–H activation in α position to a nitrogen atom in tertiary amines and β–lactams, catalyzed by ruthenium complexes, is well established [16]. However, taking into account the high reactivity of the pyrrole α-positions towards electrophilic substitution [15], the cyclization process observed for aldehyde (**2**) likely takes place via an intramolecular electrophilic aromatic substitution.

In conclusion, the above findings showed that 1-allylpyrrole (**1**), like other unsaturated pyrrolylderivatives [7], easily undergoes rhodium-catalyzed hydroformylation, allowing the preparation of the novel pyrrolylaldehydes **2** and **3** with almost complete chemoselectivity. But the original and very interesting result of the oxo process applied to 1-allylpyrrole (**1**) is the formation of the unexpected indolizine structure. The indolizine moiety with different degrees of unsaturation is present in many families of alkaloids in the animal and vegetable kingdom and it is an important target in organic synthesis [17]. The approach described here, starting from the easily available 1-allylpyrrole (**1**), can become, in our opinion, a convenient and competitive tool for the preparation of these compounds. Thus the synthesis of appropriate allylpyrroles and the choice of experimental conditions able to give selectively pyrrolylbutanals instead of pyrrolylpropanals in the oxo process are now under investigation.

2. Experimental

All reagents were of commercial quality. Silica gel (70–230 mesh) was purchased from Merck. Toluene was dried over molecular sieves and distilled under nitrogen. NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200 at 200 MHz for ^{1}H and 50 MHz for ^{13}C. Chemical shifts (δ) were referred to TMS. GC analyses were performed on a Perkin–Elmer 8700 chromatograph equipped with a 12 m × 0.22 mm BP5 capillary column, using nitrogen as the carrier gas. GC–MS analyses were performed on a Perkin–Elmer Q-Mass

910 interfaced with a Perkin–Elmer 8500 chromatograph equipped with a 30 m × 0.25 mm apolar BP1 capillary column, using helium as the carrier gas. IR spectra were recorded on a Perkin–Elmer FT-IR spectrophotometer 1760 ×. $Rh_4(CO)_{12}$ was prepared according to a well-known procedure [18,19].

2.1. Preparation of 1-allylpyrrole (*1*)

Dry DMSO (120 ml) was added to potassium hydroxide (13.2 g, 235 mmol) and the mixture was stirred for 5 min. Pyrrole (4.0 ml, 58 mmol) was then added and the mixture was stirred for 45 min. 3-Bromo-1-propene (6.5 ml, 75 mmol) was added and the mixture was stirred for a further 30 min before water (250 ml) was added. The mixture was extracted with ether and each extract was washed with water. The combined ether layers were dried (Na_2SO_4) and the solvent and the excess of 3-bromo-1-propene were removed by distillation at atmospheric pressure. The residue was distilled giving 1-allylpyrrole (**1**) (3.7 g, 60% yield) as a colorless liquid: b.p. 145°C at 760 mmHg ([20] 146–147°C).

2.2. Hydroformylation of 1-allylpyrrole (*1*); general procedure

A solution of 1-allylpyrrole (**1**) (0.2 g, 1.87 mmol) and $Rh_4(CO)_{12}$ (0.7–1.4 mg) in toluene (6 ml) was introduced by suction into an evacuated 25 ml stainless steel reaction vessel. Carbon monoxide was introduced, the autoclave was then rocked, heated to the desired temperature and hydrogen was introduced rapidly to 120 atm ($CO–H_2 = 1:1$) total pressure. When the gas absorption reached the value corresponding to the fixed conversion, the reaction mixture was siphoned out; the degree of conversion and the product distributions were determined by GC/GC–MS control, by using acetophenone as an internal standard.

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[13] MS *m/e* 137 (M^+, 46), 109 (100), 94 (82), 81 (97). IR neat 2725 cm^{-1} (ν_{OC-H}), 1714 cm^{-1}($\nu_{C=O}$).
[14] MS *m/e* 137 (M^+, 64), 136 (43), 120 (100), 117 (92), 108 (38), 91 (14).
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