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Note

Domino reaction sequences in the rhodium-catalyzed hydroformylation of 3-acetyl-1-allylpyrrole: a short route to 5,6,7,8-tetrahydroindolizines

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Abstract

When 3-acetyl-1-allylpyrrole (**1**) was subjected under hydroformylation conditions, with $Rh_4(CO)_{12}$ as catalyst precursor, to 30 atm CO/H_2 (1:1) total pressure and 140 °C, an equimolar mixture of the isomeric 5,6,7,8-tetrahydroindolizines **4′** and **5′** was obtained as the almost exclusive product. In both cases a domino hydroformylation/cyclization on the α pyrrole positions by the aldehyde **3** carbonyl group occurs which involves different intermediates: while **4′** is generated via the dihydroindolizine **4**, **5′** forms via direct reduction of 8-hydroxytetrahydroindolizine **5**, a structure that has never been observed before from 1-allylpyrroles under oxo conditions.

Keywords: Hydroformylation; 3-Acetyl-1-allylpyrrole; Rhodium; Catalysis; 5,6,7,8-Tetrahydroindolizines

1. Introduction

Domino reaction sequences are of great interest because they enable the atom-economic formation of C–C bonds, thus providing relatively easy access to complex molecular architectures [1]. Recently, we found a domino process in the intramolecular cyclodehydration of 4-pyrrolylbutanals generated by rhodium-catalyzed hydroformylation of 1-allylpyrroles: the aldehyde carbonyl group attacks the pyrrole position giving a 8-hydroxytetrahydroindolizine which immediately undergoes water elimination to a 5,6-dihydroindolizine. This process occurs very easily with unsubstituted 1-allylpyrroles or with 1-allylpyrroles having an electron-donor group at the α- or β-position [2]. In contrast, when an electron-withdrawing group (a formyl or an acetyl group) is present at the α pyrrole position, the above cyclization does not occur but a dihydroindolizine derivative is nevertheless formed via an aldol condensation involving the pyrrole formyl group and the C2 butanal carbon atom [3]. In order to extend the investigation of the rhodium catalyzed hydroformylation of N-allylpyrroles to those substituted with electron-withdrawing groups on β pyrrole position, 3-acetyl-1-allylpyrrole (**1**) was subjected to oxo conditions. We found that the linear aldehyde **3**, the main *oxo* product (Scheme 1), gives, under reaction conditions, the new isomeric acetyl substituted 5,6,7,8-tetrahydroindolizines **4′** and **5′** (1:1) (Scheme 2). Interestingly, the aldehyde **3**, in the presence only of CO and the rhodium catalyst, gives the tricyclic alcoholic species **5** in addition to dihydroindolizine **4** (Scheme 2). Although a structure of type **5** has been frequently invoked as part of the cyclization mechanism, **5** is the first 8-hydroxytetrahydroindolizine identified under rhodium-catalyzed hydroformylation of N-allylpyrroles.

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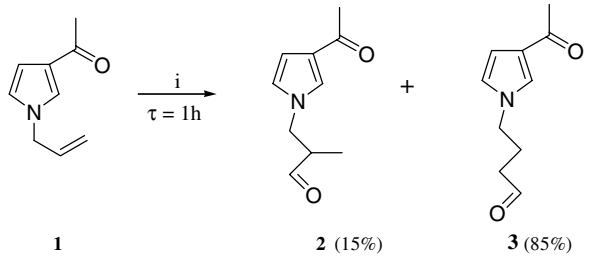


(i) $Rh_4(CO)_{12}$, CO/H_2 1:1, 30 atm, 140 °C, toluene.

Scheme 1.

