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Journal of Organometallic Chemistry 592 (1999) 69–73

Journal of Organometallic Chemistry

Stepwise hydroformylation of C,N-divinylpyrroles with $Rh_4(CO)_{12}$ under mild conditions: an original synthesis of N-vinylpyrrolylmonoaldehydes and of pyrrolyldialdehydes

Raffaello Lazzaroni [a,*], Roberta Settambolo [b], Manuela Mariani [a], Aldo Caiazzo [a]

[a] *Centro di Studio CNR per le Macromolecole Stereordinate ed Otticamente Attive, Dipartimento di Chimica e Chimica Industriale, via Risorgimento 35, 56126 Pisa, Italy*

[b] *Istituto di Chimica Quantistica ed Energetica Molecolare del CNR, Dipartimento di Chimica e Chimica Industriale, via Risorgimento 35, 56126 Pisa, Italy*

Received 2 June 1999; accepted 2 August 1999

Abstract

1,3-Divinylpyrrole and 1,2-divinylpyrrole were treated in a stainless steel autoclave with $Rh_4(CO)_{12}$ at 40°C and 120 atm of H_2/CO total pressure: for both substrates exclusive hydroformylation of the vinyl groups bonded to the ring carbon atom occurred, the branched unsaturated monoaldehydes 2-(1-vinylpyrrolyl)propanals being formed with a very high chemoselectivity and α-regioselectivity. At 80°C only 1,3-divinylpyrrole gives, via hydroformylation of N-vinyl group, the corresponding dialdehydes.

Keywords: Hydroformylation; Deuterioformylation; Pyrrolepropanols; Rhodium; Catalysis

1. Introduction

Reaction selectivity is a desired goal in organic synthesis. Among catalytic processes, the rhodium-catalyzed hydroformylation of vinyl- or vinylidenic aromatic and heteroaromatic olefins constitutes a very significant example [1–9]. Indeed with the former substrates a high or complete selectivity in the branched isomeric aldehydes was observed, while with the latter introduction of the formyl group occurred only at the terminal position of the double bond. The above findings have been successfully applied in the synthesis of various pharmaceuticals, i.e. anti-inflammatory 2-arylpropionic acids [10] and antiallergic agents [11].

Although the branched aldehyde is largely favored in the hydroformylation of aromatic or heteroaromatic vinylsubstrates, its amount can vary and depends on the electron-poor or π-excessive character of the aromatic ring as well as on the relative position of the double bond with respect to the annular heteroatom. The above effects have been widely pointed out, by various authors and by us, in the rhodium-catalyzed hydroformylation of styrene [1a], substituted styrenes [2], simple vinylpyrroles [12] and vinylpyridines [13].

In spite of the fact that the most functionalized or unfunctionalized aromatic vinylsubstrates have been submitted to hydroformylation, no examples involving divinylsubstrates containing two unsaturated groups on the same aromatic ring have been previously reported in the literature.

Owing to our interest into the selectivity of hydroformylation with respect to both mechanistic and synthetic points of view, we first investigated this research field, by hydroformylating the recently synthesized 1,3- and 1,2-divinylpyrroles (**1a** and **1b**) [14], characterized by a N-vinyl group and a C-vinyl group in 1–3 or 1–2 positions, respectively of the same pyrrole ring. These substrates seemed very interesting as precursors to pyrrolyl aldehydes as well as to providing an opportunity to investigate the reactivity of a C- and a N-vinyl group bonded to the same aromatic ring.

* Corresponding author. Tel.: +39-050-918-227; fax: +39-050-918-260.

E-mail address: lazzaroni@dcci.unipi.it (R. Lazzaroni)

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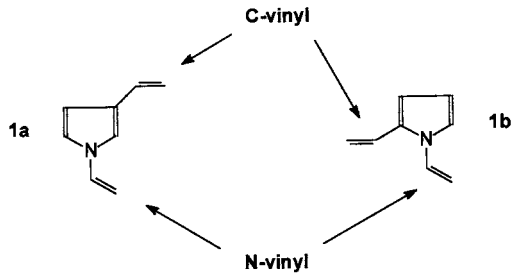
PII: S0022-328X(99)00483-0



In this paper, we report that when **1a** and **1b** were treated in a stainless steel autoclave with $Rh_4(CO)_{12}$, at 40°C and 120 atm of H_2–CO total pressure, an original and very interesting selectivity was observed: the C-vinyl group reacted faster than the N-vinyl one in both the substrates, the corresponding branched monoaldehydes 2-(1-vinylpyrrolyl)propanals **2a** and **2b** being formed with very high chemoselectivity (> 98%) and α-regioselectivity (**2a**/**3a** = 93/7; **2b**/**3b** = 98/2) (Scheme 1).

