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# A shortcut hydroformylation route to 7-formyl-5,6-dihydroindolizine from 1-allyl-2-formylpyrrole

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**Abstract**

When 1-allyl-2-formylpyrrole (**1**) was subject to hydroformylation conditions with $Rh_4(CO)_{12}$ as catalyst precursor, at 100 atm total pressure and 100°C, 7-formyl-5,6-dihydroindolizine (**2′**) was produced together with the expected branched aldehyde (**3**), the linear isomer (**2**) being obtained in traces only. An intramolecular aldol condensation between the carbon atom adjacent to the formyl group in the chain and the carbonyl group directly bonded to pyrrole ring most likely generates the indolizine structure.


*Keywords:* Hydroformylation; 1-Allyl-2-formylpyrrole; Rhodium; Catalysis; Indolizine

## 1. Introduction

Aldehydes produced via hydroformylation are not always the final products. Due to the versatile chemistry of the formyl group, hydroformylation can also be integrated in tandem or domino reaction sequences [1]. Recently we found that tandem hydroformylation–cyclization–dehydration sequence of 1-allylpyrrole very easily occurs giving 5,6-dihydroindolizine [2]. In an extension of these studies to the hydroformylation of 1-allylpyrroles substituted on aromatic rings, we investigated the easily available 1-allyl-2-formylpyrrole (**1**). We found and report here that when **1** was submitted to hydroformylation in the presence of $Rh_4(CO)_{12}$ as catalyst precursor, at complete substrate conversion, a mixture of the isomeric *oxo*-dialdehydes **2** and **3** (**2**:**3** = 46:54) was found as almost exclusive product. By heating the reaction mixture for longer times, the linear aldehyde **2** disappeared and 7-formyl-5,6-dihydroindolizine (**2′**) was obtained, whereas the branched aldehyde **3** remained unchanged (Scheme 1).

The hydroformylation experiments on 1-allyl-2-formylpyrrole (**1**) were carried out in a stainless steel autoclave, in toluene, with $Rh_4(CO)_{12}$ as catalyst precursor, at 100°C, at 100 atm total pressure ($CO:H_2$ = 1:1), using a 100:1 substrate:rhodium ratio. The substrate conversion and the composition of the reaction mixture were analysed at different times by GC and GC–MS, using acetophenone as internal standard.

The regioisomeric **3**:**2** ratio was 54:46 at partial conversion (Table 1, entry 1). This value was very similar to that observed in the case of unsubstituted 1-allylpyrrole (59:41 at the same temperature [2]), the presence of a formyl group on aromatic ring weakly affecting the regioselectivity of the reaction.

After 1 h at 100°C (Table 1, entry 2), the conversion was complete and the *oxo*-dialdehydes 4-(2-formylpyrrol-1-yl)butanal (**2**) and 2-methyl-3-(2-formylpyrrol-1-yl)propanal (**3**) were the almost exclusive isomeric products (97%). A low amount of 7-formyl-5,6-dihydroindolizine (**2′**) ($< 3\%$) was also observed. When the crude reaction mixture was allowed to stand under $CO:H_2$ pressure for longer reaction times, an increase of the dihydroindolizine **2′** was observed together with the reduction of the carbonyl group of both the branched and the linear dialdehydes **3** and **2** to the corresponding hydroxyl groups. When,

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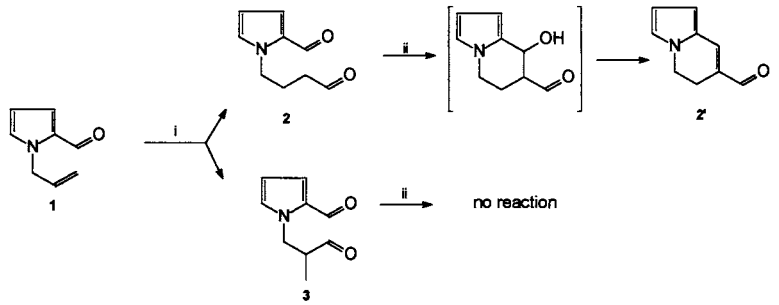


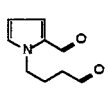
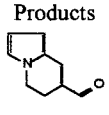
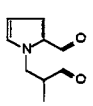

Scheme 1. (i) $Rh_4(CO)_{12}$, 100 atm $CO:H_2 = 1:1$, 100°C, toluene, 1 h. (ii) The same conditions as (i), 72 h under $N_2$ atmosphere, after CO and $H_2$ removal.

at complete substrate conversion, the $CO:H_2$ gas mixture was removed and the autoclave was heated at 100°C for additional 72 h (Table 1, entry 3c), the dialdehyde **2** disappeared and **2′** was 46% of the total products, the branched dialdehyde **3** (54%) staying unreacted during all the reaction time.