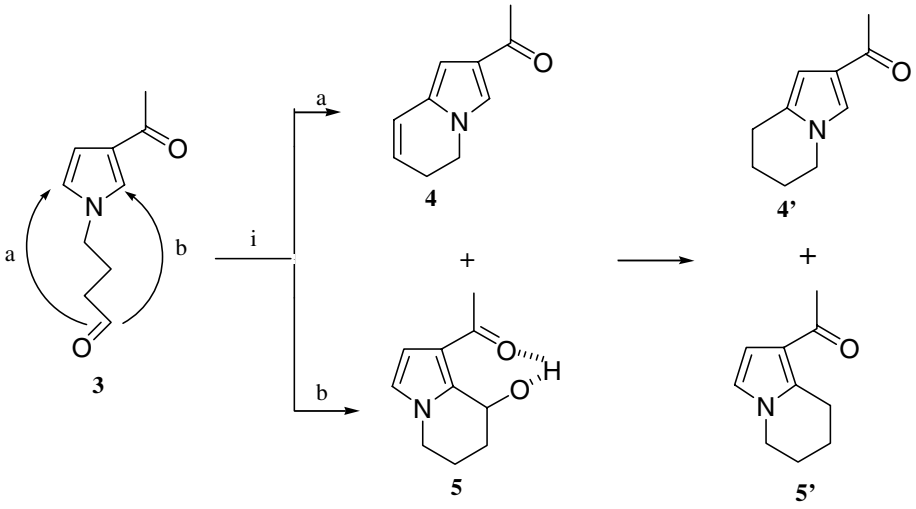
2. Results and discussion

The hydroformylation experiments on 1-allyl-3-acetylpyrrole (**1**) were carried out in a stainless steel autoclave, in toluene, with $Rh_4(CO)_{12}$ as catalyst precursor, at 30 atm total pressure (CO/H_2 = 1:1) and 140 °C, using a 200:1 substrate:Rh ratio. The substrate conversion was analysed by GC using acetophenone as internal standard.

After 1 h the starting olefin **1** was completely converted into the corresponding aldehydes, the linear isomer **3** being strongly favoured with respect to the branched one **2** (regioisomeric **3**:**2** molar ratio 85:15) (Scheme 1). This value was very similar to that observed for other 1-allylpyrroles under the above experimental conditions [2]: under these drastic conditions (high temperature, low pressure), no trace of the isomeric olefin 1-(pyrrol-1-yl)propene was found in the crude reaction mixture, at all conversions.

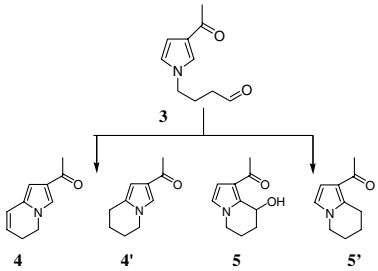
For long reaction times (τ = 48 h) (Table 1, entry 3), the linear aldehyde was completely transformed into two products, i.e., 2-acetyl-5,6,7,8-tetrahydroindolizine **4′** and 1-acetyl-5,6,7,8-tetrahydroindolizine **5′** in a 1:1 molar ratio. In contrast, the branched aldehyde **2**, which was present in very small amount, did not give cyclization products but only reduction to the corresponding alcohol.

According to the previous report [2], the formation of **4′** is explainable by an electrophilic attack of the carbonyl group of **3** on the C5 pyrrole carbon atom (route **a**, Scheme 2) via the conjugated dihydroindolizine **4**, which was identified in the crude reaction mixture at intermediate times (Table 1, entry 1). An analogous attack on pyrrole carbon atom C2 (route **b**, Scheme 2) instead of C5 occurs for the formation of **5′**: in this case the bicyclic alcohol **5** was found as a transient species (Table 1, entry 1 and 2). Note that **5** does not undergo water elimination but is converted into the tetrahydroindolizine **5′** via a direct reduction of the hydroxyl group (Table 1, entry 3). Indeed the corresponding dihydroindolizine has never been found in the crude reaction mixture. It is to be pointed out that the reduction of **4** to **4′** is faster than the transformation of tetrahydroindolizine **5** into the corresponding compound **5′**. However, it is possible to stop the reaction at the stage of formation of **4** and **5** by removing the CO/H_2 gas mixture after the complete conversion of **1** to **3** and by pressuring the reactor with CO only. In this way after 48 h the aldehyde **3** was quantitatively converted into an equimolar mixture of **4** and **5** (Table 1, entry 5). Reduction products **4′** and **5′** could not be detected. **4** and **5** were easily separated by column chromatography and characterized. The hydroxylated indolizidines have attracted special interest by virtue of their varied and pharmaceutically useful biological actions as potential antiviral, antitumor, and immunomodulating agents [4]. In particular, tetrahydroindolizines bearing both an acetyl group at C1 and a hydroxyl group at C8 show antithrombotic activity or are intermediates for the preparation of antithrombotic derivatives. They also show anti-TNF activity [5]. **5** is likely to be stabilized by an intramolecular