2. Results

The hydroformylation experiments on **1a** and **1b** were carried out in toluene with $Rh_4(CO)_{12}$ as catalytic precursor, at 40°C and 120 atm pressure (1:1 CO–H_2), using a 100/1 substrate/rhodium ratio (Scheme 1). The substrate conversion and the composition of the reaction mixtures were analysed by GC and GC/MS, using *o*-xylene as internal standard. The chemoselectivity into the aldehydes **2** and **3**, coming from exclusive functionalization of the C-vinyl, was very high for both the substrates (> 98%) (Table 1). Only traces of the monoaldehydes **2′a–b** and **3′a–b** (Scheme 1), due to the hydroformylation of the vinyl group bonded to the nitrogen atom (N-vinyl), were observed. The regioisomeric ratio **2**/**3** was higher for **1b** (98/2) than for **1a** (93/7). The chemo- and regioselectivity kept constant during the reaction proceeding (Table 1).

The double bond involved in the functionalization was easily identified by looking at the disappearance of the well-resolved signals of the protons of the C-vinyl groups [14] in the ^{1}H-NMR spectra of hydroformylation mixtures. The newly synthesized aldehydes **2a** and **2b** have been isolated by column chromatography and characterized by ^{1}H-NMR and MS analysis.

When the reaction mixture containing the 1-vinylaldehydes isomers **2a** and **3a**, arising from the hydroformylation of 1,3-divinylpyrrole (**1a**) at 40°C, was heated at 80°C, the hydroformylation of the N-vinyl took place and the dialdehydes **4a** and **5a**, due to insertion of the formyl group exclusively in the α-position of the N-vinyl moiety, were formed (**4a**/**5a** = 92/8) (at $T < 80$°C the process was very slow) (Scheme 2). An analogous result was obtained when hydroformylation at 80°C was carried out directly on 1,3-divinylpyrrole (**1a**): the formation of the 1-vinylmonoaldehydes **2a** and **3a** (**2a**/**3a** = 86/14) was observed until unconverted C-vinyl was present in the reaction mixture. At complete conversion of **1a**, the hydroformylation of the N-vinyl in **2a** and **3a** occurred, giving the dialdehyde isomers **4a** and **5a** (**4a**/**5a** = 86/14).

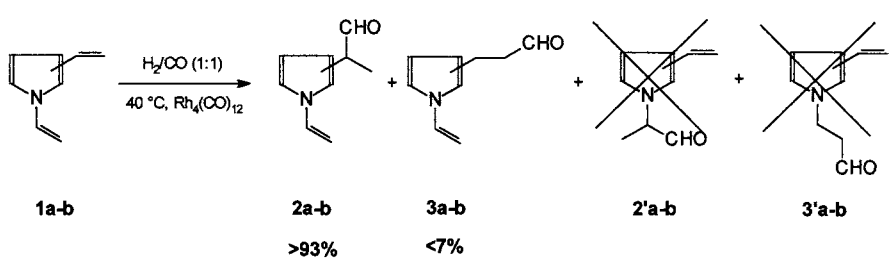
In contrast, hydroformylation experiments carried out at 80°C on **1b** gave the dialdehydes **4b** and **5b** in a very low yield and the formation of various unidentified by-products had occurred.

The aldehydes **3a**, **3b**, **4a** and **5a** have been characterized by identification of their typical signals in the ^{1}H-NMR and mass spectra of reaction mixtures and by a comparison with the spectra of the monoaldehydes coming from the hydroformylation of the single vinylpyrrole isomers [7,12].

3. Discussion and conclusion

The above findings indicate that, in the adopted experimental conditions, the C-vinyl is more reactive than the N-vinyl and chemoselective monohydroformylation to N-vinylpyrrolylpropanals takes place. Such a finding is in agreement with the higher reaction rate previously observed for 2- and 3-vinylpyrrole with respect to N-vinyl isomer [7,12].

In order to obtain more information about this, an equimolecular mixture of simple 3-vinylpyrrole [15] and N-vinylpyrrole [16] was submitted to hydroformylation at 40°C, in the presence of $Rh_4(CO)_{12}$ as catalyst precursor. We found that the former substrate was hydroformylated first, whereas the latter reacted more slowly



Scheme 1.

Table 1
Hydroformylation of 1,3-divinylpyrrole (**1a**) and 1,2-divinylpyrrole (**1b**) with $Rh_4(CO)_{12}$ as catalytic precursor, at 40°C [a]

Substrate	Reaction time (h)	Conversion (%)	[(2+3)/(2+3+2′+3′)] [b] (%)	(2/3) [c] (%)	[(2′+3′)/(2′+3′+2+3)] [b] (%)
1a	2	44	100	93/7	–
1a	15	94	98	93/7	2
1b	1	57	99	98/2	1
1b	3.5	90	98	98/2	2

[a] A 5 ml toluene solution containing 4 mmol of substrate; substrate/Rh = 100/1; 1:1 CO–H_2; 120 atm pressure; volume of the reactor vessel 25 ml. The mixture composition was determined via GLC using *o*-xylene as internal standard; ± 1% accuracy.
[b] Chemoselectivity.
[c] Regioselectivity.