Aldehydes **2** and **3** and dihydroindolizine **2′** are all new compounds and are obtained as isolated products via elution on column chromatography. The two aldehydes were separated one from each other on $SiO_2$ (hexane:AcOEt = 2:1) from a 1 h time reaction mixture (Table 1, entry 2), while 7-formyl-5,6-dihydroindolizine was separated from aldehyde **3** on $Al_2O_3$ (hexane:AcOEt = 9:1) from a 72 h time reaction mixture (Table 1, entry 3). The compounds **2**, **3** and **2′** were characterised by GC–MS and IR analyses [3–5], $^1H$- and $^{13}C$-NMR spectroscopy (Table 2).

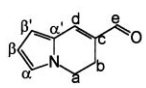
The above findings suggest that the indolizine structure **2′** comes from **2** likely via an intramolecular aldol addition between the carbon atom adjacent to the formyl group in the alkyl chain and the carbonyl group directly bonded to pyrrole ring. Then a bicyclic hydroxyaldehyde should form (Scheme 1), which very easily undergoes water elimination to give a double bond conjugated with both the pyrrole and the formyl group. In order to verify this hypothesis a sample of pure dialdehyde **2** was submitted to typical aldol condensation conditions with EtONa in absolute EtOH, at room temperature: selective formation of 7-formyl-5,6-dihydroindolizine was immediately observed, the precursor **2** resulting completely transformed into **2′**. In contrast, in absence of rhodium-catalyst, no traces of **2′** were observed by heating **2** in toluene at 100°C. On this light we can hypothesise that under hydroformylation condi-

Table 1
Composition of the crude reaction mixtures resulting from 1-allyl-2-formylpyrrole (**1**)[a] in the presence of $Rh_4(CO)_{12}$, at 100°C, with or without $CO:H_2$ gas pressure

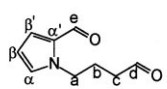
| Entry | CO (atm) | $H_2$ (atm) | Reaction Time (h) | Conversion (%)[b] | Products | | |
|---|---|---|---|---|---|---|---|
| | | | | |  **2** (%)[b] |  **2'** (%)[b] |  **3** (%)[b] |
| 1 | 50 | 50 | 0.5 | 58 | 46 | - | 54 |
| 2 | 50 | 50 | 1.0 | 100 | 43 | <3 | 54 |
| 3 | a) - | - | 1.2 | " | 39 | <7 | 54 |
| | b) - | - | 24 | " | 37 | 9 | 54 |
| | c) | | 72 | " | - | 46 | 54 |

[a]Reaction conditions: 0.5g of **1**, 10ml toluene, 7mg $Rh_4(CO)_{12}$ (substrate/Rh=100/1); autoclave volume 25 ml.
[b]Determined by GLC using acetophenone as internal standard.

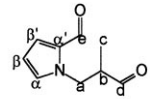
Table 2
$^{1}H$- and $^{13}C$-NMR parameters for 7-formyl-5,6-dihydroindolizine (2′), 4-(2-formylpyrrol-1-yl)butanal (2), 2-methyl-3-(2-formylpyrrol-1-yl)propanal (3)



2'