Scheme 2. (i) $Rh_4(CO)_{12}$, CO/H_2 1:1, 30 atm, 140 °C, toluene.

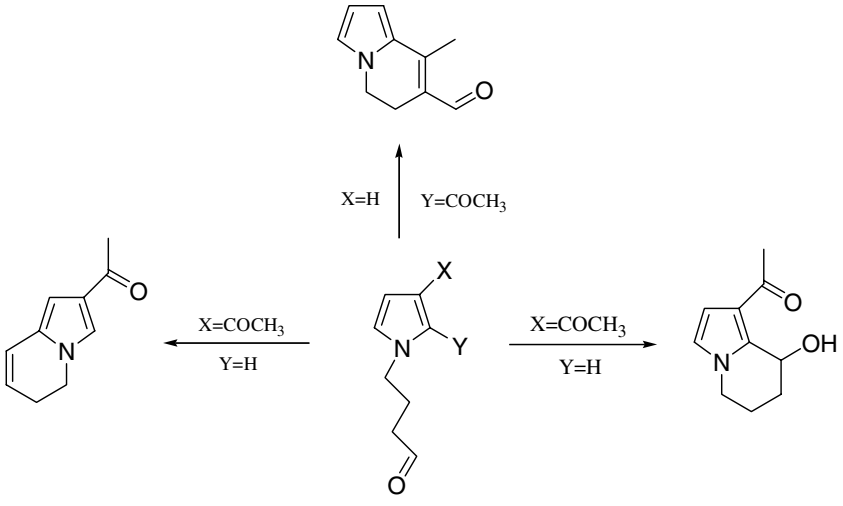
Table 1
Distribution of the cyclization products resulting from 4-(3-acetylpyrrol-1-yl)butanal (**3**)[a] in the presence of $Rh_4(CO)_{12}$, with CO/H_2 or CO only gas pressure

Entry	CO (atm)	H_2 (atm)	Reaction Time (h)	Conv. (%)[b]	 **4**	**4'**	**5**	**5'**
					(%)[b]	(%)[b]	(%)[b]	(%)[b]
1	15	15	11	58	16	5	15	6
2	15	15	24	100	-	45	30	25
3	15	15	48	100	-	45	-	55
4	30	-	23	50	25	-	25	-
5	30	-	48	100	50	-	50	-

[a] Reaction conditions: 0.2 g (1.34 mmol) of 3-acetyl-1-allylpyrrole (**1**) as the starting material, 5 ml toluene, 3 mg $Rh_4(CO)_{12}$ ($7x10^{-3}$ mmol, substrate/Rh = 200/1), 140 °C, autoclave volume 25 ml.
[b] Determined by GLC using acetophenone as internal standard.

hydrogen bond between the hydroxylic hydrogen and the carbonyl oxygen atom with consequent formation of a tricyclic structure. This factor could be the driving force for the formation of **5** in an amount (1:1 molar ratio with respect **4**) that would not be expected on the basis of otherwise unfavourable steric and electronic effects. In accord with this structural hypothesis, the IR spectrum showed a band due to OH stretching at an unexpectedly low frequency (3037 cm^{-1}). This value was independent of concentration (10^{-2}, 10^{-3}, 10^{-4} M solution in CCl_4) as expected for an intramolecular, rather than intermolecular, hydrogen bond.