(rate ratio 16:1). The regioselectivity observed for 3-vinylpyrrole ($\alpha/\beta = 92/8$) in the mixture was very similar to that obtained in the hydroformylation of 3-vinylpyrrole alone [7,12] and also of the C-vinyl in 1,3-divinylpyrrole under the same experimental conditions. A similar behavior has also been observed at higher temperatures. In fact the regioisomeric ratio **2a**/**3a** = 88/12 found in the hydroformylation of the C-vinyl group of **1a** at 80°C is in agreement with the depression of α-regioselectivity with increasing temperature which was observed in the hydroformylation of the corresponding simple 3-vinylpyrrole [12]. The comparison of the results obtained in the case of 3-vinylpyrrole together with the data relative to the hydroformylation of the C-vinyl in 1,3-divinylpyrrole seems to exclude a significant influence of the N-vinyl on the chemo- and regioselectivity when the two double bonds are on the same heteroaromatic ring. Confirmation of this comes from semiempirical calculations (CNDO) [13,17] carried out on divinyl- and monovinylpyrroles, which showed the two double bonds in the disubstituted structure. The same charge distribution was observed for the same type of vinyl group in simple monovinylpyrroles. The minor hydroformylation rate observed for N-vinyl could be due to the minor charge density in this double bond with respect to the charge density in C-vinyl. This factor could make the C-vinyl group more available than the N-vinyl one for the insertion into Rh–H bond during the catalytic cycle [3,12], the effect being equally active in the mono- as in the divinylpyrroles.

The lower hydroformylation rate observed for N-vinylpyrrole with respect to the C-vinyl one, predictable, in principle, on the basis of the results obtained in the hydroformylation of the mono vinylpyrrole isomers [7,12], is not an obvious result if we take into account the behavior of styrene and 2- or 4-vinylpyridine [18] under hydroformylation condition. When the above substrates are hydroformylated separately, styrene reacts faster than vinylpyridines. In contrast, for a mixture of styrene and vinylpyridine, the reaction rate of vinylpyridine is much higher than that of styrene. In practice, vinylpyridine prevents the styrene reactivity and only when the vinylpyridine disappears does hydroformylation of styrene take place.

In conclusion, the rhodium-catalyzed hydroformylation of the divinylpyrroles **1a** and **1b** to 1-vinylpyrrolylmonoaldehydes reported here is an original example of a chemoselective and twice regioselective reaction: in fact the insertion of the formyl group selectively occurs on C_α carbon atom of the C-vinyl group.

As 2-pyrrolylpropanals are precursors of biologically active compounds [19], the N-vinyl pyrrolylaldehydes obtained could constitute versatile intermediates in the synthesis of fine chemicals.

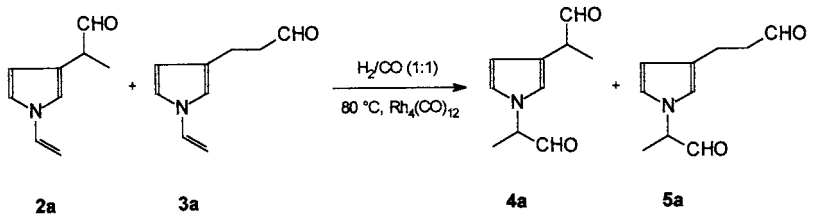
It is interesting that the dialdehydes coming from the high-temperature hydroformylation of N-vinylpyrrolyldialdehydes constitute the first example of 1,7- and 1,8-dialdehydes carrying out a pyrrole ring in the middle of the carbon atom chain. Actually dialdehydes of this type are the subject of considerable interest as cross-linking agents in the biochemistry of proteins as well as new tanning agents. They represent an alternative to the traditional chromium-based ones [20].

In the light of the above findings, hydroformylation in the presence of rhodium-based catalyst precursors is likely to be an increasingly useful synthetic method, because of its tolerance to a variety of functional groups [21–24]. In order to expand this potential, we are now carrying out studies on the rhodium-catalyzed hydroformylation of vinyl- and allylpyrroles bearing other groups on the heteroaromatic ring.

4. 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. Microanalyses were performed at Laboratorio di Microanalisi, Istituto di Chimica Organica, Facoltà di Farmacia, Università di Pisa. ^{1}H-NMR spectra (200 MHz) were recorded in $CDCl_3$. 1-vinylpyrrole [16], 3-vinylpyrrole [15], 1,3-divinylpyrrole (**1a**) [14] and 1,2-divinylpyrrole (**1b**) [14] were synthesized as described in the literature. $Rh_4(CO)_{12}$ was prepared according to a well-known procedure [25,26].