2



3

| Products | Nucleus | Chemical shifts [a] (δ [(a)]) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | α | α′ | β | β′ | a | b | c | d | e |
| **2′** | $^{1}H$ | 6.84 (s) | – | 6.27 (m) | 6.50 (m) | 4.04 (t) ($J = 7.3$ Hz) | 2.76 (t) ($J = 7.3$ Hz) | – | 7.22 (s) | 9.51(s) |
| | $^{13}C$ | 125.5 | 128.1 | 110.6 | 114.0 | 43.6 | 20.8 | 129.5 | 136.2 | 190.6 |
| **2** | $^{1}H$ | 6.95 (s) | – | 6.24 (t) ($J = 3.2$ Hz) | 6.94 (s) | 4.35 (t) ($J = 7.0$ Hz) | 2.10 (m) | 2.45 (t) ($J = 6.6$ Hz) | 9.73 (bs) | 9.52 (s) |
| | $^{13}C$ | 125.1 | 131.3 | 109.8 | 131.3 | 47.9 | 24.0 | 40.0 | 201.0 | 180.0 |
| **3** | $^{1}H$ | 7.00 (s) | – | 6.21(dd) ($J = 2.6$, 4.0 Hz) | 6.94 (dd) ($J = 1.6$, 4.0 Hz) | 4.66 (dd) ($J = 13.7$, 6.3 Hz) 4.30 (dd) ($J = 13.7$, 6.3 Hz) | 3.01 (m) | 1.12 (d) ($J = 7.2$ Hz) | 9.68 (bs) | 9.52 (bs) |
| | $^{13}C$ | 125.4 | 131.3 | 109.8 | 132.6 | 48.7 | 47.8 | 11.4 | 202.3 | 179.4 |

[a] Referred to TMS as internal standard; $CDCl_3$ as solvent.

tions the aldol condensation is promoted by a rhodium carbonyl, although at a very low rate. It is to remark that, the 3-formyl-5,6-dihydroindolizine, arising from an intramolecular attack of C5 pyrrole carbon atom on the carbonyl group of the alkyl chain of the dialdehyde **2**, previously observed in the case of simple 1-allylpyrrole hydroformylation [2], does not form, the above described aldol condensation being the exclusive process. Because of the presence of electron-withdrawing group on the pyrrole C2 carbon atom, the C5 carbon atom is not nucleophilic enough to bear the electrophilic attack of the carbonyl moiety.

Aldol condensations of oxo aldehydes under hydroformylation conditions have been often observed [6–8]. Recently several efforts have been reported in literature to combine hydroformylation with a consecutive aldol reaction in a one pot sequence [9–12]. As far as we know, the process here described constitutes the first example of tandem hydroformylation–aldol condensation sequence devoted to the synthesis of indolizine moiety. Hydro derivatives of indolizine are an interesting and topical subject because some of these occur in natural products [13]. The rhodium-catalysed hydroformylation of appropriate 1-allyl-2-formylpyrroles could be a convenient protocol for the synthesis of this class of compounds.

## 2. Experimental

All reagents were of commercial quality. Silica gel and aluminium oxide (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 ($\delta$) 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 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 [14,15].

### 2.1. Preparation of 1-allyl-2-formylpyrrole (*1*)

To a stirred mixture of 50% aqueous NaOH (20 ml) solution, 2-formylpyrrole (3.0 g, 31.6 mmol) and tetrabutylammonium hydrogen sulfate (1.2 g, 3.5 mmol) in toluene (50 ml), was added 3-chloro-1-propene (2.7 ml, 2.5 g, 32.7 mmol). 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 3.4 g (25.3 mmol, 80% yield) of **1** as a orange oil. $^1H$-NMR: $\delta$ 9.55 (s, 1H), 6.96 (m, 2H), 6.26 (t, 1H), 5.98 (m, 1H), 5.17 (d, 1H), 5.04–4.95 (m, 3H). $^{13}C$-NMR: 179.5, 134.0, 131.0, 124.3, 116.9, 110.0, 51.0.

### 2.2. Hydroformylation of 1-allyl-2-formylpyrrole (*1*)

#### 2.2.1. General procedure

A solution of 1-allyl-2-formylpyrrole (**1**) (0.5 g, 3.7 mmol) and $Rh_4(CO)_{12}$ (7 mg) in toluene (11 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 100°C and hydrogen was rapidly introduced to 100 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 products distributions were determined by GC/GC–MS control, by using acetophenone as internal standard.

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[3] **2**: MS *m/e* 147 ($M^+ - 18$, 46), 136 (27), 118 (100), 108 (36), 91 (22). IR neat 1721.1 ($\nu_{c=o}$), 1660.2 ($\nu_{c=o}$).
[4] **3**: MS *m/e* 137 ($M^+ - 28$, 40), 118 (43), 108 (31), 104 (38), 94 (100), 80 (40). IR neat 1723.9 ($\nu_{c=o}$), 1659.6 ($\nu_{c=o}$).
[5] **2′**: MS *m/e* 147 ($M^+$, 66), 146 (61), 118 (100), 117 (58), 91 (19). IR neat 1606.4 $cm^{-1}$ ($\nu_{c=c}$), 1646.7 ($\nu_{c=o}$).
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