In conclusion, the hydroformylation of 3-acetyl-1-allylpyrrole reported here constitutes an interesting extension of the reactivity of 1-allylpyrroles substituted with electron-withdrawing groups. Unlike the analogous 2-acetyl-1-allylpyrrole [3], which undergoes no electrophilic substitution but only aldol condensation (Scheme 3), the presence of the acetyl group on the β pyrrole position makes the α pyrrole positions



Scheme 3.

still available for the electrophilic attack of the carbonyl moiety. Interestingly, cyclization is much slower than hydroformylation, thus allowing either the aldehydes or the corresponding cyclization products to be recovered as required. Of these last, tetrahydroindolizines can be obtained at long reaction times under a CO/H_2 gas mixture, dihydroindolizine or 8-hydroxytetrahydroindolizine being the exclusive products under CO pressure only. Because of the interest in the hydroxylated indolizines, the rhodium-catalyzed hydroformylation of appropriate 3-carbonylsubstituted-1-allylpyrroles could be a convenient protocol for the synthesis of this class of compounds.

3. Experimental

All reagents were of commercial quality. Silica gel and alumina (70–230 mesh) were 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 ^1H 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 BP1 capillary column, using nitrogen as 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 carrier gas. IR spectra were recorded on a Perkin–Elmer FT-IR spectrophotometer 1760X. $Rh_4(CO)_{12}$ was prepared according to a well-known procedure [6,7]. 3-acetylpyrrole was prepared as reported in the literature [8].

3.1. Preparation of 1-allyl-3-acetylpyrrole (*1*)

To a stirred mixture of 50% aqueous NaOH (13 ml) solution, 3-acetylpyrrole (2.5 g, 0.027 mol) and tetrabutylammonium hydrogen sulfate (1.0 g, 3.0 mmol) in toluene (80 ml), was added 3-bromo-1-propene (2.4 ml, 0.027 mol). The mixture was then heated at 70 °C, with vigorous stirring, for 1 h. The cooled mixture was diluted with water and extracted with ether. The combined organic extracts were washed with water, dried (Na_2SO_4), and evaporated in vacuo to give a residue which was distilled at reduced pressure ($T = 40$ °C; $P = 0.3$ mmHg) giving 3.23 g (0.02 mol, 87% yield) of **1** as a yellowish oil. ^1H NMR δ 7.29 (t, $J = 2.0$ Hz, 1H, pyr-H), 6.63 (m, 2H, pyr-H), 5.89–6.05 (m, 1H, CH═), 5.12–5.32 (m, 2H, N-CH_2), 4.52 (dd, $J = 6.0$; 4.0; 1.4 Hz, 2H, CH_2═), 2.42 (s, 3H, CH_3CO). ^{13}C NMR δ 193.1 (CO), 133.0 (CH═), 125.8 (pyr-H), 122.2 (pyr-H), 118.3 (CH_2═), 109.1 (pyr-H), 52.3 (C–N), 26.9 (CH_3–). MS *m/e* 149 (M^+ 40), 134 (100), 106 (20), 94 (25), 79 (19), 66 (15), 51 (15), 41 (35).

3.2. Hydroformylation of 1-allyl-3-acetylpyrrole (*1*). General procedure

A solution of 1-allyl-3-acetylpyrrole (**1**) (0.2 g, 1.34 mmol) and $Rh_4(CO)_{12}$ (3 mg, 7×10^{-3} mmol, substrate/Rh = 200/1) 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, heated to 140 °C and hydrogen was rapidly introduced to 30 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 with use of acetophenone as internal standard.