Scheme 2.

4.1. Hydroformylation of vinyl and divinylpyrroles

4.1.1. General procedure

*4.1.1.1. 2-(1-Vinylpyrrol-3-yl)propanal (**2a**).* A solution of 1,3-divinylpyrrole (**1a**) (4.2×10^{-3} mol) and $Rh_4(CO)_{12}$ (21 mg, 2.8×10^{-5} mol) in toluene (5 ml) was introduced by suction into an evacuated 25 ml stainless steel reaction vessel. Carbon monoxide was introduced, the autoclave was then rocked and heated to 40°C and hydrogen was rapidly introduced to the desired total pressure (120 atm; 1:1 $CO-H_2$). After 3 h at 40°C the reaction was completed and regioisomeric ratio **1a**/**1b** was 92/8. From the reaction mixture 2-(1-vinylpyrrol-3-yl)propanal (**2a**) was obtained as an oily residue, by column chromatography on silica gel, by eluting with 3:1 hexane–EtOAc; ^{1}H-NMR δ 9.58 (d, 1H, $J = 1.14$ Hz), 6.80 (m, 1H), 6.72 (m, 1H), 6.70 (dd, 1H, $J = 15.7$ Hz, $J = 8.8$ Hz), 6.06 (m, 1H), 5.01 (dd, 1H, $J = 15.7$ Hz, $J = 1.5$ Hz), 4.58 (dd, 1H, $J = 8.8$ Hz, $J = 1.5$ Hz), 3.45 (m, 1H), 1.30 (d, 3H); MS *m/e* 149 (M^+, 28.5), 120 (100), 105 (9.5), 91 (14.2), 77 (15.8), 65 (12.7). Anal. Calc. for $C_9H_{11}NO$: C, 72.4; H, 7.4; N, 9.4. Found: C, 72.4; H, 7.4; N, 9.4.

*4.1.1.2. 3-(1-Vinylpyrrol-3-yl)propanal (**3a**).* ^{1}H-NMR typical signals δ 9.81 (t, 1H), 2.95–2.80 (m, 4H); MS *m/e* 149 (M^+, 51.5), 135 (29.6), 120 (61), 106 (100), 93 (64), 77 (21.8), 65 (23.4).

*4.1.1.3. 2-(1-Vinylpyrrol-2-yl)propanal (**2b**).* Prepared according to the general procedure except that **1b** was used. Colorless oil (SiO_2; hexane–EtOAc 3:1); ^{1}H-NMR δ 9.46 (d, 1H), 7.03 (m, 1H), 6.84 (dd, 1H, $J = 15.6$ Hz, $J = 8.8$ Hz), 6.21 (m, 1H), 6.05 (m, 1H), 5.13 (dd, 1H, $J = 15.6$ Hz), 4.74 (dd, 1H, $J = 8.8$ Hz,), 3.67 (q, 1H), 1.42 (d, 3H); MS *m/e* 149 (M^+, 29), 130 (4.8), 120 (100), 105 (27.7), 93 (13.8), 80 (12.5). Anal. Calc. for $C_9H_{11}NO$: C, 72.4; H, 7.4; N, 9.4. Found: C, 72.5; H, 7.4; N, 9.4.

*4.1.1.4. 3-(1-Vinylpyrrol-2-yl)propanal (**3b**).* ^{1}H-NMR typical signals δ 9.59 (t, 1H), 2.95–2.80 (m, 4H); MS *m/e* 149 (M^+, 72.2), 120 (33.3), 106 (100), 93 (70.8), 79 (50.7), 65 (18).

*4.1.1.5. 1,3-bis(1-formylethyl)pyrrole (**4a**).* ^{1}H-NMR δ 9.57 (d, 1H), 6.68 (m, 1H), 6.57 (m, 1H), 6.14 (m, 1H), 4.52 (q, 1H), 3.53–3.40 (m, 1H), 1.60 (d, 3H, $J = 7.3$ Hz), 1.37 (d, 3H, $J = 7.3$ Hz); MS *m/e* 179 (M^+, 26.5), 150 (95.3), 122 (100), 106 (17), 93 (17), 77 (20.3).

*4.1.1.6. 1-(1-Formylethyl)-3-(2-formylethyl)pyrrole (**4b**).* ^{1}H-NMR typical signals δ 9.81 (t, 2H), 2.95–2.70 (m, 4H); MS *m/e* 179 (M^+, 32.8), 150 (75), 122 (48.4), 106 (100), 94 (54.6), 79 (23.4).

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