Selected data for 4-(3-acetylpyrrol-1-yl)butanal (**3**). As a yellow oil (Al_2O_3; benzene/EtOAc = 70/30). ^1H NMR δ 9.69 (t, $J = 0.6$ Hz, 1H, COH), 7.21 (t, $J = 2.4$ Hz, 1H, pyr-H), 6.60 (m, 2H, pyr-H), 4.25 (dd, $J = 6.8$; 14.4 Hz, 2H, CH_2–N), 2.41 (t, $J = 7.6$ Hz, 2H, CH_2–CO), 2.30 (s, 3H, CH_3CO), 2.10 (m, 2H, CH_2). MS *m/e* 179 (M^+ 14), 164 (10), 161 (16), 151 (54), 146 (30), 136 (82), 94 (100), 80 (40), 71 (46), 66 (7). Selected data for 2-methyl-3-(3-acetylpyrrol-1-yl)propanal (**2**). As a yellow oil (Al_2O_3; benzene/EtOAc = 70/30). ^1H NMR δ 9.62 (d, $J = 1.1$ Hz, 1H, COH), 7.18 (t, $J = 2.0$ Hz, 1H, pyr-H), 6.51 (m, 2H, pyr-H), 3.90 (dd, $J = 6.8$; 13.8 Hz, 2H, CH_2–N), 2.81 (q, $J = 7.0$ Hz, 1H, CH–), 2.30 (s, 3H, CH_3CO), 1.11 (d, $J = 7.0$ Hz, 3H, CH_3–). MS *m/e* 179 (M^+ 7), 164 (70), 151 (66), 136 (54), 122 (5), 109 (10), 108 (24), 94 (100), 93 (19), 80 (19), 66 (13), 52 (5). Selected data for 2-acetyl-5,6,7,8-tetrahydroindolizine (**4′**). As a yellowish oil (Al_2O_3, benzene/EtOAc = 70/30). ^1H NMR δ 6.50 (d, $J = 3.0$ Hz, 1H, pyr-H), 6.47 (d, $J = 3.0$ Hz, 1H, pyr-H), 3.90 (m, 2H, CH_2–N), 2.59 (m, 2H, CH_2–), 2.30 (s, 3H, CH_3CO), 1.77 (m, 2H, CH_2), 1.53 (m, 2H, CH_2). MS *m/e* 163 (M^+ 60), 148 (100), 120 (30), 106 (10).

Selected data for 1-acetyl-5,6,7,8-tetrahydroindolizine (**5′**). ^1H NMR δ 6.99 (s, 1H, pyr-H), 6.35 (s, 1H, pyr-H), 3.90 (m, 2H, CH_2–N), 2.59 (m, 2H, CH_2–), 2.30 (s, 3H, CH_3CO), 1.85 (m, 2H, CH_2), 1.56 (m, 2H, CH_2). MS *m/e* 163 (M^+ 50), 148 (100), 120 (10), 106 (30).

Selected data for 2-acetyl-5,6-dihydroindolizine (**4**). As a yellowish oil (Al_2O_3, benzene/EtOAc = 70/30). ^1H NMR δ 7.25 (s, 1H, pyr-H), 6.50 (t, $J = 1.2$ Hz, 1H, pyr-H), 6.48 (d, $J = 9.7$ Hz, 1H, CH═), 5.74 (dt, $J = 10.0$; 4.5 Hz, 1H, CH═), 3.91 (t, $J = 7.5$ Hz, 2H, CH_2–N), 2.52 (m, 2H, CH_2–C═), 2.30 (s, 3H, CH_3CO). MS *m/e* 161 (M^+ 55), 147 (8), 146 (100), 118 (10), 117 (15), 91 (13). Selected data for 1-acetyl-8-hydroxy-5,6,7,8-tetraidroindolizine (**5**). ^1H NMR δ 6.54 (d, $J = 3.0$ Hz, 1H, pyr-H), 6.47 (d, $J = 3.0$ Hz, 1H, pyr-H), 5.95 (d, $J = 1.8$ Hz, 1H, –OH), 4.95 (q, $J = 6.0$ Hz, 1H, CH-O), 3.90 (m, 2H, CH_2–N), 2.41 (s, 3H, CH_3CO), 2.13 (m, 2H, CH_2–), 1.90 (m, 2H, CH_2–). ^{13}C NMR δ 196.7 (CO), 164.4 (pyr-H), 146.6 (pyr-H), 119.6

(pyr-H), 111.3 (pyr-H), 62.4 (CH-O), 45.8 (C–N), 29.7 (CH_2–), 28.3 (CH_2–), 27.6 (CH_3–). MS *m/e* 179 (m^+ 38), 164 (23), 161 (58), 160 (9), 146 (100), 136 (24), 120 (10), 118 (14), 117 (15), 108 (31), 80 (16).

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